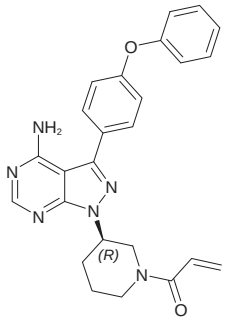
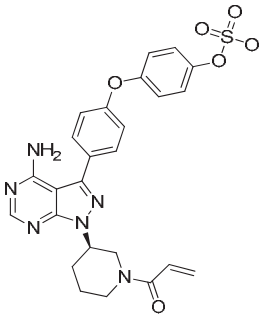
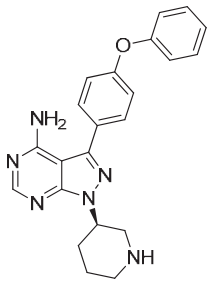
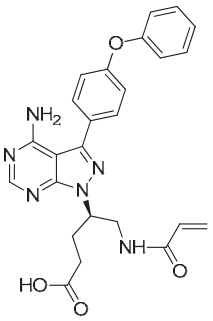
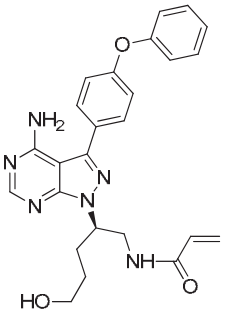
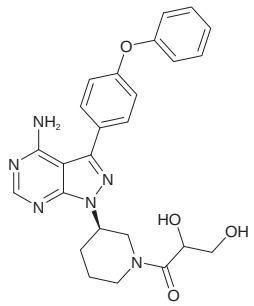
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## 略号一覧表

| 略号又は略称 | 化学名又は一般名 | 構造式 | 由来 |
|---|---|---|---|
| イブルチニブ（PCI-32765 又は JNJ-54179060） | 1-{(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one |  | 主薬 |
| PCI-45994（JNJ-63788621） | 末端フェニル基水酸化体の硫酸抱合体（M21） |  | 代謝物 |
| PCI-7503（JNJ-54243696） | アミド加水分解体（M23） |  | 代謝物 |
| PCI-45741（JNJ-55499730） | ピペリジン環の酸化的開環及びカルボン酸への酸化体（M25） |  | 代謝物 |
| PCI-45752（JNJ-55499743） | ピペリジン環の酸化的開環及び第一級アルコールへの還元体（M34） |  | 代謝物 |

| | | | |
|---|---|---|---|
| PCI-45227<br>（JNJ-54243761） | ジヒドロジオール体<br>（M37） |  | 代謝物 |

| 略号又は略称 | 名称及び内容 |
|---|---|
| CLL | 慢性リンパ性白血病（chronic lymphocytic leukemia） |
| Janssen R&D | Janssen Research & Development, LLC |
| LC-MS/MS | 液体クロマトグラフィーータンデム質量分析（liquid chromatography-tandem mass spectrometry） |
| MCL | マントル細胞リンパ腫（mantle cell lymphoma） |
| PCYC | Pharmacyclics, Inc. |
| SLL | 小リンパ球性リンパ腫（small lymphocytic lymphoma） |

## 2.7.1 生物薬剤学試験及び関連する分析法

イブルチニブ（PCI-32765 及び JNJ-54179060）について「再発又は難治性のマントル細胞リンパ腫」に対する適応を追加承認申請するにあたり，新たな生物薬剤学試験は実施していない。本モジュールでは，本申請に含む臨床試験で使用した製剤情報，及び当該臨床試験より得られた生体試料中の濃度測定に使用した分析法の概要を示す。

### 2.7.1.1 背景及び概観

#### 2.7.1.1.1 製剤開発

##### 2.7.1.1.1.1 製剤開発過程

現在，国内において承認［適応：再発又は難治性の慢性リンパ性白血病（小リンパ球性リンパ腫を含む）］されている市販用製剤は，白色不透明の 0 号硬カプセル剤に，有効成分としてイブルチニブ 140 mg，並びに添加剤として結晶セルロース，クロスカルメロースナトリウム，ラウリル硫酸ナトリウム及びステアリン酸マグネシウムを充填したものである。

本薬の開発の初期段階では，[redacted]（[redacted]社）で 40 mg，140 mg 及び 200 mg のイブルチニブを含有する 3 種類のカプセル剤を製造し，これらカプセル剤を初期の海外第 I 相及び II 相試験で使用した。その後，製造を[redacted]社から[redacted]（[redacted]社）に移管した。[redacted]社では 140 mg カプセル剤のみを製造しており，当該カプセル剤を臨床試験用製剤及び市販用製剤として使用している。【1.13.1-3 既承認資料 CTD 2.3.P.2 参照】

[redacted]社製剤と[redacted]社製剤のロット分析結果及び溶出プロファイルに差異は認められず，両製剤の同等性が示された。同様に，[redacted]社で製造した臨床試験用製剤と市販用製剤についても，両製剤の同等性が示された。【1.13.1-3 既承認資料 CTD 2.3.P.2 参照】

##### 2.7.1.1.1.2 製剤

本申請に含む臨床試験のうち，開発初期に実施した海外第 II 相試験（PCYC-1104-CA 試験）では[redacted]社製剤及び[redacted]社製剤の両方を使用したが，その他の臨床試験では[redacted]社製剤のみを使用した。[redacted]社製剤及び[redacted]社製剤について，本申請に含む臨床試験で使用した製剤の曝露サイクルの割合を表 2.7.1-1 に示す。各臨床試験で使用した製剤及びロット番号の一覧は付録-1 に示す。

表 2.7.1-1 製剤の曝露サイクルの割合

| 実施地域 | 開発の相 | 試験番号 | カプセルの含量（mg） | [redacted]社製剤 | [redacted]社製剤 |
|---|---|---|---|---|---|
| 国内 | II | PCI-32765MCL2002 | 140 | 100% | 0% |
| 海外 | I | PCI-32765CLL1007 | 140 | 100% | 0% |
| 海外 | II | PCYC-1104-CA | 140 | 87% | 13% |
| 海外 | II | PCI-32765MCL2001 | 140 | 100% | 0% |
| 海外 | III | PCI-32765MCL3001 | 140 | 100% | 0% |

参照元：各試験総括報告書（PCI-32765MCL2002：【5.3.5.2.1】，PCI-32765CLL1007：【5.3.4.1.1】，PCYC-1104-CA：【5.3.5.2.2-1】，PCI-32765MCL2001：【5.3.5.2.3-1】，PCI-32765MCL3001：【5.3.5.1.1】）

### 2.7.1.1.2　分析法

#### 2.7.1.1.2.1　イブルチニブ及び代謝物濃度の測定

血漿中イブルチニブ及び代謝物 PCI-45227（M37）濃度を，液体クロマトグラフィーータンデム質量分析（LC-MS/MS）法で定量した。本申請に含む臨床試験で使用した分析法は，再発又は難治性の慢性リンパ性白血病（小リンパ球性リンパ腫を含む）（2016 年 3 月承認）の承認申請（初回申請）時に提出したものと同一である。

また，PCI-45227（M37）を除く代謝物［JNJ-63788621（M21），JNJ-54243696（M23），JNJ-55499730（M25），JNJ-54243800（M26），及び JNJ-55499743（M34）］の血漿中濃度を，申請者（Janssen R&D）により確立された手法（LC-MS/MS 法）を用いて定量した。

本申請に含む臨床試験で使用した分析法の一覧を表 2.7.1-2 に示す。

表 2.7.1-2 各臨床試験における薬物濃度測定法

| 分析機関<br>（分析法番号） | 生体<br>試料 | 分析対象 | 定量範囲<br>（ng/mL） | 対象試験番号 | バリデーション<br>試験報告書<br>添付場所 |
|---|---|---|---|---|---|
| [redacted] 社 [a]<br>（AV11-PCI32765-01/10-088-Hu-Z-BMV） | 血漿 | イブルチニブ<br>PCI-45227 | 0.500 – 100<br>0.500 – 100 | PCYC-1104-CA | 評価資料<br>5.3.1.4.1 |
| [redacted] 社 [a,b]<br>（BA10399/JNJ-R2120A3; 12-156-Hu-Z-BMV） | 血漿 | イブルチニブ<br>PCI-45227 | 0.500 – 100<br>0.500 – 100 | PCI-32765MCL3001<br>PCI-32765MCL2001 | 参考資料<br>5.3.1.4.2 |
| [redacted] 社 [b]<br>（BA10667/JNJ-R3221; 14-112-Hu-Z-BMV） | 血漿 | イブルチニブ<br>PCI-45227 | 0.500 – 100<br>0.500 – 100 | PCI-32765MCL2002<br>PCI-32765MCL3001<br>PCI-32765CLL1007 | 評価資料<br>5.3.1.4.3 |
| Janssen R&D | 血漿 | JNJ-63788621<br>JNJ-54243696<br>JNJ-55499730<br>JNJ-54243800<br>JNJ-55499743 | 1.00 – 1000<br>0.100 – 100<br>1.00 – 1000<br>1.00 - 1000<br>1.00 –1000 | PCI-32765CLL1007 | NA [c] |

[a] これら分析法のクロスバリデーションを実施した【1.13.1-3 既承認資料 CTD 2.7.1.1.3.2 参照】
[b] これら分析法のクロスバリデーションを実施した【1.13.1-3 既承認資料 CTD 2.7.1.1.3.2 参照】
[c] 測定報告書（QBSS-PCI-32765CLL1007-plasma-JNJ-63788621-JNJ-54243696-JNJ-55499730-JNJ-55499743-JNJ-54243800）を試験総括報告書に添付した【5.3.4.1.1】

### 2.7.1.2　個々の試験結果の要約

該当なし

### 2.7.1.3　全試験を通しての結果の比較と解析

該当なし

## 2.7.1.4　付録

**付録-1 本申請に含む臨床試験で使用した製剤**

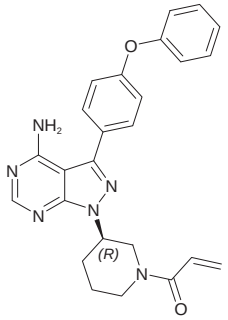
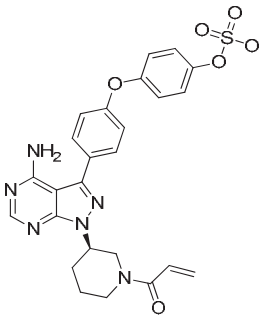
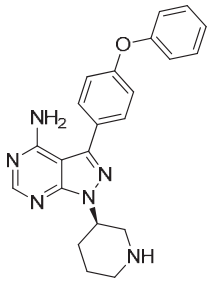
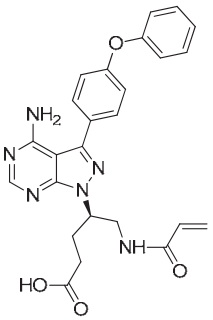
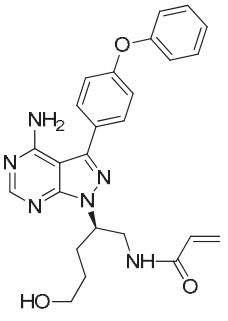
| 試験番号 | 製剤 | 製造施設 | ロット番号 |
|---|---|---|---|
| PCI-32765MCL2002 | 140 mg カプセル | [redacted] | L0403953 |
| PCYC-1104-CA | 140 mg カプセル | [redacted] | 10-0119 |
| | 140 mg カプセル | [redacted] | L0304110, L0304897, L0305448, L0305985, L0307025, L0307693, L0308265, L0308266 |
| PCI-32765MCL3001 | 140 mg カプセル | [redacted] | L0308541, L0309801, L0400217, L0400218, L0308541, L0402420, L0404313, L0404955, L0407872A, L0409196A |
| PCI-32765MCL2001 | 140 mg カプセル | [redacted] | L0308541, L0308792, L0400218 |
| PCI-32765CLL1007 | 140 mg カプセル | [redacted] | L0309801, L0406225 |

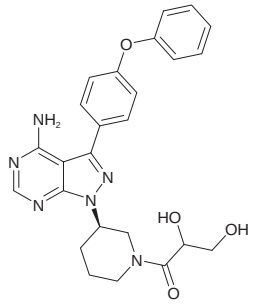
参照元：各試験総括報告書（PCI-32765MCL2002：【5.3.5.2.1】，PCI-32765CLL1007：【5.3.4.1.1】，PCYC-1104-CA：【5.3.5.2.2-1】，PCI-32765MCL2001：【5.3.5.2.3-1】，PCI-32765MCL3001：【5.3.5.1.1】）

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## 略号一覧表

| 略号又は略称 | 化学名又は一般名 | 構造式 | 由来 |
|---|---|---|---|
| イブルチニブ（PCI-32765 又は JNJ-54179060） | 1-{(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one |  | 主薬 |
| PCI-45994（JNJ-63788621） | 末端フェニル基水酸化体の硫酸抱合体（M21） |  | 代謝物 |
| PCI-7503（JNJ-54243696） | アミド加水分解体（M23） |  | 代謝物 |
| PCI-45741（JNJ-55499730） | ピペリジン環の酸化的開環及びカルボン酸への酸化体（M25） |  | 代謝物 |
| PCI-45752（JNJ-55499743） | ピペリジン環の酸化的開環及び第一級アルコールへの還元体（M34） |  | 代謝物 |

| | | | |
|---|---|---|---|
| PCI-45227<br>（JNJ-54243761） | ジヒドロジオール体<br>（M37） |  | 代謝物 |

| 略号又は略称 | 名称及び内容 |
|---|---|
| AUC | 血漿中濃度－時間曲線下面積（area under the plasma concentration-time curve） |
| $AUC_{\infty}$ | 0 時間から無限大時間までの血漿中濃度－時間曲線下面積（area under the plasma concentration-time curve from time zero to infinite time） |
| $AUC_{last}$ | 0 時間から最終定量可能時間までの血漿中濃度－時間曲線下面積（area under the plasma concentration-time curve from time zero to the last quantifiable time） |
| $AUC_{t}$ | 0 時間から t 時間までの血漿中濃度－時間曲線下面積（area under the plasma concentration-time curve from time zero to time t） |
| BCRP | 乳がん耐性たん白質（breast cancer resistance protein） |
| BTK | ブルトン型チロシンキナーゼ（Bruton’s tyrosine kinase） |
| CI | 信頼区間（confidence interval） |
| $C_{max}$ | 最高血漿中濃度（maximum plasma concentration） |
| CL | 全身クリアランス（total body clearance） |
| CLL | 慢性リンパ性白血病（chronic lymphocytic leukemia） |
| CR | 完全奏功（complete response） |
| CRi | complete response with incomplete blood count recovery |
| CV | 変動係数（coefficient of variation） |
| CYP | チトクローム P450（cytochrome P450） |
| ECG | 心電図（electrocardiogram） |
| $IC_{50}$ | 50%阻害濃度（50% inhibitory concentration） |
| Janssen R&D | Janssen Research & Development, LLC |
| MCL | マントル細胞リンパ腫（mantle cell lymphoma） |
| MTD | 最大耐量（maximum tolerated dose） |
| MPR | 代謝物/親化合物比（metabolite to parent ratio） |
| MRP | 多剤耐性関連たん白質（multidrug resistance-associated protein） |
| nPR | nodular partial response |
| OATP | 有機アニオン輸送ポリペプチド（organic anion transporting polypeptide） |
| OCT | 有機カチオントランスポーター（organic cation transporter） |
| ORR | 全奏効率（overall response ratio） |
| PBPK | 生理学的薬物動態（physiologically-based pharmacokinetic(s)） |
| PD | 疾患進行（progressive disease） |
| PFS | 無増悪生存期間（progression-free survival） |

| 略号又は略称 | 名称及び内容 |
|---|---|
| P-gp | P-糖たん白質（P-glycoprotein） |
| PR | 部分奏功（partial response） |
| PR | 心臓の電気的周期における P 波の開始から QRS 波の開始までの時間（measure of the time between the start of the P wave and the start of the QRS wave in the heart’s electrical cycle） |
| PRL | partial response with lymphocytosis |
| Q/F | みかけのコンパートメント間クリアランス（apparent inter-compartmental flow） |
| QRS | 心電図上の QRS 波（combination of Q, R, and S waves seen on an electrocardiogram） |
| QT | 心臓の電気的周期における Q 波の開始から T 波の終了までの時間（measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle） |
| QTcB | Bazett 法を使って心拍数で補正した QT 間隔（QT interval corrected for heart rate using Bazett's Formula） |
| QTcF | Fridericia 法を使って心拍数で補正した QT 間隔（QT interval corrected for heart rate using Fridericia's Formula） |
| QTcP | 試験固有の補正係数（power）を用い QT と RR の相関を補正した QT 間隔 |
| RR | 心臓の電気的周期における R 波から R 波までの時間（measure of the time between the R waves in the heart’s electrical cycle） |
| RUV | 説明のつかない残差変動（residual unexplained variability） |
| SD | 標準偏差（standard deviation） |
| SD | 安定（stable disease） |
| SLL | 小リンパ球性リンパ腫（small lymphocytic lymphoma） |
| $t_{1/2}$ | 消失半減期（elimination half-life） |
| $t_{max}$ | 最高血漿中濃度到達時間（time to reach the maximum blood or plasma concentration） |
| $V_c$ | 中枢コンパートメントの分布容積（volume of distribution of the central compartment） |
| $Vd_{ss}$ | 定常状態における分布容積（volume of distribution at steady state） |

## 2.7.2 臨床薬理試験

イブルチニブ（PCI-32765 及び JNJ-54179060）について「再発又は難治性のマントル細胞リンパ腫（MCL）」に対する適応を追加承認申請するにあたり，表 2.7.2-1 に示す臨床試験で薬物動態を評価した。

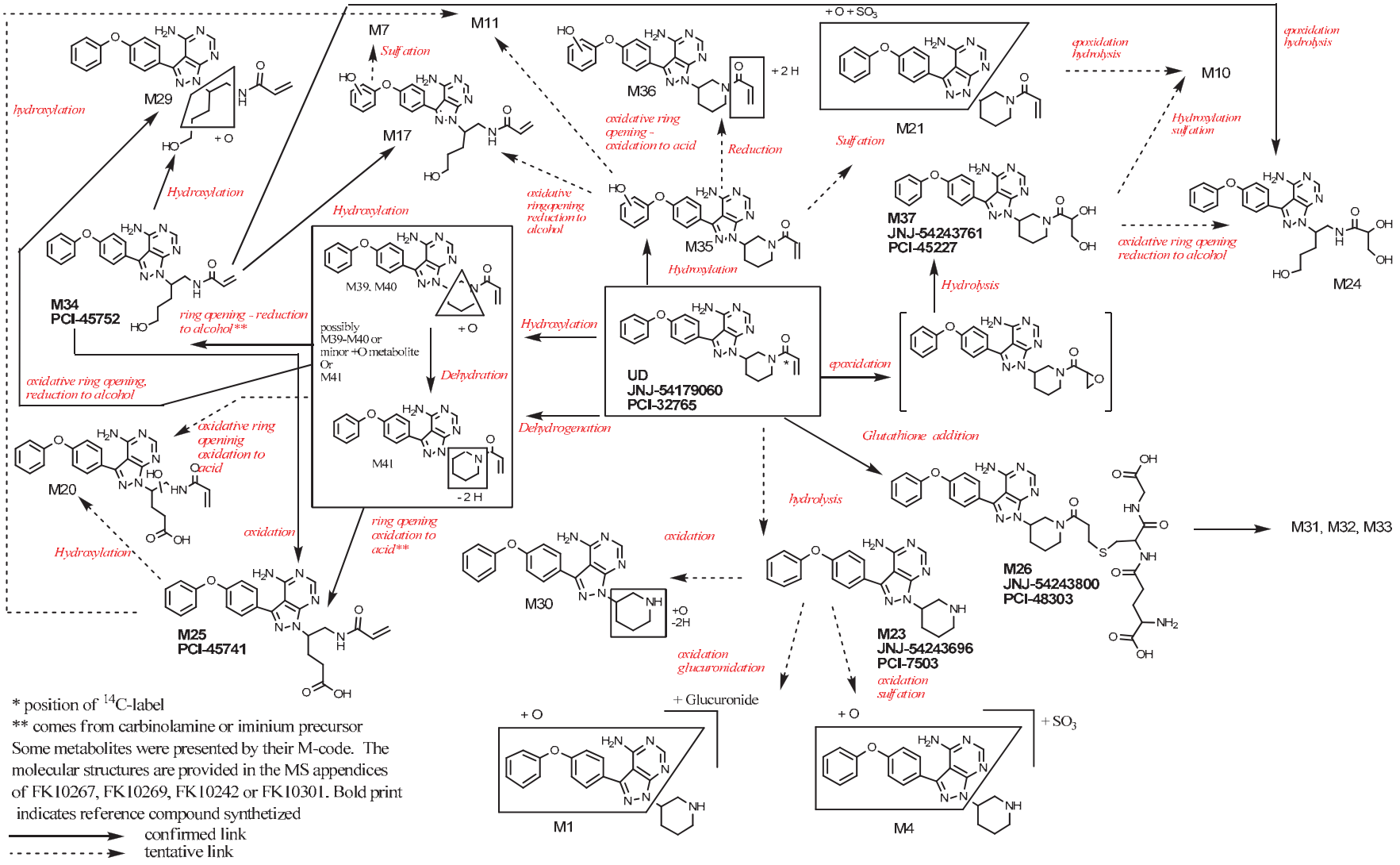
### 2.7.2.1 背景及び概観

本項では，再発又は難治性の慢性リンパ性白血病（CLL）［小リンパ球性リンパ腫（SLL）を含む］に対する適応（2016 年 3 月承認）の承認申請（初回申請）時以降に得られたヒト生体試料を用いた試験の概観，及び本申請に含む臨床試験で実施した薬物動態評価の概要を示す。

#### 2.7.2.1.1 ヒト生体試料を用いて実施した試験

##### 2.7.2.1.1.1 代謝

マスバランス試験［PCI-32765CLL1004（CLL1004）試験］の結果から推定されたイブルチニブの代謝経路を図 2.7.2-1 に示す【1.13.1-3 既承認資料 CTD 2.7.2.1.1.4 参照】。また，CLL1004 試験における放射能検出分析より，ヒト血漿中の重要な代謝物として，M21，M23，M25，M34，及び PCI-45227（M37）が示唆された【1.13.1-3 既承認資料 CTD 2.7.2.3.2.4 参照】。海外で実施した PCI-32765FLR2002（FLR2002）試験（用量 560 mg/日）で得られた血漿試料を用い，これら代謝物の濃度推移を評価したところ，M21，M23，M25，M34 及び M37 が定常状態における血漿中の重要な代謝物（AUC が未変化体の 25%以上）であることが示された【2.6.4.5.1.5 参照】。なお，M21，M23，M25，M34 及び M37 のブルトン型チロシンキナーゼ（BTK）に対する 50%阻害濃度（$IC_{50}$）中央値［イブルチニブの $IC_{50}$（0.39 nM）に対する活性比］はそれぞれ，621 nM（<1/1500），33.1 nM（<1/80），899 nM（<1/2000），80.7 nM（<1/200），6.16 nM（1/15）であった【2.6.2.6 及び 1.13.1-3 既承認資料 CTD 2.6.2.2.3 参照】。




* position of $^{14}C$-label
** comes from carbinolamine or iminium precursor
Some metabolites were presented by their M-code. The molecular structures are provided in the MS appendices of FK10267, FK10269, FK10242 or FK10301. Bold print indicates reference compound synthetized

confirmed link
tentative link

参照元：1.13.1-3 既承認資料 CTD 2.7.2.1.1.4

図 2.7.2-1 ヒトにおけるイブルチニブの推定代謝経路

#### 2.7.2.1.1.2 酵素の誘導及び阻害

代謝物 M21 は，チトクローム P450（CYP）2C8 に対して比較的強い阻害活性（$IC_{50}$：9.5 μmol/L）を，CYP2C9 に対して弱い阻害活性（$IC_{50}$：54～75 μmol/L）を示した。その他の CYP 分子種に対する阻害活性はほとんど認められなかった。静的薬物速度論に基づく考察から，M21 による CYP2C8 に対する臨床的に意義のある阻害作用が生じる可能性は低いと考えられた（予測 AUC 比：1.023）。【2.6.4.5.2.2 (2) 参照】

初回申請時に実施した *in vitro* 試験及び生理学的薬物動態（PBPK）モデルを用いた検討から，イブルチニブが消化管 CYP3A を軽度に阻害する可能性が示唆されていた【1.13.1-3 既承認資料 CTD 2.7.2.1.1.5 参照】。その後，CYP3A に対するイブルチニブの可逆的阻害について，より適切な実験条件の下で再検討し，新たに阻害定数（$K_i$）を算出した（worst case での $K_i$：1.34 μmol/L）。この $K_i$ 値及び PBPK モデルを用いた検討により，イブルチニブはミダゾラム（CYP3A の典型的基質）の曝露量に大きな影響を及ぼさないことが示され（予測 AUC 比：1.15），イブルチニブによる CYP3A に対する臨床的に意義のある阻害作用が生じる可能性は低いと考えられた。【2.6.4.5.2.2 (1) 参照】

CYP1A2，CYP2B6，CYP2C8，CYP2C9，CYP2C19，及び CYP2D6 に対するイブルチニブの時間依存的阻害について検討したところ，CYP2C9 について $IC_{50}$ の最も大きなシフトが認められた。PBPK モデルを用いた検討により，イブルチニブは S-ワルファリン（CYP2C9 の典型的基質）の曝露量に大きな影響を及ぼさないことが示され（予測 AUC 比：1.04），イブルチニブによる CYP2C9 に対する臨床的に意義のある時間依存的阻害作用が生じる可能性は低いと考えられた。【2.6.4.5.2.2 (1) 参照】

ヒト肝細胞を用い CYP1A2 及び CYP2B6 に対するイブルチニブの誘導活性について再検討したところ，CYP2B6 に対する弱い誘導活性が認められた【2.6.4.5.2.1 参照】。PBPK モデルを用いた検討により，イブルチニブはブプロピオン（CYP2B6 の典型的基質）の曝露量に影響を及ぼさないことが示され，イブルチニブによる CYP2B6 に対する臨床的に意義のある誘導作用が生じる可能性は低いと考えられた【2.6.4.5.2.1 参照】。CYP2B6 への誘導活性が認められたことから，イブルチニブが constitutive androstane receptor（CAR）による調節を受ける他の酵素及びトランスポーターの発現にも影響を及ぼす可能性があるものの，現時点において，臨床上の重要性は不明である。

初回申請時に提出した *in vitro* 試験では，CYP3A4 に対するイブルチニブの誘導活性は認められなかったものの，イブルチニブは速やかに代謝されるため，解釈には注意が必要である【2.6.4.5.2.1 参照】。しかし，これまでに得られた臨床薬物動態データから，イブルチニブは CYP3A 活性の変動に大きく影響を受ける CYP3A 基質であることが示されているが，単回投与時の曝露量から反復投与時の曝露量を予測可能であることから【1.13.1-3 既承認資料 CTD 2.7.2.2.1.5 参照】，イブルチニブによる臨床的に意義のある CYP3A 活性の変動が生じる可能性は低いと考えられた。

#### 2.7.2.1.1.3 トランスポーターを介した薬物相互作用

*In vitro* 試験より，イブルチニブは，有機カチオントランスポーター（OCT）2 を除き，P-糖たん白質（P-gp）及びその他の主要なトランスポーターの基質ではないことが示された。【2.6.4.7.1.1 参照】

イブルチニブは，臨床曝露量で全身循環性の P-gp 及び多剤耐性関連たん白質（MRP）1 を阻害する可能性は低いものの，全身循環性の乳がん耐性たん白質（BCRP）を阻害する可能性は否定することができない【2.6.4.7.1.2 (5) 1)参照】。また，イブルチニブは消化管の P-gp 及び BCRP を阻害する可能性があるが，その阻害の程度は顕著ではないと考えられた【1.13.1-3 既承認資料 CTD 2.6.4.7.3.2 参照】。

M21 は，BCRP，有機アニオン輸送ポリペプチド（OATP）1B1，及び OATP1B3 の基質であることが示された。なお，M21 は P-gp の基質ではなかった。【2.6.4.7.1.1 参照】

M21 は，BCRP 及び MRP1 に対する阻害活性（$IC_{50}$ はそれぞれ 2.31 μmol/L 及び 0.123 μmol/L）を示した。カットオフ基準に基づく考察において，阻害薬濃度（[I]）/$IC_{50}$ 比（[I]/$IC_{50}$）がそれぞれ 0.1 以上であったことから，M21 が臨床曝露量で BCRP 及び MRP1 を阻害する可能性を否定することはできない。【2.6.4.7.1.2 参照】

### 2.7.2.1.2 臨床薬理試験

#### 2.7.2.1.2.1 概観

本申請に含むすべての臨床試験でイブルチニブの薬物動態を検討した。試験一覧を表 2.7.2-1 に示す。各試験の概要については【2.7.6】に示す。

なお，国内試験を対象とした母集団薬物動態解析［2.7.2.2.1.3(2) 参照］は，初回申請で提出した PCI-32765-JPN-101（JPN-101）試験より得られた血漿中濃度データを含めて実施した。海外試験を対象とした母集団薬物動態解析［2.7.2.2.1.3(1)参照］及び曝露量－反応解析［2.7.2.2.2.2 参照］は，初回申請で報告した PCYC-04753（04753）試験，PCYC-1102-CA（1102）試験，及び PCYC-1112-CA（1112）試験，並びに初回申請及び本申請には含まれない PCYC-1117-CA（1117）試験，PCYC-1115-CA（1115）試験，及び PCI-32765CLL3001（CLL3001）試験より得られた血漿中濃度データを含めて実施した。

表 2.7.2-1 本申請に含む臨床試験の一覧

| 実施場所 | 相 | 試験番号 | 試験の主目的 | 対象被験者 | N[a] | 用量（mg） | 治験総括報告書添付場所 |
|---|---|---|---|---|---|---|---|
| 国内 | II | PCI-32765MCL2002 | 有効性 | 日本人 MCL 患者 | 16 | 560 | 評価資料 5.3.5.2.1 |
| 海外 | I | PCI-32765CLL1007 | Part 1：安全性及び忍容性<br>Part 2：Thorough QT | 外国人健康被験者 | Part 1：8<br>Part 2：20[b] | 840/1680 | 評価資料 5.3.4.1.1 |

| 実施場所 | 相 | 試験番号 | 試験の主目的 | 対象被験者 | N[a] | 用量（mg） | 治験総括報告書添付場所 |
|---|---|---|---|---|---|---|---|
| 海外 | II | PCYC-1104-CA | 有効性 | 外国人 MCL 患者 | 48 | 560 | 評価資料 5.3.5.2.2-1 5.3.5.2.2-2 |
| 海外 | II | PCI-32765MCL2001 | 有効性 | 外国人 MCL 患者 | 119 | 560 | 参考資料 5.3.5.2.3-1 5.3.5.2.3-2 |
| 海外 | III | PCI-32765MCL3001 | 有効性 | 外国人 MCL 患者 | 135[c] | 560 | 評価資料 5.3.5.1.1 |

MCL：マントル細胞リンパ腫
[a] 薬物動態解析対象集団
[b] 全投与集団
[c] イブルチニブ投与群

#### 2.7.2.1.2.2 評価方法

薬物動態を検討したいずれの試験においても血漿試料を採取し，液体クロマトグラフィーータンデム質量分析法（LC-MS/MS 法）で血漿中イブルチニブ及びジヒドロジオール代謝物 PCI-45227（M37）濃度を測定した。CLL1007 試験ではその他の代謝物（M21，M23，M25，M26 及び M34）の血漿中濃度も測定した。【2.7.1.1.2 参照】

#### 2.7.2.1.2.3 薬物動態解析法

薬物動態パラメータは，実採血時間を用いたノンコンパートメント法により算出した。本項では，特別な記載がない限り，算術平均値を代表値として使用した。

母集団薬物動態解析では，非線形混合効果モデルを用いてモデルパラメータを推定した。

### 2.7.2.2 個々の試験結果の要約

#### 2.7.2.2.1 薬物動態試験

##### 2.7.2.2.1.1 健康被験者での薬物動態試験

**(1) 海外 PCI-32765CLL1007 試験【評価資料 5.3.4.1.1】**

PCI-32765CLL1007（CLL1007）試験は，外国人健康成人被験者を対象とした 2 パートからなる第 I 相試験であった。パート 1 では，非盲検，2 期逐次デザインで，イブルチニブ 840 及び 1680 mg を単回経口投与したときの安全性及び忍容性並びに薬物動態を評価した。パート 2 では，二重盲検，4 期クロスオーバーデザインで，イブルチニブ 840 及び 1680 mg，モキシフロキサシン（400 mg，陽性対照）並びにプラセボを単回経口投与したときの QT/QTc 間隔及び心電図形態学に及ぼす影響並びに薬物動態を評価した。イブルチニブの曝露量（$C_{max}$）が最大となるように，いずれのパートにおいても，被験者は治験薬投与の 2 時間後に高脂肪食を摂取した【1.13.1-3 既承認資料 CTD 2.7.2.3.2.2 (1) 参照】。

パート 1 では 8 例の被験者を組み入れ，すべての被験者がイブルチニブ 840 及び 1680 mg の投与を受けた。パート 2 では，当初 64 例の組入れを計画していたが，1 例の被験者でイブルチニブ 1680 mg 投与期後に Grade 4 の肝酵素上昇が発現したため，20 例の被験者を組み入れたところで試験を中止した。その結果，パート 2 では，13 例が 840 mg イブルチニブを，14 例が 1680 mg イブルチニブを，13 例がプラセボを，14 例がモキシフロキサシンの投与を受けた。

ノンコンパートメント解析により求められたイブルチニブ 840 及び 1680 mg を単回経口投与したときの血漿中イブルチニブの薬物動態パラメータ（パート 2）を表 2.7.2-2 に示す。イブルチニブの $t_{max}$ 及び $t_{1/2}$ について用量間の差異は認められなかった。パート 1 においても同様の結果が得られた（付録 1）。また，探索的に用量比例性を評価した結果，$C_{max}$ は用量比例的な増加を示したが，AUC はやや用量比例性を上回る増加を示した【5.3.4.1.1 CSR Section 5.2.1.1 p.56 参照】。

PCI-45227（M37）についても同様の結果が得られた（付録 2）。

**表 2.7.2-2 外国人健康成人被験者にイブルチニブ 840 及び 1680 mg を単回経口投与したときの血漿中イブルチニブの薬物動態パラメータ［CLL1007 試験，パート 2］**

| | | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $AUC_{\infty}$ (ng·h/mL) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| 840 mg | N | 13 | 13 | 13 | 13 |
| | Mean (CV%) | 304 (59.4) | – | 1239 (54.6) | 6.0 (30.3) |
| | Median | 312 | 3.02 | 1232 | 6.1 |
| | Range | 60.0 – 67.0 | 1.52 – 6.03 | 293 – 2703 | 3.5 – 9.7 |
| 1680 mg | N | 14 | 14 | 14 | 14 |
| | Mean (CV%) | 719 (68.3) | – | 3832 (54.6) | 6.9 (26.6) |
| | Median | 638 | 4.06 | 3491 | 6.1 |
| | Range | 261 – 1890 | 2.07 – 6.03 | 1036 – 8307 | 4.8 – 10.3 |

参照元：5.3.4.1.1 PCI-32765CLL1007 試験 CSR Table 9

また，イブルチニブ 1680 mg を単回投与したときの 5 種類の代謝物（M21，M23，M25，M26 及び M34）の血漿中濃度を測定したところ，M23 を除き，FLR2002 試験で得られた定常状態における代謝物の血漿中濃度と同様の結果が得られた（2.7.2.1.1.1 参照）。イブルチニブ単回投与後の M23 の血漿中濃度は，反復投与後に比べて低値であった。【5.3.4.1.1 CSR Section 5.2.1.2 p.57 参照】

### 2.7.2.2.1.2 患者での薬物動態試験

#### (1) 国内 PCI-32765MCL2002 試験【評価資料 5.3.5.2.1】

PCI-32765MCL2002（MCL2002）試験は，再発又は難治性の MCL 患者を対象とした多施設共同，単群，第 II 相試験であった。疾患進行，完全奏効（CR）到達後の再発，耐容不能な毒性の発現，又は治験終了のいずれか早い時点まで，28 日間を 1 サイクルとして，イブルチニブ 560 mg（1 日 1 回）を経口投与した。サイクル 1 及び 2 の 1 日目に薬物濃度測定用のスパース試料を採取した。得られた薬物濃度データは母集団薬物動態解析により評価した。母集団薬物動態解析の結果は 2.7.2.2.1.3(2)に示す。

### (2) 海外 PCYC-1104-CA 試験【評価資料 5.3.5.2.2-1 及び 5.3.5.2.2-2】

PCYC-1104-CA（1104）試験は，病理学的に MCL と診断され 1 レジメン以上 5 レジメン以下の前治療を受けた後に再発した患者（外国人）を対象とした非盲検，多施設共同，第 II 相試験であった。被験者をボルテミゾブの治療歴に基づき 2 つのコホートに組み入れた。疾患進行，耐容不能な毒性の発現，又は長期継続試験への参加のいずれか早い時点まで，28 日間を 1 サイクルとして，イブルチニブ 560 mg（1 日 1 回）を経口投与した。米国の施設に組み入れられた被験者（全体集団の約 4 割）からのみ，サイクル 1 に薬物濃度測定用試料を採取し，血漿中イブルチニブ及び PCI-45227 の薬物動態を検討した。得られた薬物濃度データはノンコンパートメント解析及び母集団薬物動態解析（2.7.2.2.1.3(1) 参照）により評価した。

ノンコンパートメント解析により求められたイブルチニブ 560 mg を経口投与したときの血漿中イブルチニブの薬物動態パラメータを表 2.7.2-3 に示す。イブルチニブの吸収は速やかであり（$t_{max}$ 中央値：2 時間），その後速やかに消失した（$t_{1/2}$：6～8 時間）。ばらつきは大きかったものの，定常状態（8 日目）の $C_{max}$ 及び $AUC_{24}$ は，単回投与後（1 日目）に比べて増加した。$AUC_{24}$ の累積率は 1.40 であった。なお，サイクル 1 期間中のトラフ濃度が 8 日目以降増加しなかったことから【5.3.5.2.2-1 CSR Section 5.1 p.48 参照】，反復投与の開始後 1 週間以内に定常状態に到達したと考えられた。ボルテミゾブの治療歴の有無はイブルチニブの薬物動態に明らかな影響を及ぼさなかった【5.3.5.2.2-1 CSR Section 5.1 p.48 参照】。

PCI-45227 についても同様の結果が得られた（付録 2）。

表 2.7.2-3 MCL 患者にイブルチニブ 560 mg/日を経口投与したときの
血漿中イブルチニブの薬物動態パラメータ［1104 試験，サイクル 1］

| | | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $AUC_{24}$ (ng·h/mL) | $t_{1/2}$ (h) | 累積率 ($AUC_{24}$) |
|---|---|---|---|---|---|---|
| Day 1 | N | 48 | 48 | 45 | 20 | NA |
| | Mean (CV%) | 147 (97.6) | — | 802 (83.2) | 5.89 (33.3) | NA |
| | Median | 116 | 2.00 | 646 | 5.25 | NA |
| | Range | 7.86 – 890 | 0.75 – 22.75 | 57.7 – 3794 | 3.12 – 11.49 | NA |
| Day 8 | N | 45 | 45 | 43 | 21 | 42 |
| | Mean (CV%) | 164 (99.9) | — | 953 (74.0) | 8.48 (72.5) | 1.40 (53.8) |
| | Median | 102 | 2.00 | 830 | 6.92 | 1.26 |
| | Range | 5.23 – 956 | 0.00 – 4.12 | 115 – 3372 | 3.99 – 33.06 | 0.27 – 3.53 |

NA：Not applicable
参照元：5.3.5.2.2-1 PCYC-1104-CA 試験 CSR Table 13

### (3) 海外 PCI-32765MCL2001 試験【参考資料 5.3.5.2.3-1 及び 5.3.5.2.3-2】

PCI-32765MCL2001（MCL2001）試験は，ボルテゾミブ治療中又は治療後に疾患進行が認められた MCL 患者（外国人）を対象とした多施設共同，単群，第 II 相試験であった。疾患進行，CR 到達後の再発，耐容不能な毒性の発現，又は試験終了のいずれか早い時点まで，21 日間を 1 サイクルとして，イブルチニブ 560 mg（1 日 1 回）を経口投与した。サイクル 1 及び 2 の 1 日目に薬

物濃度測定用のスパース試料を採取した。得られた薬物濃度データは母集団薬物動態解析により評価した。母集団薬物動態解析の結果は 2.7.2.2.1.3(1)に示す。

#### (4) 海外 PCI-32765MCL3001 試験【評価資料 5.3.5.1.1】

PCI-32765MCL3001（MCL3001）試験は，1 レジメン以上の前治療を受けた再発又は難治性の MCL 患者（外国人）を対象に，イブルチニブとテムシロリムスの有効性及び安全性を比較するランダム化，実薬対照，非盲検，多施設共同，第 III 相試験であった。イブルチニブ群では，疾患進行，耐容不能な毒性の発現，又は試験終了のいずれか早い時点まで，21 日間を 1 サイクルとして，イブルチニブ 560 mg（1 日 1 回）を経口投与した。イブルチニブ群では，サイクル 1，2 及び 3 の 1 日目に薬物濃度測定用のスパース試料を採取した。得られた薬物濃度データは母集団薬物動態解析により評価した。母集団薬物動態解析の結果は 2.7.2.2.1.3(1)に示す。

### 2.7.2.2.1.3 母集団薬物動態解析

#### (1) 海外で実施した臨床試験成績に基づく母集団薬物動態解析【参考資料 5.3.3.5.1】

最新の海外試験データに基づき，初回申請時に報告した母集団薬物動態モデル【1.13.1-3 既承認資料 CTD 2.7.2.2.1.5 参照】をアップデートした。本解析には，1104 試験，MCL2001 試験，及び MCL3001 試験に加え，初回申請で報告した 04753 試験，1102 試験，及び 1112 試験，並びに初回申請及び本申請には含まれない 1115 試験，1117 試験，及び CLL3001 試験を統合したデータセットを用いた。さらに，内因性要因及び外因性要因がイブルチニブの薬物動態に及ぼす影響を再評価した。

本解析に用いたイブルチニブの血漿中濃度の統合データは，初回申請時に報告した解析で用いたデータ（04753 試験，1102 試験，及び 1104 試験の統合データ）とよい重なりを示し，初回申請時の最終モデル【1.13.1-3 既承認資料 CTD 2.7.2.2.1.5 参照】を大きく改変することなく適用可能であると考えられた。そこで，薬物動態モデルには，初回申請時と同じ 0 次－1 次吸収及び 1 次消失を伴う線形 2－コンパートメントモデルを用いた。最終モデルのパラメータ推定値を表 2.7.2-4 に示す。

**表 2.7.2-4 最終モデルでのパラメータ推定値**
**（海外で実施した臨床試験成績に基づく母集団薬物動態解析）**

| Parameter | Population mean estimate | %SEM | BSV (CV%) | %SEM |
|---|---|---|---|---|
| CL/F (L/h) | 1100 | 2.11 | 0 FIX | NA |
| V2/F (L) | 436 | 13.2 | 154.6 | 11.1 |
| Q/F (L/h) | 709 | 6.25 | 64.9 | 17.1 |
| V3/F (L) | 8660 | 4.45 | 56.0 | 21.0 |
| $k_a$ ($h^{-1}$) | 0.451 | 4.04 | 0 FIX | NA |
| ALAG1 (h) | 0.226 | 7.39 | 72.5 | 11.8 |
| D1 fast/mod fast (h) | 1.29 | 3.99 | 0 FIX | NA |
| D1 fed (h) | 3.29 FIX | NA | 0 FIX | NA |
| F1 mod fast/fed | 1 FIX | NA | 67.5 | 5.29 |
| F1 fast | 0.666 FIX | NA | 67.5 | 5.29 |
| Effect of CYP3A inhibitors on F1 (ratio) | 1.59 | 4.82 | － | － |

| Parameter | Population mean estimate | %SEM | BSV (CV%) | %SEM |
|---|---|---|---|---|
| Effect of age on F1 (power) | 0.699 | 19.6 | — | — |
| RUV (Studies 04753, 1102, 1104, 1112) (CV%) | 71.9 | 1.29 | — | — |
| RUV (Studies 1115, 1117) (CV%) | 48.8 | 5.50 | — | — |
| RUV (Studies CLL3001, MCL2001, MCL3001) (CV%) | 81.3 | 1.66 | — | — |

CL/F：apparent (oral) drug clearance，V2/F：apparent central volume of distribution，Q/F：apparent inter-compartmental flow，V3/F：apparent peripheral volume of distribution，$k_a$：first-order absorption rate constant，ALAG1：temporal delay (lag time) before absorption process is started，D1：duration of zero-order input，F1：relative bioavailability，RUV：residual unexplained variability，SEM：relative standard error of the mean parameter，BSV：between-subject variability，CV%：percent coefficient of variation，NA：not applicable，FIX：fixed in the model

本解析の最終モデルにおいて，経口クリアランス（CL/F）及び分布容積（V2/F と V3/F の和）はそれぞれ 1100 L/h 及び 9000 L と推定され，初回申請時に報告した最終モデルとよい一致を示した。最終モデルには，初回申請時の最終モデルで採用した共変量である，相対的バイオアベイラビリティ（F1；食後投与及び modified fasting 投与に比べ，絶食時投与で低下する）及び 0 次インプット持続時間（D1；絶食時投与及び modified fasting 投与に比べ，食後投与で延長する）に及ぼす食事の影響を保持した。しかし，初回申請時の最終モデルで採用した体重の分布容積への影響及び制酸薬の D1 への影響は，本解析では統計学的に有意な共変量とはならなかった。一方，本解析の最終モデルでは，CYP3A 阻害薬の併用及び年齢の F1 への影響が有意な共変量として新たに採用された（これらは，初回申請時の解析では，有意な共変量ではなかった）。中程度及び強力な CYP3A 阻害薬の併用は，イブルチニブの血漿中曝露量を母集団平均で 59%［95% 信頼区間（CI）：44～74%］増加させることが推定された。年齢はイブルチニブの血漿中曝露量に影響を及ぼし，本解析対象集団の中央値である 67 歳に比べて，81 歳（解析対象集団の 95 パーセンタイル値）では 14%増加，49 歳（解析対象集団の 5 パーセンタイル値）では 20%減少することが推定された。解析対象集団の多くが白人（86%）であったことから，人種の影響を「白人」と「白人以外」のカテゴリに分けて評価したが，有意な共変量とはならなかった。

本解析の最終モデルを用いて予測したイブルチニブの定常状態における血漿中曝露量（$AUC_{ss}$）は，試験間でおおむね一定であった。

### (2) 国内で実施した臨床試験成績に基づく母集団薬物動態解析【参考資料 5.3.3.5.2】

国内で実施した臨床試験 2 試験を対象とした母集団薬物動態解析を実施した。解析は，再発又は難治性の MCL 患者を対象とした MCL2002 試験，及び初回申請に含めた B 細胞腫瘍患者を対象とした JPN-101 試験で得られたデータを統合して実施した。海外試験を対象とした母集団薬物動態解析［海外試験モデル，2.7.2.2.1.3 (1)］では解析対象集団の多くが白人であり，人種の影響を十分に検討できなかったことから，国内試験を対象とした本解析の対象集団（日本人）でモデルを再検討した。海外試験モデルを用い日本人データに対して Bayesian feedback による個別パラメータ推定及び Visual Predictive Check（VPC）を実施したところ，日本人データは海外試験モデルで適切に記述されることが示唆された。さらに，海外試験モデルと同じモデル構造を適用し，

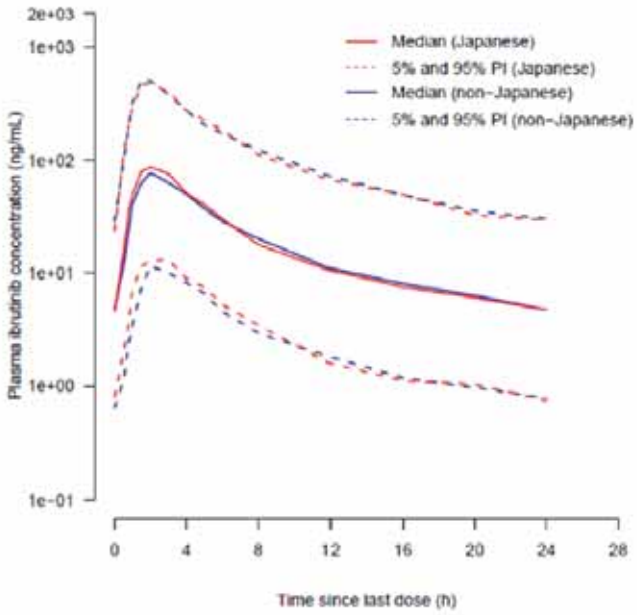
日本人データに対して母集団平均パラメータ及び変量効果を推定した。なお，日本人データのサンプルサイズ（N=31）は共変量解析を実施するには不十分と考えられたことから，共変量解析は実施せず，共変量パラメータを海外試験モデルで得られた値に固定した。最終モデルのパラメータ推定値を表 2.7.2-5 に示す。

**表 2.7.2-5 最終モデルでのパラメータ推定値**
**（国内で実施した臨床試験成績に基づく母集団薬物動態解析）**

| Parameter | Population mean estimate | %SEM | BSV (CV%) | %SEM |
|---|---|---|---|---|
| CL/F (L/h) | 983 | 14.1 | 0 FIX | NA |
| V2/F (L) | 1320 | 41.4 | 87.2 | 69.9 |
| Q/F (L/h) | 608 | 30.6 | 77.5 | 39.0 |
| V3/F (L) | 6720 | 25.7 | 49.8 | 29.7 |
| $k_a$ ($h^{-1}$) | 0.575 | 13.5 | 0 FIX | NA |
| ALAG1 (h) | 0.153 | 35.3 | 72.6 | 59.2 |
| D1 fast/mod fast (h) | 0.931 | 17.2 | 0 FIX | NA |
| D1 fed (h) | 3.29 FIX | NA | 0 FIX | NA |
| F1 mod fast/fed | 1 FIX | NA | 57.8 | 33.2 |
| F1 fast | 0.666 FIX | NA | 57.8 | 33.2 |
| Effect of CYP3A inhibitors on F1 (ratio) | 1.59 FIX | NA | — | — |
| Effect of age on F1 (power) | 0.699 FIX | NA | — | — |
| RUV (Study JPN-101) (CV%) | 52.8 | 15.7 | — | — |
| RUV (Study MCL2002 (CV%) | 85.1 | 23.5 | — | — |

CL/F：apparent (oral) drug clearance，V2/F：apparent central volume of distribution，Q/F：apparent inter-compartmental flow，V3/F：apparent peripheral volume of distribution，$k_a$：first-order absorption rate constant，ALAG1：temporal delay (lag time) before absorption process is started，D1：duration of zero-order input，F1：relative bioavailability，RUV：residual unexplained variability，SEM：relative standard error of the mean parameter，BSV：between-subject variability，CV%：percent coefficient of variation，NA：not applicable，FIX：fixed in the model

本解析の最終モデル（国内試験モデル）において，CL/F 及び分布容積（V2/F と V3/F の和）はそれぞれ 983 L/h および 8040 L と推定され，海外試験モデルによる推定値と同程度であった。国内試験モデルを用いた血漿中濃度推移のシミュレーションは，海外試験モデルを用いたシミュレーションとよい一致を示し（図 2.7.2-2），日本人と外国人の薬物動態に差異はないと考えられた。




Steady-state concentration was simulated for each population (N=1000), with age distribution (mean=65, sd=10, range=40-90) and no-comedication of CYP3A inhibitors, under modified fasting condition, at 560 mg dose. The highest RUV value was used in each population (85.1% for the Japanese model; 81.3% for the non-Japanese model).

**図 2.7.2-2 イブルチニブの血漿中濃度推移のシミュレーション**
**（modified fasting 条件，CYP3A 阻害薬の併用なし）**
**［国内試験モデル及び海外試験モデルの比較］**

### 2.7.2.2.2 薬力学試験

#### 2.7.2.2.2.1 心血管安全性評価

**(1) PCI-32765CLL1007 試験【評価資料 5.3.4.1.1】**

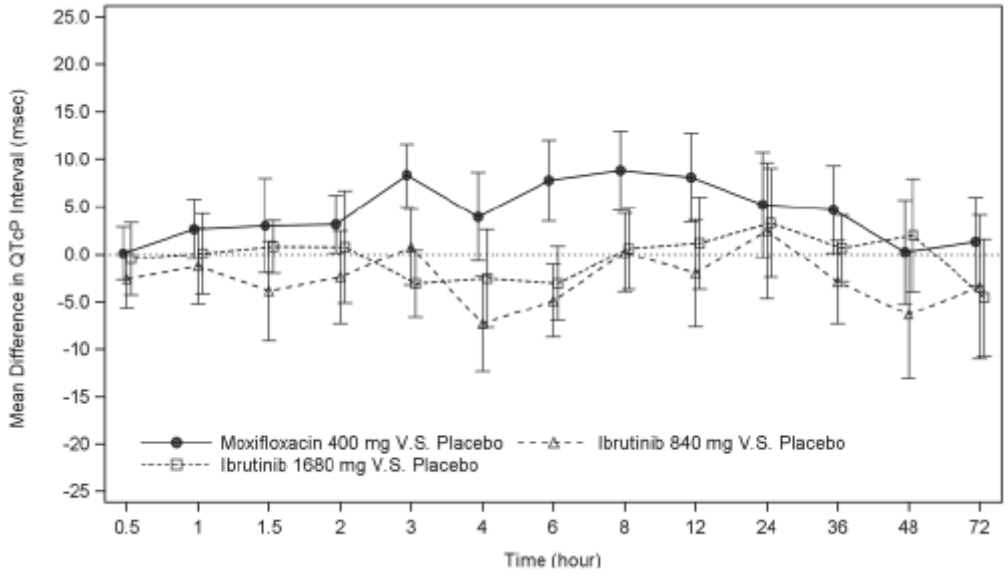
CLL1007 試験のパート 2 では，ICH-E14 ガイドラインにのっとり，ランダム化，二重盲検，プラセボ及び陽性対照，4 期クロスオーバーデザインの QT/QTc 評価試験（thorough QT 試験）として，イブルチニブが QT/QTc 間隔及び心電図形態学に及ぼす影響を評価した。被験者はそれぞれ，イブルチニブ 840 mg（thorough QT 試験における治療用量として），イブルチニブ 1680 mg［治療用量を超える用量（supratherapeutic dose）として］，モキシフロキサシン 400 mg（陽性対照）及びプラセボの単回経口投与を受けた。イブルチニブの曝露量（$C_{max}$）が最大となるように，被験者は治験薬投与の 2 時間後に高脂肪食を摂取した【1.13.1-3 既承認資料 CTD 2.7.2.3.2.2 (1) 参照】。規定した各時点において心電図の triplicate 測定を実施し，平均値を各時点の評価に用いた。

パート 2 では，当初 64 例の組入れを計画していたが，1 例の被験者でイブルチニブ 1680 mg の投与期後に Grade 4 の肝酵素上昇が発現したため，20 例の被験者を組み入れたところで試験を中止した。その結果，パート 2 では，13 例が 840 mg イブルチニブを，14 例が 1680 mg イブルチニブを，13 例がプラセボを，14 例がモキシフロキサシンの投与を受けた。

心電図パラメータとして，心拍数並びに QT 間隔（QT），RR 間隔（RR），QRS 間隔（QRS）及び PR 間隔（PR）を測定した。QT については，Fridericia 法（QTcF），Bazett 法（QTcB），及び試験固有の補正係数（power）を用い QT と RR の相関を補正した値（QTcP）を求めた。なお，QTcP の算出には，補正係数 0.2052 を用いた。ベースラインにおける QT 及び QTc と RR の相関

を線形回帰により評価したところ，QTcP で傾きが最小となったことから，QTcP を QT/QTc の評価における主要パラメータとした。

イブルチニブ及びモキシフロキサシンを投与したときの QTcP のベースラインからの変化量のプラセボとの差（ΔΔQTcP）の経時変化を図 2.7.2-3 に図示した。イブルチニブ 840 及び 1680 mg を投与したときの ΔΔQTcP はそれぞれ-7.3～2.5 msec 及び-4.6～3.3 msec の範囲で推移した。一方，陽性対照であるモキシフロキサシンの ΔΔQTcP は 0.1～8.8 msec の範囲で推移した。なお，QTcF 及び QTcB についても同様の傾向が認められた【5.3.4.1.1 CSR Section 5.2.2.2 p.62 参照】。イブルチニブ投与群では QTc の短縮が認められたが，これは臨床的に意義のあるものではないと考えられた。



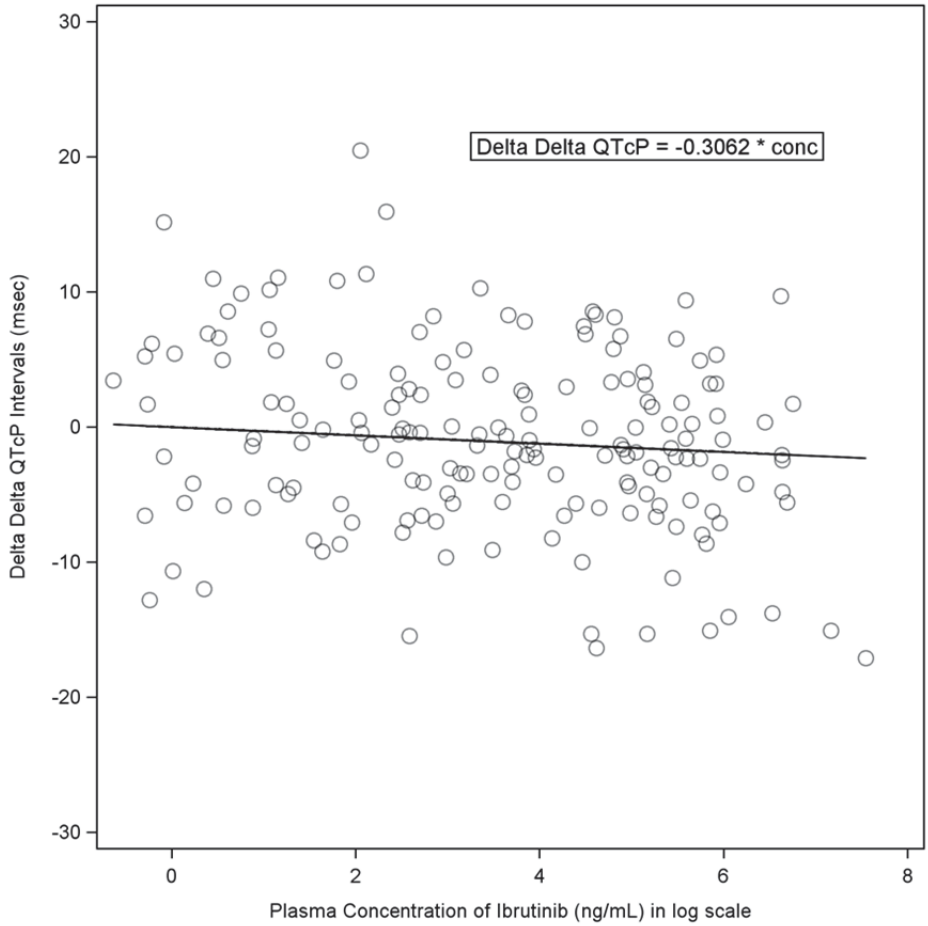

参照元：5.3.4.1.1 （PCI-32765CLL1007 試験 CSR Figure 9）

**図 2.7.2-3 イブルチニブ及びモキシフロキサシンを投与したときの ΔΔQTcP［平均（SD）］**

いずれのイブルチニブ用量，測定時点，及びいずれの補正法においても，最小二乗平均 ΔΔQTc の 90%信頼区間（CI）の上限は 10 msec 未満（ICH-E14 ガイドラインで推奨される閾値）であった【5.3.4.1.1 CSR Section 5.2.2.2 p.62 参照】。したがって，イブルチニブには QTc を延長する作用はないと考えられた。また，いずれのイブルチニブ用量においても，最小二乗平均 ΔΔQTc の 90%CI の下限は 0 msec を超えなかった。一方，陽性対照であるモキシフロキサシンを投与したとき，最小二乗平均 ΔΔQTc はピーク付近で 5 msec を超過した。また，その 90%CI の上限は複数の測定時点で 10 msec を，90%CI の下限は多くの時点で 0 msec を超過していた。

線形混合効果モデルを用い，ΔΔQTc と血漿中イブルチニブ又は PCI-45227 濃度の相関を検討した結果，負の相関が認められた。ΔΔQTcP 及び血漿中イブルチニブ濃度の個別値のプロットを図 2.7.2-4 に示す。当該モデルを用いたとき，イブルチニブ 840 及び 1680 mg 用量における $C_{max}$ での ΔΔQTcP（90%CI）は，それぞれ-1.92 msec（-4.23～0.39）及び-5.27 msec（-9.41～-1.13）と推定された。また，血漿中イブルチニブ及び PCI-45227 濃度が 100 ng/mL 増加すると，ΔΔQTcP はそ

れぞれおよそ 0.8 msec 減少することが推定された。また，ΔΔQTcF 及び ΔΔQTcB についても同様の結果が得られた【5.3.4.1.1 CSR Section 5.2.3 p.76 参照】。




Note: A linear mixed model was used with concentration as a predictor and subject as a random effect (random slope model without intercept), since the intercept is not significant from random slope random intercept model. p-value is 0.2588 for slope fixed effect term.

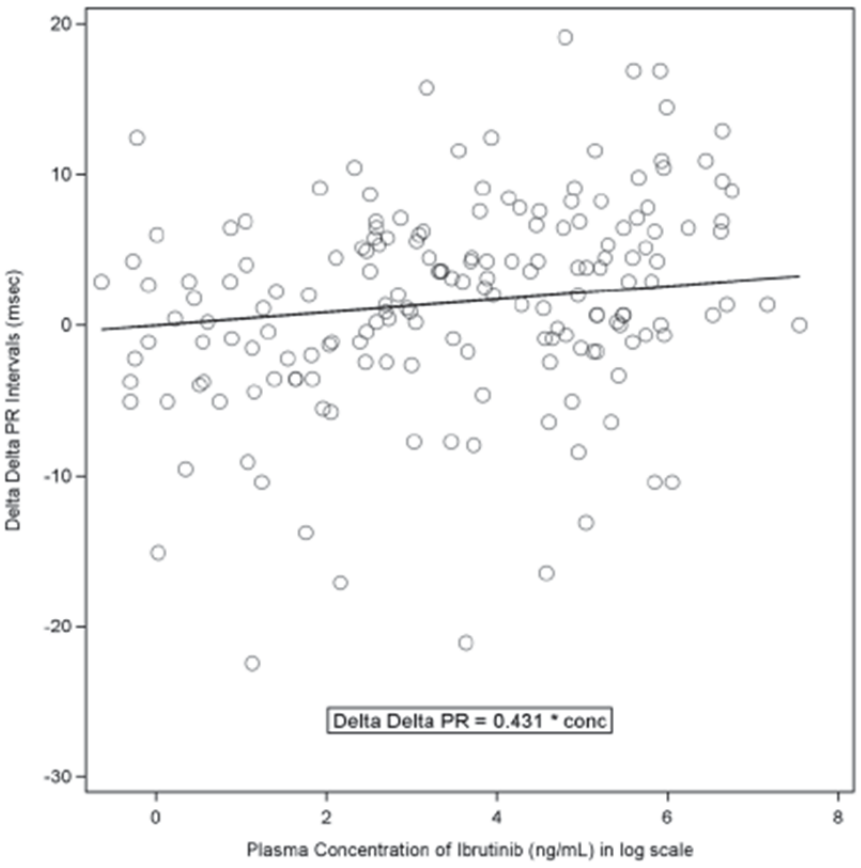
Note: The X-axis shows the natural log of the concentration, ie. $2 = e^2 = 7.4$ ng/mL; $6 = e^6 = 403$ ng/mL.

参照元：5.3.4.1.1 （PCI-32765CLL1007 試験 CSR Figure 13）

**図 2.7.2-4 ΔΔQTcP 及び血漿中イブルチニブ濃度の関係**

PR 間隔が 200 msec を超えた被験者は認められなかったが，投与後 3～36 時間の範囲において，PR のベースラインからの変化量は，プラセボに比較してイブルチニブ投与群で大きく，モキシフロキサシン投与群で小さい傾向が認められた【5.3.4.1.1 CSR Section 5.2.2.3 p.74 参照】。イブルチニブ投与群で認められた PR の延長は臨床的に意義のあるものではないと考えられた。

ΔΔPR と血漿中イブルチニブ又は PCI-45227 濃度の相関を線形混合モデルにより検討した結果，正の相関が認められた。ΔΔPR 及び血漿中イブルチニブ濃度の個別値のプロットを図 2.7.2-5 に示す。血漿中イブルチニブ及び PCI-45227 濃度が 100 ng/mL 増加すると，ΔΔPR はそれぞれおよそ 0.8 msec 及び 1.4 msec 増加することが推定された。




Note: A linear mixed model was used with concentration as a predictor and subject as a random effect (random slope model without intercept), since the intercept is not significant from random slope random intercept model.
p-value is 0.1674 for slope fixed effect term.
Note: The X-axis shows the natural log of the concentration, ie, $2 = e^2 = 7.4$ ng/mL; $6 = e^6 = 403$ ng/mL

参照元：5.3.4.1.1 （PCI-32765CLL1007 試験 CSR Figure 15）

**図 2.7.2-5 ΔΔPR 及び血漿中イブルチニブ濃度の関係**

### 2.7.2.2.2.2 曝露量－反応解析【参考資料 5.3.4.2.1 及び 5.3.4.2.2】

初期の海外臨床試験 3 試験（04753 試験，1102 試験及び 1104 試験）を対象として実施した母集団薬物動態解析データ【1.13.1-3 既承認資料 CTD 2.7.2.2.1.5 参照】を用い，曝露量－反応（exposure-response，E-R）解析を実施した（N=245）。その後さらに，海外臨床試験 9 試験（04753 試験，1102 試験，1104 試験，1117 試験，MCL2001 試験，MCL3001 試験，1112 試験，1115 試験，及び CLL3001 試験）を対象として実施した母集団薬物動態解析データ［2.7.2.2.1.3(1) 参照］を用いて同様の E-R 解析を実施した（N=1201）。本項では，最新の解析結果に基づき結果を記載する。

#### (1) 有効性

有効性のカテゴリカルな指標として tumor response を用い，best tumor response に基づく全奏効率（ORR）［完全奏功（CR）＋部分奏功（PR）＋CR with incomplete blood count recovery（CRi）＋nodular partial response（nPR）＋PR with lymphocytosis（PRL）（CRi，nPR，PRL は CLL のみ）］又は奏功なし（no response）［安定（SD）＋疾患進行（PD）］の 2 値変数に分類し，海

外試験 9 試験を対象とした母集団薬物動態解析で推定されたイブルチニブ曝露量（$AUC_{ss}$：定常状態における AUC）との相関をロジスティック回帰分析により検討した。解析の結果，CLL 患者（1102，1117，1112，1115，CLL3001 及び 04753 試験の該当被験者）（N=820）及び MCL 患者（1104，MCL2001，MCL3001，及び 04753 試験の該当被験者）（N=300）のいずれの集団においても，意義のある相関は認められなかった。臨床曝露量における高い BTK 活性部位占有率が示唆されたことからも【1.13.1-3 既承認資料 CTD 2.7.2.3.6.1 (1) 参照】，臨床推奨用量において有効性は最大レベルに到達していると考えられた。

**(2) 安全性（出血事象，心房細動，好中球減少，肝機能検査値異常，及び感染症）**

以下に示した安全性の指標について，それぞれ発現の有無を 2 値変数とし，海外試験 9 試験を対象とした母集団薬物動態解析で推定されたイブルチニブ曝露量（$AUC_{ss}$）との相関をロジスティック回帰分析により検討した（N=1201）。

- Treatment-emergent adverse event（TEAE）としての出血事象［大出血事象及びグレードを問わないすべての出血事象］の発現有り／無し
- TEAE としての心房細動（グレードを問わない）の発現有り／無し
- 臨床検査値に基づく好中球減少［イブルチニブ投与開始 3 又は 6 ヵ月以内に発現した，グレードを問わない悪化，若しくは 2 グレード以上の悪化又はグレード 3 以上への悪化の絶対好中球数（ANC）減少］の発現有り／無し
- 肝機能検査値異常［イブルチニブ投与開始から最終投与 30 日以内までに発現した，グレードを問わない悪化，若しくは 2 グレード以上の悪化又はグレード 3 以上への悪化のアラニンアミノトランスフェラーゼ（ALT）上昇，アスパラギン酸アミノトランスフェラーゼ（AST）上昇，又は総ビリルビン上昇］の発現有り／無し

解析の結果，心房細動，好中球減少，及び肝機能検査値異常とイブルチニブ曝露量に意義のある相関は認められなかった。一方，イブルチニブ曝露量の増加に伴い，出血事象の発現が増加する傾向が認められた。

そこで，CLL 及び MCL の各適応症に対する臨床推奨用量を投与された部分集団（420 mg/日の投与を受けた CLL 患者，又は 560 mg/日の投与を受けた MCL 患者）について解析を行ったところ，420 mg/日の投与を受けた CLL 患者集団（N=797）では明確な相関は認められなかった。一方，560 mg/日の投与を受けた MCL 患者集団（N=306）では相関が認められた。560 mg/日の投与を受けた MCL 患者集団において，単変量ロジスティック回帰分析で推定された，大出血事象及びグレードを問わないすべての出血事象との相関の回帰式の傾き（99%信頼区間）はそれぞれ，0.0009（0.0000～0.0018）及び 0.0008（0.0001～0.0015）であった。さらに，グレードを問わないすべての出血事象に対して，イブルチニブ曝露量以外の影響因子を考慮した多変量ロジスティック回帰分析を行ったところ，420 mg/日を投与された CLL 患者集団ではイブルチニブ曝露量との相関は認められなかったが，560 mg/日を投与された MCL 患者集団ではイブルチニブ曝露量との相関が認められた［傾き（99%信頼区間）：0.0008（0.0001～0.0015）］。

また，感染症及び出血事象について，初期の海外試験 3 試験を対象とした母集団薬物動態解析で推定されたイブルチニブ曝露量との相関を評価したが，意義のある相関は認められなかった。

### 2.7.2.3 全試験を通しての結果の比較と解析

本項では，初回申請時以降に新たに得られたデータ，及び本申請に含む臨床試験で得られたデータに基づき評価を行う。

#### 2.7.2.3.1 イブルチニブ及び代謝物の薬物動態特性

##### 2.7.2.3.1.1 単回及び反復経口投与時の薬物動態

日本人 B 細胞腫瘍患者（JPN-101 試験）【1.13.1-3 既承認資料 CTD 2.7.2.2.1.2 (1)】及び外国人 MCL 患者（1104 試験）にイブルチニブ 560 mg/日を投与したときの 1 日目（単回投与）及び 8 日目（反復投与，定常状態）の薬物動態パラメータを表 2.7.2-6 に示す。また，個別パラメータ値及び中央値を図 2.7.2-6 及び図 2.7.2-7 に図示する。

イブルチニブの吸収は速やかであり（$t_{max}$ 中央値：1～2 時間），その後速やかに消失した（$t_{1/2}$：5～8 時間）。ばらつきは大きかったものの，定常状態の $C_{max}$ 及び $AUC_{24}$ は，単回投与後に比べて増加した（$AUC_{24}$ に基づく累積率：1.4～1.5）。

薬物動態のばらつきは大きく，日本人例数は限られていたものの，イブルチニブ 560 mg/日を投与したときの日本人の $C_{max}$ 及び $AUC_{24}$ の分布は外国人の分布の範囲内であり，日本人と外国人のイブルチニブの薬物動態に明確な差異は認められなかった。

**表 2.7.2-6 日本人 B 細胞腫瘍患者（JPN-101 試験）及び外国人 MCL 患者（1104 試験）にイブルチニブ 560 mg/日を経口投与したときのイブルチニブの薬物動態パラメータ［平均（CV%）］**

| 試験番号 | | N | $C_{max}$ (ng/mL) | $t_{max}$ [a] (h) | $AUC_{24}$ (ng·h/mL) | $t_{1/2}$ (h) | 累積率 ($AUC_{24}$) |
|---|---|---|---|---|---|---|---|
| PCI-32765-JPN-101（日本人） | Day 1 | 6 | 94.6 (69.2) | 1.48 (0.98 – 3.92) | 419 (57.0) | 6.34 [b] (NC) | — |
| | Day 8 | 6 | 105 (65.0) | 2.00 (0.97 – 4.00) | 639 (74.5) | 5.31 [b] (NC) | 1.52 (38.1) |
| PCYC-1104-CA（外国人） | Day 1 | 48 | 147 (97.6) | 2.00 (0.75 – 22.75) | 802 [c] (83.2) | 5.89 [d] (33.3) | — |
| | Day 8 | 45 | 164 (99.9) | 2.00 (0.00 – 4.12) | 953 [e] (74.0) | 8.48 [f] (72.5) | 1.40 [g] (53.8) |

[a] 中央値（範囲），[b] N=2，[c] N=45，[d] N=20，[e] N=43，[f] N=21，[g] N=42
参照元：1.13.1-3 既承認資料 2.7.2.2.1.2 (1)，5.3.5.2.2-1（PCYC-1104-CA 試験 CSR Table 13）

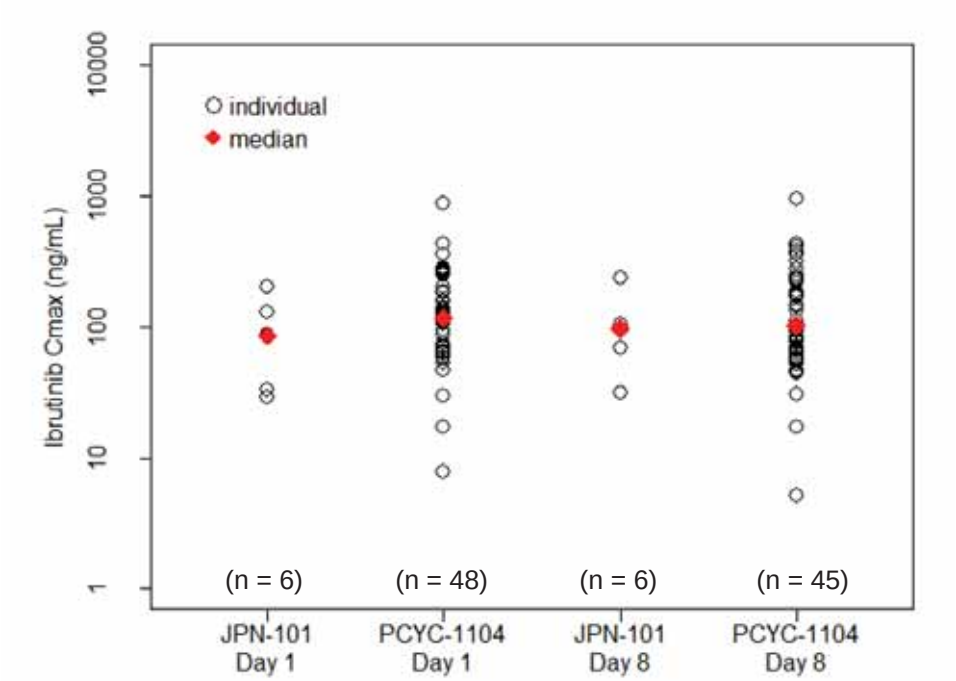



図 2.7.2-6 日本人 B 細胞腫瘍患者（JPN-101 試験）及び外国人 MCL 患者（1104 試験）にイブルチニブ 560 mg/日を経口投与したときの $C_{max}$（1 日目及び 8 日目）の比較
（○：個別値，◆：中央値）

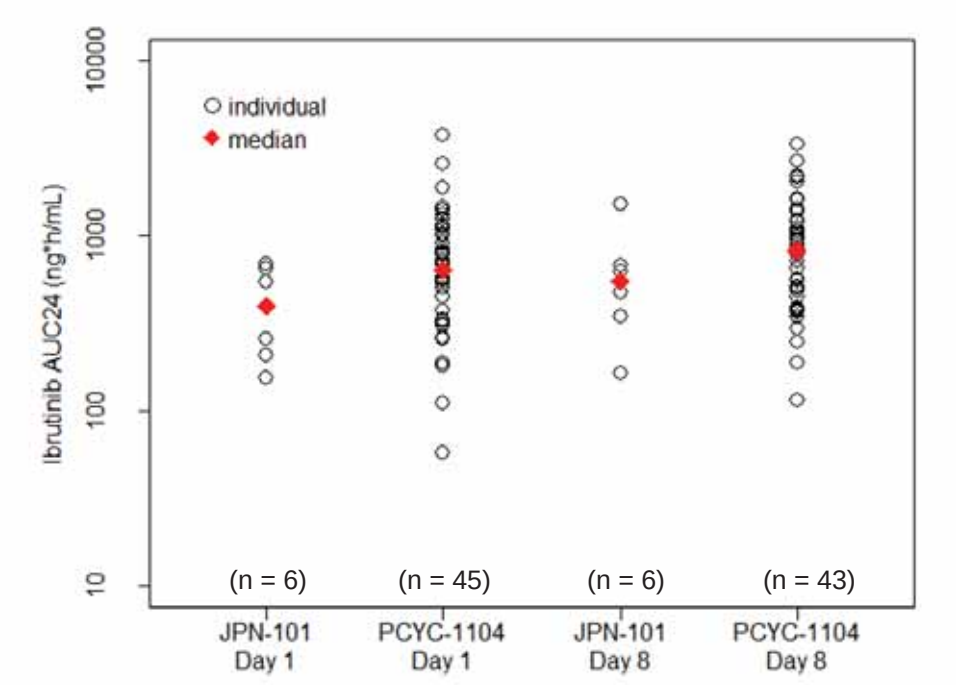



図 2.7.2-7 日本人 B 細胞腫瘍患者（JPN-101 試験）及び外国人 MCL 患者（1104 試験）にイブルチニブ 560 mg/日を経口投与したときの $AUC_{24}$（1 日目及び 8 日目）の比較
（○：個別値，◆：中央値）

#### 2.7.2.3.1.2 用量比例性

用量比例性の評価を主目的とした試験は実施していないが，イブルチニブ 70～840 mg を投与したときのイブルチニブの曝露量に非線形性は認められなかった【1.13.1-3 既承認資料 CTD 2.7.2.3.1.5 参照】。CLL1007 験において，840 mg 及び 1680 mg のイブルチニブを単回投与したとき，イブルチニブの $C_{max}$ はおおむね用量に比例して増加したが，AUC は用量比例性をわずかに上回った。

#### 2.7.2.3.1.3 分布

**(1) トランスポーター**

*In vitro* 試験より，イブルチニブは，OCT2 を除き，P-gp 及びその他のトランスポーターの基質ではないことが示された。また，M21 は，BCRP，OATP1B1，及び OATP1B3 の基質であることが示された。

#### 2.7.2.3.1.4 代謝

**(1) 代謝物の薬物動態**

FLR2002 試験（用量 560 mg/日）で得られた血漿試料から，M21，M23，M25，M34 及び PCI-45227（M37）が定常状態における血漿中の重要な代謝物（AUC が未変化体の 25%以上）であることが示された。

### 2.7.2.3.2 内因性要因の影響

#### 2.7.2.3.2.1 年齢

海外試験を対象とした母集団薬物動態解析において，年齢はイブルチニブの相対的バイオアベイラビリティ（F1）に有意な影響を及ぼす共変量として同定され，当該解析対象集団の中央値である 67 歳に比べたときの曝露量（AUC）は，81 歳では 14%増加，49 歳では 20%減少することが推定された。

#### 2.7.2.3.2.2 性別

海外試験を対象とした母集団薬物動態解析において，性別の影響は認められなかった。

#### 2.7.2.3.2.3 体重及び関連する体格尺度

初回申請時に実施した母集団薬物動態解析では，体重が分布容積に対する有意な共変量として同定された【1.13.1-3 既承認資料 CTD 2.7.2.3.3.3 参照】。しかし，本申請で実施した海外試験を対象とした母集団薬物動態解析において，体重はモデルパラメータに影響を及ぼす有意な共変量として採用されなかった。いずれの解析においても，体重は本薬の曝露量（AUC）に意義のある影響を及ぼさないと考えられた。

#### 2.7.2.3.2.4 肝機能障害

軽度，中等度及び重度の肝機能障害を有する被験者を対象とした PCI-32765CLL1006 試験において，肝機能障害の悪化に伴い，イブルチニブの曝露量及び非結合型分率が増加することが示された。【1.13.1-3 既承認資料 CTD 2.7.2.3.3.4 参照】

国内外で実施した B 細胞腫瘍患者を対象とし有効性及び安全性を評価した臨床試験では，重篤な肝機能障害を有する被験者を組入れから除外していた。しかし，本申請で実施した海外試験を対象とした母集団薬物動態解析の解析対象集団（1202 例）を，NCI organ dysfunction working group（NCI-ODWG）基準による肝機能障害の重症度に基づき分類したところ，179 例が軽度肝機能障害を，12 例が中等度の肝機能障害を有していた（ベースライン）。そこで，当該母集団薬物動態解析において，NCI-ODWG 分類に基づく肝機能障害重症度，総ビリルビン値，及びアスパラギン酸アミノトランスフェラーゼ（AST）値（いずれもベースライン）について共変量解析を実施したが，いずれも統計学的に有意な影響は認められなかった。

#### 2.7.2.3.2.5 腎機能障害

海外試験を対象とした母集団薬物動態解析において，統計学的に有意な腎機能の影響は認められなかった。

#### 2.7.2.3.2.6 人種/民族

2.7.2.3.1.1 に示すとおり，JPN-101 試験（日本人）及び 1104 試験（外国人）で得られた薬物動態パラメータを比較した結果，日本人被験者の例数は限られているものの，明確な差異は認められなかった。

母集団薬物動態解析では，海外試験の解析対象集団（N=1202）の大多数が白人であったこと，当該集団に比較し国内試験の日本人の例数（N=31）が極めて限られていたことから，日本人と外国人の薬物動態の比較について，共変量解析に基づく評価は実施しなかった。しかし，国内試験を対象とした母集団薬物動態解析において，国内試験モデルを用いた血漿中濃度シミュレーションは，海外試験モデルを用いたシミュレーションとよい一致を示したことから，日本人と外国人の薬物動態に差異はないと考えられた。

### 2.7.2.3.3 外因性要因の影響

#### 2.7.2.3.3.1 薬物相互作用

**(1) 他の薬剤がイブルチニブの薬物動態に及ぼす影響**

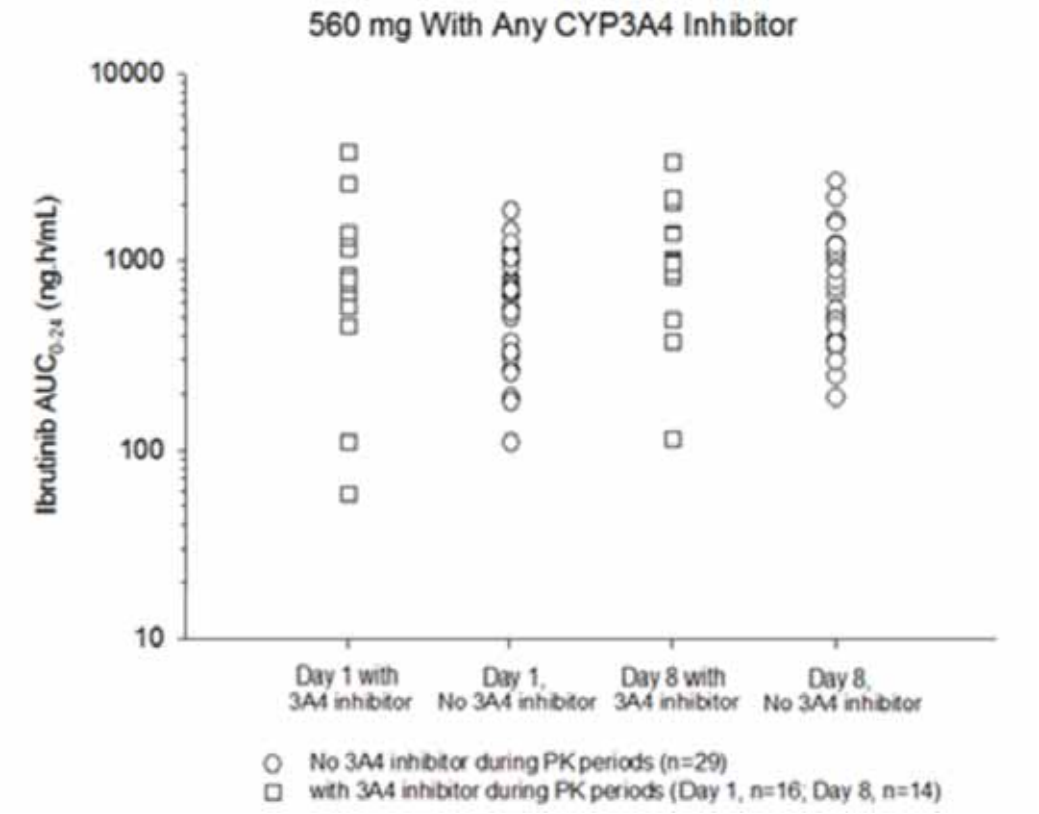
**1) CYP3A 阻害剤**

イブルチニブは CYP3A によりほぼ完全に代謝されることから，CYP3A 阻害剤の併用はイブルチニブの血漿中曝露量を増加させる可能性がある。【1.13.1-3 既承認資料 CTD 2.7.2.3.5.1 (1) 参照】

海外試験を対象とした母集団薬物動態解析において，中程度及び強力な CYP3A 阻害薬の併用は，イブルチニブの血漿中曝露量を母集団平均で 59%増加させることが推定された。なお，初回

申請時に実施した母集団薬物動態解析では CYP3A 阻害薬の併用は有意な共変量とならなかったが，これは，当該解析では阻害強度分類によらずすべての CYP3A 阻害剤を解析対象に含めていたことなどが原因として考えられる [3)] 。

また，外国人 MCL 患者を対象とした 1104 試験（用量 560 mg/日）の薬物動態データを用いて，CYP3A 阻害剤併用がイブルチニブの曝露量に及ぼす影響を検討した。薬物濃度測定用試料を採取した期間中の CYP3A 阻害剤の併用の有無別で被験者を分類し，イブルチニブの曝露量を比較した結果を図 2.7.2-8 に示す。なお，強力な CYP3A 阻害剤を併用した被験者はおらず，併用群で使用されたのはすべて中程度又は弱い CYP3A 阻害剤であった。中程度又は弱い CYP3A 阻害剤を併用した被験者の曝露量（$AUC_{24}$）の分布は，併用がなかった被験者と大きく異ならなかった。




Moderate CYP3A inhibitors: ciprofloxacin, diltiazem, fluconazole

Mild CYP3A inhibitors: alprazoram, amlodipine, atorvastatin, ranitidine

参照元：5.3.5.2.2-1（PCYC-1104-CA 試験 CSR）一部改変

**図 2.7.2-8 外国人 MCL 患者にイブルチニブ 560 mg/日を投与したときの（中程度又は弱い）CYP3A 阻害剤併用の有無別のイブルチニブの $AUC_{24}$（1104 試験）**

### 2) トランスポーターの阻害剤

*In vitro* 試験より，イブルチニブは OCT2 の基質であること，並びに代謝物 M21 は BCRP, OATP1B1 及び OATP1B3 の基質であることが示された。これらに関する臨床試験は実施していない。

(2) イブルチニブが他の薬剤の薬物動態に及ぼす影響

*In vitro* 試験及び PBPK モデルによるシミュレーションの結果から，イブルチニブ及び代謝物 M21，M23，M25，M34 及び M37（PCI-45227）が CYP で代謝される薬剤の薬物動態に臨床的に意義のある影響を及ぼす可能性は低いと考えられた。なお，これまでに得られた臨床薬物動態データから，イブルチニブは CYP3A 活性の変動に大きく影響を受ける CYP3A 基質であることが示されているが，単回投与時の曝露量から反復投与時の曝露量を予測可能であることから，イブルチニブによる臨床的に意義のある CYP3A 活性の変動が生じる可能性は低いと考えられた。

イブルチニブが臨床曝露量で全身循環性の P-gp 及び MRP1 を阻害する可能性は低いものの，全身循環性の BCRP を阻害する可能性は否定することができない。イブルチニブは消化管の P-gp 及び BCRP を阻害する可能性があるが，その阻害の程度は顕著ではないと考えられた。また，*in vitro* 試験において，代謝物 M21 は BCRP 及び MRP1 に対する阻害活性を示し，カットオフ基準に基づく考察から，臨床曝露量で全身循環性の BCRP 及び MRP1 を阻害する可能性が示唆された。上記を除き，トランスポーターを介した臨床的に意義のある薬物相互作用が起こる可能性は低いと考えられる。

## 2.7.2.3.4 薬物動態－薬力学関係及び曝露量－反応関係

### 2.7.2.3.4.1 有効性

有効性の指標として tumor response を用い，海外臨床試験 9 試験を対象とした母集団薬物動態解析で推定されたイブルチニブの曝露量（$AUC_{ss}$）との相関を評価したところ，いずれの解析対象集団においても，意義のある相関は認められなかった。

### 2.7.2.3.4.2 安全性

(1) QT/QTc 間隔

CLL1007 試験のパート 2 では，ICH-E14 ガイドラインにのっとり，thorough QT 試験として，イブルチニブ 840 及び 1680 mg を単回投与したときの QT/QTc 間隔及び心電図形態学に及ぼす影響を評価した。試験が途中で中止されたために評価対象例数は計画よりも少なかったものの，いずれのイブルチニブ用量においても，最小二乗平均 ΔΔQTc の 90%CI の上限は 10 msec 未満（ICH-E14 ガイドラインで推奨される閾値）であり，イブルチニブには QTc を延長する作用はないと考えられた。また，いずれのイブルチニブ用量においても，最小二乗平均 ΔΔQTc の 90%CI の下限は 0 msec を超えなかった。ΔΔQTc と薬物濃度の相関を検討した結果，負の相関が認められ，血漿中イブルチニブ及び PCI-45227 濃度が 100 ng/mL 増加すると，ΔΔQTcP がそれぞれおよそ 0.8 msec 減少することが推定された。また，ΔΔPR と薬物濃度の相関を検討した結果，正の相関が認められ，血漿中イブルチニブ及び PCI-45227 濃度が 100 ng/mL 増加すると，ΔΔPR がそれぞれおよそ 0.8 及び 1.4 msec 増加することが推定された。イブルチニブ投与群で認められた QTc の短縮及び PR の延長は，臨床的に意義のあるものではないと考えられた。

**(2) 出血事象，心房細動，好中球減少，肝機能検査値異常，及び感染症**

有害事象のうち出血事象，心房細動，好中球減少及び肝機能検査値異常の発現に対して，海外臨床試験 9 試験を対象とした母集団薬物動態解析で推定されたイブルチニブの曝露量（$AUC_{ss}$）との相関を評価したところ，$AUC_{ss}$ の増加に伴い出血事象の発現が増加する傾向が認められた。その他の有害事象について意義のある相関は認められなかった。

また，有害事象のうち感染症及び出血事象について，初期の海外臨床試験 3 試験を対象とした母集団薬物動態解析で推定されたイブルチニブの曝露量（$AUC_{ss}$）との相関を評価したが，意義のある相関は認められなかった。

### 2.7.2.3.4.3 用法・用量の根拠

MCL の治療に対する推奨用法・用量は 560 mg の 1 日 1 回投与である。

海外における MCL の治療に対する推奨用法・用量は，海外で実施した 04753 試験並びに 1104 試験での薬物動態，薬力学，及び臨床（安全性及び有効性）評価に基づき決定した。

04753 試験は，外国人再発性 B 細胞腫瘍患者 66 例を対象とした第 I 相，用量漸増試験であり，イブルチニブ 1.25～12.5 mg/kg/日（560 mg/日の固定用量を含む）を間欠投与又は連日投与した。2.5～12.5 mg/kg/日の用量範囲で，投与 4 時間及び 24 時間後のいずれの時点においても，BTK 活性部位占有率はすべて 90%を超えていた【1.13.1-3 既承認資料 CTD 2.7.2.2.1.2 (2) 参照】。04753 試験では 9 例の再発又は難治性 MCL 患者がイブルチニブの投与を受け，9 例のうち 7 例が PR 以上であった（CR 3 例，PR 4 例）[1)]。9 例のうち，5 例は 560 mg/日の固定用量を，1 例が 8.3 mg/kg を投与されていた[1)]。04753 試験の結果から，イブルチニブ 560 mg/日投与による ORR に基づく有効性が確認され，安全性プロファイルも良好であった。

04753 試験では，間欠投与及び連日投与のいずれでも MTD に達しなかったことから，以降の臨床試験では 1 日 1 回の連日投与レジメンを選択した。04753 試験の結果に基づき，再発又は難治性の外国人 MCL 患者を対象とした 1104 試験では，イブルチニブを 560 mg/日の固定用量で投与した。1104 試験では持続的で高い奏効率及び許容可能な安全性が示され，再発又は難治性の MCL に対する 560 mg/日用量の適切性が支持された。また，1104 試験と同様にイブルチニブを 560 mg/日の固定用量で投与した MCL3001 試験でも，主要評価項目である無増悪生存期間（PFS）の中央値はイブルチニブ群で 14.6 カ月，テムシロリムス群で 6.2 カ月であり，イブルチニブ群でテムシロリムス群と比較し統計学的に有意で臨床的に意義のある PFS の改善（$p<0.0001$，ハザード比 0.43）が示された。【2.5.6.3 参照】

国内における MCL の治療に対する推奨用法・用量は，上記の 04753 試験，1104 試験，及び MCL3001 試験に加え，国内で実施した JPN-101 試験及び MCL2002 試験での薬物動態，薬力学，及び臨床（安全性及び有効性）評価に基づき決定した。

国内で実施した MCL2002 試験のイブルチニブの用法・用量は，1104 試験においてイブルチニブ 560 mg/日投与により高い ORR を示したこと，及び国内の用量漸増試験である JPN-101 試験の結果から決定した。JPN-101 試験の結果から，日本人にイブルチニブ 560 mg/日を投与したときの薬物動態及び BTK 活性部位占有率に外国人との差異は認められなかった【1.13.1-3 既承認資料 CTD 2.7.2.2.1.2 (1) 及び 2.7.2.3.2.6 参照】。また，JPN-101 試験に組み入れられた MCL 患者 2 例は，イブルチニブ 560 mg/日の投与後，いずれも 2 サイクル以内に奏効が認められ，うち 1 例は CR

に達した[2)]。JPN-101 試験の結果，日本人におけるイブルチニブ 560 mg/日の投与の忍容性が確認された。MCL2002 試験の結果，再発又は難治性の日本人 MCL 患者におけるイブルチニブ 560 mg/日の高い奏効率及び良好な安全性が確認された。

以上より，再発又は難治性の日本人 MCL 患者に対するイブルチニブの推奨用法・用量として，海外と同じ 560 mg（140 mg カプセル x 4）の 1 日 1 回投与を選択した。

## 2.7.2.4 付録

### 付録 1 健康被験者及び B 細胞性腫瘍患者にイブルチニブを単回及び反復経口投与したときのイブルチニブの薬物動態パラメータ

| | | | | Mean (SD); $t_{max}$: Median (Range) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dose | | | $t_{max}$ | $C_{max}$ | Acc. Ratio $C_{max}$ | $AUC_{24}$ | Acc. Ratio $AUC_{24}$ | $t_{1/2}$ | Vd/F | CL/F |
| Study ID | mg | Treatment Group | N | h | ng/mL | | ng·h/mL | | h | L | L/h |
| PCI-32765CLL1007 (healthy subjects) | 840 SD | Part 1 | 8 | 3.00 (2.00-4.00) | 248 (82.6) | − | 1048 (350) | − | 6.0 (1.6) | 7654 (3589) | 903 (472) |
| | 840 SD | Part 2 | 13 | 3.02 (1.52-6.03) | 304 (181) | − | 1200 (650) | − | 6.0 (1.8) | 7554 (4709) | 970 (734) |
| | 1680 SD | Part 1 | 8 | 3.00 (2.00-6.00) | 567 (282) | − | 2850 (1465) | − | 6.5 (1.3) | 6857 (4416) | 691 (363) |
| | 1680 SD | Part 2 | 14 | 4.06 (2.07-6.03) | 719 (491) | − | 3656 (2050) | − | 6.9 (1.8) | 6693 (6176) | 599 (380) |
| PCYC-1104 (subjects with MCL) | 560 SD | Bortezomib exposed and bortezomib naïve | 48 | 2.0 (0.75-22.8) | 147 (143) | − | 802 (668) [a] | − | 5.89 (1.96) [b] | 8251 (6572) | 982 (787) |
| | 560 MD | Bortezomib exposed and bortezomib naïve | 45 | 2.00 (0.00-4.12) | 164 (164) | 1.41 (1.26) | 953 (705) [c] | 1.40 (0.75) [d] | 8.48 (6.15) [e] | - | - |

Acc. ratio = Accumulation ratio
[a] N=45, [b] N=20, [c] N=43, [d] N=42, [e] N=21

付録 2 健康被験者及び B 細胞性腫瘍患者にイブルチニブを単回及び反復経口投与したときの PCI-45227 の薬物動態パラメータ

| | | | | Mean (SD); $t_{max}$: Median (Range) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study ID | Dose mg | Treatment Group | N | $t_{max}$ h | $C_{max}$ ng/mL | Acc. Ratio $C_{max}$ ng/mL | $AUC_{24}$ ng·h/mL | Acc. Ratio $AUC_{24}$ | $t_{1/2}$ h | MPR $C_{max}$ | MPR $AUC_{24}$ |
| PCI-32765CLL1007 (healthy subjects) | 840 SD | Part 1 | 8 | 3.00 (2.00-6.00) | 304 (58.4) | – | 2643 (574) | – | 10.0 (1.7) | 1.25 (0.47) | 2.56 (0.86) |
| | 840 SD | Part 2 | 13 | 3.02 (2.07-6.03) | 256 (76.4) | – | 2073 (522) | – | 11.1 (3.1) | 1.22 (0.98) | 2.15 (1.27) |
| | 1680 SD | Part 1 | 8 | 4.00 (2.00-6.00) | 534 (146) | – | 5192 (1864) | – | 9.1 (1.7) | 1.06 (0.49) | 1.89 (0.58) |
| | 1680 SD | Part 2 | 14 | 4.07 (2.07-6.03) | 468 (169) | – | 4348 (1507) | – | 10.7 (1.7) | 0.89 (0.65) | 1.43 (0.91) |
| PCYC-1104 (subjects with MCL) | 560 SD | Bortezomib exposed and bortezomib naïve | 48 | 2.0 (0.92-6.08) | 112 (54.0) | – | 1052 (583) [a] | – | 6.89 (1.53) [b] | 1.14 (1.06) | 1.65 (1.13) [c] |
| | 560 MD | Bortezomib exposed and bortezomib naïve | 45 | 2.00 (0.97-4.12) | 122 (59.0) | 1.41 (1.26) | 1263 (707) [d] | 1.41 (0.89) [e] | 9.18 (3.68) [b] | 1.19 (1.16) | 1.65 (1.09) [f] |

Acc. ratio = Accumulation ratio

MPR = Metabolite to parent ratio, corrected for molecular weight [PK Parameter(metabolite)/Molecular weight(metabolite)]/[PK Parameter(parent)/Molecular weight(parent)]

[a] N=46, [b] N=28, [c] N=45, [d] N=44, [e] N=42, [f] N=43

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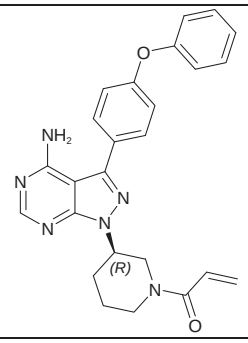
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# 略号一覧表

| 略号又は略称 | 化学名又は一般名 | 構造式 | 由来 |
|---|---|---|---|
| イブルチニブ（PCI-32765 又は JNJ-54179060） | 1-{(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one |  | 主薬 |

| 略号又は略称 | 名称及び内容 |
|---|---|
| BTK | ブルトン型チロシンキナーゼ（Bruton’s Tyrosine Kinase） |
| CI | 信頼区間（confidence interval） |
| CR | 完全奏効（complete response） |
| CSR | 治験総括報告書（clinical study report） |
| CT | コンピュータ断層撮影（computed tomography） |
| DOR | 奏効持続期間（duration of response） |
| ECOG | Eastern Cooperative Oncology Group |
| EQ | EuroQol |
| FACT-Lym | Functional Assessment of Cancer Therapy-Lymphoma |
| FISH | 蛍光 in-situ ハイブリダイゼーション（fluorescence in situ hybridization） |
| IHC | 免疫組織化学（immunohistochemistry） |
| IRC | 独立評価委員会（Independent Review Committee） |
| ITT | intent-to-treat |
| LD | 長径（longest diameter） |
| LDH | 乳酸脱水素酵素（lactate dehydrogenase） |
| MCL | マントル細胞リンパ腫（mantle cell lymphoma） |
| MIPI | マントル細胞リンパ腫国際予後指標（Mantle Cell Lymphoma International Prognostic Index） |
| NE | not estimable |
| ORR | 全奏効率（overall response rate） |
| OS | 全生存期間（overall survival） |
| PFS | 無増悪生存期間（progression-free survival） |
| PR | 部分奏効（partial response） |
| SD | 安定（stable disease） |
| SPD | 腫瘍の二方向積和（Sum of the products of the diameters） |
| USA | United States of America |
| WBC | 白血球（white blood cell） |

## 2.7.3 臨床的有効性

### 2.7.3.1 背景及び概観

イブルチニブはブルトン型チロシンキナーゼ（BTK）阻害剤である。イブルチニブは，国内で2016年3月に420 mgを1日1回経口投与する用法・用量で「再発又は難治性の慢性リンパ性白血病（CLL）［小リンパ球性リンパ腫（SLL）を含む］」で承認されている。今回，新効能として560 mgを1日1回経口投与する用法・用量で「再発又は難治性のマントル細胞リンパ腫（MCL）」を申請する。

臨床的有効性では，イブルチニブの再発又は難治性MCLに対する有効性を評価するために，再発又は難治性MCL患者を対象として実施した国内及び海外臨床4試験［国内第II相試験（PCI-32765MCL2002試験），海外第II相試験（PCYC-1104-CA試験），海外第III相試験（PCI-32765MCL3001試験）及び海外第II相試験（PCI-32765MCL2001試験）］を用いた。

再発又は難治性MCLに対するイブルチニブの有効性評価に用いた臨床試験を表 2.7.3-1に示す。国内第II相試験（PCI-32765MCL2002試験）は，イブルチニブの有用性が認められた海外第II相試験（PCYC-1104-CA試験）と同様の対象患者及び計画で実施しており，これら2試験及び国内において本疾患の適応では未承認であるテムシロリムスを比較対照とした海外第III相試験（PCI-32765MCL3001試験）を評価資料とした。また，ボルテゾミブ既治療のMCL患者を対象とした海外第II相試験（PCI-32765MCL2001試験）は，参考資料とした。

**表 2.7.3-1 有効性評価に用いた臨床試験**

| 実施地域 | 開発の相 | 試験番号 | 有効性評価に用いたデータカットオフ日又は試験完了日 | | 評価/参考資料 | 資料番号 |
|---|---|---|---|---|---|---|
| 国内 | 第II相 | PCI-32765MCL2002 | [redacted]年[redacted]月[redacted]日 | 継続中 | 評価 | 5.3.5.2.1 |
| 海外 | 第II相 | PCYC-1104-CA [a] | 主要解析に用いたデータカットオフ日：[redacted]年[redacted]月[redacted]日<br><br>最終解析に用いたデータカットオフ日：2014年3月[redacted]日 | 完了 | 評価 | 主要解析時報告書：5.3.5.2.2-1<br><br>最終報告書：5.3.5.2.2-2 |
| | 第III相 | PCI-32765MCL3001 | 2015年4月22日 | 継続中 | 評価 | 5.3.5.1.1 |
| | 第II相 | PCI-32765MCL2001 [a] | 主要解析に用いたデータカットオフ日：[redacted]年[redacted]月[redacted]日<br><br>最終解析に用いたデータカットオフ日：2015年5月[redacted]日 | 完了 | 参考 | 主要解析時報告書：5.3.5.2.3-1<br><br>最終報告書：5.3.5.2.3-2 |

[a] 有効性は，主要解析時の結果を記載した。

本項では，表 2.7.3-1に記載した試験番号の表記「PCYC-」及び「-CA」，並びに「PCI-32765」を省略して記載する。

有効性評価に用いた 4 試験の臨床試験概要を表 2.7.3-2 に示す。

国内第 II 相試験である MCL2002 試験は，再発又は難治性の MCL 患者にイブルチニブ 560 mg/日を投与する試験である。イブルチニブを投与した 16 例を全投与集団とした。ベースライン後に 1 回以上の腫瘍評価が 16 例全例で適切に実施され，当該 16 例を抗腫瘍効果の評価可能な解析対象集団とし，すべての有効性を評価した。治験総括報告書（CSR）に記載した解析結果（データカットオフ日：[redacted] 年 [redacted] 月 [redacted] 日）を 2.7.3.3 項に提示した。

海外第 II 相試験である 1104 試験は，再発又は難治性の MCL 患者にイブルチニブ 560 mg/日を投与する試験であり，組み入れられた 115 例の被験者のうち，イブルチニブを投与した 111 例を全投与集団とし，すべての有効性を評価した。また，有効性の結果は，ボルテゾミブ未治療の 63 例及びボルテゾミブ既治療の 48 例の 2 つのコホート別にも示した。CSR に記載した解析結果（主要解析のデータカットオフ日：[redacted] 年 [redacted] 月 [redacted] 日）を 2.7.3.3 項に提示した。

海外第 III 相試験である MCL3001 試験は，再発又は難治性の MCL 患者にイブルチニブ 560 mg/日又はテムシロリムスを投与したときの有効性を比較する試験である。ランダム化された再発又は難治性の MCL 患者 280 例（イブルチニブ群 139 例，テムシロリムス群 141 例）を intent-to-treat（ITT）集団とし，すべての有効性を評価した。CSR に記載した解析結果（データカットオフ日：2015 年 4 月 22 日）を 2.7.3.3 項に提示した。

海外第 II 相試験である MCL2001 試験は，ボルテゾミブ治療中又は治療後に疾患進行が認められた MCL 患者にイブルチニブ 560 mg/日を投与する試験であり，組み入れられた 120 例の被験者全例にイブルチニブを投与した。そのうち，抗腫瘍効果の評価可能な被験者は 110 例であった。有効性の評価では，主要評価項目は抗腫瘍効果の評価可能な解析対象集団，副次評価項目は全投与集団に対して実施した。CSR に記載した解析結果（主要解析のデータカットオフ日：[redacted] 年 [redacted] 月 [redacted] 日）を 2.7.3.3 項に提示した。

表 2.7.3-2 有効性評価に用いた臨床試験概要

| 試験番号<br>開発の相<br>（進行状況） | 試験名 | 用法・用量 | 被験者数 |
|---|---|---|---|
| PCI-32765<br>MCL2002<br>第 II 相<br>（継続中） | BTK 阻害剤イブルチニブの再発又は難治性の MCL 患者を対象とした第 II 相試験 | イブルチニブを 560 mg/日で投与したときの日本人における再発又は難治性の MCL 患者に対する有効性，安全性，及び薬物動態を検討した試験 | 全投与集団：16 例<br>抗腫瘍効果の評価可能な解析対象集団：16 例 |
| PCYC-1104-CA<br>第 II 相<br>（完了） | BTK 阻害剤 PCI-32765 の再発又は難治性の MCL 患者を対象とした多施設共同，第 II 相試験 | イブルチニブを 560 mg/日で投与したときの再発又は難治性の MCL 患者（ボルテゾミブ未治療及びボルテゾミブ既治療）に対する有効性及び安全性を検討した試験 | 登録例数：115 例<br>全投与集団：111 例<br>－ボルテゾミブ未治療例数：63 例<br>－ボルテゾミブ既治療例数：48 例 |
| PCI-32765<br>MCL3001<br>第 III 相<br>（継続中） | 1 レジメン以上の前治療を受けた再発又は難治性の MCL 患者を対象とした，BTK 阻害剤イブルチニブとテムシロリムスを比較するランダム化，実薬対照，非盲検，多施設共同，第 III 相試験 | イブルチニブ 560 mg/日及びテムシロリムスを投与したときの再発又は難治性の MCL 患者に対する有効性及び安全性を検討した試験<br><br>イブルチニブ群<br>：21 日間を 1 サイクルとし，560 mg を 1 日 1 回経口投与<br>テムシロリムス群<br>：21 日間を 1 サイクルとし，最初のサイクルは 175 mg，以降は 75 mg の用量で Day 1，8，15 に静脈内投与 | ITT 集団：280 例<br>－イブルチニブ群：139 例<br>－テムシロリムス群：141 例 |
| PCI-32765<br>MCL2001<br>第 II 相<br>（完了） | ボルテゾミブ治療中又は治療後に疾患進行が認められた MCL 患者を対象とした，BTK 阻害剤イブルチニブの有効性及び安全性を検討する第 II 相，多施設共同，単群試験 | イブルチニブを 560 mg/日で投与したときのボルテゾミブ治療中又は治療後に疾患進行が認められた MCL 患者に対する有効性及び安全性を検討した試験 | 登録例数：120 例<br>全投与集団：120 例<br>抗腫瘍効果の評価可能な解析対象集団：110 例 |

Key: BTK=ブルトン型チロシンキナーゼ，ITT=intent-to-treat，MCL=マントル細胞リンパ腫

有効性評価に用いた 4 試験（MCL2002，1104，MCL3001 及び MCL2001 試験）の結果は，試験ごとに記載し，併合解析は行わなかった。

### 2.7.3.1.1 有効性を評価した各試験のデザイン

4 試験すべてにおいて，イブルチニブは 560 mg/日の固定用量とした。被験者は 1 日 1 回，140 mg カプセルを 4 カプセル服用した。イブルチニブ投与による毒性が認められた場合，イブルチニブの減量を可能とし，1 段階の減量は 420 mg/日（3 カプセル），2 段階の減量は 280 mg/日（2 カプセル）の用量とした。

#### (1) 国内第 II 相試験（MCL2002 試験）

MCL2002 試験は，再発又は難治性の MCL 患者を対象とした多施設共同，単群，第 II 相試験である。

本試験の目的は，1 レジメン以上 5 レジメン以下の前治療を実施した後に疾患進行が認められた再発又は難治性の MCL 患者を対象に，イブルチニブ単剤治療による有効性及び安全性を評価し，さらにイブルチニブの薬物動態を探索的に検討することであった。

本試験の主な選択基準は，20 歳以上の日本人被験者で，病理学的に（中央病理診断医により）cyclin D1 の共発現又は t(11;14) 転座により MCL と確定診断され，コンピュータ断層撮影（CT）による断面画像にて直交する二方向の測定可能な病変を有し，Eastern Cooperative Oncology Group（ECOG）performance status が 0 又は 1 で，1 レジメン以上 5 レジメン以下の MCL に対する治療歴を有していることとした。被験者は，直近の治療レジメンで少なくとも部分奏効（PR）に達しなかった，又は当該治療後に疾患進行が認められていることとした。

疾患進行，完全奏効（CR）到達後の再発，耐容不能な毒性の発現，又は試験終了のいずれか早い時点まで，28 日間を 1 サイクルとして 1 日 1 回，経口でイブルチニブを 560 mg 投与した。

### (2) 海外第 II 相試験（1104 試験）

1104 試験は，病理学的に MCL と診断され 1 レジメン以上 5 レジメン以下の前治療を受けた後に再発した患者を対象とした，第 II 相，非盲検，非ランダム化，多施設共同試験である。

本試験の目的は，ボルテゾミブ既治療及びボルテゾミブ未治療の 2 つのコホートに分けた MCL 患者を対象に，イブルチニブの有効性及び安全性を評価することであった。

本試験の主な選択基準は，18 歳以上の男女で，病理学的に cyclin D1 の共発現又は t(11;14) 転座により MCL と確定診断され，CT による断面画像にて直交する二方向の測定可能な病変を有し，ECOG performance status が 2 以下で，1 レジメン以上 5 レジメン以下の MCL に対する治療歴を有していることとした。ボルテゾミブの曝露は，被験者が単剤又は併用療法レジメンの一部として少なくとも 2 サイクル以上の投与を受けた場合に既治療とした。被験者は，直近の治療レジメンで少なくとも PR に達しなかった，又は当該治療後に疾患進行が認められていることとした。

疾患進行，耐容不能な毒性の発現，又は長期継続試験への参加のいずれか早い時点まで，28 日間を 1 サイクルとして 1 日 1 回，休薬なしでイブルチニブを 560 mg 投与した。

### (3) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験は，1 レジメン以上の前治療を受けた再発又は難治性の MCL 患者を対象に，イブルチニブとテムシロリムスの有効性及び安全性を比較するランダム化，実薬対照，非盲検，多施設共同，第 III 相試験である。

本試験の主要目的は，1 レジメン以上のリツキシマブ併用の化学療法を受けた再発又は難治性の MCL 患者を対象に，イブルチニブ投与がテムシロリムス投与と比較して無増悪生存期間（PFS）を延長するかどうかを検討することであった。主な副次目的は，イブルチニブの全奏効率（ORR），全生存期間（OS），1 年 OS 率，奏効持続期間（DOR），及び安全性をテムシロリムスと比較し，イブルチニブの薬物動態プロファイルを評価することであった。

本試験の主な選択基準は，18 歳以上で，MCL と確定診断され，1 レジメン以上のリツキシマブ併用の化学療法を受けており，再発又は疾患進行が認められ，ECOG performance status が 0 又は 1 で，少なくとも 1 カ所の測定可能病変を有していることとした。

約 280 例の被験者を前治療数及びマントル細胞リンパ腫国際予後指標（MIPI）簡略版のスコアで層別化し，イブルチニブ群又はテムシロリムス群に 1:1 の比でランダムに割り付けることとした。

イブルチニブ群は 21 日間を 1 サイクルとして 1 日 1 回，経口でイブルチニブを 560 mg 投与した。テムシロリムス群は 21 日間を 1 サイクルとし，テムシロリムスを最初のサイクルは 175 mg，以降は 75 mg の用量で Day 1，8，15 に静脈内投与した。両群ともに，疾患進行，又は耐容不能な毒性の発現のいずれか早い時点まで投与を継続した。さらに，テムシロリムス群の被験者で独立評価委員会（IRC）判定により疾患進行が認められた場合，イブルチニブ群へのクロスオーバーを可能とし，疾患進行，耐容不能な毒性の発現，又は試験終了まで，21 日間を 1 サイクルとして 1 日 1 回，経口でイブルチニブを 560 mg 投与した。

#### (4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験は，ボルテゾミブ治療中又は治療後に疾患進行が認められた MCL 患者を対象とした多施設共同，単群，第 II 相試験である。

本試験の主要目的は，1 レジメン以上のリツキシマブ併用の化学療法を受けており，ボルテゾミブ治療中又は治療後に疾患進行が認められた MCL 患者を対象に，イブルチニブの ORR を IRC により評価することであった。主な副次目的は，イブルチニブの DOR，PFS，OS，安全性及び薬物動態を評価することであった。

本試験の主な選択基準は，18 歳以上で，中央判定により病理学的に MCL と確定診断され，CT による測定可能病変を有し，1 レジメン以上のリツキシマブ併用の化学療法を受けており，少なくとも 2 サイクル以上のボルテゾミブ治療後（単剤又は併用投与）に疾患進行が認められ，ECOG performance status が 2 以下の患者であることとした。

疾患進行，CR 到達後の再発，耐容不能な毒性の発現，又は試験終了のいずれか早い時点まで，21 日間を 1 サイクルとして 1 日 1 回，経口でイブルチニブを 560 mg 投与した。投与を中止した被験者には，生存状況，後治療，及びその他の悪性腫瘍の発現状況に関する追跡調査を実施した。

### 2.7.3.1.2 有効性の主な評価項目及び解析方法

#### 2.7.3.1.2.1 効果判定規準等

有効性評価は，改訂版「悪性リンパ腫効果判定規準」[1)] に従い IRC 又は治験担当医師が実施した。

CT スキャン（禁忌でない限り造影剤を使用）を胸部，腹部，骨盤，及びその他の疾患部位（頸部など）に実施した。CR を確定するためにポジトロンエミッショントモグラフィー（PET）を実施した。また，ベースライン時に消化管への浸潤が認められた被験者は CR 確定時に内視鏡検査を実施することとし，骨髄浸潤が認められた被験者は CR 確定時に骨髄生検を実施することとした。

さらに，MCL2002 試験，MCL3001 試験及び MCL2001 試験では，CT で適切に画像化できない場合，磁気共鳴画像（MRI）を用いることとした。

(1) 国内第 II 相試験（MCL2002 試験）

MCL2002 試験では，主要解析における有効性は IRC が評価し，投与継続の判断にかかわる有効性評価は治験担当医師が実施した。腫瘍評価は，イブルチニブの投与開始から最初の 24 週間は 8 週ごと，その後は疾患進行，死亡，試験参加の同意撤回，又は試験終了のいずれか早い時点まで 12 週ごとに実施した。治験担当医師により判定された有効性も副次的に評価した。

(2) 海外第 II 相試験（1104 試験）

1104 試験では，有効性は治験担当医師が評価した。腫瘍評価は 28 日間を 1 サイクルとしてサイクル 3，5，7 の Day 1，その後は疾患進行が認められるまで 3 サイクルごとに実施した。さらに，探索的な解析では IRC が放射線画像及び臨床データから有効性を評価した。

(3) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験では，有効性は IRC が盲検下で評価し，投与継続の判断は治験担当医師が実施した。また，治験担当医師も有効性を評価した。腫瘍評価は，投与開始から最初の 15 カ月間は 9 週ごと，その後は疾患進行，死亡，又はデータカットオフのいずれか早い時点まで 24 週ごとに実施した。疾患進行が認められる前に投与を中止した被験者は，疾患進行，死亡，又はデータカットオフのいずれか早い時点まで，スケジュールに従い定期的な腫瘍評価を継続した。

(4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験では，主要解析に関する有効性は IRC が評価した。腫瘍評価は，イブルチニブの投与開始から最初の 15 カ月間は 9 週ごと，その後は疾患進行，死亡，又は試験終了のいずれか早い時点まで 24 週ごとに実施した。疾患進行が認められた被験者に対して，9 週ごとに生存状況及び MCL の後治療に関する情報を収集した。さらに，感度分析では治験担当医師が有効性を評価した。

2.7.3.1.2.2 解析対象集団

各試験の主たる有効性解析対象集団を表 2.7.3-3 に示す。MCL2002 試験及び MCL2001 試験（主要評価項目）は抗腫瘍効果の評価可能な解析対象集団，1104 試験及び MCL2001 試験（副次評価項目）は全投与集団，MCL3001 試験は ITT 集団に対して解析した。

表 2.7.3-3 本申請で用いた各試験の主たる有効性解析対象集団

| 試験番号 | 主たる有効性解析対象集団 | 定義 |
|---|---|---|
| PCI-32765MCL2002 | 抗腫瘍効果の評価可能な解析対象集団 | イブルチニブを 1 回以上投与され，ベースライン後の適切な腫瘍評価 [a] を 1 回以上実施したすべての被験者 |
| PCYC-1104-CA | 全投与集団 | イブルチニブを 1 回以上投与されたすべての被験者 |
| PCI-32765MCL3001 | ITT 集団 | ランダム化されたすべての被験者 |
| PCI-32765MCL2001 | 抗腫瘍効果の評価可能な解析対象集団（主要評価項目） | イブルチニブを 1 回以上投与され，ベースライン後の適切な腫瘍評価 [a] を 1 回以上実施したすべての被験者 |
| | 全投与集団（副次評価項目） | イブルチニブを 1 回以上投与されたすべての被験者 |

Key: ITT=intent-to-treat，MCL=マントル細胞リンパ腫
[a] 適切な腫瘍評価とは，疾患進行の有無を正確に示す十分な証拠があることとした。疾患進行による死亡が認められた被験者は適切な腫瘍評価が実施されたとみなした。

### 2.7.3.1.2.3 有効性評価項目及び統計解析

各試験の有効性評価項目を表 2.7.3-4 に示す。本項では各試験の主な有効性評価項目の結果を提示した。

表 2.7.3-4 各試験の有効性評価項目

| 試験番号<br>開発の相 | CSR に記載した有効性評価項目 | 主な有効性評価項目 |
|---|---|---|
| PCI-32765MCL2002<br>第 II 相 | 主要評価項目：ORR [a, b]<br>副次評価項目：奏効到達期間 [a]，DOR [a]，PFS [a]，及び腫瘍径の変化率 [a] | ・ ORR<br>・ 奏効到達期間<br>・ DOR<br>・ PFS<br>・ OS |
| PCYC-1104-CA<br>第 II 相 | 主要評価項目：ORR [b]<br>副次評価項目：DOR [a, b]，奏効到達期間 [b]，PFS [b]，OS，及び ECOG performance status のスコア変化<br>探索的評価項目：ORR [a] | |
| PCI-32765MCL3001<br>第 III 相 | 主要評価項目：PFS [a, b]<br>副次評価項目：ORR [a, b]，DOR [a]，奏効到達期間 [a]，OS，1 年 OS 率，後治療開始までの期間，FACT-Lym，及び EQ-5D-5L | |
| PCI-32765MCL2001<br>第 II 相 | 主要評価項目：ORR [a, b]<br>副次評価項目：奏効到達期間 [a, b]，DOR [a, b]，PFS [a, b]，OS，FACT-Lym，及び EQ-5D-5L | |

Key: CSR=治験総括報告書，DOR=奏効持続期間，ECOG=Eastern Cooperative Oncology Group，EQ=EuroQol，FACT-Lym=Functional Assessment of Cancer Therapy-Lymphoma，IRC=独立評価委員会，MCL=マントル細胞リンパ腫，ORR=全奏効率，OS=全生存期間，PFS=無増悪生存期間
[a] IRC 判定に基づく評価
[b] 治験担当医師判定に基づく評価

また，有効性の各評価項目の定義及び解析方法を以下に示す。解析の詳細は，各試験の統計解析計画書に記載した。

全奏効率（ORR）

ORR の定義は，最良総合効果が CR 又は PR となった被験者（奏効例）の割合とした。

ORR 及び対応する信頼区間（CI）を算出した。MCL2002 試験では 90% CI，1104 試験では 95% CI を正確二項分布によりそれぞれ算出し，MCL2001 試験では 95% CI を二項分布の正規近似により算出した。

さらに，MCL3001 試験では，イブルチニブ群とテムシロリムス群の ORR を層別 Cochran Mantel-Haenszel 検定を用いて比較した。層別因子は前治療数（1 又は 2 vs. 3 以上）及び MIPI 簡易版のスコア［Low-risk (0-3) vs. Intermediate risk (4-5) vs. High risk (6-11)］とした。イブルチニブ群のテムシロリムス群に対する相対危険度及びその 95% CI を算出した。

奏効到達期間（Time to Response）

奏効到達期間の定義は，投与開始日又はランダム化された日から奏効（PR 又は CR）が最初に認められた日までの期間とした（初回奏効到達期間）。また，MCL3001 試験及び MCL2001 試験では，最良効果到達期間（投与開始日又はランダム化された日から最良の奏効が最初に認められた日までの期間）も評価した。さらに，MCL2002 試験，1104 試験及び MCL3001 試験では，CR 到達期間（投与開始日又はランダム化された日から CR が最初に認められた日までの期間）も評価した。

これらの到達期間は，奏効例に対する記述統計量を算出した。

奏効持続期間（DOR）

DOR の定義は，奏効例を対象に，奏効（PR 又は CR）が最初に認められた日から疾患進行，CR 到達後の再発，又は死亡が最初に認められた日までのいずれか早いほうの期間とした。

DOR は Kaplan-Meier 法を用いて推定し，疾患進行が認められず生存しているか生存状況が不明の被験者は，腫瘍評価を実施した最後の日をもって打ち切りとした。

無増悪生存期間（PFS）

PFS の定義は，投与開始日又はランダム化された日から，疾患進行，CR 到達後の再発，又は死亡が認められた日までのいずれか早いほうの期間とした。

PFS は Kaplan-Meier 法を用いて推定し，疾患進行が認められず生存しているか生存状況が不明の被験者は，腫瘍評価を実施した最後の日をもって打ち切りとした。

さらに，MCL3001 試験では，イブルチニブ群とテムシロリムス群の PFS の比較を層別 log-rank 検定を用いて実施した。層別因子は前治療数及び MIPI 簡略版のスコアとした。イブルチニブ群のテムシロリムス群に対するハザード比及びその 95% CI を，層別 Cox 比例ハザードモデルにより算出した。

全生存期間（OS）

OS の定義は，投与開始日又はランダム化された日から死亡が認められた日までの期間とした。

OS は Kaplan-Meier 法を用いて推定し，死亡が認められないか生存状況が不明の被験者は，生存を確認した最後の日をもってデータを打ち切りとした。

さらに，MCL3001 試験では，イブルチニブ群とテムシロリムス群の OS の比較を PFS と同一の解析方法を用いて実施した。

#### 2.7.3.1.2.4 被験者数の設定

**(1) 国内第 II 相試験（MCL2002 試験）**

MCL2002 試験では，1104 試験の結果を参考に ORR を 60%と推測すると，有意水準 0.05（片側）で ORR が臨床的な閾値の 20%以上であることを示すためには，94%の検出力で 14 例の抗腫瘍効果の評価可能な被験者が必要となる。有効性の評価不能症例を 10%と想定し，約 16 例の被験者を組み入れることとした。

主要解析は，全ての被験者が 28 日間を 1 サイクルとしてサイクル 7 の Day 1 の有効性評価を終了（又はそれ以前に投与を中止）した時点をデータカットオフとして実施した。

**(2) 海外第 II 相試験（1104 試験）**

1104 試験では，ボルテゾミブの治療歴（ボルテゾミブ未治療及びボルテゾミブ既治療）に基づき，約 115 例を並行して 2 つのコホートに組み入れることとした。症例数の算出には第 II 相試験で用いられる Simon の 2 段階デザイン（最適法）を用いた。ボルテゾミブ未治療のコホートでは，第 1 段階で 25 例を組み入れることとし，少なくとも 6 例が奏効を達成するとした場合，ORR が臨床的な閾値の 20%以下であるという帰無仮説を棄却するためには，このコホートに計 65 例の被験者を組み入れる必要がある。最終解析時の症例数が 65 例，ORR が閾値の 20%に対して 40%である場合，有意水準 0.01（片側）では検出力は 91%となる。ボルテゾミブ既治療のコホートでは，第 1 段階で 25 例を組み入れることとし，少なくとも 5 例が奏効を達成するとした場合，ORR が臨床的な閾値の 15%以下であるという帰無仮説を棄却するためには，このコホートに計 50 例の被験者を組み入れる必要がある。最終解析時の症例数が 50 例，ORR が閾値の 15%に対して 35%である場合，有意水準 0.01（片側）では検出力は 80%以上となる。

有効性の解析では，本試験に組み入れられた最後の被験者が少なくとも 9 カ月間以上の追跡調査を経過した時点をデータカットオフとした。

**(3) 海外第 III 相試験（MCL3001 試験）**

MCL3001 試験では，主要解析時に 178 例の PFS イベントを評価するため約 280 例（各群 140 例ずつ）の被験者を組み入れることとした。イブルチニブ群はテムシロリムス群と比較して PFS の中央値を 57%延長するとした場合（PFS が指数分布に従うと仮定すると，テムシロリムス群に対するイブルチニブ群のハザード比は 0.64 に相当する），178 例の PFS イベントでは有意水準 0.025（片側），検出力 85%以上で統計学的に有意となる。

PFS の主要解析は，PFS イベント数が約 178 例に達した時点をデータカットオフとして実施した。

#### (4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験では，ORR を 56%（1104 試験のすべてのサブグループで得られた最も低値）と推測すると，有意水準 0.025（片側）で ORR が 40%以上であることを示すためには，90%の検出力で 101 例の抗腫瘍効果の評価可能な被験者が必要となる。

主要評価項目である ORR の最終解析は最終被験者の組入れから約 1 年後に実施した。帰無仮説に対して有意水準 0.025（片側）で検定を行い，95% CI の下限値が 40%を上回った場合に棄却することとした。

### 2.7.3.2 個々の試験結果の要約

#### 2.7.3.2.1 国内第 II 相試験（MCL2002 試験）

#### (1) 被験者内訳，被験者背景及び治験薬への曝露状況

[redacted]年[redacted]月[redacted]日のデータカットオフ時点において，再発又は難治性の MCL 患者 16 例に 560 mg/日のイブルチニブを 1 回以上投与し，全例がベースライン後の適切な腫瘍評価を 1 回以上実施した。

年齢の中央値（範囲）は 72.0（55～83）歳であり，被験者の 75.0%が 65 歳以上であった。ECOG performance status が 0 の被験者の割合は 75.0%，1 の被験者の割合は 25.0%であった（表 2.7.3-9）。

ベースライン時では，MCL の初回診断から投与開始までの期間の中央値（範囲）は 50.64（9.7～118.0）カ月であった。MIPI 簡略版のスコアは Intermediate risk（56.3%）の被験者が最も多く，次いで Low risk（25.0%），High risk（18.8%）の順であった。前治療のレジメン数の中央値は 2.5 レジメンであった（表 2.7.3-10）。

投与期間の中央値（範囲）は 6.46（2.8～8.3）カ月であった（表 2.7.3-17）。

#### (2) 有効性の結果

すべての有効性解析は，16 例の抗腫瘍効果の評価可能な解析対象集団を対象として実施した。有効性は IRC が評価し，治験担当医師判定による結果も副次的に評価した。主要な有効性の結果を以下に示す。なお，OS の要約統計量は集計しなかった。

- ORR は 87.5%（90% CI：65.6-97.7）であり，最良効果が CR の被験者の割合は 12.5%，PR の被験者の割合は 75.0%であった（表 2.7.3-21）。
- 治験担当医師判定に基づく ORR は 93.8%であり，最良効果が CR 及び PR に到達した被験者の割合は，それぞれ 6.3%及び 87.5%であった（【5.3.5.2.1 CSR Table 10 p61】）。
- 奏効例（14 例）の DOR の中央値は推定できず，データカットオフ時点で疾患進行又は死亡が認められなかった被験者の割合は 85.7%であった（表 2.7.3-29）。
- 奏効例（14 例）の初回奏効到達期間の中央値（範囲）は 1.84（0.7～5.3）カ月，CR 例（2 例）の CR 到達期間の中央値（範囲）は 2.84（1.8～3.8）カ月であった（表 2.7.3-25）。

・ PFS の中央値は推定できなかった。6 カ月 PFS 率は 88%と推定された（表 2.7.3-33）。

・ 16 例の被験者全例に腫瘍の二方向積和の減少が認められ，うち 14 例はベースライン時より最大で 50%以上減少した（図 2.7.3-1）。

#### 2.7.3.2.2 海外第 II 相試験（1104 試験）

**(1) 被験者内訳，被験者背景及び治験薬への曝露状況**

[redacted]年[redacted]月[redacted]日のデータカットオフ時点において，組み入れられた再発又は難治性の MCL 患者 115 例のうち，111 例に 560 mg/日のイブルチニブを 1 回以上投与した。

年齢の中央値（範囲）は 68.0（40.0～84.0）歳であり，被験者の 63.1%が 65 歳以上であった（表 2.7.3-11）。

ベースライン時では，MCL の初回診断からの期間の中央値（範囲）は 42.3（2.5～223）カ月であった。MIPI 簡略版のスコアは High risk（48.6%）の被験者が最も多く，次いで Intermediate risk（37.8%），Low risk（13.5%）の順であった。前治療のレジメン数の中央値は 3.0 レジメンであった。ECOG performance status が 0 の被験者の割合は 45.9%，1 の被験者の割合は 43.2%であった（表 2.7.3-12）。

投与期間の中央値（範囲）は 8.3（0.7～21.4）カ月であった（表 2.7.3-18）。

**(2) 有効性の結果**

すべての有効性解析は，111 例の全投与集団を対象として実施した。また，解析結果は，ボルテゾミブ未治療の 63 例及びボルテゾミブ既治療の 48 例の 2 つのコホート別にも示した。有効性は治験担当医師が評価し，探索的解析では IRC も評価した。主要な有効性の結果を以下に示す。

・ ORR は 67.6%（95% CI：58.0-76.1）であり，最良効果が CR の被験者の割合は 20.7%，PR の被験者の割合は 46.8%であった（表 2.7.3-22）。

・ IRC 判定に基づく ORR は 68.5%であり，最良効果が CR 及び PR に到達した被験者の割合は，それぞれ 20.7%及び 47.7%であった（【5.3.5.2.2-1 CSR TEFRSP04B p301】）。

・ 奏効例（75 例）の DOR の中央値は 17.5 カ月（95% CI：15.8-NE）と推定され，データカットオフ時点で疾患進行又は死亡が認められなかった被験者の割合は 68.0%であった（表 2.7.3-30）。

・ 奏効例（75 例）の初回奏効到達期間の中央値（範囲）は 1.9（1.4～13.7）カ月，CR 例（23 例）の CR 到達期間の中央値（範囲）は 5.5（1.7～11.5）カ月であった（表 2.7.3-26）。

・ 各評価時点で CR と評価された被験者の割合（CR 率）は投与開始 2 カ月目の 3.6%から 12 カ月目の 20.7%まで経時的に上昇した（図 2.7.3-2）。

・ PFS の中央値は 13.9 カ月（95% CI：7.0-NE）と推定された。また，6 カ月 PFS 率は 62.8%，18 カ月 PFS 率は 41.6%と推定された（表 2.7.3-34）。

・ OS の中央値は推定できなかった。18 カ月 OS 率は 58.2%と推定された（表 2.7.3-37）。

#### 2.7.3.2.3 海外第 III 相試験（MCL3001 試験）

**(1) 被験者内訳，被験者背景及び治験薬への曝露状況**

2015 年 4 月 22 日のデータカットオフ時点において，再発又は難治性の MCL 患者 280 例がイブルチニブ群 139 例，又はテムシロリムス群 141 例にランダム化された。イブルチニブ群では 139 例の被験者全例に 560 mg/日のイブルチニブを 1 回以上投与し，テムシロリムス群では 141 例のうち 139 例の被験者にテムシロリムスを 1 回以上投与した。

年齢の中央値（範囲）は 68.0（34～88）歳であり，被験者の 61.8%が 65 歳以上であった。ECOG performance status が 0 の被験者の割合は 47.9%，1 の被験者の割合は 51.1%であった（表 2.7.3-13）。

ベースライン時では，MCL の初回診断からランダム化までの期間の中央値（範囲）は 42.56（2.7～298.7）カ月であった。MIPI 簡略版のスコアは Intermediate risk（47.9%）の被験者が最も多く，次いで Low risk（30.7%），High risk（21.4%）の順であった。前治療のレジメン数の中央値は 2.0 レジメンであった（表 2.7.3-14）。

投与期間の中央値（範囲）は，イブルチニブ群が 14.39（0.0～28.2）カ月，テムシロリムス群が 3.02（0.0～27.0）カ月であり，イブルチニブ群の投与期間はテムシロリムス群の 4 倍を超えた（表 2.7.3-19）。

**(2) 有効性の結果**

すべての有効性解析は，ITT 集団（イブルチニブ群 139 例，テムシロリムス群 141 例）を対象として実施した。有効性は IRC が評価し，感度分析では治験担当医師も評価した。主要な有効性の結果を以下に示す。

・ PFS の中央値はイブルチニブ群が 14.6 カ月（95% CI：10.4-NE），テムシロリムス群が 6.2 カ月（95% CI：4.2-7.9）と推定され，イブルチニブ投与はテムシロリムス投与に比べて PFS を有意に延長した［ハザード比：0.43（95% CI：0.32-0.58），p<0.0001］。また，イブルチニブ群及びテムシロリムス群の 6 カ月 PFS 率はそれぞれ 73%及び 54%，18 カ月 PFS 率はそれぞれ 48%及び 15%と推定された（表 2.7.3-35）。

・ ORR はイブルチニブ群が 71.9%であり，テムシロリムス群の 40.4%に比べて有意に高かった［相対危険度：1.78（95% CI：1.43-2.23），p<0.0001］。最良効果が CR の被験者の割合は，イブルチニブ群（18.7%）の方がテムシロリムス群（1.4%）よりも高かった（表 2.7.3-23）

・ イブルチニブ群では DOR の中央値は推定できず，奏効例（100 例）のうち 61.0%の被験者を打ち切りとした。テムシロリムス群では奏効例（57 例）の DOR の中央値は 7.0 カ月（95% CI：4.2-9.9）と推定された（表 2.7.3-31）。

・ 奏効例（イブルチニブ群 100 例，テムシロリムス群 57 例）において，初回奏効到達期間の中央値はイブルチニブ群が 2.15 カ月，テムシロリムス群が 2.14 カ月であった。CR 例（イブルチニブ群 26 例，テムシロリムス群 2 例）において，CR 到達期間の中央値はイブルチニブ群が 6.28 カ月，テムシロリムス群が 6.60 カ月であった（表 2.7.3-27）。

・ イブルチニブ群では OS の中央値は推定できず，テムシロリムス群では OS の中央値は 21.3 カ月（95% CI：13.0-NE）と推定された。18 カ月 OS 率は，イブルチニブ群が 60%，テムシロリムス群が 54%と推定された（表 2.7.3-38）。

#### 2.7.3.2.4 海外第 II 相試験（MCL2001 試験）

##### (1) 被験者内訳，被験者背景及び治験薬への曝露状況

[redacted]年[redacted]月[redacted]日のデータカットオフ時点において，組み入れられたボルテゾミブ既治療の MCL 患者 120 例全例に 560 mg/日のイブルチニブを 1 回以上投与した。そのうちベースライン後に有効性評価を 1 回以上受けた被験者は 110 例であった。

年齢の中央値（範囲）は 67.5（35～85）歳であり，被験者の 62.5%が 65 歳以上であった（表 2.7.3-15）。

ベースライン時では，MCL の初回診断からの期間の中央値（範囲）は 43.94（6.8～189.6）カ月であった。MIPI 簡略版のスコアは Intermediate risk（48.3%）の被験者が最も多く，次いで High risk（28.0%），Low risk（23.7%）の順であった。前治療のレジメン数の中央値は 2.00 レジメンであった。ECOG performance status が 0 の被験者の割合は 35.0%，1 の被験者の割合は 55.8%であった（表 2.7.3-16）。

投与期間の中央値（範囲）は 7.95（0.5～20.9）カ月であった（表 2.7.3-20）。

##### (2) 有効性の結果

有効性解析は，主要評価項目では 110 例の抗腫瘍効果の評価可能な解析対象集団，副次評価項目では 120 例の全投与集団を対象として実施した。有効性は IRC が評価し，感度分析では治験担当医師も評価した。主要な有効性の結果を以下に示す。

・ ORR は 62.7%（95% CI：53.7-71.8）であり，最良効果が CR の被験者の割合は 20.9%であった（表 2.7.3-24）。

・ 奏効例（69 例）において，初回奏効到達期間の中央値（範囲）は 2.07（1.3～6.3）カ月であった（表 2.7.3-28）。

・ 奏効例（69 例）の DOR の中央値は 14.92 カ月（95% CI：12.35-NE）と推定された（表 2.7.3-32）。

・ PFS の中央値は 10.48 カ月（95% CI：4.37-14.98）と推定された。また，6 カ月 PFS 率は 58%，18 カ月 PFS 率は 26%と推定された（表 2.7.3-36）。

・ OS の中央値は推定できなかった。18 カ月 OS 率は 61%と推定された（表 2.7.3-39）。

## 2.7.3.3 全試験を通しての結果の比較と解析

### 2.7.3.3.1 試験対象集団

#### 2.7.3.3.1.1 被験者内訳

**(1) 国内第 II 相試験（MCL2002 試験）**

MCL2002 試験では，16 例の被験者に 560 mg/日のイブルチニブを 1 回以上投与した。全例がベースライン後の適切な腫瘍評価を 1 回以上実施し，抗腫瘍効果の評価可能な解析対象集団となった。

[redacted]年[redacted]月[redacted]日のデータカットオフ時点では，解析対象集団 16 例のうち，投与を継続していた被験者の割合は 68.8%（11 例），投与を中止した被験者の割合は 31.3%（5 例）であった。投与中止の主な理由は疾患進行（25.0%，4 例）であった。

試験を終了した被験者の割合は 31.3%（5 例）であり，全例が死亡によるものであった（表 2.7.3-5）。

表 2.7.3-5 被験者内訳［MCL2002 試験：All Subjects］

| | Ibrutinib |
|---|---|
| All Subjects Obtained Informed Consent | 19 |
| Screen Failure | 3 |
| All Treated Population | 16 |
| Response-Evaluable Population | 16 (100.0%) |
| Pharmacokinetic Analysis Population | 16 (100.0%) |
| Ongoing at date of cut-off | 11 (68.8%) |
| Treatment Discontinuation | 5 (31.3%) |
| Reason for Treatment Discontinuation | |
| ADVERSE EVENT | 1 (6.3%) |
| PROGRESSIVE DISEASE | 4 (25.0%) |
| Study Discontinuation | 5 (31.3%) |
| Reason for Study Discontinuation | |
| DEATH | 5 (31.3%) |

Note: Percentages calculated with all treated population as denominator.

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 4

**(2) 海外第 II 相試験（1104 試験）**

1104 試験では，組み入れられた 115 例の被験者のうち 111 例に 560 mg/日のイブルチニブを 1 回以上投与し，その内訳はボルテゾミブ未治療が 63 例，ボルテゾミブ既治療が 48 例であった。

[redacted]年[redacted]月[redacted]日の主要解析のデータカットオフ時点では，全投与集団 111 例のうち，投与を継続していた被験者の割合は 41.4%（46 例），投与を中止した被験者の割合は 58.6%（65 例）であった。投与中止の主な理由は疾患進行（44.1%，49 例）であった。

Kaplan-Meier 法を用いて推定した試験参加期間（投与開始日から直近の生存確認日までの期間）の中央値（範囲）は 15.3［1.87（打ち切り例）～22.34］カ月であった。

試験を終了した主な理由は死亡（36.9%，41 例）であった（表 2.7.3-6）。

表 2.7.3-6 被験者内訳及び投与期間［1104 試験：All-Treated Population］

| | Ibrutinib | | |
|---|---|---|---|
| | Bortezomib-Naive (N=63) | Bortezomib-Exposed (N=48) | Total (N=111) |
| Treatment Duration (months) | | | |
| Mean (SD) | 9.2 ( 6.51) | 10.2 ( 6.42) | 9.6 ( 6.46) |
| Median | 7.4 | 10.4 | 8.3 |
| Min, Max | 0.7, 21.2 | 0.9, 21.4 | 0.7, 21.4 |
| ≤6 Months | 29 (46.0%) | 16 (33.3%) | 45 (40.5%) |
| >6 - ≤12 Months | 10 (15.9%) | 14 (29.2%) | 24 (21.6%) |
| >12 Months | 24 (38.1%) | 18 (37.5%) | 42 (37.8%) |
| Subjects Still on Treatment | 24 (38.1%) | 22 (45.8%) | 46 (41.4%) |
| Subjects Discontinued Study Treatment | 39 (61.9%) | 26 (54.2%) | 65 (58.6%) |
| Primary Reason for Study Treatment Discontinuation | | | |
| Disease Progression | 32 (50.8%) | 17 (35.4%) | 49 (44.1%) |
| Adverse Event | 4 ( 6.3%) | 5 (10.4%) | 9 ( 8.1%) |
| Investigator's Decision | 1 ( 1.6%) | 2 ( 4.2%) | 3 ( 2.7%) |
| Consent Withdrawal | 2 ( 3.2%) | 2 ( 4.2%) | 4 ( 3.6%) |
| Time on Study (Months) [a] | | | |
| Median | 16.3 | 15.3 | 15.3 |
| Min, Max | 1.97, 21.16 | 1.87+, 22.34 | 1.87+, 22.34 |
| Primary Reason for Study Termination | | | |
| Death | 24 (38.1%) | 17 (35.4%) | 41 (36.9%) |
| Consent Withdrawal | 5 ( 7.9%) | 3 ( 6.3%) | 8 ( 7.2%) |
| Lost to Follow-up | 2 ( 3.2%) | 0 | 2 ( 1.8%) |

[a] Time on study is defined as the interval between the date of first dose of study drug and the date last known alive (the same way as overall survival with reversed censoring). The Kaplan-Meier method was used to estimate the median time on study with subjects who died being censored at death date.

Note: + indicates censored observation.

### (3) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験では，280 例の被験者がイブルチニブ群 139 例，又はテムシロリムス群 141 例にランダム化された。イブルチニブ群では 139 例の被験者全例に 560 mg/日のイブルチニブを 1 回以上投与した。テムシロリムス群では 141 例のうち 139 例の被験者にテムシロリムスを 1 回以上投与した。残り 2 例の被験者はテムシロリムスの投与を受けなかった。

2015 年 4 月 22 日のデータカットオフ時点では，投与を継続していた被験者の割合は，イブルチニブ群が 46.8%（65 例），テムシロリムス群が 10.6%（15 例）であり，イブルチニブ群の方が高かった。投与を中止した被験者の割合は，イブルチニブ群が 53.2%（74 例），テムシロリムス群が 87.9%（124 例）であった。投与中止の主な理由は疾患進行又は再発であり，その割合はイブルチニブ群が 39.6%（55 例），テムシロリムス群が 41.1%（58 例）と同程度であった。

試験を終了した被験者の割合は，イブルチニブ群が 47.5%（66 例），テムシロリムス群が 55.3%（78 例）であった。試験終了の主な理由は死亡であり，その割合はイブルチニブ群が 42.4%（59 例），テムシロリムス群が 44.7%（63 例）であった（表 2.7.3-7）。

表 2.7.3-7 被験者内訳［MCL3001 試験：Intent-to-treat Analysis Set］

| | Ibrutinib | Temsirolimus | Total |
|---|---|---|---|
| Analysis set: intent-to-treat | 139 | 141 | 280 |
| Did not receive study drug | 0 | 2 (1.4%) | 2 (0.7%) |
| Still on treatment | 65 (46.8%) | 15 (10.6%) | 80 (28.6%) |
| Discontinued treatment | 74 (53.2%) | 124 (87.9%) | 198 (70.7%) |
| Reason for discontinuation | | | |
| Progressive disease or relapse | 55 (39.6%) | 58 (41.1%) | 113 (40.4%) |
| Adverse event | 9 (6.5%) | 36 (25.5%) | 45 (16.1%) |
| Death | 6 (4.3%) | 8 (5.7%) | 14 (5.0%) |
| Lost to follow-up | 0 | 0 | 0 |
| Pregnancy | 0 | 0 | 0 |
| Investigator or sponsor decision | 0 | 6 (4.3%) | 6 (2.1%) |
| Subject refuses further treatment | 4 (2.9%) | 16 (11.3%) | 20 (7.1%) |
| Analysis set: intent-to-treat subjects | 139 | 141 | 280 |
| In treatment phase | 65 (46.8%) | 15 (10.6%) | 80 (28.6%) |
| In follow-up phase | 8 (5.8%) | 48 (34.0%) | 56 (20.0%) |
| Discontinued study | 66 (47.5%) | 78 (55.3%) | 144 (51.4%) |
| Reason for discontinuation | | | |
| Death | 59 (42.4%) | 63 (44.7%) | 122 (43.6%) |
| Lost to follow-up | 1 (0.7%) | 2 (1.4%) | 3 (1.1%) |
| Withdrawal of consent | 6 (4.3%) | 13 (9.2%) | 19 (6.8%) |

Note: Percentages calculated with the number of subjects in intent-to-treat analysis set as denominator

参照元：5.3.5.1.1 MCL3001 試験 CSR Table 1, TSIDS02A

### (4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験では，組み入れられた 120 例の被験者全例に 560 mg/日のイブルチニブを 1 回以上投与した。

[redacted]年[redacted]月[redacted]日のデータカットオフ時点では，全投与集団 120 例のうち，投与を継続していた被験者の割合は 32.5%（39 例），投与を中止した被験者の割合は 67.5%（81 例）であった。投与中止の主な理由は疾患進行又は再発（44.2%，53 例）であった。

試験終了に関する集計は登録例数に対して実施したが，解析対象は全投与集団と同じ 120 例であった。被験者の 45.8%（55 例）が試験を終了し，主な理由は死亡（36.7%，44 例）であった（表 2.7.3-8）。

表 2.7.3-8 被験者内訳［MCL2001 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Population: all-treated | 120 |
| Treatment ongoing | 39 (32.5%) |
| Discontinued treatment | 81 (67.5%) |
| Reason for discontinuation | |
| Progressive Disease or Relapse | 53 (44.2%) |
| Adverse event | 8 (6.7%) |
| Investigator or Sponsor decision | 3 (2.5%) |
| Death | 8 (6.7%) |
| Subject refuses further treatment with study drug per protocol | 9 (7.5%) |
| | |
| Population: all-enrolled | 120 |
| On study | 65 (54.2%) |
| Discontinued from the study | 55 (45.8%) |
| Reason for discontinuation | |
| Withdrawal of consent | 10 (8.3%) |
| Lost to follow-up | 1 (0.8%) |
| Sponsor ends the study | 0 |
| Death | 44 (36.7%) |

Note: Percentages are calculated with the number of subjects with non-missing values for each parameter as the denominator.

参照元：5.3.5.2.3-1 MCL2001 試験 CSR Table 1, Table 2

### 2.7.3.3.1.2 人口統計学的特性及びベースラインの疾患特性等

#### (1) 国内第 II 相試験（MCL2002 試験）

MCL2002 試験の人口統計学的特性を表 2.7.3-9 に示す。

日本人の全投与集団 16 例において，年齢の中央値（範囲）は 72.0（55～83）歳であり，65 歳以上の被験者の割合は 75.0%（12 例）であった。性別では男性（75.0%）の被験者が多かった。また，ECOG performance status が 0 の被験者の割合は 75.0%（12 例），1 の被験者の割合は 25.0%（4 例）であった。

表 2.7.3-9 人口統計学的特性［MCL2002 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Age (years) | |
| N | 16 |
| < 65 | 4 (25.0%) |
| >= 65 | 12 (75.0%) |
| < 70 | 7 (43.8%) |
| >= 70 | 9 (56.3%) |
| Mean (SD) | 71.4 (8.62) |
| Median | 72.0 |
| Range | (55; 83) |
| Sex | |
| N | 16 |
| Male | 12 (75.0%) |
| Female | 4 (25.0%) |
| Weight (kg) | |
| N | 16 |
| Mean (SD) | 58.34 (11.590) |
| Median | 55.30 |
| Range | (38.4; 85.0) |
| ECOG | |
| N | 16 |
| 0 | 12 (75.0%) |
| 1 | 4 (25.0%) |

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 5

MCL2002 試験のベースラインの疾患特性を表 2.7.3-10 に示す。

MCL の初回診断から投与開始までの期間の中央値（範囲）は 50.64（9.7～118.0）カ月であり，被験者の 75.0%（12 例）がステージ IV であった。芽球様細胞の組織学的所見を有する被験者，及び B 症状を有する被験者はいずれもいなかった。MIPI 簡略版のスコアは Intermediate risk（56.3%）の被験者が最も多く，次いで Low risk（25.0%），High risk（18.8%）の順であった。前治療のレジメン数の中央値（範囲）は 2.5（1～4）レジメンであった。試験参加前の直近の前治療に対する奏効評価が PR 以上に達しなかったと定義される難治性疾患を有する被験者の割合は 25.0 %（4 例）であった。ベースライン時に長径が 10 cm 以上の bulky disease を有する被験者の割合は 6.3%（1 例）であった。節外病変が認められた被験者の割合は 43.8%（7 例）であった。骨髄浸潤が認められた被験者の割合は，生検による陽性診断が 43.8%（7 例），骨髄穿刺による陽性診断が 56.3%（9 例）であった。

表 2.7.3-10 ベースラインの疾患特性［MCL2002 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Duration of Disease (months) [a] | |
| N | 16 |
| Mean (SD) | 59.84 (35.563) |
| Median | 50.64 |
| Range | (9.7; 118.0) |
| Ann Arbor stage | |
| N | 16 |
| I | 1 (6.3%) |
| II | 0 |
| III | 3 (18.8%) |
| IV | 12 (75.0%) |
| Type of Histology | |
| N | 16 |
| Diffuse | 13 (81.3%) |
| Nodular | 3 (18.8%) |
| Blastoid | 0 |
| Other | 0 |
| B-symptoms | |
| N | 16 |
| Yes | 0 |
| No | 16 (100.0%) |
| Simplified MIPI score | |
| N | 16 |
| Low risk (0-3) | 4 (25.0%) |
| Intermediate risk (4-5) | 9 (56.3%) |
| High risk (6-11) | 3 (18.8%) |
| Number of Prior Regimens | |
| N | 16 |
| Mean (SD) | 2.3 (1.20) |
| Median | 2.5 |
| Range | (1; 4) |
| Best Response of Last Therapy/Regimen | |
| N | 16 |
| COMPLETE RESPONSE | 9 (56.3%) |
| PARTIAL RESPONSE | 3 (18.8%) |
| STABLE DISEASE | 3 (18.8%) |
| PROGRESSIVE DISEASE | 1 (6.3%) |
| Tumor bulk (cm) [b] | |
| N | 16 |
| < 10 | 15 (93.8%) |
| >=10 | 1 (6.3%) |
| Extranodal site [c] | |
| Yes | 7 (43.8%) |
| Bone Marrow Biopsy | |
| Histology Negative | 7 (43.8%) |
| Histology Positive | 4 (25.0%) |
| Histology Indeterminate | 2 (12.5%) |
| Histology Indeterminate: Positive by IHC | 3 (18.8%) |
| Histology Indeterminate: Positive by Karyotype | 0 |
| Histology Indeterminate: Positive by FISH | 0 |
| Bone Marrow Aspirate | |
| Histology Negative | 6 (37.5%) |
| Histology Positive | 6 (37.5%) |
| Histology Indeterminate | 1 (6.3%) |
| Histology Indeterminate: Positive by IHC | 1 (6.3%) |
| Histology Indeterminate: Positive by Karyotype | 0 |
| Histology Indeterminate: Positive by FISH | 2 (12.5%) |
| Prior Radiotherapy | |
| Yes | 3 (18.8%) |

[a] (Date of First Dose of Ibrutinib - Date of Initial Diagnosis +1) / 365.25×12
[b] Tumor bulk (cm) is derived using the largest diameter among measurable lesions.
[c] Extranodal site is defined as any measurable or unmeasurable extranodal lesions except for spleen.

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 6, TSIDEM05

### (2) 海外第 II 相試験（1104 試験）

1104 試験の人口統計学的特性を表 2.7.3-11 に示す。

全投与集団 111 例において，年齢の中央値（範囲）は 68.0（40.0～84.0）歳であり，65 歳以上の被験者の割合は 63.1%（70 例）であった。性別では男性（76.6%），人種では白人（91.9%）の被験者が多かった。

表 2.7.3-11 人口統計学的特性［1104 試験：All-Treated Population］

| | Ibrutinib | | |
|---|---|---|---|
| | Bortezomib-Naive (N=63) | Bortezomib-Exposed (N=48) | Total (N=111) |
| Age (years) | | | |
| N | 63 | 48 | 111 |
| Mean (SD) | 66.9 ( 8.57) | 67.4 ( 8.64) | 67.1 ( 8.57) |
| Median | 66.0 | 69.0 | 68.0 |
| Min, Max | 46.0, 83.0 | 40.0, 84.0 | 40.0, 84.0 |
| Age Group | | | |
| <65 | 25 (39.7%) | 16 (33.3%) | 41 (36.9%) |
| ≥65 | 38 (60.3%) | 32 (66.7%) | 70 (63.1%) |
| ≥70 | 24 (38.1%) | 22 (45.8%) | 46 (41.4%) |
| ≥75 | 15 (23.8%) | 8 (16.7%) | 23 (20.7%) |
| Sex | | | |
| Male | 46 (73.0%) | 39 (81.3%) | 85 (76.6%) |
| Female | 17 (27.0%) | 9 (18.8%) | 26 (23.4%) |
| Ethnicity | | | |
| Hispanic or Latino | 2 ( 3.2%) | 3 ( 6.3%) | 5 ( 4.5%) |
| Not Hispanic or Latino | 61 (96.8%) | 45 (93.8%) | 106 (95.5%) |
| Race | | | |
| Asian | 0 | 1 ( 2.1%) | 1 ( 0.9%) |
| Black or African American | 2 ( 3.2%) | 3 ( 6.3%) | 5 ( 4.5%) |
| Native Hawaiian or Other Pacific Islander | 1 ( 1.6%) | 0 | 1 ( 0.9%) |
| White | 60 (95.2%) | 42 (87.5%) | 102 (91.9%) |
| Other | 0 | 2 ( 4.2%) | 2 ( 1.8%) |
| Region | | | |
| USA | 36 (57.1%) | 42 (87.5%) | 78 (70.3%) |
| Europe | 27 (42.9%) | 6 (12.5%) | 33 (29.7%) |

Key: USA=United States of America

1104 試験のベースラインの疾患特性を表 2.7.3-12 に示す。

MCL の初回診断からの期間の中央値（範囲）は 42.3（2.5～223）カ月であった。B 症状を有する被験者の割合は 26.1%（29 例）であった。全被験者に対し，免疫組織化学（IHC）法による cyclin D1 の過剰発現，蛍光 in-situ ハイブリダイゼーション（FISH）法による t(11,14) 転座，又はその両方を用いた MCL の分子レベルの確定診断を実施した。MIPI 簡略版のスコアは High risk（48.6%）の被験者が最も多く，次いで Intermediate risk（37.8%），Low risk（13.5%）の順であった。骨髄浸潤又は節外病変が認められていることと定義される進行性疾患は 72.1%（80 例）の被験者に認められた。前治療のレジメン数の中央値（範囲）は 3.0（1.0～5.0）レジメンであった。難治性疾患を有する被験者の割合は 45.0%（50 例）であった。ベースライン時に長径が 5 cm 以上及び 10 cm 以上の bulky disease を有する被験者の割合は，それぞれ 38.7%（43 例）及び 8.1%（9 例）であった。ECOG performance status が 0 の被験者の割合は 45.9%（51 例），1 の被験者の割合は 43.2%（48 例）であった。全体的に，被験者集団の疾患特性は，再発性又は難治性 MCL

の一般的な患者集団を反映しており，ボルテゾミブ未治療とボルテゾミブ既治療の被験者間で，臨床的に意味のある差は認められなかった。

表 2.7.3-12 ベースラインの疾患特性［1104 試験：All-Treated Population］

| | Ibrutinib | | |
|---|---|---|---|
| | Bortezomib-Naive (N=63) | Bortezomib-Exposed (N=48) | Total (N=111) |
| Time since initial diagnosis (months) | | | |
| Mean (SD) | 45.8 (45.45) | 59.2 (39.62) | 51.6 (43.35) |
| Median | 29.0 | 48.3 | 42.3 |
| Min, Max | 2.5, 213 | 6.6, 223 | 2.5, 223 |
| B Symptoms | | | |
| Yes | 19 (30.2%) | 10 (20.8%) | 29 (26.1%) |
| No | 39 (61.9%) | 37 (77.1%) | 76 (68.5%) |
| Unknown | 5 ( 7.9%) | 1 ( 2.1%) | 6 ( 5.4%) |
| Molecular Confirmation of Mantle Cell Lymphoma | | | |
| FISH Only | 9 (14.3%) | 6 (12.5%) | 15 (13.5%) |
| IHC Only | 44 (69.8%) | 33 (68.8%) | 77 (69.4%) |
| Both FISH and IHC | 10 (15.9%) | 9 (18.8%) | 19 (17.1%) |
| Simplified MIPI score [a] | | | |
| Low risk (0-3) | 9 (14.3%) | 6 (12.5%) | 15 (13.5%) |
| Intermediate risk (4-5) | 24 (38.1%) | 18 (37.5%) | 42 (37.8%) |
| High risk (6-11) | 30 (47.6%) | 24 (50.0%) | 54 (48.6%) |
| Advance Disease (Extranodal/Bone Marrow Involvement) | | | |
| Yes | 49 (77.8%) | 31 (64.6%) | 80 (72.1%) |
| Number of Prior Therapy Regimens | | | |
| Mean (SD) | 2.6 ( 1.40) | 3.3 ( 1.34) | 2.9 ( 1.41) |
| Median | 2.0 | 3.0 | 3.0 |
| Min, Max | 1.0, 5.0 | 1.0, 5.0 | 1.0, 5.0 |
| Prior lenalidomide | 9 (14.3%) | 18 (37.5%) | 27 (24.3%) |
| Refractory disease | 27 (42.9%) | 23 (47.9%) | 50 (45.0%) |
| Received prior radiotherapy | 16 (25.4%) | 12 (25.0%) | 28 (25.2%) |
| Received prior cancer surgery | 17 (27.0%) | 10 (20.8%) | 27 (24.3%) |
| Tumor bulk (≥5 cm) | 26 (41.3%) | 17 (35.4%) | 43 (38.7%) |
| Tumor bulk (≥10 cm) | 6 ( 9.5%) | 3 ( 6.3%) | 9 ( 8.1%) |
| ECOG Performance Status Score | | | |
| 0 | 28 (44.4%) | 23 (47.9%) | 51 (45.9%) |
| 1 | 25 (39.7%) | 23 (47.9%) | 48 (43.2%) |
| 2 | 9 (14.3%) | 2 ( 4.2%) | 11 ( 9.9%) |
| >2 | 1 ( 1.6%) | 0 | 1 ( 0.9%) |
| LDH > upper limit normal | | | |
| Yes | 47 (74.6%) | 42 (87.5%) | 89 (80.2%) |

Key: ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; LDH=lactate dehydrogenase; MIPI=Mantle Cell Lymphoma International Prognostic Index; WBC=white blood cell
[a] Derived using the following 4 prognostic factors: age, ECOG, LDH, and WBC at baseline. If a subject had LDH and/or WBC values missing at baseline then it was derived using rest of the prognostic factors

### (3) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験の人口統計学的特性を表 2.7.3-13 に示す。

ITT 集団 280 例において，年齢の中央値（範囲）は 68.0（34～88）歳であり，65 歳以上の被験者の割合は 61.8%（173 例）であった。性別では男性（74.3%），人種では白人（87.1%）の被験者が多かった。また，ECOG performance status が 0 の被験者の割合は 47.9%（134 例），1 の被験者の割合は 51.1%（143 例）であった。

人口統計学的特性は対象とする患者集団を反映しており，イブルチニブ群とテムシロリムス群の被験者間でおおむね同様であった。

表 2.7.3-13 人口統計学的特性［MCL3001 試験：Intent-to-treat Analysis Set］

| | Ibrutinib | Temsirolimus | Total |
|---|---|---|---|
| Analysis set: intent-to-treat | 139 | 141 | 280 |
| Age (years) | | | |
| N | 139 | 141 | 280 |
| Mean (SD) | 66.7 (8.7) | 67.1 (9.8) | 66.9 (9.3) |
| Median | 67.0 | 68.0 | 68.0 |
| Range | (39; 84) | (34; 88) | (34; 88) |
| < 65 | 53 (38.1%) | 54 (38.3%) | 107 (38.2%) |
| >= 65 | 86 (61.9%) | 87 (61.7%) | 173 (61.8%) |
| Sex | | | |
| N | 139 | 141 | 280 |
| Male | 100 (71.9%) | 108 (76.6%) | 208 (74.3%) |
| Female | 39 (28.1%) | 33 (23.4%) | 72 (25.7%) |
| Race | | | |
| N | 139 | 141 | 280 |
| White | 115 (82.7%) | 129 (91.5%) | 244 (87.1%) |
| Asian | 16 (11.5%) | 5 (3.5%) | 21 (7.5%) |
| Other | 3 (2.2%) | 4 (2.8%) | 7 (2.5%) |
| Unknown/ not reported | 5 (3.6%) | 3 (2.1%) | 8 (2.9%) |
| Ethnicity | | | |
| N | 139 | 141 | 280 |
| Hispanic or Latino | 7 (5.0%) | 11 (7.8%) | 18 (6.4%) |
| Not Hispanic or Latino | 127 (91.4%) | 127 (90.1%) | 254 (90.7%) |
| Unknown/ not reported | 5 (3.6%) | 3 (2.1%) | 8 (2.9%) |
| ECOG performance status | | | |
| N | 139 | 141 | 280 |
| 0 | 67 (48.2%) | 67 (47.5%) | 134 (47.9%) |
| 1 | 71 (51.1%) | 72 (51.1%) | 143 (51.1%) |
| 2 | 1 (0.7%) | 2 (1.4%) | 3 (1.1%) |

Key: ECOG=Eastern Cooperative Oncology Group

参照元：5.3.5.1.1 MCL3001 試験 CSR Table 2

MCL3001 試験のベースラインの疾患特性を表 2.7.3-14 に示す。

MCL の初回診断からランダム化までの期間の中央値（範囲）は 42.56（2.7～298.7）カ月であり，被験者の 82.9%（232 例）がステージ IV であった。芽球様細胞の組織学的所見を有する被験者の割合は 11.8%（33 例），B 症状を有する被験者の割合は 25.7%（72 例）であった。MIPI 簡略版のスコアは Intermediate risk（47.9%）の被験者が最も多く，次いで Low risk（30.7%），High risk（21.4%）の順であった。前治療のレジメン数の中央値（範囲）は 2.0（1～9）レジメンであった。難治性疾患を有する被験者の割合は 29.6%（83 例）であった。前治療でボルテゾミブの投与を受けていた被験者の割合は 17.9%（50 例）であった。ベースライン時に長径が 5 cm 以上及び 10 cm 以上の bulky disease を有する被験者の割合は，それぞれ 53.4%（149 例）及び 17.2%（48 例）であった。節外病変が認められた被験者の割合は 60.0%（168 例），骨髄浸潤が認められた被験者の割合は 53.9%（151 例）であった。

ベースラインの疾患特性はイブルチニブ群とテムシロリムス群の被験者間でおおむね同様であった。

表 2.7.3-14 ベースラインの疾患特性［MCL3001 試験：Intent-to-treat Analysis Set］

| | Ibrutinib | Temsirolimus | Total |
|---|---|---|---|
| Analysis set: intent-to-treat | 139 | 141 | 280 |
| Time from initial diagnosis to randomization (months) | | | |
| N | 139 | 141 | 280 |
| Mean (SD) | 49.98 (42.71) | 51.17 (33.60) | 50.58 (38.33) |
| Median | 38.90 | 46.23 | 42.56 |
| Range | (4.2; 298.7) | (2.7; 159.8) | (2.7; 298.7) |
| Stage of MCL at study entry | | | |
| N | 139 | 141 | 280 |
| I | 3 (2.2%) | 2 (1.4%) | 5 (1.8%) |
| II | 7 (5.0%) | 5 (3.5%) | 12 (4.3%) |
| III | 17 (12.2%) | 14 (9.9%) | 31 (11.1%) |
| IV | 112 (80.6%) | 120 (85.1%) | 232 (82.9%) |
| Types of histology | | | |
| N | 139 | 141 | 280 |
| Blastoid | 16 (11.5%) | 17 (12.1%) | 33 (11.8%) |
| Diffuse | 56 (40.3%) | 61 (43.3%) | 117 (41.8%) |
| Nodular | 38 (27.3%) | 40 (28.4%) | 78 (27.9%) |
| Other | 9 (6.5%) | 5 (3.5%) | 14 (5.0%) |
| Unknown | 20 (14.4%) | 18 (12.8%) | 38 (13.6%) |
| Baseline lymphoma symptoms [a] | | | |
| Yes | 78 (56.1%) | 69 (48.9%) | 147 (52.5%) |
| B symptoms | 33 (23.7%) | 39 (27.7%) | 72 (25.7%) |
| Other MCL-related symptoms | 65 (46.8%) | 57 (40.4%) | 122 (43.6%) |
| Simplified MCL international prognostic index | | | |
| N | 139 | 141 | 280 |
| Low risk (1-3) | 44 (31.7%) | 42 (29.8%) | 86 (30.7%) |
| Intermediate risk (4-5) | 65 (46.8%) | 69 (48.9%) | 134 (47.9%) |
| High risk (6-11) | 30 (21.6%) | 30 (21.3%) | 60 (21.4%) |
| Prior lines of therapy | | | |
| N | 139 | 141 | 280 |
| Mean (SD) | 2.1 (1.4) | 2.2 (1.3) | 2.2 (1.3) |
| Median | 2.0 | 2.0 | 2.0 |
| Range | (1; 9) | (1; 9) | (1; 9) |
| Types of treatment indication | | | |
| N | 139 | 141 | 280 |
| Relapsed disease [b] | 103 (74.1%) | 94 (66.7%) | 197 (70.4%) |
| Refractory disease [c] | 36 (25.9%) | 47 (33.3%) | 83 (29.6%) |
| Prior cancer-related surgery | 39 (28.1%) | 33 (23.4%) | 72 (25.7%) |
| Prior radiotherapy | 26 (18.7%) | 26 (18.4%) | 52 (18.6%) |
| Prior bortezomib | 30 (21.6%) | 20 (14.2%) | 50 (17.9%) |
| Tumor bulk (largest diameter) | | | |
| < 5 cm | 64 (46.4%) | 66 (46.8%) | 130 (46.6%) |
| >= 5 cm | 74 (53.6%) | 75 (53.2%) | 149 (53.4%) |
| >= 10 cm | 22 (15.9%) | 26 (18.4%) | 48 (17.2%) |
| Extranodal disease | | | |
| Yes | 83 (59.7%) | 85 (60.3%) | 168 (60.0%) |
| Bone marrow involvement [d] | | | |
| Yes | 66 (47.5%) | 85 (60.3%) | 151 (53.9%) |

Key: MCL=mantle cell lymphoma
[a] Subjects belong to multiple categories are counted multiple times.
[b] Relapsed disease was defined as relapsed or disease progression after achieving at least partial response to the last regimen prior to study entry.
[c] Refractory disease was defined as failure to achieve at least partial response to the last regimen prior to study entry.
[d] Subjects with positive bone marrow aspirate or biopsy results at baseline.

参照元：5.3.5.1.1 MCL3001 試験 CSR Table 3, Table 4, Table 5

### (4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験の人口統計学的特性を表 2.7.3-15 に示す。

全投与集団 120 例において，年齢の中央値（範囲）は 67.5（35～85）歳であり，65 歳以上の被験者の割合は 62.5%（75 例）であった。性別では男性（86.7%），人種では白人（94.2%）の被験者が多かった。

表 2.7.3-15 人口統計学的特性［MCL2001 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Population: all treated | 120 |
| Age (years) | |
| N | 120 |
| Mean (SD) | 66.7 (9.98) |
| Median | 67.5 |
| Range | (35; 85) |
| < 65 | 45 (37.5%) |
| ≥ 65 | 75 (62.5%) |
| Sex | |
| N | 120 |
| Male | 104 (86.7%) |
| Female | 16 (13.3%) |
| Ethnicity | |
| N | 120 |
| Hispanic or Latino | 4 (3.3%) |
| Not Hispanic or Latino | 97 (80.8%) |
| Unknown/not reported | 19 (15.8%) |
| Race | |
| N | 120 |
| White | 113 (94.2%) |
| Black or African American | 2 (1.7%) |
| Unknown/not reported | 5 (4.2%) |
| Region | |
| N | 120 |
| United States | 83 (69.2%) |
| Europe | 37 (30.8%) |

Note: Percentages are calculated with the number of subjects with non-missing values for each parameter as the denominator.

参照元：5.3.5.2.3-1 MCL2001 試験 CSR Table 3

MCL2001 試験のベースラインの疾患特性を表 2.7.3-16 に示す。

MCL の初回診断からの期間の中央値（範囲）は 43.94（6.8～189.6）カ月であり，被験者の 77.5%（93 例）がステージ IV であった。芽球様細胞の組織学的所見を有する被験者の割合は 9.2%（11 例），B 症状を有する被験者の割合は 15.0%（18 例）であった。MIPI 簡略版のスコアは Intermediate risk（48.3%）の被験者が最も多く，次いで High risk（28.0%），Low risk（23.7%）の順であった。前治療のレジメン数の中央値（範囲）は 2.00（1.0～8.0）レジメンであった。ベースライン時に長径が 5 cm 以上及び 10 cm 以上の bulky disease を有する被験者の割合は，それぞれ 52.5%（63 例）及び 14.2%（17 例）であった。節外病変が認められた被験者の割合は 60.0%（72 例），骨髄浸潤が認められた被験者の割合は 41.7%（50 例）であった。ECOG performance status が 0 の被験者の割合は 35.0%（42 例），1 の被験者の割合は 55.8%（67 例）であった。

表 2.7.3-16 ベースラインの疾患特性［MCL2001 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Population: all-treated | 120 |
| Time from initial diagnosis to first dose (months) | |
| N | 120 |
| Mean (SD) | 53.72 (36.151) |
| Median | 43.94 |
| Range | (6.8; 189.6) |
| Stage of MCL at study entry | |
| N | 120 |
| I | 2 (1.7%) |
| II | 9 (7.5%) |
| III | 16 (13.3%) |
| IV | 93 (77.5%) |
| Types of Histology | |
| N | 120 |
| Blastoid | 11 (9.2%) |
| Diffuse | 62 (51.7%) |
| Nodular | 29 (24.2%) |
| Other | 18 (15.0%) |
| Baseline lymphoma symptom [a] | |
| N | 120 |
| Yes | 59 (49.2%) |
| B-symptoms | 18 (15.0%) |
| Other MCL-related symptoms | 55 (45.8%) |
| Simplified MCL international prognostic index | |
| N | 118 |
| Low risk (1-3) | 28 (23.7%) |
| Intermediate risk (4-5) | 57 (48.3%) |
| High risk (6-11) | 33 (28.0%) |
| Prior lines of therapy | |
| N | 120 |
| Mean (SD) | 2.66 (1.267) |
| Median | 2.00 |
| Range | (1.0; 8.0) |
| Prior cancer-related surgery | 29 (24.2%) |
| Prior radiotherapy | 28 (23.3%) |
| Bulky disease (LD≥5 cm) | 63 (52.5%) |
| Bulky disease (LD ≥10 cm) | 17 (14.2%) |
| Extranodal disease [b] | 72 (60.0%) |
| Bone marrow involvement [c] | 50 (41.7%) |
| ECOG Performance Status | |
| N | 120 |
| 0 | 42 (35.0%) |
| 1 | 67 (55.8%) |
| 2 | 11 (9.2%) |

Key: ECOG=Eastern Cooperative Oncology Group; LD=longest diameter; MCL=Mantle Cell Lymphoma
[a] Subjects belong to multiple categories are counted multiple times.
[b] Extranodal disease include gastrointestinal disease, liver/lung/spleen/fluid involvement,etc.
[c] Subjects with positive bone marrow aspirate or biopsy results at baseline.

Note: Percentages are calculated with the number of subjects with non-missing values for each parameter as the denominator.

参照元：5.3.5.2.3-1 MCL2001 試験 CSR Table 4, Table 5, Table 7

### 2.7.3.3.2 治験薬の曝露

#### (1) 国内第 II 相試験（MCL2002 試験）

MCL2002 試験では，データカットオフ時点での投与期間の中央値（範囲）は 6.46（2.8～8.3）カ月であった。イブルチニブの 1 日平均投与量の中央値は 557.99 mg/日，相対用量強度の中央値は 99.64%であった。被験者の 12.5%（2 例）がイブルチニブの用量を減量した（表 2.7.3-17）。

表 2.7.3-17 治験薬の曝露及び用量変更［MCL2002 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Duration of Treatment (months) [a] | |
| N | 16 |
| <= 6 | 7 (43.8%) |
| > 6 <= 12 | 9 (56.3%) |
| > 12 | 0 |
| Mean (SD) | 6.14 (1.730) |
| Median | 6.46 |
| Range | (2.8; 8.3) |
| Total Cumulative Dose ($x10^3$mg) [b] | |
| N | 16 |
| Mean (SD) | 96.67 (29.721) |
| Median | 100.80 |
| Range | (46.3; 141.1) |
| Dose Intensity (mg/day) [c] | |
| N | 16 |
| Mean (SD) | 520.48 (76.548) |
| Median | 557.99 |
| Range | (268.0; 560.0) |
| Relative Dose Intensity (%) [d] | |
| N | 16 |
| < 70% | 1 (6.3%) |
| 70% - < 90% | 4 (25.0%) |
| >= 90% | 11 (68.8%) |
| Mean (SD) | 92.94 (13.669) |
| Median | 99.64 |
| Range | (47.9; 100.0) |
| Dose Reduction | 2 (12.5%) |
| ADVERSE EVENT | 2 (12.5%) |

[a] The duration of treatment (in months, day/365.25×12) is defined as the date of last dose minus the date of first dose of Ibrutinib plus 1.
[b] Total cumulative dose ($\times10^3$ mg) is the sum of all given doses.
[c] Dose intensity (mg/day) is derived by the total cumulative dose (mg) divided by the duration of treatment (days).
[d] Relative dose intensity (%) is derived by 100×dose intensity (mg/day) divided by 560.

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 8, TSIEXP02

### (2) 海外第 II 相試験（1104 試験）

1104 試験では，データカットオフ時点での投与期間の中央値（範囲）は 8.3（0.7～21.4）カ月であった。イブルチニブの 1 日平均投与量の中央値は 550.0 mg/日，相対用量強度の中央値は 98.2%であった。被験者の 9.9%（11 例）が 1 段階の減量を，4.5%（5 例）が 2 段階の減量を行った（表 2.7.3-18）。

表 2.7.3-18 治験薬の曝露及び用量変更［1104 試験：All-Treated Population］

| | Ibrutinib | | |
|---|---|---|---|
| | Bortezomib-Naive (N=63) | Bortezomib-Exposed (N=48) | Total (N=111) |
| Treatment Duration (months) | | | |
| N | 63 | 48 | 111 |
| Mean (SD) | 9.2 ( 6.5) | 10.2 ( 6.4) | 9.6 ( 6.5) |
| Median | 7.4 | 10.4 | 8.3 |
| Min, Max | 0.7, 21.2 | 0.9, 21.4 | 0.7, 21.4 |
| Total Cumulative Dose Received (grams) | | | |
| N | 63 | 48 | 111 |
| Mean (SD) | 145.0 (102.8) | 161.7 (104.4) | 152.2 (103.3) |
| Median | 113.1 | 154.8 | 125.4 |
| Min, Max | 11.8, 328.2 | 15.1, 338.8 | 11.8, 338.8 |
| Average Daily Dose (mg/day) | | | |
| N | 63 | 48 | 111 |
| Mean (SD) | 523.6 (58.4) | 521.0 (61.5) | 522.5 (59.5) |
| Median | 550.9 | 549.7 | 550.0 |
| Min, Max | 307.3, 566.7 | 277.7, 560.0 | 277.7, 566.7 |
| Relative Dose Intensity [a] (%) | | | |
| N | 63 | 48 | 111 |
| Mean (SD) | 93.5 (10.4) | 93.0 (11.0) | 93.3 (10.6) |
| Median | 98.4 | 98.2 | 98.2 |
| Min, Max | 54.9, 101 | 49.6, 100 | 49.6, 101 |
| <70% | 4 ( 6.3%) | 3 ( 6.3%) | 7 ( 6.3%) |
| 70% - <%90 | 9 (14.3%) | 8 (16.7%) | 17 (15.3%) |
| ≥90% | 50 (79.4%) | 37 (77.1%) | 87 (78.4%) |
| Number of Dose Reductions | | | |
| 1 | 4 ( 6.3%) | 7 (14.6%) | 11 ( 9.9%) |
| 2 | 3 ( 4.8%) | 2 ( 4.2%) | 5 ( 4.5%) |

[a] Relative dose intensity (%) is calculated as the percentage of total cumulative dose received/planned total cumulative dose during the treatment period.

参照元：5.3.5.2.2-1 1104 試験 CSR Table 11, Table 12

### (3) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験では，治験薬の曝露の解析は安全性解析対象集団に対して実施し，その内訳はイブルチニブ群が 139 例，テムシロリムス群が 139 例であった。

データカットオフ時点での投与期間の中央値（範囲）は，イブルチニブ群が 14.39（0.0～28.2）カ月，テムシロリムス群が 3.02（0.0～27.0）カ月であり，イブルチニブ群の投与期間はテムシロリムス群の 4 倍を超えた。相対用量強度の中央値は，イブルチニブ群が 99.85%，テムシロリムス群が 81.82%であった。用量を減量した被験者の割合は，イブルチニブ群が 4.3%（6 例），テムシロリムス群が 43.9%（61 例）であり，イブルチニブ群の方が低かった（表 2.7.3-19）。

表 2.7.3-19 治験薬の曝露及び用量変更［MCL3001 試験：Safety Analysis Set］

| | Ibrutinib | Temsirolimus |
|---|---|---|
| Analysis set: safety | 139 | 139 |
| Treatment duration (months) | | |
| N | 139 | 139 |
| Mean (SD) | 13.27 (8.31) | 6.04 (6.80) |
| Median | 14.39 | 3.02 |
| Range | (0.0; 28.2) | (0.0; 27.0) |
| Total dose (g for ibrutinib and mg for temsirolimus) | | |
| N | 139 | 139 |
| Mean (SD) | 217.19 (137.97) | 1650.32 (1672.32) |
| Median | 235.76 | 1000.00 |
| Range | (0.6; 452.5) | (75.0; 8400.0) |
| Relative dose intensity (%) | | |
| N | 139 | 139 |
| Mean (SD) | 96.29 (8.15) | 76.49 (21.44) |
| Median | 99.85 | 81.82 |
| Range | (30.3; 100.0) | (30.0; 100.0) |
| < 75% | 3 (2.2%) | 59 (42.4%) |
| >= 75% - < 90% | 12 (8.6%) | 29 (20.9%) |
| >= 90% | 124 (89.2%) | 51 (36.7%) |
| Subjects with any dose reduction | 6 (4.3%) | 61 (43.9%) |
| Dose reduced once | 6 (4.3%) | 34 (24.5%) |
| Dose reduced twice | 0 | 27 (19.4%) |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.

参照元：5.3.5.1.1 MCL3001 試験 CSR Table 7, TSIEXP02

### (4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験では，治験薬の曝露及び用量変更の解析は安全性解析対象集団に対して実施し，全投与集団と同じ 120 例の被験者が解析対象であった。

データカットオフ時点での投与期間の中央値（範囲）は 7.95（0.5～20.9）カ月であった。イブルチニブの 1 日平均投与量の中央値は 549.83 mg/日，相対用量強度の中央値は 96.52%であった。被験者の 4.2%（5 例）が 1 段階の減量を，2.5%（3 例）が 2 段階の減量を行った（表 2.7.3-20）。

表 2.7.3-20 治験薬の曝露及び用量変更［MCL2001 試験：Safety Population］

| | Ibrutinib |
|---|---|
| Population: safety | 120 |
| Treatment duration (months) | |
| N | 120 |
| Mean (SD) | 8.74 (6.297) |
| Median | 7.95 |
| Range | (0.5; 20.9) |
| Total dose (grams) | |
| N | 120 |
| Mean (SD) | 140.0 (101.1) |
| Median | 130.9 |
| Range | (7.8: 355.6) |
| Dose intensity (mg/day) | |
| N | 120 |
| Mean (SD) | 530.94 (47.235) |
| Median | 549.83 |
| Range | (328.1; 560.0) |
| Relative dose intensity (%) | |
| N | 120 |
| Mean (SD) | 93.04 (9.709) |
| Median | 96.52 |
| Range | (46.0; 100.0) |
| <70% | 4 (3.3%) |
| 70% - <%90 | 25 (20.8%) |
| ≥90% | 91 (75.8%) |
| Subjects with any dose reductions | 8 (6.7%) |
| 1 | 5 (4.2%) |
| 2 | 3 (2.5%) |

Note: Percentages calculated with the number of subjects in safety population as denominator.

参照元：5.3.5.2.3-1 MCL2001 試験 CSR Table 10, Table 11

### 2.7.3.3.3 全有効性試験の結果の比較検討

#### 2.7.3.3.3.1 奏効率（Response Rate）

**(1) 国内第 II 相試験（MCL2002 試験）**

MCL2002 試験では，抗腫瘍効果の評価可能な解析対象集団 16 例において，IRC 判定に基づく ORR は 87.5%（14 例，90% CI：65.6-97.7）であった。90% CI の下限値は，治験実施計画書であらかじめ設定した値である 20%を大きく上回った。最良効果が CR の被験者の割合は 12.5%（2 例），PR の被験者の割合は 75.0%（12 例）であった（表 2.7.3-21）。

また，治験担当医師判定に基づく ORR は 93.8%であり，そのうち最良効果が CR 及び PR に到達した被験者の割合は，それぞれ 6.3%及び 87.5%であった（【5.3.5.2.1 CSR Table 10 p61】）。

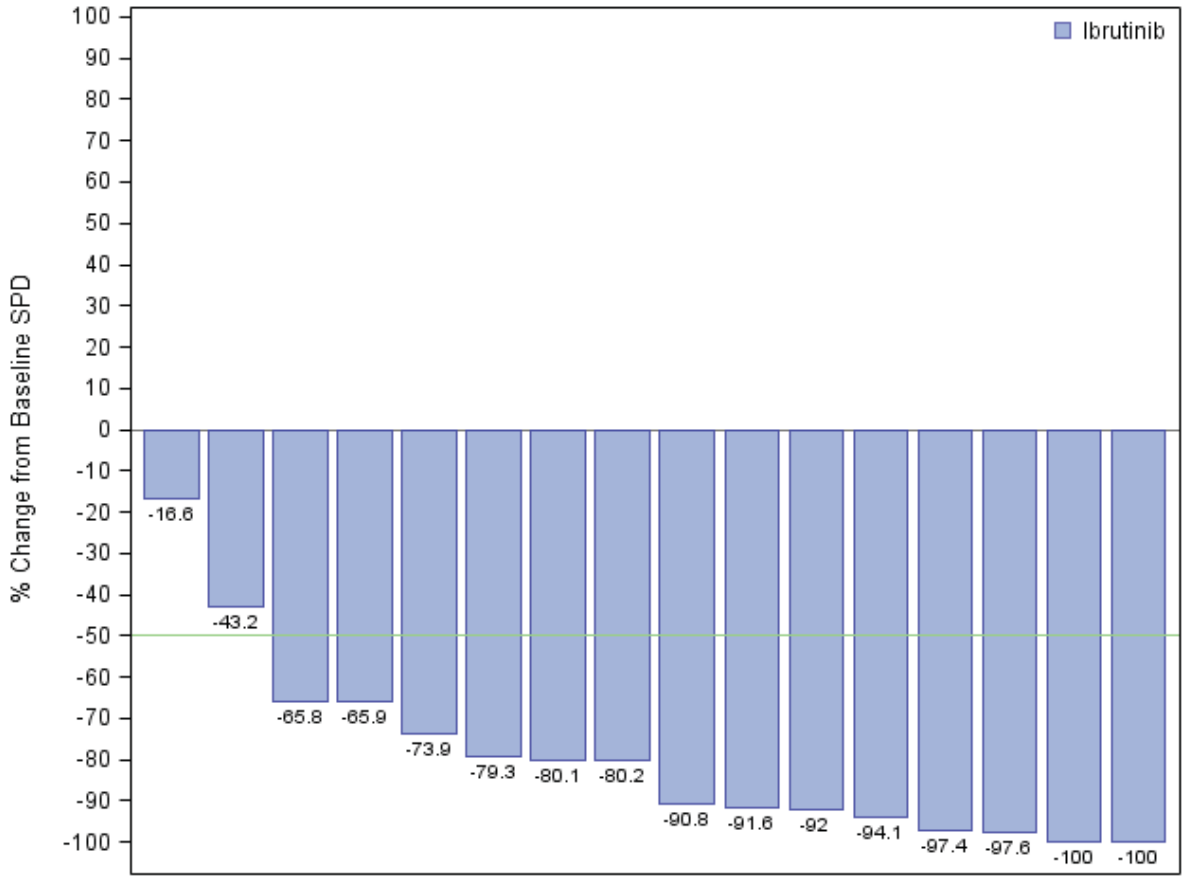
さらに，16 例の被験者全例に腫瘍の二方向積和の減少が認められ，うち 14 例はベースライン時より最大で 50%以上減少した（図 2.7.3-1）。

表 2.7.3-21 奏効率（Response Rate）－IRC 判定［MCL2002 試験：Response-Evaluable Population］

| | Ibrutinib |
|---|---|
| Analysis Set: Response-Evaluable Population | 16 |
| Best Overall Response | |
| CR | 2 (12.5%) |
| PR | 12 (75.0%) |
| SD | 2 (12.5%) |
| PD | 0 |
| ORR (CR or PR) | 14 (87.5%) |
| Exact 90% CI | (65.6, 97.7) |

Key: CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease; ORR=Overall Response Rate

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 9




Key: SPD=Sum of the products of the diameters.

参照元：5.3.5.2.1 MCL2002 試験 CSR Figure 2

図 2.7.3-1 腫瘍の二方向積和の最大変化率［MCL2002 試験：Response-Evaluable Population］

### (2) 海外第 II 相試験（1104 試験）

1104 試験の全投与集団 111 例において，治験担当医師判定に基づく ORR は 67.6%（75 例，95% CI：58.0-76.1）であった。最良効果が CR の被験者の割合は 20.7%（23 例，95% CI：13.6-29.5），PR の被験者の割合は 46.8%（52 例）であった。ボルテゾミブ既治療及びボルテゾミブ

未治療の被験者の ORR は，それぞれ全投与集団で認められた割合と同程度であった（表 2.7.3-22）。

また，探索的評価項目として解析した IRC 判定に基づく ORR は 68.5%であり，そのうち最良効果が CR 及び PR に到達した被験者の割合は，それぞれ 20.7%及び 47.7%であった（【5.3.5.2.2-1 CSR TEFRSP04B p301】）。治験担当医師が判定した奏効例の 94.7%が IRC による判定と一致した（【5.3.5.2.2-1 CSR Table 17 p62】）。全体的に，IRC 判定による奏効の評価は治験担当医師判定による結果と同様であった。

表 2.7.3-22 奏効率（Response Rate）－治験担当医師判定［1104 試験：All-Treated Population］

| | Ibrutinib | | |
|---|---|---|---|
| | Bortezomib-Naive (N=63) | Bortezomib-Exposed (N=48) | Total (N=111) |
| Best Disease Response | | | |
| Complete Response (CR) | 12 (19.0%) | 11 (22.9%) | 23 (20.7%) |
| 95% CI | (10.2%, 30.9%) | (12.0%, 37.3%) | (13.6%, 29.5%) |
| Partial Response (PR) | 31 (49.2%) | 21 (43.8%) | 52 (46.8%) |
| Stable Disease (SD) | 8 (12.7%) | 8 (16.7%) | 16 (14.4%) |
| Progressive Disease (PD) | 12 (19.0%) | 7 (14.6%) | 19 (17.1%) |
| Not Evaluable [a] | 0 | 1 ( 2.1%) | 1 ( 0.9%) |
| Overall Response Rate (CR+PR) | | | |
| n (%) | 43 (68.3%) | 32 (66.7%) | 75 (67.6%) |
| 95% CI [b] | (55.3%, 79.4%) | (51.6%, 79.6%) | (58.0%, 76.1%) |

[a] No post-baseline assessment
[b] Based on exact binomial distribution.

### (3) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験の各群の ITT 集団（イブルチニブ群 139 例，テムシロリムス群 141 例）において，IRC 判定に基づく ORR はイブルチニブ群が 71.9%（100 例）であり，テムシロリムス群の 40.4%（57 例）に比べて有意に高かった［相対危険度：1.78（95% CI：1.43-2.23），p<0.0001］。最良効果が CR の被験者の割合は，イブルチニブ群（18.7%）の方がテムシロリムス群（1.4%）よりも高かった（表 2.7.3-23）。

また，治験担当医師判定に基づく ORR はイブルチニブ群が 77.0%であり，テムシロリムス群の 46.1%に比べて有意に高かった（p<0.0001）。最良効果が CR の被験者の割合は，イブルチニブ群が 23.0%，テムシロリムス群が 2.1%であった（【5.3.5.1.1 CSR TEFRSP02 p612】）。全体的に，治験担当医師判定による奏効の評価は IRC 判定による結果と同様であった。

表 2.7.3-23 奏効率（Response Rate）－IRC 判定［MCL3001 試験：Intent-to-treat Analysis Set］

| | Ibrutinib | Temsirolimus |
|---|---|---|
| Analysis set: intent-to-treat | 139 | 141 |
| Overall Response Rate [a] (CR, PR) | 100 (71.9%) | 57 (40.4%) |
| Relative Risk (CI) | | 1.78 (1.43, 2.23) [c] |
| p-value [b] | | <0.0001 |
| Best response | | |
| Complete Response (CR) | 26 (18.7%) | 2 (1.4%) |
| Partial Response (PR) | 74 (53.2%) | 55 (39.0%) |
| Stable Disease (SD) | 15 (10.8%) | 43 (30.5%) |
| Progressive Disease (PD) | 15 (10.8%) | 23 (16.3%) |
| No Evidence of Disease (NED) | 2 (1.4%) | 1 (0.7%) |
| Not Evaluable (NE) | 7 (5.0%) | 15 (10.6%) |
| Missing | 0 | 2 (1.4%) |

[a] Response rate is estimated using the crude proportion of responders based on the best overall response.
[b] Stratified Cochran Mantel-Haenszel test
[c] In the MCL3001 clinical study report, the odds ratio is reported: 3.98 (95% CI: 2.38, 6.65).

### (4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験では，抗腫瘍効果の評価可能な解析対象集団 110 例において，IRC 判定に基づく ORR は 62.7%（69 例，95% CI：53.7-71.8）であった。95% CI の下限値は，治験実施計画書であらかじめ設定した閾値である 40%を上回り，イブルチニブ投与の有効性が示された（p<0.001，片側検定）。最良効果が CR の被験者の割合は 20.9%（23 例，95% CI：13.3-28.5）であった（表 2.7.3-24）。

また，治験担当医師判定に基づく ORR は 66.4%であり，そのうち最良効果が CR に到達した被験者の割合は 18.2%であった（【5.3.5.2.3-1 CSR Table 13 p52】）。IRC が判定した奏効例の 90.0%が治験担当医師による判定と一致した（【5.3.5.2.3-1 CSR TEFRSP07 p169】）。

表 2.7.3-24 奏効率（Response Rate）－IRC 判定［MCL2001 試験：Response-Evaluable Population］

| | Ibrutinib | | |
|---|---|---|---|
| | N (%) | 95% CI | p-value [a] |
| Population: response evaluable | 110 | | |
| Best Response | | | |
| Complete response (CR) | 23 (20.9%) | (13.3%, 28.5%) | |
| Partial response (PR) | 46 (41.8%) | (32.6%, 51.0%) | |
| Overall response (CR+PR) | 69 (62.7%) | (53.7%, 71.8%) | < 0.001 |
| Stable disease | 16 (14.5%) | (8.0%, 21.1%) | |
| Progressive disease | 25 (22.7%) | (14.9%, 30.6%) | |

[a] Based on 40% response rate under the null hypothesis and normal approximation to binomial.
参照元：5.3.5.2.3-1 MCL2001 試験 CSR Table 12

## 2.7.3.3.3.2　奏効到達期間（Time to Response）

### (1) 国内第 II 相試験（MCL2002 試験）

MCL2002 試験では，IRC 判定に基づく奏効例（14 例）において，初回奏効到達期間の中央値（範囲）は 1.84（0.7～5.3）カ月であった。また，CR 例（2 例）において，CR 到達期間の中央値（範囲）は 2.84（1.8～3.8）カ月であった（表 2.7.3-25）。

表 2.7.3-25 奏効到達期間（Time to Response）－IRC 判定［MCL2002 試験：Response-Evaluable Population］

| | Ibrutinib |
|---|---|
| Analysis Set: Response-Evaluable Population | 16 |
| Responder (CR or PR) | 14 |
| Time to initial response (months) [a] | |
| Median | 1.84 |
| Range | (0.7; 5.3) |
| Responder (CR) | 2 |
| Time to CR (months) [b] | |
| Median | 2.84 |
| Range | (1.8; 3.8) |

Key: CR=Complete Response, PR=Partial Response
[a] Time to initial response were derived for subjects who achieved CR or PR
[b] Time to CR was derived for subjects who achieved CR.
参照元：5.3.5.2.1 MCL2002 試験 CSR Table 12

### (2) 海外第 II 相試験（1104 試験）

1104 試験では，治験担当医師判定に基づく奏効例（75 例）において，初回奏効到達期間の中央値（範囲）は 1.9（1.4～13.7）カ月であった。また，CR 例（23 例）において，CR 到達期間の中央値（範囲）は 5.5（1.7～11.5）カ月であった（表 2.7.3-26）。

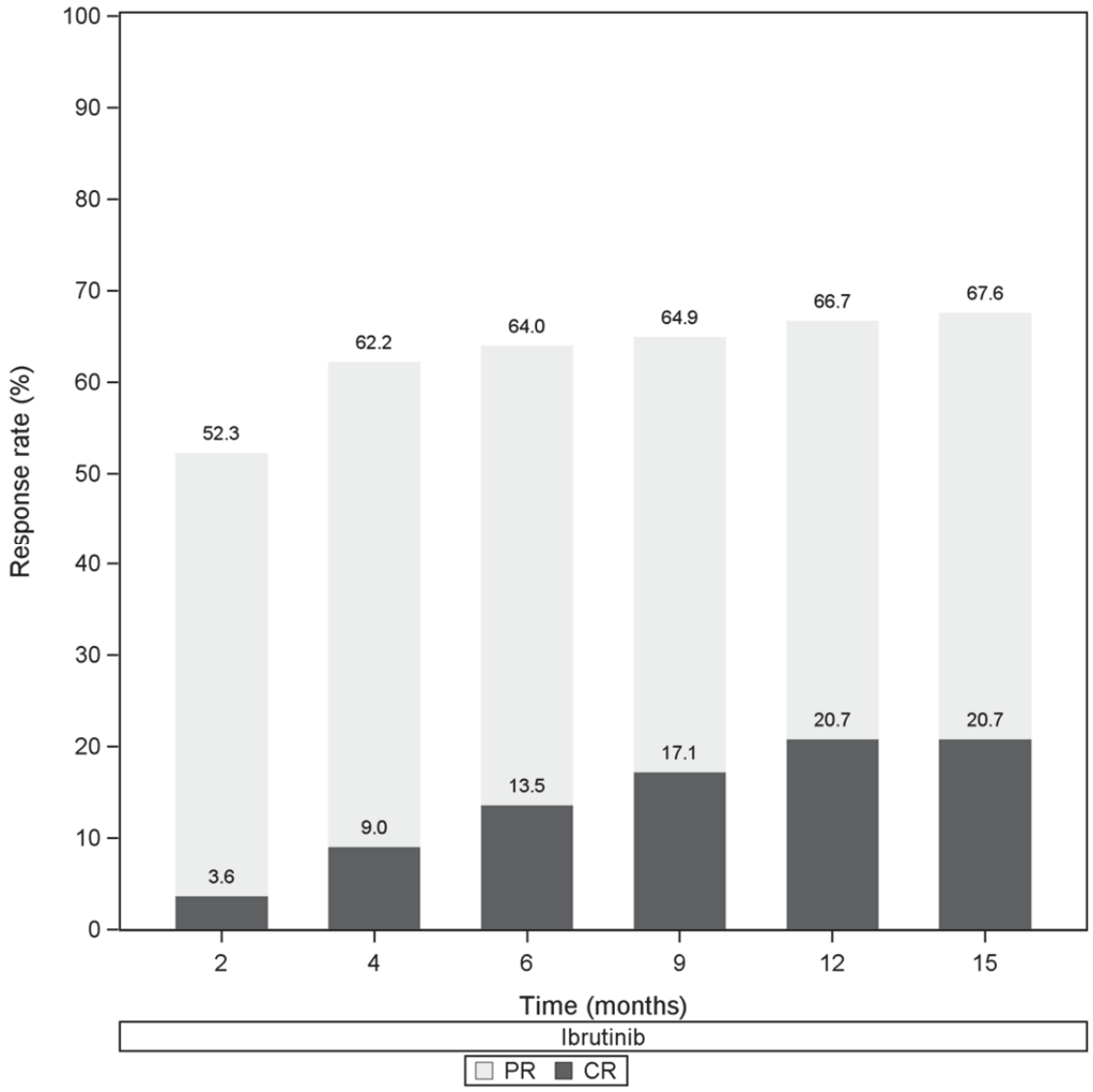
さらに，各評価時点の CR 率は投与開始 2 カ月目の 3.6%から 12 カ月目の 20.7%まで経時的に上昇し，最初の奏効が認められた後もイブルチニブの投与を継続することにより CR 率が向上することが示された（図 2.7.3-2）。

表 2.7.3-26 奏効到達期間（Time to Response）－治験担当医師判定［1104 試験：All-Treated Population］

| | Ibrutinib | | |
|---|---|---|---|
| | Bortezomib-Naive (N=63) | Bortezomib-Exposed (N=48) | Total (N=111) |
| Time to initial response (months) [a] | | | |
| N | 43 | 32 | 75 |
| Median | 1.9 | 1.8 | 1.9 |
| Min, Max | 1.4, 11.1 | 1.6, 13.7 | 1.4, 13.7 |
| Time to complete response (months) [b] | | | |
| N | 12 | 11 | 23 |
| Median | 6.7 | 5.3 | 5.5 |
| Min, Max | 1.7, 11.5 | 1.7, 11.1 | 1.7, 11.5 |

[a] Time to initial response is calculated as the number of months from first dose date of study treatment to first documented PR for subjects who achieved PR or better.
[b] Time to CR is calculated as the number of months from first dose date of study treatment to first documented CR.

Note: The above summaries are based on descriptive statistics.
参照元：5.3.5.2.2-1 1104 試験 CSR Table 20




Key: CR=complete response; PR=partial response

Note: Percentages calculated with 111 subjects in all treated population as denominator.

参照元：5.3.5.2.2-1 1104 試験 CSR Figure 11

**図 2.7.3-2 CR 率及び奏効率の経時的推移［1104 試験：All-Treated Population］**

### (3) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験では，IRC 判定に基づく奏効例（イブルチニブ群 100 例，テムシロリムス群 57 例）において，初回奏効到達期間及び最良効果到達期間の中央値は，イブルチニブ群がそれぞれ 2.15 カ月及び 2.17 カ月，テムシロリムス群がそれぞれ 2.14 カ月及び 2.14 カ月であり，投与群間で同程度であった。また，CR 例（イブルチニブ群 26 例，テムシロリムス群 2 例）において，CR 到達期間の中央値はイブルチニブ群が 6.28 カ月であり，テムシロリムス群の 6.60 カ月と同程度であった（表 2.7.3-27）。

表 2.7.3-27 奏効到達期間（Time to Response）－IRC 判定［MCL3001 試験：Intent-to-treat Analysis Set］

| | Ibrutinib | Temsirolimus |
|---|---|---|
| Analysis set: intent-to-treat | 139 | 141 |
| Responder (CR or PR) | 100 | 57 |
| Time to initial response (months) [a] | | |
| Median | 2.15 | 2.14 |
| Range | (0.5; 10.4) | (0.9; 12.0) |
| Time to best response (months) [a] | | |
| Median | 2.17 | 2.14 |
| Range | (0.5; 20.9) | (0.9; 12.0) |
| Responder (CR) | 26 | 2 |
| Time to CR (months) [b] | | |
| Median | 6.28 | 6.60 |
| Range | (2.1; 20.9) | (6.2; 7.0) |

Key: CR=complete response, NE=not estimable, PR=partial response
[a] Time to initial response and best response were derived for subjects who achieved CR or PR.
[b] Time to CR was derived for subjects who achieved CR.
参照元：5.3.5.1.1 MCL3001 試験 CSR Table 13

### (4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験では，IRC 判定に基づく奏効例（69 例）において，初回奏効到達期間の中央値（範囲）は 2.07（1.3～6.3）カ月であり，最良効果到達期間の中央値（範囲）である 2.14（1.3～10.6）カ月と同程度であった（表 2.7.3-28）。

また，治験担当医師判定に基づく奏効例（77 例）において，初回奏効到達期間の中央値（範囲）は 2.07（1.3～8.2）カ月，最良効果到達期間の中央値（範囲）は 2.10（1.3～14.8）カ月であった（【5.3.5.2.3-1 CSR TEFRSP22 p171】）。

表 2.7.3-28 奏効到達期間（Time to Response）－IRC 判定［MCL2001 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Population: all-treated [a] | 69 |
| Responder (complete or partial response) | 69 |
| Time to initial response (months) | |
| Mean (SD) | 2.37 (1.045) |
| Median | 2.07 |
| Range | (1.3; 6.3) |
| Time to best response (months) | |
| Mean (SD) | 3.62 (2.346) |
| Median | 2.14 |
| Range | (1.3; 10.6) |

[a] Included responders only.
参照元：5.3.5.2.3-1 MCL2001 試験 CSR Table 14

## 2.7.3.3.3.3 奏効持続期間（DOR）

### (1) 国内第 II 相試験（MCL2002 試験）

MCL2002 試験では，IRC 判定に基づく奏効例（14 例）のうち 85.7%（12 例）の被験者を打ち切りとしたため，DOR の中央値は Kaplan-Meier 法を用いて推定できなかった（表 2.7.3-29）。

表 2.7.3-29 奏効持続期間（DOR）－IRC 判定［MCL2002 試験：Response-Evaluable Population］

| | Ibrutinib |
|---|---|
| Analysis Set: Response-Evaluable Population | 16 |
| Responder (CR or PR) | 14 |
| Progressed or died (event) | 2 (14.3%) |
| Censored | 12 (85.7%) |
| Duration of Response (months) | |
| Median (95% CI) | NE (2.79, NE) |
| Range | (1.1, 6.4+) |
| 3-months duration rate (95% CI) | 0.83 (0.47, 0.96) |
| 6-months duration rate (95% CI) | 0.83 (0.47, 0.96) |

Key: CR=Complete Response, PR=Partial Response, NE=Not Estimable, '+'=Censored Observation

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 11

### (2) 海外第 II 相試験（1104 試験）

1104 試験では，治験担当医師判定に基づく奏効例（75 例）のうち 32.0%（24 例）の被験者に疾患進行又は死亡が認められ，DOR の解析では残り 68.0%（51 例）を打ち切りとした。Kaplan-Meier 法を用いて推定した DOR の中央値は 17.5 カ月（95% CI：15.8-NE）であった（表 2.7.3-30）。

また，IRC 判定に基づく奏効例（76 例）において，Kaplan-Meier 法を用いて推定した DOR の中央値は 19.58 カ月であり，治験担当医師判定による結果と同程度であった（【5.3.5.2.2-1 CSR TEFRSP05B p303】）。

表 2.7.3-30 奏効持続期間（DOR）－治験担当医師判定［1104 試験：All-Treated Population］

| | Ibrutinib | | |
|---|---|---|---|
| | Bortezomib-Naive (N=63) | Bortezomib-Exposed (N=48) | Total (N=111) |
| Responders (CR+PR) | 43 | 32 | 75 |
| Events | 17 (39.5%) | 7 (21.9%) | 24 (32.0%) |
| Progressed | 16 (37.2%) | 6 (18.8%) | 22 (29.3%) |
| Died without documentation of progression | 1 ( 2.3%) | 1 ( 3.1%) | 2 ( 2.7%) |
| Censored | 26 (60.5%) | 25 (78.1%) | 51 (68.0%) |
| Duration of response (months) [a] | | | |
| Median (95% CI) | 15.8 ( 5.6, NE) | NE (NE, NE) | 17.5 (15.8, NE) |
| Min, Max | 0.03+, 17.51+ | 1.68, 19.58+ | 0.03+, 19.58+ |
| 6-month event-free rate (95% CI) | 65.8 (49.1, 78.1) | 86.5 (67.9, 94.8) | 74.6 (62.7, 83.2) |
| 12-month event-free rate (95% CI) | 63.1 (46.4, 75.9) | 73.7 (52.2, 86.7) | 67.9 (55.4, 77.7) |

Key: CR=complete response; NE=Not estimable; PR=partial response
[a] Kaplan-Meier product limit estimates.

Note: + indicates censored observation.
Note: All percentage calculations are based on the number of subjects with response (CR+PR).

### (3) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験では，Kaplan-Meier 法を用いて推定した試験参加期間（ランダム化された日から死亡日又は直近のデータ収集日までの期間）の各群の中央値は，イブルチニブ群が 20.44 カ月，テムシロリムス群が 19.65 カ月と同程度であった（【5.3.5.1.1 CSR TSIDS04A p1040】）。イブル

チニブ群では IRC 判定に基づく奏効例（100 例）のうち 61.0%（61 例）の被験者を打ち切りとした。DOR の中央値は Kaplan-Meier 法を用いて推定できなかった（95% CI の下限値：16.2 カ月）。

テムシロリムス群では IRC 判定に基づく奏効例（57 例）のうち 73.7%（42 例）の被験者に疾患進行又は死亡が認められ，DOR の解析では残り 26.3%（15 例）を打ち切りとした。Kaplan-Meier 法を用いて推定したテムシロリムス群の DOR の中央値は 7.0 カ月（95% CI：4.2-9.9）であった。また，18 カ月 DOR 率はイブルチニブ群が 58%と推定され，テムシロリムス群の 20%よりも高かった（表 2.7.3-31）。

表 2.7.3-31 奏効持続期間（DOR）－IRC 判定［MCL3001 試験：Intent-to-treat Analysis Set］

| | Ibrutinib | Temsirolimus |
|---|---|---|
| Analysis set: intent-to-treat | 139 | 141 |
| Responder (CR or PR) | 100 | 57 |
| Progressed or died (event) | 39 (39.0%) | 42 (73.7%) |
| Censored | 61 (61.0%) | 15 (26.3%) |
| Duration of response (months) [a] | | |
| 25% quantile (95% CI) | 7.9 (4.7, 12.4) | 4.0 (2.1, 5.1) |
| Median (95% CI) | NE (16.2, NE) | 7.0 (4.2, 9.9) |
| 75% quantile (95% CI) | NE (NE, NE) | 14.9 (9.5, 23.5) |
| 6-months DOR rate (95% CI) | 0.83 (0.74, 0.89) | 0.60 (0.46, 0.72) |
| 12-months DOR rate (95% CI) | 0.69 (0.59, 0.77) | 0.26 (0.15, 0.38) |
| 18-months DOR rate (95% CI) | 0.58 (0.46, 0.68) | 0.20 (0.09, 0.35) |
| 24-months DOR rate (95% CI) | 0.51 (0.35, 0.65) | 0.00 (NE, NE) |

[a] Duration of response was derived for subjects who achieved CR or PR.

参照元：5.3.5.1.1 MCL3001 試験 CSR Table 12

### (4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験では，IRC 判定に基づく奏効例（69 例）のうち 33.3%（23 例）の被験者に疾患進行又は死亡が認められ，DOR の解析では残り 66.7%（46 例）を打ち切りとした。Kaplan-Meier 法を用いて推定した DOR の中央値は 14.92 カ月（95% CI：12.35-NE）であった（表 2.7.3-32）。

また，治験担当医師判定に基づく奏効例（77 例）において，Kaplan-Meier 法を用いて推定した DOR の中央値は 12.94 カ月であった（【5.3.5.2.3-1 CSR TEFRSP14 p170】）。

表 2.7.3-32 奏効持続期間（DOR）－IRC 判定［MCL2001 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Population: all-treated [a] | 69 |
| Responder (complete or partial response) | |
| Progressed or died | 23 (33.3%) |
| Censored | 46 (66.7%) |
| Duration of response (months) [b] | |
| 25th percentile (95% CI) | 9.69 (4.17, 12.45) |
| Median (95% CI) | 14.92 (12.35, NE) |
| 75th percentile (95% CI) | NE (14.92, NE) |

[a] Included responders only.
[b] Based on Kaplan-Meier estimate.

参照元：5.3.5.2.3-1 MCL2001 試験 CSR Table 15

#### 2.7.3.3.3.4 無増悪生存期間（PFS）

##### (1) 国内第 II 相試験（MCL2002 試験）

MCL2002 試験では，抗腫瘍効果の評価可能な解析対象集団（16 例）のうち 12.5%（2 例）の被験者に IRC 判定に基づく疾患進行又は死亡が認められ，PFS の解析では残り 87.5%（14 例）を打ち切りとしたため，PFS の中央値は Kaplan-Meier 法を用いて推定できなかった。また，6 カ月 PFS 率は 88%（95% CI：59-97）と推定された（表 2.7.3-33）。

表 2.7.3-33 無増悪生存期間（PFS）－IRC 判定［MCL2002 試験：Response-Evaluable Population］

| | Ibrutinib |
|---|---|
| Analysis Set: Response-Evaluable Population | 16 |
| Progressed or died (event) | 2 (12.5%) |
| Censored | 14 (87.5%) |
| Progression-free survival (months) | |
| Median (95% CI) | NE (NE, NE) |
| Range | (2.8, 8.0+) |
| 6-months PFS rate (95% CI) | 0.88 (0.59, 0.97) |

Key: NE=Not Estimable, PFS=Progression-free Survival, '+'=Censored Observation

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 13

##### (2) 海外第 II 相試験（1104 試験）

1104 試験の Kaplan-Meier 法を用いて推定した PFS を表 2.7.3-34 に，PFS の Kaplan-Meier 曲線を図 2.7.3-3 に示す。

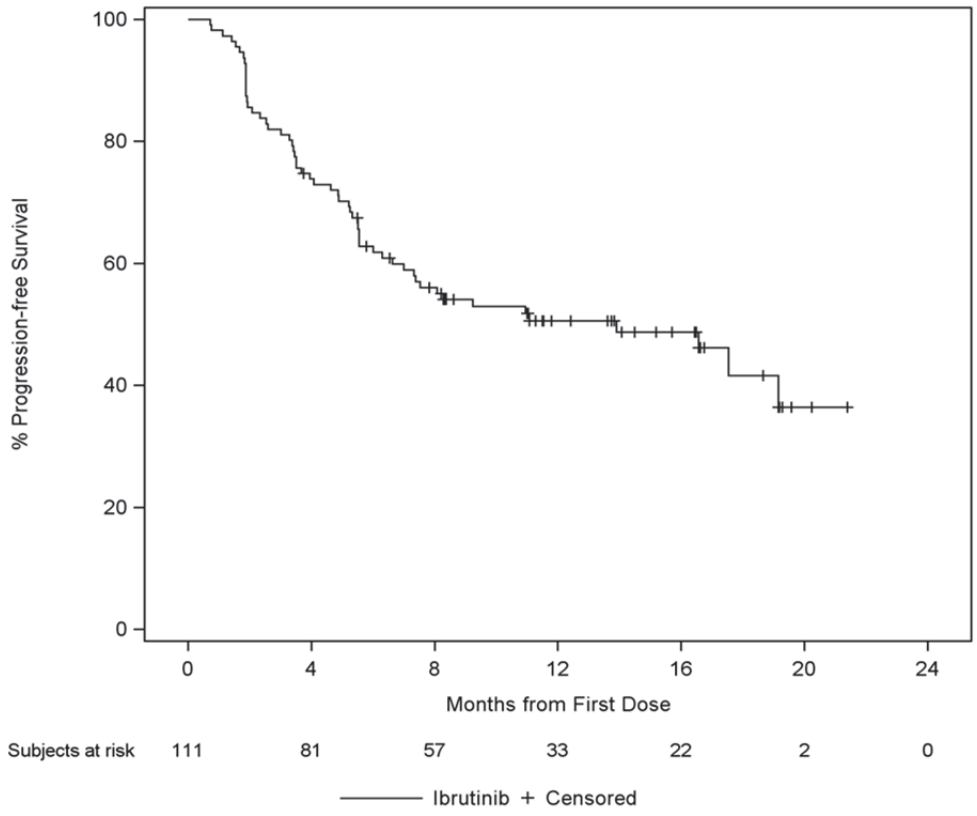
全投与集団（111 例）のうち 51.4%（57 例）の被験者に治験担当医師判定に基づく疾患進行又は死亡が認められ，PFS の解析では残り 48.6%（54 例）を打ち切りとした。Kaplan-Meier 法を用いて推定した PFS の中央値は 13.9 カ月（95% CI：7.0-NE）であった。また，6 カ月 PFS 率は 62.8%（95% CI：53.0-71.1），18 カ月 PFS 率は 41.6%（95% CI：28.7-53.9）と推定された。

表 2.7.3-34 無増悪生存期間（PFS）ー治験担当医師判定［1104 試験：All-Treated Population］

| | Ibrutinib | | |
|---|---|---|---|
| | Bortezomib-Naive (N=63) | Bortezomib-Exposed (N=48) | Total (N=111) |
| Subject status | | | |
| Events | 36 (57.1%) | 21 (43.8%) | 57 (51.4%) |
| Progressed | 35 (55.6%) | 18 (37.5%) | 53 (47.7%) |
| Died without documentation of progression | 1 ( 1.6%) | 3 ( 6.3%) | 4 ( 3.6%) |
| Censored | 27 (42.9%) | 27 (56.3%) | 54 (48.6%) |
| Progression-free survival (months) [a] | | | |
| Median (95% CI) | 7.4 ( 5.3, 19.2) | 16.6 ( 8.3, NE) | 13.9 ( 7.0, NE) |
| Min, Max | 0.72, 19.29+ | 0.76, 21.39+ | 0.72, 21.39+ |
| 6-month progression-free survival rate (95% CI) | 55.2 (42.0, 66.5) | 72.8 (57.8, 83.2) | 62.8 (53.0, 71.1) |
| 12-month progression-free survival rate (95% CI) | 46.7 (34.0, 58.6) | 54.7 (38.5, 68.3) | 50.6 (40.6, 59.7) |
| 18-month progression-free survival rate (95% CI) | 35.2 (17.7, 53.2) | 48.6 (30.5, 64.6) | 41.6 (28.7, 53.9) |

Key: NE=not estimable
[a] Kaplan-Meier product limit estimates.

Note: + indicates censored observation.




Note: Subjects who received subsequent anti-cancer therapy prior to disease progression were censored.
参照元：5.3.5.2.2-1 1104 試験 CSR Figure 12

図 2.7.3-3 無増悪生存期間（PFS）の Kaplan-Meier 曲線ー治験担当医師判定［1104 試験：All-Treated Population］

### (3) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験の Kaplan-Meier 法を用いて推定した PFS を表 2.7.3-35 に，PFS の Kaplan-Meier 曲線を図 2.7.3-4 に示す。

ITT 集団（イブルチニブ群 139 例，テムシロリムス群 141 例）において，イブルチニブ群では 52.5%（73 例），テムシロリムス群では 78.7%（111 例）の被験者に IRC 判定に基づく疾患進行又は死亡が認められた。Kaplan-Meier 法を用いて推定した PFS の中央値は，イブルチニブ群が 14.6 カ月（95% CI：10.4-NE），テムシロリムス群が 6.2 カ月（95% CI：4.2-7.9）であり，イブルチニブ投与はテムシロリムス投与に比べて PFS を有意に延長した（p<0.0001）。ハザード比は 0.43（95% CI：0.32-0.58）であり，イブルチニブ投与はテムシロリムス投与に比べて疾患進行又は死亡のリスクを 57%低下した（p<0.0001）。また，イブルチニブ群及びテムシロリムス群の 6 カ月 PFS 率はそれぞれ 73%（95% CI：65-80）及び 54%（95% CI：45-62），18 カ月 PFS 率はそれぞれ 48%（95% CI：40-57）及び 15%（95% CI：10-23）と推定された。

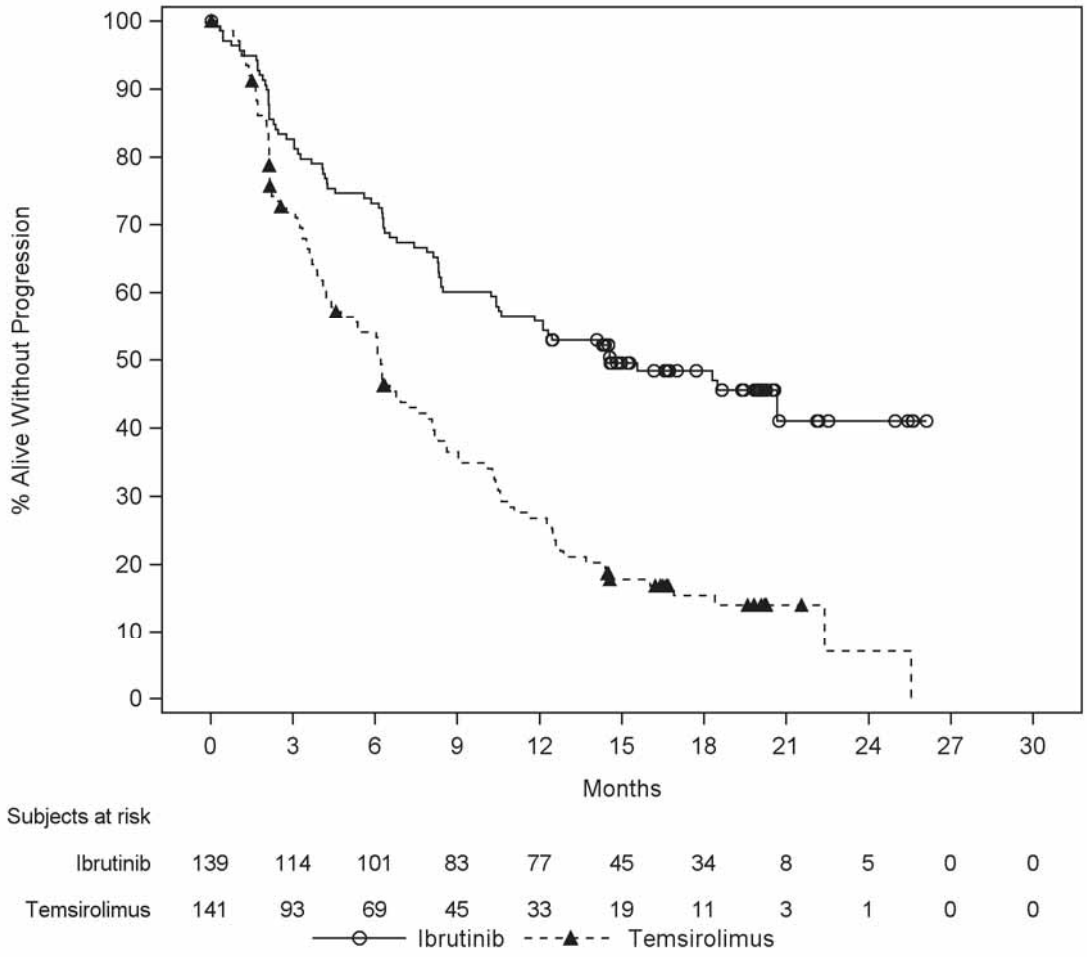
さらに，治験担当医師判定に基づき推定した PFS の中央値は，イブルチニブ群が 15.6 カ月（95% CI：10.6-NE），テムシロリムス群が 6.2 カ月（95% CI：4.2-7.8）であり，両群ともに IRC 判定による値とそれぞれ同程度であった（【5.3.5.1.1 CSR TEFPFS07 p609】）。

表 2.7.3-35 無増悪生存期間（PFS）－IRC 判定［MCL3001 試験：Intent-to-treat Analysis Set］

| | Ibrutinib | Temsirolimus |
|---|---|---|
| Analysis set: intent-to-treat | 139 | 141 |
| Subject status | | |
| Progressed or died (event) | 73 (52.5%) | 111 (78.7%) |
| Censored | 66 (47.5%) | 30 (21.3%) |
| Progression-free survival (months) [a] | | |
| 25% quantile (95% CI) | 4.5 (3.1, 6.8) | 2.2 (2.1, 3.5) |
| Median (95% CI) | 14.6 (10.4, NE) | 6.2 (4.2, 7.9) |
| 75% quantile (95% CI) | NE (NE, NE) | 12.5 (10.3, 14.6) |
| 6-months PFS rate (95% CI) | 0.73 (0.65, 0.80) | 0.54 (0.45, 0.62) |
| 12-months PFS rate (95% CI) | 0.56 (0.47, 0.64) | 0.27 (0.19, 0.35) |
| 18-months PFS rate (95% CI) | 0.48 (0.40, 0.57) | 0.15 (0.10, 0.23) |
| 24-months PFS rate (95% CI) | 0.41 (0.29, 0.52) | 0.07 (0.01, 0.22) |
| P-value [b] | < 0.0001 | |
| Hazard ratio (95% CI) [c] | 0.43 (0.32, 0.58) | |

Key: NE=not estimable
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on stratified Log rank test with MIPI and prior lines of therapy from IWRS as stratification factors.
[c] Based on stratified Cox´s model with MIPI and prior lines of therapy from IWRS as stratification factors.
A hazard ratio <1 indicates an advantage for Ibrutinib.

参照元：5.3.5.1.1 MCL3001 試験 CSR Table 8




参照元：5.3.5.1.1 MCL3001 試験 CSR Figure 2

**図 2.7.3-4 無増悪生存期間（PFS）の Kaplan-Meier 曲線－IRC 判定［MCL3001 試験：Intent-to-treat Analysis Set］**

### (4) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験では，全投与集団（120 例）のうち 56.7%（68 例）の被験者に IRC 判定に基づく疾患進行又は死亡が認められ，PFS の解析では残り 43.3%（52 例）を打ち切りとした。Kaplan-Meier 法を用いて推定した PFS の中央値は 10.48 カ月（95% CI：4.37-14.98）であった。また，6 カ月 PFS 率は 58%（95% CI：49-67），18 カ月 PFS 率は 26%（95% CI：11-45）と推定された（表 2.7.3-36）。

さらに，治験担当医師判定に基づき推定した PFS の中央値は 10.12 カ月（95% CI：6.21-13.80）であった（【5.3.5.2.3-1 CSR TEFPFS06 p166】）。

表 2.7.3-36 無増悪生存期間（PFS）－IRC 判定［MCL2001 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Population: all treated | 120 |
| Subject status | 120 |
| Progressed or died | 68 (56.7%) |
| Censored | 52 (43.3%) |
| Progression-free survival (PFS) (months) [a] | |
| 25th percentile (95% CI) | 2.17 (1.94, 4.11) |
| Median (95% CI) | 10.48 (4.37, 14.98) |
| 75th percentile (95% CI) | 18.53 (14.98, NE) |
| 6-months PFS rate (95% CI) | 0.58 (0.49, 0.67) |
| 12-months PFS rate (95% CI) | 0.47 (0.38, 0.56) |
| 18-months PFS rate (95% CI) | 0.26 (0.11, 0.45) |

[a] Based on Kaplan-Meier estimate.

参照元：5.3.5.2.3-1 MCL2001 試験 CSR Table 16

### 2.7.3.3.3.5　全生存期間（OS）

#### (1) 海外第 II 相試験（1104 試験）

1104 試験の Kaplan-Meier 法を用いて推定した OS を表 2.7.3-37 に，OS の Kaplan-Meier 曲線を図 2.7.3-5 に示す。

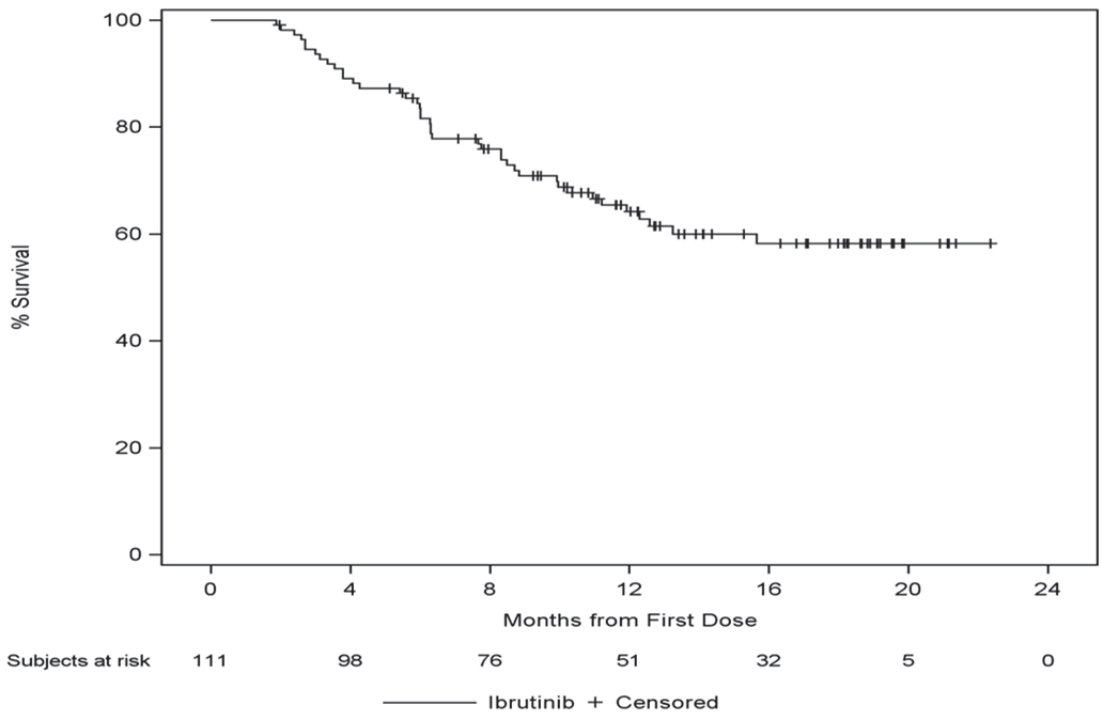
1104 試験では，Kaplan-Meier 法を用いて推定した試験参加期間の中央値は 15.3 カ月であった（2.7.3.3.1.1(2)参照）。全投与集団（111 例）のうち 36.9%（41 例）の被験者が死亡し，OS の解析では残り 63.1%（70 例）を打ち切りとした。OS の中央値は Kaplan-Meier 法を用いて推定できなかった。また，18 カ月 OS 率は 58.2%（95% CI：47.3-67.6）と推定された。

表 2.7.3-37 全生存期間（OS）［1104 試験：All-Treated Population］

| | Ibrutinib | | |
|---|---|---|---|
| | Bortezomib-Naive (N=63) | Bortezomib-Exposed (N=48) | Total (N=111) |
| Subject status | | | |
| Death of any cause (event) | 24 (38.1%) | 17 (35.4%) | 41 (36.9%) |
| Censored | 39 (61.9%) | 31 (64.6%) | 70 (63.1%) |
| Overall survival (months) [a] | | | |
| Median (95% CI) | NE (10.0, NE) | NE (11.9, NE) | NE (13.2, NE) |
| Min, Max | 1.97+, 21.16+ | 1.87, 22.34+ | 1.87, 22.34+ |
| 6-month overall survival rate (95% CI) | 80.4 (68.1, 88.4) | 87.5 (74.2, 94.2) | 83.5 (75.1, 89.3) |
| 12-month overall survival rate (95% CI) | 62.4 (48.6, 73.5) | 65.7 (49.2, 77.9) | 64.2 (54.0, 72.7) |
| 18-month overall survival rate (95% CI) | 57.8 (43.6, 69.6) | 57.9 (40.0, 72.2) | 58.2 (47.3, 67.6) |

Key: NE=not estimable
[a] Kaplan-Meier product limit estimates.

Note: + indicates censored observation.




参照元：5.3.5.2.2-1 1104 試験 CSR Figure 13

**図 2.7.3-5 全生存期間（OS）の Kaplan-Meier 曲線［1104 試験：All-Treated Population］**

### (2) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験の Kaplan-Meier 法を用いて推定した OS を表 2.7.3-38 に，OS の Kaplan-Meier 曲線を図 2.7.3-6 に示す。

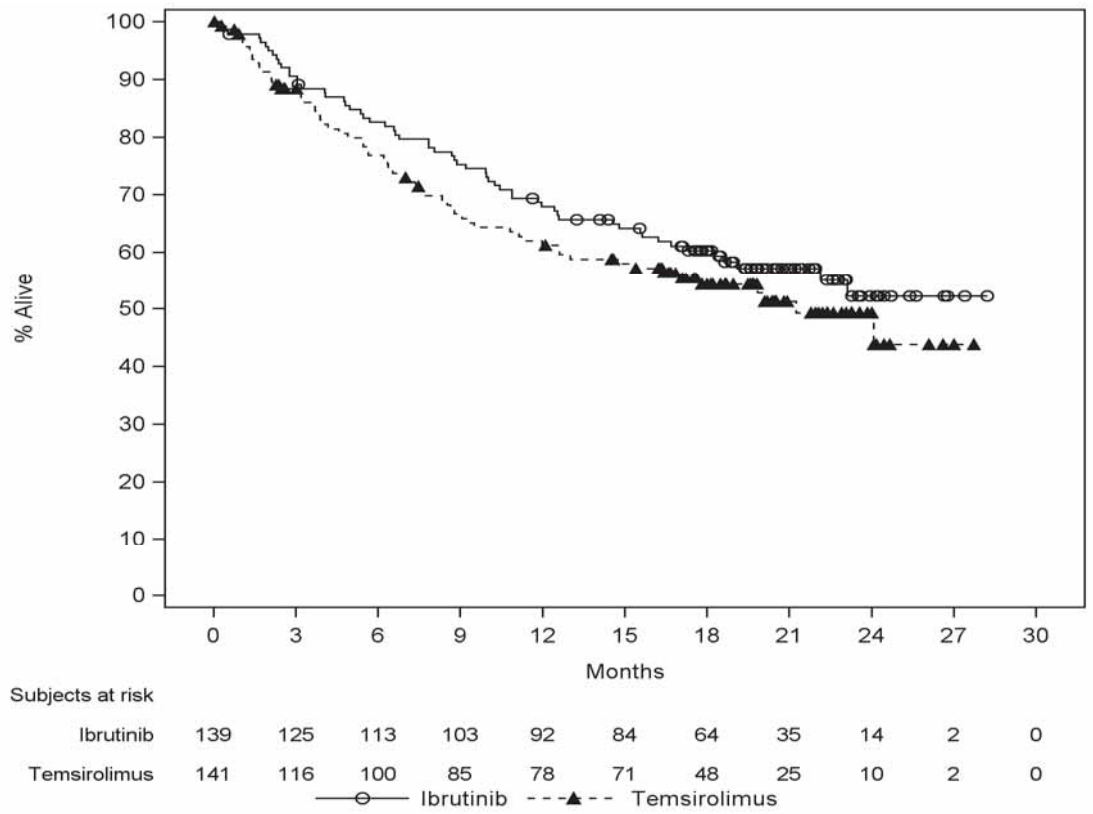
MCL3001 試験では，Kaplan-Meier 法を用いて推定した試験参加期間の中央値は全体で 20.01 カ月であった（【5.3.5.1.1 CSR TSIDS04A p1040】）。ITT 集団（イブルチニブ群 139 例，テムシロリムス群 141 例）において，イブルチニブ群では OS の中央値は推定できず，テムシロリムス群では Kaplan-Meier 法を用いて推定した OS の中央値は 21.3 カ月（95% CI：13.0-NE）であった。ハザード比は 0.76（95% CI：0.53-1.09）であり，イブルチニブ投与はテムシロリムス投与に比べて死亡のリスクを 24%低下した（p=0.1324）。なお，テムシロリムス群 141 例のうち，22.7%（32 例）の被験者が後治療でイブルチニブの投与を受けており（【5.3.5.1.1 CSR LSICM01 p336】），そのうちイブルチニブ群へクロスオーバーした被験者は 16.3%（23 例）であった（【5.3.5.1.1 CSR TCRAE01 p559】）。そのため，テムシロリムス群の OS の結果が交絡した可能性が示唆された。さらに，OS の Kaplan-Meier 曲線では，投与早期よりイブルチニブ群がテムシロリムス群よりも OS を延長する傾向を認めた。18 カ月 OS 率は，イブルチニブ群が 60%（95% CI：52-68），テムシロリムス群が 54%（95% CI：45-63）と推定された。

表 2.7.3-38 全生存期間（OS）［MCL3001 試験：Intent-to-treat Analysis Set］

| | Ibrutinib | Temsirolimus |
|---|---|---|
| Analysis set: intent-to-treat | 139 | 141 |
| Subject status | | |
| Died (event) | 59 (42.4%) | 63 (44.7%) |
| Censored | 80 (57.6%) | 78 (55.3%) |
| Overall Survival (months) [a] | | |
| 25% quantile (95% CI) | 9.2 (6.2, 12.4) | 6.4 (4.0, 8.6) |
| Median (95% CI) | NE (18.6, NE) | 21.3 (13.0, NE) |
| 75% quantile (95% CI) | NE (NE, NE) | NE (NE, NE) |
| 6-months OS rate (95% CI) | 0.83 (0.75, 0.88) | 0.77 (0.69, 0.83) |
| 12-months OS rate (95% CI) | 0.68 (0.59, 0.75) | 0.61 (0.52, 0.69) |
| 18-months OS rate (95% CI) | 0.60 (0.52, 0.68) | 0.54 (0.45, 0.63) |
| 24-months OS rate (95% CI) | 0.52 (0.41, 0.62) | 0.49 (0.39, 0.58) |
| P-value [b] | 0.1324 | |
| Hazard ratio (95% CI) [c] | 0.76 (0.53, 1.09) | |

Key: NE=not estimable
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on stratified Log rank test with MIPI and prior lines of therapy from IWRS as stratification factors.
[c] Based on stratified Cox´s model with MIPI and prior lines of therapy from IWRS as stratification factors.
A hazard ratio < 1 indicates an advantage for Ibrutinib.

参照元：5.3.5.1.1 MCL3001 試験 CSR Table 14




参照元：5.3.5.1.1 MCL3001 試験 CSR Figure 6

図 2.7.3-6 全生存期間（OS）の Kaplan-Meier 曲線［MCL3001 試験：Intent-to-treat Analysis Set］

### (3) 海外第 II 相試験（MCL2001 試験）

MCL2001 試験では，Kaplan-Meier 法を用いて推定した試験参加期間（投与開始日から直近のデータ収集日までの期間）の中央値は 14.92 カ月であった（【5.3.5.2.3-1 CSR TSIDS05 p136】）。全投与集団（120 例）のうち 36.7%（44 例）の被験者が死亡し，OS の解析では残り 63.3%（76 例）を打ち切りとした。OS の中央値は Kaplan-Meier 法を用いて推定できなかった。また，18 カ月 OS 率は 61%（95% CI：50-69）と推定された（表 2.7.3-39）。

表 2.7.3-39 全生存期間（OS）［MCL2001 試験：All-Treated Population］

| | Ibrutinib |
|---|---|
| Population: all treated | 120 |
| Subject status | 120 |
| Died | 44 (36.7%) |
| Censored | 76 (63.3%) |
| Overall survival (OS) (months) [a] | |
| 25th percentile (95% CI) | 7.43 (4.07, 11.79) |
| Median (95% CI) | NE (18.53, NE) |
| 75th percentile (95% CI) | NE (NE, NE) |
| 6-months survival rate (95% CI) | 0.77 (0.68, 0.83) |
| 12-months survival rate (95% CI) | 0.67 (0.58, 0.75) |
| 18-months survival rate (95% CI) | 0.61 (0.50, 0.69) |
| 24-months survival rate (95% CI) | 0.56 (0.43, 0.67) |

[a] Based on Kaplan-Meier estimate.

参照元：5.3.5.2.3-1 MCL2001 試験 CSR Table 17

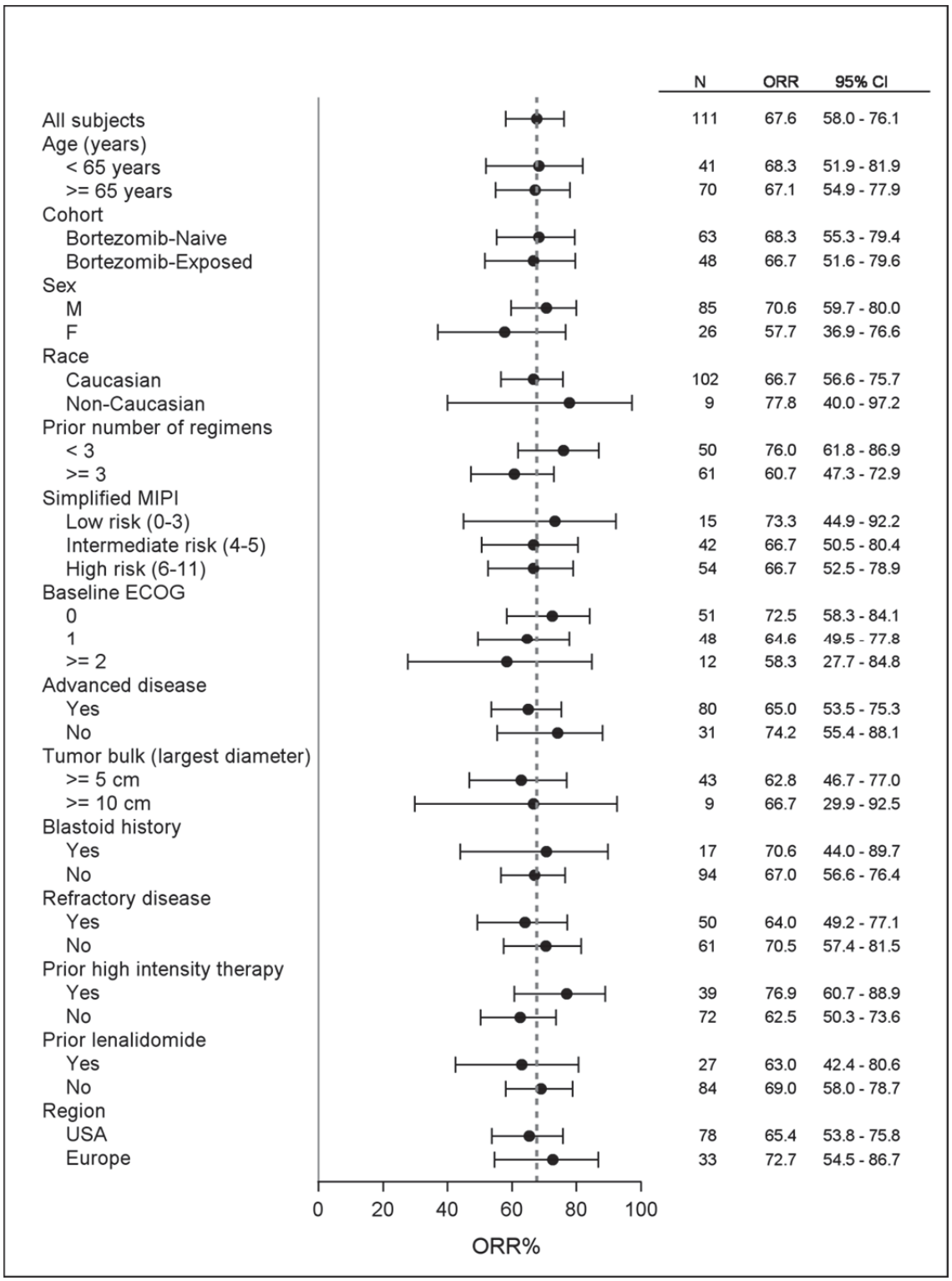
## 2.7.3.3.4 部分集団における結果の比較

1104 試験では ORR，MCL3001 試験では PFS に関して，再発又は難治性 MCL 患者の人口統計学的特性及びベースラインの疾患特性別に，部分集団解析を各試験で実施した。

### (1) 海外第 II 相試験（1104 試験）

1104 試験はランダム化試験とはせず，事前に規定した 2 つのコホート（ボルテゾミブ既治療及びボルテゾミブ未治療）に被験者を組み入れた。治験担当医師評価に基づく ORR に関して，ベースラインの予後因子及び疾患特性別に，全投与集団を対象に部分集団解析を実施した。

年齢，性別，地域，ボルテゾミブによる前治療，レナリドミドによる前治療，MIPI 簡略版によるリスク分類，難治性，又は芽球様細胞の組織学的所見などの部分集団別で ORR は同程度であり，臨床上の特性との関連性は認められなかった（図 2.7.3-7）。



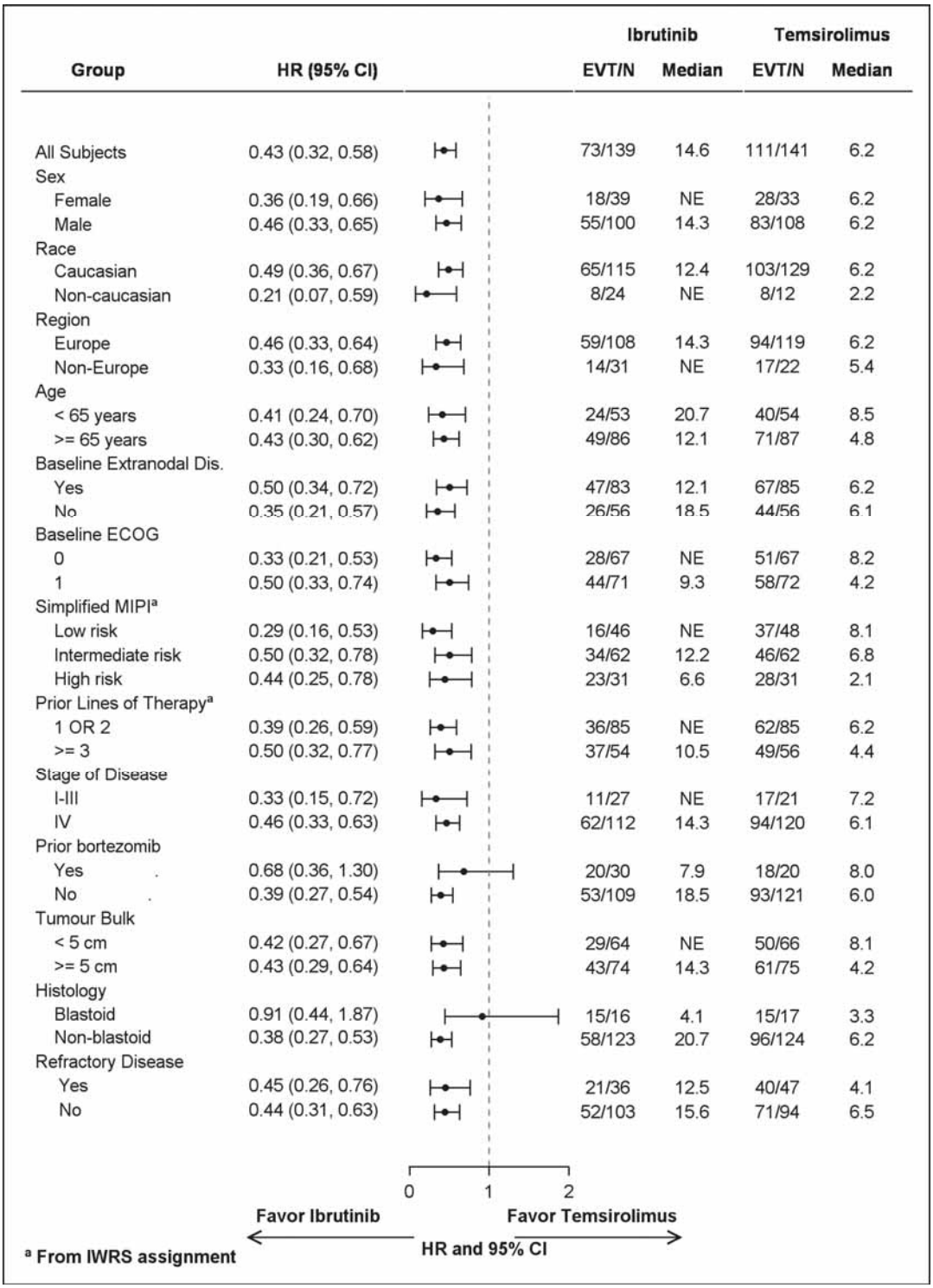

Key: ECOG=Eastern Cooperative Oncology Group; F=female; M=male; MIPI=Mantle Cell Lymphoma International Prognostic Index; ORR=overall response rate; USA=United States of America

図 2.7.3-7 全奏効率（ORR）の Forest plot［1104 試験：All-Treated Population］

### (2) 海外第 III 相試験（MCL3001 試験）

MCL3001 試験はランダム化試験であり，被験者を前治療数及び MIPI 簡略版のスコアで層別化し，イブルチニブ群又はテムシロリムス群に 1:1 の比で割り付けた。IRC 評価に基づく PFS に関して，予測した予後因子別に，ITT 集団を対象に部分集団解析を実施した。なお，イブルチニブ群のテムシロリムス群に対するハザード比及びその 95% CI は，Cox 比例ハザードモデル（層別化なし）により算出した。

年齢，性別，地域，前治療数，ベースライン時の病期及び腫瘍の大きさなどの部分集団別で PFS の解析結果は同程度であった。部分集団別の PFS のハザード比はすべての項目で 1 未満であり，ベースライン時の特性によらず，イブルチニブ投与はテムシロリムス投与に比べて PFS を延長した（図 2.7.3-8）。




参照元：5.3.5.1.1 MCL3001 試験 CSR Figure 3

図 2.7.3-8 無増悪生存期間（PFS）の Forest plot［MCL3001 試験：Intent-to-treat Analysis Set］

### 2.7.3.4 推奨用法・用量に関する臨床情報の解析

再発又は難治性の MCL 患者に対するイブルチニブの用法・用量は，海外第 I 相漸増投与試験である PCYC-04753 試験及び 1104 試験の薬物動態，薬力学評価及び臨床評価に基づき決定した。

また，日本人の再発又は難治性の MCL 患者に対するイブルチニブの用量は，海外 04753 試験，1104 試験及び MCL3001 試験に加え，用量漸増試験である JPN-101 試験及び MCL2002 試験の薬物動態，薬力学評価及び臨床評価に基づき決定した。

用法・用量に関する臨床情報の詳細は，【CTD2.5.6.3】に記載した。

### 2.7.3.5 効果の持続，耐薬性

国内及び海外で実施した臨床試験 4 試験では，再発又は難治性の MCL 患者にイブルチニブを 560 mg/日の用量で投与した。1104 試験では各評価時点で CR と評価された被験者の割合は投与開始 2 カ月目の 3.6%から 12 カ月目の 20.7%まで経時的に上昇し，投与の継続による深い奏効が認められた（2.7.3.3.3.2(2)参照）。

各試験の PFS 及び OS の Kaplan-Meier 法を用いた解析結果から，持続的な抗腫瘍効果が認められた。試験参加期間が短いため，データカットオフ時点では PFS の中央値が推定できなかった MCL2002 試験を除く 3 試験では，PFS の中央値は 10.48～14.6 カ月の範囲であり，18 カ月 PFS 率は 26～48%と推定された（2.7.3.3.3.4 参照）。また，OS に関して，試験参加期間の中央値は，1104 試験が 15.3 カ月，MCL3001 試験が 20.44 カ月（イブルチニブ群），MCL2001 試験が 14.92 カ月であったが，いずれも OS の中央値は推定できず，18 カ月 OS 率は 58.2～61%と推定された（2.7.3.3.3.5 参照）。なお，1104 試験の最終解析結果では，OS の中央値は 22.5 カ月（95% CI：13.7-NE）と推定された（【5.3.5.2.2-2 CSR Table 9 p15】）。

これらの結果から，再発又は難治性の MCL 患者に対するイブルチニブの効果は持続的であると考える。

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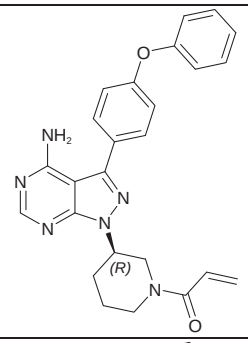
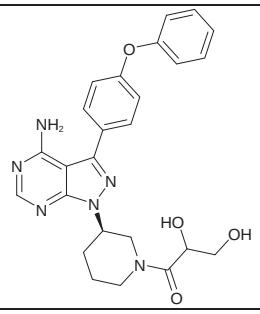
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# 略号一覧表

| 略号又は略称 | 化学名又は一般名 | 構造式 | 由来 |
|---|---|---|---|
| イブルチニブ（PCI-32765 又は JNJ-54179060） | 1-{(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one |  | 主薬 |
| PCI-45227（JNJ-54243761） | ジヒドロジオール体（M37） |  | 代謝物 |

| 略号又は略称 | 名称及び内容 |
|---|---|
| ALC | absolute lymphocyte count |
| ALT | アラニンアミノトランスフェラーゼ（alanine aminotransferase） |
| AST | アスパラギン酸アミノトランスフェラーゼ（aspartate aminotransferase） |
| AUC | 血漿中濃度―時間曲線下面積（area under the plasma concentration-time curve） |
| BTK | ブルトン型チロシンキナーゼ（Bruton’s Tyrosine Kinase） |
| CLL | 慢性リンパ性白血病（chronic lymphocytic leukemia） |
| $C_{max}$ | 最高血漿中濃度（maximum observed plasma concentration） |
| CR | 完全奏効（complete response） |
| CrCL | クレアチニン・クリアランス（creatinine clearance） |
| CSR | 治験総括報告書（clinical study report） |
| CxDy | Cycle x Day y |
| CYP | チトクローム P450（cytochrome P450） |
| EAIR | 曝露期間により調整した有害事象の発現率（exposure-adjusted incidence rate） |
| ECOG | Eastern Cooperative Oncology Group |
| EOT | end of treatment |
| ISS | Integrated Summary of Safety |
| MCL | マントル細胞リンパ腫（mantle cell lymphoma） |
| MIPI | マントル細胞リンパ腫国際予後指標（Mantle Cell Lymphoma International Prognostic Index） |
| MTD | 最大耐量（maximum tolerated dose） |
| MedDRA | 医薬品規制用語集（Medical Dictionary for Regulatory Activities） |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| PS | performance status |
| PSUR | 定期的安全性最新報告（periodic safety update report） |
| PT | 基本語（preferred term） |

| 略号又は略称 | 名称及び内容 |
|---|---|
| QTcB | Bazett formula を用いて心拍数で補正した QT 間隔（QT interval corrected for heart rate, using Bazett formula） |
| QTcF | Fridericia formula を用いて心拍数で補正した QT 間隔（QT interval corrected for heart rate, using Fridericia formula） |
| QTcP | 試験固有の補正係数を用いて心拍数で補正した QT 間隔（QT interval corrected for heart rate, using a study-specific power model） |
| SAE | serious adverse event |
| SCR | screening |
| SLL | 小リンパ球性リンパ腫（small lymphocytic lymphoma） |
| SMQ | MedDRA 標準検索式（Standardized MedDRA query） |
| SOC | 器官別大分類（system organ class） |
| TEAE | 治験薬投与後に発現した有害事象（treatment-emergent adverse event） |
| TESAE | treatment-emergent serious adverse event |

## 2.7.4 臨床的安全性

イブルチニブはブルトン型チロシンキナーゼ（BTK）阻害剤である。イブルチニブは，国内で2016年3月に420 mgを1日1回経口投与する用法・用量で「再発又は難治性の慢性リンパ性白血病（CLL）［小リンパ球性リンパ腫（SLL）を含む］」で承認されている。今回，新効能として560 mgを1日1回経口投与する用法・用量で「再発又は難治性のマントル細胞リンパ腫（MCL）」を申請する。

### 2.7.4.1 医薬品への曝露

#### 2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述

##### 2.7.4.1.1.1 安全性の評価に用いた試験

イブルチニブの再発又は難治性のMCLに対する安全性は，表2.7.4-1に示す国内試験1試験及び海外試験4試験の計5試験を用いて評価した。評価に際して，表2.7.4-1に示す区分に各試験を分類した。海外3試験（PCYC-1104-CA試験，PCI-32765MCL3001試験，PCI-32765MCL2001試験）の計370例のデータの併合解析（海外3試験併合）を実施した。安全性は，国内試験（PCI-32765MCL2002試験）及び海外3試験併合の結果を中心に評価した。PCI-32765CLL1007試験は健康成人対象の試験であり，心室再分極に与える影響を評価した結果を2.7.4.4.2項に記載した。なお，PCI-32765MCL3001試験でイブルチニブの対照薬として用いたテムシロリムスの安全性データをイブルチニブとの比較に用いた。

表2.7.4-1 安全性の評価に用いた試験

| 実施地域 | 区分 | 試験番号（資料番号） | 相 | 対象 | 資料 |
|---|---|---|---|---|---|
| 国内 | 国内の再発又は難治性MCL患者対象試験 | PCI-32765MCL2002（5.3.5.2.1） | II | 1レジメン以上5レジメン以下の前治療を実施した後に疾患進行した，再発又は難治性の日本人MCL患者 | 評価 |
| 海外 | 海外の再発又は難治性MCL患者対象試験 | PCYC-1104-CA[*1]（5.3.5.2.2-1） | II | 1レジメン以上5レジメン以下の前治療歴がある再発又は難治性MCL患者 | |
| | | PCI-32765MCL3001（5.3.5.1.1） | III | 1レジメン以上のリツキシマブを含む化学療法歴がある再発又は難治性MCL患者 | |
| | | PCI-32765MCL2001（5.3.5.2.3-1）[*2] | II | 1レジメン以上のリツキシマブを含む化学療法歴があり，2サイクル以上のボルテゾミブを含む前治療を実施した後に疾患進行したMCL患者 | 参考 |
| | 健康成人対象試験 | PCI-32765CLL1007（5.3.4.1.1） | I | 健康成人 | 評価 |

*1: 主要解析のためのデータカットオフ（[redacted]年[redacted]月[redacted]日）時点の結果を用いた。
*2: 主要解析のためのデータカットオフ（[redacted]年[redacted]月[redacted]日）時点の結果を用いた。

2.7.4 項（本項）本文では，表 2.7.4-1 に示した試験の試験番号の表記「PCYC-」及び「-CA」並びに試験番号冒頭の表記「PCI-32765」を省略して記載する。

#### 2.7.4.1.1.2 主な試験のデザイン

##### (1) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験は，1 レジメン以上 5 レジメン以下の前治療を実施した後に疾患進行した，再発又は難治性の MCL 日本人患者を対象に，イブルチニブ単剤投与による有効性及び安全性を評価し，さらにイブルチニブの薬物動態を探索的に検討する，多施設共同，単群の第 II 相試験であった。

16 例に，疾患進行，完全奏効（complete response，以下 CR）到達後の再発，耐容不能な毒性の発現又は治験終了のいずれか早い時点まで，28 日間を 1 サイクルとしてイブルチニブ 560 mg を 1 日 1 回経口投与した。

すべての被験者がサイクル 7 の 1 日目の有効性評価を完了した時点又は治験薬の投与を中止した時点をデータカットオフとした。

##### (2) 海外の再発又は難治性 MCL 患者対象試験

###### 1) 1104 試験

1104 試験は，1 レジメン以上 5 レジメン以下の前治療を実施した後に再発した MCL 患者を対象に，イブルチニブを単剤投与したときの有効性及び安全性を評価する，非ランダム化，非盲検，多施設共同，第 II 相試験であった。

ボルテゾミブの治療歴に基づき，被験者をボルテゾミブ未治療コホート（ボルテゾミブによる前治療が 2 サイクル未満）又はボルテゾミブ既治療コホート（ボルテゾミブによる前治療が 2 サイクル以上）に組み入れ，計 111 例に，疾患進行又は耐容不能な毒性の発現まで，28 日間を 1 サイクルとしてイブルチニブ 560 mg を 1 日 1 回経口投与した。

本治験に組み入れられた最後の被験者が，治験薬投与開始後少なくとも 9 カ月間経過した時点を主要解析のためのデータカットオフとした。

###### 2) MCL3001 試験

MCL3001 試験は，1 レジメン以上のリツキシマブを含む化学療法歴がある再発又は難治性 MCL 患者を対象に，イブルチニブ又はテムシロリムスを投与したときの有効性及び安全性を比較する，ランダム化，実薬対照，非盲検，多施設共同，第 III 相試験であった。

前治療数，マントル細胞リンパ腫国際予後指標（Mantle Cell Lymphoma International Prognostic Index，以下 MIPI）簡易版のスコアで層別化し，被験者をイブルチニブを経口投与する群（イブルチニブ群）又はテムシロリムスを静脈内投与する群（テムシロリムス群）に 1:1 の比でランダムに割り付け，各群 139 例に，疾患進行，CR 到達後に再発，耐容不能な毒性の発現又は治験終了のいずれか早い日まで，21 日間を 1 サイクルとして，イブルチニブ群にはイブルチニブ 560 mg を 1 日 1 回経口投与し，テムシロリムス群には各サイクルの 1，8，15 日目に，サイクル 1 ではテムシロリムス 175 mg を，サイクル 2 以降ではテムシロリムス 75 mg を静脈内投与した。

テムシロリムス群で疾患進行が認められた被験者は，イブルチニブ 560 mg の 1 日 1 回経口投与に切り替え可能とした。

疾患進行，CR 到達後に再発又は死亡が合計で約 178 件認められた時点をデータカットオフとした。

#### 3) MCL2001 試験

MCL2001 試験は，1 レジメン以上のリツキシマブを含む化学療法歴があり，2 サイクル以上のボルテゾミブを含む前治療を実施した後に疾患進行した MCL 患者を対象に，イブルチニブを単剤投与したときの有効性及び安全性を評価する，多施設共同，単群，第 II 相試験であった。

120 例に，疾患進行，CR 到達後に再発，耐容不能な毒性の発現又は治験終了のいずれか早い日まで，21 日間を 1 サイクルとしてイブルチニブ 560 mg を 1 日 1 回経口投与した。

最後の被験者の登録から約 1 年後を主要解析のためのデータカットオフとした。

### (3) 健康成人対象試験（CLL1007 試験）

CLL1007 試験は，Part 1 及び Part 2 で構成された。

Part 1 は，健康成人を対象に，治療用量を上回る用量のイブルチニブを投与したときの安全性を評価する，非盲検，単施設，2 期，逐次試験であった。第 1 期では 8 例にイブルチニブ 840 mg を単回投与した。第 2 期では，第 1 期から 7 日以上のウォッシュアウト期間の後に，最初の 3 例にイブルチニブ 1680 mg を投与し，安全性及び忍容性を評価した。この 3 例に Grade 3 以上の毒性が認められず，消化管に対する忍容性が認められたため，残る 5 例にイブルチニブ 1680 mg を投与した。

Part 2 は，健康成人を対象に，心室再分極に対するイブルチニブの作用を評価する，ランダム化，プラセボ及び実薬対照，二重盲検，単回投与，4 期クロスオーバー試験であった。64 例にイブルチニブ 1680 mg（治療用量を上回る用量），イブルチニブ 840 mg（治療用量），プラセボ及びモキシフロキサシン 400 mg を，ランダム化された投与順序でそれぞれ単回投与することとした。Part 2 はイブルチニブ 1680 mg を投与された 1 例で Grade 4 の肝酵素上昇が認められたため，試験を早期中止した。中止時点で 20 例が少なくとも 1 回治験薬の投与を受けていた。

## 2.7.4.1.1.3 安全性の評価・解析方法

### (1) 評価方法

#### 1) 有害事象

<u>有害事象</u>

本項では，有害事象として治験薬投与後に発現した有害事象（treatment-emergent adverse event，以下 TEAE）を評価した。原疾患については，予期しない症状及び徴候を有害事象とした。疾患進行については，MCL2002 試験，MCL3001 試験及び MCL2001 試験では有害事象として報告しないこととしたが，下記の重篤な有害事象の定義に該当する場合は報告対象とした。TEAE は以下のように定義した。

・ 治験薬投与後から治験薬最終投与後 30 日又は MCL に対する全身性の後治療（MCL3001 試験のテムシロリムス群のイブルチニブへの切替えを含む）の開始のいずれか早い日までに発現した有害事象（1104 試験では治験薬投与後から治験薬最終投与後 30 日に発現した有害事象）

・ 発現日が不明で治験薬投与期間中に回復した有害事象（1104 試験及び MCL2001 試験のみ）

・ 発現日にかかわらず治験薬との関連性があると判断された有害事象

・ ベースライン時に存在していたがその重症度が悪化した有害事象

重篤な有害事象

重篤な有害事象は，以下の基準に該当する有害事象と定義した。

・ 死亡

・ 生命を脅かすもの

・ 入院又は入院期間の延長が必要なもの

・ 永続的又は顕著な障害/機能不能に陥るもの

・ 先天異常・先天性欠損を来すもの

・ 医薬品（治験薬を含む）を介する感染因子伝播の疑いがあるもの（1104 試験を除く）

・ 医学的に重要なもの（1104 試験を除く）

重症度

National Cancer Institute Common Terminology Criteria for Adverse Events（以下，NCI-CTCAE）に基づき，有害事象の重症度を判定した。各試験で使用した NCI-CTCAE のバージョンは，MCL2002 試験，MCL3001 試験及び MCL2001 試験では ver. 4.03，1104 試験では ver. 4.0 であった。

本項では，重症度別の集計では Grade 3 以上の有害事象を対象とした。

治験薬との因果関係

治験担当医師がすべての有害事象について，治験薬との因果関係を評価した。各試験で用いた因果関係の評価スケールを，表 2.7.4-2 に示す。MCL2002 試験，MCL3001 試験及び MCL2001 試験では，治験実施計画書に規定していたとおり，「可能性小」，「可能性大」，「ほぼ確実」と評価された事象を治験薬との関連性がある有害事象とした。

表 2.7.4-2 治験薬との因果関係の評価

| 試験番号 | 因果関係の評価 | | | | |
|---|---|---|---|---|---|
| MCL2002 | 関連なし<br>not related | 多分なし<br>doubtful | 可能性小<br>possible | 可能性大<br>probable | ほぼ確実<br>very likely |
| 1104 | 関連なし<br>unrelated | | 可能性小<br>possibly related | | ほぼ確実<br>definitely related |
| MCL3001 | 関連なし<br>not related | 多分なし<br>doubtful | 可能性小<br>possible | 可能性大<br>probable | ほぼ確実<br>very likely |
| MCL2001 | 関連なし<br>not related | 多分なし<br>doubtful | 可能性小<br>possible | 可能性大<br>probable | ほぼ確実<br>very likely |

治験薬との関連性がある有害事象

#### 2) 臨床検査

MCL2002 試験では治験治療終了時の来院までに得られた結果，1104 試験，MCL3001 試験及び MCL2001 試験では治験薬の最終投与 30 日後又は治験治療終了時の来院のいずれか遅い時点までに得られた結果に基づき，血液学及び血液生化学の臨床検査結果を評価した。重症度は NCI-CTCAE ver. 4.03 に基づき判定した。

#### 3) バイタルサイン

MCL2002 試験では体温，脈拍数及び血圧を，1104 試験では体温，脈拍数，血圧，呼吸数を各試験のスケジュールに従い測定した。MCL2002 試験ではバイタルサインに臨床的に重要な変化が認められた場合は有害事象として収集した。また，MCL3001 試験及び MCL2001 試験ではバイタルサインを治験薬投与後の測定項目に含めなかったが，臨床的に重要な変化が認められた場合は有害事象として収集した。

#### 4) 心電図

MCL3001 試験，MCL2001 試験及び CLL1007 試験で各試験のスケジュールに従い心電図を記録した。CLL1107 試験では，心電図の結果は，治験担当医師又は指名された有資格者によって安全性が評価された後に，盲検下におかれた第三者の中央測定機関へ電子的に送付されパラメータが測定された。1104 試験ではイブルチニブ投与後に心電図を記録しなかった。MCL2002 試験ではイブルチニブ投与後の評価時点を規定せず，治験担当医師の判断で実施した。

### (2) 解析方法

#### 1) 解析対象集団

治験薬投与を 1 回以上受けた被験者を安全性解析対象集団とした。再発又は難治性 MCL 患者対象試験の安全性解析対対象集団を表 2.7.4-3 に示した。健康成人対象の CLL1007 試験の安全性解析対象集団は，Part 1 が 8 例，Part 2 が 20 例であった。

表 2.7.4-3 安全性解析対象集団

| Monotherapy studies in subjects with relapsed/refractory MCL | | | | | |
|---|---|---|---|---|---|
| Dose | 1104 試験 | MCL3001 試験 | MCL2001 試験 | Total | MCL2002 試験 |
| Ibrutinib | 111 | 139 | 120 | 370 | 16 |
| Temsirolimus | - | 139 | - | - | - |

併合解析

1104 試験，MCL3001 試験及び MCL2001 試験でイブルチニブを 1 回以上投与された被験者を主要な安全性解析対象集団とし，安全性データを併合解析した（海外 3 試験併合）。併合解析対象は 1104 試験の 111 例，MCL3001 試験のイブルチニブ群 139 例及び MCL2001 試験の 120 例の計 370 例とした（表 2.7.4-3）。なお，1104 試験及び MCL2001 試験は，主要解析のためのデータカットオフ（それぞれ [redacted] 年 [redacted] 月 [redacted] 日及び [redacted] 年 [redacted] 月 [redacted] 日）時点のデータを用いた。MCL3001 試験では，テムシロリムス群で進行が認められイブルチニブ投与を開始した被験者（23 例）は本併合解析の対象としていない。

### 2) 有害事象

有害事象名は，医薬品規制用語集（Medical Dictionary for Regulatory Activities，以下 MedDRA）を用いてコード化し，器官別大分類（system organ class，以下 SOC）及び基本語（preferred term，以下 PT）単位で集計した。患者対象試験及び海外 3 試験併合で用いた MedDRA のバージョンを表 2.7.4-4 に示す。各試験で用いた MedDRA バージョンが異なっていたため，海外 3 試験併合では 1104 試験及び MCL2001 試験の有害事象名を MedDRA ver. 17.1 で再コード化した。

表 2.7.4-4 MedDRA のバージョン

| 試験番号 | MedDRA ver. |
|---|---|
| MCL2002 | 18.0 |
| 1104 | 15.1 |
| MCL3001 | 17.1 |
| MCL2001 | 16.1 |
| 海外 3 試験併合 | 17.1 |

## 2.7.4.1.2 全般的な曝露状況

### (1) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験の曝露量及び用量強度を表 2.7.4-5 に，減量及び投与中断を表 2.7.4-付録-1 に示す。

イブルチニブの曝露期間の中央値（範囲）は，6.46（2.8 - 8.3）カ月であり，相対用量強度の中央値は 99.64%であった。安全性解析対象集団 16 例のうち，有害事象により減量した被験者は 2 例（12.5%）であり，7 日間以上投与を中断した被験者は 5 例（31.3%）であった。減量に至った有害事象については 2.7.4.2.1.4(2)a)項に記載する。

表 2.7.4-5 曝露量及び用量強度：MCL2002 試験

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Duration of Treatment (months) [a] | |
| N | 16 |
| <= 6 | 7 (43.8%) |
| > 6 <= 12 | 9 (56.3%) |
| > 12 | 0 |
| Mean (SD) | 6.14 (1.730) |
| Median | 6.46 |
| Range | (2.8; 8.3) |
| Total Number of Cycles [b] | |
| N | 16 |
| Mean (SD) | 7.1 (1.88) |
| Median | 7.5 |
| Range | (4; 10) |
| Total Cumulative Dose (x10$^3$mg) [c] | |
| N | 16 |
| Mean (SD) | 96.67 (29.721) |
| Median | 100.80 |
| Range | (46.3; 141.1) |
| Dose Intensity (mg/day) [d] | |
| N | 16 |
| Mean (SD) | 520.48 (76.548) |
| Median | 557.99 |
| Range | (268.0; 560.0) |
| Relative Dose Intensity (%) [e] | |
| N | 16 |
| < 70% | 1 (6.3%) |
| 70% - < 90% | 4 (25.0%) |
| >= 90% | 11 (68.8%) |
| Mean (SD) | 92.94 (13.669) |
| Median | 99.64 |
| Range | (47.9; 100.0) |

[a] The duration of treatment (in months, day/365.25 x 12) is defined as the date of last dose minus the date of first dose of Ibrutinib plus 1.
[b] The number of cycles is derived from the duration of treatment with each cycle length of 28 days.
[c] Total cumulative dose (×10 $^3$ mg) is the sum of all given doses.
[d] Dose intensity (mg/day) is derived by the total cumulative dose (mg) divided by the duration of treatment (days).
[e] Relative dose intensity (%) is derived by 100×dose intensity (mg/day) divided by 560.

[TSIEXP01.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsiexp01.sas] 21AUG2015, 12:31
参照元：5.3.5.2.1 MCL2002 試験 CSR Table 8

### (2) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験の主要な安全性解析対象集団の曝露量及び用量強度を表 2.7.4-6 に，減量及び投与中断を表 2.7.4-付録-2 に示す。

海外 3 試験併合（370 例）のイブルチニブの曝露期間の中央値（範囲）は，10.83（0.0 - 28.2）カ月であり，相対用量強度の中央値は 98.5%であった。30 例（8.1%）が治験薬を減量し，6.8%（25 例）が 3 回以上投与を中断した。減量に至った有害事象については 2.7.4.2.1.4(2)b)項に記載する。

各試験のイブルチニブの曝露期間の中央値（範囲）は，MCL3001 試験のイブルチニブ群で 14.39（0.0 - 28.2）カ月，1104 試験で 8.28（0.7 - 21.4）カ月，MCL2001 試験で 7.95（0.5 - 20.9）カ月であり，1104 試験及び MCL2001 試験と比較して MCL3001 試験のイブルチニブ群で長かった。

MCL3001 試験の曝露期間の中央値（最大値）は，テムシロリムス群［3.02（27.0）カ月］と比較して，イブルチニブ群［14.39（28.2）カ月］で長かった。

表 2.7.4-6 曝露量及び用量強度：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Analysis set: safety population | 111 | 120 | 139 | 139 | 370 |
| Treatment duration (months) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 9.60 (6.462) | 8.74 (6.297) | 13.27 (8.306) | 6.04 (6.796) | 10.70 (7.426) |
| Median | 8.28 | 7.95 | 14.39 | 3.02 | 10.83 |
| Range | (0.7; 21.4) | (0.5; 20.9) | (0.0; 28.2) | (0.0; 27.0) | (0.0; 28.2) |
| 0 - <3 months | 24 (21.6%) | 35 (29.2%) | 25 (18.0%) | 66 (47.5%) | 84 (22.7%) |
| 3 - <6 months | 21 (18.9%) | 14 (11.7%) | 15 (10.8%) | 26 (18.7%) | 50 (13.5%) |
| 6 - <9 months | 12 (10.8%) | 14 (11.7%) | 11 (7.9%) | 12 (8.6%) | 37 (10.0%) |
| 9 - <12 months | 12 (10.8%) | 8 (6.7%) | 8 (5.8%) | 12 (8.6%) | 28 (7.6%) |
| 12 - <15 months | 13 (11.7%) | 26 (21.7%) | 11 (7.9%) | 5 (3.6%) | 50 (13.5%) |
| 15 - <18 months | 9 (8.1%) | 15 (12.5%) | 15 (10.8%) | 5 (3.6%) | 39 (10.5%) |
| 18 - <24 months | 20 (18.0%) | 8 (6.7%) | 42 (30.2%) | 9 (6.5%) | 70 (18.9%) |
| >=24 months | 0 | 0 | 12 (8.6%) | 4 (2.9%) | 12 (3.2%) |
| Cumulative total prescribed dose (g for Ibrutinib and mg for Temsirolimus) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 163.7 (110.14) | 147.6 (103.73) | 226.3 (141.58) | 2306.3 (2228.61) | 182.0 (125.72) |
| Median | 141.1 | 135.5 | 245.3 | 1350.0 | 184.0 |
| Range | (12; 364) | (8; 356) | (1; 480) | (175; 9150) | (1; 480) |
| Cumulative total dose received (g for Ibrutinib and mg for Temsirolimus) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 152.2 (103.34) | 140.0 (101.11) | 217.2 (137.97) | 1650.3 (1672.32) | 172.6 (121.74) |
| Median | 125.4 | 130.9 | 235.8 | 1000.0 | 171.0 |
| Range | (12; 339) | (8; 356) | (1; 452) | (75; 8400) | (1; 452) |
| Average dose level per administration (mg/day for Ibrutinib and mg/week for Temsirolimus) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 522.5 (59.51) | 530.9 (47.23) | 539.2 (45.62) | 86.6 (49.87) | 531.5 (51.00) |
| Median | 550.0 | 549.8 | 559.2 | 76.5 | 554.4 |
| Range | (278; 567) | (328; 560) | (170; 560) | (23; 350) | (170; 567) |

表 2.7.4-6 曝露量及び用量強度：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合（続き）

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Relative dose intensity (%) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 93.3 (10.63) | 93.0 (9.71) | 96.3 (8.15) | 76.5 (21.44) | 94.3 (9.55) |
| Median | 98.2 | 96.5 | 99.9 | 81.8 | 98.5 |
| Range | (50; 101) | (46; 100) | (30; 100) | (30; 100) | (30; 101) |
| <75 % | 9 (8.1%) | 7 (5.8%) | 3 (2.2%) | 59 (42.4%) | 19 (5.1%) |
| 75%-<90% | 15 (13.5%) | 22 (18.3%) | 12 (8.6%) | 29 (20.9%) | 49 (13.2%) |
| ≥ 90% | 87 (78.4%) | 91 (75.8%) | 124 (89.2%) | 51 (36.7%) | 302 (81.6%) |

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参照元：5.3.5.3.1 ISS TSIEXP01

### 2.7.4.1.3 治験対象集団の人口統計学的特性及びその他の特性

#### (1) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験のベースラインの人口統計学的特性を表 2.7.4-7 に，ベースラインの疾患の特性を表 2.7.4-8 に，全身性の前治療歴及び放射線による前治療歴を表 2.7.4-9 に示す。

安全性解析対象集団 16 例での年齢の中央値（範囲）は 72.0（55 - 83）歳であり，性別は男性 12 例（75.0%），女性 4 例（25.0%）で男性が多かった。ベースラインの Eastern Cooperative Oncology Group（以下，ECOG）performance status（以下，PS）は 0（75.0%，12 例）又は 1（25.0%，4 例）であった。前治療数は，1 レジメンが 6 例（37.5%），2 レジメンが 2 例（12.5%），3 レジメン以上が 8 例（50.0%）で，前治療数の中央値（範囲）は 2.5（1 - 4）であった。罹患期間の中央値（範囲）は 50.64（9.7 - 118.0）カ月，10 cm 以上の bulky disease を有する被験者は 1 例（6.3%）であった。全例に全身性の前治療歴があり，放射線による前治療歴のある被験者は 3 例（18.8%）であった。

表 2.7.4-7 ベースラインの人口統計学的特性：MCL2002 試験

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Age (years) | |
| N | 16 |
| < 65 | 4 (25.0%) |
| >= 65 | 12 (75.0%) |
| < 70 | 7 (43.8%) |
| >= 70 | 9 (56.3%) |
| Mean (SD) | 71.4 (8.62) |
| Median | 72.0 |
| Range | (55; 83) |
| Sex | |
| N | 16 |
| Male | 12 (75.0%) |
| Female | 4 (25.0%) |
| Weight (kg) | |
| N | 16 |
| Mean (SD) | 58.34 (11.590) |
| Median | 55.30 |
| Range | (38.4; 85.0) |
| ECOG | |
| N | 16 |
| 0 | 12 (75.0%) |
| 1 | 4 (25.0%) |

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 5

表 2.7.4-8 ベースラインの疾患の特性：MCL2002 試験

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Duration of Disease (months) [a] | |
| N | 16 |
| Mean (SD) | 59.84 (35.563) |
| Median | 50.64 |
| Range | (9.7; 118.0) |
| Type of Histology | |
| N | 16 |
| Diffuse | 13 (81.3%) |
| Nodular | 3 (18.8%) |
| Blastoid | 0 |
| Other | 0 |
| Tumor bulk (cm) [b] | |
| N | 16 |
| < 10 | 15 (93.8%) |
| >=10 | 1 (6.3%) |
| Tumor burden ($cm^2$) [c] | |
| N | 16 |
| Mean (SD) | 24.22 (37.637) |
| Median | 15.51 |
| Range | (1.6; 160.7) |
| B-symptoms | |
| N | 16 |
| Yes | 0 |
| No | 16 (100.0%) |
| Simplified MIPI score | |
| N | 16 |
| Low risk (0-3) | 4 (25.0%) |
| Intermediate risk (4-5) | 9 (56.3%) |
| High risk (6-11) | 3 (18.8%) |
| Ann Arbor stage | |
| N | 16 |
| I | 1 (6.3%) |
| II | 0 |
| III | 3 (18.8%) |
| IV | 12 (75.0%) |
| Number of Prior Regimens | |
| N | 16 |
| 1 | 6 (37.5%) |
| 2 | 2 (12.5%) |
| >=3 | 8 (50.0%) |
| Mean (SD) | 2.3 (1.20) |
| Median | 2.5 |
| Range | (1; 4) |
| Best Response of Last Therapy/Regimen | |
| N | 16 |
| COMPLETE RESPONSE | 9 (56.3%) |
| PARTIAL RESPONSE | 3 (18.8%) |
| STABLE DISEASE | 3 (18.8%) |
| PROGRESSIVE DISEASE | 1 (6.3%) |
| Extranodal site [d] | |
| N | 16 |
| Yes | 7 (43.8%) |
| No | 9 (56.3%) |
| Bone Marrow Biopsy | |
| N | 16 |
| Histology Negative | 7 (43.8%) |
| Histology Positive | 4 (25.0%) |
| Histology Indeterminate | 2 (12.5%) |
| Histology Indeterminate: Positive by IHC | 3 (18.8%) |
| Histology Indeterminate: Positive by Karyotype | 0 |
| Histology Indeterminate: Positive by FISH | 0 |

表 2.7.4-8 ベースラインの疾患の特性：MCL2002 試験（続き）

| | Ibrutinib |
|---|---|
| Bone Marrow Aspirate | |
| N | 16 |
| Histology Negative | 6 (37.5%) |
| Histology Positive | 6 (37.5%) |
| Histology Indeterminate | 1 (6.3%) |
| Histology Indeterminate: Positive by IHC | 1 (6.3%) |
| Histology Indeterminate: Positive by Karyotype | 0 |
| Histology Indeterminate: Positive by FISH | 2 (12.5%) |

[a] (Date of First Dose of Ibrutinib - Date of Initial Diagnosis + 1) / 365.25 x 12
[b] Tumor bulk (cm) is derived using the largest diameter among measurable lesions.
[c] Tumor burden (cm $^2$) is defined as the sum of product of two bidimensional measurements of all measurable lesions.
[d] Extra nodal site is defined as any measurable or unmeasurable extra-nodal lesions except for spleen.

[TSIDEM02.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsidem02.sas] 14MAR2016, 16:21
参照元：5.3.5.2.1 MCL2002 試験 CSR Table 6

表 2.7.4-9 全身性の前治療歴及び放射線による前治療歴：MCL2002 試験

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Prior Systemic Therapy | |
| N | 16 |
| Yes | 16 (100.0%) |
| No | 0 |
| Prior Radiotherapy | |
| N | 16 |
| Yes | 3 (18.8%) |
| No | 13 (81.3%) |

[TSIDEM05.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsidem05.sas] 21AUG2015, 12:31
参照元：5.3.5.2.1 MCL2002 試験 CSR TSIDEM05

### (2) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験の主要な安全性解析対象集団のベースラインの人口統計学的特性及び疾患の特性を表 2.7.4-10 及び表 2.7.4-11 に示す。

海外 3 試験併合（370 例）での年齢の中央値（範囲）は 67.5（35 - 85）歳で，62.4%（231 例）が 65 歳以上であった。男性が多く（78.1%，289 例），大多数が白人（89.2%，330 例）で，ベースラインの ECOG PS が 0（43.2%，160 例）又は 1（50.3%，186 例）の被験者が多かった。初回診断から割付け又はイブルチニブの初回投与までの経過時間の中央値（範囲）は 42.37（2.5 - 298.7）カ月で，Stage IV の被験者は 79.2%（205 例），10 cm 以上の bulky disease を有する被験者は 13.0%（48 例）であった。前治療数の中央値（範囲）は 2.0（1 - 9）レジメンであり，放射線による前治療歴がある被験者は 22.2%（82 例）であった。

試験の実施国に基づき，1104 試験及び MCL2001 試験では米国の被験者が多く，MCL3001 試験のイブルチニブ群では欧州の被験者が多かった。MIPI 簡易版のスコアで High risk であった被験者は，MCL2001 試験（28.0%）及び MCL3001 試験のイブルチニブ群（21.6%）と比較して，1104 試験（48.6%）で多かった。ボルテゾミブによる前治療歴がある被験者の割合は，MCL2001 試験ではボルテゾミブによる前治療歴がある被験者を対象としたため 100%であったが，1104 試験では 43.2%，MCL3001 試験のイブルチニブ群では 21.6%であった。1104 試験及び MCL2001 試験では再発性の MCL 及び難治性の MCL の被験者の割合が同程度であったが，MCL3001 試験のイブルチニブ群では再発性の MCL の被験者が多かった［1104 試験；再発性の MCL の被験者 47.7%

及び難治性の MCL の被験者 45.0%（以降同順），MCL2001 試験；45.8%及び 54.2%，MCL3001 試験のイブルチニブ群；74.1%及び 25.9%］。Bulky disease を有する被験者は，MCL2001 試験と MCL3001 試験のイブルチニブ群では同様であったが，1104 試験では少なかった（5 cm 以上の bulky disease；1104 試験 38.7%，MCL2001 試験 52.9%，MCL3001 試験のイブルチニブ群 53.6%，10 cm 以上の bulky disease；1104 試験 8.1%，MCL2001 試験 14.3%，MCL3001 試験のイブルチニブ群 15.9%）。B 症状を有する被験者は，1104 試験（26.1%）及び MCL3001 試験のイブルチニブ群（23.7%）と比較して MCL2001 試験（15.0%）で少なかった。その他のベースラインの人口統計学的特性及び疾患の特性に顕著な偏りは認められなかった。また，MCL3001 試験の投与群間においては，ベースラインの人口統計学的特性及び疾患の特性に顕著な偏りは認められなかった。

表 2.7.4-10 ベースラインの人口統計学的特性：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Analysis set: safety population | 111 | 120 | 139 | 139 | 370 |
| Region | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| United States | 78 (70.3%) | 83 (69.2%) | 0 | 0 | 161 (43.5%) |
| Europe | 33 (29.7%) | 37 (30.8%) | 108 (77.7%) | 117 (84.2%) | 178 (48.1%) |
| ROW | 0 | 0 | 31 (22.3%) | 22 (15.8%) | 31 (8.4%) |
| Age (years) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 67.1 (8.57) | 66.7 (9.98) | 66.7 (8.68) | 67.1 (9.88) | 66.8 (9.07) |
| Median | 68.0 | 67.5 | 67.0 | 68.0 | 67.5 |
| Range | (40; 84) | (35; 85) | (39; 84) | (34; 88) | (35; 85) |
| < 65 | 41 (36.9%) | 45 (37.5%) | 53 (38.1%) | 54 (38.8%) | 139 (37.6%) |
| ≥ 65 | 70 (63.1%) | 75 (62.5%) | 86 (61.9%) | 85 (61.2%) | 231 (62.4%) |
| ≥ 70 | 46 (41.4%) | 56 (46.7%) | 58 (41.7%) | 60 (43.2%) | 160 (43.2%) |
| ≥ 75 | 23 (20.7%) | 26 (21.7%) | 29 (20.9%) | 33 (23.7%) | 78 (21.1%) |
| Sex | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Male | 85 (76.6%) | 104 (86.7%) | 100 (71.9%) | 106 (76.3%) | 289 (78.1%) |
| Female | 26 (23.4%) | 16 (13.3%) | 39 (28.1%) | 33 (23.7%) | 81 (21.9%) |
| Race | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| White | 102 (91.9%) | 113 (94.2%) | 115 (82.7%) | 127 (91.4%) | 330 (89.2%) |
| Black or African American | 5 (4.5%) | 2 (1.7%) | 0 | 0 | 7 (1.9%) |
| Asian | 1 (0.9%) | 0 | 16 (11.5%) | 5 (3.6%) | 17 (4.6%) |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| Other | 2 (1.8%) | 0 | 3 (2.2%) | 4 (2.9%) | 5 (1.4%) |
| Unknown/not reported | 0 | 5 (4.2%) | 5 (3.6%) | 3 (2.2%) | 10 (2.7%) |
| Ethnicity | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Hispanic or Latino | 5 (4.5%) | 4 (3.3%) | 7 (5.0%) | 11 (7.9%) | 16 (4.3%) |
| Not Hispanic or Latino | 106 (95.5%) | 97 (80.8%) | 127 (91.4%) | 125 (89.9%) | 330 (89.2%) |
| Unknown/not reported | 0 | 19 (15.8%) | 5 (3.6%) | 3 (2.2%) | 24 (6.5%) |
| ECOG performance status | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| 0 | 51 (45.9%) | 42 (35.0%) | 67 (48.2%) | 66 (47.5%) | 160 (43.2%) |
| 1 | 48 (43.2%) | 67 (55.8%) | 71 (51.1%) | 71 (51.1%) | 186 (50.3%) |
| 2 | 11 (9.9%) | 11 (9.2%) | 1 (0.7%) | 2 (1.4%) | 23 (6.2%) |
| >2 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |

Key: ECOG = Eastern Cooperative Oncology Group

[TSIDEM01.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsidem01.sas] 15SEP2015, 14:13
参照元：5.3.5.3.1 ISS TSIDEM01

表 2.7.4-11 ベースラインの疾患の特性：
1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Analysis set: safety population | 111 | 120 | 139 | 139 | 370 |
| Time from initial diagnosis to randomization/first dose (months) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 51.58 (43.349) | 53.72 (36.151) | 49.98 (42.708) | 51.64 (33.552) | 51.67 (40.819) |
| Median | 42.35 | 43.94 | 38.90 | 46.39 | 42.37 |
| Range | (2.5; 223.3) | (6.8; 189.6) | (4.2; 298.7) | (2.7; 159.8) | (2.5; 298.7) |
| < 36 months | 48 (43.2%) | 44 (36.7%) | 68 (48.9%) | 56 (40.3%) | 160 (43.2%) |
| ≥ 36 months | 63 (56.8%) | 76 (63.3%) | 71 (51.1%) | 83 (59.7%) | 210 (56.8%) |
| Time from end of last prior therapy to randomization/first dose (months) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 9.63 (14.696) | 9.21 (13.184) | 15.43 (18.620) | 16.49 (20.305) | 11.67 (16.082) |
| Median | 3.50 | 3.10 | 8.25 | 7.03 | 4.70 |
| Range | (0.7; 115.4) | (0.5; 62.5) | (0.4; 91.1) | (0.7; 111.2) | (0.4; 115.4) |
| Type of histology | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Blastoid | 17 (15.3%) | 11 (9.2%) | 16 (11.5%) | 17 (12.2%) | 44 (11.9%) |
| Non-blastoid | 94 (84.7%) | 109 (90.8%) | 123 (88.5%) | 122 (87.8%) | 326 (88.1%) |
| Diffuse | - | 62 (51.7%) | 56 (40.3%) | 59 (42.4%) | - |
| Nodular | - | 29 (24.2%) | 38 (27.3%) | 40 (28.8%) | - |
| Other | - | 18 (15.0%) | 9 (6.5%) | 5 (3.6%) | - |
| Unknown | - | 0 | 20 (14.4%) | 18 (12.9%) | - |
| Stage of MCL at study entry | | | | | |
| N | - | 120 | 139 | 139 | 259 |
| I-III | | | | | |
| I | - | 2 (1.7%) | 3 (2.2%) | 2 (1.4%) | 5 (1.9%) |
| II | - | 9 (7.5%) | 7 (5.0%) | 5 (3.6%) | 16 (6.2%) |
| III | - | 16 (13.3%) | 17 (12.2%) | 14 (10.1%) | 33 (12.7%) |
| IV | - | 93 (77.5%) | 112 (80.6%) | 118 (84.9%) | 205 (79.2%) |
| Simplified MIPI score | | | | | |
| N | 111 | 118 | 139 | 139 | 368 |
| Low risk (0-3) | 15 (13.5%) | 28 (23.7%) | 44 (31.7%) | 42 (30.2%) | 87 (23.6%) |
| Intermediate risk (4-5) | 42 (37.8%) | 57 (48.3%) | 65 (46.8%) | 68 (48.9%) | 164 (44.6%) |
| High risk (6-11) | 54 (48.6%) | 33 (28.0%) | 30 (21.6%) | 29 (20.9%) | 117 (31.8%) |
| Lines of prior therapy | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 2.9 (1.41) | 2.7 (1.27) | 2.1 (1.37) | 2.2 (1.33) | 2.5 (1.38) |
| Median | 3.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| Range | (1; 5) | (1; 8) | (1; 9) | (1; 9) | (1; 9) |
| < 3 | 50 (45.0%) | 63 (52.5%) | 95 (68.3%) | 91 (65.5%) | 208 (56.2%) |
| ≥ 3 | 61 (55.0%) | 57 (47.5%) | 44 (31.7%) | 48 (34.5%) | 162 (43.8%) |
| Prior bortezomib exposure | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Yes | 48 (43.2%) | 120 (100.0%) | 30 (21.6%) | 20 (14.4%) | 198 (53.5%) |
| No | 63 (56.8%) | 0 | 109 (78.4%) | 119 (85.6%) | 172 (46.5%) |
| Prior radiotherapy | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Yes | 28 (25.2%) | 28 (23.3%) | 26 (18.7%) | 26 (18.7%) | 82 (22.2%) |
| No | 83 (74.8%) | 92 (76.7%) | 113 (81.3%) | 113 (81.3%) | 288 (77.8%) |
| Types of treatment indication | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Relapsed disease [a] | 53 (47.7%) | 55 (45.8%) | 103 (74.1%) | 94 (67.6%) | 211 (57.0%) |
| Refractory disease [b] | 50 (45.0%) | 65 (54.2%) | 36 (25.9%) | 45 (32.4%) | 151 (40.8%) |
| Unknown | 8 (7.2%) | 0 | 0 | 0 | 8 (2.2%) |
| Tumor bulk (largest diameter) | | | | | |
| N | 111 | 119 | 138 | 139 | 368 |
| < 5 cm | 68 (61.3%) | 56 (47.1%) | 64 (46.4%) | 66 (47.5%) | 188 (51.1%) |
| ≥ 5 cm | 43 (38.7%) | 63 (52.9%) | 74 (53.6%) | 73 (52.5%) | 180 (48.9%) |
| ≥ 10 cm | 9 (8.1%) | 17 (14.3%) | 22 (15.9%) | 26 (18.7%) | 48 (13.0%) |

表 2.7.4-11 ベースラインの疾患の特性：
1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合（続き）

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Extra nodal disease | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Yes | 60 (54.1%) | 72 (60.0%) | 83 (59.7%) | 84 (60.4%) | 215 (58.1%) |
| No | 51 (45.9%) | 48 (40.0%) | 56 (40.3%) | 55 (39.6%) | 155 (41.9%) |
| Bone marrow involvement [c] | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Yes | 54 (48.6%) | 50 (41.7%) | 66 (47.5%) | 84 (60.4%) | 170 (45.9%) |
| No | 57 (51.4%) | 70 (58.3%) | 73 (52.5%) | 55 (39.6%) | 200 (54.1%) |
| B-symptoms | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Yes | 29 (26.1%) | 18 (15.0%) | 33 (23.7%) | 38 (27.3%) | 80 (21.6%) |
| No | 76 (68.5%) | - | - | - | - |
| Unknown | 6 (5.4%) | - | - | - | - |
| Other MCL-related symptoms | | | | | |
| N | - | 120 | 139 | 139 | 259 |
| Yes | - | 55 (45.8%) | 65 (46.8%) | 56 (40.3%) | 120 (46.3%) |

Key: MCL = Mantle Cell Lymphoma; MIPI=Mantle cell lymphoma international prognostic index.
[a] Relapsed disease was defined as relapsed or disease progression after achieving at least partial response to the last line of therapy prior to study entry.
[b] Refractory disease was defined as failure to achieve at least partial response to the last therapy prior to study entry.
[c] Subjects with positive bone marrow aspirate or biopsy results at baseline.
Prior bortezomib exposure is presented per study design for PCYC-1104 and MCL2001.

[TSIDEM02.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsidem02.sas] 15SEP2015, 16:47
参照元：5.3.5.3.1 ISS TSIDEM02

### 2.7.4.1.4　被験者の内訳

#### (1) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験の被験者の内訳を表 2.7.4-12 に示す。安全性解析対象集団 16 例のうち，データカットオフまでに投与を中止した被験者は 5 例（31.3%）であり，残り 11 例（68.8%）は投与を継続していた。中止理由は進行（4 例，25.0%）及び有害事象（1 例，6.3%）であった。

表 2.7.4-12 被験者の内訳：MCL2002 試験

| | Ibrutinib |
|---|---|
| All Subjects Obtained Informed Consent | 19 |
| Screen Failure | 3 |
| All Treated Population | 16 |
| Response Evaluable Population | 16 (100.0%) |
| Pharmacokinetic Analysis Population | 16 (100.0%) |
| Ongoing at date of cut-off | 11 (68.8%) |
| Treatment Discontinuation | 5 (31.3%) |
| Reason for Treatment Discontinuation | |
| ADVERSE EVENT | 1 (6.3%) |
| PROGRESSIVE DISEASE | 4 (25.0%) |
| Study Discontinuation | 5 (31.3%) |
| Reason for Study Discontinuation | |
| DEATH | 5 (31.3%) |

Note: Percentages calculated with all treated population as denominator.

[TSIDS01.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsids01.sas] 24AUG2015, 15:42
参照元：5.3.5.2.1 MCL2002 試験 CSR Table 4

### (2) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験の主要な安全性解析対象集団の被験者の内訳及び試験中止理由をそれぞれ表 2.7.4-13 及び表 2.7.4-14 に示す。海外 3 試験併合（370 例）でイブルチニブの投与を中止した被験者は 220 例（59.5%）であり，残り 150 例（40.5%）は投与を継続していた。主なイブルチニブの投与中止理由は，疾患進行又は再発（157 例，42.4%）であった。なお，MCL3001 試験では，テムシロリムス群（15 例，10.8%）と比較してイブルチニブ群（65 例，46.8%）で，投与を継続していた被験者が多かった。

表 2.7.4-13 被験者の内訳：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 | | Pooled Ibrutinib |
|---|---|---|---|---|---|
| | | | Ibrutinib | Temsirolimus | |
| Analysis set: safety population | 111 | 120 | 139 | 139 | 370 |
| Still on treatment | 46 (41.4%) | 39 (32.5%) | 65 (46.8%) | 15 (10.8%) | 150 (40.5%) |
| Discontinued treatment | 65 (58.6%) | 81 (67.5%) | 74 (53.2%) | 124 (89.2%) | 220 (59.5%) |
| Reason for discontinuation | | | | | |
| Progression disease or relapse | 49 (44.1%) | 53 (44.2%) | 55 (39.6%) | 58 (41.7%) | 157 (42.4%) |
| Adverse event | 9 (8.1%) | 8 (6.7%) | 9 (6.5%) | 36 (25.9%) | 26 (7.0%) |
| Death | 0 | 8 (6.7%) | 6 (4.3%) | 8 (5.8%) | 14 (3.8%) |
| Investigator or sponsor decision | 3 (2.7%) | 3 (2.5%) | 0 | 6 (4.3%) | 6 (1.6%) |
| Subject refuses further treatment | 4 (3.6%) | 9 (7.5%) | 4 (2.9%) | 16 (11.5%) | 17 (4.6%) |

Note: Percentages calculated with the number of subjects in safety population as denominator.

[TSIDS01.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsids01.sas] 15SEP2015, 15:00
参照元：5.3.5.3.1 ISS TSIDS01

表 2.7.4-14 試験中止理由：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 | | Pooled Ibrutinib |
|---|---|---|---|---|---|
| | | | Ibrutinib | Temsirolimus | |
| Analysis set: safety population | 111 | 120 | 139 | 139 | 370 |
| In treatment phase | 46 (41.4%) | 39 (32.5%) | 65 (46.8%) | 15 (10.8%) | 150 (40.5%) |
| In follow-up phase | 14 (12.6%) | 26 (21.7%) | 8 (5.8%) | 48 (34.5%) | 48 (13.0%) |
| Discontinued study | 51 (45.9%) | 55 (45.8%) | 66 (47.5%) | 76 (54.7%) | 172 (46.5%) |
| Reason for discontinuation | | | | | |
| Death | 41 (36.9%) | 44 (36.7%) | 59 (42.4%) | 62 (44.6%) | 144 (38.9%) |
| Lost to follow-up | 2 (1.8%) | 1 (0.8%) | 1 (0.7%) | 2 (1.4%) | 4 (1.1%) |
| Withdrawal of consent | 8 (7.2%) | 10 (8.3%) | 6 (4.3%) | 12 (8.6%) | 24 (6.5%) |

Note: Percentages calculated with the number of subjects in safety population as denominator.

[TSIDS02.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsids02.sas] 15SEP2015, 14:59
参照元：5.3.5.3.1 ISS TSIDS02

## 2.7.4.2 有害事象

### 2.7.4.2.1 有害事象の解析

評価資料の各試験で認められたすべての有害事象は，2.7.6 項又は各試験の CSR で各試験別に示す。1104 試験及び MCL2001 試験と比較して MCL3001 試験のイブルチニブ群で曝露期間が長かったが，本申請では曝露期間による有害事象の発現割合の調整はしていない。

### (1) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で認められた有害事象の概要を表 2.7.4-15 に示す。安全性解析対象集団（16 例）で，すべての被験者に有害事象が発現した。Grade 3 以上の有害事象は 8 例（50.0%）に発現した。死亡を含む重篤な有害事象は 5 例（31.3%），死亡は 3 例（18.8%）に発現した。有害事象により，2 例（12.5%）がイブルチニブの投与を中止し，2 例（12.5%）がイブルチニブを減量した。

表 2.7.4-15 有害事象の概要：MCL2002 試験

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Number of Subjects with TEAE | 16 (100.0%) |
| Number of Subjects with TEAE of Toxicity Grade 3 or Higher | 8 (50.0%) |
| Number of Subjects with Drug Related TEAE | 15 (93.8%) |
| Number of Subjects with Serious TEAE | 5 (31.3%) |
| Number of Subjects with Drug Related Serious TEAE | 1 (6.3%) |
| Number of Subjects with TEAE Leading to Death | 3 (18.8%) |
| Number of Subjects with TEAE Leading to Drug Withdrawn | 2 (12.5%) |
| Number of Subjects with TEAE Leading to Dose Reduction | 2 (12.5%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Drug related AE is defined as an event related to study agent (relationship to study agent is possible, probable or very likely).

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 14

### (2) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験で認められた有害事象の概要を表 2.7.4-16 に示す。海外 3 試験併合（370 例）で，ほぼすべての被験者（98.4%，364 例）に有害事象が発現した。Grade 3 以上の有害事象は 71.6%（265 例）に発現した。死亡を含む重篤な有害事象は 50.8%（188 例）に，死亡は 12.2%（45 例）に発現した。有害事象により，13.0%（48 例）がイブルチニブの投与を中止し，7.6%（28 例）がイブルチニブを減量した。

MCL3001 試験では，イブルチニブ群はテムシロリムス群よりも曝露期間が長かったにもかかわらず（曝露期間の中央値：イブルチニブ群 14.39 カ月，テムシロリムス群 3.02 カ月）（表 2.7.4-6），Grade 3 以上の有害事象，治験薬との関連性がある有害事象，重篤な有害事象，治験薬との関連性がある重篤な有害事象，投与中止に至った有害事象及び減量に至った有害事象の発現割合は，テムシロリムス群と比較してイブルチニブ群で低かった。テムシロリムス群と比較して，イブルチニブ群の安全性プロファイルは許容可能であった。総じて，イブルチニブ群の安全性プロファイルは既知のもと同様であり，新たな安全性シグナルは検出されなかった。

表 2.7.4-16 有害事象の概要：
1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Analysis Set: Safety Population | 111 | 120 | 139 | 139 | 370 |
| Any TEAE | 111 (100.0%) | 115 (95.8%) | 138 (99.3%) | 138 (99.3%) | 364 (98.4%) |
| Grade >= 3 | 84 (75.7%) | 87 (72.5%) | 94 (67.6%) | 121 (87.1%) | 265 (71.6%) |
| Drug related [a] | 98 (88.3%) | 95 (79.2%) | 115 (82.7%) | 133 (95.7%) | 308 (83.2%) |
| Grade >= 3 | 49 (44.1%) | 52 (43.3%) | 55 (39.6%) | 109 (78.4%) | 156 (42.2%) |
| Any TESAE | 62 (55.9%) | 59 (49.2%) | 67 (48.2%) | 80 (57.6%) | 188 (50.8%) |
| Grade >= 3 | 55 (49.5%) | 53 (44.2%) | 63 (45.3%) | 68 (48.9%) | 171 (46.2%) |
| Drug related [a] | 28 (25.2%) | 25 (20.8%) | 29 (20.9%) | 53 (38.1%) | 82 (22.2%) |
| TEAE leading to treatment discontinuation | 10 (9.0%) | 20 (16.7%) | 18 (12.9%) | 41 (29.5%) | 48 (13.0%) |
| TEAE leading to treatment dose reduction | 15 (13.5%) | 8 (6.7%) | 5 (3.6%) | 60 (43.2%) | 28 (7.6%) |
| TEAE with outcome death | 16 (14.4%) | 14 (11.7%) | 15 (10.8%) | 11 (7.9%) | 45 (12.2%) |
| Deaths within 30 days after last dose of study treatment [b] | 16 (14.4%) | 23 (19.2%) | 24 (17.3%) | 15 (10.8%) | 63 (17.0%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE01.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae01.sas] 26OCT2015, 14:30
参照元：5.3.5.3.1 ISS TSFAE01

### 1) MCL3001 試験の曝露期間により調整した有害事象の発現率の概要

MCL3001 試験では投与群により曝露期間に差が認められたため，有害事象の発現割合を曝露期間により調整するために，曝露期間で標準化し，100 人月あたりの有害事象の発現率を算出した。曝露期間は，投与開始日から 1) 当該有害事象を最初に発現した日，2) 当該有害事象を発現していない被験者の総曝露期間のいずれかを月数により定義した。有害事象の発現率の解析では，同一被験者が同一有害事象を複数回発現しても 1 例として集計した。曝露期間により調整した有害事象の発現率（exposure-adjusted incidence rate，以下 EAIR）は，100 人月あたりの有害事象の発現率で示し，「最初の有害事象が発現するまでの速さ（rate until the first event occurs）」と解釈した。MCL3001 試験の EAIR の詳細な解析方法は CSR の Appendix 9.1 に記載した（【5.3.5.1.1 CSR Section 7.2.3 p. 83】）。EAIR の要約を表 2.7.4-17 に示す。

すべての有害事象，Grade 3 以上の有害事象，治験薬との関連性がある有害事象，重篤な有害事象，治験薬の投与中止に至った有害事象及び死亡の EAIR は，いずれもテムシロリムス群と比較してイブルチニブ群で低かった。

表 2.7.4-17 曝露期間により調整した有害事象の発現率：MCL3001 試験

| | Ibrutinib | | | Temsirolimus | | |
|---|---|---|---|---|---|---|
| | n | 100 Patient-months at Risk[a] | EAIR[b] | n | 100 Patient-months at Risk[a] | EAIR[b] |
| Analysis set: safety | 139 | | | 139 | | |
| Any TEAE | 138 | 2.0 | 70.018 | 138 | 0.4 | 358.700 |
| Grade >= 3 | 94 | 11.3 | 8.309 | 121 | 2.2 | 54.977 |
| Drug related | 115 | 4.4 | 26.316 | 133 | 0.5 | 242.116 |
| Any TESAE | 67 | 14.5 | 4.613 | 80 | 6.5 | 12.250 |
| Grade >= 3 | 63 | 15.0 | 4.195 | 68 | 7.0 | 9.661 |
| Drug related | 29 | 15.9 | 1.820 | 53 | 7.3 | 7.272 |
| TEAE leading to treatment discontinuation | 18 | 18.5 | 0.975 | 41 | 8.4 | 4.896 |
| TEAE with outcome death | 15 | 18.5 | 0.811 | 11 | 8.5 | 1.299 |

Key: EAIR = exposure-adjusted incidence rate; TEAE= treatment-emergent adverse event; TESAE= treatment-emergent serious adverse event

[a] Patient-months at risk is the sum of the exposure times at the occurrence of the first TEAE for each subject. A patient's duration of exposure is given either by the time when the event has occurred (non-censored data), or by the total duration of treatment if the patient does not show the adverse event in question (censored data).

[b] EAIR represents the number of subjects with the event divided by 100 patient-months at risk for that event. If a patient has multiple occurrences of an event, the patient is counted only once in the numerator.

[TEAIR01.rtf] [JNJ-54179060\PCI32765MCL3001\DBR_CSR\RE_CSR\teair01.sas] 02JUL2015, 17:01

参照元：5.3.5.1.1 MCL3001 試験 CSR Table 27

### 2.7.4.2.1.1 比較的よく見られる有害事象

#### (1) すべての有害事象

##### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で発現割合が 10%以上であった有害事象を表 2.7.4-18 に，すべての有害事象を表 2.7.4-付録-3 に示す。安全性解析対象集団 16 例中 7 例以上に認められた SOC は，胃腸障害，感染症および寄生虫症，皮膚および皮下組織障害（各 10 例，62.5%），一般・全身障害および投与部位の状態（9 例，56.3%），臨床検査（8 例，50.0%）並びに血液およびリンパ系障害（7 例，43.8%）であった。4 例以上に認められた PT は，下痢及び口内炎（各 6 例，37.5%），血小板数減少（5 例，31.3%）並びに貧血（4 例，25.0%）であった。Grade 3 以上の有害事象については，2.7.4.2.1.1(2)a)項に記載する。

表 2.7.4-18 10%以上に認められた有害事象：MCL2002 試験

| | Ibrutinib | |
|---|---|---|
| | All Grade | Grade 3 or Higher |
| Analysis Set: All Treated Population | 16 | |
| Total Number of Subjects with TEAE | 16 (100.0%) | 8 (50.0%) |
| MedDRA System organ class/Preferred term | | |
| 胃腸障害 | 10 (62.5%) | 1 (6.3%) |
| 下痢 | 6 (37.5%) | 0 |
| 口内炎 | 6 (37.5%) | 1 (6.3%) |
| 便秘 | 3 (18.8%) | 0 |
| 消化不良 | 2 (12.5%) | 0 |
| 悪心 | 2 (12.5%) | 0 |
| 感染症および寄生虫症 | 10 (62.5%) | 1 (6.3%) |
| 上気道感染 | 3 (18.8%) | 0 |
| 鼻咽頭炎 | 2 (12.5%) | 0 |
| 皮膚感染 | 2 (12.5%) | 0 |
| 皮膚および皮下組織障害 | 10 (62.5%) | 0 |
| 皮膚乾燥 | 3 (18.8%) | 0 |
| 一般・全身障害および投与部位の状態 | 9 (56.3%) | 3 (18.8%) |
| 疾患進行 | 3 (18.8%) | 3 (18.8%) |
| 疲労 | 3 (18.8%) | 0 |
| 倦怠感 | 2 (12.5%) | 0 |
| 臨床検査 | 8 (50.0%) | 1 (6.3%) |
| 血小板数減少 | 5 (31.3%) | 0 |
| アラニンアミノトランスフェラーゼ増加 | 2 (12.5%) | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 2 (12.5%) | 0 |
| 血中ビリルビン増加 | 2 (12.5%) | 0 |
| 血液およびリンパ系障害 | 7 (43.8%) | 2 (12.5%) |
| 貧血 | 4 (25.0%) | 1 (6.3%) |
| 血小板減少症 | 3 (18.8%) | 0 |
| 白血球増加症 | 2 (12.5%) | 1 (6.3%) |
| リンパ球増加症 | 2 (12.5%) | 0 |
| 代謝および栄養障害 | 5 (31.3%) | 2 (12.5%) |
| 食欲減退 | 3 (18.8%) | 0 |
| 低カリウム血症 | 2 (12.5%) | 1 (6.3%) |
| 傷害、中毒および処置合併症 | 4 (25.0%) | 0 |
| 挫傷 | 2 (12.5%) | 0 |
| 裂傷 | 2 (12.5%) | 0 |
| 神経系障害 | 4 (25.0%) | 0 |
| 頭痛 | 2 (12.5%) | 0 |
| 末梢性ニューロパチー | 2 (12.5%) | 0 |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0

[TSFAE03.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsfae03.sas] 21AUG2015, 12:30

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 15

### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（370 例）で 10%以上に認められた有害事象を表 2.7.4-19 に示す。また，海外 3 試験併合で 10%以上に認められた有害事象について，1104 試験及び MCL2001 試験並びに MCL3001 試験のそれぞれの集計を表 2.7.4-付録-4 及び表 2.7.4-付録-5 に，1104 試験及び MCL2001 試験，MCL3001 試験並びに海外 3 試験併合のすべての有害事象を表 2.7.4-付録-6，表 2.7.4-付録-7 及び表 2.7.4-付録-8 に示す。

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験のイブルチニブ群のいずれにおいても 50%以上に発現した SOC は，感染症および寄生虫症，胃腸障害，一般・全身障害および

投与部位の状態，並びに呼吸器，胸郭および縦隔障害であった。海外 3 試験併合（370 例）の 20%以上に認められた PT は，下痢（39.5%，146 例），疲労（34.9%，129 例），咳嗽（21.9%，81 例），悪心（21.6%，80 例）並びに末梢性浮腫及び血小板減少症（各 20.0%，74 例）であった。また，MCL3001 試験で，テムシロリムス群と比較してイブルチニブ群で 10%以上発現割合が高かった PT は筋痙縮であった。Grade 3 以上の有害事象については，2.7.4.2.1.1(2)b)項に記載する。

**表 2.7.4-19 10%以上に認められた有害事象：海外 3 試験併合**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 370 | |
| Subjects with any TEAE | 364 (98.4%) | 265 (71.6%) |
| System organ class | | |
| Preferred term | | |
| 感染症および寄生虫症 | 263 (71.1%) | 87 (23.5%) |
| 上気道感染 | 73 (19.7%) | 3 (0.8%) |
| 肺炎 | 44 (11.9%) | 33 (8.9%) |
| 副鼻腔炎 | 39 (10.5%) | 1 (0.3%) |
| 尿路感染 | 38 (10.3%) | 6 (1.6%) |
| 胃腸障害 | 255 (68.9%) | 39 (10.5%) |
| 下痢 | 146 (39.5%) | 13 (3.5%) |
| 悪心 | 80 (21.6%) | 1 (0.3%) |
| 嘔吐 | 62 (16.8%) | 1 (0.3%) |
| 便秘 | 57 (15.4%) | 0 |
| 腹痛 | 42 (11.4%) | 13 (3.5%) |
| 一般・全身障害および投与部位の状態 | 239 (64.6%) | 38 (10.3%) |
| 疲労 | 129 (34.9%) | 16 (4.3%) |
| 末梢性浮腫 | 74 (20.0%) | 6 (1.6%) |
| 発熱 | 68 (18.4%) | 3 (0.8%) |
| 呼吸器、胸郭および縦隔障害 | 200 (54.1%) | 35 (9.5%) |
| 咳嗽 | 81 (21.9%) | 0 |
| 呼吸困難 | 69 (18.6%) | 12 (3.2%) |
| 皮膚および皮下組織障害 | 194 (52.4%) | 10 (2.7%) |
| 発疹 | 57 (15.4%) | 4 (1.1%) |
| 筋骨格系および結合組織障害 | 173 (46.8%) | 20 (5.4%) |
| 筋痙縮 | 67 (18.1%) | 0 |
| 背部痛 | 44 (11.9%) | 6 (1.6%) |
| 関節痛 | 38 (10.3%) | 2 (0.5%) |
| 血液およびリンパ系障害 | 169 (45.7%) | 109 (29.5%) |
| 血小板減少症 | 74 (20.0%) | 41 (11.1%) |
| 好中球減少症 | 70 (18.9%) | 61 (16.5%) |
| 貧血 | 63 (17.0%) | 30 (8.1%) |
| 代謝および栄養障害 | 150 (40.5%) | 52 (14.1%) |
| 食欲減退 | 62 (16.8%) | 3 (0.8%) |
| 神経系障害 | 121 (32.7%) | 9 (2.4%) |
| 頭痛 | 37 (10.0%) | 0 |
| 傷害、中毒および処置合併症 | 101 (27.3%) | 13 (3.5%) |
| 挫傷 | 46 (12.4%) | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE03APART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae03a.sas]
15SEP2015, 14:10

参照元：5.3.5.3.1 ISS TSFAE03APART3OF3

### (2) Grade 3 以上の有害事象

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で認められた Grade 3 以上の有害事象を表 2.7.4-付録-3 に示す。安全性解析対象集団 16 例のうち，Grade 3 以上の有害事象は 8 例（50.0%）に発現した。発現割合が最も高かった Grade 3 以上の有害事象は疾患進行（3 例，18.8%）であり，その他の Grade 3 以上の有害事象はいずれも各 1 例に発現した。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合で認められた Grade 3 以上の有害事象を表 2.7.4-付録-8 に示す。海外 3 試験併合（370 例）で，Grade 3 以上の有害事象は 265 例（71.6%）に発現し，5%以上に発現した有害事象は好中球減少症（16.5%，61 例），血小板減少症（11.1%，41 例），肺炎（8.9%，33 例），貧血（8.1%，30 例）であった。肺炎等の感染症については 2.7.4.2.1.5(3)b)項に，血球減少症（好中球減少症，貧血，血小板減少症）については 2.7.4.2.1.5(4)b)項に記載する。

1104 試験，MCL2001 試験及び MCL3001 試験で 10%以上に発現した有害事象をそれぞれ表 2.7.4-付録-9，表 2.7.4-付録-10 及び表 2.7.4-付録-11 に示す。MCL3001 試験で，Grade 3 以上の有害事象の発現割合は，テムシロリムス群（87.1%，139 例中 121 例）と比較してイブルチニブ群（67.6%，139 例中 94 例）で低く，いずれかの投与群で 10%以上に発現した Grade 3 以上の有害事象は，血小板減少症［イブルチニブ群 9.4%（13 例）及びテムシロリムス群 42.4%（59 例），以降同順］，好中球減少症［12.9%（18 例）及び 16.5%（23 例）］，貧血［7.9%（11 例）及び 20.1%（28 例）］並びに血小板数減少［1.4%（2 例）及び 13.7%（19 例）］であった。

### (3) 治験薬との関連性がある有害事象

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で認められたイブルチニブとの関連性がある有害事象を表 2.7.4-付録-12 に示す。安全性解析対象集団 16 例中のうち，イブルチニブとの関連性がある有害事象は 15 例（93.8%）に発現した。3 例以上に認められたイブルチニブとの関連性がある有害事象は，下痢及び血小板数減少（各 5 例，31.3%），口内炎及び貧血（各 4 例，25.0%）並びに血小板減少症，疲労及び食欲減退（各 3 例，18.8%）であった。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

1104 試験及び MCL2001 試験，MCL3001 試験並びに海外 3 試験併合で認められた治験薬との関連性がある有害事象を表 2.7.4-付録 13，表 2.7.4-付録 14 及び表 2.7.4-付録 15 に示す。海外 3 試験併合（370 例）で，イブルチニブとの関連性がある有害事象は 308 例（83.2%）に発現した。10%以上に認められたイブルチニブとの関連性がある有害事象は，下痢（27.0%，100 例），疲労（21.1%，78 例），好中球減少症（15.7%，58 例），血小板減少症（13.8%，51 例），悪心及び筋痙縮（各 12.4%，46 例）並びに発疹（10.5%，39 例）であった。Grade 3 以上のイブルチニブとの関連性がある有害事象は 156 例（42.2%）に発現し，最も発現割合が高かった事象は好中球減少症（14.1%，52 例）であった。

MCL3001 試験で認められた治験薬との関連性がある有害事象の発現割合は，イブルチニブ群で 82.7%（139 例中 115 例），テムシロリムス群で 95.7%（139 例中 133 例）であった。いずれかの投与群で 5%以上に発現した治験薬との関連性がある有害事象のうち，イブルチニブ群と比較してテムシロリムス群で発現割合が高かった事象は多数（31 事象）あったが，テムシロリムス群と比較してイブルチニブ群で発現割合が高かった事象は筋痙縮及び帯状疱疹のみであった。

#### (4) 発現時期別の有害事象

##### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で認められた有害事象の発現時期別の集計を表 2.7.4-付録-16 に示す。各時期の有害事象の発現割合は，各時期の初日の解析対象被験者数を分母，当該時期に新たに有害事象が発現した被験者を分子として算出した。同一被験者に同一事象が発現した場合は一事象として集計した。有害事象の発現割合は，投与開始後の Day 1 から Day 90 では 100%（16 例），Day 181 から Day 270 では 55.6%（9 例中 5 例）であり経時的に減少した。個別の有害事象においても継続投与により発現割合が高くなる傾向は認められず，ほとんどの有害事象の発現割合は投与開始後の Day 1 から Day 90 又は Day 91 から Day 180 で最も高かった。

##### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合で 10%以上に認められた有害事象の発現時期別の集計を表 2.7.4-付録-17 に示す。各時期の有害事象の発現割合は，当該時期がイブルチニブ投与開始からイブルチニブ最終投与後 30 日又は治験中止のいずれか早い日までに該当する被験者数を分母，当該時期に有害事象が発現した又は以前の時期に発現した有害事象が当該時期に継続していた被験者数を分子として算出した。

海外 3 試験併合（370 例）の有害事象の発現割合は，投与開始後の Day 1 から Day 90 では 92.4%（370 例中 342 例），Day 91 から Day 180 では 91.9%（308 例中 283 例），Day 181 から Day 270 では 91.5%（247 例中 226 例），Day 271 から Day 365 では 92.3%（209 例中 193 例），Day 366 以上では 92.6%（175 例中 162 例）であり，継続投与により発現割合が高くなる傾向は認められなかった。個別の有害事象においても筋痙縮を除き，ほとんどの有害事象の発現割合は投与開始後の Day 1 から Day 90 で最も高く，継続投与により発現割合が高くなる傾向は認められなかった。筋痙縮の発現割合は，投与開始後の Day 1 から Day 90 では 7.0%（26 例），Day 91 から Day 180 では 13.0%（40 例），Day 181 から Day 270 では 17.8%（44 例），Day 271 から Day 365 では 20.1%（42 例），Day 366 以上では 21.7%（38 例）であり，継続投与により高くなる傾向が認められたが，重症度はいずれも Grade 1 又は 2 であり，イブルチニブの投与中止に至った事象はなかった。

### 2.7.4.2.1.2 死亡

#### (1) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で死亡に至った有害事象の一覧を表 2.7.4-20 に示す。

MCL2002 試験で 16 例のうち，3 例（18.8%）がイブルチニブ投与後に有害事象により死亡した。死亡に至った有害事象はいずれも疾患進行であり，イブルチニブとの関連性はなかった。

表 2.7.4-20 死亡に至った有害事象の一覧：MCL2002 試験

| Treatment | Subject ID | Age/ Sex | TEAE | Reported Term | MedDRA Preferred Term | Dose at Onset of AE (mg) | Start Date/ End Date | AE Start Day | Duration (Days) | SAE | Severity Grade | Concomitant or Additional Treatment Given | Outcome | Causality | Action Taken |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ibrutinib | 81000203 | 6[redacted]/M | Y | DISEASE PROGRESSION | 疾患進行 | | 2015-01-03/ | 116 | | Y | 5 | N | FATAL | NOT RELATED | NOT APPLICABLE |
| Ibrutinib | 81000401 | 8[redacted]/M | Y | DISEASE PROGRESSION | 疾患進行 | | 2015-04-03/ | 149 | | Y | 5 | N | FATAL | NOT RELATED | NOT APPLICABLE |
| Ibrutinib | 81000501 | 7[redacted]/M | Y | PROGRESSIVE DISEASE | 疾患進行 | | 2014-11-18/ | 91 | | Y | 5 | N | FATAL | NOT RELATED | NOT APPLICABLE |

Key: TEAE=Treatment-Emergent Adverse Event, SAE=Serious Adverse Event
Note: Adverse Events are coded using MedDRA 18.0
Note: CTCAE version 4.03 was used.

[LSFAE04.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\lsfae04.sas] 21AUG2015, 12:29

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 17

### (2) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験で死亡に至った有害事象の集計を表 2.7.4-21 に示す。また，各試験で発現したすべての死亡に至った有害事象の一覧を表 2.7.4-付録-18 に示す。

海外 3 試験併合（370 例）で，1104 試験 16 例，MCL2001 試験 14 例，MCL3001 試験のイブルチニブ群 15 例の計 45 例（12.2%）がイブルチニブ投与後に有害事象により死亡した。海外 3 試験併合で 2 例以上に認められた死亡に至った有害事象は，マントル細胞リンパ腫（疾患進行，7 例，1.9%），肺炎，敗血症及び呼吸不全（各 5 例，1.4%）並びに敗血症性ショック，多臓器不全，心停止及び腎不全（各 2 例，0.5%）であった。

MCL3001 試験で死亡に至った有害事象の発現割合は，イブルチニブ群で 10.8%（139 例中 15 例），テムシロリムス群で 7.9%（139 例中 11 例）であった。

表 2.7.4-21 死亡に至った有害事象：
1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Analysis Set: Safety Population | 111 | 120 | 139 | 139 | 370 |
| Subjects with any TEAE leading to death | 16 (14.4%) | 14 (11.7%) | 15 (10.8%) | 11 (7.9%) | 45 (12.2%) |
| System organ class<br>Preferred term | | | | | |
| 感染症および寄生虫症 | 3 (2.7%) | 5 (4.2%) | 5 (3.6%) | 3 (2.2%) | 13 (3.5%) |
| 肺炎 | 1 (0.9%) | 4 (3.3%) | 0 | 1 (0.7%) | 5 (1.4%) |
| 敗血症 | 1 (0.9%) | 1 (0.8%) | 3 (2.2%) | 1 (0.7%) | 5 (1.4%) |
| 敗血症性ショック | 0 | 0 | 2 (1.4%) | 1 (0.7%) | 2 (0.5%) |
| ニューモシスチス・イロベチイ肺炎 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 8 (7.2%) | 0 | 1 (0.7%) | 0 | 9 (2.4%) |
| マントル細胞リンパ腫 | 7 (6.3%) | 0 | 0 | 0 | 7 (1.9%) |
| 悪性胸水 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| 移行上皮癌 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 呼吸器、胸郭および縦隔障害 | 2 (1.8%) | 3 (2.5%) | 3 (2.2%) | 1 (0.7%) | 8 (2.2%) |
| 呼吸不全 | 1 (0.9%) | 3 (2.5%) | 1 (0.7%) | 1 (0.7%) | 5 (1.4%) |
| 呼吸困難 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| 肺塞栓症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 肺水腫 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 一般・全身障害および投与部位の状態 | 0 | 2 (1.7%) | 2 (1.4%) | 2 (1.4%) | 4 (1.1%) |
| 多臓器不全 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 無力症 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 死亡 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 疲労 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 疼痛 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 全身健康状態低下 | 0 | 0 | 0 | 2 (1.4%) | 0 |
| 心臓障害 | 1 (0.9%) | 2 (1.7%) | 0 | 3 (2.2%) | 3 (0.8%) |
| 心停止 | 1 (0.9%) | 1 (0.8%) | 0 | 1 (0.7%) | 2 (0.5%) |
| 心血管不全 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 急性心不全 | 0 | 0 | 0 | 1 (0.7%) | 0 |
| 心肺不全 | 0 | 0 | 0 | 1 (0.7%) | 0 |
| 腎および尿路障害 | 1 (0.9%) | 0 | 2 (1.4%) | 1 (0.7%) | 3 (0.8%) |
| 腎不全 | 0 | 0 | 2 (1.4%) | 1 (0.7%) | 2 (0.5%) |
| 急性腎不全 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| 傷害、中毒および処置合併症 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 脾破裂 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 硬膜下血腫 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 血液およびリンパ系障害 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 発熱性好中球減少症 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 胃腸障害 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| 麻痺性イレウス | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| 神経系障害 | 0 | 1 (0.8%) | 0 | 1 (0.7%) | 1 (0.3%) |
| 脳症 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 虚血性脳卒中 | 0 | 0 | 0 | 1 (0.7%) | 0 |
| 血管障害 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 循環虚脱 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE10.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae10.sas] 15SEP2015, 14:11
参照元：5.3.5.3.1 ISS TSFAE10

#### 2.7.4.2.1.3 その他の重篤な有害事象

##### (1) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で認められた死亡及びその他の重篤な有害事象の一覧を表 2.7.4-22 に，集計を表 2.7.4-23 に示す。

安全性解析対象集団 16 例のうち，その他の重篤な有害事象は 2 例に計 3 件（被験者番号 81000204：高尿酸血症及び白血球増加症各 1 件，被験者番号 81001001：敗血症 1 件）発現した。このうちイブルチニブとの関連性がある重篤な有害事象は敗血症のみであった。被験者番号 81000204 に発現した重篤な有害事象は，疾患進行に関連するものであるため，いずれもイブルチニブとの因果関係は「関連なし」と判断された。

## 表 2.7.4-22 死亡及びその他の重篤な有害事象の一覧：MCL2002 試験

| Treatment | Subject ID | Age/ Sex | TEAE | Reported Term | MedDRA Preferred Term | Dose at Onset of AE (mg) | Start Date/ End Date | AE Start Day | Duration (Days) | SAE | Severity Grade | Concomitant or Additional Treatment Given | Outcome | Causality | Action Taken |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ibrutinib | 81000203 | 6[redacted]/M | Y | DISEASE PROGRESSION | 疾患進行 | | 2015-01-03/ | 116 | | Y | 5 | N | FATAL | NOT RELATED | NOT APPLICABLE |
| Ibrutinib | 81000204 | 6[redacted]/M | Y | HYPERURICEMIA | 高尿酸血症 | 560 | 2015-03-19/2015-03-20 | 143 | 2 | Y | 4 | Y | RECOVERED/ RESOLVED | NOT RELATED | DRUG WITHDRAWN |
| | | | Y | LEUKOCYTOSIS | 白血球増加症 | 560 | 2015-03-19/ | 143 | | Y | 3 | Y | NOT RECOVERED/ NOT RESOLVED | NOT RELATED | DRUG WITHDRAWN |
| Ibrutinib | 81000401 | 8[redacted]/M | Y | DISEASE PROGRESSION | 疾患進行 | | 2015-04-03/ | 149 | | Y | 5 | N | FATAL | NOT RELATED | NOT APPLICABLE |
| Ibrutinib | 81000501 | 7[redacted]/M | Y | PROGRESSIVE DISEASE | 疾患進行 | | 2014-11-18/ | 91 | | Y | 5 | N | FATAL | NOT RELATED | NOT APPLICABLE |
| Ibrutinib | 81001001 | 8[redacted]/F | Y | SEPSIS | 敗血症 | 0 | 2015-03-09/ | 138 | | Y | 4 | Y | RECOVERING /RESOLVING | POSSIBLE | DRUG WITHDRAWN |

Key: TEAE=Treatment-Emergent Adverse Event, SAE=Serious Adverse Event
Note: Adverse Events are coded using MedDRA 18.0
Note: CTCAE version 4.03 was used.

[LSFAE03.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\lsfae03.sas] 21AUG2015, 12:29

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 19

表 2.7.4-23 死亡及びその他の重篤な有害事象：MCL2002 試験

| | Ibrutinib | |
|---|---|---|
| | All Grade | Grade 3 or Higher |
| Analysis Set: All Treated Population | 16 | |
| Total Number of Subjects with Serious TEAE | 5 (31.3%) | 5 (31.3%) |
| MedDRA System organ class/Preferred term | | |
| 一般・全身障害および投与部位の状態 | 3 (18.8%) | 3 (18.8%) |
| 疾患進行 | 3 (18.8%) | 3 (18.8%) |
| 血液およびリンパ系障害 | 1 (6.3%) | 1 (6.3%) |
| 白血球増加症 | 1 (6.3%) | 1 (6.3%) |
| 感染症および寄生虫症 | 1 (6.3%) | 1 (6.3%) |
| 敗血症 | 1 (6.3%) | 1 (6.3%) |
| 代謝および栄養障害 | 1 (6.3%) | 1 (6.3%) |
| 高尿酸血症 | 1 (6.3%) | 1 (6.3%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0

[TSFAE06.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsfae06.sas] 21AUG2015, 12:30
参照元：5.3.5.2.1 MCL2002 試験 CSR Table 18

### (2) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合で 2%以上に認められた治験薬投与後に発現した死亡及びその他の重篤な有害事象について，海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験の集計を表 2.7.4-24 に示す。また，すべての死亡及びその他の重篤な有害事象を表 2.7.4-付録-19，表 2.7.4-付録-20 及び表 2.7.4-付録-21 に，各試験で発現したすべての死亡及びその他の重篤な有害事象一覧を表 2.7.4-付録-22 に示す。

海外 3 試験併合（370 例）で 188 例（50.8%）に死亡及びその他の重篤な有害事象が発現し，2%以上に認められた事象は，肺炎（32 例，8.6%），心房細動（15 例，4.1%），呼吸困難（13 例，3.5%），発熱性好中球減少症（11 例，3.0%），腹痛（10 例，2.7%），敗血症（9 例，2.4%）並びに呼吸不全，発熱，マントル細胞リンパ腫及び急性腎不全（各 8 例，2.2%）であった。発現割合が最も高かった SOC は感染症および寄生虫症（76 例，20.5%）であった。なお，肺炎はイブルチニブとの関連性がある重篤な有害事象で最も多い事象であった。

MCL3001 試験では，イブルチニブ群はテムシロリムス群よりも曝露期間が長かったにもかかわらず（曝露期間の中央値：イブルチニブ群 14.39 カ月，テムシロリムス群 3.02 カ月）（表 2.7.4-6），死亡及びその他の重篤な有害事象の発現割合はイブルチニブ群で 48.2%（139 例中 67 例），テムシロリムス群で 57.6%（139 例中 80 例）であった。両群ともに最も多く認められた事象は肺炎［イブルチニブ群 8.6%（12 例），テムシロリムス群 6.5%（9 例）］であった。

表 2.7.4-24 2%以上に認められた死亡及びその他の重篤な有害事象：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | | MCL3001 Ibrutinib | | MCL3001 Temsirolimus | | Pooled Ibrutinib | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 111 | | 120 | | 139 | | 139 | | 370 | |
| Subjects with any serious TEAE | 62 (55.9%) | 55 (49.5%) | 59 (49.2%) | 53 (44.2%) | 67 (48.2%) | 63 (45.3%) | 80 (57.6%) | 68 (48.9%) | 188 (50.8%) | 171 (46.2%) |
| System organ class | | | | | | | | | | |
| Preferred term | | | | | | | | | | |
| 感染症および寄生虫症 | 22 (19.8%) | 21 (18.9%) | 29 (24.2%) | 27 (22.5%) | 25 (18.0%) | 23 (16.5%) | 40 (28.8%) | 35 (25.2%) | 76 (20.5%) | 71 (19.2%) |
| 肺炎 | 6 (5.4%) | 6 (5.4%) | 14 (11.7%) | 13 (10.8%) | 12 (8.6%) | 11 (7.9%) | 9 (6.5%) | 8 (5.8%) | 32 (8.6%) | 30 (8.1%) |
| 敗血症 | 2 (1.8%) | 2 (1.8%) | 3 (2.5%) | 3 (2.5%) | 4 (2.9%) | 4 (2.9%) | 5 (3.6%) | 5 (3.6%) | 9 (2.4%) | 9 (2.4%) |
| 呼吸器、胸郭および縦隔障害 | 5 (4.5%) | 5 (4.5%) | 12 (10.0%) | 7 (5.8%) | 18 (12.9%) | 12 (8.6%) | 14 (10.1%) | 11 (7.9%) | 35 (9.5%) | 24 (6.5%) |
| 呼吸困難 | 2 (1.8%) | 2 (1.8%) | 5 (4.2%) | 2 (1.7%) | 6 (4.3%) | 1 (0.7%) | 5 (3.6%) | 4 (2.9%) | 13 (3.5%) | 5 (1.4%) |
| 呼吸不全 | 2 (1.8%) | 2 (1.8%) | 4 (3.3%) | 4 (3.3%) | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) | 8 (2.2%) | 8 (2.2%) |
| 一般・全身障害および投与部位の状態 | 11 (9.9%) | 5 (4.5%) | 8 (6.7%) | 5 (4.2%) | 11 (7.9%) | 6 (4.3%) | 16 (11.5%) | 8 (5.8%) | 30 (8.1%) | 16 (4.3%) |
| 発熱 | 3 (2.7%) | 1 (0.9%) | 2 (1.7%) | 1 (0.8%) | 3 (2.2%) | 1 (0.7%) | 7 (5.0%) | 2 (1.4%) | 8 (2.2%) | 3 (0.8%) |
| 血液およびリンパ系障害 | 9 (8.1%) | 9 (8.1%) | 8 (6.7%) | 8 (6.7%) | 12 (8.6%) | 12 (8.6%) | 10 (7.2%) | 9 (6.5%) | 29 (7.8%) | 29 (7.8%) |
| 発熱性好中球減少症 | 3 (2.7%) | 3 (2.7%) | 6 (5.0%) | 6 (5.0%) | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) | 11 (3.0%) | 11 (3.0%) |
| 胃腸障害 | 8 (7.2%) | 7 (6.3%) | 8 (6.7%) | 4 (3.3%) | 10 (7.2%) | 8 (5.8%) | 13 (9.4%) | 10 (7.2%) | 26 (7.0%) | 19 (5.1%) |
| 腹痛 | 3 (2.7%) | 3 (2.7%) | 3 (2.5%) | 2 (1.7%) | 4 (2.9%) | 4 (2.9%) | 1 (0.7%) | 1 (0.7%) | 10 (2.7%) | 9 (2.4%) |
| 心臓障害 | 8 (7.2%) | 8 (7.2%) | 8 (6.7%) | 6 (5.0%) | 8 (5.8%) | 6 (4.3%) | 9 (6.5%) | 7 (5.0%) | 24 (6.5%) | 20 (5.4%) |
| 心房細動 | 5 (4.5%) | 5 (4.5%) | 5 (4.2%) | 3 (2.5%) | 5 (3.6%) | 5 (3.6%) | 2 (1.4%) | 2 (1.4%) | 15 (4.1%) | 13 (3.5%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 10 (9.0%) | 10 (9.0%) | 1 (0.8%) | 1 (0.8%) | 7 (5.0%) | 6 (4.3%) | 1 (0.7%) | 1 (0.7%) | 18 (4.9%) | 17 (4.6%) |
| マントル細胞リンパ腫 | 8 (7.2%) | 8 (7.2%) | 0 | 0 | 0 | 0 | 0 | 0 | 8 (2.2%) | 8 (2.2%) |
| 腎および尿路障害 | 6 (5.4%) | 6 (5.4%) | 5 (4.2%) | 3 (2.5%) | 7 (5.0%) | 6 (4.3%) | 6 (4.3%) | 6 (4.3%) | 18 (4.9%) | 15 (4.1%) |
| 急性腎不全 | 3 (2.7%) | 3 (2.7%) | 4 (3.3%) | 2 (1.7%) | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) | 8 (2.2%) | 5 (1.4%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

参照元：5.3.5.3.1 ISS TSFAE06PART1OF3; 5.3.5.3.1 ISS TSFAE06PART2OF3; 5.3.5.3.1 ISS TSFAE06PART3OF3

#### 2.7.4.2.1.4 その他の重要な有害事象

その他の重要な有害事象として，投与中止に至った有害事象，減量に至った有害事象及び国内外の臨床試験においてイブルチニブ投与後に特徴的に認められた出血事象について評価した。

##### (1) 投与中止に至った有害事象

###### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で認められた投与中止に至った有害事象を表 2.7.4-付録-23 に示す。

安全性解析対象集団 16 例のうち 2 例（12.5%）で投与中止に至った有害事象が報告された。1 例はイブルチニブとの関連性がある Grade 4 の敗血症により中止し，他の 1 例は Grade 4 の高尿酸血症及び Grade 3 の白血球増加症（いずれも重篤な有害事象）により中止した。

###### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

1104 試験及び MCL2001 試験，MCL3001 試験並びに海外 3 試験併合で認められた投与中止に至った有害事象を表 2.7.4-付録-24，表 2.7.4-付録-25 及び表 2.7.4-付録-26 に示す。

海外 3 試験併合（370 例）で投与中止に至った有害事象は 48 例（13.0%）に発現した。2 例以上に発現した投与中止に至った有害事象は肺炎（6 例，1.6%），血小板減少症（5 例，1.4%），好中球減少症，呼吸不全，腹痛及び硬膜下血腫（各 3 例，0.8%）並びに敗血症，心停止及び急性腎不全（各 2 例，0.5%）であった。

MCL3001 試験の投与中止に至った有害事象の発現割合は，テムシロリムス群（29.5%，139 例中 41 例）と比較してイブルチニブ群（12.9%，139 例中 18 例）で低かった。3 例以上に認められた事象は，イブルチニブ群では血小板減少症（3 例，2.2%），テムシロリムス群では疲労（7 例，5.0%），血小板減少症及び肺臓炎（各 4 例，2.9%）並びに好中球減少症，無力症及び末梢性浮腫（各 3 例，2.2%）であった。

##### (2) 減量に至った有害事象

###### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で認められた減量に至った有害事象を表 2.7.4-付録-27 に示す。

減量に至った有害事象は安全性解析対象集団 16 例のうち 2 例（12.5%）に発現し，その内訳は，口内炎，血小板数減少及び全身性皮疹（各 1 例，6.3%）であった。

###### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

1104 試験及び MCL2001 試験，MCL3001 試験並びに海外 3 試験併合で認められた減量に至った有害事象を表 2.7.4-付録-28，表 2.7.4-付録-29 及び表 2.7.4-付録-30 に示す。

海外 3 試験併合（370 例）で 28 例（7.6%）が有害事象により減量し，そのうち 20 例（5.4%）は Grade 3 以上の有害事象による減量であった。2 例以上に発現した減量に至った有害事象は，好中球減少症（8 例，2.2%），下痢（6 例，1.6%），疲労（3 例，0.8%）並びに口内炎，発疹及び呼吸困難（各 2 例，0.5%）であった。

MCL3001 試験の減量に至った有害事象の発現割合は，テムシロリムス群（43.2%，139 例中 60 例）と比較してイブルチニブ群（3.6%，139 例中 5 例）で低かった。イブルチニブ群で認められた減量に至った有害事象に PT 又は SOC で 2 例以上に認められた事象はなく，一定の傾向は認められなかった。テムシロリムス群で 5 例以上に認められた事象は血小板減少症（25 例，18.0%），好中球減少症（11 例，7.9%），血小板数減少（8 例，5.8%）及び疲労（5 例，3.6%）であった。

### (3) 出血事象

出血事象は，MedDRA 標準検索式（Standardized MedDRA query，以下 SMQ）の「出血」を用いて集計した。また，大出血事象は治験薬投与中に発現した Grade 3 以上の出血事象，治験薬投与中に発現した Grade を問わないすべての重篤な出血事象並びに治験薬投与中に発現した中枢神経系の出血／血腫と定義した。

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で認められた出血事象を表 2.7.4-25 に示す。

出血事象は安全性解析対象集団 16 例のうち 5 例（31.3%）に発現し，その内訳は，挫傷（2 例，12.5%）並びに肛門出血，鼻出血，血尿，皮下出血，口腔内出血及び点状出血（各 1 例，6.3%）であった。

また，大出血事象は認められなかった。

表 2.7.4-25 出血事象：MCL2002 試験

| | Ibrutinib | |
|---|---|---|
| | All Grade | Grade 3 or Higher |
| Analysis Set: All Treated Population | 16 | |
| Total Number of Subjects with TEAE of Hemorrhage | 5 (31.3%) | 0 |
| MedDRA Preferred term | | |
| 挫傷 | 2 (12.5%) | 0 |
| 肛門出血 | 1 (6.3%) | 0 |
| 鼻出血 | 1 (6.3%) | 0 |
| 血尿 | 1 (6.3%) | 0 |
| 皮下出血 | 1 (6.3%) | 0 |
| 口腔内出血 | 1 (6.3%) | 0 |
| 点状出血 | 1 (6.3%) | 0 |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0
Note: Hemorrhagic events identified by haemorrhage terms excluding laboratory terms Standardized MedDRA Query [SMQ]

[TSFAE13.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsfae13.sas] 21AUG2015, 12:30
参照元：5.3.5.2.1 MCL2002 試験 CSR Table 22

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

1104 試験及び MCL2001 試験，MCL3001 試験並びに海外 3 試験併合で認められた出血事象を表 2.7.4-付録-31，表 2.7.4-付録-32 及び表 2.7.4-付録-33 に示す。

海外 3 試験併合（370 例）で出血事象の発現割合は 41.6%（154 例）であり，5%以上に発現した出血事象は，挫傷（12.4%，46 例），鼻出血（8.6%，32 例）及び点状出血（5.9%，22 例）であった。ほとんどの事象は Grade 1 又は 2 であり，Grade 3 以上の出血事象は 4.9%（18 例）に発

現し，その内訳は，血尿，硬膜下血腫及び出血（各 3 例，0.8%），紫斑及び処置後出血（各 2 例，0.5%）並びに鼻出血，下部消化管出血，出血性膀胱炎，脾臓出血及び硝子体出血（各 1 例，0.3%）であった。

MCL3001 試験の出血事象の発現割合は，イブルチニブ群で 39.6%（139 例中 55 例），テムシロリムス群で 32.4%（139 例中 45 例）であった。

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験で認められた大出血事象を表 2.7.4-26 に示す。

海外 3 試験併合で大出血事象の発現割合は 6.8%（25 例）であり，このうちイブルチニブの投与中止に至った事象は，硬膜下血腫（0.8%，3 例）及び脾臓出血（0.3%，1 例）であった（表 2.7.4-付録-26）。また，1 例が硬膜下血腫により死亡したが，イブルチニブとの因果関係は「関連なし」と判断された。

MCL3001 試験の大出血事象の発現割合は，イブルチニブ群で 10.1%（139 例中 14 例），テムシロリムス群で 6.5%（139 例中 9 例）であり，大出血事象の EAIR はテムシロリムス群（1.077/100 人月）と比較してイブルチニブ群（0.786/100 人月）で低かった（【5.3.5.1.1CSR TEAIR06 p. 603】）。

表 2.7.4-26 大出血事象：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | | MCL3001 Ibrutinib | | MCL3001 Temsirolimus | | Pooled Ibrutinib | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis set: safety | 111 | | 120 | | 139 | | 139 | | 370 | |
| Any Treatment-emergent Major Hemorrhage Adverse Events | 7 (6.3%) | 5 (4.5%) | 4 (3.3%) | 2 (1.7%) | 14 (10.1%) | 11 (7.9%) | 9 (6.5%) | 7 (5.0%) | 25 (6.8%) | 18 (4.9%) |
| Preferred term | | | | | | | | | | |
| 硬膜下血腫 | 4 (3.6%) | 2 (1.8%) | 0 | 0 | 2 (1.4%) | 1 (0.7%) | 0 | 0 | 6 (1.6%) | 3 (0.8%) |
| 出血 | 0 | 0 | 0 | 0 | 4 (2.9%) | 3 (2.2%) | 1 (0.7%) | 1 (0.7%) | 4 (1.1%) | 3 (0.8%) |
| 血尿 | 2 (1.8%) | 2 (1.8%) | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 3 (0.8%) | 3 (0.8%) |
| 鼻出血 | 0 | 0 | 0 | 0 | 2 (1.4%) | 1 (0.7%) | 3 (2.2%) | 2 (1.4%) | 2 (0.5%) | 1 (0.3%) |
| 頭蓋内出血 | 0 | 0 | 2 (1.7%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) | 0 |
| 処置後出血 | 0 | 0 | 0 | 0 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 0 | 2 (0.5%) | 2 (0.5%) |
| 紫斑 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 2 (0.5%) | 2 (0.5%) |
| 出血性膀胱炎 | 0 | 0 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) | 1 (0.3%) |
| 下部消化管出血 | 1 (0.9%) | 1 (0.9%) | 0 | 0 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) | 1 (0.3%) |
| 脾臓出血 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 0 | 0 | 0 | 0 | 1 (0.3%) | 1 (0.3%) |
| 硝子体出血 | 0 | 0 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) | 1 (0.3%) |
| 出血性胃炎 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7%) | 0 | 0 | 0 |
| 胃腸出血 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (1.4%) | 2 (1.4%) | 0 | 0 |
| 腸出血 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

参照元：5.3.5.3.1 ISS TSFAE19BPART1OF3; 5.3.5.3.1 ISS TSFAE19BPART2OF3; 5.3.5.3.1 ISS TSFAE19BPART3OF3

#### 2.7.4.2.1.5 器官別又は症候群別有害事象の解析

有害事象の臨床上の重要性，発現頻度又は非臨床結果に基づいて選択した特定の器官又は症候群に関する安全性を以下に要約した。

##### (1) 白血球停滞症候群

###### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験では，データカットオフ時点で，白血球停滞症候群（PT）の報告はなかった（表 2.7.4-付録-3）。

###### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

白血球停滞症候群（PT）は，1104 試験及び MCL3001 試験ではデータカットオフ時点で報告がなく，MCL2001 試験の 1 例で報告され，海外 3 試験併合（370 例）での発現割合は 0.3%であった（表 2.7.4-付録-8）。MCL2001 試験で発現した白血球停滞症候群は Grade 3 で，非重篤であり，イブルチニブとの関連性はなかった。なお，イブルチニブの投与中止又は減量には至らなかった。また，1104 試験で，リンパ球増加症に伴う白血球停滞と考えられる有害事象が認められた。詳細を以下に示す。

被験者番号 10001707（MCL2001 試験）：当該事象は Day 4 から Day 10 にかけて，Grade 2 の歩行障害を伴って発現した。スクリーニング検査では白血球数は 284.9 × $10^9$/L，リンパ球数は 253.6 × $10^9$/L であったが，Day 1（イブルチニブ初回投与前）に白血球数は 467.8 × $10^9$/L，リンパ球数は 416.3 × $10^9$/L に増加した。Day 5 に白血球数は 631.1 × $10^9$/L，リンパ球数は 606.3 × $10^9$/L にさらに増加した。イブルチニブの投与は変更されなかった。白血球除去が Day 6 から Day 22 にかけて 5 回行われた。Day 23 までに白血球数及びリンパ球数がそれぞれ 100 × $10^9$/L 未満（白血球数 84.4 × $10^9$/L，リンパ球数 77.8 × $10^9$/L）に減少した。Day 35 にコンピュータ断層撮影法スキャンで放射線学的疾患進行が認められ，イブルチニブの投与が中止された。

被験者番号 367-001（1104 試験）：当該被験者は疾患進行とは関連しない一過性のリンパ球増加症に伴う白血球停滞と考えられる有害事象を発現した。白血球数はスクリーニング検査（Day -9）では 241 × $10^9$/L であったが，Day 1 のイブルチニブ初回投与前に 378 × $10^9$/L に増加した。白血球数は Day 8 に 477 × $10^9$/L にさらに増加した。当該時点で Grade 2 の嗜眠が認められ，治験担当医師はイブルチニブとの因果関係を「可能性小」と判断した。白血球数は Day 15 までに 157 × $10^9$/L に減少した。

### (2) 過敏症

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験では，データカットオフ時点で，過敏症［蕁麻疹，血管浮腫，過敏症，薬物過敏症，アナフィラキシー反応，アナフィラキシーショック，アナフィラキシー様反応，アナフィラキシー様ショック（いずれも PT）］の報告はなかった（表 2.7.4-付録-3）。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

1104 試験及び MCL2001 試験，MCL3001 試験並びに海外 3 試験併合で認められた過敏症［蕁麻疹，血管浮腫，過敏症，薬物過敏症，アナフィラキシー反応，アナフィラキシーショック，アナフィラキシー様反応，アナフィラキシー様ショック（いずれも PT）］の集計を表 2.7.4-付録-34，表 2.7.4-付録-35 及び表 2.7.4-付録-36 に示す。

海外 3 試験併合（370 例）で，過敏症は 2.4%（9 例）に発現した。Grade 3 以上又は重篤な事象はなかった（表 2.7.4-付録-36 及び表 2.7.4-付録-21）。イブルチニブの投与中止に至った事象又は減量に至った事象はなかった（表 2.7.4-付録-26 及び表 2.7.4-付録-30）。また，血管浮腫，アナフィラキシー反応，アナフィラキシーショック，アナフィラキシー様反応，アナフィラキシー様ショックの報告はなかった。なお，イブルチニブとの関連性がある事象は，蕁麻疹（2 例，0.5%）及び過敏症（1 例，0.3%）であった（表 2.7.4-付録-15）。

MCL3001 試験で過敏症の発現割合に投与群間で差は認められなかった［イブルチニブ群 2.9%（139 例中 4 例），テムシロリムス群 5.0%（139 例中 7 例）］。発現した事象は，蕁麻疹，過敏症及び薬物過敏症であり，EAIR はイブルチニブ群及びテムシロリムス群でそれぞれ，蕁麻疹 0.22/100 人月及び 0.48/100 人月（以下同順），過敏症 0.00/100 人月及び 0.24/100 人月及び薬物過敏症 0.05/100 人月及び 0.12/100 人月であり，いずれの事象もテムシロリムス群と比較してイブルチニブ群で低かった（【5.3.5.1.1 CSR TEAIR02 p. 567】）。

### (3) 感染症

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で SOC が感染症および寄生虫症の有害事象は，安全性解析対象集団 16 例のうち 10 例（62.5%）に発現し，Grade 3 の事象は 1 例（6.3%）に発現した（表 2.7.4-付録-3）。重篤な事象及びイブルチニブの投与中止に至った事象は 1 例（6.3%）に発現した敗血症であった（表 2.7.4-23 及び表 2.7.4-付録-23）。減量に至った事象はなかった（表 2.7.4-付録-27）。なお，イブルチニブとの関連性がある事象は皮膚感染（2 例，12.5%）並びに爪囲炎，咽頭炎及び敗血症（各 1 例，6.3%）であった（表 2.7.4-付録-12）。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（370 例）で SOC が感染症および寄生虫症の有害事象は，71.1%（263 例）に発現した（表 2.7.4-付録-8）。10%以上に認められた事象は，上気道感染（19.7%，73 例），肺炎（11.9%，44 例），副鼻腔炎（10.5%，39 例）及び尿路感染（10.3%，38 例）であった。Grade 3 以上の事象は 23.5%（87 例）に発現し，2%以上に認められた Grade 3 以上の事象は，肺炎（8.9%，

33 例），敗血症（3.0%，11 例）及び蜂巣炎（2.2%，8 例）であった。重篤な事象は 20.5%（76 例）に発現した（表 2.7.4-付録-21）。死亡に至った事象は 3.5%（13 例）に発現し，その内訳は，肺炎及び敗血症（各 5 例，1.4%），敗血症性ショック（2 例，0.5%）並びにニューモシスチス・イロベチイ肺炎（1 例，0.3%）であった（表 2.7.4-21）。なお，このうちイブルチニブとの関連性がある事象は肺炎 3 例並びに敗血症及びニューモシスチス・イロベチイ肺炎各 1 例であった。ニューモシスチス・イロベチイ肺炎により死亡した被験者の主たる死因は進行であった。また，高位語が肝炎ウイルス感染の有害事象を発現した被験者は 1 例であった。当該被験者は，イブルチニブ投与開始後 336 日に重篤な Grade 3 の B 型肝炎（症例報告書記載名：Reactivation of hepatitis b viral）を発現した。当該被験者は，ベースライン時に B 型肝炎表面抗原及び B 型肝炎 e 抗原が陰性であったが，イブルチニブ投与開始後 337 日に B 型肝炎表面抗原及び B 型肝炎 e 抗原が陽性となり，B 型肝炎ウイルスデオキシリボ核酸が高値（$276 \times 10^6$ IU/mL）であることが確認された。当該事象は回復しなかったが，イブルチニブの投与はイブルチニブ投与開始後 329 日から 347 日まで中断した後に再開し，データカットオフ時点で継続していた。イブルチニブとの因果関係は「多分なし」と判断された。

MCL3001 試験で SOC が感染症および寄生虫症の有害事象の発現割合に，投与群間で差は認められなかった［イブルチニブ群 69.8%（139 例中 97 例），テムシロリムス群 71.2%（139 例中 99 例）］（表 2.7.4-付録-7）。Grade 3 以上の事象の発現割合は，イブルチニブ群［19.4%（27 例）］と比較してテムシロリムス群［30.2%（42 例）］で高かった。重篤な事象はイブルチニブ群の 18.0%（25 例）及びテムシロリムス群の 28.8%（40 例）で報告された（表 2.7.4-24）。SOC が感染症および寄生虫症の有害事象の EAIR はテムシロリムス群（30.34/100 人月）と比較してイブルチニブ群（11.68/100 人月）で低かった（【5.3.5.1.1 CSR TEAIR02 p. 567】）。

#### (4) 血球減少症

##### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で，貧血，血小板減少症及び好中球減少症（いずれも PT）は，それぞれ 4 例（25.0%），3 例（18.8%）及び 1 例（6.3%）に発現した（表 2.7.4-付録-3）。発熱性好中球減少症は発現しなかった。血小板減少症はいずれも Grade 1 又は 2 であった。Grade 3 以上の事象は，同一被験者で発現した貧血 2 件及び好中球減少症 3 件であった。これらの事象のうち，好中球減少症 1 件はデータカットオフ時点で未回復であったが，その他の 4 件は回復した。重篤な事象はなかった（表 2.7.4-23）。イブルチニブの投与中止に至った事象又は減量に至った事象はなかった（表 2.7.4-付録-23 及び表 2.7.4-付録-27）。

##### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（370 例）の貧血，血小板減少症及び好中球減少症（いずれも PT）の発現割合は，それぞれ 17.0%（63 例），20.0%（74 例）及び 18.9%（70 例）であった（表 2.7.4-付録-8）。Grade 3 以上の貧血，血小板減少症及び好中球減少症の発現割合は，それぞれ 8.1%（30 例），11.1%（41 例）及び 16.5%（61 例）であり，発現した好中球減少症の多くは Grade 3 以上であった。発熱性好中球減少症は 3.5%（13 例）に発現し，いずれも Grade 3 以上であった。このうち 1

例が死亡に至り，当該事象とイブルチニブとの因果関係は「可能性小」と判断された。貧血，血小板減少症，好中球減少症及び発熱性好中球減少症は，重篤な事象は少なく（いずれも発現割合3.0%以下），イブルチニブの投与中止に至った事象又は減量に至った事象も少なかった（いずれも発現割合 2.5%以下）（表 2.7.4-付録-21，表 2.7.4-付録-26 及び表 2.7.4-付録-30）。

MCL3001 試験で血球減少症（貧血，血小板減少症，好中球減少症及び発熱性好中球減少症）の発現割合はテムシロリムス群（71.2%，139 例中 99 例）と比較してイブルチニブ群（36.0%，139 例中 50 例）で低かった（【5.3.5.1.1 CSR TSFAE36 p. 887】）。Grade 3 又は 4 の血球減少症の発現割合はイブルチニブ群で 20.9%（29 例），テムシロリムス群で 56.1%（78 例）であった。

### (5) 二次性悪性腫瘍

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験では，データカットオフ時点で，SOC が良性，悪性および詳細不明の新生物（嚢胞およびポリープを含む）の有害事象の報告はなかった（表 2.7.4-付録-3）。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験で，イブルチニブ投与中及びフォローアップ期間に認められた固形癌，皮膚癌及び血液腫瘍を含む二次性悪性腫瘍の集計を表 2.7.4-27 に示す。

海外 3 試験併合（370 例）で，イブルチニブ投与後の二次性悪性腫瘍の発現割合は 5.7%（21 例）であり，非黒色腫皮膚癌及び非皮膚癌の発現割合はそれぞれ 3.8%（14 例）及び 1.9%（7 例）であった。2 例以上に認められた二次性悪性腫瘍は，基底細胞癌（7 例，1.9%），皮膚有棘細胞癌（5 例，1.4%）並びに扁平上皮癌及び前立腺癌（各 2 例，0.5%）であった。非黒色腫皮膚癌では基底細胞癌，扁平上皮癌及び皮膚癌（各 1 例，0.3%）が Grade 3 以上であり，非皮膚癌では急性骨髄性白血病及び胃腺癌を除くすべての事象が Grade 3 以上であった（表 2.7.4-付録-8）。重篤な事象は，前立腺癌（2 例，0.5%）並びに基底細胞癌，扁平上皮癌，膀胱癌，遠隔転移を伴う新生物，唾液腺癌及び移行上皮癌（各 1 例，0.3%）であった（表 2.7.4-付録-21）。イブルチニブの投与中止に至った事象は肺腺癌，遠隔転移を伴う新生物及び移行上皮癌（各 1 例，0.3%）であり（表 2.7.4-付録-26），減量に至った事象はなかった（表 2.7.4-付録-30）。なお，イブルチニブとの関連性がある事象は，扁平上皮癌，遠隔転移を伴う新生物及び移行上皮癌（各 1 例，0.3%）であった（表 2.7.4-付録-15）。移行上皮癌は死亡に至った事象として報告された。

MCL3001 試験で治験薬投与後の二次性悪性腫瘍の発現割合は，イブルチニブ群で 3.6%（139 例中 5 例），テムシロリムス群で 2.9%（139 例中 4 例）であった。テムシロリムス群で 2 例以上に発現した二次性悪性腫瘍は扁平上皮癌で，イブルチニブ群で 2 例以上に発現した二次性悪性腫瘍はなかった。

表 2.7.4-27 二次性悪性腫瘍：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Analysis set: safety | 111 | 120 | 139 | 139 | 370 |
| Subjects with any other malignancy | 5 (4.5%) | 11 (9.2%) | 5 (3.6%) | 4 (2.9%) | 21 (5.7%) |
| Type | | | | | |
| Preferred term | | | | | |
| Non-Melanoma Skin Cancer | 4 (3.6%) | 8 (6.7%) | 2 (1.4%) | 2 (1.4%) | 14 (3.8%) |
| 基底細胞癌 | 1 (0.9%) | 5 (4.2%) | 1 (0.7%) | 1 (0.7%) | 7 (1.9%) |
| 皮膚有棘細胞癌 | 1 (0.9%) | 4 (3.3%) | 0 | 0 | 5 (1.4%) |
| 扁平上皮癌 | 1 (0.9%) | 0 | 1 (0.7%) | 2 (1.4%) | 2 (0.5%) |
| 皮膚癌 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| Non-Skin cancer (malignant) | 1 (0.9%) | 3 (2.5%) | 3 (2.2%) | 2 (1.4%) | 7 (1.9%) |
| 前立腺癌 | 0 | 1 (0.8%) | 1 (0.7%) | 0 | 2 (0.5%) |
| 急性骨髄性白血病 | 0 | 1 (0.8%) | 0 | 1 (0.7%) | 1 (0.3%) |
| 膀胱癌 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| 肺腺癌 | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| 唾液腺癌 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 移行上皮癌 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 胃腺癌 | 0 | 0 | 0 | 1 (0.7%) | 0 |

Events include all other malignancies reported during the treatment and follow-up.
Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE21.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae21.sas] 15SEP2015, 14:13
参照元：5.3.5.3.1 ISS TSFAE21

### (6) 心臓障害

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で，SMQ の「不整脈」を用いた集計を表 2.7.4-28 に示す。

不整脈は安全性解析対象集団 16 例のうち 2 例（12.5%）に発現し，その内訳は，不整脈及び心房細動（各 1 例，6.3%）であった。不整脈の重症度は Grade 3 であった。重篤な事象，イブルチニブの投与中止に至った事象及び減量に至った事象はなかった（表 2.7.4-23，表 2.7.4-付録-23 及び表 2.7.4-付録-27）。なお，心房細動はイブルチニブとの関連性があった（表 2.7.4-付録-12）。

SOC が心臓障害の有害事象は SMQ の「不整脈」の有害事象と同一であった（表 2.7.4-付録-3）。

表 2.7.4-28 不整脈：MCL2002 試験

| | Ibrutinib | |
|---|---|---|
| | All Grade | Grade 3 or Higher |
| Analysis Set: All Treated Population | 16 | |
| Total Number of Subjects with TEAE of Cardiac Arrhythmias | 2 (12.5%) | 1 (6.3%) |
| MedDRA Preferred term | | |
| 不整脈 | 1 (6.3%) | 1 (6.3%) |
| 心房細動 | 1 (6.3%) | 0 |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0
Note: Cardiac arrhythmias SMQ will be used to identify the cardiac arrhythmias events.

[TSFAE15.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsfae15.sas] 21AUG2015, 12:30
参照元：5.3.5.2.1 MCL2002 試験 CSR Table 26

b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（370 例）で，SOC が心臓障害の有害事象は 64 例（17.3%）に発現し，Grade 3 以上の事象は 26 例（7.0%）に発現した（表 2.7.4-付録-8）。重篤な事象，イブルチニブの投与中止に至った事象及び減量に至った事象が発現した被験者は少なく，発現割合はそれぞれ 6.5%（24 例），1.1%（4 例）及び 0.3%（1 例）であった（表 2.7.4-付録-21，表 2.7.4-付録-26 及び表 2.7.4-付録-30）。心房細動（7.6%，28 例）及び頻脈（2.4%，9 例）を除いて，いずれの事象も発現割合は 2%未満であった。Grade 3 以上の心房細動は 4.6%（17 例）に発現した。心房粗動は 0.8%（3 例）に発現し，Grade 3 以上の心房粗動は 0.3%（1 例）に発現した。重篤な心房細動及び心房粗動は少なかった［重篤な心房細動 4.1%（15 例），重篤な心房粗動 0.5%（2 例）］（表 2.7.4-付録-21）。イブルチニブの投与中止に至った心房細動又は心房粗動はなかった（表 2.7.4-付録-26）。イブルチニブの減量に至った心房細動は 0.3%（1 例）に発現し，減量に至った心房粗動はなかった（表 2.7.4-付録-30）。

MCL3001 試験で認められた SOC が心臓障害の有害事象のうち，心房細動は最も発現割合が高く，イブルチニブ群の 4.3%［139 例中 6 例，Grade 3 以上は 3.6%（5 例）］，テムシロリムス群の 2.2%［139 例中 3 例，Grade 3 以上は 2 例（1.4%）］に発現した（表 2.7.4-付録-7）。すべての Grade 3 以上の心房細動が重篤な事象として報告された（表 2.7.4-付録-20）。死亡に至った心房細動，治験薬の投与中止又は減量に至った心房細動はなかった（表 2.7.4-21，表 2.7.4-付録-25 及び表 2.7.4-付録-29）。心房細動の EAIR はイブルチニブ群（0.337/100 人月）及びテムシロリムス群（0.358/100 人月）であり，投与群間で差は認められなかった（【5.3.5.1.1 CSR TEAIR02 p. 567】）。

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験で認められた SMQ「不整脈」の概要を表 2.7.4-29 に，集計を表 2.7.4-30 に示す。

海外 3 試験併合で不整脈は，57 例（15.4%）に発現した。Grade 3 以上の不整脈は 24 例（6.5%）に発現した。重篤な不整脈は 20 例（5.4%）に発現し，このうち心停止を発現した 2 例（0.5%）が死亡に至った。イブルチニブの投与中止に至った事象は 2 例（0.5%）に，減量に至った事象は 1 例（0.3%）に発現した。イブルチニブ投与開始から不整脈初回発現までの期間の中央値（範囲）は 53.0（1 - 419）日間であった。4 例以上に認められた事象は，心房細動（28 例，7.6%），頻脈（9 例，2.4%），洞性頻脈（7 例，1.9%）並びに徐脈，動悸及び失神（各 4 例，1.1%）であった。

表 2.7.4-29 不整脈の概要：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Analysis set: safety population | 111 | 120 | 139 | 139 | 370 |
| Any Treatment-emergent Cardiac Arrhythmia Adverse Events | 20 (18.0%) | 24 (20.0%) | 13 (9.4%) | 15 (10.8%) | 57 (15.4%) |
| Grade >= 3 | 9 (8.1%) | 7 (5.8%) | 8 (5.8%) | 6 (4.3%) | 24 (6.5%) |
| Fatal | 1 (0.9%) | 1 (0.8%) | 0 | 1 (0.7%) | 2 (0.5%) |
| SAE | 7 (6.3%) | 6 (5.0%) | 7 (5.0%) | 3 (2.2%) | 20 (5.4%) |
| Leading to treatment discontinuation | 1 (0.9%) | 1 (0.8%) | 0 | 0 | 2 (0.5%) |
| Leading to dose reduction | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| Time to onset of first event (days) [a] | | | | | |
| N | 20 | 24 | 13 | 15 | 57 |
| Mean (SD) | 145.3 (124.91) | 79.5 (104.29) | 50.5 (67.98) | 94.1 (110.86) | 96.0 (110.52) |
| Median | 119.5 | 43.0 | 29.0 | 49.0 | 53.0 |
| Range | (1; 393) | (1; 419) | (1; 213) | (13; 403) | (1; 419) |

[a] Days = Onset of the event – First dose date + 1.
Note: Percentages calculated with the number of subjects in safety analysis set as denominator.

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参照元：5.3.5.3.1 ISS TSFAE24

表 2.7.4-30 不整脈：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | | MCL3001 Ibrutinib | | MCL3001 Temsirolimus | | Pooled Ibrutinib | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis set: safety | 111 | | 120 | | 139 | | 139 | | 370 | |
| Any Treatment-emergent Cardiac Arrhythmias Adverse Events | 20 (18.0%) | 9 (8.1%) | 24 (20.0%) | 7 (5.8%) | 13 (9.4%) | 8 (5.8%) | 15 (10.8%) | 6 (4.3%) | 57 (15.4%) | 24 (6.5%) |
| Preferred term | | | | | | | | | | |
| 心房細動 | 9 (8.1%) | 6 (5.4%) | 13 (10.8%) | 6 (5.0%) | 6 (4.3%) | 5 (3.6%) | 3 (2.2%) | 2 (1.4%) | 28 (7.6%) | 17 (4.6%) |
| 頻脈 | 0 | 0 | 8 (6.7%) | 0 | 1 (0.7%) | 0 | 2 (1.4%) | 0 | 9 (2.4%) | 0 |
| 洞性頻脈 | 5 (4.5%) | 0 | 1 (0.8%) | 0 | 1 (0.7%) | 0 | 1 (0.7%) | 0 | 7 (1.9%) | 0 |
| 徐脈 | 0 | 0 | 3 (2.5%) | 0 | 1 (0.7%) | 0 | 0 | 0 | 4 (1.1%) | 0 |
| 動悸 | 1 (0.9%) | 0 | 0 | 0 | 3 (2.2%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) | 0 |
| 失神 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 3 (2.2%) | 3 (2.2%) | 3 (2.2%) | 3 (2.2%) | 4 (1.1%) | 4 (1.1%) |
| 心房粗動 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) | 1 (0.3%) |
| 洞性徐脈 | 2 (1.8%) | 0 | 1 (0.8%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) | 0 |
| 上室性頻脈 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 | 1 (0.7%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) | 1 (0.3%) |
| 心停止 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 2 (0.5%) | 2 (0.5%) |
| 心室性期外収縮 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) | 0 |
| 不整脈 | 0 | 0 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.7%) | 0 | 1 (0.3%) | 0 |
| 第一度房室ブロック | 1 (0.9%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) | 0 |
| 変時性応答不全 | 0 | 0 | 0 | 0 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) | 0 |
| 心拍数増加 | 0 | 0 | 1 (0.8%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) | 0 |
| 心拍数不整 | 1 (0.9%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) | 0 |
| 洞不全症候群 | 0 | 0 | 1 (0.8%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) | 0 |
| 頻脈性不整脈 | 0 | 0 | 1 (0.8%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) | 0 |
| トルサード　ド　ポアント | 1 (0.9%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) | 0 |
| 心室性不整脈 | 0 | 0 | 0 | 0 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) | 0 |
| 心室性頻脈 | 1 (0.9%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) | 0 |
| 右脚ブロック | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7%) | 0 | 0 | 0 |
| 意識消失 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.7%) | 0 | 0 | 0 |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

参照元：5.3.5.3.1 ISS TSFAE23PART1OF3; 5.3.5.3.1 ISS TSFAE23PART2OF3; 5.3.5.3.1 ISS TSFAE23PART3OF3

### (7) 発疹

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で PT に「rash」を含む有害事象は，発疹，全身性皮疹及び斑状丘疹状皮疹（各 1 例，6.3%）であり，Grade 3 以上の事象はなかった（表 2.7.4-付録-3）。重篤な事象はなかった（表 2.7.4-23）。イブルチニブの投与中止に至った事象はなく（表 2.7.4-付録-23），減量に至った事象は全身性皮疹であった（表 2.7.4-付録-27）。なお，いずれもイブルチニブとの関連性がある有害事象であった（表 2.7.4-付録-12）。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（370 例）で，発現割合が 2%以上であった PT に「rash」を含む有害事象は，発疹（57 例，15.4%），斑状丘疹状皮疹（16 例，4.3%），斑状皮疹（4 例，1.1%），紅斑性皮疹（3 例，0.8%），膿疱性皮疹，全身性皮疹，丘疹性皮疹及びそう痒性皮疹（各 2 例，0.5%）並びに毛孔性皮疹及び性器発疹（各 1 例，0.3%）であった（表 2.7.4-付録-8）。ほとんどの事象は Grade 1 又は 2 であった。このうち 1 例で発現した発疹は重篤な有害事象として報告された（表 2.7.4-付録-21）。イブルチニブの投与中止に至った事象はなく（表 2.7.4-付録-26），減量に至った事象は発疹（2 例，0.5%）並びに膿疱性皮疹及び斑状丘疹状皮疹（各 1 例，0.3%）であった（表 2.7.4-付録-30）。

### (8) 眼障害

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で SOC が眼障害の有害事象は安全性解析対象集団 16 例のうち 3 例（18.8%）に発現し，その内訳は，眼乾燥，点状角膜炎，網膜裂孔及び網膜血管障害（各 1 例，6.3%）であった（表 2.7.4-付録-3）。いずれもイブルチニブとの関連性はなかった（表 2.7.4-付録-12）。Grade 3 以上の事象は網膜血管障害であった。網膜血管障害の重症度は，発現時では Grade 3 であったが，イブルチニブの休薬後では Grade 2 であった。データカットオフ時点で網膜血管障害は未回復であった。重篤な事象，イブルチニブの投与中止に至った事象又は減量に至った事象はなかった（表 2.7.4-23，表 2.7.4-付録-23 及び表 2.7.4-付録-27）。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（370 例）で，SOC が眼障害の有害事象は 22.2%（82 例）に報告された（表 2.7.4-付録-8）。ほとんどの事象が Grade 1 又は 2 で，Grade 3 以上の事象の発現割合は 1.4%（5 例）であった。3%以上に発現した事象は，眼乾燥（16 例，4.3%），流涙増加及び霧視（各 13 例，3.5%）並びに白内障（11 例，3.0%）であった。1 例に発現した糖尿病網膜症及び硝子体出血が重篤な事象として報告された（表 2.7.4-付録-21）。イブルチニブの投与中止に至った事象又は減量に至った事象はなかった（表 2.7.4-付録-26 及び表 2.7.4-付録-30）。

MCL3001 試験で SOC が眼障害の有害事象の発現割合は，イブルチニブ群で 21.6%（139 例中 30 例），テムシロリムス群で 18.0%（139 例中 25 例）であった（表 2.7.4-付録-7）。EAIR はテム

シロリムス群（3.403/100 人月）と比較してイブルチニブ群（1.919/100 人月）で低かった（【5.3.5.1.1 CSR TEAIR02 p. 567】）。

### (9) 腫瘍崩壊症候群

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験では，データカットオフ時点で，腫瘍崩壊症候群（PT）の報告はなかった（表 2.7.4-付録-3）。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

腫瘍崩壊症候群（PT）は，MCL3001 試験のイブルチニブ群（139 例）で 1 例（0.7%，Grade 3），テムシロリムス群で 3 例（2.2%，いずれも Grade 3 以上）に発現した（表 2.7.4-付録-7）。いずれも重篤な事象として報告されたが，死亡に至った事象はなかった（表 2.7.4-付録-20 及び表 2.7.4-21）。イブルチニブの投与中止に至った事象又は減量に至った事象はなかった（表 2.7.4-付録-25 及び表 2.7.4-付録-29）。なお，イブルチニブ群 1 例に発現した事象はイブルチニブとの因果関係を「可能性大」と判断されたが，イブルチニブの休薬後に回復した。腫瘍崩壊症候群の EAIR はテムシロリムス群（0.358/100 人月）と比較してイブルチニブ群（0.055/100 人月）で低かった（【5.3.5.1.1 CSR TEAIR02 p. 567】）。

腫瘍崩壊症候群は 1104 試験及び MCL2001 試験では認められず，海外 3 試験併合（370 例）での発現割合は 0.3%であった（表 2.7.4-付録-8）。

### (10) 間質性肺疾患

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験では，データカットオフ時点で，SMQ の「間質性肺疾患」に該当する有害事象の報告はなかったが，データカットオフ後に間質性肺疾患が 1 例に発現した。当該事象は Grade 2 の重篤な有害事象として報告された。イブルチニブとの因果関係は「可能性大」と判断され，イブルチニブの投与を中止し，[redacted]年[redacted]月[redacted]日時点で Grade 1 に軽快した。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験で認められた SMQ「間質性肺疾患」の集計を表 2.7.4-31 に示す。

海外 3 試験併合（370 例）で，間質性肺疾患は 4 例（1.1%）に発現し，その内訳は，細気管支炎及び肺浸潤（各 2 例，0.5%）であった。Grade 3 以上又は重篤な事象はなかった（表 2.7.4-31 及び表 2.7.4-付録-21）。肺浸潤 1 例を除いてイブルチニブとの関連性はなかった（表 2.7.4-付録-15）。イブルチニブの投与中止に至った事象又は減量に至った事象はなかった（表 2.7.4-付録-26 及び表 2.7.4-付録-30）。

MCL3001 試験で間質性肺疾患の発現割合は，テムシロリムス群（12.2%，139 例中 17 例）と比較してイブルチニブ群（1.4%，139 例中 2 例）で低かった。

表 2.7.4-31 間質性肺疾患：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | | MCL3001 Ibrutinib | | MCL3001 Temsirolimus | | Pooled Ibrutinib | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis set: safety | 111 | | 120 | | 139 | | 139 | | 370 | |
| Any Treatment-emergent Interstitial Lung Disease Adverse Events | 2 (1.8%) | 0 | 0 | 0 | 2 (1.4%) | 0 | 17 (12.2%) | 6 (4.3%) | 4 (1.1%) | 0 |
| Preferred term | | | | | | | | | | |
| 細気管支炎 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.7%) | 0 | 0 | 0 | 2 (0.5%) | 0 |
| 肺浸潤 | 1 (0.9%) | 0 | 0 | 0 | 1 (0.7%) | 0 | 2 (1.4%) | 1 (0.7%) | 2 (0.5%) | 0 |
| 間質性肺疾患 | 0 | 0 | 0 | 0 | 0 | 0 | 6 (4.3%) | 2 (1.4%) | 0 | 0 |
| 肺臓炎 | 0 | 0 | 0 | 0 | 0 | 0 | 10 (7.2%) | 3 (2.2%) | 0 | 0 |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

参照元：5.3.5.3.1 ISS TSFAE33PART1OF3; 5.3.5.3.1 ISS TSFAE33PART2OF3; 5.3.5.3.1 ISS TSFAE33PART3OF3

### (11) 胃腸障害

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で SOC が胃腸障害の有害事象は安全性解析対象集団 16 例中 10 例（62.5%）に発現し，発現割合が最も高かった事象は下痢及び口内炎（各 6 例，37.5%）であった（表 2.7.4-付録-3）。Grade 3 以上の事象は口内炎（1 例，6.3%）であり，重篤な事象及びイブルチニブの投与中止に至った事象はなく，減量に至った事象は口内炎（1 例，6.3%）であった（表 2.7.4-23，表 2.7.4-付録-23 及び表 2.7.4-付録-27）。MCL2002 試験では，口内炎の発現割合が比較的高かったが，そのほとんどは，Grade 1 又は 2 であった。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（370 例）で，SOC が胃腸障害の有害事象の発現割合は 68.9%（255 例）であった（表 2.7.4-付録-8）。10%以上に認められた事象は，下痢（39.5%，146 例），悪心（21.6%，80 例），嘔吐（16.8%，62 例），便秘（15.4%，57 例）及び腹痛（11.4%，42 例）であった。Grade 1 又は 2 の事象が多く，Grade 3 以上の事象の発現割合は 10.5%（39 例）で，2 例以上に認められた Grade 3 以上の事象は，下痢及び腹痛（各 13 例，3.5%），口内炎（3 例，0.8%）並びに嚥下障害，麻痺性イレウス及び小腸閉塞（各 2 例，0.5%）であった。イブルチニブの投与中止に至った事象は 0.8%（3 例）に発現し，その内訳は，腹痛（3 例，0.8%）及び吐血（1 例，0.3%）であった（表 2.7.4-付録-26）。減量に至った事象は 1.9%（7 例）に発現し，その内訳は，下痢（6 例，1.6%）及び口内炎（2 例，0.5%）であった（表 2.7.4-付録-30）。重篤な事象は 7.0%（26 例）に発現し，2 例以上に発現した重篤な事象は，腹痛（10 例，2.7%），下痢（4 例，1.1%）並びに麻痺性イレウス，悪心，小腸閉塞及び嘔吐（各 2 例，0.5%）であった（表 2.7.4-付録-21）。死亡に至った事象は，麻痺性イレウスの 1 例で，イブルチニブとの「関連なし」と判断された。

MCL3001 試験で SOC が胃腸障害の有害事象の発現割合は，イブルチニブ群で 57.6%（139 例中 80 例），テムシロリムス群で 78.4%（139 例中 109 例）であった（表 2.7.4-付録-7）。

### (12) 腎機能に関する有害事象

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で SOC が腎および尿路障害の有害事象は安全性解析対象集団 16 例中 2 例（12.5%）に発現し，その内訳は，血尿，蛋白尿，腎機能障害（各 1 例，6.3%）であった（表 2.7.4-付録-3）。血尿及び腎機能障害はイブルチニブとの関連性があった（表 2.7.4-付録-12）。Grade 3 以上の事象は腎機能障害であり，イブルチニブの休薬後に回復した。重篤な事象，イブルチニブの投与中止に至った事象又は減量に至った事象はなかった（表 2.7.4-23，表 2.7.4-付録-23，表 2.7.4-付録-27）。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（370 例）で，SOC が腎および尿路障害の有害事象の発現割合は 15.4%（57 例）であった（表 2.7.4-付録-8）。ほとんどの事象は Grade 1 又は 2 であり，Grade 3 以上の事象

は 4.6%（17 例）で認められ，2 例以上に認められた Grade 3 以上の事象は急性腎不全（6 例，1.6%），腎不全（5 例，1.4%），血尿（3 例，0.8%）及び水腎症（2 例，0.5%）であった。イブルチニブの投与中止に至った事象は 0.8%（3 例）に発現し（表 2.7.4-付録-26），減量に至った事象はなかった（表 2.7.4-付録-30）。重篤な有害事象は 18 例（4.9%）に認められ，2 例以上に認められた事象は急性腎不全（8 例，2.2%），腎不全（4 例，1.1%）及び血尿（3 例，0.8%）であった（表 2.7.4-付録-21）。なお，イブルチニブとの関連性がある重篤な事象は 4 例に認められ，その内訳は，血尿（2 例）並びに腎不全及び急性腎不全（各 1 例）であった。このうち腎不全はデータカットオフ時点で未回復であったが，それ以外の事象は回復又は軽快した。

### (13) 肝機能に関する有害事象

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験では，データカットオフ時点で，SOC が肝胆道系障害の有害事象の報告はなかった（表 2.7.4-付録-3）。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（370 例）で，SOC が肝胆道系障害の有害事象の発現割合は 3.5%（13 例）であった（表 2.7.4-付録-8）。ほとんどの事象は Grade 1 又は 2 であり，Grade 3 以上の事象の発現割合は 1.1%（4 例）であった。イブルチニブの投与中止に至った事象はなく（表 2.7.4-付録-26），減量に至った事象は 0.3%（1 例）に発現した（表 2.7.4-付録-30）。重篤な事象は 3 例（0.8%）に発現し，その内訳は，胆石症及び中毒性肝炎並びに同一被験者に発現した胆管結石及び胆管炎（各 1 例，0.3%）であった（表 2.7.4-付録-21）。このうち中毒性肝炎はイブルチニブとの因果関係を「可能性大」と判断された。当該事象はイブルチニブの休薬後に回復した。死亡に至った事象はなかった（表 2.7.4-21）。

MCL3001 試験で，SOC が肝胆道系障害の有害事象はイブルチニブ群の 4.3%（139 例中 6 例）及びテムシロリムス群の 2.9%（139 例中 4 例）に発現した（表 2.7.4-付録-7）。Grade 3 以上の事象はイブルチニブ群の 1 例（0.7%，重篤な中毒性肝炎）に発現した。テムシロリムス群では Grade 3 以上の事象はなかったが，1 例で 2 件の重篤な中毒性肝炎（Grade 1 及び 2）が発現した。SOC が肝胆道系障害の有害事象の EAIR はテムシロリムス群（0.478/100 人月）と比較してイブルチニブ群（0.338/100 人月）で低かった（【5.3.5.1.1 CSR TEAIR02 p. 567】）。

CLL1007 試験の Part 2 で，治験実施計画書に従いイブルチニブ 840 mg 及び 1680 mg を連続して（1 週間の休薬をおいて）単回投与された 1 例に，Grade 4 の肝酵素上昇が認められた。肝酵素上昇は，イブルチニブ 1680 mg の投与後に発現し，臨床検査値異常として，イブルチニブ 1680 mg 投与 8 日後に Grade 4 のアラニンアミノトランスフェラーゼ（alanine aminotransferase，以下 ALT）上昇（3312 U/L，正常範囲 ≤ 45 U/L）及び Grade 4 のアスパラギン酸アミノトランスフェラーゼ（aspartate aminotransferase，以下 AST）上昇（926 U/L，正常範囲 ≤ 40 U/L）が認められた。臨床検査値異常発現後 1 カ月以内に，AST は正常範囲内（30 U/L），ALT はほぼ正常範囲内（56 U/L）に回復した。本事象は重篤な有害事象として報告され，被験者は当該事象，Grade 2

の筋肉痛及び Grade 2 の上腹部痛により試験を中止した。肝酵素上昇とイブルチニブとの因果関係は「可能性小」と判断された。

#### 2.7.4.2.2 個別有害事象の文章による説明

評価資料とした試験で認められた，治験薬投与開始から最終投与後 30 日までの死亡を含む重篤な有害事象に関する個別症例の詳細は，2.7.6 項又は各試験の CSR に記載した。

### 2.7.4.3 臨床検査値の評価

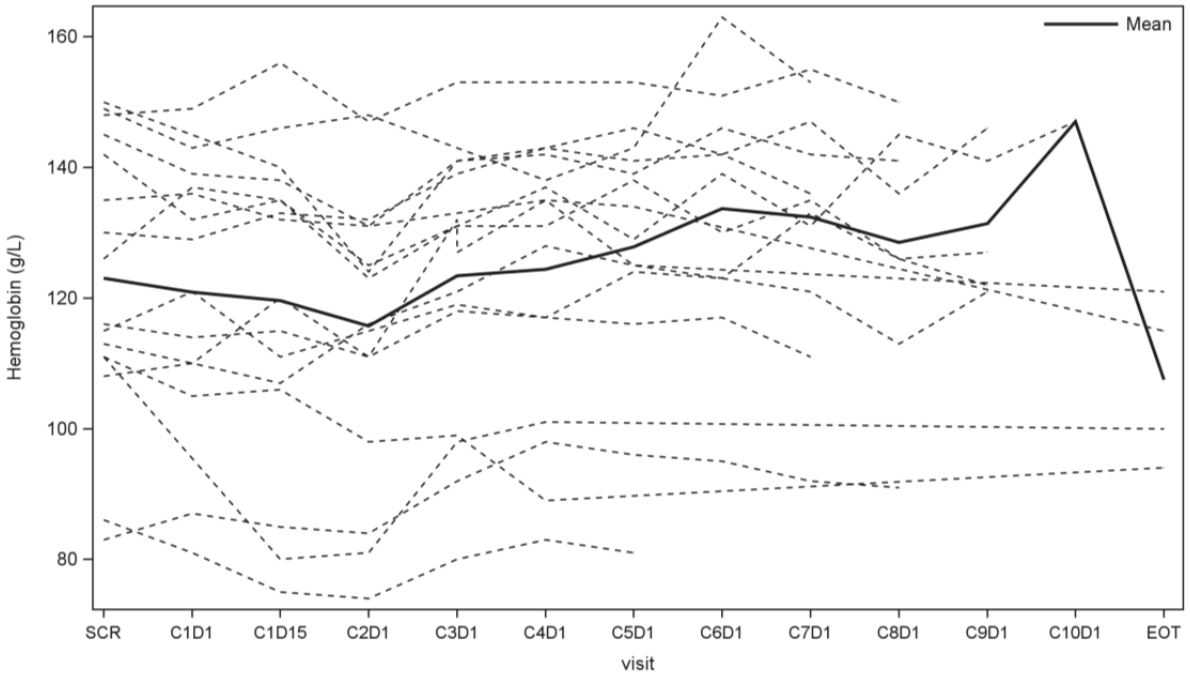
#### 2.7.4.3.1 血液学的検査

##### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験の血液学的検査のパラメータのベースラインの重症度と投与後の最高重症度を示したシフトテーブルを CSR に示す（【5.3.5.2.1 CSR Table 30 p. 83】）。

安全性解析対象集団 16 例で，Grade 3 のヘモグロビン量の減少，血小板数の減少及び好中球数（absolute neutrophil count，以下 ANC）の減少はそれぞれ 2 例（12.5%），2 例（12.5%）及び 1 例（6.3%）に認められた。Grade 4 のヘモグロビン量の減少，血小板数の減少及び ANC の減少は認められなかった。ベースラインからの 2 段階以上の悪化は，ヘモグロビン量の減少（Grade 1 から Grade 3），血小板数の減少（Grade 0 から Grade 2 及び Grade 1 から Grade 3）並びに ANC の減少（Grade 1 から Grade 3）が各 1 例（6.3%）に認められた。

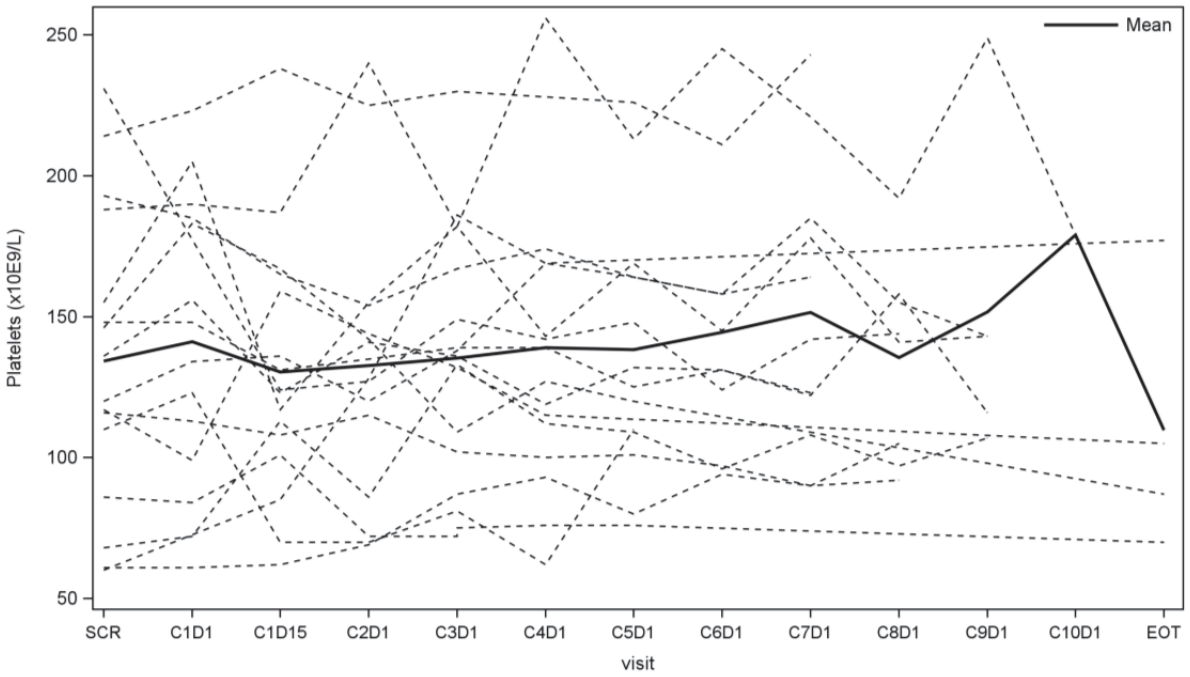
また，MCL2002 試験のヘモグロビン量，血小板数及び ANC の平均値の経時的な推移をそれぞれ図 2.7.4-1，図 2.7.4-2 及び図 2.7.4-3 に示す。いずれも投与期間を通しておおむね安定しており，大きな変動は認められなかった。




Key: SCR=Screening, CxDy=Cycle x Day y, EOT=End of Treatment
Note: Unscheduled visit have been excluded from the presentation.

[GSFLAB01.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\gsflab01.sas] 21AUG2015, 12:28
参照元：5.3.5.2.1 MCL2002 試験 CSR GSFLAB01

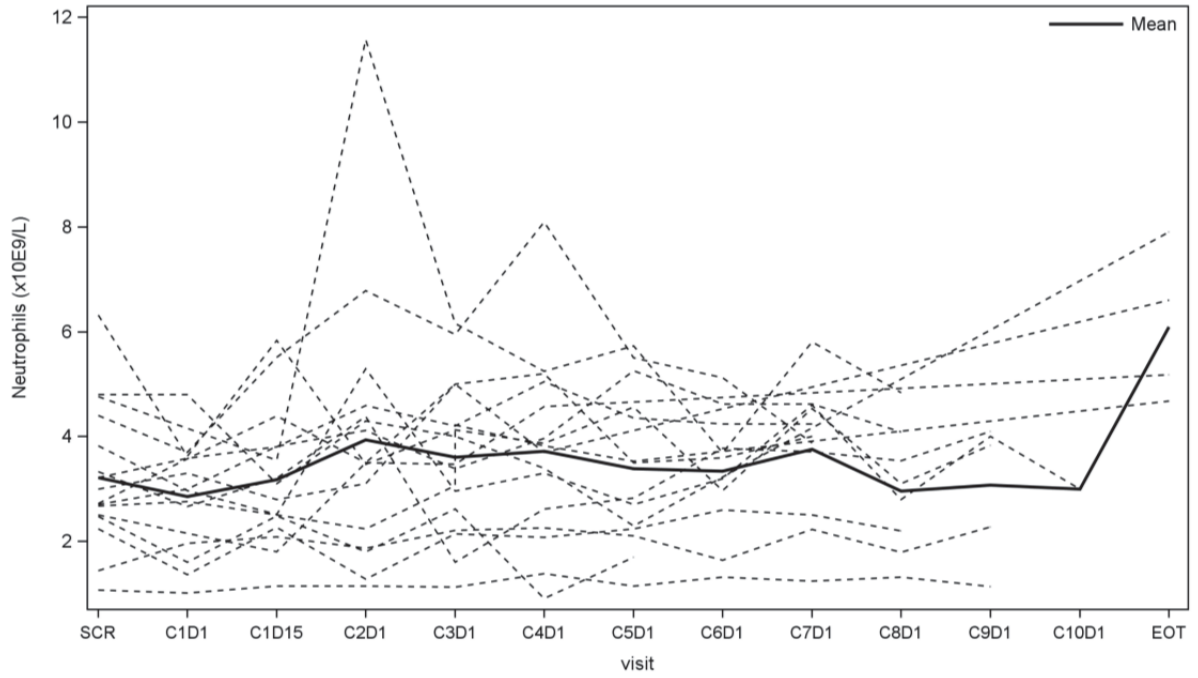
図 2.7.4-1 ヘモグロビン量の推移：MCL2002 試験




Key: SCR=Screening, CxDy=Cycle x Day y, EOT=End of Treatment
Note: Unscheduled visit have been excluded from the presentation.

[GSFLAB01.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\gsflab01.sas] 21AUG2015, 12:28
参照元：5.3.5.2.1 MCL2002 試験 CSR GSFLAB01

図 2.7.4-2 血小板数の推移：MCL2002 試験




Key: SCR=Screening, CxDy=Cycle x Day y, EOT=End of Treatment
Note: Unscheduled visit have been excluded from the presentation.

[GSFLAB01.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\gsflab01.sas] 21AUG2015, 12:28
参照元：5.3.5.2.1 MCL2002 試験 CSR GSFLAB01

図 2.7.4-3 ANC の推移：MCL2002 試験

### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験のヘモグロビン量，血小板数及び ANC の下方変動の発現割合を表 2.7.4-32 に，血液学的検査のパラメータのベースラインの重症度と投与後の最高重症度を示したシフトテーブルを表 2.7.4-付録-37 に示す。

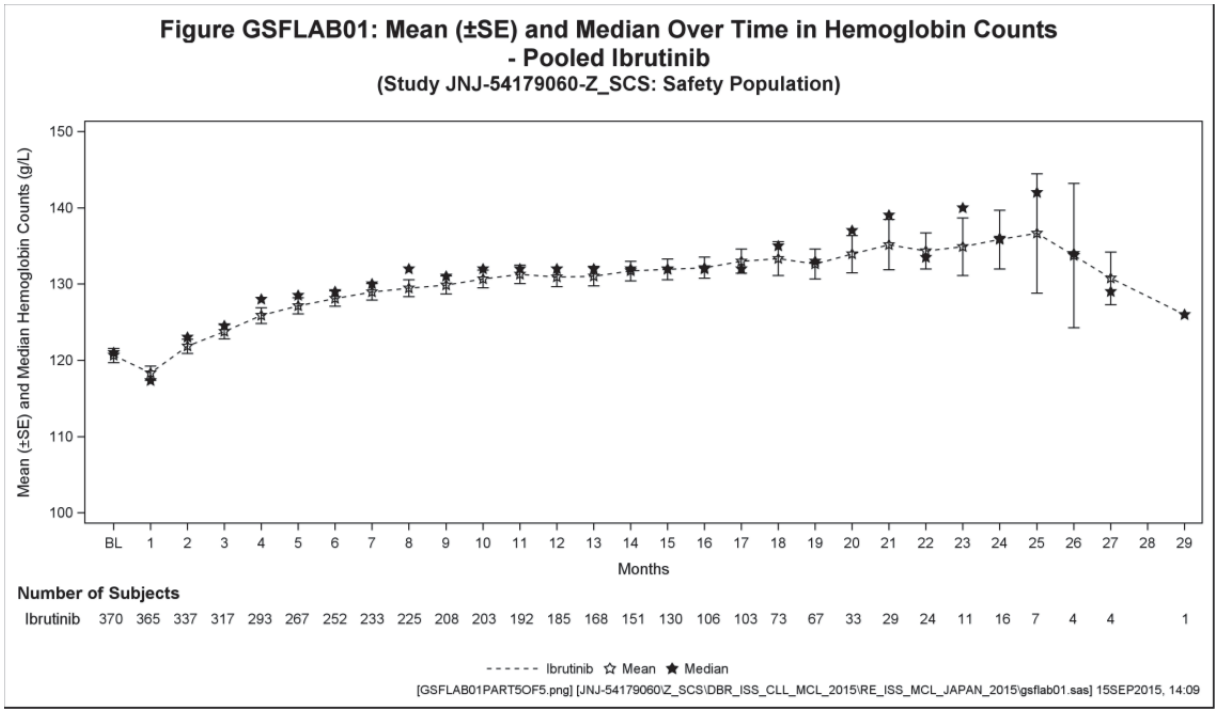
海外 3 試験併合（370 例）で，ヘモグロビン量，血小板数及び ANC の下方変動傾向が認められたが，ヘモグロビン量の減少及び血小板数の減少は Grade 1 又は 2 の減少が多かった。Grade 3 又は 4 のヘモグロビン量の減少，血小板数の減少及び ANC の減少はそれぞれ 8.4%（31 例），17.3%（64 例）及び 24.9%（92 例）に認められた。ヘモグロビン量及び血小板数は，ベースラインの Grade を維持又は 1 段階悪化した被験者が多かった。3 段階以上の悪化があった被験者は，ヘモグロビン減少，血小板数減少及び ANC の減少でそれぞれ 368 例中 3 例，368 例中 27 例及び 365 例中 67 例であった。MCL3001 試験のヘモグロビン量，血小板数及び ANC の下方変動の発現割合は，いずれもテムシロリムス群と比較してイブルチニブ群で低かった。

海外 3 試験併合のヘモグロビン量，血小板数及び ANC の平均値及び中央値の経時的な推移をそれぞれ図 2.7.4-4，図 2.7.4-5 及び図 2.7.4-6 に示し，1104 試験，MCL2001 試験及び MCL3001 試験の推移図を図 2.7.4-付録-1～図 2.7.4-付録-12 に示す。海外 3 試験併合のヘモグロビン量は増加傾向を示したが，血小板数及び ANC は，投与期間を通しておおむね安定しており，大きな変動は認められなかった。

表 2.7.4-32 血液学的検査異常値（下方変動）：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

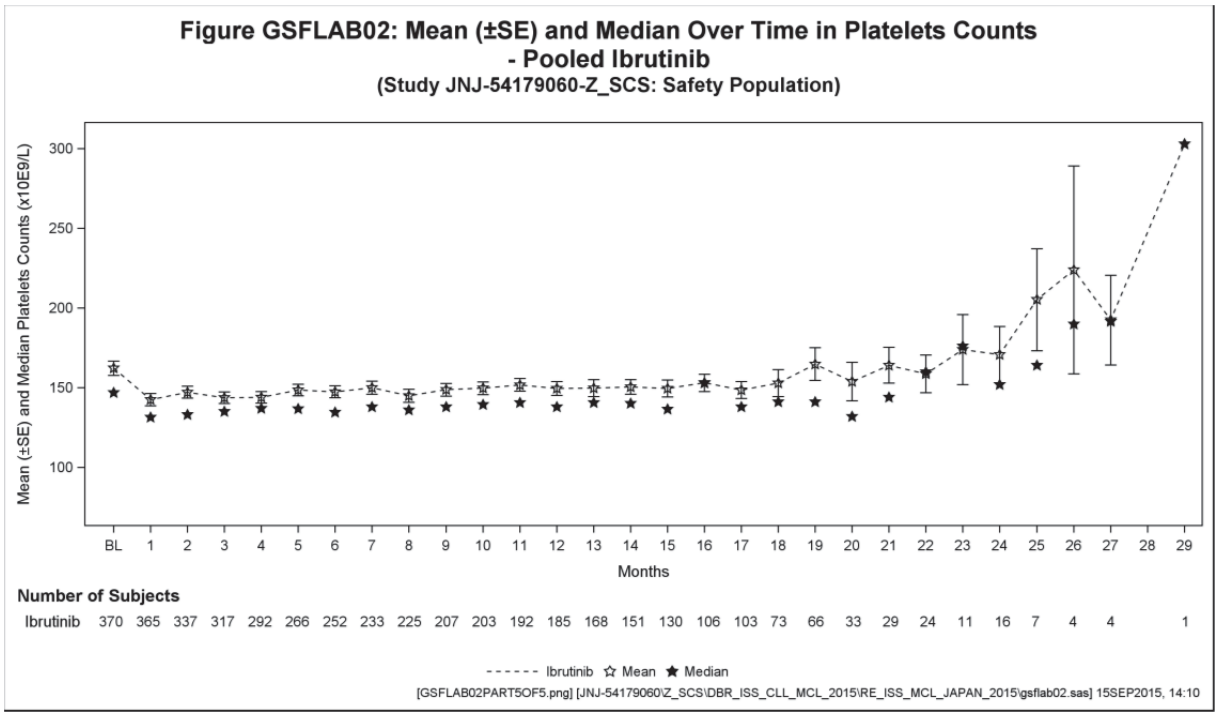
| | PCYC-1104 | | | MCL2001 | | | MCL3001 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ibrutinib | | | Ibrutinib | | | Ibrutinib | | | Temsirolimus | | | Pooled Ibrutinib | | |
| | Any Grade | Grade 1/2 | Grade 3/4 | Any Grade | Grade 1/2 | Grade 3/4 | Any Grade | Grade 1/2 | Grade 3/4 | Any Grade | Grade 1/2 | Grade 3/4 | Any Grade | Grade 1/2 | Grade 3/4 |
| Analysis set: safety population | 111 | | | 120 | | | 139 | | | 139 | | | 370 | | |
| Hemoglobin (Decrease) | 40 (36.0%) | 36 (32.4%) | 4 ( 3.6%) | 65 (54.2%) | 52 (43.3%) | 13 (10.8%) | 68 (48.9%) | 54 (38.8%) | 14 (10.1%) | 108 (77.7%) | 83 (59.7%) | 25 (18.0%) | 173 (46.8) | 142 (38.4) | 31 ( 8.4) |
| Platelets (Decrease) | 61 (55.0%) | 46 (41.4%) | 15 (13.5%) | 70 (58.3%) | 48 (40.0%) | 22 (18.3%) | 78 (56.1%) | 51 (36.7%) | 27 (19.4%) | 128 (92.1%) | 52 (37.4%) | 76 (54.7%) | 209 (56.5) | 145 (39.2) | 64 (17.3) |
| ANC (Decrease) | 50 (45.0%) | 23 (20.7%) | 27 (24.3%) | 57 (47.5%) | 24 (20.0%) | 33 (27.5%) | 60 (43.2%) | 28 (20.1%) | 32 (23.0%) | 104 (74.8%) | 68 (48.9%) | 36 (25.9%) | 167 (45.1) | 75 (20.3) | 92 (24.9) |

Key: ANC = Absolute neutrophils counts.
Note: Only subjects whose grade worsened from baseline were counted in numerator. Percentages are calculated with the number of subjects in safety population as the denominators.
参照元：5.3.5.3.1 ISS TSFLAB04PART1OF3; 5.3.5.3.1 ISS TSFLAB04PART2OF3; 5.3.5.3.1 ISS TSFLAB04PART3OF3



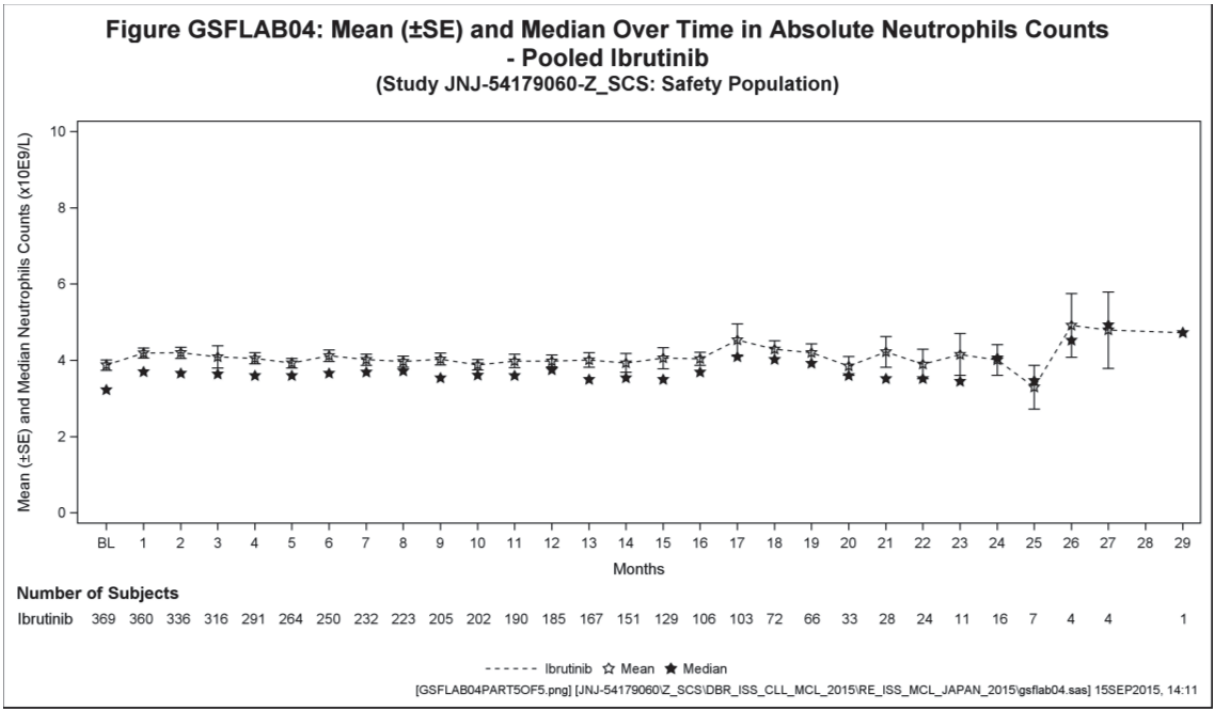

参照元：5.3.5.3.1 ISS GSFLAB01PART5OF5

図 2.7.4-4 ヘモグロビン量の推移：海外 3 試験併合




参照元：5.3.5.3.1 ISS GSFLAB02 PART5OF5

図 2.7.4-5 血小板数の推移：海外 3 試験併合




参照元：5.3.5.3.1 ISS GSFLAB04 PART5OF5

図 2.7.4-6 ANC の推移：海外 3 試験併合

### 2.7.4.3.1.1 リンパ球絶対数

一過性のリンパ球増加症はイブルチニブの薬力学的な影響として認められており，BTK 介在性の細胞のホーミング及び接着の阻害によって腫瘍細胞のリンパ節から末梢血中への動員が引き起こされる [1)] 。この現象を検討するため，リンパ球増加症を，リンパ球絶対数がベースラインから50%以上増加し，絶対数が 5.0 × $10^9$/L を超えた状態と定義し，リンパ球増加症の回復は，リンパ球絶対数がベースラインまで減少した状態又は 5.0 × $10^9$/L 未満となった状態と定義した [2)] 。

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験のリンパ球増加症の発現割合，発現時期及び発現期間を表 2.7.4-33 に示す。

安全性解析対象集団の 16 例中 7 例（43.8%）がイブルチニブ投与後にリンパ球増加症を発現した。投与後のリンパ球増加症の発現時期の中央値（範囲）は，2.14（1.1 - 21.3）週であった。Kaplan-Meier 法による回復までの期間の中央値（95%信頼区間）は 11.14（2.14 - 13.86）週で，投与後にリンパ球増加症を発現した被験者の約半数（4 例，57.1%）が回復した。

1 例で Grade 3 の重篤な白血球増加症が報告された。当該事象は疾患進行によるものと考えられ，イブルチニブとの因果関係は「関連なし」と判断された。白血球絶対数は，リンパ球増加症発現時（Day 143）で 386.9 × $10^9$/L であった。

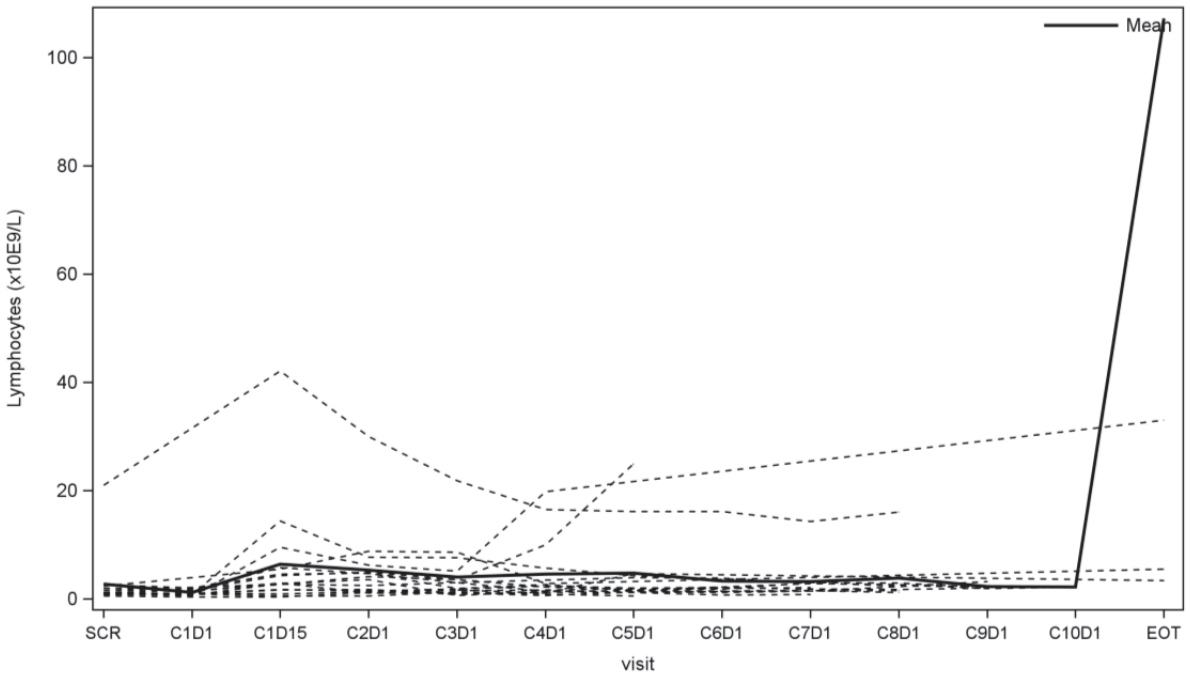
また，リンパ球絶対数の平均値の経時的な推移を図 2.7.4-7 に示す。リンパ球絶対数の平均値は投与期間を通しておおむね安定しており，大きな変動は認められなかった。

表 2.7.4-33 リンパ球増加症の概要：MCL2002 試験

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Subjects with Baseline and Any Post-baseline ALC Measurements | |
| N | 16 |
| With Lymphocytosis | 7 (43.8%) |
| Without Lymphocytosis | 9 (56.3%) |
| Time to Lymphocytosis (weeks)[a] | |
| N | 7 |
| Median | 2.14 |
| Range | (1.1, 21.3) |
| Duration of Lymphocytosis (weeks)[b] | |
| N | 7 |
| Resolved (event) | 4 (57.1%) |
| Not Resolved (censored) | 3 (42.9%) |
| Median (95% CI) | 11.14 (2.14, 13.86) |
| Range | (0.1+, 13.9) |

Key: ALC=Absolute Lymphocyte Count, '+'=Censored Observation
Note: Lymphocytosis was defined as ALC increasing >= 50% from baseline and achieving level >= $5x10^9$/L
Note: Resolution of Lymphocytosis occurred when ALC decreased to the baseline level or lower or achieving level of < $5x10^9$/L for subjects with lymphocytosis.
[a] Number of weeks from first dose date of study treatment to first post-baseline ALC which met the lymphocytosis criteria. Descriptive statistics are presented.
[b] Number of weeks from first post-baseline ALC which met the lymphocytosis criteria to the earliest date of the following ALC which met the resolution of lymphocytosis criteria or date of censoring (date of last non-missing ALC). The Kaplan-Meier method was used to estimate the median time.

[TSFLAB01.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsflab01.sas] 21AUG2015, 12:30
参照元：5.3.5.2.1 MCL2002 試験 CSR Table 31




Key: SCR=Screening, CxDy=Cycle x Day y, EOT=End of Treatment
Note: Unscheduled visit have been excluded from the presentation.
Note: One outlier (Subject 81000204´s Lymphocytes 386.9 x10E9/L) at EOT was removed from the individual connected-line due to the readability. This subject ended treatment with PD and SAE.

[GSFLAB01.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\gsflab01.sas] 21AUG2015, 12:28
参照元：5.3.5.2.1 MCL2002 試験 CSR GSFLAB01

図 2.7.4-7 リンパ球絶対数の推移：MCL2002 試験

b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験のベースラインの血液学的検査値を表 2.7.4-付録-38 に，リンパ球増加症の発現割合，発現時期及び発現期間を表 2.7.4-34 に，海外 3 試験併合のリンパ球絶対数の平均値及び中央値の経時的な推移を図 2.7.4-8 に，1104 試験，MCL2001 試験及び MCL3001 試験のリンパ球絶対数の平均値及び中央値の経時的な推移をそれぞれ図 2.7.4-付録-13，図 2.7.4-付録-14，図 2.7.4-付録-15 及び図 2.7.4-付録-16 に示す。

海外 3 試験併合（365 例）で 122 例（33.4%）がイブルチニブ投与後にリンパ球増加症を発現した。投与後のリンパ球増加症の発現時期の中央値（範囲）は 3.14（0.1 - 99.1）週であった。Kaplan-Meier 法による回復までの期間の中央値（95%信頼区間）は 7.1（5.4 - 9.1）週で，投与後にリンパ球増加症を発現したほとんどの被験者（77.0%，94 例）が回復した。

MCL3001 試験でリンパ球増加症はイブルチニブ群で 38.2%（136 例中 52 例），テムシロリムス群で 22.6%（137 例中 31 例）に発現した。投与後のリンパ球増加症の発現時期の中央値（範囲）はイブルチニブ群で 3.14（0.3 - 99.1）週，テムシロリムス群で 2.86（0.3 - 58.3）週であった。Kaplan-Meier 法による回復までの期間の中央値（95%信頼区間）は，イブルチニブ群で 6.1（3.1 - 9.1）週，テムシロリムス群で 2.1（1.1 - 6.1）週で，それぞれ 82.7%（52 例中 43 例）及び 71.0%（31 例中 22 例）の被験者が回復した。

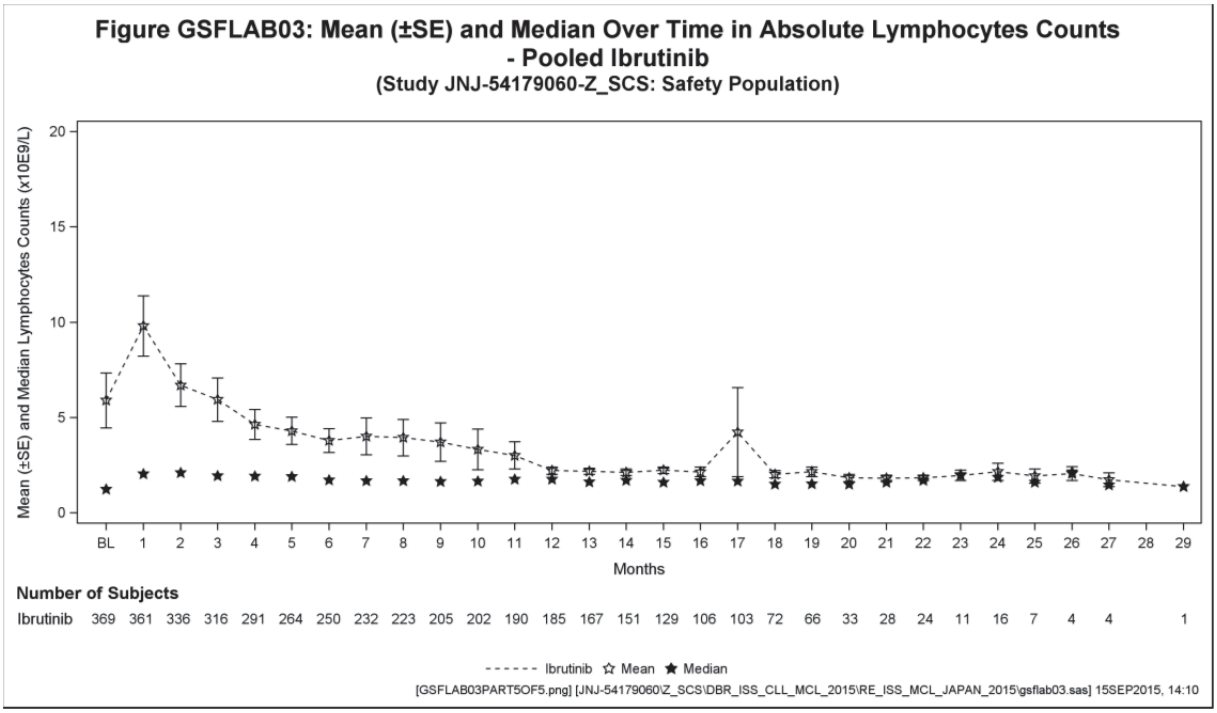
表 2.7.4-34 リンパ球増加症の概要：1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 | MCL2001 | MCL3001 | | Pooled |
|---|---|---|---|---|---|
| | Ibrutinib | Ibrutinib | Ibrutinib | Temsirolimus | Ibrutinib |
| Analysis set: safety population | 111 | 120 | 139 | 139 | 370 |
| Subjects with baseline and any post-baseline ALC measurements | 110 | 119 | 136 | 137 | 365 |
| With lymphocytosis | 37 (33.6%) | 33 (27.7%) | 52 (38.2%) | 31 (22.6%) | 122 (33.4%) |
| Without lymphocytosis | 73 (66.4%) | 86 (72.3%) | 84 (61.8%) | 106 (77.4%) | 243 (66.6%) |
| Time to peak ALC for subjects who had lymphocytosis (weeks) | | | | | |
| N | 37 | 33 | 52 | 31 | 122 |
| Mean (SD) | 12.24 (18.015) | 11.83 (14.963) | 16.34 (23.577) | 13.25 (19.625) | 13.87 (19.865) |
| Median | 4.14 | 6.14 | 3.14 | 5.14 | 4.29 |
| Range | (1.0; 68.1) | (0.7; 55.1) | (1.0; 99.1) | (0.3; 85.1) | (0.7; 99.1) |
| Time to treatment-emergent lymphocytosis (weeks)[a] | | | | | |
| N | 37 | 33 | 52 | 31 | 122 |
| Mean (SD) | 6.93 (14.778) | 8.25 (13.187) | 11.02 (20.094) | 6.60 (12.554) | 9.03 (16.863) |
| Median | 1.14 | 3.14 | 3.14 | 2.86 | 3.14 |
| Range | (0.1; 64.3) | (0.7; 55.0) | (0.3; 99.1) | (0.3; 58.3) | (0.1; 99.1) |
| Duration of treatment-emergent lymphocytosis (weeks)[b] | | | | | |
| N | 37 | 33 | 52 | 31 | 122 |
| Resolved (event) | 25 (67.6%) | 26 (78.8%) | 43 (82.7%) | 22 (71.0%) | 94 (77.0%) |
| Not resolved (censored) | 12 (32.4%) | 7 (21.2%) | 9 (17.3%) | 9 (29.0%) | 28 (23.0%) |
| Median (95% CI) | 8.0 (5.4, 14.1) | 6.1 (3.1, 10.3) | 6.1 (3.1, 9.1) | 2.1 (1.1, 6.1) | 7.1 (5.4, 9.1) |
| Range | (0.1+, 35.1) | (0.3, 30.1+) | (0.1+, 43.3+) | (0.1+, 20.3) | (0.1+, 43.3+) |

Key: ALC= Absolute lymphocyte count, + = censored value.
Note: Lymphocytosis was defined as ALC increasing >=50% from baseline and achieving level >= 5x10E9 /L.
Resolution of Lymphocytosis occurred when ALC decreased to the baseline level or lower or achieving level of < 5x10E9/L for subjects with lymphocytosis.
[a] Time to lymphocytosis was defined as the number of weeks from first dose date of study treatment to first post-baseline ALC which met the lymphocytosis criteria. Descriptive statistics are presented.
[b] Duration of lymphocytosis was defined as the number of weeks from first post-baseline ALC which met the lymphocytosis criteria to the earliest date of the following ALC which met the resolution of lymphocytosis criteria or date of censoring (date of last non-missing ALC). The Kaplan-Meier method was used to estimate the median time.
Percentages are calculated with the number of subjects who had a baseline and any post-baseline ALC.

[TSFLAB08.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsflab08.sas] 15SEP2015, 14:12

参照元：5.3.5.3.1 ISS TSFLAB08




参照元：5.3.5.3.1 ISS GSFLAB03PART5OF5

図 2.7.4-8 リンパ球絶対数の推移：海外 3 試験併合

### 2.7.4.3.2 血液生化学検査

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験の血液生化学検査のパラメータのベースラインの重症度と投与後の最高重症度を示したシフトテーブルを CSR に示す（【5.3.5.2.1 CSR TSFLAB03 p. 174】）。

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験の血液生化学検査のパラメータのベースラインの重症度と投与後の最高重症度を示したシフトテーブルを表 2.7.4-付録-39 に示す。

#### 2.7.4.3.2.1 肝機能異常

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験で，イブルチニブ投与後に，Grade 3 又は 4 の ALT，AST 又はビリルビン値の増加は認められなかった。

また，MCL2002 試験の ALT，AST 及びビリルビンの平均値の経時的な推移を CSR に示す（【5.3.5.2.1 CSR GSFLAB01 p. 178】）。投与期間中の肝機能検査値に一定の傾向は認められなかった。

肝機能に関する有害事象については 2.7.4.2.1.5(13)a)項に記載した。

b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合で，ALT，AST 又は総ビリルビン値が増加した被験者は少なかった。認められた ALT，AST 又は総ビリルビン値の増加のほとんどは Grade 1 又は 2 であり，Grade 3 の ALT 増加は 365 例中 5 例（1.4%），Grade 3 の AST 増加は 365 例中 1 例（0.3%），Grade 4 の AST 増加は 365 例中 2 例（0.5%），Grade 3 の総ビリルビン増加は 366 例中 5 例（1.4%），Grade 4 の総ビリルビン増加は 366 例中 1 例（0.3%）に認められ，Grade 4 の ALT 増加は認められなかった。

肝機能に関する有害事象については 2.7.4.2.1.5(13)b)項に記載した。

### 2.7.4.3.2.2 血清クレアチニン異常

a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験の安全性解析対象集団 16 例のうち，Grade 3 の血清クレアチニン増加が 1 例（6.3%）に認められたが，Grade 4 の血清クレアチニン増加は認められなかった。Grade 3 の血清クレアチニン増加が認められた被験者は腎機能異常を有しており，ベースラインで Grade 2 の血清クレアチニン増加が認められていた。

また，血清クレアチニンの平均値の経時的な推移を CSR に示す（【5.3.5.2.1 CSR GSFLAB01 p. 178】）。血清クレアチニンの平均値は，投与期間を通しておおむね安定しており，大きな変動は認められなかった。

腎機能に関する有害事象については 2.7.4.2.1.5(12)a)項に記載した。

b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合（367 例）で，血清クレアチニン値が増加した被験者は少なかった。認められた血清クレアチニン値の増加のほとんどは Grade 1 又は 2 であり，Grade 3 の血清クレアチニン増加は 5 例（1.4%），Grade 4 の血清クレアチニン増加は 1 例（0.3%）に認められた。

海外 3 試験併合のクレアチニン・クリアランス（creatinine clearance，以下 CrCL）のベースラインからのシフトテーブルを表 2.7.4-付録-40 に示す。海外 3 試験併合（366 例）の 264 例がベースラインの値を維持し，7 例（1.9%）が CrCL≧60 mL/分から CrCL <30 mL/分に，77 例（21%）が CrCL ≧ 60 mL/分から 30 mL/分 ≦ CrCL<60 mL/分に，8 例（2.2%）が 30 mL/分 ≦ CrCL<60 mL/分から CrCL < 30 mL/分に悪化した。

腎機能に関する有害事象については 2.7.4.2.1.5(12)b)項に記載した。

### 2.7.4.3.2.3 血清電解質異常

a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

安全性解析対象集団 16 例で，イブルチニブ投与後に血清カリウム及び血清ナトリウムの減少が，それぞれ 5 例（31.3%）及び 4 例（25%）に認められたが，ほとんどの減少は Grade 1 又は 2 であった。Grade 3 以上の減少は，Grade 3 の血清カリウム減少が 1 例（6.3%）に認められた。また，Grade 1 の血清カリウム増加が 1 例（6.3%）に認められ，血清ナトリウム増加は認められなかった（【5.3.5.2.1 CSR TSFLAB03 p. 174】）。

b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合で，イブルチニブ投与後の血清カリウム及び血清ナトリウムが減少又は増加した被験者は少なかった。認められた血清カリウム及び血清ナトリウムの減少又は増加のほとんどは Grade 1 又は 2 であった。血清カリウム減少は，Grade 3 が 367 例中 14 例（3.8%），Grade 4 が 367 例中 2 例（0.5%）に認められ，血清カリウム増加は，Grade 3 が 367 例中 3 例（0.8%），Grade 4 が 367 例中 4 例（1.1%）に認められた。血清ナトリウム減少は，Grade 3 が 368 例中 14 例（3.8%），Grade 4 が 368 例中 3 例（0.8%）に認められ，血清ナトリウム増加は，Grade 3 が 368 例中 1 例（0.3%）に認められ，Grade 4 の血清ナトリウム増加は認められなかった。

## 2.7.4.4 バイタルサイン，身体的所見及び安全性に関連する他の観察項目

### 2.7.4.4.1 バイタルサイン

a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験では，バイタルサインについて解析を実施していない。

b) 海外の再発又は難治性 MCL 患者対象試験（1104 試験）

1104 試験では，臨床的に重要な変化は認められなかった。

### 2.7.4.4.2 心電図

a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験では，イブルチニブ投与後の心電図の評価時点を規定せず，治験担当医師の判断で心電図を記録した。MCL2002 試験では，心電図について解析を実施していない。

b) 海外の再発又は難治性 MCL 患者対象試験（MCL2001 試験，MCL3001 試験）

MCL2001 試験（120 例）で，治験担当医師により臨床的に重要であると判断された異常は 15 例（12.5%）に認められた（【5.3.5.2.3-1 CSR TSFECG04 p. 298】）。このうち，心房細動は 11 例に認められた。

6 例（5.3%）に投与期間中に心電図で QT 延長が認められた。このうち 3 例は，ベースラインで QT 間隔の延長が認められていた。いずれも治験担当医師により臨床的に重要ではないと判断されたため有害事象として報告されなかった。QT 延長が認められた被験者のベースラインの Fridericia formula を用いて心拍数で補正した QT 間隔（QT interval corrected for heart rate, using Fridericia formula，以下 QTcF）の範囲は 407 - 501 msec であり，ベースラインから 60 msec を超える QTcF の延長は認められなかった（【5.3.5.2.3-1 CSR LSFECG05 p. 215】）。

治験薬投与開始後に 2 例で QTcF が 500 msec 以上となったが，いずれの被験者もベースラインの QTcF が 500 msec 以上であった。2 例（1.7%）で投与期間中に 60 msec を超える延長が認められたが（【5.3.5.2.3-1 CSR TSFECG03 p. 297】），いずれも QTcF は 500 msec 以上ではなく

（【5.3.5.2.3-1 CSR LSFECG06 p. 218】），治験担当医師により臨床的に重要ではないと判断された。

ベースラインの QTcF の平均値（範囲）は 426（356 - 584）msec であった。ベースラインからの変化量の平均値は，サイクル 1 の Day 1 で-3.8 msec，サイクル 2 の Day 1 で-11.8 msec であった（【5.3.5.2.3-1 CSR TSFECG01 p. 295】）。

MCL3001 試験のイブルチニブ群のベースライン及びベースライン後に少なくとも 1 回心電図を記録した 62 例で，Bazett formula を用いて心拍数で補正した QT 間隔（QT interval corrected for heart rate, using Bazett formula，以下 QTcB）に，60 msec を超える延長が 3 例（4.8%），30 msec 以上 60 msec 以下の延長が 9 例（14.5%）に認められた。QTcF に，60 msec を超える延長が 2 例（3.2%），30 msec 以上 60 msec 以下の延長が 4 例（6.5%）に認められた（【5.3.5.1.1 CSR TSFECG05 p. 926】）。60 msec を超える QTcB 又は QTcF の延長が認められた被験者のうち 1 例で，ベースラインからサイクル 2 の Day 1 投与後 2 時間に，QTcB が 88 msec 延長し，QTcF が 70 msec 延長した。（【5.3.5.1.1 CSR LSFECG01 p. 298】）。当該被験者はベースラインで徐脈が認められており，心拍数が正常範囲内に増加した後に心電図を記録した。ベースライン後に数値的な QTc 延長が認められたが，その値は正常範囲内であり，この所見の臨床的な重要性は限定的であった。2 例で QTcB 及び QTcF がいずれも 500 msec 超となったが，いずれの被験者も試験期間中に 500 msec 未満に短縮した。

### c) 健康成人対象試験（CLL1007 試験）

Part 1 では，臨床的に重要な変化は認められなかった。

Part 2 では，心電図解析の結果，イブルチニブを治療用量（840 mg）又は治療用量を上回る用量（1680 mg）で投与したときに，QT/QTc 間隔の延長が起こらないことが示唆された。QT については，QTcF，QTcB 及び試験固有の補正係数を用いて心拍数で補正した QT 間隔（QT interval corrected for heart-rate, using a study-specific power model，以下 QTcP）を求め，QTcP を QT/QTc 間隔の評価における主要パラメータとした。プラセボ，イブルチニブ 840 mg 又はイブルチニブ 1680 mg を投与したときの QTcP の平均値は，ベースラインと比べて投与後の多くの評価時点で短縮した。対照的に，モキシフロキサシン 400 mg を投与したときの QTcP の平均値は，ベースラインと比べて投与後の多くの評価時点で延長した。いずれの治験薬を投与した被験者でも，投与後に QTcP，QTcF 又は QTcB が 450 msec 超となった又はベースラインから 60 msec を超えて延長した被験者は認められなかった。プラセボ，イブルチニブ 840 mg 又はイブルチニブ 1680 mg を投与した被験者で，ベースラインから 30 msec を超えて延長した被験者は認められなかった。また，イブルチニブの血漿中濃度がピークに達したときの，ベースラインからの変化量のプラセボとの差の推定値（90%信頼区間）は，イブルチニブ 840 mg を投与した被験者で-1.9178 msec（-4.23，0.39），イブルチニブ 1680 mg を投与した被験者で -5.2706 msec（-9.41，-1.13）であった。イブルチニブのいずれの用量を投与した被験者でも臨床的に重要な影響は認められず，他の心電図パラメータ又は心電図波形でも臨床的に重要な影響は認められなかった。

## 2.7.4.5 特別な患者集団及び状況下における安全性

### 2.7.4.5.1 内因性要因

#### 2.7.4.5.1.1 年齢

**a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）**

MCL2002 試験の有害事象を，65 歳未満及び 65 歳以上の年齢別並びに 70 歳未満及び 70 歳以上の年齢別に集計した。65 歳未満及び 65 歳以上の年齢別の有害事象の概要を表 2.7.4-35 に，70 歳未満及び 70 歳以上の年齢別の有害事象の概要を表 2.7.4-36 に示す。組入れ時点で，安全性解析対象集団の 75.0%（12/16 例）が 65 歳以上，56.3%（9/16 例）が 70 歳以上であった（表 2.7.4-7）。

65 歳未満及び 65 歳以上の年齢別の有害事象の概要では，65 歳未満の被験者が 4 例と少数であり，部分集団の差異についての明確な解釈は困難であるものの，顕著な差異は認められなかった。また，70 歳未満及び 70 歳以上の年齢別の有害事象の概要では，顕著な差異は認められなかった。

表 2.7.4-35 65 歳未満及び 65 歳以上の年齢別の有害事象の概要：MCL2002 試験

| | Ibrutinib | | |
|---|---|---|---|
| | Age Group | | |
| | < 65 | >= 65 | All |
| Analysis Set: All Treated Population | 4 | 12 | 16 |
| Number of Subjects with TEAE | 4 (100.0%) | 12 (100.0%) | 16 (100.0%) |
| Number of Subjects with TEAE of Toxicity Grade 3 or Higher | 2 (50.0%) | 6 (50.0%) | 8 (50.0%) |
| Number of Subjects with Drug Related TEAE | 4 (100.0%) | 11 (91.7%) | 15 (93.8%) |
| Number of Subjects with Serious TEAE | 1 (25.0%) | 4 (33.3%) | 5 (31.3%) |
| Number of Subjects with Drug Related Serious TEAE | 0 | 1 (8.3%) | 1 (6.3%) |
| Number of Subjects with TEAE Leading to Death | 0 | 3 (25.0%) | 3 (18.8%) |
| Number of Subjects with TEAE Leading to Drug Withdrawn | 1 (25.0%) | 1 (8.3%) | 2 (12.5%) |
| Number of Subjects with TEAE Leading to Dose Reduction | 1 (25.0%) | 1 (8.3%) | 2 (12.5%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Drug related AE is defined as an event related to study agent (relationship to study agent is possible, probable or very likely).

参照元：5.3.5.2.1 MCL2002 試験 CSR TSFAE02A

表 2.7.4-36 70 歳未満及び 70 歳以上の年齢別の有害事象の概要：MCL2002 試験

| | Ibrutinib | | |
|---|---|---|---|
| | Age Group | | |
| | < 70 | >= 70 | All |
| Analysis Set: All Treated Population | 7 | 9 | 16 |
| Number of Subjects with TEAE | 7 (100.0%) | 9 (100.0%) | 16 (100.0%) |
| Number of Subjects with TEAE of Toxicity Grade 3 or Higher | 3 (42.9%) | 5 (55.6%) | 8 (50.0%) |
| Number of Subjects with Drug Related TEAE | 6 (85.7%) | 9 (100.0%) | 15 (93.8%) |
| Number of Subjects with Serious TEAE | 2 (28.6%) | 3 (33.3%) | 5 (31.3%) |
| Number of Subjects with Drug Related Serious TEAE | 0 | 1 (11.1%) | 1 (6.3%) |
| Number of Subjects with TEAE Leading to Death | 1 (14.3%) | 2 (22.2%) | 3 (18.8%) |
| Number of Subjects with TEAE Leading to Drug Withdrawn | 1 (14.3%) | 1 (11.1%) | 2 (12.5%) |
| Number of Subjects with TEAE Leading to Dose Reduction | 2 (28.6%) | 0 | 2 (12.5%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Drug related AE is defined as an event related to study agent (relationship to study agent is possible, probable or very likely).

参照元：5.3.5.2.1 MCL2002 試験 CSR TSFAE02A_1

b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験の有害事象を，65 歳未満及び 65 歳以上の年齢別，70 歳未満及び 70 歳以上の年齢別並びに 75 歳未満及び 75 歳以上の年齢別に集計した。海外 3 試験併合の年齢別の有害事象の概要をそれぞれ表 2.7.4-37，表 2.7.4-38 及び表 2.7.4-39 に，1104 試験及び MCL2001 試験並びに MCL3001 試験の年齢別の有害事象の概要を表 2.7.4-付録-41～表 2.7.4-付録-46 に示す。また，海外 3 試験併合の 65 歳未満及び 65 歳以上，70 歳未満及び 70 歳以上並びに 75 歳未満及び 75 歳以上の年齢別の有害事象の集計をそれぞれ表 2.7.4-付録-47，表 2.7.4-付録-48 及び表 2.7.4-付録-49 に示す。組入れ時点で，海外 3 試験併合（370 例）の 62.4%（231 例）が 65 歳以上，43.2%（160 例）が 70 歳以上，21.1%（78 例）が 75 歳以上であった（表 2.7.4-10）。

海外 3 試験併合で，重篤な有害事象［65 歳未満：35.3%（139 例中 49 例），65 歳以上：60.2%（231 例中 139 例），70 歳未満：41.4%（210 例中 87 例），70 歳以上：63.1%（160 例中 101 例），75 歳未満：47.3%（292 例中 138 例），75 歳以上：64.1%（78 例中 50 例）］，Grade 3 以上の重篤な有害事象［65 歳未満：30.2%（139 例中 42 例），65 歳以上 55.8%（231 例中 129 例），70 歳未満：37.1%（210 例中 78 例），70 歳以上：58.1%（160 例中 93 例），75 歳未満：42.8%（292 例中 125 例），75 歳以上：59.0%（78 例中 46 例）］及び Grade 3 以上の有害事象［65 歳未満：59.7%（139 例中 83 例），65 歳以上：78.8%（231 例中 182 例），70 歳未満：65.2%（210 例中 137 例），70 歳以上：80.0%（160 例中 128 例），75 歳未満：68.2%（292 例中 199 例），75 歳以上：84.6%（78 例中 66 例）］は高齢の被験者で発現割合が高くなる傾向が認められた。65 歳未満と 65 歳以上で発現割合に 5%以上差が認められた Grade 3 以上の有害事象は，肺炎［65 歳未満：5.0%（139 例中 7 例），65 歳以上：11.3%（231 例中 26 例）］，呼吸困難［65 歳未満：0%（139 例中 0 例），65 歳以上：5.2%（231 例中 12 例）］及び貧血［65 歳未満：5.0%（139 例中 7 例），65 歳以上：10.0%（231 例中 23 例）］，70 歳未満と 70 歳以上では，肺炎［70 歳未満：6.2%（210 例中 13 例），70 歳以上：12.5%（160 例中 20 例）］，疲労［70 歳未満：1.9%（210 例中 4 例），70 歳以上：7.5%（160 例中 12 例）］及び心房細動［70 歳未満：2.4%（210 例中 5 例），70 歳以上：7.5%（160 例中 12 例）］，75 歳未満と 75 歳以上では，貧血［75 歳未満：6.2%（292 例中 18 例），75 歳以上：15.4%（78 例中 12 例）］であった。

表 2.7.4-37 65 歳未満及び 65 歳以上の年齢別の有害事象の概要：海外 3 試験併合

| | Pooled Ibrutinib | |
|---|---|---|
| | Age (years) | |
| | >= 65 | < 65 |
| Analysis Set: Safety Population | 231 | 139 |
| Any TEAE | 229 (99.1%) | 135 (97.1%) |
| Grade >= 3 | 182 (78.8%) | 83 (59.7%) |
| Drug related [a] | 191 (82.7%) | 117 (84.2%) |
| Grade >= 3 | 113 (48.9%) | 43 (30.9%) |
| Any TESAE | 139 (60.2%) | 49 (35.3%) |
| Grade >= 3 | 129 (55.8%) | 42 (30.2%) |
| Drug related [a] | 65 (28.1%) | 17 (12.2%) |
| TEAE leading to treatment discontinuation | 38 (16.5%) | 10 (7.2%) |
| TEAE leading to treatment dose reduction | 22 (9.5%) | 6 (4.3%) |
| TEAE with outcome death | 34 (14.7%) | 11 (7.9%) |
| Deaths within 30 days after last dose of study treatment [b] | 45 (19.5%) | 18 (12.9%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE11APART3OF3

表 2.7.4-38 70 歳未満及び 70 歳以上の年齢別の有害事象の概要：海外 3 試験併合

| | Pooled Ibrutinib | |
|---|---|---|
| | Age (years) | |
| | >= 70 | < 70 |
| Analysis Set: Safety Population | 160 | 210 |
| Any TEAE | 158 (98.8%) | 206 (98.1%) |
| Grade >= 3 | 128 (80.0%) | 137 (65.2%) |
| Drug related [a] | 137 (85.6%) | 171 (81.4%) |
| Grade >= 3 | 82 (51.3%) | 74 (35.2%) |
| Any TESAE | 101 (63.1%) | 87 (41.4%) |
| Grade >= 3 | 93 (58.1%) | 78 (37.1%) |
| Drug related [a] | 47 (29.4%) | 35 (16.7%) |
| TEAE leading to treatment discontinuation | 28 (17.5%) | 20 (9.5%) |
| TEAE leading to treatment dose reduction | 13 (8.1%) | 15 (7.1%) |
| TEAE with outcome death | 25 (15.6%) | 20 (9.5%) |
| Deaths within 30 days after last dose of study treatment [b] | 32 (20.0%) | 31 (14.8%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE11BPART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae11b.sas]
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参照元：5.3.5.3.1 ISS TSFAE11BPART3OF3

表 2.7.4-39 75 歳未満及び 75 歳以上の年齢別の有害事象の概要：海外 3 試験併合

| | Pooled Ibrutinib | |
|---|---|---|
| | Age (years) | |
| | >= 75 | < 75 |
| Analysis Set: Safety Population | 78 | 292 |
| Any TEAE | 78 (100.0%) | 286 (97.9%) |
| Grade >= 3 | 66 (84.6%) | 199 (68.2%) |
| Drug related [a] | 69 (88.5%) | 239 (81.8%) |
| Grade >= 3 | 39 (50.0%) | 117 (40.1%) |
| Any TESAE | 50 (64.1%) | 138 (47.3%) |
| Grade >= 3 | 46 (59.0%) | 125 (42.8%) |
| Drug related [a] | 21 (26.9%) | 61 (20.9%) |
| TEAE leading to treatment discontinuation | 14 (17.9%) | 34 (11.6%) |
| TEAE leading to treatment dose reduction | 6 (7.7%) | 22 (7.5%) |
| TEAE with outcome death | 11 (14.1%) | 34 (11.6%) |
| Deaths within 30 days after last dose of study treatment [b] | 15 (19.2%) | 48 (16.4%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE11CPART3OF3

### 2.7.4.5.1.2　性別

#### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験の有害事象を性別に集計した。性別の有害事象の概要を表 2.7.4-40 に示す。安全性解析対象集団の男性は 75.0%（12/16 例）であった（表 2.7.4-7）。

女性被験者が 4 例と少数であり，部分集団の差異についての明確な解釈は困難であるものの，有害事象の概要に顕著な差異は認められなかった。

表 2.7.4-40 性別の有害事象の概要：MCL2002 試験

| | Ibrutinib | | |
|---|---|---|---|
| | Sex | | |
| | Male | Female | All |
| Analysis Set: All Treated Population | 12 | 4 | 16 |
| Number of Subjects with TEAE | 12 (100.0%) | 4 (100.0%) | 16 (100.0%) |
| Number of Subjects with TEAE of Toxicity Grade 3 or Higher | 6 (50.0%) | 2 (50.0%) | 8 (50.0%) |
| Number of Subjects with Drug Related TEAE | 11 (91.7%) | 4 (100.0%) | 15 (93.8%) |
| Number of Subjects with Serious TEAE | 4 (33.3%) | 1 (25.0%) | 5 (31.3%) |
| Number of Subjects with Drug Related Serious TEAE | 0 | 1 (25.0%) | 1 (6.3%) |
| Number of Subjects with TEAE Leading to Death | 3 (25.0%) | 0 | 3 (18.8%) |
| Number of Subjects with TEAE Leading to Drug Withdrawn | 1 (8.3%) | 1 (25.0%) | 2 (12.5%) |
| Number of Subjects with TEAE Leading to Dose Reduction | 1 (8.3%) | 1 (25.0%) | 2 (12.5%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Drug related AE is defined as an event related to study agent (relationship to study agent is possible, probable or very likely).

参照元：5.3.5.2.1 MCL2002 試験 CSR TSFAE02B

#### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験の有害事象を性別に集計した。海外 3 試験併合での性別の有害事象の概要を表 2.7.4-41 に，1104 試験及び MCL2001 試験並びに

MCL3001 試験の性別の有害事象の概要を表 2.7.4-付録-50 及び表 2.7.4-付録-51 に示す。また，海外 3 試験併合の性別の有害事象の集計を表 2.7.4-付録-52 に示す。海外 3 試験併合（370 例）で男性は 78.1%（289 例）であった（表 2.7.4-10）。

海外 3 試験併合で，重篤な有害事象［男性：54.7%（289 例中 158 例），女性：37.0%（81 例中 30 例）］，Grade 3 以上の重篤な有害事象［男性：49.8%（144 例），女性：33.3%（27 例）］，Grade 3 以上の有害事象［男性：75.4%（218 例），女性：58.0%（47 例）］及びイブルチニブとの関連性がある Grade 3 以上の有害事象［男性：44.6%（129 例），女性：33.3%（27 例）］は男性被験者で発現割合が高い傾向が認められた。性別で 5%以上差が認められた Grade 3 以上の有害事象は，肺炎［男性：10.0%（29 例），女性：4.9%（4 例）］，好中球減少症［男性：17.6%（51 例），女性：12.3%（10 例）］，貧血［男性：6.9%（20 例），女性：12.3%（10 例）］及び低カリウム血症［男性：2.8%（8 例），女性：8.6%（7 例）］であった。

**表 2.7.4-41 性別の有害事象の概要：海外 3 試験併合**

| | Pooled Ibrutinib | |
|---|---|---|
| | Sex | |
| | Male | Female |
| Analysis Set: Safety Population | 289 | 81 |
| Any TEAE | 285 (98.6%) | 79 (97.5%) |
| Grade >= 3 | 218 (75.4%) | 47 (58.0%) |
| Drug related [a] | 241 (83.4%) | 67 (82.7%) |
| Grade >= 3 | 129 (44.6%) | 27 (33.3%) |
| Any TESAE | 158 (54.7%) | 30 (37.0%) |
| Grade >= 3 | 144 (49.8%) | 27 (33.3%) |
| Drug related [a] | 69 (23.9%) | 13 (16.0%) |
| TEAE leading to treatment discontinuation | 41 (14.2%) | 7 (8.6%) |
| TEAE leading to treatment dose reduction | 24 (8.3%) | 4 (4.9%) |
| TEAE with outcome death | 40 (13.8%) | 5 (6.2%) |
| Deaths within 30 days after last dose of study treatment [b] | 52 (18.0%) | 11 (13.6%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE12PART3OF3

#### 2.7.4.5.1.3 人種

MCL2002 試験は全例が日本人被験者であり，人種別の集計はしていない。

海外 3 試験併合の解析対象例の大多数が白人（89.2%，370 例中 330 例）であったことから，人種別の集計はしていない。

#### 2.7.4.5.1.4 ベースラインの肝機能

##### a) 国内の再発又は難治性 MCL 患者対象試験（MCL2002 試験）

MCL2002 試験の有害事象をベースラインの肝機能別に集計した。ベースラインの肝機能は，ベースラインの ALT，AST 又は総ビリルビンのいずれかが正常範囲上限を超えた場合を異常とした。ベースラインの肝機能別の有害事象の概要を表 2.7.4-42 に示す。また，ベースラインの肝

機能別の有害事象の集計を表 2.7.4-付録-53 に示す。安全性解析対象集団 16 例で，5 例にベースラインで肝機能に異常があった。

ベースラインで肝機能に異常があった被験者が 5 例と少数であり，部分集団の差異についての明確な解釈は困難であるものの，有害事象の概要に顕著な差異は認められなかった。

表 2.7.4-42 ベースラインの肝機能別の有害事象の概要：MCL2002 試験

| | Ibrutinib | | |
|---|---|---|---|
| | Baseline Liver Function Abnormality | | |
| | Normal | Abnormal | All |
| Analysis Set: All Treated Population | 11 | 5 | 16 |
| Number of Subjects with TEAE | 11 (100.0%) | 5 (100.0%) | 16 (100.0%) |
| Number of Subjects with TEAE of Toxicity Grade 3 or Higher | 5 (45.5%) | 3 (60.0%) | 8 (50.0%) |
| Number of Subjects with Drug Related TEAE | 10 (90.9%) | 5 (100.0%) | 15 (93.8%) |
| Number of Subjects with Serious TEAE | 3 (27.3%) | 2 (40.0%) | 5 (31.3%) |
| Number of Subjects with Drug Related Serious TEAE | 1 (9.1%) | 0 | 1 (6.3%) |
| Number of Subjects with TEAE Leading to Death | 1 (9.1%) | 2 (40.0%) | 3 (18.8%) |
| Number of Subjects with TEAE Leading to Drug Withdrawn | 2 (18.2%) | 0 | 2 (12.5%) |
| Number of Subjects with TEAE Leading to Dose Reduction | 2 (18.2%) | 0 | 2 (12.5%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Drug related AE is defined as an event related to study agent (relationship to study agent is possible, probable or very likely).

参照元：5.3.5.2.1 MCL2002 試験 CSR TSFAE02E

### b) 海外の再発又は難治性 MCL 患者対象試験（海外 3 試験併合）

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験の有害事象をベースラインの肝機能別に集計した。ベースラインの肝機能は，ベースラインの ALT 又は総ビリルビンのいずれかが正常範囲上限を超えた場合を異常とした。海外 3 試験併合でのベースラインの肝機能別の有害事象の概要を表 2.7.4-43 に，1104 試験及び MCL2001 試験並びに MCL3001 試験のベースラインの肝機能別の有害事象の概要を表 2.7.4-付録-54 及び表 2.7.4-付録-55 に示す。また，海外 3 試験併合のベースラインの肝機能別の有害事象の集計を表 2.7.4-付録-56 に示す。海外 3 試験併合（369 例）で 49 例にベースラインで肝機能に異常があった。

海外 3 試験併合で，イブルチニブ最終投与後 30 日以内の死亡［肝機能正常：15.3%（320 例中 49 例），肝機能異常：26.5%（49 例中 13 例）］及び Grade 3 以上の有害事象［肝機能正常：70.0%（224 例），肝機能異常：81.6%（40 例）］はベースラインで肝機能に異常があった被験者で発現割合が高い傾向が認められた。ベースラインの肝機能別で 5%以上差が認められた Grade 3 又は 4 の有害事象は，血小板減少症［肝機能正常：9.7%（31 例），肝機能異常：20.4%（10 例）］，貧血［肝機能正常：6.9%（22 例），肝機能異常：16.3%（8 例）］であった。ベースラインの肝機能別で 5%以上差が認められた Grade 5 の有害事象はなかった。

表 2.7.4-43 ベースラインの肝機能別の有害事象の概要：海外 3 試験併合

| | Pooled Ibrutinib | |
|---|---|---|
| | Baseline Hepatic Abnormality | |
| | Normal | Not Normal |
| Analysis Set: Safety Population | 320 | 49 |
| Any TEAE | 314 (98.1%) | 49 (100.0%) |
| Grade >= 3 | 224 (70.0%) | 40 (81.6%) |
| Drug related [a] | 266 (83.1%) | 41 (83.7%) |
| Grade >= 3 | 136 (42.5%) | 19 (38.8%) |
| Any TESAE | 162 (50.6%) | 25 (51.0%) |
| Grade >= 3 | 147 (45.9%) | 23 (46.9%) |
| Drug related [a] | 72 (22.5%) | 10 (20.4%) |
| TEAE leading to treatment discontinuation | 39 (12.2%) | 9 (18.4%) |
| TEAE leading to treatment dose reduction | 25 (7.8%) | 3 (6.1%) |
| TEAE with outcome death | 37 (11.6%) | 7 (14.3%) |
| Deaths within 30 days after last dose of study treatment [b] | 49 (15.3%) | 13 (26.5%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE31PART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae31.sas] 26OCT2015, 14:30

参照元：5.3.5.3.1 ISS TSFAE31PART3OF3

## 2.7.4.5.2　外因性要因

### 2.7.4.5.2.1　前治療数（MCL2002 試験）

MCL2002 試験の有害事象を前治療数別（1，2 及び 3 レジメン以上）に集計した。安全性解析対象集団 16 例で，前治療数は，6 例（37.5%）が 1 レジメン，2 例（12.5%）が 2 レジメン，8 例（50.0%）が 3 レジメン以上であった（表 2.7.4-8）。前治療数別の有害事象の概要を表 2.7.4-44 に示す。

有害事象の概要に前治療数による顕著な差異は認められなかった。

表 2.7.4-44 前治療数別の有害事象の概要：MCL2002 試験

| | Ibrutinib | | | |
|---|---|---|---|---|
| | Number of Prior Lines of Treatment | | | |
| | 1 | 2 | >=3 | All |
| Analysis Set: All Treated Population | 6 | 2 | 8 | 16 |
| Number of Subjects with TEAE | 6 (100.0%) | 2 (100.0%) | 8 (100.0%) | 16 (100.0%) |
| Number of Subjects with TEAE of Toxicity Grade 3 or Higher | 3 (50.0%) | 2 (100.0%) | 3 (37.5%) | 8 (50.0%) |
| Number of Subjects with Drug Related TEAE | 5 (83.3%) | 2 (100.0%) | 8 (100.0%) | 15 (93.8%) |
| Number of Subjects with Serious TEAE | 1 (16.7%) | 1 (50.0%) | 3 (37.5%) | 5 (31.3%) |
| Number of Subjects with Drug Related Serious TEAE | 0 | 0 | 1 (12.5%) | 1 (6.3%) |
| Number of Subjects with TEAE Leading to Death | 1 (16.7%) | 0 | 2 (25.0%) | 3 (18.8%) |
| Number of Subjects with TEAE Leading to Drug Withdrawn | 0 | 1 (50.0%) | 1 (12.5%) | 2 (12.5%) |
| Number of Subjects with TEAE Leading to Dose Reduction | 1 (16.7%) | 0 | 1 (12.5%) | 2 (12.5%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Drug related AE is defined as an event related to study agent (relationship to study agent is possible, probable or very likely).

参照元：5.3.5.2.1 MCL2002 試験 CSR TSFAE02D

#### 2.7.4.5.2.2 食事の影響

本薬による食事の影響に関する情報は再発又は難治性の CLL/SLL 申請時に提示しており，その後，新たな知見は得られていない。再発又は難治性の CLL/SLL 申請時には，再発又は難治性の CLL/SLL 患者を対象にイブルチニブ 420 mg/日を空腹時投与又は高脂肪，高カロリー朝食後に投与する 2 期クロスオーバーデザインの試験で，食後投与の最高血漿中濃度（maximum observed plasma concentration，以下 $C_{max}$）及び血漿中濃度—時間曲線下面積（area under the plasma concentration-time curve，以下 AUC）がそれぞれ空腹時投与の 2.32 倍及び 1.65 倍であったこと，別の健康成人を対象とした食事の影響試験でも同様の結果が得られたことを提示した（【1.13.1-3 既承認資料 CTD2.7.2.3.2.2(1)】項参照）。

### 2.7.4.5.3 薬物相互作用

#### (1) チトクローム P450 3A 阻害剤又は誘導剤との併用投与について（海外 3 試験併合）

強力又は中等度のチトクローム P450（cytochrome P450，以下 CYP）3A 阻害剤とイブルチニブを併用することは避け，CYP3A 阻害がより少ない代替薬の使用を検討すべきである。中等度の CYP3A 阻害剤（例えば，フルコナゾール，ダルナビル，エリスロマイシン，ジルチアゼム，アタザナビル，アプレピタント，アンプレナビル，ホスアンプレナビル，クリゾチニブ，イマチニブ，ベラパミル及びシプロフロキサシン）を使用しなければならない場合は，イブルチニブの減量（140 mg/日）が推奨される。

イブルチニブと強力な CYP3A 誘導剤（例えば，リファンピシン，フェニトイン及びセントジョンズワート）を併用した場合，イブルチニブの血漿中濃度が低下するため，CYP3A 誘導がより少ない代替薬の使用を検討すべきである。しかしながら，血漿中濃度の低下は，イブルチニブのベネフィットプロファイルに好ましくない影響があるが，安全性プロファイルには理論的に否定的な影響はない。

海外 3 試験併合，1104 試験，MCL2001 試験及び MCL3001 試験の有害事象を CYP3A 阻害剤併用有無別及び CYP3A 阻害剤の力価別に集計した。海外 3 試験併合の CYP3A 阻害剤併用有無別及び CYP3A 阻害剤の力価別の有害事象の概要をそれぞれ表 2.7.4-46 及び表 2.7.4-47 に示し，1104 試験及び MCL2001 試験並びに MCL3001 試験の有害事象の概要を表 2.7.4-付録-57～表 2.7.4-付録-60 に示す。また，海外 3 試験併合の CYP3A 阻害剤併用有無別及び CYP3A 阻害剤の力価別の有害事象の集計をそれぞれ表 2.7.4-付録-61 及び表 2.7.4-付録-62 に示す。

海外 3 試験併合（370 例）で，CYP3A 阻害剤を併用した被験者は 148 例（40.0%）であり，5%以上の被験者で併用された CYP3A 阻害剤はシプロフロキサシン（14.3%，53 例），アジスロマイシン（14.1%，52 例），フルコナゾール（6.5%，24 例）及びクラリスロマイシン（5.7%，21 例）であった（表 2.7.4-45）。また，強力な CYP3A 阻害剤を併用した被験者は 24 例（6.5%）であった。

海外 3 試験併合で，CYP3A 阻害剤併用の有無別では，イブルチニブとの関連性がある重篤な有害事象［併用有：31.8%（148 例中 47 例），併用無：15.8%（222 例中 35 例）］，イブルチニブとの関連性がある Grade 3 以上の有害事象［併用有：54.1%（80 例），併用無：34.2%（76 例）］及びイブルチニブとの関連性がある有害事象［併用有：90.5%（134 例），併用無：78.4%

（174 例）］は CYP3A 阻害剤を併用した被験者で発現割合が高い傾向が認められた。また，CYP3A 阻害剤の力価別では，イブルチニブとの関連性がある重篤な有害事象［強力な CYP3A 阻害剤：50.0%（24 例中 12 例），非強力な CYP3A 阻害剤：28.2%（124 例中 35 例）］及びイブルチニブとの関連性がある Grade 3 以上の有害事象［強力な CYP3A 阻害剤：66.7%（16 例），非強力な CYP3A 阻害剤：51.6%（64 例）］は強力な CYP3A 阻害剤を併用した被験者で発現割合が高い傾向が認められた。

表 2.7.4-45 CYP3A 阻害剤及び誘導剤併用投与：
1104 試験，MCL2001 試験，MCL3001 試験，海外 3 試験併合

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 | | Pooled Ibrutinib |
|---|---|---|---|---|---|
| | | | Ibrutinib | Temsirolimus | |
| Analysis Set: Safety Population | 111 | 120 | 139 | 139 | 370 |
| Subjects with concomitant usage of CYP3A inhibitor | 60 (54.1%) | 41 (34.2%) | 47 (33.8%) | 53 (38.1%) | 148 (40.0%) |
| Strength/Preferred term | | | | | |
| Strong | 7 (6.3%) | 3 (2.5%) | 14 (10.1%) | 12 (8.6%) | 24 (6.5%) |
| Clarithromycin | 6 (5.4%) | 2 (1.7%) | 13 (9.4%) | 10 (7.2%) | 21 (5.7%) |
| Itraconazole | 1 (0.9%) | 0 | 2 (1.4%) | 3 (2.2%) | 3 (0.8%) |
| Ketoconazole | 0 | 1 (0.8%) | 0 | 0 | 1 (0.3%) |
| Moderate | 20 (18.0%) | 9 (7.5%) | 10 (7.2%) | 21 (15.1%) | 39 (10.5%) |
| Diltiazem | 4 (3.6%) | 3 (2.5%) | 1 (0.7%) | 1 (0.7%) | 8 (2.2%) |
| Erythromycin | 1 (0.9%) | 0 | 3 (2.2%) | 1 (0.7%) | 4 (1.1%) |
| Fluconazole | 14 (12.6%) | 5 (4.2%) | 5 (3.6%) | 19 (13.7%) | 24 (6.5%) |
| Verapamil | 1 (0.9%) | 1 (0.8%) | 1 (0.7%) | 0 | 3 (0.8%) |
| Weak | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| Cimetidine | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| Other | 45 (40.5%) | 33 (27.5%) | 31 (22.3%) | 42 (30.2%) | 109 (29.5%) |
| Amiodarone | 2 (1.8%) | 1 (0.8%) | 1 (0.7%) | 1 (0.7%) | 4 (1.1%) |
| Azithromycin | 23 (20.7%) | 20 (16.7%) | 9 (6.5%) | 11 (7.9%) | 52 (14.1%) |
| Chloramphenicol | 4 (3.6%) | 1 (0.8%) | 4 (2.9%) | 1 (0.7%) | 9 (2.4%) |
| Ciprofloxacin | 20 (18.0%) | 13 (10.8%) | 20 (14.4%) | 32 (23.0%) | 53 (14.3%) |
| Fluvoxamine | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| Norfloxacin | 1 (0.9%) | 0 | 0 | 1 (0.7%) | 1 (0.3%) |
| Voriconazole | 3 (2.7%) | 2 (1.7%) | 2 (1.4%) | 1 (0.7%) | 7 (1.9%) |
| Subjects with concomitant usage of CYP3A inducer | 11 (9.9%) | 7 (5.8%) | 10 (7.2%) | 18 (12.9%) | 28 (7.6%) |
| Strength/Preferred term | | | | | |
| Strong | 2 (1.8%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| Carbamazepine | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| Phenytoin | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| Rifampicin | 1 (0.9%) | 0 | 0 | 0 | 1 (0.3%) |
| Weak | 9 (8.1%) | 7 (5.8%) | 9 (6.5%) | 18 (12.9%) | 25 (6.8%) |
| Pioglitazone | 2 (1.8%) | 0 | 0 | 0 | 2 (0.5%) |
| Prednisone | 7 (6.3%) | 7 (5.8%) | 9 (6.5%) | 18 (12.9%) | 23 (6.2%) |

Note: Percentages calculated with the number of subjects in safety population as denominator.

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参照元：5.3.5.3.1 ISS TSICM01

表 2.7.4-46 CYP3A 阻害剤併用有無別の有害事象の概要：海外 3 試験併合

| | Pooled Ibrutinib | |
|---|---|---|
| | CYP3A Inhibitor | |
| | Yes | No |
| Analysis Set: Safety Population | 148 | 222 |
| Any TEAE | 148 (100.0%) | 216 (97.3%) |
| Grade >= 3 | 111 (75.0%) | 154 (69.4%) |
| Drug related [a] | 134 (90.5%) | 174 (78.4%) |
| Grade >= 3 | 80 (54.1%) | 76 (34.2%) |
| Any TESAE | 87 (58.8%) | 101 (45.5%) |
| Grade >= 3 | 79 (53.4%) | 92 (41.4%) |
| Drug related [a] | 47 (31.8%) | 35 (15.8%) |
| TEAE leading to treatment discontinuation | 16 (10.8%) | 32 (14.4%) |
| TEAE leading to treatment dose reduction | 16 (10.8%) | 12 (5.4%) |
| TEAE with outcome death | 18 (12.2%) | 27 (12.2%) |
| Deaths within 30 days after last dose of study treatment [b] | 23 (15.5%) | 40 (18.0%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE14APART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae14a.sas]
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参照元：5.3.5.3.1 ISS TSFAE14APART3OF3

表 2.7.4-47 CYP3A 阻害剤の力価別の有害事象の概要：海外 3 試験併合

| | Pooled Ibrutinib | |
|---|---|---|
| | CYP3A Inhibitor | |
| | Strong | non-Strong |
| Analysis Set: Safety Population | 24 | 124 |
| Any TEAE | 24 (100.0%) | 124 (100.0%) |
| Grade >= 3 | 16 (66.7%) | 95 (76.6%) |
| Drug related [a] | 22 (91.7%) | 112 (90.3%) |
| Grade >= 3 | 16 (66.7%) | 64 (51.6%) |
| Any TESAE | 16 (66.7%) | 71 (57.3%) |
| Grade >= 3 | 14 (58.3%) | 65 (52.4%) |
| Drug related [a] | 12 (50.0%) | 35 (28.2%) |
| TEAE leading to treatment discontinuation | 4 (16.7%) | 12 (9.7%) |
| TEAE leading to treatment dose reduction | 3 (12.5%) | 13 (10.5%) |
| TEAE with outcome death | 4 (16.7%) | 14 (11.3%) |
| Deaths within 30 days after last dose of study treatment [b] | 5 (20.8%) | 18 (14.5%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE14BPART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae14b.sas]
26OCT2015, 14:28

参照元：5.3.5.3.1 ISS TSFAE14BPART3OF3

### 2.7.4.5.4 妊娠及び授乳時の使用

妊娠及び催奇形性

イブルチニブの妊婦を対象とした臨床試験は実施していない。非臨床試験の結果から，イブルチニブを妊婦に投与すると胎児に害を及ぼす可能性がある。

妊娠ラットで，着床後胚損失率の増加，心血管系の奇形及び胎児の体重減少への影響が示唆された。また，妊娠ウサギで，着床後胚損失率の増加及び胎児の骨格異常（胸骨分節の癒合）への影響が示唆された。

授乳時の使用

イブルチニブ及び代謝物の乳汁中への移行は不明である。乳汁中へ移行する薬剤は多く，授乳婦にイブルチニブを投与することにより乳児に重篤な副作用が発現する可能性があることから，イブルチニブ投与期間中の授乳は中止するべきである。

### 2.7.4.5.5 過量投与

イブルチニブの過量投与に関する検討は，いずれの試験においても実施していない。再発性 B 細胞腫瘍患者を対象とした用量漸増第 I 相試験（04753 試験）では，最大耐量（maximum tolerated dose，以下 MTD）に到達しなかった。これまでに実施された臨床試験で患者に投与された最高用量は 04753 試験の 12.5 mg/kg であり，1 日量に換算するとおよそ 1400 mg/日である。CLL1007 試験で健康成人に 1680 mg/日が投与され，Grade 4 の肝酵素上昇（AST 及び ALT）が 1 例に認められた。イブルチニブに特異的な解毒剤はない。推奨用量を超える量のイブルチニブを摂取した患者はよく観察し，支持療法を行うべきである。

### 2.7.4.5.6 薬物乱用

イブルチニブによる依存性や薬物乱用の可能性を示唆する報告はない。イブルチニブはチロシンキナーゼ阻害剤であり，薬理学的又は構造的にも薬物乱用に関与する可能性は低い。イブルチニブの乱用を評価する臨床試験は実施していない。イブルチニブの臨床試験に参加した被験者で，薬物乱用，誤用又は依存性は報告されていない。

### 2.7.4.5.7 離脱症状及び反跳現象

イブルチニブの離脱症状及び反跳現象を検討する試験は実施していない。

### 2.7.4.5.8 自動車運転及び機械操作に対する影響又は精神機能の障害

イブルチニブの投与を受けた一部の患者で，疲労，浮動性めまい及び無力症の有害事象が報告されており，運転等危険を伴う機械の操作を行う際は注意喚起が必要であると考える。

## 2.7.4.6 市販後データ

イブルチニブの国際誕生日は，イブルチニブ（カプセル）が米国にて承認された 2013 年 11 月 13 日である。

イブルチニブは，定期的安全性最新報告（periodic safety update report，以下 PSUR）第 4 報のデータベースロック（2015 年 11 月 12 日）時点で，米国，欧州等の 63 カ国で承認されている。

2014 年 5 月 13 日から 2015 年 11 月 12 日までに，市販後に報告された重篤な有害事象の一覧を表 2.7.4-付録-61 に示す。有害事象は MedDRA/J（version 18.1）を用いて読み替えた。PSUR 第 2 報～第 4 報について，市販後の曝露状況及び安全性データの概要を 2.7.4.6.1 項に示す。

### 2.7.4.6.1 PSUR 第 2 報～第 4 報

#### (1) PSUR 第 2 報（期間：2014 年 5 月 13 日～2014 年 11 月 12 日）

累計報告期間（2013 年 11 月 13 日～2014 年 10 月 31 日）に，およそ 1,068 人（[redacted] 人月）が治験依頼者の臨床試験でイブルチニブの投与を受けた。同期間に，市販後にイブルチニブが曝露された患者はおよそ 10,884 人（[redacted] 人月）であった。当該期間中に，イブルチニブの安全性に関する新たな知見は認められなかった。

#### (2) PSUR 第 3 報（PBRER/PSUR 第 1 報）（期間：2014 年 10 月 21 日～2015 年 4 月 20 日）

2015 年 4 月 20 日までの累計で，およそ 2,261 人が臨床試験でイブルチニブの投与を受けた。2015 年 4 月 30 日までの累計出荷量（[redacted] mg）に基づく市販後のイブルチニブの推定曝露は [redacted] 人月であった。また，PSUR 第 2 報からの期間（2014 年 11 月 1 日～2015 年 4 月 30 日）の出荷量（[redacted] mg）に基づく市販後のイブルチニブの推定曝露は [redacted] 人月であった。イブルチニブの安全性プロファイルは引き続き良好であった。

#### (3) PSUR 第 4 報（PBRER/PSUR 第 2 報）（期間：2015 年 4 月 21 日～2015 年 11 月 12 日）

2015 年 11 月 12 日までの累計で，およそ 2,937 人が臨床試験でイブルチニブの投与を受けた。2015 年 10 月 31 日までの累計出荷量（[redacted] mg）に基づく市販後のイブルチニブの推定曝露は [redacted] 人月であった。また，PSUR 第 3 報（PBRER/PSUR 第 1 報）からの期間（2015 年 5 月 1 日～2015 年 10 月 31 日）の出荷量（[redacted] mg）に基づく市販後のイブルチニブの推定曝露は [redacted] 人月であった。イブルチニブの安全性プロファイルは引き続き良好であった。

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表 2.7.4-付録-1 Dose Modification; All Treated Population (Study PCI-32765MCL2002)

**TSIEXP02: Dose Modification; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Total Number of Subjects with Any Dose Modification | 8 (50.0%) |
| Dose Reduction | 2 (12.5%) |
| ADVERSE EVENT | 2 (12.5%) |
| Dose Delay | 8 (50.0%) |
| ADVERSE EVENT | 6 (37.5%) |
| OTHER | 5 (31.3%) |
| Dose delay of 7 or more consecutive days | 5 (31.3%) |

[TSIEXP02.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsiexp02.sas] 21AUG2015, 12:31

参照元：5.3.5.2.1 MCL2002 試験 CSR TSIEXP02

表 2.7.4-付録-2 Dose Modification; Safety Population (MCL-ISS)

**TSIEXP02: Dose Modification; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 Ibrutinib | MCL3001 Temsirolimus | Pooled Ibrutinib |
|---|---|---|---|---|---|
| Analysis set: safety population | 111 | 120 | 139 | 139 | 370 |
| Subjects with any dose modification (reduction or withholding) | 45 (40.5%) | 44 (36.7%) | 48 (34.5%) | 126 (90.6%) | 137 (37.0%) |
| Subjects with any dose reductions | 16 (14.4%) | 8 (6.7%) | 6 (4.3%) | 61 (43.9%) | 30 (8.1%) |
| 1 | 11 (9.9%) | 5 (4.2%) | 6 (4.3%) | 34 (24.5%) | 22 (5.9%) |
| 2 | 5 (4.5%) | 3 (2.5%) | 0 | 27 (19.4%) | 8 (2.2%) |
| Subjets with any dose witholding | 44 (39.6%) | 44 (36.7%) | 48 (34.5%) | 120 (86.3%) | 136 (36.8%) |
| 1 | 25 (22.5%) | 27 (22.5%) | 30 (21.6%) | 46 (33.1%) | 82 (22.2%) |
| 2 | 11 (9.9%) | 8 (6.7%) | 10 (7.2%) | 25 (18.0%) | 29 (7.8%) |
| >= 3 | 8 (7.2%) | 9 (7.5%) | 8 (5.8%) | 49 (35.3%) | 25 (6.8%) |

Note: Percentages calculated with the number of subjects in safety population as denominator.

[TSIEXP02.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsiexp02.sas] 15SEP2015, 14:13

参照元：5.3.5.3.1 ISS TSIEXP02

表 2.7.4-付録-3 Treatment-Emergent Adverse Events by Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)

**TSFAE05: Treatment-Emergent Adverse Events by Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib | |
|---|---|---|
| | All Grade | Grade 3 or Higher |
| Analysis Set: All Treated Population | 16 | |
| Total Number of Subjects with TEAE | 16 (100.0%) | 8 (50.0%) |
| MedDRA System organ class/Preferred term | | |
| 胃腸障害 | 10 (62.5%) | 1 (6.3%) |
| 下痢 | 6 (37.5%) | 0 |
| 口内炎 | 6 (37.5%) | 1 (6.3%) |
| 便秘 | 3 (18.8%) | 0 |
| 消化不良 | 2 (12.5%) | 0 |
| 悪心 | 2 (12.5%) | 0 |
| 上腹部痛 | 1 (6.3%) | 0 |
| 肛門出血 | 1 (6.3%) | 0 |
| 舌痛 | 1 (6.3%) | 0 |
| 口腔内出血 | 1 (6.3%) | 0 |
| 感染症および寄生虫症 | 10 (62.5%) | 1 (6.3%) |
| 上気道感染 | 3 (18.8%) | 0 |
| 鼻咽頭炎 | 2 (12.5%) | 0 |
| 皮膚感染 | 2 (12.5%) | 0 |
| 感染 | 1 (6.3%) | 0 |
| インフルエンザ | 1 (6.3%) | 0 |
| 爪囲炎 | 1 (6.3%) | 0 |
| 咽頭炎 | 1 (6.3%) | 0 |
| 敗血症 | 1 (6.3%) | 1 (6.3%) |
| 扁桃炎 | 1 (6.3%) | 0 |
| 皮膚および皮下組織障害 | 10 (62.5%) | 0 |
| 皮膚乾燥 | 3 (18.8%) | 0 |
| 皮膚炎 | 1 (6.3%) | 0 |
| 湿疹 | 1 (6.3%) | 0 |
| 皮下出血 | 1 (6.3%) | 0 |
| 爪変色 | 1 (6.3%) | 0 |
| 爪破損 | 1 (6.3%) | 0 |
| 点状出血 | 1 (6.3%) | 0 |
| そう痒症 | 1 (6.3%) | 0 |
| 発疹 | 1 (6.3%) | 0 |
| 全身性皮疹 | 1 (6.3%) | 0 |
| 斑状丘疹状皮疹 | 1 (6.3%) | 0 |
| 皮膚脆弱性 | 1 (6.3%) | 0 |
| 一般・全身障害および投与部位の状態 | 9 (56.3%) | 3 (18.8%) |
| 疾患進行 | 3 (18.8%) | 3 (18.8%) |
| 疲労 | 3 (18.8%) | 0 |
| 倦怠感 | 2 (12.5%) | 0 |
| 胸部不快感 | 1 (6.3%) | 0 |
| インフルエンザ様疾患 | 1 (6.3%) | 0 |
| 臨床検査 | 8 (50.0%) | 1 (6.3%) |
| 血小板数減少 | 5 (31.3%) | 0 |
| アラニンアミノトランスフェラーゼ増加 | 2 (12.5%) | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 2 (12.5%) | 0 |
| 血中ビリルビン増加 | 2 (12.5%) | 0 |
| 血中アルカリホスファターゼ増加 | 1 (6.3%) | 0 |
| 血中クレアチニン増加 | 1 (6.3%) | 0 |
| γ－グルタミルトランスフェラーゼ増加 | 1 (6.3%) | 0 |
| リンパ球数減少 | 1 (6.3%) | 0 |
| リンパ球数増加 | 1 (6.3%) | 1 (6.3%) |
| 血液およびリンパ系障害 | 7 (43.8%) | 2 (12.5%) |

**TSFAE05: Treatment-Emergent Adverse Events by Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib | |
|---|---|---|
| | All Grade | Grade 3 or Higher |
| 貧血 | 4 (25.0%) | 1 (6.3%) |
| 血小板減少症 | 3 (18.8%) | 0 |
| 白血球増加症 | 2 (12.5%) | 1 (6.3%) |
| リンパ球増加症 | 2 (12.5%) | 0 |
| 好中球減少症 | 1 (6.3%) | 1 (6.3%) |
| 代謝および栄養障害 | 5 (31.3%) | 2 (12.5%) |
| 食欲減退 | 3 (18.8%) | 0 |
| 低カリウム血症 | 2 (12.5%) | 1 (6.3%) |
| 高尿酸血症 | 1 (6.3%) | 1 (6.3%) |
| 低ナトリウム血症 | 1 (6.3%) | 0 |
| 低リン酸血症 | 1 (6.3%) | 0 |
| 傷害、中毒および処置合併症 | 4 (25.0%) | 0 |
| 挫傷 | 2 (12.5%) | 0 |
| 裂傷 | 2 (12.5%) | 0 |
| 関節脱臼 | 1 (6.3%) | 0 |
| 神経系障害 | 4 (25.0%) | 0 |
| 頭痛 | 2 (12.5%) | 0 |
| 末梢性ニューロパチー | 2 (12.5%) | 0 |
| 体位性めまい | 1 (6.3%) | 0 |
| 眼障害 | 3 (18.8%) | 1 (6.3%) |
| 眼乾燥 | 1 (6.3%) | 0 |
| 点状角膜炎 | 1 (6.3%) | 0 |
| 網膜裂孔 | 1 (6.3%) | 0 |
| 網膜血管障害 | 1 (6.3%) | 1 (6.3%) |
| 筋骨格系および結合組織障害 | 3 (18.8%) | 0 |
| 関節炎 | 1 (6.3%) | 0 |
| 筋痙縮 | 1 (6.3%) | 0 |
| 骨炎 | 1 (6.3%) | 0 |
| 心臓障害 | 2 (12.5%) | 1 (6.3%) |
| 不整脈 | 1 (6.3%) | 1 (6.3%) |
| 心房細動 | 1 (6.3%) | 0 |
| 精神障害 | 2 (12.5%) | 0 |
| 譫妄 | 1 (6.3%) | 0 |
| うつ病 | 1 (6.3%) | 0 |
| 腎および尿路障害 | 2 (12.5%) | 1 (6.3%) |
| 血尿 | 1 (6.3%) | 0 |
| 蛋白尿 | 1 (6.3%) | 0 |
| 腎機能障害 | 1 (6.3%) | 1 (6.3%) |
| 呼吸器、胸郭および縦隔障害 | 2 (12.5%) | 0 |
| 鼻出血 | 1 (6.3%) | 0 |
| 鼻漏 | 1 (6.3%) | 0 |
| 血管障害 | 1 (6.3%) | 1 (6.3%) |
| 高血圧 | 1 (6.3%) | 1 (6.3%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0

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参照元：5.3.5.2.1 MCL2002 試験 CSR TSFAE05

表 2.7.4-付録-4 Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Pooled Ibrutinib by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE03APART1OF3: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Pooled Ibrutinib by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 111 | | 120 | |
| Subjects with any TEAE | 111 (100%) | 84 (75.7%) | 115 (95.8%) | 87 (72.5%) |
| System organ class | | | | |
| Preferred term | | | | |
| 感染症および寄生虫症 | 86 (77.5%) | 28 (25.2%) | 80 (66.7%) | 32 (26.7%) |
| 上気道感染 | 26 (23.4%) | 0 | 21 (17.5%) | 0 |
| 肺炎 | 13 (11.7%) | 7 (6.3%) | 18 (15.0%) | 15 (12.5%) |
| 副鼻腔炎 | 14 (12.6%) | 1 (0.9%) | 15 (12.5%) | 0 |
| 尿路感染 | 16 (14.4%) | 3 (2.7%) | 12 (10.0%) | 2 (1.7%) |
| 胃腸障害 | 91 (82.0%) | 13 (11.7%) | 84 (70.0%) | 12 (10.0%) |
| 下痢 | 55 (49.5%) | 6 (5.4%) | 51 (42.5%) | 3 (2.5%) |
| 悪心 | 34 (30.6%) | 0 | 26 (21.7%) | 1 (0.8%) |
| 嘔吐 | 25 (22.5%) | 0 | 21 (17.5%) | 1 (0.8%) |
| 便秘 | 28 (25.2%) | 0 | 17 (14.2%) | 0 |
| 腹痛 | 19 (17.1%) | 6 (5.4%) | 12 (10.0%) | 2 (1.7%) |
| 一般・全身障害および投与部位の状態 | 80 (72.1%) | 11 (9.9%) | 85 (70.8%) | 12 (10.0%) |
| 疲労 | 46 (41.4%) | 5 (4.5%) | 52 (43.3%) | 5 (4.2%) |
| 末梢性浮腫 | 28 (25.2%) | 2 (1.8%) | 28 (23.3%) | 4 (3.3%) |
| 発熱 | 20 (18.0%) | 1 (0.9%) | 25 (20.8%) | 1 (0.8%) |
| 呼吸器、胸郭および縦隔障害 | 60 (54.1%) | 9 (8.1%) | 68 (56.7%) | 10 (8.3%) |
| 咳嗽 | 20 (18.0%) | 0 | 30 (25.0%) | 0 |
| 呼吸困難 | 30 (27.0%) | 5 (4.5%) | 23 (19.2%) | 3 (2.5%) |
| 皮膚および皮下組織障害 | 72 (64.9%) | 4 (3.6%) | 63 (52.5%) | 3 (2.5%) |
| 発疹 | 18 (16.2%) | 2 (1.8%) | 21 (17.5%) | 1 (0.8%) |
| 筋骨格系および結合組織障害 | 61 (55.0%) | 5 (4.5%) | 60 (50.0%) | 7 (5.8%) |
| 筋痙縮 | 16 (14.4%) | 0 | 25 (20.8%) | 0 |
| 背部痛 | 14 (12.6%) | 1 (0.9%) | 14 (11.7%) | 1 (0.8%) |
| 関節痛 | 12 (10.8%) | 0 | 18 (15.0%) | 1 (0.8%) |
| 血液およびリンパ系障害 | 51 (45.9%) | 34 (30.6%) | 63 (52.5%) | 44 (36.7%) |
| 血小板減少症 | 20 (18.0%) | 12 (10.8%) | 29 (24.2%) | 16 (13.3%) |
| 好中球減少症 | 20 (18.0%) | 18 (16.2%) | 28 (23.3%) | 25 (20.8%) |
| 貧血 | 15 (13.5%) | 11 (9.9%) | 23 (19.2%) | 8 (6.7%) |
| 代謝および栄養障害 | 53 (47.7%) | 15 (13.5%) | 46 (38.3%) | 15 (12.5%) |
| 食欲減退 | 23 (20.7%) | 2 (1.8%) | 14 (11.7%) | 0 |
| 神経系障害 | 44 (39.6%) | 1 (0.9%) | 38 (31.7%) | 4 (3.3%) |
| 頭痛 | 12 (10.8%) | 0 | 12 (10.0%) | 0 |
| 傷害、中毒および処置合併症 | 34 (30.6%) | 4 (3.6%) | 36 (30.0%) | 2 (1.7%) |
| 挫傷 | 19 (17.1%) | 0 | 17 (14.2%) | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE03APART1OF3

表 2.7.4-付録-5 Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Pooled Ibrutinib by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE03APART2OF3: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Pooled Ibrutinib by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 139 | | 139 | |
| Subjects with any TEAE | 138 (99.3%) | 94 (67.6%) | 138 (99.3%) | 121 (87.1%) |
| System organ class | | | | |
| Preferred term | | | | |
| 感染症および寄生虫症 | 97 (69.8%) | 27 (19.4%) | 99 (71.2%) | 42 (30.2%) |
| 上気道感染 | 26 (18.7%) | 3 (2.2%) | 16 (11.5%) | 1 (0.7%) |
| 肺炎 | 13 (9.4%) | 11 (7.9%) | 17 (12.2%) | 9 (6.5%) |
| 副鼻腔炎 | 10 (7.2%) | 0 | 7 (5.0%) | 1 (0.7%) |
| 尿路感染 | 10 (7.2%) | 1 (0.7%) | 9 (6.5%) | 3 (2.2%) |
| 胃腸障害 | 80 (57.6%) | 14 (10.1%) | 109 (78.4%) | 25 (18.0%) |
| 下痢 | 40 (28.8%) | 4 (2.9%) | 43 (30.9%) | 6 (4.3%) |
| 悪心 | 20 (14.4%) | 0 | 30 (21.6%) | 0 |
| 嘔吐 | 16 (11.5%) | 0 | 10 (7.2%) | 1 (0.7%) |
| 便秘 | 12 (8.6%) | 0 | 21 (15.1%) | 0 |
| 腹痛 | 11 (7.9%) | 5 (3.6%) | 11 (7.9%) | 2 (1.4%) |
| 一般・全身障害および投与部位の状態 | 74 (53.2%) | 15 (10.8%) | 99 (71.2%) | 29 (20.9%) |
| 疲労 | 31 (22.3%) | 6 (4.3%) | 40 (28.8%) | 10 (7.2%) |
| 末梢性浮腫 | 18 (12.9%) | 0 | 31 (22.3%) | 3 (2.2%) |
| 発熱 | 23 (16.5%) | 1 (0.7%) | 29 (20.9%) | 3 (2.2%) |
| 呼吸器、胸郭および縦隔障害 | 72 (51.8%) | 16 (11.5%) | 82 (59.0%) | 19 (13.7%) |
| 咳嗽 | 31 (22.3%) | 0 | 31 (22.3%) | 0 |
| 呼吸困難 | 16 (11.5%) | 4 (2.9%) | 17 (12.2%) | 5 (3.6%) |
| 皮膚および皮下組織障害 | 59 (42.4%) | 3 (2.2%) | 69 (49.6%) | 5 (3.6%) |
| 発疹 | 18 (12.9%) | 1 (0.7%) | 24 (17.3%) | 0 |
| 筋骨格系および結合組織障害 | 52 (37.4%) | 8 (5.8%) | 49 (35.3%) | 8 (5.8%) |
| 筋痙縮 | 26 (18.7%) | 0 | 4 (2.9%) | 0 |
| 背部痛 | 16 (11.5%) | 4 (2.9%) | 15 (10.8%) | 1 (0.7%) |
| 関節痛 | 8 (5.8%) | 1 (0.7%) | 9 (6.5%) | 2 (1.4%) |
| 血液およびリンパ系障害 | 55 (39.6%) | 31 (22.3%) | 104 (74.8%) | 80 (57.6%) |
| 血小板減少症 | 25 (18.0%) | 13 (9.4%) | 78 (56.1%) | 59 (42.4%) |
| 好中球減少症 | 22 (15.8%) | 18 (12.9%) | 36 (25.9%) | 23 (16.5%) |
| 貧血 | 25 (18.0%) | 11 (7.9%) | 60 (43.2%) | 28 (20.1%) |
| 代謝および栄養障害 | 51 (36.7%) | 22 (15.8%) | 88 (63.3%) | 46 (33.1%) |
| 食欲減退 | 25 (18.0%) | 1 (0.7%) | 26 (18.7%) | 4 (2.9%) |
| 神経系障害 | 39 (28.1%) | 4 (2.9%) | 52 (37.4%) | 10 (7.2%) |
| 頭痛 | 13 (9.4%) | 0 | 17 (12.2%) | 0 |
| 傷害、中毒および処置合併症 | 31 (22.3%) | 7 (5.0%) | 27 (19.4%) | 4 (2.9%) |
| 挫傷 | 10 (7.2%) | 0 | 3 (2.2%) | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE03APART2OF3

表 2.7.4-付録-6 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 111 | | 120 | |
| Subjects with any TEAE | 111 (100%) | 84 (75.7%) | 115 (95.8%) | 87 (72.5%) |
| System organ class | | | | |
| Preferred term | | | | |
| 感染症および寄生虫症 | 86 (77.5%) | 28 (25.2%) | 80 (66.7%) | 32 (26.7%) |
| 上気道感染 | 26 (23.4%) | 0 | 21 (17.5%) | 0 |
| 肺炎 | 13 (11.7%) | 7 (6.3%) | 18 (15.0%) | 15 (12.5%) |
| 副鼻腔炎 | 14 (12.6%) | 1 (0.9%) | 15 (12.5%) | 0 |
| 尿路感染 | 16 (14.4%) | 3 (2.7%) | 12 (10.0%) | 2 (1.7%) |
| 鼻咽頭炎 | 9 (8.1%) | 0 | 6 (5.0%) | 0 |
| 結膜炎 | 7 (6.3%) | 0 | 3 (2.5%) | 0 |
| 気管支炎 | 8 (7.2%) | 2 (1.8%) | 6 (5.0%) | 2 (1.7%) |
| 蜂巣炎 | 9 (8.1%) | 3 (2.7%) | 8 (6.7%) | 4 (3.3%) |
| 帯状疱疹 | 5 (4.5%) | 0 | 0 | 0 |
| 鼻炎 | 5 (4.5%) | 0 | 3 (2.5%) | 0 |
| 毛包炎 | 5 (4.5%) | 0 | 6 (5.0%) | 0 |
| 爪囲炎 | 3 (2.7%) | 0 | 2 (1.7%) | 0 |
| 下気道感染 | 4 (3.6%) | 2 (1.8%) | 3 (2.5%) | 1 (0.8%) |
| 皮膚感染 | 4 (3.6%) | 0 | 3 (2.5%) | 0 |
| 口腔ヘルペス | 4 (3.6%) | 0 | 4 (3.3%) | 0 |
| 気道感染 | 2 (1.8%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 敗血症 | 2 (1.8%) | 2 (1.8%) | 4 (3.3%) | 4 (3.3%) |
| 胃腸炎 | 4 (3.6%) | 1 (0.9%) | 2 (1.7%) | 1 (0.8%) |
| 咽頭炎 | 0 | 0 | 0 | 0 |
| ウイルス感染 | 2 (1.8%) | 0 | 0 | 0 |
| 感染 | 2 (1.8%) | 0 | 0 | 0 |
| クロストリジウム・ディフィシレ大腸炎 | 3 (2.7%) | 2 (1.8%) | 2 (1.7%) | 1 (0.8%) |
| 眼感染 | 2 (1.8%) | 0 | 2 (1.7%) | 0 |
| 歯肉炎 | 0 | 0 | 3 (2.5%) | 0 |
| 口腔カンジダ症 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| クロストリジウム・ディフィシレ感染 | 2 (1.8%) | 1 (0.9%) | 2 (1.7%) | 0 |
| インフルエンザ | 1 (0.9%) | 0 | 0 | 0 |
| 限局性感染 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 中耳炎 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 歯周炎 | 0 | 0 | 0 | 0 |
| 歯感染 | 3 (2.7%) | 0 | 1 (0.8%) | 0 |
| 菌血症 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 気管支肺炎 | 0 | 0 | 0 | 0 |
| 膀胱炎 | 0 | 0 | 1 (0.8%) | 0 |
| 耳感染 | 0 | 0 | 2 (1.7%) | 0 |
| ウイルス性胃腸炎 | 0 | 0 | 3 (2.5%) | 1 (0.8%) |
| 単純ヘルペス | 2 (1.8%) | 0 | 0 | 0 |
| 喉頭炎 | 0 | 0 | 0 | 0 |
| 爪感染 | 1 (0.9%) | 0 | 0 | 0 |
| 外耳炎 | 0 | 0 | 0 | 0 |
| ブドウ球菌感染 | 3 (2.7%) | 0 | 0 | 0 |
| ウイルス性上気道感染 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 急性副鼻腔炎 | 0 | 0 | 1 (0.8%) | 0 |
| 細気管支炎 | 1 (0.9%) | 0 | 0 | 0 |
| 医療機器関連感染 | 0 | 0 | 1 (0.8%) | 0 |
| 憩室炎 | 2 (1.8%) | 0 | 0 | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 感染性小腸結腸炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 丹毒 | 0 | 0 | 0 | 0 |
| 真菌感染 | 0 | 0 | 2 (1.7%) | 0 |
| 皮膚真菌感染 | 0 | 0 | 1 (0.8%) | 0 |
| 真菌性性器感染 | 1 (0.9%) | 0 | 0 | 0 |
| ヘルペスウイルス感染 | 1 (0.9%) | 0 | 0 | 0 |
| 麦粒腫 | 0 | 0 | 2 (1.7%) | 0 |
| 爪真菌症 | 1 (0.9%) | 0 | 0 | 0 |
| レンサ球菌性咽頭炎 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| ニューモシスチス・イロベチイ肺炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 細菌性肺炎 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 膿疱性皮疹 | 1 (0.9%) | 0 | 0 | 0 |
| 敗血症性ショック | 0 | 0 | 0 | 0 |
| ブドウ球菌性菌血症 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 歯膿瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 細菌性尿路感染 | 0 | 0 | 1 (0.8%) | 0 |
| 尿路性敗血症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 外陰部腟カンジダ症 | 0 | 0 | 1 (0.8%) | 0 |
| 創傷感染 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 腹部膿瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 四肢膿瘍 | 0 | 0 | 0 | 0 |
| ダニ皮膚炎 | 0 | 0 | 0 | 0 |
| 膿疱性ざ瘡 | 0 | 0 | 1 (0.8%) | 0 |
| 肛門膿瘍 | 1 (0.9%) | 0 | 0 | 0 |
| 肛門カンジダ症 | 0 | 0 | 1 (0.8%) | 0 |
| 虫垂炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 穿孔性虫垂炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 異型肺炎 | 0 | 0 | 1 (0.8%) | 0 |
| 細菌尿 | 0 | 0 | 0 | 0 |
| カンジダ性亀頭炎 | 0 | 0 | 0 | 0 |
| 胆道感染 | 0 | 0 | 0 | 0 |
| ブラストシスティス感染 | 0 | 0 | 0 | 0 |
| 体部白癬 | 0 | 0 | 1 (0.8%) | 0 |
| 乳房蜂巣炎 | 0 | 0 | 0 | 0 |
| カンピロバクター胃腸炎 | 0 | 0 | 0 | 0 |
| カンピロバクター感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| カンジダ感染 | 0 | 0 | 0 | 0 |
| 眼窩蜂巣炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 感染性胆嚢炎 | 0 | 0 | 0 | 0 |
| 慢性副鼻腔炎 | 0 | 0 | 0 | 0 |
| シトロバクター感染 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 涙嚢炎 | 0 | 0 | 0 | 0 |
| ウイルス性脳炎 | 0 | 0 | 0 | 0 |
| 精巣上体炎 | 0 | 0 | 0 | 0 |
| 喉頭蓋炎 | 0 | 0 | 0 | 0 |
| 細菌性眼感染 | 1 (0.9%) | 0 | 0 | 0 |
| 真菌血症 | 0 | 0 | 0 | 0 |
| ヘリコバクター胃潰瘍 | 0 | 0 | 0 | 0 |
| 消化管感染 | 0 | 0 | 0 | 0 |
| ウイルス性消化管感染 | 1 (0.9%) | 0 | 0 | 0 |
| 性器カンジダ症 | 0 | 0 | 1 (0.8%) | 0 |
| 血腫感染 | 0 | 0 | 1 (0.8%) | 0 |
| ヘモフィルス感染 | 1 (0.9%) | 0 | 0 | 0 |
| Ｂ型肝炎 | 0 | 0 | 0 | 0 |
| ヒストプラスマ症 | 1 (0.9%) | 0 | 0 | 0 |
| 埋込み部位感染 | 1 (0.9%) | 0 | 0 | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 切開部位感染 | 1 (0.9%) | 0 | 0 | 0 |
| クレブシエラ感染 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 口唇感染 | 1 (0.9%) | 0 | 0 | 0 |
| 細菌性下気道感染 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 肺感染 | 0 | 0 | 0 | 0 |
| ライム病 | 0 | 0 | 1 (0.8%) | 0 |
| 乳腺炎 | 0 | 0 | 0 | 0 |
| 水疱性鼓膜炎 | 0 | 0 | 0 | 0 |
| 爪床感染 | 0 | 0 | 1 (0.8%) | 0 |
| 眼帯状疱疹 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 口腔真菌感染 | 0 | 0 | 1 (0.8%) | 0 |
| 乳頭腫ウイルス感染 | 1 (0.9%) | 0 | 0 | 0 |
| クリプトコッカス性肺炎 | 1 (0.9%) | 0 | 0 | 0 |
| クレブシエラ菌性肺炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 処置後感染 | 0 | 0 | 1 (0.8%) | 0 |
| 肺結核 | 0 | 0 | 0 | 0 |
| 腎盂腎炎 | 0 | 0 | 0 | 0 |
| 膿皮症 | 0 | 0 | 0 | 0 |
| レンサ球菌性膿皮症 | 0 | 0 | 0 | 0 |
| 狂犬病 | 0 | 0 | 1 (0.8%) | 0 |
| 直腸膿瘍 | 1 (0.9%) | 0 | 0 | 0 |
| ウイルス性気道感染 | 0 | 0 | 0 | 0 |
| 軟部組織感染 | 0 | 0 | 0 | 0 |
| ブドウ球菌皮膚感染 | 0 | 0 | 1 (0.8%) | 0 |
| レンサ球菌感染 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 皮下組織膿瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 足部白癬 | 1 (0.9%) | 0 | 0 | 0 |
| 扁桃炎 | 0 | 0 | 0 | 0 |
| 気管炎 | 0 | 0 | 0 | 0 |
| 真菌性尿路感染 | 0 | 0 | 1 (0.8%) | 0 |
| シュードモナス性尿路感染 | 1 (0.9%) | 0 | 0 | 0 |
| 眼瞼膿瘍 | 0 | 0 | 0 | 0 |
| 急性扁桃炎 | 0 | 0 | 0 | 0 |
| 真菌性肛門感染 | 0 | 0 | 0 | 0 |
| 気管支肺アスペルギルス症 | 0 | 0 | 0 | 0 |
| 大腸菌性菌血症 | 0 | 0 | 0 | 0 |
| 感染性大腸炎 | 0 | 0 | 0 | 0 |
| 真菌性喉頭炎 | 0 | 0 | 0 | 0 |
| 肝膿瘍 | 0 | 0 | 0 | 0 |
| 大葉性肺炎 | 0 | 0 | 0 | 0 |
| リンパ管炎 | 0 | 0 | 0 | 0 |
| 粘膜感染 | 0 | 0 | 0 | 0 |
| 好中球減少性敗血症 | 0 | 0 | 0 | 0 |
| ニューモシスチス・イロベチイ感染 | 0 | 0 | 0 | 0 |
| 大腸菌性肺炎 | 0 | 0 | 0 | 0 |
| 細菌性気道感染 | 0 | 0 | 0 | 0 |
| アスペルギルス性副鼻腔炎 | 0 | 0 | 0 | 0 |
| ブドウ球菌性敗血症 | 0 | 0 | 0 | 0 |
| 癜風 | 0 | 0 | 0 | 0 |
| 気管気管支炎 | 0 | 0 | 0 | 0 |
| 胃腸障害 | 91 (82.0%) | 13 (11.7%) | 84 (70.0%) | 12 (10.0%) |
| 下痢 | 55 (49.5%) | 6 (5.4%) | 51 (42.5%) | 3 (2.5%) |
| 悪心 | 34 (30.6%) | 0 | 26 (21.7%) | 1 (0.8%) |
| 嘔吐 | 25 (22.5%) | 0 | 21 (17.5%) | 1 (0.8%) |
| 便秘 | 28 (25.2%) | 0 | 17 (14.2%) | 0 |
| 腹痛 | 19 (17.1%) | 6 (5.4%) | 12 (10.0%) | 2 (1.7%) |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 口内炎 | 13 (11.7%) | 1 (0.9%) | 14 (11.7%) | 2 (1.7%) |
| 消化不良 | 12 (10.8%) | 0 | 7 (5.8%) | 0 |
| 上腹部痛 | 6 (5.4%) | 0 | 2 (1.7%) | 0 |
| 腹部膨満 | 4 (3.6%) | 0 | 3 (2.5%) | 0 |
| 口内乾燥 | 6 (5.4%) | 0 | 5 (4.2%) | 0 |
| 胃食道逆流性疾患 | 4 (3.6%) | 0 | 5 (4.2%) | 0 |
| 嚥下障害 | 3 (2.7%) | 0 | 2 (1.7%) | 1 (0.8%) |
| 腹部不快感 | 3 (2.7%) | 0 | 0 | 0 |
| 口腔内痛 | 4 (3.6%) | 0 | 3 (2.5%) | 0 |
| 口腔内潰瘍形成 | 2 (1.8%) | 0 | 5 (4.2%) | 0 |
| 放屁 | 5 (4.5%) | 0 | 1 (0.8%) | 0 |
| 胃炎 | 5 (4.5%) | 0 | 1 (0.8%) | 0 |
| 心窩部不快感 | 3 (2.7%) | 0 | 0 | 0 |
| 舌痛 | 1 (0.9%) | 0 | 4 (3.3%) | 0 |
| 痔核 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| アフタ性口内炎 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| おくび | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| イレウス | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 直腸出血 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 舌潰瘍 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 下腹部痛 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| 齲歯 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 軟便 | 2 (1.8%) | 0 | 0 | 0 |
| 食中毒 | 0 | 0 | 1 (0.8%) | 0 |
| 排便回数増加 | 1 (0.9%) | 0 | 0 | 0 |
| 胃潰瘍 | 0 | 0 | 0 | 0 |
| 歯肉出血 | 0 | 0 | 0 | 0 |
| 歯肉浮腫 | 2 (1.8%) | 0 | 0 | 0 |
| 吐血 | 0 | 0 | 0 | 0 |
| 麻痺性イレウス | 2 (1.8%) | 2 (1.8%) | 0 | 0 |
| 鼠径ヘルニア | 0 | 0 | 2 (1.7%) | 0 |
| 口唇潰瘍 | 1 (0.9%) | 0 | 0 | 0 |
| 下部消化管出血 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 口腔内出血 | 1 (0.9%) | 0 | 0 | 0 |
| 歯周病 | 1 (0.9%) | 0 | 0 | 0 |
| 肛門周囲痛 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 直腸炎 | 1 (0.9%) | 0 | 0 | 0 |
| 直腸裂 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 小腸閉塞 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 歯痛 | 0 | 0 | 2 (1.7%) | 0 |
| 裂肛 | 0 | 0 | 0 | 0 |
| 肛門直腸障害 | 0 | 0 | 0 | 0 |
| 萎縮性舌炎 | 0 | 0 | 0 | 0 |
| バレット食道 | 1 (0.9%) | 0 | 0 | 0 |
| 口唇炎 | 1 (0.9%) | 0 | 0 | 0 |
| 大腸炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 歯不快感 | 0 | 0 | 1 (0.8%) | 0 |
| 血性下痢 | 0 | 0 | 0 | 0 |
| 十二指腸狭窄 | 0 | 0 | 0 | 0 |
| 十二指腸潰瘍 | 0 | 0 | 0 | 0 |
| 十二指腸炎 | 0 | 0 | 0 | 0 |
| 十二指腸胃逆流 | 0 | 0 | 0 | 0 |
| 便失禁 | 1 (0.9%) | 0 | 0 | 0 |
| 糞塊 | 0 | 0 | 0 | 0 |
| 胃前庭部毛細血管拡張症 | 1 (0.9%) | 0 | 0 | 0 |
| 出血性胃炎 | 0 | 0 | 1 (0.8%) | 0 |
| 歯肉痛 | 0 | 0 | 1 (0.8%) | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 血便排泄 | 1 (0.9%) | 0 | 0 | 0 |
| 痔出血 | 0 | 0 | 1 (0.8%) | 0 |
| 過敏性腸症候群 | 1 (0.9%) | 0 | 0 | 0 |
| 口唇水疱 | 1 (0.9%) | 0 | 0 | 0 |
| 口唇びらん | 0 | 0 | 0 | 0 |
| 口唇痛 | 0 | 0 | 1 (0.8%) | 0 |
| 口唇腫脹 | 1 (0.9%) | 0 | 0 | 0 |
| 弛緩歯 | 0 | 0 | 1 (0.8%) | 0 |
| メレナ | 0 | 0 | 0 | 0 |
| 嚥下痛 | 1 (0.9%) | 0 | 0 | 0 |
| 口蓋障害 | 1 (0.9%) | 0 | 0 | 0 |
| 慢性膵炎 | 1 (0.9%) | 0 | 0 | 0 |
| 舌突出 | 0 | 0 | 0 | 0 |
| 直腸潰瘍 | 0 | 0 | 0 | 0 |
| 唾液腺結石 | 0 | 0 | 0 | 0 |
| 変色歯 | 0 | 0 | 1 (0.8%) | 0 |
| 歯の障害 | 0 | 0 | 0 | 0 |
| 歯の脱落 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 痔瘻 | 0 | 0 | 0 | 0 |
| 肛門直腸不快感 | 0 | 0 | 0 | 0 |
| 腸炎 | 0 | 0 | 0 | 0 |
| 変色便 | 0 | 0 | 0 | 0 |
| 胃腸出血 | 0 | 0 | 0 | 0 |
| 胃腸毒性 | 0 | 0 | 0 | 0 |
| 歯肉障害 | 0 | 0 | 0 | 0 |
| 歯肉退縮 | 0 | 0 | 0 | 0 |
| 舌炎 | 0 | 0 | 0 | 0 |
| 腸出血 | 0 | 0 | 0 | 0 |
| 口唇乾燥 | 0 | 0 | 0 | 0 |
| 口唇浮腫 | 0 | 0 | 0 | 0 |
| 食道炎 | 0 | 0 | 0 | 0 |
| 口腔知覚不全 | 0 | 0 | 0 | 0 |
| 口腔粘膜びらん | 0 | 0 | 0 | 0 |
| 口腔粘膜紅斑 | 0 | 0 | 0 | 0 |
| 排便痛 | 0 | 0 | 0 | 0 |
| 上部消化管出血 | 0 | 0 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 80 (72.1%) | 11 (9.9%) | 85 (70.8%) | 12 (10.0%) |
| 疲労 | 46 (41.4%) | 5 (4.5%) | 52 (43.3%) | 5 (4.2%) |
| 末梢性浮腫 | 28 (25.2%) | 2 (1.8%) | 28 (23.3%) | 4 (3.3%) |
| 発熱 | 20 (18.0%) | 1 (0.9%) | 25 (20.8%) | 1 (0.8%) |
| 無力症 | 12 (10.8%) | 2 (1.8%) | 9 (7.5%) | 2 (1.7%) |
| 悪寒 | 7 (6.3%) | 0 | 6 (5.0%) | 0 |
| 胸痛 | 4 (3.6%) | 0 | 8 (6.7%) | 0 |
| 末梢腫脹 | 4 (3.6%) | 0 | 10 (8.3%) | 1 (0.8%) |
| インフルエンザ様疾患 | 8 (7.2%) | 0 | 4 (3.3%) | 0 |
| 疼痛 | 3 (2.7%) | 0 | 5 (4.2%) | 1 (0.8%) |
| 非心臓性胸痛 | 5 (4.5%) | 2 (1.8%) | 3 (2.5%) | 0 |
| 粘膜の炎症 | 4 (3.6%) | 0 | 0 | 0 |
| 全身健康状態低下 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 倦怠感 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 局所腫脹 | 2 (1.8%) | 0 | 1 (0.8%) | 1 (0.8%) |
| 多臓器不全 | 0 | 0 | 0 | 0 |
| 胸部不快感 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 歩行障害 | 0 | 0 | 2 (1.7%) | 0 |
| 全身性浮腫 | 1 (0.9%) | 0 | 2 (1.7%) | 1 (0.8%) |
| 注射部位内出血 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 乾燥症 | 1 (0.9%) | 0 | 0 | 0 |
| 腋窩痛 | 1 (0.9%) | 0 | 0 | 0 |
| 早期満腹 | 0 | 0 | 1 (0.8%) | 0 |
| 重力性浮腫 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 低体温 | 0 | 0 | 1 (0.8%) | 0 |
| 炎症 | 0 | 0 | 0 | 0 |
| 浮腫 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 活動状態低下 | 1 (0.9%) | 0 | 0 | 0 |
| カテーテル留置部位関連反応 | 0 | 0 | 0 | 0 |
| 死亡 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 医療機器リーク | 1 (0.9%) | 0 | 0 | 0 |
| 顔面浮腫 | 0 | 0 | 0 | 0 |
| 異常感 | 1 (0.9%) | 0 | 0 | 0 |
| 冷感 | 0 | 0 | 0 | 0 |
| 熱感 | 0 | 0 | 0 | 0 |
| 治癒不良 | 0 | 0 | 0 | 0 |
| 硬結 | 1 (0.9%) | 0 | 0 | 0 |
| 注入部位血管外漏出 | 0 | 0 | 0 | 0 |
| 注射部位紅斑 | 1 (0.9%) | 0 | 0 | 0 |
| 注射部位漏出 | 1 (0.9%) | 0 | 0 | 0 |
| 注射部位出血 | 0 | 0 | 1 (0.8%) | 0 |
| 注射部位疼痛 | 1 (0.9%) | 0 | 0 | 0 |
| 注射部位反応 | 1 (0.9%) | 0 | 0 | 0 |
| 先行疾患の改善 | 0 | 0 | 0 | 0 |
| 温度変化不耐症 | 0 | 0 | 1 (0.8%) | 0 |
| 評価不能の事象 | 1 (0.9%) | 0 | 0 | 0 |
| 医療機器関連の血栓症 | 0 | 0 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 60 (54.1%) | 9 (8.1%) | 68 (56.7%) | 10 (8.3%) |
| 咳嗽 | 20 (18.0%) | 0 | 30 (25.0%) | 0 |
| 呼吸困難 | 30 (27.0%) | 5 (4.5%) | 23 (19.2%) | 3 (2.5%) |
| 鼻出血 | 12 (10.8%) | 0 | 8 (6.7%) | 0 |
| 口腔咽頭痛 | 10 (9.0%) | 0 | 11 (9.2%) | 0 |
| 胸水 | 6 (5.4%) | 1 (0.9%) | 7 (5.8%) | 2 (1.7%) |
| 湿性咳嗽 | 3 (2.7%) | 0 | 6 (5.0%) | 0 |
| 鼻閉 | 1 (0.9%) | 0 | 9 (7.5%) | 0 |
| 呼吸不全 | 2 (1.8%) | 2 (1.8%) | 6 (5.0%) | 6 (5.0%) |
| 鼻漏 | 1 (0.9%) | 0 | 7 (5.8%) | 0 |
| 発声障害 | 3 (2.7%) | 0 | 3 (2.5%) | 0 |
| 慢性閉塞性肺疾患 | 1 (0.9%) | 1 (0.9%) | 3 (2.5%) | 1 (0.8%) |
| アレルギー性鼻炎 | 4 (3.6%) | 0 | 0 | 0 |
| 副鼻腔うっ血 | 3 (2.7%) | 0 | 3 (2.5%) | 0 |
| 上気道うっ血 | 0 | 0 | 6 (5.0%) | 0 |
| 低酸素症 | 1 (0.9%) | 1 (0.9%) | 3 (2.5%) | 2 (1.7%) |
| しゃっくり | 1 (0.9%) | 0 | 3 (2.5%) | 0 |
| 気胸 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| 喀血 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 鼻部不快感 | 0 | 0 | 2 (1.7%) | 0 |
| 肺水腫 | 0 | 0 | 1 (0.8%) | 0 |
| ラ音 | 2 (1.8%) | 0 | 0 | 0 |
| 喘鳴 | 0 | 0 | 1 (0.8%) | 0 |
| 無気肺 | 0 | 0 | 1 (0.8%) | 0 |
| 労作性呼吸困難 | 0 | 0 | 1 (0.8%) | 0 |
| 肺硬化 | 2 (1.8%) | 0 | 0 | 0 |
| 肺浸潤 | 1 (0.9%) | 0 | 0 | 0 |
| 鼻の炎症 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 肺塞栓症 | 1 (0.9%) | 0 | 0 | 0 |
| 気道うっ血 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 急性肺水腫 | 0 | 0 | 0 | 0 |
| 喘息 | 0 | 0 | 1 (0.8%) | 0 |
| 気管支反応性亢進 | 0 | 0 | 0 | 0 |
| 気管支分泌物貯留 | 0 | 0 | 1 (0.8%) | 0 |
| 気管支拡張症 | 0 | 0 | 1 (0.8%) | 0 |
| 慢性気管支炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 肺気腫 | 0 | 0 | 1 (0.8%) | 0 |
| 上気道分泌増加 | 0 | 0 | 0 | 0 |
| 鼻乾燥 | 0 | 0 | 0 | 0 |
| 鼻潰瘍 | 0 | 0 | 0 | 0 |
| 副鼻腔不快感 | 0 | 0 | 1 (0.8%) | 0 |
| 副鼻腔分泌過多 | 1 (0.9%) | 0 | 0 | 0 |
| 咽頭紅斑 | 0 | 0 | 1 (0.8%) | 0 |
| 胸膜炎 | 0 | 0 | 0 | 0 |
| 胸膜痛 | 0 | 0 | 0 | 0 |
| 肺腫瘤 | 0 | 0 | 1 (0.8%) | 0 |
| 呼吸性アシドーシス | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 呼吸窮迫 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 拘束性肺疾患 | 1 (0.9%) | 0 | 0 | 0 |
| 副鼻腔障害 | 1 (0.9%) | 0 | 0 | 0 |
| くしゃみ | 0 | 0 | 0 | 0 |
| 頻呼吸 | 0 | 0 | 1 (0.8%) | 0 |
| 扁桃肥大 | 0 | 0 | 1 (0.8%) | 0 |
| 上気道咳症候群 | 0 | 0 | 1 (0.8%) | 0 |
| 間質性肺疾患 | 0 | 0 | 0 | 0 |
| 咽頭潰瘍 | 0 | 0 | 0 | 0 |
| 肺臓炎 | 0 | 0 | 0 | 0 |
| 皮膚および皮下組織障害 | 72 (64.9%) | 4 (3.6%) | 63 (52.5%) | 3 (2.5%) |
| 発疹 | 18 (16.2%) | 2 (1.8%) | 21 (17.5%) | 1 (0.8%) |
| そう痒症 | 8 (7.2%) | 0 | 8 (6.7%) | 0 |
| 点状出血 | 10 (9.0%) | 0 | 6 (5.0%) | 0 |
| 皮膚病変 | 9 (8.1%) | 0 | 6 (5.0%) | 0 |
| 斑状丘疹状皮疹 | 8 (7.2%) | 0 | 3 (2.5%) | 1 (0.8%) |
| 皮膚乾燥 | 6 (5.4%) | 0 | 6 (5.0%) | 0 |
| 斑状出血 | 6 (5.4%) | 0 | 3 (2.5%) | 0 |
| 紅斑 | 3 (2.7%) | 0 | 5 (4.2%) | 0 |
| 寝汗 | 5 (4.5%) | 0 | 6 (5.0%) | 0 |
| 脱毛症 | 5 (4.5%) | 0 | 2 (1.7%) | 0 |
| ざ瘡様皮膚炎 | 2 (1.8%) | 0 | 2 (1.7%) | 0 |
| 紫斑 | 3 (2.7%) | 0 | 1 (0.8%) | 1 (0.8%) |
| 多汗症 | 1 (0.9%) | 0 | 4 (3.3%) | 0 |
| 皮膚亀裂 | 1 (0.9%) | 0 | 0 | 0 |
| 嵌入爪 | 2 (1.8%) | 0 | 3 (2.5%) | 0 |
| 爪破損 | 3 (2.7%) | 0 | 0 | 0 |
| 蕁麻疹 | 1 (0.9%) | 0 | 0 | 0 |
| 水疱 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 全身性そう痒症 | 0 | 0 | 3 (2.5%) | 0 |
| 斑状皮疹 | 4 (3.6%) | 1 (0.9%) | 0 | 0 |
| 皮膚腫瘤 | 0 | 0 | 4 (3.3%) | 0 |
| 皮膚潰瘍 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| ざ瘡 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 褥瘡性潰瘍 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 0 |
| 湿疹 | 0 | 0 | 0 | 0 |
| 紅斑性皮疹 | 3 (2.7%) | 0 | 0 | 0 |
| 皮膚色素過剰 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 皮膚嚢腫 | 0 | 0 | 2 (1.7%) | 0 |
| 接触性皮膚炎 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 皮下出血 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 間擦疹 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 皮膚疼痛 | 0 | 0 | 1 (0.8%) | 0 |
| 全身性皮疹 | 0 | 0 | 1 (0.8%) | 0 |
| 丘疹性皮疹 | 0 | 0 | 1 (0.8%) | 0 |
| そう痒性皮疹 | 0 | 0 | 1 (0.8%) | 0 |
| 皮膚変色 | 2 (1.8%) | 0 | 0 | 0 |
| 毛細血管炎 | 0 | 0 | 1 (0.8%) | 0 |
| 皮膚炎 | 0 | 0 | 1 (0.8%) | 0 |
| アレルギー性皮膚炎 | 1 (0.9%) | 0 | 0 | 0 |
| 水疱性皮膚炎 | 0 | 0 | 1 (0.8%) | 0 |
| 皮脂欠乏性湿疹 | 0 | 0 | 0 | 0 |
| 貨幣状湿疹 | 0 | 0 | 0 | 0 |
| 過敏性血管炎 | 0 | 0 | 0 | 0 |
| 爪床出血 | 0 | 0 | 0 | 0 |
| 爪床障害 | 0 | 0 | 1 (0.8%) | 0 |
| 爪床の炎症 | 0 | 0 | 0 | 0 |
| 爪の不快感 | 0 | 0 | 0 | 0 |
| 爪の障害 | 1 (0.9%) | 0 | 0 | 0 |
| 爪ジストロフィー | 0 | 0 | 0 | 0 |
| 爪線状隆起 | 1 (0.9%) | 0 | 0 | 0 |
| 爪痛 | 0 | 0 | 0 | 0 |
| 爪甲脱落症 | 0 | 0 | 1 (0.8%) | 0 |
| 手掌・足底発赤知覚不全症候群 | 0 | 0 | 0 | 0 |
| 脂肪織炎 | 0 | 0 | 0 | 0 |
| 色素沈着障害 | 0 | 0 | 0 | 0 |
| 毛孔性皮疹 | 0 | 0 | 1 (0.8%) | 0 |
| 皮膚色素減少 | 1 (0.9%) | 0 | 0 | 0 |
| 皮膚刺激 | 0 | 0 | 1 (0.8%) | 0 |
| 皮膚腫脹 | 0 | 0 | 1 (0.8%) | 0 |
| 乾皮症 | 0 | 0 | 0 | 0 |
| 皮膚アミロイドーシス | 0 | 0 | 0 | 0 |
| 異汗性湿疹 | 0 | 0 | 0 | 0 |
| 多形紅斑 | 0 | 0 | 0 | 0 |
| 爪甲離床症 | 0 | 0 | 0 | 0 |
| 痒疹 | 0 | 0 | 0 | 0 |
| 皮膚硬結 | 0 | 0 | 0 | 0 |
| うっ滞性皮膚炎 | 0 | 0 | 0 | 0 |
| 顔面腫脹 | 0 | 0 | 0 | 0 |
| 筋骨格系および結合組織障害 | 61 (55.0%) | 5 (4.5%) | 60 (50.0%) | 7 (5.8%) |
| 筋痙縮 | 16 (14.4%) | 0 | 25 (20.8%) | 0 |
| 背部痛 | 14 (12.6%) | 1 (0.9%) | 14 (11.7%) | 1 (0.8%) |
| 関節痛 | 12 (10.8%) | 0 | 18 (15.0%) | 1 (0.8%) |
| 筋肉痛 | 14 (12.6%) | 0 | 13 (10.8%) | 1 (0.8%) |
| 四肢痛 | 12 (10.8%) | 0 | 12 (10.0%) | 2 (1.7%) |
| 筋骨格痛 | 6 (5.4%) | 0 | 10 (8.3%) | 0 |
| 筋力低下 | 5 (4.5%) | 1 (0.9%) | 4 (3.3%) | 1 (0.8%) |
| 側腹部痛 | 3 (2.7%) | 2 (1.8%) | 3 (2.5%) | 0 |
| 頚部痛 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 変形性関節症 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 肢径部痛 | 2 (1.8%) | 1 (0.9%) | 2 (1.7%) | 0 |
| 四肢不快感 | 0 | 0 | 3 (2.5%) | 0 |
| 筋骨格硬直 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 骨痛 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 関節硬直 | 2 (1.8%) | 0 | 0 | 0 |
| 関節腫脹 | 0 | 0 | 2 (1.7%) | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 運動性低下 | 2 (1.8%) | 0 | 0 | 0 |
| 筋骨格系胸痛 | 2 (1.8%) | 0 | 0 | 0 |
| ミオパチー | 1 (0.9%) | 0 | 1 (0.8%) | 1 (0.8%) |
| 軟部組織障害 | 1 (0.9%) | 0 | 0 | 0 |
| 関節炎 | 0 | 0 | 1 (0.8%) | 0 |
| 滑液包炎 | 0 | 0 | 0 | 0 |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 0 | 0 | 0 | 0 |
| 外骨腫 | 0 | 0 | 0 | 0 |
| 痛風性関節炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 椎間板変性症 | 1 (0.9%) | 0 | 0 | 0 |
| 椎間板突出 | 0 | 0 | 0 | 0 |
| 関節拘縮 | 1 (0.9%) | 0 | 0 | 0 |
| 関節滲出液 | 0 | 0 | 1 (0.8%) | 0 |
| 関節ロック | 0 | 0 | 1 (0.8%) | 0 |
| 筋緊張 | 0 | 0 | 1 (0.8%) | 0 |
| 筋攣縮 | 0 | 0 | 1 (0.8%) | 0 |
| 筋骨格不快感 | 1 (0.9%) | 0 | 0 | 0 |
| 頚部腫瘤 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 骨壊死 | 0 | 0 | 0 | 0 |
| 骨粗鬆症 | 1 (0.9%) | 0 | 0 | 0 |
| 顎痛 | 0 | 0 | 1 (0.8%) | 0 |
| 横紋筋融解症 | 0 | 0 | 0 | 0 |
| 滑液嚢腫 | 1 (0.9%) | 0 | 0 | 0 |
| 腱痛 | 0 | 0 | 0 | 0 |
| 椎間孔狭窄 | 0 | 0 | 1 (0.8%) | 0 |
| 関節障害 | 0 | 0 | 0 | 0 |
| 軟骨石灰化症 | 0 | 0 | 0 | 0 |
| 鼡径部腫瘤 | 0 | 0 | 0 | 0 |
| 椎間板圧迫 | 0 | 0 | 0 | 0 |
| 筋拘縮 | 0 | 0 | 0 | 0 |
| 骨炎 | 0 | 0 | 0 | 0 |
| 筋肉減少症 | 0 | 0 | 0 | 0 |
| 脊椎痛 | 0 | 0 | 0 | 0 |
| 弾発指 | 0 | 0 | 0 | 0 |
| 血液およびリンパ系障害 | 51 (45.9%) | 34 (30.6%) | 63 (52.5%) | 44 (36.7%) |
| 血小板減少症 | 20 (18.0%) | 12 (10.8%) | 29 (24.2%) | 16 (13.3%) |
| 好中球減少症 | 20 (18.0%) | 18 (16.2%) | 28 (23.3%) | 25 (20.8%) |
| 貧血 | 15 (13.5%) | 11 (9.9%) | 23 (19.2%) | 8 (6.7%) |
| 発熱性好中球減少症 | 4 (3.6%) | 4 (3.6%) | 6 (5.0%) | 6 (5.0%) |
| 白血球減少症 | 7 (6.3%) | 4 (3.6%) | 4 (3.3%) | 2 (1.7%) |
| 白血球増加症 | 3 (2.7%) | 0 | 1 (0.8%) | 1 (0.8%) |
| 内出血発生の増加傾向 | 5 (4.5%) | 0 | 0 | 0 |
| リンパ球減少症 | 1 (0.9%) | 0 | 0 | 0 |
| リンパ球増加症 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| リンパ節痛 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| リンパ節症 | 1 (0.9%) | 0 | 0 | 0 |
| 脾腫 | 1 (0.9%) | 0 | 0 | 0 |
| 骨髄機能不全 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 凝血異常 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 溶血 | 0 | 0 | 0 | 0 |
| 鉄欠乏性貧血 | 1 (0.9%) | 0 | 0 | 0 |
| 白血球停滞症候群 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 汎血球減少症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 後腹膜リンパ節腫脹 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 脾臓出血 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 脾臓梗塞 | 0 | 0 | 0 | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 血小板増加症 | 0 | 0 | 1 (0.8%) | 0 |
| リンパ節炎 | 0 | 0 | 0 | 0 |
| 好中球増加症 | 0 | 0 | 0 | 0 |
| 代謝および栄養障害 | 53 (47.7%) | 15 (13.5%) | 46 (38.3%) | 15 (12.5%) |
| 食欲減退 | 23 (20.7%) | 2 (1.8%) | 14 (11.7%) | 0 |
| 低カリウム血症 | 9 (8.1%) | 2 (1.8%) | 14 (11.7%) | 5 (4.2%) |
| 高尿酸血症 | 15 (13.5%) | 5 (4.5%) | 5 (4.2%) | 4 (3.3%) |
| 脱水 | 13 (11.7%) | 4 (3.6%) | 6 (5.0%) | 2 (1.7%) |
| 低マグネシウム血症 | 4 (3.6%) | 0 | 9 (7.5%) | 0 |
| 高カリウム血症 | 1 (0.9%) | 0 | 3 (2.5%) | 0 |
| 低ナトリウム血症 | 6 (5.4%) | 4 (3.6%) | 5 (4.2%) | 3 (2.5%) |
| 低アルブミン血症 | 1 (0.9%) | 1 (0.9%) | 8 (6.7%) | 3 (2.5%) |
| 高血糖 | 4 (3.6%) | 0 | 2 (1.7%) | 1 (0.8%) |
| 低カルシウム血症 | 2 (1.8%) | 0 | 2 (1.7%) | 0 |
| 低血糖症 | 2 (1.8%) | 0 | 2 (1.7%) | 0 |
| 低リン酸血症 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 水分過負荷 | 1 (0.9%) | 0 | 0 | 0 |
| 痛風 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 酵素異常 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 高コレステロール血症 | 1 (0.9%) | 0 | 0 | 0 |
| 高ナトリウム血症 | 0 | 0 | 2 (1.7%) | 0 |
| 高リン酸塩血症 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 過小食 | 0 | 0 | 0 | 0 |
| 乳酸アシドーシス | 0 | 0 | 1 (0.8%) | 0 |
| アルコール不耐性 | 1 (0.9%) | 0 | 0 | 0 |
| 悪液質 | 0 | 0 | 0 | 0 |
| 糖尿病 | 0 | 0 | 0 | 0 |
| 糖尿病性ケトアシドーシス | 0 | 0 | 0 | 0 |
| 高アルブミン血症 | 0 | 0 | 0 | 0 |
| 高アンモニア血症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 低蛋白血症 | 0 | 0 | 0 | 0 |
| 代謝性アシドーシス | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 腫瘍崩壊症候群 | 0 | 0 | 0 | 0 |
| ２型糖尿病 | 0 | 0 | 0 | 0 |
| 脂質異常症 | 0 | 0 | 0 | 0 |
| 電解質失調 | 0 | 0 | 0 | 0 |
| 体液貯留 | 0 | 0 | 0 | 0 |
| 耐糖能障害 | 0 | 0 | 0 | 0 |
| 高クレアチニン血症 | 0 | 0 | 0 | 0 |
| 高脂血症 | 0 | 0 | 0 | 0 |
| 高トリグリセリド血症 | 0 | 0 | 0 | 0 |
| 多飲症 | 0 | 0 | 0 | 0 |
| 神経系障害 | 44 (39.6%) | 1 (0.9%) | 38 (31.7%) | 4 (3.3%) |
| 頭痛 | 12 (10.8%) | 0 | 12 (10.0%) | 0 |
| 浮動性めまい | 16 (14.4%) | 0 | 5 (4.2%) | 0 |
| 末梢性感覚ニューロパチー | 6 (5.4%) | 0 | 5 (4.2%) | 1 (0.8%) |
| 体位性めまい | 1 (0.9%) | 0 | 8 (6.7%) | 0 |
| 錯感覚 | 4 (3.6%) | 0 | 3 (2.5%) | 0 |
| 記憶障害 | 3 (2.7%) | 0 | 3 (2.5%) | 0 |
| 末梢性ニューロパチー | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 振戦 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 感覚鈍麻 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 健忘 | 2 (1.8%) | 0 | 2 (1.7%) | 0 |
| 傾眠 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 失神 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 平衡障害 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 構語障害 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 味覚異常 | 0 | 0 | 2 (1.7%) | 0 |
| 嗜眠 | 2 (1.8%) | 0 | 0 | 0 |
| 多発ニューロパチー | 0 | 0 | 0 | 0 |
| 認知症 | 0 | 0 | 1 (0.8%) | 0 |
| 頭蓋内出血 | 0 | 0 | 2 (1.7%) | 0 |
| 過眠症 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 神経痛 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 失神寸前の状態 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 下肢静止不能症候群 | 0 | 0 | 1 (0.8%) | 0 |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 2 (1.7%) | 0 |
| 一過性脳虚血発作 | 0 | 0 | 1 (0.8%) | 0 |
| 灼熱足症候群 | 0 | 0 | 0 | 0 |
| 手根管症候群 | 0 | 0 | 0 | 0 |
| 大脳萎縮 | 0 | 0 | 0 | 0 |
| 脳血管発作 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 労作性めまい | 0 | 0 | 1 (0.8%) | 0 |
| 脳症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| てんかん | 0 | 0 | 0 | 0 |
| 顔面部神経痛 | 0 | 0 | 0 | 0 |
| 顔面不全麻痺 | 0 | 0 | 0 | 0 |
| 頭部不快感 | 1 (0.9%) | 0 | 0 | 0 |
| 腰髄神経根障害 | 0 | 0 | 0 | 0 |
| 片頭痛 | 1 (0.9%) | 0 | 0 | 0 |
| 前兆を伴う片頭痛 | 1 (0.9%) | 0 | 0 | 0 |
| 筋痙直 | 0 | 0 | 0 | 0 |
| ミオクローヌス | 0 | 0 | 0 | 0 |
| 眼振 | 1 (0.9%) | 0 | 0 | 0 |
| 腓骨神経麻痺 | 1 (0.9%) | 0 | 0 | 0 |
| ヘルペス後神経痛 | 0 | 0 | 0 | 0 |
| 坐骨神経痛 | 1 (0.9%) | 0 | 0 | 0 |
| 感覚障害 | 1 (0.9%) | 0 | 0 | 0 |
| 会話障害 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 緊張性頭痛 | 1 (0.9%) | 0 | 0 | 0 |
| 一過性全健忘 | 1 (0.9%) | 0 | 0 | 0 |
| 血管性脳症 | 0 | 0 | 0 | 0 |
| 失声症 | 0 | 0 | 0 | 0 |
| 運動失調 | 0 | 0 | 0 | 0 |
| 脳虚血 | 0 | 0 | 0 | 0 |
| 認知障害 | 0 | 0 | 0 | 0 |
| 糖尿病性ニューロパチー | 0 | 0 | 0 | 0 |
| 注意力障害 | 0 | 0 | 0 | 0 |
| 異常感覚 | 0 | 0 | 0 | 0 |
| 虚血性脳卒中 | 0 | 0 | 0 | 0 |
| 意識消失 | 0 | 0 | 0 | 0 |
| 末梢性感覚運動ニューロパチー | 0 | 0 | 0 | 0 |
| 精神運動亢進 | 0 | 0 | 0 | 0 |
| 臨床検査 | 26 (23.4%) | 4 (3.6%) | 33 (27.5%) | 14 (11.7%) |
| 血中クレアチニン増加 | 6 (5.4%) | 0 | 11 (9.2%) | 0 |
| 血小板数減少 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 体重減少 | 3 (2.7%) | 0 | 3 (2.5%) | 0 |
| 血中アルカリホスファターゼ増加 | 1 (0.9%) | 0 | 6 (5.0%) | 2 (1.7%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 3 (2.7%) | 0 | 2 (1.7%) | 0 |
| 血中ビリルビン増加 | 2 (1.8%) | 0 | 5 (4.2%) | 1 (0.8%) |
| 好中球数減少 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| アラニンアミノトランスフェラーゼ増加 | 3 (2.7%) | 0 | 0 | 0 |
| 血中尿酸増加 | 0 | 0 | 4 (3.3%) | 3 (2.5%) |
| リンパ球数増加 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 体重増加 | 3 (2.7%) | 0 | 1 (0.8%) | 0 |
| 活性化部分トロンボプラスチン時間延長 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 0 |
| 血中乳酸脱水素酵素増加 | 0 | 0 | 3 (2.5%) | 0 |
| 白血球数減少 | 0 | 0 | 3 (2.5%) | 3 (2.5%) |
| 血中免疫グロブリンG減少 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 国際標準比増加 | 2 (1.8%) | 2 (1.8%) | 1 (0.8%) | 1 (0.8%) |
| 白血球数増加 | 1 (0.9%) | 0 | 0 | 0 |
| 血中ブドウ糖増加 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 血中免疫グロブリンM減少 | 0 | 0 | 0 | 0 |
| 血圧上昇 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| Ｃ－反応性蛋白増加 | 1 (0.9%) | 0 | 0 | 0 |
| 心雑音 | 2 (1.8%) | 0 | 0 | 0 |
| γ－グルタミルトランスフェラーゼ増加 | 0 | 0 | 0 | 0 |
| 糸球体濾過率減少 | 2 (1.8%) | 0 | 0 | 0 |
| ヘモグロビン減少 | 0 | 0 | 0 | 0 |
| 免疫グロブリン減少 | 0 | 0 | 0 | 0 |
| リンパ球数減少 | 0 | 0 | 0 | 0 |
| トランスアミナーゼ上昇 | 0 | 0 | 1 (0.8%) | 0 |
| アミラーゼ増加 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| アスペルギルス検査陽性 | 1 (0.9%) | 0 | 0 | 0 |
| 血中アルブミン減少 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 血中重炭酸塩増加 | 0 | 0 | 0 | 0 |
| 血中ビリルビン異常 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 血中クロール減少 | 0 | 0 | 1 (0.8%) | 0 |
| 血中コレステロール増加 | 1 (0.9%) | 0 | 0 | 0 |
| 血中クレアチン増加 | 0 | 0 | 1 (0.8%) | 0 |
| 血中免疫グロブリンＡ減少 | 0 | 0 | 0 | 0 |
| 血中鉄減少 | 1 (0.9%) | 0 | 0 | 0 |
| 血中マグネシウム減少 | 0 | 0 | 0 | 0 |
| 血中リン減少 | 1 (0.9%) | 0 | 0 | 0 |
| 血中カリウム減少 | 0 | 0 | 0 | 0 |
| 呼吸音異常 | 1 (0.9%) | 0 | 0 | 0 |
| 二酸化炭素減少 | 0 | 0 | 1 (0.8%) | 0 |
| 胸部コンピュータ断層撮影異常 | 0 | 0 | 1 (0.8%) | 0 |
| 駆出率減少 | 0 | 0 | 1 (0.8%) | 0 |
| グリコヘモグロビン増加 | 0 | 0 | 0 | 0 |
| ヘモフィルス検査陽性 | 1 (0.9%) | 0 | 0 | 0 |
| 心拍数増加 | 0 | 0 | 1 (0.8%) | 0 |
| 心拍数不整 | 1 (0.9%) | 0 | 0 | 0 |
| 肝酵素上昇 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 深吸気量減少 | 0 | 0 | 0 | 0 |
| 肝機能検査異常 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 黄斑部反射異常 | 1 (0.9%) | 0 | 0 | 0 |
| 平均赤血球容積増加 | 1 (0.9%) | 0 | 0 | 0 |
| 血小板凝集異常 | 0 | 0 | 0 | 0 |
| 尿量減少 | 1 (0.9%) | 0 | 0 | 0 |
| 超低比重リポ蛋白増加 | 0 | 0 | 1 (0.8%) | 0 |
| 肺活量異常 | 0 | 0 | 0 | 0 |
| 血中重炭酸塩減少 | 0 | 0 | 0 | 0 |
| 血中カルシウム減少 | 0 | 0 | 0 | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 血中フィブリノゲン増加 | 0 | 0 | 0 | 0 |
| 起立血圧低下 | 0 | 0 | 0 | 0 |
| 収縮期血圧上昇 | 0 | 0 | 0 | 0 |
| 血中ナトリウム減少 | 0 | 0 | 0 | 0 |
| 血中トリグリセリド増加 | 0 | 0 | 0 | 0 |
| 血中尿素増加 | 0 | 0 | 0 | 0 |
| ＥＣＯＧパフォーマンスステータス悪化 | 0 | 0 | 0 | 0 |
| 好酸球数増加 | 0 | 0 | 0 | 0 |
| 低比重リポ蛋白増加 | 0 | 0 | 0 | 0 |
| 平均赤血球容積減少 | 0 | 0 | 0 | 0 |
| 好中球数増加 | 0 | 0 | 0 | 0 |
| 酸素飽和度低下 | 0 | 0 | 0 | 0 |
| レスピロウイルス検査陽性 | 0 | 0 | 0 | 0 |
| 視力検査異常 | 0 | 0 | 0 | 0 |
| 傷害、中毒および処置合併症 | 34 (30.6%) | 4 (3.6%) | 36 (30.0%) | 2 (1.7%) |
| 挫傷 | 19 (17.1%) | 0 | 17 (14.2%) | 0 |
| 転倒 | 8 (7.2%) | 2 (1.8%) | 6 (5.0%) | 0 |
| 節足動物咬傷 | 1 (0.9%) | 0 | 4 (3.3%) | 0 |
| 処置による疼痛 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 硬膜下血腫 | 4 (3.6%) | 2 (1.8%) | 0 | 0 |
| 外傷性血腫 | 2 (1.8%) | 0 | 0 | 0 |
| 裂傷 | 3 (2.7%) | 0 | 1 (0.8%) | 0 |
| 皮膚擦過傷 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| サンバーン | 1 (0.9%) | 0 | 3 (2.5%) | 0 |
| 創傷 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 動物咬傷 | 0 | 0 | 3 (2.5%) | 1 (0.8%) |
| 頭部損傷 | 1 (0.9%) | 0 | 0 | 0 |
| 靭帯捻挫 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 腰椎骨折 | 0 | 0 | 0 | 0 |
| 処置後出血 | 0 | 0 | 1 (0.8%) | 0 |
| 骨挫傷 | 1 (0.9%) | 0 | 0 | 0 |
| 擦過傷 | 0 | 0 | 1 (0.8%) | 0 |
| 顔面骨骨折 | 0 | 0 | 1 (0.8%) | 0 |
| 四肢損傷 | 0 | 0 | 0 | 0 |
| 眼窩周囲挫傷 | 0 | 0 | 1 (0.8%) | 0 |
| 肋骨骨折 | 0 | 0 | 0 | 0 |
| 皮膚創傷 | 1 (0.9%) | 0 | 0 | 0 |
| 脊椎圧迫骨折 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 脾破裂 | 0 | 0 | 0 | 0 |
| 熱傷 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 動物による引っかき傷 | 0 | 0 | 1 (0.8%) | 0 |
| 足関節部骨折 | 0 | 0 | 1 (0.8%) | 0 |
| 第２度熱傷 | 0 | 0 | 1 (0.8%) | 0 |
| 眼挫傷 | 0 | 0 | 0 | 0 |
| 眼外傷 | 1 (0.9%) | 0 | 0 | 0 |
| 足骨折 | 0 | 0 | 1 (0.8%) | 0 |
| 眼内異物 | 0 | 0 | 0 | 0 |
| 外傷性血尿 | 0 | 0 | 1 (0.8%) | 0 |
| 関節損傷 | 0 | 0 | 0 | 0 |
| 過量投与 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 処置後便秘 | 1 (0.9%) | 0 | 0 | 0 |
| 処置後血尿 | 0 | 0 | 0 | 0 |
| 処置後腫脹 | 0 | 0 | 0 | 0 |
| 外傷後疼痛 | 1 (0.9%) | 0 | 0 | 0 |
| 陰嚢血腫 | 0 | 0 | 0 | 0 |
| 皮下血腫 | 0 | 0 | 0 | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 脛骨骨折 | 0 | 0 | 1 (0.8%) | 0 |
| 歯牙破折 | 0 | 0 | 1 (0.8%) | 0 |
| 術後尿閉 | 1 (0.9%) | 0 | 0 | 0 |
| 創合併症 | 0 | 0 | 1 (0.8%) | 0 |
| アルコール中毒 | 0 | 0 | 0 | 0 |
| 背部損傷 | 0 | 0 | 0 | 0 |
| 腓骨骨折 | 0 | 0 | 0 | 0 |
| 体内異物 | 0 | 0 | 0 | 0 |
| 注入に伴う反応 | 0 | 0 | 0 | 0 |
| 靭帯断裂 | 0 | 0 | 0 | 0 |
| 四肢外傷性切断 | 0 | 0 | 0 | 0 |
| 眼窩周囲血腫 | 0 | 0 | 0 | 0 |
| 橈骨骨折 | 0 | 0 | 0 | 0 |
| 瘢痕 | 0 | 0 | 0 | 0 |
| 皮膚損傷 | 0 | 0 | 0 | 0 |
| 各種物質毒性 | 0 | 0 | 0 | 0 |
| 輸血反応 | 0 | 0 | 0 | 0 |
| 眼障害 | 26 (23.4%) | 0 | 26 (21.7%) | 3 (2.5%) |
| 眼乾燥 | 5 (4.5%) | 0 | 6 (5.0%) | 0 |
| 流涙増加 | 8 (7.2%) | 0 | 2 (1.7%) | 0 |
| 霧視 | 2 (1.8%) | 0 | 8 (6.7%) | 0 |
| 白内障 | 6 (5.4%) | 0 | 4 (3.3%) | 3 (2.5%) |
| 視力低下 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 眼窩周囲浮腫 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 結膜出血 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 眼痛 | 0 | 0 | 1 (0.8%) | 0 |
| 眼充血 | 2 (1.8%) | 0 | 0 | 0 |
| 睫毛乱生 | 0 | 0 | 2 (1.7%) | 0 |
| 硝子体浮遊物 | 2 (1.8%) | 0 | 0 | 0 |
| 糖尿病網膜症 | 1 (0.9%) | 0 | 0 | 0 |
| 複視 | 0 | 0 | 0 | 0 |
| 眼出血 | 0 | 0 | 1 (0.8%) | 0 |
| 眼刺激 | 0 | 0 | 0 | 0 |
| 眼瞼下垂 | 1 (0.9%) | 0 | 0 | 0 |
| 羞明 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 眼瞼炎 | 0 | 0 | 0 | 0 |
| 片側失明 | 0 | 0 | 0 | 0 |
| 結膜充血 | 0 | 0 | 0 | 0 |
| 眼瞼内反 | 0 | 0 | 1 (0.8%) | 0 |
| 眼脂 | 0 | 0 | 0 | 0 |
| 眼の炎症 | 1 (0.9%) | 0 | 0 | 0 |
| 眼そう痒症 | 0 | 0 | 1 (0.8%) | 0 |
| 眼の異物感 | 0 | 0 | 0 | 0 |
| 緑内障 | 0 | 0 | 1 (0.8%) | 0 |
| 角膜炎 | 0 | 0 | 1 (0.8%) | 0 |
| 黄斑変性 | 0 | 0 | 1 (0.8%) | 0 |
| マイボーム腺機能不全 | 0 | 0 | 1 (0.8%) | 0 |
| 眼血管障害 | 0 | 0 | 0 | 0 |
| 開放隅角緑内障 | 0 | 0 | 0 | 0 |
| 動揺視 | 0 | 0 | 0 | 0 |
| 老視 | 0 | 0 | 0 | 0 |
| 網膜剥離 | 1 (0.9%) | 0 | 0 | 0 |
| 強膜出血 | 1 (0.9%) | 0 | 0 | 0 |
| 視力障害 | 0 | 0 | 1 (0.8%) | 0 |
| 硝子体出血 | 0 | 0 | 0 | 0 |
| 眼球乾燥症 | 0 | 0 | 0 | 0 |
| 眼瞼紅斑 | 0 | 0 | 0 | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 眼の障害 | 0 | 0 | 0 | 0 |
| 眼部腫脹 | 0 | 0 | 0 | 0 |
| 眼瞼機能障害 | 0 | 0 | 0 | 0 |
| 眼瞼浮腫 | 0 | 0 | 0 | 0 |
| 血管障害 | 20 (18.0%) | 5 (4.5%) | 32 (26.7%) | 12 (10.0%) |
| 高血圧 | 11 (9.9%) | 4 (3.6%) | 14 (11.7%) | 5 (4.2%) |
| 低血圧 | 7 (6.3%) | 2 (1.8%) | 7 (5.8%) | 2 (1.7%) |
| 血腫 | 0 | 0 | 2 (1.7%) | 0 |
| 深部静脈血栓症 | 0 | 0 | 7 (5.8%) | 2 (1.7%) |
| 潮紅 | 1 (0.9%) | 0 | 3 (2.5%) | 0 |
| 出血 | 0 | 0 | 0 | 0 |
| 起立性低血圧 | 2 (1.8%) | 0 | 0 | 0 |
| 静脈炎 | 0 | 0 | 1 (0.8%) | 0 |
| 血圧変動 | 1 (0.9%) | 0 | 0 | 0 |
| リンパ浮腫 | 0 | 0 | 2 (1.7%) | 2 (1.7%) |
| 表在性血栓性静脈炎 | 0 | 0 | 0 | 0 |
| 大動脈硬化症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 循環虚脱 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| ほてり | 0 | 0 | 1 (0.8%) | 0 |
| 高血圧クリーゼ | 0 | 0 | 1 (0.8%) | 0 |
| 末梢血管障害 | 0 | 0 | 0 | 0 |
| 末梢静脈疾患 | 0 | 0 | 1 (0.8%) | 0 |
| 静脈瘤 | 1 (0.9%) | 0 | 0 | 0 |
| 塞栓症 | 0 | 0 | 0 | 0 |
| 頚静脈血栓症 | 0 | 0 | 0 | 0 |
| 静脈瘤性潰瘍 | 0 | 0 | 0 | 0 |
| 心臓障害 | 22 (19.8%) | 11 (9.9%) | 29 (24.2%) | 9 (7.5%) |
| 心房細動 | 9 (8.1%) | 6 (5.4%) | 13 (10.8%) | 6 (5.0%) |
| 頻脈 | 0 | 0 | 8 (6.7%) | 0 |
| 洞性頻脈 | 5 (4.5%) | 0 | 1 (0.8%) | 0 |
| 徐脈 | 0 | 0 | 3 (2.5%) | 0 |
| 動悸 | 1 (0.9%) | 0 | 0 | 0 |
| 心房粗動 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 0 |
| 洞性徐脈 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 上室性頻脈 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 不安定狭心症 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| 心停止 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 心不全 | 2 (1.8%) | 2 (1.8%) | 0 | 0 |
| 心室性期外収縮 | 0 | 0 | 1 (0.8%) | 0 |
| 急性心筋梗塞 | 0 | 0 | 0 | 0 |
| 不整脈 | 0 | 0 | 0 | 0 |
| 冠動脈硬化症 | 0 | 0 | 0 | 0 |
| 第一度房室ブロック | 1 (0.9%) | 0 | 0 | 0 |
| うっ血性心不全 | 0 | 0 | 0 | 0 |
| 心血管不全 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 変時性応答不全 | 0 | 0 | 0 | 0 |
| 冠動脈疾患 | 0 | 0 | 0 | 0 |
| 冠動脈閉塞 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| チアノーゼ | 0 | 0 | 1 (0.8%) | 0 |
| 僧帽弁閉鎖不全症 | 1 (0.9%) | 0 | 0 | 0 |
| 心筋梗塞 | 1 (0.9%) | 0 | 0 | 0 |
| 心嚢液貯留 | 0 | 0 | 1 (0.8%) | 0 |
| 心膜炎 | 0 | 0 | 0 | 0 |
| 洞不全症候群 | 0 | 0 | 1 (0.8%) | 0 |
| ストレス心筋症 | 0 | 0 | 1 (0.8%) | 0 |
| 頻脈性不整脈 | 0 | 0 | 1 (0.8%) | 0 |
| トルサード　ド　ポアント | 1 (0.9%) | 0 | 0 | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 三尖弁疾患 | 0 | 0 | 1 (0.8%) | 0 |
| 心室性不整脈 | 0 | 0 | 0 | 0 |
| 心室性頻脈 | 1 (0.9%) | 0 | 0 | 0 |
| 狭心症 | 0 | 0 | 0 | 0 |
| 右脚ブロック | 0 | 0 | 0 | 0 |
| 急性心不全 | 0 | 0 | 0 | 0 |
| 慢性心不全 | 0 | 0 | 0 | 0 |
| 心肺不全 | 0 | 0 | 0 | 0 |
| 冠動脈狭窄 | 0 | 0 | 0 | 0 |
| 心筋虚血 | 0 | 0 | 0 | 0 |
| 精神障害 | 26 (23.4%) | 2 (1.8%) | 21 (17.5%) | 3 (2.5%) |
| 不眠症 | 11 (9.9%) | 0 | 9 (7.5%) | 0 |
| 不安 | 6 (5.4%) | 0 | 2 (1.7%) | 0 |
| 錯乱状態 | 3 (2.7%) | 1 (0.9%) | 5 (4.2%) | 1 (0.8%) |
| うつ病 | 6 (5.4%) | 1 (0.9%) | 4 (3.3%) | 0 |
| 激越 | 3 (2.7%) | 0 | 1 (0.8%) | 0 |
| 譫妄 | 0 | 0 | 1 (0.8%) | 0 |
| 希死念慮を有するうつ病 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 多幸気分 | 1 (0.9%) | 0 | 0 | 0 |
| 幻聴 | 0 | 0 | 1 (0.8%) | 0 |
| 幻視 | 0 | 0 | 0 | 0 |
| 易刺激性 | 1 (0.9%) | 0 | 0 | 0 |
| リビドー減退 | 1 (0.9%) | 0 | 0 | 0 |
| 躁病 | 1 (0.9%) | 0 | 0 | 0 |
| 精神障害 | 0 | 0 | 0 | 0 |
| 精神状態変化 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 悪夢 | 0 | 0 | 0 | 0 |
| パニック発作 | 1 (0.9%) | 0 | 0 | 0 |
| パニック障害 | 0 | 0 | 0 | 0 |
| 感情不安定 | 0 | 0 | 0 | 0 |
| 広場恐怖症 | 0 | 0 | 0 | 0 |
| 抑うつ気分 | 0 | 0 | 0 | 0 |
| 睡眠異常 | 0 | 0 | 0 | 0 |
| 気分動揺 | 0 | 0 | 0 | 0 |
| 腎および尿路障害 | 18 (16.2%) | 6 (5.4%) | 22 (18.3%) | 3 (2.5%) |
| 血尿 | 6 (5.4%) | 2 (1.8%) | 4 (3.3%) | 0 |
| 急性腎不全 | 5 (4.5%) | 3 (2.7%) | 5 (4.2%) | 2 (1.7%) |
| 排尿困難 | 2 (1.8%) | 0 | 4 (3.3%) | 0 |
| 腎不全 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 0 |
| 頻尿 | 3 (2.7%) | 0 | 3 (2.5%) | 0 |
| 水腎症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 腎機能障害 | 2 (1.8%) | 0 | 0 | 0 |
| 尿閉 | 0 | 0 | 3 (2.5%) | 0 |
| 尿路閉塞 | 2 (1.8%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 腎結石症 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| 夜間頻尿 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 腎嚢胞 | 0 | 0 | 1 (0.8%) | 0 |
| 慢性腎不全 | 0 | 0 | 0 | 0 |
| 尿失禁 | 2 (1.8%) | 0 | 0 | 0 |
| 高窒素血症 | 1 (0.9%) | 0 | 0 | 0 |
| 膀胱刺激症状 | 0 | 0 | 1 (0.8%) | 0 |
| 出血性膀胱炎 | 0 | 0 | 0 | 0 |
| 緊張性膀胱 | 0 | 0 | 1 (0.8%) | 0 |
| 失禁 | 0 | 0 | 0 | 0 |
| 尿意切迫 | 1 (0.9%) | 0 | 0 | 0 |
| 閉塞性尿路疾患 | 1 (0.9%) | 0 | 0 | 0 |
| 乏尿 | 0 | 0 | 0 | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 腎仙痛 | 0 | 0 | 0 | 0 |
| 有痛性排尿困難 | 0 | 0 | 0 | 0 |
| 尿路痛 | 1 (0.9%) | 0 | 0 | 0 |
| 糖尿 | 0 | 0 | 0 | 0 |
| 白血球尿 | 0 | 0 | 0 | 0 |
| 排尿異常 | 0 | 0 | 0 | 0 |
| 多尿 | 0 | 0 | 0 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 16 (14.4%) | 11 (9.9%) | 12 (10.0%) | 2 (1.7%) |
| マントル細胞リンパ腫 | 8 (7.2%) | 8 (7.2%) | 0 | 0 |
| 基底細胞癌 | 1 (0.9%) | 0 | 5 (4.2%) | 0 |
| 皮膚有棘細胞癌 | 1 (0.9%) | 0 | 4 (3.3%) | 0 |
| 膀胱移行上皮癌 | 0 | 0 | 0 | 0 |
| 前立腺癌 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 扁平上皮癌 | 1 (0.9%) | 0 | 0 | 0 |
| 急性骨髄性白血病 | 0 | 0 | 1 (0.8%) | 0 |
| 良性新生物 | 0 | 0 | 0 | 0 |
| 膀胱癌 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 肺腺癌 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 悪性胸水 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 遠隔転移を伴う新生物 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 口腔乳頭腫 | 1 (0.9%) | 0 | 0 | 0 |
| 唾液腺癌 | 0 | 0 | 0 | 0 |
| 皮膚癌 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 皮膚乳頭腫 | 1 (0.9%) | 0 | 0 | 0 |
| 胸腺腫 | 0 | 0 | 0 | 0 |
| 移行上皮癌 | 0 | 0 | 0 | 0 |
| 腫瘍フレア | 0 | 0 | 1 (0.8%) | 0 |
| 胃腺癌 | 0 | 0 | 0 | 0 |
| 耳および迷路障害 | 6 (5.4%) | 1 (0.9%) | 10 (8.3%) | 1 (0.8%) |
| 回転性めまい | 1 (0.9%) | 0 | 4 (3.3%) | 0 |
| 耳鳴 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 耳痛 | 2 (1.8%) | 0 | 2 (1.7%) | 0 |
| 聴力低下 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 耳垢栓塞 | 0 | 0 | 2 (1.7%) | 0 |
| 耳不快感 | 0 | 0 | 1 (0.8%) | 0 |
| 難聴 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 耳出血 | 0 | 0 | 0 | 0 |
| 聴覚過敏 | 1 (0.9%) | 0 | 0 | 0 |
| 老人性難聴 | 0 | 0 | 0 | 0 |
| 耳部腫脹 | 0 | 0 | 0 | 0 |
| 聴覚障害 | 0 | 0 | 0 | 0 |
| 生殖系および乳房障害 | 6 (5.4%) | 4 (3.6%) | 7 (5.8%) | 1 (0.8%) |
| 良性前立腺肥大症 | 0 | 0 | 2 (1.7%) | 0 |
| 血精液症 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 性器浮腫 | 2 (1.8%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 勃起不全 | 0 | 0 | 2 (1.7%) | 0 |
| 骨盤痛 | 0 | 0 | 0 | 0 |
| 腟出血 | 1 (0.9%) | 0 | 0 | 0 |
| 後天性包茎 | 0 | 0 | 0 | 0 |
| 乳房血腫 | 0 | 0 | 0 | 0 |
| 乳房腫瘤 | 0 | 0 | 0 | 0 |
| 乳房痛 | 1 (0.9%) | 0 | 0 | 0 |
| 性器発疹 | 0 | 0 | 0 | 0 |
| 陰茎痛 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 陰嚢腫瘤 | 0 | 0 | 1 (0.8%) | 0 |

**TSFAE02PART1OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 陰嚢浮腫 | 0 | 0 | 0 | 0 |
| 陰嚢痛 | 0 | 0 | 0 | 0 |
| 子宮腟脱 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 外陰腟痛 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 外陰腟そう痒症 | 0 | 0 | 0 | 0 |
| 性器水疱 | 0 | 0 | 0 | 0 |
| 前立腺炎 | 0 | 0 | 0 | 0 |
| 陰嚢紅斑 | 0 | 0 | 0 | 0 |
| 外陰腟乾燥 | 0 | 0 | 0 | 0 |
| 免疫系障害 | 7 (6.3%) | 0 | 8 (6.7%) | 0 |
| 低ｙグロブリン血症 | 0 | 0 | 3 (2.5%) | 0 |
| 節足動物咬傷アレルギー | 1 (0.9%) | 0 | 3 (2.5%) | 0 |
| 過敏症 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 季節性アレルギー | 3 (2.7%) | 0 | 0 | 0 |
| 薬物過敏症 | 1 (0.9%) | 0 | 0 | 0 |
| 造影剤アレルギー | 0 | 0 | 0 | 0 |
| 食物アレルギー | 0 | 0 | 1 (0.8%) | 0 |
| 肝胆道系障害 | 3 (2.7%) | 0 | 4 (3.3%) | 3 (2.5%) |
| 高ビリルビン血症 | 2 (1.8%) | 0 | 1 (0.8%) | 1 (0.8%) |
| 胆石症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 胆管結石 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 胆管炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 肝不全 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 肝機能異常 | 1 (0.9%) | 0 | 0 | 0 |
| 中毒性肝炎 | 0 | 0 | 0 | 0 |
| 陶器様胆嚢 | 0 | 0 | 1 (0.8%) | 0 |
| 胆汁うっ滞 | 0 | 0 | 0 | 0 |
| 薬物性肝障害 | 0 | 0 | 0 | 0 |
| 肝障害 | 0 | 0 | 0 | 0 |
| 内分泌障害 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 甲状腺機能低下症 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 甲状腺機能亢進症 | 0 | 0 | 0 | 0 |
| 性腺機能低下 | 0 | 0 | 0 | 0 |
| 先天性、家族性および遺伝性障害 | 0 | 0 | 0 | 0 |
| 臍血腫 | 0 | 0 | 0 | 0 |
| 外科および内科処置 | 0 | 0 | 0 | 0 |
| 抜歯 | 0 | 0 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE02PART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae02.sas] 15SEP2015, 14:10

参照元：5.3.5.3.1 ISS TSFAE02PART1OF3

表 2.7.4-付録-7 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 139 | | 139 | |
| Subjects with any TEAE | 138 (99.3%) | 94 (67.6%) | 138 (99.3%) | 121 (87.1%) |
| System organ class | | | | |
| Preferred term | | | | |
| 感染症および寄生虫症 | 97 (69.8%) | 27 (19.4%) | 99 (71.2%) | 42 (30.2%) |
| 上気道感染 | 26 (18.7%) | 3 (2.2%) | 16 (11.5%) | 1 (0.7%) |
| 肺炎 | 13 (9.4%) | 11 (7.9%) | 17 (12.2%) | 9 (6.5%) |
| 副鼻腔炎 | 10 (7.2%) | 0 | 7 (5.0%) | 1 (0.7%) |
| 尿路感染 | 10 (7.2%) | 1 (0.7%) | 9 (6.5%) | 3 (2.2%) |
| 鼻咽頭炎 | 15 (10.8%) | 0 | 16 (11.5%) | 0 |
| 結膜炎 | 16 (11.5%) | 0 | 7 (5.0%) | 0 |
| 気管支炎 | 6 (4.3%) | 0 | 7 (5.0%) | 0 |
| 蜂巣炎 | 1 (0.7%) | 1 (0.7%) | 4 (2.9%) | 0 |
| 帯状疱疹 | 9 (6.5%) | 0 | 6 (4.3%) | 2 (1.4%) |
| 鼻炎 | 6 (4.3%) | 0 | 5 (3.6%) | 0 |
| 毛包炎 | 2 (1.4%) | 0 | 4 (2.9%) | 0 |
| 爪囲炎 | 8 (5.8%) | 0 | 5 (3.6%) | 0 |
| 下気道感染 | 5 (3.6%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| 皮膚感染 | 5 (3.6%) | 1 (0.7%) | 2 (1.4%) | 1 (0.7%) |
| 口腔ヘルペス | 3 (2.2%) | 0 | 15 (10.8%) | 0 |
| 気道感染 | 8 (5.8%) | 0 | 15 (10.8%) | 3 (2.2%) |
| 敗血症 | 5 (3.6%) | 5 (3.6%) | 5 (3.6%) | 5 (3.6%) |
| 胃腸炎 | 4 (2.9%) | 0 | 3 (2.2%) | 3 (2.2%) |
| 咽頭炎 | 7 (5.0%) | 1 (0.7%) | 2 (1.4%) | 0 |
| ウイルス感染 | 5 (3.6%) | 0 | 3 (2.2%) | 0 |
| 感染 | 4 (2.9%) | 2 (1.4%) | 2 (1.4%) | 0 |
| クロストリジウム・ディフィシレ大腸炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 眼感染 | 1 (0.7%) | 0 | 0 | 0 |
| 歯肉炎 | 2 (1.4%) | 0 | 3 (2.2%) | 0 |
| 口腔カンジダ症 | 2 (1.4%) | 0 | 7 (5.0%) | 2 (1.4%) |
| クロストリジウム・ディフィシレ感染 | 0 | 0 | 1 (0.7%) | 0 |
| インフルエンザ | 3 (2.2%) | 0 | 3 (2.2%) | 0 |
| 限局性感染 | 1 (0.7%) | 0 | 0 | 0 |
| 中耳炎 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 歯周炎 | 4 (2.9%) | 0 | 0 | 0 |
| 歯感染 | 0 | 0 | 3 (2.2%) | 1 (0.7%) |
| 菌血症 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 気管支肺炎 | 3 (2.2%) | 1 (0.7%) | 2 (1.4%) | 1 (0.7%) |
| 膀胱炎 | 2 (1.4%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 耳感染 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| ウイルス性胃腸炎 | 0 | 0 | 1 (0.7%) | 0 |
| 単純ヘルペス | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 喉頭炎 | 3 (2.2%) | 1 (0.7%) | 0 | 0 |
| 爪感染 | 2 (1.4%) | 0 | 2 (1.4%) | 0 |
| 外耳炎 | 3 (2.2%) | 0 | 0 | 0 |
| ブドウ球菌感染 | 0 | 0 | 0 | 0 |
| ウイルス性上気道感染 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 急性副鼻腔炎 | 1 (0.7%) | 0 | 0 | 0 |
| 細気管支炎 | 1 (0.7%) | 0 | 0 | 0 |
| 医療機器関連感染 | 1 (0.7%) | 1 (0.7%) | 3 (2.2%) | 2 (1.4%) |
| 憩室炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 感染性小腸結腸炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 丹毒 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 真菌感染 | 0 | 0 | 2 (1.4%) | 0 |
| 皮膚真菌感染 | 1 (0.7%) | 0 | 0 | 0 |
| 真菌性性器感染 | 1 (0.7%) | 0 | 0 | 0 |
| ヘルペスウイルス感染 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 麦粒腫 | 0 | 0 | 0 | 0 |
| 爪真菌症 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| レンサ球菌性咽頭炎 | 0 | 0 | 0 | 0 |
| ニューモシスチス・イロベチイ肺炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 細菌性肺炎 | 0 | 0 | 0 | 0 |
| 膿疱性皮疹 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 敗血症性ショック | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| ブドウ球菌性菌血症 | 0 | 0 | 1 (0.7%) | 0 |
| 歯膿瘍 | 1 (0.7%) | 0 | 4 (2.9%) | 1 (0.7%) |
| 細菌性尿路感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 尿路性敗血症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 外陰部腟カンジダ症 | 1 (0.7%) | 0 | 0 | 0 |
| 創傷感染 | 0 | 0 | 0 | 0 |
| 腹部膿瘍 | 0 | 0 | 0 | 0 |
| 四肢膿瘍 | 1 (0.7%) | 0 | 0 | 0 |
| ダニ皮膚炎 | 1 (0.7%) | 0 | 0 | 0 |
| 膿疱性ざ瘡 | 0 | 0 | 0 | 0 |
| 肛門膿瘍 | 0 | 0 | 0 | 0 |
| 肛門カンジダ症 | 0 | 0 | 0 | 0 |
| 虫垂炎 | 0 | 0 | 0 | 0 |
| 穿孔性虫垂炎 | 0 | 0 | 0 | 0 |
| 異型肺炎 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 細菌尿 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| カンジダ性亀頭炎 | 1 (0.7%) | 0 | 0 | 0 |
| 胆道感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| ブラストシスティス感染 | 1 (0.7%) | 0 | 0 | 0 |
| 体部白癬 | 0 | 0 | 0 | 0 |
| 乳房蜂巣炎 | 1 (0.7%) | 0 | 0 | 0 |
| カンピロバクター胃腸炎 | 1 (0.7%) | 0 | 0 | 0 |
| カンピロバクター感染 | 0 | 0 | 0 | 0 |
| カンジダ感染 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 眼窩蜂巣炎 | 0 | 0 | 0 | 0 |
| 感染性胆嚢炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 慢性副鼻腔炎 | 1 (0.7%) | 0 | 0 | 0 |
| シトロバクター感染 | 0 | 0 | 0 | 0 |
| 涙嚢炎 | 1 (0.7%) | 0 | 0 | 0 |
| ウイルス性脳炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 精巣上体炎 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 喉頭蓋炎 | 1 (0.7%) | 0 | 0 | 0 |
| 細菌性眼感染 | 0 | 0 | 0 | 0 |
| 真菌血症 | 1 (0.7%) | 0 | 0 | 0 |
| ヘリコバクター胃潰瘍 | 1 (0.7%) | 0 | 0 | 0 |
| 消化管感染 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| ウイルス性消化管感染 | 0 | 0 | 1 (0.7%) | 0 |
| 性器カンジダ症 | 0 | 0 | 1 (0.7%) | 0 |
| 血腫感染 | 0 | 0 | 0 | 0 |
| ヘモフィルス感染 | 0 | 0 | 0 | 0 |
| Ｂ型肝炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| ヒストプラスマ症 | 0 | 0 | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 埋込み部位感染 | 0 | 0 | 0 | 0 |
| 切開部位感染 | 0 | 0 | 0 | 0 |
| クレブシエラ感染 | 0 | 0 | 0 | 0 |
| 口唇感染 | 0 | 0 | 0 | 0 |
| 細菌性下気道感染 | 0 | 0 | 0 | 0 |
| 肺感染 | 1 (0.7%) | 1 (0.7%) | 2 (1.4%) | 2 (1.4%) |
| ライム病 | 0 | 0 | 0 | 0 |
| 乳腺炎 | 1 (0.7%) | 0 | 0 | 0 |
| 水疱性鼓膜炎 | 1 (0.7%) | 0 | 0 | 0 |
| 爪床感染 | 0 | 0 | 0 | 0 |
| 眼帯状疱疹 | 0 | 0 | 0 | 0 |
| 口腔真菌感染 | 0 | 0 | 1 (0.7%) | 0 |
| 乳頭腫ウイルス感染 | 0 | 0 | 0 | 0 |
| クリプトコッカス性肺炎 | 0 | 0 | 0 | 0 |
| クレブシエラ菌性肺炎 | 0 | 0 | 0 | 0 |
| 処置後感染 | 0 | 0 | 0 | 0 |
| 肺結核 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 腎盂腎炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 膿皮症 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| レンサ球菌性膿皮症 | 1 (0.7%) | 0 | 0 | 0 |
| 狂犬病 | 0 | 0 | 0 | 0 |
| 直腸膿瘍 | 0 | 0 | 0 | 0 |
| ウイルス性気道感染 | 1 (0.7%) | 0 | 0 | 0 |
| 軟部組織感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| ブドウ球菌皮膚感染 | 0 | 0 | 0 | 0 |
| レンサ球菌感染 | 0 | 0 | 0 | 0 |
| 皮下組織膿瘍 | 0 | 0 | 0 | 0 |
| 足部白癬 | 0 | 0 | 0 | 0 |
| 扁桃炎 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 気管炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 真菌性尿路感染 | 0 | 0 | 0 | 0 |
| シュードモナス性尿路感染 | 0 | 0 | 0 | 0 |
| 眼瞼膿瘍 | 0 | 0 | 1 (0.7%) | 0 |
| 急性扁桃炎 | 0 | 0 | 1 (0.7%) | 0 |
| 真菌性肛門感染 | 0 | 0 | 1 (0.7%) | 0 |
| 気管支肺アスペルギルス症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 大腸菌性菌血症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 感染性大腸炎 | 0 | 0 | 1 (0.7%) | 0 |
| 真菌性喉頭炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 肝膿瘍 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 大葉性肺炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| リンパ管炎 | 0 | 0 | 1 (0.7%) | 0 |
| 粘膜感染 | 0 | 0 | 1 (0.7%) | 0 |
| 好中球減少性敗血症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| ニューモシスチス・イロベチイ感染 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 大腸菌性肺炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 細菌性気道感染 | 0 | 0 | 1 (0.7%) | 0 |
| アスペルギルス性副鼻腔炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| ブドウ球菌性敗血症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 癜風 | 0 | 0 | 1 (0.7%) | 0 |
| 気管気管支炎 | 0 | 0 | 1 (0.7%) | 0 |
| 胃腸障害 | 80 (57.6%) | 14 (10.1%) | 109 (78.4%) | 25 (18.0%) |
| 下痢 | 40 (28.8%) | 4 (2.9%) | 43 (30.9%) | 6 (4.3%) |
| 悪心 | 20 (14.4%) | 0 | 30 (21.6%) | 0 |
| 嘔吐 | 16 (11.5%) | 0 | 10 (7.2%) | 1 (0.7%) |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 便秘 | 12 (8.6%) | 0 | 21 (15.1%) | 0 |
| 腹痛 | 11 (7.9%) | 5 (3.6%) | 11 (7.9%) | 2 (1.4%) |
| 口内炎 | 4 (2.9%) | 0 | 29 (20.9%) | 5 (3.6%) |
| 消化不良 | 9 (6.5%) | 0 | 1 (0.7%) | 0 |
| 上腹部痛 | 8 (5.8%) | 1 (0.7%) | 3 (2.2%) | 0 |
| 腹部膨満 | 7 (5.0%) | 0 | 0 | 0 |
| 口内乾燥 | 3 (2.2%) | 0 | 2 (1.4%) | 0 |
| 胃食道逆流性疾患 | 4 (2.9%) | 0 | 4 (2.9%) | 0 |
| 嚥下障害 | 4 (2.9%) | 1 (0.7%) | 2 (1.4%) | 0 |
| 腹部不快感 | 5 (3.6%) | 0 | 2 (1.4%) | 0 |
| 口腔内痛 | 1 (0.7%) | 1 (0.7%) | 9 (6.5%) | 3 (2.2%) |
| 口腔内潰瘍形成 | 0 | 0 | 8 (5.8%) | 1 (0.7%) |
| 放屁 | 0 | 0 | 1 (0.7%) | 0 |
| 胃炎 | 0 | 0 | 0 | 0 |
| 心窩部不快感 | 2 (1.4%) | 0 | 0 | 0 |
| 舌痛 | 0 | 0 | 1 (0.7%) | 0 |
| 痔核 | 2 (1.4%) | 0 | 6 (4.3%) | 0 |
| アフタ性口内炎 | 1 (0.7%) | 0 | 4 (2.9%) | 0 |
| おくび | 1 (0.7%) | 0 | 0 | 0 |
| イレウス | 0 | 0 | 0 | 0 |
| 直腸出血 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 舌潰瘍 | 0 | 0 | 1 (0.7%) | 0 |
| 下腹部痛 | 0 | 0 | 1 (0.7%) | 0 |
| 齲歯 | 1 (0.7%) | 0 | 0 | 0 |
| 軟便 | 0 | 0 | 0 | 0 |
| 食中毒 | 1 (0.7%) | 0 | 0 | 0 |
| 排便回数増加 | 1 (0.7%) | 0 | 0 | 0 |
| 胃潰瘍 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 歯肉出血 | 2 (1.4%) | 0 | 0 | 0 |
| 歯肉浮腫 | 0 | 0 | 0 | 0 |
| 吐血 | 2 (1.4%) | 0 | 0 | 0 |
| 麻痺性イレウス | 0 | 0 | 0 | 0 |
| 鼠径ヘルニア | 0 | 0 | 0 | 0 |
| 口唇潰瘍 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 下部消化管出血 | 1 (0.7%) | 0 | 2 (1.4%) | 1 (0.7%) |
| 口腔内出血 | 1 (0.7%) | 0 | 0 | 0 |
| 歯周病 | 1 (0.7%) | 0 | 0 | 0 |
| 肛門周囲痛 | 0 | 0 | 1 (0.7%) | 0 |
| 直腸炎 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 直腸裂 | 0 | 0 | 0 | 0 |
| 小腸閉塞 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 歯痛 | 0 | 0 | 1 (0.7%) | 0 |
| 裂肛 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 肛門直腸障害 | 1 (0.7%) | 0 | 0 | 0 |
| 萎縮性舌炎 | 1 (0.7%) | 0 | 0 | 0 |
| バレット食道 | 0 | 0 | 0 | 0 |
| 口唇炎 | 0 | 0 | 1 (0.7%) | 0 |
| 大腸炎 | 0 | 0 | 2 (1.4%) | 0 |
| 歯不快感 | 0 | 0 | 0 | 0 |
| 血性下痢 | 1 (0.7%) | 0 | 0 | 0 |
| 十二指腸狭窄 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 十二指腸潰瘍 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 十二指腸炎 | 1 (0.7%) | 0 | 0 | 0 |
| 十二指腸胃逆流 | 1 (0.7%) | 0 | 0 | 0 |
| 便失禁 | 0 | 0 | 0 | 0 |
| 糞塊 | 1 (0.7%) | 0 | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 胃前庭部毛細血管拡張症 | 0 | 0 | 0 | 0 |
| 出血性胃炎 | 0 | 0 | 1 (0.7%) | 0 |
| 歯肉痛 | 0 | 0 | 0 | 0 |
| 血便排泄 | 0 | 0 | 1 (0.7%) | 0 |
| 痔出血 | 0 | 0 | 0 | 0 |
| 過敏性腸症候群 | 0 | 0 | 0 | 0 |
| 口唇水疱 | 0 | 0 | 0 | 0 |
| 口唇びらん | 1 (0.7%) | 0 | 0 | 0 |
| 口唇痛 | 0 | 0 | 0 | 0 |
| 口唇腫脹 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 弛緩歯 | 0 | 0 | 0 | 0 |
| メレナ | 1 (0.7%) | 0 | 0 | 0 |
| 嚥下痛 | 0 | 0 | 0 | 0 |
| 口蓋障害 | 0 | 0 | 0 | 0 |
| 慢性膵炎 | 0 | 0 | 0 | 0 |
| 舌突出 | 1 (0.7%) | 0 | 0 | 0 |
| 直腸潰瘍 | 1 (0.7%) | 0 | 0 | 0 |
| 唾液腺結石 | 1 (0.7%) | 0 | 0 | 0 |
| 変色歯 | 0 | 0 | 0 | 0 |
| 歯の障害 | 1 (0.7%) | 0 | 0 | 0 |
| 歯の脱落 | 0 | 0 | 0 | 0 |
| 痔瘻 | 0 | 0 | 1 (0.7%) | 0 |
| 肛門直腸不快感 | 0 | 0 | 1 (0.7%) | 0 |
| 腸炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 変色便 | 0 | 0 | 1 (0.7%) | 0 |
| 胃腸出血 | 0 | 0 | 2 (1.4%) | 2 (1.4%) |
| 胃腸毒性 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 歯肉障害 | 0 | 0 | 1 (0.7%) | 0 |
| 歯肉退縮 | 0 | 0 | 1 (0.7%) | 0 |
| 舌炎 | 0 | 0 | 1 (0.7%) | 0 |
| 腸出血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 口唇乾燥 | 0 | 0 | 1 (0.7%) | 0 |
| 口唇浮腫 | 0 | 0 | 2 (1.4%) | 0 |
| 食道炎 | 0 | 0 | 1 (0.7%) | 0 |
| 口腔知覚不全 | 0 | 0 | 1 (0.7%) | 0 |
| 口腔粘膜びらん | 0 | 0 | 1 (0.7%) | 0 |
| 口腔粘膜紅斑 | 0 | 0 | 1 (0.7%) | 0 |
| 排便痛 | 0 | 0 | 1 (0.7%) | 0 |
| 上部消化管出血 | 0 | 0 | 1 (0.7%) | 0 |
| 一般・全身障害および投与部位の状態 | 74 (53.2%) | 15 (10.8%) | 99 (71.2%) | 29 (20.9%) |
| 疲労 | 31 (22.3%) | 6 (4.3%) | 40 (28.8%) | 10 (7.2%) |
| 末梢性浮腫 | 18 (12.9%) | 0 | 31 (22.3%) | 3 (2.2%) |
| 発熱 | 23 (16.5%) | 1 (0.7%) | 29 (20.9%) | 3 (2.2%) |
| 無力症 | 11 (7.9%) | 1 (0.7%) | 27 (19.4%) | 3 (2.2%) |
| 悪寒 | 5 (3.6%) | 0 | 6 (4.3%) | 0 |
| 胸痛 | 3 (2.2%) | 0 | 4 (2.9%) | 0 |
| 末梢腫脹 | 1 (0.7%) | 0 | 4 (2.9%) | 0 |
| インフルエンザ様疾患 | 2 (1.4%) | 0 | 3 (2.2%) | 0 |
| 疼痛 | 3 (2.2%) | 0 | 3 (2.2%) | 2 (1.4%) |
| 非心臓性胸痛 | 0 | 0 | 1 (0.7%) | 0 |
| 粘膜の炎症 | 2 (1.4%) | 1 (0.7%) | 21 (15.1%) | 6 (4.3%) |
| 全身健康状態低下 | 4 (2.9%) | 1 (0.7%) | 5 (3.6%) | 3 (2.2%) |
| 倦怠感 | 2 (1.4%) | 0 | 4 (2.9%) | 0 |
| 局所腫脹 | 1 (0.7%) | 0 | 0 | 0 |
| 多臓器不全 | 4 (2.9%) | 4 (2.9%) | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 胸部不快感 | 0 | 0 | 1 (0.7%) | 0 |
| 歩行障害 | 1 (0.7%) | 0 | 0 | 0 |
| 全身性浮腫 | 0 | 0 | 2 (1.4%) | 0 |
| 注射部位内出血 | 0 | 0 | 0 | 0 |
| 乾燥症 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 腋窩痛 | 1 (0.7%) | 0 | 0 | 0 |
| 早期満腹 | 1 (0.7%) | 0 | 0 | 0 |
| 重力性浮腫 | 0 | 0 | 0 | 0 |
| 低体温 | 1 (0.7%) | 0 | 0 | 0 |
| 炎症 | 2 (1.4%) | 0 | 2 (1.4%) | 1 (0.7%) |
| 浮腫 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 活動状態低下 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| カテーテル留置部位関連反応 | 1 (0.7%) | 0 | 0 | 0 |
| 死亡 | 0 | 0 | 0 | 0 |
| 医療機器リーク | 0 | 0 | 0 | 0 |
| 顔面浮腫 | 1 (0.7%) | 0 | 3 (2.2%) | 0 |
| 異常感 | 0 | 0 | 0 | 0 |
| 冷感 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 熱感 | 1 (0.7%) | 0 | 0 | 0 |
| 治癒不良 | 1 (0.7%) | 0 | 0 | 0 |
| 硬結 | 0 | 0 | 0 | 0 |
| 注入部位血管外漏出 | 1 (0.7%) | 0 | 0 | 0 |
| 注射部位紅斑 | 0 | 0 | 0 | 0 |
| 注射部位漏出 | 0 | 0 | 0 | 0 |
| 注射部位出血 | 0 | 0 | 0 | 0 |
| 注射部位疼痛 | 0 | 0 | 0 | 0 |
| 注射部位反応 | 0 | 0 | 0 | 0 |
| 先行疾患の改善 | 1 (0.7%) | 0 | 0 | 0 |
| 温度変化不耐症 | 0 | 0 | 0 | 0 |
| 評価不能の事象 | 0 | 0 | 0 | 0 |
| 医療機器関連の血栓症 | 0 | 0 | 1 (0.7%) | 0 |
| 呼吸器、胸郭および縦隔障害 | 72 (51.8%) | 16 (11.5%) | 82 (59.0%) | 19 (13.7%) |
| 咳嗽 | 31 (22.3%) | 0 | 31 (22.3%) | 0 |
| 呼吸困難 | 16 (11.5%) | 4 (2.9%) | 17 (12.2%) | 5 (3.6%) |
| 鼻出血 | 12 (8.6%) | 1 (0.7%) | 33 (23.7%) | 2 (1.4%) |
| 口腔咽頭痛 | 8 (5.8%) | 0 | 8 (5.8%) | 0 |
| 胸水 | 10 (7.2%) | 4 (2.9%) | 5 (3.6%) | 0 |
| 湿性咳嗽 | 6 (4.3%) | 0 | 4 (2.9%) | 0 |
| 鼻閉 | 3 (2.2%) | 0 | 4 (2.9%) | 1 (0.7%) |
| 呼吸不全 | 2 (1.4%) | 2 (1.4%) | 2 (1.4%) | 2 (1.4%) |
| 鼻漏 | 1 (0.7%) | 0 | 0 | 0 |
| 発声障害 | 2 (1.4%) | 0 | 4 (2.9%) | 0 |
| 慢性閉塞性肺疾患 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| アレルギー性鼻炎 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 副鼻腔うっ血 | 0 | 0 | 0 | 0 |
| 上気道うっ血 | 0 | 0 | 0 | 0 |
| 低酸素症 | 1 (0.7%) | 1 (0.7%) | 2 (1.4%) | 0 |
| しゃっくり | 0 | 0 | 0 | 0 |
| 気胸 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 喀血 | 0 | 0 | 0 | 0 |
| 鼻部不快感 | 1 (0.7%) | 0 | 0 | 0 |
| 肺水腫 | 2 (1.4%) | 1 (0.7%) | 2 (1.4%) | 1 (0.7%) |
| ラ音 | 1 (0.7%) | 0 | 0 | 0 |
| 喘鳴 | 2 (1.4%) | 0 | 0 | 0 |
| 無気肺 | 1 (0.7%) | 0 | 0 | 0 |
| 労作性呼吸困難 | 1 (0.7%) | 0 | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 肺硬化 | 0 | 0 | 0 | 0 |
| 肺浸潤 | 1 (0.7%) | 0 | 2 (1.4%) | 1 (0.7%) |
| 鼻の炎症 | 0 | 0 | 0 | 0 |
| 肺塞栓症 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 気道うっ血 | 0 | 0 | 0 | 0 |
| 急性肺水腫 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 喘息 | 0 | 0 | 0 | 0 |
| 気管支反応性亢進 | 1 (0.7%) | 0 | 0 | 0 |
| 気管支分泌物貯留 | 0 | 0 | 0 | 0 |
| 気管支拡張症 | 0 | 0 | 0 | 0 |
| 慢性気管支炎 | 0 | 0 | 1 (0.7%) | 0 |
| 肺気腫 | 0 | 0 | 0 | 0 |
| 上気道分泌増加 | 1 (0.7%) | 0 | 0 | 0 |
| 鼻乾燥 | 1 (0.7%) | 0 | 0 | 0 |
| 鼻潰瘍 | 1 (0.7%) | 0 | 0 | 0 |
| 副鼻腔不快感 | 0 | 0 | 0 | 0 |
| 副鼻腔分泌過多 | 0 | 0 | 0 | 0 |
| 咽頭紅斑 | 0 | 0 | 0 | 0 |
| 胸膜炎 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 胸膜痛 | 1 (0.7%) | 0 | 0 | 0 |
| 肺腫瘤 | 0 | 0 | 0 | 0 |
| 呼吸性アシドーシス | 0 | 0 | 0 | 0 |
| 呼吸窮迫 | 0 | 0 | 0 | 0 |
| 拘束性肺疾患 | 0 | 0 | 0 | 0 |
| 副鼻腔障害 | 0 | 0 | 0 | 0 |
| くしゃみ | 1 (0.7%) | 0 | 0 | 0 |
| 頻呼吸 | 0 | 0 | 0 | 0 |
| 扁桃肥大 | 0 | 0 | 0 | 0 |
| 上気道咳症候群 | 0 | 0 | 0 | 0 |
| 間質性肺疾患 | 0 | 0 | 6 (4.3%) | 2 (1.4%) |
| 咽頭潰瘍 | 0 | 0 | 1 (0.7%) | 0 |
| 肺臓炎 | 0 | 0 | 10 (7.2%) | 3 (2.2%) |
| 皮膚および皮下組織障害 | 59 (42.4%) | 3 (2.2%) | 69 (49.6%) | 5 (3.6%) |
| 発疹 | 18 (12.9%) | 1 (0.7%) | 24 (17.3%) | 0 |
| そう痒症 | 12 (8.6%) | 0 | 18 (12.9%) | 1 (0.7%) |
| 点状出血 | 6 (4.3%) | 0 | 0 | 0 |
| 皮膚病変 | 5 (3.6%) | 0 | 8 (5.8%) | 1 (0.7%) |
| 斑状丘疹状皮疹 | 5 (3.6%) | 1 (0.7%) | 7 (5.0%) | 1 (0.7%) |
| 皮膚乾燥 | 2 (1.4%) | 0 | 4 (2.9%) | 0 |
| 斑状出血 | 4 (2.9%) | 0 | 1 (0.7%) | 0 |
| 紅斑 | 3 (2.2%) | 0 | 5 (3.6%) | 0 |
| 寝汗 | 0 | 0 | 2 (1.4%) | 0 |
| 脱毛症 | 3 (2.2%) | 0 | 2 (1.4%) | 0 |
| ざ瘡様皮膚炎 | 4 (2.9%) | 0 | 3 (2.2%) | 0 |
| 紫斑 | 3 (2.2%) | 1 (0.7%) | 0 | 0 |
| 多汗症 | 1 (0.7%) | 0 | 0 | 0 |
| 皮膚亀裂 | 5 (3.6%) | 0 | 1 (0.7%) | 0 |
| 嵌入爪 | 0 | 0 | 1 (0.7%) | 0 |
| 爪破損 | 2 (1.4%) | 0 | 6 (4.3%) | 0 |
| 蕁麻疹 | 4 (2.9%) | 0 | 4 (2.9%) | 0 |
| 水疱 | 1 (0.7%) | 0 | 0 | 0 |
| 全身性そう痒症 | 1 (0.7%) | 0 | 5 (3.6%) | 0 |
| 斑状皮疹 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚腫瘤 | 0 | 0 | 0 | 0 |
| 皮膚潰瘍 | 1 (0.7%) | 0 | 3 (2.2%) | 1 (0.7%) |
| ざ瘡 | 0 | 0 | 5 (3.6%) | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 褥瘡性潰瘍 | 0 | 0 | 0 | 0 |
| 湿疹 | 3 (2.2%) | 0 | 3 (2.2%) | 0 |
| 紅斑性皮疹 | 0 | 0 | 0 | 0 |
| 皮膚色素過剰 | 0 | 0 | 0 | 0 |
| 皮膚嚢腫 | 0 | 0 | 0 | 0 |
| 接触性皮膚炎 | 0 | 0 | 0 | 0 |
| 皮下出血 | 0 | 0 | 0 | 0 |
| 間擦疹 | 0 | 0 | 0 | 0 |
| 皮膚疼痛 | 1 (0.7%) | 0 | 0 | 0 |
| 全身性皮疹 | 1 (0.7%) | 0 | 7 (5.0%) | 1 (0.7%) |
| 丘疹性皮疹 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| そう痒性皮疹 | 1 (0.7%) | 0 | 0 | 0 |
| 皮膚変色 | 0 | 0 | 0 | 0 |
| 毛細血管炎 | 0 | 0 | 0 | 0 |
| 皮膚炎 | 0 | 0 | 2 (1.4%) | 0 |
| アレルギー性皮膚炎 | 0 | 0 | 1 (0.7%) | 0 |
| 水疱性皮膚炎 | 0 | 0 | 1 (0.7%) | 0 |
| 皮脂欠乏性湿疹 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 貨幣状湿疹 | 1 (0.7%) | 0 | 0 | 0 |
| 過敏性血管炎 | 1 (0.7%) | 0 | 0 | 0 |
| 爪床出血 | 1 (0.7%) | 0 | 0 | 0 |
| 爪床障害 | 0 | 0 | 0 | 0 |
| 爪床の炎症 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 爪の不快感 | 1 (0.7%) | 0 | 0 | 0 |
| 爪の障害 | 0 | 0 | 5 (3.6%) | 0 |
| 爪ジストロフィー | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 爪線状隆起 | 0 | 0 | 0 | 0 |
| 爪痛 | 1 (0.7%) | 0 | 0 | 0 |
| 爪甲脱落症 | 0 | 0 | 0 | 0 |
| 手掌・足底発赤知覚不全症候群 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 脂肪織炎 | 1 (0.7%) | 0 | 0 | 0 |
| 色素沈着障害 | 1 (0.7%) | 0 | 0 | 0 |
| 毛孔性皮疹 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚色素減少 | 0 | 0 | 0 | 0 |
| 皮膚刺激 | 0 | 0 | 0 | 0 |
| 皮膚腫脹 | 0 | 0 | 0 | 0 |
| 乾皮症 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 皮膚アミロイドーシス | 0 | 0 | 1 (0.7%) | 0 |
| 異汗性湿疹 | 0 | 0 | 1 (0.7%) | 0 |
| 多形紅斑 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 爪甲離床症 | 0 | 0 | 1 (0.7%) | 0 |
| 痒疹 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚硬結 | 0 | 0 | 1 (0.7%) | 0 |
| うっ滞性皮膚炎 | 0 | 0 | 1 (0.7%) | 0 |
| 顔面腫脹 | 0 | 0 | 3 (2.2%) | 0 |
| 筋骨格系および結合組織障害 | 52 (37.4%) | 8 (5.8%) | 49 (35.3%) | 8 (5.8%) |
| 筋痙縮 | 26 (18.7%) | 0 | 4 (2.9%) | 0 |
| 背部痛 | 16 (11.5%) | 4 (2.9%) | 15 (10.8%) | 1 (0.7%) |
| 関節痛 | 8 (5.8%) | 1 (0.7%) | 9 (6.5%) | 2 (1.4%) |
| 筋肉痛 | 5 (3.6%) | 0 | 5 (3.6%) | 0 |
| 四肢痛 | 4 (2.9%) | 0 | 12 (8.6%) | 1 (0.7%) |
| 筋骨格痛 | 1 (0.7%) | 0 | 4 (2.9%) | 1 (0.7%) |
| 筋力低下 | 4 (2.9%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 側腹部痛 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 頚部痛 | 3 (2.2%) | 0 | 2 (1.4%) | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 変形性関節症 | 3 (2.2%) | 1 (0.7%) | 0 | 0 |
| 鼡径部痛 | 0 | 0 | 1 (0.7%) | 0 |
| 四肢不快感 | 1 (0.7%) | 0 | 0 | 0 |
| 筋骨格硬直 | 0 | 0 | 0 | 0 |
| 骨痛 | 0 | 0 | 3 (2.2%) | 2 (1.4%) |
| 関節硬直 | 0 | 0 | 0 | 0 |
| 関節腫脹 | 0 | 0 | 2 (1.4%) | 0 |
| 運動性低下 | 0 | 0 | 0 | 0 |
| 筋骨格系胸痛 | 0 | 0 | 1 (0.7%) | 0 |
| ミオパチー | 0 | 0 | 0 | 0 |
| 軟部組織障害 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 関節炎 | 0 | 0 | 0 | 0 |
| 滑液包炎 | 1 (0.7%) | 0 | 0 | 0 |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 外骨腫 | 1 (0.7%) | 0 | 0 | 0 |
| 痛風性関節炎 | 0 | 0 | 1 (0.7%) | 0 |
| 椎間板変性症 | 0 | 0 | 0 | 0 |
| 椎間板突出 | 1 (0.7%) | 0 | 0 | 0 |
| 関節拘縮 | 0 | 0 | 0 | 0 |
| 関節滲出液 | 0 | 0 | 0 | 0 |
| 関節ロック | 0 | 0 | 0 | 0 |
| 筋緊張 | 0 | 0 | 0 | 0 |
| 筋攣縮 | 0 | 0 | 0 | 0 |
| 筋骨格不快感 | 0 | 0 | 0 | 0 |
| 頚部腫瘤 | 0 | 0 | 0 | 0 |
| 骨壊死 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 骨粗鬆症 | 0 | 0 | 0 | 0 |
| 顎痛 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 横紋筋融解症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 滑液嚢腫 | 0 | 0 | 0 | 0 |
| 腱痛 | 1 (0.7%) | 0 | 0 | 0 |
| 椎間孔狭窄 | 0 | 0 | 0 | 0 |
| 関節障害 | 0 | 0 | 1 (0.7%) | 0 |
| 軟骨石灰化症 | 0 | 0 | 1 (0.7%) | 0 |
| 鼡径部腫瘤 | 0 | 0 | 1 (0.7%) | 0 |
| 椎間板圧迫 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 筋拘縮 | 0 | 0 | 1 (0.7%) | 0 |
| 骨炎 | 0 | 0 | 1 (0.7%) | 0 |
| 筋肉減少症 | 0 | 0 | 1 (0.7%) | 0 |
| 脊椎痛 | 0 | 0 | 1 (0.7%) | 0 |
| 弾発指 | 0 | 0 | 1 (0.7%) | 0 |
| 血液およびリンパ系障害 | 55 (39.6%) | 31 (22.3%) | 104 (74.8%) | 80 (57.6%) |
| 血小板減少症 | 25 (18.0%) | 13 (9.4%) | 78 (56.1%) | 59 (42.4%) |
| 好中球減少症 | 22 (15.8%) | 18 (12.9%) | 36 (25.9%) | 23 (16.5%) |
| 貧血 | 25 (18.0%) | 11 (7.9%) | 60 (43.2%) | 28 (20.1%) |
| 発熱性好中球減少症 | 3 (2.2%) | 3 (2.2%) | 2 (1.4%) | 2 (1.4%) |
| 白血球減少症 | 2 (1.4%) | 0 | 6 (4.3%) | 0 |
| 白血球増加症 | 3 (2.2%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| 内出血発生の増加傾向 | 0 | 0 | 0 | 0 |
| リンパ球減少症 | 4 (2.9%) | 0 | 6 (4.3%) | 5 (3.6%) |
| リンパ球増加症 | 2 (1.4%) | 2 (1.4%) | 3 (2.2%) | 0 |
| リンパ節痛 | 0 | 0 | 0 | 0 |
| リンパ節症 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 脾腫 | 1 (0.7%) | 0 | 0 | 0 |
| 骨髄機能不全 | 0 | 0 | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 凝血異常 | 0 | 0 | 0 | 0 |
| 溶血 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 鉄欠乏性貧血 | 0 | 0 | 3 (2.2%) | 0 |
| 白血球停滞症候群 | 0 | 0 | 0 | 0 |
| 汎血球減少症 | 0 | 0 | 0 | 0 |
| 後腹膜リンパ節腫脹 | 0 | 0 | 0 | 0 |
| 脾臓出血 | 0 | 0 | 0 | 0 |
| 脾臓梗塞 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 血小板増加症 | 0 | 0 | 0 | 0 |
| リンパ節炎 | 0 | 0 | 1 (0.7%) | 0 |
| 好中球増加症 | 0 | 0 | 1 (0.7%) | 0 |
| 代謝および栄養障害 | 51 (36.7%) | 22 (15.8%) | 88 (63.3%) | 46 (33.1%) |
| 食欲減退 | 25 (18.0%) | 1 (0.7%) | 26 (18.7%) | 4 (2.9%) |
| 低カリウム血症 | 11 (7.9%) | 8 (5.8%) | 24 (17.3%) | 12 (8.6%) |
| 高尿酸血症 | 5 (3.6%) | 1 (0.7%) | 2 (1.4%) | 1 (0.7%) |
| 脱水 | 3 (2.2%) | 1 (0.7%) | 5 (3.6%) | 2 (1.4%) |
| 低マグネシウム血症 | 8 (5.8%) | 1 (0.7%) | 4 (2.9%) | 0 |
| 高カリウム血症 | 9 (6.5%) | 5 (3.6%) | 3 (2.2%) | 1 (0.7%) |
| 低ナトリウム血症 | 1 (0.7%) | 1 (0.7%) | 7 (5.0%) | 6 (4.3%) |
| 低アルブミン血症 | 2 (1.4%) | 0 | 6 (4.3%) | 0 |
| 高血糖 | 3 (2.2%) | 1 (0.7%) | 26 (18.7%) | 10 (7.2%) |
| 低カルシウム血症 | 2 (1.4%) | 0 | 3 (2.2%) | 0 |
| 低血糖症 | 0 | 0 | 4 (2.9%) | 1 (0.7%) |
| 低リン酸血症 | 2 (1.4%) | 2 (1.4%) | 5 (3.6%) | 4 (2.9%) |
| 水分過負荷 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 痛風 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 酵素異常 | 0 | 0 | 0 | 0 |
| 高コレステロール血症 | 1 (0.7%) | 0 | 18 (12.9%) | 3 (2.2%) |
| 高ナトリウム血症 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 高リン酸塩血症 | 0 | 0 | 0 | 0 |
| 過小食 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 乳酸アシドーシス | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| アルコール不耐性 | 0 | 0 | 0 | 0 |
| 悪液質 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 糖尿病 | 1 (0.7%) | 1 (0.7%) | 7 (5.0%) | 2 (1.4%) |
| 糖尿病性ケトアシドーシス | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 高アルブミン血症 | 1 (0.7%) | 0 | 0 | 0 |
| 高アンモニア血症 | 0 | 0 | 0 | 0 |
| 低蛋白血症 | 1 (0.7%) | 0 | 0 | 0 |
| 代謝性アシドーシス | 0 | 0 | 0 | 0 |
| 腫瘍崩壊症候群 | 1 (0.7%) | 1 (0.7%) | 3 (2.2%) | 3 (2.2%) |
| ２型糖尿病 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 脂質異常症 | 0 | 0 | 1 (0.7%) | 0 |
| 電解質失調 | 0 | 0 | 1 (0.7%) | 0 |
| 体液貯留 | 0 | 0 | 1 (0.7%) | 0 |
| 耐糖能障害 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 高クレアチニン血症 | 0 | 0 | 1 (0.7%) | 0 |
| 高脂血症 | 0 | 0 | 3 (2.2%) | 1 (0.7%) |
| 高トリグリセリド血症 | 0 | 0 | 25 (18.0%) | 13 (9.4%) |
| 多飲症 | 0 | 0 | 1 (0.7%) | 0 |
| 神経系障害 | 39 (28.1%) | 4 (2.9%) | 52 (37.4%) | 10 (7.2%) |
| 頭痛 | 13 (9.4%) | 0 | 17 (12.2%) | 0 |
| 浮動性めまい | 5 (3.6%) | 0 | 4 (2.9%) | 0 |
| 末梢性感覚ニューロパチー | 3 (2.2%) | 0 | 3 (2.2%) | 1 (0.7%) |
| 体位性めまい | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 錯感覚 | 1 (0.7%) | 0 | 3 (2.2%) | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 記憶障害 | 1 (0.7%) | 0 | 0 | 0 |
| 末梢性ニューロパチー | 4 (2.9%) | 0 | 3 (2.2%) | 0 |
| 振戦 | 3 (2.2%) | 0 | 2 (1.4%) | 1 (0.7%) |
| 感覚鈍麻 | 3 (2.2%) | 0 | 1 (0.7%) | 0 |
| 健忘 | 0 | 0 | 3 (2.2%) | 0 |
| 傾眠 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 失神 | 3 (2.2%) | 3 (2.2%) | 3 (2.2%) | 3 (2.2%) |
| 平衡障害 | 0 | 0 | 0 | 0 |
| 構語障害 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 味覚異常 | 1 (0.7%) | 0 | 7 (5.0%) | 0 |
| 嗜眠 | 1 (0.7%) | 0 | 4 (2.9%) | 0 |
| 多発ニューロパチー | 3 (2.2%) | 1 (0.7%) | 2 (1.4%) | 1 (0.7%) |
| 認知症 | 1 (0.7%) | 0 | 0 | 0 |
| 頭蓋内出血 | 0 | 0 | 0 | 0 |
| 過眠症 | 0 | 0 | 1 (0.7%) | 0 |
| 神経痛 | 0 | 0 | 4 (2.9%) | 1 (0.7%) |
| 失神寸前の状態 | 0 | 0 | 0 | 0 |
| 下肢静止不能症候群 | 1 (0.7%) | 0 | 0 | 0 |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 0 | 0 |
| 一過性脳虚血発作 | 1 (0.7%) | 0 | 0 | 0 |
| 灼熱足症候群 | 1 (0.7%) | 0 | 0 | 0 |
| 手根管症候群 | 1 (0.7%) | 0 | 0 | 0 |
| 大脳萎縮 | 1 (0.7%) | 0 | 0 | 0 |
| 脳血管発作 | 0 | 0 | 1 (0.7%) | 0 |
| 労作性めまい | 0 | 0 | 0 | 0 |
| 脳症 | 0 | 0 | 0 | 0 |
| てんかん | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 顔面部神経痛 | 1 (0.7%) | 0 | 0 | 0 |
| 顔面不全麻痺 | 1 (0.7%) | 0 | 0 | 0 |
| 頭部不快感 | 0 | 0 | 1 (0.7%) | 0 |
| 腰髄神経根障害 | 1 (0.7%) | 0 | 0 | 0 |
| 片頭痛 | 0 | 0 | 0 | 0 |
| 前兆を伴う片頭痛 | 0 | 0 | 0 | 0 |
| 筋痙直 | 1 (0.7%) | 0 | 0 | 0 |
| ミオクローヌス | 1 (0.7%) | 0 | 0 | 0 |
| 眼振 | 0 | 0 | 0 | 0 |
| 腓骨神経麻痺 | 0 | 0 | 1 (0.7%) | 0 |
| ヘルペス後神経痛 | 1 (0.7%) | 0 | 0 | 0 |
| 坐骨神経痛 | 0 | 0 | 1 (0.7%) | 0 |
| 感覚障害 | 0 | 0 | 0 | 0 |
| 会話障害 | 0 | 0 | 0 | 0 |
| 緊張性頭痛 | 0 | 0 | 0 | 0 |
| 一過性全健忘 | 0 | 0 | 0 | 0 |
| 血管性脳症 | 1 (0.7%) | 0 | 0 | 0 |
| 失声症 | 0 | 0 | 1 (0.7%) | 0 |
| 運動失調 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 脳虚血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 認知障害 | 0 | 0 | 1 (0.7%) | 0 |
| 糖尿病性ニューロパチー | 0 | 0 | 1 (0.7%) | 0 |
| 注意力障害 | 0 | 0 | 1 (0.7%) | 0 |
| 異常感覚 | 0 | 0 | 1 (0.7%) | 0 |
| 虚血性脳卒中 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 意識消失 | 0 | 0 | 1 (0.7%) | 0 |
| 末梢性感覚運動ニューロパチー | 0 | 0 | 1 (0.7%) | 0 |
| 精神運動亢進 | 0 | 0 | 1 (0.7%) | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 臨床検査 | 53 (38.1%) | 17 (12.2%) | 64 (46.0%) | 29 (20.9%) |
| 血中クレアチニン増加 | 14 (10.1%) | 0 | 17 (12.2%) | 0 |
| 血小板数減少 | 12 (8.6%) | 2 (1.4%) | 23 (16.5%) | 19 (13.7%) |
| 体重減少 | 6 (4.3%) | 0 | 18 (12.9%) | 0 |
| 血中アルカリホスファターゼ増加 | 4 (2.9%) | 0 | 9 (6.5%) | 1 (0.7%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 5 (3.6%) | 1 (0.7%) | 10 (7.2%) | 0 |
| 血中ビリルビン増加 | 3 (2.2%) | 1 (0.7%) | 0 | 0 |
| 好中球数減少 | 7 (5.0%) | 7 (5.0%) | 10 (7.2%) | 5 (3.6%) |
| アラニンアミノトランスフェラーゼ増加 | 4 (2.9%) | 1 (0.7%) | 9 (6.5%) | 0 |
| 血中尿酸増加 | 3 (2.2%) | 0 | 0 | 0 |
| リンパ球数増加 | 5 (3.6%) | 3 (2.2%) | 1 (0.7%) | 1 (0.7%) |
| 体重増加 | 2 (1.4%) | 0 | 0 | 0 |
| 活性化部分トロンボプラスチン時間延長 | 2 (1.4%) | 0 | 0 | 0 |
| 血中乳酸脱水素酵素増加 | 2 (1.4%) | 0 | 7 (5.0%) | 1 (0.7%) |
| 白血球数減少 | 2 (1.4%) | 2 (1.4%) | 6 (4.3%) | 2 (1.4%) |
| 血中免疫グロブリンG減少 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 国際標準比増加 | 0 | 0 | 2 (1.4%) | 0 |
| 白血球数増加 | 2 (1.4%) | 1 (0.7%) | 2 (1.4%) | 1 (0.7%) |
| 血中ブドウ糖増加 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 血中免疫グロブリンM減少 | 2 (1.4%) | 0 | 0 | 0 |
| 血圧上昇 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| Ｃ－反応性蛋白増加 | 1 (0.7%) | 0 | 4 (2.9%) | 1 (0.7%) |
| 心雑音 | 0 | 0 | 0 | 0 |
| γ－グルタミルトランスフェラーゼ増加 | 2 (1.4%) | 0 | 0 | 0 |
| 糸球体濾過率減少 | 0 | 0 | 0 | 0 |
| ヘモグロビン減少 | 2 (1.4%) | 2 (1.4%) | 0 | 0 |
| 免疫グロブリン減少 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| リンパ球数減少 | 2 (1.4%) | 0 | 2 (1.4%) | 1 (0.7%) |
| トランスアミナーゼ上昇 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| アミラーゼ増加 | 0 | 0 | 0 | 0 |
| アスペルギルス検査陽性 | 0 | 0 | 0 | 0 |
| 血中アルブミン減少 | 0 | 0 | 1 (0.7%) | 0 |
| 血中重炭酸塩増加 | 1 (0.7%) | 0 | 0 | 0 |
| 血中ビリルビン異常 | 0 | 0 | 0 | 0 |
| 血中クロール減少 | 0 | 0 | 0 | 0 |
| 血中コレステロール増加 | 0 | 0 | 6 (4.3%) | 2 (1.4%) |
| 血中クレアチン増加 | 0 | 0 | 0 | 0 |
| 血中免疫グロブリンA減少 | 1 (0.7%) | 0 | 0 | 0 |
| 血中鉄減少 | 0 | 0 | 1 (0.7%) | 0 |
| 血中マグネシウム減少 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 血中リン減少 | 0 | 0 | 3 (2.2%) | 1 (0.7%) |
| 血中カリウム減少 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 呼吸音異常 | 0 | 0 | 0 | 0 |
| 二酸化炭素減少 | 0 | 0 | 0 | 0 |
| 胸部コンピュータ断層撮影異常 | 0 | 0 | 0 | 0 |
| 駆出率減少 | 0 | 0 | 0 | 0 |
| グリコヘモグロビン増加 | 1 (0.7%) | 0 | 0 | 0 |
| ヘモフィルス検査陽性 | 0 | 0 | 0 | 0 |
| 心拍数増加 | 0 | 0 | 0 | 0 |
| 心拍数不整 | 0 | 0 | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 肝酵素上昇 | 0 | 0 | 0 | 0 |
| 深吸気量減少 | 1 (0.7%) | 0 | 0 | 0 |
| 肝機能検査異常 | 0 | 0 | 0 | 0 |
| 黄斑部反射異常 | 0 | 0 | 0 | 0 |
| 平均赤血球容積増加 | 0 | 0 | 0 | 0 |
| 血小板凝集異常 | 1 (0.7%) | 0 | 0 | 0 |
| 尿量減少 | 0 | 0 | 0 | 0 |
| 超低比重リポ蛋白増加 | 0 | 0 | 0 | 0 |
| 肺活量異常 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 血中重炭酸塩減少 | 0 | 0 | 1 (0.7%) | 0 |
| 血中カルシウム減少 | 0 | 0 | 2 (1.4%) | 0 |
| 血中フィブリノゲン増加 | 0 | 0 | 2 (1.4%) | 0 |
| 起立血圧低下 | 0 | 0 | 1 (0.7%) | 0 |
| 収縮期血圧上昇 | 0 | 0 | 1 (0.7%) | 0 |
| 血中ナトリウム減少 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 血中トリグリセリド増加 | 0 | 0 | 4 (2.9%) | 2 (1.4%) |
| 血中尿素増加 | 0 | 0 | 1 (0.7%) | 0 |
| ＥＣＯＧパフォーマンスステータス悪化 | 0 | 0 | 1 (0.7%) | 0 |
| 好酸球数増加 | 0 | 0 | 1 (0.7%) | 0 |
| 低比重リポ蛋白増加 | 0 | 0 | 1 (0.7%) | 0 |
| 平均赤血球容積減少 | 0 | 0 | 1 (0.7%) | 0 |
| 好中球数増加 | 0 | 0 | 1 (0.7%) | 0 |
| 酸素飽和度低下 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| レスピロウイルス検査陽性 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 視力検査異常 | 0 | 0 | 1 (0.7%) | 0 |
| 傷害、中毒および処置合併症 | 31 (22.3%) | 7 (5.0%) | 27 (19.4%) | 4 (2.9%) |
| 挫傷 | 10 (7.2%) | 0 | 3 (2.2%) | 0 |
| 転倒 | 3 (2.2%) | 2 (1.4%) | 2 (1.4%) | 0 |
| 節足動物咬傷 | 1 (0.7%) | 0 | 3 (2.2%) | 0 |
| 処置による疼痛 | 3 (2.2%) | 0 | 0 | 0 |
| 硬膜下血腫 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 外傷性血腫 | 4 (2.9%) | 0 | 0 | 0 |
| 裂傷 | 0 | 0 | 0 | 0 |
| 皮膚擦過傷 | 1 (0.7%) | 0 | 0 | 0 |
| サンバーン | 0 | 0 | 1 (0.7%) | 0 |
| 創傷 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 動物咬傷 | 0 | 0 | 0 | 0 |
| 頭部損傷 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 靭帯捻挫 | 1 (0.7%) | 0 | 0 | 0 |
| 腰椎骨折 | 3 (2.2%) | 1 (0.7%) | 0 | 0 |
| 処置後出血 | 2 (1.4%) | 2 (1.4%) | 2 (1.4%) | 0 |
| 骨挫傷 | 1 (0.7%) | 0 | 0 | 0 |
| 擦過傷 | 1 (0.7%) | 0 | 0 | 0 |
| 顔面骨骨折 | 1 (0.7%) | 0 | 0 | 0 |
| 四肢損傷 | 2 (1.4%) | 0 | 0 | 0 |
| 眼窩周囲挫傷 | 1 (0.7%) | 0 | 0 | 0 |
| 肋骨骨折 | 2 (1.4%) | 0 | 0 | 0 |
| 皮膚創傷 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 脊椎圧迫骨折 | 0 | 0 | 0 | 0 |
| 脾破裂 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| 熱傷 | 0 | 0 | 1 (0.7%) | 0 |
| 動物による引っかき傷 | 0 | 0 | 0 | 0 |
| 足関節部骨折 | 0 | 0 | 0 | 0 |
| 第２度熱傷 | 0 | 0 | 0 | 0 |
| 眼挫傷 | 1 (0.7%) | 0 | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 眼外傷 | 0 | 0 | 1 (0.7%) | 0 |
| 足骨折 | 0 | 0 | 1 (0.7%) | 0 |
| 眼内異物 | 1 (0.7%) | 0 | 0 | 0 |
| 外傷性血尿 | 0 | 0 | 0 | 0 |
| 関節損傷 | 1 (0.7%) | 0 | 0 | 0 |
| 過量投与 | 0 | 0 | 0 | 0 |
| 処置後便秘 | 0 | 0 | 0 | 0 |
| 処置後血尿 | 1 (0.7%) | 0 | 0 | 0 |
| 処置後腫脹 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 外傷後疼痛 | 0 | 0 | 0 | 0 |
| 陰嚢血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 皮下血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 脛骨骨折 | 0 | 0 | 0 | 0 |
| 歯牙破折 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 術後尿閉 | 0 | 0 | 0 | 0 |
| 創合併症 | 0 | 0 | 0 | 0 |
| アルコール中毒 | 0 | 0 | 1 (0.7%) | 0 |
| 背部損傷 | 0 | 0 | 1 (0.7%) | 0 |
| 腓骨骨折 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 体内異物 | 0 | 0 | 1 (0.7%) | 0 |
| 注入に伴う反応 | 0 | 0 | 1 (0.7%) | 0 |
| 靭帯断裂 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 四肢外傷性切断 | 0 | 0 | 1 (0.7%) | 0 |
| 眼窩周囲血腫 | 0 | 0 | 1 (0.7%) | 0 |
| 橈骨骨折 | 0 | 0 | 1 (0.7%) | 0 |
| 瘢痕 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚損傷 | 0 | 0 | 1 (0.7%) | 0 |
| 各種物質毒性 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 輸血反応 | 0 | 0 | 1 (0.7%) | 0 |
| 眼障害 | 30 (21.6%) | 2 (1.4%) | 25 (18.0%) | 4 (2.9%) |
| 眼乾燥 | 5 (3.6%) | 0 | 1 (0.7%) | 0 |
| 流涙増加 | 3 (2.2%) | 0 | 0 | 0 |
| 霧視 | 3 (2.2%) | 0 | 4 (2.9%) | 0 |
| 白内障 | 1 (0.7%) | 0 | 5 (3.6%) | 4 (2.9%) |
| 視力低下 | 3 (2.2%) | 0 | 1 (0.7%) | 0 |
| 眼窩周囲浮腫 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 結膜出血 | 1 (0.7%) | 0 | 5 (3.6%) | 0 |
| 眼痛 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 眼充血 | 1 (0.7%) | 0 | 0 | 0 |
| 睫毛乱生 | 1 (0.7%) | 0 | 0 | 0 |
| 硝子体浮遊物 | 1 (0.7%) | 0 | 0 | 0 |
| 糖尿病網膜症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 複視 | 2 (1.4%) | 0 | 0 | 0 |
| 眼出血 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 眼刺激 | 2 (1.4%) | 0 | 2 (1.4%) | 0 |
| 眼瞼下垂 | 1 (0.7%) | 0 | 0 | 0 |
| 羞明 | 0 | 0 | 0 | 0 |
| 眼瞼炎 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 片側失明 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 結膜充血 | 1 (0.7%) | 0 | 0 | 0 |
| 眼瞼内反 | 0 | 0 | 0 | 0 |
| 眼脂 | 1 (0.7%) | 0 | 0 | 0 |
| 眼の炎症 | 0 | 0 | 1 (0.7%) | 0 |
| 眼そう痒症 | 0 | 0 | 3 (2.2%) | 0 |
| 眼の異物感 | 1 (0.7%) | 0 | 0 | 0 |
| 緑内障 | 0 | 0 | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 角膜炎 | 0 | 0 | 0 | 0 |
| 黄斑変性 | 0 | 0 | 0 | 0 |
| マイボーム腺機能不全 | 0 | 0 | 0 | 0 |
| 眼血管障害 | 1 (0.7%) | 0 | 0 | 0 |
| 開放隅角緑内障 | 1 (0.7%) | 0 | 0 | 0 |
| 動揺視 | 1 (0.7%) | 0 | 0 | 0 |
| 老視 | 1 (0.7%) | 0 | 0 | 0 |
| 網膜剥離 | 0 | 0 | 0 | 0 |
| 強膜出血 | 0 | 0 | 0 | 0 |
| 視力障害 | 0 | 0 | 0 | 0 |
| 硝子体出血 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 眼球乾燥症 | 1 (0.7%) | 0 | 0 | 0 |
| 眼瞼紅斑 | 0 | 0 | 1 (0.7%) | 0 |
| 眼の障害 | 0 | 0 | 1 (0.7%) | 0 |
| 眼部腫脹 | 0 | 0 | 2 (1.4%) | 0 |
| 眼瞼機能障害 | 0 | 0 | 1 (0.7%) | 0 |
| 眼瞼浮腫 | 0 | 0 | 1 (0.7%) | 0 |
| 血管障害 | 29 (20.9%) | 9 (6.5%) | 19 (13.7%) | 5 (3.6%) |
| 高血圧 | 10 (7.2%) | 4 (2.9%) | 5 (3.6%) | 2 (1.4%) |
| 低血圧 | 7 (5.0%) | 1 (0.7%) | 3 (2.2%) | 2 (1.4%) |
| 血腫 | 10 (7.2%) | 0 | 3 (2.2%) | 0 |
| 深部静脈血栓症 | 0 | 0 | 4 (2.9%) | 0 |
| 潮紅 | 0 | 0 | 0 | 0 |
| 出血 | 4 (2.9%) | 3 (2.2%) | 1 (0.7%) | 1 (0.7%) |
| 起立性低血圧 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 静脈炎 | 2 (1.4%) | 0 | 0 | 0 |
| 血圧変動 | 1 (0.7%) | 0 | 0 | 0 |
| リンパ浮腫 | 0 | 0 | 1 (0.7%) | 0 |
| 表在性血栓性静脈炎 | 2 (1.4%) | 0 | 0 | 0 |
| 大動脈硬化症 | 0 | 0 | 0 | 0 |
| 循環虚脱 | 0 | 0 | 0 | 0 |
| ほてり | 0 | 0 | 1 (0.7%) | 0 |
| 高血圧クリーゼ | 0 | 0 | 0 | 0 |
| 末梢血管障害 | 1 (0.7%) | 0 | 0 | 0 |
| 末梢静脈疾患 | 0 | 0 | 0 | 0 |
| 静脈瘤 | 0 | 0 | 0 | 0 |
| 塞栓症 | 0 | 0 | 1 (0.7%) | 0 |
| 頚静脈血栓症 | 0 | 0 | 1 (0.7%) | 0 |
| 静脈瘤性潰瘍 | 0 | 0 | 1 (0.7%) | 0 |
| 心臓障害 | 13 (9.4%) | 6 (4.3%) | 19 (13.7%) | 7 (5.0%) |
| 心房細動 | 6 (4.3%) | 5 (3.6%) | 3 (2.2%) | 2 (1.4%) |
| 頻脈 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 洞性頻脈 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 徐脈 | 1 (0.7%) | 0 | 0 | 0 |
| 動悸 | 3 (2.2%) | 0 | 2 (1.4%) | 0 |
| 心房粗動 | 0 | 0 | 0 | 0 |
| 洞性徐脈 | 0 | 0 | 0 | 0 |
| 上室性頻脈 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 不安定狭心症 | 0 | 0 | 0 | 0 |
| 心停止 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 心不全 | 0 | 0 | 0 | 0 |
| 心室性期外収縮 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 急性心筋梗塞 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 不整脈 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 冠動脈硬化症 | 1 (0.7%) | 0 | 0 | 0 |
| 第一度房室ブロック | 0 | 0 | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| うっ血性心不全 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 心血管不全 | 0 | 0 | 0 | 0 |
| 変時性応答不全 | 1 (0.7%) | 0 | 0 | 0 |
| 冠動脈疾患 | 1 (0.7%) | 0 | 0 | 0 |
| 冠動脈閉塞 | 0 | 0 | 0 | 0 |
| チアノーゼ | 0 | 0 | 0 | 0 |
| 僧帽弁閉鎖不全症 | 0 | 0 | 0 | 0 |
| 心筋梗塞 | 0 | 0 | 0 | 0 |
| 心嚢液貯留 | 0 | 0 | 0 | 0 |
| 心膜炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 洞不全症候群 | 0 | 0 | 0 | 0 |
| ストレス心筋症 | 0 | 0 | 0 | 0 |
| 頻脈性不整脈 | 0 | 0 | 0 | 0 |
| トルサード　ド　ポアント | 0 | 0 | 0 | 0 |
| 三尖弁疾患 | 0 | 0 | 0 | 0 |
| 心室性不整脈 | 1 (0.7%) | 0 | 0 | 0 |
| 心室性頻脈 | 0 | 0 | 0 | 0 |
| 狭心症 | 0 | 0 | 3 (2.2%) | 0 |
| 右脚ブロック | 0 | 0 | 1 (0.7%) | 0 |
| 急性心不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 慢性心不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 心肺不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 冠動脈狭窄 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 心筋虚血 | 0 | 0 | 1 (0.7%) | 0 |
| 精神障害 | 16 (11.5%) | 2 (1.4%) | 29 (20.9%) | 3 (2.2%) |
| 不眠症 | 6 (4.3%) | 0 | 15 (10.8%) | 0 |
| 不安 | 5 (3.6%) | 0 | 1 (0.7%) | 0 |
| 錯乱状態 | 4 (2.9%) | 2 (1.4%) | 3 (2.2%) | 2 (1.4%) |
| うつ病 | 2 (1.4%) | 0 | 6 (4.3%) | 0 |
| 激越 | 1 (0.7%) | 0 | 0 | 0 |
| 譫妄 | 0 | 0 | 0 | 0 |
| 希死念慮を有するうつ病 | 0 | 0 | 0 | 0 |
| 多幸気分 | 0 | 0 | 0 | 0 |
| 幻聴 | 0 | 0 | 0 | 0 |
| 幻視 | 1 (0.7%) | 0 | 0 | 0 |
| 易刺激性 | 0 | 0 | 0 | 0 |
| リビドー減退 | 0 | 0 | 0 | 0 |
| 躁病 | 0 | 0 | 0 | 0 |
| 精神障害 | 1 (0.7%) | 0 | 0 | 0 |
| 精神状態変化 | 0 | 0 | 0 | 0 |
| 悪夢 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| パニック発作 | 0 | 0 | 0 | 0 |
| パニック障害 | 1 (0.7%) | 0 | 0 | 0 |
| 感情不安定 | 0 | 0 | 1 (0.7%) | 0 |
| 広場恐怖症 | 0 | 0 | 1 (0.7%) | 0 |
| 抑うつ気分 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 睡眠異常 | 0 | 0 | 1 (0.7%) | 0 |
| 気分動揺 | 0 | 0 | 1 (0.7%) | 0 |
| 腎および尿路障害 | 17 (12.2%) | 8 (5.8%) | 20 (14.4%) | 6 (4.3%) |
| 血尿 | 4 (2.9%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 急性腎不全 | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 排尿困難 | 2 (1.4%) | 0 | 4 (2.9%) | 0 |
| 腎不全 | 4 (2.9%) | 4 (2.9%) | 4 (2.9%) | 4 (2.9%) |
| 頻尿 | 0 | 0 | 6 (4.3%) | 0 |
| 水腎症 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 腎機能障害 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 尿閉 | 0 | 0 | 1 (0.7%) | 0 |
| 尿路閉塞 | 0 | 0 | 0 | 0 |
| 腎結石症 | 0 | 0 | 0 | 0 |
| 夜間頻尿 | 0 | 0 | 0 | 0 |
| 腎嚢胞 | 1 (0.7%) | 0 | 0 | 0 |
| 慢性腎不全 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 尿失禁 | 0 | 0 | 0 | 0 |
| 高窒素血症 | 0 | 0 | 0 | 0 |
| 膀胱刺激症状 | 0 | 0 | 0 | 0 |
| 出血性膀胱炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 緊張性膀胱 | 0 | 0 | 0 | 0 |
| 失禁 | 1 (0.7%) | 0 | 0 | 0 |
| 尿意切迫 | 0 | 0 | 1 (0.7%) | 0 |
| 閉塞性尿路疾患 | 0 | 0 | 0 | 0 |
| 乏尿 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 腎仙痛 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 有痛性排尿困難 | 1 (0.7%) | 0 | 0 | 0 |
| 尿路痛 | 0 | 0 | 0 | 0 |
| 糖尿 | 0 | 0 | 1 (0.7%) | 0 |
| 白血球尿 | 0 | 0 | 1 (0.7%) | 0 |
| 排尿異常 | 0 | 0 | 1 (0.7%) | 0 |
| 多尿 | 0 | 0 | 1 (0.7%) | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 8 (5.8%) | 6 (4.3%) | 1 (0.7%) | 1 (0.7%) |
| マントル細胞リンパ腫 | 0 | 0 | 0 | 0 |
| 基底細胞癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 皮膚有棘細胞癌 | 0 | 0 | 0 | 0 |
| 膀胱移行上皮癌 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 前立腺癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 扁平上皮癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 急性骨髄性白血病 | 0 | 0 | 0 | 0 |
| 良性新生物 | 1 (0.7%) | 0 | 0 | 0 |
| 膀胱癌 | 0 | 0 | 0 | 0 |
| 肺腺癌 | 0 | 0 | 0 | 0 |
| 悪性胸水 | 0 | 0 | 0 | 0 |
| 遠隔転移を伴う新生物 | 0 | 0 | 0 | 0 |
| 口腔乳頭腫 | 0 | 0 | 0 | 0 |
| 唾液腺癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 皮膚癌 | 0 | 0 | 0 | 0 |
| 皮膚乳頭腫 | 0 | 0 | 0 | 0 |
| 胸腺腫 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 移行上皮癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 腫瘍フレア | 0 | 0 | 0 | 0 |
| 胃腺癌 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 耳および迷路障害 | 14 (10.1%) | 0 | 9 (6.5%) | 0 |
| 回転性めまい | 6 (4.3%) | 0 | 2 (1.4%) | 0 |
| 耳鳴 | 4 (2.9%) | 0 | 1 (0.7%) | 0 |
| 耳痛 | 1 (0.7%) | 0 | 3 (2.2%) | 0 |
| 聴力低下 | 3 (2.2%) | 0 | 1 (0.7%) | 0 |
| 耳垢栓塞 | 0 | 0 | 0 | 0 |
| 耳不快感 | 1 (0.7%) | 0 | 0 | 0 |
| 難聴 | 0 | 0 | 0 | 0 |
| 耳出血 | 1 (0.7%) | 0 | 0 | 0 |
| 聴覚過敏 | 0 | 0 | 0 | 0 |
| 老人性難聴 | 1 (0.7%) | 0 | 0 | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 耳部腫脹 | 0 | 0 | 1 (0.7%) | 0 |
| 聴覚障害 | 0 | 0 | 1 (0.7%) | 0 |
| 生殖系および乳房障害 | 13 (9.4%) | 2 (1.4%) | 5 (3.6%) | 1 (0.7%) |
| 良性前立腺肥大症 | 2 (1.4%) | 0 | 0 | 0 |
| 血精液症 | 1 (0.7%) | 0 | 0 | 0 |
| 性器浮腫 | 0 | 0 | 0 | 0 |
| 勃起不全 | 0 | 0 | 1 (0.7%) | 0 |
| 骨盤痛 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 腟出血 | 1 (0.7%) | 0 | 0 | 0 |
| 後天性包茎 | 1 (0.7%) | 0 | 0 | 0 |
| 乳房血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 乳房腫瘤 | 1 (0.7%) | 0 | 0 | 0 |
| 乳房痛 | 0 | 0 | 0 | 0 |
| 性器発疹 | 1 (0.7%) | 0 | 0 | 0 |
| 陰茎痛 | 0 | 0 | 0 | 0 |
| 陰嚢腫瘤 | 0 | 0 | 0 | 0 |
| 陰嚢浮腫 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 陰嚢痛 | 1 (0.7%) | 0 | 0 | 0 |
| 子宮腟脱 | 0 | 0 | 0 | 0 |
| 外陰腟痛 | 0 | 0 | 0 | 0 |
| 外陰腟そう痒症 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 性器水疱 | 0 | 0 | 1 (0.7%) | 0 |
| 前立腺炎 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 陰嚢紅斑 | 0 | 0 | 1 (0.7%) | 0 |
| 外陰腟乾燥 | 0 | 0 | 1 (0.7%) | 0 |
| 免疫系障害 | 4 (2.9%) | 0 | 5 (3.6%) | 1 (0.7%) |
| 低ッグロブリン血症 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 節足動物咬傷アレルギー | 0 | 0 | 1 (0.7%) | 0 |
| 過敏症 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 季節性アレルギー | 0 | 0 | 0 | 0 |
| 薬物過敏症 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 造影剤アレルギー | 1 (0.7%) | 0 | 0 | 0 |
| 食物アレルギー | 0 | 0 | 0 | 0 |
| 肝胆道系障害 | 6 (4.3%) | 1 (0.7%) | 4 (2.9%) | 0 |
| 高ビリルビン血症 | 3 (2.2%) | 0 | 0 | 0 |
| 胆石症 | 2 (1.4%) | 0 | 0 | 0 |
| 胆管結石 | 0 | 0 | 0 | 0 |
| 胆管炎 | 0 | 0 | 0 | 0 |
| 肝不全 | 0 | 0 | 0 | 0 |
| 肝機能異常 | 0 | 0 | 0 | 0 |
| 中毒性肝炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 陶器様胆嚢 | 0 | 0 | 0 | 0 |
| 胆汁うっ滞 | 0 | 0 | 1 (0.7%) | 0 |
| 薬物性肝障害 | 0 | 0 | 1 (0.7%) | 0 |
| 肝障害 | 0 | 0 | 1 (0.7%) | 0 |
| 内分泌障害 | 2 (1.4%) | 0 | 3 (2.2%) | 0 |
| 甲状腺機能低下症 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 甲状腺機能亢進症 | 0 | 0 | 1 (0.7%) | 0 |
| 性腺機能低下 | 0 | 0 | 1 (0.7%) | 0 |
| 先天性、家族性および遺伝性障害 | 1 (0.7%) | 0 | 0 | 0 |
| 臍血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 外科および内科処置 | 0 | 0 | 1 (0.7%) | 0 |
| 抜歯 | 0 | 0 | 1 (0.7%) | 0 |

**TSFAE02PART2OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE02PART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae02.sas] 15SEP2015, 14:10

参照元：5.3.5.3.1 ISS TSFAE02PART2OF3

表 2.7.4-付録-8 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 370 | |
| Subjects with any TEAE | 364 (98.4%) | 265 (71.6%) |
| System organ class | | |
| Preferred term | | |
| 感染症および寄生虫症 | 263 (71.1%) | 87 (23.5%) |
| 上気道感染 | 73 (19.7%) | 3 (0.8%) |
| 肺炎 | 44 (11.9%) | 33 (8.9%) |
| 副鼻腔炎 | 39 (10.5%) | 1 (0.3%) |
| 尿路感染 | 38 (10.3%) | 6 (1.6%) |
| 鼻咽頭炎 | 30 (8.1%) | 0 |
| 結膜炎 | 26 (7.0%) | 0 |
| 気管支炎 | 20 (5.4%) | 4 (1.1%) |
| 蜂巣炎 | 18 (4.9%) | 8 (2.2%) |
| 帯状疱疹 | 14 (3.8%) | 0 |
| 鼻炎 | 14 (3.8%) | 0 |
| 毛包炎 | 13 (3.5%) | 0 |
| 爪囲炎 | 13 (3.5%) | 0 |
| 下気道感染 | 12 (3.2%) | 5 (1.4%) |
| 皮膚感染 | 12 (3.2%) | 1 (0.3%) |
| 口腔ヘルペス | 11 (3.0%) | 0 |
| 気道感染 | 11 (3.0%) | 2 (0.5%) |
| 敗血症 | 11 (3.0%) | 11 (3.0%) |
| 胃腸炎 | 10 (2.7%) | 2 (0.5%) |
| 咽頭炎 | 7 (1.9%) | 1 (0.3%) |
| ウイルス感染 | 7 (1.9%) | 0 |
| 感染 | 6 (1.6%) | 2 (0.5%) |
| クロストリジウム・ディフィシレ大腸炎 | 5 (1.4%) | 3 (0.8%) |
| 眼感染 | 5 (1.4%) | 0 |
| 歯肉炎 | 5 (1.4%) | 0 |
| 口腔カンジダ症 | 5 (1.4%) | 0 |
| クロストリジウム・ディフィシレ感染 | 4 (1.1%) | 1 (0.3%) |
| インフルエンザ | 4 (1.1%) | 0 |
| 限局性感染 | 4 (1.1%) | 0 |
| 中耳炎 | 4 (1.1%) | 0 |
| 歯周炎 | 4 (1.1%) | 0 |
| 歯感染 | 4 (1.1%) | 0 |
| 菌血症 | 3 (0.8%) | 2 (0.5%) |
| 気管支肺炎 | 3 (0.8%) | 1 (0.3%) |
| 膀胱炎 | 3 (0.8%) | 0 |
| 耳感染 | 3 (0.8%) | 0 |
| ウイルス性胃腸炎 | 3 (0.8%) | 1 (0.3%) |
| 単純ヘルペス | 3 (0.8%) | 0 |
| 喉頭炎 | 3 (0.8%) | 1 (0.3%) |
| 爪感染 | 3 (0.8%) | 0 |
| 外耳炎 | 3 (0.8%) | 0 |
| ブドウ球菌感染 | 3 (0.8%) | 0 |
| ウイルス性上気道感染 | 3 (0.8%) | 0 |
| 急性副鼻腔炎 | 2 (0.5%) | 0 |
| 細気管支炎 | 2 (0.5%) | 0 |
| 医療機器関連感染 | 2 (0.5%) | 1 (0.3%) |
| 憩室炎 | 2 (0.5%) | 0 |
| 感染性小腸結腸炎 | 2 (0.5%) | 2 (0.5%) |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 丹毒 | 2 (0.5%) | 0 |
| 真菌感染 | 2 (0.5%) | 0 |
| 皮膚真菌感染 | 2 (0.5%) | 0 |
| 真菌性性器感染 | 2 (0.5%) | 0 |
| ヘルペスウイルス感染 | 2 (0.5%) | 0 |
| 麦粒腫 | 2 (0.5%) | 0 |
| 爪真菌症 | 2 (0.5%) | 0 |
| レンサ球菌性咽頭炎 | 2 (0.5%) | 0 |
| ニューモシスチス・イロベチイ肺炎 | 2 (0.5%) | 2 (0.5%) |
| 細菌性肺炎 | 2 (0.5%) | 2 (0.5%) |
| 膿疱性皮疹 | 2 (0.5%) | 0 |
| 敗血症性ショック | 2 (0.5%) | 2 (0.5%) |
| ブドウ球菌性菌血症 | 2 (0.5%) | 1 (0.3%) |
| 歯膿瘍 | 2 (0.5%) | 1 (0.3%) |
| 細菌性尿路感染 | 2 (0.5%) | 1 (0.3%) |
| 尿路性敗血症 | 2 (0.5%) | 2 (0.5%) |
| 外陰部腟カンジダ症 | 2 (0.5%) | 0 |
| 創傷感染 | 2 (0.5%) | 1 (0.3%) |
| 腹部膿瘍 | 1 (0.3%) | 1 (0.3%) |
| 四肢膿瘍 | 1 (0.3%) | 0 |
| ダニ皮膚炎 | 1 (0.3%) | 0 |
| 膿疱性ざ瘡 | 1 (0.3%) | 0 |
| 肛門膿瘍 | 1 (0.3%) | 0 |
| 肛門カンジダ症 | 1 (0.3%) | 0 |
| 虫垂炎 | 1 (0.3%) | 1 (0.3%) |
| 穿孔性虫垂炎 | 1 (0.3%) | 1 (0.3%) |
| 異型肺炎 | 1 (0.3%) | 0 |
| 細菌尿 | 1 (0.3%) | 0 |
| カンジダ性亀頭炎 | 1 (0.3%) | 0 |
| 胆道感染 | 1 (0.3%) | 1 (0.3%) |
| ブラストシスティス感染 | 1 (0.3%) | 0 |
| 体部白癬 | 1 (0.3%) | 0 |
| 乳房蜂巣炎 | 1 (0.3%) | 0 |
| カンピロバクター胃腸炎 | 1 (0.3%) | 0 |
| カンピロバクター感染 | 1 (0.3%) | 1 (0.3%) |
| カンジダ感染 | 1 (0.3%) | 0 |
| 眼窩蜂巣炎 | 1 (0.3%) | 1 (0.3%) |
| 感染性胆嚢炎 | 1 (0.3%) | 1 (0.3%) |
| 慢性副鼻腔炎 | 1 (0.3%) | 0 |
| シトロバクター感染 | 1 (0.3%) | 1 (0.3%) |
| 涙嚢炎 | 1 (0.3%) | 0 |
| ウイルス性脳炎 | 1 (0.3%) | 1 (0.3%) |
| 精巣上体炎 | 1 (0.3%) | 0 |
| 喉頭蓋炎 | 1 (0.3%) | 0 |
| 細菌性眼感染 | 1 (0.3%) | 0 |
| 真菌血症 | 1 (0.3%) | 0 |
| ヘリコバクター胃潰瘍 | 1 (0.3%) | 0 |
| 消化管感染 | 1 (0.3%) | 0 |
| ウイルス性消化管感染 | 1 (0.3%) | 0 |
| 性器カンジダ症 | 1 (0.3%) | 0 |
| 血腫感染 | 1 (0.3%) | 0 |
| ヘモフィルス感染 | 1 (0.3%) | 0 |
| Ｂ型肝炎 | 1 (0.3%) | 1 (0.3%) |
| ヒストプラスマ症 | 1 (0.3%) | 0 |
| 埋込み部位感染 | 1 (0.3%) | 0 |
| 切開部位感染 | 1 (0.3%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| クレブシエラ感染 | 1 (0.3%) | 1 (0.3%) |
| 口唇感染 | 1 (0.3%) | 0 |
| 細菌性下気道感染 | 1 (0.3%) | 1 (0.3%) |
| 肺感染 | 1 (0.3%) | 1 (0.3%) |
| ライム病 | 1 (0.3%) | 0 |
| 乳腺炎 | 1 (0.3%) | 0 |
| 水疱性鼓膜炎 | 1 (0.3%) | 0 |
| 爪床感染 | 1 (0.3%) | 0 |
| 眼帯状疱疹 | 1 (0.3%) | 1 (0.3%) |
| 口腔真菌感染 | 1 (0.3%) | 0 |
| 乳頭腫ウイルス感染 | 1 (0.3%) | 0 |
| クリプトコッカス性肺炎 | 1 (0.3%) | 0 |
| クレブシエラ菌性肺炎 | 1 (0.3%) | 1 (0.3%) |
| 処置後感染 | 1 (0.3%) | 0 |
| 肺結核 | 1 (0.3%) | 1 (0.3%) |
| 腎盂腎炎 | 1 (0.3%) | 1 (0.3%) |
| 膿皮症 | 1 (0.3%) | 0 |
| レンサ球菌性膿皮症 | 1 (0.3%) | 0 |
| 狂犬病 | 1 (0.3%) | 0 |
| 直腸膿瘍 | 1 (0.3%) | 0 |
| ウイルス性気道感染 | 1 (0.3%) | 0 |
| 軟部組織感染 | 1 (0.3%) | 1 (0.3%) |
| ブドウ球菌皮膚感染 | 1 (0.3%) | 0 |
| レンサ球菌感染 | 1 (0.3%) | 1 (0.3%) |
| 皮下組織膿瘍 | 1 (0.3%) | 1 (0.3%) |
| 足部白癬 | 1 (0.3%) | 0 |
| 扁桃炎 | 1 (0.3%) | 0 |
| 気管炎 | 1 (0.3%) | 1 (0.3%) |
| 真菌性尿路感染 | 1 (0.3%) | 0 |
| シュードモナス性尿路感染 | 1 (0.3%) | 0 |
| 眼瞼膿瘍 | 0 | 0 |
| 急性扁桃炎 | 0 | 0 |
| 真菌性肛門感染 | 0 | 0 |
| 気管支肺アスペルギルス症 | 0 | 0 |
| 大腸菌性菌血症 | 0 | 0 |
| 感染性大腸炎 | 0 | 0 |
| 真菌性喉頭炎 | 0 | 0 |
| 肝膿瘍 | 0 | 0 |
| 大葉性肺炎 | 0 | 0 |
| リンパ管炎 | 0 | 0 |
| 粘膜感染 | 0 | 0 |
| 好中球減少性敗血症 | 0 | 0 |
| ニューモシスチス・イロベチイ感染 | 0 | 0 |
| 大腸菌性肺炎 | 0 | 0 |
| 細菌性気道感染 | 0 | 0 |
| アスペルギルス性副鼻腔炎 | 0 | 0 |
| ブドウ球菌性敗血症 | 0 | 0 |
| 癜風 | 0 | 0 |
| 気管気管支炎 | 0 | 0 |
| 胃腸障害 | 255 (68.9%) | 39 (10.5%) |
| 下痢 | 146 (39.5%) | 13 (3.5%) |
| 悪心 | 80 (21.6%) | 1 (0.3%) |
| 嘔吐 | 62 (16.8%) | 1 (0.3%) |
| 便秘 | 57 (15.4%) | 0 |
| 腹痛 | 42 (11.4%) | 13 (3.5%) |
| 口内炎 | 31 (8.4%) | 3 (0.8%) |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 消化不良 | 28 (7.6%) | 0 |
| 上腹部痛 | 16 (4.3%) | 1 (0.3%) |
| 腹部膨満 | 14 (3.8%) | 0 |
| 口内乾燥 | 14 (3.8%) | 0 |
| 胃食道逆流性疾患 | 13 (3.5%) | 0 |
| 嚥下障害 | 9 (2.4%) | 2 (0.5%) |
| 腹部不快感 | 8 (2.2%) | 0 |
| 口腔内痛 | 8 (2.2%) | 1 (0.3%) |
| 口腔内潰瘍形成 | 7 (1.9%) | 0 |
| 放屁 | 6 (1.6%) | 0 |
| 胃炎 | 6 (1.6%) | 0 |
| 心窩部不快感 | 5 (1.4%) | 0 |
| 舌痛 | 5 (1.4%) | 0 |
| 痔核 | 4 (1.1%) | 0 |
| アフタ性口内炎 | 3 (0.8%) | 1 (0.3%) |
| おくび | 3 (0.8%) | 0 |
| イレウス | 3 (0.8%) | 0 |
| 直腸出血 | 3 (0.8%) | 0 |
| 舌潰瘍 | 3 (0.8%) | 0 |
| 下腹部痛 | 2 (0.5%) | 1 (0.3%) |
| 齲歯 | 2 (0.5%) | 1 (0.3%) |
| 軟便 | 2 (0.5%) | 0 |
| 食中毒 | 2 (0.5%) | 0 |
| 排便回数増加 | 2 (0.5%) | 0 |
| 胃潰瘍 | 2 (0.5%) | 1 (0.3%) |
| 歯肉出血 | 2 (0.5%) | 0 |
| 歯肉浮腫 | 2 (0.5%) | 0 |
| 吐血 | 2 (0.5%) | 0 |
| 麻痺性イレウス | 2 (0.5%) | 2 (0.5%) |
| 鼠径ヘルニア | 2 (0.5%) | 0 |
| 口唇潰瘍 | 2 (0.5%) | 0 |
| 下部消化管出血 | 2 (0.5%) | 1 (0.3%) |
| 口腔内出血 | 2 (0.5%) | 0 |
| 歯周病 | 2 (0.5%) | 0 |
| 肛門周囲痛 | 2 (0.5%) | 1 (0.3%) |
| 直腸炎 | 2 (0.5%) | 0 |
| 直腸裂 | 2 (0.5%) | 0 |
| 小腸閉塞 | 2 (0.5%) | 2 (0.5%) |
| 歯痛 | 2 (0.5%) | 0 |
| 裂肛 | 1 (0.3%) | 0 |
| 肛門直腸障害 | 1 (0.3%) | 0 |
| 萎縮性舌炎 | 1 (0.3%) | 0 |
| バレット食道 | 1 (0.3%) | 0 |
| 口唇炎 | 1 (0.3%) | 0 |
| 大腸炎 | 1 (0.3%) | 1 (0.3%) |
| 歯不快感 | 1 (0.3%) | 0 |
| 血性下痢 | 1 (0.3%) | 0 |
| 十二指腸狭窄 | 1 (0.3%) | 1 (0.3%) |
| 十二指腸潰瘍 | 1 (0.3%) | 1 (0.3%) |
| 十二指腸炎 | 1 (0.3%) | 0 |
| 十二指腸胃逆流 | 1 (0.3%) | 0 |
| 便失禁 | 1 (0.3%) | 0 |
| 糞塊 | 1 (0.3%) | 0 |
| 胃前庭部毛細血管拡張症 | 1 (0.3%) | 0 |
| 出血性胃炎 | 1 (0.3%) | 0 |
| 歯肉痛 | 1 (0.3%) | 0 |
| 血便排泄 | 1 (0.3%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 痔出血 | 1 (0.3%) | 0 |
| 過敏性腸症候群 | 1 (0.3%) | 0 |
| 口唇水疱 | 1 (0.3%) | 0 |
| 口唇びらん | 1 (0.3%) | 0 |
| 口唇痛 | 1 (0.3%) | 0 |
| 口唇腫脹 | 1 (0.3%) | 0 |
| 弛緩歯 | 1 (0.3%) | 0 |
| メレナ | 1 (0.3%) | 0 |
| 嚥下痛 | 1 (0.3%) | 0 |
| 口蓋障害 | 1 (0.3%) | 0 |
| 慢性膵炎 | 1 (0.3%) | 0 |
| 舌突出 | 1 (0.3%) | 0 |
| 直腸潰瘍 | 1 (0.3%) | 0 |
| 唾液腺結石 | 1 (0.3%) | 0 |
| 変色歯 | 1 (0.3%) | 0 |
| 歯の障害 | 1 (0.3%) | 0 |
| 歯の脱落 | 1 (0.3%) | 1 (0.3%) |
| 痔瘻 | 0 | 0 |
| 肛門直腸不快感 | 0 | 0 |
| 腸炎 | 0 | 0 |
| 変色便 | 0 | 0 |
| 胃腸出血 | 0 | 0 |
| 胃腸毒性 | 0 | 0 |
| 歯肉障害 | 0 | 0 |
| 歯肉退縮 | 0 | 0 |
| 舌炎 | 0 | 0 |
| 腸出血 | 0 | 0 |
| 口唇乾燥 | 0 | 0 |
| 口唇浮腫 | 0 | 0 |
| 食道炎 | 0 | 0 |
| 口腔知覚不全 | 0 | 0 |
| 口腔粘膜びらん | 0 | 0 |
| 口腔粘膜紅斑 | 0 | 0 |
| 排便痛 | 0 | 0 |
| 上部消化管出血 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 239 (64.6%) | 38 (10.3%) |
| 疲労 | 129 (34.9%) | 16 (4.3%) |
| 末梢性浮腫 | 74 (20.0%) | 6 (1.6%) |
| 発熱 | 68 (18.4%) | 3 (0.8%) |
| 無力症 | 32 (8.6%) | 5 (1.4%) |
| 悪寒 | 18 (4.9%) | 0 |
| 胸痛 | 15 (4.1%) | 0 |
| 末梢腫脹 | 15 (4.1%) | 1 (0.3%) |
| インフルエンザ様疾患 | 14 (3.8%) | 0 |
| 疼痛 | 11 (3.0%) | 1 (0.3%) |
| 非心臓性胸痛 | 8 (2.2%) | 2 (0.5%) |
| 粘膜の炎症 | 6 (1.6%) | 1 (0.3%) |
| 全身健康状態低下 | 5 (1.4%) | 2 (0.5%) |
| 倦怠感 | 5 (1.4%) | 0 |
| 局所腫脹 | 4 (1.1%) | 1 (0.3%) |
| 多臓器不全 | 4 (1.1%) | 4 (1.1%) |
| 胸部不快感 | 3 (0.8%) | 0 |
| 歩行障害 | 3 (0.8%) | 0 |
| 全身性浮腫 | 3 (0.8%) | 1 (0.3%) |
| 注射部位内出血 | 3 (0.8%) | 0 |
| 乾燥症 | 3 (0.8%) | 1 (0.3%) |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 腋窩痛 | 2 (0.5%) | 0 |
| 早期満腹 | 2 (0.5%) | 0 |
| 重力性浮腫 | 2 (0.5%) | 0 |
| 低体温 | 2 (0.5%) | 0 |
| 炎症 | 2 (0.5%) | 0 |
| 浮腫 | 2 (0.5%) | 0 |
| 活動状態低下 | 2 (0.5%) | 1 (0.3%) |
| カテーテル留置部位関連反応 | 1 (0.3%) | 0 |
| 死亡 | 1 (0.3%) | 1 (0.3%) |
| 医療機器リーク | 1 (0.3%) | 0 |
| 顔面浮腫 | 1 (0.3%) | 0 |
| 異常感 | 1 (0.3%) | 0 |
| 冷感 | 1 (0.3%) | 0 |
| 熱感 | 1 (0.3%) | 0 |
| 治癒不良 | 1 (0.3%) | 0 |
| 硬結 | 1 (0.3%) | 0 |
| 注入部位血管外漏出 | 1 (0.3%) | 0 |
| 注射部位紅斑 | 1 (0.3%) | 0 |
| 注射部位漏出 | 1 (0.3%) | 0 |
| 注射部位出血 | 1 (0.3%) | 0 |
| 注射部位疼痛 | 1 (0.3%) | 0 |
| 注射部位反応 | 1 (0.3%) | 0 |
| 先行疾患の改善 | 1 (0.3%) | 0 |
| 温度変化不耐症 | 1 (0.3%) | 0 |
| 評価不能の事象 | 1 (0.3%) | 0 |
| 医療機器関連の血栓症 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 200 (54.1%) | 35 (9.5%) |
| 咳嗽 | 81 (21.9%) | 0 |
| 呼吸困難 | 69 (18.6%) | 12 (3.2%) |
| 鼻出血 | 32 (8.6%) | 1 (0.3%) |
| 口腔咽頭痛 | 29 (7.8%) | 0 |
| 胸水 | 23 (6.2%) | 7 (1.9%) |
| 湿性咳嗽 | 15 (4.1%) | 0 |
| 鼻閉 | 13 (3.5%) | 0 |
| 呼吸不全 | 10 (2.7%) | 10 (2.7%) |
| 鼻漏 | 9 (2.4%) | 0 |
| 発声障害 | 8 (2.2%) | 0 |
| 慢性閉塞性肺疾患 | 6 (1.6%) | 4 (1.1%) |
| アレルギー性鼻炎 | 6 (1.6%) | 0 |
| 副鼻腔うっ血 | 6 (1.6%) | 0 |
| 上気道うっ血 | 6 (1.6%) | 0 |
| 低酸素症 | 5 (1.4%) | 4 (1.1%) |
| しゃっくり | 4 (1.1%) | 0 |
| 気胸 | 4 (1.1%) | 2 (0.5%) |
| 喀血 | 3 (0.8%) | 0 |
| 鼻部不快感 | 3 (0.8%) | 0 |
| 肺水腫 | 3 (0.8%) | 1 (0.3%) |
| ラ音 | 3 (0.8%) | 0 |
| 喘鳴 | 3 (0.8%) | 0 |
| 無気肺 | 2 (0.5%) | 0 |
| 労作性呼吸困難 | 2 (0.5%) | 0 |
| 肺硬化 | 2 (0.5%) | 0 |
| 肺浸潤 | 2 (0.5%) | 0 |
| 鼻の炎症 | 2 (0.5%) | 0 |
| 肺塞栓症 | 2 (0.5%) | 1 (0.3%) |
| 気道うっ血 | 2 (0.5%) | 0 |
| 急性肺水腫 | 1 (0.3%) | 1 (0.3%) |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 喘息 | 1 (0.3%) | 0 |
| 気管支反応性亢進 | 1 (0.3%) | 0 |
| 気管支分泌物貯留 | 1 (0.3%) | 0 |
| 気管支拡張症 | 1 (0.3%) | 0 |
| 慢性気管支炎 | 1 (0.3%) | 1 (0.3%) |
| 肺気腫 | 1 (0.3%) | 0 |
| 上気道分泌増加 | 1 (0.3%) | 0 |
| 鼻乾燥 | 1 (0.3%) | 0 |
| 鼻潰瘍 | 1 (0.3%) | 0 |
| 副鼻腔不快感 | 1 (0.3%) | 0 |
| 副鼻腔分泌過多 | 1 (0.3%) | 0 |
| 咽頭紅斑 | 1 (0.3%) | 0 |
| 胸膜炎 | 1 (0.3%) | 0 |
| 胸膜痛 | 1 (0.3%) | 0 |
| 肺腫瘤 | 1 (0.3%) | 0 |
| 呼吸性アシドーシス | 1 (0.3%) | 1 (0.3%) |
| 呼吸窮迫 | 1 (0.3%) | 1 (0.3%) |
| 拘束性肺疾患 | 1 (0.3%) | 0 |
| 副鼻腔障害 | 1 (0.3%) | 0 |
| くしゃみ | 1 (0.3%) | 0 |
| 頻呼吸 | 1 (0.3%) | 0 |
| 扁桃肥大 | 1 (0.3%) | 0 |
| 上気道咳症候群 | 1 (0.3%) | 0 |
| 間質性肺疾患 | 0 | 0 |
| 咽頭潰瘍 | 0 | 0 |
| 肺臓炎 | 0 | 0 |
| 皮膚および皮下組織障害 | 194 (52.4%) | 10 (2.7%) |
| 発疹 | 57 (15.4%) | 4 (1.1%) |
| そう痒症 | 28 (7.6%) | 0 |
| 点状出血 | 22 (5.9%) | 0 |
| 皮膚病変 | 20 (5.4%) | 0 |
| 斑状丘疹状皮疹 | 16 (4.3%) | 2 (0.5%) |
| 皮膚乾燥 | 14 (3.8%) | 0 |
| 斑状出血 | 13 (3.5%) | 0 |
| 紅斑 | 11 (3.0%) | 0 |
| 寝汗 | 11 (3.0%) | 0 |
| 脱毛症 | 10 (2.7%) | 0 |
| ざ瘡様皮膚炎 | 8 (2.2%) | 0 |
| 紫斑 | 7 (1.9%) | 2 (0.5%) |
| 多汗症 | 6 (1.6%) | 0 |
| 皮膚亀裂 | 6 (1.6%) | 0 |
| 嵌入爪 | 5 (1.4%) | 0 |
| 爪破損 | 5 (1.4%) | 0 |
| 蕁麻疹 | 5 (1.4%) | 0 |
| 水疱 | 4 (1.1%) | 0 |
| 全身性そう痒症 | 4 (1.1%) | 0 |
| 斑状皮疹 | 4 (1.1%) | 1 (0.3%) |
| 皮膚腫瘤 | 4 (1.1%) | 0 |
| 皮膚潰瘍 | 4 (1.1%) | 0 |
| ざ瘡 | 3 (0.8%) | 0 |
| 褥瘡性潰瘍 | 3 (0.8%) | 1 (0.3%) |
| 湿疹 | 3 (0.8%) | 0 |
| 紅斑性皮疹 | 3 (0.8%) | 0 |
| 皮膚色素過剰 | 3 (0.8%) | 0 |
| 皮膚嚢腫 | 2 (0.5%) | 0 |
| 接触性皮膚炎 | 2 (0.5%) | 0 |
| 皮下出血 | 2 (0.5%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 間擦疹 | 2 (0.5%) | 0 |
| 皮膚疼痛 | 2 (0.5%) | 0 |
| 全身性皮疹 | 2 (0.5%) | 0 |
| 丘疹性皮疹 | 2 (0.5%) | 0 |
| そう痒性皮疹 | 2 (0.5%) | 0 |
| 皮膚変色 | 2 (0.5%) | 0 |
| 毛細血管炎 | 1 (0.3%) | 0 |
| 皮膚炎 | 1 (0.3%) | 0 |
| アレルギー性皮膚炎 | 1 (0.3%) | 0 |
| 水疱性皮膚炎 | 1 (0.3%) | 0 |
| 皮脂欠乏性湿疹 | 1 (0.3%) | 0 |
| 貨幣状湿疹 | 1 (0.3%) | 0 |
| 過敏性血管炎 | 1 (0.3%) | 0 |
| 爪床出血 | 1 (0.3%) | 0 |
| 爪床障害 | 1 (0.3%) | 0 |
| 爪床の炎症 | 1 (0.3%) | 0 |
| 爪の不快感 | 1 (0.3%) | 0 |
| 爪の障害 | 1 (0.3%) | 0 |
| 爪ジストロフィー | 1 (0.3%) | 0 |
| 爪線状隆起 | 1 (0.3%) | 0 |
| 爪痛 | 1 (0.3%) | 0 |
| 爪甲脱落症 | 1 (0.3%) | 0 |
| 手掌・足底発赤知覚不全症候群 | 1 (0.3%) | 0 |
| 脂肪織炎 | 1 (0.3%) | 0 |
| 色素沈着障害 | 1 (0.3%) | 0 |
| 毛孔性皮疹 | 1 (0.3%) | 0 |
| 皮膚色素減少 | 1 (0.3%) | 0 |
| 皮膚刺激 | 1 (0.3%) | 0 |
| 皮膚腫脹 | 1 (0.3%) | 0 |
| 乾皮症 | 1 (0.3%) | 0 |
| 皮膚アミロイドーシス | 0 | 0 |
| 異汗性湿疹 | 0 | 0 |
| 多形紅斑 | 0 | 0 |
| 爪甲離床症 | 0 | 0 |
| 痒疹 | 0 | 0 |
| 皮膚硬結 | 0 | 0 |
| うっ滞性皮膚炎 | 0 | 0 |
| 顔面腫脹 | 0 | 0 |
| 筋骨格系および結合組織障害 | 173 (46.8%) | 20 (5.4%) |
| 筋痙縮 | 67 (18.1%) | 0 |
| 背部痛 | 44 (11.9%) | 6 (1.6%) |
| 関節痛 | 38 (10.3%) | 2 (0.5%) |
| 筋肉痛 | 32 (8.6%) | 1 (0.3%) |
| 四肢痛 | 28 (7.6%) | 2 (0.5%) |
| 筋骨格痛 | 17 (4.6%) | 0 |
| 筋力低下 | 13 (3.5%) | 3 (0.8%) |
| 側腹部痛 | 8 (2.2%) | 2 (0.5%) |
| 頚部痛 | 6 (1.6%) | 0 |
| 変形性関節症 | 5 (1.4%) | 2 (0.5%) |
| 肢径部痛 | 4 (1.1%) | 1 (0.3%) |
| 四肢不快感 | 4 (1.1%) | 0 |
| 筋骨格硬直 | 3 (0.8%) | 0 |
| 骨痛 | 2 (0.5%) | 0 |
| 関節硬直 | 2 (0.5%) | 0 |
| 関節腫脹 | 2 (0.5%) | 0 |
| 運動性低下 | 2 (0.5%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 筋骨格系胸痛 | 2 (0.5%) | 0 |
| ミオパチー | 2 (0.5%) | 1 (0.3%) |
| 軟部組織障害 | 2 (0.5%) | 0 |
| 関節炎 | 1 (0.3%) | 0 |
| 滑液包炎 | 1 (0.3%) | 0 |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 1 (0.3%) | 1 (0.3%) |
| 外骨腫 | 1 (0.3%) | 0 |
| 痛風性関節炎 | 1 (0.3%) | 1 (0.3%) |
| 椎間板変性症 | 1 (0.3%) | 0 |
| 椎間板突出 | 1 (0.3%) | 0 |
| 関節拘縮 | 1 (0.3%) | 0 |
| 関節滲出液 | 1 (0.3%) | 0 |
| 関節ロック | 1 (0.3%) | 0 |
| 筋緊張 | 1 (0.3%) | 0 |
| 筋攣縮 | 1 (0.3%) | 0 |
| 筋骨格不快感 | 1 (0.3%) | 0 |
| 頚部腫瘤 | 1 (0.3%) | 1 (0.3%) |
| 骨壊死 | 1 (0.3%) | 1 (0.3%) |
| 骨粗鬆症 | 1 (0.3%) | 0 |
| 顎痛 | 1 (0.3%) | 0 |
| 横紋筋融解症 | 1 (0.3%) | 1 (0.3%) |
| 滑液嚢腫 | 1 (0.3%) | 0 |
| 腱痛 | 1 (0.3%) | 0 |
| 椎間孔狭窄 | 1 (0.3%) | 0 |
| 関節障害 | 0 | 0 |
| 軟骨石灰化症 | 0 | 0 |
| 肛径部腫瘤 | 0 | 0 |
| 椎間板圧迫 | 0 | 0 |
| 筋拘縮 | 0 | 0 |
| 骨炎 | 0 | 0 |
| 筋肉減少症 | 0 | 0 |
| 脊椎痛 | 0 | 0 |
| 弾発指 | 0 | 0 |
| 血液およびリンパ系障害 | 169 (45.7%) | 109 (29.5%) |
| 血小板減少症 | 74 (20.0%) | 41 (11.1%) |
| 好中球減少症 | 70 (18.9%) | 61 (16.5%) |
| 貧血 | 63 (17.0%) | 30 (8.1%) |
| 発熱性好中球減少症 | 13 (3.5%) | 13 (3.5%) |
| 白血球減少症 | 13 (3.5%) | 6 (1.6%) |
| 白血球増加症 | 7 (1.9%) | 3 (0.8%) |
| 内出血発生の増加傾向 | 5 (1.4%) | 0 |
| リンパ球減少症 | 5 (1.4%) | 0 |
| リンパ球増加症 | 4 (1.1%) | 3 (0.8%) |
| リンパ節痛 | 2 (0.5%) | 1 (0.3%) |
| リンパ節症 | 2 (0.5%) | 0 |
| 脾腫 | 2 (0.5%) | 0 |
| 骨髄機能不全 | 1 (0.3%) | 1 (0.3%) |
| 凝血異常 | 1 (0.3%) | 1 (0.3%) |
| 溶血 | 1 (0.3%) | 1 (0.3%) |
| 鉄欠乏性貧血 | 1 (0.3%) | 0 |
| 白血球停滞症候群 | 1 (0.3%) | 1 (0.3%) |
| 汎血球減少症 | 1 (0.3%) | 1 (0.3%) |
| 後腹膜リンパ節腫脹 | 1 (0.3%) | 1 (0.3%) |
| 脾臓出血 | 1 (0.3%) | 1 (0.3%) |
| 脾臓梗塞 | 1 (0.3%) | 1 (0.3%) |
| 血小板増加症 | 1 (0.3%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| リンパ節炎 | 0 | 0 |
| 好中球増加症 | 0 | 0 |
| 代謝および栄養障害 | 150 (40.5%) | 52 (14.1%) |
| 食欲減退 | 62 (16.8%) | 3 (0.8%) |
| 低カリウム血症 | 34 (9.2%) | 15 (4.1%) |
| 高尿酸血症 | 25 (6.8%) | 10 (2.7%) |
| 脱水 | 22 (5.9%) | 7 (1.9%) |
| 低マグネシウム血症 | 21 (5.7%) | 1 (0.3%) |
| 高カリウム血症 | 13 (3.5%) | 5 (1.4%) |
| 低ナトリウム血症 | 12 (3.2%) | 8 (2.2%) |
| 低アルブミン血症 | 11 (3.0%) | 4 (1.1%) |
| 高血糖 | 9 (2.4%) | 2 (0.5%) |
| 低カルシウム血症 | 6 (1.6%) | 0 |
| 低血糖症 | 4 (1.1%) | 0 |
| 低リン酸血症 | 4 (1.1%) | 4 (1.1%) |
| 水分過負荷 | 3 (0.8%) | 0 |
| 痛風 | 3 (0.8%) | 0 |
| 酵素異常 | 2 (0.5%) | 1 (0.3%) |
| 高コレステロール血症 | 2 (0.5%) | 0 |
| 高ナトリウム血症 | 2 (0.5%) | 0 |
| 高リン酸塩血症 | 2 (0.5%) | 0 |
| 過小食 | 2 (0.5%) | 1 (0.3%) |
| 乳酸アシドーシス | 2 (0.5%) | 1 (0.3%) |
| アルコール不耐性 | 1 (0.3%) | 0 |
| 悪液質 | 1 (0.3%) | 1 (0.3%) |
| 糖尿病 | 1 (0.3%) | 1 (0.3%) |
| 糖尿病性ケトアシドーシス | 1 (0.3%) | 1 (0.3%) |
| 高アルブミン血症 | 1 (0.3%) | 0 |
| 高アンモニア血症 | 1 (0.3%) | 1 (0.3%) |
| 低蛋白血症 | 1 (0.3%) | 0 |
| 代謝性アシドーシス | 1 (0.3%) | 1 (0.3%) |
| 腫瘍崩壊症候群 | 1 (0.3%) | 1 (0.3%) |
| ２型糖尿病 | 1 (0.3%) | 0 |
| 脂質異常症 | 0 | 0 |
| 電解質失調 | 0 | 0 |
| 体液貯留 | 0 | 0 |
| 耐糖能障害 | 0 | 0 |
| 高クレアチニン血症 | 0 | 0 |
| 高脂血症 | 0 | 0 |
| 高トリグリセリド血症 | 0 | 0 |
| 多飲症 | 0 | 0 |
| 神経系障害 | 121 (32.7%) | 9 (2.4%) |
| 頭痛 | 37 (10.0%) | 0 |
| 浮動性めまい | 26 (7.0%) | 0 |
| 末梢性感覚ニューロパチー | 14 (3.8%) | 1 (0.3%) |
| 体位性めまい | 10 (2.7%) | 0 |
| 錯感覚 | 8 (2.2%) | 0 |
| 記憶障害 | 7 (1.9%) | 0 |
| 末梢性ニューロパチー | 7 (1.9%) | 0 |
| 振戦 | 6 (1.6%) | 0 |
| 感覚鈍麻 | 5 (1.4%) | 1 (0.3%) |
| 健忘 | 4 (1.1%) | 0 |
| 傾眠 | 4 (1.1%) | 0 |
| 失神 | 4 (1.1%) | 4 (1.1%) |
| 平衡障害 | 3 (0.8%) | 0 |
| 構語障害 | 3 (0.8%) | 2 (0.5%) |
| 味覚異常 | 3 (0.8%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 嗜眠 | 3 (0.8%) | 0 |
| 多発ニューロパチー | 3 (0.8%) | 1 (0.3%) |
| 認知症 | 2 (0.5%) | 0 |
| 頭蓋内出血 | 2 (0.5%) | 0 |
| 過眠症 | 2 (0.5%) | 0 |
| 神経痛 | 2 (0.5%) | 0 |
| 失神寸前の状態 | 2 (0.5%) | 0 |
| 下肢静止不能症候群 | 2 (0.5%) | 0 |
| 副鼻腔炎に伴う頭痛 | 2 (0.5%) | 0 |
| 一過性脳虚血発作 | 2 (0.5%) | 0 |
| 灼熱足症候群 | 1 (0.3%) | 0 |
| 手根管症候群 | 1 (0.3%) | 0 |
| 大脳萎縮 | 1 (0.3%) | 0 |
| 脳血管発作 | 1 (0.3%) | 1 (0.3%) |
| 労作性めまい | 1 (0.3%) | 0 |
| 脳症 | 1 (0.3%) | 1 (0.3%) |
| てんかん | 1 (0.3%) | 1 (0.3%) |
| 顔面部神経痛 | 1 (0.3%) | 0 |
| 顔面不全麻痺 | 1 (0.3%) | 0 |
| 頭部不快感 | 1 (0.3%) | 0 |
| 腰髄神経根障害 | 1 (0.3%) | 0 |
| 片頭痛 | 1 (0.3%) | 0 |
| 前兆を伴う片頭痛 | 1 (0.3%) | 0 |
| 筋痙直 | 1 (0.3%) | 0 |
| ミオクローヌス | 1 (0.3%) | 0 |
| 眼振 | 1 (0.3%) | 0 |
| 腓骨神経麻痺 | 1 (0.3%) | 0 |
| ヘルペス後神経痛 | 1 (0.3%) | 0 |
| 坐骨神経痛 | 1 (0.3%) | 0 |
| 感覚障害 | 1 (0.3%) | 0 |
| 会話障害 | 1 (0.3%) | 1 (0.3%) |
| 緊張性頭痛 | 1 (0.3%) | 0 |
| 一過性全健忘 | 1 (0.3%) | 0 |
| 血管性脳症 | 1 (0.3%) | 0 |
| 失声症 | 0 | 0 |
| 運動失調 | 0 | 0 |
| 脳虚血 | 0 | 0 |
| 認知障害 | 0 | 0 |
| 糖尿病性ニューロパチー | 0 | 0 |
| 注意力障害 | 0 | 0 |
| 異常感覚 | 0 | 0 |
| 虚血性脳卒中 | 0 | 0 |
| 意識消失 | 0 | 0 |
| 末梢性感覚運動ニューロパチー | 0 | 0 |
| 精神運動亢進 | 0 | 0 |
| 臨床検査 | 112 (30.3%) | 35 (9.5%) |
| 血中クレアチニン増加 | 31 (8.4%) | 0 |
| 血小板数減少 | 14 (3.8%) | 2 (0.5%) |
| 体重減少 | 12 (3.2%) | 0 |
| 血中アルカリホスファターゼ増加 | 11 (3.0%) | 2 (0.5%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 10 (2.7%) | 1 (0.3%) |
| 血中ビリルビン増加 | 10 (2.7%) | 2 (0.5%) |
| 好中球数減少 | 9 (2.4%) | 8 (2.2%) |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| アラニンアミノトランスフェラーゼ増加 | 7 (1.9%) | 1 (0.3%) |
| 血中尿酸増加 | 7 (1.9%) | 3 (0.8%) |
| リンパ球数増加 | 6 (1.6%) | 4 (1.1%) |
| 体重増加 | 6 (1.6%) | 0 |
| 活性化部分トロンボプラスチン時間延長 | 5 (1.4%) | 1 (0.3%) |
| 血中乳酸脱水素酵素増加 | 5 (1.4%) | 0 |
| 白血球数減少 | 5 (1.4%) | 5 (1.4%) |
| 血中免疫グロブリンG減少 | 3 (0.8%) | 0 |
| 国際標準比増加 | 3 (0.8%) | 3 (0.8%) |
| 白血球数増加 | 3 (0.8%) | 1 (0.3%) |
| 血中ブドウ糖増加 | 2 (0.5%) | 2 (0.5%) |
| 血中免疫グロブリンM減少 | 2 (0.5%) | 0 |
| 血圧上昇 | 2 (0.5%) | 2 (0.5%) |
| Ｃ－反応性蛋白増加 | 2 (0.5%) | 0 |
| 心雑音 | 2 (0.5%) | 0 |
| γ－グルタミルトランスフェラーゼ増加 | 2 (0.5%) | 0 |
| 糸球体濾過率減少 | 2 (0.5%) | 0 |
| ヘモグロビン減少 | 2 (0.5%) | 2 (0.5%) |
| 免疫グロブリン減少 | 2 (0.5%) | 0 |
| リンパ球数減少 | 2 (0.5%) | 0 |
| トランスアミナーゼ上昇 | 2 (0.5%) | 0 |
| アミラーゼ増加 | 1 (0.3%) | 1 (0.3%) |
| アスペルギルス検査陽性 | 1 (0.3%) | 0 |
| 血中アルブミン減少 | 1 (0.3%) | 1 (0.3%) |
| 血中重炭酸塩増加 | 1 (0.3%) | 0 |
| 血中ビリルビン異常 | 1 (0.3%) | 1 (0.3%) |
| 血中クロール減少 | 1 (0.3%) | 0 |
| 血中コレステロール増加 | 1 (0.3%) | 0 |
| 血中クレアチン増加 | 1 (0.3%) | 0 |
| 血中免疫グロブリンＡ減少 | 1 (0.3%) | 0 |
| 血中鉄減少 | 1 (0.3%) | 0 |
| 血中マグネシウム減少 | 1 (0.3%) | 0 |
| 血中リン減少 | 1 (0.3%) | 0 |
| 血中カリウム減少 | 1 (0.3%) | 0 |
| 呼吸音異常 | 1 (0.3%) | 0 |
| 二酸化炭素減少 | 1 (0.3%) | 0 |
| 胸部コンピュータ断層撮影異常 | 1 (0.3%) | 0 |
| 駆出率減少 | 1 (0.3%) | 0 |
| グリコヘモグロビン増加 | 1 (0.3%) | 0 |
| ヘモフィルス検査陽性 | 1 (0.3%) | 0 |
| 心拍数増加 | 1 (0.3%) | 0 |
| 心拍数不整 | 1 (0.3%) | 0 |
| 肝酵素上昇 | 1 (0.3%) | 1 (0.3%) |
| 深吸気量減少 | 1 (0.3%) | 0 |
| 肝機能検査異常 | 1 (0.3%) | 1 (0.3%) |
| 黄斑部反射異常 | 1 (0.3%) | 0 |
| 平均赤血球容積増加 | 1 (0.3%) | 0 |
| 血小板凝集異常 | 1 (0.3%) | 0 |
| 尿量減少 | 1 (0.3%) | 0 |
| 超低比重リポ蛋白増加 | 1 (0.3%) | 0 |
| 肺活量異常 | 1 (0.3%) | 1 (0.3%) |
| 血中重炭酸塩減少 | 0 | 0 |
| 血中カルシウム減少 | 0 | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 血中フィブリノゲン増加 | 0 | 0 |
| 起立血圧低下 | 0 | 0 |
| 収縮期血圧上昇 | 0 | 0 |
| 血中ナトリウム減少 | 0 | 0 |
| 血中トリグリセリド増加 | 0 | 0 |
| 血中尿素増加 | 0 | 0 |
| ＥＣＯＧパフォーマンスステータス悪化 | 0 | 0 |
| 好酸球数増加 | 0 | 0 |
| 低比重リポ蛋白増加 | 0 | 0 |
| 平均赤血球容積減少 | 0 | 0 |
| 好中球数増加 | 0 | 0 |
| 酸素飽和度低下 | 0 | 0 |
| レスピロウイルス検査陽性 | 0 | 0 |
| 視力検査異常 | 0 | 0 |
| 傷害、中毒および処置合併症 | 101 (27.3%) | 13 (3.5%) |
| 挫傷 | 46 (12.4%) | 0 |
| 転倒 | 17 (4.6%) | 4 (1.1%) |
| 節足動物咬傷 | 6 (1.6%) | 0 |
| 処置による疼痛 | 6 (1.6%) | 0 |
| 硬膜下血腫 | 6 (1.6%) | 3 (0.8%) |
| 外傷性血腫 | 6 (1.6%) | 0 |
| 裂傷 | 4 (1.1%) | 0 |
| 皮膚擦過傷 | 4 (1.1%) | 0 |
| サンバーン | 4 (1.1%) | 0 |
| 創傷 | 4 (1.1%) | 0 |
| 動物咬傷 | 3 (0.8%) | 1 (0.3%) |
| 頭部損傷 | 3 (0.8%) | 0 |
| 靭帯捻挫 | 3 (0.8%) | 0 |
| 腰椎骨折 | 3 (0.8%) | 1 (0.3%) |
| 処置後出血 | 3 (0.8%) | 2 (0.5%) |
| 骨挫傷 | 2 (0.5%) | 0 |
| 擦過傷 | 2 (0.5%) | 0 |
| 顔面骨骨折 | 2 (0.5%) | 0 |
| 四肢損傷 | 2 (0.5%) | 0 |
| 眼窩周囲挫傷 | 2 (0.5%) | 0 |
| 肋骨骨折 | 2 (0.5%) | 0 |
| 皮膚創傷 | 2 (0.5%) | 0 |
| 脊椎圧迫骨折 | 2 (0.5%) | 1 (0.3%) |
| 脾破裂 | 2 (0.5%) | 2 (0.5%) |
| 熱傷 | 2 (0.5%) | 0 |
| 動物による引っかき傷 | 1 (0.3%) | 0 |
| 足関節部骨折 | 1 (0.3%) | 0 |
| 第２度熱傷 | 1 (0.3%) | 0 |
| 眼挫傷 | 1 (0.3%) | 0 |
| 眼外傷 | 1 (0.3%) | 0 |
| 足骨折 | 1 (0.3%) | 0 |
| 眼内異物 | 1 (0.3%) | 0 |
| 外傷性血尿 | 1 (0.3%) | 0 |
| 関節損傷 | 1 (0.3%) | 0 |
| 過量投与 | 1 (0.3%) | 1 (0.3%) |
| 処置後便秘 | 1 (0.3%) | 0 |
| 処置後血尿 | 1 (0.3%) | 0 |
| 処置後腫脹 | 1 (0.3%) | 1 (0.3%) |
| 外傷後疼痛 | 1 (0.3%) | 0 |
| 陰嚢血腫 | 1 (0.3%) | 0 |
| 皮下血腫 | 1 (0.3%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 脛骨骨折 | 1 (0.3%) | 0 |
| 歯牙破折 | 1 (0.3%) | 0 |
| 術後尿閉 | 1 (0.3%) | 0 |
| 創合併症 | 1 (0.3%) | 0 |
| アルコール中毒 | 0 | 0 |
| 背部損傷 | 0 | 0 |
| 腓骨骨折 | 0 | 0 |
| 体内異物 | 0 | 0 |
| 注入に伴う反応 | 0 | 0 |
| 靭帯断裂 | 0 | 0 |
| 四肢外傷性切断 | 0 | 0 |
| 眼窩周囲血腫 | 0 | 0 |
| 橈骨骨折 | 0 | 0 |
| 瘢痕 | 0 | 0 |
| 皮膚損傷 | 0 | 0 |
| 各種物質毒性 | 0 | 0 |
| 輸血反応 | 0 | 0 |
| 眼障害 | 82 (22.2%) | 5 (1.4%) |
| 眼乾燥 | 16 (4.3%) | 0 |
| 流涙増加 | 13 (3.5%) | 0 |
| 霧視 | 13 (3.5%) | 0 |
| 白内障 | 11 (3.0%) | 3 (0.8%) |
| 視力低下 | 6 (1.6%) | 0 |
| 眼窩周囲浮腫 | 5 (1.4%) | 1 (0.3%) |
| 結膜出血 | 3 (0.8%) | 0 |
| 眼痛 | 3 (0.8%) | 0 |
| 眼充血 | 3 (0.8%) | 0 |
| 睫毛乱生 | 3 (0.8%) | 0 |
| 硝子体浮遊物 | 3 (0.8%) | 0 |
| 糖尿病網膜症 | 2 (0.5%) | 1 (0.3%) |
| 複視 | 2 (0.5%) | 0 |
| 眼出血 | 2 (0.5%) | 0 |
| 眼刺激 | 2 (0.5%) | 0 |
| 眼瞼下垂 | 2 (0.5%) | 0 |
| 羞明 | 2 (0.5%) | 0 |
| 眼瞼炎 | 1 (0.3%) | 0 |
| 片側失明 | 1 (0.3%) | 1 (0.3%) |
| 結膜充血 | 1 (0.3%) | 0 |
| 眼瞼内反 | 1 (0.3%) | 0 |
| 眼脂 | 1 (0.3%) | 0 |
| 眼の炎症 | 1 (0.3%) | 0 |
| 眼そう痒症 | 1 (0.3%) | 0 |
| 眼の異物感 | 1 (0.3%) | 0 |
| 緑内障 | 1 (0.3%) | 0 |
| 角膜炎 | 1 (0.3%) | 0 |
| 黄斑変性 | 1 (0.3%) | 0 |
| マイボーム腺機能不全 | 1 (0.3%) | 0 |
| 眼血管障害 | 1 (0.3%) | 0 |
| 開放隅角緑内障 | 1 (0.3%) | 0 |
| 動揺視 | 1 (0.3%) | 0 |
| 老視 | 1 (0.3%) | 0 |
| 網膜剥離 | 1 (0.3%) | 0 |
| 強膜出血 | 1 (0.3%) | 0 |
| 視力障害 | 1 (0.3%) | 0 |
| 硝子体出血 | 1 (0.3%) | 1 (0.3%) |
| 眼球乾燥症 | 1 (0.3%) | 0 |
| 眼瞼紅斑 | 0 | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 眼の障害 | 0 | 0 |
| 眼部腫脹 | 0 | 0 |
| 眼瞼機能障害 | 0 | 0 |
| 眼瞼浮腫 | 0 | 0 |
| 血管障害 | 81 (21.9%) | 26 (7.0%) |
| 高血圧 | 35 (9.5%) | 13 (3.5%) |
| 低血圧 | 21 (5.7%) | 5 (1.4%) |
| 血腫 | 12 (3.2%) | 0 |
| 深部静脈血栓症 | 7 (1.9%) | 2 (0.5%) |
| 潮紅 | 4 (1.1%) | 0 |
| 出血 | 4 (1.1%) | 3 (0.8%) |
| 起立性低血圧 | 3 (0.8%) | 1 (0.3%) |
| 静脈炎 | 3 (0.8%) | 0 |
| 血圧変動 | 2 (0.5%) | 0 |
| リンパ浮腫 | 2 (0.5%) | 2 (0.5%) |
| 表在性血栓性静脈炎 | 2 (0.5%) | 0 |
| 大動脈硬化症 | 1 (0.3%) | 1 (0.3%) |
| 循環虚脱 | 1 (0.3%) | 1 (0.3%) |
| ほてり | 1 (0.3%) | 0 |
| 高血圧クリーゼ | 1 (0.3%) | 0 |
| 末梢血管障害 | 1 (0.3%) | 0 |
| 末梢静脈疾患 | 1 (0.3%) | 0 |
| 静脈瘤 | 1 (0.3%) | 0 |
| 塞栓症 | 0 | 0 |
| 頚静脈血栓症 | 0 | 0 |
| 静脈瘤性潰瘍 | 0 | 0 |
| 心臓障害 | 64 (17.3%) | 26 (7.0%) |
| 心房細動 | 28 (7.6%) | 17 (4.6%) |
| 頻脈 | 9 (2.4%) | 0 |
| 洞性頻脈 | 7 (1.9%) | 0 |
| 徐脈 | 4 (1.1%) | 0 |
| 動悸 | 4 (1.1%) | 0 |
| 心房粗動 | 3 (0.8%) | 1 (0.3%) |
| 洞性徐脈 | 3 (0.8%) | 0 |
| 上室性頻脈 | 3 (0.8%) | 1 (0.3%) |
| 不安定狭心症 | 2 (0.5%) | 1 (0.3%) |
| 心停止 | 2 (0.5%) | 2 (0.5%) |
| 心不全 | 2 (0.5%) | 2 (0.5%) |
| 心室性期外収縮 | 2 (0.5%) | 0 |
| 急性心筋梗塞 | 1 (0.3%) | 1 (0.3%) |
| 不整脈 | 1 (0.3%) | 0 |
| 冠動脈硬化症 | 1 (0.3%) | 0 |
| 第一度房室ブロック | 1 (0.3%) | 0 |
| うっ血性心不全 | 1 (0.3%) | 0 |
| 心血管不全 | 1 (0.3%) | 1 (0.3%) |
| 変時性応答不全 | 1 (0.3%) | 0 |
| 冠動脈疾患 | 1 (0.3%) | 0 |
| 冠動脈閉塞 | 1 (0.3%) | 1 (0.3%) |
| チアノーゼ | 1 (0.3%) | 0 |
| 僧帽弁閉鎖不全症 | 1 (0.3%) | 0 |
| 心筋梗塞 | 1 (0.3%) | 0 |
| 心嚢液貯留 | 1 (0.3%) | 0 |
| 心膜炎 | 1 (0.3%) | 1 (0.3%) |
| 洞不全症候群 | 1 (0.3%) | 0 |
| ストレス心筋症 | 1 (0.3%) | 0 |
| 頻脈性不整脈 | 1 (0.3%) | 0 |
| トルサード　ド　ポアント | 1 (0.3%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 三尖弁疾患 | 1 (0.3%) | 0 |
| 心室性不整脈 | 1 (0.3%) | 0 |
| 心室性頻脈 | 1 (0.3%) | 0 |
| 狭心症 | 0 | 0 |
| 右脚ブロック | 0 | 0 |
| 急性心不全 | 0 | 0 |
| 慢性心不全 | 0 | 0 |
| 心肺不全 | 0 | 0 |
| 冠動脈狭窄 | 0 | 0 |
| 心筋虚血 | 0 | 0 |
| 精神障害 | 63 (17.0%) | 7 (1.9%) |
| 不眠症 | 26 (7.0%) | 0 |
| 不安 | 13 (3.5%) | 0 |
| 錯乱状態 | 12 (3.2%) | 4 (1.1%) |
| うつ病 | 12 (3.2%) | 1 (0.3%) |
| 激越 | 5 (1.4%) | 0 |
| 譫妄 | 1 (0.3%) | 0 |
| 希死念慮を有するうつ病 | 1 (0.3%) | 1 (0.3%) |
| 多幸気分 | 1 (0.3%) | 0 |
| 幻聴 | 1 (0.3%) | 0 |
| 幻視 | 1 (0.3%) | 0 |
| 易刺激性 | 1 (0.3%) | 0 |
| リビドー減退 | 1 (0.3%) | 0 |
| 躁病 | 1 (0.3%) | 0 |
| 精神障害 | 1 (0.3%) | 0 |
| 精神状態変化 | 1 (0.3%) | 1 (0.3%) |
| 悪夢 | 1 (0.3%) | 0 |
| パニック発作 | 1 (0.3%) | 0 |
| パニック障害 | 1 (0.3%) | 0 |
| 感情不安定 | 0 | 0 |
| 広場恐怖症 | 0 | 0 |
| 抑うつ気分 | 0 | 0 |
| 睡眠異常 | 0 | 0 |
| 気分動揺 | 0 | 0 |
| 腎および尿路障害 | 57 (15.4%) | 17 (4.6%) |
| 血尿 | 14 (3.8%) | 3 (0.8%) |
| 急性腎不全 | 12 (3.2%) | 6 (1.6%) |
| 排尿困難 | 8 (2.2%) | 0 |
| 腎不全 | 7 (1.9%) | 5 (1.4%) |
| 頻尿 | 6 (1.6%) | 0 |
| 水腎症 | 3 (0.8%) | 2 (0.5%) |
| 腎機能障害 | 3 (0.8%) | 0 |
| 尿閉 | 3 (0.8%) | 0 |
| 尿路閉塞 | 3 (0.8%) | 1 (0.3%) |
| 腎結石症 | 2 (0.5%) | 1 (0.3%) |
| 夜間頻尿 | 2 (0.5%) | 0 |
| 腎嚢胞 | 2 (0.5%) | 0 |
| 慢性腎不全 | 2 (0.5%) | 0 |
| 尿失禁 | 2 (0.5%) | 0 |
| 高窒素血症 | 1 (0.3%) | 0 |
| 膀胱刺激症状 | 1 (0.3%) | 0 |
| 出血性膀胱炎 | 1 (0.3%) | 1 (0.3%) |
| 緊張性膀胱 | 1 (0.3%) | 0 |
| 失禁 | 1 (0.3%) | 0 |
| 尿意切迫 | 1 (0.3%) | 0 |
| 閉塞性尿路疾患 | 1 (0.3%) | 0 |
| 乏尿 | 1 (0.3%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 腎仙痛 | 1 (0.3%) | 0 |
| 有痛性排尿困難 | 1 (0.3%) | 0 |
| 尿路痛 | 1 (0.3%) | 0 |
| 糖尿 | 0 | 0 |
| 白血球尿 | 0 | 0 |
| 排尿異常 | 0 | 0 |
| 多尿 | 0 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 36 (9.7%) | 19 (5.1%) |
| マントル細胞リンパ腫 | 8 (2.2%) | 8 (2.2%) |
| 基底細胞癌 | 7 (1.9%) | 1 (0.3%) |
| 皮膚有棘細胞癌 | 5 (1.4%) | 0 |
| 膀胱移行上皮癌 | 2 (0.5%) | 1 (0.3%) |
| 前立腺癌 | 2 (0.5%) | 2 (0.5%) |
| 扁平上皮癌 | 2 (0.5%) | 1 (0.3%) |
| 急性骨髄性白血病 | 1 (0.3%) | 0 |
| 良性新生物 | 1 (0.3%) | 0 |
| 膀胱癌 | 1 (0.3%) | 1 (0.3%) |
| 肺腺癌 | 1 (0.3%) | 1 (0.3%) |
| 悪性胸水 | 1 (0.3%) | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 1 (0.3%) | 1 (0.3%) |
| 口腔乳頭腫 | 1 (0.3%) | 0 |
| 唾液腺癌 | 1 (0.3%) | 1 (0.3%) |
| 皮膚癌 | 1 (0.3%) | 1 (0.3%) |
| 皮膚乳頭腫 | 1 (0.3%) | 0 |
| 胸腺腫 | 1 (0.3%) | 1 (0.3%) |
| 移行上皮癌 | 1 (0.3%) | 1 (0.3%) |
| 腫瘍フレア | 1 (0.3%) | 0 |
| 胃腺癌 | 0 | 0 |
| 耳および迷路障害 | 30 (8.1%) | 2 (0.5%) |
| 回転性めまい | 11 (3.0%) | 0 |
| 耳鳴 | 6 (1.6%) | 0 |
| 耳痛 | 5 (1.4%) | 0 |
| 聴力低下 | 4 (1.1%) | 1 (0.3%) |
| 耳垢栓塞 | 2 (0.5%) | 0 |
| 耳不快感 | 2 (0.5%) | 0 |
| 難聴 | 1 (0.3%) | 1 (0.3%) |
| 耳出血 | 1 (0.3%) | 0 |
| 聴覚過敏 | 1 (0.3%) | 0 |
| 老人性難聴 | 1 (0.3%) | 0 |
| 耳部腫脹 | 0 | 0 |
| 聴覚障害 | 0 | 0 |
| 生殖系および乳房障害 | 26 (7.0%) | 7 (1.9%) |
| 良性前立腺肥大症 | 4 (1.1%) | 0 |
| 血精液症 | 4 (1.1%) | 0 |
| 性器浮腫 | 3 (0.8%) | 2 (0.5%) |
| 勃起不全 | 2 (0.5%) | 0 |
| 骨盤痛 | 2 (0.5%) | 1 (0.3%) |
| 腟出血 | 2 (0.5%) | 0 |
| 後天性包茎 | 1 (0.3%) | 0 |
| 乳房血腫 | 1 (0.3%) | 0 |
| 乳房腫瘤 | 1 (0.3%) | 0 |
| 乳房痛 | 1 (0.3%) | 0 |
| 性器発疹 | 1 (0.3%) | 0 |
| 陰茎痛 | 1 (0.3%) | 1 (0.3%) |
| 陰嚢腫瘤 | 1 (0.3%) | 0 |

**TSFAE02PART3OF3: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 陰嚢浮腫 | 1 (0.3%) | 1 (0.3%) |
| 陰嚢痛 | 1 (0.3%) | 0 |
| 子宮腟脱 | 1 (0.3%) | 1 (0.3%) |
| 外陰腟痛 | 1 (0.3%) | 1 (0.3%) |
| 外陰腟そう痒症 | 1 (0.3%) | 0 |
| 性器水疱 | 0 | 0 |
| 前立腺炎 | 0 | 0 |
| 陰嚢紅斑 | 0 | 0 |
| 外陰腟乾燥 | 0 | 0 |
| 免疫系障害 | 19 (5.1%) | 0 |
| 低ｙグロブリン血症 | 5 (1.4%) | 0 |
| 節足動物咬傷アレルギー | 4 (1.1%) | 0 |
| 過敏症 | 3 (0.8%) | 0 |
| 季節性アレルギー | 3 (0.8%) | 0 |
| 薬物過敏症 | 2 (0.5%) | 0 |
| 造影剤アレルギー | 1 (0.3%) | 0 |
| 食物アレルギー | 1 (0.3%) | 0 |
| 肝胆道系障害 | 13 (3.5%) | 4 (1.1%) |
| 高ビリルビン血症 | 6 (1.6%) | 1 (0.3%) |
| 胆石症 | 3 (0.8%) | 1 (0.3%) |
| 胆管結石 | 1 (0.3%) | 1 (0.3%) |
| 胆管炎 | 1 (0.3%) | 1 (0.3%) |
| 肝不全 | 1 (0.3%) | 1 (0.3%) |
| 肝機能異常 | 1 (0.3%) | 0 |
| 中毒性肝炎 | 1 (0.3%) | 1 (0.3%) |
| 陶器様胆嚢 | 1 (0.3%) | 0 |
| 胆汁うっ滞 | 0 | 0 |
| 薬物性肝障害 | 0 | 0 |
| 肝障害 | 0 | 0 |
| 内分泌障害 | 5 (1.4%) | 0 |
| 甲状腺機能低下症 | 5 (1.4%) | 0 |
| 甲状腺機能亢進症 | 0 | 0 |
| 性腺機能低下 | 0 | 0 |
| 先天性、家族性および遺伝性障害 | 1 (0.3%) | 0 |
| 臍血腫 | 1 (0.3%) | 0 |
| 外科および内科処置 | 0 | 0 |
| 抜歯 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE02PART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae02.sas] 15SEP2015, 14:10

参照元：5.3.5.3.1 ISS TSFAE02PART3OF3

表 2.7.4-付録-9 Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study PCYC-1104 by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)

**TSFAE03B: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study PCYC-1104 by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 111 | |
| Subjects with any TEAE | 111 (100%) | 84 (75.7%) |
| System organ class | | |
| Preferred term | | |
| 胃腸障害 | 91 (82.0%) | 13 (11.7%) |
| 下痢 | 55 (49.5%) | 6 (5.4%) |
| 悪心 | 34 (30.6%) | 0 |
| 便秘 | 28 (25.2%) | 0 |
| 嘔吐 | 25 (22.5%) | 0 |
| 腹痛 | 19 (17.1%) | 6 (5.4%) |
| 口内炎 | 13 (11.7%) | 1 (0.9%) |
| 消化不良 | 12 (10.8%) | 0 |
| 感染症および寄生虫症 | 86 (77.5%) | 28 (25.2%) |
| 上気道感染 | 26 (23.4%) | 0 |
| 尿路感染 | 16 (14.4%) | 3 (2.7%) |
| 副鼻腔炎 | 14 (12.6%) | 1 (0.9%) |
| 肺炎 | 13 (11.7%) | 7 (6.3%) |
| 一般・全身障害および投与部位の状態 | 80 (72.1%) | 11 (9.9%) |
| 疲労 | 46 (41.4%) | 5 (4.5%) |
| 末梢性浮腫 | 28 (25.2%) | 2 (1.8%) |
| 発熱 | 20 (18.0%) | 1 (0.9%) |
| 無力症 | 12 (10.8%) | 2 (1.8%) |
| 皮膚および皮下組織障害 | 72 (64.9%) | 4 (3.6%) |
| 発疹 | 18 (16.2%) | 2 (1.8%) |
| 筋骨格系および結合組織障害 | 61 (55.0%) | 5 (4.5%) |
| 筋痙縮 | 16 (14.4%) | 0 |
| 背部痛 | 14 (12.6%) | 1 (0.9%) |
| 筋肉痛 | 14 (12.6%) | 0 |
| 関節痛 | 12 (10.8%) | 0 |
| 四肢痛 | 12 (10.8%) | 0 |
| 呼吸器、胸郭および縦隔障害 | 60 (54.1%) | 9 (8.1%) |
| 呼吸困難 | 30 (27.0%) | 5 (4.5%) |
| 咳嗽 | 20 (18.0%) | 0 |
| 鼻出血 | 12 (10.8%) | 0 |
| 代謝および栄養障害 | 53 (47.7%) | 15 (13.5%) |
| 食欲減退 | 23 (20.7%) | 2 (1.8%) |
| 高尿酸血症 | 15 (13.5%) | 5 (4.5%) |
| 脱水 | 13 (11.7%) | 4 (3.6%) |
| 血液およびリンパ系障害 | 51 (45.9%) | 34 (30.6%) |
| 好中球減少症 | 20 (18.0%) | 18 (16.2%) |
| 血小板減少症 | 20 (18.0%) | 12 (10.8%) |
| 貧血 | 15 (13.5%) | 11 (9.9%) |
| 神経系障害 | 44 (39.6%) | 1 (0.9%) |
| 浮動性めまい | 16 (14.4%) | 0 |
| 頭痛 | 12 (10.8%) | 0 |
| 傷害、中毒および処置合併症 | 34 (30.6%) | 4 (3.6%) |
| 挫傷 | 19 (17.1%) | 0 |

**TSFAE03B: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study PCYC-1104 by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE03B.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae03b.sas] 15SEP2015, 16:34
参照元：5.3.5.3.1 ISS TSFAE03B

表 2.7.4-付録-10 Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study MCL2001 by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)

**TSFAE03C: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study MCL2001 by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL2001 Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 120 | |
| Subjects with any TEAE | 115 (95.8%) | 87 (72.5%) |
| System organ class | | |
| Preferred term | | |
| 一般・全身障害および投与部位の状態 | 85 (70.8%) | 12 (10.0%) |
| 疲労 | 52 (43.3%) | 5 (4.2%) |
| 末梢性浮腫 | 28 (23.3%) | 4 (3.3%) |
| 発熱 | 25 (20.8%) | 1 (0.8%) |
| 胃腸障害 | 84 (70.0%) | 12 (10.0%) |
| 下痢 | 51 (42.5%) | 3 (2.5%) |
| 悪心 | 26 (21.7%) | 1 (0.8%) |
| 嘔吐 | 21 (17.5%) | 1 (0.8%) |
| 便秘 | 17 (14.2%) | 0 |
| 口内炎 | 14 (11.7%) | 2 (1.7%) |
| 腹痛 | 12 (10.0%) | 2 (1.7%) |
| 感染症および寄生虫症 | 80 (66.7%) | 32 (26.7%) |
| 上気道感染 | 21 (17.5%) | 0 |
| 肺炎 | 18 (15.0%) | 15 (12.5%) |
| 副鼻腔炎 | 15 (12.5%) | 0 |
| 尿路感染 | 12 (10.0%) | 2 (1.7%) |
| 呼吸器、胸郭および縦隔障害 | 68 (56.7%) | 10 (8.3%) |
| 咳嗽 | 30 (25.0%) | 0 |
| 呼吸困難 | 23 (19.2%) | 3 (2.5%) |
| 血液およびリンパ系障害 | 63 (52.5%) | 44 (36.7%) |
| 血小板減少症 | 29 (24.2%) | 16 (13.3%) |
| 好中球減少症 | 28 (23.3%) | 25 (20.8%) |
| 貧血 | 23 (19.2%) | 8 (6.7%) |
| 皮膚および皮下組織障害 | 63 (52.5%) | 3 (2.5%) |
| 発疹 | 21 (17.5%) | 1 (0.8%) |
| 筋骨格系および結合組織障害 | 60 (50.0%) | 7 (5.8%) |
| 筋痙縮 | 25 (20.8%) | 0 |
| 関節痛 | 18 (15.0%) | 1 (0.8%) |
| 背部痛 | 14 (11.7%) | 1 (0.8%) |
| 筋肉痛 | 13 (10.8%) | 1 (0.8%) |
| 四肢痛 | 12 (10.0%) | 2 (1.7%) |
| 代謝および栄養障害 | 46 (38.3%) | 15 (12.5%) |
| 食欲減退 | 14 (11.7%) | 0 |
| 低カリウム血症 | 14 (11.7%) | 5 (4.2%) |
| 神経系障害 | 38 (31.7%) | 4 (3.3%) |
| 頭痛 | 12 (10.0%) | 0 |
| 傷害、中毒および処置合併症 | 36 (30.0%) | 2 (1.7%) |
| 挫傷 | 17 (14.2%) | 0 |
| 血管障害 | 32 (26.7%) | 12 (10.0%) |
| 高血圧 | 14 (11.7%) | 5 (4.2%) |
| 心臓障害 | 29 (24.2%) | 9 (7.5%) |
| 心房細動 | 13 (10.8%) | 6 (5.0%) |

**TSFAE03C: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study MCL2001 by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL2001 Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE03C.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae03c.sas] 15SEP2015, 16:34
参照元：5.3.5.3.1 ISS TSFAE03C

表 2.7.4-付録-11 Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study MCL3001 by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)

**TSFAE03D: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study MCL3001 by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 139 | | 139 | |
| Subjects with any TEAE | 138 (99.3%) | 94 (67.6%) | 138 (99.3%) | 121 (87.1%) |
| System organ class | | | | |
| Preferred term | | | | |
| 感染症および寄生虫症 | 97 (69.8%) | 27 (19.4%) | 99 (71.2%) | 42 (30.2%) |
| 上気道感染 | 26 (18.7%) | 3 (2.2%) | 16 (11.5%) | 1 (0.7%) |
| 結膜炎 | 16 (11.5%) | 0 | 7 (5.0%) | 0 |
| 鼻咽頭炎 | 15 (10.8%) | 0 | 16 (11.5%) | 0 |
| 肺炎 | 13 (9.4%) | 11 (7.9%) | 17 (12.2%) | 9 (6.5%) |
| 気道感染 | 8 (5.8%) | 0 | 15 (10.8%) | 3 (2.2%) |
| 口腔ヘルペス | 3 (2.2%) | 0 | 15 (10.8%) | 0 |
| 胃腸障害 | 80 (57.6%) | 14 (10.1%) | 109 (78.4%) | 25 (18.0%) |
| 下痢 | 40 (28.8%) | 4 (2.9%) | 43 (30.9%) | 6 (4.3%) |
| 悪心 | 20 (14.4%) | 0 | 30 (21.6%) | 0 |
| 嘔吐 | 16 (11.5%) | 0 | 10 (7.2%) | 1 (0.7%) |
| 便秘 | 12 (8.6%) | 0 | 21 (15.1%) | 0 |
| 口内炎 | 4 (2.9%) | 0 | 29 (20.9%) | 5 (3.6%) |
| 一般・全身障害および投与部位の状態 | 74 (53.2%) | 15 (10.8%) | 99 (71.2%) | 29 (20.9%) |
| 疲労 | 31 (22.3%) | 6 (4.3%) | 40 (28.8%) | 10 (7.2%) |
| 発熱 | 23 (16.5%) | 1 (0.7%) | 29 (20.9%) | 3 (2.2%) |
| 末梢性浮腫 | 18 (12.9%) | 0 | 31 (22.3%) | 3 (2.2%) |
| 無力症 | 11 (7.9%) | 1 (0.7%) | 27 (19.4%) | 3 (2.2%) |
| 粘膜の炎症 | 2 (1.4%) | 1 (0.7%) | 21 (15.1%) | 6 (4.3%) |
| 呼吸器、胸郭および縦隔障害 | 72 (51.8%) | 16 (11.5%) | 82 (59.0%) | 19 (13.7%) |
| 咳嗽 | 31 (22.3%) | 0 | 31 (22.3%) | 0 |
| 呼吸困難 | 16 (11.5%) | 4 (2.9%) | 17 (12.2%) | 5 (3.6%) |
| 鼻出血 | 12 (8.6%) | 1 (0.7%) | 33 (23.7%) | 2 (1.4%) |
| 皮膚および皮下組織障害 | 59 (42.4%) | 3 (2.2%) | 69 (49.6%) | 5 (3.6%) |
| 発疹 | 18 (12.9%) | 1 (0.7%) | 24 (17.3%) | 0 |
| そう痒症 | 12 (8.6%) | 0 | 18 (12.9%) | 1 (0.7%) |
| 血液およびリンパ系障害 | 55 (39.6%) | 31 (22.3%) | 104 (74.8%) | 80 (57.6%) |
| 貧血 | 25 (18.0%) | 11 (7.9%) | 60 (43.2%) | 28 (20.1%) |
| 血小板減少症 | 25 (18.0%) | 13 (9.4%) | 78 (56.1%) | 59 (42.4%) |
| 好中球減少症 | 22 (15.8%) | 18 (12.9%) | 36 (25.9%) | 23 (16.5%) |
| 臨床検査 | 53 (38.1%) | 17 (12.2%) | 64 (46.0%) | 29 (20.9%) |
| 血中クレアチニン増加 | 14 (10.1%) | 0 | 17 (12.2%) | 0 |
| 血小板数減少 | 12 (8.6%) | 2 (1.4%) | 23 (16.5%) | 19 (13.7%) |
| 体重減少 | 6 (4.3%) | 0 | 18 (12.9%) | 0 |
| 筋骨格系および結合組織障害 | 52 (37.4%) | 8 (5.8%) | 49 (35.3%) | 8 (5.8%) |
| 筋痙縮 | 26 (18.7%) | 0 | 4 (2.9%) | 0 |
| 背部痛 | 16 (11.5%) | 4 (2.9%) | 15 (10.8%) | 1 (0.7%) |
| 代謝および栄養障害 | 51 (36.7%) | 22 (15.8%) | 88 (63.3%) | 46 (33.1%) |
| 食欲減退 | 25 (18.0%) | 1 (0.7%) | 26 (18.7%) | 4 (2.9%) |
| 低カリウム血症 | 11 (7.9%) | 8 (5.8%) | 24 (17.3%) | 12 (8.6%) |
| 高血糖 | 3 (2.2%) | 1 (0.7%) | 26 (18.7%) | 10 (7.2%) |
| 高コレステロール血症 | 1 (0.7%) | 0 | 18 (12.9%) | 3 (2.2%) |
| 高トリグリセリド血症 | 0 | 0 | 25 (18.0%) | 13 (9.4%) |
| 神経系障害 | 39 (28.1%) | 4 (2.9%) | 52 (37.4%) | 10 (7.2%) |
| 頭痛 | 13 (9.4%) | 0 | 17 (12.2%) | 0 |
| 精神障害 | 16 (11.5%) | 2 (1.4%) | 29 (20.9%) | 3 (2.2%) |

**TSFAE03D: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Study MCL3001 by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 不眠症 | 6 (4.3%) | 0 | 15 (10.8%) | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE03D.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae03d.sas] 15SEP2015, 16:34
参照元：5.3.5.3.1 ISS TSFAE03D

表 2.7.4-付録-12 Drug Related Treatment-Emergent Adverse Events; All Treated Population (Study PCI-32765MCL2002)

**TSFAE04: Drug Related Treatment-Emergent Adverse Events; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib |
|---|---|
| Analysis Set: All Treated Population | 16 |
| Total Number of Subjects with Drug Related TEAE | 15 (93.8%) |
| MedDRA System organ class/Preferred term | |
| 胃腸障害 | 8 (50.0%) |
| 下痢 | 5 (31.3%) |
| 口内炎 | 4 (25.0%) |
| 悪心 | 2 (12.5%) |
| 上腹部痛 | 1 (6.3%) |
| 便秘 | 1 (6.3%) |
| 消化不良 | 1 (6.3%) |
| 舌痛 | 1 (6.3%) |
| 口腔内出血 | 1 (6.3%) |
| 臨床検査 | 7 (43.8%) |
| 血小板数減少 | 5 (31.3%) |
| 血中ビリルビン増加 | 2 (12.5%) |
| アラニンアミノトランスフェラーゼ増加 | 1 (6.3%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 1 (6.3%) |
| リンパ球数減少 | 1 (6.3%) |
| リンパ球数増加 | 1 (6.3%) |
| 皮膚および皮下組織障害 | 7 (43.8%) |
| 皮膚乾燥 | 1 (6.3%) |
| 皮下出血 | 1 (6.3%) |
| 爪破損 | 1 (6.3%) |
| 点状出血 | 1 (6.3%) |
| 発疹 | 1 (6.3%) |
| 全身性皮疹 | 1 (6.3%) |
| 斑状丘疹状皮疹 | 1 (6.3%) |
| 皮膚脆弱性 | 1 (6.3%) |
| 血液およびリンパ系障害 | 6 (37.5%) |
| 貧血 | 4 (25.0%) |
| 血小板減少症 | 3 (18.8%) |
| リンパ球増加症 | 2 (12.5%) |
| 白血球増加症 | 1 (6.3%) |
| 好中球減少症 | 1 (6.3%) |
| 一般・全身障害および投与部位の状態 | 6 (37.5%) |
| 疲労 | 3 (18.8%) |
| 倦怠感 | 2 (12.5%) |
| インフルエンザ様疾患 | 1 (6.3%) |
| 感染症および寄生虫症 | 5 (31.3%) |
| 皮膚感染 | 2 (12.5%) |
| 爪囲炎 | 1 (6.3%) |
| 咽頭炎 | 1 (6.3%) |
| 敗血症 | 1 (6.3%) |
| 代謝および栄養障害 | 5 (31.3%) |
| 食欲減退 | 3 (18.8%) |
| 低カリウム血症 | 2 (12.5%) |
| 低ナトリウム血症 | 1 (6.3%) |
| 低リン酸血症 | 1 (6.3%) |
| 傷害、中毒および処置合併症 | 2 (12.5%) |
| 裂傷 | 2 (12.5%) |
| 挫傷 | 1 (6.3%) |
| 筋骨格系および結合組織障害 | 2 (12.5%) |
| 筋痙縮 | 1 (6.3%) |
| 骨炎 | 1 (6.3%) |
| 神経系障害 | 2 (12.5%) |

**TSFAE04: Drug Related Treatment-Emergent Adverse Events; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib |
|---|---|
| 末梢性ニューロパチー | 2 (12.5%) |
| 頭痛 | 1 (6.3%) |
| 腎および尿路障害 | 2 (12.5%) |
| 血尿 | 1 (6.3%) |
| 腎機能障害 | 1 (6.3%) |
| 心臓障害 | 1 (6.3%) |
| 心房細動 | 1 (6.3%) |
| 呼吸器、胸郭および縦隔障害 | 1 (6.3%) |
| 鼻出血 | 1 (6.3%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0
Note: Drug related AE is defined as an event related to study agent (relationship to study agent is possible, probable or very likely).

[TSFAE04.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsfae04.sas] 21AUG2015, 12:30
参照元：5.3.5.2.1 MCL2002 試験 CSR TSFAE04

表 2.7.4-付録-13 Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE04PART1OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 111 | | 120 | |
| Subjects with any drug related TEAE | 98 (88.3%) | 49 (44.1%) | 95 (79.2%) | 52 (43.3%) |
| System organ class | | | | |
| Preferred term | | | | |
| 胃腸障害 | 56 (50.5%) | 7 (6.3%) | 54 (45.0%) | 6 (5.0%) |
| 下痢 | 39 (35.1%) | 5 (4.5%) | 34 (28.3%) | 3 (2.5%) |
| 悪心 | 20 (18.0%) | 0 | 13 (10.8%) | 0 |
| 嘔吐 | 10 (9.0%) | 0 | 6 (5.0%) | 0 |
| 口内炎 | 6 (5.4%) | 1 (0.9%) | 9 (7.5%) | 2 (1.7%) |
| 腹痛 | 6 (5.4%) | 1 (0.9%) | 6 (5.0%) | 0 |
| 便秘 | 10 (9.0%) | 0 | 4 (3.3%) | 0 |
| 消化不良 | 8 (7.2%) | 0 | 2 (1.7%) | 0 |
| 腹部不快感 | 3 (2.7%) | 0 | 0 | 0 |
| 口内乾燥 | 3 (2.7%) | 0 | 3 (2.5%) | 0 |
| 上腹部痛 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 放屁 | 5 (4.5%) | 0 | 0 | 0 |
| 腹部膨満 | 0 | 0 | 1 (0.8%) | 0 |
| 胃食道逆流性疾患 | 1 (0.9%) | 0 | 0 | 0 |
| アフタ性口内炎 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| 心窩部不快感 | 2 (1.8%) | 0 | 0 | 0 |
| 舌痛 | 0 | 0 | 3 (2.5%) | 0 |
| 嚥下障害 | 2 (1.8%) | 0 | 0 | 0 |
| おくび | 0 | 0 | 1 (0.8%) | 0 |
| 排便回数増加 | 1 (0.9%) | 0 | 0 | 0 |
| 胃炎 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 下部消化管出血 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 口腔内痛 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 直腸炎 | 1 (0.9%) | 0 | 0 | 0 |
| 舌潰瘍 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 萎縮性舌炎 | 0 | 0 | 0 | 0 |
| 歯不快感 | 0 | 0 | 1 (0.8%) | 0 |
| 血性下痢 | 0 | 0 | 0 | 0 |
| 十二指腸炎 | 0 | 0 | 0 | 0 |
| 便失禁 | 1 (0.9%) | 0 | 0 | 0 |
| 軟便 | 1 (0.9%) | 0 | 0 | 0 |
| 歯肉出血 | 0 | 0 | 0 | 0 |
| 歯肉浮腫 | 1 (0.9%) | 0 | 0 | 0 |
| 歯肉痛 | 0 | 0 | 1 (0.8%) | 0 |
| 吐血 | 0 | 0 | 0 | 0 |
| イレウス | 0 | 0 | 1 (0.8%) | 0 |
| 過敏性腸症候群 | 1 (0.9%) | 0 | 0 | 0 |
| 口唇潰瘍 | 0 | 0 | 0 | 0 |
| 口腔内潰瘍形成 | 0 | 0 | 1 (0.8%) | 0 |
| 小腸閉塞 | 0 | 0 | 0 | 0 |
| 歯痛 | 0 | 0 | 1 (0.8%) | 0 |
| 裂肛 | 0 | 0 | 0 | 0 |
| 肛門直腸不快感 | 0 | 0 | 0 | 0 |
| 口唇炎 | 0 | 0 | 0 | 0 |
| 大腸炎 | 0 | 0 | 0 | 0 |
| 腸炎 | 0 | 0 | 0 | 0 |
| 出血性胃炎 | 0 | 0 | 0 | 0 |
| 胃腸出血 | 0 | 0 | 0 | 0 |
| 胃腸毒性 | 0 | 0 | 0 | 0 |

**TSFAE04PART1OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 痔核 | 0 | 0 | 0 | 0 |
| 腸出血 | 0 | 0 | 0 | 0 |
| 口唇腫脹 | 0 | 0 | 0 | 0 |
| 食道炎 | 0 | 0 | 0 | 0 |
| 口腔知覚不全 | 0 | 0 | 0 | 0 |
| 口腔粘膜びらん | 0 | 0 | 0 | 0 |
| 口腔粘膜紅斑 | 0 | 0 | 0 | 0 |
| 排便痛 | 0 | 0 | 0 | 0 |
| 感染症および寄生虫症 | 41 (36.9%) | 16 (14.4%) | 33 (27.5%) | 14 (11.7%) |
| 上気道感染 | 13 (11.7%) | 0 | 5 (4.2%) | 0 |
| 肺炎 | 5 (4.5%) | 4 (3.6%) | 7 (5.8%) | 6 (5.0%) |
| 帯状疱疹 | 2 (1.8%) | 0 | 0 | 0 |
| 副鼻腔炎 | 2 (1.8%) | 1 (0.9%) | 5 (4.2%) | 0 |
| 気管支炎 | 5 (4.5%) | 2 (1.8%) | 2 (1.7%) | 1 (0.8%) |
| 結膜炎 | 2 (1.8%) | 0 | 0 | 0 |
| 尿路感染 | 3 (2.7%) | 0 | 4 (3.3%) | 1 (0.8%) |
| 毛包炎 | 2 (1.8%) | 0 | 4 (3.3%) | 0 |
| 下気道感染 | 1 (0.9%) | 0 | 1 (0.8%) | 1 (0.8%) |
| 爪囲炎 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 気道感染 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 敗血症 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 皮膚感染 | 0 | 0 | 2 (1.7%) | 0 |
| 歯肉炎 | 0 | 0 | 2 (1.7%) | 0 |
| 蜂巣炎 | 3 (2.7%) | 2 (1.8%) | 0 | 0 |
| 胃腸炎 | 1 (0.9%) | 0 | 1 (0.8%) | 1 (0.8%) |
| 鼻咽頭炎 | 1 (0.9%) | 0 | 0 | 0 |
| 口腔ヘルペス | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 鼻炎 | 1 (0.9%) | 0 | 0 | 0 |
| 菌血症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| クロストリジウム・ディフィシレ感染 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| ヘルペスウイルス感染 | 1 (0.9%) | 0 | 0 | 0 |
| 感染 | 1 (0.9%) | 0 | 0 | 0 |
| 中耳炎 | 0 | 0 | 1 (0.8%) | 0 |
| ニューモシスチス・イロベチイ肺炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 腹部膿瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 四肢膿瘍 | 0 | 0 | 0 | 0 |
| 肛門膿瘍 | 1 (0.9%) | 0 | 0 | 0 |
| 異型肺炎 | 0 | 0 | 1 (0.8%) | 0 |
| カンジダ性亀頭炎 | 0 | 0 | 0 | 0 |
| 気管支肺炎 | 0 | 0 | 0 | 0 |
| カンピロバクター胃腸炎 | 0 | 0 | 0 | 0 |
| 眼窩蜂巣炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| クロストリジウム・ディフィシレ大腸炎 | 1 (0.9%) | 0 | 0 | 0 |
| 感染性小腸結腸炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 喉頭蓋炎 | 0 | 0 | 0 | 0 |
| 丹毒 | 0 | 0 | 0 | 0 |
| 真菌感染 | 0 | 0 | 1 (0.8%) | 0 |
| インフルエンザ | 0 | 0 | 0 | 0 |
| 口唇感染 | 1 (0.9%) | 0 | 0 | 0 |
| 肺感染 | 0 | 0 | 0 | 0 |
| 水疱性鼓膜炎 | 0 | 0 | 0 | 0 |
| 爪感染 | 0 | 0 | 0 | 0 |
| 眼帯状疱疹 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 口腔真菌感染 | 0 | 0 | 1 (0.8%) | 0 |

**TSFAE04PART1OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 外耳炎 | 0 | 0 | 0 | 0 |
| 咽頭炎 | 0 | 0 | 0 | 0 |
| 細菌性肺炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| クリプトコッカス性肺炎 | 1 (0.9%) | 0 | 0 | 0 |
| クレブシエラ菌性肺炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 肺結核 | 0 | 0 | 0 | 0 |
| 腎盂腎炎 | 0 | 0 | 0 | 0 |
| 膿疱性皮疹 | 1 (0.9%) | 0 | 0 | 0 |
| ブドウ球菌性菌血症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| ブドウ球菌感染 | 1 (0.9%) | 0 | 0 | 0 |
| 皮下組織膿瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 尿路性敗血症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| ウイルス性上気道感染 | 0 | 0 | 0 | 0 |
| 急性扁桃炎 | 0 | 0 | 0 | 0 |
| カンジダ感染 | 0 | 0 | 0 | 0 |
| 膀胱炎 | 0 | 0 | 0 | 0 |
| 医療機器関連感染 | 0 | 0 | 0 | 0 |
| 憩室炎 | 0 | 0 | 0 | 0 |
| 精巣上体炎 | 0 | 0 | 0 | 0 |
| 消化管感染 | 0 | 0 | 0 | 0 |
| 性器カンジダ症 | 0 | 0 | 0 | 0 |
| 単純ヘルペス | 0 | 0 | 0 | 0 |
| 肝膿瘍 | 0 | 0 | 0 | 0 |
| 大葉性肺炎 | 0 | 0 | 0 | 0 |
| リンパ管炎 | 0 | 0 | 0 | 0 |
| 粘膜感染 | 0 | 0 | 0 | 0 |
| 爪真菌症 | 0 | 0 | 0 | 0 |
| 口腔カンジダ症 | 0 | 0 | 0 | 0 |
| ニューモシスチス・イロベチイ感染 | 0 | 0 | 0 | 0 |
| 膿皮症 | 0 | 0 | 0 | 0 |
| 癜風 | 0 | 0 | 0 | 0 |
| 歯膿瘍 | 0 | 0 | 0 | 0 |
| 歯感染 | 0 | 0 | 0 | 0 |
| ウイルス感染 | 0 | 0 | 0 | 0 |
| 血液およびリンパ系障害 | 30 (27.0%) | 24 (21.6%) | 45 (37.5%) | 36 (30.0%) |
| 好中球減少症 | 16 (14.4%) | 15 (13.5%) | 24 (20.0%) | 23 (19.2%) |
| 血小板減少症 | 12 (10.8%) | 7 (6.3%) | 19 (15.8%) | 10 (8.3%) |
| 貧血 | 7 (6.3%) | 5 (4.5%) | 9 (7.5%) | 3 (2.5%) |
| 発熱性好中球減少症 | 3 (2.7%) | 3 (2.7%) | 6 (5.0%) | 6 (5.0%) |
| 白血球減少症 | 4 (3.6%) | 2 (1.8%) | 4 (3.3%) | 2 (1.7%) |
| 白血球増加症 | 1 (0.9%) | 0 | 1 (0.8%) | 1 (0.8%) |
| リンパ球減少症 | 1 (0.9%) | 0 | 0 | 0 |
| リンパ球増加症 | 0 | 0 | 1 (0.8%) | 0 |
| 溶血 | 0 | 0 | 0 | 0 |
| 汎血球減少症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 血小板増加症 | 0 | 0 | 1 (0.8%) | 0 |
| 鉄欠乏性貧血 | 0 | 0 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 38 (34.2%) | 3 (2.7%) | 38 (31.7%) | 3 (2.5%) |
| 疲労 | 27 (24.3%) | 2 (1.8%) | 29 (24.2%) | 3 (2.5%) |
| 発熱 | 8 (7.2%) | 0 | 6 (5.0%) | 0 |
| 無力症 | 4 (3.6%) | 1 (0.9%) | 5 (4.2%) | 0 |
| 末梢性浮腫 | 4 (3.6%) | 0 | 3 (2.5%) | 0 |
| 粘膜の炎症 | 3 (2.7%) | 0 | 0 | 0 |
| 悪寒 | 2 (1.8%) | 0 | 2 (1.7%) | 0 |
| 疼痛 | 0 | 0 | 2 (1.7%) | 0 |

**TSFAE04PART1OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| インフルエンザ様疾患 | 3 (2.7%) | 0 | 0 | 0 |
| 胸痛 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 末梢腫脹 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 乾燥症 | 1 (0.9%) | 0 | 0 | 0 |
| 顔面浮腫 | 0 | 0 | 0 | 0 |
| 冷感 | 0 | 0 | 0 | 0 |
| 熱感 | 0 | 0 | 0 | 0 |
| 歩行障害 | 0 | 0 | 1 (0.8%) | 0 |
| 重力性浮腫 | 0 | 0 | 1 (0.8%) | 0 |
| 治癒不良 | 0 | 0 | 0 | 0 |
| 倦怠感 | 1 (0.9%) | 0 | 0 | 0 |
| 先行疾患の改善 | 0 | 0 | 0 | 0 |
| 全身健康状態低下 | 0 | 0 | 0 | 0 |
| 非心臓性胸痛 | 0 | 0 | 0 | 0 |
| 浮腫 | 0 | 0 | 0 | 0 |
| 活動状態低下 | 0 | 0 | 0 | 0 |
| 皮膚および皮下組織障害 | 35 (31.5%) | 3 (2.7%) | 31 (25.8%) | 2 (1.7%) |
| 発疹 | 12 (10.8%) | 2 (1.8%) | 15 (12.5%) | 0 |
| 点状出血 | 8 (7.2%) | 0 | 3 (2.5%) | 0 |
| そう痒症 | 4 (3.6%) | 0 | 1 (0.8%) | 0 |
| 斑状丘疹状皮疹 | 3 (2.7%) | 0 | 3 (2.5%) | 1 (0.8%) |
| 紫斑 | 3 (2.7%) | 0 | 1 (0.8%) | 1 (0.8%) |
| ざ瘡様皮膚炎 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 皮膚乾燥 | 2 (1.8%) | 0 | 3 (2.5%) | 0 |
| 皮膚病変 | 1 (0.9%) | 0 | 3 (2.5%) | 0 |
| 脱毛症 | 0 | 0 | 2 (1.7%) | 0 |
| 斑状出血 | 0 | 0 | 1 (0.8%) | 0 |
| 爪破損 | 2 (1.8%) | 0 | 0 | 0 |
| ざ瘡 | 0 | 0 | 2 (1.7%) | 0 |
| 湿疹 | 0 | 0 | 0 | 0 |
| 多汗症 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 寝汗 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 全身性そう痒症 | 0 | 0 | 1 (0.8%) | 0 |
| 全身性皮疹 | 0 | 0 | 1 (0.8%) | 0 |
| 斑状皮疹 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 皮膚色素過剰 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 蕁麻疹 | 1 (0.9%) | 0 | 0 | 0 |
| 水疱 | 1 (0.9%) | 0 | 0 | 0 |
| 毛細血管炎 | 0 | 0 | 1 (0.8%) | 0 |
| 褥瘡性潰瘍 | 0 | 0 | 1 (0.8%) | 0 |
| 貨幣状湿疹 | 0 | 0 | 0 | 0 |
| 紅斑 | 0 | 0 | 1 (0.8%) | 0 |
| 爪の不快感 | 0 | 0 | 0 | 0 |
| 爪ジストロフィー | 0 | 0 | 0 | 0 |
| 皮膚疼痛 | 0 | 0 | 1 (0.8%) | 0 |
| 手掌・足底発赤知覚不全症候群 | 0 | 0 | 0 | 0 |
| 紅斑性皮疹 | 1 (0.9%) | 0 | 0 | 0 |
| 毛孔性皮疹 | 0 | 0 | 1 (0.8%) | 0 |
| 丘疹性皮疹 | 0 | 0 | 1 (0.8%) | 0 |
| そう痒性皮疹 | 0 | 0 | 1 (0.8%) | 0 |
| 皮膚亀裂 | 0 | 0 | 0 | 0 |
| 皮膚刺激 | 0 | 0 | 1 (0.8%) | 0 |
| 皮膚腫瘤 | 0 | 0 | 1 (0.8%) | 0 |
| 皮膚潰瘍 | 0 | 0 | 0 | 0 |
| 乾皮症 | 0 | 0 | 0 | 0 |
| 皮膚炎 | 0 | 0 | 0 | 0 |

**TSFAE04PART1OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| アレルギー性皮膚炎 | 0 | 0 | 0 | 0 |
| 水疱性皮膚炎 | 0 | 0 | 0 | 0 |
| 異汗性湿疹 | 0 | 0 | 0 | 0 |
| 皮脂欠乏性湿疹 | 0 | 0 | 0 | 0 |
| 多形紅斑 | 0 | 0 | 0 | 0 |
| 爪の障害 | 0 | 0 | 0 | 0 |
| 痒疹 | 0 | 0 | 0 | 0 |
| 皮膚硬結 | 0 | 0 | 0 | 0 |
| うっ滞性皮膚炎 | 0 | 0 | 0 | 0 |
| 筋骨格系および結合組織障害 | 21 (18.9%) | 0 | 26 (21.7%) | 1 (0.8%) |
| 筋痙縮 | 10 (9.0%) | 0 | 22 (18.3%) | 0 |
| 筋肉痛 | 5 (4.5%) | 0 | 6 (5.0%) | 0 |
| 関節痛 | 1 (0.9%) | 0 | 4 (3.3%) | 1 (0.8%) |
| 四肢痛 | 1 (0.9%) | 0 | 3 (2.5%) | 0 |
| 背部痛 | 2 (1.8%) | 0 | 0 | 0 |
| 側腹部痛 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 筋力低下 | 1 (0.9%) | 0 | 0 | 0 |
| 胤径部痛 | 1 (0.9%) | 0 | 0 | 0 |
| 関節硬直 | 1 (0.9%) | 0 | 0 | 0 |
| 関節腫脹 | 0 | 0 | 1 (0.8%) | 0 |
| 四肢不快感 | 0 | 0 | 0 | 0 |
| 筋攣縮 | 0 | 0 | 1 (0.8%) | 0 |
| 筋骨格痛 | 1 (0.9%) | 0 | 0 | 0 |
| 頚部痛 | 1 (0.9%) | 0 | 0 | 0 |
| 腱痛 | 0 | 0 | 0 | 0 |
| 骨痛 | 0 | 0 | 0 | 0 |
| 筋肉減少症 | 0 | 0 | 0 | 0 |
| 軟部組織障害 | 0 | 0 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 18 (16.2%) | 1 (0.9%) | 19 (15.8%) | 0 |
| 咳嗽 | 6 (5.4%) | 0 | 10 (8.3%) | 0 |
| 呼吸困難 | 8 (7.2%) | 1 (0.9%) | 5 (4.2%) | 0 |
| 鼻出血 | 5 (4.5%) | 0 | 2 (1.7%) | 0 |
| 鼻閉 | 1 (0.9%) | 0 | 0 | 0 |
| 口腔咽頭痛 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 胸水 | 0 | 0 | 1 (0.8%) | 0 |
| 湿性咳嗽 | 0 | 0 | 3 (2.5%) | 0 |
| 気道うっ血 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 上気道うっ血 | 0 | 0 | 2 (1.7%) | 0 |
| 急性肺水腫 | 0 | 0 | 0 | 0 |
| 発声障害 | 1 (0.9%) | 0 | 0 | 0 |
| 喀血 | 0 | 0 | 1 (0.8%) | 0 |
| しゃっくり | 1 (0.9%) | 0 | 0 | 0 |
| 低酸素症 | 0 | 0 | 0 | 0 |
| 肺浸潤 | 1 (0.9%) | 0 | 0 | 0 |
| 鼻潰瘍 | 0 | 0 | 0 | 0 |
| 副鼻腔不快感 | 0 | 0 | 1 (0.8%) | 0 |
| 咽頭紅斑 | 0 | 0 | 1 (0.8%) | 0 |
| 胸膜炎 | 0 | 0 | 0 | 0 |
| 胸膜痛 | 0 | 0 | 0 | 0 |
| 肺塞栓症 | 0 | 0 | 0 | 0 |
| アレルギー性鼻炎 | 1 (0.9%) | 0 | 0 | 0 |
| 鼻漏 | 0 | 0 | 1 (0.8%) | 0 |
| 副鼻腔うっ血 | 1 (0.9%) | 0 | 0 | 0 |
| 間質性肺疾患 | 0 | 0 | 0 | 0 |
| 咽頭潰瘍 | 0 | 0 | 0 | 0 |
| 肺臓炎 | 0 | 0 | 0 | 0 |
| 呼吸不全 | 0 | 0 | 0 | 0 |

**TSFAE04PART1OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 代謝および栄養障害 | 25 (22.5%) | 7 (6.3%) | 15 (12.5%) | 2 (1.7%) |
| 食欲減退 | 13 (11.7%) | 0 | 8 (6.7%) | 0 |
| 高尿酸血症 | 8 (7.2%) | 3 (2.7%) | 0 | 0 |
| 低カリウム血症 | 2 (1.8%) | 0 | 4 (3.3%) | 0 |
| 脱水 | 4 (3.6%) | 1 (0.9%) | 2 (1.7%) | 1 (0.8%) |
| 低ナトリウム血症 | 3 (2.7%) | 3 (2.7%) | 1 (0.8%) | 0 |
| 低マグネシウム血症 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 低アルブミン血症 | 0 | 0 | 3 (2.5%) | 0 |
| 低カルシウム血症 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 痛風 | 1 (0.9%) | 0 | 0 | 0 |
| 高血糖 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 高カリウム血症 | 0 | 0 | 1 (0.8%) | 0 |
| 低血糖症 | 1 (0.9%) | 0 | 0 | 0 |
| 低リン酸血症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 腫瘍崩壊症候群 | 0 | 0 | 0 | 0 |
| 悪液質 | 0 | 0 | 0 | 0 |
| 糖尿病 | 0 | 0 | 0 | 0 |
| 脂質異常症 | 0 | 0 | 0 | 0 |
| 耐糖能障害 | 0 | 0 | 0 | 0 |
| 高コレステロール血症 | 0 | 0 | 0 | 0 |
| 高脂血症 | 0 | 0 | 0 | 0 |
| 高ナトリウム血症 | 0 | 0 | 0 | 0 |
| 高トリグリセリド血症 | 0 | 0 | 0 | 0 |
| 臨床検査 | 14 (12.6%) | 0 | 13 (10.8%) | 8 (6.7%) |
| 血中クレアチニン増加 | 3 (2.7%) | 0 | 4 (3.3%) | 0 |
| 血小板数減少 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 好中球数減少 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| アラニンアミノトランスフェラーゼ増加 | 3 (2.7%) | 0 | 0 | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 3 (2.7%) | 0 | 1 (0.8%) | 0 |
| リンパ球数増加 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 血中アルカリホスファターゼ増加 | 1 (0.9%) | 0 | 2 (1.7%) | 1 (0.8%) |
| 体重減少 | 2 (1.8%) | 0 | 0 | 0 |
| 体重増加 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 白血球数減少 | 0 | 0 | 3 (2.5%) | 3 (2.5%) |
| 活性化部分トロンボプラスチン時間延長 | 0 | 0 | 2 (1.7%) | 0 |
| 血中尿酸増加 | 0 | 0 | 2 (1.7%) | 2 (1.7%) |
| 血中乳酸脱水素酵素増加 | 0 | 0 | 2 (1.7%) | 0 |
| 糸球体濾過率減少 | 2 (1.8%) | 0 | 0 | 0 |
| ヘモグロビン減少 | 0 | 0 | 0 | 0 |
| 免疫グロブリン減少 | 0 | 0 | 0 | 0 |
| リンパ球数減少 | 0 | 0 | 0 | 0 |
| 白血球数増加 | 0 | 0 | 0 | 0 |
| 血中ビリルビン増加 | 0 | 0 | 1 (0.8%) | 0 |
| 血中クレアチン増加 | 0 | 0 | 1 (0.8%) | 0 |
| 血中免疫グロブリンM減少 | 0 | 0 | 0 | 0 |
| Ｃ－反応性蛋白増加 | 1 (0.9%) | 0 | 0 | 0 |
| 胸部コンピュータ断層撮影異常 | 0 | 0 | 1 (0.8%) | 0 |
| 平均赤血球容積増加 | 1 (0.9%) | 0 | 0 | 0 |
| 血小板凝集異常 | 0 | 0 | 0 | 0 |
| トランスアミナーゼ上昇 | 0 | 0 | 0 | 0 |
| 血中アルブミン減少 | 0 | 0 | 0 | 0 |
| 血中重炭酸塩減少 | 0 | 0 | 0 | 0 |

**TSFAE04PART1OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 血中カルシウム減少 | 0 | 0 | 0 | 0 |
| 血中コレステロール増加 | 0 | 0 | 0 | 0 |
| 血中フィブリノゲン増加 | 0 | 0 | 0 | 0 |
| 血中ブドウ糖増加 | 0 | 0 | 0 | 0 |
| 血中免疫グロブリンG減少 | 0 | 0 | 0 | 0 |
| 血中鉄減少 | 0 | 0 | 0 | 0 |
| 血中リン減少 | 0 | 0 | 0 | 0 |
| 血中カリウム減少 | 0 | 0 | 0 | 0 |
| 血中トリグリセリド増加 | 0 | 0 | 0 | 0 |
| 血中尿素増加 | 0 | 0 | 0 | 0 |
| ＥＣＯＧパフォーマンスステータス悪化 | 0 | 0 | 0 | 0 |
| 好酸球数増加 | 0 | 0 | 0 | 0 |
| 国際標準比増加 | 0 | 0 | 0 | 0 |
| 低比重リポ蛋白増加 | 0 | 0 | 0 | 0 |
| 平均赤血球容積減少 | 0 | 0 | 0 | 0 |
| 好中球数増加 | 0 | 0 | 0 | 0 |
| 神経系障害 | 13 (11.7%) | 0 | 14 (11.7%) | 1 (0.8%) |
| 頭痛 | 8 (7.2%) | 0 | 4 (3.3%) | 0 |
| 浮動性めまい | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 錯感覚 | 1 (0.9%) | 0 | 3 (2.5%) | 0 |
| 末梢性感覚ニューロパチー | 4 (3.6%) | 0 | 0 | 0 |
| 味覚異常 | 0 | 0 | 2 (1.7%) | 0 |
| 嗜眠 | 1 (0.9%) | 0 | 0 | 0 |
| 末梢性ニューロパチー | 0 | 0 | 1 (0.8%) | 0 |
| 多発ニューロパチー | 0 | 0 | 0 | 0 |
| 失神 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 振戦 | 0 | 0 | 1 (0.8%) | 0 |
| 平衡障害 | 0 | 0 | 1 (0.8%) | 0 |
| 灼熱足症候群 | 0 | 0 | 0 | 0 |
| 体位性めまい | 0 | 0 | 1 (0.8%) | 0 |
| てんかん | 0 | 0 | 0 | 0 |
| 頭蓋内出血 | 0 | 0 | 1 (0.8%) | 0 |
| 頭部不快感 | 1 (0.9%) | 0 | 0 | 0 |
| 感覚鈍麻 | 0 | 0 | 1 (0.8%) | 0 |
| 片頭痛 | 1 (0.9%) | 0 | 0 | 0 |
| 前兆を伴う片頭痛 | 1 (0.9%) | 0 | 0 | 0 |
| 失神寸前の状態 | 1 (0.9%) | 0 | 0 | 0 |
| 下肢静止不能症候群 | 0 | 0 | 1 (0.8%) | 0 |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 1 (0.8%) | 0 |
| 傾眠 | 0 | 0 | 0 | 0 |
| 失声症 | 0 | 0 | 0 | 0 |
| 認知障害 | 0 | 0 | 0 | 0 |
| 注意力障害 | 0 | 0 | 0 | 0 |
| 過眠症 | 0 | 0 | 0 | 0 |
| 神経痛 | 0 | 0 | 0 | 0 |
| 精神運動亢進 | 0 | 0 | 0 | 0 |
| 眼障害 | 7 (6.3%) | 0 | 6 (5.0%) | 0 |
| 眼乾燥 | 2 (1.8%) | 0 | 3 (2.5%) | 0 |
| 霧視 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 視力低下 | 0 | 0 | 0 | 0 |
| 眼痛 | 0 | 0 | 0 | 0 |
| 眼窩周囲浮腫 | 1 (0.9%) | 0 | 0 | 0 |
| 白内障 | 0 | 0 | 1 (0.8%) | 0 |
| 結膜出血 | 0 | 0 | 0 | 0 |
| 複視 | 0 | 0 | 0 | 0 |
| 眼刺激 | 0 | 0 | 0 | 0 |

**TSFAE04PART1OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 眼そう痒症 | 0 | 0 | 1 (0.8%) | 0 |
| 緑内障 | 0 | 0 | 1 (0.8%) | 0 |
| 流涙増加 | 1 (0.9%) | 0 | 0 | 0 |
| 眼血管障害 | 0 | 0 | 0 | 0 |
| 動揺視 | 0 | 0 | 0 | 0 |
| 羞明 | 1 (0.9%) | 0 | 0 | 0 |
| 睫毛乱生 | 0 | 0 | 0 | 0 |
| 硝子体浮遊物 | 1 (0.9%) | 0 | 0 | 0 |
| 眼部腫脹 | 0 | 0 | 0 | 0 |
| 血管障害 | 5 (4.5%) | 2 (1.8%) | 6 (5.0%) | 3 (2.5%) |
| 高血圧 | 3 (2.7%) | 2 (1.8%) | 2 (1.7%) | 1 (0.8%) |
| 低血圧 | 2 (1.8%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 血腫 | 0 | 0 | 0 | 0 |
| 潮紅 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 血圧変動 | 0 | 0 | 0 | 0 |
| 深部静脈血栓症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 出血 | 0 | 0 | 0 | 0 |
| ほてり | 0 | 0 | 1 (0.8%) | 0 |
| 表在性血栓性静脈炎 | 0 | 0 | 0 | 0 |
| 傷害、中毒および処置合併症 | 6 (5.4%) | 0 | 4 (3.3%) | 0 |
| 挫傷 | 4 (3.6%) | 0 | 4 (3.3%) | 0 |
| 処置後出血 | 0 | 0 | 0 | 0 |
| 硬膜下血腫 | 1 (0.9%) | 0 | 0 | 0 |
| 外傷性血腫 | 0 | 0 | 0 | 0 |
| 転倒 | 1 (0.9%) | 0 | 0 | 0 |
| 関節損傷 | 0 | 0 | 0 | 0 |
| 裂傷 | 1 (0.9%) | 0 | 0 | 0 |
| 靭帯捻挫 | 0 | 0 | 0 | 0 |
| 脾破裂 | 0 | 0 | 0 | 0 |
| 皮下血腫 | 0 | 0 | 0 | 0 |
| 注入に伴う反応 | 0 | 0 | 0 | 0 |
| 皮膚創傷 | 0 | 0 | 0 | 0 |
| 歯牙破折 | 0 | 0 | 0 | 0 |
| 各種物質毒性 | 0 | 0 | 0 | 0 |
| 創傷 | 0 | 0 | 0 | 0 |
| 心臓障害 | 8 (7.2%) | 5 (4.5%) | 6 (5.0%) | 2 (1.7%) |
| 心房細動 | 5 (4.5%) | 4 (3.6%) | 4 (3.3%) | 2 (1.7%) |
| 洞性頻脈 | 2 (1.8%) | 0 | 0 | 0 |
| 急性心筋梗塞 | 0 | 0 | 0 | 0 |
| 心房粗動 | 0 | 0 | 1 (0.8%) | 0 |
| 徐脈 | 0 | 0 | 1 (0.8%) | 0 |
| 心不全 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 動悸 | 0 | 0 | 0 | 0 |
| 心膜炎 | 0 | 0 | 0 | 0 |
| 洞性徐脈 | 0 | 0 | 1 (0.8%) | 0 |
| 頻脈 | 0 | 0 | 1 (0.8%) | 0 |
| トルサード　ド　ポアント | 1 (0.9%) | 0 | 0 | 0 |
| 急性心不全 | 0 | 0 | 0 | 0 |
| 腎および尿路障害 | 9 (8.1%) | 1 (0.9%) | 3 (2.5%) | 0 |
| 血尿 | 3 (2.7%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 頻尿 | 3 (2.7%) | 0 | 1 (0.8%) | 0 |
| 急性腎不全 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 腎不全 | 0 | 0 | 1 (0.8%) | 0 |
| 排尿困難 | 1 (0.9%) | 0 | 0 | 0 |
| 夜間頻尿 | 1 (0.9%) | 0 | 0 | 0 |
| 腎機能障害 | 0 | 0 | 0 | 0 |
| 尿失禁 | 1 (0.9%) | 0 | 0 | 0 |

**TSFAE04PART1OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 尿路痛 | 1 (0.9%) | 0 | 0 | 0 |
| 慢性腎不全 | 0 | 0 | 0 | 0 |
| 尿閉 | 0 | 0 | 0 | 0 |
| 精神障害 | 3 (2.7%) | 0 | 4 (3.3%) | 2 (1.7%) |
| 錯乱状態 | 1 (0.9%) | 0 | 2 (1.7%) | 1 (0.8%) |
| 不眠症 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 不安 | 0 | 0 | 0 | 0 |
| リビドー減退 | 1 (0.9%) | 0 | 0 | 0 |
| 精神状態変化 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 抑うつ気分 | 0 | 0 | 0 | 0 |
| うつ病 | 0 | 0 | 0 | 0 |
| 耳および迷路障害 | 2 (1.8%) | 0 | 2 (1.7%) | 0 |
| 回転性めまい | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 耳痛 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 聴力低下 | 0 | 0 | 0 | 0 |
| 老人性難聴 | 0 | 0 | 0 | 0 |
| 耳部腫脹 | 0 | 0 | 0 | 0 |
| 生殖系および乳房障害 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 勃起不全 | 0 | 0 | 2 (1.7%) | 0 |
| 血精液症 | 1 (0.9%) | 0 | 0 | 0 |
| 乳房腫瘤 | 0 | 0 | 0 | 0 |
| 性器発疹 | 0 | 0 | 0 | 0 |
| 前立腺炎 | 0 | 0 | 0 | 0 |
| 肝胆道系障害 | 2 (1.8%) | 0 | 0 | 0 |
| 高ビリルビン血症 | 1 (0.9%) | 0 | 0 | 0 |
| 肝機能異常 | 1 (0.9%) | 0 | 0 | 0 |
| 中毒性肝炎 | 0 | 0 | 0 | 0 |
| 薬物性肝障害 | 0 | 0 | 0 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 遠隔転移を伴う新生物 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 扁平上皮癌 | 0 | 0 | 0 | 0 |
| 移行上皮癌 | 0 | 0 | 0 | 0 |
| 腫瘍フレア | 0 | 0 | 1 (0.8%) | 0 |
| 免疫系障害 | 0 | 0 | 1 (0.8%) | 0 |
| 低ｙグロブリン血症 | 0 | 0 | 0 | 0 |
| 過敏症 | 0 | 0 | 1 (0.8%) | 0 |
| 内分泌障害 | 0 | 0 | 0 | 0 |
| 甲状腺機能低下症 | 0 | 0 | 0 | 0 |
| 甲状腺機能亢進症 | 0 | 0 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately. An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
Adverse events were coded using MedDRA version 17.1.

[TSFAE04PART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae04.sas] 22OCT2015, 16:07

参照元：5.3.5.3.1 ISS TSFAE04PART1OF3

表 2.7.4-付録-14 Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 139 | | 139 | |
| Subjects with any drug related TEAE | 115 (82.7%) | 55 (39.6%) | 133 (95.7%) | 109 (78.4%) |
| System organ class | | | | |
| Preferred term | | | | |
| 胃腸障害 | 50 (36.0%) | 6 (4.3%) | 78 (56.1%) | 21 (15.1%) |
| 下痢 | 27 (19.4%) | 4 (2.9%) | 28 (20.1%) | 6 (4.3%) |
| 悪心 | 13 (9.4%) | 0 | 19 (13.7%) | 0 |
| 嘔吐 | 6 (4.3%) | 0 | 4 (2.9%) | 0 |
| 口内炎 | 3 (2.2%) | 0 | 23 (16.5%) | 5 (3.6%) |
| 腹痛 | 5 (3.6%) | 0 | 4 (2.9%) | 0 |
| 便秘 | 3 (2.2%) | 0 | 10 (7.2%) | 0 |
| 消化不良 | 6 (4.3%) | 0 | 0 | 0 |
| 腹部不快感 | 4 (2.9%) | 0 | 0 | 0 |
| 口内乾燥 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 上腹部痛 | 3 (2.2%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 放屁 | 0 | 0 | 0 | 0 |
| 腹部膨満 | 3 (2.2%) | 0 | 0 | 0 |
| 胃食道逆流性疾患 | 3 (2.2%) | 0 | 1 (0.7%) | 0 |
| アフタ性口内炎 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 心窩部不快感 | 1 (0.7%) | 0 | 0 | 0 |
| 舌痛 | 0 | 0 | 1 (0.7%) | 0 |
| 嚥下障害 | 0 | 0 | 1 (0.7%) | 0 |
| おくび | 1 (0.7%) | 0 | 0 | 0 |
| 排便回数増加 | 1 (0.7%) | 0 | 0 | 0 |
| 胃炎 | 0 | 0 | 0 | 0 |
| 下部消化管出血 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 口腔内痛 | 0 | 0 | 6 (4.3%) | 3 (2.2%) |
| 直腸炎 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 舌潰瘍 | 0 | 0 | 0 | 0 |
| 萎縮性舌炎 | 1 (0.7%) | 0 | 0 | 0 |
| 歯不快感 | 0 | 0 | 0 | 0 |
| 血性下痢 | 1 (0.7%) | 0 | 0 | 0 |
| 十二指腸炎 | 1 (0.7%) | 0 | 0 | 0 |
| 便失禁 | 0 | 0 | 0 | 0 |
| 軟便 | 0 | 0 | 0 | 0 |
| 歯肉出血 | 1 (0.7%) | 0 | 0 | 0 |
| 歯肉浮腫 | 0 | 0 | 0 | 0 |
| 歯肉痛 | 0 | 0 | 0 | 0 |
| 吐血 | 1 (0.7%) | 0 | 0 | 0 |
| イレウス | 0 | 0 | 0 | 0 |
| 過敏性腸症候群 | 0 | 0 | 0 | 0 |
| 口唇潰瘍 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 口腔内潰瘍形成 | 0 | 0 | 5 (3.6%) | 1 (0.7%) |
| 小腸閉塞 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 歯痛 | 0 | 0 | 0 | 0 |
| 裂肛 | 0 | 0 | 1 (0.7%) | 0 |
| 肛門直腸不快感 | 0 | 0 | 1 (0.7%) | 0 |
| 口唇炎 | 0 | 0 | 1 (0.7%) | 0 |
| 大腸炎 | 0 | 0 | 2 (1.4%) | 0 |
| 腸炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 出血性胃炎 | 0 | 0 | 1 (0.7%) | 0 |
| 胃腸出血 | 0 | 0 | 2 (1.4%) | 2 (1.4%) |

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 胃腸毒性 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 痔核 | 0 | 0 | 3 (2.2%) | 0 |
| 腸出血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 口唇腫脹 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 食道炎 | 0 | 0 | 1 (0.7%) | 0 |
| 口腔知覚不全 | 0 | 0 | 1 (0.7%) | 0 |
| 口腔粘膜びらん | 0 | 0 | 1 (0.7%) | 0 |
| 口腔粘膜紅斑 | 0 | 0 | 1 (0.7%) | 0 |
| 排便痛 | 0 | 0 | 1 (0.7%) | 0 |
| 感染症および寄生虫症 | 46 (33.1%) | 13 (9.4%) | 62 (44.6%) | 26 (18.7%) |
| 上気道感染 | 6 (4.3%) | 1 (0.7%) | 6 (4.3%) | 0 |
| 肺炎 | 9 (6.5%) | 8 (5.8%) | 11 (7.9%) | 6 (4.3%) |
| 帯状疱疹 | 8 (5.8%) | 0 | 5 (3.6%) | 2 (1.4%) |
| 副鼻腔炎 | 3 (2.2%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 気管支炎 | 1 (0.7%) | 0 | 3 (2.2%) | 0 |
| 結膜炎 | 6 (4.3%) | 0 | 4 (2.9%) | 0 |
| 尿路感染 | 1 (0.7%) | 0 | 4 (2.9%) | 1 (0.7%) |
| 毛包炎 | 0 | 0 | 3 (2.2%) | 0 |
| 下気道感染 | 4 (2.9%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| 爪囲炎 | 4 (2.9%) | 0 | 2 (1.4%) | 0 |
| 気道感染 | 4 (2.9%) | 0 | 9 (6.5%) | 1 (0.7%) |
| 敗血症 | 3 (2.2%) | 3 (2.2%) | 4 (2.9%) | 4 (2.9%) |
| 皮膚感染 | 3 (2.2%) | 0 | 1 (0.7%) | 0 |
| 歯肉炎 | 2 (1.4%) | 0 | 2 (1.4%) | 0 |
| 蜂巣炎 | 0 | 0 | 2 (1.4%) | 0 |
| 胃腸炎 | 1 (0.7%) | 0 | 2 (1.4%) | 2 (1.4%) |
| 鼻咽頭炎 | 2 (1.4%) | 0 | 4 (2.9%) | 0 |
| 口腔ヘルペス | 0 | 0 | 6 (4.3%) | 0 |
| 鼻炎 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 菌血症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| クロストリジウム・ディフィシレ感染 | 0 | 0 | 0 | 0 |
| ヘルペスウイルス感染 | 1 (0.7%) | 0 | 0 | 0 |
| 感染 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 中耳炎 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| ニューモシスチス・イロベチイ肺炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 腹部膿瘍 | 0 | 0 | 0 | 0 |
| 四肢膿瘍 | 1 (0.7%) | 0 | 0 | 0 |
| 肛門膿瘍 | 0 | 0 | 0 | 0 |
| 異型肺炎 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| カンジダ性亀頭炎 | 1 (0.7%) | 0 | 0 | 0 |
| 気管支肺炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| カンピロバクター胃腸炎 | 1 (0.7%) | 0 | 0 | 0 |
| 眼窩蜂巣炎 | 0 | 0 | 0 | 0 |
| クロストリジウム・ディフィシレ大腸炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 感染性小腸結腸炎 | 0 | 0 | 0 | 0 |
| 喉頭蓋炎 | 1 (0.7%) | 0 | 0 | 0 |
| 丹毒 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 真菌感染 | 0 | 0 | 0 | 0 |
| インフルエンザ | 1 (0.7%) | 0 | 0 | 0 |
| 口唇感染 | 0 | 0 | 0 | 0 |
| 肺感染 | 1 (0.7%) | 1 (0.7%) | 2 (1.4%) | 2 (1.4%) |
| 水疱性鼓膜炎 | 1 (0.7%) | 0 | 0 | 0 |
| 爪感染 | 1 (0.7%) | 0 | 0 | 0 |

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 眼帯状疱疹 | 0 | 0 | 0 | 0 |
| 口腔真菌感染 | 0 | 0 | 1 (0.7%) | 0 |
| 外耳炎 | 1 (0.7%) | 0 | 0 | 0 |
| 咽頭炎 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 細菌性肺炎 | 0 | 0 | 0 | 0 |
| クリプトコッカス性肺炎 | 0 | 0 | 0 | 0 |
| クレブシエラ菌性肺炎 | 0 | 0 | 0 | 0 |
| 肺結核 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 腎盂腎炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 膿疱性皮疹 | 0 | 0 | 2 (1.4%) | 0 |
| ブドウ球菌性菌血症 | 0 | 0 | 1 (0.7%) | 0 |
| ブドウ球菌感染 | 0 | 0 | 0 | 0 |
| 皮下組織膿瘍 | 0 | 0 | 0 | 0 |
| 尿路性敗血症 | 0 | 0 | 0 | 0 |
| ウイルス性上気道感染 | 1 (0.7%) | 0 | 0 | 0 |
| 急性扁桃炎 | 0 | 0 | 1 (0.7%) | 0 |
| カンジダ感染 | 0 | 0 | 2 (1.4%) | 0 |
| 膀胱炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 医療機器関連感染 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 憩室炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 精巣上体炎 | 0 | 0 | 1 (0.7%) | 0 |
| 消化管感染 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 性器カンジダ症 | 0 | 0 | 1 (0.7%) | 0 |
| 単純ヘルペス | 0 | 0 | 1 (0.7%) | 0 |
| 肝膿瘍 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 大葉性肺炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| リンパ管炎 | 0 | 0 | 1 (0.7%) | 0 |
| 粘膜感染 | 0 | 0 | 1 (0.7%) | 0 |
| 爪真菌症 | 0 | 0 | 1 (0.7%) | 0 |
| 口腔カンジダ症 | 0 | 0 | 5 (3.6%) | 1 (0.7%) |
| ニューモシスチス・イロベチイ感染 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 膿皮症 | 0 | 0 | 1 (0.7%) | 0 |
| 癜風 | 0 | 0 | 1 (0.7%) | 0 |
| 歯膿瘍 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 歯感染 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| ウイルス感染 | 0 | 0 | 2 (1.4%) | 0 |
| 血液およびリンパ系障害 | 43 (30.9%) | 24 (17.3%) | 93 (66.9%) | 70 (50.4%) |
| 好中球減少症 | 18 (12.9%) | 14 (10.1%) | 33 (23.7%) | 20 (14.4%) |
| 血小板減少症 | 20 (14.4%) | 7 (5.0%) | 72 (51.8%) | 53 (38.1%) |
| 貧血 | 15 (10.8%) | 5 (3.6%) | 43 (30.9%) | 18 (12.9%) |
| 発熱性好中球減少症 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| 白血球減少症 | 1 (0.7%) | 0 | 5 (3.6%) | 0 |
| 白血球増加症 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| リンパ球減少症 | 2 (1.4%) | 0 | 4 (2.9%) | 3 (2.2%) |
| リンパ球増加症 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 溶血 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 汎血球減少症 | 0 | 0 | 0 | 0 |
| 血小板増加症 | 0 | 0 | 0 | 0 |
| 鉄欠乏性貧血 | 0 | 0 | 2 (1.4%) | 0 |
| 一般・全身障害および投与部位の状態 | 42 (30.2%) | 7 (5.0%) | 74 (53.2%) | 23 (16.5%) |
| 疲労 | 22 (15.8%) | 4 (2.9%) | 32 (23.0%) | 9 (6.5%) |
| 発熱 | 5 (3.6%) | 0 | 15 (10.8%) | 1 (0.7%) |
| 無力症 | 8 (5.8%) | 1 (0.7%) | 22 (15.8%) | 2 (1.4%) |
| 末梢性浮腫 | 4 (2.9%) | 0 | 11 (7.9%) | 3 (2.2%) |

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 粘膜の炎症 | 2 (1.4%) | 1 (0.7%) | 20 (14.4%) | 6 (4.3%) |
| 悪寒 | 0 | 0 | 2 (1.4%) | 0 |
| 疼痛 | 2 (1.4%) | 0 | 1 (0.7%) | 1 (0.7%) |
| インフルエンザ様疾患 | 0 | 0 | 1 (0.7%) | 0 |
| 胸痛 | 0 | 0 | 2 (1.4%) | 0 |
| 末梢腫脹 | 0 | 0 | 1 (0.7%) | 0 |
| 乾燥症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 顔面浮腫 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 冷感 | 1 (0.7%) | 0 | 0 | 0 |
| 熱感 | 1 (0.7%) | 0 | 0 | 0 |
| 歩行障害 | 0 | 0 | 0 | 0 |
| 重力性浮腫 | 0 | 0 | 0 | 0 |
| 治癒不良 | 1 (0.7%) | 0 | 0 | 0 |
| 倦怠感 | 0 | 0 | 2 (1.4%) | 0 |
| 先行疾患の改善 | 1 (0.7%) | 0 | 0 | 0 |
| 全身健康状態低下 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 非心臓性胸痛 | 0 | 0 | 1 (0.7%) | 0 |
| 浮腫 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 活動状態低下 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 皮膚および皮下組織障害 | 34 (24.5%) | 3 (2.2%) | 58 (41.7%) | 5 (3.6%) |
| 発疹 | 12 (8.6%) | 1 (0.7%) | 20 (14.4%) | 0 |
| 点状出血 | 2 (1.4%) | 0 | 0 | 0 |
| そう痒症 | 7 (5.0%) | 0 | 15 (10.8%) | 1 (0.7%) |
| 斑状丘疹状皮疹 | 3 (2.2%) | 1 (0.7%) | 4 (2.9%) | 1 (0.7%) |
| 紫斑 | 3 (2.2%) | 1 (0.7%) | 0 | 0 |
| ざ瘡様皮膚炎 | 3 (2.2%) | 0 | 3 (2.2%) | 0 |
| 皮膚乾燥 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 皮膚病変 | 1 (0.7%) | 0 | 6 (4.3%) | 1 (0.7%) |
| 脱毛症 | 2 (1.4%) | 0 | 2 (1.4%) | 0 |
| 斑状出血 | 2 (1.4%) | 0 | 0 | 0 |
| 爪破損 | 1 (0.7%) | 0 | 6 (4.3%) | 0 |
| ざ瘡 | 0 | 0 | 5 (3.6%) | 0 |
| 湿疹 | 2 (1.4%) | 0 | 2 (1.4%) | 0 |
| 多汗症 | 0 | 0 | 0 | 0 |
| 寝汗 | 0 | 0 | 0 | 0 |
| 全身性そう痒症 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 全身性皮疹 | 1 (0.7%) | 0 | 6 (4.3%) | 1 (0.7%) |
| 斑状皮疹 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚色素過剰 | 0 | 0 | 0 | 0 |
| 蕁麻疹 | 1 (0.7%) | 0 | 3 (2.2%) | 0 |
| 水疱 | 0 | 0 | 0 | 0 |
| 毛細血管炎 | 0 | 0 | 0 | 0 |
| 褥瘡性潰瘍 | 0 | 0 | 0 | 0 |
| 貨幣状湿疹 | 1 (0.7%) | 0 | 0 | 0 |
| 紅斑 | 0 | 0 | 1 (0.7%) | 0 |
| 爪の不快感 | 1 (0.7%) | 0 | 0 | 0 |
| 爪ジストロフィー | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 皮膚疼痛 | 0 | 0 | 0 | 0 |
| 手掌・足底発赤知覚不全症候群 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 紅斑性皮疹 | 0 | 0 | 0 | 0 |
| 毛孔性皮疹 | 0 | 0 | 1 (0.7%) | 0 |
| 丘疹性皮疹 | 0 | 0 | 1 (0.7%) | 0 |
| そう痒性皮疹 | 0 | 0 | 0 | 0 |
| 皮膚亀裂 | 1 (0.7%) | 0 | 0 | 0 |
| 皮膚刺激 | 0 | 0 | 0 | 0 |

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 皮膚腫瘤 | 0 | 0 | 0 | 0 |
| 皮膚潰瘍 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 乾皮症 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 皮膚炎 | 0 | 0 | 1 (0.7%) | 0 |
| アレルギー性皮膚炎 | 0 | 0 | 1 (0.7%) | 0 |
| 水疱性皮膚炎 | 0 | 0 | 1 (0.7%) | 0 |
| 異汗性湿疹 | 0 | 0 | 1 (0.7%) | 0 |
| 皮脂欠乏性湿疹 | 0 | 0 | 1 (0.7%) | 0 |
| 多形紅斑 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 爪の障害 | 0 | 0 | 5 (3.6%) | 0 |
| 痒疹 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚硬結 | 0 | 0 | 1 (0.7%) | 0 |
| うっ滞性皮膚炎 | 0 | 0 | 1 (0.7%) | 0 |
| 筋骨格系および結合組織障害 | 18 (12.9%) | 0 | 14 (10.1%) | 2 (1.4%) |
| 筋痙縮 | 14 (10.1%) | 0 | 1 (0.7%) | 0 |
| 筋肉痛 | 3 (2.2%) | 0 | 2 (1.4%) | 0 |
| 関節痛 | 4 (2.9%) | 0 | 4 (2.9%) | 1 (0.7%) |
| 四肢痛 | 0 | 0 | 2 (1.4%) | 0 |
| 背部痛 | 0 | 0 | 2 (1.4%) | 0 |
| 側腹部痛 | 0 | 0 | 0 | 0 |
| 筋力低下 | 1 (0.7%) | 0 | 0 | 0 |
| 胤径部痛 | 0 | 0 | 0 | 0 |
| 関節硬直 | 0 | 0 | 0 | 0 |
| 関節腫脹 | 0 | 0 | 1 (0.7%) | 0 |
| 四肢不快感 | 1 (0.7%) | 0 | 0 | 0 |
| 筋攣縮 | 0 | 0 | 0 | 0 |
| 筋骨格痛 | 0 | 0 | 1 (0.7%) | 0 |
| 頚部痛 | 0 | 0 | 0 | 0 |
| 腱痛 | 1 (0.7%) | 0 | 0 | 0 |
| 骨痛 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 筋肉減少症 | 0 | 0 | 1 (0.7%) | 0 |
| 軟部組織障害 | 0 | 0 | 1 (0.7%) | 0 |
| 呼吸器、胸郭および縦隔障害 | 23 (16.5%) | 5 (3.6%) | 46 (33.1%) | 9 (6.5%) |
| 咳嗽 | 7 (5.0%) | 0 | 15 (10.8%) | 0 |
| 呼吸困難 | 4 (2.9%) | 1 (0.7%) | 6 (4.3%) | 2 (1.4%) |
| 鼻出血 | 9 (6.5%) | 0 | 19 (13.7%) | 2 (1.4%) |
| 鼻閉 | 2 (1.4%) | 0 | 0 | 0 |
| 口腔咽頭痛 | 0 | 0 | 2 (1.4%) | 0 |
| 胸水 | 2 (1.4%) | 2 (1.4%) | 0 | 0 |
| 湿性咳嗽 | 0 | 0 | 0 | 0 |
| 気道うっ血 | 0 | 0 | 0 | 0 |
| 上気道うっ血 | 0 | 0 | 0 | 0 |
| 急性肺水腫 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 発声障害 | 0 | 0 | 1 (0.7%) | 0 |
| 喀血 | 0 | 0 | 0 | 0 |
| しゃっくり | 0 | 0 | 0 | 0 |
| 低酸素症 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 肺浸潤 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 鼻潰瘍 | 1 (0.7%) | 0 | 0 | 0 |
| 副鼻腔不快感 | 0 | 0 | 0 | 0 |
| 咽頭紅斑 | 0 | 0 | 0 | 0 |
| 胸膜炎 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 胸膜痛 | 1 (0.7%) | 0 | 0 | 0 |
| 肺塞栓症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| アレルギー性鼻炎 | 0 | 0 | 0 | 0 |
| 鼻漏 | 0 | 0 | 0 | 0 |

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 副鼻腔うっ血 | 0 | 0 | 0 | 0 |
| 間質性肺疾患 | 0 | 0 | 5 (3.6%) | 2 (1.4%) |
| 咽頭潰瘍 | 0 | 0 | 1 (0.7%) | 0 |
| 肺臓炎 | 0 | 0 | 8 (5.8%) | 1 (0.7%) |
| 呼吸不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 代謝および栄養障害 | 16 (11.5%) | 5 (3.6%) | 65 (46.8%) | 36 (25.9%) |
| 食欲減退 | 9 (6.5%) | 0 | 17 (12.2%) | 3 (2.2%) |
| 高尿酸血症 | 3 (2.2%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 低カリウム血症 | 3 (2.2%) | 2 (1.4%) | 13 (9.4%) | 8 (5.8%) |
| 脱水 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 低ナトリウム血症 | 1 (0.7%) | 1 (0.7%) | 3 (2.2%) | 2 (1.4%) |
| 低マグネシウム血症 | 2 (1.4%) | 0 | 3 (2.2%) | 0 |
| 低アルブミン血症 | 0 | 0 | 3 (2.2%) | 0 |
| 低カルシウム血症 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 痛風 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 高血糖 | 0 | 0 | 22 (15.8%) | 9 (6.5%) |
| 高カリウム血症 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 低血糖症 | 0 | 0 | 1 (0.7%) | 0 |
| 低リン酸血症 | 0 | 0 | 2 (1.4%) | 2 (1.4%) |
| 腫瘍崩壊症候群 | 1 (0.7%) | 1 (0.7%) | 3 (2.2%) | 3 (2.2%) |
| 悪液質 | 0 | 0 | 1 (0.7%) | 0 |
| 糖尿病 | 0 | 0 | 5 (3.6%) | 2 (1.4%) |
| 脂質異常症 | 0 | 0 | 1 (0.7%) | 0 |
| 耐糖能障害 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 高コレステロール血症 | 0 | 0 | 12 (8.6%) | 3 (2.2%) |
| 高脂血症 | 0 | 0 | 3 (2.2%) | 1 (0.7%) |
| 高ナトリウム血症 | 0 | 0 | 1 (0.7%) | 0 |
| 高トリグリセリド血症 | 0 | 0 | 17 (12.2%) | 10 (7.2%) |
| 臨床検査 | 28 (20.1%) | 8 (5.8%) | 45 (32.4%) | 20 (14.4%) |
| 血中クレアチニン増加 | 4 (2.9%) | 0 | 7 (5.0%) | 0 |
| 血小板数減少 | 8 (5.8%) | 0 | 20 (14.4%) | 16 (11.5%) |
| 好中球数減少 | 6 (4.3%) | 6 (4.3%) | 10 (7.2%) | 5 (3.6%) |
| アラニンアミノトランスフェラーゼ増加 | 2 (1.4%) | 0 | 7 (5.0%) | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 1 (0.7%) | 0 | 7 (5.0%) | 0 |
| リンパ球数増加 | 4 (2.9%) | 2 (1.4%) | 0 | 0 |
| 血中アルカリホスファターゼ増加 | 1 (0.7%) | 0 | 6 (4.3%) | 1 (0.7%) |
| 体重減少 | 2 (1.4%) | 0 | 13 (9.4%) | 0 |
| 体重増加 | 1 (0.7%) | 0 | 0 | 0 |
| 白血球数減少 | 1 (0.7%) | 1 (0.7%) | 5 (3.6%) | 2 (1.4%) |
| 活性化部分トロンボプラスチン時間延長 | 1 (0.7%) | 0 | 0 | 0 |
| 血中尿酸増加 | 1 (0.7%) | 0 | 0 | 0 |
| 血中乳酸脱水素酵素増加 | 0 | 0 | 4 (2.9%) | 0 |
| 糸球体濾過率減少 | 0 | 0 | 0 | 0 |
| ヘモグロビン減少 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 免疫グロブリン減少 | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| リンパ球数減少 | 2 (1.4%) | 0 | 2 (1.4%) | 1 (0.7%) |
| 白血球数増加 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 血中ビリルビン増加 | 0 | 0 | 0 | 0 |
| 血中クレアチン増加 | 0 | 0 | 0 | 0 |
| 血中免疫グロブリンM減少 | 1 (0.7%) | 0 | 0 | 0 |
| Ｃ－反応性蛋白増加 | 0 | 0 | 2 (1.4%) | 0 |

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 胸部コンピュータ断層撮影異常 | 0 | 0 | 0 | 0 |
| 平均赤血球容積増加 | 0 | 0 | 0 | 0 |
| 血小板凝集異常 | 1 (0.7%) | 0 | 0 | 0 |
| トランスアミナーゼ上昇 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 血中アルブミン減少 | 0 | 0 | 1 (0.7%) | 0 |
| 血中重炭酸塩減少 | 0 | 0 | 1 (0.7%) | 0 |
| 血中カルシウム減少 | 0 | 0 | 2 (1.4%) | 0 |
| 血中コレステロール増加 | 0 | 0 | 4 (2.9%) | 1 (0.7%) |
| 血中フィブリノゲン増加 | 0 | 0 | 2 (1.4%) | 0 |
| 血中ブドウ糖増加 | 0 | 0 | 1 (0.7%) | 0 |
| 血中免疫グロブリンG減少 | 0 | 0 | 1 (0.7%) | 0 |
| 血中鉄減少 | 0 | 0 | 1 (0.7%) | 0 |
| 血中リン減少 | 0 | 0 | 3 (2.2%) | 1 (0.7%) |
| 血中カリウム減少 | 0 | 0 | 2 (1.4%) | 0 |
| 血中トリグリセリド増加 | 0 | 0 | 2 (1.4%) | 0 |
| 血中尿素増加 | 0 | 0 | 1 (0.7%) | 0 |
| ＥＣＯＧパフォーマンスステータス悪化 | 0 | 0 | 1 (0.7%) | 0 |
| 好酸球数増加 | 0 | 0 | 1 (0.7%) | 0 |
| 国際標準比増加 | 0 | 0 | 2 (1.4%) | 0 |
| 低比重リポ蛋白増加 | 0 | 0 | 1 (0.7%) | 0 |
| 平均赤血球容積減少 | 0 | 0 | 1 (0.7%) | 0 |
| 好中球数増加 | 0 | 0 | 1 (0.7%) | 0 |
| 神経系障害 | 15 (10.8%) | 2 (1.4%) | 28 (20.1%) | 5 (3.6%) |
| 頭痛 | 6 (4.3%) | 0 | 6 (4.3%) | 0 |
| 浮動性めまい | 3 (2.2%) | 0 | 2 (1.4%) | 0 |
| 錯感覚 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 末梢性感覚ニューロパチー | 1 (0.7%) | 0 | 3 (2.2%) | 1 (0.7%) |
| 味覚異常 | 1 (0.7%) | 0 | 7 (5.0%) | 0 |
| 嗜眠 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 末梢性ニューロパチー | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 多発ニューロパチー | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 失神 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 振戦 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 平衡障害 | 0 | 0 | 0 | 0 |
| 灼熱足症候群 | 1 (0.7%) | 0 | 0 | 0 |
| 体位性めまい | 0 | 0 | 0 | 0 |
| てんかん | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 頭蓋内出血 | 0 | 0 | 0 | 0 |
| 頭部不快感 | 0 | 0 | 0 | 0 |
| 感覚鈍麻 | 0 | 0 | 0 | 0 |
| 片頭痛 | 0 | 0 | 0 | 0 |
| 前兆を伴う片頭痛 | 0 | 0 | 0 | 0 |
| 失神寸前の状態 | 0 | 0 | 0 | 0 |
| 下肢静止不能症候群 | 0 | 0 | 0 | 0 |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 0 | 0 |
| 傾眠 | 1 (0.7%) | 0 | 0 | 0 |
| 失声症 | 0 | 0 | 1 (0.7%) | 0 |
| 認知障害 | 0 | 0 | 1 (0.7%) | 0 |
| 注意力障害 | 0 | 0 | 1 (0.7%) | 0 |
| 過眠症 | 0 | 0 | 1 (0.7%) | 0 |
| 神経痛 | 0 | 0 | 3 (2.2%) | 1 (0.7%) |
| 精神運動亢進 | 0 | 0 | 1 (0.7%) | 0 |
| 眼障害 | 15 (10.8%) | 1 (0.7%) | 11 (7.9%) | 3 (2.2%) |
| 眼乾燥 | 4 (2.9%) | 0 | 1 (0.7%) | 0 |

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 霧視 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 視力低下 | 3 (2.2%) | 0 | 1 (0.7%) | 0 |
| 眼痛 | 2 (1.4%) | 0 | 0 | 0 |
| 眼窩周囲浮腫 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 白内障 | 0 | 0 | 3 (2.2%) | 3 (2.2%) |
| 結膜出血 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 複視 | 1 (0.7%) | 0 | 0 | 0 |
| 眼刺激 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 眼そう痒症 | 0 | 0 | 3 (2.2%) | 0 |
| 緑内障 | 0 | 0 | 0 | 0 |
| 流涙増加 | 0 | 0 | 0 | 0 |
| 眼血管障害 | 1 (0.7%) | 0 | 0 | 0 |
| 動揺視 | 1 (0.7%) | 0 | 0 | 0 |
| 羞明 | 0 | 0 | 0 | 0 |
| 睫毛乱生 | 1 (0.7%) | 0 | 0 | 0 |
| 硝子体浮遊物 | 0 | 0 | 0 | 0 |
| 眼部腫脹 | 0 | 0 | 1 (0.7%) | 0 |
| 血管障害 | 11 (7.9%) | 1 (0.7%) | 5 (3.6%) | 2 (1.4%) |
| 高血圧 | 2 (1.4%) | 0 | 2 (1.4%) | 1 (0.7%) |
| 低血圧 | 2 (1.4%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 血腫 | 4 (2.9%) | 0 | 0 | 0 |
| 潮紅 | 0 | 0 | 0 | 0 |
| 血圧変動 | 1 (0.7%) | 0 | 0 | 0 |
| 深部静脈血栓症 | 0 | 0 | 1 (0.7%) | 0 |
| 出血 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| ほてり | 0 | 0 | 1 (0.7%) | 0 |
| 表在性血栓性静脈炎 | 1 (0.7%) | 0 | 0 | 0 |
| 傷害、中毒および処置合併症 | 11 (7.9%) | 3 (2.2%) | 5 (3.6%) | 2 (1.4%) |
| 挫傷 | 4 (2.9%) | 0 | 0 | 0 |
| 処置後出血 | 2 (1.4%) | 2 (1.4%) | 0 | 0 |
| 硬膜下血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 外傷性血腫 | 2 (1.4%) | 0 | 0 | 0 |
| 転倒 | 0 | 0 | 0 | 0 |
| 関節損傷 | 1 (0.7%) | 0 | 0 | 0 |
| 裂傷 | 0 | 0 | 0 | 0 |
| 靭帯捻挫 | 1 (0.7%) | 0 | 0 | 0 |
| 脾破裂 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 皮下血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 注入に伴う反応 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚創傷 | 0 | 0 | 1 (0.7%) | 0 |
| 歯牙破折 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 各種物質毒性 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 創傷 | 0 | 0 | 1 (0.7%) | 0 |
| 心臓障害 | 5 (3.6%) | 5 (3.6%) | 4 (2.9%) | 1 (0.7%) |
| 心房細動 | 4 (2.9%) | 4 (2.9%) | 1 (0.7%) | 0 |
| 洞性頻脈 | 1 (0.7%) | 0 | 0 | 0 |
| 急性心筋梗塞 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 心房粗動 | 0 | 0 | 0 | 0 |
| 徐脈 | 0 | 0 | 0 | 0 |
| 心不全 | 0 | 0 | 0 | 0 |
| 動悸 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 心膜炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 洞性徐脈 | 0 | 0 | 0 | 0 |
| 頻脈 | 0 | 0 | 1 (0.7%) | 0 |
| トルサード　ド　ポアント | 0 | 0 | 0 | 0 |
| 急性心不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 腎および尿路障害 | 3 (2.2%) | 2 (1.4%) | 6 (4.3%) | 3 (2.2%) |
| 血尿 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 頻尿 | 0 | 0 | 1 (0.7%) | 0 |
| 急性腎不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 腎不全 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 排尿困難 | 0 | 0 | 0 | 0 |
| 夜間頻尿 | 0 | 0 | 0 | 0 |
| 腎機能障害 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 尿失禁 | 0 | 0 | 0 | 0 |
| 尿路痛 | 0 | 0 | 0 | 0 |
| 慢性腎不全 | 0 | 0 | 1 (0.7%) | 0 |
| 尿閉 | 0 | 0 | 1 (0.7%) | 0 |
| 精神障害 | 3 (2.2%) | 1 (0.7%) | 6 (4.3%) | 2 (1.4%) |
| 錯乱状態 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 不眠症 | 1 (0.7%) | 0 | 3 (2.2%) | 0 |
| 不安 | 1 (0.7%) | 0 | 0 | 0 |
| リビドー減退 | 0 | 0 | 0 | 0 |
| 精神状態変化 | 0 | 0 | 0 | 0 |
| 抑うつ気分 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| うつ病 | 0 | 0 | 1 (0.7%) | 0 |
| 耳および迷路障害 | 3 (2.2%) | 0 | 4 (2.9%) | 0 |
| 回転性めまい | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| 耳痛 | 0 | 0 | 1 (0.7%) | 0 |
| 聴力低下 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 老人性難聴 | 1 (0.7%) | 0 | 0 | 0 |
| 耳部腫脹 | 0 | 0 | 1 (0.7%) | 0 |
| 生殖系および乳房障害 | 3 (2.2%) | 0 | 1 (0.7%) | 0 |
| 勃起不全 | 0 | 0 | 0 | 0 |
| 血精液症 | 1 (0.7%) | 0 | 0 | 0 |
| 乳房腫瘤 | 1 (0.7%) | 0 | 0 | 0 |
| 性器発疹 | 1 (0.7%) | 0 | 0 | 0 |
| 前立腺炎 | 0 | 0 | 1 (0.7%) | 0 |
| 肝胆道系障害 | 3 (2.2%) | 1 (0.7%) | 2 (1.4%) | 0 |
| 高ビリルビン血症 | 2 (1.4%) | 0 | 0 | 0 |
| 肝機能異常 | 0 | 0 | 0 | 0 |
| 中毒性肝炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 薬物性肝障害 | 0 | 0 | 1 (0.7%) | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 2 (1.4%) | 2 (1.4%) | 0 | 0 |
| 遠隔転移を伴う新生物 | 0 | 0 | 0 | 0 |
| 扁平上皮癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 移行上皮癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 腫瘍フレア | 0 | 0 | 0 | 0 |
| 免疫系障害 | 2 (1.4%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 低γグロブリン血症 | 2 (1.4%) | 0 | 0 | 0 |
| 過敏症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 内分泌障害 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 甲状腺機能低下症 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 甲状腺機能亢進症 | 0 | 0 | 1 (0.7%) | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately. An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
Adverse events were coded using MedDRA version 17.1.

**TSFAE04PART2OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |

[TSFAE04PART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae04.sas] 22OCT2015, 16:07

参照元：5.3.5.3.1 ISS TSFAE04PART2OF3

表 2.7.4-付録-15 Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)

**TSFAE04PART3OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 370 | |
| Subjects with any drug related TEAE | 308 (83.2%) | 156 (42.2%) |
| System organ class | | |
| Preferred term | | |
| 胃腸障害 | 160 (43.2%) | 19 (5.1%) |
| 下痢 | 100 (27.0%) | 12 (3.2%) |
| 悪心 | 46 (12.4%) | 0 |
| 嘔吐 | 22 (5.9%) | 0 |
| 口内炎 | 18 (4.9%) | 3 (0.8%) |
| 腹痛 | 17 (4.6%) | 1 (0.3%) |
| 便秘 | 17 (4.6%) | 0 |
| 消化不良 | 16 (4.3%) | 0 |
| 腹部不快感 | 7 (1.9%) | 0 |
| 口内乾燥 | 7 (1.9%) | 0 |
| 上腹部痛 | 6 (1.6%) | 1 (0.3%) |
| 放屁 | 5 (1.4%) | 0 |
| 腹部膨満 | 4 (1.1%) | 0 |
| 胃食道逆流性疾患 | 4 (1.1%) | 0 |
| アフタ性口内炎 | 3 (0.8%) | 1 (0.3%) |
| 心窩部不快感 | 3 (0.8%) | 0 |
| 舌痛 | 3 (0.8%) | 0 |
| 嚥下障害 | 2 (0.5%) | 0 |
| おくび | 2 (0.5%) | 0 |
| 排便回数増加 | 2 (0.5%) | 0 |
| 胃炎 | 2 (0.5%) | 0 |
| 下部消化管出血 | 2 (0.5%) | 1 (0.3%) |
| 口腔内痛 | 2 (0.5%) | 0 |
| 直腸炎 | 2 (0.5%) | 0 |
| 舌潰瘍 | 2 (0.5%) | 0 |
| 萎縮性舌炎 | 1 (0.3%) | 0 |
| 歯不快感 | 1 (0.3%) | 0 |
| 血性下痢 | 1 (0.3%) | 0 |
| 十二指腸炎 | 1 (0.3%) | 0 |
| 便失禁 | 1 (0.3%) | 0 |
| 軟便 | 1 (0.3%) | 0 |
| 歯肉出血 | 1 (0.3%) | 0 |
| 歯肉浮腫 | 1 (0.3%) | 0 |
| 歯肉痛 | 1 (0.3%) | 0 |
| 吐血 | 1 (0.3%) | 0 |
| イレウス | 1 (0.3%) | 0 |
| 過敏性腸症候群 | 1 (0.3%) | 0 |
| 口唇潰瘍 | 1 (0.3%) | 0 |
| 口腔内潰瘍形成 | 1 (0.3%) | 0 |
| 小腸閉塞 | 1 (0.3%) | 1 (0.3%) |
| 歯痛 | 1 (0.3%) | 0 |
| 裂肛 | 0 | 0 |
| 肛門直腸不快感 | 0 | 0 |
| 口唇炎 | 0 | 0 |
| 大腸炎 | 0 | 0 |
| 腸炎 | 0 | 0 |
| 出血性胃炎 | 0 | 0 |
| 胃腸出血 | 0 | 0 |
| 胃腸毒性 | 0 | 0 |
| 痔核 | 0 | 0 |

**TSFAE04PART3OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 腸出血 | 0 | 0 |
| 口唇腫脹 | 0 | 0 |
| 食道炎 | 0 | 0 |
| 口腔知覚不全 | 0 | 0 |
| 口腔粘膜びらん | 0 | 0 |
| 口腔粘膜紅斑 | 0 | 0 |
| 排便痛 | 0 | 0 |
| 感染症および寄生虫症 | 120 (32.4%) | 43 (11.6%) |
| 上気道感染 | 24 (6.5%) | 1 (0.3%) |
| 肺炎 | 21 (5.7%) | 18 (4.9%) |
| 帯状疱疹 | 10 (2.7%) | 0 |
| 副鼻腔炎 | 10 (2.7%) | 1 (0.3%) |
| 気管支炎 | 8 (2.2%) | 3 (0.8%) |
| 結膜炎 | 8 (2.2%) | 0 |
| 尿路感染 | 8 (2.2%) | 1 (0.3%) |
| 毛包炎 | 6 (1.6%) | 0 |
| 下気道感染 | 6 (1.6%) | 3 (0.8%) |
| 爪囲炎 | 6 (1.6%) | 0 |
| 気道感染 | 6 (1.6%) | 1 (0.3%) |
| 敗血症 | 5 (1.4%) | 5 (1.4%) |
| 皮膚感染 | 5 (1.4%) | 0 |
| 歯肉炎 | 4 (1.1%) | 0 |
| 蜂巣炎 | 3 (0.8%) | 2 (0.5%) |
| 胃腸炎 | 3 (0.8%) | 1 (0.3%) |
| 鼻咽頭炎 | 3 (0.8%) | 0 |
| 口腔ヘルペス | 3 (0.8%) | 0 |
| 鼻炎 | 3 (0.8%) | 0 |
| 菌血症 | 2 (0.5%) | 2 (0.5%) |
| クロストリジウム・ディフィシレ感染 | 2 (0.5%) | 0 |
| ヘルペスウイルス感染 | 2 (0.5%) | 0 |
| 感染 | 2 (0.5%) | 0 |
| 中耳炎 | 2 (0.5%) | 0 |
| ニューモシスチス・イロベチイ肺炎 | 2 (0.5%) | 2 (0.5%) |
| 腹部膿瘍 | 1 (0.3%) | 1 (0.3%) |
| 四肢膿瘍 | 1 (0.3%) | 0 |
| 肛門膿瘍 | 1 (0.3%) | 0 |
| 異型肺炎 | 1 (0.3%) | 0 |
| カンジダ性亀頭炎 | 1 (0.3%) | 0 |
| 気管支肺炎 | 1 (0.3%) | 1 (0.3%) |
| カンピロバクター胃腸炎 | 1 (0.3%) | 0 |
| 眼窩蜂巣炎 | 1 (0.3%) | 1 (0.3%) |
| クロストリジウム・ディフィシレ大腸炎 | 1 (0.3%) | 0 |
| 感染性小腸結腸炎 | 1 (0.3%) | 1 (0.3%) |
| 喉頭蓋炎 | 1 (0.3%) | 0 |
| 丹毒 | 1 (0.3%) | 0 |
| 真菌感染 | 1 (0.3%) | 0 |
| インフルエンザ | 1 (0.3%) | 0 |
| 口唇感染 | 1 (0.3%) | 0 |
| 肺感染 | 1 (0.3%) | 1 (0.3%) |
| 水疱性鼓膜炎 | 1 (0.3%) | 0 |
| 爪感染 | 1 (0.3%) | 0 |
| 眼帯状疱疹 | 1 (0.3%) | 1 (0.3%) |
| 口腔真菌感染 | 1 (0.3%) | 0 |
| 外耳炎 | 1 (0.3%) | 0 |

**TSFAE04PART3OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 咽頭炎 | 1 (0.3%) | 0 |
| 細菌性肺炎 | 1 (0.3%) | 1 (0.3%) |
| クリプトコッカス性肺炎 | 1 (0.3%) | 0 |
| クレブシエラ菌性肺炎 | 1 (0.3%) | 1 (0.3%) |
| 肺結核 | 1 (0.3%) | 1 (0.3%) |
| 腎盂腎炎 | 1 (0.3%) | 1 (0.3%) |
| 膿疱性皮疹 | 1 (0.3%) | 0 |
| ブドウ球菌性菌血症 | 1 (0.3%) | 1 (0.3%) |
| ブドウ球菌感染 | 1 (0.3%) | 0 |
| 皮下組織膿瘍 | 1 (0.3%) | 1 (0.3%) |
| 尿路性敗血症 | 1 (0.3%) | 1 (0.3%) |
| ウイルス性上気道感染 | 1 (0.3%) | 0 |
| 急性扁桃炎 | 0 | 0 |
| カンジダ感染 | 0 | 0 |
| 膀胱炎 | 0 | 0 |
| 医療機器関連感染 | 0 | 0 |
| 憩室炎 | 0 | 0 |
| 精巣上体炎 | 0 | 0 |
| 消化管感染 | 0 | 0 |
| 性器カンジダ症 | 0 | 0 |
| 単純ヘルペス | 0 | 0 |
| 肝膿瘍 | 0 | 0 |
| 大葉性肺炎 | 0 | 0 |
| リンパ管炎 | 0 | 0 |
| 粘膜感染 | 0 | 0 |
| 爪真菌症 | 0 | 0 |
| 口腔カンジダ症 | 0 | 0 |
| ニューモシスチス・イロベチイ感染 | 0 | 0 |
| 膿皮症 | 0 | 0 |
| 癜風 | 0 | 0 |
| 歯膿瘍 | 0 | 0 |
| 歯感染 | 0 | 0 |
| ウイルス感染 | 0 | 0 |
| 血液およびリンパ系障害 | 118 (31.9%) | 84 (22.7%) |
| 好中球減少症 | 58 (15.7%) | 52 (14.1%) |
| 血小板減少症 | 51 (13.8%) | 24 (6.5%) |
| 貧血 | 31 (8.4%) | 13 (3.5%) |
| 発熱性好中球減少症 | 11 (3.0%) | 11 (3.0%) |
| 白血球減少症 | 9 (2.4%) | 4 (1.1%) |
| 白血球増加症 | 4 (1.1%) | 2 (0.5%) |
| リンパ球減少症 | 3 (0.8%) | 0 |
| リンパ球増加症 | 2 (0.5%) | 1 (0.3%) |
| 溶血 | 1 (0.3%) | 1 (0.3%) |
| 汎血球減少症 | 1 (0.3%) | 1 (0.3%) |
| 血小板増加症 | 1 (0.3%) | 0 |
| 鉄欠乏性貧血 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 118 (31.9%) | 13 (3.5%) |
| 疲労 | 78 (21.1%) | 9 (2.4%) |
| 発熱 | 19 (5.1%) | 0 |
| 無力症 | 17 (4.6%) | 2 (0.5%) |
| 末梢性浮腫 | 11 (3.0%) | 0 |
| 粘膜の炎症 | 5 (1.4%) | 1 (0.3%) |
| 悪寒 | 4 (1.1%) | 0 |
| 疼痛 | 4 (1.1%) | 0 |
| インフルエンザ様疾患 | 3 (0.8%) | 0 |

**TSFAE04PART3OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 胸痛 | 2 (0.5%) | 0 |
| 末梢腫脹 | 2 (0.5%) | 0 |
| 乾燥症 | 2 (0.5%) | 1 (0.3%) |
| 顔面浮腫 | 1 (0.3%) | 0 |
| 冷感 | 1 (0.3%) | 0 |
| 熱感 | 1 (0.3%) | 0 |
| 歩行障害 | 1 (0.3%) | 0 |
| 重力性浮腫 | 1 (0.3%) | 0 |
| 治癒不良 | 1 (0.3%) | 0 |
| 倦怠感 | 1 (0.3%) | 0 |
| 先行疾患の改善 | 1 (0.3%) | 0 |
| 全身健康状態低下 | 0 | 0 |
| 非心臓性胸痛 | 0 | 0 |
| 浮腫 | 0 | 0 |
| 活動状態低下 | 0 | 0 |
| 皮膚および皮下組織障害 | 100 (27.0%) | 8 (2.2%) |
| 発疹 | 39 (10.5%) | 3 (0.8%) |
| 点状出血 | 13 (3.5%) | 0 |
| そう痒症 | 12 (3.2%) | 0 |
| 斑状丘疹状皮疹 | 9 (2.4%) | 2 (0.5%) |
| 紫斑 | 7 (1.9%) | 2 (0.5%) |
| ざ瘡様皮膚炎 | 6 (1.6%) | 0 |
| 皮膚乾燥 | 6 (1.6%) | 0 |
| 皮膚病変 | 5 (1.4%) | 0 |
| 脱毛症 | 4 (1.1%) | 0 |
| 斑状出血 | 3 (0.8%) | 0 |
| 爪破損 | 3 (0.8%) | 0 |
| ざ瘡 | 2 (0.5%) | 0 |
| 湿疹 | 2 (0.5%) | 0 |
| 多汗症 | 2 (0.5%) | 0 |
| 寝汗 | 2 (0.5%) | 0 |
| 全身性そう痒症 | 2 (0.5%) | 0 |
| 全身性皮疹 | 2 (0.5%) | 0 |
| 斑状皮疹 | 2 (0.5%) | 1 (0.3%) |
| 皮膚色素過剰 | 2 (0.5%) | 0 |
| 蕁麻疹 | 2 (0.5%) | 0 |
| 水疱 | 1 (0.3%) | 0 |
| 毛細血管炎 | 1 (0.3%) | 0 |
| 褥瘡性潰瘍 | 1 (0.3%) | 0 |
| 貨幣状湿疹 | 1 (0.3%) | 0 |
| 紅斑 | 1 (0.3%) | 0 |
| 爪の不快感 | 1 (0.3%) | 0 |
| 爪ジストロフィー | 1 (0.3%) | 0 |
| 皮膚疼痛 | 1 (0.3%) | 0 |
| 手掌・足底発赤知覚不全症候群 | 1 (0.3%) | 0 |
| 紅斑性皮疹 | 1 (0.3%) | 0 |
| 毛孔性皮疹 | 1 (0.3%) | 0 |
| 丘疹性皮疹 | 1 (0.3%) | 0 |
| そう痒性皮疹 | 1 (0.3%) | 0 |
| 皮膚亀裂 | 1 (0.3%) | 0 |
| 皮膚刺激 | 1 (0.3%) | 0 |
| 皮膚腫瘤 | 1 (0.3%) | 0 |
| 皮膚潰瘍 | 1 (0.3%) | 0 |
| 乾皮症 | 1 (0.3%) | 0 |
| 皮膚炎 | 0 | 0 |
| アレルギー性皮膚炎 | 0 | 0 |

**TSFAE04PART3OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 水疱性皮膚炎 | 0 | 0 |
| 異汗性湿疹 | 0 | 0 |
| 皮脂欠乏性湿疹 | 0 | 0 |
| 多形紅斑 | 0 | 0 |
| 爪の障害 | 0 | 0 |
| 痒疹 | 0 | 0 |
| 皮膚硬結 | 0 | 0 |
| うっ滞性皮膚炎 | 0 | 0 |
| 筋骨格系および結合組織障害 | 65 (17.6%) | 1 (0.3%) |
| 筋痙縮 | 46 (12.4%) | 0 |
| 筋肉痛 | 14 (3.8%) | 0 |
| 関節痛 | 9 (2.4%) | 1 (0.3%) |
| 四肢痛 | 4 (1.1%) | 0 |
| 背部痛 | 2 (0.5%) | 0 |
| 側腹部痛 | 2 (0.5%) | 0 |
| 筋力低下 | 2 (0.5%) | 0 |
| 肌径部痛 | 1 (0.3%) | 0 |
| 関節硬直 | 1 (0.3%) | 0 |
| 関節腫脹 | 1 (0.3%) | 0 |
| 四肢不快感 | 1 (0.3%) | 0 |
| 筋攣縮 | 1 (0.3%) | 0 |
| 筋骨格痛 | 1 (0.3%) | 0 |
| 頚部痛 | 1 (0.3%) | 0 |
| 腱痛 | 1 (0.3%) | 0 |
| 骨痛 | 0 | 0 |
| 筋肉減少症 | 0 | 0 |
| 軟部組織障害 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 60 (16.2%) | 6 (1.6%) |
| 咳嗽 | 23 (6.2%) | 0 |
| 呼吸困難 | 17 (4.6%) | 2 (0.5%) |
| 鼻出血 | 16 (4.3%) | 0 |
| 鼻閉 | 3 (0.8%) | 0 |
| 口腔咽頭痛 | 3 (0.8%) | 0 |
| 胸水 | 3 (0.8%) | 2 (0.5%) |
| 湿性咳嗽 | 3 (0.8%) | 0 |
| 気道うっ血 | 2 (0.5%) | 0 |
| 上気道うっ血 | 2 (0.5%) | 0 |
| 急性肺水腫 | 1 (0.3%) | 1 (0.3%) |
| 発声障害 | 1 (0.3%) | 0 |
| 喀血 | 1 (0.3%) | 0 |
| しゃっくり | 1 (0.3%) | 0 |
| 低酸素症 | 1 (0.3%) | 1 (0.3%) |
| 肺浸潤 | 1 (0.3%) | 0 |
| 鼻潰瘍 | 1 (0.3%) | 0 |
| 副鼻腔不快感 | 1 (0.3%) | 0 |
| 咽頭紅斑 | 1 (0.3%) | 0 |
| 胸膜炎 | 1 (0.3%) | 0 |
| 胸膜痛 | 1 (0.3%) | 0 |
| 肺塞栓症 | 1 (0.3%) | 1 (0.3%) |
| アレルギー性鼻炎 | 1 (0.3%) | 0 |
| 鼻漏 | 1 (0.3%) | 0 |
| 副鼻腔うっ血 | 1 (0.3%) | 0 |
| 間質性肺疾患 | 0 | 0 |
| 咽頭潰瘍 | 0 | 0 |
| 肺臓炎 | 0 | 0 |
| 呼吸不全 | 0 | 0 |
| 代謝および栄養障害 | 56 (15.1%) | 14 (3.8%) |

**TSFAE04PART3OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 食欲減退 | 30 (8.1%) | 0 |
| 高尿酸血症 | 11 (3.0%) | 4 (1.1%) |
| 低カリウム血症 | 9 (2.4%) | 2 (0.5%) |
| 脱水 | 6 (1.6%) | 2 (0.5%) |
| 低ナトリウム血症 | 5 (1.4%) | 4 (1.1%) |
| 低マグネシウム血症 | 4 (1.1%) | 0 |
| 低アルブミン血症 | 3 (0.8%) | 0 |
| 低カルシウム血症 | 3 (0.8%) | 0 |
| 痛風 | 2 (0.5%) | 0 |
| 高血糖 | 2 (0.5%) | 0 |
| 高カリウム血症 | 1 (0.3%) | 0 |
| 低血糖症 | 1 (0.3%) | 0 |
| 低リン酸血症 | 1 (0.3%) | 1 (0.3%) |
| 腫瘍崩壊症候群 | 1 (0.3%) | 1 (0.3%) |
| 悪液質 | 0 | 0 |
| 糖尿病 | 0 | 0 |
| 脂質異常症 | 0 | 0 |
| 耐糖能障害 | 0 | 0 |
| 高コレステロール血症 | 0 | 0 |
| 高脂血症 | 0 | 0 |
| 高ナトリウム血症 | 0 | 0 |
| 高トリグリセリド血症 | 0 | 0 |
| 臨床検査 | 55 (14.9%) | 16 (4.3%) |
| 血中クレアチニン増加 | 11 (3.0%) | 0 |
| 血小板数減少 | 10 (2.7%) | 0 |
| 好中球数減少 | 8 (2.2%) | 7 (1.9%) |
| アラニンアミノトランスフェラーゼ増加 | 5 (1.4%) | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 5 (1.4%) | 0 |
| リンパ球数増加 | 5 (1.4%) | 3 (0.8%) |
| 血中アルカリホスファターゼ増加 | 4 (1.1%) | 1 (0.3%) |
| 体重減少 | 4 (1.1%) | 0 |
| 体重増加 | 4 (1.1%) | 0 |
| 白血球数減少 | 4 (1.1%) | 4 (1.1%) |
| 活性化部分トロンボプラスチン時間延長 | 3 (0.8%) | 0 |
| 血中尿酸増加 | 3 (0.8%) | 2 (0.5%) |
| 血中乳酸脱水素酵素増加 | 2 (0.5%) | 0 |
| 糸球体濾過率減少 | 2 (0.5%) | 0 |
| ヘモグロビン減少 | 2 (0.5%) | 1 (0.3%) |
| 免疫グロブリン減少 | 2 (0.5%) | 0 |
| リンパ球数減少 | 2 (0.5%) | 0 |
| 白血球数増加 | 2 (0.5%) | 1 (0.3%) |
| 血中ビリルビン増加 | 1 (0.3%) | 0 |
| 血中クレアチン増加 | 1 (0.3%) | 0 |
| 血中免疫グロブリンM減少 | 1 (0.3%) | 0 |
| Ｃ－反応性蛋白増加 | 1 (0.3%) | 0 |
| 胸部コンピュータ断層撮影異常 | 1 (0.3%) | 0 |
| 平均赤血球容積増加 | 1 (0.3%) | 0 |
| 血小板凝集異常 | 1 (0.3%) | 0 |
| トランスアミナーゼ上昇 | 1 (0.3%) | 0 |
| 血中アルブミン減少 | 0 | 0 |
| 血中重炭酸塩減少 | 0 | 0 |
| 血中カルシウム減少 | 0 | 0 |

**TSFAE04PART3OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 血中コレステロール増加 | 0 | 0 |
| 血中フィブリノゲン増加 | 0 | 0 |
| 血中ブドウ糖増加 | 0 | 0 |
| 血中免疫グロブリンG減少 | 0 | 0 |
| 血中鉄減少 | 0 | 0 |
| 血中リン減少 | 0 | 0 |
| 血中カリウム減少 | 0 | 0 |
| 血中トリグリセリド増加 | 0 | 0 |
| 血中尿素増加 | 0 | 0 |
| ＥＣＯＧパフォーマンスステータス悪化 | 0 | 0 |
| 好酸球数増加 | 0 | 0 |
| 国際標準比増加 | 0 | 0 |
| 低比重リポ蛋白増加 | 0 | 0 |
| 平均赤血球容積減少 | 0 | 0 |
| 好中球数増加 | 0 | 0 |
| 神経系障害 | 42 (11.4%) | 3 (0.8%) |
| 頭痛 | 18 (4.9%) | 0 |
| 浮動性めまい | 6 (1.6%) | 0 |
| 錯感覚 | 5 (1.4%) | 0 |
| 末梢性感覚ニューロパチー | 5 (1.4%) | 0 |
| 味覚異常 | 3 (0.8%) | 0 |
| 嗜眠 | 2 (0.5%) | 0 |
| 末梢性ニューロパチー | 2 (0.5%) | 0 |
| 多発ニューロパチー | 2 (0.5%) | 1 (0.3%) |
| 失神 | 2 (0.5%) | 2 (0.5%) |
| 振戦 | 2 (0.5%) | 0 |
| 平衡障害 | 1 (0.3%) | 0 |
| 灼熱足症候群 | 1 (0.3%) | 0 |
| 体位性めまい | 1 (0.3%) | 0 |
| てんかん | 1 (0.3%) | 1 (0.3%) |
| 頭蓋内出血 | 1 (0.3%) | 0 |
| 頭部不快感 | 1 (0.3%) | 0 |
| 感覚鈍麻 | 1 (0.3%) | 0 |
| 片頭痛 | 1 (0.3%) | 0 |
| 前兆を伴う片頭痛 | 1 (0.3%) | 0 |
| 失神寸前の状態 | 1 (0.3%) | 0 |
| 下肢静止不能症候群 | 1 (0.3%) | 0 |
| 副鼻腔炎に伴う頭痛 | 1 (0.3%) | 0 |
| 傾眠 | 1 (0.3%) | 0 |
| 失声症 | 0 | 0 |
| 認知障害 | 0 | 0 |
| 注意力障害 | 0 | 0 |
| 過眠症 | 0 | 0 |
| 神経痛 | 0 | 0 |
| 精神運動亢進 | 0 | 0 |
| 眼障害 | 28 (7.6%) | 1 (0.3%) |
| 眼乾燥 | 9 (2.4%) | 0 |
| 霧視 | 3 (0.8%) | 0 |
| 視力低下 | 3 (0.8%) | 0 |
| 眼痛 | 2 (0.5%) | 0 |
| 眼窩周囲浮腫 | 2 (0.5%) | 1 (0.3%) |
| 白内障 | 1 (0.3%) | 0 |
| 結膜出血 | 1 (0.3%) | 0 |
| 複視 | 1 (0.3%) | 0 |
| 眼刺激 | 1 (0.3%) | 0 |
| 眼そう痒症 | 1 (0.3%) | 0 |

**TSFAE04PART3OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 緑内障 | 1 (0.3%) | 0 |
| 流涙増加 | 1 (0.3%) | 0 |
| 眼血管障害 | 1 (0.3%) | 0 |
| 動揺視 | 1 (0.3%) | 0 |
| 羞明 | 1 (0.3%) | 0 |
| 睫毛乱生 | 1 (0.3%) | 0 |
| 硝子体浮遊物 | 1 (0.3%) | 0 |
| 眼部腫脹 | 0 | 0 |
| 血管障害 | 22 (5.9%) | 6 (1.6%) |
| 高血圧 | 7 (1.9%) | 3 (0.8%) |
| 低血圧 | 5 (1.4%) | 2 (0.5%) |
| 血腫 | 4 (1.1%) | 0 |
| 潮紅 | 3 (0.8%) | 0 |
| 血圧変動 | 1 (0.3%) | 0 |
| 深部静脈血栓症 | 1 (0.3%) | 1 (0.3%) |
| 出血 | 1 (0.3%) | 1 (0.3%) |
| ほてり | 1 (0.3%) | 0 |
| 表在性血栓性静脈炎 | 1 (0.3%) | 0 |
| 傷害、中毒および処置合併症 | 21 (5.7%) | 3 (0.8%) |
| 挫傷 | 12 (3.2%) | 0 |
| 処置後出血 | 2 (0.5%) | 2 (0.5%) |
| 硬膜下血腫 | 2 (0.5%) | 0 |
| 外傷性血腫 | 2 (0.5%) | 0 |
| 転倒 | 1 (0.3%) | 0 |
| 関節損傷 | 1 (0.3%) | 0 |
| 裂傷 | 1 (0.3%) | 0 |
| 靭帯捻挫 | 1 (0.3%) | 0 |
| 脾破裂 | 1 (0.3%) | 1 (0.3%) |
| 皮下血腫 | 1 (0.3%) | 0 |
| 注入に伴う反応 | 0 | 0 |
| 皮膚創傷 | 0 | 0 |
| 歯牙破折 | 0 | 0 |
| 各種物質毒性 | 0 | 0 |
| 創傷 | 0 | 0 |
| 心臓障害 | 19 (5.1%) | 12 (3.2%) |
| 心房細動 | 13 (3.5%) | 10 (2.7%) |
| 洞性頻脈 | 3 (0.8%) | 0 |
| 急性心筋梗塞 | 1 (0.3%) | 1 (0.3%) |
| 心房粗動 | 1 (0.3%) | 0 |
| 徐脈 | 1 (0.3%) | 0 |
| 心不全 | 1 (0.3%) | 1 (0.3%) |
| 動悸 | 1 (0.3%) | 0 |
| 心膜炎 | 1 (0.3%) | 1 (0.3%) |
| 洞性徐脈 | 1 (0.3%) | 0 |
| 頻脈 | 1 (0.3%) | 0 |
| トルサード　ド　ポアント | 1 (0.3%) | 0 |
| 急性心不全 | 0 | 0 |
| 腎および尿路障害 | 15 (4.1%) | 3 (0.8%) |
| 血尿 | 5 (1.4%) | 2 (0.5%) |
| 頻尿 | 4 (1.1%) | 0 |
| 急性腎不全 | 3 (0.8%) | 0 |
| 腎不全 | 2 (0.5%) | 1 (0.3%) |
| 排尿困難 | 1 (0.3%) | 0 |
| 夜間頻尿 | 1 (0.3%) | 0 |
| 腎機能障害 | 1 (0.3%) | 0 |
| 尿失禁 | 1 (0.3%) | 0 |
| 尿路痛 | 1 (0.3%) | 0 |

**TSFAE04PART3OF3: Incidence of Treatment-emergent Drug Related Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 慢性腎不全 | 0 | 0 |
| 尿閉 | 0 | 0 |
| 精神障害 | 10 (2.7%) | 3 (0.8%) |
| 錯乱状態 | 4 (1.1%) | 2 (0.5%) |
| 不眠症 | 3 (0.8%) | 0 |
| 不安 | 1 (0.3%) | 0 |
| リビドー減退 | 1 (0.3%) | 0 |
| 精神状態変化 | 1 (0.3%) | 1 (0.3%) |
| 抑うつ気分 | 0 | 0 |
| うつ病 | 0 | 0 |
| 耳および迷路障害 | 7 (1.9%) | 0 |
| 回転性めまい | 4 (1.1%) | 0 |
| 耳痛 | 2 (0.5%) | 0 |
| 聴力低下 | 1 (0.3%) | 0 |
| 老人性難聴 | 1 (0.3%) | 0 |
| 耳部腫脹 | 0 | 0 |
| 生殖系および乳房障害 | 6 (1.6%) | 0 |
| 勃起不全 | 2 (0.5%) | 0 |
| 血精液症 | 2 (0.5%) | 0 |
| 乳房腫瘤 | 1 (0.3%) | 0 |
| 性器発疹 | 1 (0.3%) | 0 |
| 前立腺炎 | 0 | 0 |
| 肝胆道系障害 | 5 (1.4%) | 1 (0.3%) |
| 高ビリルビン血症 | 3 (0.8%) | 0 |
| 肝機能異常 | 1 (0.3%) | 0 |
| 中毒性肝炎 | 1 (0.3%) | 1 (0.3%) |
| 薬物性肝障害 | 0 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 4 (1.1%) | 3 (0.8%) |
| 遠隔転移を伴う新生物 | 1 (0.3%) | 1 (0.3%) |
| 扁平上皮癌 | 1 (0.3%) | 1 (0.3%) |
| 移行上皮癌 | 1 (0.3%) | 1 (0.3%) |
| 腫瘍フレア | 1 (0.3%) | 0 |
| 免疫系障害 | 3 (0.8%) | 0 |
| 低ｙグロブリン血症 | 2 (0.5%) | 0 |
| 過敏症 | 1 (0.3%) | 0 |
| 内分泌障害 | 1 (0.3%) | 0 |
| 甲状腺機能低下症 | 1 (0.3%) | 0 |
| 甲状腺機能亢進症 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately. An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
Adverse events were coded using MedDRA version 17.1.

[TSFAE04PART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae04.sas] 22OCT2015, 16:07

参照元：5.3.5.3.1 ISS TSFAE04PART3OF3

表 2.7.4-付録-16 Treatment-Emergent Adverse Events by Period; All Treated Population (Study PCI-32765MCL2002)

**TSFAE12: Treatment-Emergent Adverse Events by Period; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib | | | | | |
|---|---|---|---|---|---|---|
| | Total | Day1-90 | Day91-180 | Day181-270 | Day271-365 | >=Day 366 |
| Analysis Set: All Treated Population | 16 | 16 | 16 | 9 | 0 | 0 |
| Total Number of Subjects with TEAE | 16 (100.0%) | 16 (100.0%) | 14 (87.5%) | 5 (55.6%) | 0 | 0 |
| MedDRA System organ class/Preferred term | | | | | | |
| 胃腸障害 | 10 (62.5%) | 10 (62.5%) | 2 (12.5%) | 1 (11.1%) | - | - |
| 下痢 | 6 (37.5%) | 5 (31.3%) | 2 (12.5%) | 0 | - | - |
| 口内炎 | 6 (37.5%) | 6 (37.5%) | 0 | 0 | - | - |
| 便秘 | 3 (18.8%) | 3 (18.8%) | 1 (6.3%) | 0 | - | - |
| 消化不良 | 2 (12.5%) | 2 (12.5%) | 1 (6.3%) | 0 | - | - |
| 悪心 | 2 (12.5%) | 2 (12.5%) | 0 | 0 | - | - |
| 上腹部痛 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 肛門出血 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 舌痛 | 1 (6.3%) | 0 | 0 | 1 (11.1%) | - | - |
| 口腔内出血 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 感染症および寄生虫症 | 10 (62.5%) | 4 (25.0%) | 6 (37.5%) | 2 (22.2%) | - | - |
| 上気道感染 | 3 (18.8%) | 3 (18.8%) | 0 | 0 | - | - |
| 鼻咽頭炎 | 2 (12.5%) | 0 | 2 (12.5%) | 0 | - | - |
| 皮膚感染 | 2 (12.5%) | 0 | 1 (6.3%) | 1 (11.1%) | - | - |
| 感染 | 1 (6.3%) | 0 | 0 | 1 (11.1%) | - | - |
| インフルエンザ | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 爪囲炎 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 咽頭炎 | 1 (6.3%) | 1 (6.3%) | 1 (6.3%) | 0 | - | - |
| 敗血症 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 扁桃炎 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 皮膚および皮下組織障害 | 10 (62.5%) | 5 (31.3%) | 3 (18.8%) | 3 (33.3%) | - | - |
| 皮膚乾燥 | 3 (18.8%) | 1 (6.3%) | 1 (6.3%) | 1 (11.1%) | - | - |
| 皮膚炎 | 1 (6.3%) | 0 | 0 | 1 (11.1%) | - | - |
| 湿疹 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 皮下出血 | 1 (6.3%) | 0 | 0 | 1 (11.1%) | - | - |
| 爪変色 | 1 (6.3%) | 0 | 0 | 1 (11.1%) | - | - |
| 爪破損 | 1 (6.3%) | 0 | 0 | 1 (11.1%) | - | - |
| 点状出血 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| そう痒症 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 発疹 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 全身性皮疹 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 斑状丘疹状皮疹 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 皮膚脆弱性 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 一般・全身障害および投与部位の状態 | 9 (56.3%) | 5 (31.3%) | 5 (31.3%) | 0 | - | - |
| 疾患進行 | 3 (18.8%) | 0 | 3 (18.8%) | 0 | - | - |
| 疲労 | 3 (18.8%) | 2 (12.5%) | 1 (6.3%) | 0 | - | - |
| 倦怠感 | 2 (12.5%) | 2 (12.5%) | 0 | 0 | - | - |
| 胸部不快感 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| インフルエンザ様疾患 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 臨床検査 | 8 (50.0%) | 8 (50.0%) | 4 (25.0%) | 3 (33.3%) | - | - |
| 血小板数減少 | 5 (31.3%) | 5 (31.3%) | 4 (25.0%) | 3 (33.3%) | - | - |
| アラニンアミノトランスフェラーゼ増加 | 2 (12.5%) | 2 (12.5%) | 0 | 0 | - | - |
| アスパラギン酸アミノトランスフェラーゼ増加 | 2 (12.5%) | 2 (12.5%) | 0 | 0 | - | - |
| 血中ビリルビン増加 | 2 (12.5%) | 2 (12.5%) | 0 | 0 | - | - |
| 血中アルカリホスファターゼ増加 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |

**TSFAE12: Treatment-Emergent Adverse Events by Period; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib | | | | | |
|---|---|---|---|---|---|---|
| | Total | Day1-90 | Day91-180 | Day181-270 | Day271-365 | >=Day 366 |
| 血中クレアチニン増加 | 1 (6.3%) | 1 (6.3%) | 1 (6.3%) | 0 | - | - |
| γ－グルタミルトランスフェラーゼ増加 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| リンパ球数減少 | 1 (6.3%) | 1 (6.3%) | 1 (6.3%) | 0 | - | - |
| リンパ球数増加 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 血液およびリンパ系障害 | 7 (43.8%) | 6 (37.5%) | 4 (25.0%) | 1 (11.1%) | - | - |
| 貧血 | 4 (25.0%) | 4 (25.0%) | 1 (6.3%) | 0 | - | - |
| 血小板減少症 | 3 (18.8%) | 3 (18.8%) | 2 (12.5%) | 1 (11.1%) | - | - |
| 白血球増加症 | 2 (12.5%) | 1 (6.3%) | 2 (12.5%) | 0 | - | - |
| リンパ球増加症 | 2 (12.5%) | 2 (12.5%) | 0 | 0 | - | - |
| 好中球減少症 | 1 (6.3%) | 1 (6.3%) | 1 (6.3%) | 0 | - | - |
| 代謝および栄養障害 | 5 (31.3%) | 5 (31.3%) | 3 (18.8%) | 0 | - | - |
| 食欲減退 | 3 (18.8%) | 2 (12.5%) | 1 (6.3%) | 0 | - | - |
| 低カリウム血症 | 2 (12.5%) | 1 (6.3%) | 2 (12.5%) | 0 | - | - |
| 高尿酸血症 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 低ナトリウム血症 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 低リン酸血症 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 傷害、中毒および処置合併症 | 4 (25.0%) | 3 (18.8%) | 2 (12.5%) | 0 | - | - |
| 挫傷 | 2 (12.5%) | 1 (6.3%) | 1 (6.3%) | 0 | - | - |
| 裂傷 | 2 (12.5%) | 2 (12.5%) | 1 (6.3%) | 0 | - | - |
| 関節脱臼 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 神経系障害 | 4 (25.0%) | 4 (25.0%) | 1 (6.3%) | 0 | - | - |
| 頭痛 | 2 (12.5%) | 2 (12.5%) | 0 | 0 | - | - |
| 末梢性ニューロパチー | 2 (12.5%) | 1 (6.3%) | 1 (6.3%) | 0 | - | - |
| 体位性めまい | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 眼障害 | 3 (18.8%) | 3 (18.8%) | 0 | 0 | - | - |
| 眼乾燥 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 点状角膜炎 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 網膜裂孔 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 網膜血管障害 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 筋骨格系および結合組織障害 | 3 (18.8%) | 2 (12.5%) | 1 (6.3%) | 0 | - | - |
| 関節炎 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 筋痙縮 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 骨炎 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 心臓障害 | 2 (12.5%) | 0 | 2 (12.5%) | 0 | - | - |
| 不整脈 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 心房細動 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 精神障害 | 2 (12.5%) | 2 (12.5%) | 1 (6.3%) | 0 | - | - |
| 譫妄 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| うつ病 | 1 (6.3%) | 1 (6.3%) | 1 (6.3%) | 0 | - | - |
| 腎および尿路障害 | 2 (12.5%) | 2 (12.5%) | 2 (12.5%) | 0 | - | - |
| 血尿 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 蛋白尿 | 1 (6.3%) | 0 | 1 (6.3%) | 0 | - | - |
| 腎機能障害 | 1 (6.3%) | 1 (6.3%) | 1 (6.3%) | 0 | - | - |
| 呼吸器、胸郭および縦隔障害 | 2 (12.5%) | 2 (12.5%) | 0 | 0 | - | - |
| 鼻出血 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 鼻漏 | 1 (6.3%) | 1 (6.3%) | 0 | 0 | - | - |
| 血管障害 | 1 (6.3%) | 1 (6.3%) | 1 (6.3%) | 1 (11.1%) | - | - |
| 高血圧 | 1 (6.3%) | 1 (6.3%) | 1 (6.3%) | 1 (11.1%) | - | - |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0
Note: Only one incidence of a type that occurs during each period is counted as the event. The numerators are the numbers of subjects who experience a new episode of that event in that period.

[TSFAE12.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsfae12.sas] 21AUG2015, 12:30

参照元：5.3.5.2.1 MCL2002 試験 CSR TSFAE12

表 2.7.4-付録-17 Prevalence Rate of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Pooled Ibrutinib by Period, System Organ Class and Preferred Term; Safety Population (MCL-ISS)

**TSFAE30: Prevalence Rate of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Pooled Ibrutinib by Period, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | |
|---|---|---|---|---|---|---|
| | Total | Day 1 - 90 | Day 91 - 180 | Day 181 - 270 | Day 271 - 365 | >= Day 366 |
| Analysis set: safety population | 370 | 370 | 308 | 247 | 209 | 175 |
| Subjects with any TEAE | 364 (98.4%) | 342 (92.4%) | 283 (91.9%) | 226 (91.5%) | 193 (92.3%) | 162 (92.6%) |
| 感染症および寄生虫症 | 263 (71.1%) | 156 (42.2%) | 134 (43.5%) | 103 (41.7%) | 91 (43.5%) | 97 (55.4%) |
| 上気道感染 | 73 (19.7%) | 28 (7.6%) | 29 (9.4%) | 17 (6.9%) | 13 (6.2%) | 28 (16.0%) |
| 肺炎 | 44 (11.9%) | 19 (5.1%) | 11 (3.6%) | 9 (3.6%) | 10 (4.8%) | 15 (8.6%) |
| 副鼻腔炎 | 39 (10.5%) | 17 (4.6%) | 13 (4.2%) | 9 (3.6%) | 3 (1.4%) | 12 (6.9%) |
| 尿路感染 | 38 (10.3%) | 18 (4.9%) | 11 (3.6%) | 11 (4.5%) | 8 (3.8%) | 7 (4.0%) |
| 胃腸障害 | 255 (68.9%) | 205 (55.4%) | 123 (39.9%) | 105 (42.5%) | 83 (39.7%) | 80 (45.7%) |
| 下痢 | 146 (39.5%) | 109 (29.5%) | 48 (15.6%) | 38 (15.4%) | 30 (14.4%) | 31 (17.7%) |
| 悪心 | 80 (21.6%) | 55 (14.9%) | 27 (8.8%) | 22 (8.9%) | 11 (5.3%) | 17 (9.7%) |
| 嘔吐 | 62 (16.8%) | 37 (10.0%) | 12 (3.9%) | 8 (3.2%) | 4 (1.9%) | 8 (4.6%) |
| 便秘 | 57 (15.4%) | 33 (8.9%) | 22 (7.1%) | 13 (5.3%) | 15 (7.2%) | 15 (8.6%) |
| 腹痛 | 42 (11.4%) | 20 (5.4%) | 16 (5.2%) | 10 (4.0%) | 8 (3.8%) | 7 (4.0%) |
| 一般・全身障害および投与部位の状態 | 239 (64.6%) | 181 (48.9%) | 121 (39.3%) | 96 (38.9%) | 71 (34.0%) | 77 (44.0%) |
| 疲労 | 129 (34.9%) | 98 (26.5%) | 62 (20.1%) | 49 (19.8%) | 45 (21.5%) | 40 (22.9%) |
| 末梢性浮腫 | 74 (20.0%) | 48 (13.0%) | 33 (10.7%) | 27 (10.9%) | 20 (9.6%) | 20 (11.4%) |
| 発熱 | 68 (18.4%) | 31 (8.4%) | 15 (4.9%) | 17 (6.9%) | 11 (5.3%) | 16 (9.1%) |
| 呼吸器、胸郭および縦隔障害 | 200 (54.1%) | 126 (34.1%) | 102 (33.1%) | 80 (32.4%) | 67 (32.1%) | 60 (34.3%) |
| 咳嗽 | 81 (21.9%) | 46 (12.4%) | 39 (12.7%) | 28 (11.3%) | 26 (12.4%) | 22 (12.6%) |
| 呼吸困難 | 69 (18.6%) | 43 (11.6%) | 22 (7.1%) | 20 (8.1%) | 17 (8.1%) | 20 (11.4%) |
| 皮膚および皮下組織障害 | 194 (52.4%) | 130 (35.1%) | 96 (31.2%) | 86 (34.8%) | 71 (34.0%) | 70 (40.0%) |
| 発疹 | 57 (15.4%) | 36 (9.7%) | 22 (7.1%) | 20 (8.1%) | 12 (5.7%) | 15 (8.6%) |
| 筋骨格系および結合組織障害 | 173 (46.8%) | 103 (27.8%) | 107 (34.7%) | 93 (37.7%) | 81 (38.8%) | 76 (43.4%) |
| 筋痙縮 | 67 (18.1%) | 26 (7.0%) | 40 (13.0%) | 44 (17.8%) | 42 (20.1%) | 38 (21.7%) |
| 背部痛 | 44 (11.9%) | 20 (5.4%) | 14 (4.5%) | 11 (4.5%) | 12 (5.7%) | 14 (8.0%) |
| 関節痛 | 38 (10.3%) | 13 (3.5%) | 17 (5.5%) | 12 (4.9%) | 12 (5.7%) | 14 (8.0%) |
| 血液およびリンパ系障害 | 169 (45.7%) | 105 (28.4%) | 84 (27.3%) | 55 (22.3%) | 45 (21.5%) | 41 (23.4%) |
| 血小板減少症 | 74 (20.0%) | 43 (11.6%) | 29 (9.4%) | 27 (10.9%) | 23 (11.0%) | 20 (11.4%) |
| 好中球減少症 | 70 (18.9%) | 29 (7.8%) | 43 (14.0%) | 20 (8.1%) | 15 (7.2%) | 15 (8.6%) |
| 貧血 | 63 (17.0%) | 43 (11.6%) | 17 (5.5%) | 18 (7.3%) | 14 (6.7%) | 12 (6.9%) |
| 代謝および栄養障害 | 150 (40.5%) | 93 (25.1%) | 58 (18.8%) | 39 (15.8%) | 35 (16.7%) | 37 (21.1%) |
| 食欲減退 | 62 (16.8%) | 41 (11.1%) | 23 (7.5%) | 11 (4.5%) | 8 (3.8%) | 12 (6.9%) |

**TSFAE30: Prevalence Rate of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Pooled Ibrutinib by Period, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | |
|---|---|---|---|---|---|---|
| | Total | Day 1 - 90 | Day 91 - 180 | Day 181 - 270 | Day 271 - 365 | >= Day 366 |
| 神経系障害 | 121 (32.7%) | 76 (20.5%) | 59 (19.2%) | 46 (18.6%) | 42 (20.1%) | 45 (25.7%) |
| 頭痛 | 37 (10.0%) | 23 (6.2%) | 11 (3.6%) | 9 (3.6%) | 10 (4.8%) | 9 (5.1%) |
| 傷害、中毒および処置合併症 | 101 (27.3%) | 35 (9.5%) | 35 (11.4%) | 39 (15.8%) | 36 (17.2%) | 36 (20.6%) |
| 挫傷 | 46 (12.4%) | 12 (3.2%) | 14 (4.5%) | 21 (8.5%) | 15 (7.2%) | 15 (8.6%) |

Key: TEAE = Treatment-emergent adverse event.
Note: For percentage calculation, the numerator is the number of subjects who experienced a new episode of the corresponding event in the current period, or an episode started in the prior period and lasted to current period, the denominator is the number of subjects at risk at current AE reporting period, where AE reporting period is defined by the time from first dose date to last dose date + 30 or study exit date whichever occurred first
Adverse events were coded using MedDRA version 17.1.

[TSFAE30.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae30.sas] 15SEP2015, 14:13

参照元：5.3.5.3.1 ISS TSFAE30

表 2.7.4-付録-18 Listing of Treatment-emergent Adverse Events Leading to Death; Safety Population (MCL-ISS)

**LSFAE01: Listing of Treatment-emergent Adverse Events Leading to Death; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PCYC-1104 | Ibrutinib | 006-004 | 7[redacted]/Male/ White | 560 mg | Pneumonia | 肺炎 | 5 | Yes | 2011-10-01/ | 74/ | Possible/ Drug withdrawn | Fatal |
| | | 200-005 | 7[redacted]/Female/ White | | Dyspnea | 呼吸困難 | 5 | Yes | 2011-07-13/ | 49/ | Not related/ | Fatal |
| | | 217-006 | 7[redacted]/Male/ White | 560 mg | Acute renal failure | 急性腎不全 | 5 | Yes | 2011-11-02/ | 78/ | Not related/ | Fatal |
| | | 217-008 | 7[redacted]/Male/ White | | Mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-02-03/ | 73/ | Not related/ | Fatal |
| | | 350-001 | 6[redacted]/Male/ White | | Malignant pleural effusion | 悪性胸水 | 5 | Yes | 2012-02-21/ | 63/ | Not related/ | Fatal |
| | | 354-001 | 6[redacted]/Male/ White | | Paralytec ileus | 麻痺性イレウス | 5 | Yes | 2012-03-17/ | 108/ | Not related/ | Fatal |
| | | 363-001 | 7[redacted]/Male/ White | | Pneumonia - etiology pneumocystis jiroveci | ニューモシスチス・イロベチイ肺炎 | 5 | Yes | 2012-07-03/ | 169/ | Possible/ | Fatal |
| | | 364-001 | 6[redacted]/Female/ White | | Mcl | マントル細胞リンパ腫 | 5 | Yes | 2012-02-13/ | 89/ | Not related/ | Fatal |
| | | 364-003 | 7[redacted]/Male/ White | | Death due to mcl | マントル細胞リンパ腫 | 5 | Yes | 2012-04-02/ | 124/ | Not related/ Drug withdrawn | Fatal |
| | | 364-007 | 6[redacted]/Female/ White | | Respiratory insufficiency | 呼吸不全 | 5 | Yes | 2012-10-14/ | 251/ | Not related/ Drug withdrawn | Fatal |
| | | 368-001 | 7[redacted]/Male/ White | | Worsening of mantle cell lymphoma worsening of mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-03-10/ | 180/ | Not related/ Dose not changed | Fatal |
| | | 368-003 | 6[redacted]/Male/ White | 560 mg | Worsening of mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-03-06/ | 169/ | Not related/ | Fatal |
| | | 368-004 | 6[redacted]/Male/ White | | Sepsis-unknown origin | 敗血症 | 5 | Yes | 2012-05-22/ | 226/ | Not related/ | Fatal |
| | | 368-007 | 7[redacted]/Male/ White | | Cardiac arrest | 心停止 | 5 | Yes | 2012-10-05/ | 341/ | Not related/ Drug withdrawn | Fatal |
| | | 368-012 | 6[redacted]/Male/ White | | Worsening of mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-05-10/ | 122/ | Not related/ | Fatal |
| | | 368-013 | 7[redacted]/Male/ White | | Worsening of mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-03-15/ | 60/ | Not related/ | Fatal |
| MCL-2001 | Ibrutinib | 10001001 | 7[redacted]/Female/ White | | Encephalopathy | 脳症 | 5 | Yes | 2012-12-18/ | 42/ | Not related/ Not applicable | Fatal |
| | | 10001401 | 6[redacted]/Male/ White | | Fatigue | 疲労 | 5 | Yes | 2013-06-26/ | 267/ | Not related/ Not applicable | Fatal |
| | | | | | Pain, nos | 疼痛 | 5 | Yes | 2013-06-26/ | 267/ | Not related/ Not applicable | Fatal |
| | | | | | Weakness-nos | 無力症 | 5 | Yes | 2013-06-26/ | 267/ | Not related/ Not applicable | Fatal |

**LSFAE01: Listing of Treatment-emergent Adverse Events Leading to Death; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 10002203 | 7[redacted]/Male/ Unknown | | Neutropenic fever | 発熱性好中球減少症 | 5 | Yes | 2013-01-22/ | 72/ | Possible/ Not applicable | Fatal |
| | | 10002206 | 7[redacted]/Male/ White | 0 mg | Respiratory failure. | 呼吸不全 | 5 | Yes | 2013-07-10/ | 91/ | Not related/ Not applicable | Fatal |
| | | 10002510 | 7[redacted]/Male/ White | 0 mg | Pneumonia | 肺炎 | 5 | Yes | 2013-04-07/ | 216/ | Possible/ Drug withdrawn | Fatal |
| | | 10002526 | 6[redacted]/Male/ White | 0 mg | Pneumonia | 肺炎 | 5 | Yes | 2013-03-06/ | 50/ | Possible/ Drug withdrawn | Fatal |
| | | 10004902 | 7[redacted]/Male/ White | 0 mg | Respiratory failure | 呼吸不全 | 5 | Yes | 2012-11-04/ | 24/ | Not related/ Drug withdrawn | Fatal |
| | | 48000101 | 7[redacted]/Male/ White | | Circulatory failure due to disease progression | 循環虚脱 | 5 | Yes | 2013-05-29/ | 136/ | Not related/ Drug withdrawn | Fatal |
| | | | | | Respiratory failure | 呼吸不全 | 5 | Yes | 2013-05-29/ | 136/ | Not related/ Drug withdrawn | Fatal |
| | | 70000102 | 4[redacted]/Male/ White | | Fatal death | 死亡 | 5 | Yes | 2013-04-13/ | 31/ | Not related/ Drug withdrawn | Fatal |
| | | 70000602 | 7[redacted]/Male/ White | | Acute cardiovascular insufficiency | 心血管不全 | 5 | Yes | 2013-04-09/ | 19/ | Not related/ Drug withdrawn | Fatal |
| | | 97200204 | 7[redacted]/Male/ White | | Pneumonia | 肺炎 | 5 | Yes | 2013-03-22/ | 59/ | Not related/ Not applicable | Fatal |
| | | 97200302 | 6[redacted]/Male/ White | 560 mg | Cardiac arrest | 心停止 | 5 | Yes | 2012-12-16/ | 21/ | Not related/ Drug withdrawn | Fatal |
| | | 97200701 | 7[redacted]/Male/ White | | Pneumonia | 肺炎 | 5 | Yes | 2013-05-08/ | 51/ | Not related/ Not applicable | Fatal |
| | | 97200702 | 6[redacted]/Male/ White | | Sepsis | 敗血症 | 5 | Yes | 2013-06-18/ | 62/ | Not related/ Drug withdrawn | Fatal |
| MCL-3001 | Ibrutinib | 38000101 | 6[redacted]/Male/ White | 560 mg | Suspected pulmonary embolism | 肺塞栓症 | 5 | Yes | 2013-06-24/ | 61/ | Possible/ Not applicable | Fatal |
| | | 38000501 | 6[redacted]/Male/ White | 0 mg | Pulmonary edema | 肺水腫 | 5 | Yes | 2013-05-27/ | 69/ | Doubtful/ Not applicable | Fatal |
| | | 39000102 | 7[redacted]/Male/ White | | Subdural hematoma | 硬膜下血腫 | 5 | Yes | 2015-01-06/ | 523/ | Not related/ Not applicable | Fatal |
| | | 46000103 | 7[redacted]/Male/ White | | Renal failure | 腎不全 | 5 | Yes | 2013-12-30/ | 376/ | Not related/ Not applicable | Fatal |
| | | 46000106 | 5[redacted]/Male/ White | | Splenic ruptur | 脾破裂 | 5 | Yes | 2013-07-05/ | 74/ | Possible/ Not applicable | Fatal |
| | | 46000108 | 6[redacted]/Male/ White | | Multiple organ failure | 多臓器不全 | 5 | Yes | 2013-06-02/ | 5/ | Not related/ Not applicable | Fatal |
| | | 46000110 | 7[redacted]/Male/ White | | Progressive urothelial cancer | 移行上皮癌 | 5 | Yes | 2014-06-12/ | 380/ | Possible/ Not applicable | Fatal |
| | | 46000406 | 7[redacted]/Male/ White | | Sepsis | 敗血症 | 5 | Yes | 2014-02-13/ | 241/ | Not related/ Not applicable | Fatal |
| | | 48001504 | 6[redacted]/Male/ White | | Multiorgan dysfunction due to mcl progession | 多臓器不全 | 5 | Yes | 2013-10-26/ | 151/ | Not related/ Not applicable | Fatal |

**LSFAE01: Listing of Treatment-emergent Adverse Events Leading to Death; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 48001506 | 8[redacted]/Female/ White | | Respiratory insufficiency due to mcl progression | 呼吸不全 | 5 | Yes | 2013-12-17/ | 189/ | Not related/ Not applicable | Fatal |
| | | 49000602 | 5[redacted]/Male/ White | | Renal failure | 腎不全 | 5 | Yes | 2013-09-18/ | 94/ | Not related/ Not applicable | Fatal |
| | | 49001202 | 7[redacted]/Male/ White | | Sepsis | 敗血症 | 5 | Yes | 2015-01-30/ | 555/ | Possible/ Not applicable | Fatal |
| | | 82000401 | 7[redacted]/Male/ Asian | | Septic shock | 敗血症性ショック | 5 | Yes | 2013-11-23/ | 269/ | Not related/ Not applicable | Fatal |
| | | 88600104 | 6[redacted]/Male/ Asian | | Sepsis | 敗血症 | 5 | Yes | 2014-01-07/ | 92/ | Not related/ Not applicable | Fatal |
| | | 88600501 | 5[redacted]/Male/ Asian | 560 mg | Septic shock | 敗血症性ショック | 5 | Yes | 2013-05-08/ | 10/ | Not related/ Not applicable | Fatal |
| | Temsirolimus | 32000701 | 6[redacted]/Male/ White | | Bilateral pneumonia | 肺炎 | 5 | Yes | 2013-11-13/ | 59/ | Possible/ Not applicable | Fatal |
| | | 34000101 | 6[redacted]/Male/ White | | Deterioration of general condition | 全身健康状態低下 | 5 | Yes | 2013-05-06/ | 25/ | Not related/ Not applicable | Fatal |
| | | 35100201 | 7[redacted]/Male/ White | | Isquemic stroke | 虚血性脳卒中 | 5 | Yes | 2013-06-05/ | 30/ | Doubtful/ Not applicable | Fatal |
| | | 35100204 | 6[redacted]/Male/ White | | Cardiac arrest | 心停止 | 5 | Yes | 2013-07-22/ | 49/ | Not related/ Not applicable | Fatal |
| | | 38000301 | 7[redacted]/Male/ White | | Acute heart failure | 急性心不全 | 5 | Yes | 2013-04-11/ | 9/ | Possible/ Not applicable | Fatal |
| | | 42002507 | 7[redacted]/Male/ White | | Septic shock | 敗血症性ショック | 5 | Yes | 2014-01-13/ | 75/ | Not related/ Not applicable | Fatal |
| | | 44001003 | 5[redacted]/Male/ White | | Renal faliure | 腎不全 | 5 | Yes | 2013-05-28/ | 62/ | Not related/ Not applicable | Fatal |
| | | 46000403 | 6[redacted]/Male/ White | | Worsening of general condition | 全身健康状態低下 | 5 | Yes | 2013-04-21/ | 32/ | Not related/ Not applicable | Fatal |
| | | 48001304 | 7[redacted]/Male/ White | | Sepsis | 敗血症 | 5 | Yes | 2013-09-09/ | 50/ | Possible/ Not applicable | Fatal |
| | | 48001508 | 7[redacted]/Male/ White | | Cardio-respiratory failure | 心肺不全 | 5 | Yes | 2013-12-22/ | 117/ | Not related/ Not applicable | Fatal |
| | | 55000107 | 7[redacted]/Female/ White | | Respiratory failure | 呼吸不全 | 5 | Yes | 2013-12-17/ | 42/ | Very likely/ Not applicable | Fatal |

[a] Start day = AE start date – first dose date (+1 if AE start date >= first dose date).
[b] Stop day = AE stop date – first dose date (+1 if AE stop date >= first dose date).
[c] Duration of AE = AE stop date – AE start date + 1.



参照元：5.3.5.3.1 ISS LSFAE01

表 2.7.4-付録-19 Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE05PART1OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 111 | | 120 | |
| Subjects with any serious TEAE | 62 (55.9%) | 55 (49.5%) | 59 (49.2%) | 53 (44.2%) |
| System organ class | | | | |
| Preferred term | | | | |
| 感染症および寄生虫症 | 22 (19.8%) | 21 (18.9%) | 29 (24.2%) | 27 (22.5%) |
| 肺炎 | 6 (5.4%) | 6 (5.4%) | 14 (11.7%) | 13 (10.8%) |
| 敗血症 | 2 (1.8%) | 2 (1.8%) | 3 (2.5%) | 3 (2.5%) |
| 蜂巣炎 | 2 (1.8%) | 2 (1.8%) | 4 (3.3%) | 4 (3.3%) |
| 尿路感染 | 4 (3.6%) | 3 (2.7%) | 1 (0.8%) | 1 (0.8%) |
| 下気道感染 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 気管支炎 | 2 (1.8%) | 2 (1.8%) | 1 (0.8%) | 1 (0.8%) |
| 胃腸炎 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| クロストリジウム・ディフィシレ大腸炎 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| ニューモシスチス・イロベチイ肺炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 細菌性肺炎 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 敗血症性ショック | 0 | 0 | 0 | 0 |
| ブドウ球菌性菌血症 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 腹部膿瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 四肢膿瘍 | 0 | 0 | 0 | 0 |
| 肛門膿瘍 | 1 (0.9%) | 0 | 0 | 0 |
| 虫垂炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 穿孔性虫垂炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 菌血症 | 0 | 0 | 0 | 0 |
| 気管支肺炎 | 0 | 0 | 0 | 0 |
| カンピロバクター感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 眼窩蜂巣炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 医療機器関連感染 | 0 | 0 | 0 | 0 |
| 感染性小腸結腸炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| ウイルス性胃腸炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| Ｂ型肝炎 | 0 | 0 | 0 | 0 |
| 感染 | 0 | 0 | 0 | 0 |
| 喉頭炎 | 0 | 0 | 0 | 0 |
| 肺感染 | 0 | 0 | 0 | 0 |
| 眼帯状疱疹 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 咽頭炎 | 0 | 0 | 0 | 0 |
| クレブシエラ菌性肺炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 肺結核 | 0 | 0 | 0 | 0 |
| 腎盂腎炎 | 0 | 0 | 0 | 0 |
| 気道感染 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 皮膚感染 | 0 | 0 | 0 | 0 |
| 軟部組織感染 | 0 | 0 | 0 | 0 |
| レンサ球菌感染 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 皮下組織膿瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 気管炎 | 0 | 0 | 0 | 0 |
| 細菌性尿路感染 | 0 | 0 | 0 | 0 |
| 尿路性敗血症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 創傷感染 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 異型肺炎 | 0 | 0 | 0 | 0 |
| 気管支肺アスペルギルス症 | 0 | 0 | 0 | 0 |
| 膀胱炎 | 0 | 0 | 0 | 0 |
| 憩室炎 | 0 | 0 | 0 | 0 |

**TSFAE05PART1OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 帯状疱疹 | 0 | 0 | 0 | 0 |
| 感染性大腸炎 | 0 | 0 | 0 | 0 |
| 真菌性喉頭炎 | 0 | 0 | 0 | 0 |
| 肝膿瘍 | 0 | 0 | 0 | 0 |
| 大葉性肺炎 | 0 | 0 | 0 | 0 |
| 好中球減少性敗血症 | 0 | 0 | 0 | 0 |
| 口腔カンジダ症 | 0 | 0 | 0 | 0 |
| ニューモシスチス・イロベチイ感染 | 0 | 0 | 0 | 0 |
| 大腸菌性肺炎 | 0 | 0 | 0 | 0 |
| 副鼻腔炎 | 0 | 0 | 0 | 0 |
| アスペルギルス性副鼻腔炎 | 0 | 0 | 0 | 0 |
| 歯感染 | 0 | 0 | 0 | 0 |
| 上気道感染 | 0 | 0 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 5 (4.5%) | 5 (4.5%) | 12 (10.0%) | 7 (5.8%) |
| 呼吸困難 | 2 (1.8%) | 2 (1.8%) | 5 (4.2%) | 2 (1.7%) |
| 呼吸不全 | 2 (1.8%) | 2 (1.8%) | 4 (3.3%) | 4 (3.3%) |
| 胸水 | 0 | 0 | 2 (1.7%) | 2 (1.7%) |
| 慢性閉塞性肺疾患 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 咳嗽 | 0 | 0 | 2 (1.7%) | 0 |
| 鼻出血 | 0 | 0 | 0 | 0 |
| 低酸素症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 気胸 | 0 | 0 | 0 | 0 |
| 肺塞栓症 | 0 | 0 | 0 | 0 |
| 肺水腫 | 0 | 0 | 0 | 0 |
| 間質性肺疾患 | 0 | 0 | 0 | 0 |
| 肺臓炎 | 0 | 0 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 11 (9.9%) | 5 (4.5%) | 8 (6.7%) | 5 (4.2%) |
| 発熱 | 3 (2.7%) | 1 (0.9%) | 2 (1.7%) | 1 (0.8%) |
| 末梢性浮腫 | 3 (2.7%) | 2 (1.8%) | 2 (1.7%) | 2 (1.7%) |
| 多臓器不全 | 0 | 0 | 0 | 0 |
| 疲労 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 全身健康状態低下 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 無力症 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| 非心臓性胸痛 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 悪寒 | 1 (0.9%) | 0 | 0 | 0 |
| 死亡 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 医療機器リーク | 1 (0.9%) | 0 | 0 | 0 |
| 倦怠感 | 0 | 0 | 1 (0.8%) | 0 |
| 疼痛 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 粘膜の炎症 | 0 | 0 | 0 | 0 |
| 浮腫 | 0 | 0 | 0 | 0 |
| 血液およびリンパ系障害 | 9 (8.1%) | 9 (8.1%) | 8 (6.7%) | 8 (6.7%) |
| 発熱性好中球減少症 | 3 (2.7%) | 3 (2.7%) | 6 (5.0%) | 6 (5.0%) |
| 血小板減少症 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 貧血 | 2 (1.8%) | 2 (1.8%) | 1 (0.8%) | 1 (0.8%) |
| 好中球減少症 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 1 (0.8%) |
| 白血球増加症 | 0 | 0 | 0 | 0 |
| リンパ球増加症 | 0 | 0 | 0 | 0 |
| 汎血球減少症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 後腹膜リンパ節腫脹 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 脾臓出血 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 脾臓梗塞 | 0 | 0 | 0 | 0 |
| 胃腸障害 | 8 (7.2%) | 7 (6.3%) | 8 (6.7%) | 4 (3.3%) |
| 腹痛 | 3 (2.7%) | 3 (2.7%) | 3 (2.5%) | 2 (1.7%) |
| 下痢 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |

**TSFAE05PART1OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 麻痺性イレウス | 2 (1.8%) | 2 (1.8%) | 0 | 0 |
| 悪心 | 0 | 0 | 2 (1.7%) | 0 |
| 小腸閉塞 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 嘔吐 | 0 | 0 | 2 (1.7%) | 0 |
| アフタ性口内炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 大腸炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 十二指腸狭窄 | 0 | 0 | 0 | 0 |
| 嚥下障害 | 0 | 0 | 0 | 0 |
| 胃潰瘍 | 0 | 0 | 0 | 0 |
| イレウス | 1 (0.9%) | 0 | 0 | 0 |
| 腸炎 | 0 | 0 | 0 | 0 |
| 出血性胃炎 | 0 | 0 | 0 | 0 |
| 胃腸出血 | 0 | 0 | 0 | 0 |
| 痔核 | 0 | 0 | 0 | 0 |
| 腸出血 | 0 | 0 | 0 | 0 |
| 下部消化管出血 | 0 | 0 | 0 | 0 |
| 口内炎 | 0 | 0 | 0 | 0 |
| 心臓障害 | 8 (7.2%) | 8 (7.2%) | 8 (6.7%) | 6 (5.0%) |
| 心房細動 | 5 (4.5%) | 5 (4.5%) | 5 (4.2%) | 3 (2.5%) |
| 心房粗動 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 心停止 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 急性心筋梗塞 | 0 | 0 | 0 | 0 |
| 不安定狭心症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 冠動脈硬化症 | 0 | 0 | 0 | 0 |
| 徐脈 | 0 | 0 | 0 | 0 |
| 心不全 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 心血管不全 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 冠動脈閉塞 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 心膜炎 | 0 | 0 | 0 | 0 |
| 上室性頻脈 | 0 | 0 | 0 | 0 |
| 狭心症 | 0 | 0 | 0 | 0 |
| 急性心不全 | 0 | 0 | 0 | 0 |
| 慢性心不全 | 0 | 0 | 0 | 0 |
| うっ血性心不全 | 0 | 0 | 0 | 0 |
| 心肺不全 | 0 | 0 | 0 | 0 |
| 冠動脈狭窄 | 0 | 0 | 0 | 0 |
| 心筋虚血 | 0 | 0 | 0 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 10 (9.0%) | 10 (9.0%) | 1 (0.8%) | 1 (0.8%) |
| マントル細胞リンパ腫 | 8 (7.2%) | 8 (7.2%) | 0 | 0 |
| 膀胱移行上皮癌 | 0 | 0 | 0 | 0 |
| 前立腺癌 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 基底細胞癌 | 0 | 0 | 0 | 0 |
| 膀胱癌 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 悪性胸水 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 遠隔転移を伴う新生物 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 唾液腺癌 | 0 | 0 | 0 | 0 |
| 扁平上皮癌 | 0 | 0 | 0 | 0 |
| 胸腺腫 | 0 | 0 | 0 | 0 |
| 移行上皮癌 | 0 | 0 | 0 | 0 |
| 胃腺癌 | 0 | 0 | 0 | 0 |
| 腎および尿路障害 | 6 (5.4%) | 6 (5.4%) | 5 (4.2%) | 3 (2.5%) |
| 急性腎不全 | 3 (2.7%) | 3 (2.7%) | 4 (3.3%) | 2 (1.7%) |
| 腎不全 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 血尿 | 2 (1.8%) | 2 (1.8%) | 0 | 0 |
| 出血性膀胱炎 | 0 | 0 | 0 | 0 |

**TSFAE05PART1OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 水腎症 | 0 | 0 | 0 | 0 |
| 腎結石症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 尿路閉塞 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 腎機能障害 | 0 | 0 | 0 | 0 |
| 傷害、中毒および処置合併症 | 5 (4.5%) | 3 (2.7%) | 4 (3.3%) | 2 (1.7%) |
| 硬膜下血腫 | 3 (2.7%) | 2 (1.8%) | 0 | 0 |
| 転倒 | 0 | 0 | 1 (0.8%) | 0 |
| 処置後出血 | 0 | 0 | 0 | 0 |
| 脊椎圧迫骨折 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 脾破裂 | 0 | 0 | 0 | 0 |
| 動物咬傷 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 腰椎骨折 | 0 | 0 | 0 | 0 |
| 過量投与 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 処置後腫脹 | 0 | 0 | 0 | 0 |
| 肋骨骨折 | 0 | 0 | 0 | 0 |
| 脛骨骨折 | 0 | 0 | 1 (0.8%) | 0 |
| 腓骨骨折 | 0 | 0 | 0 | 0 |
| 体内異物 | 0 | 0 | 0 | 0 |
| 各種物質毒性 | 0 | 0 | 0 | 0 |
| 創傷 | 0 | 0 | 0 | 0 |
| 神経系障害 | 2 (1.8%) | 0 | 6 (5.0%) | 2 (1.7%) |
| 構語障害 | 0 | 0 | 0 | 0 |
| 頭蓋内出血 | 0 | 0 | 2 (1.7%) | 0 |
| 頭痛 | 1 (0.9%) | 0 | 0 | 0 |
| 一過性脳虚血発作 | 0 | 0 | 1 (0.8%) | 0 |
| 脳血管発作 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 脳症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| てんかん | 0 | 0 | 0 | 0 |
| 顔面不全麻痺 | 0 | 0 | 0 | 0 |
| 記憶障害 | 0 | 0 | 0 | 0 |
| ミオクローヌス | 0 | 0 | 0 | 0 |
| 失神寸前の状態 | 0 | 0 | 1 (0.8%) | 0 |
| 失神 | 0 | 0 | 0 | 0 |
| 一過性全健忘 | 1 (0.9%) | 0 | 0 | 0 |
| 運動失調 | 0 | 0 | 0 | 0 |
| 脳虚血 | 0 | 0 | 0 | 0 |
| 虚血性脳卒中 | 0 | 0 | 0 | 0 |
| 神経痛 | 0 | 0 | 0 | 0 |
| 振戦 | 0 | 0 | 0 | 0 |
| 代謝および栄養障害 | 2 (1.8%) | 2 (1.8%) | 3 (2.5%) | 3 (2.5%) |
| 脱水 | 2 (1.8%) | 2 (1.8%) | 1 (0.8%) | 1 (0.8%) |
| 悪液質 | 0 | 0 | 0 | 0 |
| 糖尿病性ケトアシドーシス | 0 | 0 | 0 | 0 |
| 高尿酸血症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 低アルブミン血症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 腫瘍崩壊症候群 | 0 | 0 | 0 | 0 |
| 食欲減退 | 0 | 0 | 0 | 0 |
| 糖尿病 | 0 | 0 | 0 | 0 |
| 低カリウム血症 | 0 | 0 | 0 | 0 |
| 低ナトリウム血症 | 0 | 0 | 0 | 0 |
| 筋骨格系および結合組織障害 | 3 (2.7%) | 3 (2.7%) | 2 (1.7%) | 2 (1.7%) |
| 側腹部痛 | 2 (1.8%) | 2 (1.8%) | 0 | 0 |
| 関節痛 | 1 (0.9%) | 0 | 0 | 0 |
| 背部痛 | 0 | 0 | 0 | 0 |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 0 | 0 | 0 | 0 |
| 痛風性関節炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |

**TSFAE05PART1OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 単径部痛 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 筋力低下 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 頚部腫瘤 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 変形性関節症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 骨壊死 | 0 | 0 | 0 | 0 |
| 四肢痛 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 骨痛 | 0 | 0 | 0 | 0 |
| 椎間板圧迫 | 0 | 0 | 0 | 0 |
| 血管障害 | 1 (0.9%) | 1 (0.9%) | 4 (3.3%) | 4 (3.3%) |
| 出血 | 0 | 0 | 0 | 0 |
| 低血圧 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 循環虚脱 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 深部静脈血栓症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| リンパ浮腫 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 起立性低血圧 | 0 | 0 | 0 | 0 |
| 精神障害 | 2 (1.8%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 錯乱状態 | 2 (1.8%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 精神障害 | 0 | 0 | 0 | 0 |
| 臨床検査 | 0 | 0 | 1 (0.8%) | 0 |
| 血小板数減少 | 0 | 0 | 0 | 0 |
| 血中クレアチニン増加 | 0 | 0 | 0 | 0 |
| ヘモグロビン減少 | 0 | 0 | 0 | 0 |
| 好中球数減少 | 0 | 0 | 0 | 0 |
| トランスアミナーゼ上昇 | 0 | 0 | 1 (0.8%) | 0 |
| 肝胆道系障害 | 0 | 0 | 2 (1.7%) | 2 (1.7%) |
| 胆管結石 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 胆管炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 胆石症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 中毒性肝炎 | 0 | 0 | 0 | 0 |
| 皮膚および皮下組織障害 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 褥瘡性潰瘍 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 脂肪織炎 | 0 | 0 | 0 | 0 |
| 発疹 | 0 | 0 | 1 (0.8%) | 0 |
| 皮膚潰瘍 | 0 | 0 | 0 | 0 |
| 生殖系および乳房障害 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 骨盤痛 | 0 | 0 | 0 | 0 |
| 子宮腟脱 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 前立腺炎 | 0 | 0 | 0 | 0 |
| 眼障害 | 0 | 0 | 0 | 0 |
| 糖尿病網膜症 | 0 | 0 | 0 | 0 |
| 硝子体出血 | 0 | 0 | 0 | 0 |
| 白内障 | 0 | 0 | 0 | 0 |
| 免疫系障害 | 0 | 0 | 0 | 0 |
| 過敏症 | 0 | 0 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE05PART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae05.sas] 15SEP2015, 14:11

参照元：5.3.5.3.1 ISS TSFAE05PART1OF3

表 2.7.4-付録-20 Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE05PART2OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 139 | | 139 | |
| Subjects with any serious TEAE | 67 (48.2%) | 63 (45.3%) | 80 (57.6%) | 68 (48.9%) |
| System organ class | | | | |
| Preferred term | | | | |
| 感染症および寄生虫症 | 25 (18.0%) | 23 (16.5%) | 40 (28.8%) | 35 (25.2%) |
| 肺炎 | 12 (8.6%) | 11 (7.9%) | 9 (6.5%) | 8 (5.8%) |
| 敗血症 | 4 (2.9%) | 4 (2.9%) | 5 (3.6%) | 5 (3.6%) |
| 蜂巣炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 尿路感染 | 1 (0.7%) | 0 | 3 (2.2%) | 2 (1.4%) |
| 下気道感染 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| 気管支炎 | 0 | 0 | 0 | 0 |
| 胃腸炎 | 1 (0.7%) | 0 | 2 (1.4%) | 2 (1.4%) |
| クロストリジウム・ディフィシレ大腸炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| ニューモシスチス・イロベチイ肺炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 細菌性肺炎 | 0 | 0 | 0 | 0 |
| 敗血症性ショック | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| ブドウ球菌性菌血症 | 0 | 0 | 0 | 0 |
| 腹部膿瘍 | 0 | 0 | 0 | 0 |
| 四肢膿瘍 | 1 (0.7%) | 0 | 0 | 0 |
| 肛門膿瘍 | 0 | 0 | 0 | 0 |
| 虫垂炎 | 0 | 0 | 0 | 0 |
| 穿孔性虫垂炎 | 0 | 0 | 0 | 0 |
| 菌血症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 気管支肺炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| カンピロバクター感染 | 0 | 0 | 0 | 0 |
| 眼窩蜂巣炎 | 0 | 0 | 0 | 0 |
| 医療機器関連感染 | 1 (0.7%) | 1 (0.7%) | 2 (1.4%) | 2 (1.4%) |
| 感染性小腸結腸炎 | 0 | 0 | 0 | 0 |
| ウイルス性胃腸炎 | 0 | 0 | 0 | 0 |
| Ｂ型肝炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 感染 | 1 (0.7%) | 1 (0.7%) | 2 (1.4%) | 0 |
| 喉頭炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 肺感染 | 1 (0.7%) | 1 (0.7%) | 2 (1.4%) | 2 (1.4%) |
| 眼帯状疱疹 | 0 | 0 | 0 | 0 |
| 咽頭炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| クレブシエラ菌性肺炎 | 0 | 0 | 0 | 0 |
| 肺結核 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 腎盂腎炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 気道感染 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚感染 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 軟部組織感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| レンサ球菌感染 | 0 | 0 | 0 | 0 |
| 皮下組織膿瘍 | 0 | 0 | 0 | 0 |
| 気管炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 細菌性尿路感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 尿路性敗血症 | 0 | 0 | 0 | 0 |
| 創傷感染 | 0 | 0 | 0 | 0 |
| 異型肺炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 気管支肺アスペルギルス症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 膀胱炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 憩室炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |

**TSFAE05PART2OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 帯状疱疹 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 感染性大腸炎 | 0 | 0 | 1 (0.7%) | 0 |
| 真菌性喉頭炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 肝膿瘍 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 大葉性肺炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 好中球減少性敗血症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 口腔カンジダ症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| ニューモシスチス・イロベチイ感染 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 大腸菌性肺炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 副鼻腔炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| アスペルギルス性副鼻腔炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 歯感染 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 上気道感染 | 0 | 0 | 2 (1.4%) | 0 |
| 呼吸器、胸郭および縦隔障害 | 18 (12.9%) | 12 (8.6%) | 14 (10.1%) | 11 (7.9%) |
| 呼吸困難 | 6 (4.3%) | 1 (0.7%) | 5 (3.6%) | 4 (2.9%) |
| 呼吸不全 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| 胸水 | 3 (2.2%) | 2 (1.4%) | 0 | 0 |
| 慢性閉塞性肺疾患 | 2 (1.4%) | 2 (1.4%) | 0 | 0 |
| 咳嗽 | 1 (0.7%) | 0 | 0 | 0 |
| 鼻出血 | 2 (1.4%) | 1 (0.7%) | 2 (1.4%) | 1 (0.7%) |
| 低酸素症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 気胸 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 肺塞栓症 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 肺水腫 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 間質性肺疾患 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 肺臓炎 | 0 | 0 | 3 (2.2%) | 2 (1.4%) |
| 一般・全身障害および投与部位の状態 | 11 (7.9%) | 6 (4.3%) | 16 (11.5%) | 8 (5.8%) |
| 発熱 | 3 (2.2%) | 1 (0.7%) | 7 (5.0%) | 2 (1.4%) |
| 末梢性浮腫 | 0 | 0 | 0 | 0 |
| 多臓器不全 | 4 (2.9%) | 4 (2.9%) | 0 | 0 |
| 疲労 | 2 (1.4%) | 0 | 3 (2.2%) | 2 (1.4%) |
| 全身健康状態低下 | 2 (1.4%) | 1 (0.7%) | 5 (3.6%) | 3 (2.2%) |
| 無力症 | 0 | 0 | 0 | 0 |
| 非心臓性胸痛 | 0 | 0 | 0 | 0 |
| 悪寒 | 0 | 0 | 0 | 0 |
| 死亡 | 0 | 0 | 0 | 0 |
| 医療機器リーク | 0 | 0 | 0 | 0 |
| 倦怠感 | 0 | 0 | 1 (0.7%) | 0 |
| 疼痛 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 粘膜の炎症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 浮腫 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 血液およびリンパ系障害 | 12 (8.6%) | 12 (8.6%) | 10 (7.2%) | 9 (6.5%) |
| 発熱性好中球減少症 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| 血小板減少症 | 5 (3.6%) | 4 (2.9%) | 3 (2.2%) | 3 (2.2%) |
| 貧血 | 3 (2.2%) | 3 (2.2%) | 5 (3.6%) | 4 (2.9%) |
| 好中球減少症 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 白血球増加症 | 2 (1.4%) | 2 (1.4%) | 0 | 0 |
| リンパ球増加症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 汎血球減少症 | 0 | 0 | 0 | 0 |
| 後腹膜リンパ節腫脹 | 0 | 0 | 0 | 0 |
| 脾臓出血 | 0 | 0 | 0 | 0 |
| 脾臓梗塞 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 胃腸障害 | 10 (7.2%) | 8 (5.8%) | 13 (9.4%) | 10 (7.2%) |
| 腹痛 | 4 (2.9%) | 4 (2.9%) | 1 (0.7%) | 1 (0.7%) |

**TSFAE05PART2OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 下痢 | 2 (1.4%) | 1 (0.7%) | 4 (2.9%) | 3 (2.2%) |
| 麻痺性イレウス | 0 | 0 | 0 | 0 |
| 悪心 | 0 | 0 | 0 | 0 |
| 小腸閉塞 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 嘔吐 | 0 | 0 | 1 (0.7%) | 0 |
| アフタ性口内炎 | 0 | 0 | 0 | 0 |
| 大腸炎 | 0 | 0 | 0 | 0 |
| 十二指腸狭窄 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 嚥下障害 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 胃潰瘍 | 1 (0.7%) | 0 | 0 | 0 |
| イレウス | 0 | 0 | 0 | 0 |
| 腸炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 出血性胃炎 | 0 | 0 | 1 (0.7%) | 0 |
| 胃腸出血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 痔核 | 0 | 0 | 1 (0.7%) | 0 |
| 腸出血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 下部消化管出血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 口内炎 | 0 | 0 | 3 (2.2%) | 2 (1.4%) |
| 心臓障害 | 8 (5.8%) | 6 (4.3%) | 9 (6.5%) | 7 (5.0%) |
| 心房細動 | 5 (3.6%) | 5 (3.6%) | 2 (1.4%) | 2 (1.4%) |
| 心房粗動 | 0 | 0 | 0 | 0 |
| 心停止 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 急性心筋梗塞 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 不安定狭心症 | 0 | 0 | 0 | 0 |
| 冠動脈硬化症 | 1 (0.7%) | 0 | 0 | 0 |
| 徐脈 | 1 (0.7%) | 0 | 0 | 0 |
| 心不全 | 0 | 0 | 0 | 0 |
| 心血管不全 | 0 | 0 | 0 | 0 |
| 冠動脈閉塞 | 0 | 0 | 0 | 0 |
| 心膜炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 上室性頻脈 | 1 (0.7%) | 0 | 0 | 0 |
| 狭心症 | 0 | 0 | 1 (0.7%) | 0 |
| 急性心不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 慢性心不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| うっ血性心不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 心肺不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 冠動脈狭窄 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 心筋虚血 | 0 | 0 | 1 (0.7%) | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 7 (5.0%) | 6 (4.3%) | 1 (0.7%) | 1 (0.7%) |
| マントル細胞リンパ腫 | 0 | 0 | 0 | 0 |
| 膀胱移行上皮癌 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 前立腺癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 基底細胞癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 膀胱癌 | 0 | 0 | 0 | 0 |
| 悪性胸水 | 0 | 0 | 0 | 0 |
| 遠隔転移を伴う新生物 | 0 | 0 | 0 | 0 |
| 唾液腺癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 扁平上皮癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 胸腺腫 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 移行上皮癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 胃腺癌 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 腎および尿路障害 | 7 (5.0%) | 6 (4.3%) | 6 (4.3%) | 6 (4.3%) |
| 急性腎不全 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 腎不全 | 3 (2.2%) | 3 (2.2%) | 4 (2.9%) | 4 (2.9%) |

**TSFAE05PART2OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 血尿 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 出血性膀胱炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 水腎症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 腎結石症 | 0 | 0 | 0 | 0 |
| 尿路閉塞 | 0 | 0 | 0 | 0 |
| 腎機能障害 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 傷害、中毒および処置合併症 | 8 (5.8%) | 6 (4.3%) | 6 (4.3%) | 3 (2.2%) |
| 硬膜下血腫 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 転倒 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 処置後出血 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 0 |
| 脊椎圧迫骨折 | 0 | 0 | 0 | 0 |
| 脾破裂 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) |
| 動物咬傷 | 0 | 0 | 0 | 0 |
| 腰椎骨折 | 1 (0.7%) | 0 | 0 | 0 |
| 過量投与 | 0 | 0 | 0 | 0 |
| 処置後腫脹 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 肋骨骨折 | 1 (0.7%) | 0 | 0 | 0 |
| 脛骨骨折 | 0 | 0 | 0 | 0 |
| 腓骨骨折 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 体内異物 | 0 | 0 | 1 (0.7%) | 0 |
| 各種物質毒性 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 創傷 | 0 | 0 | 1 (0.7%) | 0 |
| 神経系障害 | 7 (5.0%) | 3 (2.2%) | 6 (4.3%) | 5 (3.6%) |
| 構語障害 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 頭蓋内出血 | 0 | 0 | 0 | 0 |
| 頭痛 | 1 (0.7%) | 0 | 0 | 0 |
| 一過性脳虚血発作 | 1 (0.7%) | 0 | 0 | 0 |
| 脳血管発作 | 0 | 0 | 1 (0.7%) | 0 |
| 脳症 | 0 | 0 | 0 | 0 |
| てんかん | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 顔面不全麻痺 | 1 (0.7%) | 0 | 0 | 0 |
| 記憶障害 | 1 (0.7%) | 0 | 0 | 0 |
| ミオクローヌス | 1 (0.7%) | 0 | 0 | 0 |
| 失神寸前の状態 | 0 | 0 | 0 | 0 |
| 失神 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 一過性全健忘 | 0 | 0 | 0 | 0 |
| 運動失調 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 脳虚血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 虚血性脳卒中 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 神経痛 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 振戦 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 代謝および栄養障害 | 5 (3.6%) | 4 (2.9%) | 8 (5.8%) | 7 (5.0%) |
| 脱水 | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 悪液質 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 糖尿病性ケトアシドーシス | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 高尿酸血症 | 0 | 0 | 0 | 0 |
| 低アルブミン血症 | 0 | 0 | 0 | 0 |
| 腫瘍崩壊症候群 | 1 (0.7%) | 1 (0.7%) | 3 (2.2%) | 3 (2.2%) |
| 食欲減退 | 0 | 0 | 2 (1.4%) | 2 (1.4%) |
| 糖尿病 | 0 | 0 | 1 (0.7%) | 0 |
| 低カリウム血症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 低ナトリウム血症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 筋骨格系および結合組織障害 | 3 (2.2%) | 3 (2.2%) | 4 (2.9%) | 3 (2.2%) |
| 側腹部痛 | 0 | 0 | 0 | 0 |
| 関節痛 | 0 | 0 | 0 | 0 |
| 背部痛 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |

**TSFAE05PART2OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 痛風性関節炎 | 0 | 0 | 0 | 0 |
| 鼡径部痛 | 0 | 0 | 0 | 0 |
| 筋力低下 | 0 | 0 | 0 | 0 |
| 頚部腫瘤 | 0 | 0 | 0 | 0 |
| 変形性関節症 | 0 | 0 | 0 | 0 |
| 骨壊死 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 四肢痛 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 骨痛 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 椎間板圧迫 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 血管障害 | 3 (2.2%) | 2 (1.4%) | 1 (0.7%) | 0 |
| 出血 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 低血圧 | 0 | 0 | 0 | 0 |
| 循環虚脱 | 0 | 0 | 0 | 0 |
| 深部静脈血栓症 | 0 | 0 | 1 (0.7%) | 0 |
| リンパ浮腫 | 0 | 0 | 0 | 0 |
| 起立性低血圧 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 精神障害 | 2 (1.4%) | 1 (0.7%) | 2 (1.4%) | 2 (1.4%) |
| 錯乱状態 | 1 (0.7%) | 1 (0.7%) | 2 (1.4%) | 2 (1.4%) |
| 精神障害 | 1 (0.7%) | 0 | 0 | 0 |
| 臨床検査 | 3 (2.2%) | 2 (1.4%) | 0 | 0 |
| 血小板数減少 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 血中クレアチニン増加 | 1 (0.7%) | 0 | 0 | 0 |
| ヘモグロビン減少 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 好中球数減少 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| トランスアミナーゼ上昇 | 0 | 0 | 0 | 0 |
| 肝胆道系障害 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 胆管結石 | 0 | 0 | 0 | 0 |
| 胆管炎 | 0 | 0 | 0 | 0 |
| 胆石症 | 0 | 0 | 0 | 0 |
| 中毒性肝炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 皮膚および皮下組織障害 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 褥瘡性潰瘍 | 0 | 0 | 0 | 0 |
| 脂肪織炎 | 1 (0.7%) | 0 | 0 | 0 |
| 発疹 | 0 | 0 | 0 | 0 |
| 皮膚潰瘍 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 生殖系および乳房障害 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 骨盤痛 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 子宮腟脱 | 0 | 0 | 0 | 0 |
| 前立腺炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 眼障害 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 糖尿病網膜症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 硝子体出血 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 白内障 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 免疫系障害 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 過敏症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE05PART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae05.sas] 15SEP2015, 14:11

参照元：5.3.5.3.1 ISS TSFAE05PART2OF3

表 2.7.4-付録-21 Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)

**TSFAE05PART3OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 370 | |
| Subjects with any serious TEAE | 188 (50.8%) | 171 (46.2%) |
| System organ class | | |
| Preferred term | | |
| 感染症および寄生虫症 | 76 (20.5%) | 71 (19.2%) |
| 肺炎 | 32 (8.6%) | 30 (8.1%) |
| 敗血症 | 9 (2.4%) | 9 (2.4%) |
| 蜂巣炎 | 7 (1.9%) | 7 (1.9%) |
| 尿路感染 | 6 (1.6%) | 4 (1.1%) |
| 下気道感染 | 4 (1.1%) | 4 (1.1%) |
| 気管支炎 | 3 (0.8%) | 3 (0.8%) |
| 胃腸炎 | 3 (0.8%) | 2 (0.5%) |
| クロストリジウム・ディフィシレ大腸炎 | 2 (0.5%) | 1 (0.3%) |
| ニューモシスチス・イロベチイ肺炎 | 2 (0.5%) | 2 (0.5%) |
| 細菌性肺炎 | 2 (0.5%) | 2 (0.5%) |
| 敗血症性ショック | 2 (0.5%) | 2 (0.5%) |
| ブドウ球菌性菌血症 | 2 (0.5%) | 1 (0.3%) |
| 腹部膿瘍 | 1 (0.3%) | 1 (0.3%) |
| 四肢膿瘍 | 1 (0.3%) | 0 |
| 肛門膿瘍 | 1 (0.3%) | 0 |
| 虫垂炎 | 1 (0.3%) | 1 (0.3%) |
| 穿孔性虫垂炎 | 1 (0.3%) | 1 (0.3%) |
| 菌血症 | 1 (0.3%) | 1 (0.3%) |
| 気管支肺炎 | 1 (0.3%) | 1 (0.3%) |
| カンピロバクター感染 | 1 (0.3%) | 1 (0.3%) |
| 眼窩蜂巣炎 | 1 (0.3%) | 1 (0.3%) |
| 医療機器関連感染 | 1 (0.3%) | 1 (0.3%) |
| 感染性小腸結腸炎 | 1 (0.3%) | 1 (0.3%) |
| ウイルス性胃腸炎 | 1 (0.3%) | 1 (0.3%) |
| Ｂ型肝炎 | 1 (0.3%) | 1 (0.3%) |
| 感染 | 1 (0.3%) | 1 (0.3%) |
| 喉頭炎 | 1 (0.3%) | 1 (0.3%) |
| 肺感染 | 1 (0.3%) | 1 (0.3%) |
| 眼帯状疱疹 | 1 (0.3%) | 1 (0.3%) |
| 咽頭炎 | 1 (0.3%) | 1 (0.3%) |
| クレブシエラ菌性肺炎 | 1 (0.3%) | 1 (0.3%) |
| 肺結核 | 1 (0.3%) | 1 (0.3%) |
| 腎盂腎炎 | 1 (0.3%) | 1 (0.3%) |
| 気道感染 | 1 (0.3%) | 1 (0.3%) |
| 皮膚感染 | 1 (0.3%) | 1 (0.3%) |
| 軟部組織感染 | 1 (0.3%) | 1 (0.3%) |
| レンサ球菌感染 | 1 (0.3%) | 1 (0.3%) |
| 皮下組織膿瘍 | 1 (0.3%) | 1 (0.3%) |
| 気管炎 | 1 (0.3%) | 1 (0.3%) |
| 細菌性尿路感染 | 1 (0.3%) | 1 (0.3%) |
| 尿路性敗血症 | 1 (0.3%) | 1 (0.3%) |
| 創傷感染 | 1 (0.3%) | 1 (0.3%) |
| 異型肺炎 | 0 | 0 |
| 気管支肺アスペルギルス症 | 0 | 0 |
| 膀胱炎 | 0 | 0 |
| 憩室炎 | 0 | 0 |
| 帯状疱疹 | 0 | 0 |

**TSFAE05PART3OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 感染性大腸炎 | 0 | 0 |
| 真菌性喉頭炎 | 0 | 0 |
| 肝膿瘍 | 0 | 0 |
| 大葉性肺炎 | 0 | 0 |
| 好中球減少性敗血症 | 0 | 0 |
| 口腔カンジダ症 | 0 | 0 |
| ニューモシスチス・イロベチイ感染 | 0 | 0 |
| 大腸菌性肺炎 | 0 | 0 |
| 副鼻腔炎 | 0 | 0 |
| アスペルギルス性副鼻腔炎 | 0 | 0 |
| 歯感染 | 0 | 0 |
| 上気道感染 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 35 (9.5%) | 24 (6.5%) |
| 呼吸困難 | 13 (3.5%) | 5 (1.4%) |
| 呼吸不全 | 8 (2.2%) | 8 (2.2%) |
| 胸水 | 5 (1.4%) | 4 (1.1%) |
| 慢性閉塞性肺疾患 | 3 (0.8%) | 3 (0.8%) |
| 咳嗽 | 3 (0.8%) | 0 |
| 鼻出血 | 2 (0.5%) | 1 (0.3%) |
| 低酸素症 | 2 (0.5%) | 2 (0.5%) |
| 気胸 | 2 (0.5%) | 1 (0.3%) |
| 肺塞栓症 | 1 (0.3%) | 1 (0.3%) |
| 肺水腫 | 1 (0.3%) | 1 (0.3%) |
| 間質性肺疾患 | 0 | 0 |
| 肺臓炎 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 30 (8.1%) | 16 (4.3%) |
| 発熱 | 8 (2.2%) | 3 (0.8%) |
| 末梢性浮腫 | 5 (1.4%) | 4 (1.1%) |
| 多臓器不全 | 4 (1.1%) | 4 (1.1%) |
| 疲労 | 3 (0.8%) | 1 (0.3%) |
| 全身健康状態低下 | 3 (0.8%) | 2 (0.5%) |
| 無力症 | 2 (0.5%) | 1 (0.3%) |
| 非心臓性胸痛 | 2 (0.5%) | 1 (0.3%) |
| 悪寒 | 1 (0.3%) | 0 |
| 死亡 | 1 (0.3%) | 1 (0.3%) |
| 医療機器リーク | 1 (0.3%) | 0 |
| 倦怠感 | 1 (0.3%) | 0 |
| 疼痛 | 1 (0.3%) | 1 (0.3%) |
| 粘膜の炎症 | 0 | 0 |
| 浮腫 | 0 | 0 |
| 血液およびリンパ系障害 | 29 (7.8%) | 29 (7.8%) |
| 発熱性好中球減少症 | 11 (3.0%) | 11 (3.0%) |
| 血小板減少症 | 7 (1.9%) | 5 (1.4%) |
| 貧血 | 6 (1.6%) | 6 (1.6%) |
| 好中球減少症 | 4 (1.1%) | 3 (0.8%) |
| 白血球増加症 | 2 (0.5%) | 2 (0.5%) |
| リンパ球増加症 | 1 (0.3%) | 1 (0.3%) |
| 汎血球減少症 | 1 (0.3%) | 1 (0.3%) |
| 後腹膜リンパ節腫脹 | 1 (0.3%) | 1 (0.3%) |
| 脾臓出血 | 1 (0.3%) | 1 (0.3%) |
| 脾臓梗塞 | 1 (0.3%) | 1 (0.3%) |
| 胃腸障害 | 26 (7.0%) | 19 (5.1%) |
| 腹痛 | 10 (2.7%) | 9 (2.4%) |
| 下痢 | 4 (1.1%) | 2 (0.5%) |
| 麻痺性イレウス | 2 (0.5%) | 2 (0.5%) |

**TSFAE05PART3OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 悪心 | 2 (0.5%) | 0 |
| 小腸閉塞 | 2 (0.5%) | 2 (0.5%) |
| 嘔吐 | 2 (0.5%) | 0 |
| アフタ性口内炎 | 1 (0.3%) | 1 (0.3%) |
| 大腸炎 | 1 (0.3%) | 1 (0.3%) |
| 十二指腸狭窄 | 1 (0.3%) | 1 (0.3%) |
| 嚥下障害 | 1 (0.3%) | 1 (0.3%) |
| 胃潰瘍 | 1 (0.3%) | 0 |
| イレウス | 1 (0.3%) | 0 |
| 腸炎 | 0 | 0 |
| 出血性胃炎 | 0 | 0 |
| 胃腸出血 | 0 | 0 |
| 痔核 | 0 | 0 |
| 腸出血 | 0 | 0 |
| 下部消化管出血 | 0 | 0 |
| 口内炎 | 0 | 0 |
| 心臓障害 | 24 (6.5%) | 20 (5.4%) |
| 心房細動 | 15 (4.1%) | 13 (3.5%) |
| 心房粗動 | 2 (0.5%) | 1 (0.3%) |
| 心停止 | 2 (0.5%) | 2 (0.5%) |
| 急性心筋梗塞 | 1 (0.3%) | 1 (0.3%) |
| 不安定狭心症 | 1 (0.3%) | 1 (0.3%) |
| 冠動脈硬化症 | 1 (0.3%) | 0 |
| 徐脈 | 1 (0.3%) | 0 |
| 心不全 | 1 (0.3%) | 1 (0.3%) |
| 心血管不全 | 1 (0.3%) | 1 (0.3%) |
| 冠動脈閉塞 | 1 (0.3%) | 1 (0.3%) |
| 心膜炎 | 1 (0.3%) | 1 (0.3%) |
| 上室性頻脈 | 1 (0.3%) | 0 |
| 狭心症 | 0 | 0 |
| 急性心不全 | 0 | 0 |
| 慢性心不全 | 0 | 0 |
| うっ血性心不全 | 0 | 0 |
| 心肺不全 | 0 | 0 |
| 冠動脈狭窄 | 0 | 0 |
| 心筋虚血 | 0 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 18 (4.9%) | 17 (4.6%) |
| マントル細胞リンパ腫 | 8 (2.2%) | 8 (2.2%) |
| 膀胱移行上皮癌 | 2 (0.5%) | 1 (0.3%) |
| 前立腺癌 | 2 (0.5%) | 2 (0.5%) |
| 基底細胞癌 | 1 (0.3%) | 1 (0.3%) |
| 膀胱癌 | 1 (0.3%) | 1 (0.3%) |
| 悪性胸水 | 1 (0.3%) | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 1 (0.3%) | 1 (0.3%) |
| 唾液腺癌 | 1 (0.3%) | 1 (0.3%) |
| 扁平上皮癌 | 1 (0.3%) | 1 (0.3%) |
| 胸腺腫 | 1 (0.3%) | 1 (0.3%) |
| 移行上皮癌 | 1 (0.3%) | 1 (0.3%) |
| 胃腺癌 | 0 | 0 |
| 腎および尿路障害 | 18 (4.9%) | 15 (4.1%) |
| 急性腎不全 | 8 (2.2%) | 5 (1.4%) |
| 腎不全 | 4 (1.1%) | 4 (1.1%) |
| 血尿 | 3 (0.8%) | 3 (0.8%) |
| 出血性膀胱炎 | 1 (0.3%) | 1 (0.3%) |
| 水腎症 | 1 (0.3%) | 1 (0.3%) |

**TSFAE05PART3OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 腎結石症 | 1 (0.3%) | 1 (0.3%) |
| 尿路閉塞 | 1 (0.3%) | 1 (0.3%) |
| 腎機能障害 | 0 | 0 |
| 傷害、中毒および処置合併症 | 17 (4.6%) | 11 (3.0%) |
| 硬膜下血腫 | 4 (1.1%) | 3 (0.8%) |
| 転倒 | 2 (0.5%) | 1 (0.3%) |
| 処置後出血 | 2 (0.5%) | 2 (0.5%) |
| 脊椎圧迫骨折 | 2 (0.5%) | 1 (0.3%) |
| 脾破裂 | 2 (0.5%) | 2 (0.5%) |
| 動物咬傷 | 1 (0.3%) | 1 (0.3%) |
| 腰椎骨折 | 1 (0.3%) | 0 |
| 過量投与 | 1 (0.3%) | 1 (0.3%) |
| 処置後腫脹 | 1 (0.3%) | 1 (0.3%) |
| 肋骨骨折 | 1 (0.3%) | 0 |
| 脛骨骨折 | 1 (0.3%) | 0 |
| 腓骨骨折 | 0 | 0 |
| 体内異物 | 0 | 0 |
| 各種物質毒性 | 0 | 0 |
| 創傷 | 0 | 0 |
| 神経系障害 | 15 (4.1%) | 5 (1.4%) |
| 構語障害 | 2 (0.5%) | 1 (0.3%) |
| 頭蓋内出血 | 2 (0.5%) | 0 |
| 頭痛 | 2 (0.5%) | 0 |
| 一過性脳虚血発作 | 2 (0.5%) | 0 |
| 脳血管発作 | 1 (0.3%) | 1 (0.3%) |
| 脳症 | 1 (0.3%) | 1 (0.3%) |
| てんかん | 1 (0.3%) | 1 (0.3%) |
| 顔面不全麻痺 | 1 (0.3%) | 0 |
| 記憶障害 | 1 (0.3%) | 0 |
| ミオクローヌス | 1 (0.3%) | 0 |
| 失神寸前の状態 | 1 (0.3%) | 0 |
| 失神 | 1 (0.3%) | 1 (0.3%) |
| 一過性全健忘 | 1 (0.3%) | 0 |
| 運動失調 | 0 | 0 |
| 脳虚血 | 0 | 0 |
| 虚血性脳卒中 | 0 | 0 |
| 神経痛 | 0 | 0 |
| 振戦 | 0 | 0 |
| 代謝および栄養障害 | 10 (2.7%) | 9 (2.4%) |
| 脱水 | 5 (1.4%) | 4 (1.1%) |
| 悪液質 | 1 (0.3%) | 1 (0.3%) |
| 糖尿病性ケトアシドーシス | 1 (0.3%) | 1 (0.3%) |
| 高尿酸血症 | 1 (0.3%) | 1 (0.3%) |
| 低アルブミン血症 | 1 (0.3%) | 1 (0.3%) |
| 腫瘍崩壊症候群 | 1 (0.3%) | 1 (0.3%) |
| 食欲減退 | 0 | 0 |
| 糖尿病 | 0 | 0 |
| 低カリウム血症 | 0 | 0 |
| 低ナトリウム血症 | 0 | 0 |
| 筋骨格系および結合組織障害 | 8 (2.2%) | 8 (2.2%) |
| 側腹部痛 | 2 (0.5%) | 2 (0.5%) |
| 関節痛 | 1 (0.3%) | 0 |
| 背部痛 | 1 (0.3%) | 1 (0.3%) |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 1 (0.3%) | 1 (0.3%) |
| 痛風性関節炎 | 1 (0.3%) | 1 (0.3%) |
| 鼡径部痛 | 1 (0.3%) | 1 (0.3%) |

**TSFAE05PART3OF3: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 筋力低下 | 1 (0.3%) | 1 (0.3%) |
| 頚部腫瘤 | 1 (0.3%) | 1 (0.3%) |
| 変形性関節症 | 1 (0.3%) | 1 (0.3%) |
| 骨壊死 | 1 (0.3%) | 1 (0.3%) |
| 四肢痛 | 1 (0.3%) | 1 (0.3%) |
| 骨痛 | 0 | 0 |
| 椎間板圧迫 | 0 | 0 |
| 血管障害 | 8 (2.2%) | 7 (1.9%) |
| 出血 | 2 (0.5%) | 1 (0.3%) |
| 低血圧 | 2 (0.5%) | 2 (0.5%) |
| 循環虚脱 | 1 (0.3%) | 1 (0.3%) |
| 深部静脈血栓症 | 1 (0.3%) | 1 (0.3%) |
| リンパ浮腫 | 1 (0.3%) | 1 (0.3%) |
| 起立性低血圧 | 1 (0.3%) | 1 (0.3%) |
| 精神障害 | 5 (1.4%) | 2 (0.5%) |
| 錯乱状態 | 4 (1.1%) | 2 (0.5%) |
| 精神障害 | 1 (0.3%) | 0 |
| 臨床検査 | 4 (1.1%) | 2 (0.5%) |
| 血小板数減少 | 2 (0.5%) | 1 (0.3%) |
| 血中クレアチニン増加 | 1 (0.3%) | 0 |
| ヘモグロビン減少 | 1 (0.3%) | 1 (0.3%) |
| 好中球数減少 | 1 (0.3%) | 1 (0.3%) |
| トランスアミナーゼ上昇 | 1 (0.3%) | 0 |
| 肝胆道系障害 | 3 (0.8%) | 3 (0.8%) |
| 胆管結石 | 1 (0.3%) | 1 (0.3%) |
| 胆管炎 | 1 (0.3%) | 1 (0.3%) |
| 胆石症 | 1 (0.3%) | 1 (0.3%) |
| 中毒性肝炎 | 1 (0.3%) | 1 (0.3%) |
| 皮膚および皮下組織障害 | 3 (0.8%) | 1 (0.3%) |
| 褥瘡性潰瘍 | 1 (0.3%) | 1 (0.3%) |
| 脂肪織炎 | 1 (0.3%) | 0 |
| 発疹 | 1 (0.3%) | 0 |
| 皮膚潰瘍 | 0 | 0 |
| 生殖系および乳房障害 | 2 (0.5%) | 2 (0.5%) |
| 骨盤痛 | 1 (0.3%) | 1 (0.3%) |
| 子宮腟脱 | 1 (0.3%) | 1 (0.3%) |
| 前立腺炎 | 0 | 0 |
| 眼障害 | 1 (0.3%) | 1 (0.3%) |
| 糖尿病網膜症 | 1 (0.3%) | 1 (0.3%) |
| 硝子体出血 | 1 (0.3%) | 1 (0.3%) |
| 白内障 | 0 | 0 |
| 免疫系障害 | 0 | 0 |
| 過敏症 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE05PART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae05.sas] 15SEP2015, 14:11

参照元：5.3.5.3.1 ISS TSFAE05PART3OF3

表 2.7.4-付録-22 Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PCYC-1104 | Ibrutinib | 006-002 | 7[redacted]/Male/ White | | Neutropenic fever | 発熱性好中球減少症 | 3 | Yes | 2012-01-11/ 2012-01-15 | 205/209/5 | Very likely/ Multiple | Recovered/resolved |
| | | 006-003 | 8[redacted]/Male/ Native Hawaiian Or Other Pacific Islander | 420 mg | Ileus | イレウス | 2 | Yes | 2012-04-15/ 2012-04-19 | 300/304/5 | Not related/ | Recovered/resolved |
| | | | | 420 mg | L3 compression fracture | 脊椎圧迫骨折 | 2 | Yes | 2012-04-14/ 2012-04-19 | 299/304/6 | Not related/ | Recovered/resolved |
| | | 006-004 | 7[redacted]/Male/ White | 560 mg | Pneumonia | 肺炎 | 5 | Yes | 2011-10-01/ | 74/ | Possible/ Drug withdrawn | Fatal |
| | | 006-005 | 6[redacted]/Male/ White | | Abdominal pain | 腹痛 | 3 | Yes | 2012-03-21/ 2012-03-23 | 176/178/3 | Not related/ | Recovered/resolved |
| | | 006-006 | 7[redacted]/Female/ White | 560 mg | Incomplete uterovaginal prolapse | 子宮腟脱 | 3 | Yes | 2012-08-24/ 2012-10-12 | 199/248/50 | Not related/ Drug interrupted | Recovered/resolved |
| | | 032-001 | 6[redacted]/Male/ White | | Neutropenic fever | 発熱性好中球減少症 | 3 | Yes | 2011-03-11/ 2011-03-13 | 18/20/3 | Possible/ Drug interrupted | Recovered/resolved |
| | | 032-002 | 6[redacted]/Male/ White | | Abdominal pain | 腹痛 | 3 | Yes | 2011-06-08/ 2011-06-18 | 94/104/11 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Right side subdural hematoma | 硬膜下血腫 | 3 | Yes | 2011-06-10/ 2011-06-27 | 96/113/18 | Not related/ Drug interrupted | Recovered/resolved |
| | | 032-003 | 5[redacted]/Male/ White | 560 mg | Neutropenic fever | 発熱性好中球減少症 | 3 | Yes | 2011-08-04/ 2011-08-09 | 150/155/6 | Possible/ Drug interrupted | Recovered/resolved |
| | | 032-005 | 7[redacted]/Male/ Black Or African American | | Acute bronchitis | 気管支炎 | 3 | Yes | 2012-11-05/ 2012-11-09 | 593/597/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Acute infectious enterocolitis | 感染性小腸結腸炎 | 3 | Yes | 2012-11-05/ 2012-11-09 | 593/597/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Atrial fibrillation | 心房細動 | 3 | Yes | 2012-05-23/ 2012-05-30 | 427/434/8 | Possible/ | Recovered/resolved |
| | | | | 560 mg | Cellulitis | 蜂巣炎 | 3 | Yes | 2011-08-18/ 2011-10-05 | 148/196/49 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | New onset atrial fibrillation | 心房細動 | 3 | Yes | 2012-03-28/ 2012-03-29 | 371/372/2 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2012-05-23/ 2012-05-30 | 427/434/8 | Not related/ Drug interrupted | Recovered/resolved |
| | | 032-007 | 5[redacted]/Male/ White | | Adynamic ileus | 麻痺性イレウス | 3 | Yes | 2012-08-30/ 2012-09-01 | 525/527/3 | Not related/ Drug interrupted | Recovered/resolved |

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 032-008 | 6[redacted]/Male/ Black Or African American | | Acute renal failure | 急性腎不全 | 3 | Yes | 2012-08-24/ 2012-09-10 | 512/529/18 | Not related/ Drug interrupted | Recovered/resolved |
| | | 032-010 | 7[redacted]/Male/ White | | Urnary tract infection | 尿路感染 | 3 | Yes | 2011-09-26/ 2011-09-28 | 140/142/3 | Not related/ | Recovered/resolved |
| | | 032-012 | 7[redacted]/Male/ White | 560 mg | Acute bronchitis | 気管支炎 | 3 | Yes | 2011-09-25/ 2011-09-29 | 136/140/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Hypotension | 低血圧 | 3 | Yes | 2012-06-03/ 2012-06-05 | 388/390/3 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | New onset atrial fibrillation | 心房細動 | 3 | Yes | 2011-09-25/ 2011-09-29 | 136/140/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2011-11-24/ 2011-11-28 | 196/200/5 | Possible/ | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2012-01-06/ 2012-01-10 | 239/243/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | 032-014 | 6[redacted]/Male/ White | | Atrial fibrillation with rapid ventricular response | 心房細動 | 3 | Yes | 2011-10-13/ 2011-10-14 | 144/145/2 | Not related/ | Recovered/resolved |
| | | 032-016 | 6[redacted]/Male/ White | | Chronic obstructive pulmonary disease acerbation | 慢性閉塞性肺疾患 | 3 | Yes | 2011-06-10/ 2011-08-02 | 10/63/54 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Chronic obstructive pulmonary disease exacerbation | 慢性閉塞性肺疾患 | 3 | Yes | 2011-09-22/ 2011-11-14 | 114/167/54 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Copd exaceration | 慢性閉塞性肺疾患 | 3 | Yes | 2012-02-24/ 2012-03-01 | 269/275/7 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Coronary artery occlusion | 冠動脈閉塞 | 3 | Yes | 2012-04-25/ 2012-04-25 | 330/330/1 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Klebsiella gram-negative pneumonia | クレブシエラ菌性肺炎 | 3 | Yes | 2011-09-22/ 2011-11-14 | 114/167/54 | Possible/ Drug interrupted | Recovered/resolved |
| | | 032-020 | 6[redacted]/Female/ White | 560 mg | Non-cardiac chest pain | 非心臓性胸痛 | 3 | Yes | 2011-10-01/ 2011-10-02 | 115/116/2 | Not related/ | Recovered/resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2011-06-14/ 2011-06-17 | 6/9/4 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2012-11-22/ 2012-11-27 | 533/538/6 | Possible/ Drug interrupted | Recovered/resolved |
| | | 032-021 | 7[redacted]/Male/ White | | Hematuria | 血尿 | 3 | Yes | 2011-07-26/ 2011-07-28 | 43/45/3 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Urinary obstruction | 尿路閉塞 | 3 | Yes | 2011-07-11/ 2011-07-16 | 28/33/6 | Not related/ Drug interrupted | Recovered/resolved |
| | | 032-022 | 6[redacted]/Male/ White | | Anemia | 貧血 | 3 | Yes | 2012-05-13/ 2012-05-17 | 336/340/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | 032-023 | 6[redacted]/Male/ White | 560 mg | Cellulitis in the chest | 蜂巣炎 | 3 | Yes | 2011-09-21/ 2011-09-27 | 94/100/7 | Possible/ Drug interrupted | Recovered/resolved |

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 032-024 | 7[redacted]/Female/ White | | Rle infection with streptococcus gallolyticus | レンサ球菌感染 | 3 | Yes | 2012-04-01/ 2012-04-17 | 284/300/17 | Not related/ Drug interrupted | Recovered/resolved |
| | | 032-030 | 7[redacted]/Male/ White | | Clostridium difficile colitis | クロストリジウム・ディフィシレ大腸炎 | 3 | Yes | 2012-09-12/ 2012-09-15 | 406/409/4 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Neutropenia | 好中球減少症 | 4 | Yes | 2012-06-08/ 2012-06-14 | 310/316/7 | Possible/ Multiple | Recovered/resolved |
| | | 038-001 | 8[redacted]/Male/ White | 560 mg | Atrial flutter | 心房粗動 | 3 | Yes | 2012-03-20/ 2012-03-22 | 322/324/3 | Not related/ | Recovered/resolved |
| | | | | 560 mg | Gastroenteritis | 胃腸炎 | 3 | Yes | 2012-03-18/ 2012-03-22 | 320/324/5 | Not related/ | Recovered/resolved |
| | | 038-002 | 6[redacted]/Male/ White | | Fever | 発熱 | 3 | Yes | 2012-09-29/ 2012-10-02 | 439/442/4 | Not related/ | Recovered/resolved |
| | | | | | Inguinal pain | 鼠径部痛 | 3 | Yes | 2012-09-25/ 2012-09-28 | 435/438/4 | Not related/ | Recovered/resolved |
| | | | | | Osteoarthritis | 変形性関節症 | 3 | Yes | 2012-07-11/ 2012-07-14 | 359/362/4 | Not related/ | Recovered/resolved |
| | | | | | Right flank pain | 側腹部痛 | 3 | Yes | 2012-09-25/ 2012-09-28 | 435/438/4 | Not related/ | Recovered/resolved |
| | | | | | Right knee pain | 関節痛 | 2 | Yes | 2012-07-11/ 2012-07-14 | 359/362/4 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Shortness of breath | 呼吸困難 | 3 | Yes | 2012-09-25/ 2012-09-28 | 435/438/4 | Not related/ | Recovered/resolved |
| | | | | | Shortness of breath | 呼吸困難 | 3 | Yes | 2012-09-29/ 2012-10-02 | 439/442/4 | Not related/ | Recovered/resolved |
| | | 200-003 | 6[redacted]/Female/ White | | Small bowel obstruction | 小腸閉塞 | 3 | Yes | 2011-07-12/ 2011-07-24 | 106/118/13 | Not related/ Drug interrupted | Recovered/resolved |
| | | 200-004 | 5[redacted]/Male/ Black Or African American | | Right lower flank pain | 側腹部痛 | 3 | Yes | 2011-07-19/ 2011-07-23 | 56/60/5 | Not related/ Drug interrupted | Recovered/resolved |
| | | 200-005 | 7[redacted]/Female/ White | | Dyspnea | 呼吸困難 | 5 | Yes | 2011-07-13/ | 49/ | Not related/ | Fatal |
| | | 200-006 | 5[redacted]/Female/ White | | Pancytopenia | 汎血球減少症 | 4 | Yes | 2011-09-30/ 2011-10-10 | 60/70/11 | Possible/ Drug interrupted | Recovered/resolved |
| | | 200-007 | 8[redacted]/Female/ White | | Atrial fibrillation | 心房細動 | 3 | Yes | 2011-10-18/ 2011-10-22 | 63/67/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | 210-003 | 8[redacted]/Male/ White | | Bacterial pneumonia | 細菌性肺炎 | 3 | Yes | 2012-03-21/ 2012-03-29 | 77/85/9 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Bacterial pneumonia | 細菌性肺炎 | 3 | Yes | 2012-02-25/ 2012-03-14 | 52/70/19 | Possible/ Drug interrupted | Recovered/resolved |
| | | 217-001 | 6[redacted]/Male/ White | 560 mg | Headache | 頭痛 | 2 | Yes | 2011-09-29/ 2011-09-30 | 99/100/2 | Possible/ | Recovered/resolved |
| | | 217-005 | 6[redacted]/Male/ White | 560 mg | Edema limbs | 末梢性浮腫 | 2 | Yes | 2011-09-08/ 2011-09-12 | 39/43/5 | Not related/ | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 217-006 | 7[redacted]/Male/ White | 560 mg | Acute renal failure | 急性腎不全 | 5 | Yes | 2011-11-02/ | 78/ | Not related/ | Fatal |
| | | 217-008 | 7[redacted]/Male/ White | 560 mg | Edema limbs, bilateral lower extremities | 末梢性浮腫 | 4 | Yes | 2012-01-04/ | 43/ | Not related/ | Not recovered/not resolved |
| | | | | | Mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-02-03/ | 73/ | Not related/ | Fatal |
| | | 217-009 | 8[redacted]/Female/ Black Or African American | | Acute kidney injury | 急性腎不全 | 3 | Yes | 2012-04-20/ 2012-04-23 | 108/111/4 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Sepsis unknown | 敗血症 | 4 | Yes | 2012-05-24/ 2012-05-29 | 142/147/6 | Possible/ Multiple | Recovered/resolved |
| | | | | | Urinary tract infection | 尿路感染 | 3 | Yes | 2012-05-09/ 2012-05-21 | 127/139/13 | Not related/ Drug interrupted | Recovered/resolved |
| | | 217-013 | 7[redacted]/Female/ White | 560 mg | Anemia | 貧血 | 3 | Yes | 2012-04-09/ 2012-04-10 | 47/48/2 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Edema limbs- bilateral lower extremities | 末梢性浮腫 | 3 | Yes | 2012-05-05/ 2012-05-08 | 73/76/4 | Not related/ | Recovered/resolved |
| | | 217-014 | 6[redacted]/Female/ White | 420 mg | Fever | 発熱 | 1 | Yes | 2012-05-26/ 2012-05-27 | 74/75/2 | Possible/ Drug interrupted | Recovered/resolved |
| | | 251-001 | 7[redacted]/Male/ White | 560 mg | Diarrhea | 下痢 | 3 | Yes | 2011-11-06/ 2011-11-22 | 17/33/17 | Possible/ Multiple | Recovered/resolved |
| | | 343-001 | 7[redacted]/Male/ White | 560 mg | Non cardiac chest pain | 非心臓性胸痛 | 2 | Yes | 2011-03-09/ 2011-03-10 | 22/23/2 | Not related/ | Recovered/resolved |
| | | | | 560 mg | Subdural hematoma | 硬膜下血腫 | 2 | Yes | 2012-09-13/ 2012-12-12 | 576/666/91 | Possible/ Multiple | Recovered/resolved |
| | | | | 560 mg | Transient global amnesia | 一過性全健忘 | 1 | Yes | 2012-02-19/ 2012-02-20 | 369/370/2 | Not related/ | Recovered/resolved |
| | | 343-002 | 6[redacted]/Male/ White | 560 mg | Abdominal pain | 腹痛 | 3 | Yes | 2011-10-03/ | 229/ | Not related/ | Not recovered/not resolved |
| | | 343-005 | 7[redacted]/Male/ White | | Bilateral subdural hematoma | 硬膜下血腫 | 3 | Yes | 2011-07-19/ 2011-07-27 | 56/64/9 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Staph bacteremia-mrsa & mssa | ブドウ球菌性菌血症 | 3 | Yes | 2011-08-25/ 2011-09-04 | 93/103/11 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Subdural hematoma | 硬膜下血腫 | 3 | Yes | 2011-08-25/ 2011-09-04 | 93/103/11 | Not related/ Multiple | Recovered/resolved |
| | | 343-007 | 7[redacted]/Male/ White | | Bladder carcinoma | 膀胱癌 | 3 | Yes | 2012-07-31/ 2012-08-10 | 210/220/11 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Metastatic adenocarcinoma | 遠隔転移を伴う新生物 | 3 | Yes | 2012-09-19/ | 260/ | Possible/ Drug withdrawn | Not recovered/not resolved |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2012-04-24/ 2012-04-28 | 112/116/5 | Possible/ Drug interrupted | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 350-001 | 6[redacted]/Male/ White | | Hypoxia | 低酸素症 | 3 | Yes | 2012-02-21/ | 63/ | Not related/ | Not recovered/not resolved |
| | | | | | Malignant pleural effusion | 悪性胸水 | 5 | Yes | 2012-02-21/ | 63/ | Not related/ | Fatal |
| | | | | 560 mg | Malignant pleural effusion | 悪性胸水 | 4 | Yes | 2012-01-25/ 2012-01-31 | 36/42/7 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Renal failure | 腎不全 | 3 | Yes | 2012-01-28/ 2012-02-25 | 39/67/29 | Not related/ | Recovered/resolved |
| | | | | | Respiratory failure | 呼吸不全 | 4 | Yes | 2012-02-21/ | 63/ | Not related/ | Not recovered/not resolved |
| | | 354-001 | 6[redacted]/Male/ White | 560 mg | Decreased general condition | 全身健康状態低下 | 3 | Yes | 2012-03-07/ | 98/ | Not related/ | Not recovered/not resolved |
| | | | | | Paralytec ileus | 麻痺性イレウス | 5 | Yes | 2012-03-17/ | 108/ | Not related/ | Fatal |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2012-02-17/ 2012-02-28 | 79/90/12 | Not related/ | Recovered/resolved |
| | | 358-001 | 7[redacted]/Male/ White | 560 mg | Infection of respiratory tract | 気道感染 | 3 | Yes | 2011-12-13/ 2011-12-16 | 8/11/4 | Possible/ | Recovered/resolved |
| | | | | 560 mg | Space occupying lesion cervical (neck) left | 頚部腫瘤 | 3 | Yes | 2012-03-21/ 2012-03-23 | 107/109/3 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 363-001 | 7[redacted]/Male/ White | | Pneumonia - etiology pneumocystis jiroveci | ニューモシスチス・イロベチイ肺炎 | 5 | Yes | 2012-07-03/ | 169/ | Possible/ | Fatal |
| | | 364-001 | 6[redacted]/Female/ White | | Mcl | マントル細胞リンパ腫 | 5 | Yes | 2012-02-13/ | 89/ | Not related/ | Fatal |
| | | 364-003 | 7[redacted]/Male/ White | | Death due to mcl | マントル細胞リンパ腫 | 5 | Yes | 2012-04-02/ | 124/ | Not related/ Drug withdrawn | Fatal |
| | | 364-005 | 7[redacted]/Male/ White | 560 mg | Retroperitoneal lymphnode increase | 後腹膜リンパ節腫脹 | 4 | Yes | 2012-06-18/ | 159/ | Not related/ | Not recovered/not resolved |
| | | 364-006 | 7[redacted]/Male/ White | 560 mg | Compression fracture of th 12 vertebrae | 脊椎圧迫骨折 | 3 | Yes | 2012-08-03/ 2013-01-24 | 191/365/175 | Not related/ | Recovered/resolved |
| | | 364-007 | 6[redacted]/Female/ White | 560 mg | Dehydration | 脱水 | 4 | Yes | 2012-02-07/ 2012-02-11 | 1/5/5 | Not related/ | Recovered/resolved |
| | | | | | Respiratory insufficiency | 呼吸不全 | 5 | Yes | 2012-10-14/ | 251/ | Not related/ Drug withdrawn | Fatal |
| | | | | | Thrombocytopenia | 血小板減少症 | 4 | Yes | 2012-10-14/ | 251/ | Possible/ Dose not changed | Not recovered/not resolved |
| | | 365-001 | 6[redacted]/Male/ White | 560 mg | Confusion | 錯乱状態 | 2 | Yes | 2012-12-18/ 2012-12-23 | 405/410/6 | Not related/ | Recovered/resolved |
| | | | | 560 mg | Leaking urinary catheter | 医療機器リーク | 1 | Yes | 2011-12-22/ 2011-12-23 | 43/44/2 | Not related/ | Recovered/resolved |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 560 mg | Urinary tract infection | 尿路感染 | 2 | Yes | 2012-03-11/ 2012-03-12 | 123/124/2 | Not related/ | Recovered/resolved |
| | | 365-002 | 7[redacted]/Male/ White | 560 mg | Chest infection | 下気道感染 | 3 | Yes | 2012-03-22/ 2012-03-28 | 113/119/7 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Confusion | 錯乱状態 | 3 | Yes | 2011-12-10/ 2011-12-12 | 10/12/3 | Not related/ | Recovered/resolved |
| | | | | | Infection right eye- orbital cellulitis | 眼窩蜂巣炎 | 3 | Yes | 2012-09-29/ 2012-10-05 | 304/310/7 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Left buttock pressure ulcer | 褥瘡性潰瘍 | 1 | Yes | 2012-05-31/ 2012-06-18 | 183/201/19 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Left buttock pressure ulcer | 褥瘡性潰瘍 | 2 | Yes | 2012-06-18/ 2012-06-25 | 201/208/8 | Not related/ | Recovered/resolved |
| | | | | | Left buttock pressure ulcer | 褥瘡性潰瘍 | 3 | Yes | 2012-06-25/ 2012-07-13 | 208/226/19 | Not related/ | Recovered/resolved |
| | | | | 560 mg | Peri anal absess | 肛門膿瘍 | 2 | Yes | 2012-06-02/ 2012-07-13 | 185/226/42 | Possible/ | Recovered/resolved |
| | | | | 560 mg | Urinary tract infection | 尿路感染 | 3 | Yes | 2012-01-23/ 2012-02-06 | 54/68/15 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Urinary tract infection | 尿路感染 | 1 | Yes | 2012-05-30/ 2012-06-07 | 182/190/9 | Not related/ | Recovered/resolved |
| | | 365-005 | 6[redacted]/Male/ White | | Mantle cell lymphoma | マントル細胞リンパ腫 | 3 | Yes | 2012-10-17/ | 245/ | Not related/ | Not recovered/not resolved |
| | | 368-001 | 7[redacted]/Male/ White | | Worsening of mantle cell lymphoma worsening of mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-03-10/ | 180/ | Not related/ Dose not changed | Fatal |
| | | 368-003 | 6[redacted]/Male/ White | 560 mg | Worsening of mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-03-06/ | 169/ | Not related/ | Fatal |
| | | 368-004 | 6[redacted]/Male/ White | 560 mg | Fast atrial fibrillation | 心房細動 | 3 | Yes | 2011-12-17/ 2011-12-21 | 69/73/5 | Possible/ | Recovered/resolved |
| | | | | | Sepsis-unknown origin | 敗血症 | 5 | Yes | 2012-05-22/ | 226/ | Not related/ | Fatal |
| | | 368-005 | 7[redacted]/Male/ White | 560 mg | Infected right leg wound | 創傷感染 | 3 | Yes | 2012-05-16/ 2012-05-23 | 206/213/8 | Not related/ | Recovered/resolved |
| | | 368-007 | 7[redacted]/Male/ White | | Cardiac arrest | 心停止 | 5 | Yes | 2012-10-05/ | 341/ | Not related/ Drug withdrawn | Fatal |
| | | | | 560 mg | Haematuria | 血尿 | 3 | Yes | 2012-04-15/ 2012-04-16 | 168/169/2 | Possible/ | Recovered/resolved |
| | | | | 560 mg | Heart failure | 心不全 | 3 | Yes | 2012-05-07/ 2012-05-15 | 190/198/9 | Not related/ | Recovered/resolved |
| | | 368-009 | 7[redacted]/Male/ White | 560 mg | Opthalmic shingles | 眼帯状疱疹 | 3 | Yes | 2012-08-21/ 2012-11-12 | 260/343/84 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Rigor | 悪寒 | 2 | Yes | 2012-06-09/ 2012-06-10 | 187/188/2 | Not related/ | Recovered/resolved |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 368-011 | 6[redacted]/Female/ White | 560 mg | Pyrexia of unknown origin | 発熱 | 2 | Yes | 2012-08-12/ 2012-08-13 | 217/218/2 | Not related/ Dose not changed | Recovered/resolved |
| | | 368-012 | 6[redacted]/Male/ White | | Worsening of mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-05-10/ | 122/ | Not related/ | Fatal |
| | | 368-013 | 7[redacted]/Male/ White | | Dehydration | 脱水 | 3 | Yes | 2012-03-06/ 2012-03-16 | 51/61/11 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Worsening of mantle cell lymphoma | マントル細胞リンパ腫 | 5 | Yes | 2012-03-15/ | 60/ | Not related/ | Fatal |
| MCL-2001 | Ibrutinib | 10000201 | 6[redacted]/Male/ White | 560 mg | Perforated appendix | 穿孔性虫垂炎 | 3 | Yes | 2012-12-14/ 2012-12-18 | 10/14/5 | Not related/ Drug interrupted | Recovered/resolved |
| | | 10000202 | 7[redacted]/Male/ White | 560 mg | Nausea | 悪心 | 2 | Yes | 2014-03-13/ 2014-03-14 | 431/432/2 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Presyncope | 失神寸前の状態 | 2 | Yes | 2014-03-13/ 2014-03-14 | 431/432/2 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Vomiting | 嘔吐 | 2 | Yes | 2014-03-13/ 2014-03-14 | 431/432/2 | Not related/ Dose not changed | Recovered/resolved |
| | | 10000802 | 8[redacted]/Male/ White | 0 mg | Cellulitis | 蜂巣炎 | 3 | Yes | 2014-02-19/ 2014-02-24 | 392/397/6 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 10001001 | 7[redacted]/Female/ White | | Encephalopathy | 脳症 | 5 | Yes | 2012-12-18/ | 42/ | Not related/ Not applicable | Fatal |
| | | | | 560 mg | Encephalopathy | 脳症 | 3 | Yes | 2012-11-22/ 2012-12-18 | 16/42/27 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 10001104 | 7[redacted]/Male/ White | 560 mg | Suspected cellulitis lue | 蜂巣炎 | 3 | Yes | 2013-03-07/ 2013-03-19 | 178/190/13 | Not related/ Dose not changed | Recovered/resolved |
| | | 10001107 | 5[redacted]/Male/ White | | Fever | 発熱 | 2 | Yes | 2013-11-08/ 2013-11-12 | 235/239/5 | Possible/ Not applicable | Recovered/resolved |
| | | 10001301 | 7[redacted]/Male/ White | 0 mg | Acute kidney injury | 急性腎不全 | 1 | Yes | 2014-02-05/ 2014-02-10 | 435/440/6 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Hypercarbonic respiratory failure | 呼吸不全 | 3 | Yes | 2014-01-17/ 2014-02-04 | 416/434/19 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Hypercarbonic respiratory failure | 呼吸不全 | 4 | Yes | 2014-02-05/ | 435/ | Not related/ Drug interrupted | Not recovered/not resolved |
| | | | | 0 mg | Lung infection pneumonia | 肺炎 | 3 | Yes | 2014-01-17/ 2014-01-26 | 416/425/10 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Lung infection pneumonia | 肺炎 | 3 | Yes | 2014-02-05/ | 435/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | 10001302 | 7[redacted]/Male/ White | 560 mg | Colitis | 大腸炎 | 3 | Yes | 2013-05-07/ 2013-06-05 | 97/126/30 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Enterocolitis infection with c-difficile toxoid | クロストリジウム・ディフィシレ大腸炎 | 2 | Yes | 2013-06-13/ | 134/ | Not related/ Dose not changed | |
| | | 10001401 | 6[redacted]/Male/ White | | Fatigue | 疲労 | 5 | Yes | 2013-06-26/ | 267/ | Not related/ Not applicable | Fatal |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Muscle weakness | 筋力低下 | 4 | Yes | 2013-06-25/ 2013-06-26 | 266/267/2 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Pain, nos | 疼痛 | 5 | Yes | 2013-06-26/ | 267/ | Not related/ Not applicable | Fatal |
| | | | | | Pain, nos | 疼痛 | 4 | Yes | 2013-06-25/ 2013-06-26 | 266/267/2 | Not related/ Not applicable | Recovered/resolved with sequelae |
| | | | | | Weakness-nos | 無力症 | 5 | Yes | 2013-06-26/ | 267/ | Not related/ Not applicable | Fatal |
| | | | | | Worsening fatigue | 疲労 | 4 | Yes | 2013-06-25/ 2013-06-26 | 266/267/2 | Not related/ Not applicable | Recovered/resolved |
| | | 10001701 | 6[redacted]/Male/ White | 560 mg | Kidney stones | 腎結石症 | 3 | Yes | 2013-02-19/ 2013-02-21 | 93/95/3 | Not related/ Dose not changed | Recovered/resolved with sequelae |
| | | 10001702 | 7[redacted]/Male/ White | 560 mg | Dyspnea | 呼吸困難 | 4 | Yes | 2012-11-19/ 2012-12-06 | 1/18/18 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-11-18/ 2013-12-07 | 365/384/20 | Possible/ Dose not changed | Recovered/resolved |
| | | 10001704 | 5[redacted]/Female/ White | | Sepsis secondary to progressive disease | 敗血症 | 4 | Yes | 2013-03-17/ 2013-04-09 | 104/127/24 | Not related/ Not applicable | Recovered/resolved |
| | | 10001707 | 6[redacted]/Male/ White | 560 mg | Intracranial hemorrhage | 頭蓋内出血 | 2 | Yes | 2013-01-28/ 2013-02-18 | 5/26/22 | Possible/ Drug interrupted | Recovered/resolved |
| | | 10002201 | 8[redacted]/Male/ Black Or African American | 560 mg | Abdominal pain | 腹痛 | 2 | Yes | 2012-10-23/ 2012-10-24 | 20/21/2 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Abdominal pain due to cholelithiasis | 胆石症 | 3 | Yes | 2012-10-25/ 2012-10-29 | 22/26/5 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Atrial fibrillation with rvr | 心房細動 | 2 | Yes | 2012-11-15/ 2012-11-17 | 43/45/3 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Cough | 咳嗽 | 1 | Yes | 2012-10-07/ 2012-10-22 | 4/19/16 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 2 | Yes | 2012-10-17/ 2012-10-19 | 14/16/3 | Doubtful/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Worsening anemia | 貧血 | 3 | Yes | 2012-10-10/ 2012-10-11 | 7/8/2 | Not related/ Drug interrupted | Recovered/resolved |
| | | 10002203 | 7[redacted]/Male/ Unknown | 560 mg | Deep vein thrombosis | 深部静脈血栓症 | 3 | Yes | 2012-12-28/ 2013-01-14 | 47/64/18 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Neutropenic fever | 発熱性好中球減少症 | 5 | Yes | 2013-01-22/ | 72/ | Possible/ Not applicable | Fatal |
| | | 10002206 | 7[redacted]/Male/ White | 0 mg | Respiratory failure | 呼吸不全 | 3 | Yes | 2013-06-27/ 2013-07-10 | 78/91/14 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Respiratory failure. | 呼吸不全 | 5 | Yes | 2013-07-10/ | 91/ | Not related/ Not applicable | Fatal |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 10002402 | 7[redacted]/Male/ White | 560 mg | Fevers- at entery 102 | 発熱 | 3 | Yes | 2013-06-09/ 2013-06-10 | 61/62/2 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Worsening dyspnea | 呼吸困難 | 3 | Yes | 2013-06-09/ 2013-06-10 | 61/62/2 | Doubtful/ Dose not changed | Recovered/resolved |
| | | 10002504 | 7[redacted]/Male/ White | 0 mg | Acute kidney injury | 急性腎不全 | 3 | Yes | 2012-09-14/ 2012-09-22 | 43/51/9 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 10002507 | 3[redacted]/Male/ White | 0 mg | Abdominal pain | 腹痛 | 3 | Yes | 2013-09-03/ 2013-09-11 | 383/391/9 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Cholangitis | 胆管炎 | 3 | Yes | 2013-03-26/ 2013-03-29 | 222/225/4 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Choledocholithiasis | 胆管結石 | 3 | Yes | 2013-03-26/ 2013-03-29 | 222/225/4 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-03-29/ 2013-04-04 | 225/231/7 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Transaminitis | トランスアミナーゼ上昇 | 2 | Yes | 2013-09-03/ 2013-09-11 | 383/391/9 | Doubtful/ Dose not changed | Recovered/resolved |
| | | 10002508 | 8[redacted]/Female/ White | 0 mg | Abscess in right side abdomen | 腹部膿瘍 | 3 | Yes | 2012-12-06/ 2013-01-24 | 106/155/50 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Pleural effusion | 胸水 | 3 | Yes | 2012-12-06/ 2013-01-24 | 106/155/50 | Not related/ Drug interrupted | Recovered/resolved |
| | | 10002510 | 7[redacted]/Male/ White | 0 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-01-10/ 2013-01-12 | 129/131/3 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2013-03-09/ 2013-03-21 | 187/199/13 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2013-04-02/ 2013-04-06 | 211/215/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 5 | Yes | 2013-04-07/ | 216/ | Possible/ Drug withdrawn | Fatal |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2012-09-13/ 2012-09-21 | 10/18/9 | Possible/ Dose not changed | Recovered/resolved |
| | | 10002514 | 7[redacted]/Male/ White | 0 mg | Atrial fibrilliation | 心房細動 | 3 | Yes | 2013-03-24/ 2013-03-24 | 178/178/1 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Mini-transient ischemic attack | 一過性脳虚血発作 | 2 | Yes | 2013-03-24/ 2013-03-24 | 178/178/1 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 10002515 | 6[redacted]/Male/ White | 0 mg | Neutropenia fever | 発熱性好中球減少症 | 4 | Yes | 2013-10-24/ 2013-10-28 | 399/403/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | 10002517 | 7[redacted]/Male/ White | 0 mg | Atrial fibrillation | 心房細動 | 3 | Yes | 2013-02-25/ 2013-02-28 | 137/140/4 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Right axillary abscess | 皮下組織膿瘍 | 3 | Yes | 2013-10-21/ 2013-10-24 | 375/378/4 | Possible/ Drug interrupted | Recovered/resolved |
| | | 10002518 | 8[redacted]/Male/ White | 0 mg | Unstable angina | 不安定狭心症 | 3 | Yes | 2012-11-19/ 2012-11-26 | 22/29/8 | Not related/ Drug interrupted | Recovered/resolved |
| | | 10002519 | 7[redacted]/Male/ White | 560 mg | Stroke | 脳血管発作 | 3 | Yes | 2012-12-22/ 2012-12-25 | 51/54/4 | Doubtful/ Dose not changed | Recovered/resolved |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 10002521 | 5[redacted]/Male/ White | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-04-04/ 2013-04-09 | 130/135/6 | Possible/ Drug interrupted | Recovered/resolved |
| | | 10002525 | 6[redacted]/Male/ White | 0 mg | Left foot cellulitus | 蜂巣炎 | 3 | Yes | 2014-04-11/ 2014-04-14 | 470/473/4 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Neutropenia | 好中球減少症 | 4 | Yes | 2013-05-24/ 2013-05-28 | 148/152/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | 10002526 | 6[redacted]/Male/ White | 0 mg | Pneumonia | 肺炎 | 5 | Yes | 2013-03-06/ | 50/ | Possible/ Drug withdrawn | Fatal |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-03-04/ 2013-03-05 | 48/49/2 | Possible/ Drug interrupted | Recovered/resolved |
| | | 10002527 | 7[redacted]/Male/ White | 560 mg | Acute appendicitis | 虫垂炎 | 3 | Yes | 2013-02-08/ 2013-02-17 | 10/19/10 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 10002601 | 8[redacted]/Male/ White | 560 mg | Atrial fibrillation | 心房細動 | 1 | Yes | 2013-02-14/ 2013-02-16 | 22/24/3 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Atrial flutter | 心房粗動 | 1 | Yes | 2013-02-14/ 2013-02-16 | 22/24/3 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Nausea | 悪心 | 2 | Yes | 2013-02-14/ 2013-02-16 | 22/24/3 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Vomiting | 嘔吐 | 2 | Yes | 2013-02-14/ 2013-02-16 | 22/24/3 | Not related/ Dose not changed | Recovered/resolved |
| | | 10002603 | 7[redacted]/Female/ White | | Febrile neutropenia | 発熱性好中球減少症 | 4 | Yes | 2013-05-29/ | 106/ | Possible/ Dose not changed | Recovering/resolving |
| | | 10002801 | 7[redacted]/Male/ White | 560 mg | Pnemonia | 肺炎 | 3 | Yes | 2013-02-01/ | 52/ | Not related/ Drug withdrawn | Recovering/resolving |
| | | 10003401 | 8[redacted]/Male/ White | 0 mg | Cellulitis | 蜂巣炎 | 3 | Yes | 2013-03-17/ 2013-03-23 | 34/40/7 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Frequent falls | 転倒 | 2 | Yes | 2013-03-13/ 2013-03-23 | 30/40/11 | Not related/ Drug interrupted | Recovered/resolved |
| | | 10004301 | 6[redacted]/Male/ White | 560 mg | Acute bronchitis,nos | 気管支炎 | 3 | Yes | 2013-03-08/ 2013-03-13 | 116/121/6 | Possible/ Drug interrupted | Recovered/resolved with sequelae |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-03-30/ 2013-04-17 | 138/156/19 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Viral enteritis | ウイルス性胃腸炎 | 3 | Yes | 2013-03-17/ 2013-03-22 | 125/130/6 | Not related/ Drug interrupted | Recovered/resolved |
| | | 10004902 | 7[redacted]/Male/ White | 0 mg | Hyperuricemia | 高尿酸血症 | 4 | Yes | 2012-10-31/ 2012-11-01 | 20/21/2 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Pleural effusion | 胸水 | 3 | Yes | 2012-10-30/ | 19/ | Not related/ Drug interrupted | Not recovered/not resolved |
| | | | | 0 mg | Respiratory failure | 呼吸不全 | 5 | Yes | 2012-11-04/ | 24/ | Not related/ Drug withdrawn | Fatal |
| | | 10004918 | 8[redacted]/Male/ White | 560 mg | Atrial fibrillation | 心房細動 | 3 | Yes | 2013-04-02/ 2013-04-04 | 21/23/3 | Possible/ Drug interrupted | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-04-11/ 2013-04-18 | 30/37/8 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Worsening dyspnea | 呼吸困難 | 2 | Yes | 2013-05-02/ | 51/ | Possible/ Drug interrupted | Not recovered/not resolved |
| | | 10005201 | 5[redacted]/Male/ White | 560 mg | Dog bite | 動物咬傷 | 4 | Yes | 2014-02-02/ 2014-02-08 | 335/341/7 | Not related/ Dose not changed | Recovered/resolved |
| | | 10007201 | 7[redacted]/Male/ White | 420 mg | Febrile neutropenia | 発熱性好中球減少症 | 3 | Yes | 2013-09-13/ 2013-09-13 | 317/317/1 | Very likely/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Non-displaced intra-articular fracture of left tibia | 脛骨骨折 | 2 | Yes | 2012-12-12/ 2013-01-08 | 42/69/28 | Not related/ Dose not changed | Recovered/resolved |
| | | 10007804 | 7[redacted]/Male/ White | 560 mg | Altered mental status (confusion) | 錯乱状態 | 2 | Yes | 2013-06-13/ 2013-06-15 | 67/69/3 | Doubtful/ Drug interrupted | Recovered/resolved with sequelae |
| | | | | 560 mg | Bilateral lower extremity pain | 四肢痛 | 3 | Yes | 2013-05-21/ 2013-06-05 | 44/59/16 | Not related/ Dose not changed | Recovered/resolved with sequelae |
| | | | | 560 mg | Bilateral lower extremity swelling | 末梢性浮腫 | 3 | Yes | 2013-05-21/ 2013-06-05 | 44/59/16 | Not related/ Dose not changed | Recovered/resolved with sequelae |
| | | | | 560 mg | Gouty arthristis | 痛風性関節炎 | 3 | Yes | 2013-04-12/ 2013-04-23 | 5/16/12 | Not related/ Drug interrupted | Recovered/resolved with sequelae |
| | | | | 560 mg | Lymphedema | リンパ浮腫 | 3 | Yes | 2013-04-12/ 2013-04-23 | 5/16/12 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Neutropenic fever | 発熱性好中球減少症 | 4 | Yes | 2013-06-23/ 2013-06-28 | 77/82/6 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Splenic hemorrhage | 脾臓出血 | 3 | Yes | 2013-06-30/ 2013-07-01 | 84/85/2 | Not related/ Drug interrupted | Recovered/resolved with sequelae |
| | | | | | Splenic hemorrhage | 脾臓出血 | 3 | Yes | 2013-07-07/ 2013-07-08 | 91/92/2 | Not related/ Drug withdrawn | Recovered/resolved |
| | | | | 0 mg | Urosepsis | 尿路性敗血症 | 3 | Yes | 2013-06-23/ 2013-07-09 | 77/93/17 | Possible/ Drug interrupted | Recovered/resolved |
| | | 33000101 | 7[redacted]/Male/ Not Reported | 560 mg | Dyspnea | 呼吸困難 | 2 | Yes | 2013-02-12/ 2013-02-18 | 61/67/7 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Sepsis | 敗血症 | 4 | Yes | 2013-04-16/ 2013-04-19 | 124/127/4 | Possible/ Not applicable | Recovered/resolved |
| | | 33000103 | 6[redacted]/Female/ Not Reported | 560 mg | Abdominal pain | 腹痛 | 3 | Yes | 2013-03-15/ 2013-04-16 | 64/96/33 | Not related/ Drug withdrawn | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 33000501 | 5[redacted]/Male/ Not Reported | | Malaise due to progressive disease | 倦怠感 | 2 | Yes | 2013-03-21/ | 92/ | Not related/ Not applicable | Not recovered/not resolved |
| | | 44000101 | 4[redacted]/Male/ White | 0 mg | Over dose of analgesics & recreational drugs | 過量投与 | 4 | Yes | 2013-01-31/ 2013-02-01 | 46/47/2 | Not related/ Drug interrupted | Recovered/resolved |
| | | 44000301 | 6[redacted]/Male/ White | 560 mg | Lower respiratory tract infection | 下気道感染 | 3 | Yes | 2012-11-24/ 2012-12-10 | 12/28/17 | Possible/ Drug interrupted | Recovered/resolved |
| | | 44000302 | 6[redacted]/Male/ White | 560 mg | Gastroenteritis | 胃腸炎 | 3 | Yes | 2013-04-12/ 2013-04-19 | 144/151/8 | Possible/ Drug interrupted | Recovered/resolved |
| | | 44000304 | 7[redacted]/Male/ White | 560 mg | Acute kidney injury | 急性腎不全 | 3 | Yes | 2013-04-25/ 2013-05-13 | 35/53/19 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 48000101 | 7[redacted]/Male/ White | | Circulatory failure due to disease progression | 循環虚脱 | 5 | Yes | 2013-05-29/ | 136/ | Not related/ Drug withdrawn | Fatal |
| | | | | 0 mg | Circulatory failure due to disease progression | 循環虚脱 | 4 | Yes | 2013-05-26/ 2013-05-29 | 133/136/4 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Respiratory failure | 呼吸不全 | 5 | Yes | 2013-05-29/ | 136/ | Not related/ Drug withdrawn | Fatal |
| | | | | 0 mg | Respiratory failure due to disease progression | 呼吸不全 | 4 | Yes | 2013-05-26/ 2013-05-29 | 133/136/4 | Not related/ Dose not changed | Recovered/resolved |
| | | 70000102 | 4[redacted]/Male/ White | | Fatal death | 死亡 | 5 | Yes | 2013-04-13/ | 31/ | Not related/ Drug withdrawn | Fatal |
| | | 70000602 | 7[redacted]/Male/ White | | Acute cardiovascular insufficiency | 心血管不全 | 5 | Yes | 2013-04-09/ | 19/ | Not related/ Drug withdrawn | Fatal |
| | | | | 0 mg | Acute cardiovascular insufficiency | 心血管不全 | | Yes | 2013-04-08/ 2013-04-09 | 18/19/2 | Not related/ Drug interrupted | Recovered/resolved |
| | | 97200201 | 6[redacted]/Male/ White | 560 mg | Cough | 咳嗽 | 2 | Yes | 2012-11-29/ 2013-02-14 | 4/81/78 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Diarrhea | 下痢 | 2 | Yes | 2012-12-08/ 2012-12-14 | 13/19/7 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Neutropenia | 好中球減少症 | 2 | Yes | 2013-01-25/ 2013-01-28 | 61/64/4 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Neutropenic fever | 発熱性好中球減少症 | 3 | Yes | 2012-12-09/ 2012-12-09 | 14/14/1 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Neutropenic fever | 発熱性好中球減少症 | 4 | Yes | 2012-12-10/ 2012-12-12 | 15/17/3 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Neutropenic fever | 発熱性好中球減少症 | 3 | Yes | 2012-12-12/ 2012-12-13 | 17/18/2 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Neutropenic fever | 発熱性好中球減少症 | 4 | Yes | 2012-12-07/ 2012-12-09 | 12/14/3 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Neutropenic fever | 発熱性好中球減少症 | 4 | Yes | 2013-01-24/ 2013-01-25 | 60/61/2 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Nonspecific skin eruption | 発疹 | 2 | Yes | 2012-12-05/ 2012-12-13 | 10/18/9 | Possible/ Drug interrupted | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 560 mg | Rash | 発疹 | 2 | Yes | 2012-12-05/ 2012-12-13 | 10/18/9 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Thrombocytopenia | 血小板減少症 | 1 | Yes | 2012-12-04/ 2012-12-19 | 9/24/16 | Possible/ Dose not changed | Recovered/resolved |
| | | 97200203 | 7[redacted]/Male/ White | 0 mg | Intracranial hemmmorhage | 頭蓋内出血 | 2 | Yes | 2013-02-07/ | 52/ | Not related/ Drug interrupted | Recovering/resolving |
| | | 97200204 | 7[redacted]/Male/ White | 560 mg | Dyspnea | 呼吸困難 | 2 | Yes | 2013-03-15/ | 52/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | | | 560 mg | Hypoalbuminemia | 低アルブミン血症 | 3 | Yes | 2013-02-13/ | 22/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | | | 560 mg | Peripheral edema | 末梢性浮腫 | 3 | Yes | 2013-02-27/ | 36/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | | | | Pneumonia | 肺炎 | 5 | Yes | 2013-03-22/ | 59/ | Not related/ Not applicable | Fatal |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2013-03-19/ 2013-03-22 | 56/59/4 | Not related/ Not applicable | Recovered/resolved |
| | | 97200302 | 6[redacted]/Male/ White | 560 mg | Cardiac arrest | 心停止 | 5 | Yes | 2012-12-16/ | 21/ | Not related/ Drug withdrawn | Fatal |
| | | 97200304 | 6[redacted]/Male/ White | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-12-27/ 2014-01-06 | 290/300/11 | Not related/ Dose not changed | Recovered/resolved |
| | | 97200401 | 7[redacted]/Male/ White | 0 mg | Prostatic adenocarcinoma | 前立腺癌 | 3 | Yes | 2014-02-17/ | 309/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | 97200601 | 6[redacted]/Male/ White | 0 mg | Bacterial pneumonia | 細菌性肺炎 | 3 | Yes | 2014-02-03/ 2014-02-16 | 405/418/14 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Oral aphtae | アフタ性口内炎 | 3 | Yes | 2014-02-03/ 2014-02-04 | 405/406/2 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 2 | Yes | 2013-09-11/ 2013-09-12 | 260/261/2 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Pneumonia left | 肺炎 | 3 | Yes | 2013-11-09/ 2013-11-11 | 319/321/3 | Not related/ Dose not changed | Recovered/resolved |
| | | 97200701 | 7[redacted]/Male/ White | 560 mg | Acute (mild) renal failure | 急性腎不全 | 2 | Yes | 2013-04-02/ 2013-04-04 | 15/17/3 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Campylobacter infection | カンピロバクター感染 | 3 | Yes | 2013-04-13/ 2013-04-17 | 26/30/5 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Dehydration | 脱水 | 3 | Yes | 2013-04-02/ 2013-04-05 | 15/18/4 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Generalized weakness | 無力症 | 2 | Yes | 2013-04-13/ 2013-04-17 | 26/30/5 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Hypotention | 低血圧 | 3 | Yes | 2013-04-13/ 2013-04-17 | 26/30/5 | Possible/ Dose not changed | Recovered/resolved |

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Pneumonia | 肺炎 | 4 | Yes | 2013-05-01/ 2013-05-07 | 44/50/7 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 5 | Yes | 2013-05-08/ | 51/ | Not related/ Not applicable | Fatal |
| | | 97200702 | 6[redacted]/Male/ White | 560 mg | Mrsa bacteremia | ブドウ球菌性菌血症 | 2 | Yes | 2013-04-19/ | 2/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | | | | Sepsis | 敗血症 | 5 | Yes | 2013-06-18/ | 62/ | Not related/ Drug withdrawn | Fatal |
| | | | | 560 mg | Sepsis | 敗血症 | 4 | Yes | 2013-05-27/ 2013-06-17 | 40/61/22 | Not related/ Dose not changed | Recovered/resolved with sequelae |
| | | | | 560 mg | Urinary tract infection | 尿路感染 | 3 | Yes | 2013-05-21/ | 34/ | Not related/ Dose not changed | Not recovered/not resolved |
| MCL-3001 | Ibrutinib | 11000101 | 7[redacted]/Male/ White | 560 mg | Small bowel obstruction | 小腸閉塞 | 4 | Yes | 2013-11-08/ 2013-11-10 | 24/26/3 | Possible/ Drug interrupted | Recovered/resolved |
| | | 11000102 | 6[redacted]/Female/ White | | Abdominal pain | 腹痛 | 3 | Yes | 2014-02-05/ | 107/ | Not related/ Not applicable | Not recovered/not resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2014-01-05/ 2014-01-15 | 76/86/11 | Not related/ Drug interrupted | Recovered/resolved |
| | | 11000401 | 6[redacted]/Male/ White | 0 mg | Atrial fibrillation | 心房細動 | 3 | Yes | 2013-09-15/ 2013-09-16 | 83/84/2 | Probable/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Bacteremia | 菌血症 | 3 | Yes | 2013-08-20/ 2013-09-06 | 57/74/18 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Pneumonia | 肺炎 | 3 | Yes | 2014-12-01/ 2014-12-07 | 525/531/7 | Possible/ Drug interrupted | Recovered/resolved with sequelae |
| | | | | 420 mg | Pneumonia | 肺炎 | 3 | Yes | 2015-01-23/ 2015-01-28 | 578/583/6 | Possible/ Drug interrupted | Recovered/resolved with sequelae |
| | | | | 0 mg | Pseudo gout | ピロリン酸カルシウム結晶性軟骨石灰化症 | 3 | Yes | 2013-10-25/ 2013-11-13 | 123/142/20 | Doubtful/ Dose not changed | Recovered/resolved |
| | | 31000102 | 7[redacted]/Male/ White | 560 mg | Anaemia | 貧血 | 3 | Yes | 2014-01-31/ 2014-02-12 | 138/150/13 | Not related/ Dose not changed | Recovered/resolved with sequelae |
| | | | | 560 mg | Dyspnoea | 呼吸困難 | 2 | Yes | 2013-11-18/ 2014-02 | 64/153/90 | Doubtful/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Hemorrhage,post-procedural,rectal | 処置後出血 | 4 | Yes | 2014-03-20/ 2014-03-22 | 186/188/3 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Pleural effusion | 胸水 | 2 | Yes | 2013-10-31/ 2013-11-26 | 46/72/27 | Possible/ Dose not changed | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Pleural effusion | 胸水 | 3 | Yes | 2013-11-27/ 2013-11-29 | 73/75/3 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Pleural effusion | 胸水 | 3 | Yes | 2014-01-22/ 2014-01-30 | 129/137/9 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-11-03/ 2013-11-08 | 49/54/6 | Possible/ Dose not changed | Recovered/resolved |
| | | 32000101 | 6[redacted]/Male/ White | 560 mg | Atrial fibrillation intermittent | 心房細動 | 2 | Yes | 2013-01-29/ 2013-02-04 | 21/27/7 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Atrial fibrillation intermittent | 心房細動 | 3 | Yes | 2013-02-05/ 2013-02-06 | 28/29/2 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Bradycardia intermittent | 徐脈 | 2 | Yes | 2013-03-03/ 2013-03-05 | 54/56/3 | Doubtful/ Dose not changed | Recovered/resolved with sequelae |
| | | | | 560 mg | Mental breakdown | 精神障害 | 2 | Yes | 2013-09-12/ 2013-11-05 | 247/301/55 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Pericarditis | 心膜炎 | 3 | Yes | 2013-08-13/ 2013-09-23 | 217/258/42 | Possible/ Drug interrupted | Recovered/resolved |
| | | 33000403 | 7[redacted]/Male/ Unknown | 560 mg | Squamous cell carcinoma of the concha of the left ear | 扁平上皮癌 | 3 | Yes | 2014-11-27/ 2015-03-31 | 400/524/125 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Transient ischemic attacks | 一過性脳虚血発作 | 2 | Yes | 2015-04-02/ 2015-04-10 | 526/534/9 | Not related/ Drug interrupted | Recovered/resolved |
| | | 33000502 | 7[redacted]/Female/ Unknown | 560 mg | Febrile neutropenia | 発熱性好中球減少症 | 3 | Yes | 2014-08-30/ 2014-09-03 | 375/379/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | 34000201 | 7[redacted]/Male/ White | 560 mg | Salivary gland carcinoma | 唾液腺癌 | 3 | Yes | 2014-04-04/ 2014-07-12 | 354/453/100 | Not related/ Drug interrupted | Recovered/resolved |
| | | 34000405 | 8[redacted]/Male/ White | 560 mg | Constitutional syndrome | 悪液質 | 3 | Yes | 2014-02-06/ 2014-03-12 | 93/127/35 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 35300103 | 6[redacted]/Female/ White | 0 mg | Gastric ulcers | 胃潰瘍 | 2 | Yes | 2013-02-26/ | 6/ | Not related/ Drug interrupted | Not recovered/not resolved |
| | | | | 0 mg | Low platelets | 血小板数減少 | 3 | Yes | 2013-02-26/ | 6/ | Not related/ Drug interrupted | Not recovered/not resolved |
| | | | | 0 mg | Pelvic pain | 骨盤痛 | 3 | Yes | 2013-03-10/ | 18/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | 36000301 | 5[redacted]/Male/ White | 560 mg | Diabetic ketoacidosis | 糖尿病性ケトアシドーシス | 3 | Yes | 2014-10-15/ 2014-10-19 | 546/550/5 | Doubtful/ Dose not changed | Recovered/resolved |
| | | 36000303 | 7[redacted]/Female/ White | 560 mg | Atrial fibrillation | 心房細動 | 3 | Yes | 2014-04-18/ 2014-04-20 | 172/174/3 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Gastroenteritis acute | 胃腸炎 | 2 | Yes | 2014-11-23/ 2014-11-26 | 391/394/4 | Not related/ Dose not changed | Recovered/resolved |

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 36000401 | 7[redacted]/Male/ White | 560 mg | Atrial fibrillation | 心房細動 | 3 | Yes | 2013-06-11/ 2013-06-26 | 55/70/16 | Doubtful/ Drug interrupted | Recovered/resolved with sequelae |
| | | | | | Atrial fibrillation | 心房細動 | 3 | Yes | 2013-07-03/ 2013-07-09 | 77/83/7 | Doubtful/ Drug interrupted | Recovered/resolved with sequelae |
| | | 38000101 | 6[redacted]/Male/ White | 560 mg | Suspected pulmonary embolism | 肺塞栓症 | 5 | Yes | 2013-06-24/ | 61/ | Possible/ Not applicable | Fatal |
| | | 38000501 | 6[redacted]/Male/ White | 0 mg | Pulmonary edema | 肺水腫 | 5 | Yes | 2013-05-27/ | 69/ | Doubtful/ Not applicable | Fatal |
| | | | | 0 mg | Splenic infarctions | 脾臓梗塞 | 3 | Yes | 2013-05-21/ | 63/ | Doubtful/ Drug interrupted | Not recovered/not resolved |
| | | | | 0 mg | Trombocytopenia | 血小板減少症 | 3 | Yes | 2013-05-21/ 2013-05-22 | 63/64/2 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Trombocytopenia | 血小板減少症 | 4 | Yes | 2013-05-23/ | 65/ | Not related/ Drug interrupted | Not recovered/not resolved |
| | | 38000701 | 7[redacted]/Male/ White | 560 mg | Acute not q myocardial infarction | 急性心筋梗塞 | 3 | Yes | 2013-04-02/ 2013-04-10 | 1/9/9 | Possible/ Drug withdrawn | Recovered/resolved |
| | | 38000703 | 7[redacted]/Male/ White | 0 mg | Acute laryngitis | 喉頭炎 | 3 | Yes | 2014-09-24/ 2014-09-30 | 476/482/7 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Acute tracheitis | 気管炎 | 3 | Yes | 2014-09-24/ 2014-09-30 | 476/482/7 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Toxic hepatitis | 中毒性肝炎 | 3 | Yes | 2013-08-28/ 2013-09-18 | 84/105/22 | Probable/ Drug interrupted | Recovered/resolved |
| | | 39000101 | 6[redacted]/Male/ White | | Dyspnea | 呼吸困難 | 1 | Yes | 2014-05-23/ 2014-05-31 | 428/436/9 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Fever | 発熱 | 2 | Yes | 2014-05-19/ 2014-05-27 | 424/432/9 | Not related/ Not applicable | Recovered/resolved |
| | | | | 0 mg | Lymphocitosis | リンパ球増加症 | 3 | Yes | 2013-03-28/ 2013-04-01 | 7/11/5 | Probable/ Dose not changed | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 2 | Yes | 2014-05-23/ 2014-06-19 | 428/455/28 | Not related/ Not applicable | Recovered/resolved |
| | | | | 0 mg | Progressive dyspnea | 呼吸困難 | 2 | Yes | 2013-03-28/ 2013-04-03 | 7/13/7 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Tumor syndrome lysis | 腫瘍崩壊症候群 | 3 | Yes | 2013-03-28/ 2013-04-03 | 7/13/7 | Probable/ Drug interrupted | Recovered/resolved |
| | | 39000102 | 7[redacted]/Male/ White | 560 mg | Fatigue | 疲労 | 2 | Yes | 2014-12-01/ | 487/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | | | 560 mg | Headache | 頭痛 | 2 | Yes | 2014-12-01/ | 487/ | Not related/ Dose not changed | Not recovered/not resolved |

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 0 mg | Leukocytosis | 白血球増加症 | 3 | Yes | 2013-08-05/ 2013-08-16 | 4/15/12 | Probable/ Drug interrupted | Recovered/resolved |
| | | | | | Subdural hematoma | 硬膜下血腫 | 5 | Yes | 2015-01-06/ | 523/ | Not related/ Not applicable | Fatal |
| | | | | 560 mg | Subdural hematoma | 硬膜下血腫 | 4 | Yes | 2014-12-15/ 2015-01-05 | 501/522/22 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 39000202 | 7[redacted]/Male/ White | 0 mg | Papillary bladder carcinoma | 膀胱移行上皮癌 | 2 | Yes | 2014-09-08/ 2014-09-11 | 425/428/4 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Papillary bladder carcinoma | 膀胱移行上皮癌 | 2 | Yes | 2015-03-02/ 2015-03-05 | 600/603/4 | Not related/ Drug interrupted | Recovered/resolved |
| | | 39000402 | 7[redacted]/Male/ White | 0 mg | Anemia | 貧血 | 3 | Yes | 2014-01-10/ 2014-01-22 | 185/197/13 | Not related/ Drug withdrawn | Recovered/resolved |
| | | | | 0 mg | Trombocytopenia | 血小板減少症 | 3 | Yes | 2014-01-10/ 2014-01-22 | 185/197/13 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 42002401 | 6[redacted]/Male/ White | 0 mg | Adenocarcinoma of the prostate | 前立腺癌 | 3 | Yes | 2014-02-26/ | 279/ | Not related/ Dose not changed | |
| | | 42002502 | 7[redacted]/Male/ White | 560 mg | Epiparoxysm | てんかん | 3 | Yes | 2013-07-24/ 2013-08-01 | 14/22/9 | Possible/ Dose not changed | Recovered/resolved with sequelae |
| | | | | 0 mg | Pneumocystis pneumonia | ニューモシスチス・イロベチイ肺炎 | 3 | Yes | 2013-09-12/ 2013-09-27 | 64/79/16 | Probable/ Drug interrupted | Recovered/resolved with sequelae |
| | | | | 0 mg | Thrombocytopenia | 血小板減少症 | 4 | Yes | 2013-09-27/ 2013-10-15 | 79/97/19 | Probable/ Drug withdrawn | Recovered/resolved |
| | | 42002503 | 7[redacted]/Male/ White | 0 mg | Bronchopneumonia | 気管支肺炎 | 3 | Yes | 2015-03-13/ 2015-03-19 | 569/575/7 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Lung infection | 肺感染 | 2 | Yes | 2013-10-25/ 2013-11-01 | 65/72/8 | Possible/ Dose not changed | Recovered/resolved with sequelae |
| | | | | 0 mg | Pneumonia | 肺炎 | 3 | Yes | 2014-12-30/ 2015-01-08 | 496/505/10 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Soft tissue infection in the right axillar region | 軟部組織感染 | 3 | Yes | 2013-08-28/ 2013-10-03 | 7/43/37 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 140 mg | Worsening lung infection | 肺感染 | 3 | Yes | 2014-02-26/ 2014-03-12 | 189/203/15 | Possible/ Drug interrupted | Recovered/resolved with sequelae |
| | | 44000106 | 4[redacted]/Male/ White | | Back pain (due to progressive disease) | 背部痛 | 3 | Yes | 2013-09-29/ 2013-10-04 | 49/54/6 | Not related/ Dose not changed | Recovered/resolved with sequelae |
| | | | | 560 mg | Fever | 発熱 | 1 | Yes | 2013-09-05/ 2013-09-06 | 25/26/2 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Fever | 発熱 | 1 | Yes | 2013-09-23/ 2013-09-27 | 43/47/5 | Possible/ Dose not changed | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 44000205 | 6[redacted]/Male/ White | | Bleeding in area of tonsils following tonsillar biopsy. | 処置後出血 | 4 | Yes | 2014-07-28/ 2014-08 | 281/299/19 | Possible/ Not applicable | Recovered/resolved |
| | | | | | Confusion | 錯乱状態 | 3 | Yes | 2014-08-07/ 2014-08-14 | 291/298/8 | Doubtful/ Not applicable | Recovered/resolved |
| | | | | | Dehydration | 脱水 | 3 | Yes | 2014-07-25/ 2014-07-26 | 278/279/2 | Not related/ Not applicable | Recovered/resolved |
| | | | | 420 mg | Pneumothorax | 気胸 | 3 | Yes | 2014-03-31/ 2014-04-02 | 162/164/3 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | | Swelling in area of tonsils following tonsillar biopsy. | 処置後腫脹 | 4 | Yes | 2014-07-28/ 2014-08 | 281/299/19 | Not related/ Not applicable | Recovered/resolved |
| | | 44000207 | 7[redacted]/Female/ White | | Dysphagia | 嚥下障害 | 3 | Yes | 2014-04-07/ 2014-06-03 | 148/205/58 | Not related/ Not applicable | Recovered/resolved |
| | | 44000208 | 6[redacted]/Male/ White | 560 mg | Chest - infection | 下気道感染 | 3 | Yes | 2014-02-03/ 2014-02-07 | 77/81/5 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Chest infection | 下気道感染 | 3 | Yes | 2014-12-01/ 2014-12-04 | 378/381/4 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Chest infection | 下気道感染 | 3 | Yes | 2015-02-02/ 2015-02-05 | 441/444/4 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Chest infection | 下気道感染 | 3 | Yes | 2014-01-17/ 2014-01-24 | 60/67/8 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Chest infection | 下気道感染 | 3 | Yes | 2014-04-05/ 2014-04-28 | 138/161/24 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | | Chest infection | 下気道感染 | 3 | Yes | 2014-05-19/ 2014-05-20 | 182/183/2 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Chest infection | 下気道感染 | 3 | Yes | 2014-08-06/ 2014-08-27 | 261/282/22 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Exacerbation of copd | 慢性閉塞性肺疾患 | 3 | Yes | 2013-12-11/ 2013-12-14 | 23/26/4 | Doubtful/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Infection nos | 感染 | 3 | Yes | 2013-12-11/ 2013-12-14 | 23/26/4 | Doubtful/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Lower respiratory tract infection | 下気道感染 | 3 | Yes | 2014-11-02/ 2014-11-03 | 349/350/2 | Possible/ Dose not changed | Recovered/resolved |
| | | 44000303 | 6[redacted]/Male/ White | 560 mg | Syncope | 失神 | 3 | Yes | 2013-04-27/ | 3/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | 44000502 | 6[redacted]/Male/ White | | Hydronephrosis | 水腎症 | 3 | Yes | 2014-10-23/ 2014-11-04 | 388/400/13 | Not related/ Not applicable | Recovered/resolved |
| | | 44000605 | 7[redacted]/Female/ White | 560 mg | Chest infection | 下気道感染 | 3 | Yes | 2013-10-24/ 2013-10-30 | 21/27/7 | Probable/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Hypoxia | 低酸素症 | 3 | Yes | 2013-10-31/ 2013-11-01 | 28/29/2 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Thrombocytopenia | 血小板減少症 | 4 | Yes | 2013-11-06/ 2014-01-09 | 34/98/65 | Possible/ Drug withdrawn | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 44001005 | 7[redacted]/Male/ White | 560 mg | Acute kidney injury | 急性腎不全 | 2 | Yes | 2014-03-29/ 2014-05-01 | 250/283/34 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Community acquired pneumonia | 肺炎 | 2 | Yes | 2014-03-13/ 2014-03-24 | 234/245/12 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Dehydration | 脱水 | 2 | Yes | 2014-03-29/ 2014-05-01 | 250/283/34 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Fall | 転倒 | 3 | Yes | 2014-03-13/ 2014-03-13 | 234/234/1 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Fall | 転倒 | 3 | Yes | 2014-05-19/ 2014-05-19 | 301/301/1 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Pneumonia | 肺炎 | 3 | Yes | 2014-06-30/ 2014-07-09 | 343/352/10 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Postural hypotension | 起立性低血圧 | 3 | Yes | 2014-03-29/ 2014-05-01 | 250/283/34 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Septic | 敗血症 | 4 | Yes | 2014-06-30/ 2014-07-09 | 343/352/10 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Shortness of breath | 呼吸困難 | 2 | Yes | 2014-03-13/ 2014-03-24 | 234/245/12 | Not related/ Drug interrupted | Recovered/resolved |
| | | 46000103 | 7[redacted]/Male/ White | 560 mg | Abdominal pain | 腹痛 | 3 | Yes | 2013-12-19/ 2013-12-23 | 365/369/5 | Not related/ Drug withdrawn | Recovered/resolved |
| | | | | | Renal failure | 腎不全 | 4 | Yes | 2013-12-27/ 2013-12-29 | 373/375/3 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Renal failure | 腎不全 | 5 | Yes | 2013-12-30/ | 376/ | Not related/ Not applicable | Fatal |
| | | | | 560 mg | Right-sided facial paresis | 顔面不全麻痺 | 2 | Yes | 2013-11-06/ | 322/ | Not related/ Drug interrupted | Not recovered/not resolved |
| | | 46000106 | 5[redacted]/Male/ White | 0 mg | Neutropenic fever | 発熱性好中球減少症 | 3 | Yes | 2013-06-22/ 2013-06-27 | 61/66/6 | Very likely/ Drug interrupted | Recovered/resolved |
| | | | | | Splenic ruptur | 脾破裂 | 5 | Yes | 2013-07-05/ | 74/ | Possible/ Not applicable | Fatal |
| | | 46000107 | 7[redacted]/Male/ White | 0 mg | Fatigue | 疲労 | 2 | Yes | 2013-10-18/ 2013-11-15 | 172/200/29 | Not related/ Dose not changed | Recovered/resolved |
| | | 46000108 | 6[redacted]/Male/ White | | Multiple organ failure | 多臓器不全 | 5 | Yes | 2013-06-02/ | 5/ | Not related/ Not applicable | Fatal |
| | | | | 560 mg | Multiple organ failure | 多臓器不全 | 4 | Yes | 2013-06-01/ 2013-06-01 | 4/4/1 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 46000110 | 7[redacted]/Male/ White | 560 mg | Hematuria | 血尿 | 3 | Yes | 2014-03-24/ 2014-03-29 | 300/305/6 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Hematuria | 血尿 | 3 | Yes | 2014-04-27/ | 334/ | Possible/ Dose not changed | Recovering/resolving |
| | | | | 560 mg | Papillary urothelial carcinoma of the bladder | 膀胱移行上皮癌 | 3 | Yes | 2013-08-21/ 2014-05-14 | 85/351/267 | Not related/ Dose not changed | Recovered/resolved |

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2014-02-11/ 2014-03-04 | 259/280/22 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Progressive urothelial cancer | 移行上皮癌 | 5 | Yes | 2014-06-12/ | 380/ | Possible/ Not applicable | Fatal |
| | | | | 560 mg | Progressive urothelial cancer | 移行上皮癌 | 4 | Yes | 2014-05-23/ 2014-06-11 | 360/379/20 | Possible/ Drug withdrawn | Recovered/resolved |
| | | | | 560 mg | Suspected progression of urothelial cancer | 移行上皮癌 | 4 | Yes | 2014-05-15/ 2014-05-16 | 352/353/2 | Possible/ Dose not changed | Recovered/resolved |
| | | 46000201 | 7[redacted]/Female/ White | | Fever | 発熱 | 3 | Yes | 2013-04-18/ 2013-04-22 | 44/48/5 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Forgetful | 記憶障害 | 1 | Yes | 2013-04-18/ 2013-04-18 | 44/44/1 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Respiratory insufficiency due to tracheostomy stenosis | 呼吸不全 | 4 | Yes | 2013-04-09/ 2013-04-12 | 35/38/4 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Speech impairment | 構語障害 | 1 | Yes | 2013-04-18/ 2013-04-24 | 44/50/7 | Not related/ Not applicable | Recovered/resolved with sequelae |
| | | 46000204 | 7[redacted]/Male/ White | 560 mg | General deteriorating condition | 全身健康状態低下 | 4 | Yes | 2013-11-15/ 2013-11-25 | 60/70/11 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 46000401 | 5[redacted]/Male/ White | | Low hemoglobinvalue | ヘモグロビン減少 | 3 | Yes | 2013-05-20/ 2013-06-17 | 133/161/29 | Doubtful/ Not applicable | Recovered/resolved |
| | | | | | Low neutrophils | 好中球数減少 | 4 | Yes | 2013-05-23/ 2013-05-27 | 136/140/5 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Low thrombocytes | 血小板数減少 | 2 | Yes | 2013-05-27/ 2013-06-16 | 140/160/21 | Doubtful/ Not applicable | Recovered/resolved |
| | | 46000406 | 7[redacted]/Male/ White | 560 mg | Cough | 咳嗽 | 2 | Yes | 2014-01-21/ 2014-02-04 | 218/232/15 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Creatinine increased | 血中クレアチニン増加 | 1 | Yes | 2014-02-07/ 2014-02-08 | 235/236/2 | Not related/ Not applicable | Recovered/resolved |
| | | | | 560 mg | Diarrhoea | 下痢 | 2 | Yes | 2013-12-25/ | 191/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | | | 560 mg | Dyspnea | 呼吸困難 | 2 | Yes | 2014-01-21/ | 218/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | | | | Neutropenia | 好中球減少症 | 4 | Yes | 2014-02-06/ | 234/ | Not related/ Not applicable | Not recovered/not resolved |
| | | | | | Sepsis | 敗血症 | 4 | Yes | 2014-02-06/ 2014-02-12 | 234/240/7 | Not related/ Not applicable | Recovered/resolved with sequelae |
| | | | | | Sepsis | 敗血症 | 5 | Yes | 2014-02-13/ | 241/ | Not related/ Not applicable | Fatal |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Thrombocytopenia | 血小板減少症 | 2 | Yes | 2014-02-06/ 2014-02-07 | 234/235/2 | Not related/ Not applicable | Recovered/resolved |
| | | 48000403 | 6[redacted]/Female/ White | | Multiorgan insufficiency due to disease progression | 多臓器不全 | 4 | Yes | 2015-02-02/ 2015-02-03 | 580/581/2 | Not related/ Not applicable | Recovered/resolved |
| | | 48000503 | 7[redacted]/Male/ White | 560 mg | Chronic bronchopulmonary obstructive disease | 慢性閉塞性肺疾患 | 3 | Yes | 2013-11-21/ | 150/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | 48001504 | 6[redacted]/Male/ White | | Multiorgan dysfunction due to mcl progession | 多臓器不全 | 5 | Yes | 2013-10-26/ | 151/ | Not related/ Not applicable | Fatal |
| | | | | 560 mg | Pneumonia | 肺炎 | 4 | Yes | 2013-10-18/ 2013-10-26 | 143/151/9 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 48001506 | 8[redacted]/Female/ White | | Respiratory insufficiency due to mcl progression | 呼吸不全 | 5 | Yes | 2013-12-17/ | 189/ | Not related/ Not applicable | Fatal |
| | | 48001510 | 6[redacted]/Male/ White | 560 mg | Anemia | 貧血 | 3 | Yes | 2013-11-13/ 2013-11-18 | 22/27/6 | Not related/ Drug interrupted | Recovered/resolved |
| | | 49000101 | 5[redacted]/Male/ White | 0 mg | Diabetical retinopathy | 糖尿病網膜症 | 3 | Yes | 2013-09-24/ 2013-09-25 | 55/56/2 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Vitreous hemorrhage | 硝子体出血 | 4 | Yes | 2013-08-02/ 2013-08-22 | 2/22/21 | Not related/ Dose not changed | Recovered/resolved with sequelae |
| | | 49000301 | 6[redacted]/Male/ White | 560 mg | Basal cell carcinoma | 基底細胞癌 | 3 | Yes | 2014-06-20/ 2014-09-10 | 320/402/83 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Hemorrhagic cystitis | 出血性膀胱炎 | 4 | Yes | 2015-03-23/ 2015-04-07 | 596/611/16 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Nitrite positive urinary tract infection | 尿路感染 | 2 | Yes | 2015-02-15/ 2015-02-20 | 560/565/6 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Nitrite positive urinary tract infection with proteus mirabilis | 細菌性尿路感染 | 3 | Yes | 2015-01-05/ 2015-01-13 | 519/527/9 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-12-03/ 2013-12-17 | 121/135/15 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Suspected decreased general condition | 全身健康状態低下 | 1 | Yes | 2013-09-30/ 2014-01-03 | 57/152/96 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Urinary tract infection | 尿路感染 | 2 | Yes | 2015-03-11/ 2015-03-19 | 584/592/9 | Not related/ Dose not changed | Recovered/resolved |
| | | 49000402 | 6[redacted]/Male/ White | 0 mg | E-coli port infection | 医療機器関連感染 | 3 | Yes | 2014-12-30/ 2015-01-07 | 421/429/9 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2014-12-28/ 2015-01-07 | 419/429/11 | Possible/ Drug interrupted | Recovered/resolved |
| | | 49000502 | 5[redacted]/Male/ White | 0 mg | Worsening of necrosis: head of femur left | 骨壊死 | 3 | Yes | 2013-12-18/ 2013-12-18 | 136/136/1 | Not related/ Drug interrupted | Recovered/resolved |
| | | 49000602 | 5[redacted]/Male/ White | | Blood loss due to splenic rupture | 出血 | 4 | Yes | 2013-09-08/ 2013-09-08 | 84/84/1 | Not related/ Not applicable | Recovered/resolved |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Renal failure | 腎不全 | 5 | Yes | 2013-09-18/ | 94/ | Not related/ Not applicable | Fatal |
| | | | | | Renale failure | 腎不全 | 3 | Yes | 2013-09-13/ 2013-09-17 | 89/93/5 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Splenic rupture | 脾破裂 | 3 | Yes | 2013-09-08/ 2013-09-08 | 84/84/1 | Not related/ Not applicable | Recovered/resolved |
| | | 49000801 | 7[redacted]/Male/ White | 0 mg | Coronary sclerosis | 冠動脈硬化症 | 1 | Yes | 2013-12-03/ 2013-12-10 | 70/77/8 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Dysarthria | 構語障害 | 3 | Yes | 2014-02-04/ 2014-02-18 | 133/147/15 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | 420 mg | Myoclonus | ミオクローヌス | 2 | Yes | 2015-01-13/ 2015-03-03 | 476/525/50 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Pneumonia | 肺炎 | 3 | Yes | 2013-10-24/ 2013-10-31 | 30/37/8 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 4 | Yes | 2014-06-28/ 2014-07-15 | 277/294/18 | Possible/ Drug interrupted | Recovered/resolved |
| | | 49001202 | 7[redacted]/Male/ White | 560 mg | 3 broken ribs | 肋骨骨折 | 2 | Yes | 2014-12-19/ 2014-12-30 | 513/524/12 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Pneumonia | 肺炎 | 3 | Yes | 2014-04-18/ 2014-04-26 | 268/276/9 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2014-12-19/ 2014-12-30 | 513/524/12 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Pyelonephritis | 腎盂腎炎 | 3 | Yes | 2015-01-15/ | 540/ | Possible/ Not applicable | Not recovered/not resolved |
| | | | | | Renal failure | 腎不全 | 3 | Yes | 2015-01-15/ | 540/ | Possible/ Not applicable | Not recovered/not resolved |
| | | | | | Sepsis | 敗血症 | 4 | Yes | 2015-01-15/ 2015-01-29 | 540/554/15 | Possible/ Not applicable | Recovered/resolved |
| | | | | | Sepsis | 敗血症 | 5 | Yes | 2015-01-30/ | 555/ | Possible/ Not applicable | Fatal |
| | | 49001205 | 7[redacted]/Male/ White | 560 mg | Index finger right side phlegmon caused by foreign body (thorn) | 蜂巣炎 | 3 | Yes | 2014-03-19/ 2014-03-22 | 163/166/4 | Not related/ Dose not changed | Recovered/resolved |
| | | 49001501 | 6[redacted]/Male/ White | 0 mg | Duodenal stenosis | 十二指腸狭窄 | 4 | Yes | 2013-08-20/ 2013-09-14 | 23/48/26 | Not related/ Dose not changed | Recovered/resolved |
| | | 52000301 | 6[redacted]/Female/ Unknown | 560 mg | Epistaxis | 鼻出血 | 2 | Yes | 2013-10-16/ 2013-10-18 | 72/74/3 | Probable/ Dose not changed | Recovered/resolved |
| | | 55000103 | 6[redacted]/Male/ White | 560 mg | Abdominal pain | 腹痛 | 3 | Yes | 2013-12-22/ 2013-12-24 | 143/145/3 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 560 mg | Dyspnea | 呼吸困難 | 4 | Yes | 2013-12-22/ 2013-12-24 | 143/145/3 | Not related/ Drug interrupted | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 55000401 | 7[redacted]/Female/ White | 560 mg | Atrial fibrillation | 心房細動 | 4 | Yes | 2014-03-09/ 2014-03-31 | 181/203/23 | Very likely/ Drug interrupted | Recovered/resolved |
| | | | | | Atrial fibrillation | 心房細動 | 4 | Yes | 2014-05-27/ 2014-06-04 | 260/268/9 | Very likely/ Drug interrupted | Recovered/resolved |
| | | 57000102 | 6[redacted]/Male/ Other | 0 mg | Abscess in left elbow | 四肢膿瘍 | 2 | Yes | 2014-06-09/ 2014-06-24 | 260/275/16 | Probable/ Dose reduced | Recovered/resolved |
| | | | | 560 mg | Pleural effusion right | 胸水 | 3 | Yes | 2013-10-17/ 2013-12-03 | 25/72/48 | Probable/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Pulmonary tuberculosis | 肺結核 | 3 | Yes | 2013-10-23/ 2014-05-14 | 31/234/204 | Possible/ Dose not changed | Recovered/resolved |
| | | 57000104 | 6[redacted]/Male/ Other | 560 mg | Abdominal pain due to mantle cell lymphoma | 腹痛 | 3 | Yes | 2014-01-01/ | 57/ | Not related/ Drug withdrawn | Not recovered/not resolved |
| | | 82000101 | 7[redacted]/Male/ Asian | 560 mg | Epistaxis | 鼻出血 | 3 | Yes | 2013-05-21/ 2013-05-22 | 22/23/2 | Doubtful/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Supraventricular tachycardia | 上室性頻脈 | 2 | Yes | 2013-11-28/ 2013-11-29 | 213/214/2 | Doubtful/ Dose not changed | Recovered/resolved |
| | | 82000203 | 7[redacted]/Male/ Asian | 560 mg | Pleural effusion,aggravated | 胸水 | 2 | Yes | 2013-11-03/ 2013-11-05 | 90/92/3 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Pneumothorax | 気胸 | 2 | Yes | 2013-11-05/ 2013-12-11 | 92/128/37 | Not related/ Drug interrupted | Recovered/resolved with sequelae |
| | | 82000401 | 7[redacted]/Male/ Asian | 560 mg | Diarrhea | 下痢 | 3 | Yes | 2013-10-17/ 2013-10-24 | 232/239/8 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Pharyngitis | 咽頭炎 | 4 | Yes | 2013-11-21/ | 267/ | Not related/ Not applicable | Not recovered/not resolved |
| | | | | 560 mg | Pharyngitis | 咽頭炎 | 3 | Yes | 2013-10-26/ 2013-11-20 | 241/266/26 | Not related/ Dose not changed | Recovered/resolved with sequelae |
| | | | | | Septic shock | 敗血症性ショック | 4 | Yes | 2013-11-21/ 2013-11-22 | 267/268/2 | Not related/ Not applicable | Recovered/resolved with sequelae |
| | | | | | Septic shock | 敗血症性ショック | 5 | Yes | 2013-11-23/ | 269/ | Not related/ Not applicable | Fatal |
| | | 88600102 | 5[redacted]/Male/ Asian | 560 mg | Blood loss due to transverse process fractures | 出血 | 2 | Yes | 2014-08-06/ 2014-08-29 | 328/351/24 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | 0 mg | Reactivation of hepatitis b viral | Ｂ型肝炎 | 3 | Yes | 2014-08-14/ | 336/ | Doubtful/ Not applicable | Not recovered/not resolved |
| | | | | 560 mg | Transverse process fractures from left l1 to l5 | 腰椎骨折 | 2 | Yes | 2014-08-06/ 2014-08-29 | 328/351/24 | Not related/ Drug interrupted | Recovered/resolved |
| | | 88600103 | 4[redacted]/Female/ Asian | 0 mg | Leukocytosis | 白血球増加症 | 3 | Yes | 2015-02-06/ 2015-03-10 | 501/533/33 | Not related/ Dose not changed | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 560 mg | Skin infection | 皮膚感染 | 3 | Yes | 2013-09-30/ 2013-10-16 | 7/23/17 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 560 mg | Skin panniculitis on extremities | 脂肪織炎 | 2 | Yes | 2014-10-08/ 2014-11-18 | 380/421/42 | Not related/ Dose not changed | Recovered/resolved |
| | | | | 0 mg | Thymoma type b1 | 胸腺腫 | 3 | Yes | 2014-03-31/ 2014-04-07 | 189/196/8 | Not related/ Dose not changed | Recovered/resolved |
| | | 88600104 | 6[redacted]/Male/ Asian | | Sepsis | 敗血症 | 4 | Yes | 2014-01-06/ 2014-01-07 | 91/92/2 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Sepsis | 敗血症 | 5 | Yes | 2014-01-07/ | 92/ | Not related/ Not applicable | Fatal |
| | | 88600501 | 5[redacted]/Male/ Asian | 560 mg | Multiple organ failure | 多臓器不全 | 4 | Yes | 2013-05-08/ | 10/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | | | 560 mg | Septic shock | 敗血症性ショック | 5 | Yes | 2013-05-08/ | 10/ | Not related/ Not applicable | Fatal |
| | | | | 560 mg | Short of breath | 呼吸困難 | 2 | Yes | 2013-05-06/ | 8/ | Not related/ Dose not changed | Not recovered/not resolved |
| | Temsirolimus | 11000103 | 4[redacted]/Female/ White | | Leg pain (bone) - | 骨痛 | 3 | Yes | 2014-01/ | 80/ | Not related/ Not applicable | Not recovered/not resolved |
| | | | | | Shortness of breath | 呼吸困難 | 3 | Yes | 2014-01/ | 80/ | Possible/ Not applicable | Not recovered/not resolved |
| | | 11000202 | 7[redacted]/Male/ White | | Left clavicular area skin infection | 皮膚感染 | 3 | Yes | 2013-12-03/ 2013-12-07 | 57/61/5 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 11000402 | 7[redacted]/Male/ White | | Urinary tract infection | 尿路感染 | 3 | Yes | 2013-07-11/ 2013-07-31 | 15/35/21 | Probable/ Drug withdrawn | Recovered/resolved |
| | | 32000103 | 7[redacted]/Female/ White | | Coronary artery stenosis | 冠動脈狭窄 | 3 | Yes | 2014-01-21/ 2014-03-10 | 246/294/49 | Not related/ Drug withdrawn | Recovered/resolved with sequelae |
| | | 32000203 | 7[redacted]/Female/ White | | Adenocarcinoma stomach | 胃腺癌 | 3 | Yes | 2013-07-22/ 2013-08-01 | 7/17/11 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Interstitial pneumonia | 間質性肺疾患 | 3 | Yes | 2013-07-22/ 2013-07-31 | 7/16/10 | Probable/ Drug interrupted | Recovered/resolved |
| | | 32000501 | 8[redacted]/Male/ White | | Angina pectoris | 狭心症 | 2 | Yes | 2014-05-16/ 2014-05-30 | 486/500/15 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Diarrhea | 下痢 | 2 | Yes | 2014-08-05/ 2014-08-22 | 567/584/18 | Very likely/ Drug interrupted | Recovered/resolved |
| | | | | 75 mg | Diarrhea | 下痢 | 2 | Yes | 2014-07-31/ 2014-08-04 | 562/566/5 | Very likely/ Dose not changed | Recovered/resolved |
| | | 32000701 | 6[redacted]Male/ White | | Bilateral pneumonia | 肺炎 | 3 | Yes | 2013-11-10/ 2013-11-12 | 56/58/3 | Possible/ Drug interrupted | Recovered/resolved |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Bilateral pneumonia | 肺炎 | 5 | Yes | 2013-11-13/ | 59/ | Possible/ Not applicable | Fatal |
| | | | | | Tumorlysis | 腫瘍崩壊症候群 | 3 | Yes | 2013-09-19/ 2013-09-26 | 4/11/8 | Probable/ Drug interrupted | Recovered/resolved |
| | | 32000703 | 7[redacted]/Female/ White | | Renal insufficiency | 腎不全 | 3 | Yes | 2014-05-28/ 2014-06-05 | 198/206/9 | Not related/ Not applicable | Recovered/resolved |
| | | 33000201 | 7[redacted]/Male/ White | | Prostatitis (urinary burning) | 前立腺炎 | 3 | Yes | 2013-07-16/ 2013-07-23 | 13/20/8 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 34000101 | 6[redacted]/Male/ White | | Deterioration of general condition | 全身健康状態低下 | 5 | Yes | 2013-05-06/ | 25/ | Not related/ Not applicable | Fatal |
| | | | | | Tumor lysis syndrome | 腫瘍崩壊症候群 | 3 | Yes | 2013-04-13/ 2013-04-19 | 2/8/7 | Possible/ Dose not changed | Recovered/resolved |
| | | 34000103 | 6[redacted]/Female/ White | | Acute diverticulitis | 憩室炎 | 3 | Yes | 2014-04-30/ 2014-05-09 | 296/305/10 | Possible/ Drug withdrawn | Recovered/resolved |
| | | | | | Hepatic abcess | 肝膿瘍 | 3 | Yes | 2014-05-23/ 2014-06-13 | 319/340/22 | Possible/ Drug withdrawn | Recovered/resolved |
| | | | | | Infectious colitis | 感染性大腸炎 | 2 | Yes | 2014-02-04/ 2014-02-25 | 211/232/22 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 34000202 | 5[redacted]/Male/ White | | Ataxia | 運動失調 | 4 | Yes | 2013-07-25/ 2013-09-11 | 100/148/49 | Not related/ Drug withdrawn | Recovered/resolved |
| | | 34000302 | 8[redacted]/Male/ White | | Acute gastroenteritis | 胃腸炎 | 3 | Yes | 2014-02-27/ 2014-03-10 | 232/243/12 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Acute renal failure | 急性腎不全 | 3 | Yes | 2014-02-27/ 2014-03-10 | 232/243/12 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Hypokalemia | 低カリウム血症 | 3 | Yes | 2014-02-28/ 2014-03-06 | 233/239/7 | Possible/ Drug interrupted | Recovered/resolved |
| | | 34000401 | 7[redacted]/Male/ White | | Fever | 発熱 | 2 | Yes | 2013-03-01/ 2013-03-06 | 9/14/6 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Fever syndrome | 発熱 | 2 | Yes | 2013-04-02/ 2013-04-15 | 41/54/14 | Not related/ Dose reduced | Recovered/resolved |
| | | | | | Fever syndrome | 発熱 | 2 | Yes | 2013-04-26/ 2013-05-08 | 65/77/13 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Fever syndrome | 発熱 | 2 | Yes | 2013-05-10/ 2013-05-17 | 79/86/8 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Urinary tract infection | 尿路感染 | 3 | Yes | 2013-03-10/ 2013-03-22 | 18/30/13 | Not related/ Drug interrupted | Recovered/resolved |
| | | 34000403 | 6[redacted]/Male/ White | | Fever syndrome | 発熱 | 4 | Yes | 2013-07-19/ 2013-08-02 | 89/103/15 | Possible/ Drug withdrawn | Recovered/resolved |
| | | 34000501 | 5[redacted]/Male/ White | | Back pain | 背部痛 | 2 | Yes | 2014-09-01/ 2014-09-08 | 312/319/8 | Not related/ Not applicable | Recovered/resolved |
| | | 34000603 | 4[redacted]/Male/ White | | Anorexia | 食欲減退 | 3 | Yes | 2013-11-11/ 2013-11-14 | 98/101/4 | Probable/ Drug withdrawn | Recovered/resolved |
| | | | | | Dehydration | 脱水 | 2 | Yes | 2013-10-15/ 2013-10-21 | 71/77/7 | Possible/ Drug interrupted | Recovered/resolved |

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Diarrhea | 下痢 | 3 | Yes | 2013-10-06/ 2013-10-21 | 62/77/16 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Diarrhea | 下痢 | 3 | Yes | 2013-11-11/ 2013-11-14 | 98/101/4 | Very likely/ Drug withdrawn | Recovered/resolved |
| | | | | | Drug toxicity (probable) | 各種物質毒性 | 3 | Yes | 2013-10-10/ 2013-10-21 | 66/77/12 | Probable/ Drug interrupted | Recovered/resolved |
| | | | | | Fever | 発熱 | 1 | Yes | 2013-10-10/ 2013-10-16 | 66/72/7 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Fever | 発熱 | 1 | Yes | 2013-11-06/ 2013-11-14 | 93/101/9 | Very likely/ Drug withdrawn | Recovered/resolved |
| | | | | | Malaise | 倦怠感 | 2 | Yes | 2013-10-10/ 2013-10-21 | 66/77/12 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Malaise | 倦怠感 | 2 | Yes | 2013-11-11/ 2013-11-14 | 98/101/4 | Very likely/ Drug withdrawn | Recovered/resolved |
| | | | | | Pulmonary embolism | 肺塞栓症 | 3 | Yes | 2013-11-28/ 2014-01-23 | 115/171/57 | Not related/ Not applicable | Recovered/resolved |
| | | 34000702 | 5[redacted]/Male/ White | | Probable invasive pulmonary aspergillosis. | 気管支肺アスペルギルス症 | 4 | Yes | 2013-08-13/ 2013-09-16 | 90/124/35 | Not related/ Drug interrupted | Recovered/resolved |
| | | 34000703 | 6[redacted]/Male/ White | | Pneumonia (escherichia coli culture positive) | 大腸菌性肺炎 | 3 | Yes | 2013-08-14/ 2013-08-20 | 51/57/7 | Not related/ Drug interrupted | Recovered/resolved |
| | | 35100201 | 7[redacted]/Male/ White | | Atrial fibrillation | 心房細動 | 3 | Yes | 2013-06-02/ 2013-06-03 | 27/28/2 | Doubtful/ Not applicable | Recovered/resolved |
| | | | | | Hyponatremia | 低ナトリウム血症 | 4 | Yes | 2013-05-14/ 2013-05-16 | 8/10/3 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Hyponatremia | 低ナトリウム血症 | 3 | Yes | 2013-05-16/ 2013-05-22 | 10/16/7 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Isquemic stroke | 虚血性脳卒中 | 4 | Yes | 2013-06-02/ 2013-06-04 | 27/29/3 | Doubtful/ Not applicable | Recovered/resolved |
| | | | | | Isquemic stroke | 虚血性脳卒中 | 5 | Yes | 2013-06-05/ | 30/ | Doubtful/ Not applicable | Fatal |
| | | | | | Sinusitis | 副鼻腔炎 | 3 | Yes | 2013-05-22/ | 16/ | Possible/ Dose not changed | Not recovered/not resolved |
| | | 35100204 | 6[redacted]/Male/ White | | Cardiac arrest | 心停止 | 5 | Yes | 2013-07-22/ | 49/ | Not related/ Not applicable | Fatal |
| | | | | | Fatigue | 疲労 | 3 | Yes | 2013-07-11/ | 38/ | Possible/ Drug withdrawn | Not recovered/not resolved |
| | | 35300106 | 7[redacted]/Male/ White | | Stomatitis | 口内炎 | 3 | Yes | 2013-08-16/ 2013-09-02 | 10/27/18 | Possible/ Drug interrupted | Recovered/resolved |
| | | 36000201 | 7[redacted]/Male/ White | | Pneumonia | 肺炎 | 3 | Yes | 2013-04-04/ 2013-04-12 | 31/39/9 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 36000203 | 6[redacted]/Male/ White | | Deep vein thrombosis | 深部静脈血栓症 | 2 | Yes | 2013-11-14/ 2013-11-19 | 84/89/6 | Doubtful/ Dose not changed | Recovered/resolved |

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Sepsis | 敗血症 | 4 | Yes | 2014-01-05/ 2014-01-14 | 136/145/10 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 36000302 | 8[redacted]/Female/ White | | Gastroenteritis | 胃腸炎 | 3 | Yes | 2013-05-16/ 2013-05-21 | 4/9/6 | Very likely/ Dose not changed | Recovered/resolved |
| | | | | | Vomiting | 嘔吐 | 2 | Yes | 2013-05-30/ 2013-06-12 | 18/31/14 | Very likely/ Drug interrupted | Recovered/resolved |
| | | | | | Worsening of edema | 浮腫 | 3 | Yes | 2013-06-07/ 2013-06-26 | 26/45/20 | Possible/ Drug withdrawn | Recovered/resolved |
| | | 36000403 | 6[redacted]/Male/ White | | Pneumonitis | 肺臓炎 | 3 | Yes | 2014-02-11/ 2014-02-20 | 110/119/10 | Probable/ Drug withdrawn | Recovered/resolved with sequelae |
| | | 36000601 | 4[redacted]/Male/ White | | Epistaxis | 鼻出血 | 2 | Yes | 2013-07-24/ 2013-07-25 | 16/17/2 | Doubtful/ Dose not changed | Recovered/resolved |
| | | 38000301 | 7[redacted]/Male/ White | | Acute heart failure | 急性心不全 | 5 | Yes | 2013-04-11/ | 9/ | Possible/ Not applicable | Fatal |
| | | | | | Anemia | 貧血 | 4 | Yes | 2013-04-10/ | 8/ | Possible/ Drug interrupted | Not recovered/not resolved |
| | | | | | Gastro-intestinal bleeding | 胃腸出血 | 3 | Yes | 2013-04-10/ | 8/ | Possible/ Drug interrupted | Not recovered/not resolved |
| | | | | | Haemorragic gastritis | 出血性胃炎 | 2 | Yes | 2013-04-10/ | 8/ | Possible/ Drug interrupted | Not recovered/not resolved |
| | | 38000502 | 6[redacted]/Male/ White | | Fever | 発熱 | 2 | Yes | 2013-04-02/ 2013-04-08 | 14/20/7 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Left-sided pneumonia | 肺炎 | 3 | Yes | 2013-04-08/ 2013-04-17 | 20/29/10 | Not related/ Drug interrupted | Recovered/resolved |
| | | 38000503 | 6[redacted]/Male/ White | | Right sided lower-lobe pneumonia | 大葉性肺炎 | 3 | Yes | 2013-04-16/ 2013-04-29 | 6/19/14 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Right-sided pneumonia | 肺炎 | 3 | Yes | 2013-05-03/ 2013-05-10 | 23/30/8 | Possible/ Dose reduced | Recovered/resolved |
| | | | | | Toxic hepatitis | 中毒性肝炎 | 2 | Yes | 2013-05-23/ 2013-06-02 | 43/53/11 | Very likely/ Drug interrupted | Recovered/resolved |
| | | | | | Toxic hepatitis | 中毒性肝炎 | 1 | Yes | 2013-06-03/ 2013-06-06 | 54/57/4 | Very likely/ Drug interrupted | Recovered/resolved |
| | | 39000204 | 8[redacted]/Female/ White | | Dyspnea | 呼吸困難 | 3 | Yes | 2014-01-04/ 2014-01-10 | 137/143/7 | Not related/ Not applicable | Recovered/resolved |
| | | 39000401 | 6[redacted]/Male/ White | | Pneumonia | 肺炎 | 3 | Yes | 2013-12-23/ 2014-01-08 | 216/232/17 | Possible/ Drug interrupted | Recovered/resolved |
| | | 39000406 | 6[redacted]/Male/ White | | Ground glass opacity seen on a thoracic ct (interstitial pulmonary fibrosis) | 間質性肺疾患 | 2 | Yes | 2014-01-31/ 2014-09-03 | 66/281/216 | Not related/ Drug withdrawn | Recovered/resolved |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 39000601 | 6[redacted]/Male/ White | | Ruptured spleen | 脾破裂 | 4 | Yes | 2015-02-11/ 2015-02-24 | 454/467/14 | Not related/ Drug interrupted | Recovered/resolved |
| | | 42002301 | 7[redacted]/Male/ White | | Enterorrhagy | 腸出血 | 3 | Yes | 2013-06-04/ 2013-06-19 | 27/42/16 | Possible/ Drug withdrawn | Recovered/resolved with sequelae |
| | | 42002306 | 7[redacted]/Male/ White | | Acute mycotic laryngitis | 真菌性喉頭炎 | 3 | Yes | 2013-11-04/ 2013-11-12 | 12/20/9 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 42002507 | 7[redacted]/Male/ White | | Atypical pneumony | 異型肺炎 | 3 | Yes | 2014-01-09/ | 71/ | Possible/ Drug withdrawn | Not recovered/not resolved |
| | | | | | Septic shock | 敗血症性ショック | 5 | Yes | 2014-01-13/ | 75/ | Not related/ Not applicable | Fatal |
| | | 44000101 | 6[redacted]/Male/ White | | Pulmonary oedema | 肺水腫 | 4 | Yes | 2013-12-08/ | 243/ | Not related/ Not applicable | Not recovered/not resolved |
| | | | | | Renal failure | 腎不全 | 4 | Yes | 2013-12-08/ | 243/ | Not related/ Not applicable | Not recovered/not resolved |
| | | | | | Splenic pain due to disease progression | 腹痛 | 3 | Yes | 2013-12-08/ 2013-12-20 | 243/255/13 | Not related/ Not applicable | Recovered/resolved |
| | | 44000104 | 8[redacted]/Male/ White | | Fatigue | 疲労 | 2 | Yes | 2013-07-01/ 2013-07-26 | 42/67/26 | Probable/ Drug interrupted | Recovered/resolved |
| | | 44000107 | 8[redacted]/Female/ White | | Acute confusion | 錯乱状態 | 3 | Yes | 2013-11-13/ | 29/ | Not related/ Drug withdrawn | Not recovered/not resolved |
| | | 44000206 | 6[redacted]/Male/ White | | Chest infection | 下気道感染 | 3 | Yes | 2013-12-16/ 2013-12-24 | 43/51/9 | Probable/ Dose not changed | Recovered/resolved |
| | | | | | Infection - pneumocystis jiroveci | ニューモシスチス・イロベチイ感染 | 3 | Yes | 2013-11-14/ 2013-12-01 | 11/28/18 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Lower respiratory tract infection | 下気道感染 | 3 | Yes | 2013-11-07/ 2013-11-13 | 4/10/7 | Very likely/ Dose not changed | Recovered/resolved |
| | | | | | Tumour lysis syndrome | 腫瘍崩壊症候群 | 3 | Yes | 2013-11-05/ 2013-11-07 | 2/4/3 | Very likely/ Dose not changed | Recovered/resolved |
| | | 44000301 | 7[redacted]/Male/ White | 175 mg | Bladder infection | 膀胱炎 | 3 | Yes | 2013-01-17/ 2013-02-06 | 8/28/21 | Probable/ Drug interrupted | Recovered/resolved |
| | | | | | Infection in leg ulcer | 皮膚潰瘍 | 3 | Yes | 2013-03-02/ | 52/ | Possible/ Drug interrupted | Not recovered/not resolved |
| | | | | | Oral candidiasis | 口腔カンジダ症 | 3 | Yes | 2013-03-12/ 2013-03-22 | 62/72/11 | Not related/ Not applicable | Recovered/resolved |
| | | | | | Thrombocytopenia | 血小板減少症 | 3 | Yes | 2013-01-21/ 2013-02-06 | 12/28/17 | Probable/ Drug interrupted | Recovered/resolved |
| | | 44000304 | 6[redacted]/Male/ White | | Lung infection | 肺感染 | 3 | Yes | 2013-09-19/ 2013-10-04 | 78/93/16 | Possible/ Drug interrupted | Recovered/resolved |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 44000604 | 6[redacted]/Male/ White | 175 mg | Allergic reaction | 過敏症 | 3 | Yes | 2013-09-27/ 2013-09-28 | 1/2/2 | Probable/ Dose not changed | Recovered/resolved |
| | | | | 75 mg | Allergic reaction | 過敏症 | 2 | Yes | 2013-10-18/ 2013-10-22 | 22/26/5 | Very likely/ Dose not changed | Recovered/resolved |
| | | 44000701 | 6[redacted]/Male/ White | | Febrile neutropenia | 発熱性好中球減少症 | 3 | Yes | 2013-09-02/ 2013-09-18 | 50/66/17 | Possible/ Dose reduced | Recovered/resolved |
| | | | | | Pneumocystis carinii pneumonia | ニューモシスチス・イロベチイ肺炎 | 3 | Yes | 2013-09-01/ 2013-09-26 | 49/74/26 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Sepsis | 敗血症 | 3 | Yes | 2013-09-01/ 2013-09-18 | 49/66/18 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Sepsis | 敗血症 | 3 | Yes | 2013-09-30/ 2013-10-04 | 78/82/5 | Probable/ Drug interrupted | Recovered/resolved |
| | | 44000702 | 7[redacted]/Male/ White | | Dyspnea | 呼吸困難 | 3 | Yes | 2013-11-05/ 2013-11-17 | 50/62/13 | Probable/ Drug interrupted | Recovered/resolved |
| | | | | | Dyspnea | 呼吸困難 | 3 | Yes | 2014-01-26/ 2014-02 | 132/152/21 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Lung infection | 肺感染 | 3 | Yes | 2013-12-28/ 2014-01-24 | 103/130/28 | Possible/ Drug interrupted | Recovered/resolved with sequelae |
| | | 44000802 | 5[redacted]/Male/ White | | Neuropathic pain (both feet) | 神経痛 | 3 | Yes | 2014-01-28/ | 104/ | Very likely/ Drug withdrawn | Not recovered/not resolved |
| | | 44000901 | 7[redacted]/Male/ White | | Neutropenia | 好中球減少症 | 4 | Yes | 2013-09-26/ 2013-09-30 | 220/224/5 | Possible/ Dose reduced | Recovered/resolved |
| | | | | | Neutropenia | 好中球減少症 | 3 | Yes | 2013-10-14/ 2013-10-18 | 238/242/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Neutropenia | 好中球減少症 | 4 | Yes | 2013-10-18/ 2013-10-24 | 242/248/7 | Possible/ Dose reduced | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2014-08-29/ 2014-09-19 | 557/578/22 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | | Pneumonia | 肺炎 | 3 | Yes | 2014-09-28/ 2014-11-12 | 587/632/46 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Stomatitis | 口内炎 | 3 | Yes | 2013-09-18/ 2013-09-30 | 212/224/13 | Possible/ Dose reduced | Recovered/resolved |
| | | 44001003 | 5[redacted]/Male/ White | 175 mg | Pyrexia of unknown origin | 発熱 | 3 | Yes | 2013-03-28/ 2013-04-03 | 1/7/7 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Renal faliure | 腎不全 | 5 | Yes | 2013-05-28/ | 62/ | Not related/ Not applicable | Fatal |
| | | | | | Sepsis | 敗血症 | 4 | Yes | 2013-04-09/ 2013-04-15 | 13/19/7 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Sepsis | 敗血症 | 4 | Yes | 2013-05-12/ 2013-05-22 | 46/56/11 | Probable/ Dose not changed | Recovered/resolved |

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| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 46000105 | 7[redacted]/Male/ White | | Thrombocytopenia | 血小板減少症 | 4 | Yes | 2013-04-22/ | 7/ | Very likely/ Drug withdrawn | Not recovered/not resolved |
| | | 46000112 | 7[redacted]/Male/ White | 75 mg | Dyspnea | 呼吸困難 | 3 | Yes | 2013-11-13/ 2013-11-15 | 29/31/3 | Not related/ Drug withdrawn | Recovered/resolved |
| | | | | | Neutropenic sepsis | 好中球減少性敗血症 | 4 | Yes | 2013-12-01/ 2013-12-09 | 47/55/9 | Doubtful/ Not applicable | Recovered/resolved |
| | | 46000202 | 7[redacted]/Female/ White | | Fever | 発熱 | 2 | Yes | 2013-05-12/ 2013-05-13 | 19/20/2 | Doubtful/ Not applicable | Recovered/resolved |
| | | | | | Lumbar compression in lower back | 椎間板圧迫 | 3 | Yes | 2014-07-24/ | 457/ | Not related/ Drug interrupted | Not recovered/not resolved |
| | | | | 50 mg | Septicemia | 敗血症 | 4 | Yes | 2014-08-06/ 2014-08-26 | 470/490/21 | Very likely/ Drug interrupted | Recovered/resolved |
| | | 46000403 | 6[redacted]/Male/ White | | Dyspnoea | 呼吸困難 | 1 | Yes | 2013-04-02/ 2013-04-05 | 13/16/4 | Doubtful/ Dose not changed | Recovered/resolved |
| | | | | | Generalized infection of unknown cause | 感染 | 2 | Yes | 2013-04-02/ | 13/ | Possible/ Drug interrupted | Not recovered/not resolved |
| | | | | | Nosebleeding | 鼻出血 | 3 | Yes | 2013-04-02/ 2013-04-03 | 13/14/2 | Probable/ Dose not changed | Recovered/resolved |
| | | | | | Thrombocytopenia | 血小板減少症 | 4 | Yes | 2013-04-02/ 2013-04-05 | 13/16/4 | Doubtful/ Dose not changed | Recovered/resolved |
| | | | | | Worsening of general condition | 全身健康状態低下 | 5 | Yes | 2013-04-21/ | 32/ | Not related/ Not applicable | Fatal |
| | | 46000404 | 7[redacted]/Male/ White | | Suspect general infection | 感染 | 2 | Yes | 2013-09-17/ 2013-09-18 | 125/126/2 | Not related/ Not applicable | Recovered/resolved |
| | | 48000401 | 6[redacted]/Female/ White | 75 mg | Anemia | 貧血 | 3 | Yes | 2013-07-17/ 2013-07-25 | 36/44/9 | Probable/ Dose not changed | Recovered/resolved |
| | | | | | Renal failure | 腎不全 | 3 | Yes | 2013-07-24/ 2013-08-22 | 43/72/30 | Probable/ Not applicable | Recovered/resolved |
| | | 48000501 | 6[redacted]/Male/ White | 75 mg | Anemia | 貧血 | 2 | Yes | 2013-05-29/ 2013-06-06 | 35/43/9 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 175 mg | Diabetes | 糖尿病 | 2 | Yes | 2013-05-09/ 2013-05-15 | 15/21/7 | Very likely/ Drug interrupted | Recovered/resolved |
| | | | | | Diarrhea | 下痢 | 3 | Yes | 2013-05-14/ 2013-05-22 | 20/28/9 | Very likely/ Drug interrupted | Recovered/resolved |
| | | 48001302 | 5[redacted]/Female/ White | | Pneumonitis | 肺臓炎 | 2 | Yes | 2014-04-09/ 2014-04-15 | 323/329/7 | Very likely/ Drug interrupted | Recovered/resolved |
| | | | | | Rectal hemorrhage after polipectomy | 処置後出血 | 2 | Yes | 2014-08-19/ 2014-08-20 | 455/456/2 | Not related/ Not applicable | Recovered/resolved |
| | | 48001304 | 7[redacted]/Male/ White | | Multifocal cerebral ischaemia | 脳虚血 | 4 | Yes | 2013-09-06/ | 47/ | Doubtful/ Dose not changed | Not recovered/not resolved |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Sepsis | 敗血症 | 4 | Yes | 2013-09-07/ 2013-09-09 | 48/50/3 | Possible/ Dose not changed | Recovered/resolved with sequelae |
| | | | | | Sepsis | 敗血症 | 5 | Yes | 2013-09-09/ | 50/ | Possible/ Not applicable | Fatal |
| | | 48001401 | 5[redacted]/Male/ White | | Tooth infection | 歯感染 | 3 | Yes | 2013-08-29/ 2013-09-02 | 32/36/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | 48001501 | 7[redacted]/Male/ White | 50 mg | Anemia | 貧血 | 3 | Yes | 2013-07-03/ 2013-07-23 | 57/77/21 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Cataract of right eye | 白内障 | 3 | Yes | 2014-09-11/ 2015-04-01 | 492/694/203 | Possible/ Dose not changed | Recovered/resolved |
| | | | | 50 mg | Clostridium difficile colitis | クロストリジウム・ディフィシレ大腸炎 | 3 | Yes | 2014-11-19/ 2014-12-02 | 561/574/14 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Diarrhea | 下痢 | 3 | Yes | 2015-03-03/ 2015-03-19 | 665/681/17 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Foreign body in soft tissues | 体内異物 | 2 | Yes | 2014-02-12/ 2014-02-12 | 281/281/1 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Ischemic heart disease | 心筋虚血 | 2 | Yes | 2014-08-21/ 2014-08-22 | 471/472/2 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Upper respiratory tract infection | 上気道感染 | 2 | Yes | 2014-02-03/ 2014-02-12 | 272/281/10 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Urinary tract infection | 尿路感染 | 2 | Yes | 2013-07-18/ 2013-08-03 | 72/88/17 | Possible/ Drug interrupted | Recovered/resolved |
| | | 48001502 | 5[redacted]/Male/ White | | Anemia | 貧血 | 3 | Yes | 2014-05-21/ 2014-05-26 | 351/356/6 | Very likely/ Drug interrupted | Recovered/resolved |
| | | | | 50 mg | Anemia | 貧血 | 3 | Yes | 2014-07-02/ 2014-07-24 | 393/415/23 | Possible/ Dose reduced | Recovered/resolved |
| | | 48001508 | 7[redacted]/Male/ White | | Cardio-respiratory failure | 心肺不全 | 5 | Yes | 2013-12-22/ | 117/ | Not related/ Not applicable | Fatal |
| | | | | | Chronic heart failure (nyha iii) | 慢性心不全 | 3 | Yes | 2013-09-17/ 2013-09-19 | 21/23/3 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Respiratory tract infection | 気道感染 | 2 | Yes | 2013-12-17/ | 112/ | Possible/ Dose not changed | Not recovered/not resolved |
| | | 48001509 | 5[redacted]/Male/ White | | Atrial fibrillation | 心房細動 | 3 | Yes | 2014-02-26/ 2014-02-28 | 141/143/3 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | | Atrial fibrillation | 心房細動 | 2 | Yes | 2014-07-03/ 2014-07-08 | 268/273/6 | Possible/ Dose not changed | Recovered/resolved |
| | | 49000603 | 7[redacted]/Male/ White | | Fracture of fibular right | 腓骨骨折 | 3 | Yes | 2013-12-03/ 2014-02-11 | 29/99/71 | Not related/ Not applicable | Recovered/resolved |
| | | 49000701 | 6[redacted]/Male/ White | | Fever | 発熱 | 2 | Yes | 2014-03-12/ 2014-03-12 | 140/140/1 | Not related/ Drug interrupted | Recovered/resolved |
| | | 49001204 | 6[redacted]/Female/ White | | Deterioration of the general condition | 全身健康状態低下 | 3 | Yes | 2013-10-02/ 2013-10-08 | 23/29/7 | Possible/ Dose not changed | Recovered/resolved |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Mucositis | 粘膜の炎症 | 3 | Yes | 2013-10-02/ 2013-10-08 | 23/29/7 | Possible/ Dose not changed | Recovered/resolved |
| | | | | | Whole body pain | 疼痛 | 3 | Yes | 2013-10-02/ 2013-10-08 | 23/29/7 | Possible/ Dose not changed | Recovered/resolved |
| | | 49001701 | 6[redacted]/Male/ White | | Port infection | 医療機器関連感染 | 3 | Yes | 2013-11-13/ 2013-12-04 | 24/45/22 | Not related/ Dose not changed | Recovered/resolved |
| | | | | | Reduced general condition | 全身健康状態低下 | 2 | Yes | 2013-12-15/ 2013-12-19 | 56/60/5 | Not related/ Not applicable | Recovered/resolved |
| | | 49001702 | 6[redacted]/Male/ White | | Reduced general condition | 全身健康状態低下 | 2 | Yes | 2013-11-12/ | 37/ | Not related/ Dose not changed | Not recovered/not resolved |
| | | | | 75 mg | Reduced general condition | 全身健康状態低下 | 2 | Yes | 2013-10-28/ 2013-11-05 | 22/30/9 | Not related/ Dose not changed | Recovered/resolved |
| | | 55000107 | 7[redacted]/Female/ White | | Pneumonia | 肺炎 | 4 | Yes | 2013-12-16/ | 41/ | Very likely/ Not applicable | Not recovered/not resolved |
| | | | | | Respiratory failure | 呼吸不全 | 5 | Yes | 2013-12-17/ | 42/ | Very likely/ Not applicable | Fatal |
| | | 55000403 | 6[redacted]/Female/ White | | Implantable catheter infection | 医療機器関連感染 | 3 | Yes | 2014-12-11/ 2014-12-15 | 435/439/5 | Possible/ Drug interrupted | Recovered/resolved |
| | | 55000404 | 8[redacted]/Male/ White | | Congestive heart failure | うっ血性心不全 | 4 | Yes | 2014-10-03/ 2014-10-27 | 358/382/25 | Not related/ Drug interrupted | Recovered/resolved |
| | | | | | Herpes zoster | 帯状疱疹 | 3 | Yes | 2013-11-23/ 2013-12-02 | 44/53/10 | Very likely/ Drug interrupted | Recovered/resolved |
| | | | | | Loss of renal function | 腎機能障害 | 3 | Yes | 2014-01-02/ 2014-01-06 | 84/88/5 | Possible/ Dose reduced | Recovered/resolved |
| | | | | | Loss of renal function' | 腎機能障害 | 3 | Yes | 2014-10-03/ 2014-10-27 | 358/382/25 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | | Lower gastrointestinal bleeding | 下部消化管出血 | 3 | Yes | 2014-06-24/ 2014-07-01 | 257/264/8 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | | | | Neuropathic pain | 神経痛 | 2 | Yes | 2013-12-30/ 2014-01-09 | 81/91/11 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | | Tremors widespread | 振戦 | 3 | Yes | 2013-12-08/ 2013-12-13 | 59/64/6 | Very likely/ Drug interrupted | Recovered/resolved |
| | | 55000701 | 8[redacted]/Female/ White | | Inappetence | 食欲減退 | 3 | Yes | 2013-10-13/ 2013-10-15 | 26/28/3 | Very likely/ Dose not changed | Recovered/resolved |
| | | | | | Stroke | 脳血管発作 | 2 | Yes | 2013-12-17/ 2013-12-24 | 91/98/8 | Not related/ Drug withdrawn | Recovered/resolved with sequelae |
| | | 57000101 | 7[redacted]/Male/ Other | | Pain in extremity | 四肢痛 | 3 | Yes | 2013-10-08/ | 68/ | Not related/ Not applicable | Recovering/resolving |
| | | 57000105 | 5[redacted]/Male/ Other | | Pneumonia in study | 肺炎 | 2 | Yes | 2014-02-03/ 2014-05-30 | 69/185/117 | Probable/ Drug withdrawn | Recovered/resolved |

**LSFAE02: Listing of Treatment-emergent Serious Adverse Events; Safety Population (MCL-ISS)**

| Study | Treatment | Subject ID | Age/Sex/ Race | Dose at Onset of Event | Reported Term | MedDRA Preferred Term | Toxicity Grade | SAE | AE Start/ Stop Date | AE Start Day[a]/ Stop Day[b]/ Duration[c] | Causality/ Action Taken | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 57000201 | 6[redacted]/Male/ Other | | Pneumonitis due mcl | 肺臓炎 | 3 | Yes | 2014-03-27/ 2014-04-15 | 150/169/20 | Not related/ Drug withdrawn | Recovered/resolved |
| | | | | | Sinusitis due to aspergillus | アスペルギルス性副鼻腔炎 | 3 | Yes | 2014-03-21/ 2014-07-08 | 144/253/110 | Not related/ Drug interrupted | Recovered/resolved |
| | | 57000202 | 6[redacted]/Male/ Other | | Enterocolitis | 腸炎 | 3 | Yes | 2013-11-03/ 2013-11-14 | 11/22/12 | Possible/ Drug interrupted | Recovered/resolved |
| | | 70000702 | 7[redacted]/Female/ White | | Pneumonia (middle lobe of right lung) | 肺炎 | 3 | Yes | 2014-04-09/ 2014-04-27 | 185/203/19 | Doubtful/ Drug interrupted | Recovered/resolved |
| | | 82000202 | 6[redacted]/Female/ Asian | | Confusion | 錯乱状態 | 2 | Yes | 2013-06-22/ 2013-07-18 | 31/57/27 | Possible/ Drug interrupted | Recovered/resolved |
| | | | | 75 mg | Confusion | 錯乱状態 | 3 | Yes | 2013-07-19/ | 58/ | Possible/ Drug withdrawn | Not recovered/not resolved |
| | | | | 75 mg | Fatigue | 疲労 | 3 | Yes | 2013-07-19/ | 58/ | Possible/ Drug withdrawn | Not recovered/not resolved |
| | | 82000403 | 7[redacted]/Male/ Asian | | Upper respiratory infection | 上気道感染 | 2 | Yes | 2013-06-14/ 2013-06-27 | 66/79/14 | Not related/ Dose not changed | Recovered/resolved |
| | | 88600402 | 6[redacted]/Male/ Asian | | Hemorrhoid | 痔核 | 2 | Yes | 2013-10-11/ 2013-11-01 | 11/32/22 | Probable/ Dose not changed | Recovered/resolved |
| | | | | | Oral mucositis | 口内炎 | 2 | Yes | 2013-10-11/ 2013-11-25 | 11/56/46 | Probable/ Dose not changed | Recovered/resolved |
| | | | | | Perineal and inguinal erosive wound | 創傷 | 2 | Yes | 2013-10-16/ | 16/ | Probable/ Drug interrupted | Not recovered/not resolved |

[a] Start day = AE start date – first dose date (+1 if AE start date >= first dose date).
[b] Stop day = AE stop date – first dose date (+1 if AE stop date >= first dose date).
[c] Duration of AE = AE stop date – AE start date + 1.



参照元：5.3.5.3.1 ISS LSFAE02

表 2.7.4-付録-23 Treatment-Emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)

**TSFAE08: Treatment-Emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib | |
|---|---|---|
| | All Grade | Grade 3 or Higher |
| Analysis Set: All Treated Population | 16 | |
| Total Number of Subjects with TEAE Leading to Drug Withdrawn | 2 (12.5%) | 2 (12.5%) |
| MedDRA System organ class/Preferred term | | |
| 血液およびリンパ系障害 | 1 (6.3%) | 1 (6.3%) |
| 白血球増加症 | 1 (6.3%) | 1 (6.3%) |
| 感染症および寄生虫症 | 1 (6.3%) | 1 (6.3%) |
| 敗血症 | 1 (6.3%) | 1 (6.3%) |
| 代謝および栄養障害 | 1 (6.3%) | 1 (6.3%) |
| 高尿酸血症 | 1 (6.3%) | 1 (6.3%) |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0

[TSFAE08.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsfae08.sas] 21AUG2015, 12:30
参照元：5.3.5.2.1 MCL2002 試験 CSR Table 20

表 2.7.4-付録-24 Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE08PART1OF3: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 111 | | 120 | |
| Subjects with any TEAE leading to drug withdrawn | 10 (9.0%) | 9 (8.1%) | 20 (16.7%) | 19 (15.8%) |
| System organ class | | | | |
| Preferred term | | | | |
| 血液およびリンパ系障害 | 0 | 0 | 5 (4.2%) | 5 (4.2%) |
| 血小板減少症 | 0 | 0 | 2 (1.7%) | 2 (1.7%) |
| 好中球減少症 | 0 | 0 | 2 (1.7%) | 2 (1.7%) |
| 貧血 | 0 | 0 | 0 | 0 |
| 溶血 | 0 | 0 | 0 | 0 |
| 白血球増加症 | 0 | 0 | 0 | 0 |
| 脾臓出血 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 感染症および寄生虫症 | 2 (1.8%) | 2 (1.8%) | 4 (3.3%) | 4 (3.3%) |
| 肺炎 | 1 (0.9%) | 1 (0.9%) | 3 (2.5%) | 3 (2.5%) |
| 敗血症 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 尿路感染 | 0 | 0 | 0 | 0 |
| 異型肺炎 | 0 | 0 | 0 | 0 |
| 憩室炎 | 0 | 0 | 0 | 0 |
| 毛包炎 | 0 | 0 | 0 | 0 |
| 肝膿瘍 | 0 | 0 | 0 | 0 |
| 臨床検査 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 活性化部分トロンボプラスチン時間延長 | 0 | 0 | 0 | 0 |
| アラニンアミノトランスフェラーゼ増加 | 0 | 0 | 0 | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 0 | 0 | 0 | 0 |
| 血中アルカリホスファターゼ増加 | 0 | 0 | 0 | 0 |
| 血中ビリルビン異常 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 血中尿酸増加 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| Ｃ－反応性蛋白増加 | 0 | 0 | 0 | 0 |
| γ－グルタミルトランスフェラーゼ増加 | 0 | 0 | 0 | 0 |
| 好中球数減少 | 0 | 0 | 0 | 0 |
| 血中クレアチニン増加 | 0 | 0 | 0 | 0 |
| 血中乳酸脱水素酵素増加 | 0 | 0 | 0 | 0 |
| 心臓障害 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 2 (1.7%) |
| 心停止 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 急性心筋梗塞 | 0 | 0 | 0 | 0 |
| 心血管不全 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 冠動脈狭窄 | 0 | 0 | 0 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 2 (1.8%) | 2 (1.8%) | 1 (0.8%) | 1 (0.8%) |
| 肺腺癌 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| マントル細胞リンパ腫 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 遠隔転移を伴う新生物 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 移行上皮癌 | 0 | 0 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 2 (1.7%) |
| 呼吸不全 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 2 (1.7%) |
| 呼吸困難 | 0 | 0 | 0 | 0 |

**TSFAE08PART1OF3: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 咳嗽 | 0 | 0 | 0 | 0 |
| 鼻出血 | 0 | 0 | 0 | 0 |
| 間質性肺疾患 | 0 | 0 | 0 | 0 |
| 肺浸潤 | 0 | 0 | 0 | 0 |
| 肺臓炎 | 0 | 0 | 0 | 0 |
| 胃腸障害 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 腹痛 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 吐血 | 0 | 0 | 0 | 0 |
| アフタ性口内炎 | 0 | 0 | 0 | 0 |
| 下痢 | 0 | 0 | 0 | 0 |
| 腸出血 | 0 | 0 | 0 | 0 |
| 口内炎 | 0 | 0 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 死亡 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 全身健康状態低下 | 0 | 0 | 0 | 0 |
| 多臓器不全 | 0 | 0 | 0 | 0 |
| 無力症 | 0 | 0 | 0 | 0 |
| 疲労 | 0 | 0 | 0 | 0 |
| 倦怠感 | 0 | 0 | 0 | 0 |
| 粘膜の炎症 | 0 | 0 | 0 | 0 |
| 浮腫 | 0 | 0 | 0 | 0 |
| 末梢性浮腫 | 0 | 0 | 0 | 0 |
| 疼痛 | 0 | 0 | 0 | 0 |
| 発熱 | 0 | 0 | 0 | 0 |
| 傷害、中毒および処置合併症 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 硬膜下血腫 | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| 腎および尿路障害 | 0 | 0 | 3 (2.5%) | 2 (1.7%) |
| 急性腎不全 | 0 | 0 | 2 (1.7%) | 2 (1.7%) |
| 尿路閉塞 | 0 | 0 | 1 (0.8%) | 0 |
| 腎不全 | 0 | 0 | 0 | 0 |
| 代謝および栄養障害 | 0 | 0 | 0 | 0 |
| 悪液質 | 0 | 0 | 0 | 0 |
| 食欲減退 | 0 | 0 | 0 | 0 |
| 高トリグリセリド血症 | 0 | 0 | 0 | 0 |
| 筋骨格系および結合組織障害 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 頚部腫瘤 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 関節痛 | 0 | 0 | 0 | 0 |
| 筋肉痛 | 0 | 0 | 0 | 0 |
| 四肢痛 | 0 | 0 | 0 | 0 |
| 神経系障害 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 脳症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 運動失調 | 0 | 0 | 0 | 0 |
| 脳血管発作 | 0 | 0 | 0 | 0 |
| 神経痛 | 0 | 0 | 0 | 0 |
| 末梢性ニューロパチー | 0 | 0 | 0 | 0 |
| 多発ニューロパチー | 0 | 0 | 0 | 0 |
| 血管障害 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 循環虚脱 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 眼障害 | 0 | 0 | 0 | 0 |
| 白内障 | 0 | 0 | 0 | 0 |
| 精神障害 | 0 | 0 | 0 | 0 |
| 錯乱状態 | 0 | 0 | 0 | 0 |
| 抑うつ気分 | 0 | 0 | 0 | 0 |
| 生殖系および乳房障害 | 0 | 0 | 0 | 0 |
| 前立腺炎 | 0 | 0 | 0 | 0 |

**TSFAE08PART1OF3: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 皮膚および皮下組織障害 | 0 | 0 | 0 | 0 |
| ざ瘡 | 0 | 0 | 0 | 0 |
| 爪破損 | 0 | 0 | 0 | 0 |
| そう痒症 | 0 | 0 | 0 | 0 |
| 発疹 | 0 | 0 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE08PART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae08.sas] 15SEP2015, 14:11

参照元：5.3.5.3.1 ISS TSFAE08PART1OF3

表 2.7.4-付録-25 Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE08PART2OF3: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 139 | | 139 | |
| Subjects with any TEAE leading to drug withdrawn | 18 (12.9%) | 15 (10.8%) | 41 (29.5%) | 30 (21.6%) |
| System organ class | | | | |
| Preferred term | | | | |
| 血液およびリンパ系障害 | 5 (3.6%) | 4 (2.9%) | 7 (5.0%) | 7 (5.0%) |
| 血小板減少症 | 3 (2.2%) | 3 (2.2%) | 4 (2.9%) | 4 (2.9%) |
| 好中球減少症 | 1 (0.7%) | 1 (0.7%) | 3 (2.2%) | 3 (2.2%) |
| 貧血 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 溶血 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 白血球増加症 | 1 (0.7%) | 0 | 0 | 0 |
| 脾臓出血 | 0 | 0 | 0 | 0 |
| 感染症および寄生虫症 | 3 (2.2%) | 1 (0.7%) | 6 (4.3%) | 3 (2.2%) |
| 肺炎 | 2 (1.4%) | 1 (0.7%) | 2 (1.4%) | 0 |
| 敗血症 | 0 | 0 | 0 | 0 |
| 尿路感染 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| 異型肺炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 憩室炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 毛包炎 | 0 | 0 | 1 (0.7%) | 0 |
| 肝膿瘍 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 臨床検査 | 3 (2.2%) | 1 (0.7%) | 2 (1.4%) | 1 (0.7%) |
| 活性化部分トロンボプラスチン時間延長 | 1 (0.7%) | 0 | 0 | 0 |
| アラニンアミノトランスフェラーゼ増加 | 1 (0.7%) | 0 | 0 | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 1 (0.7%) | 0 | 0 | 0 |
| 血中アルカリホスファターゼ増加 | 1 (0.7%) | 0 | 0 | 0 |
| 血中ビリルビン異常 | 0 | 0 | 0 | 0 |
| 血中尿酸増加 | 0 | 0 | 0 | 0 |
| Ｃ－反応性蛋白増加 | 1 (0.7%) | 0 | 0 | 0 |
| γ－グルタミルトランスフェラーゼ増加 | 1 (0.7%) | 0 | 0 | 0 |
| 好中球数減少 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 血中クレアチニン増加 | 0 | 0 | 1 (0.7%) | 0 |
| 血中乳酸脱水素酵素増加 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 心臓障害 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 心停止 | 0 | 0 | 0 | 0 |
| 急性心筋梗塞 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 心血管不全 | 0 | 0 | 0 | 0 |
| 冠動脈狭窄 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 肺腺癌 | 0 | 0 | 0 | 0 |
| マントル細胞リンパ腫 | 0 | 0 | 0 | 0 |
| 遠隔転移を伴う新生物 | 0 | 0 | 0 | 0 |
| 移行上皮癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 1 (0.7%) | 1 (0.7%) | 9 (6.5%) | 6 (4.3%) |
| 呼吸不全 | 0 | 0 | 0 | 0 |

**TSFAE08PART2OF3: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 呼吸困難 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| 咳嗽 | 0 | 0 | 1 (0.7%) | 0 |
| 鼻出血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 間質性肺疾患 | 0 | 0 | 1 (0.7%) | 0 |
| 肺浸潤 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 肺臓炎 | 0 | 0 | 4 (2.9%) | 3 (2.2%) |
| 胃腸障害 | 2 (1.4%) | 2 (1.4%) | 5 (3.6%) | 2 (1.4%) |
| 腹痛 | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 0 |
| 吐血 | 1 (0.7%) | 0 | 0 | 0 |
| アフタ性口内炎 | 0 | 0 | 1 (0.7%) | 0 |
| 下痢 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 腸出血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 口内炎 | 0 | 0 | 1 (0.7%) | 0 |
| 一般・全身障害および投与部位の状態 | 2 (1.4%) | 2 (1.4%) | 15 (10.8%) | 8 (5.8%) |
| 死亡 | 0 | 0 | 0 | 0 |
| 全身健康状態低下 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 多臓器不全 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 無力症 | 0 | 0 | 3 (2.2%) | 0 |
| 疲労 | 0 | 0 | 7 (5.0%) | 5 (3.6%) |
| 倦怠感 | 0 | 0 | 1 (0.7%) | 0 |
| 粘膜の炎症 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 浮腫 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 末梢性浮腫 | 0 | 0 | 3 (2.2%) | 0 |
| 疼痛 | 0 | 0 | 1 (0.7%) | 0 |
| 発熱 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 傷害、中毒および処置合併症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 硬膜下血腫 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 腎および尿路障害 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 急性腎不全 | 0 | 0 | 0 | 0 |
| 尿路閉塞 | 0 | 0 | 0 | 0 |
| 腎不全 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 代謝および栄養障害 | 1 (0.7%) | 1 (0.7%) | 4 (2.9%) | 2 (1.4%) |
| 悪液質 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 食欲減退 | 0 | 0 | 2 (1.4%) | 2 (1.4%) |
| 高トリグリセリド血症 | 0 | 0 | 1 (0.7%) | 0 |
| 筋骨格系および結合組織障害 | 0 | 0 | 3 (2.2%) | 0 |
| 頚部腫瘤 | 0 | 0 | 0 | 0 |
| 関節痛 | 0 | 0 | 1 (0.7%) | 0 |
| 筋肉痛 | 0 | 0 | 1 (0.7%) | 0 |
| 四肢痛 | 0 | 0 | 1 (0.7%) | 0 |
| 神経系障害 | 0 | 0 | 4 (2.9%) | 3 (2.2%) |
| 脳症 | 0 | 0 | 0 | 0 |
| 運動失調 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 脳血管発作 | 0 | 0 | 1 (0.7%) | 0 |
| 神経痛 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 末梢性ニューロパチー | 0 | 0 | 1 (0.7%) | 0 |
| 多発ニューロパチー | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 血管障害 | 0 | 0 | 0 | 0 |
| 循環虚脱 | 0 | 0 | 0 | 0 |
| 眼障害 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 白内障 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 精神障害 | 0 | 0 | 3 (2.2%) | 3 (2.2%) |
| 錯乱状態 | 0 | 0 | 2 (1.4%) | 2 (1.4%) |
| 抑うつ気分 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |

**TSFAE08PART2OF3: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 生殖系および乳房障害 | 0 | 0 | 1 (0.7%) | 0 |
| 前立腺炎 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚および皮下組織障害 | 0 | 0 | 4 (2.9%) | 1 (0.7%) |
| ざ瘡 | 0 | 0 | 1 (0.7%) | 0 |
| 爪破損 | 0 | 0 | 1 (0.7%) | 0 |
| そう痒症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 発疹 | 0 | 0 | 2 (1.4%) | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE08PART2OF3

表 2.7.4-付録-26 Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)

**TSFAE08PART3OF3: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 370 | |
| Subjects with any TEAE leading to drug withdrawn | 48 (13.0%) | 43 (11.6%) |
| System organ class | | |
| Preferred term | | |
| 血液およびリンパ系障害 | 10 (2.7%) | 9 (2.4%) |
| 血小板減少症 | 5 (1.4%) | 5 (1.4%) |
| 好中球減少症 | 3 (0.8%) | 3 (0.8%) |
| 貧血 | 1 (0.3%) | 1 (0.3%) |
| 溶血 | 1 (0.3%) | 1 (0.3%) |
| 白血球増加症 | 1 (0.3%) | 0 |
| 脾臓出血 | 1 (0.3%) | 1 (0.3%) |
| 感染症および寄生虫症 | 9 (2.4%) | 7 (1.9%) |
| 肺炎 | 6 (1.6%) | 5 (1.4%) |
| 敗血症 | 2 (0.5%) | 2 (0.5%) |
| 尿路感染 | 1 (0.3%) | 0 |
| 異型肺炎 | 0 | 0 |
| 憩室炎 | 0 | 0 |
| 毛包炎 | 0 | 0 |
| 肝膿瘍 | 0 | 0 |
| 臨床検査 | 5 (1.4%) | 3 (0.8%) |
| 活性化部分トロンボプラスチン時間延長 | 1 (0.3%) | 0 |
| アラニンアミノトランスフェラーゼ増加 | 1 (0.3%) | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 1 (0.3%) | 0 |
| 血中アルカリホスファターゼ増加 | 1 (0.3%) | 0 |
| 血中ビリルビン異常 | 1 (0.3%) | 1 (0.3%) |
| 血中尿酸増加 | 1 (0.3%) | 1 (0.3%) |
| Ｃ－反応性蛋白増加 | 1 (0.3%) | 0 |
| γ－グルタミルトランスフェラーゼ増加 | 1 (0.3%) | 0 |
| 好中球数減少 | 1 (0.3%) | 1 (0.3%) |
| 血中クレアチニン増加 | 0 | 0 |
| 血中乳酸脱水素酵素増加 | 0 | 0 |
| 心臓障害 | 4 (1.1%) | 4 (1.1%) |
| 心停止 | 2 (0.5%) | 2 (0.5%) |
| 急性心筋梗塞 | 1 (0.3%) | 1 (0.3%) |
| 心血管不全 | 1 (0.3%) | 1 (0.3%) |
| 冠動脈狭窄 | 0 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 4 (1.1%) | 4 (1.1%) |
| 肺腺癌 | 1 (0.3%) | 1 (0.3%) |
| マントル細胞リンパ腫 | 1 (0.3%) | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 1 (0.3%) | 1 (0.3%) |
| 移行上皮癌 | 1 (0.3%) | 1 (0.3%) |
| 呼吸器、胸郭および縦隔障害 | 4 (1.1%) | 4 (1.1%) |
| 呼吸不全 | 3 (0.8%) | 3 (0.8%) |
| 呼吸困難 | 1 (0.3%) | 1 (0.3%) |
| 咳嗽 | 0 | 0 |

**TSFAE08PART3OF3: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 鼻出血 | 0 | 0 |
| 間質性肺疾患 | 0 | 0 |
| 肺浸潤 | 0 | 0 |
| 肺臓炎 | 0 | 0 |
| 胃腸障害 | 3 (0.8%) | 3 (0.8%) |
| 腹痛 | 3 (0.8%) | 3 (0.8%) |
| 吐血 | 1 (0.3%) | 0 |
| アフタ性口内炎 | 0 | 0 |
| 下痢 | 0 | 0 |
| 腸出血 | 0 | 0 |
| 口内炎 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 3 (0.8%) | 3 (0.8%) |
| 死亡 | 1 (0.3%) | 1 (0.3%) |
| 全身健康状態低下 | 1 (0.3%) | 1 (0.3%) |
| 多臓器不全 | 1 (0.3%) | 1 (0.3%) |
| 無力症 | 0 | 0 |
| 疲労 | 0 | 0 |
| 倦怠感 | 0 | 0 |
| 粘膜の炎症 | 0 | 0 |
| 浮腫 | 0 | 0 |
| 末梢性浮腫 | 0 | 0 |
| 疼痛 | 0 | 0 |
| 発熱 | 0 | 0 |
| 傷害、中毒および処置合併症 | 3 (0.8%) | 2 (0.5%) |
| 硬膜下血腫 | 3 (0.8%) | 2 (0.5%) |
| 腎および尿路障害 | 3 (0.8%) | 2 (0.5%) |
| 急性腎不全 | 2 (0.5%) | 2 (0.5%) |
| 尿路閉塞 | 1 (0.3%) | 0 |
| 腎不全 | 0 | 0 |
| 代謝および栄養障害 | 1 (0.3%) | 1 (0.3%) |
| 悪液質 | 1 (0.3%) | 1 (0.3%) |
| 食欲減退 | 0 | 0 |
| 高トリグリセリド血症 | 0 | 0 |
| 筋骨格系および結合組織障害 | 1 (0.3%) | 1 (0.3%) |
| 頚部腫瘤 | 1 (0.3%) | 1 (0.3%) |
| 関節痛 | 0 | 0 |
| 筋肉痛 | 0 | 0 |
| 四肢痛 | 0 | 0 |
| 神経系障害 | 1 (0.3%) | 1 (0.3%) |
| 脳症 | 1 (0.3%) | 1 (0.3%) |
| 運動失調 | 0 | 0 |
| 脳血管発作 | 0 | 0 |
| 神経痛 | 0 | 0 |
| 末梢性ニューロパチー | 0 | 0 |
| 多発ニューロパチー | 0 | 0 |
| 血管障害 | 1 (0.3%) | 1 (0.3%) |
| 循環虚脱 | 1 (0.3%) | 1 (0.3%) |
| 眼障害 | 0 | 0 |
| 白内障 | 0 | 0 |
| 精神障害 | 0 | 0 |
| 錯乱状態 | 0 | 0 |
| 抑うつ気分 | 0 | 0 |
| 生殖系および乳房障害 | 0 | 0 |
| 前立腺炎 | 0 | 0 |
| 皮膚および皮下組織障害 | 0 | 0 |

**TSFAE08PART3OF3: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawn by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| ざ瘡 | 0 | 0 |
| 爪破損 | 0 | 0 |
| そう痒症 | 0 | 0 |
| 発疹 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE08PART3OF3

## 表 2.7.4-付録-27 Treatment-Emergent Adverse Events Leading to Dose Reduction by Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)

**TSFAE10: Treatment-Emergent Adverse Events Leading to Dose Reduction by Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib | |
|---|---|---|
| | All Grade | Grade 3 or Higher |
| Analysis Set: All Treated Population | 16 | |
| Total Number of Subjects with TEAE Leading to Dose Reduction | 2 (12.5%) | 1 (6.3%) |
| MedDRA System organ class/Preferred term | | |
| 胃腸障害 | 1 (6.3%) | 1 (6.3%) |
| 口内炎 | 1 (6.3%) | 1 (6.3%) |
| 臨床検査 | 1 (6.3%) | 0 |
| 血小板数減少 | 1 (6.3%) | 0 |
| 皮膚および皮下組織障害 | 1 (6.3%) | 0 |
| 全身性皮疹 | 1 (6.3%) | 0 |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0

[TSFAE10.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsfae10.sas] 21AUG2015, 12:30

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 21

表 2.7.4-付録-28 Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE09PART1OF3: Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 111 | | 120 | |
| Subjects with any TEAE leading to dose reduction | 15 (13.5%) | 11 (9.9%) | 8 (6.7%) | 6 (5.0%) |
| System organ class | | | | |
| Preferred term | | | | |
| 血液およびリンパ系障害 | 6 (5.4%) | 6 (5.4%) | 3 (2.5%) | 3 (2.5%) |
| 好中球減少症 | 5 (4.5%) | 5 (4.5%) | 3 (2.5%) | 3 (2.5%) |
| 発熱性好中球減少症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 血小板減少症 | 0 | 0 | 0 | 0 |
| 貧血 | 0 | 0 | 0 | 0 |
| 胃腸障害 | 3 (2.7%) | 3 (2.7%) | 3 (2.5%) | 2 (1.7%) |
| 下痢 | 3 (2.7%) | 3 (2.7%) | 2 (1.7%) | 1 (0.8%) |
| 口内炎 | 0 | 0 | 2 (1.7%) | 1 (0.8%) |
| 胃腸毒性 | 0 | 0 | 0 | 0 |
| 口腔内潰瘍形成 | 0 | 0 | 0 | 0 |
| 口腔知覚不全 | 0 | 0 | 0 | 0 |
| 感染症および寄生虫症 | 3 (2.7%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 四肢膿瘍 | 0 | 0 | 0 | 0 |
| クロストリジウム・ディフィシレ大腸炎 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 膿疱性皮疹 | 1 (0.9%) | 0 | 0 | 0 |
| 副鼻腔炎 | 1 (0.9%) | 0 | 0 | 0 |
| 皮膚感染 | 0 | 0 | 1 (0.8%) | 0 |
| 口腔カンジダ症 | 0 | 0 | 0 | 0 |
| 肺炎 | 0 | 0 | 0 | 0 |
| 膿皮症 | 0 | 0 | 0 | 0 |
| 皮膚および皮下組織障害 | 1 (0.9%) | 1 (0.9%) | 2 (1.7%) | 1 (0.8%) |
| 発疹 | 1 (0.9%) | 1 (0.9%) | 1 (0.8%) | 0 |
| 紫斑 | 0 | 0 | 0 | 0 |
| 斑状丘疹状皮疹 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| そう痒症 | 0 | 0 | 0 | 0 |
| 全身性皮疹 | 0 | 0 | 0 | 0 |
| うっ滞性皮膚炎 | 0 | 0 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 2 (1.8%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 疲労 | 2 (1.8%) | 1 (0.9%) | 1 (0.8%) | 1 (0.8%) |
| 末梢性浮腫 | 0 | 0 | 1 (0.8%) | 0 |
| 粘膜の炎症 | 0 | 0 | 0 | 0 |
| 発熱 | 0 | 0 | 0 | 0 |
| 代謝および栄養障害 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 食欲減退 | 0 | 0 | 0 | 0 |
| 低ナトリウム血症 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 筋骨格系および結合組織障害 | 1 (0.9%) | 0 | 1 (0.8%) | 1 (0.8%) |
| 関節痛 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 筋肉痛 | 1 (0.9%) | 0 | 0 | 0 |
| 軟部組織障害 | 0 | 0 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 1 (0.9%) | 0 | 0 | 0 |
| 呼吸困難 | 1 (0.9%) | 0 | 0 | 0 |
| 間質性肺疾患 | 0 | 0 | 0 | 0 |
| 肺臓炎 | 0 | 0 | 0 | 0 |
| 肺水腫 | 0 | 0 | 0 | 0 |
| 心臓障害 | 1 (0.9%) | 0 | 0 | 0 |

**TSFAE09PART1OF3: Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 心房細動 | 1 (0.9%) | 0 | 0 | 0 |
| 肝胆道系障害 | 1 (0.9%) | 0 | 0 | 0 |
| 肝機能異常 | 1 (0.9%) | 0 | 0 | 0 |
| 薬物性肝障害 | 0 | 0 | 0 | 0 |
| 臨床検査 | 0 | 0 | 1 (0.8%) | 0 |
| 血中アルカリホスファターゼ増加 | 0 | 0 | 1 (0.8%) | 0 |
| 好中球数減少 | 0 | 0 | 0 | 0 |
| 血小板数減少 | 0 | 0 | 0 | 0 |
| 神経系障害 | 0 | 0 | 0 | 0 |
| 嗜眠 | 0 | 0 | 0 | 0 |
| 神経痛 | 0 | 0 | 0 | 0 |
| 末梢性感覚ニューロパチー | 0 | 0 | 0 | 0 |
| 多発ニューロパチー | 0 | 0 | 0 | 0 |
| 血管障害 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 高血圧 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 腎および尿路障害 | 0 | 0 | 0 | 0 |
| 腎機能障害 | 0 | 0 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE09PART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae09.sas] 15SEP2015, 14:11

参照元：5.3.5.3.1 ISS TSFAE09PART1OF3

表 2.7.4-付録-29 Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term; Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE09PART2OF3: Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 139 | | 139 | |
| Subjects with any TEAE leading to dose reduction | 5 (3.6%) | 3 (2.2%) | 60 (43.2%) | 40 (28.8%) |
| System organ class | | | | |
| Preferred term | | | | |
| 血液およびリンパ系障害 | 1 (0.7%) | 1 (0.7%) | 34 (24.5%) | 25 (18.0%) |
| 好中球減少症 | 0 | 0 | 11 (7.9%) | 9 (6.5%) |
| 発熱性好中球減少症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 血小板減少症 | 1 (0.7%) | 1 (0.7%) | 25 (18.0%) | 16 (11.5%) |
| 貧血 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 胃腸障害 | 1 (0.7%) | 1 (0.7%) | 6 (4.3%) | 3 (2.2%) |
| 下痢 | 1 (0.7%) | 1 (0.7%) | 2 (1.4%) | 0 |
| 口内炎 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 胃腸毒性 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 口腔内潰瘍形成 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 口腔知覚不全 | 0 | 0 | 1 (0.7%) | 0 |
| 感染症および寄生虫症 | 1 (0.7%) | 0 | 4 (2.9%) | 2 (1.4%) |
| 四肢膿瘍 | 1 (0.7%) | 0 | 0 | 0 |
| クロストリジウム・ディフィシレ大腸炎 | 0 | 0 | 0 | 0 |
| 膿疱性皮疹 | 0 | 0 | 0 | 0 |
| 副鼻腔炎 | 0 | 0 | 0 | 0 |
| 皮膚感染 | 0 | 0 | 0 | 0 |
| 口腔カンジダ症 | 0 | 0 | 1 (0.7%) | 0 |
| 肺炎 | 0 | 0 | 2 (1.4%) | 2 (1.4%) |
| 膿皮症 | 0 | 0 | 1 (0.7%) | 0 |
| 皮膚および皮下組織障害 | 1 (0.7%) | 1 (0.7%) | 5 (3.6%) | 1 (0.7%) |
| 発疹 | 0 | 0 | 0 | 0 |
| 紫斑 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 斑状丘疹状皮疹 | 0 | 0 | 2 (1.4%) | 0 |
| そう痒症 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 全身性皮疹 | 0 | 0 | 1 (0.7%) | 0 |
| うっ滞性皮膚炎 | 0 | 0 | 1 (0.7%) | 0 |
| 一般・全身障害および投与部位の状態 | 0 | 0 | 9 (6.5%) | 2 (1.4%) |
| 疲労 | 0 | 0 | 5 (3.6%) | 2 (1.4%) |
| 末梢性浮腫 | 0 | 0 | 1 (0.7%) | 0 |
| 粘膜の炎症 | 0 | 0 | 2 (1.4%) | 0 |
| 発熱 | 0 | 0 | 2 (1.4%) | 0 |
| 代謝および栄養障害 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 食欲減退 | 1 (0.7%) | 0 | 2 (1.4%) | 0 |
| 低ナトリウム血症 | 0 | 0 | 0 | 0 |
| 筋骨格系および結合組織障害 | 0 | 0 | 1 (0.7%) | 0 |
| 関節痛 | 0 | 0 | 0 | 0 |
| 筋肉痛 | 0 | 0 | 0 | 0 |
| 軟部組織障害 | 0 | 0 | 1 (0.7%) | 0 |
| 呼吸器、胸郭および縦隔障害 | 1 (0.7%) | 0 | 6 (4.3%) | 1 (0.7%) |
| 呼吸困難 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 間質性肺疾患 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 肺臓炎 | 0 | 0 | 3 (2.2%) | 0 |
| 肺水腫 | 0 | 0 | 1 (0.7%) | 0 |

**TSFAE09PART2OF3: Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 心臓障害 | 0 | 0 | 0 | 0 |
| 心房細動 | 0 | 0 | 0 | 0 |
| 肝胆道系障害 | 0 | 0 | 1 (0.7%) | 0 |
| 肝機能異常 | 0 | 0 | 0 | 0 |
| 薬物性肝障害 | 0 | 0 | 1 (0.7%) | 0 |
| 臨床検査 | 0 | 0 | 10 (7.2%) | 8 (5.8%) |
| 血中アルカリホスファターゼ増加 | 0 | 0 | 0 | 0 |
| 好中球数減少 | 0 | 0 | 2 (1.4%) | 2 (1.4%) |
| 血小板数減少 | 0 | 0 | 8 (5.8%) | 6 (4.3%) |
| 神経系障害 | 1 (0.7%) | 0 | 4 (2.9%) | 1 (0.7%) |
| 嗜眠 | 1 (0.7%) | 0 | 0 | 0 |
| 神経痛 | 0 | 0 | 1 (0.7%) | 0 |
| 末梢性感覚ニューロパチー | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 多発ニューロパチー | 0 | 0 | 1 (0.7%) | 0 |
| 血管障害 | 0 | 0 | 0 | 0 |
| 高血圧 | 0 | 0 | 0 | 0 |
| 腎および尿路障害 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |
| 腎機能障害 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE09PART2OF3

表 2.7.4-付録-30 Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)

**TSFAE09PART3OF3: Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis Set: Safety Population | 370 | |
| Subjects with any TEAE leading to dose reduction | 28 (7.6%) | 20 (5.4%) |
| System organ class | | |
| Preferred term | | |
| 血液およびリンパ系障害 | 10 (2.7%) | 10 (2.7%) |
| 好中球減少症 | 8 (2.2%) | 8 (2.2%) |
| 発熱性好中球減少症 | 1 (0.3%) | 1 (0.3%) |
| 血小板減少症 | 1 (0.3%) | 1 (0.3%) |
| 貧血 | 0 | 0 |
| 胃腸障害 | 7 (1.9%) | 6 (1.6%) |
| 下痢 | 6 (1.6%) | 5 (1.4%) |
| 口内炎 | 2 (0.5%) | 1 (0.3%) |
| 胃腸毒性 | 0 | 0 |
| 口腔内潰瘍形成 | 0 | 0 |
| 口腔知覚不全 | 0 | 0 |
| 感染症および寄生虫症 | 5 (1.4%) | 1 (0.3%) |
| 四肢膿瘍 | 1 (0.3%) | 0 |
| クロストリジウム・ディフィシレ大腸炎 | 1 (0.3%) | 1 (0.3%) |
| 膿疱性皮疹 | 1 (0.3%) | 0 |
| 副鼻腔炎 | 1 (0.3%) | 0 |
| 皮膚感染 | 1 (0.3%) | 0 |
| 口腔カンジダ症 | 0 | 0 |
| 肺炎 | 0 | 0 |
| 膿皮症 | 0 | 0 |
| 皮膚および皮下組織障害 | 4 (1.1%) | 3 (0.8%) |
| 発疹 | 2 (0.5%) | 1 (0.3%) |
| 紫斑 | 1 (0.3%) | 1 (0.3%) |
| 斑状丘疹状皮疹 | 1 (0.3%) | 1 (0.3%) |
| そう痒症 | 0 | 0 |
| 全身性皮疹 | 0 | 0 |
| うっ滞性皮膚炎 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 3 (0.8%) | 2 (0.5%) |
| 疲労 | 3 (0.8%) | 2 (0.5%) |
| 末梢性浮腫 | 1 (0.3%) | 0 |
| 粘膜の炎症 | 0 | 0 |
| 発熱 | 0 | 0 |
| 代謝および栄養障害 | 2 (0.5%) | 1 (0.3%) |
| 食欲減退 | 1 (0.3%) | 0 |
| 低ナトリウム血症 | 1 (0.3%) | 1 (0.3%) |
| 筋骨格系および結合組織障害 | 2 (0.5%) | 1 (0.3%) |
| 関節痛 | 1 (0.3%) | 1 (0.3%) |
| 筋肉痛 | 1 (0.3%) | 0 |
| 軟部組織障害 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 2 (0.5%) | 0 |
| 呼吸困難 | 2 (0.5%) | 0 |
| 間質性肺疾患 | 0 | 0 |
| 肺臓炎 | 0 | 0 |
| 肺水腫 | 0 | 0 |
| 心臓障害 | 1 (0.3%) | 0 |
| 心房細動 | 1 (0.3%) | 0 |

**TSFAE09PART3OF3: Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 肝胆道系障害 | 1 (0.3%) | 0 |
| 肝機能異常 | 1 (0.3%) | 0 |
| 薬物性肝障害 | 0 | 0 |
| 臨床検査 | 1 (0.3%) | 0 |
| 血中アルカリホスファターゼ増加 | 1 (0.3%) | 0 |
| 好中球数減少 | 0 | 0 |
| 血小板数減少 | 0 | 0 |
| 神経系障害 | 1 (0.3%) | 0 |
| 嗜眠 | 1 (0.3%) | 0 |
| 神経痛 | 0 | 0 |
| 末梢性感覚ニューロパチー | 0 | 0 |
| 多発ニューロパチー | 0 | 0 |
| 血管障害 | 1 (0.3%) | 1 (0.3%) |
| 高血圧 | 1 (0.3%) | 1 (0.3%) |
| 腎および尿路障害 | 0 | 0 |
| 腎機能障害 | 0 | 0 |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE09PART3OF3

表 2.7.4-付録-31 Incidence of Treatment-emergent Hemorrhage Adverse Events by Preferred Term; Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE19APART1OF3: Incidence of Treatment-emergent Hemorrhage Adverse Events by Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis set: safety | 111 | | 120 | |
| Any Treatment-emergent Hemorrhage Adverse Events | 54 (48.6%) | 5 (4.5%) | 45 (37.5%) | 2 (1.7%) |
| Preferred term | | | | |
| 挫傷 | 19 (17.1%) | 0 | 17 (14.2%) | 0 |
| 鼻出血 | 12 (10.8%) | 0 | 8 (6.7%) | 0 |
| 点状出血 | 10 (9.0%) | 0 | 6 (5.0%) | 0 |
| 血尿 | 6 (5.4%) | 2 (1.8%) | 4 (3.3%) | 0 |
| 斑状出血 | 6 (5.4%) | 0 | 3 (2.5%) | 0 |
| 血腫 | 0 | 0 | 2 (1.7%) | 0 |
| 紫斑 | 3 (2.7%) | 0 | 1 (0.8%) | 1 (0.8%) |
| 硬膜下血腫 | 4 (3.6%) | 2 (1.8%) | 0 | 0 |
| 外傷性血腫 | 2 (1.8%) | 0 | 0 | 0 |
| 内出血発生の増加傾向 | 5 (4.5%) | 0 | 0 | 0 |
| 血精液症 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 出血 | 0 | 0 | 0 | 0 |
| 結膜出血 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 喀血 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 注射部位内出血 | 1 (0.9%) | 0 | 2 (1.7%) | 0 |
| 処置後出血 | 0 | 0 | 1 (0.8%) | 0 |
| 直腸出血 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 骨挫傷 | 1 (0.9%) | 0 | 0 | 0 |
| 眼出血 | 0 | 0 | 1 (0.8%) | 0 |
| 歯肉出血 | 0 | 0 | 0 | 0 |
| 吐血 | 0 | 0 | 0 | 0 |
| 頭蓋内出血 | 0 | 0 | 2 (1.7%) | 0 |
| 皮下出血 | 1 (0.9%) | 0 | 1 (0.8%) | 0 |
| 下部消化管出血 | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| 口腔内出血 | 1 (0.9%) | 0 | 0 | 0 |
| 眼窩周囲挫傷 | 0 | 0 | 1 (0.8%) | 0 |
| 腟出血 | 1 (0.9%) | 0 | 0 | 0 |
| 乳房血腫 | 0 | 0 | 0 | 0 |
| 出血性膀胱炎 | 0 | 0 | 0 | 0 |
| 血性下痢 | 0 | 0 | 0 | 0 |
| 耳出血 | 0 | 0 | 0 | 0 |
| 眼挫傷 | 0 | 0 | 0 | 0 |
| 出血性胃炎 | 0 | 0 | 1 (0.8%) | 0 |
| 血便排泄 | 1 (0.9%) | 0 | 0 | 0 |
| 血腫感染 | 0 | 0 | 1 (0.8%) | 0 |
| 外傷性血尿 | 0 | 0 | 1 (0.8%) | 0 |
| 痔出血 | 0 | 0 | 1 (0.8%) | 0 |
| 注射部位出血 | 0 | 0 | 1 (0.8%) | 0 |
| メレナ | 0 | 0 | 0 | 0 |
| 爪床出血 | 0 | 0 | 0 | 0 |
| 処置後血尿 | 0 | 0 | 0 | 0 |
| 強膜出血 | 1 (0.9%) | 0 | 0 | 0 |
| 陰嚢血腫 | 0 | 0 | 0 | 0 |
| 脾臓出血 | 0 | 0 | 1 (0.8%) | 1 (0.8%) |
| 皮下血腫 | 0 | 0 | 0 | 0 |
| 臍血腫 | 0 | 0 | 0 | 0 |
| 硝子体出血 | 0 | 0 | 0 | 0 |
| 胃腸出血 | 0 | 0 | 0 | 0 |
| 腸出血 | 0 | 0 | 0 | 0 |
| 眼窩周囲血腫 | 0 | 0 | 0 | 0 |

**TSFAE19APART1OF3: Incidence of Treatment-emergent Hemorrhage Adverse Events by Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 上部消化管出血 | 0 | 0 | 0 | 0 |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE19APART1OF3

表 2.7.4-付録-32 Incidence of Treatment-emergent Hemorrhage Adverse Events by Preferred Term; Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE19APART2OF3: Incidence of Treatment-emergent Hemorrhage Adverse Events by Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis set: safety | 139 | | 139 | |
| Any Treatment-emergent Hemorrhage Adverse Events | 55 (39.6%) | 11 (7.9%) | 45 (32.4%) | 7 (5.0%) |
| Preferred term | | | | |
| 挫傷 | 10 (7.2%) | 0 | 3 (2.2%) | 0 |
| 鼻出血 | 12 (8.6%) | 1 (0.7%) | 33 (23.7%) | 2 (1.4%) |
| 点状出血 | 6 (4.3%) | 0 | 0 | 0 |
| 血尿 | 4 (2.9%) | 1 (0.7%) | 1 (0.7%) | 0 |
| 斑状出血 | 4 (2.9%) | 0 | 1 (0.7%) | 0 |
| 血腫 | 10 (7.2%) | 0 | 3 (2.2%) | 0 |
| 紫斑 | 3 (2.2%) | 1 (0.7%) | 0 | 0 |
| 硬膜下血腫 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| 外傷性血腫 | 4 (2.9%) | 0 | 0 | 0 |
| 内出血発生の増加傾向 | 0 | 0 | 0 | 0 |
| 血精液症 | 1 (0.7%) | 0 | 0 | 0 |
| 出血 | 4 (2.9%) | 3 (2.2%) | 1 (0.7%) | 1 (0.7%) |
| 結膜出血 | 1 (0.7%) | 0 | 5 (3.6%) | 0 |
| 喀血 | 0 | 0 | 0 | 0 |
| 注射部位内出血 | 0 | 0 | 0 | 0 |
| 処置後出血 | 2 (1.4%) | 2 (1.4%) | 2 (1.4%) | 0 |
| 直腸出血 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 骨挫傷 | 1 (0.7%) | 0 | 0 | 0 |
| 眼出血 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| 歯肉出血 | 2 (1.4%) | 0 | 0 | 0 |
| 吐血 | 2 (1.4%) | 0 | 0 | 0 |
| 頭蓋内出血 | 0 | 0 | 0 | 0 |
| 皮下出血 | 0 | 0 | 0 | 0 |
| 下部消化管出血 | 1 (0.7%) | 0 | 2 (1.4%) | 1 (0.7%) |
| 口腔内出血 | 1 (0.7%) | 0 | 0 | 0 |
| 眼窩周囲挫傷 | 1 (0.7%) | 0 | 0 | 0 |
| 腟出血 | 1 (0.7%) | 0 | 0 | 0 |
| 乳房血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 出血性膀胱炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 血性下痢 | 1 (0.7%) | 0 | 0 | 0 |
| 耳出血 | 1 (0.7%) | 0 | 0 | 0 |
| 眼挫傷 | 1 (0.7%) | 0 | 0 | 0 |
| 出血性胃炎 | 0 | 0 | 1 (0.7%) | 0 |
| 血便排泄 | 0 | 0 | 1 (0.7%) | 0 |
| 血腫感染 | 0 | 0 | 0 | 0 |
| 外傷性血尿 | 0 | 0 | 0 | 0 |
| 痔出血 | 0 | 0 | 0 | 0 |
| 注射部位出血 | 0 | 0 | 0 | 0 |
| メレナ | 1 (0.7%) | 0 | 0 | 0 |
| 爪床出血 | 1 (0.7%) | 0 | 0 | 0 |
| 処置後血尿 | 1 (0.7%) | 0 | 0 | 0 |
| 強膜出血 | 0 | 0 | 0 | 0 |
| 陰嚢血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 脾臓出血 | 0 | 0 | 0 | 0 |
| 皮下血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 臍血腫 | 1 (0.7%) | 0 | 0 | 0 |
| 硝子体出血 | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| 胃腸出血 | 0 | 0 | 2 (1.4%) | 2 (1.4%) |
| 腸出血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) |

**TSFAE19APART2OF3: Incidence of Treatment-emergent Hemorrhage Adverse Events by Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| 眼窩周囲血腫 | 0 | 0 | 1 (0.7%) | 0 |
| 上部消化管出血 | 0 | 0 | 1 (0.7%) | 0 |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

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参照元：5.3.5.3.1 ISS TSFAE19APART2OF3

表 2.7.4-付録-33 Incidence of Treatment-emergent Hemorrhage Adverse Events by Preferred Term; Safety Population (MCL-ISS)

**TSFAE19APART3OF3: Incidence of Treatment-emergent Hemorrhage Adverse Events by Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis set: safety | 370 | |
| Any Treatment-emergent Hemorrhage Adverse Events | 154 (41.6%) | 18 (4.9%) |
| Preferred term | | |
| 挫傷 | 46 (12.4%) | 0 |
| 鼻出血 | 32 (8.6%) | 1 (0.3%) |
| 点状出血 | 22 (5.9%) | 0 |
| 血尿 | 14 (3.8%) | 3 (0.8%) |
| 斑状出血 | 13 (3.5%) | 0 |
| 血腫 | 12 (3.2%) | 0 |
| 紫斑 | 7 (1.9%) | 2 (0.5%) |
| 硬膜下血腫 | 6 (1.6%) | 3 (0.8%) |
| 外傷性血腫 | 6 (1.6%) | 0 |
| 内出血発生の増加傾向 | 5 (1.4%) | 0 |
| 血精液症 | 4 (1.1%) | 0 |
| 出血 | 4 (1.1%) | 3 (0.8%) |
| 結膜出血 | 3 (0.8%) | 0 |
| 喀血 | 3 (0.8%) | 0 |
| 注射部位内出血 | 3 (0.8%) | 0 |
| 処置後出血 | 3 (0.8%) | 2 (0.5%) |
| 直腸出血 | 3 (0.8%) | 0 |
| 骨挫傷 | 2 (0.5%) | 0 |
| 眼出血 | 2 (0.5%) | 0 |
| 歯肉出血 | 2 (0.5%) | 0 |
| 吐血 | 2 (0.5%) | 0 |
| 頭蓋内出血 | 2 (0.5%) | 0 |
| 皮下出血 | 2 (0.5%) | 0 |
| 下部消化管出血 | 2 (0.5%) | 1 (0.3%) |
| 口腔内出血 | 2 (0.5%) | 0 |
| 眼窩周囲挫傷 | 2 (0.5%) | 0 |
| 腟出血 | 2 (0.5%) | 0 |
| 乳房血腫 | 1 (0.3%) | 0 |
| 出血性膀胱炎 | 1 (0.3%) | 1 (0.3%) |
| 血性下痢 | 1 (0.3%) | 0 |
| 耳出血 | 1 (0.3%) | 0 |
| 眼挫傷 | 1 (0.3%) | 0 |
| 出血性胃炎 | 1 (0.3%) | 0 |
| 血便排泄 | 1 (0.3%) | 0 |
| 血腫感染 | 1 (0.3%) | 0 |
| 外傷性血尿 | 1 (0.3%) | 0 |
| 痔出血 | 1 (0.3%) | 0 |
| 注射部位出血 | 1 (0.3%) | 0 |
| メレナ | 1 (0.3%) | 0 |
| 爪床出血 | 1 (0.3%) | 0 |
| 処置後血尿 | 1 (0.3%) | 0 |
| 強膜出血 | 1 (0.3%) | 0 |
| 陰嚢血腫 | 1 (0.3%) | 0 |
| 脾臓出血 | 1 (0.3%) | 1 (0.3%) |
| 皮下血腫 | 1 (0.3%) | 0 |
| 臍血腫 | 1 (0.3%) | 0 |
| 硝子体出血 | 1 (0.3%) | 1 (0.3%) |
| 胃腸出血 | 0 | 0 |
| 腸出血 | 0 | 0 |
| 眼窩周囲血腫 | 0 | 0 |

**TSFAE19APART3OF3: Incidence of Treatment-emergent Hemorrhage Adverse Events by Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| 上部消化管出血 | 0 | 0 |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE19APART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae19a.sas] 15SEP2015, 14:13

参照元：5.3.5.3.1 ISS TSFAE19APART3OF3

## 表 2.7.4-付録-34 Incidence of Treatment-emergent Hypersensitivity Adverse Events by Preferred Term; Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE20PART1OF3: Incidence of Treatment-emergent Hypersensitivity Adverse Events by Preferred Term; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis set: safety | 111 | | 120 | |
| Any Treatment-emergent Hypersensitivity Adverse Events | 4 (3.6%) | 0 | 1 (0.8%) | 0 |
| Preferred term | | | | |
| 蕁麻疹 | 1 (0.9%) | 0 | 0 | 0 |
| 過敏症 | 2 (1.8%) | 0 | 1 (0.8%) | 0 |
| 薬物過敏症 | 1 (0.9%) | 0 | 0 | 0 |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE20PART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae20.sas] 22OCT2015, 13:25

参照元：5.3.5.3.1 ISS TSFAE20PART1OF3

## 表 2.7.4-付録-35 Incidence of Treatment-emergent Hypersensitivity Adverse Events by Preferred Term; Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE20PART2OF3: Incidence of Treatment-emergent Hypersensitivity Adverse Events by Preferred Term; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 |
| Analysis set: safety | 139 | | 139 | |
| Any Treatment-emergent Hypersensitivity Adverse Events | 4 (2.9%) | 0 | 7 (5.0%) | 1 (0.7%) |
| Preferred term | | | | |
| 蕁麻疹 | 4 (2.9%) | 0 | 4 (2.9%) | 0 |
| 過敏症 | 0 | 0 | 2 (1.4%) | 1 (0.7%) |
| 薬物過敏症 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE20PART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae20.sas] 22OCT2015, 13:25

参照元：5.3.5.3.1 ISS TSFAE20PART2OF3

表 2.7.4-付録-36 Incidence of Treatment-emergent Hypersensitivity Adverse Events by Preferred Term; Safety Population (MCL-ISS)

**TSFAE20PART3OF3: Incidence of Treatment-emergent Hypersensitivity Adverse Events by Preferred Term; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | |
|---|---|---|
| | Any Grades | Grade >=3 |
| Analysis set: safety | 370 | |
| Any Treatment-emergent Hypersensitivity Adverse Events | 9 (2.4%) | 0 |
| Preferred term | | |
| 蕁麻疹 | 5 (1.4%) | 0 |
| 過敏症 | 3 (0.8%) | 0 |
| 薬物過敏症 | 2 (0.5%) | 0 |

Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE20PART3OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae20.sas] 22OCT2015, 13:25

参照元：5.3.5.3.1 ISS TSFAE20PART3OF3

表 2.7.4-付録-37 Hematology: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)

**TSFLAB05: Hematology: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| PCYC-1104-CA /Ibrutinib | Analysis set: safety population | | 111 | | | | | |
| | Hemoglobin (Decrease) | Total | 111 (100.0%) | 9 (8.1%) | 56 (50.5%) | 40 (36.0%) | 6 (5.4%) | 0 |
| | | 0 | 27 (24.3%) | 9 (8.1%) | 13 (11.7%) | 5 (4.5%) | 0 | 0 |
| | | 1 | 59 (53.2%) | 0 | 41 (36.9%) | 18 (16.2%) | 0 | 0 |
| | | 2 | 21 (18.9%) | 0 | 1 (0.9%) | 16 (14.4%) | 4 (3.6%) | 0 |
| | | 3 | 4 (3.6%) | 0 | 1 (0.9%) | 1 (0.9%) | 2 (1.8%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Platelets (Decrease) | Total | 111 (100.0%) | 17 (15.3%) | 46 (41.4%) | 24 (21.6%) | 17 (15.3%) | 7 (6.3%) |
| | | 0 | 51 (45.9%) | 17 (15.3%) | 28 (25.2%) | 4 (3.6%) | 2 (1.8%) | 0 |
| | | 1 | 36 (32.4%) | 0 | 17 (15.3%) | 14 (12.6%) | 4 (3.6%) | 1 (0.9%) |
| | | 2 | 10 (9.0%) | 0 | 1 (0.9%) | 4 (3.6%) | 5 (4.5%) | 0 |
| | | 3 | 11 (9.9%) | 0 | 0 | 2 (1.8%) | 6 (5.4%) | 3 (2.7%) |
| | | 4 | 3 (2.7%) | 0 | 0 | 0 | 0 | 3 (2.7%) |
| | ANC (Decrease) | Total | 110 (100.0%) | 54 (49.1%) | 9 (8.2%) | 19 (17.3%) | 17 (15.5%) | 11 (10.0%) |
| | | 0 | 92 (83.6%) | 52 (47.3%) | 8 (7.3%) | 13 (11.8%) | 11 (10.0%) | 8 (7.3%) |
| | | 1 | 5 (4.5%) | 0 | 1 (0.9%) | 2 (1.8%) | 2 (1.8%) | 0 |
| | | 2 | 7 (6.4%) | 1 (0.9%) | 0 | 2 (1.8%) | 3 (2.7%) | 1 (0.9%) |
| | | 3 | 6 (5.5%) | 1 (0.9%) | 0 | 2 (1.8%) | 1 (0.9%) | 2 (1.8%) |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | WBC (Decrease) | Total | 111 (100.0%) | 76 (68.5%) | 5 (4.5%) | 18 (16.2%) | 9 (8.1%) | 3 (2.7%) |
| | | 0 | 95 (85.6%) | 72 (64.9%) | 4 (3.6%) | 12 (10.8%) | 5 (4.5%) | 2 (1.8%) |
| | | 1 | 5 (4.5%) | 3 (2.7%) | 0 | 1 (0.9%) | 1 (0.9%) | 0 |
| | | 2 | 8 (7.2%) | 1 (0.9%) | 1 (0.9%) | 4 (3.6%) | 2 (1.8%) | 0 |
| | | 3 | 3 (2.7%) | 0 | 0 | 1 (0.9%) | 1 (0.9%) | 1 (0.9%) |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| MCL2001 /Ibrutinib | Analysis set: safety population | | 120 | | | | | |
| | Hemoglobin (Decrease) | Total | 119 (100.0%) | 11 (9.2%) | 67 (56.3%) | 28 (23.5%) | 13 (10.9%) | 0 |
| | | 0 | 44 (37.0%) | 9 (7.6%) | 30 (25.2%) | 3 (2.5%) | 2 (1.7%) | 0 |
| | | 1 | 63 (52.9%) | 2 (1.7%) | 36 (30.3%) | 19 (16.0%) | 6 (5.0%) | 0 |
| | | 2 | 11 (9.2%) | 0 | 0 | 6 (5.0%) | 5 (4.2%) | 0 |
| | | 3 | 1 (0.8%) | 0 | 1 (0.8%) | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Platelets (Decrease) | Total | 119 (100.0%) | 14 (11.8%) | 66 (55.5%) | 17 (14.3%) | 11 (9.2%) | 11 (9.2%) |
| | | 0 | 60 (50.4%) | 14 (11.8%) | 36 (30.3%) | 5 (4.2%) | 2 (1.7%) | 3 (2.5%) |
| | | 1 | 47 (39.5%) | 0 | 29 (24.4%) | 7 (5.9%) | 6 (5.0%) | 5 (4.2%) |
| | | 2 | 10 (8.4%) | 0 | 1 (0.8%) | 4 (3.4%) | 3 (2.5%) | 2 (1.7%) |
| | | 3 | 2 (1.7%) | 0 | 0 | 1 (0.8%) | 0 | 1 (0.8%) |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ANC (Decrease) | Total | 119 (100.0%) | 59 (49.6%) | 14 (11.8%) | 13 (10.9%) | 11 (9.2%) | 22 (18.5%) |
| | | 0 | 98 (82.4%) | 58 (48.7%) | 13 (10.9%) | 7 (5.9%) | 9 (7.6%) | 11 (9.2%) |

**TSFLAB05: Hematology: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | | 1 | 10 (8.4%) | 1 (0.8%) | 0 | 4 (3.4%) | 1 (0.8%) | 4 (3.4%) |
| | | 2 | 10 (8.4%) | 0 | 1 (0.8%) | 2 (1.7%) | 1 (0.8%) | 6 (5.0%) |
| | | 3 | 1 (0.8%) | 0 | 0 | 0 | 0 | 1 (0.8%) |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | WBC (Decrease) | Total | 119 (100.0%) | 60 (50.4%) | 27 (22.7%) | 15 (12.6%) | 13 (10.9%) | 4 (3.4%) |
| | | 0 | 86 (72.3%) | 54 (45.4%) | 20 (16.8%) | 5 (4.2%) | 5 (4.2%) | 2 (1.7%) |
| | | 1 | 21 (17.6%) | 5 (4.2%) | 6 (5.0%) | 5 (4.2%) | 5 (4.2%) | 0 |
| | | 2 | 12 (10.1%) | 1 (0.8%) | 1 (0.8%) | 5 (4.2%) | 3 (2.5%) | 2 (1.7%) |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| MCL3001 /Ibrutinib | Analysis set: safety population | | 139 | | | | | |
| | Hemoglobin (Decrease) | Total | 138 (100.0%) | 22 (15.9%) | 72 (52.2%) | 30 (21.7%) | 14 (10.1%) | 0 |
| | | 0 | 51 (37.0%) | 19 (13.8%) | 30 (21.7%) | 1 (0.7%) | 1 (0.7%) | 0 |
| | | 1 | 74 (53.6%) | 3 (2.2%) | 39 (28.3%) | 23 (16.7%) | 9 (6.5%) | 0 |
| | | 2 | 13 (9.4%) | 0 | 3 (2.2%) | 6 (4.3%) | 4 (2.9%) | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Platelets (Decrease) | Total | 138 (100.0%) | 29 (21.0%) | 67 (48.6%) | 14 (10.1%) | 16 (11.6%) | 12 (8.7%) |
| | | 0 | 78 (56.5%) | 29 (21.0%) | 39 (28.3%) | 1 (0.7%) | 5 (3.6%) | 4 (2.9%) |
| | | 1 | 49 (35.5%) | 0 | 27 (19.6%) | 11 (8.0%) | 6 (4.3%) | 5 (3.6%) |
| | | 2 | 10 (7.2%) | 0 | 1 (0.7%) | 2 (1.4%) | 4 (2.9%) | 3 (2.2%) |
| | | 3 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.7%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ANC (Decrease) | Total | 136 (100.0%) | 72 (52.9%) | 14 (10.3%) | 18 (13.2%) | 14 (10.3%) | 18 (13.2%) |
| | | 0 | 111 (81.6%) | 68 (50.0%) | 12 (8.8%) | 10 (7.4%) | 10 (7.4%) | 11 (8.1%) |
| | | 1 | 15 (11.0%) | 4 (2.9%) | 1 (0.7%) | 6 (4.4%) | 1 (0.7%) | 3 (2.2%) |
| | | 2 | 9 (6.6%) | 0 | 1 (0.7%) | 2 (1.5%) | 3 (2.2%) | 3 (2.2%) |
| | | 3 | 1 (0.7%) | 0 | 0 | 0 | 0 | 1 (0.7%) |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | WBC (Decrease) | Total | 138 (100.0%) | 71 (51.4%) | 37 (26.8%) | 15 (10.9%) | 11 (8.0%) | 4 (2.9%) |
| | | 0 | 105 (76.1%) | 65 (47.1%) | 27 (19.6%) | 7 (5.1%) | 3 (2.2%) | 3 (2.2%) |
| | | 1 | 22 (15.9%) | 5 (3.6%) | 7 (5.1%) | 6 (4.3%) | 3 (2.2%) | 1 (0.7%) |
| | | 2 | 9 (6.5%) | 1 (0.7%) | 3 (2.2%) | 2 (1.4%) | 3 (2.2%) | 0 |
| | | 3 | 2 (1.4%) | 0 | 0 | 0 | 2 (1.4%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| MCL3001 /Temsirolimus | Analysis set: safety population | | 139 | | | | | |
| | Hemoglobin (Decrease) | Total | 138 (100.0%) | 1 (0.7%) | 47 (34.1%) | 65 (47.1%) | 25 (18.1%) | 0 |
| | | 0 | 55 (39.9%) | 1 (0.7%) | 29 (21.0%) | 18 (13.0%) | 7 (5.1%) | 0 |
| | | 1 | 67 (48.6%) | 0 | 17 (12.3%) | 36 (26.1%) | 14 (10.1%) | 0 |
| | | 2 | 15 (10.9%) | 0 | 1 (0.7%) | 10 (7.2%) | 4 (2.9%) | 0 |
| | | 3 | 1 (0.7%) | 0 | 0 | 1 (0.7%) | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |

**TSFLAB05: Hematology: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | Platelets (Decrease) | Total | 138 (100.0%) | 7 (5.1%) | 32 (23.2%) | 23 (16.7%) | 55 (39.9%) | 21 (15.2%) |
| | | 0 | 86 (62.3%) | 7 (5.1%) | 29 (21.0%) | 19 (13.8%) | 28 (20.3%) | 3 (2.2%) |
| | | 1 | 42 (30.4%) | 0 | 3 (2.2%) | 4 (2.9%) | 22 (15.9%) | 13 (9.4%) |
| | | 2 | 9 (6.5%) | 0 | 0 | 0 | 5 (3.6%) | 4 (2.9%) |
| | | 3 | 1 (0.7%) | 0 | 0 | 0 | 0 | 1 (0.7%) |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ANC (Decrease) | Total | 137 (100.0%) | 32 (23.4%) | 27 (19.7%) | 42 (30.7%) | 24 (17.5%) | 12 (8.8%) |
| | | 0 | 129 (94.2%) | 31 (22.6%) | 26 (19.0%) | 41 (29.9%) | 21 (15.3%) | 10 (7.3%) |
| | | 1 | 5 (3.6%) | 1 (0.7%) | 0 | 1 (0.7%) | 2 (1.5%) | 1 (0.7%) |
| | | 2 | 3 (2.2%) | 0 | 1 (0.7%) | 0 | 1 (0.7%) | 1 (0.7%) |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | WBC (Decrease) | Total | 138 (100.0%) | 36 (26.1%) | 43 (31.2%) | 34 (24.6%) | 20 (14.5%) | 5 (3.6%) |
| | | 0 | 102 (73.9%) | 34 (24.6%) | 37 (26.8%) | 19 (13.8%) | 9 (6.5%) | 3 (2.2%) |
| | | 1 | 35 (25.4%) | 2 (1.4%) | 6 (4.3%) | 15 (10.9%) | 10 (7.2%) | 2 (1.4%) |
| | | 2 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.7%) | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pooled Ibrutinib /Ibrutinib | Analysis set: safety population | | 370 | | | | | |
| | Hemoglobin (Decrease) | Total | 368 (100.0%) | 42 (11.4%) | 195 (53.0%) | 98 (26.6%) | 33 (9.0%) | 0 |
| | | 0 | 122 (33.2%) | 37 (10.1%) | 73 (19.8%) | 9 (2.4%) | 3 (0.8%) | 0 |
| | | 1 | 196 (53.3%) | 5 (1.4%) | 116 (31.5%) | 60 (16.3%) | 15 (4.1%) | 0 |
| | | 2 | 45 (12.2%) | 0 | 4 (1.1%) | 28 (7.6%) | 13 (3.5%) | 0 |
| | | 3 | 5 (1.4%) | 0 | 2 (0.5%) | 1 (0.3%) | 2 (0.5%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Platelets (Decrease) | Total | 368 (100.0%) | 60 (16.3%) | 179 (48.6%) | 55 (14.9%) | 44 (12.0%) | 30 (8.2%) |
| | | 0 | 189 (51.4%) | 60 (16.3%) | 103 (28.0%) | 10 (2.7%) | 9 (2.4%) | 7 (1.9%) |
| | | 1 | 132 (35.9%) | 0 | 73 (19.8%) | 32 (8.7%) | 16 (4.3%) | 11 (3.0%) |
| | | 2 | 30 (8.2%) | 0 | 3 (0.8%) | 10 (2.7%) | 12 (3.3%) | 5 (1.4%) |
| | | 3 | 14 (3.8%) | 0 | 0 | 3 (0.8%) | 7 (1.9%) | 4 (1.1%) |
| | | 4 | 3 (0.8%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| | ANC (Decrease) | Total | 365 (100.0%) | 185 (50.7%) | 37 (10.1%) | 50 (13.7%) | 42 (11.5%) | 51 (14.0%) |
| | | 0 | 301 (82.5%) | 178 (48.8%) | 33 (9.0%) | 30 (8.2%) | 30 (8.2%) | 30 (8.2%) |
| | | 1 | 30 (8.2%) | 5 (1.4%) | 2 (0.5%) | 12 (3.3%) | 4 (1.1%) | 7 (1.9%) |
| | | 2 | 26 (7.1%) | 1 (0.3%) | 2 (0.5%) | 6 (1.6%) | 7 (1.9%) | 10 (2.7%) |
| | | 3 | 8 (2.2%) | 1 (0.3%) | 0 | 2 (0.5%) | 1 (0.3%) | 4 (1.1%) |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | WBC (Decrease) | Total | 368 (100.0%) | 207 (56.3%) | 69 (18.8%) | 48 (13.0%) | 33 (9.0%) | 11 (3.0%) |
| | | 0 | 286 (77.7%) | 191 (51.9%) | 51 (13.9%) | 24 (6.5%) | 13 (3.5%) | 7 (1.9%) |
| | | 1 | 48 (13.0%) | 13 (3.5%) | 13 (3.5%) | 12 (3.3%) | 9 (2.4%) | 1 (0.3%) |
| | | 2 | 29 (7.9%) | 3 (0.8%) | 5 (1.4%) | 11 (3.0%) | 8 (2.2%) | 2 (0.5%) |
| | | 3 | 5 (1.4%) | 0 | 0 | 1 (0.3%) | 3 (0.8%) | 1 (0.3%) |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |

**TSFLAB05: Hematology: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |

Key: ANC=Absolute neutrophils counts, WBC=White blood cell counts.
Note: A subject must have both baseline and at least one post-baseline assessment to be included in this table.
Percentages are calculated with the number of subjects in safety population with baseline and any post-baseline laboratory values as denominator.

[TSFLAB05.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsflab05.sas] 15SEP2015, 14:11

参照元：5.3.5.3.1 ISS TSFLAB05

## 表 2.7.4-付録-38 Hematology Laboratory Results at Baseline; Safety Population (MCL-ISS)

**TSIDEM03: Hematology Laboratory Results at Baseline; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | MCL2001 Ibrutinib | MCL3001 | | Pooled Ibrutinib |
|---|---|---|---|---|---|
| | | | Ibrutinib | Temsirolimus | |
| Analysis set: safety population | 111 | 120 | 139 | 139 | 370 |
| Hemoglobin (g/L) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 115.5 (19.49) | 123.0 (17.87) | 122.6 (16.56) | 123.3 (18.16) | 120.6 (18.16) |
| Median | 115.0 | 124.5 | 124.0 | 124.0 | 121.0 |
| Range | (60; 151) | (79; 164) | (85; 157) | (78; 170) | (60; 164) |
| Absolute neutrophil count (x10E9/L) | | | | | |
| N | 110 | 120 | 139 | 139 | 369 |
| Mean (SD) | 3.3 (1.57) | 4.1 (2.94) | 4.1 (2.79) | 3.7 (2.54) | 3.9 (2.56) |
| Median | 3.1 | 3.5 | 3.4 | 3.2 | 3.2 |
| Range | (1; 9) | (1; 21) | (1; 14) | (1; 27) | (1; 21) |
| Absolute lymphocyte count (x10E9/L) | | | | | |
| N | 110 | 120 | 139 | 139 | 369 |
| Mean (SD) | 6.18 (24.021) | 6.69 (39.924) | 4.98 (13.523) | 4.08 (10.954) | 5.89 (27.486) |
| Median | 1.14 | 1.10 | 1.45 | 1.60 | 1.24 |
| Range | (0.2; 210.1) | (0.0; 416.3) | (0.2; 89.6) | (0.3; 78.8) | (0.0; 416.3) |
| Platelets (x10E9/L) | | | | | |
| N | 111 | 120 | 139 | 139 | 370 |
| Mean (SD) | 142.9 (85.36) | 160.1 (73.97) | 179.6 (88.86) | 178.7 (97.74) | 162.2 (84.36) |
| Median | 133.0 | 149.5 | 161.0 | 173.0 | 147.0 |
| Range | (8; 567) | (46; 460) | (48; 478) | (42; 940) | (8; 567) |

[TSIDEM03.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsidem03.sas] 15SEP2015, 14:13

参照元：5.3.5.3.1 ISS TSIDEM03

表 2.7.4-付録-39 Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| PCYC-1104-CA /Ibrutinib | Analysis set: safety population | | 111 | | | | | |
| | Sodium (increase) | Total | 111 (100.0%) | 69 (62.2%) | 41 (36.9%) | 1 (0.9%) | 0 | 0 |
| | | 0 | 97 (87.4%) | 62 (55.9%) | 34 (30.6%) | 1 (0.9%) | 0 | 0 |
| | | 1 | 14 (12.6%) | 7 (6.3%) | 7 (6.3%) | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Sodium (decrease) | Total | 111 (100.0%) | 92 (82.9%) | 11 (9.9%) | 0 | 6 (5.4%) | 2 (1.8%) |
| | | 0 | 105 (94.6%) | 90 (81.1%) | 10 (9.0%) | 0 | 3 (2.7%) | 2 (1.8%) |
| | | 1 | 4 (3.6%) | 2 (1.8%) | 1 (0.9%) | 0 | 1 (0.9%) | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 2 (1.8%) | 0 | 0 | 0 | 2 (1.8%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Magnesium (increase) | Total | 110 (100.0%) | 95 (86.4%) | 15 (13.6%) | 0 | 0 | 0 |
| | | 0 | 107 (97.3%) | 93 (84.5%) | 14 (12.7%) | 0 | 0 | 0 |
| | | 1 | 3 (2.7%) | 2 (1.8%) | 1 (0.9%) | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Magnesium (decrease) | Total | 110 (100.0%) | 59 (53.6%) | 50 (45.5%) | 1 (0.9%) | 0 | 0 |
| | | 0 | 95 (86.4%) | 57 (51.8%) | 38 (34.5%) | 0 | 0 | 0 |
| | | 1 | 14 (12.7%) | 2 (1.8%) | 11 (10.0%) | 1 (0.9%) | 0 | 0 |
| | | 2 | 1 (0.9%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (increase) | Total | 111 (100.0%) | 92 (82.9%) | 17 (15.3%) | 2 (1.8%) | 0 | 0 |
| | | 0 | 106 (95.5%) | 89 (80.2%) | 16 (14.4%) | 1 (0.9%) | 0 | 0 |
| | | 1 | 5 (4.5%) | 3 (2.7%) | 1 (0.9%) | 1 (0.9%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (decrease) | Total | 111 (100.0%) | 99 (89.2%) | 0 | 12 (10.8%) | 0 | 0 |
| | | 0 | 107 (96.4%) | 98 (88.3%) | 0 | 9 (8.1%) | 0 | 0 |
| | | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 2 | 3 (2.7%) | 1 (0.9%) | 0 | 2 (1.8%) | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 1 (0.9%) | 0 | 0 | 1 (0.9%) | 0 | 0 |
| | Albumin (decrease) | Total | 111 (100.0%) | 70 (63.1%) | 20 (18.0%) | 20 (18.0%) | 1 (0.9%) | 0 |
| | | 0 | 94 (84.7%) | 67 (60.4%) | 15 (13.5%) | 12 (10.8%) | 0 | 0 |
| | | 1 | 11 (9.9%) | 3 (2.7%) | 3 (2.7%) | 5 (4.5%) | 0 | 0 |
| | | 2 | 6 (5.4%) | 0 | 2 (1.8%) | 3 (2.7%) | 1 (0.9%) | 0 |

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total bilirubin (increase) | Total | 111 (100.0%) | 97 (87.4%) | 10 (9.0%) | 4 (3.6%) | 0 | 0 |
| | | 0 | 108 (97.3%) | 96 (86.5%) | 10 (9.0%) | 2 (1.8%) | 0 | 0 |
| | | 1 | 3 (2.7%) | 1 (0.9%) | 0 | 2 (1.8%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Creatinine (increase) | Total | 111 (100.0%) | 12 (10.8%) | 87 (78.4%) | 12 (10.8%) | 0 | 0 |
| | | 0 | 92 (82.9%) | 11 (9.9%) | 74 (66.7%) | 7 (6.3%) | 0 | 0 |
| | | 1 | 16 (14.4%) | 1 (0.9%) | 12 (10.8%) | 3 (2.7%) | 0 | 0 |
| | | 2 | 3 (2.7%) | 0 | 1 (0.9%) | 2 (1.8%) | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Creatinine clearance (decrease) | Total | 111 (100.0%) | 37 (33.3%) | 34 (30.6%) | 38 (34.2%) | 2 (1.8%) | 0 |
| | | 0 | 52 (46.8%) | 35 (31.5%) | 13 (11.7%) | 4 (3.6%) | 0 | 0 |
| | | 1 | 38 (34.2%) | 2 (1.8%) | 19 (17.1%) | 16 (14.4%) | 1 (0.9%) | 0 |
| | | 2 | 20 (18.0%) | 0 | 2 (1.8%) | 17 (15.3%) | 1 (0.9%) | 0 |
| | | 3 | 1 (0.9%) | 0 | 0 | 1 (0.9%) | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ALT (increase) | Total | 111 (100.0%) | 104 (93.7%) | 6 (5.4%) | 1 (0.9%) | 0 | 0 |
| | | 0 | 111 (100.0%) | 104 (93.7%) | 6 (5.4%) | 1 (0.9%) | 0 | 0 |
| | | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | AST (increase) | Total | 110 (100.0%) | 85 (77.3%) | 24 (21.8%) | 1 (0.9%) | 0 | 0 |
| | | 0 | 104 (94.5%) | 82 (74.5%) | 22 (20.0%) | 0 | 0 | 0 |
| | | 1 | 6 (5.5%) | 3 (2.7%) | 2 (1.8%) | 1 (0.9%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ALP (increase) | Total | 111 (100.0%) | 70 (63.1%) | 36 (32.4%) | 4 (3.6%) | 1 (0.9%) | 0 |
| | | 0 | 89 (80.2%) | 67 (60.4%) | 20 (18.0%) | 2 (1.8%) | 0 | 0 |
| | | 1 | 21 (18.9%) | 3 (2.7%) | 15 (13.5%) | 2 (1.8%) | 1 (0.9%) | 0 |
| | | 2 | 1 (0.9%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| MCL2001 /Ibrutinib | Analysis set: safety population | | 120 | | | | | |
| | Sodium (increase) | Total | 119 (100.0%) | 104 (87.4%) | 10 (8.4%) | 5 (4.2%) | 0 | 0 |
| | | 0 | 117 (98.3%) | 102 (85.7%) | 10 (8.4%) | 5 (4.2%) | 0 | 0 |
| | | 1 | 2 (1.7%) | 2 (1.7%) | 0 | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Sodium (decrease) | Total | 119 (100.0%) | 76 (63.9%) | 38 (31.9%) | 0 | 4 (3.4%) | 1 (0.8%) |
| | | 0 | 113 (95.0%) | 76 (63.9%) | 34 (28.6%) | 0 | 3 (2.5%) | 0 |
| | | 1 | 6 (5.0%) | 0 | 4 (3.4%) | 0 | 1 (0.8%) | 1 (0.8%) |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Magnesium (increase) | Total | 112 (100.0%) | 109 (97.3%) | 2 (1.8%) | 0 | 1 (0.9%) | 0 |
| | | 0 | 112 (100.0%) | 109 (97.3%) | 2 (1.8%) | 0 | 1 (0.9%) | 0 |
| | | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Magnesium (decrease) | Total | 112 (100.0%) | 73 (65.2%) | 37 (33.0%) | 2 (1.8%) | 0 | 0 |
| | | 0 | 97 (86.6%) | 71 (63.4%) | 25 (22.3%) | 1 (0.9%) | 0 | 0 |
| | | 1 | 15 (13.4%) | 2 (1.8%) | 12 (10.7%) | 1 (0.9%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (increase) | Total | 119 (100.0%) | 98 (82.4%) | 16 (13.4%) | 4 (3.4%) | 0 | 1 (0.8%) |
| | | 0 | 112 (94.1%) | 92 (77.3%) | 15 (12.6%) | 4 (3.4%) | 0 | 1 (0.8%) |
| | | 1 | 5 (4.2%) | 4 (3.4%) | 1 (0.8%) | 0 | 0 | 0 |
| | | 2 | 1 (0.8%) | 1 (0.8%) | 0 | 0 | 0 | 0 |
| | | 3 | 1 (0.8%) | 1 (0.8%) | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (decrease) | Total | 119 (100.0%) | 94 (79.0%) | 0 | 19 (16.0%) | 5 (4.2%) | 1 (0.8%) |
| | | 0 | 116 (97.5%) | 93 (78.2%) | 0 | 17 (14.3%) | 5 (4.2%) | 1 (0.8%) |
| | | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 2 | 3 (2.5%) | 1 (0.8%) | 0 | 2 (1.7%) | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Albumin (decrease) | Total | 119 (100.0%) | 59 (49.6%) | 27 (22.7%) | 27 (22.7%) | 6 (5.0%) | 0 |
| | | 0 | 96 (80.7%) | 58 (48.7%) | 19 (16.0%) | 18 (15.1%) | 1 (0.8%) | 0 |
| | | 1 | 16 (13.4%) | 0 | 7 (5.9%) | 8 (6.7%) | 1 (0.8%) | 0 |
| | | 2 | 7 (5.9%) | 1 (0.8%) | 1 (0.8%) | 1 (0.8%) | 4 (3.4%) | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total bilirubin (increase) | Total | 119 (100.0%) | 88 (73.9%) | 17 (14.3%) | 12 (10.1%) | 2 (1.7%) | 0 |
| | | 0 | 111 (93.3%) | 86 (72.3%) | 15 (12.6%) | 9 (7.6%) | 1 (0.8%) | 0 |
| | | 1 | 6 (5.0%) | 1 (0.8%) | 2 (1.7%) | 3 (2.5%) | 0 | 0 |
| | | 2 | 2 (1.7%) | 1 (0.8%) | 0 | 0 | 1 (0.8%) | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | Creatinine (increase) | Total | 119 (100.0%) | 66 (55.5%) | 35 (29.4%) | 17 (14.3%) | 1 (0.8%) | 0 |
| | | 0 | 96 (80.7%) | 66 (55.5%) | 23 (19.3%) | 6 (5.0%) | 1 (0.8%) | 0 |
| | | 1 | 20 (16.8%) | 0 | 12 (10.1%) | 8 (6.7%) | 0 | 0 |
| | | 2 | 3 (2.5%) | 0 | 0 | 3 (2.5%) | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Creatinine clearance (decrease) | Total | 118 (100.0%) | 36 (30.5%) | 38 (32.2%) | 40 (33.9%) | 4 (3.4%) | 0 |
| | | 0 | 62 (52.5%) | 35 (29.7%) | 22 (18.6%) | 5 (4.2%) | 0 | 0 |
| | | 1 | 30 (25.4%) | 1 (0.8%) | 14 (11.9%) | 14 (11.9%) | 1 (0.8%) | 0 |
| | | 2 | 25 (21.2%) | 0 | 2 (1.7%) | 21 (17.8%) | 2 (1.7%) | 0 |
| | | 3 | 1 (0.8%) | 0 | 0 | 0 | 1 (0.8%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ALT (increase) | Total | 119 (100.0%) | 93 (78.2%) | 24 (20.2%) | 0 | 2 (1.7%) | 0 |
| | | 0 | 109 (91.6%) | 89 (74.8%) | 19 (16.0%) | 0 | 1 (0.8%) | 0 |
| | | 1 | 10 (8.4%) | 4 (3.4%) | 5 (4.2%) | 0 | 1 (0.8%) | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | AST (increase) | Total | 119 (100.0%) | 82 (68.9%) | 34 (28.6%) | 2 (1.7%) | 1 (0.8%) | 0 |
| | | 0 | 103 (86.6%) | 76 (63.9%) | 26 (21.8%) | 0 | 1 (0.8%) | 0 |
| | | 1 | 16 (13.4%) | 6 (5.0%) | 8 (6.7%) | 2 (1.7%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ALP (increase) | Total | 119 (100.0%) | 78 (65.5%) | 31 (26.1%) | 8 (6.7%) | 2 (1.7%) | 0 |
| | | 0 | 98 (82.4%) | 76 (63.9%) | 17 (14.3%) | 3 (2.5%) | 2 (1.7%) | 0 |
| | | 1 | 20 (16.8%) | 2 (1.7%) | 13 (10.9%) | 5 (4.2%) | 0 | 0 |
| | | 2 | 1 (0.8%) | 0 | 1 (0.8%) | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| MCL3001 /Ibrutinib | Analysis set: safety population | | 139 | | | | | |
| | Sodium (increase) | Total | 138 (100.0%) | 108 (78.3%) | 24 (17.4%) | 5 (3.6%) | 1 (0.7%) | 0 |
| | | 0 | 135 (97.8%) | 105 (76.1%) | 24 (17.4%) | 5 (3.6%) | 1 (0.7%) | 0 |
| | | 1 | 3 (2.2%) | 3 (2.2%) | 0 | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Sodium (decrease) | Total | 138 (100.0%) | 88 (63.8%) | 44 (31.9%) | 0 | 6 (4.3%) | 0 |
| | | 0 | 131 (94.9%) | 87 (63.0%) | 40 (29.0%) | 0 | 4 (2.9%) | 0 |
| | | 1 | 7 (5.1%) | 1 (0.7%) | 4 (2.9%) | 0 | 2 (1.4%) | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | Magnesium (increase) | Total | 128 (100.0%) | 121 (94.5%) | 4 (3.1%) | 0 | 3 (2.3%) | 0 |
| | | 0 | 122 (95.3%) | 120 (93.8%) | 2 (1.6%) | 0 | 0 | 0 |
| | | 1 | 3 (2.3%) | 1 (0.8%) | 2 (1.6%) | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 3 (2.3%) | 0 | 0 | 0 | 3 (2.3%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Magnesium (decrease) | Total | 128 (100.0%) | 85 (66.4%) | 37 (28.9%) | 4 (3.1%) | 2 (1.6%) | 0 |
| | | 0 | 115 (89.8%) | 82 (64.1%) | 30 (23.4%) | 2 (1.6%) | 1 (0.8%) | 0 |
| | | 1 | 12 (9.4%) | 3 (2.3%) | 6 (4.7%) | 2 (1.6%) | 1 (0.8%) | 0 |
| | | 2 | 1 (0.8%) | 0 | 1 (0.8%) | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (increase) | Total | 137 (100.0%) | 96 (70.1%) | 25 (18.2%) | 10 (7.3%) | 3 (2.2%) | 3 (2.2%) |
| | | 0 | 129 (94.2%) | 92 (67.2%) | 23 (16.8%) | 9 (6.6%) | 2 (1.5%) | 3 (2.2%) |
| | | 1 | 8 (5.8%) | 4 (2.9%) | 2 (1.5%) | 1 (0.7%) | 1 (0.7%) | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (decrease) | Total | 137 (100.0%) | 101 (73.7%) | 0 | 26 (19.0%) | 9 (6.6%) | 1 (0.7%) |
| | | 0 | 129 (94.2%) | 99 (72.3%) | 0 | 24 (17.5%) | 5 (3.6%) | 1 (0.7%) |
| | | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 2 | 8 (5.8%) | 2 (1.5%) | 0 | 2 (1.5%) | 4 (2.9%) | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Albumin (decrease) | Total | 134 (100.0%) | 80 (59.7%) | 33 (24.6%) | 20 (14.9%) | 1 (0.7%) | 0 |
| | | 0 | 115 (85.8%) | 79 (59.0%) | 23 (17.2%) | 13 (9.7%) | 0 | 0 |
| | | 1 | 16 (11.9%) | 1 (0.7%) | 9 (6.7%) | 5 (3.7%) | 1 (0.7%) | 0 |
| | | 2 | 3 (2.2%) | 0 | 1 (0.7%) | 2 (1.5%) | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total bilirubin (increase) | Total | 136 (100.0%) | 90 (66.2%) | 27 (19.9%) | 15 (11.0%) | 3 (2.2%) | 1 (0.7%) |
| | | 0 | 128 (94.1%) | 90 (66.2%) | 26 (19.1%) | 9 (6.6%) | 2 (1.5%) | 1 (0.7%) |
| | | 1 | 6 (4.4%) | 0 | 1 (0.7%) | 5 (3.7%) | 0 | 0 |
| | | 2 | 1 (0.7%) | 0 | 0 | 1 (0.7%) | 0 | 0 |
| | | 3 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.7%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Creatinine (increase) | Total | 137 (100.0%) | 78 (56.9%) | 38 (27.7%) | 16 (11.7%) | 4 (2.9%) | 1 (0.7%) |
| | | 0 | 118 (86.1%) | 76 (55.5%) | 30 (21.9%) | 8 (5.8%) | 3 (2.2%) | 1 (0.7%) |
| | | 1 | 16 (11.7%) | 2 (1.5%) | 7 (5.1%) | 6 (4.4%) | 1 (0.7%) | 0 |
| | | 2 | 3 (2.2%) | 0 | 1 (0.7%) | 2 (1.5%) | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Creatinine clearance (decrease) | Total | 137 (100.0%) | 23 (16.8%) | 46 (33.6%) | 58 (42.3%) | 7 (5.1%) | 3 (2.2%) |
| | | 0 | 51 (37.2%) | 22 (16.1%) | 21 (15.3%) | 6 (4.4%) | 1 (0.7%) | 1 (0.7%) |

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | | 1 | 57 (41.6%) | 1 (0.7%) | 21 (15.3%) | 32 (23.4%) | 2 (1.5%) | 1 (0.7%) |
| | | 2 | 28 (20.4%) | 0 | 4 (2.9%) | 19 (13.9%) | 4 (2.9%) | 1 (0.7%) |
| | | 3 | 1 (0.7%) | 0 | 0 | 1 (0.7%) | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ALT (increase) | Total | 135 (100.0%) | 96 (71.1%) | 32 (23.7%) | 4 (3.0%) | 3 (2.2%) | 0 |
| | | 0 | 123 (91.1%) | 89 (65.9%) | 29 (21.5%) | 2 (1.5%) | 3 (2.2%) | 0 |
| | | 1 | 12 (8.9%) | 7 (5.2%) | 3 (2.2%) | 2 (1.5%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | AST (increase) | Total | 136 (100.0%) | 86 (63.2%) | 46 (33.8%) | 2 (1.5%) | 0 | 2 (1.5%) |
| | | 0 | 124 (91.2%) | 81 (59.6%) | 40 (29.4%) | 1 (0.7%) | 0 | 2 (1.5%) |
| | | 1 | 12 (8.8%) | 5 (3.7%) | 6 (4.4%) | 1 (0.7%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ALP (increase) | Total | 136 (100.0%) | 86 (63.2%) | 41 (30.1%) | 9 (6.6%) | 0 | 0 |
| | | 0 | 118 (86.8%) | 84 (61.8%) | 29 (21.3%) | 5 (3.7%) | 0 | 0 |
| | | 1 | 16 (11.8%) | 2 (1.5%) | 11 (8.1%) | 3 (2.2%) | 0 | 0 |
| | | 2 | 1 (0.7%) | 0 | 1 (0.7%) | 0 | 0 | 0 |
| | | 3 | 1 (0.7%) | 0 | 0 | 1 (0.7%) | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| MCL3001 /Temsirolimus | Analysis set: safety population | | 139 | | | | | |
| | Sodium (increase) | Total | 138 (100.0%) | 102 (73.9%) | 33 (23.9%) | 2 (1.4%) | 1 (0.7%) | 0 |
| | | 0 | 133 (96.4%) | 101 (73.2%) | 29 (21.0%) | 2 (1.4%) | 1 (0.7%) | 0 |
| | | 1 | 5 (3.6%) | 1 (0.7%) | 4 (2.9%) | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Sodium (decrease) | Total | 138 (100.0%) | 86 (62.3%) | 37 (26.8%) | 0 | 12 (8.7%) | 3 (2.2%) |
| | | 0 | 122 (88.4%) | 84 (60.9%) | 30 (21.7%) | 0 | 6 (4.3%) | 2 (1.4%) |
| | | 1 | 16 (11.6%) | 2 (1.4%) | 7 (5.1%) | 0 | 6 (4.3%) | 1 (0.7%) |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Magnesium (increase) | Total | 86 (100.0%) | 74 (86.0%) | 9 (10.5%) | 0 | 3 (3.5%) | 0 |
| | | 0 | 84 (97.7%) | 73 (84.9%) | 9 (10.5%) | 0 | 2 (2.3%) | 0 |
| | | 1 | 1 (1.2%) | 1 (1.2%) | 0 | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 1 (1.2%) | 0 | 0 | 0 | 1 (1.2%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Magnesium (decrease) | Total | 86 (100.0%) | 53 (61.6%) | 27 (31.4%) | 5 (5.8%) | 1 (1.2%) | 0 |
| | | 0 | 76 (88.4%) | 52 (60.5%) | 21 (24.4%) | 3 (3.5%) | 0 | 0 |

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | | 1 | 10 (11.6%) | 1 (1.2%) | 6 (7.0%) | 2 (2.3%) | 1 (1.2%) | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (increase) | Total | 138 (100.0%) | 109 (79.0%) | 21 (15.2%) | 6 (4.3%) | 2 (1.4%) | 0 |
| | | 0 | 126 (91.3%) | 100 (72.5%) | 19 (13.8%) | 6 (4.3%) | 1 (0.7%) | 0 |
| | | 1 | 10 (7.2%) | 7 (5.1%) | 2 (1.4%) | 0 | 1 (0.7%) | 0 |
| | | 2 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 0 | 0 |
| | | 3 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (decrease) | Total | 138 (100.0%) | 64 (46.4%) | 0 | 59 (42.8%) | 12 (8.7%) | 3 (2.2%) |
| | | 0 | 134 (97.1%) | 64 (46.4%) | 0 | 58 (42.0%) | 10 (7.2%) | 2 (1.4%) |
| | | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 2 | 4 (2.9%) | 0 | 0 | 1 (0.7%) | 2 (1.4%) | 1 (0.7%) |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Albumin (decrease) | Total | 136 (100.0%) | 55 (40.4%) | 55 (40.4%) | 25 (18.4%) | 1 (0.7%) | 0 |
| | | 0 | 117 (86.0%) | 54 (39.7%) | 45 (33.1%) | 17 (12.5%) | 1 (0.7%) | 0 |
| | | 1 | 14 (10.3%) | 0 | 10 (7.4%) | 4 (2.9%) | 0 | 0 |
| | | 2 | 5 (3.7%) | 1 (0.7%) | 0 | 4 (2.9%) | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total bilirubin (increase) | Total | 138 (100.0%) | 125 (90.6%) | 8 (5.8%) | 4 (2.9%) | 1 (0.7%) | 0 |
| | | 0 | 132 (95.7%) | 122 (88.4%) | 7 (5.1%) | 3 (2.2%) | 0 | 0 |
| | | 1 | 5 (3.6%) | 3 (2.2%) | 1 (0.7%) | 1 (0.7%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.7%) | 0 |
| | Creatinine (increase) | Total | 138 (100.0%) | 58 (42.0%) | 50 (36.2%) | 27 (19.6%) | 3 (2.2%) | 0 |
| | | 0 | 114 (82.6%) | 57 (41.3%) | 45 (32.6%) | 10 (7.2%) | 2 (1.4%) | 0 |
| | | 1 | 21 (15.2%) | 1 (0.7%) | 5 (3.6%) | 14 (10.1%) | 1 (0.7%) | 0 |
| | | 2 | 3 (2.2%) | 0 | 0 | 3 (2.2%) | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Creatinine clearance (decrease) | Total | 137 (100.0%) | 20 (14.6%) | 42 (30.7%) | 58 (42.3%) | 15 (10.9%) | 2 (1.5%) |
| | | 0 | 56 (40.9%) | 19 (13.9%) | 24 (17.5%) | 13 (9.5%) | 0 | 0 |
| | | 1 | 41 (29.9%) | 1 (0.7%) | 17 (12.4%) | 22 (16.1%) | 1 (0.7%) | 0 |
| | | 2 | 40 (29.2%) | 0 | 1 (0.7%) | 23 (16.8%) | 14 (10.2%) | 2 (1.5%) |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ALT (increase) | Total | 138 (100.0%) | 63 (45.7%) | 62 (44.9%) | 12 (8.7%) | 1 (0.7%) | 0 |
| | | 0 | 130 (94.2%) | 62 (44.9%) | 57 (41.3%) | 10 (7.2%) | 1 (0.7%) | 0 |
| | | 1 | 7 (5.1%) | 1 (0.7%) | 4 (2.9%) | 2 (1.4%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | | 3 | 1 (0.7%) | 0 | 1 (0.7%) | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | AST (increase) | Total | 138 (100.0%) | 46 (33.3%) | 84 (60.9%) | 7 (5.1%) | 1 (0.7%) | 0 |
| | | 0 | 124 (89.9%) | 45 (32.6%) | 73 (52.9%) | 5 (3.6%) | 1 (0.7%) | 0 |
| | | 1 | 13 (9.4%) | 1 (0.7%) | 10 (7.2%) | 2 (1.4%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 1 (0.7%) | 0 | 1 (0.7%) | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ALP (increase) | Total | 138 (100.0%) | 70 (50.7%) | 56 (40.6%) | 10 (7.2%) | 2 (1.4%) | 0 |
| | | 0 | 118 (85.5%) | 70 (50.7%) | 43 (31.2%) | 5 (3.6%) | 0 | 0 |
| | | 1 | 16 (11.6%) | 0 | 11 (8.0%) | 4 (2.9%) | 1 (0.7%) | 0 |
| | | 2 | 3 (2.2%) | 0 | 2 (1.4%) | 1 (0.7%) | 0 | 0 |
| | | 3 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.7%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pooled Ibrutinib /Ibrutinib | Analysis set: safety population | | 370 | | | | | |
| | Sodium (increase) | Total | 368 (100.0%) | 281 (76.4%) | 75 (20.4%) | 11 (3.0%) | 1 (0.3%) | 0 |
| | | 0 | 349 (94.8%) | 269 (73.1%) | 68 (18.5%) | 11 (3.0%) | 1 (0.3%) | 0 |
| | | 1 | 19 (5.2%) | 12 (3.3%) | 7 (1.9%) | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Sodium (decrease) | Total | 368 (100.0%) | 256 (69.6%) | 93 (25.3%) | 0 | 16 (4.3%) | 3 (0.8%) |
| | | 0 | 349 (94.8%) | 253 (68.8%) | 84 (22.8%) | 0 | 10 (2.7%) | 2 (0.5%) |
| | | 1 | 17 (4.6%) | 3 (0.8%) | 9 (2.4%) | 0 | 4 (1.1%) | 1 (0.3%) |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 2 (0.5%) | 0 | 0 | 0 | 2 (0.5%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Magnesium (increase) | Total | 350 (100.0%) | 325 (92.9%) | 21 (6.0%) | 0 | 4 (1.1%) | 0 |
| | | 0 | 341 (97.4%) | 322 (92.0%) | 18 (5.1%) | 0 | 1 (0.3%) | 0 |
| | | 1 | 6 (1.7%) | 3 (0.9%) | 3 (0.9%) | 0 | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 3 (0.9%) | 0 | 0 | 0 | 3 (0.9%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Magnesium (decrease) | Total | 350 (100.0%) | 217 (62.0%) | 124 (35.4%) | 7 (2.0%) | 2 (0.6%) | 0 |
| | | 0 | 307 (87.7%) | 210 (60.0%) | 93 (26.6%) | 3 (0.9%) | 1 (0.3%) | 0 |
| | | 1 | 41 (11.7%) | 7 (2.0%) | 29 (8.3%) | 4 (1.1%) | 1 (0.3%) | 0 |
| | | 2 | 2 (0.6%) | 0 | 2 (0.6%) | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (increase) | Total | 367 (100.0%) | 286 (77.9%) | 58 (15.8%) | 16 (4.4%) | 3 (0.8%) | 4 (1.1%) |
| | | 0 | 347 (94.6%) | 273 (74.4%) | 54 (14.7%) | 14 (3.8%) | 2 (0.5%) | 4 (1.1%) |
| | | 1 | 18 (4.9%) | 11 (3.0%) | 4 (1.1%) | 2 (0.5%) | 1 (0.3%) | 0 |
| | | 2 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 |

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | | 3 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Potassium (decrease) | Total | 367 (100.0%) | 294 (80.1%) | 0 | 57 (15.5%) | 14 (3.8%) | 2 (0.5%) |
| | | 0 | 352 (95.9%) | 290 (79.0%) | 0 | 50 (13.6%) | 10 (2.7%) | 2 (0.5%) |
| | | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 2 | 14 (3.8%) | 4 (1.1%) | 0 | 6 (1.6%) | 4 (1.1%) | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 1 (0.3%) | 0 | 0 | 1 (0.3%) | 0 | 0 |
| | Albumin (decrease) | Total | 364 (100.0%) | 209 (57.4%) | 80 (22.0%) | 67 (18.4%) | 8 (2.2%) | 0 |
| | | 0 | 305 (83.8%) | 204 (56.0%) | 57 (15.7%) | 43 (11.8%) | 1 (0.3%) | 0 |
| | | 1 | 43 (11.8%) | 4 (1.1%) | 19 (5.2%) | 18 (4.9%) | 2 (0.5%) | 0 |
| | | 2 | 16 (4.4%) | 1 (0.3%) | 4 (1.1%) | 6 (1.6%) | 5 (1.4%) | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total bilirubin (increase) | Total | 366 (100.0%) | 275 (75.1%) | 54 (14.8%) | 31 (8.5%) | 5 (1.4%) | 1 (0.3%) |
| | | 0 | 347 (94.8%) | 272 (74.3%) | 51 (13.9%) | 20 (5.5%) | 3 (0.8%) | 1 (0.3%) |
| | | 1 | 15 (4.1%) | 2 (0.5%) | 3 (0.8%) | 10 (2.7%) | 0 | 0 |
| | | 2 | 3 (0.8%) | 1 (0.3%) | 0 | 1 (0.3%) | 1 (0.3%) | 0 |
| | | 3 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Creatinine (increase) | Total | 367 (100.0%) | 156 (42.5%) | 160 (43.6%) | 45 (12.3%) | 5 (1.4%) | 1 (0.3%) |
| | | 0 | 306 (83.4%) | 153 (41.7%) | 127 (34.6%) | 21 (5.7%) | 4 (1.1%) | 1 (0.3%) |
| | | 1 | 52 (14.2%) | 3 (0.8%) | 31 (8.4%) | 17 (4.6%) | 1 (0.3%) | 0 |
| | | 2 | 9 (2.5%) | 0 | 2 (0.5%) | 7 (1.9%) | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Creatinine clearance (decrease) | Total | 366 (100.0%) | 96 (26.2%) | 118 (32.2%) | 136 (37.2%) | 13 (3.6%) | 3 (0.8%) |
| | | 0 | 165 (45.1%) | 92 (25.1%) | 56 (15.3%) | 15 (4.1%) | 1 (0.3%) | 1 (0.3%) |
| | | 1 | 125 (34.2%) | 4 (1.1%) | 54 (14.8%) | 62 (16.9%) | 4 (1.1%) | 1 (0.3%) |
| | | 2 | 73 (19.9%) | 0 | 8 (2.2%) | 57 (15.6%) | 7 (1.9%) | 1 (0.3%) |
| | | 3 | 3 (0.8%) | 0 | 0 | 2 (0.5%) | 1 (0.3%) | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | ALT (increase) | Total | 365 (100.0%) | 293 (80.3%) | 62 (17.0%) | 5 (1.4%) | 5 (1.4%) | 0 |
| | | 0 | 343 (94.0%) | 282 (77.3%) | 54 (14.8%) | 3 (0.8%) | 4 (1.1%) | 0 |
| | | 1 | 22 (6.0%) | 11 (3.0%) | 8 (2.2%) | 2 (0.5%) | 1 (0.3%) | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | AST (increase) | Total | 365 (100.0%) | 253 (69.3%) | 104 (28.5%) | 5 (1.4%) | 1 (0.3%) | 2 (0.5%) |
| | | 0 | 331 (90.7%) | 239 (65.5%) | 88 (24.1%) | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| | | 1 | 34 (9.3%) | 14 (3.8%) | 16 (4.4%) | 4 (1.1%) | 0 | 0 |
| | | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |

**TSFLAB07: Chemistry: Shift from Baseline to Worst Grade During Treatment; Safety Population (MCL-ISS)**

| Study/Treatment | Parameter | Baseline Grade | Maximum Grade On Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total | 0 | 1 | 2 | 3 | 4 |
| | ALP (increase) | Total | 366 (100.0%) | 234 (63.9%) | 108 (29.5%) | 21 (5.7%) | 3 (0.8%) | 0 |
| | | 0 | 305 (83.3%) | 227 (62.0%) | 66 (18.0%) | 10 (2.7%) | 2 (0.5%) | 0 |
| | | 1 | 57 (15.6%) | 7 (1.9%) | 39 (10.7%) | 10 (2.7%) | 1 (0.3%) | 0 |
| | | 2 | 3 (0.8%) | 0 | 3 (0.8%) | 0 | 0 | 0 |
| | | 3 | 1 (0.3%) | 0 | 0 | 1 (0.3%) | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 | 0 | 0 |

Note: A subject must have both baseline and at least one post-baseline assessment to be included in this table.
Percentages are calculated with the number of subjects in safety population with baseline and any post-baseline laboratory values as denominator.

[TSFLAB07.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsflab07.sas] 15SEP2015, 14:12

参照元：5.3.5.3.1 ISS TSFLAB07

表 2.7.4-付録-40 Shift from Baseline in Creatinine Clearance (ml/min); Safety Population (MCL-ISS)

**TSFLAB09: Shift from Baseline in Creatinine Clearance (ml/min); Safety Population (MCL-ISS)**

| Study | Treatment | Population/Baseline Value | Minimum Post-Baseline Value | | | |
|---|---|---|---|---|---|---|
| | | | Total | >=60 | <60 – 30 | <30 |
| PCYC-1104 | Ibrutinib | Analysis Set: Safety Population | 111 | | | |
| | | Total | 111 (100%) | 71 (64%) | 38 (34.2%) | 2 (1.8%) |
| | | >=60 | 90 (81.1%) | 69 (62.2%) | 20 (18%) | 1 (0.9%) |
| | | <60-30 | 20 (18%) | 2 (1.8%) | 17 (15.3%) | 1 (0.9%) |
| | | <30 | 1 (0.9%) | 0 | 1 (0.9%) | 0 |
| MCL2001 | Ibrutinib | Analysis Set: Safety Population | 120 | | | |
| | | Total | 118 (100%) | 74 (62.7%) | 40 (33.9%) | 4 (3.4%) |
| | | >=60 | 92 (78%) | 72 (61%) | 19 (16.1%) | 1 (0.8%) |
| | | <60-30 | 25 (21.2%) | 2 (1.7%) | 21 (17.8%) | 2 (1.7%) |
| | | <30 | 1 (0.8%) | 0 | 0 | 1 (0.8%) |
| MCL3001 | Ibrutinib | Analysis Set: Safety Population | 139 | | | |
| | | Total | 137 (100%) | 69 (50.4%) | 58 (42.3%) | 10 (7.3%) |
| | | >=60 | 108 (78.8%) | 65 (47.4%) | 38 (27.7%) | 5 (3.6%) |
| | | <60-30 | 28 (20.4%) | 4 (2.9%) | 19 (13.9%) | 5 (3.6%) |
| | | <30 | 1 (0.7%) | 0 | 1 (0.7%) | 0 |
| MCL3001 | Temsirolimus | Analysis Set: Safety Population | 139 | | | |
| | | Total | 137 (100%) | 62 (45.3%) | 58 (42.3%) | 17 (12.4%) |
| | | >=60 | 97 (70.8%) | 61 (44.5%) | 35 (25.5%) | 1 (0.7%) |
| | | <60-30 | 40 (29.2%) | 1 (0.7%) | 23 (16.8%) | 16 (11.7%) |
| | | <30 | 0 | 0 | 0 | 0 |
| Pooled Ibrutinib | Ibrutinib | Analysis Set: Safety Population | 370 | | | |
| | | Total | 366 (100%) | 214 (58.5%) | 136 (37.2%) | 16 (4.4%) |
| | | >=60 | 290 (79.2%) | 206 (56.3%) | 77 (21%) | 7 (1.9%) |
| | | <60-30 | 73 (19.9%) | 8 (2.2%) | 57 (15.6%) | 8 (2.2%) |
| | | <30 | 3 (0.8%) | 0 | 2 (0.5%) | 1 (0.3%) |

A subject must have both baseline and at least one post-baseline assessment to be included in this table.
Percentages are calculated with the number of subjects in safety population with baseline and any post-baseline laboratory values as denominator.

[TSFLAB09.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsflab09.sas] 15SEP2015, 14:12

参照元：5.3.5.3.1 ISS TSFLAB09

表 2.7.4-付録-41 Overall Summary of Treatment-emergent Adverse Events by Age Group (>=65 vs. <65); Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE11APART1OF3: Overall Summary of Treatment-emergent Adverse Events by Age Group (>=65 vs. <65); Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Age (years) | | Age (years) | |
| | >= 65 | < 65 | >= 65 | < 65 |
| Analysis Set: Safety Population | 70 | 41 | 75 | 45 |
| Any TEAE | 70 (100.0%) | 41 (100.0%) | 73 (97.3%) | 42 (93.3%) |
| Grade >= 3 | 58 (82.9%) | 26 (63.4%) | 62 (82.7%) | 25 (55.6%) |
| Drug related [a] | 61 (87.1%) | 37 (90.2%) | 60 (80.0%) | 35 (77.8%) |
| Grade >= 3 | 34 (48.6%) | 15 (36.6%) | 39 (52.0%) | 13 (28.9%) |
| Any TESAE | 47 (67.1%) | 15 (36.6%) | 47 (62.7%) | 12 (26.7%) |
| Grade >= 3 | 44 (62.9%) | 11 (26.8%) | 44 (58.7%) | 9 (20.0%) |
| Drug related [a] | 23 (32.9%) | 5 (12.2%) | 20 (26.7%) | 5 (11.1%) |
| TEAE leading to treatment discontinuation | 10 (14.3%) | 0 | 16 (21.3%) | 4 (8.9%) |
| TEAE leading to treatment dose reduction | 12 (17.1%) | 3 (7.3%) | 6 (8.0%) | 2 (4.4%) |
| TEAE with outcome death | 13 (18.6%) | 3 (7.3%) | 12 (16.0%) | 2 (4.4%) |
| Deaths within 30 days after last dose of study treatment [b] | 13 (18.6%) | 3 (7.3%) | 17 (22.7%) | 6 (13.3%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE11APART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae11a.sas]
26OCT2015, 14:30

参照元：5.3.5.3.1 ISS TSFAE11APART1OF3

表 2.7.4-付録-42 Overall Summary of Treatment-emergent Adverse Events by Age Group (>=65 vs. <65); Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE11APART2OF3: Overall Summary of Treatment-emergent Adverse Events by Age Group (>=65 vs. <65); Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Age (years) | | Age (years) | |
| | >= 65 | < 65 | >= 65 | < 65 |
| Analysis Set: Safety Population | 86 | 53 | 85 | 54 |
| Any TEAE | 86 (100.0%) | 52 (98.1%) | 85 (100.0%) | 53 (98.1%) |
| Grade >= 3 | 62 (72.1%) | 32 (60.4%) | 77 (90.6%) | 44 (81.5%) |
| Drug related [a] | 70 (81.4%) | 45 (84.9%) | 81 (95.3%) | 52 (96.3%) |
| Grade >= 3 | 40 (46.5%) | 15 (28.3%) | 68 (80.0%) | 41 (75.9%) |
| Any TESAE | 45 (52.3%) | 22 (41.5%) | 54 (63.5%) | 26 (48.1%) |
| Grade >= 3 | 41 (47.7%) | 22 (41.5%) | 49 (57.6%) | 19 (35.2%) |
| Drug related [a] | 22 (25.6%) | 7 (13.2%) | 35 (41.2%) | 18 (33.3%) |
| TEAE leading to treatment discontinuation | 12 (14.0%) | 6 (11.3%) | 27 (31.8%) | 14 (25.9%) |
| TEAE leading to treatment dose reduction | 4 (4.7%) | 1 (1.9%) | 38 (44.7%) | 22 (40.7%) |
| TEAE with outcome death | 9 (10.5%) | 6 (11.3%) | 8 (9.4%) | 3 (5.6%) |
| Deaths within 30 days after last dose of study treatment [b] | 15 (17.4%) | 9 (17.0%) | 12 (14.1%) | 3 (5.6%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE11APART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae11a.sas]
26OCT2015, 14:30

参照元：5.3.5.3.1 ISS TSFAE11APART2OF3

表 2.7.4-付録-43 Overall Summary of Treatment-emergent Adverse Events by Age Group (>=70 vs. <70); Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE11BPART1OF3: Overall Summary of Treatment-emergent Adverse Events by Age Group (>=70 vs. <70); Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Age (years) | | Age (years) | |
| | >= 70 | < 70 | >= 70 | < 70 |
| Analysis Set: Safety Population | 46 | 65 | 56 | 64 |
| Any TEAE | 46 (100.0%) | 65 (100.0%) | 54 (96.4%) | 61 (95.3%) |
| Grade >= 3 | 40 (87.0%) | 44 (67.7%) | 45 (80.4%) | 42 (65.6%) |
| Drug related [a] | 42 (91.3%) | 56 (86.2%) | 44 (78.6%) | 51 (79.7%) |
| Grade >= 3 | 23 (50.0%) | 26 (40.0%) | 26 (46.4%) | 26 (40.6%) |
| Any TESAE | 33 (71.7%) | 29 (44.6%) | 35 (62.5%) | 24 (37.5%) |
| Grade >= 3 | 31 (67.4%) | 24 (36.9%) | 32 (57.1%) | 21 (32.8%) |
| Drug related [a] | 17 (37.0%) | 11 (16.9%) | 13 (23.2%) | 12 (18.8%) |
| TEAE leading to treatment discontinuation | 8 (17.4%) | 2 (3.1%) | 9 (16.1%) | 11 (17.2%) |
| TEAE leading to treatment dose reduction | 8 (17.4%) | 7 (10.8%) | 4 (7.1%) | 4 (6.3%) |
| TEAE with outcome death | 9 (19.6%) | 7 (10.8%) | 9 (16.1%) | 5 (7.8%) |
| Deaths within 30 days after last dose of study treatment [b] | 9 (19.6%) | 7 (10.8%) | 12 (21.4%) | 11 (17.2%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE11BPART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae11b.sas]
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参照元：5.3.5.3.1 ISS TSFAE11BPART1OF3

表 2.7.4-付録-44 Overall Summary of Treatment-emergent Adverse Events by Age Group (>=70 vs. <70); Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE11BPART2OF3: Overall Summary of Treatment-emergent Adverse Events by Age Group (>=70 vs. <70); Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Age (years) | | Age (years) | |
| | >= 70 | < 70 | >= 70 | < 70 |
| Analysis Set: Safety Population | 58 | 81 | 60 | 79 |
| Any TEAE | 58 (100.0%) | 80 (98.8%) | 60 (100.0%) | 78 (98.7%) |
| Grade >= 3 | 43 (74.1%) | 51 (63.0%) | 54 (90.0%) | 67 (84.8%) |
| Drug related [a] | 51 (87.9%) | 64 (79.0%) | 57 (95.0%) | 76 (96.2%) |
| Grade >= 3 | 33 (56.9%) | 22 (27.2%) | 46 (76.7%) | 63 (79.7%) |
| Any TESAE | 33 (56.9%) | 34 (42.0%) | 37 (61.7%) | 43 (54.4%) |
| Grade >= 3 | 30 (51.7%) | 33 (40.7%) | 33 (55.0%) | 35 (44.3%) |
| Drug related [a] | 17 (29.3%) | 12 (14.8%) | 23 (38.3%) | 30 (38.0%) |
| TEAE leading to treatment discontinuation | 11 (19.0%) | 7 (8.6%) | 22 (36.7%) | 19 (24.1%) |
| TEAE leading to treatment dose reduction | 1 (1.7%) | 4 (4.9%) | 28 (46.7%) | 32 (40.5%) |
| TEAE with outcome death | 7 (12.1%) | 8 (9.9%) | 6 (10.0%) | 5 (6.3%) |
| Deaths within 30 days after last dose of study treatment [b] | 11 (19.0%) | 13 (16.0%) | 9 (15.0%) | 6 (7.6%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE11BPART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae11b.sas]
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参照元：5.3.5.3.1 ISS TSFAE11BPART2OF3

表 2.7.4-付録-45 Overall Summary of Treatment-emergent Adverse Events by Age Group (>=75 vs. <75); Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE11CPART1OF3: Overall Summary of Treatment-emergent Adverse Events by Age Group (>=75 vs. <75); Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Age (years) | | Age (years) | |
| | >= 75 | < 75 | >= 75 | < 75 |
| Analysis Set: Safety Population | 23 | 88 | 26 | 94 |
| Any TEAE | 23 (100.0%) | 88 (100.0%) | 26 (100.0%) | 89 (94.7%) |
| Grade >= 3 | 22 (95.7%) | 62 (70.5%) | 21 (80.8%) | 66 (70.2%) |
| Drug related [a] | 21 (91.3%) | 77 (87.5%) | 23 (88.5%) | 72 (76.6%) |
| Grade >= 3 | 12 (52.2%) | 37 (42.0%) | 12 (46.2%) | 40 (42.6%) |
| Any TESAE | 17 (73.9%) | 45 (51.1%) | 16 (61.5%) | 43 (45.7%) |
| Grade >= 3 | 16 (69.6%) | 39 (44.3%) | 15 (57.7%) | 38 (40.4%) |
| Drug related [a] | 7 (30.4%) | 21 (23.9%) | 8 (30.8%) | 17 (18.1%) |
| TEAE leading to treatment discontinuation | 3 (13.0%) | 7 (8.0%) | 4 (15.4%) | 16 (17.0%) |
| TEAE leading to treatment dose reduction | 4 (17.4%) | 11 (12.5%) | 2 (7.7%) | 6 (6.4%) |
| TEAE with outcome death | 5 (21.7%) | 11 (12.5%) | 2 (7.7%) | 12 (12.8%) |
| Deaths within 30 days after last dose of study treatment [b] | 5 (21.7%) | 11 (12.5%) | 4 (15.4%) | 19 (20.2%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE11CPART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae11c.sas]
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参照元：5.3.5.3.1 ISS TSFAE11CPART1OF3

表 2.7.4-付録-46 Overall Summary of Treatment-emergent Adverse Events by Age Group (>=75 vs. <75); Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE11CPART2OF3: Overall Summary of Treatment-emergent Adverse Events by Age Group (>=75 vs. <75); Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Age (years) | | Age (years) | |
| | >= 75 | < 75 | >= 75 | < 75 |
| Analysis Set: Safety Population | 29 | 110 | 33 | 106 |
| Any TEAE | 29 (100.0%) | 109 (99.1%) | 33 (100.0%) | 105 (99.1%) |
| Grade >= 3 | 23 (79.3%) | 71 (64.5%) | 30 (90.9%) | 91 (85.8%) |
| Drug related [a] | 25 (86.2%) | 90 (81.8%) | 31 (93.9%) | 102 (96.2%) |
| Grade >= 3 | 15 (51.7%) | 40 (36.4%) | 26 (78.8%) | 83 (78.3%) |
| Any TESAE | 17 (58.6%) | 50 (45.5%) | 19 (57.6%) | 61 (57.5%) |
| Grade >= 3 | 15 (51.7%) | 48 (43.6%) | 16 (48.5%) | 52 (49.1%) |
| Drug related [a] | 6 (20.7%) | 23 (20.9%) | 11 (33.3%) | 42 (39.6%) |
| TEAE leading to treatment discontinuation | 7 (24.1%) | 11 (10.0%) | 13 (39.4%) | 28 (26.4%) |
| TEAE leading to treatment dose reduction | 0 | 5 (4.5%) | 14 (42.4%) | 46 (43.4%) |
| TEAE with outcome death | 4 (13.8%) | 11 (10.0%) | 3 (9.1%) | 8 (7.5%) |
| Deaths within 30 days after last dose of study treatment [b] | 6 (20.7%) | 18 (16.4%) | 6 (18.2%) | 9 (8.5%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE11CPART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae11c.sas]
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参照元：5.3.5.3.1 ISS TSFAE11CPART2OF3

表 2.7.4-付録-47 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| Analysis set: safety | 231 | | 139 | | 370 |
| Subjects with any TEAE | 229 (99.1%) | 182 (78.8%) | 135 (97.1%) | 83 (59.7%) | 364 (98.4%) |
| System organ class | | | | | |
| Preferred term | | | | | |
| 感染症および寄生虫症 | 165 (71.4%) | 67 (29.0%) | 98 (70.5%) | 20 (14.4%) | 263 (71.1%) |
| 上気道感染 | 37 (16.0%) | 1 (0.4%) | 36 (25.9%) | 2 (1.4%) | 73 (19.7%) |
| 肺炎 | 33 (14.3%) | 26 (11.3%) | 11 (7.9%) | 7 (5.0%) | 44 (11.9%) |
| 副鼻腔炎 | 23 (10.0%) | 0 | 16 (11.5%) | 1 (0.7%) | 39 (10.5%) |
| 尿路感染 | 27 (11.7%) | 5 (2.2%) | 11 (7.9%) | 1 (0.7%) | 38 (10.3%) |
| 鼻咽頭炎 | 22 (9.5%) | 0 | 8 (5.8%) | 0 | 30 (8.1%) |
| 結膜炎 | 18 (7.8%) | 0 | 8 (5.8%) | 0 | 26 (7.0%) |
| 気管支炎 | 15 (6.5%) | 3 (1.3%) | 5 (3.6%) | 1 (0.7%) | 20 (5.4%) |
| 蜂巣炎 | 15 (6.5%) | 8 (3.5%) | 3 (2.2%) | 0 | 18 (4.9%) |
| 帯状疱疹 | 10 (4.3%) | 0 | 4 (2.9%) | 0 | 14 (3.8%) |
| 鼻炎 | 9 (3.9%) | 0 | 5 (3.6%) | 0 | 14 (3.8%) |
| 毛包炎 | 10 (4.3%) | 0 | 3 (2.2%) | 0 | 13 (3.5%) |
| 爪囲炎 | 10 (4.3%) | 0 | 3 (2.2%) | 0 | 13 (3.5%) |
| 下気道感染 | 9 (3.9%) | 3 (1.3%) | 3 (2.2%) | 2 (1.4%) | 12 (3.2%) |
| 皮膚感染 | 9 (3.9%) | 0 | 3 (2.2%) | 1 (0.7%) | 12 (3.2%) |
| 口腔ヘルペス | 6 (2.6%) | 0 | 5 (3.6%) | 0 | 11 (3.0%) |
| 気道感染 | 9 (3.9%) | 2 (0.9%) | 2 (1.4%) | 0 | 11 (3.0%) |
| 敗血症 | 9 (3.9%) | 9 (3.9%) | 2 (1.4%) | 2 (1.4%) | 11 (3.0%) |
| 胃腸炎 | 4 (1.7%) | 2 (0.9%) | 6 (4.3%) | 0 | 10 (2.7%) |
| 咽頭炎 | 5 (2.2%) | 1 (0.4%) | 2 (1.4%) | 0 | 7 (1.9%) |
| ウイルス感染 | 3 (1.3%) | 0 | 4 (2.9%) | 0 | 7 (1.9%) |
| 感染 | 4 (1.7%) | 1 (0.4%) | 2 (1.4%) | 1 (0.7%) | 6 (1.6%) |
| クロストリジウム・ディフィシレ大腸炎 | 4 (1.7%) | 2 (0.9%) | 1 (0.7%) | 1 (0.7%) | 5 (1.4%) |
| 眼感染 | 4 (1.7%) | 0 | 1 (0.7%) | 0 | 5 (1.4%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯肉炎 | 2 (0.9%) | 0 | 3 (2.2%) | 0 | 5 (1.4%) |
| 口腔カンジダ症 | 5 (2.2%) | 0 | 0 | 0 | 5 (1.4%) |
| クロストリジウム・ディフィシレ感染 | 3 (1.3%) | 0 | 1 (0.7%) | 1 (0.7%) | 4 (1.1%) |
| インフルエンザ | 3 (1.3%) | 0 | 1 (0.7%) | 0 | 4 (1.1%) |
| 限局性感染 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| 中耳炎 | 4 (1.7%) | 0 | 0 | 0 | 4 (1.1%) |
| 歯周炎 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| 歯感染 | 0 | 0 | 4 (2.9%) | 0 | 4 (1.1%) |
| 菌血症 | 1 (0.4%) | 0 | 2 (1.4%) | 2 (1.4%) | 3 (0.8%) |
| 気管支肺炎 | 3 (1.3%) | 1 (0.4%) | 0 | 0 | 3 (0.8%) |
| 膀胱炎 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 耳感染 | 1 (0.4%) | 0 | 2 (1.4%) | 0 | 3 (0.8%) |
| ウイルス性胃腸炎 | 2 (0.9%) | 1 (0.4%) | 1 (0.7%) | 0 | 3 (0.8%) |
| 単純ヘルペス | 0 | 0 | 3 (2.2%) | 0 | 3 (0.8%) |
| 喉頭炎 | 3 (1.3%) | 1 (0.4%) | 0 | 0 | 3 (0.8%) |
| 爪感染 | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 外耳炎 | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| ブドウ球菌感染 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| ウイルス性上気道感染 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 急性副鼻腔炎 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 細気管支炎 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 医療機器関連感染 | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| 憩室炎 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 感染性小腸結腸炎 | 2 (0.9%) | 2 (0.9%) | 0 | 0 | 2 (0.5%) |
| 丹毒 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 真菌感染 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚真菌感染 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 真菌性性器感染 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| ヘルペスウイルス感染 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 麦粒腫 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 爪真菌症 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| レンサ球菌性咽頭炎 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| ニューモシスチス・イロベチイ肺炎 | 2 (0.9%) | 2 (0.9%) | 0 | 0 | 2 (0.5%) |
| 細菌性肺炎 | 2 (0.9%) | 2 (0.9%) | 0 | 0 | 2 (0.5%) |
| 膿疱性皮疹 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 敗血症性ショック | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 1 (0.7%) | 2 (0.5%) |
| ブドウ球菌性菌血症 | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| 歯膿瘍 | 1 (0.4%) | 0 | 1 (0.7%) | 1 (0.7%) | 2 (0.5%) |
| 細菌性尿路感染 | 0 | 0 | 2 (1.4%) | 1 (0.7%) | 2 (0.5%) |
| 尿路性敗血症 | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 1 (0.7%) | 2 (0.5%) |
| 外陰部腟カンジダ症 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 創傷感染 | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 0 | 2 (0.5%) |
| 腹部膿瘍 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 四肢膿瘍 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ダニ皮膚炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 膿疱性ざ瘡 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 肛門膿瘍 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 肛門カンジダ症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 虫垂炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 穿孔性虫垂炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 異型肺炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 細菌尿 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| カンジダ性亀頭炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 胆道感染 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| ブラストシスティス感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 体部白癬 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房蜂巣炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| カンピロバクター胃腸炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| カンピロバクター感染 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| カンジダ感染 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 眼窩蜂巣炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 感染性胆嚢炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性副鼻腔炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| シトロバクター感染 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 涙嚢炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性脳炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 精巣上体炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 喉頭蓋炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 細菌性眼感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 真菌血症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘリコバクター胃潰瘍 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 消化管感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性消化管感染 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 性器カンジダ症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 血腫感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘモフィルス感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| Ｂ型肝炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| ヒストプラスマ症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 埋込み部位感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 切開部位感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| クレブシエラ感染 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 口唇感染 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 細菌性下気道感染 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 肺感染 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| ライム病 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 乳腺炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 水疱性鼓膜炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼帯状疱疹 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 口腔真菌感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳頭腫ウイルス感染 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| クリプトコッカス性肺炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| クレブシエラ菌性肺炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 処置後感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 肺結核 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 腎盂腎炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 膿皮症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| レンサ球菌性膿皮症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 狂犬病 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 直腸膿瘍 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性気道感染 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 軟部組織感染 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| ブドウ球菌皮膚感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| レンサ球菌感染 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 皮下組織膿瘍 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 足部白癬 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 扁桃炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 気管炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 真菌性尿路感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| シュードモナス性尿路感染 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 胃腸障害 | 167 (72.3%) | 30 (13.0%) | 88 (63.3%) | 9 (6.5%) | 255 (68.9%) |
| 下痢 | 97 (42.0%) | 11 (4.8%) | 49 (35.3%) | 2 (1.4%) | 146 (39.5%) |
| 悪心 | 59 (25.5%) | 1 (0.4%) | 21 (15.1%) | 0 | 80 (21.6%) |
| 嘔吐 | 47 (20.3%) | 1 (0.4%) | 15 (10.8%) | 0 | 62 (16.8%) |
| 便秘 | 40 (17.3%) | 0 | 17 (12.2%) | 0 | 57 (15.4%) |
| 腹痛 | 24 (10.4%) | 8 (3.5%) | 18 (12.9%) | 5 (3.6%) | 42 (11.4%) |
| 口内炎 | 18 (7.8%) | 3 (1.3%) | 13 (9.4%) | 0 | 31 (8.4%) |
| 消化不良 | 14 (6.1%) | 0 | 14 (10.1%) | 0 | 28 (7.6%) |
| 上腹部痛 | 9 (3.9%) | 0 | 7 (5.0%) | 1 (0.7%) | 16 (4.3%) |
| 腹部膨満 | 8 (3.5%) | 0 | 6 (4.3%) | 0 | 14 (3.8%) |
| 口内乾燥 | 7 (3.0%) | 0 | 7 (5.0%) | 0 | 14 (3.8%) |
| 胃食道逆流性疾患 | 8 (3.5%) | 0 | 5 (3.6%) | 0 | 13 (3.5%) |
| 嚥下障害 | 7 (3.0%) | 2 (0.9%) | 2 (1.4%) | 0 | 9 (2.4%) |
| 腹部不快感 | 3 (1.3%) | 0 | 5 (3.6%) | 0 | 8 (2.2%) |
| 口腔内痛 | 6 (2.6%) | 1 (0.4%) | 2 (1.4%) | 0 | 8 (2.2%) |
| 口腔内潰瘍形成 | 4 (1.7%) | 0 | 3 (2.2%) | 0 | 7 (1.9%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 放屁 | 5 (2.2%) | 0 | 1 (0.7%) | 0 | 6 (1.6%) |
| 胃炎 | 6 (2.6%) | 0 | 0 | 0 | 6 (1.6%) |
| 心窩部不快感 | 4 (1.7%) | 0 | 1 (0.7%) | 0 | 5 (1.4%) |
| 舌痛 | 4 (1.7%) | 0 | 1 (0.7%) | 0 | 5 (1.4%) |
| 痔核 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| アフタ性口内炎 | 1 (0.4%) | 1 (0.4%) | 2 (1.4%) | 0 | 3 (0.8%) |
| おくび | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| イレウス | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 直腸出血 | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 舌潰瘍 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 下腹部痛 | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 0 | 2 (0.5%) |
| 齲歯 | 1 (0.4%) | 0 | 1 (0.7%) | 1 (0.7%) | 2 (0.5%) |
| 軟便 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 食中毒 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 排便回数増加 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 胃潰瘍 | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 0 | 2 (0.5%) |
| 歯肉出血 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 歯肉浮腫 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 吐血 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 麻痺性イレウス | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 1 (0.7%) | 2 (0.5%) |
| 臍径ヘルニア | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 口唇潰瘍 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 下部消化管出血 | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 0 | 2 (0.5%) |
| 口腔内出血 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 歯周病 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 肛門周囲痛 | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| 直腸炎 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 直腸裂 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 小腸閉塞 | 2 (0.9%) | 2 (0.9%) | 0 | 0 | 2 (0.5%) |
| 歯痛 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 裂肛 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 肛門直腸障害 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 萎縮性舌炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| バレット食道 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 口唇炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 大腸炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 歯不快感 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 血性下痢 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 十二指腸狭窄 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 十二指腸潰瘍 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 十二指腸炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 十二指腸胃逆流 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 便失禁 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 糞塊 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 胃前庭部毛細血管拡張症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 出血性胃炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 歯肉痛 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 血便排泄 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 痔出血 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 過敏性腸症候群 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 口唇水疱 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇びらん | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇腫脹 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 弛緩歯 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| メレナ | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 嚥下痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 口蓋障害 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 慢性膵炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 舌突出 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 直腸潰瘍 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 唾液腺結石 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 変色歯 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 歯の障害 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯の脱落 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 一般・全身障害および投与部位の状態 | 159 (68.8%) | 28 (12.1%) | 80 (57.6%) | 10 (7.2%) | 239 (64.6%) |
| 疲労 | 81 (35.1%) | 12 (5.2%) | 48 (34.5%) | 4 (2.9%) | 129 (34.9%) |
| 末梢性浮腫 | 58 (25.1%) | 6 (2.6%) | 16 (11.5%) | 0 | 74 (20.0%) |
| 発熱 | 37 (16.0%) | 3 (1.3%) | 31 (22.3%) | 0 | 68 (18.4%) |
| 無力症 | 23 (10.0%) | 3 (1.3%) | 9 (6.5%) | 2 (1.4%) | 32 (8.6%) |
| 悪寒 | 11 (4.8%) | 0 | 7 (5.0%) | 0 | 18 (4.9%) |
| 胸痛 | 9 (3.9%) | 0 | 6 (4.3%) | 0 | 15 (4.1%) |
| 末梢腫脹 | 13 (5.6%) | 1 (0.4%) | 2 (1.4%) | 0 | 15 (4.1%) |
| インフルエンザ様疾患 | 8 (3.5%) | 0 | 6 (4.3%) | 0 | 14 (3.8%) |
| 疼痛 | 4 (1.7%) | 0 | 7 (5.0%) | 1 (0.7%) | 11 (3.0%) |
| 非心臓性胸痛 | 7 (3.0%) | 1 (0.4%) | 1 (0.7%) | 1 (0.7%) | 8 (2.2%) |
| 粘膜の炎症 | 5 (2.2%) | 1 (0.4%) | 1 (0.7%) | 0 | 6 (1.6%) |
| 全身健康状態低下 | 3 (1.3%) | 2 (0.9%) | 2 (1.4%) | 0 | 5 (1.4%) |
| 倦怠感 | 3 (1.3%) | 0 | 2 (1.4%) | 0 | 5 (1.4%) |
| 局所腫脹 | 4 (1.7%) | 1 (0.4%) | 0 | 0 | 4 (1.1%) |
| 多臓器不全 | 1 (0.4%) | 1 (0.4%) | 3 (2.2%) | 3 (2.2%) | 4 (1.1%) |
| 胸部不快感 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 歩行障害 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 全身性浮腫 | 3 (1.3%) | 1 (0.4%) | 0 | 0 | 3 (0.8%) |
| 注射部位内出血 | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 乾燥症 | 2 (0.9%) | 1 (0.4%) | 1 (0.7%) | 0 | 3 (0.8%) |
| 腋窩痛 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 早期満腹 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 重力性浮腫 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 低体温 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 炎症 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 浮腫 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 活動状態低下 | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 0 | 2 (0.5%) |
| カテーテル留置部位関連反応 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 死亡 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 医療機器リーク | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 顔面浮腫 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 異常感 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 冷感 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 熱感 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 治癒不良 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 硬結 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 注入部位血管外漏出 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 注射部位紅斑 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位漏出 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位出血 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位疼痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位反応 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 先行疾患の改善 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 温度変化不耐症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 評価不能の事象 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸器、胸郭および縦隔障害 | 137 (59.3%) | 29 (12.6%) | 63 (45.3%) | 6 (4.3%) | 200 (54.1%) |
| 咳嗽 | 51 (22.1%) | 0 | 30 (21.6%) | 0 | 81 (21.9%) |
| 呼吸困難 | 57 (24.7%) | 12 (5.2%) | 12 (8.6%) | 0 | 69 (18.6%) |
| 鼻出血 | 22 (9.5%) | 1 (0.4%) | 10 (7.2%) | 0 | 32 (8.6%) |
| 口腔咽頭痛 | 17 (7.4%) | 0 | 12 (8.6%) | 0 | 29 (7.8%) |
| 胸水 | 20 (8.7%) | 6 (2.6%) | 3 (2.2%) | 1 (0.7%) | 23 (6.2%) |
| 湿性咳嗽 | 10 (4.3%) | 0 | 5 (3.6%) | 0 | 15 (4.1%) |
| 鼻閉 | 10 (4.3%) | 0 | 3 (2.2%) | 0 | 13 (3.5%) |
| 呼吸不全 | 9 (3.9%) | 9 (3.9%) | 1 (0.7%) | 1 (0.7%) | 10 (2.7%) |
| 鼻漏 | 5 (2.2%) | 0 | 4 (2.9%) | 0 | 9 (2.4%) |
| 発声障害 | 6 (2.6%) | 0 | 2 (1.4%) | 0 | 8 (2.2%) |
| 慢性閉塞性肺疾患 | 5 (2.2%) | 3 (1.3%) | 1 (0.7%) | 1 (0.7%) | 6 (1.6%) |
| アレルギー性鼻炎 | 1 (0.4%) | 0 | 5 (3.6%) | 0 | 6 (1.6%) |
| 副鼻腔うっ血 | 3 (1.3%) | 0 | 3 (2.2%) | 0 | 6 (1.6%) |
| 上気道うっ血 | 3 (1.3%) | 0 | 3 (2.2%) | 0 | 6 (1.6%) |
| 低酸素症 | 3 (1.3%) | 3 (1.3%) | 2 (1.4%) | 1 (0.7%) | 5 (1.4%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| しゃっくり | 4 (1.7%) | 0 | 0 | 0 | 4 (1.1%) |
| 気胸 | 4 (1.7%) | 2 (0.9%) | 0 | 0 | 4 (1.1%) |
| 喀血 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 鼻部不快感 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 肺水腫 | 2 (0.9%) | 0 | 1 (0.7%) | 1 (0.7%) | 3 (0.8%) |
| ラ音 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 喘鳴 | 1 (0.4%) | 0 | 2 (1.4%) | 0 | 3 (0.8%) |
| 無気肺 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 労作性呼吸困難 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 肺硬化 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 肺浸潤 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 鼻の炎症 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 肺塞栓症 | 1 (0.4%) | 0 | 1 (0.7%) | 1 (0.7%) | 2 (0.5%) |
| 気道うっ血 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 急性肺水腫 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 喘息 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 気管支反応性亢進 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 気管支分泌物貯留 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 気管支拡張症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 慢性気管支炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 肺気腫 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 上気道分泌増加 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 鼻乾燥 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 鼻潰瘍 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 副鼻腔不快感 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 副鼻腔分泌過多 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 咽頭紅斑 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸膜炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 胸膜痛 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 肺腫瘤 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸性アシドーシス | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 呼吸窮迫 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 拘束性肺疾患 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 副鼻腔障害 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| くしゃみ | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 頻呼吸 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 扁桃肥大 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 上気道咳症候群 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚および皮下組織障害 | 123 (53.2%) | 8 (3.5%) | 71 (51.1%) | 2 (1.4%) | 194 (52.4%) |
| 発疹 | 36 (15.6%) | 2 (0.9%) | 21 (15.1%) | 2 (1.4%) | 57 (15.4%) |
| そう痒症 | 19 (8.2%) | 0 | 9 (6.5%) | 0 | 28 (7.6%) |
| 点状出血 | 12 (5.2%) | 0 | 10 (7.2%) | 0 | 22 (5.9%) |
| 皮膚病変 | 11 (4.8%) | 0 | 9 (6.5%) | 0 | 20 (5.4%) |
| 斑状丘疹状皮疹 | 9 (3.9%) | 2 (0.9%) | 7 (5.0%) | 0 | 16 (4.3%) |
| 皮膚乾燥 | 9 (3.9%) | 0 | 5 (3.6%) | 0 | 14 (3.8%) |
| 斑状出血 | 9 (3.9%) | 0 | 4 (2.9%) | 0 | 13 (3.5%) |
| 紅斑 | 9 (3.9%) | 0 | 2 (1.4%) | 0 | 11 (3.0%) |
| 寝汗 | 7 (3.0%) | 0 | 4 (2.9%) | 0 | 11 (3.0%) |
| 脱毛症 | 8 (3.5%) | 0 | 2 (1.4%) | 0 | 10 (2.7%) |
| ざ瘡様皮膚炎 | 7 (3.0%) | 0 | 1 (0.7%) | 0 | 8 (2.2%) |
| 紫斑 | 4 (1.7%) | 2 (0.9%) | 3 (2.2%) | 0 | 7 (1.9%) |
| 多汗症 | 1 (0.4%) | 0 | 5 (3.6%) | 0 | 6 (1.6%) |
| 皮膚亀裂 | 3 (1.3%) | 0 | 3 (2.2%) | 0 | 6 (1.6%) |
| 嵌入爪 | 0 | 0 | 5 (3.6%) | 0 | 5 (1.4%) |
| 爪破損 | 4 (1.7%) | 0 | 1 (0.7%) | 0 | 5 (1.4%) |
| 蕁麻疹 | 2 (0.9%) | 0 | 3 (2.2%) | 0 | 5 (1.4%) |
| 水疱 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| 全身性そう痒症 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| 斑状皮疹 | 2 (0.9%) | 1 (0.4%) | 2 (1.4%) | 0 | 4 (1.1%) |
| 皮膚腫瘤 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| 皮膚潰瘍 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| ざ瘡 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 褥瘡性潰瘍 | 3 (1.3%) | 1 (0.4%) | 0 | 0 | 3 (0.8%) |
| 湿疹 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 紅斑性皮疹 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 皮膚色素過剰 | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 皮膚嚢腫 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 接触性皮膚炎 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 皮下出血 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 間擦疹 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 皮膚疼痛 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 全身性皮疹 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 丘疹性皮疹 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| そう痒性皮疹 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 皮膚変色 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 毛細血管炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| アレルギー性皮膚炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 水疱性皮膚炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮脂欠乏性湿疹 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 貨幣状湿疹 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 過敏性血管炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床出血 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床障害 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床の炎症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪の不快感 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪の障害 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪ジストロフィー | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪線状隆起 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪甲脱落症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 手掌・足底発赤知覚不全症候群 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 脂肪織炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 色素沈着障害 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 毛孔性皮疹 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 皮膚色素減少 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 皮膚刺激 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 皮膚腫脹 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 乾皮症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 筋骨格系および結合組織障害 | 111 (48.1%) | 13 (5.6%) | 62 (44.6%) | 7 (5.0%) | 173 (46.8%) |
| 筋痙縮 | 46 (19.9%) | 0 | 21 (15.1%) | 0 | 67 (18.1%) |
| 背部痛 | 29 (12.6%) | 4 (1.7%) | 15 (10.8%) | 2 (1.4%) | 44 (11.9%) |
| 関節痛 | 22 (9.5%) | 1 (0.4%) | 16 (11.5%) | 1 (0.7%) | 38 (10.3%) |
| 筋肉痛 | 23 (10.0%) | 1 (0.4%) | 9 (6.5%) | 0 | 32 (8.6%) |
| 四肢痛 | 19 (8.2%) | 2 (0.9%) | 9 (6.5%) | 0 | 28 (7.6%) |
| 筋骨格痛 | 13 (5.6%) | 0 | 4 (2.9%) | 0 | 17 (4.6%) |
| 筋力低下 | 8 (3.5%) | 1 (0.4%) | 5 (3.6%) | 2 (1.4%) | 13 (3.5%) |
| 側腹部痛 | 4 (1.7%) | 1 (0.4%) | 4 (2.9%) | 1 (0.7%) | 8 (2.2%) |
| 頚部痛 | 4 (1.7%) | 0 | 2 (1.4%) | 0 | 6 (1.6%) |
| 変形性関節症 | 4 (1.7%) | 2 (0.9%) | 1 (0.7%) | 0 | 5 (1.4%) |
| 肩径部痛 | 3 (1.3%) | 1 (0.4%) | 1 (0.7%) | 0 | 4 (1.1%) |
| 四肢不快感 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| 筋骨格硬直 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 骨痛 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 関節硬直 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 関節腫脹 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 運動性低下 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 筋骨格系胸痛 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| ミオパチー | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| 軟部組織障害 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 関節炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 滑液包炎 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 外骨腫 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 痛風性関節炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 椎間板変性症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 椎間板突出 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 関節拘縮 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 関節滲出液 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 関節ロック | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋緊張 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋攣縮 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 筋骨格不快感 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 頚部腫瘤 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 骨壊死 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 骨粗鬆症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 顎痛 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 横紋筋融解症 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 滑液嚢腫 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 腱痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 椎間孔狭窄 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 血液およびリンパ系障害 | 109 (47.2%) | 73 (31.6%) | 60 (43.2%) | 36 (25.9%) | 169 (45.7%) |
| 血小板減少症 | 50 (21.6%) | 30 (13.0%) | 24 (17.3%) | 11 (7.9%) | 74 (20.0%) |
| 好中球減少症 | 45 (19.5%) | 40 (17.3%) | 25 (18.0%) | 21 (15.1%) | 70 (18.9%) |
| 貧血 | 44 (19.0%) | 23 (10.0%) | 19 (13.7%) | 7 (5.0%) | 63 (17.0%) |
| 発熱性好中球減少症 | 7 (3.0%) | 7 (3.0%) | 6 (4.3%) | 6 (4.3%) | 13 (3.5%) |
| 白血球減少症 | 7 (3.0%) | 2 (0.9%) | 6 (4.3%) | 4 (2.9%) | 13 (3.5%) |
| 白血球増加症 | 4 (1.7%) | 1 (0.4%) | 3 (2.2%) | 2 (1.4%) | 7 (1.9%) |
| 内出血発生の増加傾向 | 3 (1.3%) | 0 | 2 (1.4%) | 0 | 5 (1.4%) |
| リンパ球減少症 | 3 (1.3%) | 0 | 2 (1.4%) | 0 | 5 (1.4%) |
| リンパ球増加症 | 1 (0.4%) | 1 (0.4%) | 3 (2.2%) | 2 (1.4%) | 4 (1.1%) |
| リンパ節痛 | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| リンパ節症 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 脾腫 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 骨髄機能不全 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 凝血異常 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 溶血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 鉄欠乏性貧血 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 白血球停滞症候群 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 汎血球減少症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 後腹膜リンパ節腫脹 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 脾臓出血 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 脾臓梗塞 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 血小板増加症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 代謝および栄養障害 | 104 (45.0%) | 39 (16.9%) | 46 (33.1%) | 13 (9.4%) | 150 (40.5%) |
| 食欲減退 | 48 (20.8%) | 3 (1.3%) | 14 (10.1%) | 0 | 62 (16.8%) |
| 低カリウム血症 | 23 (10.0%) | 13 (5.6%) | 11 (7.9%) | 2 (1.4%) | 34 (9.2%) |
| 高尿酸血症 | 16 (6.9%) | 8 (3.5%) | 9 (6.5%) | 2 (1.4%) | 25 (6.8%) |
| 脱水 | 17 (7.4%) | 7 (3.0%) | 5 (3.6%) | 0 | 22 (5.9%) |
| 低マグネシウム血症 | 11 (4.8%) | 0 | 10 (7.2%) | 1 (0.7%) | 21 (5.7%) |
| 高カリウム血症 | 8 (3.5%) | 2 (0.9%) | 5 (3.6%) | 3 (2.2%) | 13 (3.5%) |
| 低ナトリウム血症 | 10 (4.3%) | 6 (2.6%) | 2 (1.4%) | 2 (1.4%) | 12 (3.2%) |
| 低アルブミン血症 | 10 (4.3%) | 4 (1.7%) | 1 (0.7%) | 0 | 11 (3.0%) |
| 高血糖 | 7 (3.0%) | 1 (0.4%) | 2 (1.4%) | 1 (0.7%) | 9 (2.4%) |
| 低カルシウム血症 | 3 (1.3%) | 0 | 3 (2.2%) | 0 | 6 (1.6%) |
| 低血糖症 | 4 (1.7%) | 0 | 0 | 0 | 4 (1.1%) |
| 低リン酸血症 | 2 (0.9%) | 2 (0.9%) | 2 (1.4%) | 2 (1.4%) | 4 (1.1%) |
| 水分過負荷 | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 痛風 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 酵素異常 | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| 高コレステロール血症 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 高ナトリウム血症 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 高リン酸塩血症 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 過小食 | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 0 | 2 (0.5%) |
| 乳酸アシドーシス | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| アルコール不耐性 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 悪液質 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 糖尿病 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 糖尿病性ケトアシドーシス | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 高アルブミン血症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 高アンモニア血症 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 低蛋白血症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 代謝性アシドーシス | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 腫瘍崩壊症候群 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| ２型糖尿病 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 神経系障害 | 84 (36.4%) | 6 (2.6%) | 37 (26.6%) | 3 (2.2%) | 121 (32.7%) |
| 頭痛 | 22 (9.5%) | 0 | 15 (10.8%) | 0 | 37 (10.0%) |
| 浮動性めまい | 18 (7.8%) | 0 | 8 (5.8%) | 0 | 26 (7.0%) |
| 末梢性感覚ニューロパチー | 6 (2.6%) | 1 (0.4%) | 8 (5.8%) | 0 | 14 (3.8%) |
| 体位性めまい | 9 (3.9%) | 0 | 1 (0.7%) | 0 | 10 (2.7%) |
| 錯感覚 | 5 (2.2%) | 0 | 3 (2.2%) | 0 | 8 (2.2%) |
| 記憶障害 | 6 (2.6%) | 0 | 1 (0.7%) | 0 | 7 (1.9%) |
| 末梢性ニューロパチー | 6 (2.6%) | 0 | 1 (0.7%) | 0 | 7 (1.9%) |
| 振戦 | 4 (1.7%) | 0 | 2 (1.4%) | 0 | 6 (1.6%) |
| 感覚鈍麻 | 1 (0.4%) | 0 | 4 (2.9%) | 1 (0.7%) | 5 (1.4%) |
| 健忘 | 4 (1.7%) | 0 | 0 | 0 | 4 (1.1%) |
| 傾眠 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| 失神 | 2 (0.9%) | 2 (0.9%) | 2 (1.4%) | 2 (1.4%) | 4 (1.1%) |
| 平衡障害 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 構語障害 | 3 (1.3%) | 2 (0.9%) | 0 | 0 | 3 (0.8%) |
| 味覚異常 | 1 (0.4%) | 0 | 2 (1.4%) | 0 | 3 (0.8%) |
| 嗜眠 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 多発ニューロパチー | 3 (1.3%) | 1 (0.4%) | 0 | 0 | 3 (0.8%) |
| 認知症 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 頭蓋内出血 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 過眠症 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 神経痛 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 失神寸前の状態 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 下肢静止不能症候群 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 一過性脳虚血発作 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 灼熱足症候群 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 手根管症候群 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 大脳萎縮 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 脳血管発作 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 労作性めまい | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 脳症 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| てんかん | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 顔面部神経痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 顔面不全麻痺 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 頭部不快感 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 腰髄神経根障害 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 片頭痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 前兆を伴う片頭痛 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 筋痙直 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ミオクローヌス | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼振 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 腓骨神経麻痺 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘルペス後神経痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 坐骨神経痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 感覚障害 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 会話障害 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 緊張性頭痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 一過性全健忘 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 血管性脳症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 臨床検査 | 72 (31.2%) | 26 (11.3%) | 40 (28.8%) | 9 (6.5%) | 112 (30.3%) |
| 血中クレアチニン増加 | 21 (9.1%) | 0 | 10 (7.2%) | 0 | 31 (8.4%) |
| 血小板数減少 | 8 (3.5%) | 1 (0.4%) | 6 (4.3%) | 1 (0.7%) | 14 (3.8%) |
| 体重減少 | 10 (4.3%) | 0 | 2 (1.4%) | 0 | 12 (3.2%) |
| 血中アルカリホスファターゼ増加 | 9 (3.9%) | 2 (0.9%) | 2 (1.4%) | 0 | 11 (3.0%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 7 (3.0%) | 1 (0.4%) | 3 (2.2%) | 0 | 10 (2.7%) |
| 血中ビリルビン増加 | 6 (2.6%) | 1 (0.4%) | 4 (2.9%) | 1 (0.7%) | 10 (2.7%) |
| 好中球数減少 | 6 (2.6%) | 5 (2.2%) | 3 (2.2%) | 3 (2.2%) | 9 (2.4%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| アラニンアミノトランスフェラーゼ増加 | 6 (2.6%) | 1 (0.4%) | 1 (0.7%) | 0 | 7 (1.9%) |
| 血中尿酸増加 | 4 (1.7%) | 2 (0.9%) | 3 (2.2%) | 1 (0.7%) | 7 (1.9%) |
| リンパ球数増加 | 5 (2.2%) | 3 (1.3%) | 1 (0.7%) | 1 (0.7%) | 6 (1.6%) |
| 体重増加 | 0 | 0 | 6 (4.3%) | 0 | 6 (1.6%) |
| 活性化部分トロンボプラスチン時間延長 | 3 (1.3%) | 1 (0.4%) | 2 (1.4%) | 0 | 5 (1.4%) |
| 血中乳酸脱水素酵素増加 | 3 (1.3%) | 0 | 2 (1.4%) | 0 | 5 (1.4%) |
| 白血球数減少 | 4 (1.7%) | 4 (1.7%) | 1 (0.7%) | 1 (0.7%) | 5 (1.4%) |
| 血中免疫グロブリンG減少 | 0 | 0 | 3 (2.2%) | 0 | 3 (0.8%) |
| 国際標準比増加 | 3 (1.3%) | 3 (1.3%) | 0 | 0 | 3 (0.8%) |
| 白血球数増加 | 2 (0.9%) | 0 | 1 (0.7%) | 1 (0.7%) | 3 (0.8%) |
| 血中ブドウ糖増加 | 2 (0.9%) | 2 (0.9%) | 0 | 0 | 2 (0.5%) |
| 血中免疫グロブリンM減少 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 血圧上昇 | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 1 (0.7%) | 2 (0.5%) |
| Ｃ－反応性蛋白増加 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 心雑音 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| γ－グルタミルトランスフェラーゼ増加 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 糸球体濾過率減少 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| ヘモグロビン減少 | 0 | 0 | 2 (1.4%) | 2 (1.4%) | 2 (0.5%) |
| 免疫グロブリン減少 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| リンパ球数減少 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| トランスアミナーゼ上昇 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| アミラーゼ増加 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| アスペルギルス検査陽性 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 血中アルブミン減少 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 血中重炭酸塩増加 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中ビリルビン異常 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 血中クロール減少 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 血中コレステロール増加 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中クレアチン増加 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 血中免疫グロブリンA減少 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 血中鉄減少 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中マグネシウム減少 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 血中リン減少 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中カリウム減少 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 呼吸音異常 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 二酸化炭素減少 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸部コンピュータ断層撮影異常 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 駆出率減少 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| グリコヘモグロビン増加 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘモフィルス検査陽性 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 心拍数増加 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 心拍数不整 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 肝酵素上昇 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 深吸気量減少 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 肝機能検査異常 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 黄斑部反射異常 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 平均赤血球容積増加 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 血小板凝集異常 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 尿量減少 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 超低比重リポ蛋白増加 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 肺活量異常 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 傷害、中毒および処置合併症 | 69 (29.9%) | 8 (3.5%) | 32 (23.0%) | 5 (3.6%) | 101 (27.3%) |
| 挫傷 | 29 (12.6%) | 0 | 17 (12.2%) | 0 | 46 (12.4%) |
| 転倒 | 16 (6.9%) | 3 (1.3%) | 1 (0.7%) | 1 (0.7%) | 17 (4.6%) |
| 節足動物咬傷 | 1 (0.4%) | 0 | 5 (3.6%) | 0 | 6 (1.6%) |
| 処置による疼痛 | 5 (2.2%) | 0 | 1 (0.7%) | 0 | 6 (1.6%) |
| 硬膜下血腫 | 5 (2.2%) | 2 (0.9%) | 1 (0.7%) | 1 (0.7%) | 6 (1.6%) |
| 外傷性血腫 | 6 (2.6%) | 0 | 0 | 0 | 6 (1.6%) |
| 裂傷 | 4 (1.7%) | 0 | 0 | 0 | 4 (1.1%) |
| 皮膚擦過傷 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| サンバーン | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 創傷 | 3 (1.3%) | 0 | 1 (0.7%) | 0 | 4 (1.1%) |
| 動物咬傷 | 1 (0.4%) | 0 | 2 (1.4%) | 1 (0.7%) | 3 (0.8%) |
| 頭部損傷 | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 靭帯捻挫 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 腰椎骨折 | 2 (0.9%) | 1 (0.4%) | 1 (0.7%) | 0 | 3 (0.8%) |
| 処置後出血 | 3 (1.3%) | 2 (0.9%) | 0 | 0 | 3 (0.8%) |
| 骨挫傷 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 擦過傷 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 顔面骨骨折 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 四肢損傷 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 眼窩周囲挫傷 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 肋骨骨折 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚創傷 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 脊椎圧迫骨折 | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| 脾破裂 | 0 | 0 | 2 (1.4%) | 2 (1.4%) | 2 (0.5%) |
| 熱傷 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 動物による引っかき傷 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 足関節部骨折 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 第２度熱傷 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 眼挫傷 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼外傷 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 足骨折 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 眼内異物 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 外傷性血尿 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 関節損傷 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 過量投与 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 処置後便秘 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 処置後血尿 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 処置後腫脹 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 外傷後疼痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢血腫 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮下血腫 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 脛骨骨折 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 歯牙破折 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 術後尿閉 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 創合併症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 眼障害 | 53 (22.9%) | 3 (1.3%) | 29 (20.9%) | 2 (1.4%) | 82 (22.2%) |
| 眼乾燥 | 10 (4.3%) | 0 | 6 (4.3%) | 0 | 16 (4.3%) |
| 流涙増加 | 12 (5.2%) | 0 | 1 (0.7%) | 0 | 13 (3.5%) |
| 霧視 | 7 (3.0%) | 0 | 6 (4.3%) | 0 | 13 (3.5%) |
| 白内障 | 8 (3.5%) | 2 (0.9%) | 3 (2.2%) | 1 (0.7%) | 11 (3.0%) |
| 視力低下 | 3 (1.3%) | 0 | 3 (2.2%) | 0 | 6 (1.6%) |
| 眼窩周囲浮腫 | 4 (1.7%) | 1 (0.4%) | 1 (0.7%) | 0 | 5 (1.4%) |
| 結膜出血 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 眼痛 | 1 (0.4%) | 0 | 2 (1.4%) | 0 | 3 (0.8%) |
| 眼充血 | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 睫毛乱生 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 硝子体浮遊物 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 糖尿病網膜症 | 1 (0.4%) | 0 | 1 (0.7%) | 1 (0.7%) | 2 (0.5%) |
| 複視 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 眼出血 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 眼刺激 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 眼瞼下垂 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 羞明 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 眼瞼炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 片側失明 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 結膜充血 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 眼瞼内反 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 眼脂 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼の炎症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 眼そう痒症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 眼の異物感 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 緑内障 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 角膜炎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 黄斑変性 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| マイボーム腺機能不全 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼血管障害 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 開放隅角緑内障 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 動揺視 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 老視 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 網膜剥離 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 強膜出血 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 視力障害 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 硝子体出血 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 眼球乾燥症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 血管障害 | 55 (23.8%) | 19 (8.2%) | 26 (18.7%) | 7 (5.0%) | 81 (21.9%) |
| 高血圧 | 23 (10.0%) | 10 (4.3%) | 12 (8.6%) | 3 (2.2%) | 35 (9.5%) |
| 低血圧 | 15 (6.5%) | 5 (2.2%) | 6 (4.3%) | 0 | 21 (5.7%) |
| 血腫 | 8 (3.5%) | 0 | 4 (2.9%) | 0 | 12 (3.2%) |
| 深部静脈血栓症 | 6 (2.6%) | 2 (0.9%) | 1 (0.7%) | 0 | 7 (1.9%) |
| 潮紅 | 3 (1.3%) | 0 | 1 (0.7%) | 0 | 4 (1.1%) |
| 出血 | 0 | 0 | 4 (2.9%) | 3 (2.2%) | 4 (1.1%) |
| 起立性低血圧 | 3 (1.3%) | 1 (0.4%) | 0 | 0 | 3 (0.8%) |
| 静脈炎 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 血圧変動 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| リンパ浮腫 | 2 (0.9%) | 2 (0.9%) | 0 | 0 | 2 (0.5%) |
| 表在性血栓性静脈炎 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 大動脈硬化症 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 循環虚脱 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| ほてり | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 高血圧クリーゼ | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 末梢血管障害 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 末梢静脈疾患 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 静脈瘤 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 心臓障害 | 49 (21.2%) | 23 (10.0%) | 15 (10.8%) | 3 (2.2%) | 64 (17.3%) |
| 心房細動 | 23 (10.0%) | 14 (6.1%) | 5 (3.6%) | 3 (2.2%) | 28 (7.6%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 頻脈 | 7 (3.0%) | 0 | 2 (1.4%) | 0 | 9 (2.4%) |
| 洞性頻脈 | 2 (0.9%) | 0 | 5 (3.6%) | 0 | 7 (1.9%) |
| 徐脈 | 3 (1.3%) | 0 | 1 (0.7%) | 0 | 4 (1.1%) |
| 動悸 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| 心房粗動 | 3 (1.3%) | 1 (0.4%) | 0 | 0 | 3 (0.8%) |
| 洞性徐脈 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 上室性頻脈 | 3 (1.3%) | 1 (0.4%) | 0 | 0 | 3 (0.8%) |
| 不安定狭心症 | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| 心停止 | 2 (0.9%) | 2 (0.9%) | 0 | 0 | 2 (0.5%) |
| 心不全 | 2 (0.9%) | 2 (0.9%) | 0 | 0 | 2 (0.5%) |
| 心室性期外収縮 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 急性心筋梗塞 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 不整脈 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 冠動脈硬化症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 第一度房室ブロック | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| うっ血性心不全 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 心血管不全 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 変時性応答不全 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 冠動脈疾患 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 冠動脈閉塞 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| チアノーゼ | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 僧帽弁閉鎖不全症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 心筋梗塞 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 心嚢液貯留 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 心膜炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 洞不全症候群 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| ストレス心筋症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 頻脈性不整脈 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| トルサード　ド　ポアント | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 三尖弁疾患 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 心室性不整脈 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 心室性頻脈 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 精神障害 | 42 (18.2%) | 7 (3.0%) | 21 (15.1%) | 0 | 63 (17.0%) |
| 不眠症 | 17 (7.4%) | 0 | 9 (6.5%) | 0 | 26 (7.0%) |
| 不安 | 6 (2.6%) | 0 | 7 (5.0%) | 0 | 13 (3.5%) |
| 錯乱状態 | 11 (4.8%) | 4 (1.7%) | 1 (0.7%) | 0 | 12 (3.2%) |
| うつ病 | 10 (4.3%) | 1 (0.4%) | 2 (1.4%) | 0 | 12 (3.2%) |
| 激越 | 5 (2.2%) | 0 | 0 | 0 | 5 (1.4%) |
| 譫妄 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 希死念慮を有するうつ病 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 多幸気分 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 幻聴 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 幻視 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 易刺激性 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| リビドー減退 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 躁病 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 精神障害 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 精神状態変化 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 悪夢 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| パニック発作 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| パニック障害 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 腎および尿路障害 | 43 (18.6%) | 14 (6.1%) | 14 (10.1%) | 3 (2.2%) | 57 (15.4%) |
| 血尿 | 12 (5.2%) | 3 (1.3%) | 2 (1.4%) | 0 | 14 (3.8%) |
| 急性腎不全 | 12 (5.2%) | 6 (2.6%) | 0 | 0 | 12 (3.2%) |
| 排尿困難 | 7 (3.0%) | 0 | 1 (0.7%) | 0 | 8 (2.2%) |
| 腎不全 | 5 (2.2%) | 3 (1.3%) | 2 (1.4%) | 2 (1.4%) | 7 (1.9%) |
| 頻尿 | 5 (2.2%) | 0 | 1 (0.7%) | 0 | 6 (1.6%) |
| 水腎症 | 2 (0.9%) | 2 (0.9%) | 1 (0.7%) | 0 | 3 (0.8%) |
| 腎機能障害 | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 尿閉 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 尿路閉塞 | 2 (0.9%) | 1 (0.4%) | 1 (0.7%) | 0 | 3 (0.8%) |
| 腎結石症 | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 0 | 2 (0.5%) |
| 夜間頻尿 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 腎嚢胞 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性腎不全 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 尿失禁 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 高窒素血症 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 膀胱刺激症状 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 出血性膀胱炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 緊張性膀胱 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 失禁 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 尿意切迫 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 閉塞性尿路疾患 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 乏尿 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 腎仙痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 有痛性排尿困難 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 尿路痛 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 25 (10.8%) | 12 (5.2%) | 11 (7.9%) | 7 (5.0%) | 36 (9.7%) |
| マントル細胞リンパ腫 | 6 (2.6%) | 6 (2.6%) | 2 (1.4%) | 2 (1.4%) | 8 (2.2%) |
| 基底細胞癌 | 4 (1.7%) | 0 | 3 (2.2%) | 1 (0.7%) | 7 (1.9%) |
| 皮膚有棘細胞癌 | 5 (2.2%) | 0 | 0 | 0 | 5 (1.4%) |
| 膀胱移行上皮癌 | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| 前立腺癌 | 2 (0.9%) | 2 (0.9%) | 0 | 0 | 2 (0.5%) |
| 扁平上皮癌 | 2 (0.9%) | 1 (0.4%) | 0 | 0 | 2 (0.5%) |
| 急性骨髄性白血病 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 良性新生物 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 膀胱癌 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 肺腺癌 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 悪性胸水 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 口腔乳頭腫 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 唾液腺癌 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 皮膚癌 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 皮膚乳頭腫 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸腺腫 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 移行上皮癌 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 腫瘍フレア | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 耳および迷路障害 | 22 (9.5%) | 2 (0.9%) | 8 (5.8%) | 0 | 30 (8.1%) |
| 回転性めまい | 9 (3.9%) | 0 | 2 (1.4%) | 0 | 11 (3.0%) |
| 耳鳴 | 3 (1.3%) | 0 | 3 (2.2%) | 0 | 6 (1.6%) |
| 耳痛 | 3 (1.3%) | 0 | 2 (1.4%) | 0 | 5 (1.4%) |
| 聴力低下 | 4 (1.7%) | 1 (0.4%) | 0 | 0 | 4 (1.1%) |
| 耳垢栓塞 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 耳不快感 | 2 (0.9%) | 0 | 0 | 0 | 2 (0.5%) |
| 難聴 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 耳出血 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 聴覚過敏 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 老人性難聴 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 生殖系および乳房障害 | 14 (6.1%) | 5 (2.2%) | 12 (8.6%) | 2 (1.4%) | 26 (7.0%) |
| 良性前立腺肥大症 | 3 (1.3%) | 0 | 1 (0.7%) | 0 | 4 (1.1%) |
| 血精液症 | 2 (0.9%) | 0 | 2 (1.4%) | 0 | 4 (1.1%) |
| 性器浮腫 | 3 (1.3%) | 2 (0.9%) | 0 | 0 | 3 (0.8%) |
| 勃起不全 | 0 | 0 | 2 (1.4%) | 0 | 2 (0.5%) |
| 骨盤痛 | 0 | 0 | 2 (1.4%) | 1 (0.7%) | 2 (0.5%) |
| 腟出血 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 後天性包茎 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 乳房血腫 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房腫瘤 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房痛 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 性器発疹 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 陰茎痛 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 陰嚢腫瘤 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢浮腫 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 陰嚢痛 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 子宮腟脱 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 外陰腟痛 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 外陰腟そう痒症 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |

**TSFAE15A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=65 vs. <65) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 65 | | < 65 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 免疫系障害 | 13 (5.6%) | 0 | 6 (4.3%) | 0 | 19 (5.1%) |
| 低ｙグロブリン血症 | 3 (1.3%) | 0 | 2 (1.4%) | 0 | 5 (1.4%) |
| 節足動物咬傷アレルギー | 3 (1.3%) | 0 | 1 (0.7%) | 0 | 4 (1.1%) |
| 過敏症 | 2 (0.9%) | 0 | 1 (0.7%) | 0 | 3 (0.8%) |
| 季節性アレルギー | 3 (1.3%) | 0 | 0 | 0 | 3 (0.8%) |
| 薬物過敏症 | 1 (0.4%) | 0 | 1 (0.7%) | 0 | 2 (0.5%) |
| 造影剤アレルギー | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 食物アレルギー | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 肝胆道系障害 | 8 (3.5%) | 3 (1.3%) | 5 (3.6%) | 1 (0.7%) | 13 (3.5%) |
| 高ビリルビン血症 | 4 (1.7%) | 1 (0.4%) | 2 (1.4%) | 0 | 6 (1.6%) |
| 胆石症 | 1 (0.4%) | 1 (0.4%) | 2 (1.4%) | 0 | 3 (0.8%) |
| 胆管結石 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 胆管炎 | 0 | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.3%) |
| 肝不全 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 肝機能異常 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 中毒性肝炎 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.3%) |
| 陶器様胆嚢 | 1 (0.4%) | 0 | 0 | 0 | 1 (0.3%) |
| 内分泌障害 | 4 (1.7%) | 0 | 1 (0.7%) | 0 | 5 (1.4%) |
| 甲状腺機能低下症 | 4 (1.7%) | 0 | 1 (0.7%) | 0 | 5 (1.4%) |
| 先天性、家族性および遺伝性障害 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |
| 臍血腫 | 0 | 0 | 1 (0.7%) | 0 | 1 (0.3%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE15A.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae15a.sas] 15SEP2015, 14:12

参照元：5.3.5.3.1 ISS TSFAE15A

表 2.7.4-付録-48 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| Analysis set: safety | 160 | | 210 | | 370 |
| Subjects with any TEAE | 158 (98.8%) | 128 (80.0%) | 206 (98.1%) | 137 (65.2%) | 364 (98.4%) |
| System organ class | | | | | |
| Preferred term | | | | | |
| 感染症および寄生虫症 | 107 (66.9%) | 47 (29.4%) | 156 (74.3%) | 40 (19.0%) | 263 (71.1%) |
| 上気道感染 | 25 (15.6%) | 1 (0.6%) | 48 (22.9%) | 2 (1.0%) | 73 (19.7%) |
| 肺炎 | 26 (16.3%) | 20 (12.5%) | 18 (8.6%) | 13 (6.2%) | 44 (11.9%) |
| 副鼻腔炎 | 11 (6.9%) | 0 | 28 (13.3%) | 1 (0.5%) | 39 (10.5%) |
| 尿路感染 | 20 (12.5%) | 4 (2.5%) | 18 (8.6%) | 2 (1.0%) | 38 (10.3%) |
| 鼻咽頭炎 | 12 (7.5%) | 0 | 18 (8.6%) | 0 | 30 (8.1%) |
| 結膜炎 | 12 (7.5%) | 0 | 14 (6.7%) | 0 | 26 (7.0%) |
| 気管支炎 | 9 (5.6%) | 2 (1.3%) | 11 (5.2%) | 2 (1.0%) | 20 (5.4%) |
| 蜂巣炎 | 13 (8.1%) | 6 (3.8%) | 5 (2.4%) | 2 (1.0%) | 18 (4.9%) |
| 帯状疱疹 | 4 (2.5%) | 0 | 10 (4.8%) | 0 | 14 (3.8%) |
| 鼻炎 | 6 (3.8%) | 0 | 8 (3.8%) | 0 | 14 (3.8%) |
| 毛包炎 | 6 (3.8%) | 0 | 7 (3.3%) | 0 | 13 (3.5%) |
| 爪囲炎 | 4 (2.5%) | 0 | 9 (4.3%) | 0 | 13 (3.5%) |
| 下気道感染 | 3 (1.9%) | 2 (1.3%) | 9 (4.3%) | 3 (1.4%) | 12 (3.2%) |
| 皮膚感染 | 4 (2.5%) | 0 | 8 (3.8%) | 1 (0.5%) | 12 (3.2%) |
| 口腔ヘルペス | 3 (1.9%) | 0 | 8 (3.8%) | 0 | 11 (3.0%) |
| 気道感染 | 5 (3.1%) | 2 (1.3%) | 6 (2.9%) | 0 | 11 (3.0%) |
| 敗血症 | 6 (3.8%) | 6 (3.8%) | 5 (2.4%) | 5 (2.4%) | 11 (3.0%) |
| 胃腸炎 | 3 (1.9%) | 1 (0.6%) | 7 (3.3%) | 1 (0.5%) | 10 (2.7%) |
| 咽頭炎 | 5 (3.1%) | 1 (0.6%) | 2 (1.0%) | 0 | 7 (1.9%) |
| ウイルス感染 | 2 (1.3%) | 0 | 5 (2.4%) | 0 | 7 (1.9%) |
| 感染 | 4 (2.5%) | 1 (0.6%) | 2 (1.0%) | 1 (0.5%) | 6 (1.6%) |
| クロストリジウム・ディフィシレ大腸炎 | 3 (1.9%) | 1 (0.6%) | 2 (1.0%) | 2 (1.0%) | 5 (1.4%) |
| 眼感染 | 4 (2.5%) | 0 | 1 (0.5%) | 0 | 5 (1.4%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯肉炎 | 1 (0.6%) | 0 | 4 (1.9%) | 0 | 5 (1.4%) |
| 口腔カンジダ症 | 5 (3.1%) | 0 | 0 | 0 | 5 (1.4%) |
| クロストリジウム・ディフィシレ感染 | 2 (1.3%) | 0 | 2 (1.0%) | 1 (0.5%) | 4 (1.1%) |
| インフルエンザ | 3 (1.9%) | 0 | 1 (0.5%) | 0 | 4 (1.1%) |
| 限局性感染 | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| 中耳炎 | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| 歯周炎 | 1 (0.6%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 歯感染 | 0 | 0 | 4 (1.9%) | 0 | 4 (1.1%) |
| 菌血症 | 1 (0.6%) | 0 | 2 (1.0%) | 2 (1.0%) | 3 (0.8%) |
| 気管支肺炎 | 2 (1.3%) | 1 (0.6%) | 1 (0.5%) | 0 | 3 (0.8%) |
| 膀胱炎 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 耳感染 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| ウイルス性胃腸炎 | 1 (0.6%) | 0 | 2 (1.0%) | 1 (0.5%) | 3 (0.8%) |
| 単純ヘルペス | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 喉頭炎 | 3 (1.9%) | 1 (0.6%) | 0 | 0 | 3 (0.8%) |
| 爪感染 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 外耳炎 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| ブドウ球菌感染 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| ウイルス性上気道感染 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 急性副鼻腔炎 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 細気管支炎 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 医療機器関連感染 | 1 (0.6%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 憩室炎 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 感染性小腸結腸炎 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 丹毒 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 真菌感染 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 皮膚真菌感染 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 真菌性性器感染 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| ヘルペスウイルス感染 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 麦粒腫 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 爪真菌症 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| レンサ球菌性咽頭炎 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| ニューモシスチス・イロベチイ肺炎 | 2 (1.3%) | 2 (1.3%) | 0 | 0 | 2 (0.5%) |
| 細菌性肺炎 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 膿疱性皮疹 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 敗血症性ショック | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| ブドウ球菌性菌血症 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 歯膿瘍 | 1 (0.6%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 細菌性尿路感染 | 0 | 0 | 2 (1.0%) | 1 (0.5%) | 2 (0.5%) |
| 尿路性敗血症 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 外陰部腟カンジダ症 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 創傷感染 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 腹部膿瘍 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 四肢膿瘍 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| ダニ皮膚炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 膿疱性ざ瘡 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 肛門膿瘍 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 肛門カンジダ症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 虫垂炎 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 穿孔性虫垂炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 異型肺炎 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 細菌尿 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| カンジダ性亀頭炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 胆道感染 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| ブラストシスティス感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 体部白癬 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 乳房蜂巣炎 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| カンピロバクター胃腸炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| カンピロバクター感染 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| カンジダ感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼窩蜂巣炎 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 感染性胆嚢炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性副鼻腔炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| シトロバクター感染 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 涙嚢炎 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性脳炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 精巣上体炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 喉頭蓋炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 細菌性眼感染 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 真菌血症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘリコバクター胃潰瘍 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 消化管感染 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性消化管感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 性器カンジダ症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 血腫感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| ヘモフィルス感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| Ｂ型肝炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| ヒストプラスマ症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 埋込み部位感染 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 切開部位感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| クレブシエラ感染 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 口唇感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 細菌性下気道感染 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 肺感染 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| ライム病 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 乳腺炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 水疱性鼓膜炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪床感染 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼帯状疱疹 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 口腔真菌感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 乳頭腫ウイルス感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| クリプトコッカス性肺炎 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| クレブシエラ菌性肺炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 処置後感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 肺結核 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 腎盂腎炎 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 膿皮症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| レンサ球菌性膿皮症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 狂犬病 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 直腸膿瘍 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性気道感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 軟部組織感染 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| ブドウ球菌皮膚感染 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| レンサ球菌感染 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 皮下組織膿瘍 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 足部白癬 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 扁桃炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 気管炎 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 真菌性尿路感染 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| シュードモナス性尿路感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 胃腸障害 | 115 (71.9%) | 19 (11.9%) | 140 (66.7%) | 20 (9.5%) | 255 (68.9%) |
| 下痢 | 68 (42.5%) | 9 (5.6%) | 78 (37.1%) | 4 (1.9%) | 146 (39.5%) |
| 悪心 | 42 (26.3%) | 1 (0.6%) | 38 (18.1%) | 0 | 80 (21.6%) |
| 嘔吐 | 31 (19.4%) | 1 (0.6%) | 31 (14.8%) | 0 | 62 (16.8%) |
| 便秘 | 24 (15.0%) | 0 | 33 (15.7%) | 0 | 57 (15.4%) |
| 腹痛 | 16 (10.0%) | 5 (3.1%) | 26 (12.4%) | 8 (3.8%) | 42 (11.4%) |
| 口内炎 | 10 (6.3%) | 1 (0.6%) | 21 (10.0%) | 2 (1.0%) | 31 (8.4%) |
| 消化不良 | 11 (6.9%) | 0 | 17 (8.1%) | 0 | 28 (7.6%) |
| 上腹部痛 | 5 (3.1%) | 0 | 11 (5.2%) | 1 (0.5%) | 16 (4.3%) |
| 腹部膨満 | 6 (3.8%) | 0 | 8 (3.8%) | 0 | 14 (3.8%) |
| 口内乾燥 | 5 (3.1%) | 0 | 9 (4.3%) | 0 | 14 (3.8%) |
| 胃食道逆流性疾患 | 6 (3.8%) | 0 | 7 (3.3%) | 0 | 13 (3.5%) |
| 嚥下障害 | 5 (3.1%) | 2 (1.3%) | 4 (1.9%) | 0 | 9 (2.4%) |
| 腹部不快感 | 2 (1.3%) | 0 | 6 (2.9%) | 0 | 8 (2.2%) |
| 口腔内痛 | 6 (3.8%) | 1 (0.6%) | 2 (1.0%) | 0 | 8 (2.2%) |
| 口腔内潰瘍形成 | 3 (1.9%) | 0 | 4 (1.9%) | 0 | 7 (1.9%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 放屁 | 5 (3.1%) | 0 | 1 (0.5%) | 0 | 6 (1.6%) |
| 胃炎 | 4 (2.5%) | 0 | 2 (1.0%) | 0 | 6 (1.6%) |
| 心窩部不快感 | 1 (0.6%) | 0 | 4 (1.9%) | 0 | 5 (1.4%) |
| 舌痛 | 4 (2.5%) | 0 | 1 (0.5%) | 0 | 5 (1.4%) |
| 痔核 | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| アフタ性口内炎 | 0 | 0 | 3 (1.4%) | 1 (0.5%) | 3 (0.8%) |
| おくび | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| イレウス | 3 (1.9%) | 0 | 0 | 0 | 3 (0.8%) |
| 直腸出血 | 3 (1.9%) | 0 | 0 | 0 | 3 (0.8%) |
| 舌潰瘍 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 下腹部痛 | 0 | 0 | 2 (1.0%) | 1 (0.5%) | 2 (0.5%) |
| 齲歯 | 1 (0.6%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 軟便 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 食中毒 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 排便回数増加 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 胃潰瘍 | 0 | 0 | 2 (1.0%) | 1 (0.5%) | 2 (0.5%) |
| 歯肉出血 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 歯肉浮腫 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 吐血 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 麻痺性イレウス | 0 | 0 | 2 (1.0%) | 2 (1.0%) | 2 (0.5%) |
| 鼡径ヘルニア | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 口唇潰瘍 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 下部消化管出血 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 口腔内出血 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 歯周病 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 肛門周囲痛 | 2 (1.3%) | 1 (0.6%) | 0 | 0 | 2 (0.5%) |
| 直腸炎 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 直腸裂 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 小腸閉塞 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 歯痛 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 裂肛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 肛門直腸障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 萎縮性舌炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| バレット食道 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 口唇炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 大腸炎 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 歯不快感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血性下痢 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 十二指腸狭窄 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 十二指腸潰瘍 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 十二指腸炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 十二指腸胃逆流 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 便失禁 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 糞塊 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 胃前庭部毛細血管拡張症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 出血性胃炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 歯肉痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血便排泄 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 痔出血 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 過敏性腸症候群 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 口唇水疱 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇びらん | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 口唇腫脹 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 弛緩歯 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| メレナ | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 嚥下痛 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 口蓋障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 慢性膵炎 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 舌突出 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 直腸潰瘍 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 唾液腺結石 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 変色歯 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 歯の障害 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯の脱落 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 一般・全身障害および投与部位の状態 | 115 (71.9%) | 22 (13.8%) | 124 (59.0%) | 16 (7.6%) | 239 (64.6%) |
| 疲労 | 64 (40.0%) | 12 (7.5%) | 65 (31.0%) | 4 (1.9%) | 129 (34.9%) |
| 末梢性浮腫 | 46 (28.8%) | 5 (3.1%) | 28 (13.3%) | 1 (0.5%) | 74 (20.0%) |
| 発熱 | 22 (13.8%) | 2 (1.3%) | 46 (21.9%) | 1 (0.5%) | 68 (18.4%) |
| 無力症 | 17 (10.6%) | 2 (1.3%) | 15 (7.1%) | 3 (1.4%) | 32 (8.6%) |
| 悪寒 | 9 (5.6%) | 0 | 9 (4.3%) | 0 | 18 (4.9%) |
| 胸痛 | 8 (5.0%) | 0 | 7 (3.3%) | 0 | 15 (4.1%) |
| 末梢腫脹 | 12 (7.5%) | 1 (0.6%) | 3 (1.4%) | 0 | 15 (4.1%) |
| インフルエンザ様疾患 | 5 (3.1%) | 0 | 9 (4.3%) | 0 | 14 (3.8%) |
| 疼痛 | 4 (2.5%) | 0 | 7 (3.3%) | 1 (0.5%) | 11 (3.0%) |
| 非心臓性胸痛 | 5 (3.1%) | 0 | 3 (1.4%) | 2 (1.0%) | 8 (2.2%) |
| 粘膜の炎症 | 3 (1.9%) | 1 (0.6%) | 3 (1.4%) | 0 | 6 (1.6%) |
| 全身健康状態低下 | 2 (1.3%) | 1 (0.6%) | 3 (1.4%) | 1 (0.5%) | 5 (1.4%) |
| 倦怠感 | 2 (1.3%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 局所腫脹 | 3 (1.9%) | 1 (0.6%) | 1 (0.5%) | 0 | 4 (1.1%) |
| 多臓器不全 | 0 | 0 | 4 (1.9%) | 4 (1.9%) | 4 (1.1%) |
| 胸部不快感 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 歩行障害 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 全身性浮腫 | 3 (1.9%) | 1 (0.6%) | 0 | 0 | 3 (0.8%) |
| 注射部位内出血 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 乾燥症 | 0 | 0 | 3 (1.4%) | 1 (0.5%) | 3 (0.8%) |
| 腋窩痛 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 早期満腹 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 重力性浮腫 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 低体温 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 炎症 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 浮腫 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 活動状態低下 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 0 | 2 (0.5%) |
| カテーテル留置部位関連反応 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 死亡 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 医療機器リーク | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 顔面浮腫 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 異常感 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 冷感 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 熱感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 治癒不良 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 硬結 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 注入部位血管外漏出 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 注射部位紅斑 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 注射部位漏出 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 注射部位出血 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位疼痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 注射部位反応 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 先行疾患の改善 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 温度変化不耐症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 評価不能の事象 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 呼吸器、胸郭および縦隔障害 | 96 (60.0%) | 21 (13.1%) | 104 (49.5%) | 14 (6.7%) | 200 (54.1%) |
| 咳嗽 | 38 (23.8%) | 0 | 43 (20.5%) | 0 | 81 (21.9%) |
| 呼吸困難 | 39 (24.4%) | 9 (5.6%) | 30 (14.3%) | 3 (1.4%) | 69 (18.6%) |
| 鼻出血 | 16 (10.0%) | 1 (0.6%) | 16 (7.6%) | 0 | 32 (8.6%) |
| 口腔咽頭痛 | 15 (9.4%) | 0 | 14 (6.7%) | 0 | 29 (7.8%) |
| 胸水 | 15 (9.4%) | 4 (2.5%) | 8 (3.8%) | 3 (1.4%) | 23 (6.2%) |
| 湿性咳嗽 | 7 (4.4%) | 0 | 8 (3.8%) | 0 | 15 (4.1%) |
| 鼻閉 | 9 (5.6%) | 0 | 4 (1.9%) | 0 | 13 (3.5%) |
| 呼吸不全 | 8 (5.0%) | 8 (5.0%) | 2 (1.0%) | 2 (1.0%) | 10 (2.7%) |
| 鼻漏 | 3 (1.9%) | 0 | 6 (2.9%) | 0 | 9 (2.4%) |
| 発声障害 | 4 (2.5%) | 0 | 4 (1.9%) | 0 | 8 (2.2%) |
| 慢性閉塞性肺疾患 | 3 (1.9%) | 2 (1.3%) | 3 (1.4%) | 2 (1.0%) | 6 (1.6%) |
| アレルギー性鼻炎 | 1 (0.6%) | 0 | 5 (2.4%) | 0 | 6 (1.6%) |
| 副鼻腔うっ血 | 2 (1.3%) | 0 | 4 (1.9%) | 0 | 6 (1.6%) |
| 上気道うっ血 | 1 (0.6%) | 0 | 5 (2.4%) | 0 | 6 (1.6%) |
| 低酸素症 | 3 (1.9%) | 3 (1.9%) | 2 (1.0%) | 1 (0.5%) | 5 (1.4%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| しゃっくり | 4 (2.5%) | 0 | 0 | 0 | 4 (1.1%) |
| 気胸 | 3 (1.9%) | 1 (0.6%) | 1 (0.5%) | 1 (0.5%) | 4 (1.1%) |
| 喀血 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 鼻部不快感 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 肺水腫 | 2 (1.3%) | 0 | 1 (0.5%) | 1 (0.5%) | 3 (0.8%) |
| ラ音 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 喘鳴 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 無気肺 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 労作性呼吸困難 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 肺硬化 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 肺浸潤 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 鼻の炎症 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 肺塞栓症 | 0 | 0 | 2 (1.0%) | 1 (0.5%) | 2 (0.5%) |
| 気道うっ血 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 急性肺水腫 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 喘息 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 気管支反応性亢進 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 気管支分泌物貯留 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 気管支拡張症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 慢性気管支炎 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 肺気腫 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 上気道分泌増加 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 鼻乾燥 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 鼻潰瘍 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 副鼻腔不快感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 副鼻腔分泌過多 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 咽頭紅斑 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 胸膜炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 胸膜痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 肺腫瘤 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 呼吸性アシドーシス | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 呼吸窮迫 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 拘束性肺疾患 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 副鼻腔障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| くしゃみ | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 頻呼吸 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 扁桃肥大 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 上気道咳症候群 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚および皮下組織障害 | 82 (51.3%) | 5 (3.1%) | 112 (53.3%) | 5 (2.4%) | 194 (52.4%) |
| 発疹 | 23 (14.4%) | 0 | 34 (16.2%) | 4 (1.9%) | 57 (15.4%) |
| そう痒症 | 13 (8.1%) | 0 | 15 (7.1%) | 0 | 28 (7.6%) |
| 点状出血 | 10 (6.3%) | 0 | 12 (5.7%) | 0 | 22 (5.9%) |
| 皮膚病変 | 8 (5.0%) | 0 | 12 (5.7%) | 0 | 20 (5.4%) |
| 斑状丘疹状皮疹 | 6 (3.8%) | 2 (1.3%) | 10 (4.8%) | 0 | 16 (4.3%) |
| 皮膚乾燥 | 4 (2.5%) | 0 | 10 (4.8%) | 0 | 14 (3.8%) |
| 斑状出血 | 4 (2.5%) | 0 | 9 (4.3%) | 0 | 13 (3.5%) |
| 紅斑 | 6 (3.8%) | 0 | 5 (2.4%) | 0 | 11 (3.0%) |
| 寝汗 | 4 (2.5%) | 0 | 7 (3.3%) | 0 | 11 (3.0%) |
| 脱毛症 | 5 (3.1%) | 0 | 5 (2.4%) | 0 | 10 (2.7%) |
| ざ瘡様皮膚炎 | 4 (2.5%) | 0 | 4 (1.9%) | 0 | 8 (2.2%) |
| 紫斑 | 3 (1.9%) | 1 (0.6%) | 4 (1.9%) | 1 (0.5%) | 7 (1.9%) |
| 多汗症 | 0 | 0 | 6 (2.9%) | 0 | 6 (1.6%) |
| 皮膚亀裂 | 2 (1.3%) | 0 | 4 (1.9%) | 0 | 6 (1.6%) |
| 嵌入爪 | 0 | 0 | 5 (2.4%) | 0 | 5 (1.4%) |
| 爪破損 | 1 (0.6%) | 0 | 4 (1.9%) | 0 | 5 (1.4%) |
| 蕁麻疹 | 2 (1.3%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 水疱 | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| 全身性そう痒症 | 1 (0.6%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 斑状皮疹 | 1 (0.6%) | 1 (0.6%) | 3 (1.4%) | 0 | 4 (1.1%) |
| 皮膚腫瘤 | 1 (0.6%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 皮膚潰瘍 | 1 (0.6%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| ざ瘡 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 褥瘡性潰瘍 | 3 (1.9%) | 1 (0.6%) | 0 | 0 | 3 (0.8%) |
| 湿疹 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 紅斑性皮疹 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 皮膚色素過剰 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 皮膚嚢腫 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 接触性皮膚炎 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 皮下出血 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 間擦疹 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 皮膚疼痛 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 全身性皮疹 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 丘疹性皮疹 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| そう痒性皮疹 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 皮膚変色 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 毛細血管炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 皮膚炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| アレルギー性皮膚炎 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 水疱性皮膚炎 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮脂欠乏性湿疹 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 貨幣状湿疹 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 過敏性血管炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪床出血 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪床障害 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床の炎症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪の不快感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪の障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪ジストロフィー | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪線状隆起 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪痛 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪甲脱落症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 手掌・足底発赤知覚不全症候群 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 脂肪織炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 色素沈着障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 毛孔性皮疹 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 皮膚色素減少 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 皮膚刺激 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 皮膚腫脹 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 乾皮症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 筋骨格系および結合組織障害 | 82 (51.3%) | 9 (5.6%) | 91 (43.3%) | 11 (5.2%) | 173 (46.8%) |
| 筋痙縮 | 33 (20.6%) | 0 | 34 (16.2%) | 0 | 67 (18.1%) |
| 背部痛 | 22 (13.8%) | 3 (1.9%) | 22 (10.5%) | 3 (1.4%) | 44 (11.9%) |
| 関節痛 | 15 (9.4%) | 1 (0.6%) | 23 (11.0%) | 1 (0.5%) | 38 (10.3%) |
| 筋肉痛 | 16 (10.0%) | 0 | 16 (7.6%) | 1 (0.5%) | 32 (8.6%) |
| 四肢痛 | 15 (9.4%) | 2 (1.3%) | 13 (6.2%) | 0 | 28 (7.6%) |
| 筋骨格痛 | 8 (5.0%) | 0 | 9 (4.3%) | 0 | 17 (4.6%) |
| 筋力低下 | 5 (3.1%) | 1 (0.6%) | 8 (3.8%) | 2 (1.0%) | 13 (3.5%) |
| 側腹部痛 | 2 (1.3%) | 0 | 6 (2.9%) | 2 (1.0%) | 8 (2.2%) |
| 頚部痛 | 2 (1.3%) | 0 | 4 (1.9%) | 0 | 6 (1.6%) |
| 変形性関節症 | 2 (1.3%) | 0 | 3 (1.4%) | 2 (1.0%) | 5 (1.4%) |
| 肢径部痛 | 1 (0.6%) | 0 | 3 (1.4%) | 1 (0.5%) | 4 (1.1%) |
| 四肢不快感 | 1 (0.6%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 筋骨格硬直 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 骨痛 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 関節硬直 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 関節腫脹 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 運動性低下 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 筋骨格系胸痛 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| ミオパチー | 2 (1.3%) | 1 (0.6%) | 0 | 0 | 2 (0.5%) |
| 軟部組織障害 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 関節炎 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 滑液包炎 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 外骨腫 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 痛風性関節炎 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 椎間板変性症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 椎間板突出 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 関節拘縮 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 関節滲出液 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 関節ロック | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋緊張 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋攣縮 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 筋骨格不快感 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 頚部腫瘤 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 骨壊死 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 骨粗鬆症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 顎痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 横紋筋融解症 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 滑液嚢腫 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 腱痛 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 椎間孔狭窄 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血液およびリンパ系障害 | 76 (47.5%) | 51 (31.9%) | 93 (44.3%) | 58 (27.6%) | 169 (45.7%) |
| 血小板減少症 | 31 (19.4%) | 18 (11.3%) | 43 (20.5%) | 23 (11.0%) | 74 (20.0%) |
| 好中球減少症 | 28 (17.5%) | 26 (16.3%) | 42 (20.0%) | 35 (16.7%) | 70 (18.9%) |
| 貧血 | 31 (19.4%) | 17 (10.6%) | 32 (15.2%) | 13 (6.2%) | 63 (17.0%) |
| 発熱性好中球減少症 | 6 (3.8%) | 6 (3.8%) | 7 (3.3%) | 7 (3.3%) | 13 (3.5%) |
| 白血球減少症 | 5 (3.1%) | 1 (0.6%) | 8 (3.8%) | 5 (2.4%) | 13 (3.5%) |
| 白血球増加症 | 4 (2.5%) | 1 (0.6%) | 3 (1.4%) | 2 (1.0%) | 7 (1.9%) |
| 内出血発生の増加傾向 | 1 (0.6%) | 0 | 4 (1.9%) | 0 | 5 (1.4%) |
| リンパ球減少症 | 1 (0.6%) | 0 | 4 (1.9%) | 0 | 5 (1.4%) |
| リンパ球増加症 | 1 (0.6%) | 1 (0.6%) | 3 (1.4%) | 2 (1.0%) | 4 (1.1%) |
| リンパ節痛 | 2 (1.3%) | 1 (0.6%) | 0 | 0 | 2 (0.5%) |
| リンパ節症 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 脾腫 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 骨髄機能不全 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 凝血異常 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 溶血 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 鉄欠乏性貧血 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 白血球停滞症候群 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 汎血球減少症 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 後腹膜リンパ節腫脹 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 脾臓出血 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 脾臓梗塞 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 血小板増加症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 代謝および栄養障害 | 68 (42.5%) | 26 (16.3%) | 82 (39.0%) | 26 (12.4%) | 150 (40.5%) |
| 食欲減退 | 32 (20.0%) | 2 (1.3%) | 30 (14.3%) | 1 (0.5%) | 62 (16.8%) |
| 低カリウム血症 | 17 (10.6%) | 10 (6.3%) | 17 (8.1%) | 5 (2.4%) | 34 (9.2%) |
| 高尿酸血症 | 13 (8.1%) | 7 (4.4%) | 12 (5.7%) | 3 (1.4%) | 25 (6.8%) |
| 脱水 | 12 (7.5%) | 5 (3.1%) | 10 (4.8%) | 2 (1.0%) | 22 (5.9%) |
| 低マグネシウム血症 | 8 (5.0%) | 0 | 13 (6.2%) | 1 (0.5%) | 21 (5.7%) |
| 高カリウム血症 | 5 (3.1%) | 0 | 8 (3.8%) | 5 (2.4%) | 13 (3.5%) |
| 低ナトリウム血症 | 6 (3.8%) | 3 (1.9%) | 6 (2.9%) | 5 (2.4%) | 12 (3.2%) |
| 低アルブミン血症 | 8 (5.0%) | 3 (1.9%) | 3 (1.4%) | 1 (0.5%) | 11 (3.0%) |
| 高血糖 | 6 (3.8%) | 1 (0.6%) | 3 (1.4%) | 1 (0.5%) | 9 (2.4%) |
| 低カルシウム血症 | 2 (1.3%) | 0 | 4 (1.9%) | 0 | 6 (1.6%) |
| 低血糖症 | 4 (2.5%) | 0 | 0 | 0 | 4 (1.1%) |
| 低リン酸血症 | 2 (1.3%) | 2 (1.3%) | 2 (1.0%) | 2 (1.0%) | 4 (1.1%) |
| 水分過負荷 | 3 (1.9%) | 0 | 0 | 0 | 3 (0.8%) |
| 痛風 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 酵素異常 | 1 (0.6%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 高コレステロール血症 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 高ナトリウム血症 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 高リン酸塩血症 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 過小食 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 乳酸アシドーシス | 1 (0.6%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| アルコール不耐性 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 悪液質 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 糖尿病 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 糖尿病性ケトアシドーシス | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 高アルブミン血症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 高アンモニア血症 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 低蛋白血症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 代謝性アシドーシス | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 腫瘍崩壊症候群 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| ２型糖尿病 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 神経系障害 | 63 (39.4%) | 5 (3.1%) | 58 (27.6%) | 4 (1.9%) | 121 (32.7%) |
| 頭痛 | 19 (11.9%) | 0 | 18 (8.6%) | 0 | 37 (10.0%) |
| 浮動性めまい | 12 (7.5%) | 0 | 14 (6.7%) | 0 | 26 (7.0%) |
| 末梢性感覚ニューロパチー | 3 (1.9%) | 1 (0.6%) | 11 (5.2%) | 0 | 14 (3.8%) |
| 体位性めまい | 7 (4.4%) | 0 | 3 (1.4%) | 0 | 10 (2.7%) |
| 錯感覚 | 4 (2.5%) | 0 | 4 (1.9%) | 0 | 8 (2.2%) |
| 記憶障害 | 5 (3.1%) | 0 | 2 (1.0%) | 0 | 7 (1.9%) |
| 末梢性ニューロパチー | 4 (2.5%) | 0 | 3 (1.4%) | 0 | 7 (1.9%) |
| 振戦 | 3 (1.9%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 感覚鈍麻 | 1 (0.6%) | 0 | 4 (1.9%) | 1 (0.5%) | 5 (1.4%) |
| 健忘 | 3 (1.9%) | 0 | 1 (0.5%) | 0 | 4 (1.1%) |
| 傾眠 | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| 失神 | 1 (0.6%) | 1 (0.6%) | 3 (1.4%) | 3 (1.4%) | 4 (1.1%) |
| 平衡障害 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 構語障害 | 3 (1.9%) | 2 (1.3%) | 0 | 0 | 3 (0.8%) |
| 味覚異常 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 嗜眠 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 多発ニューロパチー | 3 (1.9%) | 1 (0.6%) | 0 | 0 | 3 (0.8%) |
| 認知症 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 頭蓋内出血 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 過眠症 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 神経痛 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 失神寸前の状態 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 下肢静止不能症候群 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 一過性脳虚血発作 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 灼熱足症候群 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 手根管症候群 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 大脳萎縮 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 脳血管発作 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 労作性めまい | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 脳症 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| てんかん | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 顔面部神経痛 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 顔面不全麻痺 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 頭部不快感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 腰髄神経根障害 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 片頭痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 前兆を伴う片頭痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 筋痙直 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| ミオクローヌス | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼振 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 腓骨神経麻痺 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| ヘルペス後神経痛 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 坐骨神経痛 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 感覚障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 会話障害 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 緊張性頭痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 一過性全健忘 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 血管性脳症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 臨床検査 | 53 (33.1%) | 16 (10.0%) | 59 (28.1%) | 19 (9.0%) | 112 (30.3%) |
| 血中クレアチニン増加 | 16 (10.0%) | 0 | 15 (7.1%) | 0 | 31 (8.4%) |
| 血小板数減少 | 4 (2.5%) | 0 | 10 (4.8%) | 2 (1.0%) | 14 (3.8%) |
| 体重減少 | 10 (6.3%) | 0 | 2 (1.0%) | 0 | 12 (3.2%) |
| 血中アルカリホスファターゼ増加 | 7 (4.4%) | 2 (1.3%) | 4 (1.9%) | 0 | 11 (3.0%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 5 (3.1%) | 1 (0.6%) | 5 (2.4%) | 0 | 10 (2.7%) |
| 血中ビリルビン増加 | 5 (3.1%) | 1 (0.6%) | 5 (2.4%) | 1 (0.5%) | 10 (2.7%) |
| 好中球数減少 | 5 (3.1%) | 4 (2.5%) | 4 (1.9%) | 4 (1.9%) | 9 (2.4%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| アラニンアミノトランスフェラーゼ増加 | 4 (2.5%) | 0 | 3 (1.4%) | 1 (0.5%) | 7 (1.9%) |
| 血中尿酸増加 | 4 (2.5%) | 2 (1.3%) | 3 (1.4%) | 1 (0.5%) | 7 (1.9%) |
| リンパ球数増加 | 2 (1.3%) | 1 (0.6%) | 4 (1.9%) | 3 (1.4%) | 6 (1.6%) |
| 体重増加 | 0 | 0 | 6 (2.9%) | 0 | 6 (1.6%) |
| 活性化部分トロンボプラスチン時間延長 | 3 (1.9%) | 1 (0.6%) | 2 (1.0%) | 0 | 5 (1.4%) |
| 血中乳酸脱水素酵素増加 | 1 (0.6%) | 0 | 4 (1.9%) | 0 | 5 (1.4%) |
| 白血球数減少 | 2 (1.3%) | 2 (1.3%) | 3 (1.4%) | 3 (1.4%) | 5 (1.4%) |
| 血中免疫グロブリンG減少 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 国際標準比増加 | 3 (1.9%) | 3 (1.9%) | 0 | 0 | 3 (0.8%) |
| 白血球数増加 | 1 (0.6%) | 0 | 2 (1.0%) | 1 (0.5%) | 3 (0.8%) |
| 血中ブドウ糖増加 | 2 (1.3%) | 2 (1.3%) | 0 | 0 | 2 (0.5%) |
| 血中免疫グロブリンM減少 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 血圧上昇 | 0 | 0 | 2 (1.0%) | 2 (1.0%) | 2 (0.5%) |
| Ｃ－反応性蛋白増加 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 心雑音 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| γ－グルタミルトランスフェラーゼ増加 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 糸球体濾過率減少 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| ヘモグロビン減少 | 0 | 0 | 2 (1.0%) | 2 (1.0%) | 2 (0.5%) |
| 免疫グロブリン減少 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| リンパ球数減少 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| トランスアミナーゼ上昇 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| アミラーゼ増加 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| アスペルギルス検査陽性 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血中アルブミン減少 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 血中重炭酸塩増加 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中ビリルビン異常 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 血中クロール減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血中コレステロール増加 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中クレアチン増加 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 血中免疫グロブリンA減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血中鉄減少 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中マグネシウム減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血中リン減少 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中カリウム減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 呼吸音異常 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 二酸化炭素減少 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸部コンピュータ断層撮影異常 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 駆出率減少 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| グリコヘモグロビン増加 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘモフィルス検査陽性 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心拍数増加 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 心拍数不整 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 肝酵素上昇 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 深吸気量減少 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 肝機能検査異常 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 黄斑部反射異常 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 平均赤血球容積増加 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血小板凝集異常 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 尿量減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 超低比重リポ蛋白増加 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 肺活量異常 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 傷害、中毒および処置合併症 | 52 (32.5%) | 7 (4.4%) | 49 (23.3%) | 6 (2.9%) | 101 (27.3%) |
| 挫傷 | 23 (14.4%) | 0 | 23 (11.0%) | 0 | 46 (12.4%) |
| 転倒 | 14 (8.8%) | 2 (1.3%) | 3 (1.4%) | 2 (1.0%) | 17 (4.6%) |
| 節足動物咬傷 | 1 (0.6%) | 0 | 5 (2.4%) | 0 | 6 (1.6%) |
| 処置による疼痛 | 2 (1.3%) | 0 | 4 (1.9%) | 0 | 6 (1.6%) |
| 硬膜下血腫 | 5 (3.1%) | 2 (1.3%) | 1 (0.5%) | 1 (0.5%) | 6 (1.6%) |
| 外傷性血腫 | 4 (2.5%) | 0 | 2 (1.0%) | 0 | 6 (1.6%) |
| 裂傷 | 4 (2.5%) | 0 | 0 | 0 | 4 (1.1%) |
| 皮膚擦過傷 | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| サンバーン | 1 (0.6%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 創傷 | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| 動物咬傷 | 1 (0.6%) | 0 | 2 (1.0%) | 1 (0.5%) | 3 (0.8%) |
| 頭部損傷 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 靭帯捻挫 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 腰椎骨折 | 2 (1.3%) | 1 (0.6%) | 1 (0.5%) | 0 | 3 (0.8%) |
| 処置後出血 | 2 (1.3%) | 1 (0.6%) | 1 (0.5%) | 1 (0.5%) | 3 (0.8%) |
| 骨挫傷 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 擦過傷 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 顔面骨骨折 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 四肢損傷 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 眼窩周囲挫傷 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 肋骨骨折 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚創傷 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 脊椎圧迫骨折 | 2 (1.3%) | 1 (0.6%) | 0 | 0 | 2 (0.5%) |
| 脾破裂 | 0 | 0 | 2 (1.0%) | 2 (1.0%) | 2 (0.5%) |
| 熱傷 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 動物による引っかき傷 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 足関節部骨折 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 第２度熱傷 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼挫傷 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼外傷 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 足骨折 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼内異物 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 外傷性血尿 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 関節損傷 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 過量投与 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 処置後便秘 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 処置後血尿 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 処置後腫脹 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 外傷後疼痛 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢血腫 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮下血腫 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 脛骨骨折 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 歯牙破折 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 術後尿閉 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 創合併症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼障害 | 33 (20.6%) | 3 (1.9%) | 49 (23.3%) | 2 (1.0%) | 82 (22.2%) |
| 眼乾燥 | 5 (3.1%) | 0 | 11 (5.2%) | 0 | 16 (4.3%) |
| 流涙増加 | 9 (5.6%) | 0 | 4 (1.9%) | 0 | 13 (3.5%) |
| 霧視 | 6 (3.8%) | 0 | 7 (3.3%) | 0 | 13 (3.5%) |
| 白内障 | 3 (1.9%) | 2 (1.3%) | 8 (3.8%) | 1 (0.5%) | 11 (3.0%) |
| 視力低下 | 3 (1.9%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 眼窩周囲浮腫 | 3 (1.9%) | 1 (0.6%) | 2 (1.0%) | 0 | 5 (1.4%) |
| 結膜出血 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 眼痛 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 眼充血 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 睫毛乱生 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 硝子体浮遊物 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 糖尿病網膜症 | 0 | 0 | 2 (1.0%) | 1 (0.5%) | 2 (0.5%) |
| 複視 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 眼出血 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 眼刺激 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 眼瞼下垂 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 羞明 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 眼瞼炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 片側失明 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 結膜充血 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼瞼内反 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼脂 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼の炎症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼そう痒症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼の異物感 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 緑内障 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 角膜炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 黄斑変性 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| マイボーム腺機能不全 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼血管障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 開放隅角緑内障 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 動揺視 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 老視 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 網膜剥離 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 強膜出血 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 視力障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 硝子体出血 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 眼球乾燥症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血管障害 | 42 (26.3%) | 17 (10.6%) | 39 (18.6%) | 9 (4.3%) | 81 (21.9%) |
| 高血圧 | 19 (11.9%) | 8 (5.0%) | 16 (7.6%) | 5 (2.4%) | 35 (9.5%) |
| 低血圧 | 14 (8.8%) | 5 (3.1%) | 7 (3.3%) | 0 | 21 (5.7%) |
| 血腫 | 5 (3.1%) | 0 | 7 (3.3%) | 0 | 12 (3.2%) |
| 深部静脈血栓症 | 4 (2.5%) | 2 (1.3%) | 3 (1.4%) | 0 | 7 (1.9%) |
| 潮紅 | 1 (0.6%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 出血 | 0 | 0 | 4 (1.9%) | 3 (1.4%) | 4 (1.1%) |
| 起立性低血圧 | 3 (1.9%) | 1 (0.6%) | 0 | 0 | 3 (0.8%) |
| 静脈炎 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 血圧変動 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| リンパ浮腫 | 2 (1.3%) | 2 (1.3%) | 0 | 0 | 2 (0.5%) |
| 表在性血栓性静脈炎 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 大動脈硬化症 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 循環虚脱 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| ほてり | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 高血圧クリーゼ | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 末梢血管障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 末梢静脈疾患 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 静脈瘤 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 心臓障害 | 36 (22.5%) | 18 (11.3%) | 28 (13.3%) | 8 (3.8%) | 64 (17.3%) |
| 心房細動 | 17 (10.6%) | 12 (7.5%) | 11 (5.2%) | 5 (2.4%) | 28 (7.6%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 頻脈 | 5 (3.1%) | 0 | 4 (1.9%) | 0 | 9 (2.4%) |
| 洞性頻脈 | 2 (1.3%) | 0 | 5 (2.4%) | 0 | 7 (1.9%) |
| 徐脈 | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| 動悸 | 1 (0.6%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 心房粗動 | 3 (1.9%) | 1 (0.6%) | 0 | 0 | 3 (0.8%) |
| 洞性徐脈 | 2 (1.3%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 上室性頻脈 | 2 (1.3%) | 0 | 1 (0.5%) | 1 (0.5%) | 3 (0.8%) |
| 不安定狭心症 | 2 (1.3%) | 1 (0.6%) | 0 | 0 | 2 (0.5%) |
| 心停止 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 心不全 | 2 (1.3%) | 2 (1.3%) | 0 | 0 | 2 (0.5%) |
| 心室性期外収縮 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 急性心筋梗塞 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 不整脈 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 冠動脈硬化症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 第一度房室ブロック | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| うっ血性心不全 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心血管不全 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 変時性応答不全 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 冠動脈疾患 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 冠動脈閉塞 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| チアノーゼ | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 僧帽弁閉鎖不全症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 心筋梗塞 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心嚢液貯留 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 心膜炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 洞不全症候群 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| ストレス心筋症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 頻脈性不整脈 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| トルサード　ド　ポアント | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 三尖弁疾患 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 心室性不整脈 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心室性頻脈 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 精神障害 | 31 (19.4%) | 5 (3.1%) | 32 (15.2%) | 2 (1.0%) | 63 (17.0%) |
| 不眠症 | 13 (8.1%) | 0 | 13 (6.2%) | 0 | 26 (7.0%) |
| 不安 | 5 (3.1%) | 0 | 8 (3.8%) | 0 | 13 (3.5%) |
| 錯乱状態 | 8 (5.0%) | 3 (1.9%) | 4 (1.9%) | 1 (0.5%) | 12 (3.2%) |
| うつ病 | 4 (2.5%) | 0 | 8 (3.8%) | 1 (0.5%) | 12 (3.2%) |
| 激越 | 5 (3.1%) | 0 | 0 | 0 | 5 (1.4%) |
| 譫妄 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 希死念慮を有するうつ病 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 多幸気分 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 幻聴 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 幻視 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 易刺激性 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| リビドー減退 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 躁病 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 精神障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 精神状態変化 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 悪夢 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| パニック発作 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| パニック障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 腎および尿路障害 | 31 (19.4%) | 10 (6.3%) | 26 (12.4%) | 7 (3.3%) | 57 (15.4%) |
| 血尿 | 6 (3.8%) | 3 (1.9%) | 8 (3.8%) | 0 | 14 (3.8%) |
| 急性腎不全 | 10 (6.3%) | 4 (2.5%) | 2 (1.0%) | 2 (1.0%) | 12 (3.2%) |
| 排尿困難 | 5 (3.1%) | 0 | 3 (1.4%) | 0 | 8 (2.2%) |
| 腎不全 | 5 (3.1%) | 3 (1.9%) | 2 (1.0%) | 2 (1.0%) | 7 (1.9%) |
| 頻尿 | 3 (1.9%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 水腎症 | 1 (0.6%) | 1 (0.6%) | 2 (1.0%) | 1 (0.5%) | 3 (0.8%) |
| 腎機能障害 | 3 (1.9%) | 0 | 0 | 0 | 3 (0.8%) |
| 尿閉 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 尿路閉塞 | 2 (1.3%) | 1 (0.6%) | 1 (0.5%) | 0 | 3 (0.8%) |
| 腎結石症 | 0 | 0 | 2 (1.0%) | 1 (0.5%) | 2 (0.5%) |
| 夜間頻尿 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 腎嚢胞 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性腎不全 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 尿失禁 | 2 (1.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 高窒素血症 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 膀胱刺激症状 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 出血性膀胱炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 緊張性膀胱 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 失禁 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 尿意切迫 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 閉塞性尿路疾患 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 乏尿 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 腎仙痛 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 有痛性排尿困難 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 尿路痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 21 (13.1%) | 9 (5.6%) | 15 (7.1%) | 10 (4.8%) | 36 (9.7%) |
| マントル細胞リンパ腫 | 4 (2.5%) | 4 (2.5%) | 4 (1.9%) | 4 (1.9%) | 8 (2.2%) |
| 基底細胞癌 | 4 (2.5%) | 0 | 3 (1.4%) | 1 (0.5%) | 7 (1.9%) |
| 皮膚有棘細胞癌 | 5 (3.1%) | 0 | 0 | 0 | 5 (1.4%) |
| 膀胱移行上皮癌 | 2 (1.3%) | 1 (0.6%) | 0 | 0 | 2 (0.5%) |
| 前立腺癌 | 1 (0.6%) | 1 (0.6%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 扁平上皮癌 | 2 (1.3%) | 1 (0.6%) | 0 | 0 | 2 (0.5%) |
| 急性骨髄性白血病 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 良性新生物 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 膀胱癌 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 肺腺癌 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 悪性胸水 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 口腔乳頭腫 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 唾液腺癌 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 皮膚癌 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 皮膚乳頭腫 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 胸腺腫 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 移行上皮癌 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 腫瘍フレア | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 耳および迷路障害 | 16 (10.0%) | 2 (1.3%) | 14 (6.7%) | 0 | 30 (8.1%) |
| 回転性めまい | 8 (5.0%) | 0 | 3 (1.4%) | 0 | 11 (3.0%) |
| 耳鳴 | 1 (0.6%) | 0 | 5 (2.4%) | 0 | 6 (1.6%) |
| 耳痛 | 2 (1.3%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 聴力低下 | 3 (1.9%) | 1 (0.6%) | 1 (0.5%) | 0 | 4 (1.1%) |
| 耳垢栓塞 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 耳不快感 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 難聴 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 耳出血 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 聴覚過敏 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 老人性難聴 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 生殖系および乳房障害 | 10 (6.3%) | 5 (3.1%) | 16 (7.6%) | 2 (1.0%) | 26 (7.0%) |
| 良性前立腺肥大症 | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| 血精液症 | 1 (0.6%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 性器浮腫 | 3 (1.9%) | 2 (1.3%) | 0 | 0 | 3 (0.8%) |
| 勃起不全 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 骨盤痛 | 0 | 0 | 2 (1.0%) | 1 (0.5%) | 2 (0.5%) |
| 腟出血 | 1 (0.6%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 後天性包茎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 乳房血腫 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房腫瘤 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 乳房痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 性器発疹 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 陰茎痛 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 陰嚢腫瘤 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 陰嚢浮腫 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 陰嚢痛 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 子宮腟脱 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 外陰腟痛 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 外陰腟そう痒症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE15B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=70 vs. <70) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 70 | | < 70 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 免疫系障害 | 6 (3.8%) | 0 | 13 (6.2%) | 0 | 19 (5.1%) |
| 低ｙグロブリン血症 | 2 (1.3%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 節足動物咬傷アレルギー | 2 (1.3%) | 0 | 2 (1.0%) | 0 | 4 (1.1%) |
| 過敏症 | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 季節性アレルギー | 1 (0.6%) | 0 | 2 (1.0%) | 0 | 3 (0.8%) |
| 薬物過敏症 | 0 | 0 | 2 (1.0%) | 0 | 2 (0.5%) |
| 造影剤アレルギー | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 食物アレルギー | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 肝胆道系障害 | 8 (5.0%) | 3 (1.9%) | 5 (2.4%) | 1 (0.5%) | 13 (3.5%) |
| 高ビリルビン血症 | 4 (2.5%) | 1 (0.6%) | 2 (1.0%) | 0 | 6 (1.6%) |
| 胆石症 | 1 (0.6%) | 1 (0.6%) | 2 (1.0%) | 0 | 3 (0.8%) |
| 胆管結石 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 胆管炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 肝不全 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 肝機能異常 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 中毒性肝炎 | 1 (0.6%) | 1 (0.6%) | 0 | 0 | 1 (0.3%) |
| 陶器様胆嚢 | 1 (0.6%) | 0 | 0 | 0 | 1 (0.3%) |
| 内分泌障害 | 2 (1.3%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 甲状腺機能低下症 | 2 (1.3%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 先天性、家族性および遺伝性障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 臍血腫 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE15B.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae15b.sas] 15SEP2015, 14:12

参照元：5.3.5.3.1 ISS TSFAE15B

表 2.7.4-付録-49 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| Analysis set: safety | 78 | | 292 | | 370 |
| Subjects with any TEAE | 78 (100.0%) | 66 (84.6%) | 286 (97.9%) | 199 (68.2%) | 364 (98.4%) |
| System organ class | | | | | |
| Preferred term | | | | | |
| 感染症および寄生虫症 | 49 (62.8%) | 22 (28.2%) | 214 (73.3%) | 65 (22.3%) | 263 (71.1%) |
| 上気道感染 | 12 (15.4%) | 1 (1.3%) | 61 (20.9%) | 2 (0.7%) | 73 (19.7%) |
| 肺炎 | 10 (12.8%) | 8 (10.3%) | 34 (11.6%) | 25 (8.6%) | 44 (11.9%) |
| 副鼻腔炎 | 5 (6.4%) | 0 | 34 (11.6%) | 1 (0.3%) | 39 (10.5%) |
| 尿路感染 | 9 (11.5%) | 1 (1.3%) | 29 (9.9%) | 5 (1.7%) | 38 (10.3%) |
| 鼻咽頭炎 | 5 (6.4%) | 0 | 25 (8.6%) | 0 | 30 (8.1%) |
| 結膜炎 | 5 (6.4%) | 0 | 21 (7.2%) | 0 | 26 (7.0%) |
| 気管支炎 | 3 (3.8%) | 0 | 17 (5.8%) | 4 (1.4%) | 20 (5.4%) |
| 蜂巣炎 | 6 (7.7%) | 3 (3.8%) | 12 (4.1%) | 5 (1.7%) | 18 (4.9%) |
| 帯状疱疹 | 2 (2.6%) | 0 | 12 (4.1%) | 0 | 14 (3.8%) |
| 鼻炎 | 3 (3.8%) | 0 | 11 (3.8%) | 0 | 14 (3.8%) |
| 毛包炎 | 0 | 0 | 13 (4.5%) | 0 | 13 (3.5%) |
| 爪囲炎 | 1 (1.3%) | 0 | 12 (4.1%) | 0 | 13 (3.5%) |
| 下気道感染 | 0 | 0 | 12 (4.1%) | 5 (1.7%) | 12 (3.2%) |
| 皮膚感染 | 2 (2.6%) | 0 | 10 (3.4%) | 1 (0.3%) | 12 (3.2%) |
| 口腔ヘルペス | 2 (2.6%) | 0 | 9 (3.1%) | 0 | 11 (3.0%) |
| 気道感染 | 3 (3.8%) | 1 (1.3%) | 8 (2.7%) | 1 (0.3%) | 11 (3.0%) |
| 敗血症 | 3 (3.8%) | 3 (3.8%) | 8 (2.7%) | 8 (2.7%) | 11 (3.0%) |
| 胃腸炎 | 2 (2.6%) | 1 (1.3%) | 8 (2.7%) | 1 (0.3%) | 10 (2.7%) |
| 咽頭炎 | 1 (1.3%) | 0 | 6 (2.1%) | 1 (0.3%) | 7 (1.9%) |
| ウイルス感染 | 0 | 0 | 7 (2.4%) | 0 | 7 (1.9%) |
| 感染 | 0 | 0 | 6 (2.1%) | 2 (0.7%) | 6 (1.6%) |
| クロストリジウム・ディフィシレ大腸炎 | 0 | 0 | 5 (1.7%) | 3 (1.0%) | 5 (1.4%) |
| 眼感染 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯肉炎 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| 口腔カンジダ症 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| クロストリジウム・ディフィシレ感染 | 1 (1.3%) | 0 | 3 (1.0%) | 1 (0.3%) | 4 (1.1%) |
| インフルエンザ | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 限局性感染 | 0 | 0 | 4 (1.4%) | 0 | 4 (1.1%) |
| 中耳炎 | 2 (2.6%) | 0 | 2 (0.7%) | 0 | 4 (1.1%) |
| 歯周炎 | 0 | 0 | 4 (1.4%) | 0 | 4 (1.1%) |
| 歯感染 | 0 | 0 | 4 (1.4%) | 0 | 4 (1.1%) |
| 菌血症 | 0 | 0 | 3 (1.0%) | 2 (0.7%) | 3 (0.8%) |
| 気管支肺炎 | 0 | 0 | 3 (1.0%) | 1 (0.3%) | 3 (0.8%) |
| 膀胱炎 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 耳感染 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| ウイルス性胃腸炎 | 0 | 0 | 3 (1.0%) | 1 (0.3%) | 3 (0.8%) |
| 単純ヘルペス | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 喉頭炎 | 1 (1.3%) | 1 (1.3%) | 2 (0.7%) | 0 | 3 (0.8%) |
| 爪感染 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 外耳炎 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| ブドウ球菌感染 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| ウイルス性上気道感染 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 急性副鼻腔炎 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 細気管支炎 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 医療機器関連感染 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 憩室炎 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 感染性小腸結腸炎 | 0 | 0 | 2 (0.7%) | 2 (0.7%) | 2 (0.5%) |
| 丹毒 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 真菌感染 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 皮膚真菌感染 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 真菌性性器感染 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| ヘルペスウイルス感染 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 麦粒腫 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 爪真菌症 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| レンサ球菌性咽頭炎 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| ニューモシスチス・イロベチイ肺炎 | 1 (1.3%) | 1 (1.3%) | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| 細菌性肺炎 | 1 (1.3%) | 1 (1.3%) | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| 膿疱性皮疹 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 敗血症性ショック | 0 | 0 | 2 (0.7%) | 2 (0.7%) | 2 (0.5%) |
| ブドウ球菌性菌血症 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 歯膿瘍 | 1 (1.3%) | 0 | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| 細菌性尿路感染 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 尿路性敗血症 | 0 | 0 | 2 (0.7%) | 2 (0.7%) | 2 (0.5%) |
| 外陰部腟カンジダ症 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 創傷感染 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 腹部膿瘍 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 四肢膿瘍 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| ダニ皮膚炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 膿疱性ざ瘡 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 肛門膿瘍 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 肛門カンジダ症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 虫垂炎 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 穿孔性虫垂炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 異型肺炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 細菌尿 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| カンジダ性亀頭炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 胆道感染 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| ブラストシスティス感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 体部白癬 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 乳房蜂巣炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| カンピロバクター胃腸炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| カンピロバクター感染 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| カンジダ感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼窩蜂巣炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 感染性胆嚢炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性副鼻腔炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| シトロバクター感染 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 涙嚢炎 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性脳炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 精巣上体炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 喉頭蓋炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 細菌性眼感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 真菌血症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| ヘリコバクター胃潰瘍 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 消化管感染 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性消化管感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 性器カンジダ症 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血腫感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| ヘモフィルス感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| Ｂ型肝炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| ヒストプラスマ症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 埋込み部位感染 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 切開部位感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| クレブシエラ感染 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 口唇感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 細菌性下気道感染 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 肺感染 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| ライム病 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 乳腺炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 水疱性鼓膜炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 爪床感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼帯状疱疹 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 口腔真菌感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 乳頭腫ウイルス感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| クリプトコッカス性肺炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| クレブシエラ菌性肺炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 処置後感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 肺結核 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 腎盂腎炎 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 膿皮症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| レンサ球菌性膿皮症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 狂犬病 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 直腸膿瘍 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| ウイルス性気道感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 軟部組織感染 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| ブドウ球菌皮膚感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| レンサ球菌感染 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 皮下組織膿瘍 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 足部白癬 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 扁桃炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 気管炎 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 真菌性尿路感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| シュードモナス性尿路感染 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 胃腸障害 | 58 (74.4%) | 10 (12.8%) | 197 (67.5%) | 29 (9.9%) | 255 (68.9%) |
| 下痢 | 36 (46.2%) | 3 (3.8%) | 110 (37.7%) | 10 (3.4%) | 146 (39.5%) |
| 悪心 | 21 (26.9%) | 1 (1.3%) | 59 (20.2%) | 0 | 80 (21.6%) |
| 嘔吐 | 14 (17.9%) | 1 (1.3%) | 48 (16.4%) | 0 | 62 (16.8%) |
| 便秘 | 16 (20.5%) | 0 | 41 (14.0%) | 0 | 57 (15.4%) |
| 腹痛 | 12 (15.4%) | 4 (5.1%) | 30 (10.3%) | 9 (3.1%) | 42 (11.4%) |
| 口内炎 | 3 (3.8%) | 1 (1.3%) | 28 (9.6%) | 2 (0.7%) | 31 (8.4%) |
| 消化不良 | 6 (7.7%) | 0 | 22 (7.5%) | 0 | 28 (7.6%) |
| 上腹部痛 | 4 (5.1%) | 0 | 12 (4.1%) | 1 (0.3%) | 16 (4.3%) |
| 腹部膨満 | 2 (2.6%) | 0 | 12 (4.1%) | 0 | 14 (3.8%) |
| 口内乾燥 | 2 (2.6%) | 0 | 12 (4.1%) | 0 | 14 (3.8%) |
| 胃食道逆流性疾患 | 3 (3.8%) | 0 | 10 (3.4%) | 0 | 13 (3.5%) |
| 嚥下障害 | 2 (2.6%) | 1 (1.3%) | 7 (2.4%) | 1 (0.3%) | 9 (2.4%) |
| 腹部不快感 | 1 (1.3%) | 0 | 7 (2.4%) | 0 | 8 (2.2%) |
| 口腔内痛 | 1 (1.3%) | 0 | 7 (2.4%) | 1 (0.3%) | 8 (2.2%) |
| 口腔内潰瘍形成 | 3 (3.8%) | 0 | 4 (1.4%) | 0 | 7 (1.9%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 放屁 | 4 (5.1%) | 0 | 2 (0.7%) | 0 | 6 (1.6%) |
| 胃炎 | 2 (2.6%) | 0 | 4 (1.4%) | 0 | 6 (1.6%) |
| 心窩部不快感 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| 舌痛 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| 痔核 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| アフタ性口内炎 | 0 | 0 | 3 (1.0%) | 1 (0.3%) | 3 (0.8%) |
| おくび | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| イレウス | 3 (3.8%) | 0 | 0 | 0 | 3 (0.8%) |
| 直腸出血 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 舌潰瘍 | 2 (2.6%) | 0 | 1 (0.3%) | 0 | 3 (0.8%) |
| 下腹部痛 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 齲歯 | 1 (1.3%) | 0 | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| 軟便 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 食中毒 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 排便回数増加 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 胃潰瘍 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 歯肉出血 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 歯肉浮腫 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 吐血 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 麻痺性イレウス | 0 | 0 | 2 (0.7%) | 2 (0.7%) | 2 (0.5%) |
| 鼠径ヘルニア | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 口唇潰瘍 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 下部消化管出血 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 口腔内出血 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 歯周病 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 肛門周囲痛 | 2 (2.6%) | 1 (1.3%) | 0 | 0 | 2 (0.5%) |
| 直腸炎 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 直腸裂 | 2 (2.6%) | 0 | 0 | 0 | 2 (0.5%) |
| 小腸閉塞 | 1 (1.3%) | 1 (1.3%) | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| 歯痛 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 裂肛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 肛門直腸障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 萎縮性舌炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| バレット食道 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 口唇炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 大腸炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 歯不快感 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血性下痢 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 十二指腸狭窄 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 十二指腸潰瘍 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 十二指腸炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 十二指腸胃逆流 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 便失禁 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 糞塊 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 胃前庭部毛細血管拡張症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 出血性胃炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 歯肉痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血便排泄 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 痔出血 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 過敏性腸症候群 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 口唇水疱 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 口唇びらん | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 口唇腫脹 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 弛緩歯 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| メレナ | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 嚥下痛 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 口蓋障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 慢性膵炎 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 舌突出 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 直腸潰瘍 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 唾液腺結石 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 変色歯 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 歯の障害 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯の脱落 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 一般・全身障害および投与部位の状態 | 55 (70.5%) | 8 (10.3%) | 184 (63.0%) | 30 (10.3%) | 239 (64.6%) |
| 疲労 | 29 (37.2%) | 3 (3.8%) | 100 (34.2%) | 13 (4.5%) | 129 (34.9%) |
| 末梢性浮腫 | 21 (26.9%) | 1 (1.3%) | 53 (18.2%) | 5 (1.7%) | 74 (20.0%) |
| 発熱 | 10 (12.8%) | 1 (1.3%) | 58 (19.9%) | 2 (0.7%) | 68 (18.4%) |
| 無力症 | 14 (17.9%) | 2 (2.6%) | 18 (6.2%) | 3 (1.0%) | 32 (8.6%) |
| 悪寒 | 4 (5.1%) | 0 | 14 (4.8%) | 0 | 18 (4.9%) |
| 胸痛 | 4 (5.1%) | 0 | 11 (3.8%) | 0 | 15 (4.1%) |
| 末梢腫脹 | 6 (7.7%) | 1 (1.3%) | 9 (3.1%) | 0 | 15 (4.1%) |
| インフルエンザ様疾患 | 2 (2.6%) | 0 | 12 (4.1%) | 0 | 14 (3.8%) |
| 疼痛 | 2 (2.6%) | 0 | 9 (3.1%) | 1 (0.3%) | 11 (3.0%) |
| 非心臓性胸痛 | 3 (3.8%) | 0 | 5 (1.7%) | 2 (0.7%) | 8 (2.2%) |
| 粘膜の炎症 | 1 (1.3%) | 0 | 5 (1.7%) | 1 (0.3%) | 6 (1.6%) |
| 全身健康状態低下 | 1 (1.3%) | 1 (1.3%) | 4 (1.4%) | 1 (0.3%) | 5 (1.4%) |
| 倦怠感 | 2 (2.6%) | 0 | 3 (1.0%) | 0 | 5 (1.4%) |
| 局所腫脹 | 2 (2.6%) | 1 (1.3%) | 2 (0.7%) | 0 | 4 (1.1%) |
| 多臓器不全 | 0 | 0 | 4 (1.4%) | 4 (1.4%) | 4 (1.1%) |
| 胸部不快感 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 歩行障害 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 全身性浮腫 | 2 (2.6%) | 0 | 1 (0.3%) | 1 (0.3%) | 3 (0.8%) |
| 注射部位内出血 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 乾燥症 | 0 | 0 | 3 (1.0%) | 1 (0.3%) | 3 (0.8%) |
| 腋窩痛 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 早期満腹 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 重力性浮腫 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 低体温 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 炎症 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 浮腫 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 活動状態低下 | 1 (1.3%) | 1 (1.3%) | 1 (0.3%) | 0 | 2 (0.5%) |
| カテーテル留置部位関連反応 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 死亡 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 医療機器リーク | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 顔面浮腫 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 異常感 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 冷感 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 熱感 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 治癒不良 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 硬結 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 注入部位血管外漏出 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 注射部位紅斑 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 注射部位漏出 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 注射部位出血 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位疼痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 注射部位反応 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 先行疾患の改善 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 温度変化不耐症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 評価不能の事象 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 呼吸器、胸郭および縦隔障害 | 50 (64.1%) | 10 (12.8%) | 150 (51.4%) | 25 (8.6%) | 200 (54.1%) |
| 咳嗽 | 23 (29.5%) | 0 | 58 (19.9%) | 0 | 81 (21.9%) |
| 呼吸困難 | 17 (21.8%) | 5 (6.4%) | 52 (17.8%) | 7 (2.4%) | 69 (18.6%) |
| 鼻出血 | 5 (6.4%) | 0 | 27 (9.2%) | 1 (0.3%) | 32 (8.6%) |
| 口腔咽頭痛 | 9 (11.5%) | 0 | 20 (6.8%) | 0 | 29 (7.8%) |
| 胸水 | 6 (7.7%) | 2 (2.6%) | 17 (5.8%) | 5 (1.7%) | 23 (6.2%) |
| 湿性咳嗽 | 5 (6.4%) | 0 | 10 (3.4%) | 0 | 15 (4.1%) |
| 鼻閉 | 5 (6.4%) | 0 | 8 (2.7%) | 0 | 13 (3.5%) |
| 呼吸不全 | 4 (5.1%) | 4 (5.1%) | 6 (2.1%) | 6 (2.1%) | 10 (2.7%) |
| 鼻漏 | 2 (2.6%) | 0 | 7 (2.4%) | 0 | 9 (2.4%) |
| 発声障害 | 4 (5.1%) | 0 | 4 (1.4%) | 0 | 8 (2.2%) |
| 慢性閉塞性肺疾患 | 1 (1.3%) | 1 (1.3%) | 5 (1.7%) | 3 (1.0%) | 6 (1.6%) |
| アレルギー性鼻炎 | 0 | 0 | 6 (2.1%) | 0 | 6 (1.6%) |
| 副鼻腔うっ血 | 1 (1.3%) | 0 | 5 (1.7%) | 0 | 6 (1.6%) |
| 上気道うっ血 | 1 (1.3%) | 0 | 5 (1.7%) | 0 | 6 (1.6%) |
| 低酸素症 | 0 | 0 | 5 (1.7%) | 4 (1.4%) | 5 (1.4%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| しゃっくり | 3 (3.8%) | 0 | 1 (0.3%) | 0 | 4 (1.1%) |
| 気胸 | 2 (2.6%) | 0 | 2 (0.7%) | 2 (0.7%) | 4 (1.1%) |
| 喀血 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 鼻部不快感 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 肺水腫 | 1 (1.3%) | 0 | 2 (0.7%) | 1 (0.3%) | 3 (0.8%) |
| ラ音 | 2 (2.6%) | 0 | 1 (0.3%) | 0 | 3 (0.8%) |
| 喘鳴 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 無気肺 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 労作性呼吸困難 | 2 (2.6%) | 0 | 0 | 0 | 2 (0.5%) |
| 肺硬化 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 肺浸潤 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 鼻の炎症 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 肺塞栓症 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 気道うっ血 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 急性肺水腫 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 喘息 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 気管支反応性亢進 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 気管支分泌物貯留 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 気管支拡張症 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 慢性気管支炎 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 肺気腫 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 上気道分泌増加 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 鼻乾燥 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 鼻潰瘍 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 副鼻腔不快感 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 副鼻腔分泌過多 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 咽頭紅斑 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 胸膜炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 胸膜痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 肺腫瘤 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 呼吸性アシドーシス | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 呼吸窮迫 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 拘束性肺疾患 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 副鼻腔障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| くしゃみ | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 頻呼吸 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 扁桃肥大 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 上気道咳症候群 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚および皮下組織障害 | 36 (46.2%) | 1 (1.3%) | 158 (54.1%) | 9 (3.1%) | 194 (52.4%) |
| 発疹 | 10 (12.8%) | 0 | 47 (16.1%) | 4 (1.4%) | 57 (15.4%) |
| そう痒症 | 6 (7.7%) | 0 | 22 (7.5%) | 0 | 28 (7.6%) |
| 点状出血 | 5 (6.4%) | 0 | 17 (5.8%) | 0 | 22 (5.9%) |
| 皮膚病変 | 1 (1.3%) | 0 | 19 (6.5%) | 0 | 20 (5.4%) |
| 斑状丘疹状皮疹 | 4 (5.1%) | 1 (1.3%) | 12 (4.1%) | 1 (0.3%) | 16 (4.3%) |
| 皮膚乾燥 | 4 (5.1%) | 0 | 10 (3.4%) | 0 | 14 (3.8%) |
| 斑状出血 | 3 (3.8%) | 0 | 10 (3.4%) | 0 | 13 (3.5%) |
| 紅斑 | 1 (1.3%) | 0 | 10 (3.4%) | 0 | 11 (3.0%) |
| 寝汗 | 2 (2.6%) | 0 | 9 (3.1%) | 0 | 11 (3.0%) |
| 脱毛症 | 3 (3.8%) | 0 | 7 (2.4%) | 0 | 10 (2.7%) |
| ざ瘡様皮膚炎 | 2 (2.6%) | 0 | 6 (2.1%) | 0 | 8 (2.2%) |
| 紫斑 | 1 (1.3%) | 0 | 6 (2.1%) | 2 (0.7%) | 7 (1.9%) |
| 多汗症 | 0 | 0 | 6 (2.1%) | 0 | 6 (1.6%) |
| 皮膚亀裂 | 1 (1.3%) | 0 | 5 (1.7%) | 0 | 6 (1.6%) |
| 嵌入爪 | 0 | 0 | 5 (1.7%) | 0 | 5 (1.4%) |
| 爪破損 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| 蕁麻疹 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| 水疱 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 全身性そう痒症 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 斑状皮疹 | 0 | 0 | 4 (1.4%) | 1 (0.3%) | 4 (1.1%) |
| 皮膚腫瘤 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 皮膚潰瘍 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| ざ瘡 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 褥瘡性潰瘍 | 1 (1.3%) | 0 | 2 (0.7%) | 1 (0.3%) | 3 (0.8%) |
| 湿疹 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 紅斑性皮疹 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 皮膚色素過剰 | 2 (2.6%) | 0 | 1 (0.3%) | 0 | 3 (0.8%) |
| 皮膚嚢腫 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 接触性皮膚炎 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 皮下出血 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 間擦疹 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 皮膚疼痛 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 全身性皮疹 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 丘疹性皮疹 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| そう痒性皮疹 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 皮膚変色 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 毛細血管炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 皮膚炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| アレルギー性皮膚炎 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 水疱性皮膚炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 皮脂欠乏性湿疹 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 貨幣状湿疹 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 過敏性血管炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 爪床出血 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 爪床障害 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床の炎症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 爪の不快感 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 爪の障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 爪ジストロフィー | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 爪線状隆起 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 爪痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 爪甲脱落症 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 手掌・足底発赤知覚不全症候群 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 脂肪織炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 色素沈着障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 毛孔性皮疹 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 皮膚色素減少 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 皮膚刺激 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 皮膚腫脹 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 乾皮症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 筋骨格系および結合組織障害 | 39 (50.0%) | 4 (5.1%) | 134 (45.9%) | 16 (5.5%) | 173 (46.8%) |
| 筋痙縮 | 16 (20.5%) | 0 | 51 (17.5%) | 0 | 67 (18.1%) |
| 背部痛 | 17 (21.8%) | 3 (3.8%) | 27 (9.2%) | 3 (1.0%) | 44 (11.9%) |
| 関節痛 | 6 (7.7%) | 0 | 32 (11.0%) | 2 (0.7%) | 38 (10.3%) |
| 筋肉痛 | 7 (9.0%) | 0 | 25 (8.6%) | 1 (0.3%) | 32 (8.6%) |
| 四肢痛 | 8 (10.3%) | 1 (1.3%) | 20 (6.8%) | 1 (0.3%) | 28 (7.6%) |
| 筋骨格痛 | 3 (3.8%) | 0 | 14 (4.8%) | 0 | 17 (4.6%) |
| 筋力低下 | 1 (1.3%) | 0 | 12 (4.1%) | 3 (1.0%) | 13 (3.5%) |
| 側腹部痛 | 2 (2.6%) | 0 | 6 (2.1%) | 2 (0.7%) | 8 (2.2%) |
| 頚部痛 | 1 (1.3%) | 0 | 5 (1.7%) | 0 | 6 (1.6%) |
| 変形性関節症 | 0 | 0 | 5 (1.7%) | 2 (0.7%) | 5 (1.4%) |
| 肢径部痛 | 0 | 0 | 4 (1.4%) | 1 (0.3%) | 4 (1.1%) |
| 四肢不快感 | 0 | 0 | 4 (1.4%) | 0 | 4 (1.1%) |
| 筋骨格硬直 | 2 (2.6%) | 0 | 1 (0.3%) | 0 | 3 (0.8%) |
| 骨痛 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 関節硬直 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 関節腫脹 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 運動性低下 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 筋骨格系胸痛 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| ミオパチー | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 軟部組織障害 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 関節炎 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 滑液包炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 外骨腫 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 痛風性関節炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 椎間板変性症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 椎間板突出 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 関節拘縮 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 関節滲出液 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 関節ロック | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋緊張 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 筋攣縮 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 筋骨格不快感 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 頚部腫瘤 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 骨壊死 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 骨粗鬆症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 顎痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 横紋筋融解症 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 滑液嚢腫 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 腱痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 椎間孔狭窄 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血液およびリンパ系障害 | 41 (52.6%) | 27 (34.6%) | 128 (43.8%) | 82 (28.1%) | 169 (45.7%) |
| 血小板減少症 | 19 (24.4%) | 8 (10.3%) | 55 (18.8%) | 33 (11.3%) | 74 (20.0%) |
| 好中球減少症 | 12 (15.4%) | 12 (15.4%) | 58 (19.9%) | 49 (16.8%) | 70 (18.9%) |
| 貧血 | 18 (23.1%) | 12 (15.4%) | 45 (15.4%) | 18 (6.2%) | 63 (17.0%) |
| 発熱性好中球減少症 | 4 (5.1%) | 4 (5.1%) | 9 (3.1%) | 9 (3.1%) | 13 (3.5%) |
| 白血球減少症 | 3 (3.8%) | 1 (1.3%) | 10 (3.4%) | 5 (1.7%) | 13 (3.5%) |
| 白血球増加症 | 1 (1.3%) | 0 | 6 (2.1%) | 3 (1.0%) | 7 (1.9%) |
| 内出血発生の増加傾向 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| リンパ球減少症 | 0 | 0 | 5 (1.7%) | 0 | 5 (1.4%) |
| リンパ球増加症 | 1 (1.3%) | 1 (1.3%) | 3 (1.0%) | 2 (0.7%) | 4 (1.1%) |
| リンパ節痛 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| リンパ節症 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 脾腫 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 骨髄機能不全 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 凝血異常 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 溶血 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 鉄欠乏性貧血 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 白血球停滞症候群 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 汎血球減少症 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 後腹膜リンパ節腫脹 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 脾臓出血 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 脾臓梗塞 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 血小板増加症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 代謝および栄養障害 | 28 (35.9%) | 13 (16.7%) | 122 (41.8%) | 39 (13.4%) | 150 (40.5%) |
| 食欲減退 | 16 (20.5%) | 2 (2.6%) | 46 (15.8%) | 1 (0.3%) | 62 (16.8%) |
| 低カリウム血症 | 6 (7.7%) | 3 (3.8%) | 28 (9.6%) | 12 (4.1%) | 34 (9.2%) |
| 高尿酸血症 | 8 (10.3%) | 4 (5.1%) | 17 (5.8%) | 6 (2.1%) | 25 (6.8%) |
| 脱水 | 3 (3.8%) | 2 (2.6%) | 19 (6.5%) | 5 (1.7%) | 22 (5.9%) |
| 低マグネシウム血症 | 4 (5.1%) | 0 | 17 (5.8%) | 1 (0.3%) | 21 (5.7%) |
| 高カリウム血症 | 2 (2.6%) | 0 | 11 (3.8%) | 5 (1.7%) | 13 (3.5%) |
| 低ナトリウム血症 | 4 (5.1%) | 3 (3.8%) | 8 (2.7%) | 5 (1.7%) | 12 (3.2%) |
| 低アルブミン血症 | 3 (3.8%) | 2 (2.6%) | 8 (2.7%) | 2 (0.7%) | 11 (3.0%) |
| 高血糖 | 2 (2.6%) | 0 | 7 (2.4%) | 2 (0.7%) | 9 (2.4%) |
| 低カルシウム血症 | 0 | 0 | 6 (2.1%) | 0 | 6 (1.6%) |
| 低血糖症 | 3 (3.8%) | 0 | 1 (0.3%) | 0 | 4 (1.1%) |
| 低リン酸血症 | 2 (2.6%) | 2 (2.6%) | 2 (0.7%) | 2 (0.7%) | 4 (1.1%) |
| 水分過負荷 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 痛風 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 酵素異常 | 1 (1.3%) | 0 | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| 高コレステロール血症 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 高ナトリウム血症 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 高リン酸塩血症 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 過小食 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 乳酸アシドーシス | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| アルコール不耐性 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 悪液質 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 糖尿病 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 糖尿病性ケトアシドーシス | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 高アルブミン血症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 高アンモニア血症 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 低蛋白血症 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 代謝性アシドーシス | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 腫瘍崩壊症候群 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| ２型糖尿病 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 神経系障害 | 25 (32.1%) | 0 | 96 (32.9%) | 9 (3.1%) | 121 (32.7%) |
| 頭痛 | 8 (10.3%) | 0 | 29 (9.9%) | 0 | 37 (10.0%) |
| 浮動性めまい | 6 (7.7%) | 0 | 20 (6.8%) | 0 | 26 (7.0%) |
| 末梢性感覚ニューロパチー | 0 | 0 | 14 (4.8%) | 1 (0.3%) | 14 (3.8%) |
| 体位性めまい | 5 (6.4%) | 0 | 5 (1.7%) | 0 | 10 (2.7%) |
| 錯感覚 | 1 (1.3%) | 0 | 7 (2.4%) | 0 | 8 (2.2%) |
| 記憶障害 | 3 (3.8%) | 0 | 4 (1.4%) | 0 | 7 (1.9%) |
| 末梢性ニューロパチー | 3 (3.8%) | 0 | 4 (1.4%) | 0 | 7 (1.9%) |
| 振戦 | 1 (1.3%) | 0 | 5 (1.7%) | 0 | 6 (1.6%) |
| 感覚鈍麻 | 0 | 0 | 5 (1.7%) | 1 (0.3%) | 5 (1.4%) |
| 健忘 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 傾眠 | 0 | 0 | 4 (1.4%) | 0 | 4 (1.1%) |
| 失神 | 0 | 0 | 4 (1.4%) | 4 (1.4%) | 4 (1.1%) |
| 平衡障害 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 構語障害 | 1 (1.3%) | 0 | 2 (0.7%) | 2 (0.7%) | 3 (0.8%) |
| 味覚異常 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 嗜眠 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 多発ニューロパチー | 0 | 0 | 3 (1.0%) | 1 (0.3%) | 3 (0.8%) |
| 認知症 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 頭蓋内出血 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 過眠症 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 神経痛 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 失神寸前の状態 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 下肢静止不能症候群 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 一過性脳虚血発作 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 灼熱足症候群 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 手根管症候群 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 大脳萎縮 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 脳血管発作 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 労作性めまい | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 脳症 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| てんかん | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 顔面部神経痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 顔面不全麻痺 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 頭部不快感 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 腰髄神経根障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 片頭痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 前兆を伴う片頭痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 筋痙直 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| ミオクローヌス | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼振 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 腓骨神経麻痺 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| ヘルペス後神経痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 坐骨神経痛 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 感覚障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 会話障害 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 緊張性頭痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 一過性全健忘 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血管性脳症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 臨床検査 | 32 (41.0%) | 10 (12.8%) | 80 (27.4%) | 25 (8.6%) | 112 (30.3%) |
| 血中クレアチニン増加 | 11 (14.1%) | 0 | 20 (6.8%) | 0 | 31 (8.4%) |
| 血小板数減少 | 1 (1.3%) | 0 | 13 (4.5%) | 2 (0.7%) | 14 (3.8%) |
| 体重減少 | 4 (5.1%) | 0 | 8 (2.7%) | 0 | 12 (3.2%) |
| 血中アルカリホスファターゼ増加 | 5 (6.4%) | 2 (2.6%) | 6 (2.1%) | 0 | 11 (3.0%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 1 (1.3%) | 0 | 9 (3.1%) | 1 (0.3%) | 10 (2.7%) |
| 血中ビリルビン増加 | 4 (5.1%) | 1 (1.3%) | 6 (2.1%) | 1 (0.3%) | 10 (2.7%) |
| 好中球数減少 | 3 (3.8%) | 3 (3.8%) | 6 (2.1%) | 5 (1.7%) | 9 (2.4%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| アラニンアミノトランスフェラーゼ増加 | 3 (3.8%) | 0 | 4 (1.4%) | 1 (0.3%) | 7 (1.9%) |
| 血中尿酸増加 | 3 (3.8%) | 2 (2.6%) | 4 (1.4%) | 1 (0.3%) | 7 (1.9%) |
| リンパ球数増加 | 1 (1.3%) | 0 | 5 (1.7%) | 4 (1.4%) | 6 (1.6%) |
| 体重増加 | 0 | 0 | 6 (2.1%) | 0 | 6 (1.6%) |
| 活性化部分トロンボプラスチン時間延長 | 2 (2.6%) | 1 (1.3%) | 3 (1.0%) | 0 | 5 (1.4%) |
| 血中乳酸脱水素酵素増加 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| 白血球数減少 | 1 (1.3%) | 1 (1.3%) | 4 (1.4%) | 4 (1.4%) | 5 (1.4%) |
| 血中免疫グロブリンG減少 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 国際標準比増加 | 1 (1.3%) | 1 (1.3%) | 2 (0.7%) | 2 (0.7%) | 3 (0.8%) |
| 白血球数増加 | 1 (1.3%) | 0 | 2 (0.7%) | 1 (0.3%) | 3 (0.8%) |
| 血中ブドウ糖増加 | 2 (2.6%) | 2 (2.6%) | 0 | 0 | 2 (0.5%) |
| 血中免疫グロブリンM減少 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 血圧上昇 | 0 | 0 | 2 (0.7%) | 2 (0.7%) | 2 (0.5%) |
| Ｃ－反応性蛋白増加 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 心雑音 | 2 (2.6%) | 0 | 0 | 0 | 2 (0.5%) |
| γ－グルタミルトランスフェラーゼ増加 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 糸球体濾過率減少 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| ヘモグロビン減少 | 0 | 0 | 2 (0.7%) | 2 (0.7%) | 2 (0.5%) |
| 免疫グロブリン減少 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| リンパ球数減少 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| トランスアミナーゼ上昇 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| アミラーゼ増加 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| アスペルギルス検査陽性 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血中アルブミン減少 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 血中重炭酸塩増加 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血中ビリルビン異常 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 血中クロール減少 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血中コレステロール増加 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血中クレアチン増加 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 血中免疫グロブリンA減少 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血中鉄減少 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血中マグネシウム減少 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血中リン減少 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血中カリウム減少 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 呼吸音異常 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 二酸化炭素減少 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸部コンピュータ断層撮影異常 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 駆出率減少 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| グリコヘモグロビン増加 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| ヘモフィルス検査陽性 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 心拍数増加 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 心拍数不整 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 肝酵素上昇 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 深吸気量減少 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 肝機能検査異常 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 黄斑部反射異常 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 平均赤血球容積増加 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血小板凝集異常 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 尿量減少 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 超低比重リポ蛋白増加 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 肺活量異常 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 傷害、中毒および処置合併症 | 22 (28.2%) | 2 (2.6%) | 79 (27.1%) | 11 (3.8%) | 101 (27.3%) |
| 挫傷 | 9 (11.5%) | 0 | 37 (12.7%) | 0 | 46 (12.4%) |
| 転倒 | 4 (5.1%) | 0 | 13 (4.5%) | 4 (1.4%) | 17 (4.6%) |
| 節足動物咬傷 | 0 | 0 | 6 (2.1%) | 0 | 6 (1.6%) |
| 処置による疼痛 | 2 (2.6%) | 0 | 4 (1.4%) | 0 | 6 (1.6%) |
| 硬膜下血腫 | 1 (1.3%) | 0 | 5 (1.7%) | 3 (1.0%) | 6 (1.6%) |
| 外傷性血腫 | 3 (3.8%) | 0 | 3 (1.0%) | 0 | 6 (1.6%) |
| 裂傷 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 皮膚擦過傷 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| サンバーン | 0 | 0 | 4 (1.4%) | 0 | 4 (1.1%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 創傷 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 動物咬傷 | 0 | 0 | 3 (1.0%) | 1 (0.3%) | 3 (0.8%) |
| 頭部損傷 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 靭帯捻挫 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 腰椎骨折 | 1 (1.3%) | 1 (1.3%) | 2 (0.7%) | 0 | 3 (0.8%) |
| 処置後出血 | 0 | 0 | 3 (1.0%) | 2 (0.7%) | 3 (0.8%) |
| 骨挫傷 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 擦過傷 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 顔面骨骨折 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 四肢損傷 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 眼窩周囲挫傷 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 肋骨骨折 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 皮膚創傷 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 脊椎圧迫骨折 | 2 (2.6%) | 1 (1.3%) | 0 | 0 | 2 (0.5%) |
| 脾破裂 | 0 | 0 | 2 (0.7%) | 2 (0.7%) | 2 (0.5%) |
| 熱傷 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 動物による引っかき傷 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 足関節部骨折 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 第２度熱傷 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼挫傷 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼外傷 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 足骨折 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼内異物 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 外傷性血尿 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 関節損傷 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 過量投与 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 処置後便秘 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 処置後血尿 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 処置後腫脹 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 外傷後疼痛 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢血腫 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 皮下血腫 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 脛骨骨折 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 歯牙破折 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 術後尿閉 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 創合併症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼障害 | 17 (21.8%) | 2 (2.6%) | 65 (22.3%) | 3 (1.0%) | 82 (22.2%) |
| 眼乾燥 | 3 (3.8%) | 0 | 13 (4.5%) | 0 | 16 (4.3%) |
| 流涙増加 | 5 (6.4%) | 0 | 8 (2.7%) | 0 | 13 (3.5%) |
| 霧視 | 3 (3.8%) | 0 | 10 (3.4%) | 0 | 13 (3.5%) |
| 白内障 | 1 (1.3%) | 1 (1.3%) | 10 (3.4%) | 2 (0.7%) | 11 (3.0%) |
| 視力低下 | 1 (1.3%) | 0 | 5 (1.7%) | 0 | 6 (1.6%) |
| 眼窩周囲浮腫 | 2 (2.6%) | 1 (1.3%) | 3 (1.0%) | 0 | 5 (1.4%) |
| 結膜出血 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 眼痛 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 眼充血 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 睫毛乱生 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 硝子体浮遊物 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 糖尿病網膜症 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 複視 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 眼出血 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 眼刺激 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 眼瞼下垂 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 羞明 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 眼瞼炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 片側失明 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 結膜充血 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼瞼内反 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼脂 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼の炎症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼そう痒症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼の異物感 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 緑内障 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 角膜炎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 黄斑変性 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| マイボーム腺機能不全 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 眼血管障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 開放隅角緑内障 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 動揺視 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 老視 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 網膜剥離 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 強膜出血 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 視力障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 硝子体出血 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 眼球乾燥症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 血管障害 | 22 (28.2%) | 5 (6.4%) | 59 (20.2%) | 21 (7.2%) | 81 (21.9%) |
| 高血圧 | 11 (14.1%) | 4 (5.1%) | 24 (8.2%) | 9 (3.1%) | 35 (9.5%) |
| 低血圧 | 6 (7.7%) | 1 (1.3%) | 15 (5.1%) | 4 (1.4%) | 21 (5.7%) |
| 血腫 | 4 (5.1%) | 0 | 8 (2.7%) | 0 | 12 (3.2%) |
| 深部静脈血栓症 | 1 (1.3%) | 0 | 6 (2.1%) | 2 (0.7%) | 7 (1.9%) |
| 潮紅 | 0 | 0 | 4 (1.4%) | 0 | 4 (1.1%) |
| 出血 | 0 | 0 | 4 (1.4%) | 3 (1.0%) | 4 (1.1%) |
| 起立性低血圧 | 1 (1.3%) | 0 | 2 (0.7%) | 1 (0.3%) | 3 (0.8%) |
| 静脈炎 | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 血圧変動 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| リンパ浮腫 | 1 (1.3%) | 1 (1.3%) | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| 表在性血栓性静脈炎 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 大動脈硬化症 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 循環虚脱 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| ほてり | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 高血圧クリーゼ | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 末梢血管障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 末梢静脈疾患 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 静脈瘤 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 心臓障害 | 17 (21.8%) | 9 (11.5%) | 47 (16.1%) | 17 (5.8%) | 64 (17.3%) |
| 心房細動 | 8 (10.3%) | 5 (6.4%) | 20 (6.8%) | 12 (4.1%) | 28 (7.6%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 頻脈 | 2 (2.6%) | 0 | 7 (2.4%) | 0 | 9 (2.4%) |
| 洞性頻脈 | 1 (1.3%) | 0 | 6 (2.1%) | 0 | 7 (1.9%) |
| 徐脈 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 動悸 | 0 | 0 | 4 (1.4%) | 0 | 4 (1.1%) |
| 心房粗動 | 2 (2.6%) | 1 (1.3%) | 1 (0.3%) | 0 | 3 (0.8%) |
| 洞性徐脈 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 上室性頻脈 | 0 | 0 | 3 (1.0%) | 1 (0.3%) | 3 (0.8%) |
| 不安定狭心症 | 1 (1.3%) | 1 (1.3%) | 1 (0.3%) | 0 | 2 (0.5%) |
| 心停止 | 0 | 0 | 2 (0.7%) | 2 (0.7%) | 2 (0.5%) |
| 心不全 | 1 (1.3%) | 1 (1.3%) | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| 心室性期外収縮 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 急性心筋梗塞 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 不整脈 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 冠動脈硬化症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 第一度房室ブロック | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| うっ血性心不全 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 心血管不全 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 変時性応答不全 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 冠動脈疾患 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 冠動脈閉塞 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| チアノーゼ | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 僧帽弁閉鎖不全症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 心筋梗塞 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 心嚢液貯留 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 心膜炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 洞不全症候群 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ストレス心筋症 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 頻脈性不整脈 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| トルサード　ド　ポアント | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 三尖弁疾患 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 心室性不整脈 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 心室性頻脈 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 精神障害 | 16 (20.5%) | 1 (1.3%) | 47 (16.1%) | 6 (2.1%) | 63 (17.0%) |
| 不眠症 | 7 (9.0%) | 0 | 19 (6.5%) | 0 | 26 (7.0%) |
| 不安 | 2 (2.6%) | 0 | 11 (3.8%) | 0 | 13 (3.5%) |
| 錯乱状態 | 3 (3.8%) | 1 (1.3%) | 9 (3.1%) | 3 (1.0%) | 12 (3.2%) |
| うつ病 | 3 (3.8%) | 0 | 9 (3.1%) | 1 (0.3%) | 12 (3.2%) |
| 激越 | 4 (5.1%) | 0 | 1 (0.3%) | 0 | 5 (1.4%) |
| 譫妄 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 希死念慮を有するうつ病 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 多幸気分 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 幻聴 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 幻視 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 易刺激性 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| リビドー減退 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 躁病 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 精神障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 精神状態変化 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 悪夢 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| パニック発作 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| パニック障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 腎および尿路障害 | 17 (21.8%) | 7 (9.0%) | 40 (13.7%) | 10 (3.4%) | 57 (15.4%) |
| 血尿 | 2 (2.6%) | 1 (1.3%) | 12 (4.1%) | 2 (0.7%) | 14 (3.8%) |
| 急性腎不全 | 5 (6.4%) | 4 (5.1%) | 7 (2.4%) | 2 (0.7%) | 12 (3.2%) |
| 排尿困難 | 3 (3.8%) | 0 | 5 (1.7%) | 0 | 8 (2.2%) |
| 腎不全 | 2 (2.6%) | 2 (2.6%) | 5 (1.7%) | 3 (1.0%) | 7 (1.9%) |
| 頻尿 | 2 (2.6%) | 0 | 4 (1.4%) | 0 | 6 (1.6%) |
| 水腎症 | 1 (1.3%) | 1 (1.3%) | 2 (0.7%) | 1 (0.3%) | 3 (0.8%) |
| 腎機能障害 | 2 (2.6%) | 0 | 1 (0.3%) | 0 | 3 (0.8%) |
| 尿閉 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 尿路閉塞 | 0 | 0 | 3 (1.0%) | 1 (0.3%) | 3 (0.8%) |
| 腎結石症 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 夜間頻尿 | 2 (2.6%) | 0 | 0 | 0 | 2 (0.5%) |
| 腎嚢胞 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性腎不全 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 尿失禁 | 2 (2.6%) | 0 | 0 | 0 | 2 (0.5%) |
| 高窒素血症 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 膀胱刺激症状 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 出血性膀胱炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 緊張性膀胱 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 失禁 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 尿意切迫 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 閉塞性尿路疾患 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 乏尿 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 腎仙痛 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 有痛性排尿困難 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 尿路痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 8 (10.3%) | 3 (3.8%) | 28 (9.6%) | 16 (5.5%) | 36 (9.7%) |
| マントル細胞リンパ腫 | 1 (1.3%) | 1 (1.3%) | 7 (2.4%) | 7 (2.4%) | 8 (2.2%) |
| 基底細胞癌 | 1 (1.3%) | 0 | 6 (2.1%) | 1 (0.3%) | 7 (1.9%) |
| 皮膚有棘細胞癌 | 3 (3.8%) | 0 | 2 (0.7%) | 0 | 5 (1.4%) |
| 膀胱移行上皮癌 | 1 (1.3%) | 1 (1.3%) | 1 (0.3%) | 0 | 2 (0.5%) |
| 前立腺癌 | 0 | 0 | 2 (0.7%) | 2 (0.7%) | 2 (0.5%) |
| 扁平上皮癌 | 1 (1.3%) | 0 | 1 (0.3%) | 1 (0.3%) | 2 (0.5%) |
| 急性骨髄性白血病 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 良性新生物 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 膀胱癌 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 肺腺癌 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 悪性胸水 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 口腔乳頭腫 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 唾液腺癌 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 皮膚癌 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 皮膚乳頭腫 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 胸腺腫 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 移行上皮癌 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 腫瘍フレア | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 耳および迷路障害 | 8 (10.3%) | 1 (1.3%) | 22 (7.5%) | 1 (0.3%) | 30 (8.1%) |
| 回転性めまい | 4 (5.1%) | 0 | 7 (2.4%) | 0 | 11 (3.0%) |
| 耳鳴 | 0 | 0 | 6 (2.1%) | 0 | 6 (1.6%) |
| 耳痛 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| 聴力低下 | 1 (1.3%) | 1 (1.3%) | 3 (1.0%) | 0 | 4 (1.1%) |
| 耳垢栓塞 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 耳不快感 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 難聴 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 耳出血 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 聴覚過敏 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 老人性難聴 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 生殖系および乳房障害 | 8 (10.3%) | 5 (6.4%) | 18 (6.2%) | 2 (0.7%) | 26 (7.0%) |
| 良性前立腺肥大症 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 血精液症 | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 性器浮腫 | 3 (3.8%) | 2 (2.6%) | 0 | 0 | 3 (0.8%) |
| 勃起不全 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 骨盤痛 | 0 | 0 | 2 (0.7%) | 1 (0.3%) | 2 (0.5%) |
| 腟出血 | 1 (1.3%) | 0 | 1 (0.3%) | 0 | 2 (0.5%) |
| 後天性包茎 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 乳房血腫 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房腫瘤 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 乳房痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 性器発疹 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 陰茎痛 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 陰嚢腫瘤 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 陰嚢浮腫 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 陰嚢痛 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 子宮腟脱 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 外陰腟痛 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 外陰腟そう痒症 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

**TSFAE15C: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Age Group (>=75 vs. <75) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Age (years) | | | | |
| | >= 75 | | < 75 | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 免疫系障害 | 3 (3.8%) | 0 | 16 (5.5%) | 0 | 19 (5.1%) |
| 低γグロブリン血症 | 1 (1.3%) | 0 | 4 (1.4%) | 0 | 5 (1.4%) |
| 節足動物咬傷アレルギー | 1 (1.3%) | 0 | 3 (1.0%) | 0 | 4 (1.1%) |
| 過敏症 | 1 (1.3%) | 0 | 2 (0.7%) | 0 | 3 (0.8%) |
| 季節性アレルギー | 0 | 0 | 3 (1.0%) | 0 | 3 (0.8%) |
| 薬物過敏症 | 0 | 0 | 2 (0.7%) | 0 | 2 (0.5%) |
| 造影剤アレルギー | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 食物アレルギー | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 肝胆道系障害 | 6 (7.7%) | 2 (2.6%) | 7 (2.4%) | 2 (0.7%) | 13 (3.5%) |
| 高ビリルビン血症 | 3 (3.8%) | 1 (1.3%) | 3 (1.0%) | 0 | 6 (1.6%) |
| 胆石症 | 1 (1.3%) | 1 (1.3%) | 2 (0.7%) | 0 | 3 (0.8%) |
| 胆管結石 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 胆管炎 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 肝不全 | 0 | 0 | 1 (0.3%) | 1 (0.3%) | 1 (0.3%) |
| 肝機能異常 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 中毒性肝炎 | 1 (1.3%) | 1 (1.3%) | 0 | 0 | 1 (0.3%) |
| 陶器様胆嚢 | 1 (1.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 内分泌障害 | 2 (2.6%) | 0 | 3 (1.0%) | 0 | 5 (1.4%) |
| 甲状腺機能低下症 | 2 (2.6%) | 0 | 3 (1.0%) | 0 | 5 (1.4%) |
| 先天性、家族性および遺伝性障害 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |
| 臍血腫 | 0 | 0 | 1 (0.3%) | 0 | 1 (0.3%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE15C.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae15c.sas] 15SEP2015, 14:12

参照元：5.3.5.3.1 ISS TSFAE15C

表 2.7.4-付録-50 Overall Summary of Treatment-emergent Adverse Events by Sex (Male vs. Female); Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE12PART1OF3: Overall Summary of Treatment-emergent Adverse Events by Sex (Male vs. Female); Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Sex | | Sex | |
| | Male | Female | Male | Female |
| Analysis Set: Safety Population | 85 | 26 | 104 | 16 |
| Any TEAE | 85 (100.0%) | 26 (100.0%) | 101 (97.1%) | 14 (87.5%) |
| Grade >= 3 | 65 (76.5%) | 19 (73.1%) | 76 (73.1%) | 11 (68.8%) |
| Drug related [a] | 77 (90.6%) | 21 (80.8%) | 83 (79.8%) | 12 (75.0%) |
| Grade >= 3 | 38 (44.7%) | 11 (42.3%) | 45 (43.3%) | 7 (43.8%) |
| Any TESAE | 49 (57.6%) | 13 (50.0%) | 54 (51.9%) | 5 (31.3%) |
| Grade >= 3 | 44 (51.8%) | 11 (42.3%) | 48 (46.2%) | 5 (31.3%) |
| Drug related a | 22 (25.9%) | 6 (23.1%) | 23 (22.1%) | 2 (12.5%) |
| TEAE leading to treatment discontinuation | 7 (8.2%) | 3 (11.5%) | 17 (16.3%) | 3 (18.8%) |
| TEAE leading to treatment dose reduction | 14 (16.5%) | 1 (3.8%) | 5 (4.8%) | 3 (18.8%) |
| TEAE with outcome death | 13 (15.3%) | 3 (11.5%) | 13 (12.5%) | 1 (6.3%) |
| Deaths within 30 days after last dose of study treatment [b] | 13 (15.3%) | 3 (11.5%) | 18 (17.3%) | 5 (31.3%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE12PART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae12.sas] 26OCT2015, 14:29

参照元：5.3.5.3.1 ISS TSFAE12PART1OF3

表 2.7.4-付録-51 Overall Summary of Treatment-emergent Adverse Events by Sex (Male vs. Female); Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE12PART2OF3: Overall Summary of Treatment-emergent Adverse Events by Sex (Male vs. Female); Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Sex | | Sex | |
| | Male | Female | Male | Female |
| Analysis Set: Safety Population | 100 | 39 | 106 | 33 |
| Any TEAE | 99 (99.0%) | 39 (100.0%) | 105 (99.1%) | 33 (100.0%) |
| Grade >= 3 | 77 (77.0%) | 17 (43.6%) | 92 (86.8%) | 29 (87.9%) |
| Drug related [a] | 81 (81.0%) | 34 (87.2%) | 100 (94.3%) | 33 (100.0%) |
| Grade >= 3 | 46 (46.0%) | 9 (23.1%) | 84 (79.2%) | 25 (75.8%) |
| Any TESAE | 55 (55.0%) | 12 (30.8%) | 63 (59.4%) | 17 (51.5%) |
| Grade >= 3 | 52 (52.0%) | 11 (28.2%) | 52 (49.1%) | 16 (48.5%) |
| Drug related [a] | 24 (24.0%) | 5 (12.8%) | 41 (38.7%) | 12 (36.4%) |
| TEAE leading to treatment discontinuation | 17 (17.0%) | 1 (2.6%) | 28 (26.4%) | 13 (39.4%) |
| TEAE leading to treatment dose reduction | 5 (5.0%) | 0 | 44 (41.5%) | 16 (48.5%) |
| TEAE with outcome death | 14 (14.0%) | 1 (2.6%) | 10 (9.4%) | 1 (3.0%) |
| Deaths within 30 days after last dose of study treatment [b] | 21 (21.0%) | 3 (7.7%) | 13 (12.3%) | 2 (6.1%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE12PART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae12.sas] 26OCT2015, 14:29

参照元：5.3.5.3.1 ISS TSFAE12PART2OF3

表 2.7.4-付録-52 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| Analysis set: safety | 289 | | 81 | | 370 |
| Subjects with any TEAE | 285 (98.6%) | 218 (75.4%) | 79 (97.5%) | 47 (58.0%) | 364 (98.4%) |
| System organ class | | | | | |
| Preferred term | | | | | |
| 感染症および寄生虫症 | 205 (70.9%) | 75 (26.0%) | 58 (71.6%) | 12 (14.8%) | 263 (71.1%) |
| 上気道感染 | 52 (18.0%) | 2 (0.7%) | 21 (25.9%) | 1 (1.2%) | 73 (19.7%) |
| 肺炎 | 38 (13.1%) | 29 (10.0%) | 6 (7.4%) | 4 (4.9%) | 44 (11.9%) |
| 副鼻腔炎 | 31 (10.7%) | 1 (0.3%) | 8 (9.9%) | 0 | 39 (10.5%) |
| 尿路感染 | 24 (8.3%) | 5 (1.7%) | 14 (17.3%) | 1 (1.2%) | 38 (10.3%) |
| 鼻咽頭炎 | 25 (8.7%) | 0 | 5 (6.2%) | 0 | 30 (8.1%) |
| 結膜炎 | 17 (5.9%) | 0 | 9 (11.1%) | 0 | 26 (7.0%) |
| 気管支炎 | 17 (5.9%) | 4 (1.4%) | 3 (3.7%) | 0 | 20 (5.4%) |
| 蜂巣炎 | 16 (5.5%) | 8 (2.8%) | 2 (2.5%) | 0 | 18 (4.9%) |
| 帯状疱疹 | 11 (3.8%) | 0 | 3 (3.7%) | 0 | 14 (3.8%) |
| 鼻炎 | 12 (4.2%) | 0 | 2 (2.5%) | 0 | 14 (3.8%) |
| 毛包炎 | 11 (3.8%) | 0 | 2 (2.5%) | 0 | 13 (3.5%) |
| 爪囲炎 | 8 (2.8%) | 0 | 5 (6.2%) | 0 | 13 (3.5%) |
| 下気道感染 | 10 (3.5%) | 4 (1.4%) | 2 (2.5%) | 1 (1.2%) | 12 (3.2%) |
| 皮膚感染 | 10 (3.5%) | 0 | 2 (2.5%) | 1 (1.2%) | 12 (3.2%) |
| 口腔ヘルペス | 7 (2.4%) | 0 | 4 (4.9%) | 0 | 11 (3.0%) |
| 気道感染 | 7 (2.4%) | 2 (0.7%) | 4 (4.9%) | 0 | 11 (3.0%) |
| 敗血症 | 8 (2.8%) | 8 (2.8%) | 3 (3.7%) | 3 (3.7%) | 11 (3.0%) |
| 胃腸炎 | 7 (2.4%) | 2 (0.7%) | 3 (3.7%) | 0 | 10 (2.7%) |
| 咽頭炎 | 5 (1.7%) | 1 (0.3%) | 2 (2.5%) | 0 | 7 (1.9%) |
| ウイルス感染 | 4 (1.4%) | 0 | 3 (3.7%) | 0 | 7 (1.9%) |
| 感染 | 5 (1.7%) | 2 (0.7%) | 1 (1.2%) | 0 | 6 (1.6%) |
| クロストリジウム・ディフィシレ大腸炎 | 4 (1.4%) | 2 (0.7%) | 1 (1.2%) | 1 (1.2%) | 5 (1.4%) |
| 眼感染 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯肉炎 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |
| 口腔カンジダ症 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |
| クロストリジウム・ディフィシレ感染 | 4 (1.4%) | 1 (0.3%) | 0 | 0 | 4 (1.1%) |
| インフルエンザ | 3 (1.0%) | 0 | 1 (1.2%) | 0 | 4 (1.1%) |
| 限局性感染 | 3 (1.0%) | 0 | 1 (1.2%) | 0 | 4 (1.1%) |
| 中耳炎 | 3 (1.0%) | 0 | 1 (1.2%) | 0 | 4 (1.1%) |
| 歯周炎 | 2 (0.7%) | 0 | 2 (2.5%) | 0 | 4 (1.1%) |
| 歯感染 | 2 (0.7%) | 0 | 2 (2.5%) | 0 | 4 (1.1%) |
| 菌血症 | 2 (0.7%) | 1 (0.3%) | 1 (1.2%) | 1 (1.2%) | 3 (0.8%) |
| 気管支肺炎 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| 膀胱炎 | 1 (0.3%) | 0 | 2 (2.5%) | 0 | 3 (0.8%) |
| 耳感染 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| ウイルス性胃腸炎 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| 単純ヘルペス | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 喉頭炎 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| 爪感染 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 外耳炎 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| ブドウ球菌感染 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| ウイルス性上気道感染 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 急性副鼻腔炎 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 細気管支炎 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 医療機器関連感染 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 憩室炎 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 感染性小腸結腸炎 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 丹毒 | 0 | 0 | 2 (2.5%) | 0 | 2 (0.5%) |
| 真菌感染 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚真菌感染 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 真菌性性器感染 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| ヘルペスウイルス感染 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 麦粒腫 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 爪真菌症 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| レンサ球菌性咽頭炎 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| ニューモシスチス・イロベチイ肺炎 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 細菌性肺炎 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 膿疱性皮疹 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 敗血症性ショック | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| ブドウ球菌性菌血症 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 歯膿瘍 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 細菌性尿路感染 | 1 (0.3%) | 1 (0.3%) | 1 (1.2%) | 0 | 2 (0.5%) |
| 尿路性敗血症 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 外陰部腟カンジダ症 | 0 | 0 | 2 (2.5%) | 0 | 2 (0.5%) |
| 創傷感染 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 腹部膿瘍 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 四肢膿瘍 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ダニ皮膚炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 膿疱性ざ瘡 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 肛門膿瘍 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 肛門カンジダ症 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 虫垂炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 穿孔性虫垂炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 異型肺炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 細菌尿 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| カンジダ性亀頭炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 胆道感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| ブラストシスティス感染 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 体部白癬 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房蜂巣炎 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| カンピロバクター胃腸炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| カンピロバクター感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| カンジダ感染 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 眼窩蜂巣炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 感染性胆嚢炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性副鼻腔炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| シトロバクター感染 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 涙嚢炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性脳炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 精巣上体炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 喉頭蓋炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 細菌性眼感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 真菌血症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘリコバクター胃潰瘍 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 消化管感染 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| ウイルス性消化管感染 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 性器カンジダ症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血腫感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘモフィルス感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| Ｂ型肝炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| ヒストプラスマ症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 埋込み部位感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 切開部位感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| クレブシエラ感染 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 口唇感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 細菌性下気道感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 肺感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| ライム病 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳腺炎 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 水疱性鼓膜炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼帯状疱疹 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 口腔真菌感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳頭腫ウイルス感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| クリプトコッカス性肺炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| クレブシエラ菌性肺炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 処置後感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 肺結核 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 腎盂腎炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 膿皮症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| レンサ球菌性膿皮症 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 狂犬病 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 直腸膿瘍 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性気道感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 軟部組織感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| ブドウ球菌皮膚感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| レンサ球菌感染 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 皮下組織膿瘍 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 足部白癬 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 扁桃炎 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 気管炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 真菌性尿路感染 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| シュードモナス性尿路感染 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 胃腸障害 | 201 (69.6%) | 33 (11.4%) | 54 (66.7%) | 6 (7.4%) | 255 (68.9%) |
| 下痢 | 115 (39.8%) | 12 (4.2%) | 31 (38.3%) | 1 (1.2%) | 146 (39.5%) |
| 悪心 | 57 (19.7%) | 1 (0.3%) | 23 (28.4%) | 0 | 80 (21.6%) |
| 嘔吐 | 38 (13.1%) | 1 (0.3%) | 24 (29.6%) | 0 | 62 (16.8%) |
| 便秘 | 46 (15.9%) | 0 | 11 (13.6%) | 0 | 57 (15.4%) |
| 腹痛 | 31 (10.7%) | 10 (3.5%) | 11 (13.6%) | 3 (3.7%) | 42 (11.4%) |
| 口内炎 | 23 (8.0%) | 3 (1.0%) | 8 (9.9%) | 0 | 31 (8.4%) |
| 消化不良 | 23 (8.0%) | 0 | 5 (6.2%) | 0 | 28 (7.6%) |
| 上腹部痛 | 12 (4.2%) | 1 (0.3%) | 4 (4.9%) | 0 | 16 (4.3%) |
| 腹部膨満 | 10 (3.5%) | 0 | 4 (4.9%) | 0 | 14 (3.8%) |
| 口内乾燥 | 9 (3.1%) | 0 | 5 (6.2%) | 0 | 14 (3.8%) |
| 胃食道逆流性疾患 | 7 (2.4%) | 0 | 6 (7.4%) | 0 | 13 (3.5%) |
| 嚥下障害 | 8 (2.8%) | 1 (0.3%) | 1 (1.2%) | 1 (1.2%) | 9 (2.4%) |
| 腹部不快感 | 4 (1.4%) | 0 | 4 (4.9%) | 0 | 8 (2.2%) |
| 口腔内痛 | 7 (2.4%) | 1 (0.3%) | 1 (1.2%) | 0 | 8 (2.2%) |
| 口腔内潰瘍形成 | 7 (2.4%) | 0 | 0 | 0 | 7 (1.9%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 放屁 | 4 (1.4%) | 0 | 2 (2.5%) | 0 | 6 (1.6%) |
| 胃炎 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 心窩部不快感 | 3 (1.0%) | 0 | 2 (2.5%) | 0 | 5 (1.4%) |
| 舌痛 | 5 (1.7%) | 0 | 0 | 0 | 5 (1.4%) |
| 痔核 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| アフタ性口内炎 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| おくび | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| イレウス | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 直腸出血 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 舌潰瘍 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 下腹部痛 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 齲歯 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 軟便 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 食中毒 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 排便回数増加 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 胃潰瘍 | 1 (0.3%) | 1 (0.3%) | 1 (1.2%) | 0 | 2 (0.5%) |
| 歯肉出血 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 歯肉浮腫 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 吐血 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 麻痺性イレウス | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 鼠径ヘルニア | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 口唇潰瘍 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 下部消化管出血 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 口腔内出血 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 歯周病 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 肛門周囲痛 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 直腸炎 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 直腸裂 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 小腸閉塞 | 1 (0.3%) | 1 (0.3%) | 1 (1.2%) | 1 (1.2%) | 2 (0.5%) |
| 歯痛 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 裂肛 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 肛門直腸障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 萎縮性舌炎 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| バレット食道 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 大腸炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 歯不快感 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血性下痢 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 十二指腸狭窄 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 十二指腸潰瘍 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 十二指腸炎 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 十二指腸胃逆流 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 便失禁 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 糞塊 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 胃前庭部毛細血管拡張症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 出血性胃炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 歯肉痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血便排泄 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 痔出血 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 過敏性腸症候群 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 口唇水疱 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇びらん | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇腫脹 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 弛緩歯 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| メレナ | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 嚥下痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 口蓋障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 慢性膵炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 舌突出 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 直腸潰瘍 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 唾液腺結石 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 変色歯 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 歯の障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯の脱落 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 一般・全身障害および投与部位の状態 | 188 (65.1%) | 24 (8.3%) | 51 (63.0%) | 14 (17.3%) | 239 (64.6%) |
| 疲労 | 98 (33.9%) | 10 (3.5%) | 31 (38.3%) | 6 (7.4%) | 129 (34.9%) |
| 末梢性浮腫 | 59 (20.4%) | 3 (1.0%) | 15 (18.5%) | 3 (3.7%) | 74 (20.0%) |
| 発熱 | 50 (17.3%) | 2 (0.7%) | 18 (22.2%) | 1 (1.2%) | 68 (18.4%) |
| 無力症 | 27 (9.3%) | 4 (1.4%) | 5 (6.2%) | 1 (1.2%) | 32 (8.6%) |
| 悪寒 | 14 (4.8%) | 0 | 4 (4.9%) | 0 | 18 (4.9%) |
| 胸痛 | 12 (4.2%) | 0 | 3 (3.7%) | 0 | 15 (4.1%) |
| 末梢腫脹 | 14 (4.8%) | 1 (0.3%) | 1 (1.2%) | 0 | 15 (4.1%) |
| インフルエンザ様疾患 | 11 (3.8%) | 0 | 3 (3.7%) | 0 | 14 (3.8%) |
| 疼痛 | 10 (3.5%) | 1 (0.3%) | 1 (1.2%) | 0 | 11 (3.0%) |
| 非心臓性胸痛 | 6 (2.1%) | 0 | 2 (2.5%) | 2 (2.5%) | 8 (2.2%) |
| 粘膜の炎症 | 4 (1.4%) | 0 | 2 (2.5%) | 1 (1.2%) | 6 (1.6%) |
| 全身健康状態低下 | 5 (1.7%) | 2 (0.7%) | 0 | 0 | 5 (1.4%) |
| 倦怠感 | 3 (1.0%) | 0 | 2 (2.5%) | 0 | 5 (1.4%) |
| 局所腫脹 | 4 (1.4%) | 1 (0.3%) | 0 | 0 | 4 (1.1%) |
| 多臓器不全 | 3 (1.0%) | 3 (1.0%) | 1 (1.2%) | 1 (1.2%) | 4 (1.1%) |
| 胸部不快感 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 歩行障害 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 全身性浮腫 | 2 (0.7%) | 0 | 1 (1.2%) | 1 (1.2%) | 3 (0.8%) |
| 注射部位内出血 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 乾燥症 | 1 (0.3%) | 0 | 2 (2.5%) | 1 (1.2%) | 3 (0.8%) |
| 腋窩痛 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 早期満腹 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 重力性浮腫 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 低体温 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 炎症 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 浮腫 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 活動状態低下 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| カテーテル留置部位関連反応 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 死亡 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 医療機器リーク | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 顔面浮腫 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 異常感 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 冷感 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 熱感 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 治癒不良 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 硬結 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 注入部位血管外漏出 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 注射部位紅斑 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位漏出 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位出血 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位疼痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位反応 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 先行疾患の改善 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 温度変化不耐症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 評価不能の事象 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸器、胸郭および縦隔障害 | 163 (56.4%) | 24 (8.3%) | 37 (45.7%) | 11 (13.6%) | 200 (54.1%) |
| 咳嗽 | 69 (23.9%) | 0 | 12 (14.8%) | 0 | 81 (21.9%) |
| 呼吸困難 | 58 (20.1%) | 8 (2.8%) | 11 (13.6%) | 4 (4.9%) | 69 (18.6%) |
| 鼻出血 | 29 (10.0%) | 1 (0.3%) | 3 (3.7%) | 0 | 32 (8.6%) |
| 口腔咽頭痛 | 27 (9.3%) | 0 | 2 (2.5%) | 0 | 29 (7.8%) |
| 胸水 | 19 (6.6%) | 5 (1.7%) | 4 (4.9%) | 2 (2.5%) | 23 (6.2%) |
| 湿性咳嗽 | 14 (4.8%) | 0 | 1 (1.2%) | 0 | 15 (4.1%) |
| 鼻閉 | 10 (3.5%) | 0 | 3 (3.7%) | 0 | 13 (3.5%) |
| 呼吸不全 | 6 (2.1%) | 6 (2.1%) | 4 (4.9%) | 4 (4.9%) | 10 (2.7%) |
| 鼻漏 | 8 (2.8%) | 0 | 1 (1.2%) | 0 | 9 (2.4%) |
| 発声障害 | 6 (2.1%) | 0 | 2 (2.5%) | 0 | 8 (2.2%) |
| 慢性閉塞性肺疾患 | 6 (2.1%) | 4 (1.4%) | 0 | 0 | 6 (1.6%) |
| アレルギー性鼻炎 | 4 (1.4%) | 0 | 2 (2.5%) | 0 | 6 (1.6%) |
| 副鼻腔うっ血 | 6 (2.1%) | 0 | 0 | 0 | 6 (1.6%) |
| 上気道うっ血 | 6 (2.1%) | 0 | 0 | 0 | 6 (1.6%) |
| 低酸素症 | 3 (1.0%) | 2 (0.7%) | 2 (2.5%) | 2 (2.5%) | 5 (1.4%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| しゃっくり | 3 (1.0%) | 0 | 1 (1.2%) | 0 | 4 (1.1%) |
| 気胸 | 4 (1.4%) | 2 (0.7%) | 0 | 0 | 4 (1.1%) |
| 喀血 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 鼻部不快感 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 肺水腫 | 2 (0.7%) | 1 (0.3%) | 1 (1.2%) | 0 | 3 (0.8%) |
| ラ音 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 喘鳴 | 1 (0.3%) | 0 | 2 (2.5%) | 0 | 3 (0.8%) |
| 無気肺 | 0 | 0 | 2 (2.5%) | 0 | 2 (0.5%) |
| 労作性呼吸困難 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 肺硬化 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 肺浸潤 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 鼻の炎症 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 肺塞栓症 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 気道うっ血 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 急性肺水腫 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 喘息 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 気管支反応性亢進 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 気管支分泌物貯留 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 気管支拡張症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 慢性気管支炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 肺気腫 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 上気道分泌増加 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 鼻乾燥 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 鼻潰瘍 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 副鼻腔不快感 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 副鼻腔分泌過多 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 咽頭紅斑 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸膜炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸膜痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 肺腫瘤 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸性アシドーシス | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 呼吸窮迫 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 拘束性肺疾患 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 副鼻腔障害 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| くしゃみ | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 頻呼吸 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 扁桃肥大 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 上気道咳症候群 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚および皮下組織障害 | 156 (54.0%) | 9 (3.1%) | 38 (46.9%) | 1 (1.2%) | 194 (52.4%) |
| 発疹 | 48 (16.6%) | 4 (1.4%) | 9 (11.1%) | 0 | 57 (15.4%) |
| そう痒症 | 23 (8.0%) | 0 | 5 (6.2%) | 0 | 28 (7.6%) |
| 点状出血 | 16 (5.5%) | 0 | 6 (7.4%) | 0 | 22 (5.9%) |
| 皮膚病変 | 17 (5.9%) | 0 | 3 (3.7%) | 0 | 20 (5.4%) |
| 斑状丘疹状皮疹 | 12 (4.2%) | 2 (0.7%) | 4 (4.9%) | 0 | 16 (4.3%) |
| 皮膚乾燥 | 13 (4.5%) | 0 | 1 (1.2%) | 0 | 14 (3.8%) |
| 斑状出血 | 12 (4.2%) | 0 | 1 (1.2%) | 0 | 13 (3.5%) |
| 紅斑 | 10 (3.5%) | 0 | 1 (1.2%) | 0 | 11 (3.0%) |
| 寝汗 | 8 (2.8%) | 0 | 3 (3.7%) | 0 | 11 (3.0%) |
| 脱毛症 | 3 (1.0%) | 0 | 7 (8.6%) | 0 | 10 (2.7%) |
| ざ瘡様皮膚炎 | 6 (2.1%) | 0 | 2 (2.5%) | 0 | 8 (2.2%) |
| 紫斑 | 6 (2.1%) | 1 (0.3%) | 1 (1.2%) | 1 (1.2%) | 7 (1.9%) |
| 多汗症 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 皮膚亀裂 | 3 (1.0%) | 0 | 3 (3.7%) | 0 | 6 (1.6%) |
| 嵌入爪 | 5 (1.7%) | 0 | 0 | 0 | 5 (1.4%) |
| 爪破損 | 3 (1.0%) | 0 | 2 (2.5%) | 0 | 5 (1.4%) |
| 蕁麻疹 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |
| 水疱 | 3 (1.0%) | 0 | 1 (1.2%) | 0 | 4 (1.1%) |
| 全身性そう痒症 | 3 (1.0%) | 0 | 1 (1.2%) | 0 | 4 (1.1%) |
| 斑状皮疹 | 3 (1.0%) | 1 (0.3%) | 1 (1.2%) | 0 | 4 (1.1%) |
| 皮膚腫瘤 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| 皮膚潰瘍 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| ざ瘡 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 褥瘡性潰瘍 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| 湿疹 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 紅斑性皮疹 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 皮膚色素過剰 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 皮膚嚢腫 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 接触性皮膚炎 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 皮下出血 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 間擦疹 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 皮膚疼痛 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 全身性皮疹 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 丘疹性皮疹 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| そう痒性皮疹 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚変色 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 毛細血管炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| アレルギー性皮膚炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 水疱性皮膚炎 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 皮脂欠乏性湿疹 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 貨幣状湿疹 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 過敏性血管炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床出血 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床の炎症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪の不快感 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪の障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪ジストロフィー | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 爪線状隆起 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪甲脱落症 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 手掌・足底発赤知覚不全症候群 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 脂肪織炎 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 色素沈着障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 毛孔性皮疹 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚色素減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 皮膚刺激 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚腫脹 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 乾皮症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋骨格系および結合組織障害 | 138 (47.8%) | 17 (5.9%) | 35 (43.2%) | 3 (3.7%) | 173 (46.8%) |
| 筋痙縮 | 53 (18.3%) | 0 | 14 (17.3%) | 0 | 67 (18.1%) |
| 背部痛 | 36 (12.5%) | 5 (1.7%) | 8 (9.9%) | 1 (1.2%) | 44 (11.9%) |
| 関節痛 | 33 (11.4%) | 2 (0.7%) | 5 (6.2%) | 0 | 38 (10.3%) |
| 筋肉痛 | 26 (9.0%) | 1 (0.3%) | 6 (7.4%) | 0 | 32 (8.6%) |
| 四肢痛 | 20 (6.9%) | 2 (0.7%) | 8 (9.9%) | 0 | 28 (7.6%) |
| 筋骨格痛 | 16 (5.5%) | 0 | 1 (1.2%) | 0 | 17 (4.6%) |
| 筋力低下 | 10 (3.5%) | 2 (0.7%) | 3 (3.7%) | 1 (1.2%) | 13 (3.5%) |
| 側腹部痛 | 6 (2.1%) | 2 (0.7%) | 2 (2.5%) | 0 | 8 (2.2%) |
| 頚部痛 | 4 (1.4%) | 0 | 2 (2.5%) | 0 | 6 (1.6%) |
| 変形性関節症 | 3 (1.0%) | 2 (0.7%) | 2 (2.5%) | 0 | 5 (1.4%) |
| 肢径部痛 | 4 (1.4%) | 1 (0.3%) | 0 | 0 | 4 (1.1%) |
| 四肢不快感 | 3 (1.0%) | 0 | 1 (1.2%) | 0 | 4 (1.1%) |
| 筋骨格硬直 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 骨痛 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 関節硬直 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 関節腫脹 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 運動性低下 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 筋骨格系胸痛 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| ミオパチー | 1 (0.3%) | 0 | 1 (1.2%) | 1 (1.2%) | 2 (0.5%) |
| 軟部組織障害 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 関節炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 滑液包炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 外骨腫 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 痛風性関節炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 椎間板変性症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 椎間板突出 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 関節拘縮 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 関節滲出液 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 関節ロック | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋緊張 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋攣縮 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋骨格不快感 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 頚部腫瘤 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 骨壊死 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 骨粗鬆症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 顎痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 横紋筋融解症 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 滑液嚢腫 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 腱痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 椎間孔狭窄 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血液およびリンパ系障害 | 132 (45.7%) | 87 (30.1%) | 37 (45.7%) | 22 (27.2%) | 169 (45.7%) |
| 血小板減少症 | 55 (19.0%) | 32 (11.1%) | 19 (23.5%) | 9 (11.1%) | 74 (20.0%) |
| 好中球減少症 | 58 (20.1%) | 51 (17.6%) | 12 (14.8%) | 10 (12.3%) | 70 (18.9%) |
| 貧血 | 44 (15.2%) | 20 (6.9%) | 19 (23.5%) | 10 (12.3%) | 63 (17.0%) |
| 発熱性好中球減少症 | 9 (3.1%) | 9 (3.1%) | 4 (4.9%) | 4 (4.9%) | 13 (3.5%) |
| 白血球減少症 | 12 (4.2%) | 5 (1.7%) | 1 (1.2%) | 1 (1.2%) | 13 (3.5%) |
| 白血球増加症 | 5 (1.7%) | 2 (0.7%) | 2 (2.5%) | 1 (1.2%) | 7 (1.9%) |
| 内出血発生の増加傾向 | 5 (1.7%) | 0 | 0 | 0 | 5 (1.4%) |
| リンパ球減少症 | 3 (1.0%) | 0 | 2 (2.5%) | 0 | 5 (1.4%) |
| リンパ球増加症 | 2 (0.7%) | 1 (0.3%) | 2 (2.5%) | 2 (2.5%) | 4 (1.1%) |
| リンパ節痛 | 1 (0.3%) | 0 | 1 (1.2%) | 1 (1.2%) | 2 (0.5%) |
| リンパ節症 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 脾腫 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 骨髄機能不全 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 凝血異常 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 溶血 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 鉄欠乏性貧血 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 白血球停滞症候群 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 汎血球減少症 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 後腹膜リンパ節腫脹 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 脾臓出血 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 脾臓梗塞 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 血小板増加症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 代謝および栄養障害 | 113 (39.1%) | 39 (13.5%) | 37 (45.7%) | 13 (16.0%) | 150 (40.5%) |
| 食欲減退 | 48 (16.6%) | 2 (0.7%) | 14 (17.3%) | 1 (1.2%) | 62 (16.8%) |
| 低カリウム血症 | 22 (7.6%) | 8 (2.8%) | 12 (14.8%) | 7 (8.6%) | 34 (9.2%) |
| 高尿酸血症 | 19 (6.6%) | 9 (3.1%) | 6 (7.4%) | 1 (1.2%) | 25 (6.8%) |
| 脱水 | 18 (6.2%) | 5 (1.7%) | 4 (4.9%) | 2 (2.5%) | 22 (5.9%) |
| 低マグネシウム血症 | 15 (5.2%) | 1 (0.3%) | 6 (7.4%) | 0 | 21 (5.7%) |
| 高カリウム血症 | 9 (3.1%) | 4 (1.4%) | 4 (4.9%) | 1 (1.2%) | 13 (3.5%) |
| 低ナトリウム血症 | 6 (2.1%) | 5 (1.7%) | 6 (7.4%) | 3 (3.7%) | 12 (3.2%) |
| 低アルブミン血症 | 11 (3.8%) | 4 (1.4%) | 0 | 0 | 11 (3.0%) |
| 高血糖 | 4 (1.4%) | 1 (0.3%) | 5 (6.2%) | 1 (1.2%) | 9 (2.4%) |
| 低カルシウム血症 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 低血糖症 | 3 (1.0%) | 0 | 1 (1.2%) | 0 | 4 (1.1%) |
| 低リン酸血症 | 2 (0.7%) | 2 (0.7%) | 2 (2.5%) | 2 (2.5%) | 4 (1.1%) |
| 水分過負荷 | 1 (0.3%) | 0 | 2 (2.5%) | 0 | 3 (0.8%) |
| 痛風 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 酵素異常 | 0 | 0 | 2 (2.5%) | 1 (1.2%) | 2 (0.5%) |
| 高コレステロール血症 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 高ナトリウム血症 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 高リン酸塩血症 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 過小食 | 1 (0.3%) | 1 (0.3%) | 1 (1.2%) | 0 | 2 (0.5%) |
| 乳酸アシドーシス | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| アルコール不耐性 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 悪液質 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 糖尿病 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 糖尿病性ケトアシドーシス | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 高アルブミン血症 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 高アンモニア血症 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 低蛋白血症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 代謝性アシドーシス | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 腫瘍崩壊症候群 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| ２型糖尿病 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 神経系障害 | 94 (32.5%) | 8 (2.8%) | 27 (33.3%) | 1 (1.2%) | 121 (32.7%) |
| 頭痛 | 29 (10.0%) | 0 | 8 (9.9%) | 0 | 37 (10.0%) |
| 浮動性めまい | 21 (7.3%) | 0 | 5 (6.2%) | 0 | 26 (7.0%) |
| 末梢性感覚ニューロパチー | 10 (3.5%) | 1 (0.3%) | 4 (4.9%) | 0 | 14 (3.8%) |
| 体位性めまい | 5 (1.7%) | 0 | 5 (6.2%) | 0 | 10 (2.7%) |
| 錯感覚 | 7 (2.4%) | 0 | 1 (1.2%) | 0 | 8 (2.2%) |
| 記憶障害 | 4 (1.4%) | 0 | 3 (3.7%) | 0 | 7 (1.9%) |
| 末梢性ニューロパチー | 7 (2.4%) | 0 | 0 | 0 | 7 (1.9%) |
| 振戦 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 感覚鈍麻 | 3 (1.0%) | 1 (0.3%) | 2 (2.5%) | 0 | 5 (1.4%) |
| 健忘 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| 傾眠 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| 失神 | 4 (1.4%) | 4 (1.4%) | 0 | 0 | 4 (1.1%) |
| 平衡障害 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 構語障害 | 1 (0.3%) | 1 (0.3%) | 2 (2.5%) | 1 (1.2%) | 3 (0.8%) |
| 味覚異常 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 嗜眠 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 多発ニューロパチー | 2 (0.7%) | 1 (0.3%) | 1 (1.2%) | 0 | 3 (0.8%) |
| 認知症 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 頭蓋内出血 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 過眠症 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 神経痛 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 失神寸前の状態 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 下肢静止不能症候群 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 副鼻腔炎に伴う頭痛 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 一過性脳虚血発作 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 灼熱足症候群 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 手根管症候群 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 大脳萎縮 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 脳血管発作 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 労作性めまい | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 脳症 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| てんかん | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 顔面部神経痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 顔面不全麻痺 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 頭部不快感 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 腰髄神経根障害 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 片頭痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 前兆を伴う片頭痛 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 筋痙直 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ミオクローヌス | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼振 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 腓骨神経麻痺 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘルペス後神経痛 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 坐骨神経痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 感覚障害 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 会話障害 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 緊張性頭痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 一過性全健忘 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血管性脳症 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 臨床検査 | 91 (31.5%) | 27 (9.3%) | 21 (25.9%) | 8 (9.9%) | 112 (30.3%) |
| 血中クレアチニン増加 | 26 (9.0%) | 0 | 5 (6.2%) | 0 | 31 (8.4%) |
| 血小板数減少 | 10 (3.5%) | 1 (0.3%) | 4 (4.9%) | 1 (1.2%) | 14 (3.8%) |
| 体重減少 | 9 (3.1%) | 0 | 3 (3.7%) | 0 | 12 (3.2%) |
| 血中アルカリホスファターゼ増加 | 8 (2.8%) | 2 (0.7%) | 3 (3.7%) | 0 | 11 (3.0%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 8 (2.8%) | 1 (0.3%) | 2 (2.5%) | 0 | 10 (2.7%) |
| 血中ビリルビン増加 | 8 (2.8%) | 1 (0.3%) | 2 (2.5%) | 1 (1.2%) | 10 (2.7%) |
| 好中球数減少 | 7 (2.4%) | 6 (2.1%) | 2 (2.5%) | 2 (2.5%) | 9 (2.4%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| アラニンアミノトランスフェラーゼ増加 | 5 (1.7%) | 1 (0.3%) | 2 (2.5%) | 0 | 7 (1.9%) |
| 血中尿酸増加 | 5 (1.7%) | 2 (0.7%) | 2 (2.5%) | 1 (1.2%) | 7 (1.9%) |
| リンパ球数増加 | 5 (1.7%) | 4 (1.4%) | 1 (1.2%) | 0 | 6 (1.6%) |
| 体重増加 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 活性化部分トロンボプラスチン時間延長 | 4 (1.4%) | 0 | 1 (1.2%) | 1 (1.2%) | 5 (1.4%) |
| 血中乳酸脱水素酵素増加 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |
| 白血球数減少 | 4 (1.4%) | 4 (1.4%) | 1 (1.2%) | 1 (1.2%) | 5 (1.4%) |
| 血中免疫グロブリンG減少 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 国際標準比増加 | 1 (0.3%) | 1 (0.3%) | 2 (2.5%) | 2 (2.5%) | 3 (0.8%) |
| 白血球数増加 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| 血中ブドウ糖増加 | 1 (0.3%) | 1 (0.3%) | 1 (1.2%) | 1 (1.2%) | 2 (0.5%) |
| 血中免疫グロブリンM減少 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 血圧上昇 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| Ｃ－反応性蛋白増加 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 心雑音 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| γ－グルタミルトランスフェラーゼ増加 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 糸球体濾過率減少 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| ヘモグロビン減少 | 1 (0.3%) | 1 (0.3%) | 1 (1.2%) | 1 (1.2%) | 2 (0.5%) |
| 免疫グロブリン減少 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| リンパ球数減少 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| トランスアミナーゼ上昇 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| アミラーゼ増加 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| アスペルギルス検査陽性 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中アルブミン減少 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 血中重炭酸塩増加 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中ビリルビン異常 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 血中クロール減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中コレステロール増加 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中クレアチン増加 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 血中免疫グロブリンA減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中鉄減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中マグネシウム減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中リン減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中カリウム減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸音異常 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 二酸化炭素減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸部コンピュータ断層撮影異常 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 駆出率減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| グリコヘモグロビン増加 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘモフィルス検査陽性 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 心拍数増加 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 心拍数不整 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 肝酵素上昇 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 深吸気量減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 肝機能検査異常 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 黄斑部反射異常 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 平均赤血球容積増加 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 血小板凝集異常 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 尿量減少 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 超低比重リポ蛋白増加 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 肺活量異常 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 傷害、中毒および処置合併症 | 82 (28.4%) | 12 (4.2%) | 19 (23.5%) | 1 (1.2%) | 101 (27.3%) |
| 挫傷 | 36 (12.5%) | 0 | 10 (12.3%) | 0 | 46 (12.4%) |
| 転倒 | 15 (5.2%) | 4 (1.4%) | 2 (2.5%) | 0 | 17 (4.6%) |
| 節足動物咬傷 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 処置による疼痛 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 硬膜下血腫 | 6 (2.1%) | 3 (1.0%) | 0 | 0 | 6 (1.6%) |
| 外傷性血腫 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 裂傷 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| 皮膚擦過傷 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| サンバーン | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 創傷 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| 動物咬傷 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| 頭部損傷 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 靭帯捻挫 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 腰椎骨折 | 2 (0.7%) | 0 | 1 (1.2%) | 1 (1.2%) | 3 (0.8%) |
| 処置後出血 | 3 (1.0%) | 2 (0.7%) | 0 | 0 | 3 (0.8%) |
| 骨挫傷 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 擦過傷 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 顔面骨骨折 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 四肢損傷 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 眼窩周囲挫傷 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 肋骨骨折 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚創傷 | 0 | 0 | 2 (2.5%) | 0 | 2 (0.5%) |
| 脊椎圧迫骨折 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 脾破裂 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 熱傷 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 動物による引っかき傷 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 足関節部骨折 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 第２度熱傷 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼挫傷 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼外傷 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 足骨折 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼内異物 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 外傷性血尿 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 関節損傷 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 過量投与 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 処置後便秘 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 処置後血尿 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 処置後腫脹 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 外傷後疼痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢血腫 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮下血腫 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 脛骨骨折 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 歯牙破折 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 術後尿閉 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 創合併症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼障害 | 64 (22.1%) | 3 (1.0%) | 18 (22.2%) | 2 (2.5%) | 82 (22.2%) |
| 眼乾燥 | 13 (4.5%) | 0 | 3 (3.7%) | 0 | 16 (4.3%) |
| 流涙増加 | 9 (3.1%) | 0 | 4 (4.9%) | 0 | 13 (3.5%) |
| 霧視 | 11 (3.8%) | 0 | 2 (2.5%) | 0 | 13 (3.5%) |
| 白内障 | 7 (2.4%) | 1 (0.3%) | 4 (4.9%) | 2 (2.5%) | 11 (3.0%) |
| 視力低下 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 眼窩周囲浮腫 | 4 (1.4%) | 1 (0.3%) | 1 (1.2%) | 0 | 5 (1.4%) |
| 結膜出血 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 眼痛 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 眼充血 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 睫毛乱生 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 硝子体浮遊物 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 糖尿病網膜症 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 複視 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 眼出血 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 眼刺激 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 眼瞼下垂 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 羞明 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 眼瞼炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 片側失明 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 結膜充血 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼瞼内反 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼脂 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼の炎症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼そう痒症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼の異物感 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 緑内障 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 角膜炎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 黄斑変性 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| マイボーム腺機能不全 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼血管障害 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 開放隅角緑内障 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 動揺視 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 老視 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 網膜剥離 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 強膜出血 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 視力障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 硝子体出血 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 眼球乾燥症 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 血管障害 | 65 (22.5%) | 20 (6.9%) | 16 (19.8%) | 6 (7.4%) | 81 (21.9%) |
| 高血圧 | 25 (8.7%) | 9 (3.1%) | 10 (12.3%) | 4 (4.9%) | 35 (9.5%) |
| 低血圧 | 16 (5.5%) | 2 (0.7%) | 5 (6.2%) | 3 (3.7%) | 21 (5.7%) |
| 血腫 | 10 (3.5%) | 0 | 2 (2.5%) | 0 | 12 (3.2%) |
| 深部静脈血栓症 | 5 (1.7%) | 1 (0.3%) | 2 (2.5%) | 1 (1.2%) | 7 (1.9%) |
| 潮紅 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| 出血 | 4 (1.4%) | 3 (1.0%) | 0 | 0 | 4 (1.1%) |
| 起立性低血圧 | 2 (0.7%) | 1 (0.3%) | 1 (1.2%) | 0 | 3 (0.8%) |
| 静脈炎 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 血圧変動 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| リンパ浮腫 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 表在性血栓性静脈炎 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 大動脈硬化症 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 循環虚脱 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| ほてり | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 高血圧クリーゼ | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 末梢血管障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 末梢静脈疾患 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 静脈瘤 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 心臓障害 | 53 (18.3%) | 22 (7.6%) | 11 (13.6%) | 4 (4.9%) | 64 (17.3%) |
| 心房細動 | 23 (8.0%) | 14 (4.8%) | 5 (6.2%) | 3 (3.7%) | 28 (7.6%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 頻脈 | 9 (3.1%) | 0 | 0 | 0 | 9 (2.4%) |
| 洞性頻脈 | 3 (1.0%) | 0 | 4 (4.9%) | 0 | 7 (1.9%) |
| 徐脈 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| 動悸 | 2 (0.7%) | 0 | 2 (2.5%) | 0 | 4 (1.1%) |
| 心房粗動 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| 洞性徐脈 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 上室性頻脈 | 2 (0.7%) | 0 | 1 (1.2%) | 1 (1.2%) | 3 (0.8%) |
| 不安定狭心症 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 心停止 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 心不全 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 心室性期外収縮 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 急性心筋梗塞 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 不整脈 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 冠動脈硬化症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 第一度房室ブロック | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| うっ血性心不全 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 心血管不全 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 変時性応答不全 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 冠動脈疾患 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 冠動脈閉塞 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| チアノーゼ | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 僧帽弁閉鎖不全症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 心筋梗塞 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 心嚢液貯留 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 心膜炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 洞不全症候群 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| ストレス心筋症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 頻脈性不整脈 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| トルサード　ド　ポアント | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 三尖弁疾患 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 心室性不整脈 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 心室性頻脈 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 精神障害 | 44 (15.2%) | 6 (2.1%) | 19 (23.5%) | 1 (1.2%) | 63 (17.0%) |
| 不眠症 | 19 (6.6%) | 0 | 7 (8.6%) | 0 | 26 (7.0%) |
| 不安 | 7 (2.4%) | 0 | 6 (7.4%) | 0 | 13 (3.5%) |
| 錯乱状態 | 12 (4.2%) | 4 (1.4%) | 0 | 0 | 12 (3.2%) |
| うつ病 | 6 (2.1%) | 1 (0.3%) | 6 (7.4%) | 0 | 12 (3.2%) |
| 激越 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |
| 譫妄 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 希死念慮を有するうつ病 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 多幸気分 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 幻聴 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 幻視 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 易刺激性 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| リビドー減退 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 躁病 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 精神障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 精神状態変化 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 悪夢 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| パニック発作 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| パニック障害 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 腎および尿路障害 | 51 (17.6%) | 16 (5.5%) | 6 (7.4%) | 1 (1.2%) | 57 (15.4%) |
| 血尿 | 12 (4.2%) | 3 (1.0%) | 2 (2.5%) | 0 | 14 (3.8%) |
| 急性腎不全 | 11 (3.8%) | 5 (1.7%) | 1 (1.2%) | 1 (1.2%) | 12 (3.2%) |
| 排尿困難 | 7 (2.4%) | 0 | 1 (1.2%) | 0 | 8 (2.2%) |
| 腎不全 | 7 (2.4%) | 5 (1.7%) | 0 | 0 | 7 (1.9%) |
| 頻尿 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 水腎症 | 3 (1.0%) | 2 (0.7%) | 0 | 0 | 3 (0.8%) |
| 腎機能障害 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 尿閉 | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 尿路閉塞 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| 腎結石症 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 夜間頻尿 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 腎嚢胞 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性腎不全 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 尿失禁 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 高窒素血症 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 膀胱刺激症状 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 出血性膀胱炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 緊張性膀胱 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 失禁 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 尿意切迫 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 閉塞性尿路疾患 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 乏尿 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 腎仙痛 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 有痛性排尿困難 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 尿路痛 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 34 (11.8%) | 17 (5.9%) | 2 (2.5%) | 2 (2.5%) | 36 (9.7%) |
| マントル細胞リンパ腫 | 7 (2.4%) | 7 (2.4%) | 1 (1.2%) | 1 (1.2%) | 8 (2.2%) |
| 基底細胞癌 | 7 (2.4%) | 1 (0.3%) | 0 | 0 | 7 (1.9%) |
| 皮膚有棘細胞癌 | 5 (1.7%) | 0 | 0 | 0 | 5 (1.4%) |
| 膀胱移行上皮癌 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 前立腺癌 | 2 (0.7%) | 2 (0.7%) | 0 | 0 | 2 (0.5%) |
| 扁平上皮癌 | 2 (0.7%) | 1 (0.3%) | 0 | 0 | 2 (0.5%) |
| 急性骨髄性白血病 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 良性新生物 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 膀胱癌 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 肺腺癌 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 悪性胸水 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 口腔乳頭腫 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 唾液腺癌 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 皮膚癌 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 皮膚乳頭腫 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸腺腫 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 移行上皮癌 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 腫瘍フレア | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 耳および迷路障害 | 24 (8.3%) | 1 (0.3%) | 6 (7.4%) | 1 (1.2%) | 30 (8.1%) |
| 回転性めまい | 10 (3.5%) | 0 | 1 (1.2%) | 0 | 11 (3.0%) |
| 耳鳴 | 5 (1.7%) | 0 | 1 (1.2%) | 0 | 6 (1.6%) |
| 耳痛 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |
| 聴力低下 | 2 (0.7%) | 1 (0.3%) | 2 (2.5%) | 0 | 4 (1.1%) |
| 耳垢栓塞 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 耳不快感 | 1 (0.3%) | 0 | 1 (1.2%) | 0 | 2 (0.5%) |
| 難聴 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 耳出血 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 聴覚過敏 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 老人性難聴 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 生殖系および乳房障害 | 19 (6.6%) | 4 (1.4%) | 7 (8.6%) | 3 (3.7%) | 26 (7.0%) |
| 良性前立腺肥大症 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| 血精液症 | 4 (1.4%) | 0 | 0 | 0 | 4 (1.1%) |
| 性器浮腫 | 3 (1.0%) | 2 (0.7%) | 0 | 0 | 3 (0.8%) |
| 勃起不全 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 骨盤痛 | 1 (0.3%) | 0 | 1 (1.2%) | 1 (1.2%) | 2 (0.5%) |
| 腟出血 | 0 | 0 | 2 (2.5%) | 0 | 2 (0.5%) |
| 後天性包茎 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房血腫 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 乳房腫瘤 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 乳房痛 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |
| 性器発疹 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 陰茎痛 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 陰嚢腫瘤 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢浮腫 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 陰嚢痛 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 子宮腟脱 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 外陰腟痛 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 外陰腟そう痒症 | 0 | 0 | 1 (1.2%) | 0 | 1 (0.3%) |

**TSFAE16: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Sex (Male vs. Female) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | Sex | | | | |
| | Male | | Female | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 免疫系障害 | 16 (5.5%) | 0 | 3 (3.7%) | 0 | 19 (5.1%) |
| 低ｙグロブリン血症 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |
| 節足動物咬傷アレルギー | 3 (1.0%) | 0 | 1 (1.2%) | 0 | 4 (1.1%) |
| 過敏症 | 2 (0.7%) | 0 | 1 (1.2%) | 0 | 3 (0.8%) |
| 季節性アレルギー | 3 (1.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 薬物過敏症 | 2 (0.7%) | 0 | 0 | 0 | 2 (0.5%) |
| 造影剤アレルギー | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 食物アレルギー | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 肝胆道系障害 | 11 (3.8%) | 3 (1.0%) | 2 (2.5%) | 1 (1.2%) | 13 (3.5%) |
| 高ビリルビン血症 | 5 (1.7%) | 1 (0.3%) | 1 (1.2%) | 0 | 6 (1.6%) |
| 胆石症 | 3 (1.0%) | 1 (0.3%) | 0 | 0 | 3 (0.8%) |
| 胆管結石 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 胆管炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 肝不全 | 0 | 0 | 1 (1.2%) | 1 (1.2%) | 1 (0.3%) |
| 肝機能異常 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 中毒性肝炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 1 (0.3%) |
| 陶器様胆嚢 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 内分泌障害 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |
| 甲状腺機能低下症 | 4 (1.4%) | 0 | 1 (1.2%) | 0 | 5 (1.4%) |
| 先天性、家族性および遺伝性障害 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 臍血腫 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE16.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae16.sas] 15SEP2015, 14:13

参照元：5.3.5.3.1 ISS TSFAE16

表 2.7.4-付録-53 Treatment-Emergent Adverse Events by Baseline Liver Function Abnormality and Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)

**TSFAE16: Treatment-Emergent Adverse Events by Baseline Liver Function Abnormality and Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib | | | |
|---|---|---|---|---|
| | All Grade | | Grade 3 or Higher | |
| | Normal | Abnormal | Normal | Abnormal |
| Analysis Set: All Treated Population | 11 | 5 | | |
| Total Number of Subjects with TEAE | 11 (100.0%) | 5 (100.0%) | 5 (45.5%) | 3 (60.0%) |
| MedDRA System organ class/Preferred term | | | | |
| 皮膚および皮下組織障害 | 9 (81.8%) | 1 (20.0%) | 0 | 0 |
| 皮膚乾燥 | 3 (27.3%) | 0 | 0 | 0 |
| 皮膚炎 | 1 (9.1%) | 0 | 0 | 0 |
| 湿疹 | 1 (9.1%) | 0 | 0 | 0 |
| 皮下出血 | 1 (9.1%) | 0 | 0 | 0 |
| 爪変色 | 1 (9.1%) | 0 | 0 | 0 |
| 爪破損 | 1 (9.1%) | 0 | 0 | 0 |
| 点状出血 | 1 (9.1%) | 0 | 0 | 0 |
| そう痒症 | 1 (9.1%) | 0 | 0 | 0 |
| 発疹 | 1 (9.1%) | 0 | 0 | 0 |
| 全身性皮疹 | 1 (9.1%) | 0 | 0 | 0 |
| 斑状丘疹状皮疹 | 1 (9.1%) | 0 | 0 | 0 |
| 皮膚脆弱性 | 0 | 1 (20.0%) | 0 | 0 |
| 臨床検査 | 7 (63.6%) | 1 (20.0%) | 1 (9.1%) | 0 |
| 血小板数減少 | 5 (45.5%) | 0 | 0 | 0 |
| 血中ビリルビン増加 | 2 (18.2%) | 0 | 0 | 0 |
| アラニンアミノトランスフェラーゼ増加 | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| アスパラギン酸アミノトランスフェラーゼ増加 | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| 血中クレアチニン増加 | 1 (9.1%) | 0 | 0 | 0 |
| リンパ球数減少 | 1 (9.1%) | 0 | 0 | 0 |
| リンパ球数増加 | 1 (9.1%) | 0 | 1 (9.1%) | 0 |
| 血中アルカリホスファターゼ増加 | 0 | 1 (20.0%) | 0 | 0 |
| γ－グルタミルトランスフェラーゼ増加 | 0 | 1 (20.0%) | 0 | 0 |
| 胃腸障害 | 6 (54.5%) | 4 (80.0%) | 1 (9.1%) | 0 |
| 下痢 | 3 (27.3%) | 3 (60.0%) | 0 | 0 |
| 口内炎 | 3 (27.3%) | 3 (60.0%) | 1 (9.1%) | 0 |
| 便秘 | 2 (18.2%) | 1 (20.0%) | 0 | 0 |
| 上腹部痛 | 1 (9.1%) | 0 | 0 | 0 |
| 消化不良 | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| 舌痛 | 1 (9.1%) | 0 | 0 | 0 |
| 口腔内出血 | 1 (9.1%) | 0 | 0 | 0 |
| 肛門出血 | 0 | 1 (20.0%) | 0 | 0 |
| 悪心 | 0 | 2 (40.0%) | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 6 (54.5%) | 3 (60.0%) | 1 (9.1%) | 2 (40.0%) |
| 疲労 | 2 (18.2%) | 1 (20.0%) | 0 | 0 |
| 胸部不快感 | 1 (9.1%) | 0 | 0 | 0 |
| 疾患進行 | 1 (9.1%) | 2 (40.0%) | 1 (9.1%) | 2 (40.0%) |
| インフルエンザ様疾患 | 1 (9.1%) | 0 | 0 | 0 |
| 倦怠感 | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| 感染症および寄生虫症 | 6 (54.5%) | 4 (80.0%) | 1 (9.1%) | 0 |
| 皮膚感染 | 2 (18.2%) | 0 | 0 | 0 |
| 上気道感染 | 2 (18.2%) | 1 (20.0%) | 0 | 0 |
| 感染 | 1 (9.1%) | 0 | 0 | 0 |
| 咽頭炎 | 1 (9.1%) | 0 | 0 | 0 |
| 敗血症 | 1 (9.1%) | 0 | 1 (9.1%) | 0 |
| 扁桃炎 | 1 (9.1%) | 0 | 0 | 0 |
| インフルエンザ | 0 | 1 (20.0%) | 0 | 0 |
| 鼻咽頭炎 | 0 | 2 (40.0%) | 0 | 0 |
| 爪囲炎 | 0 | 1 (20.0%) | 0 | 0 |

**TSFAE16: Treatment-Emergent Adverse Events by Baseline Liver Function Abnormality and Toxicity Grade 3 or Higher; All Treated Population (Study PCI-32765MCL2002)**

| | Ibrutinib | | | |
|---|---|---|---|---|
| | All Grade | | Grade 3 or Higher | |
| | Normal | Abnormal | Normal | Abnormal |
| 血液およびリンパ系障害 | 5 (45.5%) | 2 (40.0%) | 2 (18.2%) | 0 |
| 貧血 | 3 (27.3%) | 1 (20.0%) | 1 (9.1%) | 0 |
| 白血球増加症 | 2 (18.2%) | 0 | 1 (9.1%) | 0 |
| リンパ球増加症 | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| 好中球減少症 | 1 (9.1%) | 0 | 1 (9.1%) | 0 |
| 血小板減少症 | 1 (9.1%) | 2 (40.0%) | 0 | 0 |
| 筋骨格系および結合組織障害 | 3 (27.3%) | 0 | 0 | 0 |
| 関節炎 | 1 (9.1%) | 0 | 0 | 0 |
| 筋痙縮 | 1 (9.1%) | 0 | 0 | 0 |
| 骨炎 | 1 (9.1%) | 0 | 0 | 0 |
| 神経系障害 | 3 (27.3%) | 1 (20.0%) | 0 | 0 |
| 体位性めまい | 1 (9.1%) | 0 | 0 | 0 |
| 頭痛 | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| 末梢性ニューロパチー | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| 傷害、中毒および処置合併症 | 2 (18.2%) | 2 (40.0%) | 0 | 0 |
| 挫傷 | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| 関節脱臼 | 1 (9.1%) | 0 | 0 | 0 |
| 裂傷 | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| 代謝および栄養障害 | 2 (18.2%) | 3 (60.0%) | 1 (9.1%) | 1 (20.0%) |
| 食欲減退 | 1 (9.1%) | 2 (40.0%) | 0 | 0 |
| 高尿酸血症 | 1 (9.1%) | 0 | 1 (9.1%) | 0 |
| 低リン酸血症 | 1 (9.1%) | 0 | 0 | 0 |
| 低カリウム血症 | 0 | 2 (40.0%) | 0 | 1 (20.0%) |
| 低ナトリウム血症 | 0 | 1 (20.0%) | 0 | 0 |
| 精神障害 | 2 (18.2%) | 0 | 0 | 0 |
| 譫妄 | 1 (9.1%) | 0 | 0 | 0 |
| うつ病 | 1 (9.1%) | 0 | 0 | 0 |
| 腎および尿路障害 | 2 (18.2%) | 0 | 1 (9.1%) | 0 |
| 血尿 | 1 (9.1%) | 0 | 0 | 0 |
| 蛋白尿 | 1 (9.1%) | 0 | 0 | 0 |
| 腎機能障害 | 1 (9.1%) | 0 | 1 (9.1%) | 0 |
| 心臓障害 | 1 (9.1%) | 1 (20.0%) | 1 (9.1%) | 0 |
| 不整脈 | 1 (9.1%) | 0 | 1 (9.1%) | 0 |
| 心房細動 | 0 | 1 (20.0%) | 0 | 0 |
| 眼障害 | 1 (9.1%) | 2 (40.0%) | 0 | 1 (20.0%) |
| 眼乾燥 | 1 (9.1%) | 0 | 0 | 0 |
| 点状角膜炎 | 1 (9.1%) | 0 | 0 | 0 |
| 網膜裂孔 | 0 | 1 (20.0%) | 0 | 0 |
| 網膜血管障害 | 0 | 1 (20.0%) | 0 | 1 (20.0%) |
| 呼吸器、胸郭および縦隔障害 | 1 (9.1%) | 1 (20.0%) | 0 | 0 |
| 鼻出血 | 1 (9.1%) | 0 | 0 | 0 |
| 鼻漏 | 0 | 1 (20.0%) | 0 | 0 |
| 血管障害 | 1 (9.1%) | 0 | 1 (9.1%) | 0 |
| 高血圧 | 1 (9.1%) | 0 | 1 (9.1%) | 0 |

Key: TEAE=Treatment Emergent Adverse Event
Note: Adverse Events are coded using MedDRA 18.0

[TSFAE16.rtf] [JNJ-54179060\PCI32765MCL2002\DBR_CSR\RE_CSR\tsfae16.sas] 21AUG2015, 12:30

参照元：5.3.5.2.1 MCL2002 試験 CSR Table 16

表 2.7.4-付録-54 Overall Summary of Treatment-emergent Adverse Events by Baseline Hepatic Abnormality; Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE31PART1OF3: Overall Summary of Treatment-emergent Adverse Events by Baseline Hepatic Abnormality; Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | Baseline Hepatic Abnormality | |
| | Normal | Not Normal | Normal | Not Normal |
| Analysis Set: Safety Population | 101 | 9 | 100 | 20 |
| Any TEAE | 101 (100.0%) | 9 (100.0%) | 95 (95.0%) | 20 (100.0%) |
| Grade >= 3 | 74 (73.3%) | 9 (100.0%) | 72 (72.0%) | 15 (75.0%) |
| Drug related [a] | 90 (89.1%) | 7 (77.8%) | 76 (76.0%) | 19 (95.0%) |
| Grade >= 3 | 46 (45.5%) | 2 (22.2%) | 41 (41.0%) | 11 (55.0%) |
| Any TESAE | 56 (55.4%) | 5 (55.6%) | 52 (52.0%) | 7 (35.0%) |
| Grade >= 3 | 49 (48.5%) | 5 (55.6%) | 47 (47.0%) | 6 (30.0%) |
| Drug related [a] | 26 (25.7%) | 2 (22.2%) | 21 (21.0%) | 4 (20.0%) |
| TEAE leading to treatment discontinuation | 9 (8.9%) | 1 (11.1%) | 17 (17.0%) | 3 (15.0%) |
| TEAE leading to treatment dose reduction | 12 (11.9%) | 3 (33.3%) | 8 (8.0%) | 0 |
| TEAE with outcome death | 14 (13.9%) | 1 (11.1%) | 12 (12.0%) | 2 (10.0%) |
| Deaths within 30 days after last dose of study treatment [b] | 14 (13.9%) | 1 (11.1%) | 18 (18.0%) | 5 (25.0%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE31PART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae31.sas] 26OCT2015, 14:30

参照元：5.3.5.3.1 ISS TSFAE31PART1OF3

表 2.7.4-付録-55 Overall Summary of Treatment-emergent Adverse Events by Baseline Hepatic Abnormality; Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE31PART2OF3: Overall Summary of Treatment-emergent Adverse Events by Baseline Hepatic Abnormality; Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | Baseline Hepatic Abnormality | | Baseline Hepatic Abnormality | |
| | Normal | Not Normal | Normal | Not Normal |
| Analysis Set: Safety Population | 119 | 20 | 120 | 19 |
| Any TEAE | 118 (99.2%) | 20 (100.0%) | 119 (99.2%) | 19 (100.0%) |
| Grade >= 3 | 78 (65.5%) | 16 (80.0%) | 104 (86.7%) | 17 (89.5%) |
| Drug related [a] | 100 (84.0%) | 15 (75.0%) | 114 (95.0%) | 19 (100.0%) |
| Grade >= 3 | 49 (41.2%) | 6 (30.0%) | 93 (77.5%) | 16 (84.2%) |
| Any TESAE | 54 (45.4%) | 13 (65.0%) | 67 (55.8%) | 13 (68.4%) |
| Grade >= 3 | 51 (42.9%) | 12 (60.0%) | 58 (48.3%) | 10 (52.6%) |
| Drug related [a] | 25 (21.0%) | 4 (20.0%) | 43 (35.8%) | 10 (52.6%) |
| TEAE leading to treatment discontinuation | 13 (10.9%) | 5 (25.0%) | 33 (27.5%) | 8 (42.1%) |
| TEAE leading to treatment dose reduction | 5 (4.2%) | 0 | 50 (41.7%) | 10 (52.6%) |
| TEAE with outcome death | 11 (9.2%) | 4 (20.0%) | 8 (6.7%) | 3 (15.8%) |
| Deaths within 30 days after last dose of study treatment [b] | 17 (14.3%) | 7 (35.0%) | 12 (10.0%) | 3 (15.8%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE31PART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae31.sas] 26OCT2015, 14:30

参照元：5.3.5.3.1 ISS TSFAE31PART2OF3

表 2.7.4-付録-56 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| Analysis Set: Safety Population | 320 | | | 49 | | | 369 |
| Subjects with any TEAE | 314 (98.1%) | 187 (58.4%) | 37 (11.6%) | 49 (100.0%) | 33 (67.3%) | 7 (14.3%) | 363 (98.4%) |
| System organ class | | | | | | | |
| Preferred term | | | | | | | |
| 感染症および寄生虫症 | 233 (72.8%) | 65 (20.3%) | 9 (2.8%) | 30 (61.2%) | 9 (18.4%) | 4 (8.2%) | 263 (71.3%) |
| 上気道感染 | 69 (21.6%) | 3 (0.9%) | 0 | 4 (8.2%) | 0 | 0 | 73 (19.8%) |
| 肺炎 | 39 (12.2%) | 24 (7.5%) | 5 (1.6%) | 5 (10.2%) | 4 (8.2%) | 0 | 44 (11.9%) |
| 副鼻腔炎 | 36 (11.3%) | 1 (0.3%) | 0 | 3 (6.1%) | 0 | 0 | 39 (10.6%) |
| 尿路感染 | 30 (9.4%) | 5 (1.6%) | 0 | 8 (16.3%) | 1 (2.0%) | 0 | 38 (10.3%) |
| 鼻咽頭炎 | 26 (8.1%) | 0 | 0 | 4 (8.2%) | 0 | 0 | 30 (8.1%) |
| 結膜炎 | 22 (6.9%) | 0 | 0 | 4 (8.2%) | 0 | 0 | 26 (7.0%) |
| 気管支炎 | 19 (5.9%) | 4 (1.3%) | 0 | 1 (2.0%) | 0 | 0 | 20 (5.4%) |
| 蜂巣炎 | 16 (5.0%) | 8 (2.5%) | 0 | 2 (4.1%) | 0 | 0 | 18 (4.9%) |
| 帯状疱疹 | 13 (4.1%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 14 (3.8%) |
| 鼻炎 | 14 (4.4%) | 0 | 0 | 0 | 0 | 0 | 14 (3.8%) |
| 毛包炎 | 12 (3.8%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 13 (3.5%) |
| 爪囲炎 | 12 (3.8%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 13 (3.5%) |
| 下気道感染 | 11 (3.4%) | 4 (1.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 12 (3.3%) |
| 皮膚感染 | 10 (3.1%) | 1 (0.3%) | 0 | 2 (4.1%) | 0 | 0 | 12 (3.3%) |
| 口腔ヘルペス | 9 (2.8%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 11 (3.0%) |
| 気道感染 | 9 (2.8%) | 2 (0.6%) | 0 | 2 (4.1%) | 0 | 0 | 11 (3.0%) |
| 敗血症 | 9 (2.8%) | 6 (1.9%) | 3 (0.9%) | 2 (4.1%) | 0 | 2 (4.1%) | 11 (3.0%) |
| 胃腸炎 | 9 (2.8%) | 2 (0.6%) | 0 | 1 (2.0%) | 0 | 0 | 10 (2.7%) |
| 咽頭炎 | 7 (2.2%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 7 (1.9%) |
| ウイルス感染 | 6 (1.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 7 (1.9%) |
| 感染 | 5 (1.6%) | 1 (0.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 6 (1.6%) |
| クロストリジウム・ディフィシレ大腸炎 | 3 (0.9%) | 1 (0.3%) | 0 | 2 (4.1%) | 2 (4.1%) | 0 | 5 (1.4%) |
| 眼感染 | 4 (1.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 5 (1.4%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 歯肉炎 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 口腔カンジダ症 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| クロストリジウム・ディフィシレ感染 | 4 (1.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 4 (1.1%) |
| インフルエンザ | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 限局性感染 | 2 (0.6%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 4 (1.1%) |
| 中耳炎 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 歯周炎 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 歯感染 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 菌血症 | 3 (0.9%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 気管支肺炎 | 1 (0.3%) | 0 | 0 | 2 (4.1%) | 1 (2.0%) | 0 | 3 (0.8%) |
| 膀胱炎 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 耳感染 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| ウイルス性胃腸炎 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 単純ヘルペス | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 喉頭炎 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 爪感染 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 外耳炎 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| ブドウ球菌感染 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| ウイルス性上気道感染 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 急性副鼻腔炎 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 細気管支炎 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 医療機器関連感染 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 憩室炎 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 感染性小腸結腸炎 | 1 (0.3%) | 1 (0.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 2 (0.5%) |
| 丹毒 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 真菌感染 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚真菌感染 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 真菌性性器感染 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| ヘルペスウイルス感染 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 麦粒腫 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 爪真菌症 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| レンサ球菌性咽頭炎 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| ニューモシスチス・イロベチイ肺炎 | 0 | 0 | 0 | 2 (4.1%) | 1 (2.0%) | 1 (2.0%) | 2 (0.5%) |
| 細菌性肺炎 | 2 (0.6%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 膿疱性皮疹 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 敗血症性ショック | 1 (0.3%) | 0 | 1 (0.3%) | 1 (2.0%) | 0 | 1 (2.0%) | 2 (0.5%) |
| ブドウ球菌性菌血症 | 1 (0.3%) | 1 (0.3%) | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 歯膿瘍 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 細菌性尿路感染 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 尿路性敗血症 | 2 (0.6%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 外陰部腟カンジダ症 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 創傷感染 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 腹部膿瘍 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 四肢膿瘍 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ダニ皮膚炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 膿疱性ざ瘡 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肛門膿瘍 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肛門カンジダ症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 虫垂炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 穿孔性虫垂炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 異型肺炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 細菌尿 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| カンジダ性亀頭炎 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 胆道感染 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| ブラストシスティス感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 体部白癬 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 乳房蜂巣炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| カンピロバクター胃腸炎 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| カンピロバクター感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| カンジダ感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼窩蜂巣炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 感染性胆嚢炎 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 慢性副鼻腔炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| シトロバクター感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 涙嚢炎 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| ウイルス性脳炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 精巣上体炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 喉頭蓋炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 細菌性眼感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 真菌血症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ヘリコバクター胃潰瘍 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 消化管感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性消化管感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 性器カンジダ症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血腫感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ヘモフィルス感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| Ｂ型肝炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ヒストプラスマ症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 埋込み部位感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 切開部位感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| クレブシエラ感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 口唇感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 細菌性下気道感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肺感染 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| ライム病 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 乳腺炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 水疱性鼓膜炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪床感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼帯状疱疹 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 口腔真菌感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 乳頭腫ウイルス感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| クリプトコッカス性肺炎 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| クレブシエラ菌性肺炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 処置後感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 肺結核 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 腎盂腎炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 膿皮症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| レンサ球菌性膿皮症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 狂犬病 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 直腸膿瘍 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性気道感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 軟部組織感染 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| ブドウ球菌皮膚感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| レンサ球菌感染 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 皮下組織膿瘍 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 足部白癬 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 扁桃炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 気管炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 真菌性尿路感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| シュードモナス性尿路感染 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 胃腸障害 | 227 (70.9%) | 33 (10.3%) | 1 (0.3%) | 27 (55.1%) | 5 (10.2%) | 0 | 254 (68.8%) |
| 下痢 | 129 (40.3%) | 13 (4.1%) | 0 | 17 (34.7%) | 0 | 0 | 146 (39.6%) |
| 悪心 | 73 (22.8%) | 1 (0.3%) | 0 | 7 (14.3%) | 0 | 0 | 80 (21.7%) |
| 嘔吐 | 59 (18.4%) | 1 (0.3%) | 0 | 3 (6.1%) | 0 | 0 | 62 (16.8%) |
| 便秘 | 52 (16.3%) | 0 | 0 | 5 (10.2%) | 0 | 0 | 57 (15.4%) |
| 腹痛 | 37 (11.6%) | 11 (3.4%) | 0 | 4 (8.2%) | 2 (4.1%) | 0 | 41 (11.1%) |
| 口内炎 | 29 (9.1%) | 3 (0.9%) | 0 | 2 (4.1%) | 0 | 0 | 31 (8.4%) |
| 消化不良 | 27 (8.4%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 28 (7.6%) |
| 上腹部痛 | 16 (5.0%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 16 (4.3%) |
| 腹部膨満 | 13 (4.1%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 14 (3.8%) |
| 口内乾燥 | 13 (4.1%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 14 (3.8%) |
| 胃食道逆流性疾患 | 12 (3.8%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 13 (3.5%) |
| 嚥下障害 | 7 (2.2%) | 1 (0.3%) | 0 | 2 (4.1%) | 1 (2.0%) | 0 | 9 (2.4%) |
| 腹部不快感 | 8 (2.5%) | 0 | 0 | 0 | 0 | 0 | 8 (2.2%) |
| 口腔内痛 | 7 (2.2%) | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 8 (2.2%) |
| 口腔内潰瘍形成 | 6 (1.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 7 (1.9%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 放屁 | 6 (1.9%) | 0 | 0 | 0 | 0 | 0 | 6 (1.6%) |
| 胃炎 | 5 (1.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 6 (1.6%) |
| 心窩部不快感 | 3 (0.9%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 5 (1.4%) |
| 舌痛 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 痔核 | 3 (0.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 4 (1.1%) |
| アフタ性口内炎 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| おくび | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| イレウス | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 直腸出血 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 舌潰瘍 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 下腹部痛 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 齲歯 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 軟便 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 食中毒 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 排便回数増加 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 胃潰瘍 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 2 (0.5%) |
| 歯肉出血 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 歯肉浮腫 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 吐血 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 麻痺性イレウス | 2 (0.6%) | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 鼠径ヘルニア | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 口唇潰瘍 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 下部消化管出血 | 1 (0.3%) | 1 (0.3%) | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 口腔内出血 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 歯周病 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 肛門周囲痛 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 直腸炎 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 直腸裂 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 小腸閉塞 | 2 (0.6%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 歯痛 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 裂肛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肛門直腸障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 萎縮性舌炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| バレット食道 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 口唇炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 大腸炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 歯不快感 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血性下痢 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 十二指腸狭窄 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| 十二指腸潰瘍 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| 十二指腸炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 十二指腸胃逆流 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 便失禁 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 糞塊 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 胃前庭部毛細血管拡張症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 出血性胃炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 歯肉痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血便排泄 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 痔出血 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 過敏性腸症候群 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 口唇水疱 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 口唇びらん | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 口唇痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 口唇腫脹 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 弛緩歯 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| メレナ | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 嚥下痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 口蓋障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 慢性膵炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 舌突出 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 直腸潰瘍 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 唾液腺結石 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 変色歯 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 歯の障害 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 歯の脱落 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 一般・全身障害および投与部位の状態 | 202 (63.1%) | 30 (9.4%) | 2 (0.6%) | 37 (75.5%) | 4 (8.2%) | 2 (4.1%) | 239 (64.8%) |
| 疲労 | 110 (34.4%) | 14 (4.4%) | 1 (0.3%) | 19 (38.8%) | 1 (2.0%) | 0 | 129 (35.0%) |
| 末梢性浮腫 | 64 (20.0%) | 6 (1.9%) | 0 | 10 (20.4%) | 0 | 0 | 74 (20.1%) |
| 発熱 | 59 (18.4%) | 3 (0.9%) | 0 | 9 (18.4%) | 0 | 0 | 68 (18.4%) |
| 無力症 | 28 (8.8%) | 3 (0.9%) | 1 (0.3%) | 4 (8.2%) | 1 (2.0%) | 0 | 32 (8.7%) |
| 悪寒 | 18 (5.6%) | 0 | 0 | 0 | 0 | 0 | 18 (4.9%) |
| 胸痛 | 14 (4.4%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 15 (4.1%) |
| 末梢腫脹 | 13 (4.1%) | 1 (0.3%) | 0 | 2 (4.1%) | 0 | 0 | 15 (4.1%) |
| インフルエンザ様疾患 | 14 (4.4%) | 0 | 0 | 0 | 0 | 0 | 14 (3.8%) |
| 疼痛 | 11 (3.4%) | 0 | 1 (0.3%) | 0 | 0 | 0 | 11 (3.0%) |
| 非心臓性胸痛 | 7 (2.2%) | 2 (0.6%) | 0 | 1 (2.0%) | 0 | 0 | 8 (2.2%) |
| 粘膜の炎症 | 6 (1.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 6 (1.6%) |
| 全身健康状態低下 | 4 (1.3%) | 1 (0.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 5 (1.4%) |
| 倦怠感 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 局所腫脹 | 3 (0.9%) | 1 (0.3%) | 0 | 1 (2.0%) | 0 | 0 | 4 (1.1%) |
| 多臓器不全 | 1 (0.3%) | 1 (0.3%) | 0 | 3 (6.1%) | 1 (2.0%) | 2 (4.1%) | 4 (1.1%) |
| 胸部不快感 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 歩行障害 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 全身性浮腫 | 2 (0.6%) | 1 (0.3%) | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 注射部位内出血 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 乾燥症 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 腋窩痛 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 早期満腹 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 重力性浮腫 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 低体温 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 炎症 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 浮腫 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 活動状態低下 | 0 | 0 | 0 | 2 (4.1%) | 1 (2.0%) | 0 | 2 (0.5%) |
| カテーテル留置部位関連反応 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 死亡 | 1 (0.3%) | 0 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 医療機器リーク | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 顔面浮腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 異常感 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 冷感 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 熱感 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 治癒不良 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 硬結 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 注入部位血管外漏出 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位紅斑 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位漏出 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位出血 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位疼痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位反応 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 先行疾患の改善 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 温度変化不耐症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 評価不能の事象 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸器、胸郭および縦隔障害 | 170 (53.1%) | 26 (8.1%) | 7 (2.2%) | 30 (61.2%) | 1 (2.0%) | 1 (2.0%) | 200 (54.2%) |
| 咳嗽 | 72 (22.5%) | 0 | 0 | 9 (18.4%) | 0 | 0 | 81 (22.0%) |
| 呼吸困難 | 57 (17.8%) | 11 (3.4%) | 1 (0.3%) | 12 (24.5%) | 0 | 0 | 69 (18.7%) |
| 鼻出血 | 26 (8.1%) | 1 (0.3%) | 0 | 6 (12.2%) | 0 | 0 | 32 (8.7%) |
| 口腔咽頭痛 | 27 (8.4%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 29 (7.9%) |
| 胸水 | 18 (5.6%) | 6 (1.9%) | 0 | 5 (10.2%) | 1 (2.0%) | 0 | 23 (6.2%) |
| 湿性咳嗽 | 15 (4.7%) | 0 | 0 | 0 | 0 | 0 | 15 (4.1%) |
| 鼻閉 | 10 (3.1%) | 0 | 0 | 3 (6.1%) | 0 | 0 | 13 (3.5%) |
| 呼吸不全 | 9 (2.8%) | 5 (1.6%) | 4 (1.3%) | 1 (2.0%) | 0 | 1 (2.0%) | 10 (2.7%) |
| 鼻漏 | 9 (2.8%) | 0 | 0 | 0 | 0 | 0 | 9 (2.4%) |
| 発声障害 | 7 (2.2%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 8 (2.2%) |
| 慢性閉塞性肺疾患 | 6 (1.9%) | 4 (1.3%) | 0 | 0 | 0 | 0 | 6 (1.6%) |
| アレルギー性鼻炎 | 5 (1.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 6 (1.6%) |
| 副鼻腔うっ血 | 4 (1.3%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 6 (1.6%) |
| 上気道うっ血 | 5 (1.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 6 (1.6%) |
| 低酸素症 | 4 (1.3%) | 4 (1.3%) | 0 | 1 (2.0%) | 0 | 0 | 5 (1.4%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| しゃっくり | 3 (0.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 4 (1.1%) |
| 気胸 | 4 (1.3%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 喀血 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 鼻部不快感 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 肺水腫 | 3 (0.9%) | 0 | 1 (0.3%) | 0 | 0 | 0 | 3 (0.8%) |
| ラ音 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 喘鳴 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 無気肺 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 労作性呼吸困難 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 肺硬化 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 肺浸潤 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 鼻の炎症 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 肺塞栓症 | 2 (0.6%) | 0 | 1 (0.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 気道うっ血 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 急性肺水腫 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 喘息 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 気管支反応性亢進 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 気管支分泌物貯留 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 気管支拡張症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 慢性気管支炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肺気腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 上気道分泌増加 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 鼻乾燥 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 鼻潰瘍 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 副鼻腔不快感 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 副鼻腔分泌過多 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 咽頭紅斑 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 胸膜炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 胸膜痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肺腫瘤 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸性アシドーシス | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸窮迫 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 拘束性肺疾患 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 副鼻腔障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| くしゃみ | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 頻呼吸 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 扁桃肥大 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 上気道咳症候群 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚および皮下組織障害 | 170 (53.1%) | 10 (3.1%) | 0 | 23 (46.9%) | 0 | 0 | 193 (52.3%) |
| 発疹 | 51 (15.9%) | 4 (1.3%) | 0 | 6 (12.2%) | 0 | 0 | 57 (15.4%) |
| そう痒症 | 25 (7.8%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 27 (7.3%) |
| 点状出血 | 19 (5.9%) | 0 | 0 | 3 (6.1%) | 0 | 0 | 22 (6.0%) |
| 皮膚病変 | 18 (5.6%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 20 (5.4%) |
| 斑状丘疹状皮疹 | 16 (5.0%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 16 (4.3%) |
| 皮膚乾燥 | 14 (4.4%) | 0 | 0 | 0 | 0 | 0 | 14 (3.8%) |
| 斑状出血 | 10 (3.1%) | 0 | 0 | 3 (6.1%) | 0 | 0 | 13 (3.5%) |
| 紅斑 | 10 (3.1%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 11 (3.0%) |
| 寝汗 | 11 (3.4%) | 0 | 0 | 0 | 0 | 0 | 11 (3.0%) |
| 脱毛症 | 10 (3.1%) | 0 | 0 | 0 | 0 | 0 | 10 (2.7%) |
| ざ瘡様皮膚炎 | 8 (2.5%) | 0 | 0 | 0 | 0 | 0 | 8 (2.2%) |
| 紫斑 | 7 (2.2%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 7 (1.9%) |
| 多汗症 | 5 (1.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 6 (1.6%) |
| 皮膚亀裂 | 5 (1.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 6 (1.6%) |
| 嵌入爪 | 4 (1.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 5 (1.4%) |
| 爪破損 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 蕁麻疹 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 水疱 | 3 (0.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 4 (1.1%) |
| 全身性そう痒症 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 斑状皮疹 | 4 (1.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 皮膚腫瘤 | 3 (0.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 4 (1.1%) |
| 皮膚潰瘍 | 3 (0.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 4 (1.1%) |
| ざ瘡 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 褥瘡性潰瘍 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 湿疹 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 紅斑性皮疹 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 皮膚色素過剰 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 皮膚嚢腫 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 接触性皮膚炎 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 皮下出血 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 間擦疹 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚疼痛 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 全身性皮疹 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 丘疹性皮疹 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| そう痒性皮疹 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚変色 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 毛細血管炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| アレルギー性皮膚炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 水疱性皮膚炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 皮脂欠乏性湿疹 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 貨幣状湿疹 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 過敏性血管炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪床出血 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪床障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪床の炎症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪の不快感 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪の障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪ジストロフィー | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪線状隆起 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 爪甲脱落症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 手掌・足底発赤知覚不全症候群 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 脂肪織炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 色素沈着障害 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 毛孔性皮疹 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚色素減少 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 皮膚刺激 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 皮膚腫脹 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 乾皮症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 筋骨格系および結合組織障害 | 155 (48.4%) | 16 (5.0%) | 0 | 18 (36.7%) | 4 (8.2%) | 0 | 173 (46.9%) |
| 筋痙縮 | 63 (19.7%) | 0 | 0 | 4 (8.2%) | 0 | 0 | 67 (18.2%) |
| 背部痛 | 41 (12.8%) | 5 (1.6%) | 0 | 3 (6.1%) | 1 (2.0%) | 0 | 44 (11.9%) |
| 関節痛 | 37 (11.6%) | 2 (0.6%) | 0 | 1 (2.0%) | 0 | 0 | 38 (10.3%) |
| 筋肉痛 | 30 (9.4%) | 1 (0.3%) | 0 | 2 (4.1%) | 0 | 0 | 32 (8.7%) |
| 四肢痛 | 27 (8.4%) | 1 (0.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 28 (7.6%) |
| 筋骨格痛 | 17 (5.3%) | 0 | 0 | 0 | 0 | 0 | 17 (4.6%) |
| 筋力低下 | 12 (3.8%) | 3 (0.9%) | 0 | 1 (2.0%) | 0 | 0 | 13 (3.5%) |
| 側腹部痛 | 6 (1.9%) | 1 (0.3%) | 0 | 2 (4.1%) | 1 (2.0%) | 0 | 8 (2.2%) |
| 頚部痛 | 5 (1.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 6 (1.6%) |
| 変形性関節症 | 4 (1.3%) | 1 (0.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 5 (1.4%) |
| 肩径部痛 | 4 (1.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 四肢不快感 | 2 (0.6%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 4 (1.1%) |
| 筋骨格硬直 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 骨痛 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 関節硬直 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 関節腫脹 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 運動性低下 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 筋骨格系胸痛 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| ミオパチー | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 軟部組織障害 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 関節炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 滑液包炎 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 外骨腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 痛風性関節炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 椎間板変性症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 椎間板突出 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 関節拘縮 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 関節滲出液 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 関節ロック | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 筋緊張 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 筋攣縮 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 筋骨格不快感 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 頚部腫瘤 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 骨壊死 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 骨粗鬆症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 顎痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 横紋筋融解症 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| 滑液嚢腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 腱痛 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 椎間孔狭窄 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血液およびリンパ系障害 | 140 (43.8%) | 86 (26.9%) | 1 (0.3%) | 28 (57.1%) | 21 (42.9%) | 0 | 168 (45.5%) |
| 血小板減少症 | 59 (18.4%) | 31 (9.7%) | 0 | 15 (30.6%) | 10 (20.4%) | 0 | 74 (20.1%) |
| 好中球減少症 | 57 (17.8%) | 50 (15.6%) | 0 | 12 (24.5%) | 10 (20.4%) | 0 | 69 (18.7%) |
| 貧血 | 52 (16.3%) | 22 (6.9%) | 0 | 11 (22.4%) | 8 (16.3%) | 0 | 63 (17.1%) |
| 発熱性好中球減少症 | 13 (4.1%) | 12 (3.8%) | 1 (0.3%) | 0 | 0 | 0 | 13 (3.5%) |
| 白血球減少症 | 11 (3.4%) | 4 (1.3%) | 0 | 2 (4.1%) | 2 (4.1%) | 0 | 13 (3.5%) |
| 白血球増加症 | 7 (2.2%) | 3 (0.9%) | 0 | 0 | 0 | 0 | 7 (1.9%) |
| 内出血発生の増加傾向 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| リンパ球減少症 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| リンパ球増加症 | 4 (1.3%) | 3 (0.9%) | 0 | 0 | 0 | 0 | 4 (1.1%) |
| リンパ節痛 | 1 (0.3%) | 1 (0.3%) | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| リンパ節症 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 脾腫 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 骨髄機能不全 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 凝血異常 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 溶血 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| 鉄欠乏性貧血 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 白血球停滞症候群 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 汎血球減少症 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 後腹膜リンパ節腫脹 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 脾臓出血 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 脾臓梗塞 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血小板増加症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 代謝および栄養障害 | 132 (41.3%) | 47 (14.7%) | 0 | 18 (36.7%) | 5 (10.2%) | 0 | 150 (40.7%) |
| 食欲減退 | 54 (16.9%) | 3 (0.9%) | 0 | 8 (16.3%) | 0 | 0 | 62 (16.8%) |
| 低カリウム血症 | 30 (9.4%) | 13 (4.1%) | 0 | 4 (8.2%) | 2 (4.1%) | 0 | 34 (9.2%) |
| 高尿酸血症 | 21 (6.6%) | 9 (2.8%) | 0 | 4 (8.2%) | 1 (2.0%) | 0 | 25 (6.8%) |
| 脱水 | 19 (5.9%) | 7 (2.2%) | 0 | 3 (6.1%) | 0 | 0 | 22 (6.0%) |
| 低マグネシウム血症 | 17 (5.3%) | 1 (0.3%) | 0 | 4 (8.2%) | 0 | 0 | 21 (5.7%) |
| 高カリウム血症 | 12 (3.8%) | 4 (1.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 13 (3.5%) |
| 低ナトリウム血症 | 12 (3.8%) | 8 (2.5%) | 0 | 0 | 0 | 0 | 12 (3.3%) |
| 低アルブミン血症 | 8 (2.5%) | 3 (0.9%) | 0 | 3 (6.1%) | 1 (2.0%) | 0 | 11 (3.0%) |
| 高血糖 | 9 (2.8%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 9 (2.4%) |
| 低カルシウム血症 | 6 (1.9%) | 0 | 0 | 0 | 0 | 0 | 6 (1.6%) |
| 低血糖症 | 2 (0.6%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 4 (1.1%) |
| 低リン酸血症 | 4 (1.3%) | 4 (1.3%) | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 水分過負荷 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 痛風 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 酵素異常 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 高コレステロール血症 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 高ナトリウム血症 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 高リン酸塩血症 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 過小食 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 乳酸アシドーシス | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 2 (0.5%) |
| アルコール不耐性 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 悪液質 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 糖尿病 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 糖尿病性ケトアシドーシス | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 高アルブミン血症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 高アンモニア血症 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 低蛋白血症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 代謝性アシドーシス | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 腫瘍崩壊症候群 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ２型糖尿病 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 神経系障害 | 111 (34.7%) | 7 (2.2%) | 1 (0.3%) | 10 (20.4%) | 1 (2.0%) | 0 | 121 (32.8%) |
| 頭痛 | 36 (11.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 37 (10.0%) |
| 浮動性めまい | 24 (7.5%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 26 (7.0%) |
| 末梢性感覚ニューロパチー | 11 (3.4%) | 1 (0.3%) | 0 | 3 (6.1%) | 0 | 0 | 14 (3.8%) |
| 体位性めまい | 10 (3.1%) | 0 | 0 | 0 | 0 | 0 | 10 (2.7%) |
| 錯感覚 | 8 (2.5%) | 0 | 0 | 0 | 0 | 0 | 8 (2.2%) |
| 記憶障害 | 7 (2.2%) | 0 | 0 | 0 | 0 | 0 | 7 (1.9%) |
| 末梢性ニューロパチー | 7 (2.2%) | 0 | 0 | 0 | 0 | 0 | 7 (1.9%) |
| 振戦 | 6 (1.9%) | 0 | 0 | 0 | 0 | 0 | 6 (1.6%) |
| 感覚鈍麻 | 5 (1.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 健忘 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 傾眠 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 失神 | 4 (1.3%) | 4 (1.3%) | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 平衡障害 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 構語障害 | 3 (0.9%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 味覚異常 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 嗜眠 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 多発ニューロパチー | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 認知症 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 頭蓋内出血 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 過眠症 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 神経痛 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 失神寸前の状態 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 下肢静止不能症候群 | 0 | 0 | 0 | 2 (4.1%) | 0 | 0 | 2 (0.5%) |
| 副鼻腔炎に伴う頭痛 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 一過性脳虚血発作 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 灼熱足症候群 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 手根管症候群 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 大脳萎縮 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 脳血管発作 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 労作性めまい | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 脳症 | 1 (0.3%) | 0 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| てんかん | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| 顔面部神経痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 顔面不全麻痺 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 頭部不快感 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 腰髄神経根障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 片頭痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 前兆を伴う片頭痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 筋痙直 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ミオクローヌス | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼振 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 腓骨神経麻痺 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ヘルペス後神経痛 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 坐骨神経痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 感覚障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 会話障害 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 緊張性頭痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 一過性全健忘 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血管性脳症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 臨床検査 | 96 (30.0%) | 29 (9.1%) | 0 | 16 (32.7%) | 6 (12.2%) | 0 | 112 (30.4%) |
| 血中クレアチニン増加 | 28 (8.8%) | 0 | 0 | 3 (6.1%) | 0 | 0 | 31 (8.4%) |
| 血小板数減少 | 14 (4.4%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 14 (3.8%) |
| 体重減少 | 10 (3.1%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 12 (3.3%) |
| 血中アルカリホスファターゼ増加 | 10 (3.1%) | 2 (0.6%) | 0 | 1 (2.0%) | 0 | 0 | 11 (3.0%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 7 (2.2%) | 1 (0.3%) | 0 | 3 (6.1%) | 0 | 0 | 10 (2.7%) |
| 血中ビリルビン増加 | 6 (1.9%) | 2 (0.6%) | 0 | 4 (8.2%) | 0 | 0 | 10 (2.7%) |
| 好中球数減少 | 9 (2.8%) | 8 (2.5%) | 0 | 0 | 0 | 0 | 9 (2.4%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| アラニンアミノトランスフェラーゼ増加 | 6 (1.9%) | 1 (0.3%) | 0 | 1 (2.0%) | 0 | 0 | 7 (1.9%) |
| 血中尿酸増加 | 7 (2.2%) | 3 (0.9%) | 0 | 0 | 0 | 0 | 7 (1.9%) |
| リンパ球数増加 | 5 (1.6%) | 3 (0.9%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 6 (1.6%) |
| 体重増加 | 6 (1.9%) | 0 | 0 | 0 | 0 | 0 | 6 (1.6%) |
| 活性化部分トロンボプラスチン時間延長 | 5 (1.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 血中乳酸脱水素酵素増加 | 4 (1.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 5 (1.4%) |
| 白血球数減少 | 4 (1.3%) | 4 (1.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 5 (1.4%) |
| 血中免疫グロブリンG減少 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 国際標準比増加 | 3 (0.9%) | 3 (0.9%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 白血球数増加 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 血中ブドウ糖増加 | 2 (0.6%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 血中免疫グロブリンM減少 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 血圧上昇 | 1 (0.3%) | 1 (0.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 2 (0.5%) |
| Ｃ－反応性蛋白増加 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 心雑音 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| γ－グルタミルトランスフェラーゼ増加 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 糸球体濾過率減少 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| ヘモグロビン減少 | 2 (0.6%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 免疫グロブリン減少 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| リンパ球数減少 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| トランスアミナーゼ上昇 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| アミラーゼ増加 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| アスペルギルス検査陽性 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血中アルブミン減少 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| 血中重炭酸塩増加 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血中ビリルビン異常 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| 血中クロール減少 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血中コレステロール増加 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血中クレアチン増加 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 血中免疫グロブリンA減少 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血中鉄減少 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血中マグネシウム減少 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血中リン減少 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血中カリウム減少 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸音異常 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 二酸化炭素減少 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 胸部コンピュータ断層撮影異常 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 駆出率減少 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| グリコヘモグロビン増加 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ヘモフィルス検査陽性 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 心拍数増加 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 心拍数不整 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肝酵素上昇 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 深吸気量減少 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肝機能検査異常 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 黄斑部反射異常 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 平均赤血球容積増加 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血小板凝集異常 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 尿量減少 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 超低比重リポ蛋白増加 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肺活量異常 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| 傷害、中毒および処置合併症 | 88 (27.5%) | 9 (2.8%) | 2 (0.6%) | 13 (26.5%) | 2 (4.1%) | 0 | 101 (27.4%) |
| 挫傷 | 40 (12.5%) | 0 | 0 | 6 (12.2%) | 0 | 0 | 46 (12.5%) |
| 転倒 | 16 (5.0%) | 3 (0.9%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 17 (4.6%) |
| 節足動物咬傷 | 6 (1.9%) | 0 | 0 | 0 | 0 | 0 | 6 (1.6%) |
| 処置による疼痛 | 6 (1.9%) | 0 | 0 | 0 | 0 | 0 | 6 (1.6%) |
| 硬膜下血腫 | 4 (1.3%) | 1 (0.3%) | 1 (0.3%) | 2 (4.1%) | 1 (2.0%) | 0 | 6 (1.6%) |
| 外傷性血腫 | 5 (1.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 6 (1.6%) |
| 裂傷 | 3 (0.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 4 (1.1%) |
| 皮膚擦過傷 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| サンバーン | 3 (0.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 4 (1.1%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 創傷 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 動物咬傷 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 頭部損傷 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 靭帯捻挫 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 腰椎骨折 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 処置後出血 | 2 (0.6%) | 1 (0.3%) | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 3 (0.8%) |
| 骨挫傷 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 擦過傷 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 顔面骨骨折 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 四肢損傷 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 眼窩周囲挫傷 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 肋骨骨折 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 皮膚創傷 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 脊椎圧迫骨折 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 脾破裂 | 2 (0.6%) | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 2 (0.5%) |
| 熱傷 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 動物による引っかき傷 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 足関節部骨折 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 第２度熱傷 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼挫傷 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼外傷 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 足骨折 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼内異物 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 外傷性血尿 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 関節損傷 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 過量投与 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 処置後便秘 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 処置後血尿 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 処置後腫脹 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 外傷後疼痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢血腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 皮下血腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 脛骨骨折 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 歯牙破折 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 術後尿閉 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 創合併症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼障害 | 72 (22.5%) | 5 (1.6%) | 0 | 10 (20.4%) | 0 | 0 | 82 (22.2%) |
| 眼乾燥 | 13 (4.1%) | 0 | 0 | 3 (6.1%) | 0 | 0 | 16 (4.3%) |
| 流涙増加 | 10 (3.1%) | 0 | 0 | 3 (6.1%) | 0 | 0 | 13 (3.5%) |
| 霧視 | 11 (3.4%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 13 (3.5%) |
| 白内障 | 11 (3.4%) | 3 (0.9%) | 0 | 0 | 0 | 0 | 11 (3.0%) |
| 視力低下 | 4 (1.3%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 6 (1.6%) |
| 眼窩周囲浮腫 | 4 (1.3%) | 1 (0.3%) | 0 | 1 (2.0%) | 0 | 0 | 5 (1.4%) |
| 結膜出血 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 眼痛 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 眼充血 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 睫毛乱生 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 硝子体浮遊物 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 糖尿病網膜症 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 複視 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |
| 眼出血 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 眼刺激 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 眼瞼下垂 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 羞明 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 眼瞼炎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 片側失明 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 結膜充血 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼瞼内反 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 眼脂 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 眼の炎症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼そう痒症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼の異物感 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 緑内障 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 角膜炎 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 黄斑変性 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| マイボーム腺機能不全 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼血管障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 開放隅角緑内障 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 動揺視 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 老視 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 網膜剥離 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 強膜出血 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 視力障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 硝子体出血 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 眼球乾燥症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 血管障害 | 70 (21.9%) | 24 (7.5%) | 0 | 11 (22.4%) | 1 (2.0%) | 1 (2.0%) | 81 (22.0%) |
| 高血圧 | 32 (10.0%) | 12 (3.8%) | 0 | 3 (6.1%) | 1 (2.0%) | 0 | 35 (9.5%) |
| 低血圧 | 19 (5.9%) | 5 (1.6%) | 0 | 2 (4.1%) | 0 | 0 | 21 (5.7%) |
| 血腫 | 12 (3.8%) | 0 | 0 | 0 | 0 | 0 | 12 (3.3%) |
| 深部静脈血栓症 | 4 (1.3%) | 2 (0.6%) | 0 | 3 (6.1%) | 0 | 0 | 7 (1.9%) |
| 潮紅 | 3 (0.9%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 4 (1.1%) |
| 出血 | 4 (1.3%) | 3 (0.9%) | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 起立性低血圧 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 静脈炎 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 血圧変動 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| リンパ浮腫 | 2 (0.6%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 表在性血栓性静脈炎 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 大動脈硬化症 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 循環虚脱 | 0 | 0 | 0 | 1 (2.0%) | 0 | 1 (2.0%) | 1 (0.3%) |
| ほてり | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 高血圧クリーゼ | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 末梢血管障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 末梢静脈疾患 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 静脈瘤 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 心臓障害 | 54 (16.9%) | 22 (6.9%) | 3 (0.9%) | 10 (20.4%) | 1 (2.0%) | 0 | 64 (17.3%) |
| 心房細動 | 23 (7.2%) | 16 (5.0%) | 0 | 5 (10.2%) | 1 (2.0%) | 0 | 28 (7.6%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 頻脈 | 5 (1.6%) | 0 | 0 | 4 (8.2%) | 0 | 0 | 9 (2.4%) |
| 洞性頻脈 | 7 (2.2%) | 0 | 0 | 0 | 0 | 0 | 7 (1.9%) |
| 徐脈 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 動悸 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 心房粗動 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 洞性徐脈 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 上室性頻脈 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 不安定狭心症 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 心停止 | 2 (0.6%) | 0 | 2 (0.6%) | 0 | 0 | 0 | 2 (0.5%) |
| 心不全 | 2 (0.6%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 心室性期外収縮 | 0 | 0 | 0 | 2 (4.1%) | 0 | 0 | 2 (0.5%) |
| 急性心筋梗塞 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 不整脈 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 冠動脈硬化症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 第一度房室ブロック | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| うっ血性心不全 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 心血管不全 | 1 (0.3%) | 0 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 変時性応答不全 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 冠動脈疾患 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 冠動脈閉塞 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| チアノーゼ | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 僧帽弁閉鎖不全症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 心筋梗塞 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 心嚢液貯留 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 心膜炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 洞不全症候群 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| ストレス心筋症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 頻脈性不整脈 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| トルサード　ド　ポアント | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 三尖弁疾患 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 心室性不整脈 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 心室性頻脈 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 精神障害 | 58 (18.1%) | 7 (2.2%) | 0 | 5 (10.2%) | 0 | 0 | 63 (17.1%) |
| 不眠症 | 24 (7.5%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 26 (7.0%) |
| 不安 | 12 (3.8%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 13 (3.5%) |
| 錯乱状態 | 10 (3.1%) | 4 (1.3%) | 0 | 2 (4.1%) | 0 | 0 | 12 (3.3%) |
| うつ病 | 12 (3.8%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 12 (3.3%) |
| 激越 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 譫妄 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 希死念慮を有するうつ病 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 多幸気分 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 幻聴 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 幻視 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 易刺激性 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| リビドー減退 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 躁病 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 精神障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 精神状態変化 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 悪夢 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| パニック発作 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| パニック障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 腎および尿路障害 | 49 (15.3%) | 12 (3.8%) | 3 (0.9%) | 8 (16.3%) | 2 (4.1%) | 0 | 57 (15.4%) |
| 血尿 | 11 (3.4%) | 3 (0.9%) | 0 | 3 (6.1%) | 0 | 0 | 14 (3.8%) |
| 急性腎不全 | 11 (3.4%) | 4 (1.3%) | 1 (0.3%) | 1 (2.0%) | 1 (2.0%) | 0 | 12 (3.3%) |
| 排尿困難 | 5 (1.6%) | 0 | 0 | 3 (6.1%) | 0 | 0 | 8 (2.2%) |
| 腎不全 | 7 (2.2%) | 3 (0.9%) | 2 (0.6%) | 0 | 0 | 0 | 7 (1.9%) |
| 頻尿 | 5 (1.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 6 (1.6%) |
| 水腎症 | 2 (0.6%) | 2 (0.6%) | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 腎機能障害 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 尿閉 | 2 (0.6%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 3 (0.8%) |
| 尿路閉塞 | 3 (0.9%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 腎結石症 | 0 | 0 | 0 | 2 (4.1%) | 1 (2.0%) | 0 | 2 (0.5%) |
| 夜間頻尿 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 腎嚢胞 | 1 (0.3%) | 0 | 0 | 1 (2.0%) | 0 | 0 | 2 (0.5%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 慢性腎不全 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 尿失禁 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 高窒素血症 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 膀胱刺激症状 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 出血性膀胱炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 緊張性膀胱 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 失禁 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 尿意切迫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 閉塞性尿路疾患 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 乏尿 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 腎仙痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 有痛性排尿困難 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 尿路痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 34 (10.6%) | 9 (2.8%) | 8 (2.5%) | 1 (2.0%) | 1 (2.0%) | 0 | 35 (9.5%) |
| 基底細胞癌 | 7 (2.2%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 7 (1.9%) |
| マントル細胞リンパ腫 | 7 (2.2%) | 1 (0.3%) | 6 (1.9%) | 0 | 0 | 0 | 7 (1.9%) |
| 皮膚有棘細胞癌 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 膀胱移行上皮癌 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 前立腺癌 | 2 (0.6%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 扁平上皮癌 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 急性骨髄性白血病 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 良性新生物 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 膀胱癌 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肺腺癌 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 悪性胸水 | 1 (0.3%) | 0 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 口腔乳頭腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 唾液腺癌 | 0 | 0 | 0 | 1 (2.0%) | 1 (2.0%) | 0 | 1 (0.3%) |
| 皮膚癌 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚乳頭腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 胸腺腫 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 移行上皮癌 | 1 (0.3%) | 0 | 1 (0.3%) | 0 | 0 | 0 | 1 (0.3%) |
| 腫瘍フレア | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 耳および迷路障害 | 30 (9.4%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 30 (8.1%) |
| 回転性めまい | 11 (3.4%) | 0 | 0 | 0 | 0 | 0 | 11 (3.0%) |
| 耳鳴 | 6 (1.9%) | 0 | 0 | 0 | 0 | 0 | 6 (1.6%) |
| 耳痛 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 聴力低下 | 4 (1.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 耳垢栓塞 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 耳不快感 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 難聴 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 耳出血 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 聴覚過敏 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 老人性難聴 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 生殖系および乳房障害 | 26 (8.1%) | 7 (2.2%) | 0 | 0 | 0 | 0 | 26 (7.0%) |
| 良性前立腺肥大症 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 血精液症 | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 性器浮腫 | 3 (0.9%) | 2 (0.6%) | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 勃起不全 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 骨盤痛 | 2 (0.6%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 腟出血 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 後天性包茎 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 乳房血腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 乳房腫瘤 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 乳房痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 性器発疹 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 陰茎痛 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢腫瘤 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢浮腫 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢痛 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 子宮腟脱 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 外陰腟痛 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 外陰腟そう痒症 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE32: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by Baseline Hepatic Abnormality for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline Hepatic Abnormality | | | | | | |
| | Normal | | | Not Normal | | | |
| | Any Grades | Grade 3-4 | Grade 5 | Any Grades | Grade 3-4 | Grade 5 | Total Any Grades |
| 免疫系障害 | 17 (5.3%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 19 (5.1%) |
| 低γグロブリン血症 | 3 (0.9%) | 0 | 0 | 2 (4.1%) | 0 | 0 | 5 (1.4%) |
| 節足動物咬傷アレルギー | 4 (1.3%) | 0 | 0 | 0 | 0 | 0 | 4 (1.1%) |
| 過敏症 | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 季節性アレルギー | 3 (0.9%) | 0 | 0 | 0 | 0 | 0 | 3 (0.8%) |
| 薬物過敏症 | 2 (0.6%) | 0 | 0 | 0 | 0 | 0 | 2 (0.5%) |
| 造影剤アレルギー | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 食物アレルギー | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肝胆道系障害 | 8 (2.5%) | 3 (0.9%) | 0 | 5 (10.2%) | 1 (2.0%) | 0 | 13 (3.5%) |
| 高ビリルビン血症 | 3 (0.9%) | 0 | 0 | 3 (6.1%) | 1 (2.0%) | 0 | 6 (1.6%) |
| 胆石症 | 1 (0.3%) | 0 | 0 | 2 (4.1%) | 1 (2.0%) | 0 | 3 (0.8%) |
| 胆管結石 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 胆管炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肝不全 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 肝機能異常 | 0 | 0 | 0 | 1 (2.0%) | 0 | 0 | 1 (0.3%) |
| 中毒性肝炎 | 1 (0.3%) | 1 (0.3%) | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 陶器様胆嚢 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 内分泌障害 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 甲状腺機能低下症 | 5 (1.6%) | 0 | 0 | 0 | 0 | 0 | 5 (1.4%) |
| 先天性、家族性および遺伝性障害 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |
| 臍血腫 | 1 (0.3%) | 0 | 0 | 0 | 0 | 0 | 1 (0.3%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE32.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae32.sas] 15OCT2015, 15:03

参照元：5.3.5.3.1 ISS TSFAE32

表 2.7.4-付録-57 Overall Summary of Treatment-emergent Adverse Events by CYP3A Inhibitor (Yes vs. No); Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE14APART1OF3: Overall Summary of Treatment-emergent Adverse Events by CYP3A Inhibitor (Yes vs. No); Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | CYP3A Inhibitor | | CYP3A Inhibitor | |
| | Yes | No | Yes | No |
| Analysis Set: Safety Population | 60 | 51 | 41 | 79 |
| Any TEAE | 60 (100.0%) | 51 (100.0%) | 41 (100.0%) | 74 (93.7%) |
| Grade >= 3 | 43 (71.7%) | 41 (80.4%) | 36 (87.8%) | 51 (64.6%) |
| Drug related [a] | 53 (88.3%) | 45 (88.2%) | 37 (90.2%) | 58 (73.4%) |
| Grade >= 3 | 30 (50.0%) | 19 (37.3%) | 23 (56.1%) | 29 (36.7%) |
| Any TESAE | 31 (51.7%) | 31 (60.8%) | 27 (65.9%) | 32 (40.5%) |
| Grade >= 3 | 27 (45.0%) | 28 (54.9%) | 26 (63.4%) | 27 (34.2%) |
| Drug related [a] | 16 (26.7%) | 12 (23.5%) | 15 (36.6%) | 10 (12.7%) |
| TEAE leading to treatment discontinuation | 4 (6.7%) | 6 (11.8%) | 5 (12.2%) | 15 (19.0%) |
| TEAE leading to treatment dose reduction | 10 (16.7%) | 5 (9.8%) | 3 (7.3%) | 5 (6.3%) |
| TEAE with outcome death | 7 (11.7%) | 9 (17.6%) | 6 (14.6%) | 8 (10.1%) |
| Deaths within 30 days after last dose of study treatment [b] | 7 (11.7%) | 9 (17.6%) | 7 (17.1%) | 16 (20.3%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE14APART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae14a.sas]
26OCT2015, 14:28

参照元：5.3.5.3.1 ISS TSFAE14APART1OF3

表 2.7.4-付録-58 Overall Summary of Treatment-emergent Adverse Events by CYP3A Inhibitor (Yes vs. No); Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE14APART2OF3: Overall Summary of Treatment-emergent Adverse Events by CYP3A Inhibitor (Yes vs. No); Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | CYP3A Inhibitor | | CYP3A Inhibitor | |
| | Yes | No | Yes | No |
| Analysis Set: Safety Population | 47 | 92 | 53 | 86 |
| Any TEAE | 47 (100.0%) | 91 (98.9%) | 53 (100.0%) | 85 (98.8%) |
| Grade >= 3 | 32 (68.1%) | 62 (67.4%) | 51 (96.2%) | 70 (81.4%) |
| Drug related [a] | 44 (93.6%) | 71 (77.2%) | 53 (100.0%) | 80 (93.0%) |
| Grade >= 3 | 27 (57.4%) | 28 (30.4%) | 47 (88.7%) | 62 (72.1%) |
| Any TESAE | 29 (61.7%) | 38 (41.3%) | 32 (60.4%) | 48 (55.8%) |
| Grade >= 3 | 26 (55.3%) | 37 (40.2%) | 27 (50.9%) | 41 (47.7%) |
| Drug related [a] | 16 (34.0%) | 13 (14.1%) | 24 (45.3%) | 29 (33.7%) |
| TEAE leading to treatment discontinuation | 7 (14.9%) | 11 (12.0%) | 15 (28.3%) | 26 (30.2%) |
| TEAE leading to treatment dose reduction | 3 (6.4%) | 2 (2.2%) | 32 (60.4%) | 28 (32.6%) |
| TEAE with outcome death | 5 (10.6%) | 10 (10.9%) | 2 (3.8%) | 9 (10.5%) |
| Deaths within 30 days after last dose of study treatment [b] | 9 (19.1%) | 15 (16.3%) | 4 (7.5%) | 11 (12.8%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE14APART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae14a.sas]
26OCT2015, 14:28

参照元：5.3.5.3.1 ISS TSFAE14APART2OF3

表 2.7.4-付録-59 Overall Summary of Treatment-emergent Adverse Events by CYP3A Inhibitor (Strong vs. non-Strong); Safety Population in Studies PCYC-1104 and MCL2001 (MCL-ISS)

**TSFAE14BPART1OF3: Overall Summary of Treatment-emergent Adverse Events by CYP3A Inhibitor (Strong vs. non-Strong); Safety Population (MCL-ISS)**

| | PCYC-1104 Ibrutinib | | MCL2001 Ibrutinib | |
|---|---|---|---|---|
| | CYP3A Inhibitor | | CYP3A Inhibitor | |
| | Strong | non-Strong | Strong | non-Strong |
| Analysis Set: Safety Population | 7 | 53 | 3 | 38 |
| Any TEAE | 7 (100.0%) | 53 (100.0%) | 3 (100.0%) | 38 (100.0%) |
| Grade >= 3 | 3 (42.9%) | 40 (75.5%) | 3 (100.0%) | 33 (86.8%) |
| Drug related [a] | 6 (85.7%) | 47 (88.7%) | 3 (100.0%) | 34 (89.5%) |
| Grade >= 3 | 3 (42.9%) | 27 (50.9%) | 3 (100.0%) | 20 (52.6%) |
| Any TESAE | 2 (28.6%) | 29 (54.7%) | 3 (100.0%) | 24 (63.2%) |
| Grade >= 3 | 2 (28.6%) | 25 (47.2%) | 3 (100.0%) | 23 (60.5%) |
| Drug related [a] | 1 (14.3%) | 15 (28.3%) | 2 (66.7%) | 13 (34.2%) |
| TEAE leading to treatment discontinuation | 0 | 4 (7.5%) | 2 (66.7%) | 3 (7.9%) |
| TEAE leading to treatment dose reduction | 1 (14.3%) | 9 (17.0%) | 0 | 3 (7.9%) |
| TEAE with outcome death | 1 (14.3%) | 6 (11.3%) | 1 (33.3%) | 5 (13.2%) |
| Deaths within 30 days after last dose of study treatment [b] | 1 (14.3%) | 6 (11.3%) | 1 (33.3%) | 6 (15.8%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE14BPART1OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae14b.sas]
26OCT2015, 14:28

参照元：5.3.5.3.1 ISS TSFAE14BPART1OF3

表 2.7.4-付録-60 Overall Summary of Treatment-emergent Adverse Events by CYP3A Inhibitor (Strong vs. non-Strong); Safety Population in Study MCL3001 (MCL-ISS)

**TSFAE14BPART2OF3: Overall Summary of Treatment-emergent Adverse Events by CYP3A Inhibitor (Strong vs. non-Strong); Safety Population (MCL-ISS)**

| | MCL3001 | | | |
|---|---|---|---|---|
| | Ibrutinib | | Temsirolimus | |
| | CYP3A Inhibitor | | CYP3A Inhibitor | |
| | Strong | non-Strong | Strong | non-Strong |
| Analysis Set: Safety Population | 14 | 33 | 12 | 41 |
| Any TEAE | 14 (100.0%) | 33 (100.0%) | 12 (100.0%) | 41 (100.0%) |
| Grade >= 3 | 10 (71.4%) | 22 (66.7%) | 12 (100.0%) | 39 (95.1%) |
| Drug related [a] | 13 (92.9%) | 31 (93.9%) | 12 (100.0%) | 41 (100.0%) |
| Grade >= 3 | 10 (71.4%) | 17 (51.5%) | 12 (100.0%) | 35 (85.4%) |
| Any TESAE | 11 (78.6%) | 18 (54.5%) | 10 (83.3%) | 22 (53.7%) |
| Grade >= 3 | 9 (64.3%) | 17 (51.5%) | 9 (75.0%) | 18 (43.9%) |
| Drug related [a] | 9 (64.3%) | 7 (21.2%) | 7 (58.3%) | 17 (41.5%) |
| TEAE leading to treatment discontinuation | 2 (14.3%) | 5 (15.2%) | 1 (8.3%) | 14 (34.1%) |
| TEAE leading to treatment dose reduction | 2 (14.3%) | 1 (3.0%) | 11 (91.7%) | 21 (51.2%) |
| TEAE with outcome death | 2 (14.3%) | 3 (9.1%) | 0 | 2 (4.9%) |
| Deaths within 30 days after last dose of study treatment [b] | 3 (21.4%) | 6 (18.2%) | 0 | 4 (9.8%) |

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
[b] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.

[TSFAE14BPART2OF3.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae14b.sas]
26OCT2015, 14:28

参照元：5.3.5.3.1 ISS TSFAE14BPART2OF3

表 2.7.4-付録-61 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| Analysis set: safety | 148 | | 222 | | 370 |
| Subjects with any TEAE | 148 (100.0%) | 111 (75.0%) | 216 (97.3%) | 154 (69.4%) | 364 (98.4%) |
| System organ class | | | | | |
| Preferred term | | | | | |
| 感染症および寄生虫症 | 135 (91.2%) | 54 (36.5%) | 128 (57.7%) | 33 (14.9%) | 263 (71.1%) |
| 上気道感染 | 38 (25.7%) | 1 (0.7%) | 35 (15.8%) | 2 (0.9%) | 73 (19.7%) |
| 肺炎 | 32 (21.6%) | 24 (16.2%) | 12 (5.4%) | 9 (4.1%) | 44 (11.9%) |
| 副鼻腔炎 | 26 (17.6%) | 1 (0.7%) | 13 (5.9%) | 0 | 39 (10.5%) |
| 尿路感染 | 25 (16.9%) | 5 (3.4%) | 13 (5.9%) | 1 (0.5%) | 38 (10.3%) |
| 鼻咽頭炎 | 13 (8.8%) | 0 | 17 (7.7%) | 0 | 30 (8.1%) |
| 結膜炎 | 17 (11.5%) | 0 | 9 (4.1%) | 0 | 26 (7.0%) |
| 気管支炎 | 15 (10.1%) | 4 (2.7%) | 5 (2.3%) | 0 | 20 (5.4%) |
| 蜂巣炎 | 12 (8.1%) | 3 (2.0%) | 6 (2.7%) | 5 (2.3%) | 18 (4.9%) |
| 帯状疱疹 | 6 (4.1%) | 0 | 8 (3.6%) | 0 | 14 (3.8%) |
| 鼻炎 | 7 (4.7%) | 0 | 7 (3.2%) | 0 | 14 (3.8%) |
| 毛包炎 | 9 (6.1%) | 0 | 4 (1.8%) | 0 | 13 (3.5%) |
| 爪囲炎 | 7 (4.7%) | 0 | 6 (2.7%) | 0 | 13 (3.5%) |
| 下気道感染 | 10 (6.8%) | 5 (3.4%) | 2 (0.9%) | 0 | 12 (3.2%) |
| 皮膚感染 | 5 (3.4%) | 0 | 7 (3.2%) | 1 (0.5%) | 12 (3.2%) |
| 口腔ヘルペス | 3 (2.0%) | 0 | 8 (3.6%) | 0 | 11 (3.0%) |
| 気道感染 | 4 (2.7%) | 0 | 7 (3.2%) | 2 (0.9%) | 11 (3.0%) |
| 敗血症 | 6 (4.1%) | 6 (4.1%) | 5 (2.3%) | 5 (2.3%) | 11 (3.0%) |
| 胃腸炎 | 5 (3.4%) | 1 (0.7%) | 5 (2.3%) | 1 (0.5%) | 10 (2.7%) |
| 咽頭炎 | 3 (2.0%) | 1 (0.7%) | 4 (1.8%) | 0 | 7 (1.9%) |
| ウイルス感染 | 3 (2.0%) | 0 | 4 (1.8%) | 0 | 7 (1.9%) |
| 感染 | 5 (3.4%) | 2 (1.4%) | 1 (0.5%) | 0 | 6 (1.6%) |
| クロストリジウム・ディフィシレ大腸炎 | 3 (2.0%) | 2 (1.4%) | 2 (0.9%) | 1 (0.5%) | 5 (1.4%) |
| 眼感染 | 3 (2.0%) | 0 | 2 (0.9%) | 0 | 5 (1.4%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯肉炎 | 2 (1.4%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 口腔カンジダ症 | 3 (2.0%) | 0 | 2 (0.9%) | 0 | 5 (1.4%) |
| クロストリジウム・ディフィシレ感染 | 3 (2.0%) | 1 (0.7%) | 1 (0.5%) | 0 | 4 (1.1%) |
| インフルエンザ | 1 (0.7%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 限局性感染 | 1 (0.7%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 中耳炎 | 3 (2.0%) | 0 | 1 (0.5%) | 0 | 4 (1.1%) |
| 歯周炎 | 3 (2.0%) | 0 | 1 (0.5%) | 0 | 4 (1.1%) |
| 歯感染 | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| 菌血症 | 3 (2.0%) | 2 (1.4%) | 0 | 0 | 3 (0.8%) |
| 気管支肺炎 | 2 (1.4%) | 1 (0.7%) | 1 (0.5%) | 0 | 3 (0.8%) |
| 膀胱炎 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 耳感染 | 1 (0.7%) | 0 | 2 (0.9%) | 0 | 3 (0.8%) |
| ウイルス性胃腸炎 | 1 (0.7%) | 1 (0.7%) | 2 (0.9%) | 0 | 3 (0.8%) |
| 単純ヘルペス | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 喉頭炎 | 2 (1.4%) | 0 | 1 (0.5%) | 1 (0.5%) | 3 (0.8%) |
| 爪感染 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 外耳炎 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| ブドウ球菌感染 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| ウイルス性上気道感染 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 急性副鼻腔炎 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 細気管支炎 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 医療機器関連感染 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 憩室炎 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 感染性小腸結腸炎 | 2 (1.4%) | 2 (1.4%) | 0 | 0 | 2 (0.5%) |
| 丹毒 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 真菌感染 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 皮膚真菌感染 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 真菌性性器感染 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| ヘルペスウイルス感染 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 麦粒腫 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 爪真菌症 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| レンサ球菌性咽頭炎 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| ニューモシスチス・イロベチイ肺炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 細菌性肺炎 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 膿疱性皮疹 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 敗血症性ショック | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| ブドウ球菌性菌血症 | 1 (0.7%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 歯膿瘍 | 1 (0.7%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 細菌性尿路感染 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 尿路性敗血症 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 外陰部腟カンジダ症 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 創傷感染 | 2 (1.4%) | 1 (0.7%) | 0 | 0 | 2 (0.5%) |
| 腹部膿瘍 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 四肢膿瘍 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| ダニ皮膚炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 膿疱性ざ瘡 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 肛門膿瘍 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 肛門カンジダ症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 虫垂炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 穿孔性虫垂炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 異型肺炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 細菌尿 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| カンジダ性亀頭炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 胆道感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| ブラストシスティス感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 体部白癬 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房蜂巣炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| カンピロバクター胃腸炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| カンピロバクター感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| カンジダ感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼窩蜂巣炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 感染性胆嚢炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性副鼻腔炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| シトロバクター感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 涙嚢炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性脳炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 精巣上体炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 喉頭蓋炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 細菌性眼感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 真菌血症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘリコバクター胃潰瘍 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 消化管感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性消化管感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 性器カンジダ症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血腫感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| ヘモフィルス感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| Ｂ型肝炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| ヒストプラスマ症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 埋込み部位感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 切開部位感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| クレブシエラ感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 口唇感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 細菌性下気道感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 肺感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| ライム病 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 乳腺炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 水疱性鼓膜炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪床感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼帯状疱疹 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 口腔真菌感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳頭腫ウイルス感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| クリプトコッカス性肺炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| クレブシエラ菌性肺炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 処置後感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 肺結核 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 腎盂腎炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 膿皮症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| レンサ球菌性膿皮症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 狂犬病 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 直腸膿瘍 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| ウイルス性気道感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 軟部組織感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| ブドウ球菌皮膚感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| レンサ球菌感染 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 皮下組織膿瘍 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 足部白癬 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 扁桃炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 気管炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 真菌性尿路感染 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| シュードモナス性尿路感染 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 胃腸障害 | 116 (78.4%) | 20 (13.5%) | 139 (62.6%) | 19 (8.6%) | 255 (68.9%) |
| 下痢 | 72 (48.6%) | 7 (4.7%) | 74 (33.3%) | 6 (2.7%) | 146 (39.5%) |
| 悪心 | 41 (27.7%) | 0 | 39 (17.6%) | 1 (0.5%) | 80 (21.6%) |
| 嘔吐 | 31 (20.9%) | 0 | 31 (14.0%) | 1 (0.5%) | 62 (16.8%) |
| 便秘 | 33 (22.3%) | 0 | 24 (10.8%) | 0 | 57 (15.4%) |
| 腹痛 | 16 (10.8%) | 6 (4.1%) | 26 (11.7%) | 7 (3.2%) | 42 (11.4%) |
| 口内炎 | 20 (13.5%) | 3 (2.0%) | 11 (5.0%) | 0 | 31 (8.4%) |
| 消化不良 | 10 (6.8%) | 0 | 18 (8.1%) | 0 | 28 (7.6%) |
| 上腹部痛 | 7 (4.7%) | 0 | 9 (4.1%) | 1 (0.5%) | 16 (4.3%) |
| 腹部膨満 | 4 (2.7%) | 0 | 10 (4.5%) | 0 | 14 (3.8%) |
| 口内乾燥 | 4 (2.7%) | 0 | 10 (4.5%) | 0 | 14 (3.8%) |
| 胃食道逆流性疾患 | 5 (3.4%) | 0 | 8 (3.6%) | 0 | 13 (3.5%) |
| 嚥下障害 | 5 (3.4%) | 0 | 4 (1.8%) | 2 (0.9%) | 9 (2.4%) |
| 腹部不快感 | 4 (2.7%) | 0 | 4 (1.8%) | 0 | 8 (2.2%) |
| 口腔内痛 | 3 (2.0%) | 0 | 5 (2.3%) | 1 (0.5%) | 8 (2.2%) |
| 口腔内潰瘍形成 | 4 (2.7%) | 0 | 3 (1.4%) | 0 | 7 (1.9%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 放屁 | 3 (2.0%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 胃炎 | 4 (2.7%) | 0 | 2 (0.9%) | 0 | 6 (1.6%) |
| 心窩部不快感 | 4 (2.7%) | 0 | 1 (0.5%) | 0 | 5 (1.4%) |
| 舌痛 | 2 (1.4%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 痔核 | 3 (2.0%) | 0 | 1 (0.5%) | 0 | 4 (1.1%) |
| アフタ性口内炎 | 2 (1.4%) | 1 (0.7%) | 1 (0.5%) | 0 | 3 (0.8%) |
| おくび | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| イレウス | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 直腸出血 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 舌潰瘍 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 下腹部痛 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 齲歯 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 軟便 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 食中毒 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 排便回数増加 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 胃潰瘍 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 歯肉出血 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 歯肉浮腫 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 吐血 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 麻痺性イレウス | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 鼠径ヘルニア | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 口唇潰瘍 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 下部消化管出血 | 2 (1.4%) | 1 (0.7%) | 0 | 0 | 2 (0.5%) |
| 口腔内出血 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 歯周病 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 肛門周囲痛 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 直腸炎 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 直腸裂 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 小腸閉塞 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 歯痛 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 裂肛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 肛門直腸障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 萎縮性舌炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| バレット食道 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 大腸炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 歯不快感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血性下痢 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 十二指腸狭窄 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 十二指腸潰瘍 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 十二指腸炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 十二指腸胃逆流 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 便失禁 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 糞塊 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 胃前庭部毛細血管拡張症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 出血性胃炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 歯肉痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血便排泄 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 痔出血 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 過敏性腸症候群 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇水疱 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇びらん | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 口唇痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 口唇腫脹 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 弛緩歯 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| メレナ | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 嚥下痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 口蓋障害 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 慢性膵炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 舌突出 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 直腸潰瘍 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 唾液腺結石 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 変色歯 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 歯の障害 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 歯の脱落 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 一般・全身障害および投与部位の状態 | 108 (73.0%) | 13 (8.8%) | 131 (59.0%) | 25 (11.3%) | 239 (64.6%) |
| 疲労 | 59 (39.9%) | 6 (4.1%) | 70 (31.5%) | 10 (4.5%) | 129 (34.9%) |
| 末梢性浮腫 | 37 (25.0%) | 2 (1.4%) | 37 (16.7%) | 4 (1.8%) | 74 (20.0%) |
| 発熱 | 38 (25.7%) | 1 (0.7%) | 30 (13.5%) | 2 (0.9%) | 68 (18.4%) |
| 無力症 | 12 (8.1%) | 1 (0.7%) | 20 (9.0%) | 4 (1.8%) | 32 (8.6%) |
| 悪寒 | 12 (8.1%) | 0 | 6 (2.7%) | 0 | 18 (4.9%) |
| 胸痛 | 8 (5.4%) | 0 | 7 (3.2%) | 0 | 15 (4.1%) |
| 末梢腫脹 | 7 (4.7%) | 0 | 8 (3.6%) | 1 (0.5%) | 15 (4.1%) |
| インフルエンザ様疾患 | 10 (6.8%) | 0 | 4 (1.8%) | 0 | 14 (3.8%) |
| 疼痛 | 5 (3.4%) | 0 | 6 (2.7%) | 1 (0.5%) | 11 (3.0%) |
| 非心臓性胸痛 | 6 (4.1%) | 2 (1.4%) | 2 (0.9%) | 0 | 8 (2.2%) |
| 粘膜の炎症 | 2 (1.4%) | 1 (0.7%) | 4 (1.8%) | 0 | 6 (1.6%) |
| 全身健康状態低下 | 2 (1.4%) | 0 | 3 (1.4%) | 2 (0.9%) | 5 (1.4%) |
| 倦怠感 | 2 (1.4%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 局所腫脹 | 1 (0.7%) | 0 | 3 (1.4%) | 1 (0.5%) | 4 (1.1%) |
| 多臓器不全 | 0 | 0 | 4 (1.8%) | 4 (1.8%) | 4 (1.1%) |
| 胸部不快感 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 歩行障害 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 全身性浮腫 | 0 | 0 | 3 (1.4%) | 1 (0.5%) | 3 (0.8%) |
| 注射部位内出血 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 乾燥症 | 2 (1.4%) | 1 (0.7%) | 1 (0.5%) | 0 | 3 (0.8%) |
| 腋窩痛 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 早期満腹 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 重力性浮腫 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 低体温 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 炎症 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 浮腫 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 活動状態低下 | 0 | 0 | 2 (0.9%) | 1 (0.5%) | 2 (0.5%) |
| カテーテル留置部位関連反応 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 死亡 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 医療機器リーク | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 顔面浮腫 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 異常感 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 冷感 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 熱感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 治癒不良 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 硬結 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 注入部位血管外漏出 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位紅斑 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 注射部位漏出 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 注射部位出血 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 注射部位疼痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 注射部位反応 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 先行疾患の改善 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 温度変化不耐症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 評価不能の事象 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸器、胸郭および縦隔障害 | 99 (66.9%) | 19 (12.8%) | 101 (45.5%) | 16 (7.2%) | 200 (54.1%) |
| 咳嗽 | 45 (30.4%) | 0 | 36 (16.2%) | 0 | 81 (21.9%) |
| 呼吸困難 | 40 (27.0%) | 6 (4.1%) | 29 (13.1%) | 6 (2.7%) | 69 (18.6%) |
| 鼻出血 | 20 (13.5%) | 1 (0.7%) | 12 (5.4%) | 0 | 32 (8.6%) |
| 口腔咽頭痛 | 19 (12.8%) | 0 | 10 (4.5%) | 0 | 29 (7.8%) |
| 胸水 | 11 (7.4%) | 3 (2.0%) | 12 (5.4%) | 4 (1.8%) | 23 (6.2%) |
| 湿性咳嗽 | 7 (4.7%) | 0 | 8 (3.6%) | 0 | 15 (4.1%) |
| 鼻閉 | 8 (5.4%) | 0 | 5 (2.3%) | 0 | 13 (3.5%) |
| 呼吸不全 | 6 (4.1%) | 6 (4.1%) | 4 (1.8%) | 4 (1.8%) | 10 (2.7%) |
| 鼻漏 | 6 (4.1%) | 0 | 3 (1.4%) | 0 | 9 (2.4%) |
| 発声障害 | 5 (3.4%) | 0 | 3 (1.4%) | 0 | 8 (2.2%) |
| 慢性閉塞性肺疾患 | 4 (2.7%) | 2 (1.4%) | 2 (0.9%) | 2 (0.9%) | 6 (1.6%) |
| アレルギー性鼻炎 | 4 (2.7%) | 0 | 2 (0.9%) | 0 | 6 (1.6%) |
| 副鼻腔うっ血 | 2 (1.4%) | 0 | 4 (1.8%) | 0 | 6 (1.6%) |
| 上気道うっ血 | 3 (2.0%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 低酸素症 | 2 (1.4%) | 2 (1.4%) | 3 (1.4%) | 2 (0.9%) | 5 (1.4%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| しゃっくり | 3 (2.0%) | 0 | 1 (0.5%) | 0 | 4 (1.1%) |
| 気胸 | 2 (1.4%) | 1 (0.7%) | 2 (0.9%) | 1 (0.5%) | 4 (1.1%) |
| 喀血 | 1 (0.7%) | 0 | 2 (0.9%) | 0 | 3 (0.8%) |
| 鼻部不快感 | 1 (0.7%) | 0 | 2 (0.9%) | 0 | 3 (0.8%) |
| 肺水腫 | 0 | 0 | 3 (1.4%) | 1 (0.5%) | 3 (0.8%) |
| ラ音 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 喘鳴 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 無気肺 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 労作性呼吸困難 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 肺硬化 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 肺浸潤 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 鼻の炎症 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 肺塞栓症 | 0 | 0 | 2 (0.9%) | 1 (0.5%) | 2 (0.5%) |
| 気道うっ血 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 急性肺水腫 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 喘息 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 気管支反応性亢進 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 気管支分泌物貯留 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 気管支拡張症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 慢性気管支炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 肺気腫 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 上気道分泌増加 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 鼻乾燥 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 鼻潰瘍 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 副鼻腔不快感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 副鼻腔分泌過多 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 咽頭紅斑 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 胸膜炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸膜痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 肺腫瘤 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 呼吸性アシドーシス | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 呼吸窮迫 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 拘束性肺疾患 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 副鼻腔障害 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| くしゃみ | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 頻呼吸 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 扁桃肥大 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 上気道咳症候群 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚および皮下組織障害 | 91 (61.5%) | 5 (3.4%) | 103 (46.4%) | 5 (2.3%) | 194 (52.4%) |
| 発疹 | 34 (23.0%) | 3 (2.0%) | 23 (10.4%) | 1 (0.5%) | 57 (15.4%) |
| そう痒症 | 8 (5.4%) | 0 | 20 (9.0%) | 0 | 28 (7.6%) |
| 点状出血 | 11 (7.4%) | 0 | 11 (5.0%) | 0 | 22 (5.9%) |
| 皮膚病変 | 12 (8.1%) | 0 | 8 (3.6%) | 0 | 20 (5.4%) |
| 斑状丘疹状皮疹 | 8 (5.4%) | 0 | 8 (3.6%) | 2 (0.9%) | 16 (4.3%) |
| 皮膚乾燥 | 9 (6.1%) | 0 | 5 (2.3%) | 0 | 14 (3.8%) |
| 斑状出血 | 7 (4.7%) | 0 | 6 (2.7%) | 0 | 13 (3.5%) |
| 紅斑 | 6 (4.1%) | 0 | 5 (2.3%) | 0 | 11 (3.0%) |
| 寝汗 | 6 (4.1%) | 0 | 5 (2.3%) | 0 | 11 (3.0%) |
| 脱毛症 | 2 (1.4%) | 0 | 8 (3.6%) | 0 | 10 (2.7%) |
| ざ瘡様皮膚炎 | 1 (0.7%) | 0 | 7 (3.2%) | 0 | 8 (2.2%) |
| 紫斑 | 2 (1.4%) | 0 | 5 (2.3%) | 2 (0.9%) | 7 (1.9%) |
| 多汗症 | 2 (1.4%) | 0 | 4 (1.8%) | 0 | 6 (1.6%) |
| 皮膚亀裂 | 5 (3.4%) | 0 | 1 (0.5%) | 0 | 6 (1.6%) |
| 嵌入爪 | 2 (1.4%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 爪破損 | 2 (1.4%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 蕁麻疹 | 4 (2.7%) | 0 | 1 (0.5%) | 0 | 5 (1.4%) |
| 水疱 | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| 全身性そう痒症 | 1 (0.7%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 斑状皮疹 | 2 (1.4%) | 1 (0.7%) | 2 (0.9%) | 0 | 4 (1.1%) |
| 皮膚腫瘤 | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| 皮膚潰瘍 | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| ざ瘡 | 3 (2.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 褥瘡性潰瘍 | 3 (2.0%) | 1 (0.7%) | 0 | 0 | 3 (0.8%) |
| 湿疹 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 紅斑性皮疹 | 0 | 0 | 3 (1.4%) | 0 | 3 (0.8%) |
| 皮膚色素過剰 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 皮膚嚢腫 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 接触性皮膚炎 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 皮下出血 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 間擦疹 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 皮膚疼痛 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 全身性皮疹 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 丘疹性皮疹 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| そう痒性皮疹 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚変色 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 毛細血管炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| アレルギー性皮膚炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 水疱性皮膚炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 皮脂欠乏性湿疹 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 貨幣状湿疹 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 過敏性血管炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪床出血 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪床障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪床の炎症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪の不快感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪の障害 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪ジストロフィー | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪線状隆起 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 爪痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 爪甲脱落症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 手掌・足底発赤知覚不全症候群 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 脂肪織炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 色素沈着障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 毛孔性皮疹 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮膚色素減少 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 皮膚刺激 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 皮膚腫脹 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 乾皮症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋骨格系および結合組織障害 | 82 (55.4%) | 6 (4.1%) | 91 (41.0%) | 14 (6.3%) | 173 (46.8%) |
| 筋痙縮 | 36 (24.3%) | 0 | 31 (14.0%) | 0 | 67 (18.1%) |
| 背部痛 | 23 (15.5%) | 2 (1.4%) | 21 (9.5%) | 4 (1.8%) | 44 (11.9%) |
| 関節痛 | 19 (12.8%) | 1 (0.7%) | 19 (8.6%) | 1 (0.5%) | 38 (10.3%) |
| 筋肉痛 | 15 (10.1%) | 1 (0.7%) | 17 (7.7%) | 0 | 32 (8.6%) |
| 四肢痛 | 12 (8.1%) | 0 | 16 (7.2%) | 2 (0.9%) | 28 (7.6%) |
| 筋骨格痛 | 10 (6.8%) | 0 | 7 (3.2%) | 0 | 17 (4.6%) |
| 筋力低下 | 4 (2.7%) | 1 (0.7%) | 9 (4.1%) | 2 (0.9%) | 13 (3.5%) |
| 側腹部痛 | 4 (2.7%) | 1 (0.7%) | 4 (1.8%) | 1 (0.5%) | 8 (2.2%) |
| 頚部痛 | 5 (3.4%) | 0 | 1 (0.5%) | 0 | 6 (1.6%) |
| 変形性関節症 | 1 (0.7%) | 1 (0.7%) | 4 (1.8%) | 1 (0.5%) | 5 (1.4%) |
| 肩径部痛 | 2 (1.4%) | 1 (0.7%) | 2 (0.9%) | 0 | 4 (1.1%) |
| 四肢不快感 | 0 | 0 | 4 (1.8%) | 0 | 4 (1.1%) |
| 筋骨格硬直 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 骨痛 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 関節硬直 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 関節腫脹 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 運動性低下 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 筋骨格系胸痛 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| ミオパチー | 0 | 0 | 2 (0.9%) | 1 (0.5%) | 2 (0.5%) |
| 軟部組織障害 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 関節炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 滑液包炎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 外骨腫 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 痛風性関節炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 椎間板変性症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 椎間板突出 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 関節拘縮 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 関節滲出液 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 関節ロック | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋緊張 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 筋攣縮 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 筋骨格不快感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 頚部腫瘤 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 骨壊死 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 骨粗鬆症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 顎痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 横紋筋融解症 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 滑液嚢腫 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 腱痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 椎間孔狭窄 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血液およびリンパ系障害 | 73 (49.3%) | 51 (34.5%) | 96 (43.2%) | 58 (26.1%) | 169 (45.7%) |
| 血小板減少症 | 34 (23.0%) | 22 (14.9%) | 40 (18.0%) | 19 (8.6%) | 74 (20.0%) |
| 好中球減少症 | 36 (24.3%) | 30 (20.3%) | 34 (15.3%) | 31 (14.0%) | 70 (18.9%) |
| 貧血 | 30 (20.3%) | 14 (9.5%) | 33 (14.9%) | 16 (7.2%) | 63 (17.0%) |
| 発熱性好中球減少症 | 4 (2.7%) | 4 (2.7%) | 9 (4.1%) | 9 (4.1%) | 13 (3.5%) |
| 白血球減少症 | 8 (5.4%) | 4 (2.7%) | 5 (2.3%) | 2 (0.9%) | 13 (3.5%) |
| 白血球増加症 | 1 (0.7%) | 0 | 6 (2.7%) | 3 (1.4%) | 7 (1.9%) |
| 内出血発生の増加傾向 | 2 (1.4%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| リンパ球減少症 | 3 (2.0%) | 0 | 2 (0.9%) | 0 | 5 (1.4%) |
| リンパ球増加症 | 1 (0.7%) | 1 (0.7%) | 3 (1.4%) | 2 (0.9%) | 4 (1.1%) |
| リンパ節痛 | 0 | 0 | 2 (0.9%) | 1 (0.5%) | 2 (0.5%) |
| リンパ節症 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 脾腫 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 骨髄機能不全 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 凝血異常 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 溶血 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 鉄欠乏性貧血 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 白血球停滞症候群 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 汎血球減少症 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 後腹膜リンパ節腫脹 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 脾臓出血 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 脾臓梗塞 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 血小板増加症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 代謝および栄養障害 | 78 (52.7%) | 23 (15.5%) | 72 (32.4%) | 29 (13.1%) | 150 (40.5%) |
| 食欲減退 | 36 (24.3%) | 0 | 26 (11.7%) | 3 (1.4%) | 62 (16.8%) |
| 低カリウム血症 | 18 (12.2%) | 7 (4.7%) | 16 (7.2%) | 8 (3.6%) | 34 (9.2%) |
| 高尿酸血症 | 14 (9.5%) | 6 (4.1%) | 11 (5.0%) | 4 (1.8%) | 25 (6.8%) |
| 脱水 | 16 (10.8%) | 4 (2.7%) | 6 (2.7%) | 3 (1.4%) | 22 (5.9%) |
| 低マグネシウム血症 | 13 (8.8%) | 0 | 8 (3.6%) | 1 (0.5%) | 21 (5.7%) |
| 高カリウム血症 | 4 (2.7%) | 0 | 9 (4.1%) | 5 (2.3%) | 13 (3.5%) |
| 低ナトリウム血症 | 5 (3.4%) | 3 (2.0%) | 7 (3.2%) | 5 (2.3%) | 12 (3.2%) |
| 低アルブミン血症 | 7 (4.7%) | 2 (1.4%) | 4 (1.8%) | 2 (0.9%) | 11 (3.0%) |
| 高血糖 | 3 (2.0%) | 0 | 6 (2.7%) | 2 (0.9%) | 9 (2.4%) |
| 低カルシウム血症 | 3 (2.0%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 低血糖症 | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| 低リン酸血症 | 1 (0.7%) | 1 (0.7%) | 3 (1.4%) | 3 (1.4%) | 4 (1.1%) |
| 水分過負荷 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 痛風 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 酵素異常 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 高コレステロール血症 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 高ナトリウム血症 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 高リン酸塩血症 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 過小食 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 乳酸アシドーシス | 1 (0.7%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| アルコール不耐性 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 悪液質 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 糖尿病 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 糖尿病性ケトアシドーシス | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 高アルブミン血症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 高アンモニア血症 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 低蛋白血症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 代謝性アシドーシス | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 腫瘍崩壊症候群 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| ２型糖尿病 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 神経系障害 | 61 (41.2%) | 2 (1.4%) | 60 (27.0%) | 7 (3.2%) | 121 (32.7%) |
| 頭痛 | 17 (11.5%) | 0 | 20 (9.0%) | 0 | 37 (10.0%) |
| 浮動性めまい | 16 (10.8%) | 0 | 10 (4.5%) | 0 | 26 (7.0%) |
| 末梢性感覚ニューロパチー | 8 (5.4%) | 0 | 6 (2.7%) | 1 (0.5%) | 14 (3.8%) |
| 体位性めまい | 6 (4.1%) | 0 | 4 (1.8%) | 0 | 10 (2.7%) |
| 錯感覚 | 4 (2.7%) | 0 | 4 (1.8%) | 0 | 8 (2.2%) |
| 記憶障害 | 5 (3.4%) | 0 | 2 (0.9%) | 0 | 7 (1.9%) |
| 末梢性ニューロパチー | 6 (4.1%) | 0 | 1 (0.5%) | 0 | 7 (1.9%) |
| 振戦 | 3 (2.0%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 感覚鈍麻 | 1 (0.7%) | 0 | 4 (1.8%) | 1 (0.5%) | 5 (1.4%) |
| 健忘 | 3 (2.0%) | 0 | 1 (0.5%) | 0 | 4 (1.1%) |
| 傾眠 | 4 (2.7%) | 0 | 0 | 0 | 4 (1.1%) |
| 失神 | 2 (1.4%) | 2 (1.4%) | 2 (0.9%) | 2 (0.9%) | 4 (1.1%) |
| 平衡障害 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 構語障害 | 1 (0.7%) | 1 (0.7%) | 2 (0.9%) | 1 (0.5%) | 3 (0.8%) |
| 味覚異常 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 嗜眠 | 3 (2.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 多発ニューロパチー | 1 (0.7%) | 1 (0.7%) | 2 (0.9%) | 0 | 3 (0.8%) |
| 認知症 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 頭蓋内出血 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 過眠症 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 神経痛 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 失神寸前の状態 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 下肢静止不能症候群 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 副鼻腔炎に伴う頭痛 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 一過性脳虚血発作 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 灼熱足症候群 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 手根管症候群 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 大脳萎縮 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 脳血管発作 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 労作性めまい | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 脳症 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| てんかん | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 顔面部神経痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 顔面不全麻痺 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 頭部不快感 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 腰髄神経根障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 片頭痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 前兆を伴う片頭痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 筋痙直 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| ミオクローヌス | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼振 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 腓骨神経麻痺 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| ヘルペス後神経痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 坐骨神経痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 感覚障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 会話障害 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 緊張性頭痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 一過性全健忘 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 血管性脳症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 臨床検査 | 51 (34.5%) | 20 (13.5%) | 61 (27.5%) | 15 (6.8%) | 112 (30.3%) |
| 血中クレアチニン増加 | 12 (8.1%) | 0 | 19 (8.6%) | 0 | 31 (8.4%) |
| 血小板数減少 | 3 (2.0%) | 0 | 11 (5.0%) | 2 (0.9%) | 14 (3.8%) |
| 体重減少 | 11 (7.4%) | 0 | 1 (0.5%) | 0 | 12 (3.2%) |
| 血中アルカリホスファターゼ増加 | 4 (2.7%) | 1 (0.7%) | 7 (3.2%) | 1 (0.5%) | 11 (3.0%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 4 (2.7%) | 1 (0.7%) | 6 (2.7%) | 0 | 10 (2.7%) |
| 血中ビリルビン増加 | 3 (2.0%) | 0 | 7 (3.2%) | 2 (0.9%) | 10 (2.7%) |
| 好中球数減少 | 4 (2.7%) | 4 (2.7%) | 5 (2.3%) | 4 (1.8%) | 9 (2.4%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| アラニンアミノトランスフェラーゼ増加 | 4 (2.7%) | 0 | 3 (1.4%) | 1 (0.5%) | 7 (1.9%) |
| 血中尿酸増加 | 4 (2.7%) | 2 (1.4%) | 3 (1.4%) | 1 (0.5%) | 7 (1.9%) |
| リンパ球数増加 | 5 (3.4%) | 4 (2.7%) | 1 (0.5%) | 0 | 6 (1.6%) |
| 体重増加 | 3 (2.0%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 活性化部分トロンボプラスチン時間延長 | 3 (2.0%) | 1 (0.7%) | 2 (0.9%) | 0 | 5 (1.4%) |
| 血中乳酸脱水素酵素増加 | 3 (2.0%) | 0 | 2 (0.9%) | 0 | 5 (1.4%) |
| 白血球数減少 | 3 (2.0%) | 3 (2.0%) | 2 (0.9%) | 2 (0.9%) | 5 (1.4%) |
| 血中免疫グロブリンG減少 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 国際標準比増加 | 2 (1.4%) | 2 (1.4%) | 1 (0.5%) | 1 (0.5%) | 3 (0.8%) |
| 白血球数増加 | 2 (1.4%) | 1 (0.7%) | 1 (0.5%) | 0 | 3 (0.8%) |
| 血中ブドウ糖増加 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 血中免疫グロブリンM減少 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 血圧上昇 | 2 (1.4%) | 2 (1.4%) | 0 | 0 | 2 (0.5%) |
| Ｃ－反応性蛋白増加 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 心雑音 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| γ－グルタミルトランスフェラーゼ増加 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 糸球体濾過率減少 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| ヘモグロビン減少 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 免疫グロブリン減少 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| リンパ球数減少 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| トランスアミナーゼ上昇 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| アミラーゼ増加 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| アスペルギルス検査陽性 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中アルブミン減少 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 血中重炭酸塩増加 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血中ビリルビン異常 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 血中クロール減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血中コレステロール増加 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中クレアチン増加 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 血中免疫グロブリンA減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 血中鉄減少 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中マグネシウム減少 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中リン減少 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 血中カリウム減少 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 呼吸音異常 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 二酸化炭素減少 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸部コンピュータ断層撮影異常 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 駆出率減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| グリコヘモグロビン増加 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| ヘモフィルス検査陽性 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 心拍数増加 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心拍数不整 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 肝酵素上昇 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 深吸気量減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 肝機能検査異常 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 黄斑部反射異常 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 平均赤血球容積増加 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 血小板凝集異常 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 尿量減少 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 超低比重リポ蛋白増加 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 肺活量異常 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 傷害、中毒および処置合併症 | 51 (34.5%) | 5 (3.4%) | 50 (22.5%) | 8 (3.6%) | 101 (27.3%) |
| 挫傷 | 28 (18.9%) | 0 | 18 (8.1%) | 0 | 46 (12.4%) |
| 転倒 | 10 (6.8%) | 3 (2.0%) | 7 (3.2%) | 1 (0.5%) | 17 (4.6%) |
| 節足動物咬傷 | 2 (1.4%) | 0 | 4 (1.8%) | 0 | 6 (1.6%) |
| 処置による疼痛 | 3 (2.0%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 硬膜下血腫 | 1 (0.7%) | 0 | 5 (2.3%) | 3 (1.4%) | 6 (1.6%) |
| 外傷性血腫 | 2 (1.4%) | 0 | 4 (1.8%) | 0 | 6 (1.6%) |
| 裂傷 | 3 (2.0%) | 0 | 1 (0.5%) | 0 | 4 (1.1%) |
| 皮膚擦過傷 | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| サンバーン | 3 (2.0%) | 0 | 1 (0.5%) | 0 | 4 (1.1%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 創傷 | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| 動物咬傷 | 1 (0.7%) | 0 | 2 (0.9%) | 1 (0.5%) | 3 (0.8%) |
| 頭部損傷 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 靭帯捻挫 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 腰椎骨折 | 2 (1.4%) | 1 (0.7%) | 1 (0.5%) | 0 | 3 (0.8%) |
| 処置後出血 | 3 (2.0%) | 2 (1.4%) | 0 | 0 | 3 (0.8%) |
| 骨挫傷 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 擦過傷 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 顔面骨骨折 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 四肢損傷 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 眼窩周囲挫傷 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 肋骨骨折 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 皮膚創傷 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 脊椎圧迫骨折 | 0 | 0 | 2 (0.9%) | 1 (0.5%) | 2 (0.5%) |
| 脾破裂 | 0 | 0 | 2 (0.9%) | 2 (0.9%) | 2 (0.5%) |
| 熱傷 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 動物による引っかき傷 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 足関節部骨折 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 第２度熱傷 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼挫傷 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼外傷 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 足骨折 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼内異物 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 外傷性血尿 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 関節損傷 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 過量投与 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 処置後便秘 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 処置後血尿 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 処置後腫脹 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 外傷後疼痛 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 陰嚢血腫 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 皮下血腫 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 脛骨骨折 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 歯牙破折 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 術後尿閉 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 創合併症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼障害 | 41 (27.7%) | 2 (1.4%) | 41 (18.5%) | 3 (1.4%) | 82 (22.2%) |
| 眼乾燥 | 8 (5.4%) | 0 | 8 (3.6%) | 0 | 16 (4.3%) |
| 流涙増加 | 10 (6.8%) | 0 | 3 (1.4%) | 0 | 13 (3.5%) |
| 霧視 | 7 (4.7%) | 0 | 6 (2.7%) | 0 | 13 (3.5%) |
| 白内障 | 6 (4.1%) | 2 (1.4%) | 5 (2.3%) | 1 (0.5%) | 11 (3.0%) |
| 視力低下 | 1 (0.7%) | 0 | 5 (2.3%) | 0 | 6 (1.6%) |
| 眼窩周囲浮腫 | 1 (0.7%) | 0 | 4 (1.8%) | 1 (0.5%) | 5 (1.4%) |
| 結膜出血 | 1 (0.7%) | 0 | 2 (0.9%) | 0 | 3 (0.8%) |
| 眼痛 | 1 (0.7%) | 0 | 2 (0.9%) | 0 | 3 (0.8%) |
| 眼充血 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 睫毛乱生 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 硝子体浮遊物 | 1 (0.7%) | 0 | 2 (0.9%) | 0 | 3 (0.8%) |
| 糖尿病網膜症 | 1 (0.7%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 複視 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 眼出血 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 眼刺激 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 眼瞼下垂 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 羞明 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 眼瞼炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 片側失明 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 結膜充血 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼瞼内反 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼脂 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼の炎症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 眼そう痒症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼の異物感 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 緑内障 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 角膜炎 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 黄斑変性 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| マイボーム腺機能不全 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 眼血管障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 開放隅角緑内障 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 動揺視 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 老視 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 網膜剥離 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 強膜出血 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 視力障害 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 硝子体出血 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 眼球乾燥症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 血管障害 | 39 (26.4%) | 10 (6.8%) | 42 (18.9%) | 16 (7.2%) | 81 (21.9%) |
| 高血圧 | 15 (10.1%) | 5 (3.4%) | 20 (9.0%) | 8 (3.6%) | 35 (9.5%) |
| 低血圧 | 14 (9.5%) | 4 (2.7%) | 7 (3.2%) | 1 (0.5%) | 21 (5.7%) |
| 血腫 | 7 (4.7%) | 0 | 5 (2.3%) | 0 | 12 (3.2%) |
| 深部静脈血栓症 | 3 (2.0%) | 0 | 4 (1.8%) | 2 (0.9%) | 7 (1.9%) |
| 潮紅 | 0 | 0 | 4 (1.8%) | 0 | 4 (1.1%) |
| 出血 | 0 | 0 | 4 (1.8%) | 3 (1.4%) | 4 (1.1%) |
| 起立性低血圧 | 1 (0.7%) | 1 (0.7%) | 2 (0.9%) | 0 | 3 (0.8%) |
| 静脈炎 | 1 (0.7%) | 0 | 2 (0.9%) | 0 | 3 (0.8%) |
| 血圧変動 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| リンパ浮腫 | 0 | 0 | 2 (0.9%) | 2 (0.9%) | 2 (0.5%) |
| 表在性血栓性静脈炎 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 大動脈硬化症 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 循環虚脱 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| ほてり | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 高血圧クリーゼ | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 末梢血管障害 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 末梢静脈疾患 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 静脈瘤 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心臓障害 | 38 (25.7%) | 14 (9.5%) | 26 (11.7%) | 12 (5.4%) | 64 (17.3%) |
| 心房細動 | 17 (11.5%) | 11 (7.4%) | 11 (5.0%) | 6 (2.7%) | 28 (7.6%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 頻脈 | 5 (3.4%) | 0 | 4 (1.8%) | 0 | 9 (2.4%) |
| 洞性頻脈 | 5 (3.4%) | 0 | 2 (0.9%) | 0 | 7 (1.9%) |
| 徐脈 | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| 動悸 | 1 (0.7%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 心房粗動 | 3 (2.0%) | 1 (0.7%) | 0 | 0 | 3 (0.8%) |
| 洞性徐脈 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 上室性頻脈 | 3 (2.0%) | 1 (0.7%) | 0 | 0 | 3 (0.8%) |
| 不安定狭心症 | 1 (0.7%) | 0 | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 心停止 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 心不全 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| 心室性期外収縮 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 急性心筋梗塞 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 不整脈 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 冠動脈硬化症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 第一度房室ブロック | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| うっ血性心不全 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心血管不全 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 変時性応答不全 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 冠動脈疾患 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 冠動脈閉塞 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| チアノーゼ | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 僧帽弁閉鎖不全症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 心筋梗塞 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 心嚢液貯留 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心膜炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 洞不全症候群 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| ストレス心筋症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 頻脈性不整脈 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| トルサード　ド　ポアント | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 三尖弁疾患 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心室性不整脈 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 心室性頻脈 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 精神障害 | 30 (20.3%) | 3 (2.0%) | 33 (14.9%) | 4 (1.8%) | 63 (17.0%) |
| 不眠症 | 12 (8.1%) | 0 | 14 (6.3%) | 0 | 26 (7.0%) |
| 不安 | 6 (4.1%) | 0 | 7 (3.2%) | 0 | 13 (3.5%) |
| 錯乱状態 | 8 (5.4%) | 2 (1.4%) | 4 (1.8%) | 2 (0.9%) | 12 (3.2%) |
| うつ病 | 6 (4.1%) | 0 | 6 (2.7%) | 1 (0.5%) | 12 (3.2%) |
| 激越 | 1 (0.7%) | 0 | 4 (1.8%) | 0 | 5 (1.4%) |
| 譫妄 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 希死念慮を有するうつ病 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 多幸気分 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 幻聴 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 幻視 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 易刺激性 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| リビドー減退 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 躁病 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 精神障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 精神状態変化 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 悪夢 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| パニック発作 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| パニック障害 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 腎および尿路障害 | 31 (20.9%) | 10 (6.8%) | 26 (11.7%) | 7 (3.2%) | 57 (15.4%) |
| 血尿 | 10 (6.8%) | 2 (1.4%) | 4 (1.8%) | 1 (0.5%) | 14 (3.8%) |
| 急性腎不全 | 7 (4.7%) | 3 (2.0%) | 5 (2.3%) | 3 (1.4%) | 12 (3.2%) |
| 排尿困難 | 5 (3.4%) | 0 | 3 (1.4%) | 0 | 8 (2.2%) |
| 腎不全 | 5 (3.4%) | 3 (2.0%) | 2 (0.9%) | 2 (0.9%) | 7 (1.9%) |
| 頻尿 | 3 (2.0%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 水腎症 | 1 (0.7%) | 1 (0.7%) | 2 (0.9%) | 1 (0.5%) | 3 (0.8%) |
| 腎機能障害 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 尿閉 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 尿路閉塞 | 1 (0.7%) | 0 | 2 (0.9%) | 1 (0.5%) | 3 (0.8%) |
| 腎結石症 | 1 (0.7%) | 1 (0.7%) | 1 (0.5%) | 0 | 2 (0.5%) |
| 夜間頻尿 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 腎嚢胞 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 慢性腎不全 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 尿失禁 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 高窒素血症 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 膀胱刺激症状 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 出血性膀胱炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 緊張性膀胱 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 失禁 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 尿意切迫 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 閉塞性尿路疾患 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 乏尿 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 腎仙痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 有痛性排尿困難 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 尿路痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 17 (11.5%) | 9 (6.1%) | 19 (8.6%) | 10 (4.5%) | 36 (9.7%) |
| マントル細胞リンパ腫 | 2 (1.4%) | 2 (1.4%) | 6 (2.7%) | 6 (2.7%) | 8 (2.2%) |
| 基底細胞癌 | 5 (3.4%) | 1 (0.7%) | 2 (0.9%) | 0 | 7 (1.9%) |
| 皮膚有棘細胞癌 | 2 (1.4%) | 0 | 3 (1.4%) | 0 | 5 (1.4%) |
| 膀胱移行上皮癌 | 2 (1.4%) | 1 (0.7%) | 0 | 0 | 2 (0.5%) |
| 前立腺癌 | 2 (1.4%) | 2 (1.4%) | 0 | 0 | 2 (0.5%) |
| 扁平上皮癌 | 0 | 0 | 2 (0.9%) | 1 (0.5%) | 2 (0.5%) |
| 急性骨髄性白血病 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 良性新生物 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 膀胱癌 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 肺腺癌 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 悪性胸水 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 遠隔転移を伴う新生物 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 口腔乳頭腫 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 唾液腺癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 皮膚癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 皮膚乳頭腫 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 胸腺腫 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 移行上皮癌 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 腫瘍フレア | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 耳および迷路障害 | 15 (10.1%) | 0 | 15 (6.8%) | 2 (0.9%) | 30 (8.1%) |
| 回転性めまい | 5 (3.4%) | 0 | 6 (2.7%) | 0 | 11 (3.0%) |
| 耳鳴 | 3 (2.0%) | 0 | 3 (1.4%) | 0 | 6 (1.6%) |
| 耳痛 | 4 (2.7%) | 0 | 1 (0.5%) | 0 | 5 (1.4%) |
| 聴力低下 | 1 (0.7%) | 0 | 3 (1.4%) | 1 (0.5%) | 4 (1.1%) |
| 耳垢栓塞 | 1 (0.7%) | 0 | 1 (0.5%) | 0 | 2 (0.5%) |
| 耳不快感 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 難聴 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 耳出血 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 聴覚過敏 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 老人性難聴 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 生殖系および乳房障害 | 11 (7.4%) | 2 (1.4%) | 15 (6.8%) | 5 (2.3%) | 26 (7.0%) |
| 良性前立腺肥大症 | 1 (0.7%) | 0 | 3 (1.4%) | 0 | 4 (1.1%) |
| 血精液症 | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| 性器浮腫 | 1 (0.7%) | 0 | 2 (0.9%) | 2 (0.9%) | 3 (0.8%) |
| 勃起不全 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 骨盤痛 | 0 | 0 | 2 (0.9%) | 1 (0.5%) | 2 (0.5%) |
| 腟出血 | 0 | 0 | 2 (0.9%) | 0 | 2 (0.5%) |
| 後天性包茎 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房血腫 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房腫瘤 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 乳房痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 性器発疹 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 陰茎痛 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 陰嚢腫瘤 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 陰嚢浮腫 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 陰嚢痛 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 子宮腟脱 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 外陰腟痛 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 外陰腟そう痒症 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |

**TSFAE18A: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Yes vs. No) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Yes | | No | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 免疫系障害 | 12 (8.1%) | 0 | 7 (3.2%) | 0 | 19 (5.1%) |
| 低γグロブリン血症 | 3 (2.0%) | 0 | 2 (0.9%) | 0 | 5 (1.4%) |
| 節足動物咬傷アレルギー | 2 (1.4%) | 0 | 2 (0.9%) | 0 | 4 (1.1%) |
| 過敏症 | 2 (1.4%) | 0 | 1 (0.5%) | 0 | 3 (0.8%) |
| 季節性アレルギー | 3 (2.0%) | 0 | 0 | 0 | 3 (0.8%) |
| 薬物過敏症 | 2 (1.4%) | 0 | 0 | 0 | 2 (0.5%) |
| 造影剤アレルギー | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 食物アレルギー | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 肝胆道系障害 | 4 (2.7%) | 1 (0.7%) | 9 (4.1%) | 3 (1.4%) | 13 (3.5%) |
| 高ビリルビン血症 | 2 (1.4%) | 0 | 4 (1.8%) | 1 (0.5%) | 6 (1.6%) |
| 胆石症 | 0 | 0 | 3 (1.4%) | 1 (0.5%) | 3 (0.8%) |
| 胆管結石 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 胆管炎 | 1 (0.7%) | 1 (0.7%) | 0 | 0 | 1 (0.3%) |
| 肝不全 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 肝機能異常 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 中毒性肝炎 | 0 | 0 | 1 (0.5%) | 1 (0.5%) | 1 (0.3%) |
| 陶器様胆嚢 | 0 | 0 | 1 (0.5%) | 0 | 1 (0.3%) |
| 内分泌障害 | 3 (2.0%) | 0 | 2 (0.9%) | 0 | 5 (1.4%) |
| 甲状腺機能低下症 | 3 (2.0%) | 0 | 2 (0.9%) | 0 | 5 (1.4%) |
| 先天性、家族性および遺伝性障害 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |
| 臍血腫 | 1 (0.7%) | 0 | 0 | 0 | 1 (0.3%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE18A.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae18a.sas] 15SEP2015, 14:13

参照元：5.3.5.3.1 ISS TSFAE18A

表 2.7.4-付録-62 Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| Analysis set: safety | 24 | | 124 | | 148 |
| Subjects with any TEAE | 24 (100.0%) | 16 (66.7%) | 124 (100.0%) | 95 (76.6%) | 148 (100.0%) |
| System organ class | | | | | |
| Preferred term | | | | | |
| 感染症および寄生虫症 | 22 (91.7%) | 11 (45.8%) | 113 (91.1%) | 43 (34.7%) | 135 (91.2%) |
| 上気道感染 | 4 (16.7%) | 0 | 34 (27.4%) | 1 (0.8%) | 38 (25.7%) |
| 肺炎 | 5 (20.8%) | 5 (20.8%) | 27 (21.8%) | 19 (15.3%) | 32 (21.6%) |
| 副鼻腔炎 | 3 (12.5%) | 0 | 23 (18.5%) | 1 (0.8%) | 26 (17.6%) |
| 尿路感染 | 3 (12.5%) | 0 | 22 (17.7%) | 5 (4.0%) | 25 (16.9%) |
| 結膜炎 | 1 (4.2%) | 0 | 16 (12.9%) | 0 | 17 (11.5%) |
| 気管支炎 | 2 (8.3%) | 0 | 13 (10.5%) | 4 (3.2%) | 15 (10.1%) |
| 鼻咽頭炎 | 3 (12.5%) | 0 | 10 (8.1%) | 0 | 13 (8.8%) |
| 蜂巣炎 | 0 | 0 | 12 (9.7%) | 3 (2.4%) | 12 (8.1%) |
| 下気道感染 | 6 (25.0%) | 3 (12.5%) | 4 (3.2%) | 2 (1.6%) | 10 (6.8%) |
| 毛包炎 | 1 (4.2%) | 0 | 8 (6.5%) | 0 | 9 (6.1%) |
| 爪囲炎 | 1 (4.2%) | 0 | 6 (4.8%) | 0 | 7 (4.7%) |
| 鼻炎 | 1 (4.2%) | 0 | 6 (4.8%) | 0 | 7 (4.7%) |
| 帯状疱疹 | 1 (4.2%) | 0 | 5 (4.0%) | 0 | 6 (4.1%) |
| 敗血症 | 3 (12.5%) | 3 (12.5%) | 3 (2.4%) | 3 (2.4%) | 6 (4.1%) |
| 胃腸炎 | 0 | 0 | 5 (4.0%) | 1 (0.8%) | 5 (3.4%) |
| 感染 | 2 (8.3%) | 1 (4.2%) | 3 (2.4%) | 1 (0.8%) | 5 (3.4%) |
| 皮膚感染 | 0 | 0 | 5 (4.0%) | 0 | 5 (3.4%) |
| 気道感染 | 1 (4.2%) | 0 | 3 (2.4%) | 0 | 4 (2.7%) |
| 菌血症 | 0 | 0 | 3 (2.4%) | 2 (1.6%) | 3 (2.0%) |
| クロストリジウム・ディフィシレ大腸炎 | 0 | 0 | 3 (2.4%) | 2 (1.6%) | 3 (2.0%) |
| クロストリジウム・ディフィシレ感染 | 0 | 0 | 3 (2.4%) | 1 (0.8%) | 3 (2.0%) |
| 眼感染 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 口腔カンジダ症 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 口腔ヘルペス | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 中耳炎 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 歯周炎 | 2 (8.3%) | 0 | 1 (0.8%) | 0 | 3 (2.0%) |
| 咽頭炎 | 1 (4.2%) | 1 (4.2%) | 2 (1.6%) | 0 | 3 (2.0%) |
| ウイルス感染 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 気管支肺炎 | 1 (4.2%) | 0 | 1 (0.8%) | 1 (0.8%) | 2 (1.4%) |
| 膀胱炎 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 憩室炎 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 感染性小腸結腸炎 | 0 | 0 | 2 (1.6%) | 2 (1.6%) | 2 (1.4%) |
| 皮膚真菌感染 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 真菌性性器感染 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 歯肉炎 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 単純ヘルペス | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 喉頭炎 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 爪感染 | 2 (8.3%) | 0 | 0 | 0 | 2 (1.4%) |
| 外耳炎 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 膿疱性皮疹 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| ブドウ球菌感染 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 歯感染 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| ウイルス性上気道感染 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 創傷感染 | 0 | 0 | 2 (1.6%) | 1 (0.8%) | 2 (1.4%) |
| 腹部膿瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 膿疱性ざ瘡 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 急性副鼻腔炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 肛門膿瘍 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 虫垂炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 穿孔性虫垂炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 異型肺炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 胆道感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| ブラストシスティス感染 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 体部白癬 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| カンピロバクター感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| カンジダ感染 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 眼窩蜂巣炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 感染性胆嚢炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| シトロバクター感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 涙嚢炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 医療機器関連感染 | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| 耳感染 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| ウイルス性脳炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 精巣上体炎 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 細菌性眼感染 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 真菌血症 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| ヘリコバクター胃潰瘍 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| ウイルス性胃腸炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 消化管感染 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 血腫感染 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| ヘモフィルス感染 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| ヘルペスウイルス感染 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| ヒストプラスマ症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 埋込み部位感染 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 切開部位感染 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| インフルエンザ | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| クレブシエラ感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 口唇感染 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 限局性感染 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 細菌性下気道感染 | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| 肺感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 乳腺炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 水疱性鼓膜炎 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 爪真菌症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 眼帯状疱疹 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 口腔真菌感染 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| レンサ球菌性咽頭炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| ニューモシスチス・イロベチイ肺炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 細菌性肺炎 | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| クリプトコッカス性肺炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 処置後感染 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 腎盂腎炎 | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| 直腸膿瘍 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 敗血症性ショック | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| 軟部組織感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| ブドウ球菌性菌血症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| レンサ球菌感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 皮下組織膿瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 歯膿瘍 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 細菌性尿路感染 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| シュードモナス性尿路感染 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 尿路性敗血症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 外陰部腟カンジダ症 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 胃腸障害 | 20 (83.3%) | 2 (8.3%) | 96 (77.4%) | 18 (14.5%) | 116 (78.4%) |
| 下痢 | 10 (41.7%) | 1 (4.2%) | 62 (50.0%) | 6 (4.8%) | 72 (48.6%) |
| 悪心 | 8 (33.3%) | 0 | 33 (26.6%) | 0 | 41 (27.7%) |
| 便秘 | 9 (37.5%) | 0 | 24 (19.4%) | 0 | 33 (22.3%) |
| 嘔吐 | 6 (25.0%) | 0 | 25 (20.2%) | 0 | 31 (20.9%) |
| 口内炎 | 0 | 0 | 20 (16.1%) | 3 (2.4%) | 20 (13.5%) |
| 腹痛 | 3 (12.5%) | 0 | 13 (10.5%) | 6 (4.8%) | 16 (10.8%) |
| 消化不良 | 2 (8.3%) | 0 | 8 (6.5%) | 0 | 10 (6.8%) |
| 上腹部痛 | 1 (4.2%) | 0 | 6 (4.8%) | 0 | 7 (4.7%) |
| 嚥下障害 | 2 (8.3%) | 0 | 3 (2.4%) | 0 | 5 (3.4%) |
| 胃食道逆流性疾患 | 0 | 0 | 5 (4.0%) | 0 | 5 (3.4%) |
| 腹部不快感 | 1 (4.2%) | 0 | 3 (2.4%) | 0 | 4 (2.7%) |
| 腹部膨満 | 2 (8.3%) | 0 | 2 (1.6%) | 0 | 4 (2.7%) |
| 口内乾燥 | 1 (4.2%) | 0 | 3 (2.4%) | 0 | 4 (2.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 心窩部不快感 | 1 (4.2%) | 0 | 3 (2.4%) | 0 | 4 (2.7%) |
| 胃炎 | 0 | 0 | 4 (3.2%) | 0 | 4 (2.7%) |
| 口腔内潰瘍形成 | 1 (4.2%) | 0 | 3 (2.4%) | 0 | 4 (2.7%) |
| 放屁 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 痔核 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 口腔内痛 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| アフタ性口内炎 | 1 (4.2%) | 1 (4.2%) | 1 (0.8%) | 0 | 2 (1.4%) |
| 排便回数増加 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 舌痛 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| イレウス | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 下部消化管出血 | 0 | 0 | 2 (1.6%) | 1 (0.8%) | 2 (1.4%) |
| 直腸出血 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 舌潰瘍 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 下腹部痛 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 萎縮性舌炎 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| バレット食道 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 口唇炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 齲歯 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 十二指腸狭窄 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 十二指腸潰瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 便失禁 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 糞塊 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 軟便 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 食中毒 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 胃前庭部毛細血管拡張症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 胃潰瘍 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 出血性胃炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 歯肉出血 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 歯肉浮腫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 血便排泄 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 麻痺性イレウス | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 鼠径ヘルニア | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 過敏性腸症候群 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 口唇水疱 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 口唇痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 口唇腫脹 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 口唇潰瘍 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 弛緩歯 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 口腔内出血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 口蓋障害 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 歯周病 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 肛門周囲痛 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 舌突出 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 直腸裂 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 直腸潰瘍 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 小腸閉塞 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 歯の障害 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 歯の脱落 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 一般・全身障害および投与部位の状態 | 15 (62.5%) | 2 (8.3%) | 93 (75.0%) | 11 (8.9%) | 108 (73.0%) |
| 疲労 | 4 (16.7%) | 1 (4.2%) | 55 (44.4%) | 5 (4.0%) | 59 (39.9%) |
| 発熱 | 7 (29.2%) | 0 | 31 (25.0%) | 1 (0.8%) | 38 (25.7%) |
| 末梢性浮腫 | 1 (4.2%) | 0 | 36 (29.0%) | 2 (1.6%) | 37 (25.0%) |
| 無力症 | 3 (12.5%) | 0 | 9 (7.3%) | 1 (0.8%) | 12 (8.1%) |
| 悪寒 | 3 (12.5%) | 0 | 9 (7.3%) | 0 | 12 (8.1%) |
| インフルエンザ様疾患 | 2 (8.3%) | 0 | 8 (6.5%) | 0 | 10 (6.8%) |
| 胸痛 | 1 (4.2%) | 0 | 7 (5.6%) | 0 | 8 (5.4%) |
| 末梢腫脹 | 1 (4.2%) | 0 | 6 (4.8%) | 0 | 7 (4.7%) |
| 非心臓性胸痛 | 0 | 0 | 6 (4.8%) | 2 (1.6%) | 6 (4.1%) |
| 疼痛 | 1 (4.2%) | 0 | 4 (3.2%) | 0 | 5 (3.4%) |
| 歩行障害 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 全身健康状態低下 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 炎症 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 注射部位内出血 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 倦怠感 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 粘膜の炎症 | 0 | 0 | 2 (1.6%) | 1 (0.8%) | 2 (1.4%) |
| 乾燥症 | 1 (4.2%) | 1 (4.2%) | 1 (0.8%) | 0 | 2 (1.4%) |
| 腋窩痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| カテーテル留置部位関連反応 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 医療機器リーク | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 異常感 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 冷感 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 硬結 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 注入部位血管外漏出 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 注射部位出血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 局所腫脹 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 浮腫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 先行疾患の改善 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 評価不能の事象 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 呼吸器、胸郭および縦隔障害 | 18 (75.0%) | 4 (16.7%) | 81 (65.3%) | 15 (12.1%) | 99 (66.9%) |
| 咳嗽 | 5 (20.8%) | 0 | 40 (32.3%) | 0 | 45 (30.4%) |
| 呼吸困難 | 8 (33.3%) | 1 (4.2%) | 32 (25.8%) | 5 (4.0%) | 40 (27.0%) |
| 鼻出血 | 4 (16.7%) | 0 | 16 (12.9%) | 1 (0.8%) | 20 (13.5%) |
| 口腔咽頭痛 | 3 (12.5%) | 0 | 16 (12.9%) | 0 | 19 (12.8%) |
| 胸水 | 2 (8.3%) | 0 | 9 (7.3%) | 3 (2.4%) | 11 (7.4%) |
| 鼻閉 | 0 | 0 | 8 (6.5%) | 0 | 8 (5.4%) |
| 湿性咳嗽 | 1 (4.2%) | 0 | 6 (4.8%) | 0 | 7 (4.7%) |
| 呼吸不全 | 1 (4.2%) | 1 (4.2%) | 5 (4.0%) | 5 (4.0%) | 6 (4.1%) |
| 鼻漏 | 0 | 0 | 6 (4.8%) | 0 | 6 (4.1%) |
| 発声障害 | 2 (8.3%) | 0 | 3 (2.4%) | 0 | 5 (3.4%) |
| 慢性閉塞性肺疾患 | 1 (4.2%) | 1 (4.2%) | 3 (2.4%) | 1 (0.8%) | 4 (2.7%) |
| アレルギー性鼻炎 | 1 (4.2%) | 0 | 3 (2.4%) | 0 | 4 (2.7%) |
| しゃっくり | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 上気道うっ血 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 低酸素症 | 1 (4.2%) | 1 (4.2%) | 1 (0.8%) | 1 (0.8%) | 2 (1.4%) |
| 肺硬化 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 気胸 | 1 (4.2%) | 1 (4.2%) | 1 (0.8%) | 0 | 2 (1.4%) |
| 副鼻腔うっ血 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 急性肺水腫 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 気管支反応性亢進 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 気管支拡張症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 労作性呼吸困難 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 肺気腫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 喀血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 肺浸潤 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 鼻部不快感 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 鼻の炎症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 副鼻腔分泌過多 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 胸膜炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 胸膜痛 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 気道うっ血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 拘束性肺疾患 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 副鼻腔障害 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 頻呼吸 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 上気道咳症候群 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 皮膚および皮下組織障害 | 14 (58.3%) | 0 | 77 (62.1%) | 5 (4.0%) | 91 (61.5%) |
| 発疹 | 3 (12.5%) | 0 | 31 (25.0%) | 3 (2.4%) | 34 (23.0%) |
| 皮膚病変 | 0 | 0 | 12 (9.7%) | 0 | 12 (8.1%) |
| 点状出血 | 0 | 0 | 11 (8.9%) | 0 | 11 (7.4%) |
| 皮膚乾燥 | 1 (4.2%) | 0 | 8 (6.5%) | 0 | 9 (6.1%) |
| そう痒症 | 3 (12.5%) | 0 | 5 (4.0%) | 0 | 8 (5.4%) |
| 斑状丘疹状皮疹 | 1 (4.2%) | 0 | 7 (5.6%) | 0 | 8 (5.4%) |
| 斑状出血 | 1 (4.2%) | 0 | 6 (4.8%) | 0 | 7 (4.7%) |
| 紅斑 | 2 (8.3%) | 0 | 4 (3.2%) | 0 | 6 (4.1%) |
| 寝汗 | 0 | 0 | 6 (4.8%) | 0 | 6 (4.1%) |
| 皮膚亀裂 | 2 (8.3%) | 0 | 3 (2.4%) | 0 | 5 (3.4%) |
| 蕁麻疹 | 1 (4.2%) | 0 | 3 (2.4%) | 0 | 4 (2.7%) |
| ざ瘡 | 2 (8.3%) | 0 | 1 (0.8%) | 0 | 3 (2.0%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 褥瘡性潰瘍 | 0 | 0 | 3 (2.4%) | 1 (0.8%) | 3 (2.0%) |
| 脱毛症 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 水疱 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 湿疹 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 皮下出血 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 多汗症 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 嵌入爪 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 爪破損 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 紫斑 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 斑状皮疹 | 0 | 0 | 2 (1.6%) | 1 (0.8%) | 2 (1.4%) |
| 丘疹性皮疹 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| そう痒性皮疹 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 皮膚色素過剰 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 皮膚腫瘤 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 皮膚潰瘍 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 毛細血管炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 皮膚嚢腫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| ざ瘡様皮膚炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 接触性皮膚炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 皮脂欠乏性湿疹 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 間擦疹 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 爪の障害 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 爪線状隆起 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 爪甲脱落症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 全身性そう痒症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 毛孔性皮疹 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 皮膚変色 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 皮膚色素減少 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 皮膚腫脹 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 乾皮症 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 筋骨格系および結合組織障害 | 13 (54.2%) | 1 (4.2%) | 69 (55.6%) | 5 (4.0%) | 82 (55.4%) |
| 筋痙縮 | 7 (29.2%) | 0 | 29 (23.4%) | 0 | 36 (24.3%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 背部痛 | 2 (8.3%) | 0 | 21 (16.9%) | 2 (1.6%) | 23 (15.5%) |
| 関節痛 | 1 (4.2%) | 0 | 18 (14.5%) | 1 (0.8%) | 19 (12.8%) |
| 筋肉痛 | 0 | 0 | 15 (12.1%) | 1 (0.8%) | 15 (10.1%) |
| 四肢痛 | 1 (4.2%) | 0 | 11 (8.9%) | 0 | 12 (8.1%) |
| 筋骨格痛 | 0 | 0 | 10 (8.1%) | 0 | 10 (6.8%) |
| 頚部痛 | 1 (4.2%) | 0 | 4 (3.2%) | 0 | 5 (3.4%) |
| 側腹部痛 | 0 | 0 | 4 (3.2%) | 1 (0.8%) | 4 (2.7%) |
| 筋力低下 | 2 (8.3%) | 1 (4.2%) | 2 (1.6%) | 0 | 4 (2.7%) |
| 胂径部痛 | 0 | 0 | 2 (1.6%) | 1 (0.8%) | 2 (1.4%) |
| 関節硬直 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 運動性低下 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 筋骨格系胸痛 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 筋骨格硬直 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 骨痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 滑液包炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| ピロリン酸カルシウム結晶性軟骨石灰化症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 椎間板変性症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 椎間板突出 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 関節拘縮 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 関節ロック | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 関節腫脹 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 変形性関節症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 骨粗鬆症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 軟部組織障害 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 滑液嚢腫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 腱痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 代謝および栄養障害 | 13 (54.2%) | 4 (16.7%) | 65 (52.4%) | 19 (15.3%) | 78 (52.7%) |
| 食欲減退 | 8 (33.3%) | 0 | 28 (22.6%) | 0 | 36 (24.3%) |
| 低カリウム血症 | 2 (8.3%) | 1 (4.2%) | 16 (12.9%) | 6 (4.8%) | 18 (12.2%) |
| 脱水 | 2 (8.3%) | 1 (4.2%) | 14 (11.3%) | 3 (2.4%) | 16 (10.8%) |
| 高尿酸血症 | 3 (12.5%) | 2 (8.3%) | 11 (8.9%) | 4 (3.2%) | 14 (9.5%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 低マグネシウム血症 | 1 (4.2%) | 0 | 12 (9.7%) | 0 | 13 (8.8%) |
| 低アルブミン血症 | 1 (4.2%) | 0 | 6 (4.8%) | 2 (1.6%) | 7 (4.7%) |
| 低ナトリウム血症 | 0 | 0 | 5 (4.0%) | 3 (2.4%) | 5 (3.4%) |
| 高カリウム血症 | 0 | 0 | 4 (3.2%) | 0 | 4 (2.7%) |
| 高血糖 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 低カルシウム血症 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 水分過負荷 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 痛風 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 低血糖症 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 悪液質 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 糖尿病 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 糖尿病性ケトアシドーシス | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 酵素異常 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 高コレステロール血症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 高ナトリウム血症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 高リン酸塩血症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 過小食 | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| 低リン酸血症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 低蛋白血症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 乳酸アシドーシス | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 腫瘍崩壊症候群 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 血液およびリンパ系障害 | 7 (29.2%) | 6 (25.0%) | 66 (53.2%) | 45 (36.3%) | 73 (49.3%) |
| 好中球減少症 | 3 (12.5%) | 2 (8.3%) | 33 (26.6%) | 28 (22.6%) | 36 (24.3%) |
| 血小板減少症 | 6 (25.0%) | 5 (20.8%) | 28 (22.6%) | 17 (13.7%) | 34 (23.0%) |
| 貧血 | 5 (20.8%) | 4 (16.7%) | 25 (20.2%) | 10 (8.1%) | 30 (20.3%) |
| 白血球減少症 | 0 | 0 | 8 (6.5%) | 4 (3.2%) | 8 (5.4%) |
| 発熱性好中球減少症 | 0 | 0 | 4 (3.2%) | 4 (3.2%) | 4 (2.7%) |
| リンパ球減少症 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 内出血発生の増加傾向 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 鉄欠乏性貧血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 白血球増加症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| リンパ球増加症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 神経系障害 | 10 (41.7%) | 1 (4.2%) | 51 (41.1%) | 1 (0.8%) | 61 (41.2%) |
| 頭痛 | 1 (4.2%) | 0 | 16 (12.9%) | 0 | 17 (11.5%) |
| 浮動性めまい | 3 (12.5%) | 0 | 13 (10.5%) | 0 | 16 (10.8%) |
| 末梢性感覚ニューロパチー | 1 (4.2%) | 0 | 7 (5.6%) | 0 | 8 (5.4%) |
| 体位性めまい | 1 (4.2%) | 0 | 5 (4.0%) | 0 | 6 (4.1%) |
| 末梢性ニューロパチー | 2 (8.3%) | 0 | 4 (3.2%) | 0 | 6 (4.1%) |
| 記憶障害 | 0 | 0 | 5 (4.0%) | 0 | 5 (3.4%) |
| 錯感覚 | 1 (4.2%) | 0 | 3 (2.4%) | 0 | 4 (2.7%) |
| 傾眠 | 0 | 0 | 4 (3.2%) | 0 | 4 (2.7%) |
| 健忘 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 嗜眠 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 振戦 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 平衡障害 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 味覚異常 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 神経痛 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 失神 | 1 (4.2%) | 1 (4.2%) | 1 (0.8%) | 1 (0.8%) | 2 (1.4%) |
| 灼熱足症候群 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 大脳萎縮 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 認知症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 労作性めまい | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 構語障害 | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| 顔面部神経痛 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 顔面不全麻痺 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 感覚鈍麻 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 前兆を伴う片頭痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| ミオクローヌス | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 眼振 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 多発ニューロパチー | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| ヘルペス後神経痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 失神寸前の状態 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 下肢静止不能症候群 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 副鼻腔炎に伴う頭痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 緊張性頭痛 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 一過性全健忘 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 一過性脳虚血発作 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 傷害、中毒および処置合併症 | 5 (20.8%) | 2 (8.3%) | 46 (37.1%) | 3 (2.4%) | 51 (34.5%) |
| 挫傷 | 1 (4.2%) | 0 | 27 (21.8%) | 0 | 28 (18.9%) |
| 転倒 | 2 (8.3%) | 2 (8.3%) | 8 (6.5%) | 1 (0.8%) | 10 (6.8%) |
| 裂傷 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 処置後出血 | 1 (4.2%) | 1 (4.2%) | 2 (1.6%) | 1 (0.8%) | 3 (2.0%) |
| 処置による疼痛 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| サンバーン | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 節足動物咬傷 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 顔面骨骨折 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 頭部損傷 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 靭帯捻挫 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 腰椎骨折 | 1 (4.2%) | 0 | 1 (0.8%) | 1 (0.8%) | 2 (1.4%) |
| 眼窩周囲挫傷 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 肋骨骨折 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 皮膚擦過傷 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 熱傷 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 外傷性血腫 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 創傷 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 動物咬傷 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 動物による引っかき傷 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 足関節部骨折 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 骨挫傷 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 眼挫傷 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 足骨折 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 処置後腫脹 | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| 陰嚢血腫 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 硬膜下血腫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 脛骨骨折 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 歯牙破折 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 創合併症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 臨床検査 | 5 (20.8%) | 4 (16.7%) | 46 (37.1%) | 16 (12.9%) | 51 (34.5%) |
| 血中クレアチニン増加 | 1 (4.2%) | 0 | 11 (8.9%) | 0 | 12 (8.1%) |
| 体重減少 | 0 | 0 | 11 (8.9%) | 0 | 11 (7.4%) |
| リンパ球数増加 | 2 (8.3%) | 2 (8.3%) | 3 (2.4%) | 2 (1.6%) | 5 (3.4%) |
| アラニンアミノトランスフェラーゼ増加 | 0 | 0 | 4 (3.2%) | 0 | 4 (2.7%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 2 (8.3%) | 1 (4.2%) | 2 (1.6%) | 0 | 4 (2.7%) |
| 血中アルカリホスファターゼ増加 | 1 (4.2%) | 0 | 3 (2.4%) | 1 (0.8%) | 4 (2.7%) |
| 血中尿酸増加 | 0 | 0 | 4 (3.2%) | 2 (1.6%) | 4 (2.7%) |
| 好中球数減少 | 1 (4.2%) | 1 (4.2%) | 3 (2.4%) | 3 (2.4%) | 4 (2.7%) |
| 活性化部分トロンボプラスチン時間延長 | 0 | 0 | 3 (2.4%) | 1 (0.8%) | 3 (2.0%) |
| 血中ビリルビン増加 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 血中乳酸脱水素酵素増加 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 血小板数減少 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 体重増加 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 白血球数減少 | 0 | 0 | 3 (2.4%) | 3 (2.4%) | 3 (2.0%) |
| 血中免疫グロブリンG減少 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 血圧上昇 | 0 | 0 | 2 (1.6%) | 2 (1.6%) | 2 (1.4%) |
| 国際標準比増加 | 0 | 0 | 2 (1.6%) | 2 (1.6%) | 2 (1.4%) |
| トランスアミナーゼ上昇 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 白血球数増加 | 1 (4.2%) | 0 | 1 (0.8%) | 1 (0.8%) | 2 (1.4%) |
| アミラーゼ増加 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| アスペルギルス検査陽性 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 血中アルブミン減少 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 血中コレステロール増加 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 血中ブドウ糖増加 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 血中免疫グロブリンM減少 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 血中鉄減少 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 血中マグネシウム減少 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 血中リン減少 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 血中カリウム減少 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| Ｃ－反応性蛋白増加 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 二酸化炭素減少 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 胸部コンピュータ断層撮影異常 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| γ－グルタミルトランスフェラーゼ増加 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| ヘモグロビン減少 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| ヘモフィルス検査陽性 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 肝機能検査異常 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| リンパ球数減少 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 平均赤血球容積増加 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 肺活量異常 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 眼障害 | 6 (25.0%) | 0 | 35 (28.2%) | 2 (1.6%) | 41 (27.7%) |
| 流涙増加 | 0 | 0 | 10 (8.1%) | 0 | 10 (6.8%) |
| 眼乾燥 | 1 (4.2%) | 0 | 7 (5.6%) | 0 | 8 (5.4%) |
| 霧視 | 2 (8.3%) | 0 | 5 (4.0%) | 0 | 7 (4.7%) |
| 白内障 | 1 (4.2%) | 0 | 5 (4.0%) | 2 (1.6%) | 6 (4.1%) |
| 眼充血 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 睫毛乱生 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 結膜出血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 結膜充血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 糖尿病網膜症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 複視 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 眼脂 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 眼出血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 眼の炎症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 眼痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 眼の異物感 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 緑内障 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 黄斑変性 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 眼窩周囲浮腫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 羞明 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 強膜出血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 視力低下 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 視力障害 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 硝子体浮遊物 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 眼球乾燥症 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 血管障害 | 6 (25.0%) | 3 (12.5%) | 33 (26.6%) | 7 (5.6%) | 39 (26.4%) |
| 高血圧 | 0 | 0 | 15 (12.1%) | 5 (4.0%) | 15 (10.1%) |
| 低血圧 | 2 (8.3%) | 1 (4.2%) | 12 (9.7%) | 3 (2.4%) | 14 (9.5%) |
| 血腫 | 3 (12.5%) | 0 | 4 (3.2%) | 0 | 7 (4.7%) |
| 深部静脈血栓症 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 血圧変動 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 表在性血栓性静脈炎 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 循環虚脱 | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| 起立性低血圧 | 1 (4.2%) | 1 (4.2%) | 0 | 0 | 1 (0.7%) |
| 末梢血管障害 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 末梢静脈疾患 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 静脈炎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 心臓障害 | 2 (8.3%) | 1 (4.2%) | 36 (29.0%) | 13 (10.5%) | 38 (25.7%) |
| 心房細動 | 1 (4.2%) | 1 (4.2%) | 16 (12.9%) | 10 (8.1%) | 17 (11.5%) |
| 洞性頻脈 | 0 | 0 | 5 (4.0%) | 0 | 5 (3.4%) |
| 頻脈 | 0 | 0 | 5 (4.0%) | 0 | 5 (3.4%) |
| 心房粗動 | 0 | 0 | 3 (2.4%) | 1 (0.8%) | 3 (2.0%) |
| 上室性頻脈 | 0 | 0 | 3 (2.4%) | 1 (0.8%) | 3 (2.0%) |
| 徐脈 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 洞性徐脈 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 不安定狭心症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 冠動脈硬化症 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 第一度房室ブロック | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 心停止 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 心不全 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 冠動脈疾患 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| チアノーゼ | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 僧帽弁閉鎖不全症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 心筋梗塞 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 動悸 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| ストレス心筋症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 頻脈性不整脈 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| トルサード　ド　ポアント | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 心室性頻脈 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 腎および尿路障害 | 6 (25.0%) | 1 (4.2%) | 25 (20.2%) | 9 (7.3%) | 31 (20.9%) |
| 血尿 | 2 (8.3%) | 0 | 8 (6.5%) | 2 (1.6%) | 10 (6.8%) |
| 急性腎不全 | 1 (4.2%) | 0 | 6 (4.8%) | 3 (2.4%) | 7 (4.7%) |
| 排尿困難 | 2 (8.3%) | 0 | 3 (2.4%) | 0 | 5 (3.4%) |
| 腎不全 | 1 (4.2%) | 1 (4.2%) | 4 (3.2%) | 2 (1.6%) | 5 (3.4%) |
| 頻尿 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 腎機能障害 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 尿閉 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 高窒素血症 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 出血性膀胱炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 水腎症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 失禁 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 尿意切迫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 腎結石症 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 閉塞性尿路疾患 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 腎仙痛 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 慢性腎不全 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 尿失禁 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 尿路閉塞 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 尿路痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 精神障害 | 2 (8.3%) | 1 (4.2%) | 28 (22.6%) | 2 (1.6%) | 30 (20.3%) |
| 不眠症 | 2 (8.3%) | 0 | 10 (8.1%) | 0 | 12 (8.1%) |
| 錯乱状態 | 1 (4.2%) | 1 (4.2%) | 7 (5.6%) | 1 (0.8%) | 8 (5.4%) |
| 不安 | 0 | 0 | 6 (4.8%) | 0 | 6 (4.1%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| うつ病 | 0 | 0 | 6 (4.8%) | 0 | 6 (4.1%) |
| 激越 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 希死念慮を有するうつ病 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 多幸気分 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 幻視 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 易刺激性 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| リビドー減退 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 躁病 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 4 (16.7%) | 2 (8.3%) | 13 (10.5%) | 7 (5.6%) | 17 (11.5%) |
| 基底細胞癌 | 0 | 0 | 5 (4.0%) | 1 (0.8%) | 5 (3.4%) |
| 膀胱移行上皮癌 | 1 (4.2%) | 0 | 1 (0.8%) | 1 (0.8%) | 2 (1.4%) |
| マントル細胞リンパ腫 | 1 (4.2%) | 1 (4.2%) | 1 (0.8%) | 1 (0.8%) | 2 (1.4%) |
| 前立腺癌 | 1 (4.2%) | 1 (4.2%) | 1 (0.8%) | 1 (0.8%) | 2 (1.4%) |
| 皮膚有棘細胞癌 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 悪性胸水 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 唾液腺癌 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 皮膚癌 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 皮膚乳頭腫 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 移行上皮癌 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 耳および迷路障害 | 5 (20.8%) | 0 | 10 (8.1%) | 0 | 15 (10.1%) |
| 回転性めまい | 2 (8.3%) | 0 | 3 (2.4%) | 0 | 5 (3.4%) |
| 耳痛 | 1 (4.2%) | 0 | 3 (2.4%) | 0 | 4 (2.7%) |
| 耳鳴 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 耳不快感 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 耳垢栓塞 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 耳出血 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 聴力低下 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 老人性難聴 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 免疫系障害 | 4 (16.7%) | 0 | 8 (6.5%) | 0 | 12 (8.1%) |
| 低ｙグロブリン血症 | 0 | 0 | 3 (2.4%) | 0 | 3 (2.0%) |
| 季節性アレルギー | 2 (8.3%) | 0 | 1 (0.8%) | 0 | 3 (2.0%) |

**TSFAE18B: Incidence of Treatment-emergent Adverse Events by Toxicity Grade, System Organ Class, Preferred Term, and by CYP3A Inhibitor (Strong vs. non-Strong) for Pooled Ibrutinib; Safety Population (MCL-ISS)**

| | Pooled Ibrutinib | | | | |
|---|---|---|---|---|---|
| | CYP3A Inhibitor | | | | |
| | Strong | | non-Strong | | |
| | Any Grades | Grade >=3 | Any Grades | Grade >=3 | Total Any Grades |
| 節足動物咬傷アレルギー | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 薬物過敏症 | 1 (4.2%) | 0 | 1 (0.8%) | 0 | 2 (1.4%) |
| 過敏症 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 生殖系および乳房障害 | 4 (16.7%) | 0 | 7 (5.6%) | 2 (1.6%) | 11 (7.4%) |
| 血精液症 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 後天性包茎 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 良性前立腺肥大症 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 乳房血腫 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 乳房腫瘤 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 乳房痛 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 性器発疹 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 性器浮腫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 陰茎痛 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 陰嚢腫瘤 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 陰嚢痛 | 1 (4.2%) | 0 | 0 | 0 | 1 (0.7%) |
| 外陰腟痛 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 肝胆道系障害 | 0 | 0 | 4 (3.2%) | 1 (0.8%) | 4 (2.7%) |
| 高ビリルビン血症 | 0 | 0 | 2 (1.6%) | 0 | 2 (1.4%) |
| 胆管結石 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 胆管炎 | 0 | 0 | 1 (0.8%) | 1 (0.8%) | 1 (0.7%) |
| 肝機能異常 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 内分泌障害 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 甲状腺機能低下症 | 1 (4.2%) | 0 | 2 (1.6%) | 0 | 3 (2.0%) |
| 先天性、家族性および遺伝性障害 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |
| 臍血腫 | 0 | 0 | 1 (0.8%) | 0 | 1 (0.7%) |

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 17.1.

[TSFAE18B.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_MCL_JAPAN_2015\tsfae18b.sas] 15SEP2015, 14:13

参照元：5.3.5.3.1 ISS TSFAE18B

表 2.7.4-付録-63 市販後に報告された重篤な有害事象の一覧

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 血液およびリンパ系障害 | 316 | 貧血 | 75 | 33 | 42 |
| 血液およびリンパ系障害 | 316 | 慢性疾患の貧血 | 2 | 0 | 2 |
| 血液およびリンパ系障害 | 316 | 赤芽球癆 | 2 | 2 | 0 |
| 血液およびリンパ系障害 | 316 | 再生不良性貧血 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 自己免疫性溶血性貧血 | 8 | 7 | 1 |
| 血液およびリンパ系障害 | 316 | 血液障害 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 骨髄機能不全 | 3 | 3 | 0 |
| 血液およびリンパ系障害 | 316 | 骨髄毒性 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 凝血異常 | 2 | 0 | 2 |
| 血液およびリンパ系障害 | 316 | 冷式溶血性貧血 | 1 | 0 | 1 |
| 血液およびリンパ系障害 | 316 | クームス試験陽性溶血性貧血 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 血球減少症 | 4 | 3 | 1 |
| 血液およびリンパ系障害 | 316 | 播種性血管内凝固 | 2 | 2 | 0 |
| 血液およびリンパ系障害 | 316 | 発熱性好中球減少症 | 26 | 24 | 2 |
| 血液およびリンパ系障害 | 316 | 顆粒球減少症 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 溶血 | 4 | 3 | 1 |
| 血液およびリンパ系障害 | 316 | 溶血性貧血 | 7 | 5 | 2 |
| 血液およびリンパ系障害 | 316 | 出血性貧血 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 出血性素因 | 4 | 2 | 2 |
| 血液およびリンパ系障害 | 316 | 貪食細胞性組織球症 | 4 | 4 | 0 |
| 血液およびリンパ系障害 | 316 | 免疫性血小板減少性紫斑病 | 3 | 3 | 0 |
| 血液およびリンパ系障害 | 316 | 内出血発生の増加傾向 | 1 | 0 | 1 |
| 血液およびリンパ系障害 | 316 | 鉄欠乏性貧血 | 3 | 0 | 3 |
| 血液およびリンパ系障害 | 316 | 白血球増加症 | 25 | 5 | 20 |
| 血液およびリンパ系障害 | 316 | 白血球減少症 | 6 | 3 | 3 |
| 血液およびリンパ系障害 | 316 | リンパ節痛 | 2 | 1 | 1 |
| 血液およびリンパ系障害 | 316 | リンパ節症 | 29 | 8 | 21 |
| 血液およびリンパ系障害 | 316 | リンパ球増加症 | 22 | 10 | 12 |
| 血液およびリンパ系障害 | 316 | リンパ球減少症 | 1 | 0 | 1 |
| 血液およびリンパ系障害 | 316 | 好中球減少症 | 53 | 40 | 13 |
| 血液およびリンパ系障害 | 316 | 好中球増加症 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 正色素性正球性貧血 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 汎血球減少症 | 34 | 19 | 15 |
| 血液およびリンパ系障害 | 316 | 血小板破壊亢進 | 1 | 0 | 1 |
| 血液およびリンパ系障害 | 316 | 脾臓障害 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 脾血腫 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 脾臓出血 | 4 | 4 | 0 |
| 血液およびリンパ系障害 | 316 | 脾臓梗塞 | 3 | 3 | 0 |
| 血液およびリンパ系障害 | 316 | 脾腫 | 10 | 6 | 4 |
| 血液およびリンパ系障害 | 316 | 特発性血腫 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 特発性出血 | 1 | 1 | 0 |
| 血液およびリンパ系障害 | 316 | 血小板減少症 | 65 | 32 | 33 |
| 心臓障害 | 371 | 急性冠動脈症候群 | 1 | 1 | 0 |
| 心臓障害 | 371 | 急性心筋梗塞 | 5 | 5 | 0 |
| 心臓障害 | 371 | 狭心症 | 1 | 1 | 0 |
| 心臓障害 | 371 | 不安定狭心症 | 1 | 1 | 0 |
| 心臓障害 | 371 | 大動脈弁狭窄 | 1 | 1 | 0 |
| 心臓障害 | 371 | 不整脈 | 7 | 5 | 2 |
| 心臓障害 | 371 | 上室性不整脈 | 3 | 2 | 1 |
| 心臓障害 | 371 | 冠動脈硬化症 | 1 | 0 | 1 |
| 心臓障害 | 371 | 冠動脈攣縮 | 1 | 1 | 0 |
| 心臓障害 | 371 | 心房細動 | 205 | 168 | 37 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 心臓障害 | 371 | 心房粗動 | 12 | 12 | 0 |
| 心臓障害 | 371 | 房室ブロック | 1 | 1 | 0 |
| 心臓障害 | 371 | 完全房室ブロック | 3 | 3 | 0 |
| 心臓障害 | 371 | 第一度房室ブロック | 3 | 2 | 1 |
| 心臓障害 | 371 | 第二度房室ブロック | 1 | 1 | 0 |
| 心臓障害 | 371 | 徐脈 | 3 | 0 | 3 |
| 心臓障害 | 371 | 左脚ブロック | 1 | 1 | 0 |
| 心臓障害 | 371 | 右脚ブロック | 2 | 1 | 1 |
| 心臓障害 | 371 | 心停止 | 12 | 12 | 0 |
| 心臓障害 | 371 | 心障害 | 15 | 14 | 1 |
| 心臓障害 | 371 | 心不全 | 20 | 20 | 0 |
| 心臓障害 | 371 | うっ血性心不全 | 45 | 44 | 1 |
| 心臓障害 | 371 | 心粗動 | 1 | 1 | 0 |
| 心臓障害 | 371 | 心タンポナーデ | 4 | 4 | 0 |
| 心臓障害 | 371 | 心臓弁膜疾患 | 1 | 0 | 1 |
| 心臓障害 | 371 | 心肺停止 | 4 | 4 | 0 |
| 心臓障害 | 371 | 心拡大 | 5 | 5 | 0 |
| 心臓障害 | 371 | 心筋症 | 7 | 6 | 1 |
| 心臓障害 | 371 | 心毒性 | 1 | 1 | 0 |
| 心臓障害 | 371 | 伝導障害 | 2 | 2 | 0 |
| 心臓障害 | 371 | 冠動脈疾患 | 1 | 1 | 0 |
| 心臓障害 | 371 | 冠動脈不全 | 1 | 1 | 0 |
| 心臓障害 | 371 | 冠動脈閉塞 | 4 | 4 | 0 |
| 心臓障害 | 371 | 冠動脈狭窄 | 1 | 1 | 0 |
| 心臓障害 | 371 | 虚血性心筋症 | 2 | 2 | 0 |
| 心臓障害 | 371 | 左室不全 | 1 | 1 | 0 |
| 心臓障害 | 371 | 左室肥大 | 2 | 2 | 0 |
| 心臓障害 | 371 | 僧帽弁閉鎖不全症 | 2 | 2 | 0 |
| 心臓障害 | 371 | 僧帽弁狭窄症 | 1 | 1 | 0 |
| 心臓障害 | 371 | 心筋梗塞 | 19 | 19 | 0 |
| 心臓障害 | 371 | 心筋炎 | 1 | 1 | 0 |
| 心臓障害 | 371 | 動悸 | 11 | 7 | 4 |
| 心臓障害 | 371 | 心嚢液貯留 | 24 | 24 | 0 |
| 心臓障害 | 371 | 心嚢内出血 | 2 | 2 | 0 |
| 心臓障害 | 371 | 心膜炎 | 6 | 6 | 0 |
| 心臓障害 | 371 | 胸膜心膜炎 | 1 | 1 | 0 |
| 心臓障害 | 371 | 右室不全 | 1 | 1 | 0 |
| 心臓障害 | 371 | 洞性頻脈 | 4 | 1 | 3 |
| 心臓障害 | 371 | ストレス心筋症 | 1 | 1 | 0 |
| 心臓障害 | 371 | 上室性期外収縮 | 1 | 0 | 1 |
| 心臓障害 | 371 | 上室性頻脈 | 4 | 4 | 0 |
| 心臓障害 | 371 | 収縮機能障害 | 1 | 1 | 0 |
| 心臓障害 | 371 | 頻脈性不整脈 | 3 | 3 | 0 |
| 心臓障害 | 371 | 頻脈 | 9 | 6 | 3 |
| 心臓障害 | 371 | 三尖弁閉鎖不全症 | 1 | 1 | 0 |
| 心臓障害 | 371 | 心室性不整脈 | 1 | 1 | 0 |
| 心臓障害 | 371 | 心室性期外収縮 | 3 | 3 | 0 |
| 心臓障害 | 371 | 心室細動 | 7 | 7 | 0 |
| 心臓障害 | 371 | 心室性頻脈 | 4 | 3 | 1 |
| 先天性、家族性および遺伝性障害 | 5 | 形成不全 | 1 | 1 | 0 |
| 先天性、家族性および遺伝性障害 | 5 | 動静脈奇形 | 1 | 1 | 0 |
| 先天性、家族性および遺伝性障害 | 5 | 嚢胞性リンパ管腫 | 1 | 1 | 0 |
| 先天性、家族性および遺伝性障害 | 5 | 細胞遺伝学的異常 | 1 | 1 | 0 |
| 先天性、家族性および遺伝性障害 | 5 | 筋ジストロフィー | 1 | 1 | 0 |
| 耳および迷路障害 | 26 | 難聴 | 3 | 3 | 0 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 耳および迷路障害 | 26 | 片耳難聴 | 1 | 1 | 0 |
| 耳および迷路障害 | 26 | 耳出血 | 8 | 8 | 0 |
| 耳および迷路障害 | 26 | 耳痛 | 1 | 0 | 1 |
| 耳および迷路障害 | 26 | 鼓室内出血 | 3 | 3 | 0 |
| 耳および迷路障害 | 26 | 聴覚障害 | 3 | 1 | 2 |
| 耳および迷路障害 | 26 | 聴力低下 | 1 | 0 | 1 |
| 耳および迷路障害 | 26 | 感音性聴力低下 | 1 | 0 | 1 |
| 耳および迷路障害 | 26 | 突発性難聴 | 1 | 1 | 0 |
| 耳および迷路障害 | 26 | 耳鳴 | 3 | 1 | 2 |
| 耳および迷路障害 | 26 | 回転性めまい | 7 | 5 | 2 |
| 耳および迷路障害 | 26 | 頭位性回転性めまい | 1 | 1 | 0 |
| 内分泌障害 | 11 | 副腎機能不全 | 4 | 2 | 2 |
| 内分泌障害 | 11 | 甲状腺機能正常症候群 | 1 | 1 | 0 |
| 内分泌障害 | 11 | 甲状腺機能低下症 | 4 | 1 | 3 |
| 内分泌障害 | 11 | 抗利尿ホルモン不適合分泌 | 2 | 2 | 0 |
| 眼障害 | 67 | 黒内障 | 1 | 1 | 0 |
| 眼障害 | 67 | 閉塞隅角緑内障 | 1 | 1 | 0 |
| 眼障害 | 67 | 失明 | 3 | 3 | 0 |
| 眼障害 | 67 | 片側失明 | 4 | 4 | 0 |
| 眼障害 | 67 | 白内障 | 4 | 2 | 2 |
| 眼障害 | 67 | 網脈絡膜症 | 1 | 1 | 0 |
| 眼障害 | 67 | 結膜出血 | 3 | 1 | 2 |
| 眼障害 | 67 | 角膜内皮炎 | 1 | 1 | 0 |
| 眼障害 | 67 | 眼乾燥 | 2 | 0 | 2 |
| 眼障害 | 67 | 眼の障害 | 1 | 1 | 0 |
| 眼障害 | 67 | 眼出血 | 8 | 8 | 0 |
| 眼障害 | 67 | 眼運動障害 | 1 | 1 | 0 |
| 眼障害 | 67 | 眼痛 | 1 | 1 | 0 |
| 眼障害 | 67 | 眼そう痒症 | 1 | 0 | 1 |
| 眼障害 | 67 | 眼部腫脹 | 2 | 1 | 1 |
| 眼障害 | 67 | 眼瞼障害 | 1 | 0 | 1 |
| 眼障害 | 67 | 眼瞼血腫 | 1 | 1 | 0 |
| 眼障害 | 67 | 眼瞼浮腫 | 1 | 0 | 1 |
| 眼障害 | 67 | 緑内障 | 2 | 2 | 0 |
| 眼障害 | 67 | 虹彩毛様体炎 | 1 | 1 | 0 |
| 眼障害 | 67 | 虹彩癒着 | 1 | 0 | 1 |
| 眼障害 | 67 | 流涙増加 | 1 | 0 | 1 |
| 眼障害 | 67 | 黄斑変性 | 2 | 2 | 0 |
| 眼障害 | 67 | 黄斑浮腫 | 1 | 0 | 1 |
| 眼障害 | 67 | 散瞳 | 1 | 1 | 0 |
| 眼障害 | 67 | 眼充血 | 3 | 1 | 2 |
| 眼障害 | 67 | 黄疸眼 | 1 | 0 | 1 |
| 眼障害 | 67 | 光視症 | 1 | 0 | 1 |
| 眼障害 | 67 | 網膜剥離 | 2 | 2 | 0 |
| 眼障害 | 67 | 網膜障害 | 1 | 0 | 1 |
| 眼障害 | 67 | 網膜出血 | 8 | 8 | 0 |
| 眼障害 | 67 | 強膜障害 | 1 | 0 | 1 |
| 眼障害 | 67 | 霧視 | 8 | 3 | 5 |
| 眼障害 | 67 | 視力低下 | 4 | 1 | 3 |
| 眼障害 | 67 | 視力障害 | 9 | 3 | 6 |
| 眼障害 | 67 | 硝子体剥離 | 1 | 1 | 0 |
| 眼障害 | 67 | 硝子体浮遊物 | 1 | 0 | 1 |
| 眼障害 | 67 | 硝子体出血 | 2 | 2 | 0 |
| 胃腸障害 | 420 | 腹部不快感 | 7 | 1 | 6 |
| 胃腸障害 | 420 | 腹部膨満 | 11 | 2 | 9 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 胃腸障害 | 420 | 腹部ヘルニア | 1 | 0 | 1 |
| 胃腸障害 | 420 | 腹痛 | 26 | 10 | 16 |
| 胃腸障害 | 420 | 下腹部痛 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 上腹部痛 | 14 | 7 | 7 |
| 胃腸障害 | 420 | 腹部硬直 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 急性腹症 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 肛門潰瘍 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 肛門直腸不快感 | 1 | 1 | 0 |
| 胃腸障害 | 420 | アフタ性潰瘍 | 4 | 1 | 3 |
| 胃腸障害 | 420 | 腹水 | 13 | 6 | 7 |
| 胃腸障害 | 420 | 便通不規則 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 大腸炎 | 5 | 5 | 0 |
| 胃腸障害 | 420 | 虚血性大腸炎 | 2 | 2 | 0 |
| 胃腸障害 | 420 | 結腸瘻 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 便秘 | 39 | 5 | 34 |
| 胃腸障害 | 420 | 齲歯 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 下痢 | 151 | 49 | 102 |
| 胃腸障害 | 420 | 血性下痢 | 2 | 2 | 0 |
| 胃腸障害 | 420 | 憩室 | 4 | 1 | 3 |
| 胃腸障害 | 420 | 口内乾燥 | 9 | 1 | 8 |
| 胃腸障害 | 420 | 消化不良 | 4 | 0 | 4 |
| 胃腸障害 | 420 | 嚥下障害 | 15 | 4 | 11 |
| 胃腸障害 | 420 | びらん性食道炎 | 2 | 1 | 1 |
| 胃腸障害 | 420 | おくび | 1 | 0 | 1 |
| 胃腸障害 | 420 | 便量増加 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 変色便 | 5 | 0 | 5 |
| 胃腸障害 | 420 | 放屁 | 5 | 0 | 5 |
| 胃腸障害 | 420 | 排便回数増加 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 胃障害 | 2 | 1 | 1 |
| 胃腸障害 | 420 | 胃潰瘍 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 出血性胃潰瘍 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 胃炎 | 2 | 0 | 2 |
| 胃腸障害 | 420 | びらん性胃炎 | 2 | 2 | 0 |
| 胃腸障害 | 420 | 胃腸障害 | 2 | 2 | 0 |
| 胃腸障害 | 420 | 胃腸出血 | 34 | 34 | 0 |
| 胃腸障害 | 420 | 胃腸粘膜障害 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 消化管浮腫 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 消化器痛 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 胃食道逆流性疾患 | 7 | 0 | 7 |
| 胃腸障害 | 420 | 歯肉出血 | 6 | 3 | 3 |
| 胃腸障害 | 420 | 舌炎 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 舌痛 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 吐血 | 11 | 10 | 1 |
| 胃腸障害 | 420 | 血便排泄 | 10 | 8 | 2 |
| 胃腸障害 | 420 | 痔核 | 3 | 0 | 3 |
| 胃腸障害 | 420 | 裂孔ヘルニア | 2 | 1 | 1 |
| 胃腸障害 | 420 | イレウス | 2 | 2 | 0 |
| 胃腸障害 | 420 | 胃排出不全 | 3 | 0 | 3 |
| 胃腸障害 | 420 | 鼠径ヘルニア | 1 | 0 | 1 |
| 胃腸障害 | 420 | 腸出血 | 3 | 3 | 0 |
| 胃腸障害 | 420 | 腸管虚血 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 腸閉塞 | 4 | 4 | 0 |
| 胃腸障害 | 420 | 腸管穿孔 | 2 | 2 | 0 |
| 胃腸障害 | 420 | 腸管ポリープ | 1 | 0 | 1 |
| 胃腸障害 | 420 | 腸絨毛萎縮 | 1 | 0 | 1 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 胃腸障害 | 420 | 腹腔内血腫 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 腹腔内出血 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 過敏性腸症候群 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 大腸潰瘍 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 大腸穿孔 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 口唇水疱 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 口唇出血 | 2 | 0 | 2 |
| 胃腸障害 | 420 | 口唇腫脹 | 3 | 2 | 1 |
| 胃腸障害 | 420 | 限局性腹腔内液貯留 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 下部消化管出血 | 2 | 2 | 0 |
| 胃腸障害 | 420 | マロリー・ワイス症候群 | 1 | 1 | 0 |
| 胃腸障害 | 420 | メレナ | 3 | 0 | 3 |
| 胃腸障害 | 420 | 口腔内出血 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 口腔内潰瘍形成 | 2 | 1 | 1 |
| 胃腸障害 | 420 | 悪心 | 76 | 25 | 51 |
| 胃腸障害 | 420 | 胃閉塞 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 嚥下痛 | 3 | 2 | 1 |
| 胃腸障害 | 420 | 食道出血 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 食道破裂 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 食道潰瘍 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 食道炎 | 2 | 2 | 0 |
| 胃腸障害 | 420 | 口腔内不快感 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 口腔粘膜水疱形成 | 3 | 0 | 3 |
| 胃腸障害 | 420 | 口腔内痛 | 4 | 2 | 2 |
| 胃腸障害 | 420 | 膵炎 | 4 | 4 | 0 |
| 胃腸障害 | 420 | 急性膵炎 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 腹膜出血 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 反応性胃障害 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 直腸出血 | 11 | 7 | 4 |
| 胃腸障害 | 420 | 直腸ポリープ | 1 | 0 | 1 |
| 胃腸障害 | 420 | 直腸潰瘍 | 2 | 1 | 1 |
| 胃腸障害 | 420 | 後腹膜出血 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 小腸出血 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 小腸閉塞 | 6 | 6 | 0 |
| 胃腸障害 | 420 | 胃腫瘤 | 1 | 1 | 0 |
| 胃腸障害 | 420 | 口内炎 | 33 | 12 | 21 |
| 胃腸障害 | 420 | 舌腫脹 | 2 | 2 | 0 |
| 胃腸障害 | 420 | 舌乾燥 | 1 | 0 | 1 |
| 胃腸障害 | 420 | 舌出血 | 2 | 2 | 0 |
| 胃腸障害 | 420 | 歯の障害 | 2 | 0 | 2 |
| 胃腸障害 | 420 | 上部消化管出血 | 6 | 6 | 0 |
| 胃腸障害 | 420 | 嘔吐 | 46 | 20 | 26 |
| 一般・全身障害および投与部位の状態 | 815 | 歩行不能 | 5 | 1 | 4 |
| 一般・全身障害および投与部位の状態 | 815 | 医薬品副作用 | 2 | 2 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 有害事象 | 9 | 7 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 無力症 | 105 | 33 | 72 |
| 一般・全身障害および投与部位の状態 | 815 | 突出痛 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 心臓死 | 2 | 2 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 胸部不快感 | 6 | 3 | 3 |
| 一般・全身障害および投与部位の状態 | 815 | 胸痛 | 27 | 17 | 10 |
| 一般・全身障害および投与部位の状態 | 815 | 悪寒 | 27 | 8 | 19 |
| 一般・全身障害および投与部位の状態 | 815 | 状態悪化 | 3 | 3 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 死亡 | 180 | 180 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 活動性低下 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 疾患進行 | 191 | 167 | 24 |

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|---|---|---|---|---|---|
| 一般・全身障害および投与部位の状態 | 815 | 薬効低下 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 薬効不十分 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 薬効欠如 | 16 | 3 | 13 |
| 一般・全身障害および投与部位の状態 | 815 | 薬物相互作用 | 12 | 6 | 6 |
| 一般・全身障害および投与部位の状態 | 815 | 薬物不耐性 | 2 | 0 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 薬物耐性 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 薬物耐性低下 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 早期満腹 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 顔面浮腫 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 疲労 | 113 | 10 | 103 |
| 一般・全身障害および投与部位の状態 | 815 | 異常感 | 7 | 0 | 7 |
| 一般・全身障害および投与部位の状態 | 815 | 冷感 | 2 | 0 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 熱感 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | びくびく感 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 歩行障害 | 14 | 2 | 12 |
| 一般・全身障害および投与部位の状態 | 815 | 全身健康状態低下 | 7 | 4 | 3 |
| 一般・全身障害および投与部位の状態 | 815 | 全身性浮腫 | 6 | 2 | 4 |
| 一般・全身障害および投与部位の状態 | 815 | 肉芽腫 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | ヘルニア | 4 | 2 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 高熱 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 低体温 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 不明確な障害 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 治癒不良 | 3 | 1 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 炎症 | 2 | 1 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | インフルエンザ様疾患 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 局所腫脹 | 3 | 1 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 倦怠感 | 34 | 13 | 21 |
| 一般・全身障害および投与部位の状態 | 815 | 腫瘤 | 2 | 1 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 粘膜出血 | 5 | 3 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 粘膜充血 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 粘膜の炎症 | 8 | 4 | 4 |
| 一般・全身障害および投与部位の状態 | 815 | 粘膜潰瘍 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 多臓器不全 | 8 | 8 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 有害事象なし | 5 | 5 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 小結節 | 2 | 0 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 非心臓性胸痛 | 5 | 2 | 3 |
| 一般・全身障害および投与部位の状態 | 815 | 非特異反応 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 閉塞 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 浮腫 | 8 | 3 | 5 |
| 一般・全身障害および投与部位の状態 | 815 | 末梢性浮腫 | 34 | 5 | 29 |
| 一般・全身障害および投与部位の状態 | 815 | 疼痛 | 16 | 7 | 9 |
| 一般・全身障害および投与部位の状態 | 815 | 活動状態低下 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 末梢腫脹 | 29 | 6 | 23 |
| 一般・全身障害および投与部位の状態 | 815 | 気腫 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | ポリープ | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 増強的薬物相互作用 | 2 | 0 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 製品品質の問題 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 発熱 | 123 | 77 | 46 |
| 一般・全身障害および投与部位の状態 | 815 | 不活発 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 心突然死 | 1 | 1 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 突然死 | 7 | 7 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 腫脹 | 9 | 3 | 6 |
| 一般・全身障害および投与部位の状態 | 815 | 全身性炎症反応症候群 | 6 | 5 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 終末期状態 | 2 | 2 | 0 |
| 一般・全身障害および投与部位の状態 | 815 | 治療効果減弱 | 1 | 0 | 1 |

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|---|---|---|---|---|---|
| 一般・全身障害および投与部位の状態 | 815 | 予想外の治療反応 | 3 | 1 | 2 |
| 一般・全身障害および投与部位の状態 | 815 | 口渇 | 1 | 0 | 1 |
| 一般・全身障害および投与部位の状態 | 815 | 潰瘍 | 1 | 0 | 1 |
| 肝胆道系障害 | 38 | 急性肝不全 | 3 | 3 | 0 |
| 肝胆道系障害 | 38 | 胆管閉塞 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 胆管結石 | 2 | 2 | 0 |
| 肝胆道系障害 | 38 | 胆道仙痛 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 胆嚢炎 | 2 | 2 | 0 |
| 肝胆道系障害 | 38 | 急性胆嚢炎 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 胆石症 | 4 | 4 | 0 |
| 肝胆道系障害 | 38 | 胆汁うっ滞 | 4 | 4 | 0 |
| 肝胆道系障害 | 38 | 薬物性肝障害 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 胆嚢障害 | 2 | 2 | 0 |
| 肝胆道系障害 | 38 | 肝不全 | 3 | 3 | 0 |
| 肝胆道系障害 | 38 | 肝機能異常 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 肝血腫 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 肝病変 | 2 | 0 | 2 |
| 肝胆道系障害 | 38 | 肝壊死 | 2 | 2 | 0 |
| 肝胆道系障害 | 38 | 肝炎 | 2 | 2 | 0 |
| 肝胆道系障害 | 38 | 肝細胞損傷 | 2 | 2 | 0 |
| 肝胆道系障害 | 38 | 肝腫大 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 肝腎症候群 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 肝脾腫大 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 肝毒性 | 1 | 1 | 0 |
| 肝胆道系障害 | 38 | 高ビリルビン血症 | 1 | 0 | 1 |
| 肝胆道系障害 | 38 | 黄疸 | 3 | 2 | 1 |
| 肝胆道系障害 | 38 | 肝障害 | 1 | 0 | 1 |
| 肝胆道系障害 | 38 | 門脈圧亢進症 | 1 | 1 | 0 |
| 免疫系障害 | 21 | アナフィラキシーショック | 1 | 1 | 0 |
| 免疫系障害 | 21 | 免疫応答低下 | 1 | 1 | 0 |
| 免疫系障害 | 21 | 薬物過敏症 | 1 | 1 | 0 |
| 免疫系障害 | 21 | 移植片対宿主病 | 3 | 2 | 1 |
| 免疫系障害 | 21 | 肝移植片対宿主病 | 1 | 1 | 0 |
| 免疫系障害 | 21 | 皮膚移植片対宿主病 | 1 | 1 | 0 |
| 免疫系障害 | 21 | 過敏症 | 5 | 4 | 1 |
| 免疫系障害 | 21 | 低ｙグロブリン血症 | 4 | 0 | 4 |
| 免疫系障害 | 21 | 分類不能型免疫不全症 | 1 | 0 | 1 |
| 免疫系障害 | 21 | 免疫抑制 | 2 | 1 | 1 |
| 免疫系障害 | 21 | サルコイドーシス | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 膿瘍 | 4 | 3 | 1 |
| 感染症および寄生虫症 | 687 | 四肢膿瘍 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 頚部膿瘍 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 後天性免疫不全症候群 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 口角口唇炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 肛門直腸蜂巣炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 虫垂炎 | 4 | 4 | 0 |
| 感染症および寄生虫症 | 687 | 感染性関節炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | アスペルギルス感染 | 8 | 7 | 1 |
| 感染症および寄生虫症 | 687 | 異型肺炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | バチルス性菌血症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 菌血症 | 4 | 4 | 0 |
| 感染症および寄生虫症 | 687 | 細菌性下痢 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 細菌感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 細菌性敗血症 | 5 | 5 | 0 |
| 感染症および寄生虫症 | 687 | 脳膿瘍 | 8 | 8 | 0 |

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|---|---|---|---|---|---|
| 感染症および寄生虫症 | 687 | 細気管支炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 気管支炎 | 16 | 10 | 6 |
| 感染症および寄生虫症 | 687 | 気管支肺アスペルギルス症 | 8 | 8 | 0 |
| 感染症および寄生虫症 | 687 | カンジダ感染 | 6 | 0 | 6 |
| 感染症および寄生虫症 | 687 | 心臓弁疣贅 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | カテーテル留置部位蜂巣炎 | 2 | 1 | 1 |
| 感染症および寄生虫症 | 687 | カテーテル留置部位感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 蜂巣炎 | 27 | 23 | 4 |
| 感染症および寄生虫症 | 687 | ブドウ球菌性蜂巣炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 脳アスペルギルス症 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 脳トキソプラズマ症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 感染性胆嚢炎 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 慢性副鼻腔炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | クロストリジウム性菌血症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | クロストリジウム・ディフィシレ大腸炎 | 8 | 7 | 1 |
| 感染症および寄生虫症 | 687 | クロストリジウム・ディフィシレ感染 | 14 | 12 | 2 |
| 感染症および寄生虫症 | 687 | 結腸膿瘍 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 結膜炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | コロナウイルス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | クリプトコッカス症 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 膀胱炎 | 9 | 6 | 3 |
| 感染症および寄生虫症 | 687 | 大腸菌性膀胱炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | クレブシエラ膀胱炎 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | サイトメガロウイルス性大腸炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | サイトメガロウイルス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 感染性皮膚炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 医療機器関連感染 | 3 | 2 | 1 |
| 感染症および寄生虫症 | 687 | 播種性クリプトコッカス症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 播種性結核 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 憩室炎 | 4 | 3 | 1 |
| 感染症および寄生虫症 | 687 | 耳感染 | 3 | 0 | 3 |
| 感染症および寄生虫症 | 687 | 蓄膿 | 3 | 2 | 1 |
| 感染症および寄生虫症 | 687 | 脳炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | サイトメガロウイルス性脳炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 心内膜炎 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | エンテロバクター感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 腸球菌感染 | 4 | 2 | 2 |
| 感染症および寄生虫症 | 687 | エプスタイン・バーウイルス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 丹毒 | 3 | 3 | 0 |
| 感染症および寄生虫症 | 687 | 大腸菌性菌血症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 大腸菌性尿路感染 | 6 | 3 | 3 |
| 感染症および寄生虫症 | 687 | 眼感染 | 2 | 0 | 2 |
| 感染症および寄生虫症 | 687 | 真菌性眼感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | ブドウ球菌性眼感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | ウイルス性眼感染 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 真菌血症 | 2 | 1 | 1 |
| 感染症および寄生虫症 | 687 | 真菌感染 | 10 | 7 | 3 |
| 感染症および寄生虫症 | 687 | 真菌性食道炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 真菌性敗血症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 皮膚真菌感染 | 3 | 1 | 2 |

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|---|---|---|---|---|---|
| 感染症および寄生虫症 | 687 | せつ | 3 | 2 | 1 |
| 感染症および寄生虫症 | 687 | 胃感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 胃腸炎 | 3 | 3 | 0 |
| 感染症および寄生虫症 | 687 | クロストリジウム菌性胃腸炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | ウイルス性胃腸炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 消化管感染 | 3 | 1 | 2 |
| 感染症および寄生虫症 | 687 | ウイルス性消化管感染 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 肛径部膿瘍 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | Ｈ１Ｎ１インフルエンザ | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | ヘモフィルス性菌血症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | Ｂ型肝炎 | 4 | 4 | 0 |
| 感染症および寄生虫症 | 687 | 単純ヘルペス | 3 | 1 | 2 |
| 感染症および寄生虫症 | 687 | ヘルペスウイルス感染 | 3 | 2 | 1 |
| 感染症および寄生虫症 | 687 | 帯状疱疹 | 14 | 8 | 6 |
| 感染症および寄生虫症 | 687 | 麦粒腫 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 咬傷感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 感染性皮膚嚢腫 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 感染 | 40 | 31 | 9 |
| 感染症および寄生虫症 | 687 | 感染性胸水 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | インフルエンザ | 13 | 12 | 1 |
| 感染症および寄生虫症 | 687 | ＪＣウイルス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 腎感染 | 7 | 5 | 2 |
| 感染症および寄生虫症 | 687 | クレブシエラ性敗血症 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 肝膿瘍 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 限局性感染 | 9 | 8 | 1 |
| 感染症および寄生虫症 | 687 | 下気道感染 | 7 | 6 | 1 |
| 感染症および寄生虫症 | 687 | 細菌性下気道感染 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 肺感染 | 11 | 8 | 3 |
| 感染症および寄生虫症 | 687 | ライム病 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | リンパ節感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | リンパ管炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 乳様突起炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 髄膜炎 | 4 | 4 | 0 |
| 感染症および寄生虫症 | 687 | 無菌性髄膜炎 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | アスペルギルス性髄膜炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 細菌性髄膜炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | クリプトコッカス性髄膜炎 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | ブドウ球菌性髄膜炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 微胞子虫類感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 伝染性軟属腫 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | ムコール症 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | マイコバクテリウム・アビウムコンプレックス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 脊髄炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 鼻膿瘍 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 鼻咽頭炎 | 8 | 1 | 7 |
| 感染症および寄生虫症 | 687 | 好中球減少性敗血症 | 4 | 4 | 0 |
| 感染症および寄生虫症 | 687 | ノカルジア症 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 食道カンジダ症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 爪真菌症 | 2 | 0 | 2 |
| 感染症および寄生虫症 | 687 | 卵巣炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 眼帯状疱疹 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 口腔カンジダ症 | 3 | 0 | 3 |
| 感染症および寄生虫症 | 687 | 口腔ヘルペス | 5 | 2 | 3 |

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|---|---|---|---|---|---|
| 感染症および寄生虫症 | 687 | 骨髄炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 外耳炎 | 2 | 0 | 2 |
| 感染症および寄生虫症 | 687 | 中耳炎 | 2 | 1 | 1 |
| 感染症および寄生虫症 | 687 | 傍脊椎膿瘍 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | パレコウイルス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 爪囲炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 耐性病原体 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 真菌性心膜炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 直腸周囲膿瘍 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 腹膜炎 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 咽頭炎 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | レンサ球菌性咽頭炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 肺炎球菌性敗血症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | ニューモシスチス・イロベチイ肺炎 | 5 | 5 | 0 |
| 感染症および寄生虫症 | 687 | 肺炎 | 235 | 222 | 13 |
| 感染症および寄生虫症 | 687 | 細菌性肺炎 | 4 | 3 | 1 |
| 感染症および寄生虫症 | 687 | クリプトコッカス性肺炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 真菌性肺炎 | 5 | 5 | 0 |
| 感染症および寄生虫症 | 687 | ヘモフィルス性肺炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | レジオネラ菌性肺炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | マイコプラズマ性肺炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 肺炎球菌性肺炎 | 4 | 4 | 0 |
| 感染症および寄生虫症 | 687 | シュードモナス菌性肺炎 | 4 | 4 | 0 |
| 感染症および寄生虫症 | 687 | ＲＳウイルス肺炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | ブドウ球菌性肺炎 | 4 | 4 | 0 |
| 感染症および寄生虫症 | 687 | ウイルス性肺炎 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 処置後蜂巣炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 処置後感染 | 3 | 2 | 1 |
| 感染症および寄生虫症 | 687 | 進行性多巣性白質脳症 | 3 | 3 | 0 |
| 感染症および寄生虫症 | 687 | 前立腺感染 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | プロテウス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | シュードモナス性敗血症 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | シュードモナス感染 | 5 | 3 | 2 |
| 感染症および寄生虫症 | 687 | 肺結核 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 膿尿 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 膿疱性皮疹 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 腎膿瘍 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | ＲＳウイルス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 気道感染 | 9 | 6 | 3 |
| 感染症および寄生虫症 | 687 | ウイルス性気道感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 鼻炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | サルモネラ症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 敗血症 | 76 | 74 | 2 |
| 感染症および寄生虫症 | 687 | レンサ球菌性化膿性関節炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 敗血症性ショック | 26 | 26 | 0 |
| 感染症および寄生虫症 | 687 | 唾液腺炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 副鼻腔炎 | 13 | 4 | 9 |
| 感染症および寄生虫症 | 687 | 真菌性副鼻腔炎 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 皮膚感染 | 5 | 1 | 4 |
| 感染症および寄生虫症 | 687 | ブドウ球菌性菌血症 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | ブドウ球菌感染 | 12 | 9 | 3 |
| 感染症および寄生虫症 | 687 | ブドウ球菌性敗血症 | 5 | 5 | 0 |
| 感染症および寄生虫症 | 687 | ブドウ球菌皮膚感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | レンサ球菌性菌血症 | 1 | 1 | 0 |

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|---|---|---|---|---|---|
| 感染症および寄生虫症 | 687 | レンサ球菌感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 皮下組織膿瘍 | 3 | 3 | 0 |
| 感染症および寄生虫症 | 687 | 発汗熱 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 全身性カンジダ | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 全身性感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 全身性真菌症 | 4 | 4 | 0 |
| 感染症および寄生虫症 | 687 | 歯膿瘍 | 3 | 0 | 3 |
| 感染症および寄生虫症 | 687 | トキソプラズマ症 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 上気道感染 | 11 | 3 | 8 |
| 感染症および寄生虫症 | 687 | 尿路感染 | 50 | 37 | 13 |
| 感染症および寄生虫症 | 687 | シュードモナス性尿路感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 尿路性敗血症 | 2 | 2 | 0 |
| 感染症および寄生虫症 | 687 | 水痘帯状疱疹ウイルス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | ウイルス感染 | 4 | 3 | 1 |
| 感染症および寄生虫症 | 687 | ウイルス性咽頭炎 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | 皮膚ウイルス感染 | 1 | 1 | 0 |
| 感染症および寄生虫症 | 687 | 外陰部腟カンジダ症 | 1 | 0 | 1 |
| 感染症および寄生虫症 | 687 | ブドウ球菌性創感染 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 偶発的過量投与 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 術後貧血 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 足関節部骨折 | 2 | 2 | 0 |
| 傷害、中毒および処置合併症 | 405 | 節足動物咬傷 | 3 | 3 | 0 |
| 傷害、中毒および処置合併症 | 405 | 節足動物刺傷 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 挫傷 | 71 | 6 | 65 |
| 傷害、中毒および処置合併症 | 405 | 角膜擦過傷 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 投薬欠落 | 7 | 0 | 7 |
| 傷害、中毒および処置合併症 | 405 | 処方過誤 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 硬膜外血腫 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 眼挫傷 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 転倒 | 79 | 21 | 58 |
| 傷害、中毒および処置合併症 | 405 | 大腿骨頚部骨折 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 大腿骨骨折 | 4 | 4 | 0 |
| 傷害、中毒および処置合併症 | 405 | 体内異物 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 頭部損傷 | 5 | 2 | 3 |
| 傷害、中毒および処置合併症 | 405 | 股関節部骨折 | 14 | 14 | 0 |
| 傷害、中毒および処置合併症 | 405 | 上腕骨骨折 | 2 | 2 | 0 |
| 傷害、中毒および処置合併症 | 405 | 不適切な薬剤投与計画 | 21 | 0 | 21 |
| 傷害、中毒および処置合併症 | 405 | 誤った投与量の投与 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 誤用量投与 | 95 | 0 | 95 |
| 傷害、中毒および処置合併症 | 405 | 誤った投与経路 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 注入に伴う反応 | 2 | 1 | 1 |
| 傷害、中毒および処置合併症 | 405 | 角膜損傷 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 関節損傷 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 裂傷 | 3 | 2 | 1 |
| 傷害、中毒および処置合併症 | 405 | 靭帯捻挫 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 口唇損傷 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 腰椎骨折 | 2 | 2 | 0 |
| 傷害、中毒および処置合併症 | 405 | 肉離れ | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 神経損傷 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 適応外使用 | 63 | 3 | 60 |
| 傷害、中毒および処置合併症 | 405 | 過量投与 | 4 | 1 | 3 |
| 傷害、中毒および処置合併症 | 405 | 膝蓋骨骨折 | 2 | 1 | 1 |
| 傷害、中毒および処置合併症 | 405 | 骨盤骨折 | 3 | 2 | 1 |
| 傷害、中毒および処置合併症 | 405 | 眼窩周囲出血 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 化学性肺炎 | 1 | 1 | 0 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 傷害、中毒および処置合併症 | 405 | 処置後分泌物 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 処置後血腫 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 処置後出血 | 6 | 4 | 2 |
| 傷害、中毒および処置合併症 | 405 | 処置後肺塞栓症 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 外傷後疼痛 | 3 | 0 | 3 |
| 傷害、中毒および処置合併症 | 405 | 術後癒着 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 術後イレウス | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 処方に基づく過量投与 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 処方に基づく過少量投与 | 13 | 0 | 13 |
| 傷害、中毒および処置合併症 | 405 | 処置による出血 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 製品表示の混同 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 製品使用の問題 | 7 | 0 | 7 |
| 傷害、中毒および処置合併症 | 405 | 肋骨骨折 | 3 | 0 | 3 |
| 傷害、中毒および処置合併症 | 405 | 交通事故 | 2 | 1 | 1 |
| 傷害、中毒および処置合併症 | 405 | 肩甲骨骨折 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 瘢痕 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 皮膚擦過傷 | 3 | 0 | 3 |
| 傷害、中毒および処置合併症 | 405 | 脊椎圧迫骨折 | 2 | 2 | 0 |
| 傷害、中毒および処置合併症 | 405 | 脊椎骨折 | 9 | 9 | 0 |
| 傷害、中毒および処置合併症 | 405 | 脾破裂 | 3 | 3 | 0 |
| 傷害、中毒および処置合併症 | 405 | 胸骨骨折 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 皮下血腫 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 硬膜下血腫 | 44 | 44 | 0 |
| 傷害、中毒および処置合併症 | 405 | 硬膜下出血 | 4 | 4 | 0 |
| 傷害、中毒および処置合併症 | 405 | 腱断裂 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 脛骨骨折 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 歯牙破折 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 各種物質毒性 | 3 | 2 | 1 |
| 傷害、中毒および処置合併症 | 405 | 外傷性出血 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 外傷性血胸 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 外傷性頭蓋内出血 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 創傷 | 1 | 1 | 0 |
| 傷害、中毒および処置合併症 | 405 | 創合併症 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 創傷出血 | 1 | 0 | 1 |
| 傷害、中毒および処置合併症 | 405 | 手首関節骨折 | 3 | 2 | 1 |
| 臨床検査 | 378 | アラニンアミノトランスフェラーゼ増加 | 2 | 2 | 0 |
| 臨床検査 | 378 | アンモニア増加 | 2 | 0 | 2 |
| 臨床検査 | 378 | 抗凝固薬濃度治療量以上 | 2 | 0 | 2 |
| 臨床検査 | 378 | アスパラギン酸アミノトランスフェラーゼ増加 | 1 | 0 | 1 |
| 臨床検査 | 378 | 胸腔吸引 | 1 | 1 | 0 |
| 臨床検査 | 378 | 杆状核好中球百分率増加 | 1 | 1 | 0 |
| 臨床検査 | 378 | 芽球細胞数増加 | 1 | 1 | 0 |
| 臨床検査 | 378 | 血中アルカリホスファターゼ増加 | 4 | 2 | 2 |
| 臨床検査 | 378 | 血中ビリルビン異常 | 1 | 1 | 0 |
| 臨床検査 | 378 | 血中ビリルビン増加 | 3 | 2 | 1 |
| 臨床検査 | 378 | 血中カルシウム増加 | 7 | 7 | 0 |
| 臨床検査 | 378 | 血中コレステロール増加 | 1 | 1 | 0 |
| 臨床検査 | 378 | 血球数異常 | 13 | 5 | 8 |
| 臨床検査 | 378 | 血中クレアチニン増加 | 12 | 6 | 6 |
| 臨床検査 | 378 | 血中電解質異常 | 2 | 0 | 2 |
| 臨床検査 | 378 | 血中ブドウ糖減少 | 2 | 0 | 2 |
| 臨床検査 | 378 | 血中ブドウ糖増加 | 3 | 1 | 2 |

| 器官別大分類 | SOC件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 臨床検査 | 378 | 血中免疫グロブリンG減少 | 1 | 0 | 1 |
| 臨床検査 | 378 | 血中乳酸脱水素酵素増加 | 6 | 3 | 3 |
| 臨床検査 | 378 | 血中マグネシウム減少 | 3 | 1 | 2 |
| 臨床検査 | 378 | 血中カリウム減少 | 11 | 6 | 5 |
| 臨床検査 | 378 | 血中カリウム増加 | 8 | 5 | 3 |
| 臨床検査 | 378 | 血圧上昇 | 8 | 4 | 4 |
| 臨床検査 | 378 | 血中ナトリウム減少 | 3 | 2 | 1 |
| 臨床検査 | 378 | 血液検査異常 | 1 | 1 | 0 |
| 臨床検査 | 378 | 血中甲状腺刺激ホルモン増加 | 1 | 0 | 1 |
| 臨床検査 | 378 | 血中尿素増加 | 2 | 0 | 2 |
| 臨床検査 | 378 | 血中尿酸異常 | 1 | 0 | 1 |
| 臨床検査 | 378 | 血中尿酸増加 | 6 | 2 | 4 |
| 臨床検査 | 378 | 尿中血陽性 | 4 | 2 | 2 |
| 臨床検査 | 378 | ボディ・マス・インデックス減少 | 1 | 0 | 1 |
| 臨床検査 | 378 | 呼吸音異常 | 1 | 0 | 1 |
| 臨床検査 | 378 | Ｃ－反応性蛋白減少 | 1 | 0 | 1 |
| 臨床検査 | 378 | Ｃ－反応性蛋白増加 | 2 | 1 | 1 |
| 臨床検査 | 378 | 二酸化炭素増加 | 1 | 0 | 1 |
| 臨床検査 | 378 | 心雑音 | 1 | 0 | 1 |
| 臨床検査 | 378 | 心カテーテル検査 | 1 | 1 | 0 |
| 臨床検査 | 378 | ＣＤ４リンパ球減少 | 1 | 0 | 1 |
| 臨床検査 | 378 | クロストリジウム検査陽性 | 1 | 0 | 1 |
| 臨床検査 | 378 | コクサッキーウイルス検査陽性 | 1 | 0 | 1 |
| 臨床検査 | 378 | 駆出率異常 | 1 | 1 | 0 |
| 臨床検査 | 378 | 駆出率減少 | 5 | 5 | 0 |
| 臨床検査 | 378 | 心電図ＱＴ延長 | 3 | 3 | 0 |
| 臨床検査 | 378 | γ－グルタミルトランスフェラーゼ増加 | 2 | 2 | 0 |
| 臨床検査 | 378 | 糸球体濾過率減少 | 1 | 0 | 1 |
| 臨床検査 | 378 | 顆粒球数減少 | 1 | 0 | 1 |
| 臨床検査 | 378 | 顆粒球異常 | 1 | 1 | 0 |
| 臨床検査 | 378 | ヘマトクリット減少 | 5 | 0 | 5 |
| 臨床検査 | 378 | ヘモグロビン減少 | 40 | 13 | 27 |
| 臨床検査 | 378 | 心拍数異常 | 1 | 1 | 0 |
| 臨床検査 | 378 | 心拍数減少 | 6 | 3 | 3 |
| 臨床検査 | 378 | 心拍数増加 | 8 | 4 | 4 |
| 臨床検査 | 378 | 心拍数不整 | 4 | 4 | 0 |
| 臨床検査 | 378 | 肝酵素上昇 | 6 | 2 | 4 |
| 臨床検査 | 378 | 免疫グロブリン減少 | 1 | 0 | 1 |
| 臨床検査 | 378 | 国際標準比異常 | 1 | 0 | 1 |
| 臨床検査 | 378 | 国際標準比増加 | 5 | 3 | 2 |
| 臨床検査 | 378 | 臨床検査異常 | 4 | 1 | 3 |
| 臨床検査 | 378 | 肝機能検査異常 | 8 | 4 | 4 |
| 臨床検査 | 378 | リンパ節触知 | 1 | 0 | 1 |
| 臨床検査 | 378 | リンパ球数減少 | 1 | 1 | 0 |
| 臨床検査 | 378 | リンパ球数増加 | 8 | 2 | 6 |
| 臨床検査 | 378 | 好中球数減少 | 11 | 2 | 9 |
| 臨床検査 | 378 | 好中球数増加 | 1 | 1 | 0 |
| 臨床検査 | 378 | 栄養状態異常 | 1 | 0 | 1 |
| 臨床検査 | 378 | 酸素飽和度異常 | 1 | 1 | 0 |
| 臨床検査 | 378 | 酸素飽和度低下 | 2 | 1 | 1 |
| 臨床検査 | 378 | 膵酵素増加 | 1 | 0 | 1 |

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|---|---|---|---|---|---|
| 臨床検査 | 378 | 血小板数異常 | 1 | 0 | 1 |
| 臨床検査 | 378 | 血小板数減少 | 61 | 17 | 44 |
| 臨床検査 | 378 | 血小板数増加 | 1 | 0 | 1 |
| 臨床検査 | 378 | 血小板機能検査異常 | 1 | 0 | 1 |
| 臨床検査 | 378 | 前癌細胞陽性 | 1 | 0 | 1 |
| 臨床検査 | 378 | プロカルシトニン増加 | 1 | 1 | 0 |
| 臨床検査 | 378 | 総蛋白異常 | 1 | 1 | 0 |
| 臨床検査 | 378 | 総蛋白減少 | 3 | 1 | 2 |
| 臨床検査 | 378 | プロトロンビン時間延長 | 1 | 0 | 1 |
| 臨床検査 | 378 | 肺機能検査値低下 | 1 | 1 | 0 |
| 臨床検査 | 378 | 赤血球数減少 | 6 | 4 | 2 |
| 臨床検査 | 378 | 洞調律 | 1 | 1 | 0 |
| 臨床検査 | 378 | 喀痰培養陽性 | 1 | 0 | 1 |
| 臨床検査 | 378 | ブドウ球菌検査陽性 | 2 | 1 | 1 |
| 臨床検査 | 378 | トランスアミナーゼ上昇 | 1 | 0 | 1 |
| 臨床検査 | 378 | トロポニン増加 | 4 | 1 | 3 |
| 臨床検査 | 378 | ビタミンD減少 | 1 | 0 | 1 |
| 臨床検査 | 378 | 体重減少 | 44 | 3 | 41 |
| 臨床検査 | 378 | 体重増加 | 13 | 0 | 13 |
| 臨床検査 | 378 | 白血球数異常 | 1 | 0 | 1 |
| 臨床検査 | 378 | 白血球数減少 | 32 | 12 | 20 |
| 臨床検査 | 378 | 白血球数増加 | 61 | 11 | 50 |
| 臨床検査 | 378 | 尿中白血球 | 1 | 0 | 1 |
| 代謝および栄養障害 | 187 | 悪液質 | 4 | 2 | 2 |
| 代謝および栄養障害 | 187 | 食欲減退 | 49 | 6 | 43 |
| 代謝および栄養障害 | 187 | 脱水 | 46 | 30 | 16 |
| 代謝および栄養障害 | 187 | 糖尿病 | 1 | 1 | 0 |
| 代謝および栄養障害 | 187 | 糖尿病合併症 | 1 | 1 | 0 |
| 代謝および栄養障害 | 187 | 糖尿病性ケトアシドーシス | 1 | 1 | 0 |
| 代謝および栄養障害 | 187 | 拒食 | 1 | 0 | 1 |
| 代謝および栄養障害 | 187 | 電解質失調 | 7 | 4 | 3 |
| 代謝および栄養障害 | 187 | 成長障害 | 2 | 0 | 2 |
| 代謝および栄養障害 | 187 | 水分過負荷 | 3 | 1 | 2 |
| 代謝および栄養障害 | 187 | 体液貯留 | 9 | 5 | 4 |
| 代謝および栄養障害 | 187 | 痛風 | 4 | 1 | 3 |
| 代謝および栄養障害 | 187 | 高カルシウム血症 | 11 | 9 | 2 |
| 代謝および栄養障害 | 187 | 高血糖 | 7 | 0 | 7 |
| 代謝および栄養障害 | 187 | 高カリウム血症 | 2 | 0 | 2 |
| 代謝および栄養障害 | 187 | 高脂血症 | 3 | 0 | 3 |
| 代謝および栄養障害 | 187 | 高ナトリウム血症 | 1 | 0 | 1 |
| 代謝および栄養障害 | 187 | 低アルブミン血症 | 1 | 0 | 1 |
| 代謝および栄養障害 | 187 | 低カルシウム血症 | 5 | 1 | 4 |
| 代謝および栄養障害 | 187 | 低クロール血症 | 1 | 1 | 0 |
| 代謝および栄養障害 | 187 | 低血糖 | 2 | 1 | 1 |
| 代謝および栄養障害 | 187 | 低カリウム血症 | 11 | 3 | 8 |
| 代謝および栄養障害 | 187 | 低マグネシウム血症 | 6 | 1 | 5 |
| 代謝および栄養障害 | 187 | 低ナトリウム血症 | 12 | 4 | 8 |
| 代謝および栄養障害 | 187 | 低リン酸血症 | 2 | 1 | 1 |
| 代謝および栄養障害 | 187 | 鉄過剰 | 2 | 0 | 2 |
| 代謝および栄養障害 | 187 | 乳酸アシドーシス | 6 | 5 | 1 |
| 代謝および栄養障害 | 187 | 栄養障害 | 8 | 1 | 7 |
| 代謝および栄養障害 | 187 | 代謝性アシドーシス | 3 | 1 | 2 |
| 代謝および栄養障害 | 187 | 代謝障害 | 1 | 1 | 0 |
| 代謝および栄養障害 | 187 | 腫瘍崩壊症候群 | 19 | 19 | 0 |
| 代謝および栄養障害 | 187 | ２型糖尿病 | 2 | 1 | 1 |

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|---|---|---|---|---|---|
| 代謝および栄養障害 | 187 | 体重変動 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 関節痛 | 57 | 14 | 43 |
| 筋骨格系および結合組織障害 | 184 | 関節炎 | 4 | 3 | 1 |
| 筋骨格系および結合組織障害 | 184 | 関節障害 | 2 | 1 | 1 |
| 筋骨格系および結合組織障害 | 184 | 背部痛 | 25 | 8 | 17 |
| 筋骨格系および結合組織障害 | 184 | 骨障害 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 骨病変 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 骨痛 | 10 | 4 | 6 |
| 筋骨格系および結合組織障害 | 184 | 滑液包炎 | 2 | 1 | 1 |
| 筋骨格系および結合組織障害 | 184 | 頚部脊柱管狭窄症 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 軟骨炎 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | ピロリン酸カルシウム結晶性軟骨石灰化症 | 2 | 0 | 2 |
| 筋骨格系および結合組織障害 | 184 | 瘻孔 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 側腹部痛 | 2 | 0 | 2 |
| 筋骨格系および結合組織障害 | 184 | 出血性関節症 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 椎間板圧迫 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 椎間板突出 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 関節滲出液 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 関節ロック | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 関節硬直 | 2 | 0 | 2 |
| 筋骨格系および結合組織障害 | 184 | 関節腫脹 | 9 | 0 | 9 |
| 筋骨格系および結合組織障害 | 184 | 運動性低下 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 筋萎縮 | 2 | 0 | 2 |
| 筋骨格系および結合組織障害 | 184 | 筋障害 | 2 | 0 | 2 |
| 筋骨格系および結合組織障害 | 184 | 筋肉内出血 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 筋痙縮 | 24 | 5 | 19 |
| 筋骨格系および結合組織障害 | 184 | 筋攣縮 | 2 | 1 | 1 |
| 筋骨格系および結合組織障害 | 184 | 筋力低下 | 10 | 0 | 10 |
| 筋骨格系および結合組織障害 | 184 | 筋骨格系胸痛 | 2 | 1 | 1 |
| 筋骨格系および結合組織障害 | 184 | 筋骨格不快感 | 3 | 2 | 1 |
| 筋骨格系および結合組織障害 | 184 | 筋骨格痛 | 12 | 3 | 9 |
| 筋骨格系および結合組織障害 | 184 | 筋骨格硬直 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 筋肉痛 | 24 | 4 | 20 |
| 筋骨格系および結合組織障害 | 184 | ミオパチー | 2 | 1 | 1 |
| 筋骨格系および結合組織障害 | 184 | 筋炎 | 2 | 2 | 0 |
| 筋骨格系および結合組織障害 | 184 | 頚部痛 | 3 | 1 | 2 |
| 筋骨格系および結合組織障害 | 184 | 変形性関節症 | 2 | 2 | 0 |
| 筋骨格系および結合組織障害 | 184 | 骨溶解 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 骨壊死 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 骨減少症 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 骨粗鬆症性骨折 | 1 | 1 | 0 |
| 筋骨格系および結合組織障害 | 184 | 四肢痛 | 14 | 3 | 11 |
| 筋骨格系および結合組織障害 | 184 | 顎痛 | 3 | 2 | 1 |
| 筋骨格系および結合組織障害 | 184 | 足底筋膜炎 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 横紋筋融解症 | 3 | 3 | 0 |
| 筋骨格系および結合組織障害 | 184 | 軟部組織腫瘤 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 滑液嚢腫 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 腱鞘炎 | 1 | 0 | 1 |
| 筋骨格系および結合組織障害 | 184 | 弾発指 | 2 | 0 | 2 |
| 筋骨格系および結合組織障害 | 184 | 椎骨病変 | 1 | 0 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 腹部新生物 | 1 | 0 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 急性骨髄性白血病 | 1 | 1 | 0 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 腺癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 結腸腺癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 血管肉腫 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 異型線維黄色腫 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | Ｂ細胞性リンパ腫 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 基底細胞癌 | 14 | 14 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 眼の良性新生物 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 膀胱癌 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 遠隔転移を伴う脳悪性腫瘍 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 脳新生物 | 3 | 3 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 脳の悪性新生物 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 乳癌 | 7 | 7 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | バーキットリンパ腫 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 癌疼痛 | 1 | 0 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 中枢神経系リンパ腫 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 緑色腫 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 慢性リンパ性白血病 | 9 | 9 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 再発慢性リンパ性白血病 | 1 | 0 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 治療抵抗性慢性リンパ性白血病 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 慢性リンパ性白血病急性転化 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 結腸癌 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 遠隔転移を伴う結腸癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 結腸癌第３期 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 消化管間質性腫瘍 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 頭頚部癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 肝癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 遠隔転移を伴う肝癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 肝細胞癌 | 1 | 1 | 0 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 組織球肉腫 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | ホジキン病 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 虹彩黒色腫 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 良性若年性黒色腫 | 1 | 0 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 白血病肝浸潤 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 口唇および口腔内癌 | 3 | 3 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 肺腺癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 遠隔転移を伴う肺癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 肺の悪性新生物 | 5 | 5 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | リンパ腫 | 5 | 5 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | リンパ腫の転化 | 3 | 3 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 悪性黒色腫 | 6 | 6 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 悪性黒色腫第４期 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 悪性新生物進行 | 1 | 0 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 悪性胸水 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | マントル細胞リンパ腫 | 8 | 7 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 再発マントル細胞リンパ腫 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | マントル細胞リンパ腫第４期 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 骨転移 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 中枢神経系転移 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 肺転移 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 腹膜転移 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 胸膜転移 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 転移 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 遠隔転移を伴う悪性黒色腫 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 遠隔転移を伴う扁平上皮癌 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 菌状息肉症 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 骨髄異形成症候群 | 5 | 5 | 0 |

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|---|---|---|---|---|---|
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 新生物 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 悪性新生物 | 5 | 5 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 新生物進行 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 新生物再発 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 皮膚神経内分泌癌 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 非ホジキンリンパ腫 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 食道癌 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 腫瘍随伴症候群 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 前立腺癌 | 3 | 3 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 遠隔転移を伴う前立腺癌 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 再発前立腺癌 | 1 | 0 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 直腸癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 難治性癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 腎癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 腎新生物 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | リクター症候群 | 3 | 3 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 皮膚癌 | 18 | 17 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 遠隔転移を伴う皮膚癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 小細胞肺癌 | 2 | 2 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 脊髄新生物 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 扁平上皮癌 | 19 | 19 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 皮膚有棘細胞癌 | 7 | 7 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | Ｔ細胞性リンパ腫 | 1 | 0 | 1 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 甲状腺癌 | 1 | 1 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 腫瘍フレア | 3 | 3 | 0 |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 188 | 子宮平滑筋腫 | 1 | 0 | 1 |
| 神経系障害 | 309 | 味覚消失 | 1 | 0 | 1 |
| 神経系障害 | 309 | 意識変容状態 | 2 | 1 | 1 |
| 神経系障害 | 309 | 健忘 | 2 | 0 | 2 |
| 神経系障害 | 309 | 失語症 | 6 | 4 | 2 |
| 神経系障害 | 309 | 失声症 | 2 | 1 | 1 |

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|---|---|---|---|---|---|
| 神経系障害 | 309 | 運動失調 | 2 | 1 | 1 |
| 神経系障害 | 309 | 平衡障害 | 10 | 2 | 8 |
| 神経系障害 | 309 | 脳損傷 | 1 | 1 | 0 |
| 神経系障害 | 309 | 脳浮腫 | 1 | 1 | 0 |
| 神経系障害 | 309 | 灼熱感 | 4 | 0 | 4 |
| 神経系障害 | 309 | 頚動脈瘤 | 1 | 1 | 0 |
| 神経系障害 | 309 | 頚動脈狭窄 | 1 | 1 | 0 |
| 神経系障害 | 309 | 手根管症候群 | 2 | 0 | 2 |
| 神経系障害 | 309 | 馬尾症候群 | 1 | 1 | 0 |
| 神経系障害 | 309 | 中枢神経系出血 | 3 | 3 | 0 |
| 神経系障害 | 309 | 小脳微小出血 | 1 | 1 | 0 |
| 神経系障害 | 309 | 大脳動脈閉塞 | 1 | 1 | 0 |
| 神経系障害 | 309 | 脳血腫 | 1 | 1 | 0 |
| 神経系障害 | 309 | 脳出血 | 20 | 20 | 0 |
| 神経系障害 | 309 | 脳梗塞 | 2 | 2 | 0 |
| 神経系障害 | 309 | 脳微小出血 | 1 | 1 | 0 |
| 神経系障害 | 309 | 脳血管発作 | 24 | 24 | 0 |
| 神経系障害 | 309 | 頚髄症 | 1 | 1 | 0 |
| 神経系障害 | 309 | 昏睡 | 2 | 2 | 0 |
| 神経系障害 | 309 | 協調運動異常 | 1 | 0 | 1 |
| 神経系障害 | 309 | 認知症 | 1 | 1 | 0 |
| 神経系障害 | 309 | アルツハイマー型認知症 | 1 | 0 | 1 |
| 神経系障害 | 309 | 意識レベルの低下 | 1 | 0 | 1 |
| 神経系障害 | 309 | 糖尿病性高浸透圧性昏睡 | 1 | 1 | 0 |
| 神経系障害 | 309 | 注意力障害 | 1 | 1 | 0 |
| 神経系障害 | 309 | 浮動性めまい | 42 | 8 | 34 |
| 神経系障害 | 309 | 体位性めまい | 2 | 1 | 1 |
| 神経系障害 | 309 | 構語障害 | 2 | 1 | 1 |
| 神経系障害 | 309 | 味覚異常 | 4 | 0 | 4 |
| 神経系障害 | 309 | ジスキネジア | 1 | 0 | 1 |
| 神経系障害 | 309 | 塞栓性脳卒中 | 1 | 1 | 0 |
| 神経系障害 | 309 | 脳軟化 | 1 | 1 | 0 |
| 神経系障害 | 309 | 脳症 | 12 | 11 | 1 |
| 神経系障害 | 309 | 本態性振戦 | 1 | 0 | 1 |
| 神経系障害 | 309 | 全身性強直性間代性発作 | 1 | 1 | 0 |
| 神経系障害 | 309 | ギラン・バレー症候群 | 2 | 2 | 0 |
| 神経系障害 | 309 | 頭蓋内出血 | 13 | 13 | 0 |
| 神経系障害 | 309 | 出血性卒中 | 2 | 2 | 0 |
| 神経系障害 | 309 | 頭痛 | 30 | 4 | 26 |
| 神経系障害 | 309 | 不全片麻痺 | 3 | 2 | 1 |
| 神経系障害 | 309 | 肝性脳症 | 1 | 1 | 0 |
| 神経系障害 | 309 | 水頭症 | 1 | 1 | 0 |
| 神経系障害 | 309 | 感覚鈍麻 | 7 | 1 | 6 |
| 神経系障害 | 309 | 筋緊張低下 | 1 | 0 | 1 |
| 神経系障害 | 309 | 低酸素性虚血性脳症 | 3 | 2 | 1 |
| 神経系障害 | 309 | 思考散乱 | 2 | 2 | 0 |
| 神経系障害 | 309 | 虚血性脳卒中 | 1 | 1 | 0 |
| 神経系障害 | 309 | ラクナ梗塞 | 1 | 1 | 0 |
| 神経系障害 | 309 | 嗜眠 | 7 | 2 | 5 |
| 神経系障害 | 309 | 白質脳症 | 1 | 1 | 0 |
| 神経系障害 | 309 | 意識消失 | 20 | 18 | 2 |
| 神経系障害 | 309 | 記憶障害 | 4 | 0 | 4 |
| 神経系障害 | 309 | 代謝性脳症 | 3 | 3 | 0 |
| 神経系障害 | 309 | 単麻痺 | 2 | 2 | 0 |
| 神経系障害 | 309 | 運動機能障害 | 1 | 1 | 0 |

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|---|---|---|---|---|---|
| 神経系障害 | 309 | 運動障害 | 1 | 1 | 0 |
| 神経系障害 | 309 | 神経圧迫 | 1 | 0 | 1 |
| 神経系障害 | 309 | 神経痛 | 2 | 2 | 0 |
| 神経系障害 | 309 | 神経学的症状 | 1 | 1 | 0 |
| 神経系障害 | 309 | 末梢性ニューロパチー | 9 | 4 | 5 |
| 神経系障害 | 309 | 視神経炎 | 1 | 1 | 0 |
| 神経系障害 | 309 | 浸透圧性脱髄症候群 | 1 | 1 | 0 |
| 神経系障害 | 309 | 錯感覚 | 3 | 0 | 3 |
| 神経系障害 | 309 | パーキンソン発症 | 1 | 1 | 0 |
| 神経系障害 | 309 | 腓骨神経麻痺 | 1 | 0 | 1 |
| 神経系障害 | 309 | 多発ニューロパチー | 1 | 1 | 0 |
| 神経系障害 | 309 | 睡眠の質低下 | 1 | 0 | 1 |
| 神経系障害 | 309 | ヘルペス後神経痛 | 4 | 1 | 3 |
| 神経系障害 | 309 | 失神寸前の状態 | 2 | 0 | 2 |
| 神経系障害 | 309 | 痙攣発作 | 18 | 18 | 0 |
| 神経系障害 | 309 | 感覚障害 | 1 | 0 | 1 |
| 神経系障害 | 309 | 感覚消失 | 2 | 0 | 2 |
| 神経系障害 | 309 | 傾眠 | 11 | 1 | 10 |
| 神経系障害 | 309 | 会話障害 | 2 | 2 | 0 |
| 神経系障害 | 309 | 脊髄圧迫 | 1 | 1 | 0 |
| 神経系障害 | 309 | 脊髄出血 | 1 | 1 | 0 |
| 神経系障害 | 309 | 脊髄梗塞 | 1 | 1 | 0 |
| 神経系障害 | 309 | くも膜下出血 | 6 | 6 | 0 |
| 神経系障害 | 309 | 失神 | 9 | 8 | 1 |
| 神経系障害 | 309 | 一過性脳虚血発作 | 17 | 17 | 0 |
| 神経系障害 | 309 | 振戦 | 9 | 1 | 8 |
| 神経系障害 | 309 | トンネル状視野 | 1 | 0 | 1 |
| 神経系障害 | 309 | 刺激無反応 | 2 | 2 | 0 |
| 神経系障害 | 309 | 尿毒症性脳症 | 1 | 1 | 0 |
| 神経系障害 | 309 | 第７脳神経麻痺 | 3 | 2 | 1 |
| 精神障害 | 76 | 異常行動 | 1 | 1 | 0 |
| 精神障害 | 76 | 異常な夢 | 2 | 0 | 2 |
| 精神障害 | 76 | 激越 | 2 | 1 | 1 |
| 精神障害 | 76 | 不安 | 11 | 1 | 10 |
| 精神障害 | 76 | 双極性障害 | 1 | 1 | 0 |
| 精神障害 | 76 | 自殺既遂 | 1 | 1 | 0 |
| 精神障害 | 76 | 錯乱状態 | 25 | 11 | 14 |
| 精神障害 | 76 | 譫妄 | 4 | 2 | 2 |
| 精神障害 | 76 | うつ病 | 9 | 4 | 5 |
| 精神障害 | 76 | 失見当識 | 2 | 2 | 0 |
| 精神障害 | 76 | 薬物依存 | 1 | 1 | 0 |
| 精神障害 | 76 | 摂食障害 | 1 | 1 | 0 |
| 精神障害 | 76 | 情動障害 | 1 | 1 | 0 |
| 精神障害 | 76 | 幻覚 | 4 | 0 | 4 |
| 精神障害 | 76 | 幻視 | 1 | 1 | 0 |
| 精神障害 | 76 | 不眠症 | 8 | 0 | 8 |
| 精神障害 | 76 | 大うつ病 | 1 | 1 | 0 |
| 精神障害 | 76 | 精神状態変化 | 7 | 6 | 1 |
| 精神障害 | 76 | 神経過敏 | 2 | 1 | 1 |
| 精神障害 | 76 | 妄想症 | 1 | 1 | 0 |
| 精神障害 | 76 | 睡眠時随伴症 | 1 | 0 | 1 |
| 精神障害 | 76 | 凝視 | 1 | 0 | 1 |
| 精神障害 | 76 | ストレス | 1 | 0 | 1 |
| 精神障害 | 76 | 自殺念慮 | 1 | 1 | 0 |
| 精神障害 | 76 | 自殺企図 | 1 | 1 | 0 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 腎および尿路障害 | 158 | 急性腎不全 | 53 | 48 | 5 |
| 腎および尿路障害 | 158 | 急性腎前性腎不全 | 1 | 1 | 0 |
| 腎および尿路障害 | 158 | 高窒素血症 | 1 | 1 | 0 |
| 腎および尿路障害 | 158 | 膀胱障害 | 4 | 2 | 2 |
| 腎および尿路障害 | 158 | 膀胱腫瘤 | 1 | 1 | 0 |
| 腎および尿路障害 | 158 | 膀胱肉柱形成 | 1 | 0 | 1 |
| 腎および尿路障害 | 158 | 着色尿 | 1 | 0 | 1 |
| 腎および尿路障害 | 158 | 慢性腎臓病 | 2 | 0 | 2 |
| 腎および尿路障害 | 158 | 出血性膀胱炎 | 1 | 1 | 0 |
| 腎および尿路障害 | 158 | 排尿困難 | 6 | 1 | 5 |
| 腎および尿路障害 | 158 | 血尿 | 18 | 11 | 7 |
| 腎および尿路障害 | 158 | 水腎症 | 2 | 0 | 2 |
| 腎および尿路障害 | 158 | 失禁 | 2 | 0 | 2 |
| 腎および尿路障害 | 158 | 腎結石症 | 5 | 4 | 1 |
| 腎および尿路障害 | 158 | 夜間頻尿 | 4 | 0 | 4 |
| 腎および尿路障害 | 158 | 頻尿 | 4 | 0 | 4 |
| 腎および尿路障害 | 158 | 腎仙痛 | 1 | 0 | 1 |
| 腎および尿路障害 | 158 | 腎嚢胞 | 3 | 1 | 2 |
| 腎および尿路障害 | 158 | 腎障害 | 6 | 4 | 2 |
| 腎および尿路障害 | 158 | 腎不全 | 41 | 38 | 3 |
| 腎および尿路障害 | 158 | 腎機能障害 | 3 | 2 | 1 |
| 腎および尿路障害 | 158 | 腎腫瘤 | 2 | 1 | 1 |
| 腎および尿路障害 | 158 | 腎尿細管壊死 | 1 | 1 | 0 |
| 腎および尿路障害 | 158 | 膀胱出血 | 1 | 0 | 1 |
| 腎および尿路障害 | 158 | 排尿躊躇 | 1 | 0 | 1 |
| 腎および尿路障害 | 158 | 尿閉 | 12 | 3 | 9 |
| 生殖系および乳房障害 | 11 | 無月経 | 1 | 0 | 1 |
| 生殖系および乳房障害 | 11 | 良性前立腺肥大症 | 2 | 0 | 2 |
| 生殖系および乳房障害 | 11 | 膀胱瘤 | 1 | 1 | 0 |
| 生殖系および乳房障害 | 11 | 閉経期症状 | 1 | 0 | 1 |
| 生殖系および乳房障害 | 11 | 不規則月経 | 1 | 0 | 1 |
| 生殖系および乳房障害 | 11 | 性器浮腫 | 1 | 0 | 1 |
| 生殖系および乳房障害 | 11 | 前立腺出血 | 1 | 0 | 1 |
| 生殖系および乳房障害 | 11 | 前立腺腫瘤 | 1 | 1 | 0 |
| 生殖系および乳房障害 | 11 | 前立腺症 | 1 | 0 | 1 |
| 生殖系および乳房障害 | 11 | 精巣出血 | 1 | 0 | 1 |
| 生殖系および乳房障害 | 11 | 子宮腟脱 | 1 | 1 | 0 |
| 生殖系および乳房障害 | 11 | 腟分泌物 | 1 | 0 | 1 |
| 生殖系および乳房障害 | 11 | 腟出血 | 3 | 1 | 2 |
| 生殖系および乳房障害 | 11 | 外陰腟そう痒症 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 急性間質性肺臓炎 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 急性肺水腫 | 3 | 3 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 急性呼吸窮迫症候群 | 3 | 3 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 急性呼吸不全 | 14 | 14 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 誤嚥 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 喘息 | 3 | 2 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 無気肺 | 3 | 0 | 3 |
| 呼吸器、胸郭および縦隔障害 | 352 | 気管支閉塞 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 気管支痙攣 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 慢性閉塞性肺疾患 | 10 | 9 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 慢性呼吸疾患 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 咳嗽 | 36 | 8 | 28 |
| 呼吸器、胸郭および縦隔障害 | 352 | びまん性肺胞障害 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 発声障害 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 呼吸困難 | 82 | 41 | 41 |

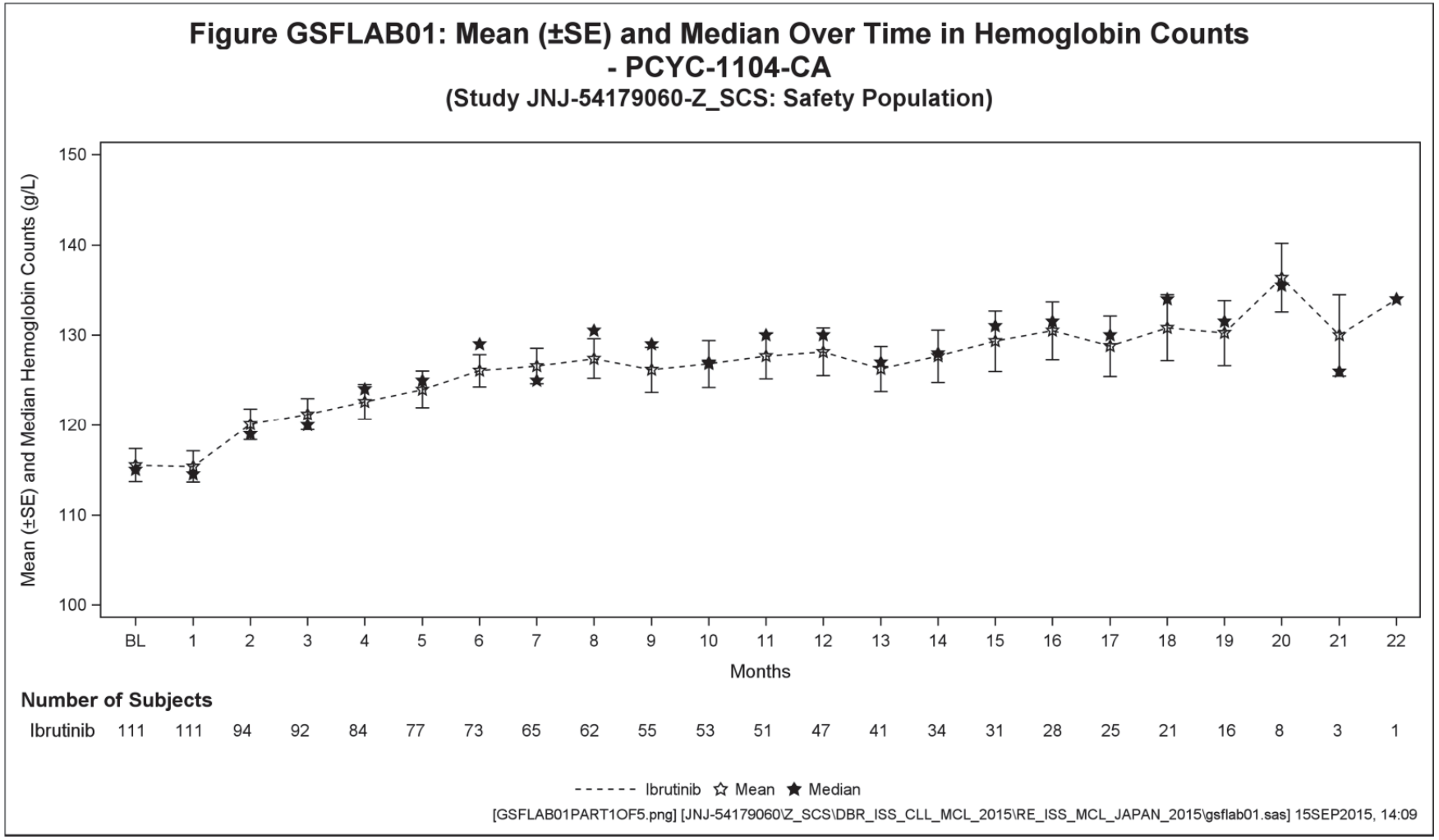
| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 呼吸器、胸郭および縦隔障害 | 352 | 労作性呼吸困難 | 6 | 2 | 4 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺気腫 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 鼻出血 | 38 | 14 | 24 |
| 呼吸器、胸郭および縦隔障害 | 352 | 喀血 | 15 | 8 | 7 |
| 呼吸器、胸郭および縦隔障害 | 352 | 血胸 | 7 | 7 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 高炭酸ガス血症 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 低酸素症 | 7 | 2 | 5 |
| 呼吸器、胸郭および縦隔障害 | 352 | 間質性肺疾患 | 4 | 4 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺障害 | 5 | 5 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺浸潤 | 5 | 3 | 2 |
| 呼吸器、胸郭および縦隔障害 | 352 | 鼻閉 | 3 | 1 | 2 |
| 呼吸器、胸郭および縦隔障害 | 352 | 鼻浮腫 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 器質化肺炎 | 3 | 2 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 口腔咽頭痛 | 10 | 2 | 8 |
| 呼吸器、胸郭および縦隔障害 | 352 | 口腔咽頭プラーク | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 起坐呼吸 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 副鼻腔分泌過多 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 咽頭浮腫 | 2 | 2 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 胸水 | 69 | 47 | 22 |
| 呼吸器、胸郭および縦隔障害 | 352 | 胸膜炎 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 誤嚥性肺炎 | 10 | 9 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺臓炎 | 14 | 14 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 気胸 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 湿性咳嗽 | 12 | 1 | 11 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺胞出血 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺うっ血 | 2 | 0 | 2 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺塞栓症 | 9 | 9 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺線維症 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺出血 | 3 | 3 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺高血圧症 | 4 | 4 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺腫瘤 | 8 | 3 | 5 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺水腫 | 17 | 15 | 2 |
| 呼吸器、胸郭および縦隔障害 | 352 | 肺毒性 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | ラ音 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 呼吸性アシドーシス | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 呼吸停止 | 2 | 2 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 呼吸障害 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 呼吸窮迫 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 呼吸不全 | 33 | 32 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 呼吸筋疲労 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 気道うっ血 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 鼻漏 | 2 | 0 | 2 |
| 呼吸器、胸郭および縦隔障害 | 352 | 低音性連続性ラ音 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 副鼻腔うっ血 | 3 | 0 | 3 |
| 呼吸器、胸郭および縦隔障害 | 352 | 副鼻腔障害 | 2 | 0 | 2 |
| 呼吸器、胸郭および縦隔障害 | 352 | 睡眠時無呼吸症候群 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | くしゃみ | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 上気道性喘鳴 | 1 | 1 | 0 |
| 呼吸器、胸郭および縦隔障害 | 352 | 咽喉病変 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 咽喉絞扼感 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 扁桃障害 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 上気道うっ血 | 1 | 0 | 1 |
| 呼吸器、胸郭および縦隔障害 | 352 | 喘鳴 | 2 | 0 | 2 |
| 皮膚および皮下組織障害 | 190 | ざ瘡 | 5 | 0 | 5 |
| 皮膚および皮下組織障害 | 190 | 脱毛症 | 4 | 0 | 4 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 皮膚および皮下組織障害 | 190 | 全頭脱毛症 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 血管浮腫 | 3 | 3 | 0 |
| 皮膚および皮下組織障害 | 190 | 水疱 | 11 | 3 | 8 |
| 皮膚および皮下組織障害 | 190 | 血性水疱 | 3 | 2 | 1 |
| 皮膚および皮下組織障害 | 190 | 冷汗 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 皮膚炎 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 糖尿病性足病変 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 薬疹 | 2 | 1 | 1 |
| 皮膚および皮下組織障害 | 190 | 皮膚乾燥 | 6 | 0 | 6 |
| 皮膚および皮下組織障害 | 190 | 斑状出血 | 6 | 0 | 6 |
| 皮膚および皮下組織障害 | 190 | 湿疹 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 紅斑 | 6 | 2 | 4 |
| 皮膚および皮下組織障害 | 190 | 全身紅斑 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 皮下出血 | 2 | 1 | 1 |
| 皮膚および皮下組織障害 | 190 | 毛髪成長異常 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 多汗症 | 2 | 0 | 2 |
| 皮膚および皮下組織障害 | 190 | 過角化 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 過敏性血管炎 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 嵌入爪 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 爪変色 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 爪の障害 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 寝汗 | 8 | 1 | 7 |
| 皮膚および皮下組織障害 | 190 | 爪破損 | 3 | 0 | 3 |
| 皮膚および皮下組織障害 | 190 | 脂肪織炎 | 2 | 1 | 1 |
| 皮膚および皮下組織障害 | 190 | 丘疹 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 腫瘍随伴性天疱瘡 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 類天疱瘡 | 3 | 2 | 1 |
| 皮膚および皮下組織障害 | 190 | 天疱瘡 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 点状出血 | 22 | 5 | 17 |
| 皮膚および皮下組織障害 | 190 | 光線過敏性反応 | 2 | 2 | 0 |
| 皮膚および皮下組織障害 | 190 | そう痒症 | 11 | 3 | 8 |
| 皮膚および皮下組織障害 | 190 | 全身性そう痒症 | 2 | 1 | 1 |
| 皮膚および皮下組織障害 | 190 | 紫斑 | 8 | 5 | 3 |
| 皮膚および皮下組織障害 | 190 | 壊疽性膿皮症 | 3 | 3 | 0 |
| 皮膚および皮下組織障害 | 190 | 発疹 | 49 | 14 | 35 |
| 皮膚および皮下組織障害 | 190 | 紅斑性皮疹 | 3 | 0 | 3 |
| 皮膚および皮下組織障害 | 190 | 全身性皮疹 | 5 | 1 | 4 |
| 皮膚および皮下組織障害 | 190 | 斑状皮疹 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 斑状丘疹状皮疹 | 4 | 3 | 1 |
| 皮膚および皮下組織障害 | 190 | 丘疹性皮疹 | 2 | 1 | 1 |
| 皮膚および皮下組織障害 | 190 | そう痒性皮疹 | 6 | 2 | 4 |
| 皮膚および皮下組織障害 | 190 | 痂皮 | 5 | 1 | 4 |
| 皮膚および皮下組織障害 | 190 | 皮膚灼熱感 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 皮膚変色 | 5 | 0 | 5 |
| 皮膚および皮下組織障害 | 190 | 皮膚障害 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 皮膚剥脱 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 皮膚亀裂 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 皮膚脆弱性 | 2 | 0 | 2 |
| 皮膚および皮下組織障害 | 190 | 皮膚出血 | 2 | 2 | 0 |
| 皮膚および皮下組織障害 | 190 | 皮膚色素過剰 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 皮膚肥厚 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 皮膚刺激 | 2 | 0 | 2 |
| 皮膚および皮下組織障害 | 190 | 皮膚病変 | 10 | 4 | 6 |
| 皮膚および皮下組織障害 | 190 | 皮膚腫瘤 | 2 | 1 | 1 |
| 皮膚および皮下組織障害 | 190 | 皮膚臭異常 | 1 | 0 | 1 |

| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 皮膚および皮下組織障害 | 190 | 皮膚反応 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 皮膚毒性 | 1 | 0 | 1 |
| 皮膚および皮下組織障害 | 190 | 皮膚潰瘍 | 5 | 3 | 2 |
| 皮膚および皮下組織障害 | 190 | スティーブンス・ジョンソン症候群 | 1 | 1 | 0 |
| 皮膚および皮下組織障害 | 190 | 顔面腫脹 | 4 | 2 | 2 |
| 皮膚および皮下組織障害 | 190 | 中毒性皮疹 | 2 | 2 | 0 |
| 皮膚および皮下組織障害 | 190 | 蕁麻疹 | 7 | 3 | 4 |
| 社会環境 | 5 | 日常生活動作障害者 | 2 | 2 | 0 |
| 社会環境 | 5 | 運動不能 | 1 | 1 | 0 |
| 社会環境 | 5 | 治療非遵守 | 2 | 0 | 2 |
| 外科および内科処置 | 34 | 骨髄移植 | 2 | 1 | 1 |
| 外科および内科処置 | 34 | 頚動脈内膜剥離術 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 胆嚢切除 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 結腸切除 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 結腸瘻造設 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 冠動脈ステント挿入 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 透析 | 2 | 2 | 0 |
| 外科および内科処置 | 34 | 耳手術 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 経腸栄養 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 胆嚢手術 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 胃バイパス | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 胃手術 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 心臓弁置換 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | ヘルニア修復 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 股関節形成 | 3 | 3 | 0 |
| 外科および内科処置 | 34 | 膝関節形成 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 肺手術 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | リンパ節切除 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 機械的換気 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 頚部手術 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 前立腺摘除 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 肩関節手術 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 植皮 | 2 | 1 | 1 |
| 外科および内科処置 | 34 | 皮膚新生物切除 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | ステント装着 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 外科手術 | 2 | 2 | 0 |
| 外科および内科処置 | 34 | 甲状腺手術 | 1 | 1 | 0 |
| 外科および内科処置 | 34 | 抜歯 | 1 | 0 | 1 |
| 外科および内科処置 | 34 | 輸血 | 1 | 1 | 0 |
| 血管障害 | 148 | 動脈瘤破裂 | 1 | 1 | 0 |
| 血管障害 | 148 | 大動脈瘤 | 1 | 0 | 1 |
| 血管障害 | 148 | 大動脈瘤破裂 | 2 | 2 | 0 |
| 血管障害 | 148 | 大動脈狭窄 | 5 | 5 | 0 |
| 血管障害 | 148 | 動脈閉塞性疾患 | 1 | 1 | 0 |
| 血管障害 | 148 | 動脈狭窄 | 1 | 0 | 1 |
| 血管障害 | 148 | 循環虚脱 | 2 | 2 | 0 |
| 血管障害 | 148 | 深部静脈血栓症 | 15 | 11 | 4 |
| 血管障害 | 148 | 血腫 | 9 | 7 | 2 |
| 血管障害 | 148 | 出血 | 36 | 28 | 8 |
| 血管障害 | 148 | ほてり | 3 | 1 | 2 |
| 血管障害 | 148 | 高血圧 | 25 | 15 | 10 |
| 血管障害 | 148 | 高血圧クリーゼ | 1 | 1 | 0 |
| 血管障害 | 148 | 低血圧 | 26 | 12 | 14 |
| 血管障害 | 148 | 血液量減少性ショック | 1 | 1 | 0 |

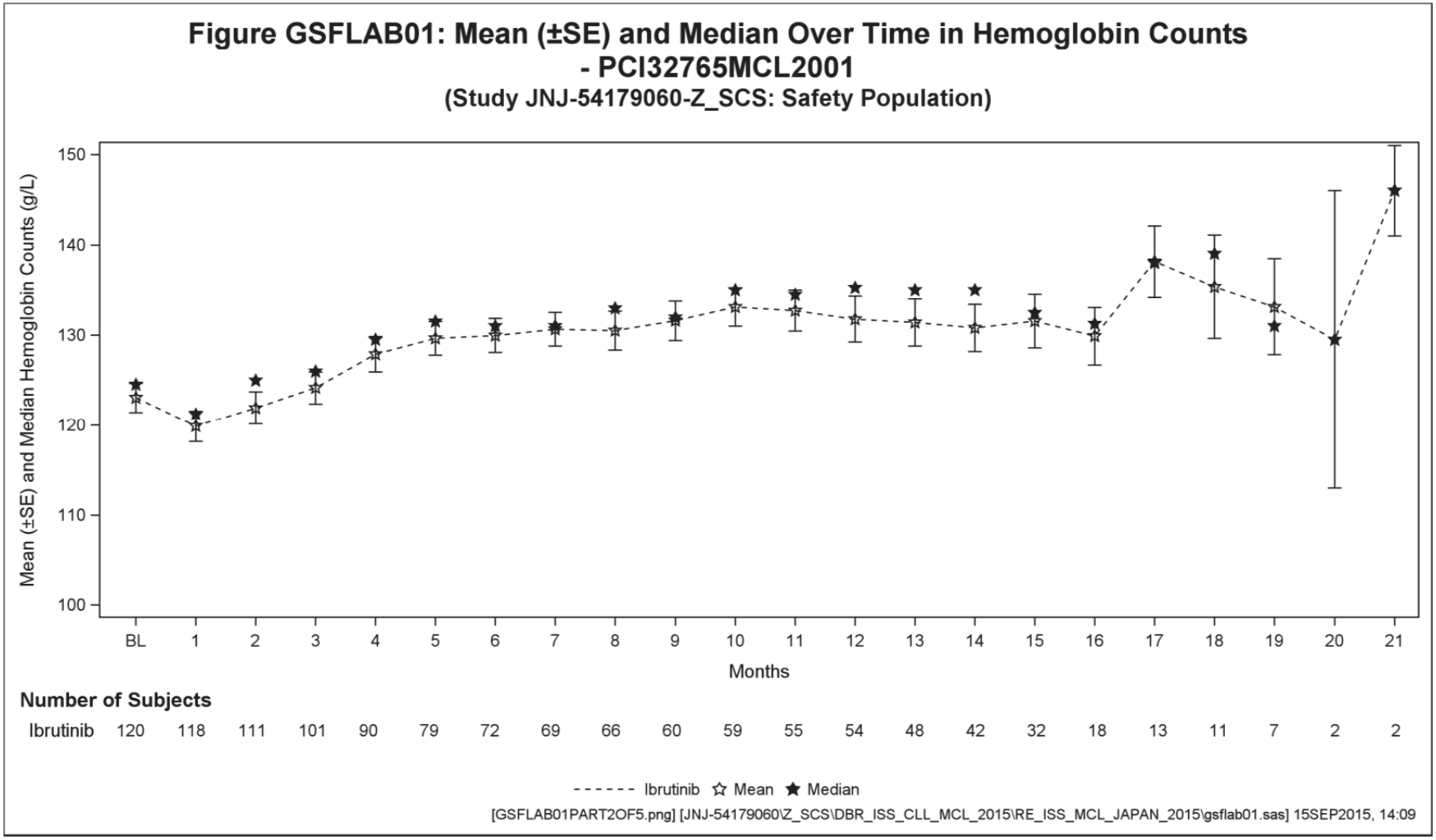
| 器官別大分類 | SOC 件数 | 基本語 | 総件数 | 重篤 | 非重篤 |
|---|---|---|---|---|---|
| 血管障害 | 148 | 内出血 | 3 | 3 | 0 |
| 血管障害 | 148 | 虚血 | 1 | 1 | 0 |
| 血管障害 | 148 | 頚静脈血栓症 | 1 | 1 | 0 |
| 血管障害 | 148 | リンパ浮腫 | 3 | 1 | 2 |
| 血管障害 | 148 | マイ・トゥルナー症候群 | 1 | 1 | 0 |
| 血管障害 | 148 | 起立性低血圧 | 3 | 2 | 1 |
| 血管障害 | 148 | 蒼白 | 1 | 0 | 1 |
| 血管障害 | 148 | 末梢静脈疾患 | 1 | 0 | 1 |
| 血管障害 | 148 | ショック | 1 | 1 | 0 |
| 血管障害 | 148 | 出血性ショック | 1 | 1 | 0 |
| 血管障害 | 148 | 表在性血栓性静脈炎 | 1 | 0 | 1 |
| 血管障害 | 148 | 血栓症 | 6 | 6 | 0 |
| 血管障害 | 148 | 血管閉塞 | 1 | 1 | 0 |
| 血管障害 | 148 | 血管炎 | 1 | 1 | 0 |
| 血管障害 | 148 | 静脈閉塞 | 1 | 1 | 0 |
| 血管障害 | 148 | 静脈血栓症 | 1 | 0 | 1 |

図 2.7.4-付録-1 Mean (±SE) and Median Over Time in Hemoglobin Counts - PCYC-1104-CA (Study JNJ-54179060-Z_SCS: Safety Population)



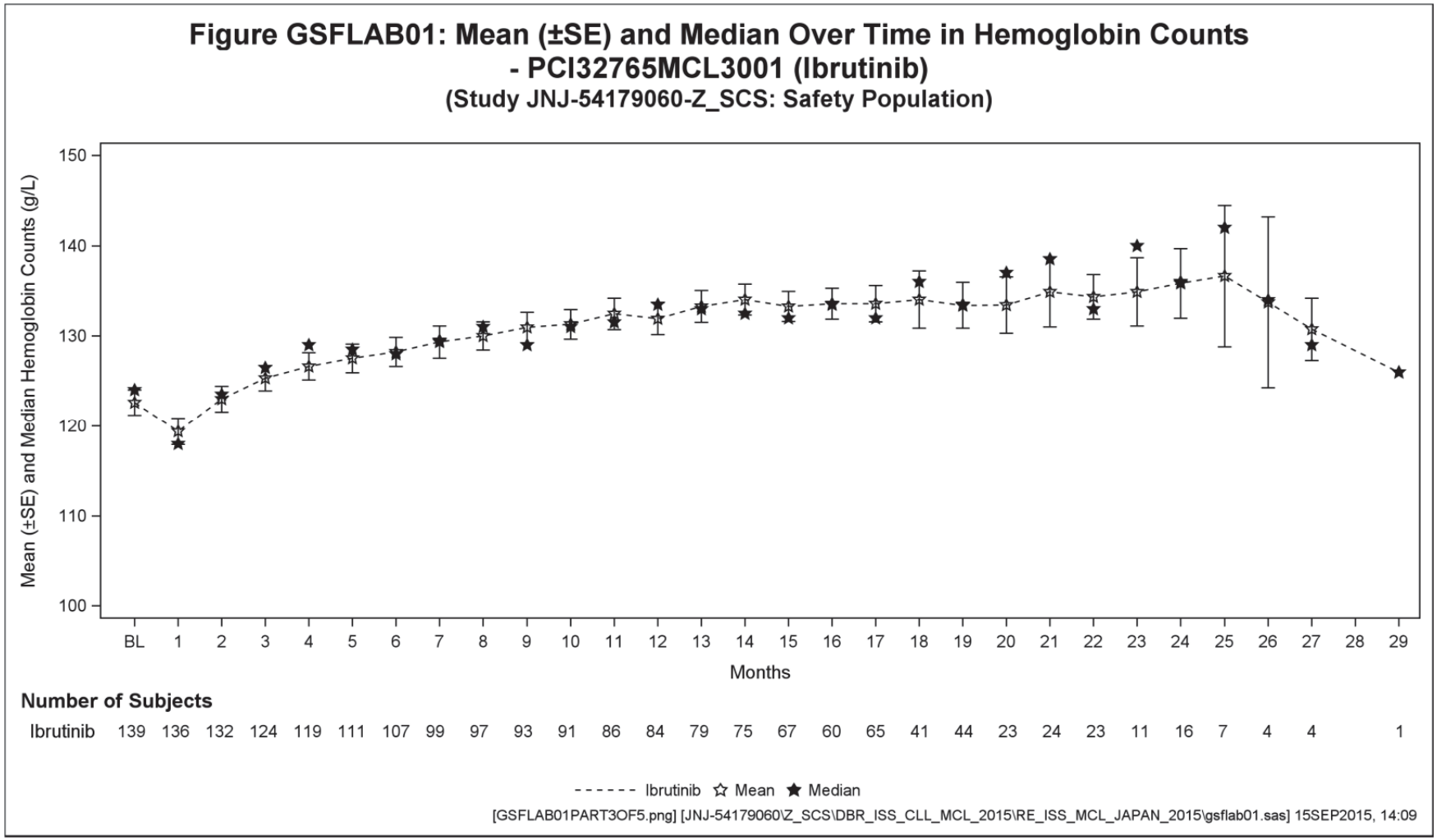

参照元：5.3.5.3.1 ISS GSFLAB01PART1OF5

図 2.7.4-付録-2 Mean (±SE) and Median Over Time in Hemoglobin Counts - PCI32765MCL2001 (Study JNJ-54179060-Z_SCS: Safety Population)



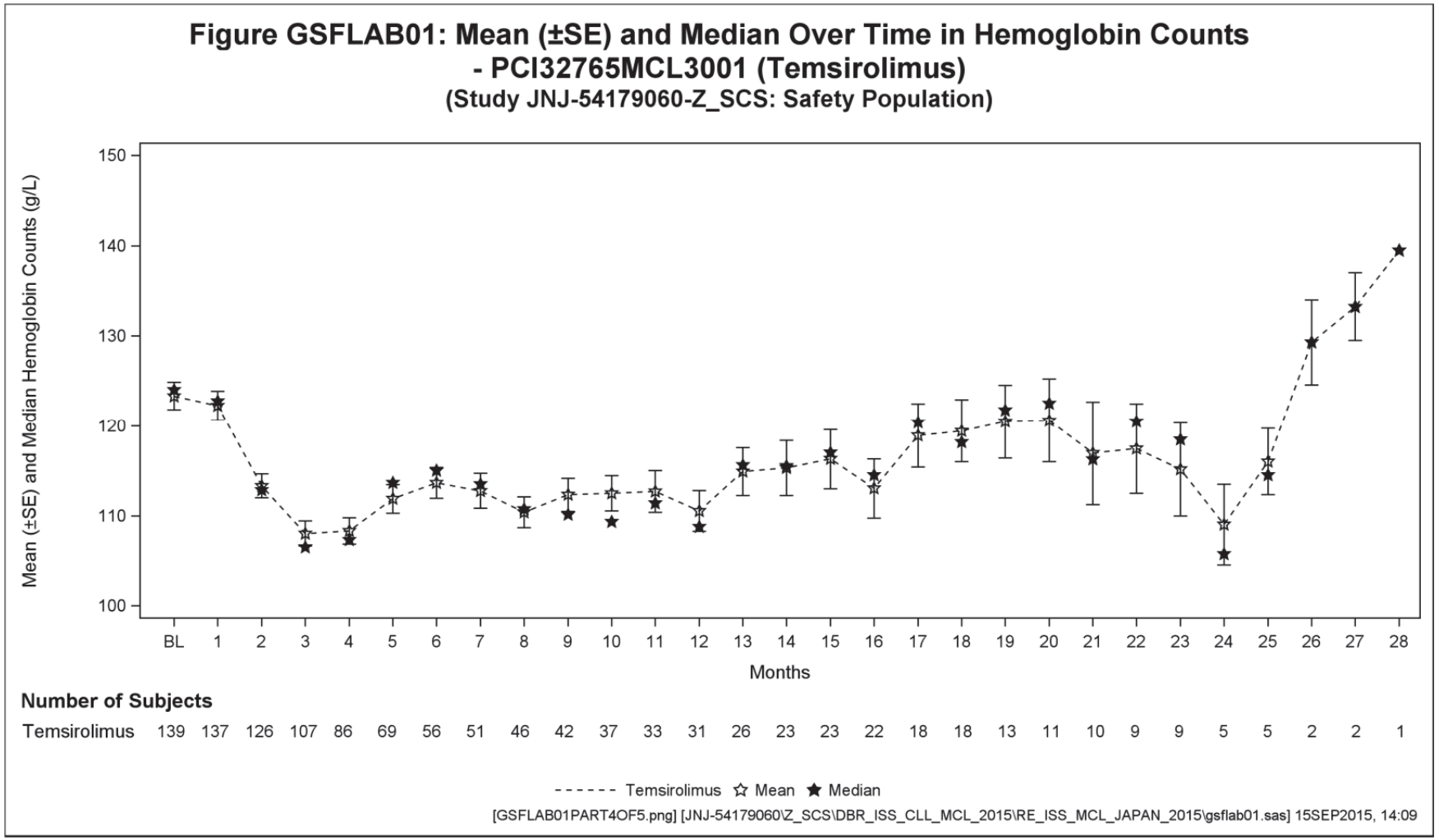

参照元：5.3.5.3.1 ISS GSFLAB01PART2OF5

図 2.7.4-付録-3 Mean (±SE) and Median Over Time in Hemoglobin Counts - PCI32765MCL3001 (Ibrutinib) (Study JNJ-54179060-Z_SCS: Safety Population)



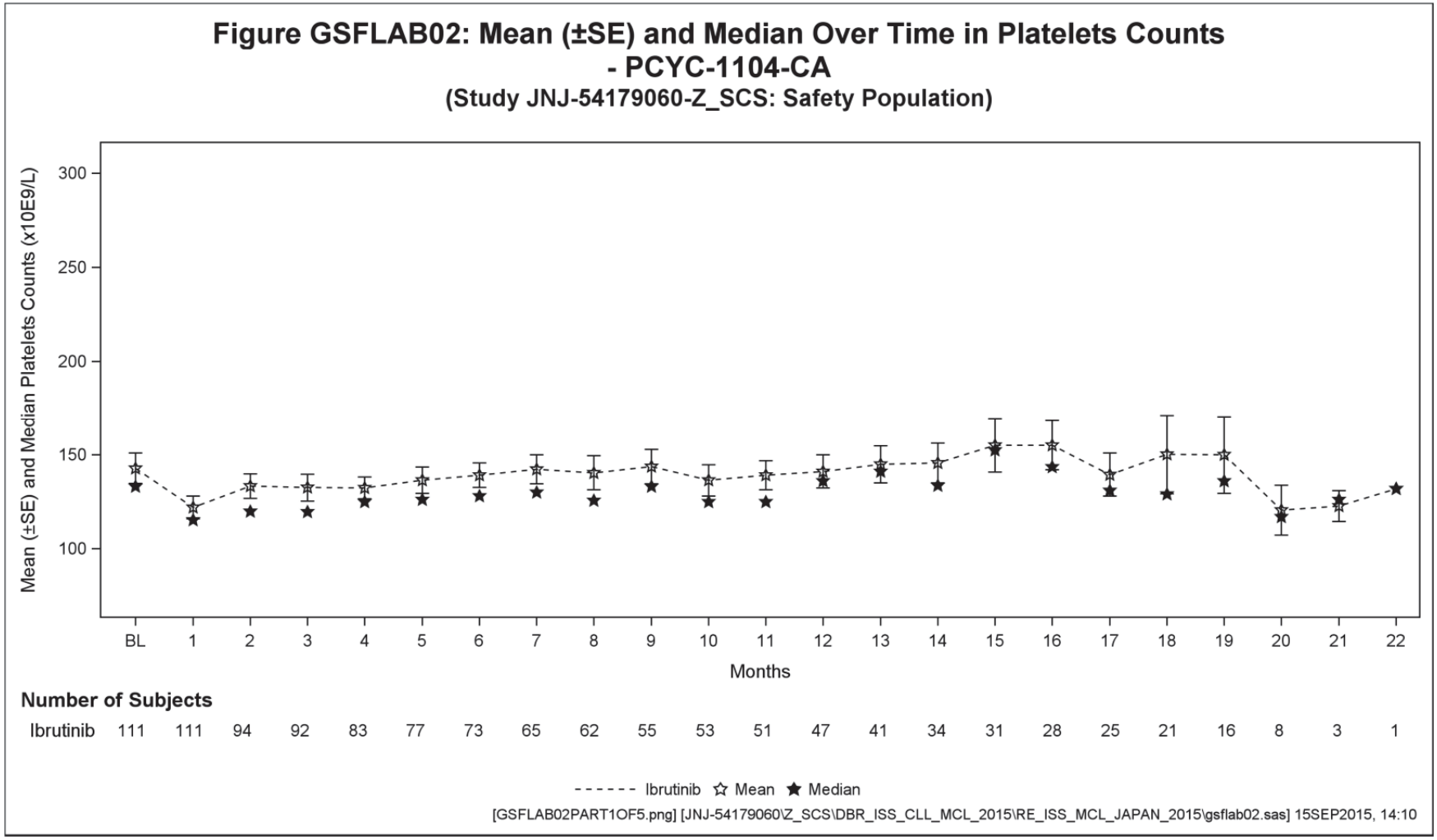

参照元：5.3.5.3.1 ISS GSFLAB01PART3OF5

図 2.7.4-付録-4 Mean (±SE) and Median Over Time in Hemoglobin Counts - PCI32765MCL3001 (Temsirolimus) (Study JNJ-54179060-Z_SCS: Safety Population)



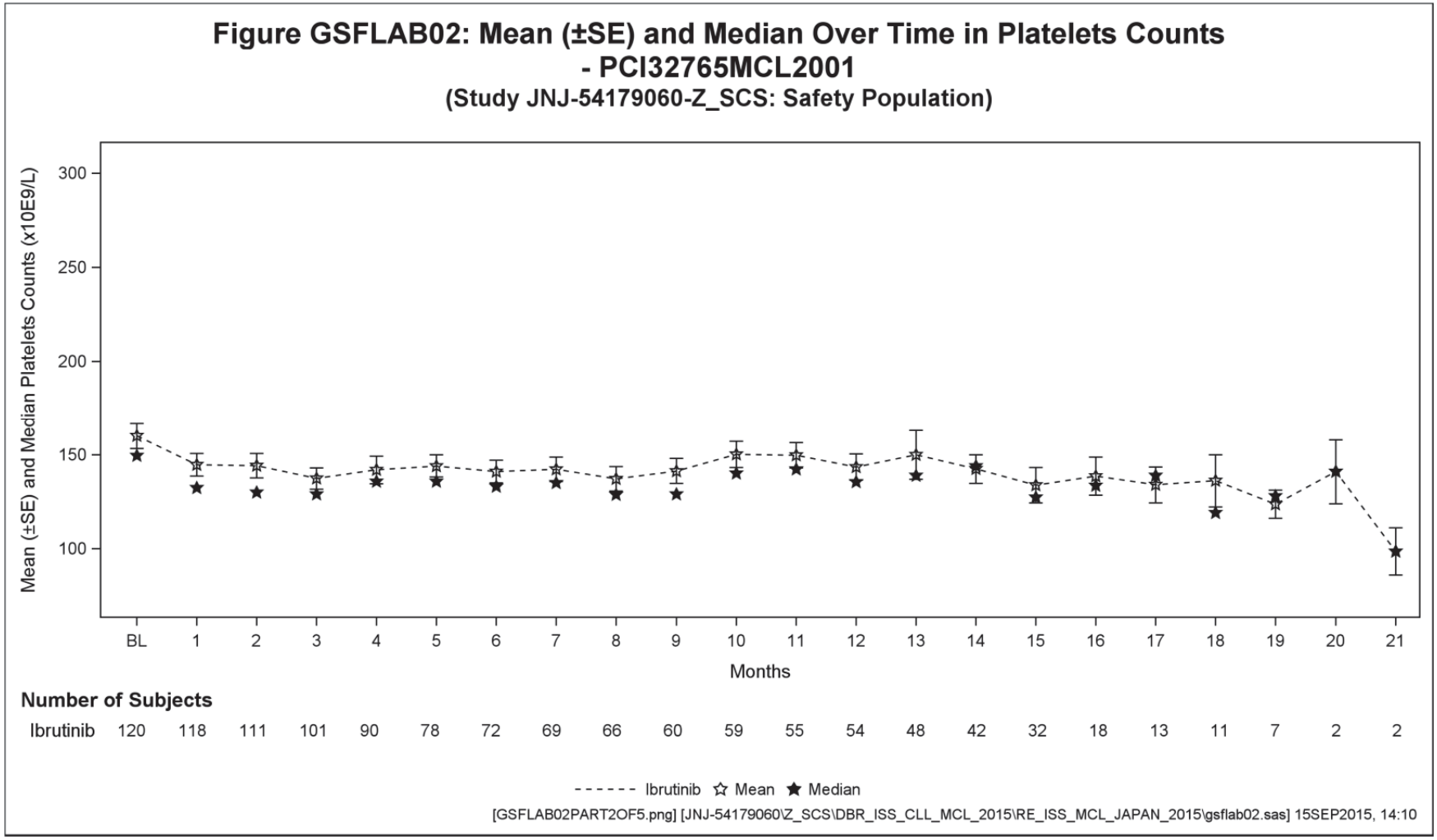

参照元：5.3.5.3.1 ISS GSFLAB01PART4OF5

図 2.7.4-付録-5 Mean (±SE) and Median Over Time in Platelets Counts - PCYC-1104-CA (Study JNJ-54179060-Z_SCS: Safety Population)



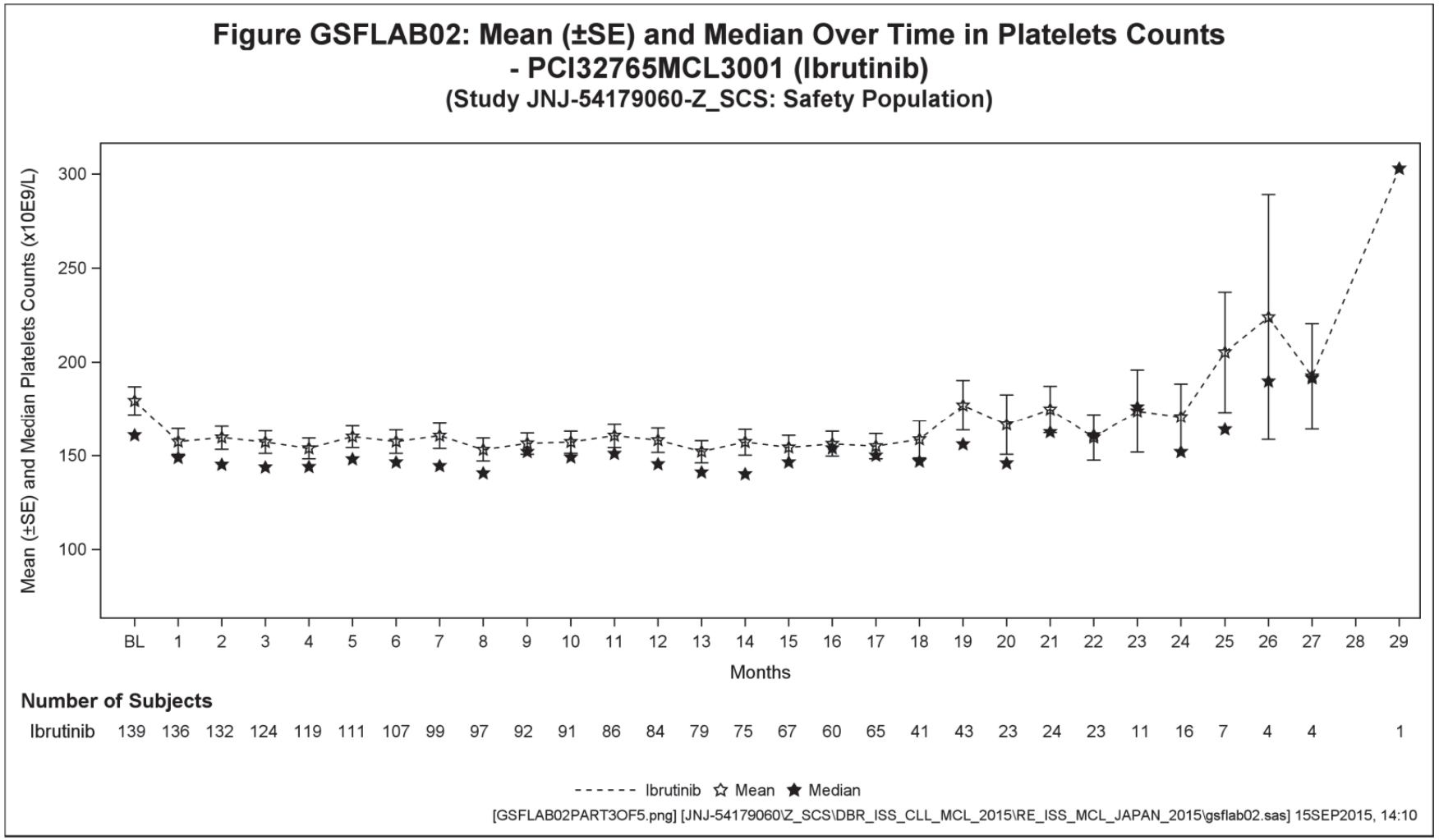

参照元：5.3.5.3.1 ISS GSFLAB02PART1OF5

図 2.7.4-付録-6 Mean (±SE) and Median Over Time in Platelets Counts - PCI32765MCL2001 (Study JNJ-54179060-Z_SCS: Safety Population)



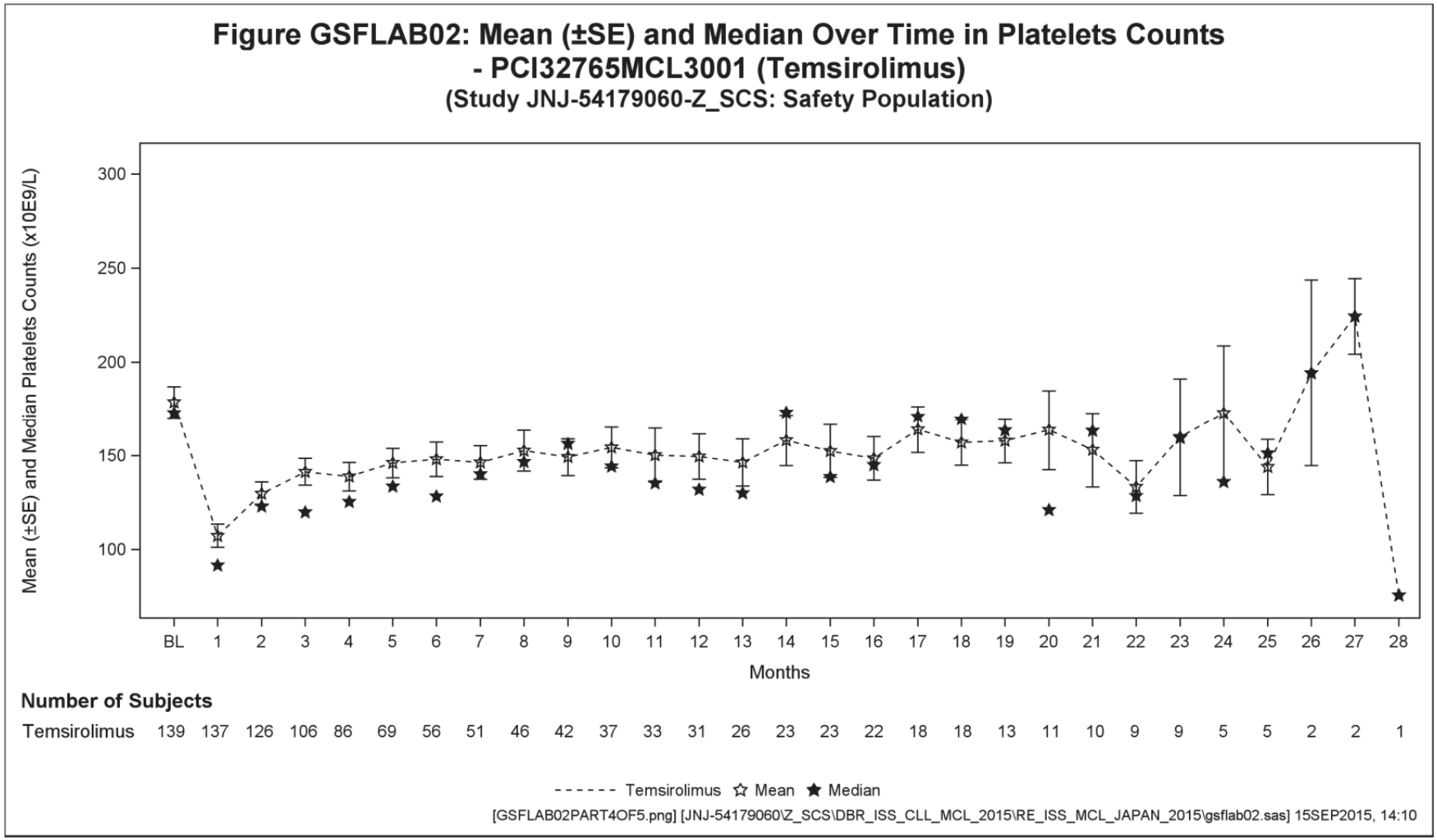

参照元：5.3.5.3.1 ISS GSFLAB02PART2OF5

図 2.7.4-付録-7 Mean (±SE) and Median Over Time in Platelets Counts - PCI32765MCL3001 (Ibrutinib) (Study JNJ-54179060-Z_SCS: Safety Population)



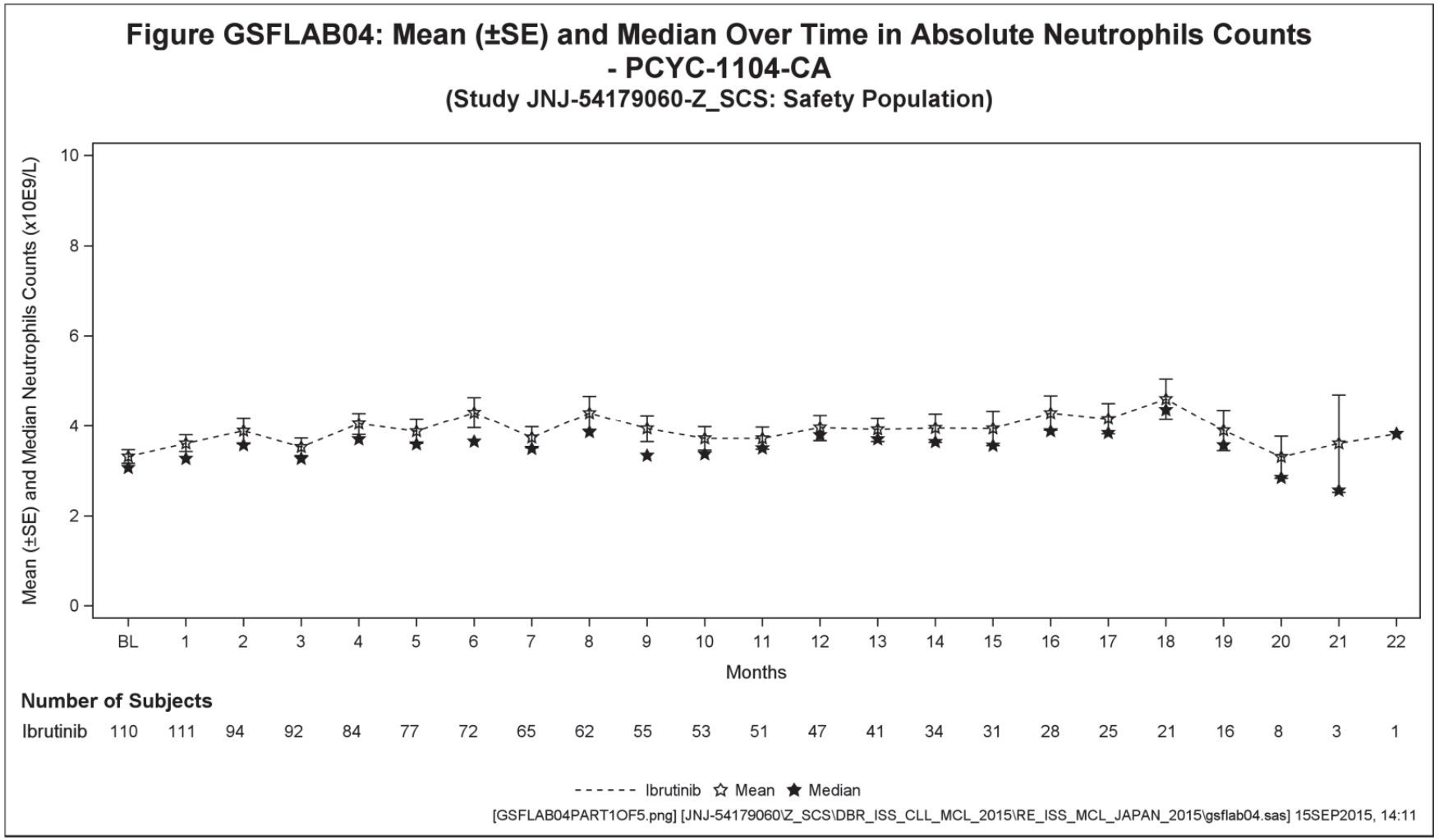

参照元：5.3.5.3.1 ISS GSFLAB02PART3OF5

図 2.7.4-付録-8 Mean (±SE) and Median Over Time in Platelets Counts - PCI32765MCL3001 (Temsirolimus) (Study JNJ-54179060-Z_SCS: Safety Population)



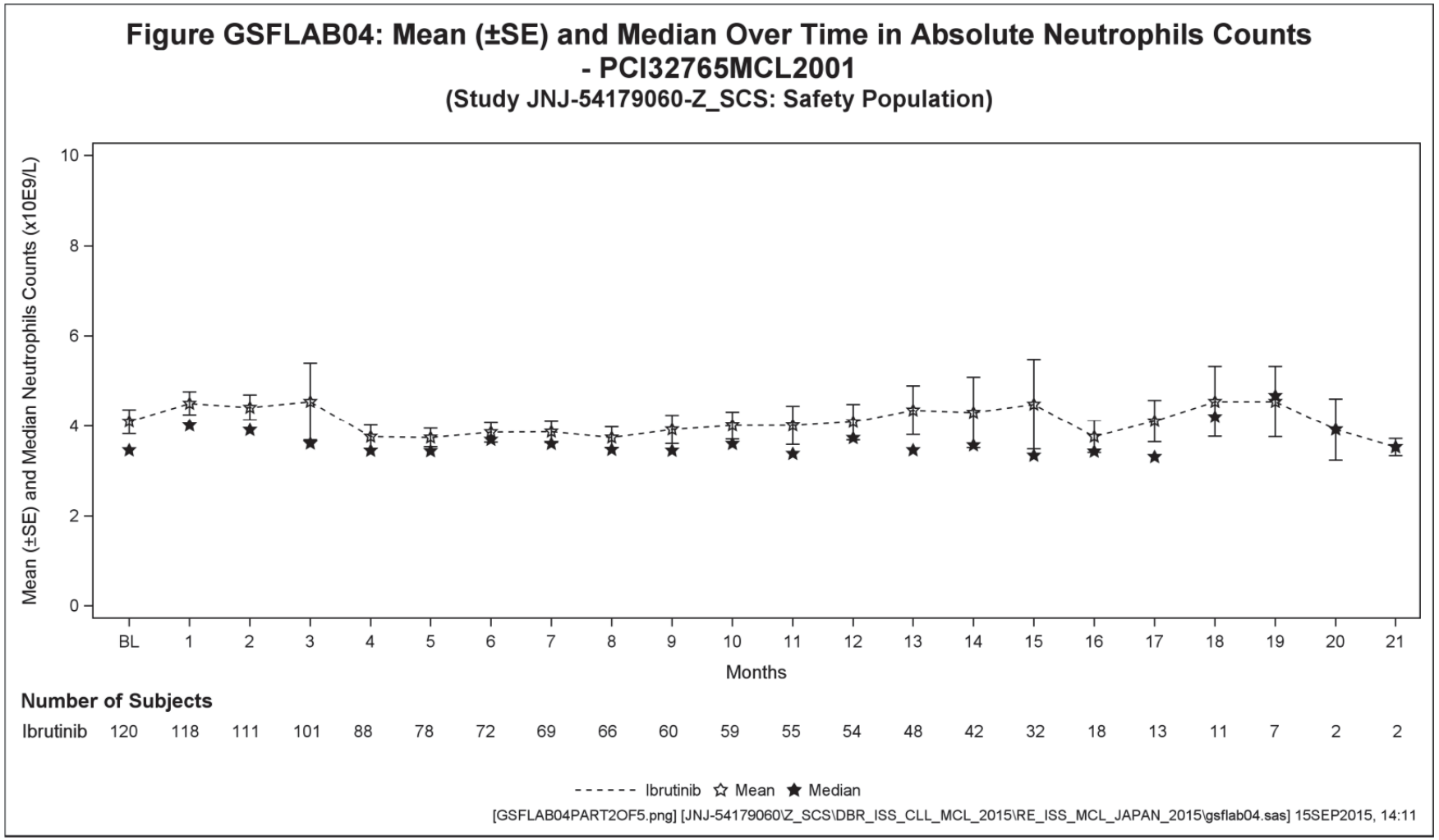

参照元：5.3.5.3.1 ISS GSFLAB02PART4OF5

図 2.7.4-付録-9 Mean (±SE) and Median Over Time in Absolute Neutrophils Counts - PCYC-1104-CA (Study JNJ-54179060-Z_SCS: Safety Population)



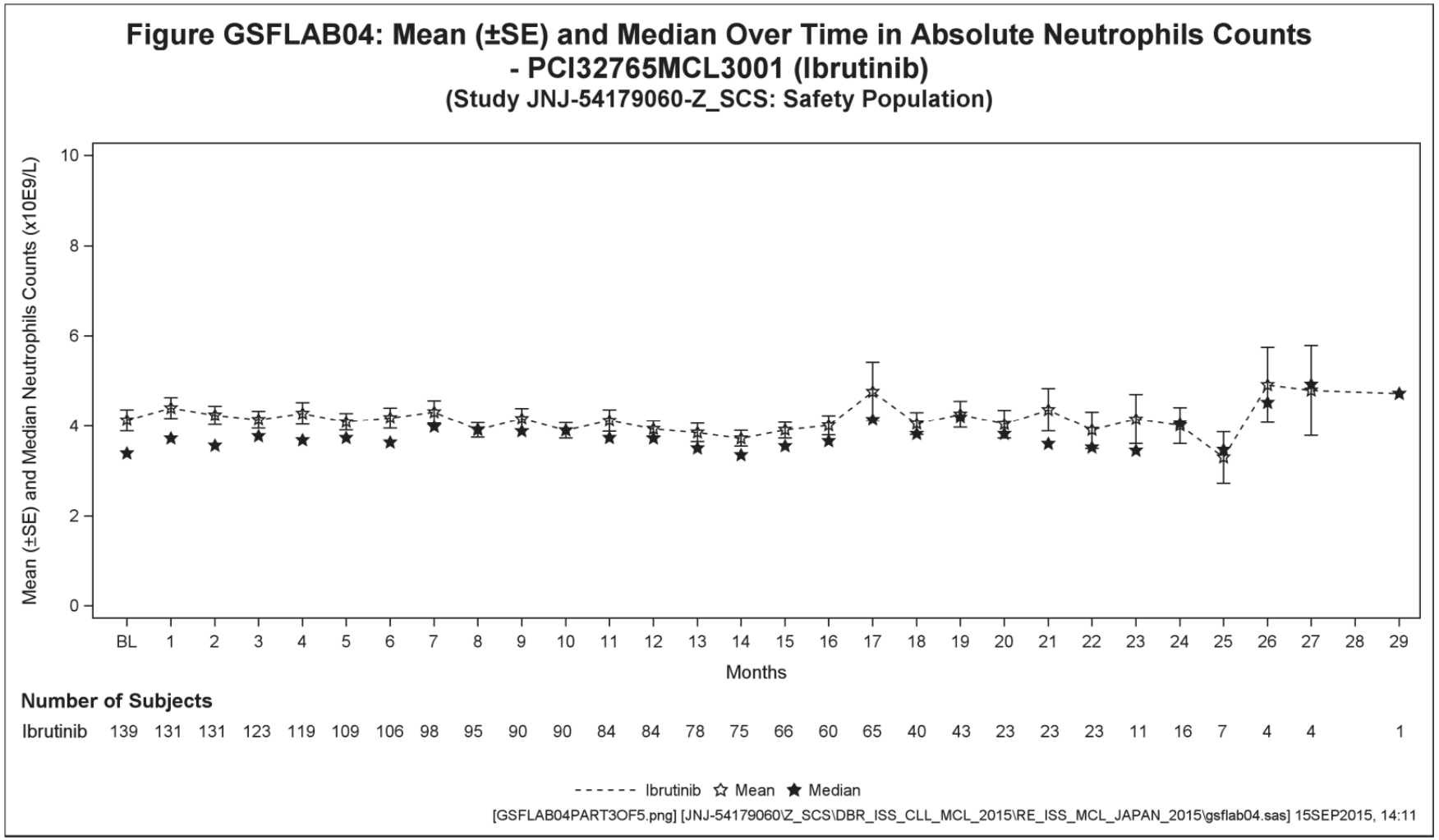

参照元：5.3.5.3.1 ISS GSFLAB04PART1OF5

図 2.7.4-付録-10 Mean (±SE) and Median Over Time in Absolute Neutrophils Counts - PCI32765MCL2001 (Study JNJ-54179060-Z_SCS: Safety Population)



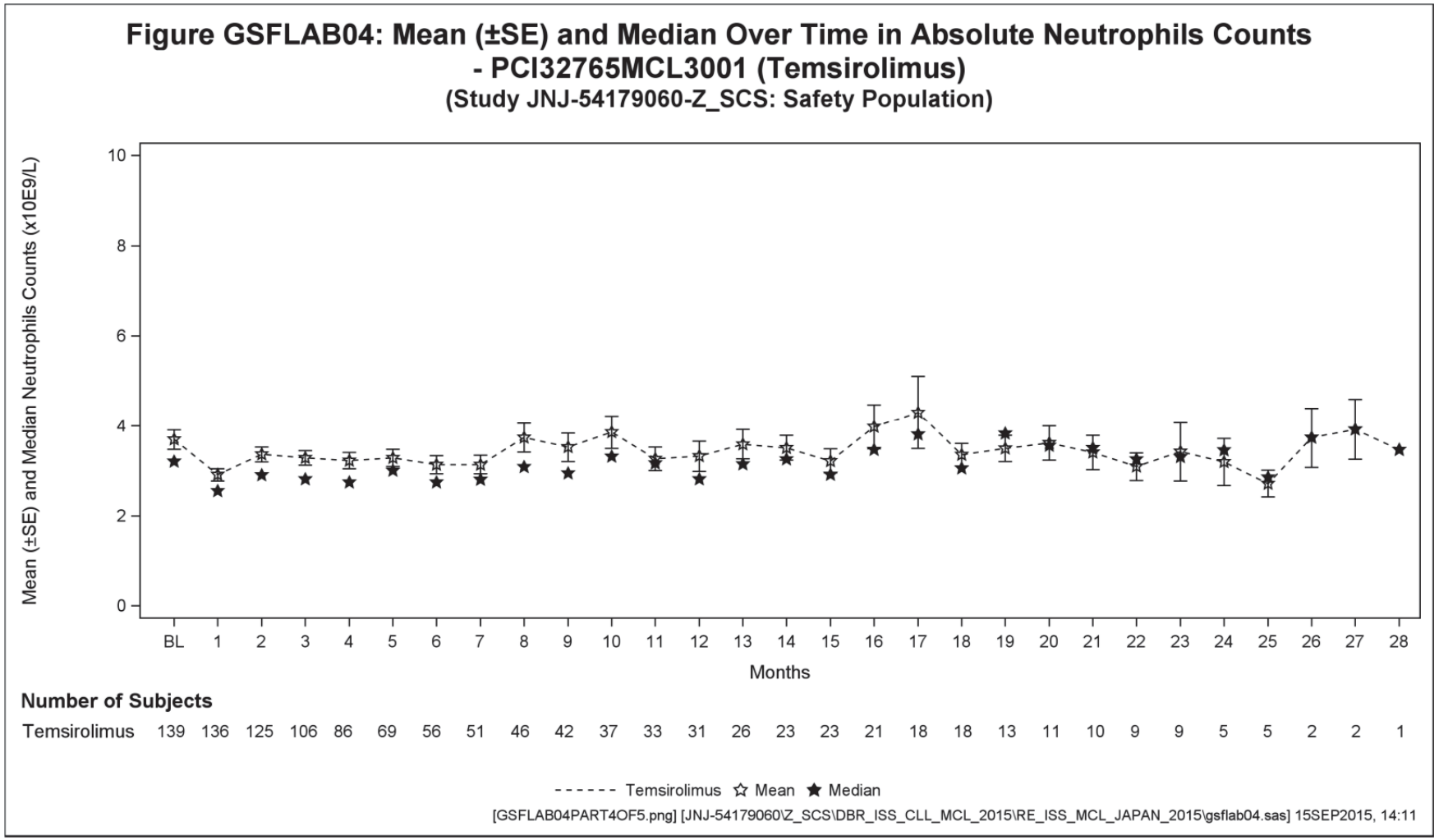

参照元：5.3.5.3.1 ISS GSFLAB04PART2OF5

図 2.7.4-付録-11 Mean (±SE) and Median Over Time in Absolute Neutrophils Counts - PCI32765MCL3001 (Ibrutinib) (Study JNJ-54179060-Z_SCS: Safety Population)



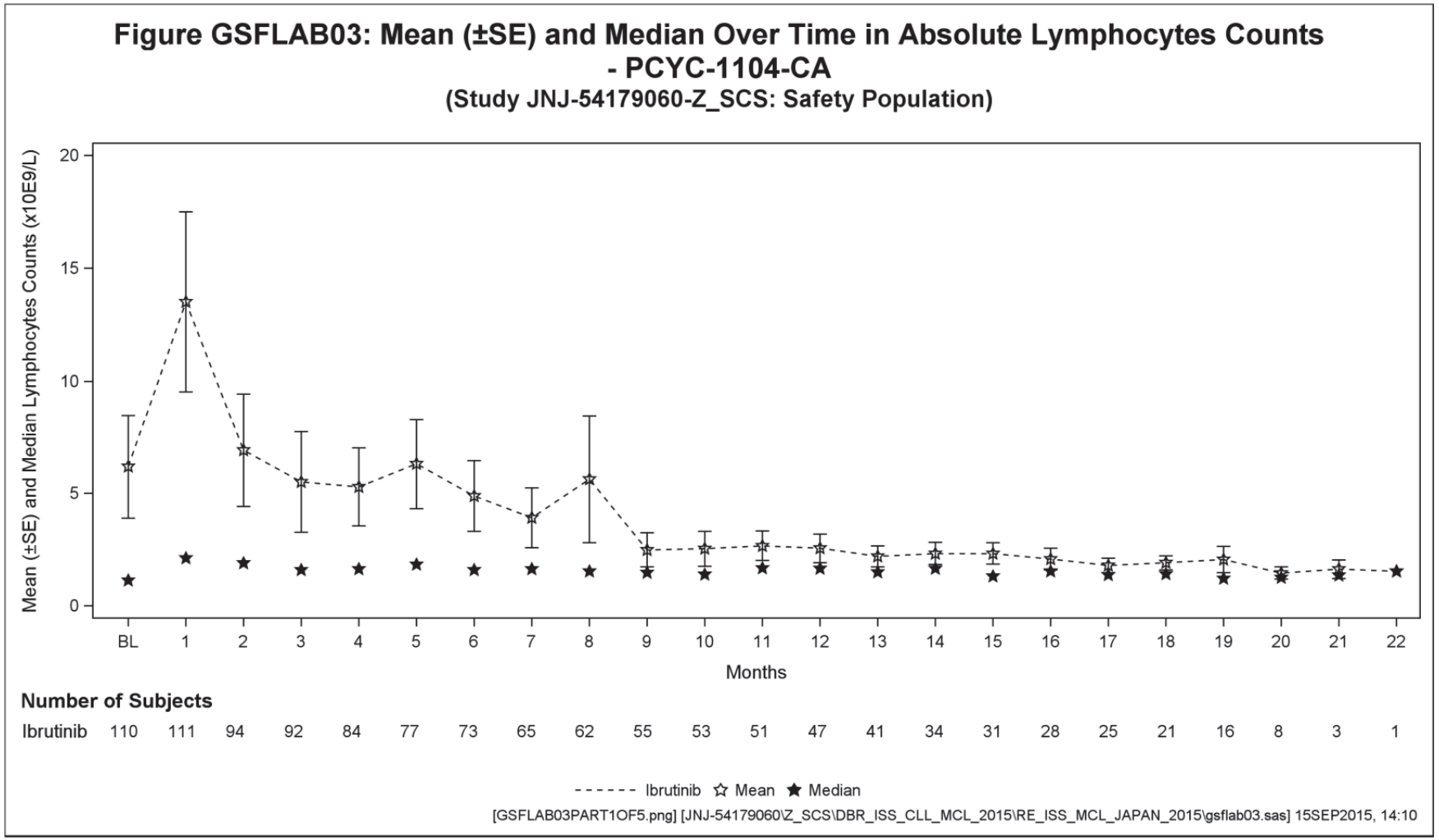

参照元：5.3.5.3.1 ISS GSFLAB04PART3OF5

図 2.7.4-付録-12 Mean (±SE) and Median Over Time in Absolute Neutrophils Counts - PCI32765MCL3001 (Temsirolimus) (Study JNJ-54179060-Z_SCS: Safety Population)



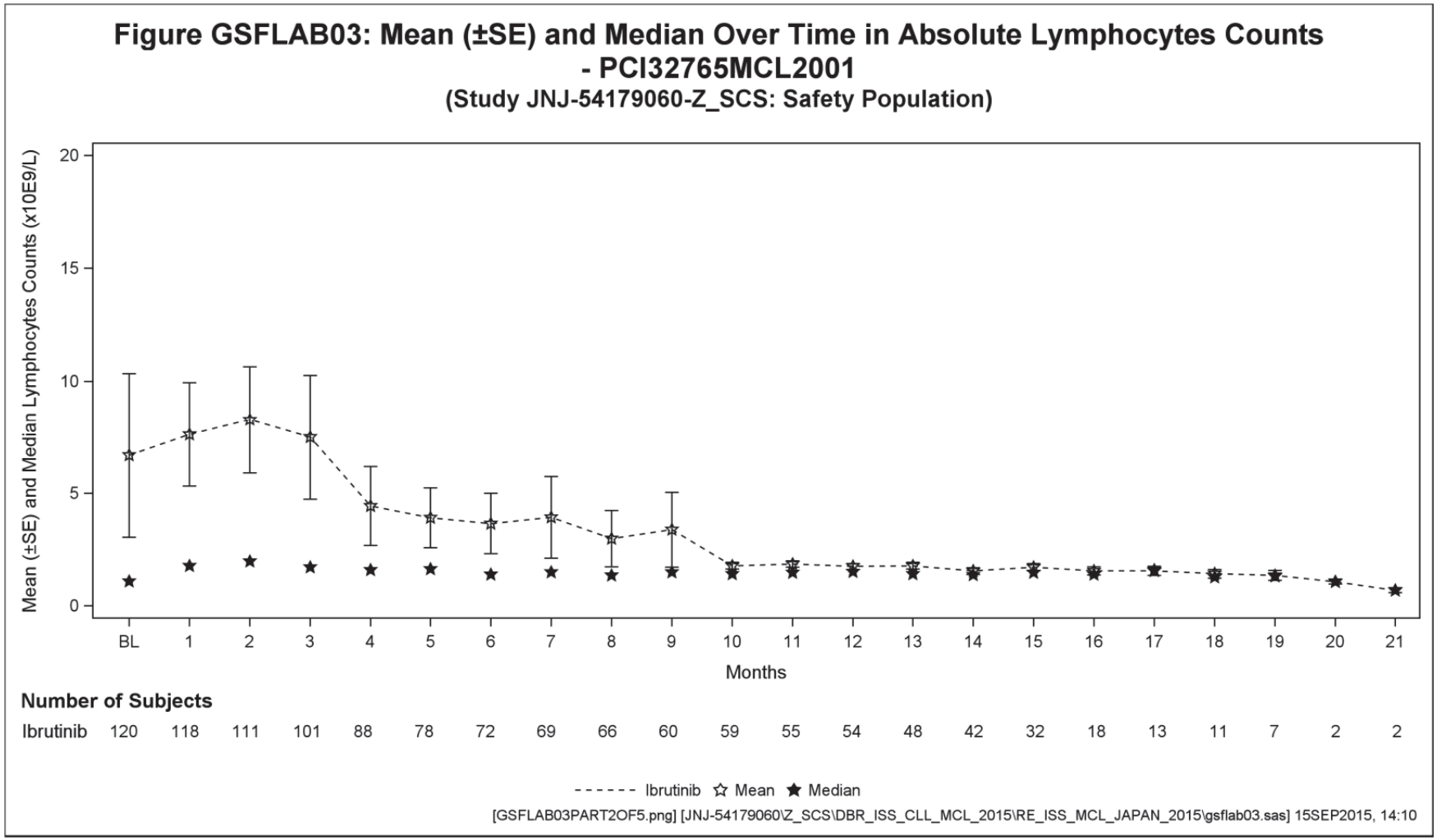

参照元：5.3.5.3.1 ISS GSFLAB04PART4OF5

図 2.7.4-付録-13 Mean (±SE) and Median Over Time in Absolute Lymphocytes Counts - PCYC-1104-CA (Study JNJ-54179060-Z_SCS: Safety Population)



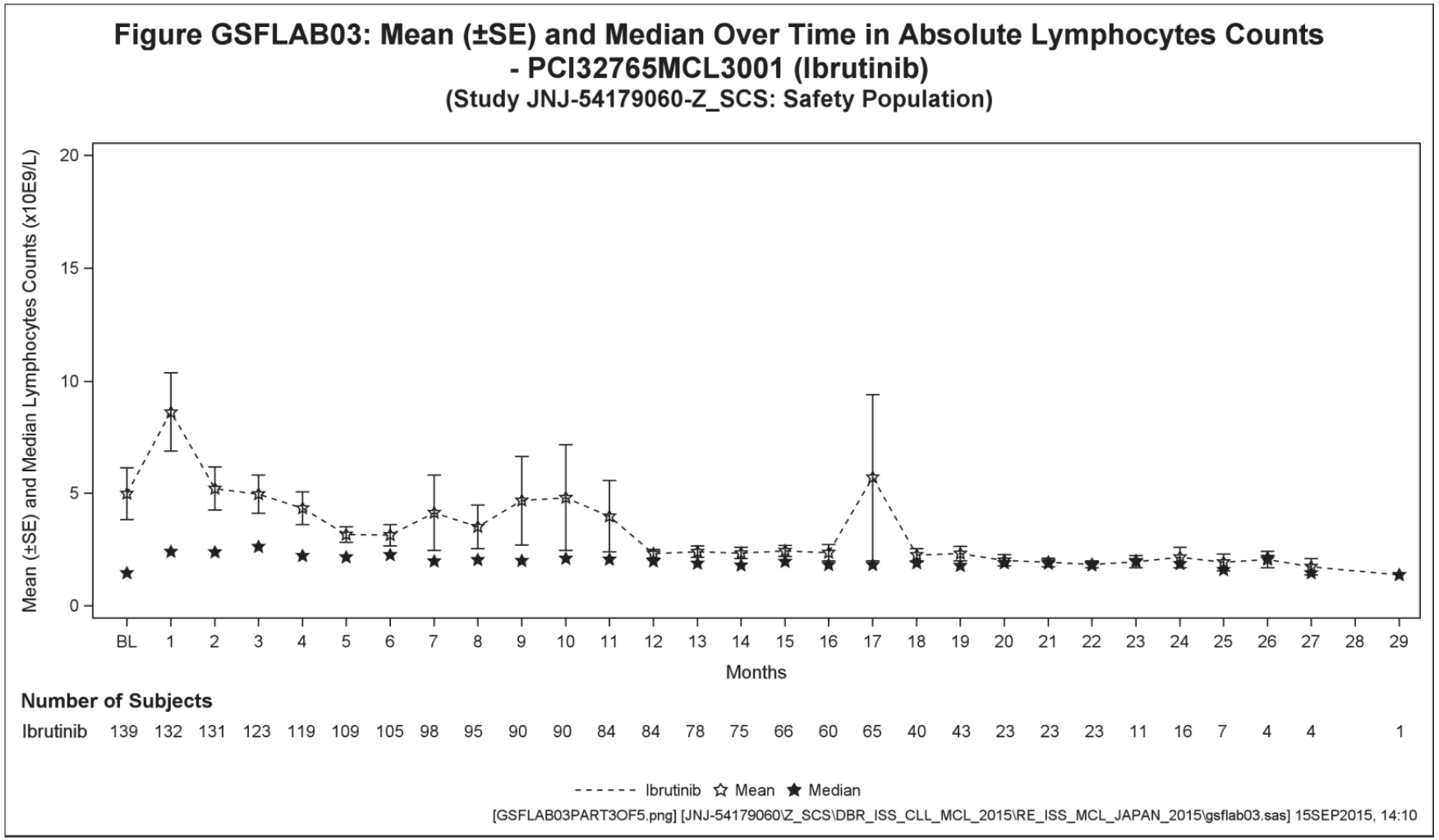

参照元：5.3.5.3.1 ISS GSFLAB03PART1OF5

図 2.7.4-付録-14 Mean (±SE) and Median Over Time in Absolute Lymphocytes Counts - PCI32765MCL2001 (Study JNJ-54179060-Z_SCS: Safety Population)



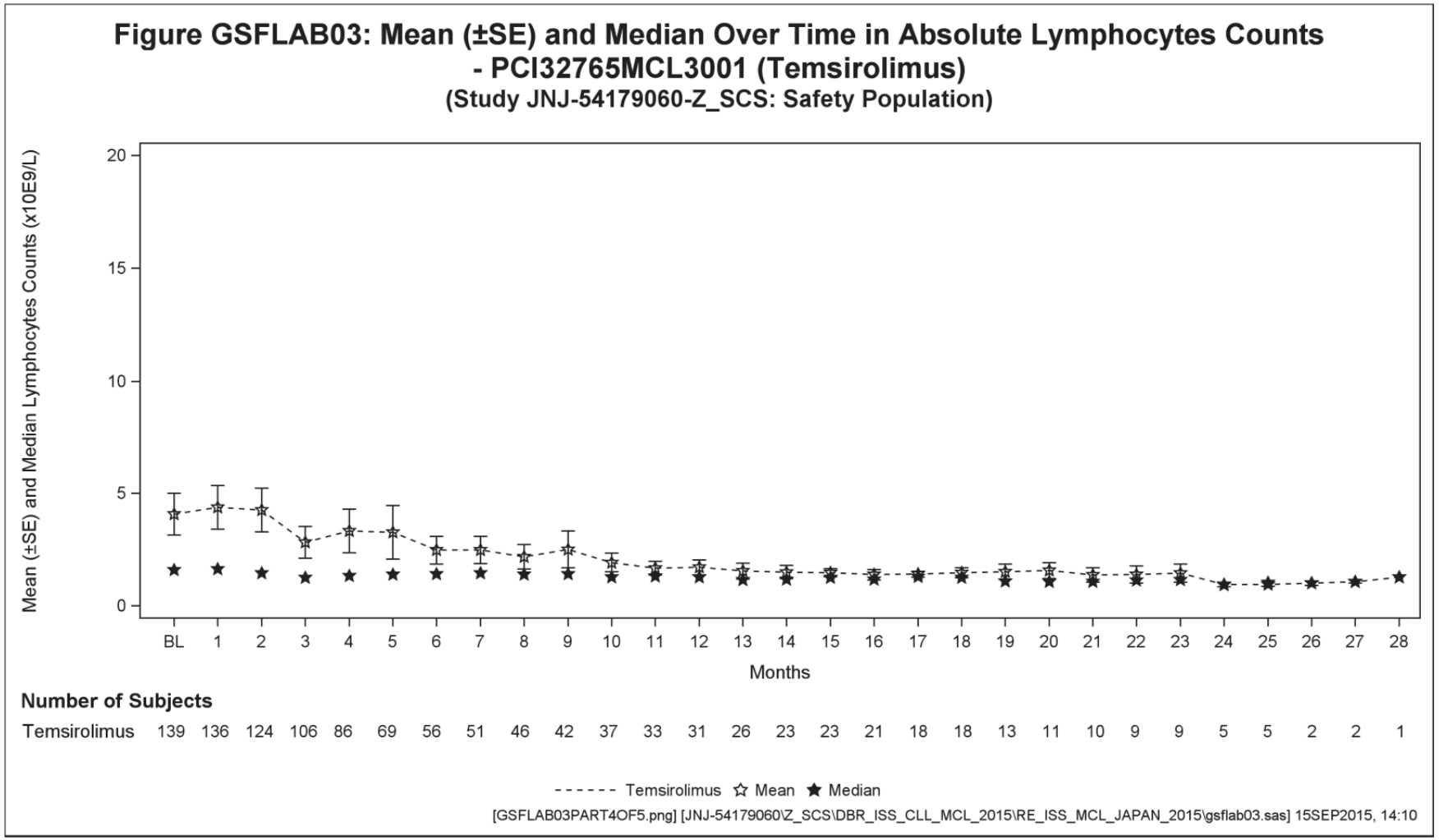

参照元：5.3.5.3.1 ISS GSFLAB03PART2OF5

図 2.7.4-付録-15 Mean (±SE) and Median Over Time in Absolute Lymphocytes Counts - PCI32765MCL3001 (Ibrutinib) (Study JNJ-54179060-Z_SCS: Safety Population)




参照元：5.3.5.3.1 ISS GSFLAB03PART3OF5

図 2.7.4-付録-16 Mean (±SE) and Median Over Time in Absolute Lymphocytes Counts - PCI32765MCL3001 (Temsirolimus) (Study JNJ-54179060-Z_SCS: Safety Population)




参照元：5.3.5.3.1 ISS GSFLAB03PART4OF5

## 2.7.5 参考文献

2.7 臨床概要における参考文献の掲載先を以下に示す。

2.7.1 生物薬剤学試験及び関連する分析法：該当なし
2.7.2 臨床薬理試験：「参考文献」の項
2.7.3 臨床的有効性：「参考文献」の項
2.7.4 臨床的安全性：「参考文献」の項

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## 2.7.6　個々の試験のまとめ

全臨床試験一覧表

| 試験の種類 | 試験番号 | 試験報告書添付場所 | 試験の目的 | 試験デザイン及び対照の種類 | 被験薬及び対照薬 投与方法　投与経路 | 被験者数 | 健康被験者又は患者の診断名 | 投与期間 | 試験の進行状況報告書の種類 |
|---|---|---|---|---|---|---|---|---|---|
| 有効性<br>安全性<br>薬物動態 | PCI-32765 MCL2002 | 5.3.5.2.1 | 主要目的<br>再発又は難治性マントル細胞リンパ腫（MCL）患者を対象に，独立判定委員会（IRC）が判定したイブルチニブの全奏効率（ORR）［完全奏効（CR）＋部分奏効（PR）］を評価する。<br><br>副次目的<br>・以下の評価項目について検討する。<br>- 奏効持続期間（DOR）<br>- 奏効到達時間<br>- 無増悪生存期間（PFS）<br>- 全生存期間（OS）<br>-安全性<br>・イブルチニブの薬物動態を探索的に検討する。 | 多施設共同，単群，第 II 相試験 | 28 日間を 1 サイクルとしてイブルチニブ 560 mg を 1 日 1 回経口投与 | 16 例 | 1 レジメン以上 5 レジメン以下の前治療を実施した後に疾患進行した，再発又は難治性の日本人 MCL 患者 | 疾患進行（又は CR 到達被験者の場合は再発），耐容不能な毒性の発現，又は試験終了時のいずれか早い時点まで | 実施中<br>中間報告書 |
| 有効性<br>安全性 | PCYC-1104-CA | 5.3.5.2.2-1<br>5.3.5.2.2-2 | 主要目的<br>再発又は難治性 MCL 患者を対象に，イブルチニブの有効性を評価する。<br><br>副次目的<br>この患者集団におけるイブルチニブの 1 日 1 回，固定用量投与レジメン（560 mg/日）の安全性を評価する。 | 非盲検，多施設共同，国際共同，第 II 相試験 | イブルチニブ 560 mg を 1 日 1 回経口投与 | ボルテゾミブ未治療コホート：<br>63 例<br><br>ボルテゾミブ既治療コホート：<br>48 例 | 1 レジメン以上 5 レジメン以下の前治療歴がある再発又は難治性 MCL 患者 | 疾患進行又は耐容不能な毒性の発現が認められるまで | 完了<br>完全な報告書 |

| 試験の種類 | 試験番号 | 試験報告書添付場所 | 試験の目的 | 試験デザイン及び対照の種類 | 被験薬及び対照薬<br>投与方法　投与経路 | 被験者数 | 健康被験者又は患者の診断名 | 投与期間 | 試験の進行状況報告書の種類 |
|---|---|---|---|---|---|---|---|---|---|
| 有効性<br>薬物動態<br>バイオマーカー<br>安全性 | PCI-32765<br>MCL3001 | 5.3.5.1.1 | 主要目的<br>1 レジメン以上のリツキシマブ併用の化学療法を前治療として受けた，再発又は難治性 MCL を対象に，イブルチニブがテムシロリムス投与と比較して，PFS を延長させるかどうか検討する。<br><br>副次目的<br>・以下の項目をテムシロリムスと比較する。<br>- イブルチニブの奏効率<br>- OS<br>- 1 年生存率<br>- DOR<br>- 安全性<br>・イブルチニブの薬物動態プロファイルの特性を評価する。 | ランダム化，実薬対照，非盲検，多施設共同，第 III 相試験 | イブルチニブ群：<br>21 日間を 1 サイクルとして，イブルチニブ 560 mg を 1 日 1 回経口投与<br><br>テムシロリムス群：<br>21 日間を 1 サイクルとして，最初のサイクルでは Day 1，Day 8，及び Day 15 にテムシロリムス 175 mg を，以降の 21 日サイクルでは，それぞれ Day 1，Day 8，及び Day 15 に 75 mg を静脈内投与 | イブルチニブ群：<br>139 例<br><br>テムシロリムス群：<br>141 例 | 1 レジメン以上のリツキシマブ併用の化学療法歴がある再発又は難治性 MCL 患者 | 疾患進行，耐容不能な毒性の発現のいずれか早い時点まで | 実施中<br>中間報告書 |

| 試験の種類 | 試験番号 | 試験報告書添付場所 | 試験の目的 | 試験デザイン及び対照の種類 | 被験薬及び対照薬投与方法　投与経路 | 被験者数 | 健康被験者又は患者の診断名 | 投与期間 | 試験の進行状況報告書の種類 |
|---|---|---|---|---|---|---|---|---|---|
| 有効性<br>安全性<br>薬物動態<br>バイオマーカー | PCI-32765<br>MCL2001 | 5.3.5.2.3-1<br>5.3.5.2.3-2 | 主要目的<br>1 レジメン以上のリツキシマブ併用の化学療法を前治療として受け，ボルテゾミブ治療後に疾患進行が認められた MCL 患者を対象に，イブルチニブの全奏効率（ORR）を IRC により評価する。<br><br>副次目的<br>・イブルチニブの DOR，PFS，OS，及び安全性を評価する。<br>・経口投与後のイブルチニブの薬物動態特性を明らかにする。<br>・イブルチニブの曝露指標に関連する臨床又はバイオマーカー情報との潜在的関連性を探索する。<br>・Functional Assessment of Cancer Therapy-Lymphoma（FACT-Lym）及び EuroQol（EQ-5D）を用いて患者報告アウトカム（PRO）を評価する。<br>・B 細胞受容体のシグナル伝達を変化させる，又は代替シグナル伝達経路を活性化するバイオマーカーを特定し，イブルチニブに対する反応との関連を探索する。 | 多施設共同，単群，第 II 相試験 | 21 日間を 1 サイクルとして，イブルチニブ 560 mg を 1 日 1 回経口投与 | 120 例 | 1 レジメン以上のリツキシマブ併用の化学療法歴があり，2 サイクル以上のボルテゾミブ治療後に疾患進行した MCL 患者 | 疾患進行，CR 到達後の再発，耐容不能な毒性の発現，又は試験終了のいずれか早い時点まで | 完了<br>完全な報告書 |

| 試験の種類 | 試験番号 | 試験報告書添付場所 | 試験の目的 | 試験デザイン及び対照の種類 | 被験薬及び対照薬<br>投与方法　投与経路 | 被験者数 | 健康被験者又は患者の診断名 | 投与期間 | 試験の進行状況報告書の種類 |
|---|---|---|---|---|---|---|---|---|---|
| 薬物動態<br>薬力学<br>ファーマコゲノミクス<br>安全性 | PCI-32765<br>CLL1007 | 5.3.4.1.1 | 主要目的<br>Part 1<br>健康成人を対象に，イブルチニブ 1680 mg を投与したときの安全性及び忍容性を評価する。<br>Part 2<br>治療用量又は治療用量を上回る用量のイブルチニブを単回投与したときの QT/QTc 間隔及び心電図への影響を評価する。<br><br>副次目的<br>Part 1 及び Part 2<br>イブルチニブ及び代謝物 PCI-45227 の薬物動態を評価する。<br>Part 2<br>他の心電図パラメータへの影響，安全性，及び忍容性を評価する。 | Part 1：<br>第 I 相，非盲検，2 期，単回投与試験<br><br>Part 2：<br>第 I 相，ランダム化，プラセボ及び実薬対照，二重盲検，単回投与，4 期クロスオーバー試験 | Part 1：<br>第 1 期では，イブルチニブ 840 mg を単回投与した。<br>第 2 期では，最初の 3 例にイブルチニブ 1680 mg を投与し，Grade 3 以上の毒性は認められず，消化管に対する忍容性が認められたため，残る 5 例にイブルチニブ 1680 mg を投与した。各投与期の間には，7 日以上のウォッシュアウト期間を設けた。<br><br>Part 2：<br>4 つの投与順序のいずれかにランダムに割り付け，イブルチニブ 1680 mg，イブルチニブ 840 mg，プラセボ，及びモキシフロキサシンを単回投与した。各投与の間には，7 日以上のウォッシュアウト期間を設けた。 | Part 1：<br>8 例<br>Part 2：<br>20 例 | 健康成人 | Part 1：<br>約 42 日<br>Part 2：<br>約 58～76 日 | 完了<br>完全な報告書 |

## 2.7.6.1　国内臨床第 II 相試験（PCI-32765MCL2002，評価資料：5.3.5.2.1）

### 2.7.6.1.1　概要

#### 2.7.6.1.1.1　計画

**(1) 治験の標題**

BTK 阻害剤イブルチニブの再発又は難治性の MCL 患者を対象とした第 II 相試験

**(2) 治験責任医師**

[redacted]，他

**(3) 公表文献（引用文献）**

該当なし

**(4) 治験実施期間**

2014 年 8 月 [redacted] 日（最初の被験者の同意取得日）～[redacted] 年 [redacted] 月 [redacted] 日（初回解析のデータカットオフ日）

**(5) 開発の相**

第 II 相

**(6) 目的**

主要目的は，再発又は難治性マントル細胞リンパ腫（mantle cell lymphoma，MCL）患者を対象に，独立判定委員会（Independent Review Committee，IRC）が判定したイブルチニブの全奏効率（overall response rate，ORR）［完全奏効（complete response，CR） + 部分奏効（partial response，PR）］を評価することである。副次目的は，奏効持続期間（duration of response，DOR），奏効到達時間，無増悪生存期間（progression-free survival，PFS），全生存期間（overall survival，OS），及びイブルチニブの安全性を評価し，イブルチニブの薬物動態を探索的に検討することである。

**(7) 治験方法**

本試験は，1 レジメン以上 5 レジメン以下の前治療を実施した後に疾患進行が認められた再発又は難治性 MCL を有する日本人被験者を対象に，イブルチニブ単剤投与による有効性及び安全性を評価し，更にイブルチニブの薬物動態を探索的に検討する，多施設共同，単群，第 II 相試験である。抗腫瘍効果の評価に必要な評価可能な被験者数 14 例を確保するため，約 16 例を組み入れることとした。適格性はスクリーニング期間中に判定した。投与期間中，疾患進行（又は CR 到達被験者の場合は再発），耐容不能な毒性の発現，又は試験終了時のいずれか早い時点まで，

28 日間を 1 サイクルとしてイブルチニブ 560 mg を 1 日 1 回経口投与した。投与サイクルは 28 日連続（中断なし）の自己投与とした。イブルチニブの用量は，毒性の重症度及び転帰に基づき，維持又は減量を可能とした。毒性の発現による減量後の再増量は禁止した。

有効性の評価は，イブルチニブの投与開始後 24 週間は 8 週ごとに，その後は疾患進行，死亡，治験参加の同意撤回，又は試験終了時のいずれか早い時点まで 12 週ごとに実施した。PFS，OS，MCL に対する後治療に関する情報を収集した。データカットオフは 2 回予定した。主要解析の初回のデータカットオフは，すべての被験者が 7 サイクル目の Day 1 の有効性評価を終了した時点か，又は 7 サイクル目の Day 1 の評価終了前にイブルチニブの投与を中止した時点と定義し，初回データカットオフまでのデータが中間報告に含まれる。被験者の追跡調査は，試験終了時，すなわち最後の被験者の登録 2 年後の時点，厚生労働省が製造販売を承認した時点，又は治験依頼者が本試験を中止した時点のいずれか早い時点まで継続することとした。2 回目のデータカットオフは試験終了時を予定した。

治験依頼者や治験実施医療機関とは独立した放射線科医及び腫瘍内科医で構成される IRC が，本試験の主要評価項目を評価するために設置された。Revised Response Criteria for Malignant Lymphoma（Cheson 2007）に従い放射線科医が判定した X 線画像評価に基づき，腫瘍内科医が奏効又は進行を判定し，全般的な奏効を評価した。

本試験では，治験依頼者や治験実施医療機関とは独立したメンバーで構成される安全性モニタリング委員会を設置した。本委員会は，本試験で新たに得られたイブルチニブの安全性情報をすべて入手した。入手した情報に基づき，本委員会は，必要に応じて治験依頼者に対し本試験の継続，中断，又は中止を勧告することとした。

### (8) 被験者数（計画時及び解析時）

本試験には適格な被験者約 16 例を組み入れることとした。イブルチニブを 1 回以上投与された被験者を安全性解析対象集団とした。抗腫瘍効果の評価可能な解析対象集団は，中央病理診断医により MCL が確定診断され，イブルチニブを 1 回以上投与され，ベースライン後に 1 回以上腫瘍評価をされた被験者と定義した。薬物動態解析対象集団は，イブルチニブ投与された解析対象集団のうち，イブルチニブ投与後の薬物動態用サンプルを 1 回以上採取されたすべての被験者とした。本試験では，19 例から同意を取得し，16 例がイブルチニブを投与された。全 16 例を薬物動態解析対象集団，抗腫瘍効果の評価可能な解析対象集団，及び安全性解析対象集団とした。

### (9) 診断及び主な組入れ基準

主な選択基準は，20 歳以上の日本人で，中央病理診断医により病理学的に MCL と確定診断されている被験者とした。また，被験者は，1 レジメン以上 5 レジメン以下の MCL に対する治療歴を有し，Revised Response Criteria for Malignant Lymphoma（Cheson 2007）に基づく測定可能病変を少なくとも 1 カ所以上有し，Eastern Cooperative Oncology Group（ECOG）Performance Status が 0 又は 1 であることとした。

### (10) 被験薬，用量及び投与方法，ロット番号

イブルチニブ硬質ゼラチンカプセルは，有効成分 140 mg を含有する経口製剤であり，28 日間を 1 サイクルとして 1 日 1 回 560 mg を投与した。1 回当たりの用量を 560 mg とするため 4 カプセルの服薬を被験者に指示した。本試験では，イブルチニブ 1 ロット（ロット番号：L0403953）を使用した。

### (11) 対照薬，用量及び投与方法，ロット番号

該当なし

### (12) 投与期間

疾患進行（又は CR 到達被験者の場合は再発），耐容不能な毒性の発現，又は試験終了時のいずれか早い時点まで，28 日間を 1 サイクルとしてイブルチニブ 560 mg を 1 日 1 回経口投与することとした。本試験の終了は，最後の被験者の登録 2 年後の時点，厚生労働省が製造販売を承認した時点，又は治験依頼者が本試験を中止した時点のいずれか早い時点と定義した。

### (13) 評価項目

有効性の評価

スクリーニング時のコンピューター断層撮影（CT）スキャンの実施を必須とした。CT で十分な画像が得られなかった場合は，腫瘍部位の評価に磁気共鳴画像（MRI）を使用可能とした。脳 MRI と腰椎穿刺は，臨床的に必要な場合のみ実施することとした。［$^{18}$F］-フルオロデオキシグルコースを用いた陽電子放射型断層撮影（positron emission tomography，PET）（頭蓋底部から大腿骨近位部）による全身スキャンは，スクリーニング時，腫瘍サイズの最大縮小時（CR 到達時又は 2 回続けて撮像した CT スキャンでさらなる腫瘍縮小が確認されなかった場合など），CR 到達後の再発時，及び CT 上で新規病変が検出され疾患進行が疑われた時点で実施することとした。ベースライン時に腫瘍が PET 検査で陰性であった被験者については，CT スキャンに基づき奏効評価を実施した。ベースライン時に消化管病変を有する被験者については，CR を確認するために内視鏡検査の実施を必須とした。

スクリーニング時に骨髄穿刺及び生検を実施した。骨髄病変を有する被験者は，CR 到達時に再度骨髄評価を実施することとした。他の腫瘍部位については，X 線画像，身体所見，必要に応じてその他の手順により評価した（試験期間中はベースライン時に用いた腫瘍評価方法と同一の方法を用いて評価した）。

有効性評価項目

主要評価項目は ORR とし，Revised Response Criteria for Malignant Lymphoma（Cheson 2007）に従い IRC が判定し，CR 又は PR に到達した抗腫瘍効果の評価可能な被験者の割合と定義した。副次評価項目は，DOR（CR 又は PR），奏効到達時間（CR 又は PR），PFS（初回投与日から疾患進行若しくは CR 到達後の再発が最初に認められた時点，又は死亡時点までを測定），及び OS（初回投与日からいかなる原因による死亡までの期間）とした。

薬物動態の評価

外国人データを用いて構築されたモデルに基づき薬物動態モデルパラメータ（経口クリアランスなど）を推定し，Bayesian feedback approach により曝露量パラメータ（投与間隔内の AUC など）を示す目的で，血漿中イブルチニブ濃度を非線形混合効果モデルにより解析した。

安全性の評価

安全性は，身体所見（リンパ腫の B 症状及び眼球の変化の評価を含む），ECOG Performance Status，臨床検査，有害事象，及び併用薬の調査結果に基づき評価した。同意取得後から最終投与後 30 日以内又は MCL に対する後治療の開始までの期間に発現した有害事象（有害事象として報告された臨床検査値異常を含む）を収集した。有害事象の程度（重症度）は，National Cancer Institute Common Terminology Criteria for Adverse Events（NCI CTCAE）第 4.03 版に基づき判定した。特に注目すべき有害事象として，Grade 3 以上，重篤な有害事象としての出血，又は中枢神経系の出血／血腫と定義する，治験薬投与中に発現した有害事象（treatment-emergent adverse event，TEAE）を大出血事象として集計した。

### (14) 統計手法

イブルチニブの粗 ORR を 60%と仮定した場合，検出力 94%，片側有意水準 0.05 で ORR が 20%以上であることを示すために，抗腫瘍効果の評価可能な被験者数として 14 例が必要であった。有効性の評価が不可能な被験者が 10%と仮定し，抗腫瘍効果の評価可能な被験者を 14 例確保するため，本試験では約 16 例の被験者を組み入れることとした。中間解析は予定しなかった。主要評価項目である IRC が判定した ORR（CR + PR）の最終解析は，最後の被験者の組入れから約 24 週間後に抗腫瘍効果の評価可能な解析対象集団に基づき実施した。奏効率及びその 90%信頼区間（CI）の算出には，二項分布に基づく直接確率法を用いた。DOR 及び PFS の分布の推定には，Kaplan-Meier 法を用いた。DOR，奏効到達時間，PFS 及び OS の解析は ORR と同じデータカットオフ時点で実施し，これらの評価項目のデータは，試験終了時，すなわち最後の被験者の登録 2 年後の時点又は厚生労働省が製造販売を承認した時点のいずれかの時点に更新することとした。安全性評価項目は，有害事象の発現割合，重症度，イブルチニブとの因果関係，イブルチニブに対する処置，有害事象の種類，被験者の身体所見における臨床的に重大な変化，バイタルサイン，臨床検査値，及び ECOG performance status とした。イブルチニブ及び代謝物 PCI-45227（測定可能かつ重要と判断された場合）の血漿中濃度は，各測定時点で記述統計量を用いて要約した。

## 2.7.6.1.1.2 結果

### (1) 対象集団

本試験では，19 例から同意を取得し，16 例がイブルチニブを投与された。

データカットオフ時点で，16 例中 11 例（68.8%）がイブルチニブの投与を継続しており，5 例（31.3%）がイブルチニブの投与を中止した。このうち 4 例は疾患進行による中止，1 例は TEAE（敗血症）による中止であった。敗血症を発現した被験者は，イブルチニブの投与中止後に疾患進行のため死亡した。イブルチニブ投与を中止した 5 例すべてが死亡により試験を中止した。

年齢の中央値は 72.0 歳（範囲：55～83 歳）であり，被験者の 75.0%（12 例）が男性，25.0%（4 例）が女性であった。

被験者の多く（75.0%）が Ann Arbor 分類で Stage IV と診断された。MCL 国際予後指標（Mantle Cell Lymphoma International Prognostic Index，MIPI）簡略版に基づく分類の内訳は，low-risk（25.0%，4 例），intermediate-risk（56.3%，9 例），及び high-risk（18.8%，3 例）であった。

被験者の半数（50.0%，8 例）が 3 レジメン以上，6 例（37.5%）が 1 レジメン，2 例（12.5%）が 2 レジメンの前治療を受けていた。難治性 MCL（直近の MCL に対する治療の最良効果が安定又は疾患進行）であった被験者は 4 例であった。

治験実施計画書からの重要な逸脱は 1 例で報告され，「用法・用量の逸脱」に分類された。当該被験者は，4 サイクル目の Day 85 から Day 97 の間，イブルチニブの投与を本人の意思で中断していた。

イブルチニブの投与期間の中央値は 6.46 カ月（範囲：2.8～8.3 カ月）であった。相対用量強度の中央値は 99.64%（範囲：47.9%～100.0%）であった。16 例中 2 例（12.5%）が TEAE のためイブルチニブが減量された。5 例（31.3%）が連続 7 日間以上イブルチニブ投与を中断した。

### (2) 有効性

抗腫瘍効果の評価可能な解析対象集団において IRC が判定した ORR（CR 又は PR）は 87.5%（14/16 例，直接確率法による 90% CI：65.6～97.7）であった。最良効果は，2 例（12.5%）が CR，12 例（75.0%）が PR であった。本試験で得られた ORR の直接確率法による 90% CI の下限が事前に定義した閾値 20%を上回ったことは，日本人の再発又は難治性 MCL 患者におけるイブルチニブの有効性を示している。イブルチニブは，被験者の年齢，性別，Ann Arbor 分類，MIPI 簡略版のスコア，前治療のレジメン数，ベースラインの難治性 MCL の有無にかかわらず有効であった。

抗腫瘍効果の評価可能な解析対象集団において治験担当医師が判定した ORR は，93.8%（15/16 例，直接確率法による 90% CI：73.6～99.7）であり，IRC が判定した ORR と同程度であった。

すべての抗腫瘍効果の評価可能な被験者（14 例）において IRC が判定した奏効到達時間の中央値は 1.84 カ月（範囲：0.7～5.3 カ月）であった。IRC が判定した DOR 及び PFS の中央値は未達であった（範囲：DOR 1.1～6.4 カ月以上，PFS 2.8～8.0 カ月以上）。Time-to-events（DOR，PFS，及び OS）の結果は，データカットオフ時点での観察期間が限られているため不十分であった。

### (3) 安全性

イブルチニブを投与された 16 例について安全性を評価したところ，日本人の再発又は難治性 MCL 患者におけるイブルチニブの安全性は概ね良好であることが示された。TEAE の多くは軽度又は中等度であり，管理可能であった。

- イブルチニブを投与された 16 例が 1 件以上の TEAE を発現した。高頻度（4 例以上）に発現した TEAE は，下痢及び口内炎（各 6 例，37.5%），血小板数減少（5 例，31.3%），貧

血（4 例，25.0%）であった。重症度が Grade 3 以上の TEAE を 1 件以上発現した被験者は 8 例（50.0%）であった。高頻度に発現した Grade 3 以上の TEAE は，疾患進行（3 例，18.8%）であり，疾患進行以外の Grade 3 以上の TEAE は 1 例に発現した。

- イブルチニブの最終投与後 30 日以内に，重篤な TEAE である疾患進行により死亡した被験者は 3 例であった。いずれもイブルチニブと関連なしと判断された。重篤な TEAE は 16 例中 5 例（31.3%）に 4 件発現し，疾患進行（3 例が死亡），高尿酸血症及び白血球増加症（1 例），敗血症（1 例）であった。高尿酸血症は発現翌日に消失したが，白血球増加症は未回復であった。いずれもイブルチニブと関連なしと判断された。敗血症は治験担当医師により軽快と報告され，イブルチニブと関連ありと判断された。いずれの被験者も疾患進行により死亡した。イブルチニブ投与の中止に至った TEAE はすべて重篤と判断された。イブルチニブの減量に至った TEAE（全身性皮疹，血小板数減少，口内炎）は 2 例に発現した。
- 出血に関連した TEAE は 5 例（31.3%）に発現し，すべて非重篤かつ Grade 1 又は Grade 2 であった。大出血事象を発現した被験者はいなかった。治験薬投与後に発現した中枢神経系の出血／血腫はなかった。出血関連の TEAE によりイブルチニブ投与を中止した被験者はいなかった。
- 過敏症に関連した TEAE は，16 例中 11 例（68.8%）に発現した。このうち 1 例は，重篤度が Grade 3 の口内炎を発現した。
- 感染に関連した TEAE は 10 例（62.5%）に発現した。このうち 1 例は，重篤な TEAE でイブルチニブ投与の中止に至った敗血症（Grade 4）を発現した。
- 血液毒性に関連した TEAE は 7 例（43.8%）に発現し，貧血 4 例（25.0%），血小板減少症 3 例（18.8%），好中球減少症 1 例（6.3%）であった。このうち 1 例は Grade 3 の貧血 2 件及び Grade 3 又は Grade 4 の好中球減少症 3 件を発現した。
- 不整脈に関連した TEAE は 2 例（12.5%）に発現し，それぞれ不整脈及び心房細動であった。不整脈は Grade 3 と判定されたが，イブルチニブの用量変更には至らなかった。
- 皮膚及び皮下組織障害は 10 例（62.5%）に発現した。皮疹に関連した TEAE は 3 例に発現し，それぞれ皮疹，全身性皮疹，斑状丘疹状皮疹であった（6.3%）。皮疹は Grade 1 又は Grade 2 と判定された。
- 眼障害は 3 例（18.8%）に発現した。このうち 1 件は網膜血管障害であり，Grade 3 と判定された。
- 腎及び尿路障害は 2 例（12.5%）に発現した。このうち 1 件は腎機能障害であり，Grade 3 と判定された。
- 本試験では，その他の悪性腫瘍，肝胆道系障害，白血球停滞症候群，又は腫瘍崩壊症候群の TEAE はなかった。
- 臨床検査結果のうちベースラインから Grade 3 又は 4 に変動した TEAE は，血液学的検査項目では，Grade 3 のヘモグロビン減少（12.5%，2 例），Grade 3 の血小板数減少（12.5%，2

例），及び Grade 3 の好中球減少（6.3%，1 例），血清生化学的検査項目では，Grade 3 のクレアチニン増加（6.3%，1 例），及び Grade 3 のカリウム減少（6.3%，1 例）であった。イブルチニブの投与後にベースラインから Grade 3 又は Grade 4 にプロトロンビン国際標準比が上昇した被験者はいなかった。また，いずれの臨床検査項目でも，ベースラインから Grade 4 に変動した被験者はいなかった。リンパ球増加症が 7 例（43.8%）に認められたが，いずれも臨床的に重要ではなかった。免疫グロブリン値に経時的変化はみられなかった。

#### 2.7.6.1.1.3　結論

本試験の結果より，イブルチニブ 560 mg の 1 日 1 回投与は，日本人の再発又は難治性 MCL 患者において，有効かつ安全性も良好であることが示唆された。

### 2.7.6.1.2　有害事象

PCI-32765MCL2002 試験開始後から主要解析のデータカットオフ時点までに発現した，すべての TEAE 及び治験薬と関連性がある TEAE を表 2.7.6.1-1 に示す。

**表 2.7.6.1-1 有害事象発現状況（PCL-32765MCL2002 試験，安全性解析対象集団）**

| MedDRA 器官別大分類<br>基本語 | TEAE | Drug-related TEAE |
|---|---|---|
| Analysis Set: All Treated Population | 16 | 16 |
| Total Number of Subjects with TEAE | 16 (100.0%) | 15 (93.8%) |
| 胃腸障害 | 10 (62.5%) | 8 (50.0%) |
| 下痢 | 6 (37.5%) | 5 (31.3%) |
| 口内炎 | 6 (37.5%) | 4 (25.0%) |
| 便秘 | 3 (18.8%) | 1 (6.3%) |
| 消化不良 | 2 (12.5%) | 1 (6.3%) |
| 悪心 | 2 (12.5%) | 2 (12.5%) |
| 上腹部痛 | 1 (6.3%) | 1 (6.3%) |
| 肛門出血 | 1 (6.3%) | 0 |
| 舌痛 | 1 (6.3%) | 1 (6.3%) |
| 口腔内出血 | 1 (6.3%) | 1 (6.3%) |
| 感染症および寄生虫症 | 10 (62.5%) | 5 (31.3%) |
| 上気道感染 | 3 (18.8%) | 0 |
| 鼻咽頭炎 | 2 (12.5%) | 0 |
| 皮膚感染 | 2 (12.5%) | 2 (12.5%) |
| 感染 | 1 (6.3%) | 0 |
| インフルエンザ | 1 (6.3%) | 0 |
| 爪囲炎 | 1 (6.3%) | 1 (6.3%) |
| 咽頭炎 | 1 (6.3%) | 1 (6.3%) |
| 敗血症 | 1 (6.3%) | 1 (6.3%) |
| 扁桃炎 | 1 (6.3%) | 0 |
| 皮膚および皮下組織障害 | 10 (62.5%) | 7 (43.8%) |
| 皮膚乾燥 | 3 (18.8%) | 1 (6.3%) |
| 皮膚炎 | 1 (6.3%) | 0 |
| 湿疹 | 1 (6.3%) | 0 |
| 皮下出血 | 1 (6.3%) | 1 (6.3%) |
| 爪変色 | 1 (6.3%) | 0 |
| 爪破損 | 1 (6.3%) | 1 (6.3%) |
| 点状出血 | 1 (6.3%) | 1 (6.3%) |
| そう痒症 | 1 (6.3%) | 0 |
| 発疹 | 1 (6.3%) | 1 (6.3%) |
| 全身性皮疹 | 1 (6.3%) | 1 (6.3%) |

| MedDRA 器官別大分類<br>基本語 | TEAE | Drug-related TEAE |
|---|---|---|
| 斑状丘疹状皮疹 | 1 (6.3%) | 1 (6.3%) |
| 皮膚脆弱性 | 1 (6.3%) | 1 (6.3%) |
| 一般・全身障害および投与部位の状態 | 9 (56.3%) | 6 (37.5%) |
| 疾患進行 | 3 (18.8%) | 0 |
| 疲労 | 3 (18.8%) | 3 (18.8%) |
| 倦怠感 | 2 (12.5%) | 2 (12.5%) |
| 胸部不快感 | 1 (6.3%) | 0 |
| インフルエンザ様疾患 | 1 (6.3%) | 1 (6.3%) |
| 臨床検査 | 8 (50.0%) | 7 (43.8%) |
| 血小板数減少 | 5 (31.3%) | 5 (31.3%) |
| アラニンアミノトランスフェラーゼ増加 | 2 (12.5%) | 1 (6.3%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 2 (12.5%) | 1 (6.3%) |
| 血中ビリルビン増加 | 2 (12.5%) | 2 (12.5%) |
| 血中アルカリホスファターゼ増加 | 1 (6.3%) | 0 |
| 血中クレアチニン増加 | 1 (6.3%) | 0 |
| γ－グルタミルトランスフェラーゼ増加 | 1 (6.3%) | 0 |
| リンパ球数減少 | 1 (6.3%) | 1 (6.3%) |
| リンパ球数増加 | 1 (6.3%) | 1 (6.3%) |
| 血液およびリンパ系障害 | 7 (43.8%) | 6 (37.5%) |
| 貧血 | 4 (25.0%) | 4 (25.0%) |
| 血小板減少症 | 3 (18.8%) | 3 (18.8%) |
| 白血球増加症 | 2 (12.5%) | 1 (6.3%) |
| リンパ球増加症 | 2 (12.5%) | 2 (12.5%) |
| 好中球減少症 | 1 (6.3%) | 1 (6.3%) |
| 代謝および栄養障害 | 5 (31.3%) | 5 (31.3%) |
| 食欲減退 | 3 (18.8%) | 3 (18.8%) |
| 低カリウム血症 | 2 (12.5%) | 2 (12.5%) |
| 高尿酸血症 | 1 (6.3%) | 0 |
| 低ナトリウム血症 | 1 (6.3%) | 1 (6.3%) |
| 低リン酸血症 | 1 (6.3%) | 1 (6.3%) |
| 傷害，中毒および処置合併症 | 4 (25.0%) | 2 (12.5%) |
| 挫傷 | 2 (12.5%) | 1 (6.3%) |
| 裂傷 | 2 (12.5%) | 2 (12.5%) |
| 関節脱臼 | 1 (6.3%) | 0 |
| 神経系障害 | 4 (25.0%) | 2 (12.5%) |
| 頭痛 | 2 (12.5%) | 1 (6.3%) |
| 末梢性ニューロパチー | 2 (12.5%) | 2 (12.5%) |
| 体位性めまい | 1 (6.3%) | 0 |
| 眼障害 | 3 (18.8%) | 0 |
| 眼乾燥 | 1 (6.3%) | 0 |
| 点状角膜炎 | 1 (6.3%) | 0 |
| 網膜裂孔 | 1 (6.3%) | 0 |
| 網膜血管障害 | 1 (6.3%) | 0 |
| 筋骨格系および結合組織障害 | 3 (18.8%) | 2 (12.5%) |
| 関節炎 | 1 (6.3%) | 0 |
| 筋痙縮 | 1 (6.3%) | 1 (6.3%) |
| 骨炎 | 1 (6.3%) | 1 (6.3%) |
| 心臓障害 | 2 (12.5%) | 1 (6.3%) |
| 不整脈 | 1 (6.3%) | 0 |
| 心房細動 | 1 (6.3%) | 1 (6.3%) |
| 精神障害 | 2 (12.5%) | 0 |
| 譫妄 | 1 (6.3%) | 0 |
| うつ病 | 1 (6.3%) | 0 |
| 腎および尿路障害 | 2 (12.5%) | 2 (12.5%) |
| 血尿 | 1 (6.3%) | 1 (6.3%) |
| 蛋白尿 | 1 (6.3%) | 0 |
| 腎機能障害 | 1 (6.3%) | 1 (6.3%) |
| 呼吸器，胸郭および縦隔障害 | 2 (12.5%) | 1 (6.3%) |
| 鼻出血 | 1 (6.3%) | 1 (6.3%) |

| MedDRA 器官別大分類<br>基本語 | TEAE | Drug-related TEAE |
|---|---|---|
| 鼻漏 | 1 (6.3%) | 0 |
| 血管障害 | 1 (6.3%) | 0 |
| 高血圧 | 1 (6.3%) | 0 |

TEAE=治験薬投与後に発現した有害事象（Treatment Emergent Adverse Event）
MedDRA/J 18.0 を用いてコード化した
「治験薬と関連性がある有害事象」は，イブルチニブとの因果関係が「可能性小」，「可能性大」，又は「ほぼ確実」と判定された有害事象と定義した
参照元：5.3.5.2.1 MCL2002 試験 CSR Attachment TSFAE04，TSFAE05

### 2.7.6.1.3　死亡及び重篤な有害事象の個別症例の詳細

(1) 有害事象による死亡例

1) イブルチニブと関連性がある死亡例

該当なし

2) イブルチニブと関連性がない死亡例

a) 被験者番号 MCL2002-81000203

■ Demographics and Baseline Characteristics

□ Country: JPN
□ Race: ASIAN
□ Age (yrs): 6[redacted]
□ Sex: Male
□ Baseline height (cm): 164
□ Baseline weight (kg): 49.6
□ Baseline BSA (m**2): 1.7
□ Baseline ECOG: 1
□ Ann arbor stage: IV
□ Prior number of regimens: 4
□ Simplified mipi score: Intermediate risk (4-5)
□ Extranodal site: Ascites; spleen
□ First study drug intake: 2014-09-10 (study day 1)
□ Last study drug intake: 2014-12-26 (study day 108)

■ Disposition Information

□ End of treatment: 2014-12-26 Progressive Disease

□ End of trial: 2015-01-03 Death

■ Fatal Adverse Events

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 疾患進行 | DISEASE PROGRESSION | 2015-01-03<br>- | 116<br>- | Y<br>5 | NOT RELATED<br>NOT APPLICABLE | N<br>FATAL | 6 |

*Note: Adverse Events are coded using MedDRA 18.0*

■ Other Serious Adverse Events

No Other Serious Adverse Events reported

■ Other Adverse Events

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 下痢 | DIARRHEA | 2014-09-15<br>- | 6<br>- | N<br>1 | PROBABLE<br>DOSE NOT CHANGED | Y<br>NOT RECOVERED/NOT RESOLVED | 5 |
| 口内炎 | MUCOSITIS ORAL | 2014-09-17<br>2014-09-18 | 8<br>2 | N<br>1 | PROBABLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 7 |

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 口内炎 | MUCOSITIS ORAL | 2014-09-18<br>2014-09-22 | 9<br>5 | N<br>2 | PROBABLE<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 8 |
| 譫妄 | DELIRIUM | 2014-09-22<br>2014-11-05 | 13<br>45 | N<br>1 | NOT RELATED<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 4 |
| 口内炎 | MUCOSITIS ORAL | 2014-09-22<br>2014-09-25 | 13<br>4 | N<br>3 | PROBABLE<br>DOSE REDUCED | Y<br>RECOVERED/RESOLVED | 9 |
| 貧血 | ANEMIA | 2014-09-24<br>- | 15<br>- | N<br>2 | PROBABLE<br>DOSE NOT CHANGED | N<br>NOT RECOVERED/NOT RESOLVED | 2 |
| 口内炎 | MUCOSITIS ORAL | 2014-09-25<br>2014-09-27 | 16<br>3 | N<br>1 | PROBABLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 10 |
| アラニンアミノトランスフェラーゼ増加 | ALT INCREASED | 2014-10-06<br>2014-11-05 | 27<br>31 | N<br>1 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 1 |
| アスパラギン酸アミノトランスフェラーゼ増加 | AST INCREASED | 2014-10-06<br>2014-11-05 | 27<br>31 | N<br>1 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 3 |

*Note: Adverse Events are coded using MedDRA 18.0*

■ Medical History

| Body System or Organ Class | Dictionary-Derived Term | Reported Term for the Medical History | End Relative to Reference Period | Toxicity Grade |
|---|---|---|---|---|
| Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) | 癌疼痛 | CANCER PAIN | DURING/AFTER | 2 |
| Gastrointestinal Disorders | 便秘 | CONSTIPATION | DURING/AFTER | 1 |
| Metabolism And Nutrition Disorders | 高尿酸血症 | HYPERURICEMIA | DURING/AFTER | 1 |
| Metabolism And Nutrition Disorders | 栄養障害 | MALNUTRITION | DURING/AFTER | 2 |
| Skin And Subcutaneous Tissue Disorders | 発疹 | RASH | DURING/AFTER | 2 |

*Note: Medical History are coded using MedDRA 18.0*

■ Disease History

| Date of initial MCL Diagnosis | Type of Histology |
|---|---|
| 2010-10-28 | DIFFUSE |

■ Study Medication

| Visit Name | Start Date of Treatment | End Date of Treatment | Study Day of Start of Treatment | Study Day of End of Treatment | Dose per Administration (mg) | Reason for Dose Adjustment | AE Sequence Number(s) |
|---|---|---|---|---|---|---|---|
| CYCLE1,DAY1 | 2014-09-10 | 2014-09-22 | 1 | 13 | 560.0 | - | - |
| CYCLE1,DAY1 | 2014-09-23 | 2014-09-24 | 14 | 15 | 0.0 | ADVERSE EVENT | 9 |
| CYCLE1,DAY1 | 2014-09-25 | 2014-10-07 | 16 | 28 | 420.0 | ADVERSE EVENT | 9 |
| CYCLE2,DAY1 | 2014-10-08 | 2014-11-04 | 29 | 56 | 420.0 | - | - |
| CYCLE3,DAY1 | 2014-11-05 | 2014-12-02 | 57 | 84 | 420.0 | - | - |
| CYCLE4,DAY1 | 2014-12-03 | 2014-12-26 | 85 | 108 | 420.0 | - | - |

■ Concomitant Medication

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication<br>Study Day of Start of Medication | End Date of Medication<br>Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| ACICLOVIR<br>(ACICLOVIR) | 2014-10-04<br>25 | 2014-12-28<br>110 | OTHER (PREVENT OF HERPES ZOSTER) | 200<br>mg | DAILY<br>ORAL | - |
| HYDROXYZINE HYDROCHLORIDE<br>(ATARAX-P) | 2014-09-05<br>-5 | 2014-09-15<br>6 | OTHER (RASH) | 25<br>mg | PRN<br>ORAL | - |
| PENTAMIDINE ISETHIONATE<br>(BENAMBAX) | -<br>- | 2014-12-03<br>85 | OTHER (PNEUMOCYSTIS CARINII PNEUMONIA) | PROPER<br>QUANTITY<br>OTHER | PRN<br>RESPIRATORY (INHALATION) | - |
| AMINO ACIDS NOS W/ELECTROLYTES NOS/GLUCOSE/TH<br>(BFLUID INJECTION) | 2014-09-18<br>9 | 2014-09-22<br>13 | OTHER (NUTRITIONAL SUPPORT) | 1000<br>mL | DAILY<br>INTRAVENOUS | - |
| ENTEROCOCCUS FAECALIS<br>(BIOFERMLN-R TABLETS) | 2014-09-18<br>9 | 2014-12-28<br>110 | ADVERSE EVENT | 1-3<br>TABLET | OTHER<br>ORAL | 5 |
| CARBOCISTEINE<br>(C-CYSTEN SYRUP) | 2014-09-21<br>12 | 2014-09-24<br>15 | ADVERSE EVENT | 4<br>mL | DAILY<br>ORAL | 8, 9 |
| DIFLORASONE DIACETATE<br>(DIFLAL OINTMENT) | 2014-08-27<br>-14 | 2014-12-28<br>110 | OTHER (RASH) | PROPER<br>QUANTITY<br>OINTMENT | PRN<br>TOPICAL | - |

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication<br>Study Day of Start of Medication | End Date of Medication<br>Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| AMINO ACIDS NOS W/COPPER/ELECTROLYTES NOS/GLU (ELNEOPA NO.1 INJECTION) | 2014-09-23<br>14 | 2014-10-07<br>28 | OTHER (NUTRITIONAL SUPPORT) | 1<br>L | DAILY<br>INTRAVENOUS | - |
| NUTRIENTS NOS (ENSURE LIQUID) | 2014-10-07<br>28 | 2014-12-28<br>110 | OTHER (NUTRITIONAL SUPPORT) | 250<br>mL | PRN<br>ORAL | - |
| FEBUXOSTAT (FEBURIC) | 2014-09-18<br>9 | 2014-12-28<br>110 | OTHER (HYPERURICEMIA) | 10<br>mg | DAILY<br>ORAL | - |
| FENTANYL (FENTANYL INJECTION) | 2014-09-18<br>9 | 2014-09-27<br>18 | OTHER (CANCER PAIN) | 336<br>mcg | DAILY<br>INTRAVENOUS | - |
| FENTANYL CITRATE (FENTOS TAPE) | 2014-10-07<br>28 | 2014-12-28<br>110 | OTHER (CANCER PAIN) | PROPER QUANTITY<br>OTHER | DAILY<br>TRANSDERMAL | - |
| GENTAMICIN SULFATE (GENTACIN OINTMENT) | 2014-09-10<br>1 | 2014-09-16<br>7 | OTHER (RASH) | PROPER QUANTITY<br>OINTMENT | PRN<br>TOPICAL | - |
| MAGNESIUM OXIDE (MAGMITT) | 2014-05-22<br>-111 | 2014-12-28<br>110 | OTHER (CONSTIPATION) | 330<br>mg | PRN<br>ORAL | - |
| MINOCYCLINE HYDROCHLORIDE (MINOMYCIN CAPSULES) | 2014-09-10<br>1 | 2014-09-16<br>7 | OTHER (RASH) | 100<br>mg | BID<br>ORAL | - |
| OLOPATADINE HYDROCHLORIDE (OLOPATADINE HYDROCHLORIDE OD TABLETS) | 2014-09-05<br>-5 | 2014-09-16<br>7 | OTHER (RASH) | 5<br>mg | BID<br>ORAL | - |
| OXYCODONE HYDROCHLORIDE (OXIFAST) | 2014-09-27<br>18 | 2014-10-07<br>28 | OTHER (CANCER PAIN) | 14.4<br>mg | DAILY<br>INTRAVENOUS | - |
| OXYCODONE HYDROCHLORIDE (OXINORM) | 2014-09-23<br>14 | 2014-12-28<br>110 | OTHER (CANCER PAIN) | 2.5<br>mg | PRN<br>ORAL | - |
| OXYCODONE HYDROCHLORIDE (OXYCONTIN) | 2014-09-05<br>-5 | 2014-09-18<br>9 | OTHER (CANCER PAIN) | 5<br>mg | BID<br>ORAL | - |
| DEXCHLORPHENIRAMINE MALEATE (POLARAMINE) | -<br>- | 2014-09-16<br>7 | OTHER (RASH) | 2<br>mg | TID<br>ORAL | - |
| PREDNISOLONE (PREDNISOLONE) | 2014-09-09<br>-1 | 2014-09-14<br>5 | OTHER (RASH) | 15<br>mg | DAILY<br>ORAL | - |
| QUETIAPINE (QUETIAPINE TABLETS) | 2014-10-03<br>24 | 2014-10-16<br>37 | ADVERSE EVENT | 25<br>mg | PRN<br>ORAL | 4 |

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication<br>Study Day of Start of Medication | End Date of Medication<br>Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| VALISONE-G<br>(RINDERON VG OINTMENT) | 2014-08-27<br>-14 | 2014-12-28<br>110 | OTHER (RASH) | PROPER QUANTITY<br>OINTMENT | PRN<br>TOPICAL | - |
| SODIUM CHLORIDE<br>(SODIUM CHLORIDE SOLUTION) | 2014-09-18<br>9 | 2014-10-07<br>28 | OTHER (NUTRITIONAL SUPPORT) | 500<br>mL | DAILY<br>INTRAVENOUS | - |
| SALBUTAMOL SULFATE<br>(SULTANOL INHALER) | -<br>- | 2014-12-03<br>85 | OTHER (PREINHALATION FOR BENAMBAX) | PROPER QUANTITY<br>PUFF | PRN<br>RESPIRATORY (INHALATION) | - |
| KETOTIFEN FUMARATE<br>(ZADITEN CAPSULES) | 2014-09-05<br>-5 | 2014-09-15<br>6 | OTHER (RASH) | 1<br>mg | QD<br>ORAL | - |
| ZINC OXIDE<br>(ZINC OXIDE OIL) | 2014-08-27<br>-14 | 2014-12-28<br>110 | OTHER (RASH) | PROPER QUANTITY<br>OINTMENT | PRN<br>TOPICAL | - |

■ Prior Systemic Therapy/Regimen

| Line of Treatment | Reported Name of Drug, Med, or Therapy | Start Date of Medication | End Date of Medication | Best Response |
|---|---|---|---|---|
| 1 | R-HIGH-CHOP,CHASER,ASCT | 2010-11-08 | 2011-02-25 | COMPLETE RESPONSE |
| 2 | MLN8237 | 2013-06-18 | 2013-08-14 | NOT EVALUABLE |
| 3 | R-BENDAMUSTINE | 2013-09-20 | 2014-02-27 | STABLE DISEASE |
| 4 | R-ESHAP | 2014-05-21 | 2014-05-26 | STABLE DISEASE |

■ Prior Radiotherapy

| Start Date of Radiotherapy<br>Study Day of Start of Radiotherapy | End Date of Radiotherapy<br>Study Day of End of Radiotherapy | Dose | Location of Radiotherapy |
|---|---|---|---|
| 2014-05-02<br>-131 | 2014-05-19<br>-114 | 30 Gray | BRAIN |
| 2014-06-25<br>-77 | 2014-06-26<br>-76 | 8 Gray | PERINEPHRIA |

■ ECOG Score

| Date of Finding<br>Study Day of Finding | Visit Name | Result |
|---|---|---|
| 2014-09-08<br>-2 | Screening | 1 |
| 2014-09-10<br>1 | Cycle1,day1 | 1 |
| 2014-09-24<br>15 | Cycle1,day15 | 1 |
| 2014-10-08<br>29 | Cycle2,day1 | 1 |
| 2014-11-05<br>57 | Cycle3,day1 | 1 |
| 2014-12-03<br>85 | Cycle4,day1 | 1 |
| 2014-12-26<br>108 | End of Treatment | 1 |

b) 被験者番号 MCL2002-81000401

■ Demographics and Baseline Characteristics

☐ Country: JPN
☐ Race: ASIAN
☐ Age (yrs): 8[redacted]
☐ Sex: Male
☐ Baseline height (cm): 158.1
☐ Baseline weight (kg): 53.1
☐ Baseline BSA (m**2): 1.7
☐ Baseline ECOG: 0
☐ Ann arbor stage: IV
☐ Prior number of regimens: 1
☐ Simplified mipi score: High risk (6-11)
☐ Extranodal site: Spleen
☐ First study drug intake: 2014-11-06 (study day 1)
☐ Last study drug intake: 2015-03-24 (study day 139)

■ Disposition Information

☐ End of treatment: 2015-03-25 Progressive Disease

☐ End of trial: 2015-04-03 Death

■ Fatal Adverse Events

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 疾患進行 | DISEASE PROGRESSION | 2015-04-03<br>- | 149<br>- | Y<br>5 | NOT RELATED<br>NOT APPLICABLE | N<br>FATAL | 6 |

*Note: Adverse Events are coded using MedDRA 18.0*

■ Other Serious Adverse Events

No Other Serious Adverse Events reported

■ Other Adverse Events

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 低ナトリウム血症 | HYPONATREMIA | 2014-11-07<br>2014-11-13 | 2<br>7 | N<br>1 | PROBABLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 11 |

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 血小板減少症 | THROMBOCYTOPENIA | 2014-11-07<br>2014-11-13 | 2<br>7 | N<br>2 | PROBABLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 13 |
| 便秘 | CONSTIPATION | 2014-11-09<br>2014-11-09 | 4<br>1 | N<br>1 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 1 |
| 便秘 | CONSTIPATION | 2014-11-10<br>2014-11-12 | 5<br>3 | N<br>2 | POSSIBLE<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 2 |
| 悪心 | NAUSEA | 2014-11-12<br>2014-11-14 | 7<br>3 | N<br>1 | PROBABLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 12 |
| 上気道感染 | UPPER RESPIRATORY INFECTION | 2014-11-18<br>2014-12-05 | 13<br>18 | N<br>1 | NOT RELATED<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 17 |
| 血小板減少症 | THROMBOCYTOPENIA | 2014-12-03<br>2015-01-05 | 28<br>34 | N<br>2 | PROBABLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 14 |
| 消化不良 | HEARTBURN | 2014-12-30<br>2015-01-18 | 55<br>20 | N<br>1 | DOUBTFUL<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 7 |
| 便秘 | CONSTIPATION | 2015-02-07<br>2015-02-11 | 94<br>5 | N<br>2 | POSSIBLE<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 3 |
| 下痢 | DIARRHEA | 2015-02-10<br>2015-02-20 | 97<br>11 | N<br>2 | DOUBTFUL<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 5 |
| 血小板減少症 | THROMBOCYTOPENIA | 2015-02-18<br>2015-02-25 | 105<br>8 | N<br>2 | PROBABLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 15 |
| 便秘 | CONSTIPATION | 2015-02-20<br>2015-02-28 | 107<br>9 | N<br>1 | POSSIBLE<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 4 |
| 低カリウム血症 | HYPOKALEMIA | 2015-02-25<br>2015-03-11 | 112<br>15 | N<br>3 | PROBABLE<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 9 |

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 消化不良 | HEARTBURN | 2015-03-06<br>- | 121<br>- | N<br>1 | DOUBTFUL<br>DOSE NOT CHANGED | Y<br>NOT RECOVERED/NOT RESOLVED | 8 |
| 血小板減少症 | THROMBOCYTOPENIA | 2015-03-11<br>2015-03-29 | 126<br>19 | N<br>2 | PROBABLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 16 |
| 低カリウム血症 | HYPOKALEMIA | 2015-03-25<br>2015-03-29 | 140<br>5 | N<br>1 | PROBABLE<br>NOT APPLICABLE | Y<br>RECOVERED/RESOLVED | 10 |

*Note: Adverse Events are coded using MedDRA 18.0*

## ■ Medical History

| Body System or Organ Class | Dictionary-Derived Term | Reported Term for the Medical History | End Relative to Reference Period | Toxicity Grade |
|---|---|---|---|---|
| Respiratory, Thoracic And Mediastinal Disorders | アレルギー性鼻炎 | ALLERGIC RHINITIS | DURING/AFTER | 1 |
| Gastrointestinal Disorders | 下痢 | DIARRHEA | DURING/AFTER | 1 |
| Cardiac Disorders | 心臓弁膜疾患 | VALVULAR DISEASE | DURING/AFTER | 1 |

*Note: Medical History are coded using MedDRA 18.0*

## ■ Disease History

| Date of initial MCL Diagnosis | Type of Histology |
|---|---|
| 2013-09-10 | DIFFUSE |

## ■ Study Medication

| Visit Name | Start Date of Treatment | End Date of Treatment | Study Day of Start of Treatment | Study Day of End of Treatment | Dose per Administration (mg) | Reason for Dose Adjustment | AE Sequence Number(s) |
|---|---|---|---|---|---|---|---|
| CYCLE1,DAY1 | 2014-11-06 | 2014-12-03 | 1 | 28 | 560.0 | - | - |
| CYCLE2,DAY1 | 2014-12-04 | 2015-01-04 | 29 | 60 | 560.0 | - | - |
| CYCLE3,DAY1 | 2015-01-05 | 2015-01-27 | 61 | 83 | 560.0 | - | - |
| CYCLE4,DAY1 | 2015-01-28 | 2015-02-24 | 84 | 111 | 560.0 | - | - |
| CYCLE5,DAY1 | 2015-02-25 | 2015-03-09 | 112 | 124 | 560.0 | - | - |
| CYCLE5,DAY1 | 2015-03-10 | 2015-03-10 | 125 | 125 | 0.0 | OTHER | - |
| CYCLE5,DAY1 | 2015-03-11 | 2015-03-24 | 126 | 139 | 560.0 | - | - |
| CYCLE5,DAY1 | 2015-03-25 | 2015-03-25 | 140 | 140 | 0.0 | OTHER | - |

■ Concomitant Medication

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication<br>Study Day of Start of Medication | End Date of Medication<br>Study Day of End of Medication | Indication | Dose<br>Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| POTASSIUM ASPARTATE<br>(ASPARA POTASSIUM) | 2015-02-25<br>112 | 2015-03-10<br>125 | ADVERSE EVENT | 300<br>mg | DAILY<br>ORAL | 9 |
| POTASSIUM ASPARTATE<br>(ASPARA POTASSIUM) | 2015-03-11<br>126 | 2015-03-24<br>139 | OTHER (PREVENTION OF HYPOKALEMIA) | 300<br>mg | DAILY<br>ORAL | - |
| POTASSIUM ASPARTATE<br>(ASPARA POTASSIUM) | 2015-03-25<br>140 | 2015-03-29<br>144 | ADVERSE EVENT | 300<br>mg | DAILY<br>ORAL | 10 |
| AMINO ACIDS NOS W/ELECTROLYTES NOS/GLUCOSE/TH<br>(BFLUID INJECTION) | 2015-03-29<br>144 | 2015-03-30<br>145 | OTHER (REPLENISHER SOLUTION) | 500<br>mL | DAILY<br>INTRAVENOUS | - |
| AMINO ACIDS NOS W/ELECTROLYTES NOS/GLUCOSE/TH<br>(BFLUID INJECTION) | 2015-03-31<br>146 | 2015-04-01<br>147 | OTHER (REPLENISHER SOLUTION) | 500<br>mL | BID<br>INTRAVENOUS | - |
| AMINO ACIDS NOS W/ELECTROLYTES NOS/GLUCOSE/TH<br>(BFLUID INJECTION) | 2015-04-02<br>148 | 2015-04-03<br>149 | OTHER (REPLENISHER SOLUTION) | 500<br>mL | DAILY<br>INTRAVENOUS | - |
| BIO-THREE<br>(BIO-THREE) | 2015-02-18<br>105 | 2015-02-19<br>106 | ADVERSE EVENT | 1<br>TABLET | TID<br>ORAL | 5 |
| BIO-THREE<br>(BIO-THREE) | 2015-02-20<br>107 | 2015-02-25<br>112 | OTHER (ADJUSTING OF THE INTESTINAL FUNCTION) | 1<br>TABLET | TID<br>ORAL | - |
| PARACETAMOL<br>(CALONAL) | 2015-04-01<br>147 | 2015-04-03<br>149 | OTHER (BACK PAIN) | 600<br>mg | TID<br>ORAL | - |
| CHLORPHENAMINE MALEATE<br>(CHLOR-TRIMETON INJECTION) | 2015-03-30<br>145 | 2015-03-30<br>145 | OTHER (INFUSION RELATED REACTION OF FFP) | 10<br>mg | DAILY<br>INTRAVENOUS | - |
| ENEMAS<br>(ENEMA) | 2015-02-10<br>97 | 2015-02-10<br>97 | ADVERSE EVENT | -<br>- | -<br>- | 3 |
| FELBINAC<br>(FELBINAC PAP) | 2015-04-01<br>147 | 2015-04-02<br>148 | OTHER (BACK PAIN) | 1<br>PATCH | DAILY<br>TRANSDERMAL | - |
| INFLUENZA VACCINE<br>(INFLUENZA HA VACCINE) | 2014-12-11<br>36 | 2014-12-11<br>36 | OTHER (PROPHYLAXIS OF INFLUENZA) | 0.5<br>mL | DAILY<br>SUBCUTANEOUS | - |
| SORBIT HARTMAN<br>(LACTEC G INJECTION) | 2015-04-03<br>149 | -<br>- | OTHER (REPLENISHER SOLUTION) | 500<br>mL | DAILY<br>INTRAVENOUS | - |

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication Study Day of Start of Medication | End Date of Medication Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| LANSOPRAZOLE<br>(LANSOPRAZOLE OD) | 2015-01-06<br>62 | 2015-01-17<br>73 | ADVERSE EVENT | 15<br>mg | DAILY<br>ORAL | 7 |
| LANSOPRAZOLE<br>(LANSOPRAZOLE OD) | 2015-01-18<br>74 | 2015-03-05<br>120 | OTHER (PROPHYLAXIS OF HEARTBURN) | 15<br>mg | PRN<br>ORAL | - |
| LANSOPRAZOLE<br>(LANSOPRAZOLE OD) | 2015-03-06<br>121 | 2015-03-29<br>144 | ADVERSE EVENT | 15<br>mg | PRN<br>ORAL | 8 |
| LANSOPRAZOLE<br>(LANSOPRAZOLE OD) | 2015-03-30<br>145 | -<br>- | ADVERSE EVENT | 15<br>mg | DAILY<br>ORAL | 8 |
| FUROSEMIDE<br>(LASIX) | 2015-04-02<br>148 | 2015-04-03<br>149 | OTHER (DIURESIS) | 10<br>mg | DAILY<br>INTRAVENOUS | - |
| MAGNESIUM OXIDE<br>(MAGLAX) | 2014-11-10<br>5 | 2014-11-11<br>6 | ADVERSE EVENT | 250<br>mg | PRN<br>ORAL | 2 |
| MAGNESIUM OXIDE<br>(MAGLAX) | 2015-02-07<br>94 | 2015-02-10<br>97 | ADVERSE EVENT | 250<br>mg | TID<br>ORAL | 3 |
| KETOPROFEN<br>(MOHRUS TAPE) | 2015-04-03<br>149 | 2015-04-03<br>149 | OTHER (BACK PAIN) | 1<br>PATCH | DAILY<br>TRANSDERMAL | - |
| MORPHINE HYDROCHLORIDE<br>(MORPHINE HYDROCHLORIDE) | 2015-04-03<br>149 | -<br>- | OTHER (BACK PAIN) | 50<br>mg | QD<br>SUBCUTANEOUS | - |
| PROCHLORPERAZINE MALEATE<br>(NOVAMIN(PROCHLORPERAZINE MALEATE)) | 2015-04-01<br>147 | 2015-04-03<br>149 | OTHER (PROPHYLAXIS OF NAUSEA) | 5<br>mg | PRN<br>ORAL | - |
| PROCHLORPERAZINE MALEATE<br>(NOVAMIN(PROCHLORPERAZINE MALEATE)) | 2015-04-02<br>148 | 2015-04-02<br>148 | OTHER (PROPHYLAXIS OF NAUSEA) | 5<br>mg | TID<br>ORAL | - |
| DANAPAROID SODIUM<br>(ORGARAN) | 2015-03-30<br>145 | 2015-04-02<br>148 | OTHER (DISSEMINATED INTRAVASCULAR COAGULATION) | 1<br>mL | BID<br>INTRAVENOUS | - |
| DANAPAROID SODIUM<br>(ORGARAN) | 2015-04-03<br>149 | 2015-04-03<br>149 | OTHER (DISSEMINATED INTRAVASCULAR COAGULATION) | 1<br>mL | DAILY<br>INTRAVENOUS | - |
| OXYCODONE HYDROCHLORIDE<br>(OXINORM(OXYCODONE HYDROCHLORIDE)) | 2015-04-01<br>147 | 2015-04-03<br>149 | OTHER (BACK PAIN) | 2.5<br>mg | PRN<br>ORAL | - |
| OXYGEN<br>(OXYGEN) | 2015-03-30<br>145 | 2015-03-30<br>145 | OTHER (INFUSION RELATED REACTION OF FFP) | PROPER OUANTITY<br>L | PRN<br>RESPIRATORY (INHALATION) | - |

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication Study Day of Start of Medication | End Date of Medication Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| OXYGEN<br>(OXYGEN) | 2015-04-03<br>149 | 2015-04-03<br>149 | OTHER (HYPOXIA) | PROPER OUANTITY<br>L | PRN<br>RESPIRATORY (INHALATION) | - |
| PA<br>(PL COMBINATION GRANULES) | 2014-11-19<br>14 | 2014-11-26<br>21 | ADVERSE EVENT | 1<br>g | PRN<br>ORAL | 17 |
| METOCLOPRAMIDE HYDROCHLORIDE<br>(PRIMPERAN INJECTION) | 2015-04-03<br>149 | 2015-04-03<br>149 | OTHER (NAUSEA) | 10<br>mg | DAILY<br>INTRAVENOUS | - |
| SENNOSIDE A+B CALCIUM<br>(PURSENNID) | 2014-11-11<br>6 | 2014-11-11<br>6 | ADVERSE EVENT | 12<br>mg | PRN<br>ORAL | 2 |
| SENNOSIDE A+B CALCIUM<br>(PURSENNID) | 2015-02-25<br>112 | 2015-02-27<br>114 | ADVERSE EVENT | 12<br>mg | PRN<br>ORAL | 4 |
| SODIUM CHLORIDE<br>(SODIUM CHLORIDE) | 2015-03-29<br>144 | 2015-03-29<br>144 | OTHER (REPLENISHER SOLUTION) | 500<br>mL | DAILY<br>INTRAVENOUS | - |
| SODIUM CHLORIDE<br>(SODIUM CHLORIDE) | 2015-03-30<br>145 | 2015-03-30<br>145 | OTHER (REPLENISHER SOLUTION) | 500<br>mL | BID<br>INTRAVENOUS | - |
| HYDROCORTISONE SODIUM SUCCINATE<br>(SOLU-CORTEF INJECTION) | 2015-03-30<br>145 | 2015-03-30<br>145 | OTHER (INFUSION RELATED REACTION OF FFP) | 100<br>mg | DAILY<br>INTRAVENOUS | - |
| UNACID /00917901/<br>(UNASYN-S KIT FOR INTRAVENOUS USE) | 2015-03-29<br>144 | 2015-03-29<br>144 | OTHER (PROPHYLAXIS OF INFECTION) | 3<br>g | BID<br>INTRAVENOUS | - |
| UNACID /00917901/<br>(UNASYN-S KIT FOR INTRAVENOUS USE) | 2015-03-30<br>145 | 2015-04-01<br>147 | OTHER (PROPHYLAXIS OF INFECTION) | 3<br>g | QID<br>INTRAVENOUS | - |
| UNACID /00917901/<br>(UNASYN-S KIT FOR INTRAVENOUS USE) | 2015-04-02<br>148 | 2015-04-02<br>148 | OTHER (PROPHYLAXIS OF INFECTION) | 6<br>g | DAILY<br>INTRAVENOUS | - |
| VITAMEDIN INTRAVENOUS<br>(VITAMEDIN FOR INTRAVENOUS INJECTION(CYANOCOBALAMIN/PYRIDOXINE HCL/THIAMINE HCL)) | 2015-03-29<br>144 | 2015-04-03<br>149 | OTHER (VITAMIN SUPPLEMENT) | 1<br>UNITS | DAILY<br>INTRAVENOUS | - |

■ Prior Systemic Therapy/Regimen

| Line of Treatment | Reported Name of Drug, Med, or Therapy | Start Date of Medication | End Date of Medication | Best Response |
|---|---|---|---|---|
| 1 | R-CHOP | 2013-10-03 | 2014-01-21 | COMPLETE RESPONSE |

## ■ Prior Radiotherapy

No Prior Radiotherapy reported

## ■ ECOG Score

| Date of Finding<br>Study Day of Finding | Visit Name | Result |
|---|---|---|
| 2014-10-16<br>-21 | Screening | 0 |
| 2014-11-06<br>1 | Cycle1,day1 | 0 |
| 2014-11-19<br>14 | Cycle1,day15 | 0 |
| 2014-12-04<br>29 | Cycle2,day1 | 0 |
| 2015-01-05<br>61 | Cycle3,day1 | 0 |
| 2015-01-28<br>84 | Cycle4,day1 | 0 |
| 2015-02-25<br>112 | Cycle5,day1 | 0 |
| 2015-03-25<br>140 | End of Treatment | 0 |

c) 被験者番号 MCL2002-81000501

■ Demographics and Baseline Characteristics

☐ Country: JPN
☐ Race: ASIAN
☐ Age (yrs): 7[redacted]
☐ Sex: Male
☐ Baseline height (cm): 171
☐ Baseline weight (kg): 57
☐ Baseline BSA (m**2): 1.9
☐ Baseline ECOG: 0
☐ Ann arbor stage: IV
☐ Prior number of regimens: 3
☐ Simplified mipi score: Intermediate risk (4-5)
☐ Extranodal site: Colon; other (bone marrow); small intestines; spleen
☐ First study drug intake: 2014-08-20 (study day 1)
☐ Last study drug intake: 2014-11-13 (study day 86)

■ Disposition Information

☐ End of treatment: 2014-11-13 Progressive Disease

☐ End of trial: 2014-11-18 Death

■ Fatal Adverse Events

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 疾患進行 | PROGRESSIVE DISEASE | 2014-11-18<br>- | 91<br>- | Y<br>5 | NOT RELATED<br>NOT APPLICABLE | N<br>FATAL | 9 |

*Note: Adverse Events are coded using MedDRA 18.0*

■ Other Serious Adverse Events

No Other Serious Adverse Events reported

■ Other Adverse Events

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 血中アルカリホスファターゼ増加 | ALP INCREASED | 2014-08-20<br>2014-09-16 | 1<br>28 | N<br>1 | NOT RELATED<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 1 |

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| アラニンアミノトランスフェラーゼ増加 | ALT INCREASED | 2014-08-20<br>2014-09-03 | 1<br>15 | N<br>1 | NOT RELATED<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 2 |
| アスパラギン酸アミノトランスフェラーゼ増加 | AST INCREASED | 2014-08-20<br>2014-09-03 | 1<br>15 | N<br>1 | NOT RELATED<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 3 |
| γ－グルタミルトランスフェラーゼ増加 | GGT INCREASED | 2014-08-20<br>2014-09-03 | 1<br>15 | N<br>2 | NOT RELATED<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 4 |
| 倦怠感 | MALAISE | 2014-08-23<br>2014-09-13 | 4<br>22 | N<br>1 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 8 |
| リンパ球増加症 | LYMPHOCYTOSIS | 2014-08-27<br>- | 8<br>- | N<br>2 | VERY LIKELY<br>DOSE NOT CHANGED | N<br>NOT RECOVERED/NOT RESOLVED | 7 |
| γ－グルタミルトランスフェラーゼ増加 | GGT INCREASED | 2014-09-03<br>2014-09-16 | 15<br>14 | N<br>1 | NOT RELATED<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 5 |
| 血小板減少症 | THROMBOCYTOPENIA | 2014-09-10<br>2014-10-01 | 22<br>22 | N<br>1 | PROBABLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 10 |
| 貧血 | WORSENING OF ANEMIA | 2014-09-10<br>- | 22<br>- | N<br>2 | POSSIBLE<br>DOSE NOT CHANGED | N<br>NOT RECOVERED/NOT RESOLVED | 12 |
| 血小板減少症 | THROMBOCYTOPENIA | 2014-10-15<br>- | 57<br>- | N<br>1 | PROBABLE<br>DOSE NOT CHANGED | N<br>NOT RECOVERED/NOT RESOLVED | 11 |
| 裂傷 | LACERATION OF FINGER | 2014-11-01<br>- | 74<br>- | N<br>1 | PROBABLE<br>DOSE NOT CHANGED | N<br>NOT RECOVERED/NOT RESOLVED | 6 |

*Note: Adverse Events are coded using MedDRA 18.0*

■ Medical History

| Body System or Organ Class | Dictionary-Derived Term | Reported Term for the Medical History | End Relative to Reference Period | Toxicity Grade |
|---|---|---|---|---|
| Immune System Disorders | 薬物過敏症 | ALLERGIC REACTION FOR BAKTAR | DURING/AFTER | 2 |
| Blood And Lymphatic System Disorders | 貧血 | ANEMIA | DURING/AFTER | 1 |
| Gastrointestinal Disorders | 便秘 | CONSTIPATION | DURING/AFTER | 2 |
| Metabolism And Nutrition Disorders | 高尿酸血症 | HYPERURICEMIA | DURING/AFTER | 1 |

*Note: Medical History are coded using MedDRA 18.0*

■ Disease History

| Date of initial MCL Diagnosis | Type of Histology |
|---|---|
| 2010-06-29 | DIFFUSE |

■ Study Medication

| Visit Name | Start Date of Treatment | End Date of Treatment | Study Day of Start of Treatment | Study Day of End of Treatment | Dose per Administration (mg) | Reason for Dose Adjustment | AE Sequence Number(s) |
|---|---|---|---|---|---|---|---|
| CYCLE1,DAY1 | 2014-08-20 | 2014-09-16 | 1 | 28 | 560.0 | - | - |
| CYCLE2,DAY1 | 2014-09-17 | 2014-10-14 | 29 | 56 | 560.0 | - | - |
| CYCLE3,DAY1 | 2014-10-15 | 2014-11-11 | 57 | 84 | 560.0 | - | - |
| CYCLE4,DAY1 | 2014-11-12 | 2014-11-13 | 85 | 86 | 560.0 | - | - |

■ Concomitant Medication

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication<br>Study Day of Start of Medication | End Date of Medication<br>Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| ACICLOVIR<br>(ACICLOVIR) | 2013-04-09<br>-498 | 2014-08-26<br>7 | OTHER (PROPHYLACTIC FOR HERPES INFECTION) | 400<br>mg | QD<br>ORAL | - |
| FEXOFENADINE HYDROCHLORIDE<br>(ALLEGRA) | 2014-08-27<br>8 | 2014-11-13<br>86 | OTHER (ALLERGIC REACTION FOR BAKTAR) | 60<br>mg | BID<br>ORAL | - |
| ALLOPURINOL<br>(ALLOPURINOL) | 2014-08-19<br>-1 | 2014-08-26<br>7 | OTHER (HYPERURICEMIA) | 100<br>mg | TID<br>ORAL | - |
| ALLOPURINOL<br>(ALLOPURINOL) | 2014-09-19<br>31 | 2014-11-13<br>86 | OTHER (HYPERURICEMIA) | 100<br>mg | DAILY<br>ORAL | - |

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication<br>Study Day of Start of Medication | End Date of Medication<br>Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| ALLOPURINOL<br>(ALOSITOL) | 2014-09-03<br>15 | 2014-09-18<br>30 | OTHER (HYPERURICEMIA) | 100<br>mg | BID<br>ORAL | - |
| BACTRIM<br>(BAKTAR) | 2013-09-19<br>-335 | 2014-11-13<br>86 | OTHER (PROPHYLACTIC FOR PNEUMOCYSTIS PNEUMONIA) | 0.5<br>g | QD<br>ORAL | - |
| PARACETAMOL<br>(CALONAL TAB.) | 2014-11-13<br>86 | 2014-11-13<br>86 | OTHER (PAIN OF PROGRESSIVE DISEASE) | 400<br>mg | PRN<br>ORAL | - |
| FEXOFENADINE HYDROCHLORIDE<br>(FEXOFENADINE HYDROCHLORIDE) | 2014-03-04<br>-169 | 2014-08-26<br>7 | OTHER (ALLERGIC REACTION FOR BAKTAR) | 30<br>mg | BID<br>ORAL | - |
| FUROSEMIDE<br>(FUROSEMIDE) | 2014-11-16<br>89 | 2014-11-16<br>89 | OTHER (RENAL DYSFUNCTION ASSOCIATED WITH PROGRESSIVE DISEASE) | UNK<br>OTHER | UNK<br>UNKNOWN | - |
| ALL OTHER THERAPEUTIC PRODUCTS<br>(HEMODIALYSIS) | 2014-11-17<br>90 | 2014-11-17<br>90 | OTHER (RENAL DYSFUNCTION ASSOCIATED WITH PROGRESSIVE DISEASE) | NOT APPLICABLE<br>OTHER | OTHER<br>OTHER | - |
| PREDNISOLONE VALEROACETATE<br>(LIDOMEX KOWA LOTION) | 2013-10-22<br>-302 | 2014-11-13<br>86 | OTHER (ALLERGIC REACTION FOR BACTAR) | PROPER QUANTITY<br>OINTMENT | DAILY<br>TOPICAL | - |
| MAGNESIUM OXIDE<br>(MAGLAX) | 2013-04-09<br>-498 | 2014-11-13<br>86 | OTHER (CONSTIPATION) | 330<br>mg | PRN<br>ORAL | - |
| LANSOPRAZOLE<br>(TAKEPRON OD TABLETS) | 2012-11-13<br>-645 | 2014-11-13<br>86 | OTHER (PROPHYLACTIC FOR GASTRITIS) | 15<br>mg | QD<br>ORAL | - |
| ACICLOVIR<br>(ZOVIRAX TABLETS) | 2014-08-27<br>8 | 2014-11-13<br>86 | OTHER (PROPHYLACTIC FOR HERPES INFECTION) | 400<br>mg | QD<br>ORAL | - |

■ Prior Systemic Therapy/Regimen

| Line of Treatment | Reported Name of Drug, Med, or Therapy | Start Date of Medication | End Date of Medication | Best Response |
|---|---|---|---|---|
| 1 | R-CHOP | 2010-07-09 | 2010-12-16 | COMPLETE RESPONSE |
| 2 | R-BENDAMUSTINE | 2012-11-22 | 2013-04-16 | PARTIAL RESPONSE |
| 3 | EPOCH-R | 2013-07-19 | 2013-09-03 | PARTIAL RESPONSE |

■ Prior Radiotherapy

| Start Date of Radiotherapy<br>Study Day of Start of Radiotherapy | End Date of Radiotherapy<br>Study Day of End of Radiotherapy | Dose | Location of Radiotherapy |
|---|---|---|---|
| 2013-09-13<br>-341 | 2013-10-22<br>-302 | 50 Gray | ASCENDING COLON |

■ ECOG Score

| Date of Finding<br>Study Day of Finding | Visit Name | Result |
|---|---|---|
| 2014-08-07<br>-13 | Screening | 0 |
| 2014-08-20<br>1 | Cycle1,day1 | 0 |
| 2014-09-03<br>15 | Cycle1,day15 | 0 |
| 2014-09-17<br>29 | Cycle2,day1 | 0 |
| 2014-10-15<br>57 | Cycle3,day1 | 0 |
| 2014-11-12<br>85 | Cycle4,day1 | 0 |
| 2014-11-13<br>86 | End of Treatment | 0 |

(2) イブルチニブと関連性がある重篤な有害事象（上記及び疾患進行を除く）

a) 被験者番号 MCL2002-81001001

■ Demographics and Baseline Characteristics

☐ Country: JPN
☐ Race: ASIAN
☐ Age (yrs): 8[redacted]
☐ Sex: Female
☐ Baseline height (cm): 140.2
☐ Baseline weight (kg): 45.3
☐ Baseline BSA (m**2): 1.4
☐ Baseline ECOG: 1
☐ Ann arbor stage: III
☐ Prior number of regimens: 3
☐ Simplified mipi score: Intermediate risk (4-5)
☐ Extranodal site: Spleen
☐ First study drug intake: 2014-10-23 (study day 1)
☐ Last study drug intake: 2015-03-08 (study day 137)

■ Disposition Information

☐ End of treatment: 2015-04-06 Adverse Event

☐ End of trial: 2015-04-19 Death

■ Fatal Adverse Events

No Fatal Adverse Events reported

■ Other Serious Adverse Events

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 敗血症 | SEPSIS | 2015-03-09<br>- | 138<br>- | Y<br>4 | POSSIBLE<br>DRUG WITHDRAWN | Y<br>RECOVERING/RESOLVING | 20 |

*Note: Adverse Events are coded using MedDRA 18.0*

■ Other Adverse Events

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 疲労 | FATIGUE | 2014-10-25<br>- | 3<br>- | N<br>1 | POSSIBLE<br>DOSE NOT CHANGED | N<br>NOT RECOVERED/NOT RESOLVED | 6 |

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 消化不良 | HEART BURN | 2014-10-25<br>- | 3<br>- | N<br>1 | POSSIBLE<br>DOSE NOT CHANGED | N<br>NOT RECOVERED/NOT RESOLVED | 7 |
| 下痢 | DIARRHEA | 2014-10-26<br>2014-11-20 | 4<br>26 | N<br>2 | POSSIBLE<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 4 |
| 貧血 | ANEMIA | 2014-11-06<br>2014-12-18 | 15<br>43 | N<br>3 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 1 |
| リンパ球数減少 | LYMPHOCYTO COUNT DECREASED | 2014-11-06<br>2014-12-18 | 15<br>43 | N<br>2 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 8 |
| 血小板数減少 | PLATELET COUNT DECREASED | 2014-11-06<br>2014-12-18 | 15<br>43 | N<br>2 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 14 |
| 腎機能障害 | RENAL DYSFUNCTION WORSENING | 2014-11-06<br>2015-02-12 | 15<br>99 | N<br>2 | POSSIBLE<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 17 |
| 下痢 | DIARRHEA | 2014-11-21<br>- | 30<br>- | N<br>1 | POSSIBLE<br>DOSE NOT CHANGED | Y<br>NOT RECOVERED/NOT RESOLVED | 5 |
| 好中球減少症 | NEUTROPENIA | 2015-01-15<br>2015-02-12 | 85<br>29 | N<br>3 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 10 |
| 血小板数減少 | PLATELET COUNT DECREASED | 2015-01-15<br>2015-02-12 | 85<br>29 | N<br>2 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 15 |
| 関節脱臼 | RIGHT SHOWLDER DISLOCATION | 2015-02-05<br>2015-02-19 | 106<br>15 | N<br>1 | NOT RELATED<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 19 |
| リンパ球数減少 | LYMPHOCYTO COUNT DECREASED | 2015-02-12<br>2015-02-19 | 113<br>8 | N<br>2 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 9 |
| 腎機能障害 | RENAL DYSFUNCTION WORSENING | 2015-02-12<br>2015-02-26 | 113<br>15 | N<br>3 | POSSIBLE<br>DRUG INTERRUPTED | Y<br>RECOVERED/RESOLVED | 18 |

| Dictionary-Derived Term | Reported Term for the Adverse Event | Start Date of Adverse Event<br>End Date of Adverse Event | Study Day of Start of Adverse Event<br>Duration (days) | Serious Event<br>Standard Toxicity Grade | Causality<br>Action Taken with Study Treatment | Concomitant or Additional Treatment Given<br>Outcome of Adverse Event | AE Sequence Number |
|---|---|---|---|---|---|---|---|
| 貧血 | ANEMIA | 2015-02-19<br>2015-02-26 | 120<br>8 | N<br>3 | POSSIBLE<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 2 |
| 血小板数減少 | PLATELET COUNT DECREASED | 2015-02-26<br>2015-03-09 | 127<br>12 | N<br>2 | NOT RELATED<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 16 |
| 好中球減少症 | NEUTROPHENIA | 2015-03-09<br>2015-03-17 | 138<br>9 | N<br>4 | POSSIBLE<br>DOSE NOT CHANGED | Y<br>RECOVERED/RESOLVED | 13 |
| 不整脈 | ARRHYTHMIA | 2015-03-15<br>- | 144<br>- | N<br>3 | DOUBTFUL<br>DOSE NOT CHANGED | Y<br>RECOVERING/RESOLVING | 3 |
| 好中球減少症 | NEUTROPENIA | 2015-03-23<br>2015-03-30 | 152<br>8 | N<br>1 | DOUBTFUL<br>DOSE NOT CHANGED | N<br>RECOVERED/RESOLVED | 11 |
| 好中球減少症 | NEUTROPENIA | 2015-03-30<br>- | 159<br>- | N<br>3 | NOT RELATED<br>DOSE NOT CHANGED | N<br>NOT RECOVERED/NOT RESOLVED | 12 |

*Note: Adverse Events are coded using MedDRA 18.0*

■ Medical History

| Body System or Organ Class | Dictionary-Derived Term | Reported Term for the Medical History | End Relative to Reference Period | Toxicity Grade |
|---|---|---|---|---|
| Cardiac Disorders | うっ血性心不全 | CARDIAC FAILURE CONGESTIVE | BEFORE | - |
| Infections And Infestations | 膀胱炎 | CYSTITIS | DURING/AFTER | 2 |
| Musculoskeletal And Connective Tissue Disorders | 骨粗鬆症 | OSTEOPOROSIS | DURING/AFTER | 1 |
| Renal And Urinary Disorders | 腎機能障害 | RENAL DYSFUNCTION | DURING/AFTER | 1 |
| Nervous System Disorders | 坐骨神経痛 | SCIATICA | DURING/AFTER | 1 |
| Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) | 大腸腺腫 | TUBULAR ADENOMA OF ASCENDING COLON | DURING/AFTER | 1 |

*Note: Medical History are coded using MedDRA 18.0*

■ Disease History

| Date of initial MCL Diagnosis | Type of Histology |
|---|---|
| 2010-12-09 | NODULAR |

■ Study Medication

| Visit Name | Start Date of Treatment | End Date of Treatment | Study Day of Start of Treatment | Study Day of End of Treatment | Dose per Administration (mg) | Reason for Dose Adjustment | AE Sequence Number(s) |
|---|---|---|---|---|---|---|---|
| CYCLE1,DAY1 | 2014-10-23 | 2014-11-19 | 1 | 28 | 560.0 | - | - |
| CYCLE2,DAY1 | 2014-11-20 | 2014-12-17 | 29 | 56 | 560.0 | - | - |
| CYCLE3,DAY1 | 2014-12-18 | 2015-01-14 | 57 | 84 | 560.0 | - | - |
| CYCLE4,DAY1 | 2015-01-15 | 2015-02-11 | 85 | 112 | 560.0 | - | - |
| CYCLE5,DAY1 | 2015-02-12 | 2015-02-25 | 113 | 126 | 0.0 | ADVERSE EVENT | 18 |
| CYCLE5,DAY1 | 2015-02-26 | 2015-03-08 | 127 | 137 | 560.0 | - | - |
| CYCLE5,DAY1 | 2015-03-09 | 2015-04-06 | 138 | 166 | 0.0 | ADVERSE EVENT | 20 |

■ Concomitant Medication

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication<br>Study Day of Start of Medication | End Date of Medication<br>Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| ALLOPURINOL<br>(ALLOPURINOL) | 2015-03-13<br>142 | 2015-03-18<br>147 | OTHER (MH3) | 100<br>mg | QD<br>ORAL | - |
| SODIUM GUALENATE HYDRATE<br>(AZUNOL GARGLE LIQUID) | 2014-10-20<br>-3 | -<br>- | OTHER (PROPHYLACTIC FOR INFECTION) | PROPER QUANTITY<br>mL | PRN<br>OTHER | - |
| BACTRIM<br>(BACTRAMIN) | 2015-03-10<br>139 | -<br>- | OTHER (PROPHYLAXIS FOR PNEUMOCYSTIS CARINII) | 1<br>TABLET | QD<br>ORAL | - |
| BISOPROLOL FUMARATE<br>(BISOPROLOL FUMARATE) | 2015-03-18<br>147 | -<br>- | ADVERSE EVENT | 2.5<br>mg | QD<br>ORAL | 3 |
| PARACETAMOL<br>(CALONAL TAB) | 2015-03-09<br>138 | -<br>- | ADVERSE EVENT | 400<br>mg | BID<br>ORAL | 20 |
| CEFCAPENE PIVOXIL HYDROCHLORIDE<br>(CEFCAPENE PIVOXIL HYDROCHLORIDE TABLETS) | 2014-12-18<br>57 | 2015-02-26<br>127 | OTHER (MH5) | 100<br>mg | PRN<br>ORAL | - |
| CEFDINIR<br>(CEFDINIR) | 2014-11-06<br>15 | 2014-11-11<br>20 | OTHER (MH5) | 100<br>mg | TID<br>ORAL | - |

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication<br>Study Day of Start of Medication | End Date of Medication<br>Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| AZOSEMIDE<br>(DIART) | 2014-08-24<br>-60 | -<br>- | OTHER (PROPHYLACTIC FOR CARDIAC FAILURE CONGESTIVE) | 15<br>mg | DAILY<br>ORAL | - |
| DICLOFENAC SODIUM<br>(DICLOFENAC SODIUM) | 2014-11-06<br>15 | -<br>- | OTHER (MH7) | PROPER QUANTITY OTHER | PRN<br>TRANSDERMAL | - |
| APIXABAN<br>(ELIQUIS TABLETS) | 2015-03-17<br>146 | -<br>- | ADVERSE EVENT | 2.5<br>mg | QD<br>ORAL | 3 |
| RALOXIFENE HYDROCHLORIDE<br>(EVISTA) | 2013-04-19<br>-552 | -<br>- | OTHER (MH4) | 60<br>mg | DAILY<br>ORAL | - |
| FEBUXOSTAT<br>(FEBURIC) | 2014-11-06<br>15 | 2014-12-17<br>56 | ADVERSE EVENT | 10<br>mg | DAILY<br>ORAL | 17 |
| FEBUXOSTAT<br>(FEBURIC) | 2015-01-15<br>85 | 2015-02-26<br>127 | ADVERSE EVENT | 10<br>mg | DAILY<br>ORAL | 17, 18 |
| FEBUXOSTAT<br>(FEBURIC) | 2015-02-27<br>128 | 2015-03-12<br>141 | OTHER (MH3) | 10<br>mg | DAILY<br>ORAL | - |
| FLUCONAZOLE<br>(FLUCONAZOLE) | 2015-03-10<br>139 | -<br>- | OTHER (PROPHYLAXIS FOR FUNGUS INFECTION) | 100<br>mg | QD<br>ORAL | - |
| FOSFOMYCIN CALCIUM<br>(FOSMICIN) | 2014-10-16<br>-7 | 2014-10-20<br>-3 | OTHER (MH5) | 500<br>mg | TID<br>ORAL | - |
| FOSFOMYCIN CALCIUM<br>(FOSMICIN) | 2014-11-14<br>23 | 2014-11-21<br>30 | OTHER (MH5) | 500<br>mg | TID<br>ORAL | - |
| FOSFOMYCIN CALCIUM<br>(FOSMICIN) | 2014-12-11<br>50 | 2014-12-18<br>57 | OTHER (MH5) | 500<br>mg | TID<br>ORAL | - |
| HEPARIN SODIUM<br>(HEPARIN SODIUM) | 2015-03-11<br>140 | 2015-03-17<br>146 | ADVERSE EVENT | 5000<br>UNITS | BID<br>INTRAVENOUS | 20 |
| INFLUENZA VACCINE<br>(INFLUENZA HA VACCINE) | 2014-12-11<br>50 | 2014-12-11<br>50 | OTHER (PROPHYLACTIC FOR INFLUENZA) | 0.5<br>mL | DAILY<br>SUBCUTANEOUS | - |
| RINGER-LACTATE<br>(LACTATE RINGER'S SOLUTION) | 2015-03-09<br>138 | 2015-03-17<br>146 | ADVERSE EVENT | 500<br>mL | TID<br>INTRAVENOUS | 20 |
| LANSOPRAZOLE<br>(LANSOPRAZOLE OD) | 2015-03-10<br>139 | -<br>- | OTHER (PROPHYLAXIS FOR GASTRIC ULCER) | 30<br>mg | QD<br>ORAL | - |
| LEVOFLOXACIN<br>(LEVOFLOXACIN HYDRATE) | 2015-03-18<br>147 | -<br>- | ADVERSE EVENT | 500<br>mg | QD<br>ORAL | 20 |
| LOXOPROFEN SODIUM<br>(LOXONIN TAPE) | 2014-10-17<br>-6 | -<br>- | OTHER (MH7) | 50<br>mg | PRN<br>TRANSDERMAL | - |

| Standardized Medication Name<br>Reported Name of Drug, Med, or Therapy | Start Date of Medication<br>Study Day of Start of Medication | End Date of Medication<br>Study Day of End of Medication | Indication | Dose Description<br>Dose Units | Dosing Frequency per Interval<br>Route of Administration | AE Sequence Number(s) |
|---|---|---|---|---|---|---|
| MEROPENEM<br>(MEROPEN) | 2015-03-09<br>138 | 2015-03-17<br>146 | ADVERSE EVENT | 1<br>g | BID<br>INTRAVENOUS | 20 |
| TELMISARTAN<br>(MICARDIS) | 2014-06-29<br>-116 | -<br>- | OTHER (PROPHYLACTIC FOR CARDIAC FAILURE CONGESTIVE) | 20<br>mg | DAILY<br>ORAL | - |
| CLOSTRIDIUM BUTYRICUM<br>(MIYA-BM FINE GRANULES) | 2014-11-06<br>15 | 2014-12-14<br>53 | ADVERSE EVENT | 1<br>g | PRN<br>ORAL | 4, 5 |
| LENOGRASTIM<br>(NEUTROGIN) | 2015-03-09<br>138 | 2015-03-11<br>140 | ADVERSE EVENT | 100<br>mcg | QD<br>SUBCUTANEOUS | 13 |
| LENOGRASTIM<br>(NEUTROGIN) | 2015-03-12<br>141 | 2015-03-16<br>145 | ADVERSE EVENT | 250<br>mcg | QD<br>SUBCUTANEOUS | 13 |
| NOREPINEPHRINE<br>(NOREPINEPHRINE) | 2015-03-09<br>138 | 2015-03-13<br>142 | ADVERSE EVENT | 1<br>mg | OTHER<br>INTRAVENOUS | 20 |
| NOREPINEPHRINE<br>(NOREPINEPHRINE) | 2015-03-14<br>143 | 2015-03-16<br>145 | ADVERSE EVENT | 1<br>mg | OTHER<br>INTRAVENOUS | 20 |
| ALFACALCIDOL<br>(ONEALFA) | 2014-10-18<br>-5 | -<br>- | OTHER (MH4) | 1<br>TABLET | DAILY<br>ORAL | - |
| BERAPROST SODIUM<br>(PROCYLIN) | 2010<br>- | -<br>- | OTHER (PROPHYLACTIC FOR CARDIAC FAILURE CONGESTIVE) | 1<br>TABLET | TID<br>ORAL | - |
| SODIUM LACTATE<br>(SODIUM LACTATE SOLUTION) | 2015-03-17<br>146 | 2015-03-19<br>148 | ADVERSE EVENT | 500<br>mL | BID<br>INTRAVENOUS | 20 |
| VERAPAMIL HYDROCHLORIDE<br>(VASOLAN) | 2015-03-15<br>144 | 2015-03-16<br>145 | ADVERSE EVENT | 5<br>mg | BID<br>INTRAVENOUS | 3 |
| VERAPAMIL HYDROCHLORIDE<br>(VASOLAN) | 2015-03-17<br>146 | 2015-03-19<br>148 | ADVERSE EVENT | 5<br>mg | QD<br>INTRAVENOUS | 3 |

■ Prior Systemic Therapy/Regimen

| Line of Treatment | Reported Name of Drug, Med, or Therapy | Start Date of Medication | End Date of Medication | Best Response |
|---|---|---|---|---|
| 1 | R-THP-COP | 2010-12-22 | 2011-06-03 | STABLE DISEASE |
| 2 | TREAKISYM | 2011-09-27 | 2012-02-07 | STABLE DISEASE |
| 3 | R-BENDAMUSTINE | 2012-12-04 | 2013-07-29 | COMPLETE RESPONSE |

■ Prior Radiotherapy

No Prior Radiotherapy reported

■ ECOG Score

| Date of Finding<br>Study Day of Finding | Visit Name | Result |
|---|---|---|
| 2014-10-07<br>-16 | Screening | 1 |
| 2014-10-23<br>1 | Cycle1,day1 | 1 |
| 2014-11-06<br>15 | Cycle1,day15 | 1 |
| 2014-11-20<br>29 | Cycle2,day1 | 1 |
| 2014-12-18<br>57 | Cycle3,day1 | 1 |
| 2015-01-15<br>85 | Cycle4,day1 | 1 |
| 2015-02-12<br>113 | Cycle5,day1 | 1 |

## 2.7.6.2 海外臨床第 II 相試験（PCYC-1104-CA，評価資料：5.3.5.2.2-1，5.3.5.2.2-2）

### 2.7.6.2.1 主要解析時（カットオフ日：[redacted] 年 [redacted] 月 [redacted] 日）

#### 2.7.6.2.1.1 概要

(1) 計画

1) 治験の標題

BTK 阻害剤 PCI-32765 の再発又は難治性の MCL 患者を対象とした多施設共同，第 II 相試験

2) 治験責任医師

[redacted] 他

3) 公表文献（引用文献）

Wang ML, Rule S, Martin P, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2013;369(6):507-16.

4) 治験実施期間

2011 年 2 月 [redacted] 日（最初の被験者の同意取得日）～[redacted] 年 [redacted] 月 [redacted] 日（主要解析のデータカットオフ日）

5) 開発の相

第 II 相

6) 目的

主要目的は，再発又は難治性マントル細胞リンパ腫（mantle cell lymphoma，MCL）患者を対象に，イブルチニブの有効性を評価することである。副次目的は，この患者集団におけるイブルチニブの 1 日 1 回，固定用量投与レジメン（560 mg/日）の安全性を評価することである。

7) 治験方法

本試験は，再発又は難治性 MCL 患者を対象として，イブルチニブの有効性及び安全性を評価する非盲検，多施設，国際共同試験である。前治療であるボルテゾミブの曝露量に基づき，2 コホートのうちいずれか一方に，並行して（ランダム化せずに）被験者を登録した。単剤又は併用療法レジメンの一部として，ボルテゾミブの前治療歴が 2 サイクル以上であった被験者をボルテゾミブ既治療コホートとした。ボルテゾミブの前治療歴が 2 サイクル未満であった被験者をボルテゾミブ未治療コホートとした。

### 8) 被験者数（計画時及び解析時）

目標被験者数は 115 例であった。本試験では 115 例が組み入れられ，イブルチニブを 1 回以上投与された 111 例を全投与集団及び安全性解析対象集団とした。

### 9) 診断及び主な組入れ基準

主な選択基準は，cyclin D1 の過剰発現又は t(11;14)転座のいずれかにより病理学的に MCL と確定診断されており，CT により測定可能な病変を有する被験者とした。また，被験者は，1 レジメン以上 5 レジメン以下の MCL に対する治療後に部分奏効（partial response，PR）に到達しなかったか，又は疾患進行が認められていることとした。

### 10) 被験薬，用量及び投与方法，ロット番号

イブルチニブ硬ゼラチンカプセルは有効成分 140 mg を含有する経口製剤であり，1 日 1 回 560 mg を投与した。本試験では，イブルチニブは [redacted] 及び [redacted] の 2 カ所の製造施設から供給した（[redacted] 製ロット番号：10-0119，[redacted] 製ロット番号：L0304110，L0304897，L0304897-1，L0305448，L0305985，L0307025，L0307693，及び L0307693A）。

### 11) 対照薬，用量及び投与方法，ロット番号

該当なし

### 12) 投与期間

疾患進行又は耐容不能な毒性の発現が認められるまで，イブルチニブを投与することとした。

### 13) 評価項目

有効性，安全性，薬物動態，及び薬力学の主要評価について，以下に示す。

有効性：

本試験の主要評価項目は全奏効率（overall response rate，ORR）とし，Revised response criteria for malignant lymphoma（Cheson 2007）に従い，治験担当医師の評価に基づく最良総合効果が完全奏効（complete response，CR）又は PR を達成した被験者の割合と定義した。主な副次的評価項目は，奏効持続期間（duration of response，DOR），無増悪生存期間（progression-free survival，PFS），及び全生存期間（overall survival，OS）とした。奏効到達期間も解析した。さらに，探索的解析の一環として，独立評価委員会（Independent Review Committee，IRC）により奏効を確認することとした。

安全性：

治験薬投与後に発現した有害事象の評価，臨床検査（血液学的検査及び血液生化学検査），バイタルサイン測定，ベースラインの心電図評価，体重，身体所見，Eastern Cooperative Oncology Group（ECOG）performance status，尿検査，血清免疫グロブリン，及び角膜検査（EU の実施医療機関のみ）により，安全性を評価することとした。

薬物動態：

イブルチニブの最高血漿中濃度（$C_{max}$），最高血漿中濃度到達時間（$t_{max}$），0 時間から最終定量可能時間までの血漿中濃度－時間曲線下面積（$AUC_{last}$），0 時間から 24 時間までの血漿中濃度－時間曲線下面積（$AUC_{0-24h}$），Day 2，8，9，15，及び 22 の投与前血漿中濃度（$C_{trough}$），最終相における消失半減期（$t_{1/2}$），0 時間から無限大時間までの血漿中濃度－時間曲線下面積（$AUC_{0-\infty}$），血管外投与後の見かけの全身クリアランス（CL/F），定常状態における見かけの全身クリアランス（$CL_{SS}/F$），及び分布容積（$Vd_z/F$）を，実際の採血時間を用いて被験者ごとに推定することとした。

薬力学：

ケモカイン／サイトカイン濃度解析用の血液サンプルは，被験者のサブセットから採取することとした。

**14) 統計手法**

主要解析は全投与集団に基づいて実施した。奏効率及びそれに対応する両側 95%信頼区間（CI）を二項分布の正規近似を用いて算出することとした。サブグループ解析を事前に定義した。DOR，PFS，及び OS の分布を Kaplan-Meier 法により推定した。さらに，PFS 及び OS について打ち切り理由を要約した。

ORR 評価のため，各コホートについて無益性に関する中間解析を 1 回計画した。ボルテゾミブ未治療コホートについて，2 段階のデザインを用いて ORR が 20%以下である（臨床的意義がないと考えられる）という帰無仮説を検証した。ボルテゾミブ既治療コホートについては，2 段階のデザインを用いて ORR が 15%以下である（臨床的意義がないと考えられる）という帰無仮説を検証した。

安全性は，有害事象の発現割合及び重症度，臨床検査，バイタルサイン，並びに身体所見を用いて解析した。すべての安全性解析は，安全性解析対象集団に基づいて行った。

個々の被験者及び平均の血漿中イブルチニブ濃度－時間プロファイルをプロットした。各時点における血漿中濃度データを，平均値，中央値，最小値，最大値，標準偏差（SD），及び変動係数（%CV）により要約した。イブルチニブの薬物動態パラメータの全推定値を，平均値，中央値，幾何平均値，最小値，最大値，SD，及び%CV により要約した。

非線形混合効果モデルを用いた母集団薬物動態解析の一環として，本試験で得られた血漿中濃度データは，血液学的悪性疾患を有する患者を対象としたイブルチニブの他の試験で得られたデータと併合することとした。母集団薬物動態解析では，血漿中薬物動態パラメータと相関する可能性のある共変量を評価することとした。また，ノンコンパートメント解析も実施した。

ケモカイン及びサイトカインの濃度変化は，限定的なサブセットのサンプルから収集したデータに基づき探索的手法により決定することとした。

### (2) 結果

#### 1) 対象集団

主要解析のデータカットオフ時点で，4 カ国，18 の実施医療機関で 115 例が本試験に組み入れられた。組み入れられた被験者のうち，4 例がイブルチニブを投与されなかった。イブルチニブを 1 回以上投与された被験者は 111 例であり，これらの被験者を全投与集団及び安全性解析対象集団とした。このうち 63 例がボルテゾミブ未治療コホート，48 例がボルテゾミブ既治療コホートであった。

投与を中止した被験者は 65 例（58.6%）であり，投与中止の理由は疾患進行が 49 例（44.1%）と最も多かった。有害事象のため投与を中止した被験者は 9 例（8.1%）であった。データカットオフ時点で，46 例（41.4%）がイブルチニブの投与を継続していた。

イブルチニブを投与された 111 例の年齢の中央値は 68 歳（範囲：40～84 歳）であり，70 例（63.1%）が 65 歳以上であった。多くの被験者が男性（85 例，76.6%）で，白人（102 例，91.9%）であった。ベースライン時の ECOG performance status は，99 例（89.1%）が 0 又は 1 であった。治験登録前の最後の治療で PR 以上の効果が得られなかった難治性疾患を有していた被験者は，50 例（45.0%）であった。

すべての被験者が全身性の化学療法を前治療として受けていた。39 例（35.1%）が，シクロホスファミドの分割投与，ビンクリスチン，ドキソルビシン，デキサメタゾン，及びメトトレキサート／シタラビン療法との交替療法［Hyper-CVAD 療法（33 例，29.7%）］及び／又は幹細胞移植（12 例，10.8%）を含む高強度療法を前治療として受けていた。また，27 例（24.3%）はレナリドミドによる前治療を受けていた。

データカットオフ時点で，イブルチニブを投与された 111 例の投与サイクル数の中央値は 9.0 サイクル（範囲：1～24 サイクル），イブルチニブの投与期間の中央値は 8.3 カ月（範囲：0.7～21.4 カ月）であった。ただし，データカットオフ時点でイブルチニブの投与を継続していた被験者は 46 例（41.4%）であった。イブルチニブの 1 日平均投与量の中央値は 550 mg/日（範囲：278～567 mg/日），相対用量強度の中央値は 98.2%であり，目標用量である 560 mg/日の 90%以上を投与された被験者の割合は 78.4%であった。

#### 2) 有効性

治験担当医師の評価に基づく ORR は，イブルチニブを投与されたすべての被験者で 67.6%（CR：20.7%，PR：46.8%），95% CI は 58.9%～76.3%であった。試験期間の推定中央値は 15.3 カ月，DOR の中央値は 17.5 カ月（95% CI 下限：15.8 カ月）であった。データカットオフ時点で，イブルチニブを投与された 111 例のうち奏効例は 75 例であり，このうち 51 例（68%）では疾患進行又は死亡は認められなかった。初回奏効到達期間の中央値は 1.9 カ月，最良効果到達期間の中央値は 5.5 カ月であった。投与継続に伴い，経時的に更に深い奏功が得られ，CR を達成した被験者数も増加した。奏効は，年齢，性別，地域，前治療数，ボルテゾミブによる治療歴，レナリドミドによる治療歴，及び高リスク因子（高スコアのマントル細胞リンパ腫国際予後指標，ベースライン時の難治性疾患，芽球様細胞の組織像など）といった関連する臨床的特徴には依存していないものと考えられた。PFS の推定中央値は 13.9 カ月であり，OS の中央値には達しておらず，46 例（41.4%）が投与を継続した。IRC による奏効の探索的解析では，ORR は 68.5%（CR：

20.7%，PR：47.7%）であり，DOR の中央値は 19.6 カ月であった。これらは治験担当医師による評価と同程度であり，IRC による評価でも治験担当医師の評価に基づく奏効例の 94.7%が奏効と判定された。

### 3) 薬物動態及び薬力学

イブルチニブの $C_{max}$ は初回投与後と反復投与後で同程度であり，大きなばらつきが認められた（%CV は 56.8%～114%であった）。AUC は Day 1 と比べて定常状態の方が高値であった。$AUC_{0\text{-}24h}$ の蓄積率は約 1.4 であり，その個別値は 0.2～3.5 に分布した。イブルチニブ濃度は二相性の消失を示し，最終相の消失半減期の平均値は単回投与後及び反復投与後のいずれも約 6 時間であった。

ジヒドロジオール代謝物 PCI-45227 の結果は親化合物と一致していた。代謝物と親化合物の $AUC_{0\text{-}24h}$ 比は約 1.7 であり，単回投与後と反復投与後では同程度であった。

ボルテゾミブ既治療コホートとボルテゾミブ未治療コホートで，薬物動態に明らかな差は認められなかった。[redacted] 製イブルチニブを投与された被験者と [redacted] 製イブルチニブを投与された被験者とでは曝露量に差が認められたが，イブルチニブの薬物動態のばらつきが大きいことから，この差は重要ではないと考えられた。

評価したケモカイン及び炎症誘発性サイトカイン 38 種類のうち 12 種類で，イブルチニブ投与後 1 週間に統計学的に有意な低下（$p < 0.05$）を示したことから，B 細胞のホーミングに対するイブルチニブの強い効果が示唆された。これは B 細胞受容体のシグナル伝達に対するイブルチニブの抑制効果と一致している。

### 4) 安全性

非盲検下でイブルチニブ 560 mg/日を投与された被験者は 111 例であり，試験期間の推定中央値は 15.3 カ月であった。すべての被験者が 1 件以上の有害事象を発現し，高頻度（25%以上）に発現した有害事象は下痢（50.5%），疲労（41.4%），悪心（30.6%），末梢性浮腫（27.9%），呼吸困難（27.0%），及び便秘（25.2%）であった。重症度が Grade 3 以上の有害事象は 84 例（75.7%）に発現し，62 例（55.9%）に重篤な有害事象が発現した。高頻度（5%以上）に発現した Grade 3 以上の有害事象は，好中球減少症（16.2%），血小板減少症（10.8%），貧血（9.9%），肺炎（6.3%），腹痛，心房細動，及び下痢（各 5.4%）であった。高頻度（5%以上）に発現した重篤な有害事象は肺炎（5.4%）であった。

減量に至った有害事象は 15 例（13.5%）に，投与中止に至った有害事象は 9 例（8.1%）に発現した。イブルチニブの最終投与後 30 日以内に死亡した被験者は 16 例（14.4%）であった。最も多かった死亡理由は疾患進行であった（16 例中 12 例）。死亡に至った 16 例中 4 例（3.6%）が有害事象により死亡に至り，このうち 2 例がイブルチニブとの因果関係を「可能性小」と判断された肺炎［1 例は MedDRA 基本語（preferred term，PT）の「肺炎」に，1 例は MedDRA PT の「ニューモシスティスジロヴェシ肺炎」にコード化された］，1 例がイブルチニブとの因果関係を「関連なし」と判断された敗血症，1 例がイブルチニブとの因果関係を「関連なし」と判断された心停止によるものであった。

(3) 結論

イブルチニブ 560 mg/日の固定用量を経口投与したときの再発又は難治性 MCL 患者の忍容性は良好であり，有効であることが示された。また，ベネフィット・リスクプロファイルは良好であった。

2.7.6.2.1.2 有害事象

PCYC-1104-CA 試験開始後から主要解析のデータカットオフ時点までに発現した，すべての有害事象及び治験薬と関連性がある有害事象を表 2.7.6.2.1-1 に示す。

表 2.7.6.2.1-1 有害事象発現状況（PCYC-1104-CA 試験，安全性解析対象集団）

| 器官別対分類<br>基本語 | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 |
| 安全性解析対象集団 | 63 | 48 | 111 | 63 | 48 | 111 |
| 治験薬投与後に有害事象を発現した被験者数 | 63 (100.0%) | 48 (100.0%) | 111 (100.0%) | 55 (87.3%) | 43 (89.6%) | 98 (88.3%) |
| 胃腸障害 | 51 (81.0%) | 40 (83.3%) | 91 (82.0%) | 28 (44.4%) | 28 (58.3%) | 56 (50.5%) |
| 下痢 | 29 (46.0%) | 27 (56.3%) | 56 (50.5%) | 18 (28.6%) | 21 (43.8%) | 39 (35.1%) |
| 悪心 | 15 (23.8%) | 19 (39.6%) | 34 (30.6%) | 8 (12.7%) | 12 (25.0%) | 20 (18.0%) |
| 便秘 | 17 (27.0%) | 11 (22.9%) | 28 (25.2%) | 5 (7.9%) | 5 (10.4%) | 10 (9.0%) |
| 嘔吐 | 12 (19.0%) | 13 (27.1%) | 25 (22.5%) | 4 (6.3%) | 6 (12.5%) | 10 (9.0%) |
| 腹痛 | 10 (15.9%) | 9 (18.8%) | 19 (17.1%) | 4 (6.3%) | 2 (4.2%) | 6 (5.4%) |
| 口内炎 | 6 (9.5%) | 7 (14.6%) | 13 (11.7%) | 2 (3.2%) | 4 (8.3%) | 6 (5.4%) |
| 消化不良 | 6 (9.5%) | 6 (12.5%) | 12 (10.8%) | 5 (7.9%) | 3 (6.3%) | 8 (7.2%) |
| 上腹部痛 | 3 (4.8%) | 3 (6.3%) | 6 (5.4%) | 0 | 2 (4.2%) | 2 (1.8%) |
| 口内乾燥 | 4 (6.3%) | 2 (4.2%) | 6 (5.4%) | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) |
| 鼓腸 | 4 (6.3%) | 1 (2.1%) | 5 (4.5%) | 4 (6.3%) | 1 (2.1%) | 5 (4.5%) |
| 胃炎 | 1 (1.6%) | 4 (8.3%) | 5 (4.5%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 腹部膨満 | 1 (1.6%) | 3 (6.3%) | 4 (3.6%) | 0 | 0 | 0 |
| 胃食道逆流性疾患 | 2 (3.2%) | 2 (4.2%) | 4 (3.6%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 口腔内痛 | 3 (4.8%) | 1 (2.1%) | 4 (3.6%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 腹部不快感 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) |
| 嚥下障害 | 0 | 3 (6.3%) | 3 (2.7%) | 0 | 2 (4.2%) | 2 (1.8%) |
| 心窩部不快感 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 歯肉浮腫 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 麻痺性イレウス | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 口腔内潰瘍形成 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 肛門周囲痛 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 舌潰瘍 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| バレット食道 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 口唇炎 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| おくび | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 便失禁 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 排便回数増加 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 胃前庭部毛細血管拡張症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 舌痛 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 血便排泄 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |

| 器官別対分類<br>基本語 | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 |
| 痔核 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| イレウス | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 過敏性腸症候群 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 口唇水疱 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 口唇腫脹 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 口唇潰瘍 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 下部消化管出血 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 口腔内出血 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 嚥下痛 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 口蓋障害 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 慢性膵炎 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 歯周病 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 直腸炎 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 直腸裂 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 直腸出血 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 小腸閉塞 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 感染症および寄生虫症 | 47 (74.6%) | 38 (79.2%) | 85 (76.6%) | 26 (41.3%) | 15 (31.3%) | 41 (36.9%) |
| 上気道感染 | 16 (25.4%) | 10 (20.8%) | 26 (23.4%) | 8 (12.7%) | 5 (10.4%) | 13 (11.7%) |
| 尿路感染 | 6 (9.5%) | 10 (20.8%) | 16 (14.4%) | 0 | 3 (6.3%) | 3 (2.7%) |
| 副鼻腔炎 | 6 (9.5%) | 8 (16.7%) | 14 (12.6%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 肺炎 | 6 (9.5%) | 7 (14.6%) | 13 (11.7%) | 3 (4.8%) | 2 (4.2%) | 5 (4.5%) |
| 蜂巣炎 | 5 (7.9%) | 4 (8.3%) | 9 (8.1%) | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) |
| 鼻咽頭炎 | 8 (12.7%) | 1 (2.1%) | 9 (8.1%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 気管支炎 | 5 (7.9%) | 3 (6.3%) | 8 (7.2%) | 4 (6.3%) | 1 (2.1%) | 5 (4.5%) |
| 毛包炎 | 2 (3.2%) | 3 (6.3%) | 5 (4.5%) | 0 | 2 (4.2%) | 2 (1.8%) |
| 帯状疱疹 | 4 (6.3%) | 1 (2.1%) | 5 (4.5%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 鼻炎 | 2 (3.2%) | 3 (6.3%) | 5 (4.5%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 胃腸炎 | 4 (6.3%) | 0 | 4 (3.6%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 下気道感染 | 3 (4.8%) | 1 (2.1%) | 4 (3.6%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 口腔ヘルペス | 3 (4.8%) | 1 (2.1%) | 4 (3.6%) | 2 (3.2%) | 0 | 2 (1.8%) |
| 皮膚感染 | 1 (1.6%) | 3 (6.3%) | 4 (3.6%) | 0 | 0 | 0 |
| クロストリジウム・ディフィシレ大腸炎 | 1 (1.6%) | 2 (4.2%) | 3 (2.7%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 爪囲炎 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 1 (1.6%) | 0 | 1 (0.9%) |
| ブドウ球菌感染 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 0 | 1 (2.1%) | 1 (0.9%) |

| 器官別対分類<br>基本語 | 有害事象<br>ボルテゾミブ未治療コホート | 有害事象<br>ボルテゾミブ既治療コホート | 有害事象<br>全体 | 治験薬と関連性がある有害事象<br>ボルテゾミブ未治療コホート | 治験薬と関連性がある有害事象<br>ボルテゾミブ既治療コホート | 治験薬と関連性がある有害事象<br>全体 |
|---|---|---|---|---|---|---|
| 歯感染 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 0 | 0 | 0 |
| 菌血症 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| クロストリジウム感染 | 2 (3.2%) | 0 | 2 (1.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 憩室炎 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 眼感染 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| 単純ヘルペス | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 感染 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 限局性感染 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| 中耳炎 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 気道感染 | 2 (3.2%) | 0 | 2 (1.8%) | 2 (3.2%) | 0 | 2 (1.8%) |
| 敗血症 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| ウイルス感染 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| 創傷感染 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 肛門膿瘍 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 細気管支炎 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 眼窩蜂巣炎 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| シトロバクター感染 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 感染性結膜炎 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| クリプトコッカス症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 感染性小腸結腸炎 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 細菌性眼感染 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| ウイルス性胃腸炎 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 真菌性性器感染 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| ヘモフィルス感染 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| ヘルペスウイルス感染 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 眼帯状疱疹 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| ヒストプラスマ症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 埋込み部位感染 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 切開部位感染 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| インフルエンザ | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| クレブシエラ感染 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 口唇感染 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 細菌性下気道感染 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 爪感染 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 爪真菌症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |

| 器官別対分類<br>基本語 | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 |
| 口腔カンジダ症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 乳頭腫ウイルス感染 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| レンサ球菌性咽頭炎 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| ニューモシスティスジロヴェシ肺炎 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 細菌性肺炎 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| クレブシエラ菌性肺炎 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 膿疱性皮疹 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 直腸膿瘍 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| ブドウ球菌性菌血症 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| レンサ球菌感染 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 足部白癬 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| シュードモナス性尿路感染 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| ウイルス性上気道感染 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 一般・全身障害および投与部位の状態 | 48 (76.2%) | 32 (66.7%) | 80 (72.1%) | 20 (31.7%) | 18 (37.5%) | 38 (34.2%) |
| 疲労 | 23 (36.5%) | 23 (47.9%) | 46 (41.4%) | 11 (17.5%) | 16 (33.3%) | 27 (24.3%) |
| 末梢性浮腫 | 17 (27.0%) | 14 (29.2%) | 31 (27.9%) | 2 (3.2%) | 3 (6.3%) | 5 (4.5%) |
| 発熱 | 14 (22.2%) | 6 (12.5%) | 20 (18.0%) | 6 (9.5%) | 2 (4.2%) | 8 (7.2%) |
| 無力症 | 9 (14.3%) | 3 (6.3%) | 12 (10.8%) | 3 (4.8%) | 1 (2.1%) | 4 (3.6%) |
| インフルエンザ様疾患 | 5 (7.9%) | 3 (6.3%) | 8 (7.2%) | 3 (4.8%) | 0 | 3 (2.7%) |
| 悪寒 | 5 (7.9%) | 2 (4.2%) | 7 (6.3%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 非心臓性胸痛 | 2 (3.2%) | 3 (6.3%) | 5 (4.5%) | 0 | 0 | 0 |
| 胸痛 | 2 (3.2%) | 2 (4.2%) | 4 (3.6%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 粘膜の炎症 | 4 (6.3%) | 0 | 4 (3.6%) | 3 (4.8%) | 0 | 3 (2.7%) |
| 疼痛 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 0 | 0 | 0 |
| 局所腫脹 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 腋窩痛 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 胸部不快感 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 捻髪音 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 医療機器リーク | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 異常感 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 全身健康状態低下 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 全身性浮腫 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 重力性浮腫 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 硬結 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 注射部位紅斑 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |

| 器官別対分類<br>基本語 | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 |
| 注射部位血管外漏出 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 注射部位血腫 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 注射部位疼痛 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 注射部位反応 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 倦怠感 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 浮腫 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 活動状態低下 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 乾燥症 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 皮膚および皮下組織障害 | 44 (69.8%) | 32 (66.7%) | 76 (68.5%) | 19 (30.2%) | 16 (33.3%) | 35 (31.5%) |
| 発疹 | 10 (15.9%) | 7 (14.6%) | 17 (15.3%) | 6 (9.5%) | 6 (12.5%) | 12 (10.8%) |
| 点状出血 | 5 (7.9%) | 5 (10.4%) | 10 (9.0%) | 5 (7.9%) | 3 (6.3%) | 8 (7.2%) |
| そう痒症 | 5 (7.9%) | 3 (6.3%) | 8 (7.2%) | 3 (4.8%) | 1 (2.1%) | 4 (3.6%) |
| 斑状丘疹状皮疹 | 4 (6.3%) | 4 (8.3%) | 8 (7.2%) | 1 (1.6%) | 2 (4.2%) | 3 (2.7%) |
| 皮膚病変 | 3 (4.8%) | 5 (10.4%) | 8 (7.2%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 皮膚乾燥 | 4 (6.3%) | 2 (4.2%) | 6 (5.4%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 斑状出血 | 5 (7.9%) | 1 (2.1%) | 6 (5.4%) | 0 | 0 | 0 |
| 脱毛症 | 4 (6.3%) | 1 (2.1%) | 5 (4.5%) | 0 | 0 | 0 |
| 内出血発生の増加傾向 | 2 (3.2%) | 3 (6.3%) | 5 (4.5%) | 0 | 0 | 0 |
| 寝汗 | 4 (6.3%) | 1 (2.1%) | 5 (4.5%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 斑状皮疹 | 1 (1.6%) | 3 (6.3%) | 4 (3.6%) | 0 | 2 (4.2%) | 2 (1.8%) |
| 紅斑 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | | | |
| 爪破損 | 3 (4.8%) | 0 | 3 (2.7%) | 2 (3.2%) | 0 | 2 (1.8%) |
| 紫斑 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) |
| 紅斑性皮疹 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 水疱 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| ざ瘡様皮膚炎 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 嵌入爪 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 皮膚変色 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| ざ瘡 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 褥瘡性潰瘍 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 皮膚炎 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| アレルギー性皮膚炎 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 接触性皮膚炎 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 皮下出血 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 多汗症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |

| 器官別対分類<br>基本語 | 有害事象<br>ボルテゾミブ未治療コホート | 有害事象<br>ボルテゾミブ既治療コホート | 有害事象<br>全体 | 治験薬と関連性がある有害事象<br>ボルテゾミブ未治療コホート | 治験薬と関連性がある有害事象<br>ボルテゾミブ既治療コホート | 治験薬と関連性がある有害事象<br>全体 |
|---|---|---|---|---|---|---|
| 間擦疹 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 爪の障害 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 爪線状隆起 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 皮膚亀裂 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 皮膚色素過剰 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 皮膚色素減少 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 皮膚潰瘍 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| サンバーン | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 蕁麻疹 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 筋骨格系および結合組織障害 | 36 (57.1%) | 25 (52.1%) | 61 (55.0%) | 11 (17.5%) | 10 (20.8%) | 21 (18.9%) |
| 筋痙縮 | 11 (17.5%) | 5 (10.4%) | 16 (14.4%) | 5 (7.9%) | 5 (10.4%) | 10 (9.0%) |
| 背部痛 | 7 (11.1%) | 7 (14.6%) | 14 (12.6%) | 2 (3.2%) | 0 | 2 (1.8%) |
| 筋肉痛 | 7 (11.1%) | 7 (14.6%) | 14 (12.6%) | 3 (4.8%) | 2 (4.2%) | 5 (4.5%) |
| 関節痛 | 10 (15.9%) | 2 (4.2%) | 12 (10.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 四肢痛 | 9 (14.3%) | 3 (6.3%) | 12 (10.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 筋骨格痛 | 2 (3.2%) | 4 (8.3%) | 6 (5.4%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 筋力低下 | 1 (1.6%) | 4 (8.3%) | 5 (4.5%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 側腹部痛 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 胤径部痛 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 関節硬直 | 2 (3.2%) | 0 | 2 (1.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 運動性低下 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 筋骨格系胸痛 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 筋骨格硬直 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 頚部痛 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 骨痛 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 椎間板変性症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 関節拘縮 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 筋骨格不快感 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| ミオパチー | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 頚部腫瘤 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 変形性関節症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 骨粗鬆症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 軟部組織障害 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 滑液嚢腫 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 呼吸器、胸郭および縦隔障害 | 28 (44.4%) | 32 (66.7%) | 60 (54.1%) | 8 (12.7%) | 10 (20.8%) | 18 (16.2%) |

| 器官別対分類<br>基本語 | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 |
| 呼吸困難 | 15 (23.8%) | 15 (31.3%) | 30 (27.0%) | 3 (4.8%) | 5 (10.4%) | 8 (7.2%) |
| 咳嗽 | 9 (14.3%) | 11 (22.9%) | 20 (18.0%) | 1 (1.6%) | 5 (10.4%) | 6 (5.4%) |
| 鼻出血 | 7 (11.1%) | 5 (10.4%) | 12 (10.8%) | 3 (4.8%) | 2 (4.2%) | 5 (4.5%) |
| 口腔咽頭痛 | 3 (4.8%) | 7 (14.6%) | 10 (9.0%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 胸水 | 3 (4.8%) | 3 (6.3%) | 6 (5.4%) | 0 | 0 | 0 |
| アレルギー性鼻炎 | 2 (3.2%) | 2 (4.2%) | 4 (3.6%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 発声障害 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 副鼻腔うっ血 | 1 (1.6%) | 2 (4.2%) | 3 (2.7%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 肺硬化 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 湿性咳嗽 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| 呼吸不全 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 慢性閉塞性肺疾患 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 喀血 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| しゃっくり | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 低酸素症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 上気道分泌増加 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 肺浸潤 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 鼻閉 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 鼻の炎症 | 1 (1.6%) | 0 | 1 (0.9%) | | | |
| 副鼻腔分泌過多 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 肺塞栓症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| ラ音 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 気道うっ血 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 拘束性肺疾患 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 鼻漏 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 副鼻腔障害 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 代謝および栄養障害 | 28 (44.4%) | 25 (52.1%) | 53 (47.7%) | 13 (20.6%) | 12 (25.0%) | 25 (22.5%) |
| 食欲減退 | 11 (17.5%) | 12 (25.0%) | 23 (20.7%) | 7 (11.1%) | 6 (12.5%) | 13 (11.7%) |
| 高尿酸血症 | 9 (14.3%) | 6 (12.5%) | 15 (13.5%) | 6 (9.5%) | 2 (4.2%) | 8 (7.2%) |
| 脱水 | 5 (7.9%) | 8 (16.7%) | 13 (11.7%) | 2 (3.2%) | 2 (4.2%) | 4 (3.6%) |
| 低カリウム血症 | 4 (6.3%) | 5 (10.4%) | 9 (8.1%) | 0 | 2 (4.2%) | 2 (1.8%) |
| 低ナトリウム血症 | 1 (1.6%) | 5 (10.4%) | 6 (5.4%) | 0 | 3 (6.3%) | 3 (2.7%) |
| 高血糖 | 2 (3.2%) | 2 (4.2%) | 4 (3.6%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 低マグネシウム血症 | 1 (1.6%) | 3 (6.3%) | 4 (3.6%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 酵素異常 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |

| 器官別対分類<br>基本語 | 有害事象<br>ボルテゾミブ未治療コホート | 有害事象<br>ボルテゾミブ既治療コホート | 有害事象<br>全体 | 治験薬と関連性がある有害事象<br>ボルテゾミブ未治療コホート | 治験薬と関連性がある有害事象<br>ボルテゾミブ既治療コホート | 治験薬と関連性がある有害事象<br>全体 |
|---|---|---|---|---|---|---|
| 低カルシウム血症 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 低血糖症 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| アルコール不耐性 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 水分過負荷 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 痛風 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 高コレステロール血症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 高カリウム血症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 高リン酸塩血症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 低アルブミン血症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 低リン酸血症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 血液およびリンパ系障害 | 32 (50.8%) | 16 (33.3%) | 48 (43.2%) | 20 (31.7%) | 10 (20.8%) | 30 (27.0%) |
| 好中球減少症 | 12 (19.0%) | 8 (16.7%) | 20 (18.0%) | 9 (14.3%) | 7 (14.6%) | 16 (14.4%) |
| 血小板減少症 | 13 (20.6%) | 7 (14.6%) | 20 (18.0%) | 8 (12.7%) | 4 (8.3%) | 12 (10.8%) |
| 貧血 | 8 (12.7%) | 7 (14.6%) | 15 (13.5%) | 4 (6.3%) | 3 (6.3%) | 7 (6.3%) |
| 白血球減少症 | 4 (6.3%) | 3 (6.3%) | 7 (6.3%) | 2 (3.2%) | 2 (4.2%) | 4 (3.6%) |
| 発熱性好中球減少症 | 3 (4.8%) | 1 (2.1%) | 4 (3.6%) | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) |
| 白血球増加症 | 3 (4.8%) | 0 | 3 (2.7%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 鉄欠乏性貧血 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| リンパ節症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| リンパ球増加症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| リンパ球減少症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 汎血球減少症 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 後腹膜リンパ節腫脹 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 脾腫 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 神経系障害 | 19 (30.2%) | 25 (52.1%) | 44 (39.6%) | 7 (11.1%) | 6 (12.5%) | 13 (11.7%) |
| 浮動性めまい | 7 (11.1%) | 9 (18.8%) | 16 (14.4%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 頭痛 | 7 (11.1%) | 5 (10.4%) | 12 (10.8%) | 5 (7.9%) | 3 (6.3%) | 8 (7.2%) |
| 末梢性感覚ニューロパチー | 3 (4.8%) | 3 (6.3%) | 6 (5.4%) | 2 (3.2%) | 2 (4.2%) | 4 (3.6%) |
| 錯感覚 | 1 (1.6%) | 3 (6.3%) | 4 (3.6%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 記憶障害 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 0 | 0 | 0 |
| 健忘 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| 嗜眠 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 傾眠 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 平衡障害 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 体位性めまい | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |

| 器官別対分類<br>基本語 | 有害事象<br>ボルテゾミブ未治療コホート | 有害事象<br>ボルテゾミブ既治療コホート | 有害事象<br>全体 | 治験薬と関連性がある有害事象<br>ボルテゾミブ未治療コホート | 治験薬と関連性がある有害事象<br>ボルテゾミブ既治療コホート | 治験薬と関連性がある有害事象<br>全体 |
|---|---|---|---|---|---|---|
| 頭部不快感 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 過眠症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 感覚鈍麻 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 片頭痛 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 前兆を伴う片頭痛 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 神経痛 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 末梢性ニューロパチー | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 眼振 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 腓骨神経麻痺 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 失神寸前の状態 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 坐骨神経痛 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 感覚障害 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 緊張性頭痛 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 一過性全健忘 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 振戦 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 傷害、中毒および処置合併症 | 19 (30.2%) | 16 (33.3%) | 35 (31.5%) | 2 (3.2%) | 4 (8.3%) | 6 (5.4%) |
| 挫傷 | 9 (14.3%) | 10 (20.8%) | 19 (17.1%) | 2 (3.2%) | 2 (4.2%) | 4 (3.6%) |
| 転倒 | 4 (6.3%) | 4 (8.3%) | 8 (7.2%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 硬膜下血腫 | 3 (4.8%) | 1 (2.1%) | 4 (3.6%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 裂傷 | 1 (1.6%) | 2 (4.2%) | 3 (2.7%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 擦過傷 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 脊椎圧迫骨折 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 外傷性血腫 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 節足動物咬傷 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 眼外傷 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 頭部損傷 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 靭帯捻挫 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 開放創 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 処置後便秘 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 外傷後疼痛 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 処置による疼痛 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 骨格損傷 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 皮膚創傷 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 熱傷 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 術後尿閉 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |

| 器官別対分類<br>基本語 | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 |
| 創傷 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 眼障害 | 12 (19.0%) | 19 (39.6%) | 31 (27.9%) | 3 (4.8%) | 5 (10.4%) | 8 (7.2%) |
| 流涙増加 | 2 (3.2%) | 6 (12.5%) | 8 (7.2%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 白内障 | 1 (1.6%) | 5 (10.4%) | 6 (5.4%) | 0 | 0 | 0 |
| 結膜炎 | 3 (4.8%) | 3 (6.3%) | 6 (5.4%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 眼乾燥 | 1 (1.6%) | 4 (8.3%) | 5 (4.5%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 眼充血 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 霧視 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 視力低下 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 硝子体浮遊物 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 結膜出血 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 糖尿病網膜症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 眼の炎症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 眼瞼下垂 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 眼窩周囲浮腫 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 羞明 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 網膜剥離 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 強膜出血 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 臨床検査 | 18 (28.6%) | 8 (16.7%) | 26 (23.4%) | 9 (14.3%) | 5 (10.4%) | 14 (12.6%) |
| 血中クレアチニン増加 | 4 (6.3%) | 2 (4.2%) | 6 (5.4%) | 3 (4.8%) | 0 | 3 (2.7%) |
| アラニンアミノトランスフェラーゼ増加 | 0 | 3 (6.3%) | 3 (2.7%) | 0 | 3 (6.3%) | 3 (2.7%) |
| アスパラギン酸アミノトランスフェラーゼ増加 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) |
| 体重減少 | 1 (1.6%) | 2 (4.2%) | 3 (2.7%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 体重増加 | 3 (4.8%) | 0 | 3 (2.7%) | 2 (3.2%) | 0 | 2 (1.8%) |
| 血中ビリルビン増加 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 心雑音 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 糸球体濾過率減少 | 2 (3.2%) | 0 | 2 (1.8%) | 2 (3.2%) | 0 | 2 (1.8%) |
| 国際標準比増加 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| 活性化部分トロンボプラスチン時間延長 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| アスペルギルス検査陽性 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 血中アルカリホスファターゼ増加 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 血中ビリルビン異常 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |

| 器官別対分類<br>基本語 | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 |
| 血中コレステロール増加 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 血中免疫グロブリンG減少 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 血中鉄減少 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 血中リン減少 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 呼吸音異常 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| Ｃ－反応性蛋白増加 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| ヘモフィルス検査陽性 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 心拍数不整 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 肝機能検査異常 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 黄斑部反射異常 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 平均赤血球容積増加 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 血小板数減少 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 尿量減少 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 白血球数増加 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 精神障害 | 15 (23.8%) | 11 (22.9%) | 26 (23.4%) | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) |
| 不眠症 | 9 (14.3%) | 2 (4.2%) | 11 (9.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 不安 | 2 (3.2%) | 4 (8.3%) | 6 (5.4%) | 0 | 0 | 0 |
| うつ病 | 3 (4.8%) | 3 (6.3%) | 6 (5.4%) | 0 | 0 | 0 |
| 激越 | 0 | 3 (6.3%) | 3 (2.7%) | 0 | 0 | 0 |
| 錯乱状態 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 異常行動 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 多幸気分 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| リビドー減退 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 躁病 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| パニック発作 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 心臓障害 | 13 (20.6%) | 9 (18.8%) | 22 (19.8%) | 5 (7.9%) | 3 (6.3%) | 8 (7.2%) |
| 心房細動 | 5 (7.9%) | 4 (8.3%) | 9 (8.1%) | 4 (6.3%) | 1 (2.1%) | 5 (4.5%) |
| 洞性頻脈 | 3 (4.8%) | 2 (4.2%) | 5 (4.5%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 心不全 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 洞性徐脈 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| 心房粗動 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 第一度房室ブロック | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 心停止 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 冠動脈閉塞 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 僧帽弁閉鎖不全症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |

| 器官別対分類<br>基本語 | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 |
| 心筋梗塞 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 動悸 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 上室性頻脈 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| トルサード　ド　ポアント | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 心室性頻脈 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 血管障害 | 10 (15.9%) | 10 (20.8%) | 20 (18.0%) | 2 (3.2%) | 3 (6.3%) | 5 (4.5%) |
| 高血圧 | 6 (9.5%) | 5 (10.4%) | 11 (9.9%) | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) |
| 低血圧 | 3 (4.8%) | 4 (8.3%) | 7 (6.3%) | 0 | 2 (4.2%) | 2 (1.8%) |
| 起立性低血圧 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| 血圧変動 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 潮紅 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 静脈瘤 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 腎および尿路障害 | 8 (12.7%) | 10 (20.8%) | 18 (16.2%) | 5 (7.9%) | 4 (8.3%) | 9 (8.1%) |
| 血尿 | 3 (4.8%) | 3 (6.3%) | 6 (5.4%) | 1 (1.6%) | 2 (4.2%) | 3 (2.7%) |
| 急性腎不全 | 2 (3.2%) | 3 (6.3%) | 5 (4.5%) | 0 | 2 (4.2%) | 2 (1.8%) |
| 頻尿 | 1 (1.6%) | 2 (4.2%) | 3 (2.7%) | 1 (1.6%) | 2 (4.2%) | 3 (2.7%) |
| 排尿困難 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 腎機能障害 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 尿失禁 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 尿路閉塞 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 0 | 0 |
| 高窒素血症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 水腎症 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 尿意切迫 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 夜間頻尿 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 閉塞性尿路疾患 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 腎不全 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 尿路痛 | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む） | 9 (14.3%) | 7 (14.6%) | 16 (14.4%) | 0 | 1 (2.1%) | 1 (0.9%) |
| マントル細胞リンパ腫 | 7 (11.1%) | 1 (2.1%) | 8 (7.2%) | 0 | 0 | 0 |
| 基底細胞癌 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 膀胱癌 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 悪性胸水 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 転移性新生物 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 口腔乳頭腫 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |

| 器官別対分類<br>基本語 | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 | ボルテゾミブ未治療コホート | ボルテゾミブ既治療コホート | 全体 |
| 皮膚癌 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 皮膚乳頭腫 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 扁平上皮癌 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 皮膚有棘細胞癌 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 免疫系障害 | 2 (3.2%) | 5 (10.4%) | 7 (6.3%) | 0 | 0 | 0 |
| 季節性アレルギー | 1 (1.6%) | 2 (4.2%) | 3 (2.7%) | 0 | 0 | 0 |
| 過敏症 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 節足動物咬傷アレルギー | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 薬物過敏症 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 耳および迷路障害 | 3 (4.8%) | 3 (6.3%) | 6 (5.4%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 耳痛 | 0 | 2 (4.2%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 聴覚過敏 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 聴力低下 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 耳鳴 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 回転性めまい | 1 (1.6%) | 0 | 1 (0.9%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 生殖系および乳房障害 | 2 (3.2%) | 4 (8.3%) | 6 (5.4%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 血精液症 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 性器浮腫 | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) | 0 | 0 | 0 |
| 乳房痛 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 陰茎痛 | 1 (1.6%) | 0 | 1 (0.9%) | 0 | 0 | 0 |
| 子宮腟脱 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 腟出血 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 外陰腟痛 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 0 | 0 |
| 肝胆道系障害 | 2 (3.2%) | 1 (2.1%) | 3 (2.7%) | 1 (1.6%) | 1 (2.1%) | 2 (1.8%) |
| 高ビリルビン血症 | 2 (3.2%) | 0 | 2 (1.8%) | 1 (1.6%) | 0 | 1 (0.9%) |
| 肝機能異常 | 0 | 1 (2.1%) | 1 (0.9%) | 0 | 1 (2.1%) | 1 (0.9%) |
| 内分泌障害 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |
| 甲状腺機能低下症 | 2 (3.2%) | 0 | 2 (1.8%) | 0 | 0 | 0 |

安全解析対象集団を母数として，発現割合（%）を算出した
MedDRA/J version 15.1 を使用して集計した
参照元：5.3.5.2.2-1 PCYC-1104-CA 試験 CSR Attachment TSFAE02，TSFAE10

### 2.7.6.2.1.3　死亡及び重篤な有害事象の個別症例の詳細

PCYC-1104-CA 試験開始後に死亡及び重篤な有害事象（SAE）を発現した被験者のうち，イブルチニブを投与された被験者における死亡に至った有害事象及びイブルチニブと関連性があるSAE を発現した被験者の詳細を示す。疾患進行による死亡については以下の叙述から除いた。また，イブルチニブと関連性がある死亡については，臨床経過を詳述した。

#### (1) 有害事象による死亡例

#### 1) イブルチニブと関連性がある死亡例

#### a) 被験者番号 1104-006-004

| | |
|---|---|
| 被験者番号 | 1104-006-004 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性があるイブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象，投与中止に至った重篤な有害事象：肺炎（Grade 5） |

被験者 1104-006-004 は，7[redacted] 歳の男性で，2008 年 6 月 16 日に蛍光 in situ ハイブリダイゼーション法（FISH）での t(11;14)転座によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，変形性関節症，慢性腰痛，高脂血症，痛風，リンパ腫による腹部不快感，便秘，上行大動脈瘤，両肺尖部肺気腫，両側頚部の頚動脈分岐部アテローム性動脈硬化症，両側胸水，新生物に対する左腎嚢胞，心嚢液貯留，ニューロパチー，下肢脱力，不眠症，両下肢浮腫，帯状疱疹噴出，寝汗，血小板減少症，及び失神寸前の状態であった。MCL に対する前治療歴は，リツキシマブ/シクロホスファミド/ドキソルビシン/prednisone/ビンクリスチン（R-CHOP），ボルテゾミブの単独療法，ベンダムスチンとリツキシマブの併用療法（BR），並びにデキサメタゾン及びレナリドミドの併用療法であった。本被験者は頚部及び頭部への放射線療法を受けた。癌に関連した手術歴はなかった。

ベースライン時に投与中であった併用薬は，シンバスタチン（高脂血症），アロプリノール（痛風），マルチビタミン剤，docusate（便秘），ガバペンチン（ニューロパチー），イブプロフェン（疼痛），オンダンセトロン（悪心），プロクロルペラジン（悪心），ゾルピデム（不眠症），及びアシクロビル（帯状疱疹）であった。ベースライン時の臨床検査結果は，好中球絶対数（ANC）$3.88 \times 10^9$/L 及び白血球数（WBC）$55.4 \times 10^9$/L であった。2011 年 7 月 20 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

Day 1 に非重篤な Grade 1 の呼吸音異常が発現した。Day 8 に非重篤な Grade 1 の捻髪音が発現した。治験担当医師により，いずれの事象もイブルチニブとの因果関係は「関連なし」と判断された。捻髪音は Day 15 に，呼吸音異常は Day 29 に回復した。

Day 74 に，本被験者は下肢脱力，錯乱，及び不安定を訴え，救急治療室を受診した。本被験者は発熱していた。頭部 CT スキャンの所見は正常であった。救急治療室での臨床検査の結果，カリウム値上昇及び白血球数増加が認められた。発現日の翌日以降にカリウム低下療法が実施され，その後フロセミド及び塩化カリウムによる治療が実施された。本被験者は集中治療室へ入院した。入院時，下肢の汎発性脱力及び錯乱が認められた。体温は 102°F，心拍数は 112 拍/分，呼吸数は 25 回/分，血圧は 101/45 mmHg，酸素飽和度は室内気下で 93%であった。胸部 X 線では，肺底部に極めて微量の胸水を伴う軽度の浸潤の疑いが認められた。再度実施した臨床検査の結果では，

カリウム 3.5 Mmol/L（正常），WBC 543 × $10^3$/μL（増加），ヘモグロビン 8.3 g/dL，ヘマトクリット 25%，及び血小板数 47 × $10^3$/μL であった。血液及び尿培養結果は陰性であった。同日（Day 74），有害事象である急性腎不全及び心不全とともに肺炎と診断された。いずれの事象もイブルチニブとの因果関係は「可能性小」と判断された。肺炎のため，イブルチニブの投与が永続的に中止され，最終投与日は Day 74 であった。静注用ブドウ糖及び塩化ナトリウム，ピペラシリン/タゾバクタム，バンコマイシン，及びレボフロキサシンによる治療が実施された。

Day 75 に Grade 2 の呼吸困難が発現し，治験担当医師によりイブルチニブとの因果関係は「可能性小」と判断された。サルブタモールによる治療が実施された。同日（Day 75），胸部 X 線に，左基底部陰影の増強，新規の網状変化，及び微量の左胸水が認められた。Day 77 に実施した胸部 X 線では，肺炎に一致する左基底部陰影の増強の可能性及び右底部の軽度の網状変化，並びに微量な両側胸水の増加が認められた。Day 78 の臨床検査結果では，WBC 493.2 × $10^3$/μL，ヘモグロビン 9.4 g/dL，ヘマトクリット 27.8%，及び血小板数 57 × $10^3$/μL であった。当初，本被験者は抗生物質療法後にわずかな改善を示したが，その後状態は悪化した。サイクル 3 では SD であったが，肝臓に新たな増悪が認められ，その後 MCL の疾患進行を臨床的に示唆する白血球増加症，腎不全及び心不全の急激な増悪が認められた。本被験者は，Day 79 に肺炎（主な死因）により死亡した。

b) 被験者番号 1104-363-001

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| 被験者番号 | 1104-363-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性があるイブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：ニューモシスティスジロヴェシ肺炎（Grade 5） |

被験者 1104-363-001 は，7[redacted] 歳の男性で，2010 年 8 月 20 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。被験者の既往歴は，静脈瘤（左下肢），白内障，人工膝関節インプラント，高血圧，胆嚢炎，及び甲状腺機能亢進症であった。MCL に対する前治療歴は，シクロホスファミド/ドキソルビシン/ビンクリスチン/プレドニゾロン（CHOP），リツキシマブの単独療法，及び BR であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，アムロジピン及びメトプロロール（高血圧），並びにチアマゾール（甲状腺機能亢進症）であった。ベースライン時の臨床検査結果は，ヘモグロビン 14.1 g/dL，白血球数（WBC）4.29 × $10^9$/L，好中球絶対数（ANC）2.85 × $10^9$/L，及び血小板数 122 × $10^9$/L であった。ベースライン時の心電図検査では，顕著な異常は認められなかった。ベースライン時の MCL 浸潤は両側腋窩，左鎖骨下，及び消化管領域にみられたが，骨髄領域への浸潤はなく，肝腫大及び脾腫大は認められなかった。2012 年 1 月 17 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

本被験者は，治験薬を減量することなく 6 サイクルにわたりイブルチニブ投与を受け，疾患は安定した状態でコントロールされていた。

Day 169 に，本被験者は重篤なニューモシスティスジロヴェシ肺炎と診断され，入院した。本事象の最終的な転帰は Day 183 の死亡であった。治験担当医師により，ニューモシスティスジロヴェシ肺炎とイブルチニブとの因果関係は「可能性小」と判断された。入院時，WBC

19.06 × $10^9$/L 及び ANC 3.43 × $10^9$/L であった。身体所見の結果，持続的な鋭い肺胞音，肺基底部内の断続性ラ音，柔軟で非有痛性の腹部浮腫，脾腫，及び浮腫が認められた。気管支鏡検査が実施され，気管支肺胞洗浄検査で採取された検体はニューモシスティスジロヴェシ陽性であった。クラリスロマイシン，トリメトプリム/スルファメトキサゾール（Septra），及びセフロキシムによる治療が実施された。疾患進行のため，イブルチニブの投与は永続的に中止され，最終投与日は Day 168 であった。

Day 170（イブルチニブ投与中止後 2 日目）の肺部の高解像度 CT スキャンでは，上葉，下葉，及び中葉内に広範囲の気管支及び細気管支肺胞陰影が認められた。病変は主に末梢及び胸膜下に位置していた。病変によっては，明らかに可視的な線維性の構成要素を有していた。肺部 CT スキャンの結果，ニューモシスティスによる病変と新たに認められた肺胞病変とは重なり合っていたが，肺胞病変は細菌性と考えられた。これらの結果からリンパ腫に関連した浸潤の存在は示唆されなかった。

Day 182（イブルチニブ投与中止後 14 日目）に，本被験者の状態は呼吸不全のため徐々に悪化した。翌日，本被験者に機械的人工換気を設置，挿管した。アシドーシス，腎不全，及び高カルシウム血症が認められた。ノルアドレナリン，フロセミド，ポリスチレンスルホン酸カルシウム，グルコサミンとインスリンの併用療法，及びメロペネムによる治療が実施された。集中治療にもかかわらず，本被験者の全身状態は継続して悪化した。Day 183（イブルチニブ投与中止後 15 日目）に，本被験者はニューモシスティスジロヴェシ肺炎により死亡した。

### 2) イブルチニブと関連性がない死亡例

#### a) 被験者番号 1104-200-005

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| 被験者番号 | 1104-200-005 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：呼吸困難（Grade 5） |

被験者 1104-200-005 は，7[redacted] 歳の白人女性で，1992 年 10 月に FISH での t(11;14)転座及び免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。特記すべき既往歴は，大腸炎，扁桃摘出，ヘルニア修復，ニューモシスティスジロヴェシ肺炎，胸腔鏡下手術，Grade 1 の呼吸困難，深部静脈血栓症，並びにスルファメトキサゾール/トリメトプリム及びベンダムスチンに対するアレルギーであった。MCL に対する前治療歴は，リツキシマブ，ボルテゾミブ及びベンダムスチンの単独療法，並びに CHOP 療法であった。癌に関連した手術歴及び放射線療法歴はなかった。

ベースライン時に投与中であった併用薬は，エソメプラゾール及びメサラジン（大腸炎），アトバコン（ニューモシスティスジロヴェシ肺炎の予防），並びに葉酸（サプリメント）であった。ベースライン時の臨床検査結果は，ヘモグロビン 10.3 g/dL，白血球数 12.6 × $10^9$/L，及び好中球絶対数 6.5 × $10^9$/L であった。2011 年 5 月 26 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

b) 被験者番号 1104-217-006

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| 被験者番号 | 1104-217-006 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：急性腎不全（Grade 5） |

被験者 1104-217-006 は，7[redacted] 歳の男性で，2010 年 11 月 13 日に FISH での t(11;14)転座及び免疫組織化学的検査での D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，高血圧，腎結石，前立腺癌，痛風，変形性関節症，胃食道逆流性疾患，高脂血症，再発基底細胞癌，黒色腫，良性甲状腺結節，心疾患，ペースメーカー，洞不全症候群，間欠性疲労，悪心，鼓腸，労作性呼吸困難，無嗅覚，咳嗽，多汗症，低カリウム血症，貧血，食欲不振，徐脈，発熱，便秘，味覚異常，浮腫，頭痛，不眠症，腹痛，腹部膨満感，下痢，股関節痛，右肩痛，洞性頻脈，ヘリコバクター・ピロリ感染，胃腸出血，アレルギー性鼻炎，及び腎機能不全であった。MCL に対する前治療歴は，リツキシマブ及びベンダムスチンであった。本被験者は，癌に関連した胃部放射線療法による治療歴を有していた。癌に関連した手術歴はなかった。

ベースライン時に投与中であった併用薬は，ジルチアゼム，メトプロロール，minoxidil，ヒドロクロロチアジド/トリアムテレン，及びテルミサルタン（すべて高血圧に対して），アロプリノール（痛風），アセトアミノフェン（関節炎に伴う疼痛），アトルバスタチン及びフェノフィブラート（高脂血症），オメプラゾール（胃食道逆流性疾患），ロラゼパム（不眠症），カリウム（低カリウム血症），モメタゾン（アレルギー性鼻炎），オキシコドン（疼痛），docusate（便秘），プロメタジン（悪心），並びに simethicone（鼓腸）であった。ベースライン時の臨床検査結果は，ヘモグロビン 95 g/L，クレアチニン 103.4 µmol/L（1.49 mg/dL），血中尿素窒素 24 mg/dL，及び白血球数 $4.1 \times 10^9$/L（3.29 K/µL）であった。2011 年 8 月 17 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

c) 被験者番号 1104-217-008

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| 被験者番号 | 1104-217-008 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：末梢性浮腫（Grade 4）<br>大出血事象：下部消化管出血（Grade 3）<br>イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：マントル細胞リンパ腫（Grade 5） |

被験者 1104-217-008 は，7[redacted] 歳の男性で，2006 年 10 月に FISH での t(11;14)転座及び免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）（異型円形細胞［慢性リンパ性白血病様］）と確定診断された。本被験者の既往歴は，再発腎結石，慢性腎疾患，レンサ球菌感染後糸球体腎炎，貧血，再発肺炎，表在性血栓性静脈炎，再発基底細胞及び扁平上皮癌，低γグロブリン血症，マイコバクテリウム・ゴルドナエ肺感染，好中球減少性敗血症，腹痛，急性腎不全，カンジダ血症，及びステノトロフォモナス肺感染であり，間欠性既往歴は，食欲不振，下痢，高尿酸血症，血小板減少症，両下肢浮腫，悪心，低カルシウム血症，高ビリルビン血症，低ナトリウム血症，及び低カリウム血症であった。MCL に対する前治療歴は，ボルテゾミブ，シクロホスファミド，ドキソルビシン，エトポシド，メトトレキサート，リツキシマブとビンクリスチンの併用療法，エベロリムスの単独療法，ベンダムスチンとリツキシマブの併用療法，レ

ナリドミドの単独療法，並びにシクロホスファミド，エトポシド，イホスファミド，及びリツキシマブの併用療法であった。癌に関連した放射線療法による治療歴は，頚部及び両眼窩への放射線療法であった。癌に関連した手術歴はなかった。

ベースライン時に投与中であった併用薬は，フルチカゾン/サルメテロール（Seretide）及びサルブタモール（呼吸困難），シプロフロキサシン，アジスロマイシン及びエタンブトール（マイコバクテリウム・ゴルドナエ肺感染），並びにロペラミド（下痢）であった。ベースライン時の臨床検査結果は，ヘモグロビン 105 g/L，クレアチニン 142.3 µmol/L，白血球数 6.8 × $10^9$/L 及び血小板数 117 × $10^9$/L であった。スクリーニング時，鼡径部，腸間膜，及び傍大動脈領域に広範囲な MCL の浸潤及び脾腫大が認められたが，骨髄への既知の浸潤は認められなかった。2011 年 11 月 23 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### d) 被験者番号 1104-350-001

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|---|---|
| 被験者番号 | 1104-350-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：悪性胸水（Grade 4）<br>イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：悪性胸水（Grade 5）<br>重篤な有害事象：腎不全（Grade 3），低酸素症（Grade 3），呼吸不全（Grade 4） |

被験者 1104-350-001 は，6[redacted] 歳の男性で，2010 年 8 月 11 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，前立腺摘除，心筋症，コントロールされている糖尿病（Grade 1），高脂血症，高血圧（Grade 2），末梢性浮腫，胸水（Grade 3），白血球減少（Grade 3），高カリウム血症（Grade 2），息切れ（Grade 3），乳酸脱水素酵素増加（Grade 2），右股関節痛（Grade 2），及び貧血（Grade 1）であった。MCL に対する前治療歴は，R-CHOP，BR，並びにベンダムスチン，リツキシマブ，及びボルテゾミブであった。癌に関連した手術歴は大腸切除であった。癌に関連した放射線療法による治療歴はなかった。

ベースライン時に投与中であった併用薬は，アムロジピン，メトプロロール及びバルサルタン（高血圧），ロスバスタチン（高脂血症），アロプリノール（尿酸血症予防），オキシコドン/アセトアミノフェン及びオキシコドン（右股関節痛），prednisone（息切れ），並びにラスブリカーゼ（腫瘍崩壊予防）であった。ベースライン時の臨床検査結果は，クレアチニン 1.1 mg/dL，ヘモグロビン 109 g/L，血小板数 184 × $10^9$/L，白血球数 1.6 × $10^9$/L，及び好中球絶対数 0.99 × $10^9$/L であった。2011 年 12 月 21 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。本被験者には横隔膜上部及び下部で数個のリンパ節浸潤を伴う顕著な疾病負荷が認められた。スクリーニング時，6 × 10 cm の広範囲でかさ高い前縦隔及び 4.7 × 7.2 cm の傍心臓腫瘤が報告された。

e) 被験者番号 1104-354-001

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| 被験者番号 | 1104-354-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：肺炎（Grade 3），全身健康状態低下（Grade 3）<br>イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：麻痺性イレウス（Grade 5） |

被験者 1104-354-001 は，6[redacted] 歳の男性で，2004 年 11 月 19 日に FISH での t(11;14)転座により芽球性マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，巨大腹部疾患，食欲不振，口腔カンジダ症，腹水，間欠性下痢，脱水，疲労，発熱性好中球減少症，間欠性気分変化，間欠性悪心，両側胸水，呼吸困難，並びに肺動脈（左上葉及び下葉）及び右下肢の血栓症であった。MCL に対する前治療歴は，R-CHOP とリツキシマブ/デキサメタゾン/シタラビン/シスプラチン（R-DHAP）の交互サイクル，及び交互サイクル後の全身照射，シタラビン/メルファラン，及び自己幹細胞移植であった。

ベースライン時に投与中であった併用薬は，アロプリノール（高尿酸血症予防），pantoprazole（胸やけ及び胃炎予防），及びトラセミド（高血圧）であった。ベースライン時の臨床検査結果は，ヘモグロビン 100 g/L，白血球数 $6.3 \times 10^9$/L，及び好中球絶対数 $4.78 \times 10^9$/L であった。ベースライン時，腋窩，胸骨後，及び傍気管領域，並びに骨髄への MCL 浸潤（25%）が認められたが，脾臓，肝臓，及び胃腸領域への浸潤は認められなかった。2011 年 12 月 1 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

f) 被験者番号 1104-364-001

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| 被験者番号 | 1104-364-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：マントル細胞リンパ腫（Grade 5） |

被験者 1104-364-001 は，6[redacted] 歳の女性で，2009 年 7 月 21 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，白子症，動脈性高血圧，胆石症，咳嗽，嗄声，及び咽頭痛であった。MCL に対する前治療歴は，R-CHOP，エトポシド/メチルプレドニゾロン/シタラビン/シスプラチン（ESHAP），シクロホスファミド，シタラビン，デキサメタゾン，ドキソルビシン，メトトレキサート，リツキシマブ，ビンクリスチン，レナリドミド，シスプラチン，エトポシド，及び prednisone であった。癌に関連した放射線療法による治療歴はなかった。

ベースライン時に投与中であった併用薬は，インダパミド，ロサルタン，メトプロロール，及びアムロジピン（すべて動脈性高血圧に対して）であった。ベースライン時の臨床検査結果は，好中球絶対数 $0.77 \times 10^9$/L 及び白血球数 $3 \times 10^9$/L であった。2011 年 11 月 17 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。投与時，頚部，腸間膜，及び縦隔リンパ節，並びに骨髄への広範囲な浸潤（60%）が認められた。

### g) 被験者番号 1104-364-003

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| 被験者番号 | 1104-364-003 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象，投与中止に至った有害事象：マントル細胞リンパ腫（Grade 5） |

被験者 1104-364-003 は，7[redacted] 歳の男性で，2011 年 7 月 28 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，前立腺肥大，左腎嚢胞，脊椎関節炎，及び黄斑領域の不均等な血管であった。MCL に対する前治療歴は R-CHOP であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，マグネシウム（低マグネシウム血症予防）及びカリウム（低カリウム血症予防）であった。ベースライン時の臨床検査結果は，ヘモグロビン 113 g/L，白血球数 $6 \times 10^9$/L，及び好中球絶対数 $4.23 \times 10^9$/L であった。本被験者は選択基準を満たし，スクリーニング時の心電図検査の結果，顕著な異常は認められなかった。2011 年 12 月 1 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

本試験登録時，頚部，縦隔，及び腸間膜領域，並びに骨髄への広範囲な MCL 浸潤（45%）が認められたが，肝腫大又は脾腫大は認められなかった。

### h) 被験者番号 1104-364-007

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| 被験者番号 | 1104-364-007 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：脱水（Grade 4），血小板減少症（Grade 4）<br>イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象，投与中止に至った有害事象：呼吸不全（Grade 5） |

被験者 1104-364-007 は，6[redacted] 歳の女性で，2009 年 11 月 24 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，子宮摘出，動脈性高血圧，胆石症，左卵巣嚢胞，結腸ポリポーシス，両側白内障手術，及び視力低下であった。MCL に対する前治療歴は，シクロホスファミド，フルダラビン，prednisone，リツキシマブ，及びビンクリスチンの併用療法（2009～2010 年），シクロホスファミド，ドキソルビシン，ミトキサントロン，prednisone，リツキシマブ，及びビンクリスチンの併用療法（2011 年），並びにテムシロリムスの単独療法であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，エナラプリル及びインダパミド（動脈性高血圧）であった。ベースライン時，縦隔，上顎，及び腸間膜領域，並びに骨髄への浸潤（17%）を伴う広範囲の疾患が認められた。ベースライン時の臨床検査結果は，ヘモグロビン 7.5 g/dL（Grade 3），白血球数 $5.2 \times 10^9$/L，好中球絶対数 $3.1 \times 10^9$/L，及び血小板数 $65 \times 10^9$/L（Grade 2）であった。ベースライン時の心電図検査では，顕著な異常は認められなかった。2012 年 2 月 7 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

i) 被験者番号 1104-368-001

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| 被験者番号 | 1104-368-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：マントル細胞リンパ腫（Grade 5） |

被験者 1104-368-001 は，7[redacted] 歳の男性で，2007 年 8 月 20 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，帯状疱疹及び眼帯状疱疹後疼痛であった。MCL に対する前治療歴は，リツキシマブ，シクロホスファミド，ビンクリスチン，及びプレドニゾロン（R-CVP），並びにシクロホスファミド及びフルダラビンであった。癌に関連した手術歴は脾摘であった。癌に関連した放射線療法による治療歴はなかった。

ベースライン時に投与中であった併用薬は，クロピドグレル（血栓予防）及びガバペンチン（眼帯状疱疹後疼痛）であった。ベースライン時の臨床検査結果は，ヘモグロビン 9.4 g/dL，白血球数 $86.4 \times 10^9$/L，好中球絶対数 $0.90 \times 10^9$/L，及び血小板数 $48 \times 10^9$/L/μL であった。ベースライン時の心電図検査では顕著な異常は認められず，選択基準を満たしていた。ベースライン時，縦隔，傍大動脈，頚部，及び腸間膜領域，並びに骨髄への MCL 浸潤（浸潤率は不明）が認められたが，脾腫大又は肝腫大は認められなかった。2011 年 9 月 13 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

j) 被験者番号 1104-368-003

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| 被験者番号 | 1104-368-003 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：マントル細胞リンパ腫（Grade 5） |

被験者 1104-368-003 は，6[redacted] 歳の男性で，2009 年 11 月 12 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。既往歴はなかった。MCL に対する前治療歴は，R-CVP，エトポシド，シスプラチン，シタラビン，及び prednisone，フルダラビン，ミトキサントロン，及びデキサメタゾン，オファツムマブの単独療法，並びに腹部放射線療法であった。癌に関連した手術歴はなかった。

ベースライン時に投与中であった併用薬はなかった。ベースライン時の臨床検査結果は，ヘモグロビン 139 g/L，白血球数 $6.7 \times 10^9$/L，好中球絶対数 $5.4 \times 10^9$/L，及び血小板数 $158 \times 10^9$/L であった。ベースライン時の心電図検査は選択基準を満たし，顕著な異常は認められなかった。2011 年 9 月 20 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

k) 被験者番号 1104-368-004

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| 被験者番号 | 1104-368-004 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：心房細動（Grade 3）<br>イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：敗血症（Grade 5） |

被験者 1104-368-004 は，6[redacted] 歳の男性で，2009 年 9 月 4 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，ヘル

ニア，静脈瘤，及び高血圧であった。MCL に対する前治療歴は，フルダラビン/シクロホスファミド（FC），シタラビンの単独療法，及びオファツムマブの単独療法であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，オメプラゾール（胃刺激症状予防），ramipril（高血圧），及びシンバスタチン（高脂血症予防）であった。ベースライン時，本被験者には傍大動脈，門脈大静脈，及び縦隔領域への浸潤を伴う広範囲の疾患がみられた。陽電子放出断層撮影（PET）スキャンは陽性で脾臓，及び骨髄で測定不能の病変が示され，70%浸潤が認められた。ベースライン時の臨床検査結果は，ヘモグロビン 86 g/L，白血球数 $23 \times 10^9$/L，好中球絶対数 $3.70 \times 10^9$/L，及び血小板数 $49 \times 10^9$/L であった。ベースライン時，ナトリウムは下限値（134～143）以下の 128 Mmol/L（mEq/L）であったが，その他の電解質には異常は認められなかった。ベースライン時の心電図検査は選択基準を満たし，顕著な異常所見は認められなかった。2011 年 10 月 10 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

l) **被験者番号 1104-368-007**

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| 被験者番号 | 1104-368-007 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象，大出血事象：血尿（Grade 3）<br>重篤な有害事象：心不全（Grade 3）<br>イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象，投与中止に至った有害事象：心停止（Grade 5） |

被験者 1104-368-007 は，7[redacted]歳の男性で，2006 年 4 月 28 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，2 型糖尿病，高血圧，血管拡張薬頚動脈過敏症，末梢性ニューロパチー（Grade 1），赤血球増加症，硬膜下血腫，うつ病，難聴，間欠性便秘，及び心不全であった。MCL に対する前治療歴は，FC，ボルテゾミブ，CHOP，及びレナリドミドの単独療法であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，buspirone 及びミルタザピン（うつ病），ロラゼパム（不安予防），アレンドロン酸（骨粗鬆症予防），カルシウム（低カルシウム血症），coloxyl・danthron 配合剤（間欠性便秘），アセチルサリチル酸（静脈血栓塞栓症予防），並びにアセトアミノフェン（疼痛予防）であった。ベースライン時の臨床検査結果は，ヘモグロビン 15.1 g/dL，血小板数 $123 \times 10^9$/L，及び白血球数 $8 \times 10^9$/L であった。ベースライン時の心電図検査では，顕著な異常は認められなかった。ベースライン時の MCL 浸潤は縦隔及び鼠径部領域で認められたが骨髄では認められず，肝腫大及び脾腫大は認められなかった。2011 年 10 月 31 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### m) 被験者番号 1104-368-012

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| 被験者番号 | 1104-368-012 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：マントル細胞リンパ腫（Grade 5） |

被験者 1104-368-012 は，6[redacted] 歳の男性で，2011 年 10 月 27 日に FISH での t(11;14)転座及び免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。既往歴はなかった。MCL に対する前治療歴は，シスプラチン，シタラビン，デキサメタゾン，リツキシマブ，及び R-CHOP であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬はなかった。ベースライン時の臨床検査結果は，ヘモグロビン 97 g/L，好中球絶対数 $2.30 \times 10^9$/L，及び白血球数 $39 \times 10^9$/L であった。2012 年 1 月 10 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

本試験登録時，頚部，縦隔，腸間膜領域，脾臓，及び骨髄への MCL 浸潤（86%）が認められた。

### n) 被験者番号 1104-368-013

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| 被験者番号 | 1104-368-013 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：脱水（Grade 3）<br>イブルチニブ最終投与後 30 日以内の死亡，重篤な有害事象：マントル細胞リンパ腫（Grade 5） |

被験者 1104-368-013 は，7[redacted] 歳の男性で，2011 年 4 月 28 日に FISH での t(11;14)転座及び免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，アンギナ，高血圧，及びそう痒症であった。MCL に対する前治療歴は，R-CHOP，CHOP，及び FC であった。癌に関連した手術歴及び放射線療法歴はなかった。

ベースライン時に投与中であった併用薬は，アムロジピン（高血圧），一硝酸イソソルビド（アンギナ），Aqueous crème（そう痒症），ビソプロロール（高血圧），セチリジン（そう痒症），ドンペリドン（悪心及び嘔吐予防），電解質/マクロゴール（便秘予防），シンバスタチン（高コレステロール血症予防），及びゾピクロン（不眠症予防）であった。2012 年 1 月 16 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。本試験登録時，肝臓，脾臓，並びに傍大動脈，腸間膜，及び縦隔領域の複数のリンパ節に加え，骨髄への広範囲な MCL 浸潤（66%浸潤）が認められた。

### (2) イブルチニブと関連性がある重篤な有害事象（上記及び疾患進行を除く）

#### 1) 被験者番号 1104-006-002

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| 被験者番号 | 1104-006-002 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 続発性悪性疾患：扁平上皮癌（Grade 1）<br>関連性がある重篤な有害事象：発熱性好中球減少症（Grade 3） |

被験者 1104-006-002 は，7[redacted] 歳の男性で，2004 年 5 月 6 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，季節性アレルギー，乾癬，胃食道逆流性疾患，甲状腺機能低下症，持続中の寝汗，手足のニューロパチー，頬部の小丘疹，胃炎，及び十二指腸炎であった。MCL に対する前治療歴は，R-CHOP 及びその後継続した強化療法としてのイブリツモマブ放射免疫療法，並びにリツキシマブ及び CAL-101 の単独療法であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，レボチロキシン（甲状腺機能低下症），オメプラゾール（胃食道逆流性疾患），及びロペラミド（下痢）であった。ベースライン時の臨床検査結果は，ヘモグロビン 117 g/L，血小板数 $101 \times 10^9$/L，白血球数 $4.8 \times 10^9$/L，及び好中球絶対数 $2.98 \times 10^9$/L であった。2011 年 6 月 21 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

#### 2) 被験者番号 1104-032-001

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| 被験者番号 | 1104-032-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：発熱性好中球減少症（Grade 3） |

被験者 1104-032-001 は，6[redacted] 歳の男性で，2006 年 2 月 7 日に FISH での染色体 t(11;14)転座によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，痔核切除，扁桃摘出，膀胱形成，胃食道逆流性疾患，血管形成，末梢血管疾患，表皮内黒色腫，霧視，眼乾燥，便秘，不安，及び下痢であった。MCL に対する前治療歴は，R-HyperCVAD 及びリツキシマブの単独療法，エトポシド，イホスファミド及びリツキシマブの併用療法，レナリドミド及びリツキシマブの併用療法，並びに自己同種骨髄幹細胞移植であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，エソメプラゾール（胃食道逆流性疾患），並びにカルシウム/ビタミン D，葉酸，マルチビタミン剤，及び亜鉛（サプリメント）であった。ベースライン時の臨床検査結果は，ヘモグロビン 139 g/L，白血球数 $4.1 \times 10^9$/L，好中球絶対数 $2.3 \times 10^9$/L，及び血小板数 $84 \times 10^9$/L であった。2011 年 2 月 22 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

#### 3) 被験者番号 1104-032-003

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| 被験者番号 | 1104-032-003 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：発熱性好中球減少症（Grade 3） |

被験者 1104-032-003 は，5[redacted] 歳の男性で，2010 年 8 月 18 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，臍ヘ

ルニア及び血小板減少症であった。MCL に対する前治療歴は，ボルテゾミブ及び R-Hyper CVAD，並びにリツキシマブの単独療法であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬はなかった。ベースライン時の臨床検査の結果は，好中球絶対数 2.84 × $10^9$/L 及び白血球数 4 × $10^9$/L であった。2011 年 3 月 8 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

#### 4) 被験者番号 1104-032-005

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| 被験者番号 | 1104-032-005 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：蜂巣炎（Grade 3）<br>関連性がある重篤な有害事象：心房細動（Grade 3）<br>関連性がある重篤な有害事象：心房細動（Grade 3）<br>重篤な有害事象：肺炎（Grade 3）<br>関連性がある重篤な有害事象：気管支炎（Grade 3）<br>関連性がある重篤な有害事象： 感染性小腸結腸炎（Grade 3） |

被験者 1104-032-005 は，7[redacted] 歳の男性で，2009 年 5 月 7 日に FISH での t(11;14)転座により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，高血圧，腎結石，慢性腎疾患，腎摘除による単腎，腎細胞癌，下肢しびれ感，疲労（Grade 1），発汗，及び腫脹であった。MCL に対する前治療歴は，61 日間の R-Hyper CVAD 療法，並びに 57 日間のシクロホスファミド，ドキソルビシン，prednisone，ビンクリスチン，及びリツキシマブによる治療（最後 2 レジメンの投与中は，ドキソルビシン 50 mg を 1 日 1 回，合計 12 回投与された）であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，ガバペンチン（下肢しびれ感），ビタミン B（サプリメント），及びバルサルタン（高血圧）であった。ベースライン時の臨床検査の結果は，好中球絶対数 4.85 × $10^9$/L 及び白血球数 7.3 × $10^9$/L であった。2011 年 3 月 23 日のベースライン時の心電図検査では，心拍数 69 bpm 及び QT 間隔 384 msec（補正 QTcB 411）であった。2011 年 3 月 24 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

#### 5) 被験者番号 1104-032-012

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| 被験者番号 | 1104-032-012 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：気管支炎（Grade 3），心房細動（Grade 3），肺炎（Grade 3），肺炎（Grade 3）<br>重篤な有害事象：低血圧（Grade 3） |

被験者 1104-032-012 は，7[redacted] 歳の男性で，2010 年 5 月 7 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，高血圧，膝関節置換，睡眠時無呼吸，骨折，パーキンソン病，良性前立腺肥大，股関節損傷に至った自動車事故，Greenfield フィルター留置，胆嚢切除，胆石，グロヴァー病，肺炎，感覚ニューロパチー，リンパ腫による皮膚そう痒，冠動脈疾患，高脂血症，アレルギー，不安障害，便秘，下肢浮腫，高尿酸血症，低カリウム血症，霧視，眼乾燥，及び流涙であった。MCL に対する前治

療歴は，R-CHOP，並びにリツキシマブ，イホスファミド，カルボプラチン，及びエトポシド（RICE）であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，アセチルサリチル酸及び一硝酸イソソルビド（冠動脈疾患），セチリジン（アレルギー），クロベタゾール（皮膚そう痒），フロセミド（下肢浮腫），ヘパリン（中心ラインのフラッシュ），メトプロロール（高血圧），ポリカルボフィル（便秘），カリウム（低カリウム血症），プラミペキソール，カルビドパ/レボドパ及び rasagiline（パーキンソン病），シンバスタチン（高脂血症），並びにトラゾドン（不安障害）であった。ベースライン時の臨床検査結果は，白血球数 $4.5 \times 10^9$/L 及び好中球絶対数 $2.4 \times 10^9$/L であった。2011 年 5 月 13 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 6) 被験者番号 1104-032-016

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| 被験者番号 | 1104-032-016 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：慢性閉塞性肺疾患（Grade 3），慢性閉塞性肺疾患（Grade 3）<br>関連性がある重篤な有害事象：クレブシエラ菌性肺炎（Grade 3）<br>重篤な有害事象：慢性閉塞性肺疾患（Grade 3），冠動脈閉塞（Grade 3） |

被験者 1104-032-016 は，6[redacted] 歳の男性で，2009 年 7 月 21 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，冠動脈疾患，高脂血症，高血圧，右冠動脈の経皮的冠インターベンション，末梢動脈疾患，頚動脈内膜剥離術，憩室炎，肺気腫，胃食道逆流性疾患，ポリープ，皮膚癌，頚部脊椎炎性脊髄症，慢性閉塞性肺疾患，心カテーテル，深部静脈血栓症，心筋梗塞，良性前立腺肥大，慢性背部痛，肺塞栓症，椎骨形成術，L3 圧迫骨折，性腺機能低下，骨粗鬆症，経尿道的前立腺摘除，貧血（Grade 1），上肢及び下肢の斑状出血性病変，間欠性疲労，血小板減少症（Grade 2），呼吸困難，記憶障害，並びに末梢性感覚ニューロパチーであった。MCL に対する前治療歴は，リツキシマブ，シクロホスファミド，デキサメタゾン，ドキソルビシン，及びビンクリスチンであった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

本試験登録時に投与中であった併用薬は，フルチカゾン/サルメテロール（Seretide，慢性閉塞性肺疾患），シンバスタチン（高脂血症），カルシウム（骨粗鬆症），ゾレドロン酸（骨粗鬆症），docusate（便秘予防），マルチビタミン剤/鉄（サプリメント），リシノプリル（高血圧），アセチルサリチル酸（冠動脈疾患），及びテストステロン（性腺機能低下）であった。ベースライン時の臨床検査結果は，ヘモグロビン 123 g/L，白血球数 $5.2 \times 10^9$/L，好中球絶対数 $3.3 \times 10^9$/L，及び血小板数 $55 \times 10^9$/L であった。ベースライン時の心電図検査は選択基準を満たしており，顕著な異常所見は認められなかった。2011 年 6 月 1 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 7) 被験者番号 1104-032-020

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| 被験者番号 | 1104-032-020 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：肺炎（Grade 3），非心臓性胸痛（Grade 3）<br>関連性がある重篤な有害事象：肺炎（Grade 3） |

被験者 1104-032-020 は，6[redacted] 歳の女性で，2007 年 3 月 16 日に FISH での t(11;14)転座及び免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，脂肪腫，帝王切開，子宮摘出による出血，肺炎，痛風，大腸菌性菌血症，高脂血症，及び右膝の関節鏡下手術であった。MCL に対する前治療歴は，R-Hyper CVAD，並びにシクロホスファミド，エトポシド，イホスファミド，及びリツキシマブ（RICE）であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，アロプリノール（痛風），アトルバスタチン（高脂血症），並びにビタミン D 配合カルシウム及びオメガ‐3 脂肪酸エチルエステル（サプリメント）であった。ベースライン時の臨床検査の結果は，白血球数 $6.9 \times 10^9$/L（K/μL），ヘモグロビン 10.5 g/dL，好中球絶対数 $3.9 \times 10^9$/L，及び血小板数 $151 \times 10^9$/L であった。ベースライン時の心電図検査では，顕著な異常は認められなかった。ベースライン時，MCL 浸潤は頚部及び鼡径部領域で認められたが，骨髄浸潤，並びに脾腫大及び肝腫大は認められなかった。2011 年 6 月 9 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 8) 被験者番号 1104-032-022

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|---|---|
| 被験者番号 | 1104-032-022 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：貧血（Grade 3） |

被験者 1104-032-022 は，6[redacted] 歳の男性で，2000 年 1 月 27 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，虫垂切除，高脂血症，脂肪腫，背部手術，良性前立腺肥大，胆嚢切除，形質細胞腫，ペニシリンアレルギー，末梢性ニューロパチー，肺炎，胃潰瘍，臍ヘルニア修復，出血性胃潰瘍，不安，うつ病，胃食道逆流性疾患，扁平上皮癌，基底細胞癌，発疹，膝痛，並びに間欠性下痢及び粘膜炎であった。MCL に対する前治療歴は，R-CHOP，フルダラビン及びリツキシマブ（2000 年），ボルテゾミブ及びデキサメタゾン，arabinofuranosyl cytidine（ARA-C）6 サイクル及びリツキシマブ，R-CHOP 2 サイクル（2009～2010 年），ベンダムスチン及びリツキシマブ 1 サイクル，サリドマイドの単独療法，並びにベンダムスチン，ボルテゾミブ，及びリツキシマブであった。癌に関連した放射線療法による治療歴は，頚部及び他の上咽頭領域に限局した放射線療法であった。癌に関連した手術歴はなかった。

ベースライン時に投与中であった併用薬は，alprazolam 及びエスシタロプラム（不安），ドキサゾシン（良性前立腺肥大），ファモチジン（胃食道逆流性疾患），オンダンセトロン（悪心及び嘔吐予防），メチルプレドニゾロン（発疹），並びに口腔用製剤（口腔ケア）であった。ベースライン時の臨床検査結果は，ヘモグロビン 9.4 g/dL，白血球数 $1.9 \times 10^9$/L，好中球絶対数 $1.5 \times 10^9$/L，及び血小板数 $69 \times 10^9$/L であった。スクリーニング時の疾患は傍大動脈腸骨及び鼡径部領域，並びに脾臓に浸潤が認められたが，肝臓及び骨髄への浸潤は認められなかった。ベー

スライン時の心電図検査では，顕著な異常は認められなかった。2011 年 6 月 13 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 9) 被験者番号 1104-032-023

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| 被験者番号 | 1104-032-023 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：蜂巣炎（Grade 3） |

被験者 1104-032-023 は，6[redacted] 歳の男性で，2009 年 12 月 22 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，高脂血症，高血圧，良性前立腺肥大症，帯状疱疹，胃食道逆流性疾患，便秘，しびれ感，及びピリピリ感，並びに Grade 2 の右下肢浮腫であった。MCL に対する前治療歴は，R-hyper CVAD，ベンダムスチン，リツキシマブ，及びボルテゾミブ単回投与であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，エナラプリル及びカルベジロール（高血圧），魚油，コレカルシフェロール及びマルチビタミン剤（サプリメント），ガバペンチン（しびれ感及びピリピリ感），プラバスタチン（高脂血症），タムスロシン（良性前立腺肥大症），及びオメプラゾール（胃食道逆流性疾患）であった。ベースライン時の臨床検査結果は，白血球数 $5.1 \times 10^9$/L，リンパ球数 $1.45 \times 10^9$/L，好中球絶対数 $2.75 \times 10^9$/L，及びヘモグロビン 94 g/L であった。2011 年 6 月 20 日，本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。同日（Day 1），眼乾燥，疲労，及び間欠性筋肉痛が発現した。

### 10) 被験者番号 1104-032-030

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| 被験者番号 | 1104-032-030 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：好中球減少症（Grade 4）<br>重篤な有害事象：クロストリジウム・ディフィシレ大腸炎（Grade 3） |

被験者 1104-032-030 は，7[redacted] 歳の男性で，2008 年 1 月 23 日に FISH での t(11;14)転座及び免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，関節炎，混合型ヘルニア，関節鏡下膝手術（5 回），人工膝関節全置換，頚骨癒合，良性前立腺肥大症，慢性 B 型肝炎感染，白内障手術，胃潰瘍，骨粗鬆症，疣贅，冠動脈疾患，末梢性ニューロパチー，三枝バイパス，霧視，間欠性下痢，記憶の変化，耳鳴，高脂血症，及びうつ病であった。MCL に対する前治療歴は，R-CHOP 及びボルテゾミブであった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，アレンドロン酸ナトリウム（骨粗鬆症），エソメプラゾール（胃潰瘍），ガバペンチン（末梢性ニューロパチー），hydrocodone/アセトアミノフェン（末梢性ニューロパチー），メロキシカム（関節炎），ロスバスタチン（高脂血症），タムスロシン（良性前立腺肥大症），ビタミン D（サプリメント），及びデュロキセチン（うつ病）であった。ベースライン時，鼡径部，縦隔，及び腸間膜領域への MCL 浸潤が認められたが，骨髄への浸潤はわずか（1%）であった。臨床検査の結果は，ヘモグロビン 112 g/L，白血球数

3.8 × $10^9$/L，血小板数 110 × $10^9$/L，及び好中球絶対数 1.46 × $10^9$/L であった。2011 年 8 月 4 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 11) 被験者番号 1104-200-006

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| 被験者番号 | 1104-200-006 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：汎血球減少症（Grade 4） |

被験者 1104-200-006 は，5[redacted] 歳の女性で，2011 年 2 月に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，クレアチニン上昇（Grade 1），高血圧，低血糖症（Grade 1），低カリウム血症（Grade 1），アルブミン低値（Grade 1），マグネシウム低値（Grade 1），脾腫（Grade 1），寝汗（Grade 1），息切れ（Grade 1），腹痛（Grade 2），貧血（Grade 2），腹水，両下肢浮腫（Grade 1），慢性的な病気の出現，結膜（Grade 1），腹部膨満（Grade 1），高カルシウム血症（Grade 1），低カルシウム血症（Grade 1），触診での左上腹部圧痛，悪心（Grade 1），頻脈（Grade 1），及び血小板減少症（Grade 3）であった。MCL に対する前治療歴は，Hyper CVAD 及び R-CHOP であった。癌に関連した放射線療法による治療歴はなかった。癌に関連した手術歴は左鼡径リンパ節生検であった。

ベースライン時に投与中であった併用薬は，アロプリノール（腫瘍崩壊予防），アムロジピン（高血圧），スルファメトキサゾール/トリメトプリム（広域抗菌予防），葉酸（サプリメント），及びバラシクロビル（帯状疱疹予防）であった。ベースライン時の臨床検査結果は，ヘモグロビン 86 g/L（8.6 g/dL），血小板数 32 × $10^9$/L，白血球数 8.4 × $10^9$/L，及び好中球絶対数 3.2 × $10^9$/L であった。2011 年 8 月 2 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。ベースライン時，骨髄への広範囲な MCL 浸潤（腫瘍細胞 70%）が認められた。

### 12) 被験者番号 1104-200-007

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| 被験者番号 | 1104-200-007 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：心房細動（Grade 3） |

被験者 1104-200-007 は，8[redacted] 歳の女性で，2009 年 9 月 24 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。特記すべき既往歴は，良性髄膜腫，乳癌，乳房腫瘤摘除，心房細動（Grade 1），蜂巣炎，B 型ウイルス性肝炎，高血圧（Grade 2），両膝関節痛（Grade 2），及び扁桃腫瘤拡大であった。MCL に対する前治療歴は，R-CVP 及びベンダムスチンの単独療法であった。癌に関連した手術歴は右扁桃生検であった。癌に関連した放射線療法による治療歴はなかった。

ベースライン時に投与中であった併用薬は，エソメプラゾール（胃食道逆流性疾患），イブプロフェン（膝痛），アムロジピン（高血圧），及び paracetamol（膝痛）であった。ベースライン時の臨床検査結果は，ヘモグロビン 9.8 g/dL，白血球数 4.8 × $10^9$/L，及び好中球絶対数 3.0 × $10^9$/L であった。ベースライン時，頚部及び鼡径部領域への MCL 浸潤が認められたが，肺

の標的病変，骨髄，肝臓，及び脾臓への浸潤は認められなかった。2011 年 8 月 17 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 13) 被験者番号 1104-210-003

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| 被験者番号 | 1104-210-003 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 続発性悪性疾患：皮膚有棘細胞癌（Grade 2）<br>関連性がある重篤な有害事象：細菌性肺炎（Grade 3）<br>重篤な有害事象：細菌性肺炎（Grade 3） |

被験者 1104-210-003 は，8[redacted] 歳の男性で，2006 年 2 月 14 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，扁桃摘出，化学療法誘発性の便秘，低血圧，痔核，平衡感覚低下，ニューロパチー（手のピリピリ感及びしびれ感，Grade 1），胃腸出血，腸管部分閉塞，前立腺腫大，胃食道逆流性疾患，労作性息切れ，放射線照射誘発性の唾液分泌量減少，化学療法誘発性の頭部及び耳うっ血，クロストリジウム・ディフィシレ感染，軽度不安，軽度うつ病，臍周囲ヘルニア，無気肺（左下葉），全身脱力（Grade 1），軽度疲労，白内障手術（両眼），手の扁平上皮癌，第一度房室ブロック，低ナトリウム血症（Grade 1），血小板減少症（Grade 1），貧血（Grade 2），左脚前枝ブロック，右脚ブロック，右前腕痛，神経圧迫による右手脱力，右前腕腫脹，血流雑音（Grade 1～2），左手背面の角化症と考えられる潰瘍性病変，尿酸増加，高血糖（Grade 2），白血球減少症（Grade 3，ベースライン時 $1.52 \times 10^9$/L），及び好中球減少症（Grade 3，ベースライン時 $0.95 \times 10^9$/L）であった。MCL に対する前治療歴は，R-CHOP，ボルテゾミブの単独療法，レナリドミドの単独療法，ベンダムスチン及びリツキシマブ，prednisone/エトポシド/プロカルバジン/シクロホスファミド及びリツキシマブ（PEP-C + Rituxan），並びに両眼窩，右硬口蓋，及び左右大腿リンパ節への放射線療法であった。癌に関連した手術歴はなかった。

ベースライン時に投与中であった併用薬は，オキシコドン（疾患による疼痛），ガバペンチン（ニューロパチー），及びドキサゾシン（前立腺腫大）であった。ベースライン時の臨床検査結果は，好中球絶対数 $0.95 \times 10^9$/L（Grade 3），白血球数 $1.52 \times 10^9$/L（Grade 3），血小板数 $133 \times 10^9$/L（Grade 1），及びヘモグロビン 85 g/L（Grade 2）であった。2012 年 1 月 5 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 14) 被験者番号 1104-217-001

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| 被験者番号 | 1104-217-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：頭痛（Grade 2） |

被験者 1104-217-001 は，6[redacted] 歳の男性で，1993 年 9 月 15 日に免疫組織化学的検査でのサイクリン D1 発現によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，間欠性頭痛，間欠性浮動性めまい，間欠性不眠症，うつ病，認知障害，下肢静止不能症候群，麻疹，扁桃摘出，ムンプス，季節性アレルギー，虫垂切除，不安，赤色食用色素，ペニシリン，及びジフェンヒドラミンに対するアレルギー，間欠性疲労，間欠性貧血，びまん性筋肉痛，間欠性血小板減少症，間欠性下痢，良性前立腺肥大，慢性副鼻腔炎，左探針及び洗浄を伴う右涙嚢鼻腔吻合，右鼻涙管探針及び洗浄を伴う左涙嚢鼻腔吻合，間欠性多汗症，椎間板変性疾患，手術を要する両

側涙管遮断，間欠性労作性呼吸困難，アテローム性動脈硬化症，胃食道逆流性疾患，高血圧，間欠性早期満腹，間欠性低カルシウム血症，間欠性食欲不振，間欠性運動失調，聴覚障害，憩室症，睡眠時無呼吸，慢性閉塞性肺疾患，間欠性低ナトリウム血症，びまん性関節痛，冠動脈疾患，高脂血症，冠動脈バイパス移植術，間欠性痔核，間欠性低カリウム血症，肺炎球菌性肺炎，菌血症，間欠性粘膜炎，間欠性便秘，間欠性悪心，起立性低血圧，胆嚢切除，複数回の腱手術，リビドー減退，性交困難，並びに両下肢浮腫であった。MCL に対する前治療歴は，chlorambucil の単独療法，シクロホスファミド及び prednisone，リツキシマブの単独療法（2 レジメン），リツキシマブ及び interleukin-2，R-CHOP，並びに自己骨髄移植であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，ロラタジン（アレルギー），アルプラゾラム及びデュロキセチン（不安），アトルバスタチン（高脂血症），バラシクロビル（水痘帯状疱疹ウイルス予防），デュタステリド及びオキシブチニン（良性前立腺肥大），プラミペキソール（下肢静止不能症候群），アセチルサリチル酸（深部静脈血栓症予防），docusate（便秘予防），オキシコドン/アセトアミノフェン（びまん性関節痛），マルチビタミン剤及びアスコルビン酸（免疫系に対するサプリメント），ビスマス（悪心予防），レボフロキサシン（細菌感染予防），鉄（鉄欠乏性貧血予防），ロラゼパム及びプロクロルペラジン（悪心），並びにスルファメトキサゾール（感染予防）であった。ベースライン時の臨床検査結果は，ヘモグロビン 113 g/L，好中球絶対数 $3.21 \times 10^9$/L，及び白血球数 $4.9 \times 10^9$/L であった。2011 年 6 月 23 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 15) 被験者番号 1104-217-009

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| 被験者番号 | 1104-217-009 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：急性腎不全（Grade 3），尿路感染（Grade 3）<br>関連性がある重篤な有害事象，投与中止に至った有害事象：敗血症（Grade 4） |

被験者 1104-217-009 は，8[redacted] 歳の女性で，2007 年 10 月に FISH での t(11;14)転座によりマントル細胞リンパ腫（MCL）と確定診断された。本被験者の特記すべき既往歴は，痛風，高血圧，2 型糖尿病，深部静脈血栓症，下大静脈フィルター留置，肺塞栓症，子宮摘出，一過性脳虚血発作，過敏性腸症候群，慢性腎機能不全，アテローム性動脈硬化症，慢性閉塞性肺疾患，憩室症，腎嚢胞，シュードモナス菌性肺炎，腫瘍崩壊症候群，アレルギー（ヨウ素，イブプロフェン，及びシプロフロキサシン），再発尿路感染，及び冠動脈疾患であった。MCL に対する前治療歴は，リツキシマブ，ボルテゾミブ，及びレナリドミドであった。癌に関連した手術歴及び放射線療法歴はなかった。

ベースライン時に投与中であった併用薬は，ヒドロクロロチアジド/トリアムテレン（Dyazide）（高血圧），ヒューマログミックス（糖尿病），クロピドグレル及びワルファリン（深部静脈血栓症予防），ロペラミド（下痢），ナプロキセン（関節炎による疼痛），ミネラル及びビタミン（免疫系サプリメント），アロプリノール（痛風，高尿酸血症，及び指の限局性浮腫），並びにコルヒチン（痛風）であった。ベースライン時の臨床検査結果は，ヘモグロビン 11.3 g/dL，血小板数 $266 \times 10^9$/L，クレアチニン 1.58 mg/dL，白血球数 $9.9 \times 10^9$/L，及び好中球絶対数 $5.3 \times 10^9$/L であった。ベースライン時の心電図検査では，顕著な異常は認められなかった。

ベースライン時の MCL 浸潤は傍大動脈領域，骨髄（40%）及び脾腫大が認められたが，肝腫大は認められなかった。2012 年 1 月 4 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 16) 被験者番号 1104-217-014

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| 被験者番号 | 1104-217-014 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：発熱（Grade 1） |

被験者 1104-217-014 は，6[redacted] 歳の女性で，2008 年 5 月に FISH での t(11;14)転座により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，高血圧，糖尿病，線維筋痛，皮膚乾燥，エプスタイン・バーウイルス，うつ病，移植片対宿主反応，胆石症，急性腎不全であり，間欠的な既往歴は，高脂血症，回転性めまい，血小板減少症，貧血，悪寒，労作性呼吸困難，疲労，発熱，頭痛，悪心，腟小出血，低血圧，高血糖，低カルシウム血症，低ナトリウム血症，下痢，高カリウム血症，高尿酸血症，味覚異常，疼痛，低マグネシウム血症，食欲不振，不眠症，発疹，洞性頻脈，及び乾性咳嗽であった。MCL に対する前治療歴は，ベンダムスチン及びリツキシマブ，R-CHOP，及びメトトレキサート，同種骨髄移植，ゲムシタビン，オキサリプラチン及びリツキシマブ，並びにボルテゾミブ及びリツキシマブであった。癌に関連した放射線療法による治療歴は，腹壁及び傍大動脈リンパ節に限局した放射線療法であった。癌に関連した手術歴はなかった。

ベースライン時に投与中であった併用薬は，ナプロキセン（頭痛），アテノロール（高血圧），アトルバスタチン（高脂血症），アセトアミノフェン（発熱），オンダンセトロン（悪心），フルコナゾール（抗真菌予防），バラシクロビル（抗ウイルス予防），プロクロルペラジン（悪心），シタロプラム（不眠症），スルファメトキサゾール/トリメトプリム（抗菌予防），マグネシウム（低マグネシウム血症），ロペラミド（下痢），オキシコドン（腹痛），及び栄養剤（食欲不振）であった。ベースライン時の臨床検査結果は，ヘモグロビン 110 g/L，白血球数 $2.4 \times 10^9$/L，及び好中球絶対数 $1.44 \times 10^9$/L であった。2012 年 3 月 14 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 17) 被験者番号 1104-251-001

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| 被験者番号 | 1104-251-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：下痢（Grade 3） |

被験者 1104-251-001 は，7[redacted] 歳の男性で，2009 年 11 月 21 日に FISH での t(11;14)転座及び免疫組織化学的検査でのサイクリン D1 発現により芽球性マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，静脈瘤切除，甲状腺機能低下症，根治的前立腺摘除，前立腺癌，発疹（左大腿上部），間欠性胃不調，貧血，ループス腎炎，慢性腎疾患，高血圧，白内障，眼異常，ヘルペス後神経痛，右下肢脱力，睡眠時無呼吸，腰椎椎弓切除，白内障手術（左眼），帯状疱疹，右膝腫脹，好中球減少症，血小板減少症，間欠性尿閉，耳下腺嚢胞，サルファ剤に対するアレルギー，クロストリジウム・ディフィシレ性下痢，便秘，胃酸逆流，不安，中心静脈カテーテル不具合，鼻の乾燥，直腸周囲発赤，ニューモシスティス肺炎，右脚ブロック，高リン酸塩血

症，並びにバンコマイシン耐性エンテロコッカスであった。MCL に対する前治療歴は，リツキシマブ，シタラビン及びメトトレキサート，並びにリツキシマブ及びボルテゾミブであった。癌に関連した放射線療法による治療歴は，右大腿領域に限局した放射線療法であった。癌に関連した手術歴はなかった。

ベースライン時に投与中であった併用薬は，レボチロキシン（甲状腺機能低下症），炭酸カルシウム（間欠性胃不調），センノシド a＋b（便秘），ビタミン D，マルチビタミン剤及びコレカルシフェロール（健康サプリメント），アシクロビル（ヘルペス後神経痛），葉酸（癌治療），ロラゼパム（不安），プラステロン（癌治療），アルテプラーゼ（中心静脈カテーテル不具合），他の皮膚病薬（直腸周囲発赤），アセトアミノフェン，prednisone，primaquine 及びスルファメトキサゾール/トリメトプリム（Bactrim）（すべてニューモシスティス肺炎に対して），クリンダマイシン（感染），センノシド/docusate（Senokot-s）（間欠性便秘），塩化ナトリウム（鼻の乾燥及び水分補給），オメプラゾール（胃酸逆流），及びセベラマー（高リン酸塩血症）であった。ベースライン時の臨床検査結果は，クレアチニン 2.45 mg/dL，ヘモグロビン 109 g/L，白血球数 $5.6 \times 10^9$/L，及び好中球絶対数 $4.23 \times 10^9$/L であった。ベースライン時の心電図検査は選択基準を満たし，顕著な異常所見はみられなかった。2011 年 10 月 18 日，本被験者は，ニューモシスティス肺炎に対する治療後退院し，クリンダマイシン及びトリメトプリム/スルファメトキサゾール（Bactrim）の投与を中止した直後であったが，primaquine 及び prednisone の投与は Day 9 まで継続した。2011 年 10 月 21 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 18) 被験者番号 1104-343-001

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| 被験者番号 | 1104-343-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：非心臓性胸痛（Grade 2），一過性全健忘（Grade 1）<br>関連性がある重篤な有害事象，投与中止に至った有害事象，大出血事象：硬膜下血腫（Grade 2） |

被験者 1104-343-001 は，7[redacted] 歳の男性で，2003 年 2 月 7 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，高コレステロール血症，結腸ポリープ，冠動脈疾患，ステント 2 本留置を伴う心筋梗塞，高脂血症，高血圧，直腸周囲瘻孔切除修復術，左前額部の扁平上皮癌切除（2005 年），扁平上皮癌切除（2010 年），ニューロパチー（Grade 1），うつ病，blespharitis，血小板減少症（Grade 1），貧血（Grade 1），一過性全健忘，及び洞性徐脈（Grade 1）であった。MCL に対する前治療歴は，HyperCVAD，ボルテゾミブ及び obatoclax，リツキシマブ及びレナリドミドの単独療法，並びに自己骨髄移植であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，ニコチン酸及びプラバスタチン（高脂血症），ロサルタン及びメトプロロール（高血圧），ビタミン B 複合体，アスコルビン酸及び魚油（サプリメント），セルトラリン及びガバペンチン（ニューロパチー），ニコチン酸アミド（ビタミンサプリメント），並びにアセチルサリチル酸（冠動脈疾患）であった。ベースライン時の臨床検査結果は，ヘモグロビン 137 g/L，血小板 $103 \times 10^9$/L，白血球数 $5 \times 10^9$/L，及び好中球絶対数 $2.4 \times 10^9$/L であった。ベースライン時の心電図検査では，顕著な異常は認められなかった。ベー

スライン時の MCL 浸潤は頚部，傍気管，後腹膜，鼠径部領域，及び骨髄に認められたが（2%），肝腫大及び脾腫大は認められなかった。2011 年 2 月 16 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 19) 被験者番号 1104-343-005

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| 被験者番号 | 1104-343-005 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象，大出血事象：硬膜下血腫（Grade 3）<br>関連性がある重篤な有害事象：ブドウ球菌性菌血症（Grade 3）<br>重篤な有害事象，投与中止に至った有害事象，大出血事象：硬膜下血腫（Grade 3） |

被験者 1104-343-005 は，7[redacted] 歳の男性で，1999 年 12 月 10 日に免疫組織化学的検査でのサイクリン D1 発現により芽球性マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，左ヘルニア修復，結腸及び膀胱癌，心臓梗塞，高コレステロール血症，リンパ球減少症（Grade 3），女性化乳房，疲労（Grade 1），並びに貧血（Grade 1）であった。MCL に対する前治療歴は，CHOP，シクロホスファミド，フルダラビン，ミトキサントロン，及びリツキシマブ，リツキシマブの単独療法，並びにベンダムスチン及びリツキシマブであった。癌に関連した放射線療法による治療歴は，結腸への放射線療法であった。

ベースライン時に投与中であった併用薬は，アセチルサリチル酸（心臓障害の予防。Day 56 に中止），マルチビタミン剤（サプリメント），及びシンバスタチン（高脂血症）であった。ベースライン時の臨床検査結果は，ヘモグロビン 111 g/L，血小板数 $165 \times 10^9$/L，及び好中球絶対数 $4.19 \times 10^9$/L であった。2011 年 5 月 25 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 20) 被験者番号 1104-343-007

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|---|---|
| 被験者番号 | 1104-343-007 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：肺炎（Grade 3）<br>重篤な有害事象，続発性悪性疾患：膀胱癌（Grade 3）<br>関連性がある重篤な有害事象，投与中止に至った有害事象，続発性悪性疾患：転移性新生物（Grade 3） |

被験者 1104-343-007 は，7[redacted] 歳の男性で，2007 年 12 月 28 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，咳嗽，喘息，気管支拡張症，慢性閉塞性肺疾患，アンギナ，末梢血管疾患，無症候性心筋梗塞，睡眠時無呼吸，高コレステロール血症，高脂血症，回転性めまい，アモキシシリン/クラブラン酸（Augmentin）に対するアレルギー，高血圧，疲労（Grade 1），貧血（Grade 1），腎仙痛，及び大腿動脈ステントであった。MCL に対する前治療歴は，R-CHOP，カルボプラチン，エトポシド，イホスファミド，メスナ，及びリツキシマブ，並びにボルテゾミブ及びレナリドミドの単独療法であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，アセチルサリチル酸，クロピドグレル及び glyceryl trinitrate（アンギナ），フロセミド及びロサルタン（高血圧），カリウム（サプリメント），サルブタモール（慢性閉塞性肺疾患），アトルバスタチン及びオメガ - 3 脂肪酸エチルエ

ステル（高コレステロール血症），カルシウム及びビタミン D（欠乏），フルチカゾン（咳嗽/慢性閉塞性肺疾患），並びに meclozine（回転性めまい）であった。ベースライン時の臨床検査結果は，ヘモグロビン 142 g/L（14.2 g/dL），白血球数 $6.2 \times 10^9$/L，好中球絶対数 $4.1 \times 10^9$/L，及び血小板数 $135 \times 10^9$/L であった。ベースライン時の心電図検査では，顕著な異常は認められなかった。ベースライン時，傍大動脈，傍気管，気管分岐部，腸骨，及び骨盤領域，並びに骨髄への MCL 浸潤（5%）が認められた。2012 年 1 月 4 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 21) 被験者番号 1104-358-001

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| 被験者番号 | 1104-358-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：気道感染（Grade 3）<br>重篤な有害事象：頚部腫瘤（Grade 3） |

被験者番号 1104-358-001 は，7[redacted] 歳の男性で，1995 年 5 月に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，浮動性めまい，鼻，左乳房，及び後頭部領域の基底細胞腫，食欲不振（Grade 1），クロストリジウム・ディフィシレ感染，単純ヘルペス感染，低カリウム血症，浮腫及び下肢痛（Grade 2），並びに不眠症であった。MCL に対する前治療歴は，prednimustine/ミトキサントロン，フルダラビン/シクロホスファミド/ミトキサントロン/リツキシマブ（R-FCM）及びリツキシマブ，ベンダムスチン及びゼヴァリン，並びにレナリドミド及びリツキシマブ/ベンダムスチン（R-benda）であった。また，本被験者は放射線療法（照射領域不明）の治療歴も有していた。癌に関連した手術歴はなかった。

ベースライン時に投与中であった併用薬は，ロペラミド（下痢），ゾルピデム（不眠症），tinzaparin（MCL による予防的抗凝固），及び metamizole（疼痛）であった。ベースライン時の臨床検査結果は，ヘモグロビン 91 g/L，好中球絶対数 $4.8 \times 10^9$/L，及び白血球数 $4.6 \times 10^9$/L であった。2011 年 12 月 6 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 22) 被験者番号 1104-364-007

本被験者の叙述は，「有害事象による死亡例」の項に記載している。

### 23) 被験者番号 1104-365-002

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| 被験者番号 | 1104-365-002 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：錯乱状態（Grade 3），尿路感染（Grade 3），下気道感染（Grade 3），尿路感染（Grade 1），褥瘡性潰瘍（Grade 1）<br>関連性がある重篤な有害事象：肛門膿瘍（Grade 2）<br>重篤な有害事象：褥瘡性潰瘍（Grade 2），褥瘡性潰瘍（Grade 3）<br>関連性がある重篤な有害事象： 眼窩蜂巣炎（Grade 3） |

被験者番号 1104-365-002 は，7[redacted] 歳の男性で，2003 年 8 月に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，

粘膜関連リンパ組織リンパ腫，右耳の聴覚障害，慢性息切れ，左鼡径部ヘルニア修復，胃潰瘍，両眼白内障，眼乾燥，両下肢浮腫，及びパーキンソン病であった。MCL に対する前治療歴は，FC，フルダラビン/シクロホスファミド/リツキシマブ（FCR），ベンダムスチン/リツキシマブ，リツキシマブ，及びレナリドミドの単独療法であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。

ベースライン時に投与中であった併用薬は，イプラトロピウム及びサルブタモール（息切れ），オメプラゾール及びランソプラゾール（胃酸逆流），docusate（便秘），アモキシシリン/クラブラン酸（Augmentin）（発熱前治療，感染），フロセミド（両足首浮腫及び過剰体液），hypromellose（眼乾燥），アセトアミノフェン及びオピオイド（発熱，背部痛，及び疼痛），ゾピクロン（不眠症），アロプリノール（腫瘍崩壊症候群予防，白血球数増加），クロラムフェニコール（赤目及び涙目），リドカイン（口唇腫脹及び潰瘍），シプロフロキサシン（眼感染，咳嗽，及び喀痰検体陽性），tinzaparin（深部静脈血栓症予防），レボドパ/カルビドパ（Sinemet）（パーキンソン病），カリウム（低カリウム血症），バンコマイシン（感染），ペチジン（悪寒），センノシド a＋b（便秘），リン酸塩及び鉄（欠乏），並びに炭水化物，脂肪酸，及びミネラル（栄養補助食品）であった。ベースライン時の臨床検査結果は，ヘモグロビン 92 g/L（9.2 g/dL），白血球数 $11.3 \times 10^9$/L，好中球絶対数 $4.9 \times 10^9$/L，及び血小板数 $129 \times 10^9$/L であった。ベースライン時の心電図検査に異常は認められなかった。ベースライン時の MCL 浸潤は，肺，縦隔，肝門脈，及び傍大動脈領域，並びに骨髄（50%）に認められたが，肝腫大及び脾腫大は認められなかった。2011 年 12 月 1 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 24) 被験者番号 1104-368-004

本被験者の叙述は，「有害事象による死亡例」の項に記載している。

### 25) 被験者番号 1104-368-007

本被験者の叙述は，「有害事象による死亡例」の項に記載している。

### 26) 被験者番号 1104-368-009

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|---|---|
| 被験者番号 | 1104-368-009 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：悪寒（Grade 2）<br>関連性がある重篤な有害事象：眼帯状疱疹（Grade 3） |

被験者 1104-368-009 は，7[redacted] 歳の男性で，2010 年 4 月 23 日に免疫組織化学的検査でのサイクリン D1 発現により定型マントル細胞リンパ腫（MCL）と確定診断された。本被験者の既往歴は，腸ポリープ，関節リウマチ，疲労，全身脱力，下気道感染，及び血小板反応であった。MCL に対する前治療歴は，2011 年 3 月までの 6 カ月間の FC であった。癌に関連した放射線療法による治療歴及び手術歴はなかった。帯状疱疹の既往歴はなかった。

ベースライン時に投与中であった併用薬は，クロルフェニラミン及びアセトアミノフェン（血小板反応），レボフロキサシン（下気道感染），並びに血小板（血小板減少症）であった。ベー

スライン時の臨床検査結果は，ヘモグロビン 101 g/L（10.1 g/dL），白血球数 $5.1 \times 10^9$/L（15.3 K/μL），好中球絶対数 $1.9 \times 10^9$/L（K/μL），及び血小板数 $8 \times 10^9$/L（K/μL）であった。ベースライン時の心電図検査に顕著な異常は認められず，QTc は 392 msec であった。ベースライン時，縦隔，傍大動脈，腋窩，腸間膜，及び鼠径部領域，並びに骨髄への MCL 浸潤（浸潤の程度は不明）が認められた。2011 年 12 月 6 日（Day 1），本被験者はイブルチニブ 560 mg の 1 日 1 回，経口投与を開始した。

### 2.7.6.2.2　最終解析時（カットオフ日：2014 年 3 月 ■ 日）

#### 2.7.6.2.2.1　概要

**(1) 計画**

計画内容は，【2.7.6.2.1.1 (1)項】を参照のこと。なお，治験実施期間は以下のとおりである。

2011 年 2 月 ■ 日～2014 年 3 月 ■ 日（最終解析のデータベースロック日）

本試験終了時に，疾患進行がなくイブルチニブの投与を継続しているすべての被験者は，イブルチニブの長期継続試験である PCI-32765CAN3001 試験（CAN3001 試験）へ参加し，長期投与後の奏効及び安全性の追跡調査を受けた。

**(2) 結果**

**1) 対象集団**

最終解析時で，イブルチニブを投与された 111 例中 82 例（73.9%）が投与を中止した。投与中止の理由は，疾患進行（55.9%），有害事象（10.8%），同意の撤回（4.5%），治験担当医師の判断（2.7%）であった。

長期継続試験（CAN3001 試験）でイブルチニブの投与を継続している被験者は 29 例（26.1%）であり，有効性及び安全性について追跡調査中である。本試験の最終解析時までに投与を中止した 82 例の主な試験中止理由は，死亡（48.6%），治験依頼者による試験中止の決定（14.4%），同意の撤回（8.1%），追跡不能（2.7%）であった。

最終解析時での平均投与期間は 12.7 カ月であり，主要解析時より長かった（9.6 カ月）。主要解析時では半数以上（58.6%）がイブルチニブの投与を中止していたため，投与期間の中央値はいずれの解析時点でも 8.3 カ月であった。追跡調査期間が延長されたため，試験参加期間の中央値は主要解析時の 15.3 カ月から最終解析時では 26.7 カ月となった。

最終解析時で，イブルチニブの 1 日平均投与量の中央値は 547.5 mg/日，相対用量強度の中央値は 97.8%であった。また，イブルチニブの減量を受けた被験者は 19 例（17.1%）であった。

**2) 有効性**

主要評価項目である治験担当医師の評価に基づく ORR の最終解析時の結果は主要解析時の結果と同様であり，主要解析時の 67.6%に対して最終解析時では 66.7%と，その変化は軽微であった。この差は，1 例において最良総合効果判定が PR から stable disease に修正されたためである。また，イブルチニブの投与期間が長くなるにつれて，2 例の最良総合効果が PR から CR となった。

奏効は IRC でも評価した。最終解析時の ORR は 68.5%であり，主要解析時の ORR と同様であった。治験担当医師の評価に基づく奏効例と IRC の評価に基づく奏効例が一致していた割合は 94.6%となり，主要解析時（94.7%）と同様であった。

副次評価項目である DOR，奏効到達期間，及び PFS の推定中央値は，主要解析の結果と同様であった。最終解析時での試験期間の中央値は 26.7 カ月，OS の推定中央値は 22.5 カ月（95% CI：13.7 カ月～推定不能）であった。治験担当医師の評価に基づく奏効例 74 例での DOR の推定中央値は 17.5 カ月（範囲：0.03～27 カ月）であった。奏効例 74 例では，初回奏効到達期間の中

央値は 1.9 カ月（範囲：1.4～13.7 カ月），CR 到達期間の中央値は 5.5 カ月（範囲：1.7～24.7 カ月）であった。治験担当医師の評価に基づく PFS の推定中央値は 13.0 カ月であった（95% CI：7.0～17.5 カ月）。

### 3) 安全性

治験薬投与後に発現した有害事象及びその他の安全性データの要約は，イブルチニブの投与を 1 回以上受けた 111 例を対象とした。治験薬投与後に発現した有害事象の発現割合について，最終解析時の平均投与期間は 12.7 カ月であり主要解析時の 9.6 カ月と比較して長いことに留意が必要である。

全体として，有害事象，治験薬投与後に発現した有害事象，Grade 3 以上の有害事象，及び重篤な有害事象の発現割合について，主要解析及び最終解析との間に特記すべき変化はなかった。

- 治験薬投与後に発現した有害事象は，すべての被験者に発現した。主要解析時と比較して，高頻度に発現した有害事象（30%を超える被験者に発現した下痢，疲労，悪心など）の全体的なプロファイルに変化はなかった。疲労（8.1%増加），関節痛（7.2%増加），及び呼吸困難（5.4%増加）以外で，主要解析時から最終解析時までに 5%以上発現割合が増加した有害事象はなかった。

- Grade 3 以上の有害事象の発現割合は 81.1%であった。高頻度（5%以上）に発現した Grade 3 以上の有害事象は，好中球減少症（17.1%），血小板減少症（12.6%），貧血（10.8%），マントル細胞リンパ腫（9.9%），肺炎（8.1%），心房細動（6.3%），腹痛（5.4%），及び下痢（5.4%）であった。マントル細胞リンパ腫（2.7%増加）を除き，主要解析時から最終解析時までに 2%以上発現割合が増加した有害事象はなかった。

- イブルチニブの最終投与後 30 日以内に死亡に至った有害事象は 18 例に発現した。このうち 1 例が血液量減少性ショックにより，1 例が疾患進行（マントル細胞リンパ腫）により，主要解析後に死亡した。

- 重篤な有害事象の発現割合は 63.1%であった。高頻度（5%以上）に発現した重篤な有害事象は，マントル細胞リンパ腫（9.9%），肺炎（7.2%），及び心房細動（6.3%）であった。マントル細胞リンパ腫（2.7%増加）を除き，主要解析時から最終解析時までに 2%以上発現割合が増加した有害事象はなかった。主要解析後に重篤な有害事象が 17 例に発現したが，これらの有害事象のほとんどが感染（主に肺炎）及び疾患進行であった。

- 投与中止に至った有害事象は 15 例（13.5%）に発現した。このうち 5 件［うっ血性心不全，マントル細胞リンパ腫，器質化肺炎，嚥下障害，及び無力症（各 1 例）］は主要解析後に発現した。

- 減量に至った有害事象は 18 例（16.2%）に発現した。このうち 4 件［記憶障害及び末梢性感覚ニューロパチー（1 例），下痢，及び肺炎（各 1 例）］は主要解析後に発現した。

- 出血性イベントの発現割合は 50.5%であった。Grade 3 又は Grade 4 の出血性イベントは 7 例（6.3%）に発現した。Grade 5 の出血性イベントの発現はなかった。高頻度（5%以上）に発現した出血性イベントは，挫傷（18.0%），鼻出血（10.8%），点状出血（9.9%），血

尿（6.3%），斑状出血（5.4%），及び内出血発生の増加傾向（5.4%）であった。また，大出血性イベントは 10 例（9.0%）に発現した。このうち，3 例の大出血性イベントは主要解析後に発現した。

- 器官別大分類（system organ class，SOC）で「感染症および寄生虫症」に分類される有害事象の発現割合は 78.4%であった。Grade 3 又は Grade 4 の「感染症および寄生虫症」に分類される有害事象の発現割合は 25.2%であった。高頻度（10%以上）に発現した感染症は，上気道感染（27.9%），尿路感染（16.2%），副鼻腔炎（15.3%），及び肺炎（13.5%）であった。「感染症および寄生虫症」に分類される重篤な有害事象の発現割合は 20.7%であった。
- 血球減少の有害事象である好中球減少症，貧血，及び血小板減少症の発現割合はそれぞれ 18.9%，18.0%，及び 21.6%であった。Grade 3 又は Grade 4 の好中球減少症，貧血，及び血小板減少症の発現割合は，それぞれ 17.1%，10.8%，及び 12.6%であった。重篤な血球減少の有害事象として，貧血が 2 例（1.8%），好中球減少症，及び血小板減少症が各 1 例（0.9%）に発現した。死亡又は投与中止に至った好中球減少症，貧血又は血小板減少症の発現はなかった。減量に至った好中球減少症の発現割合は約 5%であった。減量に至った貧血又は血小板減少症の発現はなかった。
- その他の悪性腫瘍の発現割合は，全体で 4.5%であった。主要解析から最終解析までの間に，その他の悪性腫瘍の発現はなかった。皮膚癌以外の癌では，膀胱癌及び遠隔転移を伴う新生物が 1 例に発現した。皮膚癌では基底細胞癌が 1 例，皮膚有棘細胞癌が 1 例，扁平上皮癌が 2 例に発現した。皮膚癌を発現した 4 例中 2 例は皮膚癌の既往歴を有していた。
- SOC で「心臓障害」に分類される有害事象の発現割合は 24.3%であった。最悪時での重症度が Grade 3 又は Grade 4 と判断された「心臓障害」の有害事象の発現割合は 10.8%であった。高頻度（2 例以上）に発現した有害事象は，心房細動（10.8%），洞性頻脈（4.5%），心不全（1.8%），動悸（1.8%），及び洞性徐脈（1.8%）であった。
- 最終解析時までで発現した発疹イベントは，発疹（18.0%），斑状丘疹状皮疹（8.1%），斑状皮疹（3.6%），紅斑性皮疹（2.7%），そう痒性皮疹（0.9%），及び膿疱性皮疹（0.9%）であり，ほとんどが Grade 1 又は Grade 2 であった。重篤な発疹イベント又は投与中止に至った発疹イベントはなかった。
- SOC で「眼障害」に分類される有害事象の発現割合は 33.3%であった。3 例以上（2.7%以上）に発現した「眼障害」の有害事象は，結膜炎（8.1%），流涙増加（7.2%），白内障（5.4%），眼乾燥（4.5%），眼充血（2.7%），及び霧視（2.7%）であった。「眼障害」に分類される有害事象のうち，Grade 3 以上の有害事象又は重篤な有害事象はなかった。
- SOC で「腎および尿路障害」に分類される有害事象の発現割合は 23.4%であった。Grade 3 以上の腎イベントは，「急性腎不全」（3 例）及び「腎不全」（2 例）が報告された。このうち死亡に至った事象は 1 件のみであり疾患進行に起因するものであったが，それ以外の 4 件は Grade 3 の事象であった。Grade 3 の腎イベント 5 件中 4 件は主要解析のデータカットオフ（[redacted]年[redacted]月[redacted]日）前に発現した。これらの腎イベント 4 件は，すべて既存の高血

圧及び／又は腎機能障害や，脱水，腎嚢胞，及び疾患進行などの合併症状と混同された。これ以外の 1 件は主要解析後に発現した。

- 白血球症又はアナフィラキシー反応の発現はなかった。
- Grade 3 又は Grade 4 のヘモグロビン，絶対好中球数（ANC），及び血小板の検査値異常の発現割合について，最終解析と主要解析との間に特記すべき差はなかった。最終解析時で，治験薬投与後に認められた Grade 3 又は Grade 4 のヘモグロビン，ANC，及び血小板の減少の発現割合は，それぞれ 3.6%，24.3%，及び 13.5%であった。
- 血液生化学検査において，Grade 3 又は Grade 4 の検査値異常の発現割合について，最終解析と主要解析との間に特記すべき差はなかった。アラニンアミノトランスフェラーゼ，アスパラギン酸アミノトランスフェラーゼ，及び血清クレアチニンにおけるベースライン後の最悪時の重症度が Grade 3 又は Grade 4 となった被験者はいなかった。
- 治験薬投与後に血清カリウム，血清ナトリウム，及び補正カルシウム値の低下が認められた被験者の割合は，それぞれ 11.7%，16.2%，及び 43.2%であった。これらのほとんどが Grade 1 又は Grade 2 であった。カルシウム値は，治験依頼者が決定した補正カルシウム値の正常範囲［University of California at San Francisco（UCSF）スケール］に基づき，アルブミン値が 40 g/L を超える場合に補正式［カルシウム値（mmol/L）＋0.02 × {40 - アルブミン値（g/L）}］により補正された。
- 治験薬投与後に尿酸値の重症度の Grade が悪化した被験者の割合は 28.8%であった。治験薬投与後の尿酸値の最悪値のうち，12.6%の被験者で Common Terminology Criteria for Adverse Events（CTCAE）に基づき尿酸値異常として定義したカットオフ値の 590 μmol/L を超える値を示した。有害事象としての高尿酸血症の発現割合は 17.1%であった。

### (3) 結論

本試験の最終解析から得られた有効性及び安全性の結果は，主要解析の結果と一致しており，更に追跡調査を受けた再発又は難治性 MCL 被験者においても，イブルチニブのベネフィット･リスクプロファイルが許容可能なものであることを裏付けるものであった。

#### 2.7.6.2.2.3　死亡及び重篤な有害事象の個別症例の詳細

PCYC-1104-CA 試験の主要解析のデータカットオフ後に死亡及び重篤な有害事象（SAE）を発現した被験者のうち，イブルチニブを投与された被験者における死亡に至った有害事象及びイブルチニブと関連性がある SAE を発現した被験者の詳細を示す。疾患進行による死亡については以下の叙述から除いた。また，イブルチニブと関連性がある死亡については，臨床経過を詳述した。

##### (1) 有害事象による死亡例

##### 1) イブルチニブと関連性がある死亡例

該当なし。

##### 2) イブルチニブと関連性がない死亡例

###### a) 被験者番号 1104-210-002

| | |
|---|---|
| 被験者番号 | 1104-210-002 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：マントル細胞リンパ腫（Grade 3）<br>最終投与後 30 日以内の死亡：血液量減少性ショック（Grade 5） |

被験者 1104-210-002 は，5[redacted]歳の白人女性で，本試験登録 3 年前にマントル細胞リンパ腫（MCL）と診断された。前治療歴は 4 レジメンで，シクロホスファミド及び全身照射法（2009 年），リツキシマブとシクロホスファミド/ビンクリスチン/ドキソルビシン/デキサメタゾンの多分割投与の併用療法とメトトレキサートとシタラビンの併用療法との交替療法（R-Hyper CVAD，2 レジメン），及びシタラビンの単独療法の投与歴があった。スクリーニング時の Eastern Cooperative Oncology Group（ECOG）スコアは 1 であった。関連する既往歴は，季節性アレルギー，過敏性腸症候群，顔右側及び右腕に前癌性の基底細胞病変，中耳炎，下唇のしびれ感，不安，右上腕の深部静脈血栓症，眼乾燥，夜間下肢痙攣，眼窩周囲腫脹，及び頻脈であった。

2011 年 6 月 21 日（Day 1）にイブルチニブの投与を開始し，Day 672 まで継続した。MCL の発現（Day 681）前 30 日以内に使用していた併用薬は，マクロゴール，マルチビタミン剤，生理食塩水点鼻スプレー，オメプラゾール，マグネシウム，ロラタジン，及びカルシウムであった。

###### b) 被験者番号 1104-350-002

| | |
|---|---|
| 被験者番号 | 1104-350-002 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 大出血事象：胃出血（Grade 2）<br>重篤な有害事象，最終投与後 30 日以内の死亡：MCL（Grade 5） |

被験者 1104-350-002 は，5[redacted]歳の白人男性であり，本試験登録 4 年前にマントル細胞リンパ腫（MCL）と診断された。前治療歴は 7 レジメンで，右頚部リンパ節切除（2008 年），鼡径部への放射線療法（2010 年），リツキシマブ/シクロホスファミド/ドキソルビシン/prednisone/ビンクリスチンの併用療法（R-CHOP），リツキシマブ/イホスファミド/カルボプラチン/エトポシドの併用療法（RICE），ボルテゾミブの単独療法，ベンダムスチンとリツキシマブの併用療法

（BR），リツキシマブ/フルダラビン/シクロホスファミド/ミトキサントロンの併用療法の投与歴があった。スクリーニング時の ECOG スコアは 0 であった。関連する既往歴は，2 型糖尿病，憩室炎，ニューロパチー，高血圧，及び下肢浮腫であった。

2012 年 1 月 24 日（Day 1）にイブルチニブの投与を開始し，Day 506 まで継続した。有害事象発現（Day 511）前 30 日以内に使用していた併用薬は，バルサルタン，ジルチアゼム，リシノプリル，デュロキセチン，メトホルミン，サルブタモール，レボフロキサシン，ジアゼパム，cheratussin，メトロニダゾール，ナイスタチン，ketorolac，ピペラシリン/タゾバクタム（pip/tazo），バンコマイシン，モルヒネ，hydromorphone，カリウム，イプラトロピウム，paracetamol，フィルグラスチム，oxycocet，エノキサパリン，アロプリノール，赤血球濃厚液，及びセフェピムであった。

### (2) イブルチニブと関連性がある重篤な有害事象（上記及び疾患進行を除く）

#### 1) 被験者番号 1104-032-020

| | |
|---|---|
| 被験者番号 | 1104-032-020 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：肺炎（Grade 3） |

被験者 1104-032-020 は，6[redacted] 歳の白人女性で，本試験登録 4 年前にマントル細胞リンパ腫（MCL）と診断された。前治療歴は 2 レジメンで，R-Hyper CVAD 及びリツキシマブ/イホスファミド/シクロホスファミド/エトポシドの併用療法の投与歴があった。スクリーニング時の ECOG スコアは 0 であった。関連する既往歴は，肺炎（2 回），E.coli 菌血症，持続した高脂血症，疲労，筋肉痛，霧視，記憶の変化，貧血，及び痛風であった。

イブルチニブの投与は 2011 年 6 月 9 日（Day 1）に開始し，本被験者が継続試験に移行した Day 844 まで継続した。肺炎の発現（Day 590）前 30 日以内に使用していた併用薬は，オメガ‐3 脂肪酸エチルエステル，アトルバスタチン，カルシウム/ビタミン D 配合剤，アロプリノール，docusate，及びトラマドールであった。

#### 2) 被験者番号 1104-032-024

| | |
|---|---|
| 被験者番号 | 1104-032-024 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：転倒（Grade 3）<br>大出血事象，関連性がある重篤な有害事象：外傷性血腫（Grade 3） |

被験者 1104-032-024 は，7[redacted] 歳の白人女性で，本試験登録 2 年前にマントル細胞リンパ腫（MCL）と診断された。前治療歴は 1 レジメンで，リツキシマブ/ボルテゾミブ/シクロホスファミドの併用療法の投与歴があった。スクリーニング時の ECOG スコアは 0 であった。関連する既往歴は，肺癌，持続した胃食道逆流性疾患，甲状腺機能低下症，橋本病，骨粗鬆症，脊柱管狭窄症，不安，悪心，及び嘔吐であった。

2011 年 6 月 23 日（Day 1）にイブルチニブの投与を開始し，本被験者が継続試験に移行した Day 840 まで継続した。転倒及び外傷性血腫の発現（Day 755）前 30 日以内に使用していた併用薬は，カルボキシメチルセルロース，レボチロキシン，エストラジオール，カルシウム/ビタミン D 配合剤，マルチビタミン剤，アルプラゾラム，オンダンセトロン，セチリジン/モンテルカ

スト配合剤，エソメプラゾール，メサラジン，カルシウム，メトカルバモール，口腔用製剤，口用製剤，モメタゾン，スクラルファート，シアノコバラミン，colecalciferol，paracetamol，及び蜂蜜であった。

### 3) 被験者番号 1104-032-030

| | |
|---|---|
| 被験者番号 | 1104-032-030 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象，重篤な心イベント：心房細動（Grade 3）<br>関連性がある重篤な有害事象：虚血性心筋症（Grade 3）<br>投与中止に至った有害事象，重篤な有害事象：うっ血性心不全（Grade 3） |

被験者 1104-032-030 は，7[redacted] 歳の白人男性で，本試験登録 3 年前にマントル細胞リンパ腫（MCL）と診断された。前投与歴は 2 レジメンで，R-CHOP 及びボルテゾミブの単独療法の投与歴があった。スクリーニング時の ECOG スコアは 0 であった。関連する既往歴は，冠動脈疾患，末梢性ニューロパチー，記憶の変化，霧視，耳鳴，間欠性下痢，高脂血症，うつ病，間欠性疲労，筋肉痛，うっ血性心不全，クリプトコッカス肺感染，喫煙歴，四枝血管バイパス，胃食道逆流性疾患，痛風，高血圧，QT 間隔延長，心房細動，高度貧血，黒色腫，及び直腸癌であった。

2011 年 8 月 4 日（Day 1）にイブルチニブの投与を開始し，Day 520 まで継続した。心房細動の発現（Day 522）前 30 日以内に使用していた併用薬は，タムスロシン，アレンドロン酸ナトリウム，ロスバスタチン，メロキシカム，エソメプラゾール，ビタミン D，ガバペンチン，vicodin，デュロキセチン，ナイスタチン，medinite，モキシフロキサシン，口腔用製剤，口用製剤，tobradex，プレガバリン，フルコナゾール，メトロニダゾール，及びセファレキシンであった。

### 4) 被験者番号 1104-038-004

| | |
|---|---|
| 被験者番号 | 1104-038-004 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 投与中止に至った有害事象，関連性がある重篤な有害事象：器質化肺炎（Grade 3） |

被験者 1104-038-004 は，6[redacted] 歳の白人男性で，本試験登録 9 年前にマントル細胞リンパ腫（MCL）と診断された。前治療歴は 7 レジメンで，R-Hyper CVAD，リツキシマブとボルテゾミブの併用療法，リツキシマブとフルダラビンの併用療法，リツキシマブの単独療法（2 コース），レナリドミドの単独療法，扁桃腺への放射線療法（2010 年），及び扁桃腺摘出術（2010 年）であった。スクリーニング時の ECOG スコアは 1 であった。関連する既往歴は，持続したアレルギー，右足跛行，便秘，関節痛，良性前立腺肥大症，不眠症，腎機能不全，躁病エピソード，咳嗽，ラクトース不耐性，血小板減少症，短期記憶喪失，末梢性ニューロパチー（癌治療と関連），両腕及び両下肢痙攣，口腔内痛（時折），喫煙歴，再発肺感染，並びに貧血であった。

2012 年 3 月 21 日（Day 1）にイブルチニブの投与を開始し，Day 420 まで継続した。器質化肺炎の発現（Day 435）前 30 日以内に使用していた併用薬は，アレルゲンエキス（アレルゲン名不明），マルチビタミン剤，docusate，下剤，コンドロイチン/グルコサミン配合剤，フルコナゾール，バラシクロビル，ジアゼパム，アミトリプチリン，ergocalciferol，フィナステリド，tussin DM，tilactase，クロルヘキシジン，リスペリドン，テルビナフィン，ヒドロキシジン，及びトリアムシノロンであった。

### 5) 被験者番号 1104-365-001

| | |
|---|---|
| 被験者番号 | 1104-365-001 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 関連性がある重篤な有害事象：肺炎（Grade 3）<br>重篤な有害事象：肺炎（Grade 3） |

被験者 1104-365-001 は，6[redacted] 歳の白人男性で，本試験登録 3 年前にマントル細胞リンパ腫（MCL）と診断された。前治療歴は 3 レジメンで，フルダラビンとシクロホスファミドの併用療法（FC），ビンクリスチン/prednisone/ドキソルビシン/ボルテゾミブ/シクロホスファミドの併用療法，及びシタラビンの単独療法の投与歴があった。スクリーニング時の ECOG スコアは 1 であった。関連する既往歴は，2 型糖尿病，永久的膀胱留置カテーテルを伴う尿閉，疲労，労作時息切れ，咳嗽，及びヘルペス後神経痛であった。

2011 年 11 月 10 日（Day 1）にイブルチニブの投与を開始し，Day 658 まで継続した。肺炎の発現（Day 583）前 30 日以内に使用していた併用薬は，simple linctus，インスリン，クロラムフェニコール，アシクロビル，シプロフロキサシン，ガバペンチン，及びシクリジンであった。

### 6) 被験者番号 1104-368-005

| | |
|---|---|
| 被験者番号 | 1104-368-005 |
| 治験薬 | イブルチニブ 560 mg/日，経口投与 |
| 重篤な有害事象等 | 重篤な有害事象：咬傷感染（猫による）（Grade 3）<br>関連性がある重篤な有害事象：ウイルス感染（Grade 3） |

被験者 1104-368-005 は，7[redacted] 歳の白人男性で，本試験登録 8 年前にマントル細胞リンパ腫（MCL）と診断された。前治療歴は 5 レジメンで，フルダラビンの単独療法，chlorambucil/プレドニゾロンの併用療法，FC，R-CHOP，及びレナリドミドの単独療法の投与歴があった。スクリーニング時の ECOG スコアは 1 であった。関連する既往歴は，骨髄異形成症候群，脾臓痛，貧血，湿性咳嗽，及び末梢性ニューロパチーであった。

2011 年 10 月 24 日（Day 1）にイブルチニブの投与を開始し，本被験者が継続試験に移行した Day 707 まで継続した。ウイルス感染の発現（Day 489）前 30 日以内に使用していた併用薬は，ガバペンチン，フロセミド，ドキシサイクリン，及びレボフロキサシンであった。

## 2.7.6.3 海外臨床第 III 相試験（PCI-32765MCL3001，評価資料：5.3.5.1.1）

### 2.7.6.3.1 概要

#### 2.7.6.3.1.1 計画

**(1) 治験の標題**

1 レジメン以上の前治療を受けた再発又は難治性の MCL 患者を対象とした，BTK 阻害剤イブルチニブとテムシロリムスを比較するランダム化，実薬対照，非盲検，多施設共同，第 III 相試験

**(2) 治験責任医師**

[redacted] 他

**(3) 公表文献（引用文献）**

該当なし

**(4) 治験実施期間**

2012 年 12 月 [redacted] 日～2015 年 4 月 22 日（データカットオフ日）

**(5) 開発の相**

第 III 相

**(6) 目的**

主要目的は，1 レジメン以上のリツキシマブ併用の化学療法を前治療として受けた，再発又は難治性マントル細胞リンパ腫患者（mantle cell lymphoma，MCL）を対象に，イブルチニブがテムシロリムス投与と比較して，無増悪生存期間（progression-free survival，PFS）を延長させるかどうか検討することである。

副次目的は，イブルチニブの奏効率，全生存期間（overall survival，OS），1 年生存率，奏効持続期間（duration of response，DOR），及び安全性をテムシロリムスと比較し，イブルチニブの薬物動態プロファイルの特性を評価することである。

**(7) 治験方法**

本試験は，1 レジメン以上のリツキシマブ併用の化学療法を前治療として受けた再発又は難治性 MCL 患者約 280 例を組み入れ，イブルチニブの有効性及び安全性をテムシロリムスと比較するランダム化，実薬対照，非盲検，多施設共同，第 III 相試験である。被験者を前レジメン数（1 又は 2 レジメン対 3 レジメン以上）及び MCL 国際予後指標（MCL international prognostic index，MIPI）簡略版［low-risk（0-3）対 intermediate-risk（4-5）対 high-risk（6-11）］のスコアにより層

別化し，1:1 の比でランダムに割り付けた。治験薬の割付けに対し盲検化された独立評価委員会（Independent Review Committee，IRC）が，盲検下で有効性を評価した。治験実施計画書の改訂後（第[redacted]版，[redacted]年[redacted]月），IRC により疾患進行と判断されたテムシロリムス群の被験者は，イブルチニブの投与を可能とし，疾患進行，耐容不能な毒性の発現，又は試験終了まで，21 日間を 1 サイクルとして 1 日 1 回，経口でイブルチニブを 560 mg 投与した。

**(8) 被験者数（計画時及び解析時）**

本試験は，約 280 例を組み入れるデザインとした。解析対象は 280 例であった。

**(9) 診断及び主な組入れ基準**

本試験の主な選択基準は，18 歳以上で，MCL と確定診断されていることとした。また，前治療として 1 レジメン以上のリツキシマブ併用の化学療法を受けており，再発又は疾患進行が認められていること，Eastern Cooperative Oncology Group（ECOG）performance status が 0 又は 1 であること，及び Revised Response Criteria for Malignant Lymphoma（Cheson 2007）に基づき測定可能病変を 1 カ所以上有することとした。

**(10) 被験薬，用量及び投与方法，ロット番号**

イブルチニブは微粉化した有効成分 140 mg を含有するカプセル製剤であり，560 mg を 1 日 1 回，21 日サイクルで経口投与した。被験薬のロット番号は，4366763，4367054，4367730，4368042，4369278，4369960，4366762，及び 4370176 であった。

**(11) 対照薬，用量及び投与方法，ロット番号**

最初のサイクルでは Day 1，Day 8，及び Day 15 にテムシロリムス 175 mg を，以降の 21 日サイクルでは，それぞれ Day 1，Day 8，及び Day 15 に 75 mg を静脈内投与した。対照薬のロット番号は，4366724，4367147，4367425，4367920，4367721，4369341，4369744，及び 4370154 であった。

**(12) 投与期間**

被験者は，疾患進行又は耐容不能な毒性の発現のいずれか早い時点まで，イブルチニブ又はテムシロリムスを投与された。

**(13) 評価項目**

有効性：

腫瘍評価［コンピュータ断層撮影（CT）／磁気共鳴画像（MRI）及び臨床評価］は，治験薬投与開始後 15 カ月間は 9 週ごとに，その後は疾患進行，死亡，又はデータカットオフのいずれか早い時点まで 24 週ごとに実施した。

主要評価項目は IRC が評価する PFS とし，ランダム割付け日から，完全奏効（complete response，CR）到達後の再発若しくは疾患進行，又は死亡のいずれか早い時点までの期間と定義した。副次評価項目は，全奏効率（overall response rate，ORR），OS，1 年生存率，DOR，奏効到達期間，後治療までの期間，Functional Assessment of Cancer Therapy-Lymphoma（FACT-Lym）の Lym サブスケールにおける患者報告アウトカム（patient-reported outcome，PRO）が増悪するまでの期間，並びにベースライン後の各評価時点における EuroQol（EQ-5D-5L）スコアのベースラインからの平均変化量とした。

IRC 及び実施医療機関は，Revised Response Criteria for Malignant Lymphoma（Cheson 2007）に基づき腫瘍評価を実施した。主要解析のデータカットオフ日までは，IRC が有効性を評価した。データカットオフ日以降は，治験担当医師のみが有効性を評価することとした。

疾患進行前に治験薬の投与を中止した被験者については，引き続き，疾患進行，死亡，又はデータカットオフのいずれか早い時点まで定期的に腫瘍評価を実施した。データカットオフ後，すべての被験者から生存データ，EQ-5D-5L，治験担当医師による奏効評価，及び MCL に対する後治療による最良効果又は疾患進行の結果を収集することとした。また，データカットオフ後も治験薬の投与を継続する被験者については，治験薬の投与状況，投与中又は最終投与後 30 日以内に発現した有害事象，重篤な有害事象に関連した併用薬，有害事象の発現及び回復を示す臨床検査の結果を収集することとした。

薬物動態：

イブルチニブ及び代謝物 PCI-45227 の血漿中濃度を測定するため，血液サンプルを採取した。スパース採血を実施し，母集団薬物動態モデルの開発に使用した。モデルにより予測された血漿中濃度又は曝露量パラメータ［最低血漿中濃度（$C_{min}$）又は血漿中濃度－時間曲線下面積（AUC）など］は，イブルチニブの曝露量と臨床データ又はバイオマーカーデータとの相関の探索的解析に今後用いる可能性がある。

バイオマーカー：

B 細胞受容体のシグナル伝達を変更する又は他のシグナル伝達経路を活性化するマーカーを特定し，イブルチニブの奏効性又はイブルチニブに対する抵抗性とマーカーとの関連性を探索するため，バイオマーカーの評価を計画した。イブルチニブの曝露量の測定指標と臨床データ又はバイオマーカーデータとの潜在的関連性を探索することとした。

安全性：

発現した有害事象，臨床検査，身体所見，ECOG performance status，及び併用薬の使用状況により，安全性を評価することとした。同意取得日から治験薬の最終投与後 30 日又は MCL に対する後治療の開始までの期間に発現した有害事象を収集した。有害事象の重症度は，National Cancer Institute Common Terminology Criteria for Adverse Events（NCI CTCAE）第 4.03 版に基づき判定した。大出血事象及びその他の悪性腫瘍は特に注目すべき有害事象とし，報告及びデータの収集範囲を拡大した。

### (14) 統計手法

症例数の決定：

本試験の主要解析で 178 件の PFS を評価するため，約 280 例（各群 140 例）を組み入れることとした。イブルチニブ群における PFS の中央値が，テムシロリムス群と比較して 57%延長すると仮定した場合［PFS が指数分布に従うと仮定すると，テムシロリムス群に対するイブルチニブ群のハザード比（hazard ratio，HR）は 0.64 に相当する］，本試験では有意水準 2.5%（片側），検出力 85%以上で統計学的に有意となる。本試験の終了は，ランダム割付けした被験者の 80%が死亡した時点，最後の被験者のランダム割付けから 3 年後の時点，又は治験依頼者による本試験の終了時点のいずれか早い時点と定義した。

有効性：

有効性の主要解析は，IRC が評価した PFS に基づき intent-to-treat（ITT）解析対象集団（ランダム割付けしたすべての被験者）を対象に実施した。各投与群の PFS 分布の推定には Kaplan-Meier 法を用いた。PFS について要約し，その中央値及び 95%信頼区間（CI）を示した。PFS に基づくイブルチニブの治療効果のテムシロリムスとの比較には，MIPI 簡略版及び前レジメン数によって層別化した層別 log-rank 検定を用いた。イブルチニブのテムシロリムスに対する HR 及びその 95% CI は，層別 Cox 比例ハザードモデルに基づき，ランダム割付け時の層別因子ごとに算出した。同様に，有効性の副次評価項目の解析は，ITT 解析対象集団を対象として実施した。層別 Cochran-Mantel-Haenszel 検定を用いて，ORR を投与群間で比較した。オッズ比の Mantel-Haenszel 推定値とその 95% CI も算出した。奏効到達期間及び DOR は記述統計量を用いて要約し，1 年生存率は Kaplan-Meier 法を用いて推定した。OS 率と後治療までの期間については，PFS の解析と同じ方法を用いて解析した。

FACT Lym 評価の Lym サブスケールにおける増悪までの期間及び改善までの期間については，Kaplan-Meier 法を用いて推定した。

安全性：

安全性解析対象集団は，ランダム割付け後，治験薬（イブルチニブ又はテムシロリムス）を 1 回以上投与されたすべての被験者を対象とした。

安全性は，有害事象の発現割合及び重症度，臨床検査，バイタルサイン，並びに身体所見を用いて解析した。治験薬投与後に発現した有害事象（TEAE）は，器官別及び基本語別に，投与群別，NCI 毒性グレード別（NCI CTCAE 第 4.03 版），治験薬との因果関係別，処置別に要約した。臨床検査値は記述統計量を用いて要約し，投与期間中のベースラインから最悪値への変化をシフトテーブルに示した。

## 2.7.6.3.1.2 結果

### (1) 対象集団

データカットオフ（2015 年 4 月 22 日）時点で，イブルチニブ群に割り付けられた 139 例全例がイブルチニブを，テムシロリムス群に割り付けられた 141 例のうち 139 例がテムシロリムスを投与された。データカットオフ時点で，治験薬を継続投与されていた被験者の割合は，イブルチニブ群で 46.8%，テムシロリムス群で 10.6%であった。投与中止の理由として最も多かったものは，両投与群ともに疾患進行又は再発であった（イブルチニブ群 39.6%，テムシロリムス群

41.1%）。有害事象のため投与を中止した被験者は，イブルチニブ群の方が少なかった（イブルチニブ群 6.5%，テムシロリムス群 25.5%）。

ベースラインの人口統計学的特性は MCL 患者集団の特性を反映しており，両群間でおおむね同程度であった。被験者の多くが男性（74.3%）で，白人（87.1%）であった。年齢の中央値は 68 歳（範囲：34～88 歳），65 歳以上の被験者の割合は 61.8%であった。治験登録時の病期は，被験者の多く（82.9%）がステージ IV であり，前レジメン数の中央値は 2.0，最後に前治療を受けてから本試験のベースラインまでの期間の中央値は 7.23 カ月であった。疾患特性は，両群間でおおむね同程度であった。ベースラインのリンパ腫症状，節外性病変を有する被験者数，最大径病変別に測定した腫瘍量についても両群間で同程度であった。

治験薬の投与期間の中央値は，イブルチニブ群で 14.39 カ月（範囲：0.0～28.2 カ月），テムシロリムス群で 3.02 カ月（範囲：0.0～27.0 カ月）であり，テムシロリムス群と比較してイブルチニブ群では 4 倍を超えた。サイクル数の中央値は，イブルチニブ群で 21 サイクルであったのに対し，テムシロリムス群で 5 サイクルであった。治験薬を減量された被験者数は，イブルチニブ群で 6 例（4.3%），テムシロリムス群で 61 例（43.9%）と，イブルチニブ群の方が少なかった。減量の理由は，有害事象が最も多かった（イブルチニブ群 5 例，テムシロリムス群 60 例）。治験薬を減量された被験者のうち，イブルチニブ群では全 6 例（4.3%）が 1 回減量されたのに対し，テムシロリムス群では 27 例（19.4%）が 2 回以上減量された。

### (2) 有効性

IRC による評価の結果，疾患進行又は死亡のリスクは，テムシロリムス群と比較してイブルチニブ群で 57%低下した（HR = 0.43，95% CI：0.32～0.58，p < 0.0001）。

- PFS の中央値は，イブルチニブ群で 14.6 カ月，テムシロリムス群で 6.2 カ月であった。
- 上記の結果は，後治療で打ち切った PFS と治験担当医師の評価による PFS を含め，すべての感度分析で頑健性が示された（HR = 0.43，95% CI：0.32～0.58，p < 0.0001）。
- PFS の結果は，年齢，性別，実施国，前レジメン数，ベースラインの病期，腫瘍量などの部分集団においても，全般に一貫性がみられた。

IRC 判定による ORR は，テムシロリムス群（40.4%）と比較してイブルチニブ群（71.9%）で有意に高かった（p < 0.0001）。CR 率は，テムシロリムス群（1.4%）と比較してイブルチニブ群（18.7%）で高かった。治験担当医師判定による ORR は，IRC による評価と一致していた。イブルチニブ群で奏効が認められた被験者の 39%のみが疾患進行と評価されたため，DOR の中央値は推定不能であった（95% CI：16.2 カ月～推定不能）。一方，テムシロリムス群では，奏効が認められた被験者の 73.7%に再発が認められ，DOR の中央値は 7.0 カ月であった。奏効到達期間の中央値は，イブルチニブ群で 2.15 カ月，テムシロリムス群で 2.14 カ月と，両群で同程度であった。

追跡調査期間の中央値は 20.01 カ月であり，OS の推定 HR は 0.76（95% CI：0.53～1.09，p = 0.1324）であった。この推定 HR はイブルチニブを投与された被験者における死亡リスクが 24%低下したことを示している。OS の中央値は，イブルチニブ群では未達，テムシロリムス群

では 21.3 カ月であった（ただし，テムシロリムスを投与された 23 例が疾患進行のためイブルチニブにクロスオーバーし，その後さらに 9 例が後治療としてイブルチニブを投与された）。

次の MCL 療法までの期間の中央値は，イブルチニブ群で推定不能（95% CI：上限，下限ともに推定不能），テムシロリムス群で 11.6 カ月であった（HR = 0.37，95% CI：0.25～0.53）。18 カ月時点で，イブルチニブ群の被験者の 66%が後治療を不要とした。

イブルチニブの投与は，MCL に対する後治療の臨床転帰に負の影響を及ぼさなかった。後続療法後の疾患進行又は死亡までの期間の中央値は，テムシロリムス群（11.3 カ月）と比較してイブルチニブ群（19.1 カ月）で長かった。

FACT-Lym 総スコア，FACT-Lym リンパ腫サブスケール，Functional Assessment of Cancer Therapy-General（FACT-G），及び EQ-5D-5L を用いて評価した PRO の結果から，イブルチニブ群では，テムシロリムス群と比較して改善の程度が大きく，リンパ腫症状の増悪が減少かつ遅延したことが示唆された。リンパ腫症状の増悪が認められた被験者は，イブルチニブ群（26.6%）でテムシロリムス群（51.8%）と比較して少なく，FACT-Lym サブスケールを用いて評価した，臨床的に意義のある増悪までの期間は，イブルチニブ群でテムシロリムス群と比較して長かった（HR = 0.27，95% CI：0.18～0.41，p < 0.0001）。臨床的に意義のある増悪までの期間の中央値は，イブルチニブ群では推定不能（95% CI：81.1 週～推定不能），テムシロリムス群では 9.7 週であった。

### (3) 安全性

治療歴のある MCL 患者にイブルチニブ 560 mg を 1 日 1 回投与したときの安全性プロファイルは，他の適応症への臨床使用で既知のイブルチニブの安全性プロファイルと一致していた。イブルチニブ群の投与期間の中央値（14.39 カ月）がテムシロリムス群（3.02 カ月）と比較して 4 倍を超えていたことは，TEAE の発現割合の群間比較において重要なポイントである。曝露量に大きな群間差はあるものの，TEAE の累積発現割合は，イブルチニブ群ではテムシロリムス群と比較して全体に低かった。イブルチニブ群で長期間治験薬が投与されたことを考慮の上，両群間における TEAE の発現割合をさらに解析するため，曝露量で調整した発現割合（exposure-adjusted incidence rate，EAIR）の解析，及び投与開始後から 6 カ月間の固定観察期間に基づく解析を実施した。

データカットオフ（2015 年 4 月 22 日）時点で，TEAE の分類別（すべての TEAE，Grade 3 以上の TEAE，治験薬と関連ありと判断された TEAE，重篤な TEAE，治験薬に関連ありと判断された重篤な TEAE，及び投与中止に至った TEAE）の多くで，イブルチニブ群における発現割合はテムシロリムス群と比較して低かった。投与開始後から 6 カ月間で報告された TEAE 及び EAIR の評価では，発現割合の群間差はさらに大きかった。

治験薬の投与中又は最終投与後 30 日以内に死亡した被験者は，イブルチニブ群で 24 例（17.3%），テムシロリムス群で 15 例（10.8%）であった。TEAE により死亡に至った被験者は，イブルチニブ群で 15 例（10.8%），テムシロリムス群で 11 例（7.9%）であった。これらの結果は，テムシロリムス群の被験者が有害事象又はその他の理由により，疾患進行が認められる前に治験薬の投与を中止したことに対し，イブルチニブ群の被験者は疾患進行が認められるまで治験薬を投与されたことが影響している可能性が高い。投与開始後から 6 カ月以内に TEAE により死

亡に至った被験者は，イブルチニブ群で 8 例（5.8%），テムシロリムス群で 11 例（7.9%）であった。

イブルチニブ群における TEAE の発現状況は過去の試験結果と同様であり，新たな安全性の懸念は認められなかった。イブルチニブ群で高頻度（20%以上）に発現した TEAE は，下痢（28.8%），咳嗽（22.3%），疲労（22.3%）であった。テムシロリムス群で高頻度（20%以上）に発現した TEAE は，血小板減少症（56.1%），貧血（43.2%），下痢（30.9%），疲労（28.8%），好中球減少症（25.9%），鼻出血（23.7%），咳嗽（22.3%），末梢性浮腫（22.3%），悪心（21.6%），発熱（20.9%），及び口内炎（20.9%）であった。

Grade 3 以上の TEAE は，イブルチニブ群で 67.7%，テムシロリムス群で 87.1%に発現した。高頻度（いずれかの投与群で 10%以上）に発現した Grade 3 以上の TEAE は，好中球減少症（イブルチニブ群 12.9%，テムシロリムス群 16.5%），血小板減少症（イブルチニブ群 9.4%，テムシロリムス群 42.4%），貧血（イブルチニブ群 7.9%，テムシロリムス群 20.1%）であった。Grade 3 以上の心房細動は，イブルチニブ群で 3.6%，テムシロリムス群で 1.4%に発現した。

Grade 3 又は 4 の血球減少症の発現割合が，イブルチニブ群でテムシロリムス群と比較して低かったことは，造血成長因子／サイトカイン（イブルチニブ群 12.2%，テムシロリムス群 24.5%），又は赤血球の輸血（イブルチニブ群 12.9%，テムシロリムス群 28.1%）を受けた被験者の割合がイブルチニブ群で低かったことと一致していた。

有害事象のため治験薬の投与中止に至った被験者の割合は，イブルチニブ群（6.5%）でテムシロリムス群（25.5%）と比較して低かった。治験薬の減量に至った被験者の割合は，イブルチニブ群（4.3%）でテムシロリムス群（43.9%）と比較して低かった。

治験薬投与後に発現した大出血事象は，イブルチニブ群で 10.1%，テムシロリムス群で 6.5%に発現した。大出血事象の多くは回復した。イブルチニブ群の 1 例が死亡に至った大出血事象（硬膜下血腫）を発現した。大出血事象の EAIR は，イブルチニブ群で 0.786 件/100 人月，テムシロリムス群で 1.077 件/100 人月であった。

心房細動及び高血圧の発現割合（それぞれ 4.3%及び 7.2%）は，イブルチニブ群でテムシロリムス群と比較して数値的に高かったがいずれも 10%未満であり，また，これらの有害事象により減量又は投与中止に至った被験者はいなかった。心房細動の EAIR は，イブルチニブ群（0.337 件/100 人月）とテムシロリムス群（0.358 件/100 人月）で同程度であった。高血圧の EAIR は，イブルチニブ群で 0.571 件/100 人月，テムシロリムス群で 0.614 件/100 人月であった。

テムシロリムスからイブルチニブにクロスオーバーした 23 例に発現した TEAE の発現状況及び重症度は，ランダム割付け後イブルチニブを投与された被験者に発現した TEAE と一致していた。

血液学的検査，血清生化学的検査，凝固パラメータ，及び免疫グロブリンなどの臨床検査結果に，新たな安全性の懸念は認められなかった。

#### 2.7.6.3.1.3　結論

イブルチニブ群では疾患進行又は死亡のリスクが 57%低下し（HR = 0.43，95% CI：0.32～0.58），PFS の中央値がテムシロリムス群と比較して 2.3 倍延長した（イブルチニブ群 14.6 カ月，テムシロリムス群 6.2 カ月，$p < 0.0001$）ことから，本治験の結果はイブルチニブの有効性を十分

に裏付けるものであった。また，PFS の改善は，ORR の統計学的に有意な改善（イブルチニブ群 71.9%，テムシロリムス群 40.4%）及び CR 率の改善（イブルチニブ群 18.7%，テムシロリムス群 1.4%）によっても裏付けられる。本試験期間中にテムシロリムスを投与された 23 例がイブルチニブを投与され，さらに 9 例が後治療もイブルチニブを投与され，これらの被験者の OS には改善傾向が認められた。事前に計画した PRO の解析においても，イブルチニブのさらなる臨床効果が認められた。

イブルチニブの安全性プロファイルは，イブルチニブの投与期間がテムシロリムスの投与期間の 4 倍を超えていた点でも明らかなように，テムシロリムスと比較して許容できるものであった。全般的なイブルチニブの安全性プロファイルは既知の安全性プロファイルと一致しており，本試験において新たな安全性の懸念は特定されなかった。本試験の結果から，再発又は難治性 MCL 患者の治療においてイブルチニブのベネフィット・リスクプロファイルが良好であることが示された。

## 2.7.6.4 海外臨床第 II 相試験（PCI-32765MCL2001，参考資料：5.3.5.2.3-1，5.3.5.2.3-2）

### 2.7.6.4.1 主要解析時（カットオフ日：[redacted] 年 [redacted] 月 [redacted] 日）

#### 2.7.6.4.1.1 概要

**(1) 計画**

**1) 治験の標題**

ボルテゾミブ治療中又は治療後に疾患進行が認められた MCL 患者を対象とした，BTK 阻害剤 ibrutinib の有効性及び安全性を検討する第 II 相，多施設共同，単群試験

**2) 治験責任医師**

[redacted] 他

**3) 公表文献（引用文献）**

該当なし

**4) 治験実施期間**

2012 年 7 月 [redacted] 日～[redacted] 年 [redacted] 月 [redacted] 日（データカットオフ日）

**5) 開発の相**

第 II 相

**6) 目的**

主要目的は，1 レジメン以上のリツキシマブ併用の化学療法を前治療として受け，ボルテゾミブ治療後に疾患進行が認められたマントル細胞リンパ腫（mantle cell lymphoma，MCL）患者を対象に，イブルチニブの全奏効率（overall response rate，ORR）を独立評価委員会（Independent Review Committee，IRC）により評価する。

また，副次目的を以下に示す。

- イブルチニブの奏効持続期間（duration of response，DOR），無増悪生存期間（progression-free survival，PFS），全生存期間（overall survival，OS），及び安全性を評価する
- 経口投与後のイブルチニブの薬物動態特性を明らかにする
- イブルチニブの曝露指標に関連する臨床又はバイオマーカー情報との潜在的関連性を探索する
- Functional Assessment of Cancer Therapy-Lymphoma（FACT-Lym）及び EuroQol（EQ-5D）を用いて患者報告アウトカム（patient reported outcomes，PRO）を評価する

・ B 細胞受容体のシグナル伝達を変化させる，又は代替シグナル伝達経路を活性化するバイオマーカーを特定し，イブルチニブに対する反応との関連を探索する

### 7) 治験方法

本試験は，病理学的に MCL と診断された患者を対象としてイブルチニブ単剤の有効性及び安全性を評価する，多施設共同，単群，第 II 相試験である。主な選択基準は，中央判定で MCL と確定診断され，前治療としてリツキシマブ併用の化学療法レジメンを 1 種類以上受けており，2 サイクル以上のボルテゾミブ単剤又は併用治療後に疾患進行が認められている患者とした。疾患進行，完全奏効（complete response，CR）到達後の再発，耐容不能な毒性の発現，又は試験終了のいずれか早い時点まで，すべての適格被験者に 21 日間を 1 サイクルとして，イブルチニブ 560 mg を 1 日 1 回，継続して経口投与することとした。投与中止後，生存状況，後治療，及びその他の悪性腫瘍の発現について，被験者の追跡調査を行うこととした。

全身化学療法，抗癌免疫療法，全身コルチコステロイド，実験的治療，及び放射線療法は禁止した。強力な CYP3A4/5 阻害剤の併用投与，若しくは治験実施計画書の変更の開始からワルファリン又は同等のビタミン K 拮抗剤による抗凝固療法を要することが判明している被験者は除外した。

IRC による放射線の中央判定により主要解析のための疾患評価を実施した。補助的な解析として，治験担当医師による疾患評価も行った。有効性の中間解析は実施しなかった。

### 8) 被験者数（計画時及び解析時）

本試験は，奏効評価可能な 101 例を確保するために 110 例を組み入れるデザインとした。最終的に 120 例が組み入れられ，110 例が奏効評価可能となった。全 120 例がイブルチニブを投与された。

### 9) 診断及び主な組入れ基準

中央判定により病理学的に確定診断された MCL 及び CT により測定可能な病変を有することとした。また，前治療としてリツキシマブ併用の化学療法を 1 レジメン以上受けており，Revised Response Criteria for Malignant Lymphoma（Cheson 2007）に基づきボルテゾミブ治療中又は治療後に疾患進行が認められていることとした。

### 10) 被験薬，用量及び投与方法，ロット番号

イブルチニブは 140 mg の有効成分を含有する硬ゼラチンカプセル経口製剤であり，560 mg を 1 日 1 回投与した。治験薬のロット番号は，L0308541，L0308792，L0400218，及び L0404313 であった。

### 11) 対照薬，用量及び投与方法，ロット番号

該当なし

### 12) 投与期間

疾患進行，CR 到達後の再発，耐容不能な毒性の発現，又は試験終了のいずれか早い時点まで，1 日 1 回，継続してイブルチニブを投与することとした。試験終了は最後の被験者が組み入れられてから 2 年後を予定した。

### 13) 評価項目

有効性：

主要評価項目は ORR とし，Revised Response Criteria for Malignant Lymphoma（Cheson 2007）に基づく IRC による評価で CR 又は部分奏効（partial response，PR）が得られた評価可能な被験者の割合と定義した。奏効は，イブルチニブの投与開始後 15 カ月間は 9 週ごとに，その後は疾患進行，死亡，又は治験終了のいずれか早い時点まで 24 週ごとに評価することとした。疾患進行が記録された後は，生存状況及び MCL に対する後治療の使用を評価するため，9 週ごとに被験者に連絡した。投与期間中若しくは疾患進行，死亡，又は治験終了により中止するまで，FACT-Lym 及び EQ-5D-5L PRO を用いて評価した。

安全性：

同意文書への署名後の有害事象のモニタリング，臨床検査［血液学的検査，血液生化学検査，凝固検査，血清免疫グロブリン（IgG，IgM，IgA）検査，及び β2 ミクログロブリン検査］，身体所見（項目を限定），バイタルサイン測定，Eastern Cooperative Oncology Group performance status，及び心臓評価［心電図及び心エコー／マルチゲート収集法（MUGA）］により，安全性を評価した。

薬物動態：

静脈血サンプルを，サイクル 1 及びサイクル 2 の Day 1 の投与前，投与後 1，2，4 時間に採取することとした。血漿サンプルを使用し，バリデーション済みの高特異度及び高感度の液体クロマトグラフィー／タンデム質量分析法（LC-MS/MS）を用いてイブルチニブ及び代謝物 PCI-45227 濃度を測定することとした。イブルチニブの血漿中濃度プロファイルが先行試験と一致した結果を示すか，グラフィカル・アプローチにより探索的に検討することとした。

バイオマーカー：

腫瘍［スクリーニング期間中（ただし，サイクル 1 の Day 1 以前）に採取したリンパ節生検組織又は診断的生検組織から採取］，血液，及び骨髄を評価し，イブルチニブに対する反応を予測するバイオマーカーを特定した。実施可能であれば，疾患進行時には，バイオマーカー評価用のリンパ節生検サンプル及び骨髄穿刺液を採取することとした。

### 14) 統計手法

イブルチニブの ORR を 56%と仮定し，片側有意水準 0.025 で ORR が 40%以上であることを検出力 90%で得るためには抗腫瘍効果の評価可能な被験者が 101 例必要である。抗腫瘍効果の評価可能な解析集団には，イブルチニブを 1 回以上投与され，ベースライン後の適切な腫瘍評価を 1 回以上受けたすべての被験者を含めた。

有効性の中間解析は，計画及び実施しなかった。主要評価項目である ORR の最終解析は，抗腫瘍効果の評価可能な解析集団を用い，最後の被験者の登録から約 1 年後のカットオフデータに基づき実施した。ORR の 95%信頼区間（CI）は二項分布の正規近似を用いて算出した。全体の有意水準 0.025（片側）で帰無仮説を検証し，CI の下限が 40%を超えていれば帰無仮説を棄却した。サブグループ解析を事前に定義した。CR 又は PR に到達した被験者について，奏効到達期間（time to response，TTR）及び最良奏効到達期間の記述統計量を示した。DOR（CR + PR），PFS，及び OS の分布を，全投与集団（イブルチニブを 1 回以上投与されたすべての被験者）に基づいて Kaplan-Meier 法により推定した。

FACT-Lym 及び EQ-5D-5L PRO の評価では，生データ，各時点でのベースラインからの変化量，及びベースラインから最終値までの変化量について，記述統計量（平均値，標準偏差，中央値，及び範囲）を算出した。Lym 下位尺度の悪化までの期間及び改善までの期間を Kaplan-Meier 法を用いて検討した。Lym 下位尺度の悪化及び改善は，Lym 下位尺度がベースラインから 5 ポイント以上低下又は上昇していることと定義した。FACT-Lym 評価の欠測は last observation carried forward 法で補完した。悪化／改善の定義を満たさなかった被験者は，PRO の最終評価時で打ち切った。

安全性解析は，投与期間に基づいて行った。なお，投与期間はイブルチニブの初回投与から最終投与後 30 日まで，又は MCL に対する全身性の後治療の開始までとした。イブルチニブの最終投与後 30 日以降に発現した有害事象がイブルチニブと関連ありと判断された場合は，解析対象とした。イブルチニブを投与されたすべての被験者を全投与集団（すなわち安全性解析対象集団）とし，安全性データ（有害事象及び臨床検査）の詳細な表を示した。有害事象の発現例数及び発現割合を要約した。また，その他の安全性パラメータの要約を示した。

薬物動態解析では，イブルチニブの血漿中濃度の実測値が先行試験と一致した結果を示すかをグラフィカル・アプローチにより探索した。グラフィカル・アプローチによる探索を行うため，先行試験で構築されたイブルチニブの薬物動態モデルに基づくシミュレーションに，イブルチニブの血漿中濃度の実測値の図を重ねた。

### (2) 結果

#### 1) 対象集団

120 例が組み入れられ，全 120 例がイブルチニブを 1 回以上投与された。データカットオフ時点で，イブルチニブの投与を中止した被験者は 81 例（67.5%）であった。このうち 53 例（44.2%）は疾患進行による中止，8 例（6.7%）は有害事象による中止であった。イブルチニブの投与を継続していた被験者は 39 例（32.5%）であった。

全投与集団の年齢の中央値は 67.5 歳（範囲：35～85 歳）であり，65 歳以上の被験者の割合は 62.5%であった。被験者の多くが男性（86.7%）で，白人被験者の割合は 94.2%であった。被験者の多く（77.5%）が治験登録時に病期がステージ IV の疾患を有しており，芽球様細胞の組織像が認められた被験者の割合は 9.2%であった。前治療のレジメン数の中央値は 2（範囲：1～8）であり，すべての被験者がリツキシマブ及びボルテゾミブによる前治療歴を有していた。その他の前治療は，hyper-CVAD（15.8%），CHOP/R-CHOP（40.0%），及び幹細胞移植（33.3%）であった。

投与期間の中央値は約 8.0 カ月（範囲：0.5～20.9 カ月）であり，42.5%が 18 サイクル以上イブルチニブを投与された。相対用量強度の中央値は 96.5%であった。8 例（6.7%）でイブルチニブが減量され，減量の理由は好中球減少症（3 例）が最も多かった。3 例（2.5%）は 2 回の減量を要した。

### 2) 有効性

全奏効率

抗腫瘍効果の評価可能な解析集団（n = 110）では，IRC の評価による ORR（CR + PR）は 62.7%（95% CI：53.7%～71.8%）であった。95% CI の下限値はあらかじめ設定した値である 40%を上回った（片側 p 値 < 0.001）。CR 率は 20.9%（95% CI：13.3%～28.5%）であった。ORR は，検討したほとんどの部分集団でおおむね一貫していた。

有効性の副次解析

- IRC による TTR の中央値は 2.1 カ月（範囲：1.3～6.3 カ月）であった。IRC による DOR の中央値は 14.9 カ月（95% CI：12.4 カ月～推定不能）であった。
- IRC による PFS の中央値は 10.5 カ月（95% CI：4.4～15.0 カ月）であった。1 年時での PFS は 47%であった。
- OS は中央値に到達しなかった。14.9 カ月（中央値）の追跡調査後において，18 カ月時点での OS は 61%であった。

### 3) 薬物動態

イブルチニブの血漿中濃度の実測値は，これまでの薬物動態モデルに基づいた予測値とよい重なりを示したことから，本試験における薬物動態学的挙動はこれまでの評価結果とより一致することが示された。

### 4) 患者報告アウトカム

FACT-Lym：リンパ腫サブスケールのすべてのベースライン後評価で Week 61 までの平均変化量が改善方向の変化であったことから，患者の機能改善が示された。5 ポイント以上の変化に基づき，39 例（35.8%）に投与期間中に臨床的に意義のある悪化が認められたのに対し，67 例（61.5%）にリンパ腫症状に臨床的に意義のある改善が認められた。

EQ-5D：ベースライン時の視覚的アナログ尺度（Visual Analog Scale，VAS）のスコアの平均値（SD）は 68.77（22.25）であり，10～100 の範囲で推移したことから，この方法では大きなばらつきと不均一な反応が捕捉されたことが示唆された。効用値も同じパターンであった。VAS スコア及び効用値のいずれも，投与期間中に FACT-Lym 評価で認められたパターンと類似した改善パターンを示した。

5) 安全性

安全性データは，特に記載がない限り投与期間に基づいている。安全性解析対象集団には，イブルチニブを 1 回以上投与されたすべての被験者 120 例を含めた。

有害事象の発現割合は 95.8%であり，治験担当医師によりイブルチニブと関連ありと判断された有害事象の発現割合は 79.2%であった。高頻度（20%以上）に発現した有害事象は，疲労（43.3%），下痢（42.5%），咳嗽（25.0%），血小板減少症（24.2%），好中球減少症（23.3%），末梢性浮腫（23.3%），悪心（21.7%），発熱（20.8%），及び筋痙縮（20.8%）であった。Grade 3 又は Grade 4 の有害事象の発現割合は 60.8%であり，高頻度（5%以上）に発現した Grade 3 又は Grade 4 の有害事象は好中球減少症（20.8%），血小板減少症（13.3%），肺炎（9.2%），貧血（6.7%），及び心房細動（5.0%）であった。重篤な有害事象の発現割合は 49.2%であり，高頻度（5%以上）に発現した重篤な有害事象は，肺炎（11.7%）及び発熱性好中球減少症（5.0%）であった。

イブルチニブの最終投与後 30 日以内に死亡した被験者は 23 例（19.2%）であった。このうち 13 例（10.8%）は治験担当医師により主に疾患進行に起因すると判断され，10 例（8.3%）は主に有害事象に起因すると判断された。高頻度に発現した死亡に至った有害事象は肺炎［4 例（3.3%）］であった。なお，死因が主に有害事象であると判断された 10 例中 4 例には，死亡前に放射線学的な疾患進行も認められた。

投与中止に至った有害事象は 20 例（16.7%）に発現した。2 例以上に発現した投与中止に至った有害事象は，肺炎［3 例（2.5%）］のみであった。減量に至った有害事象は 8 例（6.7%）に発現した。高頻度に発現した減量に至った有害事象は，好中球減少症［3 例（2.5%）］，下痢［2 例（1.7%）］，及び口内炎［2 例（1.7%）］であった。

下痢は 51 例（42.5%）に発現した。発現した下痢のほとんどは Grade 1 又は Grade 2 であった。Grade 3 又は Grade 4 の下痢は，3 例（2.5%）に発現した。投与中止に至った有害事象として発現した下痢はなかった。

器官別大分類「感染症および寄生虫症」の有害事象は 80 例（66.7%）に発現した。高頻度（10%以上）に発現した有害事象（基本語）は，上気道感染（17.5%），肺炎（15.0%），副鼻腔炎（12.5%），及び尿路感染（10.0%）であった。Grade 3 又は Grade 4 の感染症は 27 例（22.5%）に発現した。5 例（4.2%）に Grade 5 の感染症が発現した。高頻度に発現した Grade 3 以上の有害事象は，肺炎であった。

出血事象は 45 例（37.5%）に発現し，多くは Grade 1 又は Grade 2 の有害事象であった。高頻度に発現した出血性有害事象は，挫傷（14.2%），鼻出血（6.7%），及び点状出血（5.0%）であった。大出血は 3 例（2.5%）に発現した。このうち 1 例には，白血球症の可能性（末梢リンパ球数 $606\times10^9$/L）を背景として Day 5 に Grade 2 の頭蓋内出血が発現した。Grade 2 の頭蓋内出血は回復し，投与が再開された。ダルテパリンを使用していた 1 例に Grade 3 の脾臓出血が発現した。出血がみられた脾臓血管の塞栓術後，Grade 3 の脾臓出血は回復した。1 例に，転倒，頭部強打後にくも膜下出血が発現した。イブルチニブの投与を中断し，再開しなかった。くも膜下出血の転帰は軽快と報告された。

心房細動が 13 例（10.8%）に発現し，このうち 6 例は Grade 3 又は Grade 4 であった。心房細動を発現した 13 例中 2 例では心房粗動も発現した。イブルチニブの投与開始後，その他の悪性

腫瘍が 11 例（9.2%）に発現し，主に皮膚癌［8 例（6.7%）］であった。このほかに発現したその他の悪性腫瘍は，肺腺癌，急性骨髄性白血病，及び前立腺癌（各 1 例）であった。発現したすべてのその他の悪性腫瘍は，治験担当医師によりイブルチニブと関連なしと判断された。

血液学的検査，血液生化学検査，凝固パラメータ，及び免疫グロブリンなどの臨床検査結果に，新たな安全性の懸念を示すものは認められなかった。

### (3) 結論

イブルチニブ 560 mg の 1 日 1 回継続投与は，前治療として 1 レジメン以上のリツキシマブ併用の化学療法を受け，ボルテゾミブ治療後に疾患進行がみられた MCL 患者において，良好な忍容性を示し，迅速で持続的，かつ頑健な奏効を示した。これらの所見は，イブルチニブの良好なベネフィット・リスクプロファイルを裏付けるものである。

### 2.7.6.4.2　最終解析時（カットオフ日：2015 年 5 月 ■ 日）

#### 2.7.6.4.2.1　概要

**(1) 計画**

計画内容は，【2.7.6.4.1.1 (1)項】を参照のこと。なお，治験実施期間は以下のとおりである。

2012 年 7 月 ■ 日～2015 年 5 月 ■ 日（最終解析のデータベースロック日）

本治験終了時に，疾患進行が認められずイブルチニブの投与を継続していた 28 例中 26 例が，イブルチニブの長期継続試験である PCI-32765CAN3001 試験（CAN3001 試験）へ参加し，長期投与後の奏効及び安全性の追跡調査を受けた。

最終解析における抗腫瘍効果の評価可能な解析対象集団の定義及び解析方法は，本治験の主要解析に用いた抗腫瘍効果の評価可能な解析対象集団と同一である。本稿では，治験担当医師による抗腫瘍評価の結果のみを示す。

**(2) 結果**

**1) 対象集団**

本治験は，治験実施計画書に記載のとおり，組入れ終了から 2 年後に終了予定であった（最後の被験者の組入れ日：■■■ 年 ■ 月 ■ 日）。■■■ 年 ■ 月 ■ 日，治験依頼者は，イブルチニブ投与中又は長期追跡調査期間中であったすべての被験者に本治験の中止を要請し，最終解析時では全 120 例（100%）が本治験を中止した。最終解析時でイブルチニブ投与中であった 28 例に，イブルチニブ投与を継続できる CAN3001 試験への参加を打診したところ，26 例が CAN3001 試験でイブルチニブの継続投与を選択し，2 例が辞退した。これら 28 例は，治験担当医師又は治験依頼者の判断による投与中止とされた。主要解析時で治験担当医師又は治験依頼者の判断により投与中止とされた被験者は 3 例であった。最終解析時におけるその他の中止理由は主要解析時と同様であり，その内訳は，疾患進行又は再発による中止が 61 例（50.8%）［主要解析時 53 例（44.2%），以下同様］，有害事象による中止が 9 例（7.5%）［8 例（6.7%）］，死亡による中止が 9 例（7.5%）［8 例（6.7%）］，及び同意撤回による中止が 10 例（8.3%）［9 例（7.5%）］であった。

最終解析時での投与期間の中央値は 8 カ月（範囲：0.5～32.4 カ月）と，主要解析での投与期間の中央値（範囲：0.5～20.9 カ月）と同様であった。サイクル数の中央値も主要解析時と同じ 12 サイクルであったが，最終解析時での最大サイクル数は主要解析時の 31 サイクルから 47 サイクルに増加した。相対用量強度の中央値はほとんど変わらず，主要解析時で 96.5%（範囲：46.0%～100.0%），最終解析時で 96.4%（範囲：46.0%～100.0%）であった。

最終解析時で連続 7 日間以上イブルチニブ投与を中断した被験者は，主要解析時から 3 例増加し，合計 47 例であった（39.2%）［主要解析時 44 例（36.7%）］。同様に，有害事象及び重篤な有害事象のためイブルチニブ投与を中断した被験者の割合は，主要解析時ではそれぞれ 26.7%及び 10.0%であったが，最終解析時ではそれぞれ 30.8%及び 12.5%に増加した。

最終解析時では，イブルチニブの開始用量 560 mg から 420 mg に 1 回減量した被験者は，主要解析時と比較して 4 例増加し，合計 9 例（7.5%）であり［主要解析時 5 例（4.2%）］，さらにイ

ブルチニブ 420 mg から 280 mg に減量し，計 2 回減量した被験者数は同様であった［両解析時とも 3 例（2.5%）］。最終解析時に 1 例（0.8%）が 3 回減量した（主要解析時 0 例）。また，最終解析時に有害事象のため減量した被験者は 5 例増加し，合計 13 例（10.8%）であり［主要解析時 8 例（6.7%）］，重篤な有害事象のため減量した被験者数は同様であった［両解析時ともに 1 例（0.8%）］。

### 2) 有効性

最終解析時における抗腫瘍効果の評価可能な解析対象集団では，治験担当医師が判定した ORR は主要解析時と同様であり，66.4%（95% CI：57.5%～75.2%）であった。しかし，イブルチニブ投与により PR から CR となった被験者は，抗腫瘍効果の評価可能な解析対象集団で 7 例（6.4%），安全性解析対象集団で 8 例（6.7%）であり，最終解析時で CR であった被験者はそれぞれ 27 例（24.5%），30 例（25.0%）であった。

治験担当医師が判定した DOR 推定値の中央値は，最終解析時では主要解析時での 12.9 カ月から 21.3 カ月に延長し，イブルチニブ投与に対する持続的な奏効（PR 又は CR）が認められた。

治験担当医師が判定した PFS の中央値は主要解析時から変わらず，最終解析時においても 10.1 カ月（95% CI：6.2～13.8 カ月）であった。しかし，18 カ月 PFS 率は，最終解析時では主要評価時での 21%から 38%に上昇した。

最終解析時の追跡調査期間の中央値は 26.7 カ月であり，OS 推定値の中央値は 25.4 カ月（95% CI：17.3 カ月～推定不能）であった（主要解析時の追跡調査期間の中央値は 14.9 カ月であったが，主要解析時の OS は中央値に到達しなかった）。

### 3) 安全性

イブルチニブ投与後に発現した有害事象及びその他の安全性データは，イブルチニブを 1 回以上投与され，投与開始後の安全性データを有する被験者，すなわち安全性解析対象集団 120 例に基づき要約した。

最終解析時における安全性評価の結果は，主要解析時から 1 年経過した最終解析時においても同様であった。

有害事象を 1 件以上発現した被験者の割合は主要解析時と変わらず，最終解析時でも 95.8%であった。最終解析時で高頻度（20%以上）に発現した有害事象は，下痢（最終解析時 45.8%，主要解析時 42.5%；以下同様），疲労（43.3%，43.3%），咳嗽（29.2%，25.0%），血小板減少症（25.8%，24.2%），末梢性浮腫（24.2%，23.3%），好中球減少症（23.3.%，23.3%），貧血（22.5%，20.8%），悪心（22.5%，21.7%），筋痙縮（22.5%，20.8%），発熱（22.5%，20.8%），及び呼吸困難（20.8%，19.2%）であった。主要解析時から 1 年経過した最終解析時において，発現割合が 5%以上増加した有害事象はなかった。

Grade 3 又は Grade 4 の有害事象を発現した被験者は，主要解析時での 73 例（60.8%）から最終解析時では 77 例（64.2%）とやや増加した。最終解析時で高頻度（5%以上）に発現した Grade 3 又は Grade 4 の有害事象は，好中球減少症（最終解析時 20.8%，主要解析時 20.8%；以下同様），血小板減少症（14.2%，13.3%），肺炎（9.2%，9.2%），貧血（8.3%，6.7%），及び心房細動

（5.8%，5.0%）であった。主要解析時から 1 年経過した最終解析時において，発現割合が 2.0%以上増加した Grade 3 又は Grade 4 の有害事象はなかった。

イブルチニブと関連性がある有害事象（すなわち，治験担当医師によりイブルチニブとの因果関係が「可能性小」，「可能性大」，又は「ほぼ確実」と判断された有害事象）を発現した被験者は，主要解析時の 95 例（79.2%）から 96 例（80.0%）にやや増加した。

イブルチニブの最終投与後 30 日以内に死亡した被験者は，主要解析時の 23 例（19.2%）から 25 例（20.8%）にやや増加した。主な死因が疾患進行であった被験者は，主要解析時の 13 例（10.8%）から 14 例（11.7%）にやや増加した。同様に，主な死因が有害事象であった被験者は，主要解析時の 10 例（8.3%）から 11 例（9.2%）にやや増加した。死亡に至った有害事象を発現した被験者は，因果関係の再評価に伴い，主要解析時の 14 例（11.7%）から 13 例（10.8%）に減少した。この被験者（1 例）は，MCL に対する後治療の開始後に，有害事象（発熱性好中球減少症）により死亡した。主要解析後，治験担当医師は当該事象とイブルチニブとの因果関係を「可能性小」から「関連なし」に変更した。後治療の開始後に発現した有害事象が「関連あり」と判断されなかった場合は，治験薬投与後に発現した有害事象に該当しないことから，当該事象を治験薬投与後に発現した有害事象として分類しなかった。

重篤な有害事象を発現した被験者は，追跡調査期間の延長に伴い，主要解析時の 59 例（49.2%）から 65 例（54.2%）に増加した。重篤な有害事象を発現した被験者が，主要解析時から 2 例増加したのは無力症のみであり，その他の重篤な有害事象では，1 例の増加又は不変であった。

投与中止に至った有害事象が発現した被験者は，主要解析時の 20 例（16.7%）から 21 例（17.5%）にやや増加した。有害事象が投与中止の主な理由であった被験者は 9 例（7.5%）であった［主要解析時 8 例（6.7%）］。投与中止に至った有害事象のうち，2.0%以上で発現した有害事象は肺炎のみであった［両解析時ともに 3 例（2.5%）］。投与中止に至った無力症が最終解析時に 1 例（0.8%）報告された（主要解析時 0 例）。投与中止に至ったその他の有害事象の発現割合は主要解析時と同様であった。

減量に至った有害事象を発現した被験者は，追跡調査期間の延長に伴い，主要解析時の 8 例（6.7%）から 13 例（10.8%）に増加した。

特に注目すべき有害事象（大出血事象及び頭蓋内出血）の発現割合は，主要解析時から変わらず，3 例（2.5%）であった（頭蓋内出血 2 例，脾臓出血 1 例）。

全般的な安全性プロファイルに臨床的に意味のある変化は認められなかった。追跡調査期間の延長に伴い，血球減少症，その他の悪性腫瘍，眼障害，心房細動／粗動を含む心イベント，下痢，感染，発疹，及び腎不全を発現した被験者数と発現割合にやや増加がみられた。主要解析及び最終解析のいずれの時でも腫瘍崩壊症候群の発現はなく，白血球停滞及び高血圧を発現した被験者は主要解析時から増加しなかった［最終解析時：白血球停滞 1 例（0.8%），高血圧 14 例（11.7%）］。

最終解析時における臨床検査（血液学的検査及び血清生化学的検査）の結果から，新たな安全性の懸念は認められなかった。

**(3) 結論**

最終解析時における有効性及び安全性の結果は主要解析の結果と一致しており，長期追跡調査により，ボルテゾミブ療法後に疾患進行が認められた MCL 患者におけるイブルチニブのベネフィット・リスクプロファイルが許容できるものであることを裏付けた。

## 2.7.6.5　海外臨床第 I 相試験（PCI-32765CLL1007，評価資料：5.3.4.1.1）

### 2.7.6.5.1　概要

#### 2.7.6.5.1.1　計画

**(1) 治験の標題**

健康被験者に治療用量を上回る用量のイブルチニブを投与し，心再分極に対する作用，安全性，及び薬物動態を評価する第 I 相，ランダム化，二重盲検，プラセボ及び実薬対照，単回投与，4 期クロスオーバー探索試験

**(2) 治験責任医師**

[redacted]

**(3) 公表文献（引用文献）**

該当なし

**(4) 治験実施期間**

2014 年 10 月 [redacted] 日～2015 年 5 月 [redacted] 日（早期中止）

**(5) 開発の相**

第 I 相

**(6) 目的**

Part 1 の主要目的は，健康成人を対象に，イブルチニブ 1680 mg を投与したときの安全性及び忍容性を評価することである。Part 2 の主要目的は，治療用量又は治療用量を上回る用量のイブルチニブを単回投与したときの QT/QTc 間隔及び心電図への影響を評価することである。副次目的は，イブルチニブ及び代謝物 PCI-45227 の薬物動態（Part 1 及び Part 2），他の心電図パラメータへの影響（Part 2），安全性，及び忍容性（Part 2）を評価することである。

**(7) 治験方法**

Part 1 は非盲検，2 期，逐次デザインであった。第 1 期では，8 例すべての被験者にイブルチニブ 840 mg を単回投与した。第 2 期では，最初の 3 例にイブルチニブ 1680 mg を投与し，安全性及び忍容性を評価した。この 3 例に Grade 3 以上の毒性は認められず，消化管に対する忍容性が認められたため，残る 5 例にイブルチニブ 1680 mg を投与した。各投与期の間には，7 日以上のウォッシュアウト期間を設けた。

Part 1 でイブルチニブ 1680 mg 投与時の忍容性及び曝露量が十分であることを確認後，Part 2 を開始した。Part 2 はランダム化，プラセボ及び実薬対照，二重盲検，単回投与，4 期クロスオー

バー試験であった。すべての被験者は，ランダム化のスケジュールで規定された投与順序に従って，4 つの投与順序（表 2.7.6.5.1-1）のいずれかにランダムに割り付けられ，すべての被験者にイブルチニブ 1680 mg（治療用量を上回る用量），イブルチニブ 840 mg（治療用量），プラセボ，及びモキシフロキサシンを単回投与することとした。各投与の間には，7 日以上のウォッシュアウト期間を設けた。

イブルチニブ 840 mg は現在の承認用量（420 mg 及び 560 mg）を上回る用量である。承認された用法・用量でイブルチニブを服用している患者の，定常状態での治療曝露量を考慮し，本試験で健康被験者に投与する治療用量として設定した。イブルチニブ 1680 mg は，現在の承認用量に基づき，定常状態にある患者で想定される最も高い曝露量を考慮し設定している。

表 2.7.6.5.1-1 Part 2 における投与順序（PCI-32765CLL1007 試験）

| 投与順序 | 第 1 期 | 第 2 期 | 第 3 期 | 第 4 期 |
|---|---|---|---|---|
| 1 | A | D | B | C |
| 2 | B | A | C | D |
| 3 | C | B | D | A |
| 4 | D | C | A | B |

A：イブルチニブ 1680 mg（イブルチニブ 140 mg カプセル 12 錠）及びモキシフロキサシンに対応するプラセボカプセル（1 錠）
B：イブルチニブ 840 mg（イブルチニブ 140 mg カプセル 6 錠及びイブルチニブに対応するプラセボカプセル 6 錠）及びモキシフロキサシンに対応するプラセボカプセル（1 錠）
C：プラセボ（イブルチニブに対応するプラセボカプセル 12 錠及びモキシフロキサシンに対応するプラセボカプセル 1 錠）
D：モキシフロキサシン 400 mg（1 錠）及びイブルチニブに対応するプラセボカプセル 12 錠

### (8) 被験者数（計画時及び解析時）

Part 1：計画時 8 例，解析時 8 例。

Part 2：計画時 64 例，解析時 20 例。Part 2 は早期中止した。

### (9) 診断及び主な組入れ基準

18～55 歳の健康男女で，体格指数（BMI）18.0～30.0 kg/m$^2$，体重 50 kg 以上であることとした。また，スクリーニング時の血圧が正常であること，非喫煙者であることとした。

### (10) 被験薬，用量及び投与方法，ロット番号

Part 1，Part 2 とも，朝食に高脂肪食を摂取後 2 時間に各用量の被験薬を経口投与した。

イブルチニブ 140 mg カプセル：ロット番号 L0309801 及び L0406225

### (11) 対照薬，用量及び投与方法，ロット番号

Part 1，Part 2 とも，朝食に高脂肪食を摂取後 2 時間に各用量の対照薬を経口投与した。

イブルチニブに対応するプラセボカプセル：ロット番号 L0400219 及び L0404914

モキシフロキサシン 400 mg カプセル：ロット番号 13G17/G055

モキシフロキサシンに対応するプラセボカプセル：ロット番号 13L05/G053

### (12) 投与期間

計画時の参加期間は，Part 1 が約 42 日（スクリーニング期間を 20 日，フォローアップ期間を 10 日と仮定），Part 2 が約 58～76 日（スクリーニング期間を 21 日，フォローアップ期間を 10 ± 2 日と仮定）であった。

### (13) 評価項目

薬物動態

Part 1 では，薬物動態測定用血液を，各投与後 72 時間まで経時的に採取した。Part 2 では，薬物動態測定用血液を，各投与前及び投与後の 12 誘導心電図記録後 5 分以内に採取した。イブルチニブ，代謝物 PCI-45227，及びモキシフロキサシン（Part 2 のみ）の血漿中濃度は，バリデート済みの液体クロマトグラフィー－タンデム質量分析法を用いて測定した。薬物動態パラメータは，$C_{max}$，$t_{max}$，$AUC_{last}$，$AUC_{\infty}$，$\%AUC_{\infty,ex}$，$t_{1/2,\lambda}$，$\lambda_z$，及び代謝物／親化合物比（MPR）であった。

薬力学

Part 2 では，測定前に被験者を仰臥位で 5 分以上安静にさせた後，12 誘導心電図（triplicate）を投与前及び投与後 72 時間に 3 回連続で測定，記録した。Triplicate 測定は 5 分以内に完了した。心電図の結果は，治験責任医師による安全性の評価後，盲検下におかれた第三者の中央測定機関へ間隔計測のために電子的に送付された。薬力学的パラメータは，Bazett の補正式（QTcB），Fridericia の補正式（QTcF），及び試験特有のパワーモデルを用いた補正（QTcP）による QTc のベースラインからの変化（ΔQTc）及びイブルチニブ又はモキシフロキサシンとプラセボとの ΔQTc の差（ΔΔQTc）であった。

ファーマコゲノミクス

Part 2 では，すべての被験者から QT/QTc 間隔延長に関連する 5 つのイオンチャンネル遺伝子中の遺伝的変異を特定する目的で，血液検体を採取した。これらの変異は，試験中に QT/QTc 間隔延長が認められた場合にのみ解析することとした。本試験では，QT/QTc 間隔延長が認められなかったため，ファーマコゲノミクス解析を実施しなかった。

安全性

Part 1 及び Part 2 で身体所見，有害事象モニタリング，バイタルサイン，心電図，臨床検査値（血液学的検査，血液生化学検査）により，安全性を評価した。

### (14) 統計手法

被験者数の設定

Part 1：

実施可能性に基づき 8 例を組み入れることとした。

Part 2：

計画時の被験者数：

過去の試験結果より，ΔQTc の被験者内の標準偏差（SD）は，主要な補正法を用い 10 msec と仮定した。52 例に対し SD を 10 msec と仮定し，真の平均値の差が 5 msec である場合，ある測定時点 1 点における各用量のイブルチニブのΔΔQTc の平均値の両側 90%信頼区間（CI）の上限（片側 95% CI）が 10 msec 未満となる確率は 80%と推定された。52 例以上の被験者が，必要とするすべての評価項目を完了することを担保するために，健康被験者約 64 例（女性被験者約 20 例を含む）を本試験に組み入れることとした。

すべての測定時点におけるモキシフロキサシンのΔΔQTc の平均値を評価し，測定感度を評価した。測定感度についての統計学的評価は，あらかじめ選択した 4 点の測定時点（投与後 2，3，4，6 時間）におけるモキシフロキサシンのΔΔQTc の平均値について実施した。多重性の調整には Bonferroni 法を用いた。52 例に対し SD を 10 msec と仮定し，真の平均値の差が 10 msec 以上である場合，あらかじめ選択した 4 点の測定時点（投与後 2～6 時間）のうち 1 時点以上でモキシフロキサシンのΔΔQTc の平均値の両側 97.5% CI の下限の最大が 5 msec 超となる確率は 60%と推定された。

組入れ被験者数：

Part 2 実施中，最初の 20 例を 4 期クロスオーバー試験に組入れ，16 例が 3 期まで終了した。この 20 例のうち，第 2 期終了後に 1 例（被験者番号 07432）に Grade 4 のアラニンアミノトランスフェラーゼ増加及びアスパラギン酸アミノトランスフェラーゼ増加が認められ，本被験者は入院した。本被験者について緊急用キーコードを開封した結果，第 1 期にイブルチニブ 840 mg，第 2 期にイブルチニブ 1680 mg が投与されており，その後肝機能検査異常を発現していた（1680 mg 投与後 4 日，840 mg 投与後 11 日）。この結果を受け，本試験は，Part 2 では 20 例の組入れをもって，治験依頼者により早期中止された。

被験者の特性

Part 1 及び Part 2：

治験薬の投与を 1 回以上受けたすべての被験者を対象とし，年齢，BMI，体重，及び身長について記述統計量を用いて要約した。性別，人種，及び民族は一覧で示した。

薬物動態

Part 1 及び Part 2：

個々の被験者及び平均のイブルチニブ，代謝物 PCI-45227，及びモキシフロキサシン（Part 2 のみ）の血漿中濃度－時間曲線プロファイルをプロットした。各時点におけるイブルチニブ及び代謝物 PCI-45227 の血漿中濃度データ及び薬物動態パラメータの全推定値を，記述統計量を用いて要約した。また，探索的解析として，イブルチニブ及び代謝物 PCI-45227 の薬物動態パラメータ（$C_{max}$ 及び AUC）について，イブルチニブ 840 mg 投与時に対するイブルチニブ 1680 mg 投与時の幾何平均値の比（GMR）及びその 90% CI を線形混合効果モデルにより算出した。

薬力学及び薬物動態/薬力学

Part 1：

該当なし

Part 2：

各投与群及び各時点でのすべての心電図の測定値及びそのベースラインからの変化，並びにイブルチニブ及びモキシフロキサシンのΔΔQTc について，記述統計量を用いて要約した。ベースライン時の RR 間隔に対する QT/QTc の線形回帰分析も実施した。

線形混合効果モデルにより，濃度を予測変数，被験者を変量効果（ランダム切片モデル及びランダム係数モデル）として，イブルチニブ及び代謝物 PCI-45227 の血漿中濃度とΔΔQTc の関係を示した。

安全性

Part 1 及び Part 2：

安全性の解析は，Part 1 で治験薬の投与を 1 回以上受けたすべての被験者，又は Part 2 でいずれかの投与順序にランダム化され治験薬の投与を 1 回以上受けたすべての被験者を対象とした。有害事象は Medical Dictionary for Regulatory Activities（version 16.1）を用いてコード化し，有害事象の重症度判定には National Cancer Institute - Common Terminology Criteria for Adverse Events（version 4.03）を使用した。投与後に発現した有害事象は，すべて器官別大分類及び基本語で投与群ごとに集計した。すべての臨床検査値，バイタルサイン及び心電図について，連続変数は記述統計量を用いて，カテゴリ変数はシフト表を用いて要約した。

### 2.7.6.5.1.2 結果

#### (1) Part 1

##### 1) 対象集団

本試験の Part 1 では，男性 3 例（37.5%）及び女性 5 例（62.5%）が治験薬を投与された。年齢の中央値は 51 歳（範囲：34～55 歳）であった。すべての被験者が白人で，体重の中央値は 71.4 kg（範囲：53.7～86.2 kg），BMI の中央値は 24.1 kg/$m^2$（範囲：20.2～27.8 kg/$m^2$）であった。

8 例すべてが 2 期連続の治療期（第 1 期：イブルチニブ 840 mg 単回投与，第 2 期：イブルチニブ 1680 mg 単回投与）を完了し，安全性解析対象集団及び薬物動態解析対象集団に含まれた。Part 1 では、治験実施計画書からの重要な逸脱又は投与に関連した逸脱はなかった。

##### 2) 薬物動態

イブルチニブの曝露量（AUC）は，用量を 840 mg からその 2 倍の 1680 mg に増量したときに用量比例よりわずかに高く増加した。イブルチニブ 1680 mg 投与後の分布容積は 840 mg 投与後と同程度であったが，経口クリアランスは 840 mg 投与後と比較してより緩徐であった。半減期は，いずれの用量でも同様であった。代謝物 PCI-45227 の $C_{max}$ が用量比例より低く増加したのに対し，AUC は用量比例的に増加した。イブルチニブ 1680 mg 投与後の MPR は、840 mg 投与後と比較して低かった。

### 3) 安全性

治験薬投与後に 3 例（37.5%）に有害事象 9 件が発現したが，いずれも非重篤であり，Grade 1 又は 2 であった。Part 1 で発現したすべての有害事象の転帰は回復であった。死亡は認められず，重篤な有害事象又は投与中止に至った有害事象の発現はなかった。また，臨床的に重要な有害事象若しくは特に注目すべき有害事象（大量出血又は頭蓋内出血）の発現もなかった。

臨床検査の安全性項目（肝機能検査値上昇を含む），バイタルサイン，及び心電図パラメータに臨床的に意義のある変化は認められなかった。

## (2) Part 2

### 1) 対象集団

本試験の Part 2 は，1 例の安全性観察のため早期中止した（詳細は，2.7.6.5.1.2，(2)，5)安全性の項を参照）。早期中止時点で，計画時の被験者数 64 例のうち 20 例が Part 2 へ組み入れられ，いずれかの投与順序へランダムに割り付けられた後，治験薬の投与を 1 回以上受けた。年齢の中央値は 43.5 歳（範囲：28～54 歳）であった。被験者の多くは白人（85.0%）で，男性であった（80.0%）。体重の中央値は 74.70 kg（範囲：51.4～94.0 kg），BMI の中央値は 25.15 kg/$m^2$（範囲：18.2～28.5 kg/$m^2$）であった。

早期中止前に，4 期クロスオーバーで 4 種類の治験薬すべてを投与された被験者はいなかった。治験薬を 1 回以上投与された 20 例のうち，16 例（80.0%）が 4 種類中 3 種類，2 例（10.0%）が 2 種類，2 例（10.0%）が 1 種類の治験薬を投与された。4 種類中 3 種類の治験薬を投与された 16 例のうち，9 例がイブルチニブ 840 mg 又は 1680 mg のいずれか一方，プラセボ，及びモキシフロキサシンを投与された。全体では，13 例がプラセボ，14 例がモキシフロキサシン，13 例がイブルチニブ 840 mg，14 例がイブルチニブ 1680 mg を投与された。

### 2) 薬物動態

Part 1 の結果と同様であった。

### 3) 薬力学

**試験特有のパワーモデルを用いた補正**

補正値 0.2052 を用いて，QT/RR 関係を補正した。プラセボ，イブルチニブ 840 mg 及び 1680 mg を投与された被験者では，投与後のほとんどの時点で QTcP のベースラインからの変化（ΔQTcP）の平均値は減少した。一方，モキシフロキサシン 400 mg を投与された被験者では，投与後のほとんどの時点で平均ΔQTcP は増加した。平均ΔQTcP の最大値は，プラセボ投与で -8.7 msec，モキシフロキサシン投与で 13.9 msec，イブルチニブ 840 mg 投与で-10.3 msec，イブルチニブ 1680 mg 投与で-6.7 msec であった。

プラセボ及び実薬の両方を投与された被験者では，平均 QTcP 値は，ほとんどの時点でプラセボ投与よりモキシフロキサシン投与で高かったのに対し，イブルチニブの投与では，ほとんどの時点でいずれの用量でもプラセボ投与より低かった。すべての時点で，イブルチニブ 840 mg 及び 1680 mg の平均ΔΔQTcP の 90% CI の上限は，いずれも 10 msec 未満であった。

プラセボ，イブルチニブ 840 mg 及び 1680 mg 投与後のいずれの時点においても，QTcP にベースラインから 30 msec を超える増加が認められた被験者はいなかった。治験薬 4 種類のいずれかの投与後のいずれの時点においても，QTcP が 450 msec を超えた被験者は認められなかった。

**Fridericia の補正式及び Bazette の補正式による補正**

QTcF 及び QTcB の経時的変化は，QTcP と同様の変化パターンであった。また，最大平均ΔQTc は類似していた。すべての時点で，イブルチニブの各用量の平均ΔΔQTcF 及び平均ΔΔQTcB の 90% CI の上限は，いずれも 10 msec 未満であった。また，プラセボ，イブルチニブ 840 mg，及び 1680 mg 投与後のいずれの時点でも，QTcF 又は QTcB にベースラインから 30 msec を超える増加が認められた被験者やこれらの補正値が 450 msec を超えた被験者は認められなかった。

**その他の心電図パラメータ**

治験薬 4 種類の投与後のほとんどの時点で，PR 間隔のベースラインからの平均変化は増加した。モキシフロキサシン投与における平均変化は，プラセボと比較して，概ね同程度又は低かった。イブルチニブ 840 mg 及び 1680 mg 投与における平均変化は，投与後 3～12 時間で，プラセボと比較して大きかった。その他の心電図パラメータ又は心電図の形態に，臨床的に意義のある影響は認められなかった。

### 4) 薬物動態/薬力学

薬物動態/薬力学の結果から，イブルチニブ又は代謝物 PCI-45227 の血漿中濃度と QTc の変化とに負の相関が，PR 間隔の変化とに正の相関が示唆された。イブルチニブの治療用量を上回る 1680 mg（現在承認されている 420 mg 及び 560 mg のそれぞれ 4 倍量及び 3 倍量）の投与後の $C_{max}$ では，平均ΔΔQTcP の推定値（90% CI，以下同様）は，イブルチニブで-5.2706 msec（-9.41，-1.13），代謝物 PCI-45227 で-3.4769 msec（-7.15，0.20）であった。イブルチニブ 1680 mg 投与における 90% CI の上限は，閾値である 10 msec 未満であった。

### 5) 安全性

Part 2 では，第 2 期終了翌日に Grade 4 のアラニンアミノトランスフェラーゼ増加及びアスパラギン酸アミノトランスフェラーゼ増加が 1 例に認められた。本被験者は，第 1 期で当該事象発現の 11 日前にイブルチニブ 840 mg の投与を，第 2 期で当該事象発現の 4 日前にイブルチニブ 1680 mg を投与された。本被験者は，Grade 4 の重篤な有害事象（肝酵素上昇）及び Grade 2 の重篤な有害事象（筋肉痛及び上腹部痛）のため，本試験を中止した。肝機能異常は 1 カ月以内に回復した。肝機能異常がイブルチニブと関連性があったため，その後の投与は中止され，治験依頼者により試験が中止された。薬物動態解析では，本被験者のイブルチニブ及び代謝物 PCI-45227 の全身曝露量は，定量下限であったことが示唆された。肝酵素上昇の追加調査として解析した，他の 5 種類のイブルチニブ代謝物の曝露量も，同様に低かった。しかし，イブルチニブは初回通過効果を大きく受けやすいため，肝臓入口におけるイブルチニブ濃度は，全身濃度に比べ非常に高いことがある。そのため，特にイブルチニブ 1680 mg 投与後では，本被験者の肝臓における曝露量は他の被験者と比較して高かった可能性は否定できない。

本試験では，死亡は認められなかった。Part 2 で発現した重篤な有害事象及び Grade 3 又は 4 の有害事象は，前述の肝酵素上昇（Grade 4 のアラニンアミノトランスフェラーゼ増加及びアスパラギン酸アミノトランスフェラーゼ増加）のみであった。投与中止に至った有害事象は，上記 2 件のほかに，モキシフロキサシン投与後 3 日に 1 例に発現した胃腸炎（治験薬と関連性がない）のみであった。

有害事象の発現割合は，モキシフロキサシン 400 mg（50.0%），イブルチニブ 840 mg（46.2%）又はイブルチニブ 1680 mg（50.0%）を投与された被験者で同程度であり，プラセボを投与された被験者では 38.5%であった。実薬を投与された被験者で高頻度に発現した有害事象は，下痢及び上腹部痛（それぞれ，各薬剤及びプラセボ投与でそれぞれ 2〜3 例に発現）であった。特に注目すべき有害事象（大量出血又は頭蓋内出血）の発現はなかった。

イブルチニブ 1680 mg 投与後 4 日及び第 2 期終了後 1 日に Grade 4 のアラニンアミノトランスフェラーゼ増加及びアスパラギン酸アミノトランスフェラーゼ増加が認められた 1 例を除き，Grade 2，3 又は 4 の肝機能検査値の上昇が認められた被験者はいずれの時点でもいなかった。Grade 1 のアラニンアミノトランスフェラーゼ増加が 3 例に認められ，1 例はスクリーニング時のみ，2 例はプラセボ及びイブルチニブの投与前後に認められた。Grade 1 のビリルビン増加が 2 例に認められ，1 例はスクリーニング時のみ，1 例はプラセボ投与前のベースライン時のみであった。

その他の臨床検査の安全性項目又はバイタルサインに臨床的に意義のある変化はなかった。

#### 6) 本試験の限界

本試験の Part 2 は，計画時の被験者数 64 例のうち 20 例のみを組み入れた後，安全性の理由から中止したため，計画していた QT に対するイブルチニブの潜在的影響に関するサブグループ解析（性別）は実施しなかった。

### 2.7.6.5.1.3 結論

- Part 1 では，イブルチニブ 840 mg 単回投与及び 1680 mg 単回投与後に，臨床的な安全性の懸念は認められなかった。イブルチニブ及び代謝物 PCI-45227 の曝露量（$C_{max}$ 及び AUC）は，イブルチニブの用量を 840 mg からその 2 倍の 1680 mg に増量したときにほぼ 2 倍となったが，イブルチニブの AUC は用量比例よりも増加した。これは，イブルチニブ 1680 mg の MPR がイブルチニブ 840 mg と比較して低かったことによるものである。
- Part 2 におけるイブルチニブ及び代謝物 PCI-45227 の曝露量は，Part 1 の結果と同程度であった。最も高かった被験者の $C_{max}$ は 1890 ng/mL であり，560 mg/日（164 ng/mL）の投与後での定常状態における平均 $C_{max}$ の 10 倍以上であった。
- Part 2 の第 2 期終了後，Grade 4 のアラニンアミノトランスフェラーゼ増加及びアスパラギン酸アミノトランスフェラーゼ増加が 1 例に認められ，投与後 1 カ月以内に回復した。本被験者は，第 1 期でイブルチニブ 840 mg，第 2 期でイブルチニブの治療用量を上回る 1680 mg を投与された。本被験者以外に，イブルチニブ 1680 mg を投与された被験者に Grade 2 以上の肝機能検査値上昇は認められず，肝機能異常に関連した有害事象を発現した

被験者はいなかった。Grade 4 の有害事象の発現後，治験薬の投与を中止し，治験依頼者により本試験は中止された。計画時の組入れ被験者数の約 3 分の 1 が，本試験に既に組み入れられた後であった。

- Part 2（QT 評価試験）では，計画時の組入れ被験者数よりも少ない被験者数であったが，心電図パラメータに対するモキシフロキサシン及びプラセボの影響について，いずれも想定どおりの挙動を示し，イブルチニブによる QTc 短縮が認められた。QTc 短縮は，イブルチニブ及び代謝物 PCI-45227 の血漿中濃度と相関していた。また，イブルチニブ及び代謝物 PCI-45227 の血漿中濃度と相関していた PR 間隔の延長も認められた。これらの効果は，いずれも臨床的な問題はないと考えられた。
- Bazett の補正式，Fridericia の補正式，及び試験特有のパワーモデルを用いた QT 補正では，イブルチニブ 840 mg 及び 1680 mg のΔΔQTc の 90% CI の上限は，いずれも 10 msec 未満であり，非抗不整脈薬に対して ICH E14 ガイドラインで定めている推奨閾値であった。このことから，イブルチニブによる QTc 間隔延長は認められなかったことが示唆された。イブルチニブの 2 用量では，90% CI の下限はいずれの時点でも 0 msec を超えなかった。モキシフロキサシンでは，90% CI の下限はほとんどの時点で 0 msec を超えており，また，90% CI の上限は複数の時点で 10 msec を超えていた。

#### 2.7.6.5.2　有害事象

PCI-32765CLL1007 試験の Part 1 及び Part 2 で発現した，すべての有害事象及び治験薬と関連性がある有害事象をそれぞれ表 2.7.6.5.2-1 及び表 2.7.6.5.2-2 に示す。

表 2.7.6.5.2-1 Part 1 で発現した有害事象（PCI-32765CLL1007 試験，安全性解析対象集団）

| | 有害事象 | | | 治験薬と関連性がある有害事象 | | |
|---|---|---|---|---|---|---|
| MedDRA 器官別大分類<br>基本語 | 第 1 期<br>イブルチニブ<br>840 mg | 第 2 期<br>イブルチニブ<br>1680 mg | Part 1 全体 | 第 1 期<br>イブルチニブ<br>840 mg | 第 2 期<br>イブルチニブ<br>1680 mg | Part 1 全体 |
| 安全性解析対象集団 | 8 | 8 | 8 | 8 | 8 | 8 |
| TEAE を発現した被験者数 | 2 (25.0%) | 3 (37.5%) | 3 (37.5%) | 1 (12.5%) | 2 (25%) | 2 (25%) |
| 胃腸障害 | 1 (12.5%) | 2 (25.0%) | 2 (25.0%) | 1 (12.5%) | 2 (25%) | 2 (25%) |
| 悪心 | 1 (12.5%) | 2 (25.0%) | 2 (25.0%) | 1 (12.5%) | 2 (25%) | 2 (25%) |
| 嘔吐 | 0 | 1 (12.5%) | 1 (12.5%) | 0 | 1 (12.5%) | 1 (12.5%) |
| 神経系障害 | 2 (25.0%) | 0 | 2 (25.0%) | 0 | 0 | 0 |
| 頭痛 | 2 (25.0%) | 0 | 2 (25.0%) | 0 | 0 | 0 |
| 感染症および寄生虫症 | 0 | 1 (12.5%) | 1 (12.5%) | 0 | 0 | 0 |
| 鼻炎 | 0 | 1 (12.5%) | 1 (12.5%) | 0 | 0 | 0 |
| 筋骨格系および結合組織障害 | 1 (12.5%) | 0 | 1 (12.5%) | 0 | 0 | 0 |
| 背部痛 | 1 (12.5%) | 0 | 1 (12.5%) | 0 | 0 | 0 |
| 皮膚および皮下組織障害 | 0 | 1 (12.5%) | 1 (12.5%) | 0 | 0 | 0 |
| 小水疱性皮疹 | 0 | 1 (12.5%) | 1 (12.5%) | 0 | 0 | 0 |

注：
被験者が器官別大分類又は基本語で同一の有害事象を発現した場合は，1 例のみをカウントした
安全解析対象集団を母数として，発現割合（%）を算出した
治験責任医師によりイブルチニブとの因果関係が「可能性小」，「可能性大」，又は「ほぼ確実」と判定された有害事象を「関連性がある有害事象」と定義した
有害事象は，MedDRA/J version 16.1 を用いてコード化した
参照元：5.3.4.1.1 PCI-32765CLL1007 試験 CSR Attachment TSFAE02_P1，TSFAE34

表 2.7.6.5.2-2 Part 2 で発現した有害事象（PCI-32765CLL1007 試験，安全性解析対象集団）

| MedDRA 器官別大分類<br>基本語 | 有害事象 | | | | | 治験薬と関連性がある有害事象 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | プラセボ | モキシフロキサシン 400 mg | イブルチニブ 840 mg | イブルチニブ 1680 mg | Part 2 全体 | プラセボ | モキシフロキサシン 400 mg | イブルチニブ 840 mg | イブルチニブ 1680 mg | Part 2 全体 |
| 安全性解析対象集団 | 13 | 14 | 13 | 14 | 20 | 13 | 14 | 13 | 14 | 20 |
| TEAE を発現した被験者数 | 5 (38.5%) | 7 (50.0%) | 6 (46.2%) | 7 (50.0%) | 15 (75.0%) | 4 (30.8%) | 4 (28.6%) | 4 (30.8%) | 6 (42.9%) | 11 (55.0%) |
| 胃腸障害 | 3 (23.1%) | 5 (35.7%) | 3 (23.1%) | 5 (35.7%) | 11 (55.0%) | 3 (23.1%) | 4 (28.6%) | 3 (23.1%) | 5 (35.7%) | 10 (50.0%) |
| 下痢 | 1 (7.7%) | 2 (14.3%) | 2 (15.4%) | 3 (21.4%) | 7 (35.0%) | 1 (7.7%) | 1 (7.1%) | 2 (15.4%) | 3 (21.4%) | 6 (30.0%) |
| 上腹部痛 | 0 | 3 (21.4%) | 2 (15.4%) | 3 (21.4%) | 6 (30.0%) | 0 | 3 (21.4%) | 2 (15.4%) | 3 (21.4%) | 6 (30.0%) |
| 悪心 | 2 (15.4%) | 0 | 1 (7.7%) | 1 (7.1%) | 4 (20.0%) | 2 (15.4%) | 0 | 1 (7.7%) | 1 (7.1%) | 4 (20.0%) |
| 腹部膨満 | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) |
| 腹痛 | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) |
| 口唇乾燥 | 1 (7.7%) | 0 | 0 | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 神経系障害 | 2 (15.4%) | 2 (14.3%) | 2 (15.4%) | 1 (7.1%) | 5 (25.0%) | 2 (15.4%) | 1 (7.1%) | 0 | 0 | 3 (15.0%) |
| 頭痛 | 0 | 1 (7.1%) | 2 (15.4%) | 1 (7.1%) | 3 (15.0%) | 0 | 0 | 0 | 0 | 0 |
| 味覚異常 | 1 (7.7%) | 1 (7.1%) | 0 | 0 | 2 (10.0%) | 1 (7.7%) | 1 (7.1%) | 0 | 0 | 2 (10.0%) |
| 浮動性めまい | 1 (7.7%) | 0 | 0 | 0 | 1 (5.0%) | 1 (7.7%) | 0 | 0 | 0 | 1 (5.0%) |
| 眼障害 | 1 (7.7%) | 0 | 1 (7.7%) | 0 | 2 (10.0%) | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) |
| 眼乾燥 | 1 (7.7%) | 0 | 0 | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 眼瞼紅斑 | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) |
| 眼瞼刺激 | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) |
| 一般・全身障害および投与部位の状態 | 0 | 0 | 1 (7.7%) | 1 (7.1%) | 2 (10.0%) | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) |
| インフルエンザ様疾患 | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 倦怠感 | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) |
| 発熱 | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 感染症および寄生虫症 | 0 | 1 (7.1%) | 0 | 1 (7.1%) | 2 (10.0%) | 0 | 0 | 0 | 0 | 0 |
| 胃腸炎 | 0 | 1 (7.1%) | 0 | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 鼻咽頭炎 | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 筋骨格系および結合組織障害 | 1 (7.7%) | 0 | 1 (7.7%) | 1 (7.1%) | 2 (10.0%) | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) |
| 背部痛 | 1 (7.7%) | 0 | 0 | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 筋肉痛 | 0 | 0 | 1 (7.7%) | 1 (7.1%) | 1 (5.0%) | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) |
| 心臓障害 | 0 | 1 (7.1%) | 0 | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 動悸 | 0 | 1 (7.1%) | 0 | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 臨床検査 | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) |
| 肝酵素上昇 | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) | 0 | 0 | 0 | 1 (7.1%) | 1 (5.0%) |
| 生殖系および乳房障害 | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |

| MedDRA 器官別大分類<br>基本語 | 有害事象 | | | | | 治験薬と関連性がある有害事象 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | プラセボ | モキシフロキサシン 400 mg | イブルチニブ 840 mg | イブルチニブ 1680 mg | Part 2 全体 | プラセボ | モキシフロキサシン 400 mg | イブルチニブ 840 mg | イブルチニブ 1680 mg | Part 2 全体 |
| 勃起不全 | 0 | 0 | 1 (7.7%) | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 皮膚および皮下組織障害 | 0 | 1 (7.1%) | 0 | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |
| 紅斑 | 0 | 1 (7.1%) | 0 | 0 | 1 (5.0%) | 0 | 0 | 0 | 0 | 0 |

注：
イブルチニブの初回投与後から最終投与後 30 日以内に発現又は悪化した有害事象を TEAE と定義した
安全解析対象集団を母数として，発現割合（%）を算出した
被験者が器官別大分類又は基本語で同一の有害事象を発現した場合は，1 例のみをカウントした
有害事象は，MedDRA/J version 16.1 を用いてコード化した
参照元：5.3.4.1.1 PCI-32765CLL1007 試験 CSR Attachment TSFAE02_P2，TSFAE04_P2

#### 2.7.6.5.3　死亡及び重篤な有害事象の個別症例の詳細

PCI-32765CLL1007 試験開始後に死亡及び重篤な有害事象を発現した被験者のうち，イブルチニブを投与された被験者における，死亡に至った有害事象及びイブルチニブと関連性がある重篤な有害事象を発現した被験者の詳細及び臨床経過を示す。

##### 2.7.6.5.3.1　Part 1

**(1) 有害事象による死亡例**

**1) イブルチニブと関連性がある死亡例**

該当なし。

**2) イブルチニブと関連性がない死亡例**

該当なし。

**(2) イブルチニブと関連性がある重篤な有害事象（上記を除く）**

該当なし。

##### 2.7.6.5.3.2　Part 2

**(1) 有害事象による死亡例**

**1) イブルチニブと関連性がある死亡例**

該当なし。

**2) イブルチニブと関連性がない死亡例**

該当なし。

**(2) イブルチニブと関連性がある重篤な有害事象（上記を除く）**

**1) 被験者番号 1007-07432**

| | |
|---|---|
| 被験者番号 | 1007-07432 |
| 治験薬 | イブルチニブ 840 mg，経口投与（第 1 期），1680 mg，経口投与（第 2 期） |
| 重篤な有害事象等 | 治験薬と関連性がある重篤な有害事象，投与中止に至った有害事象：肝酵素増加（Grade 4），筋肉痛（Grade 2），上腹部痛（Grade 2） |

被験者 1107-07432 は，4[redacted]歳の女性で，肝機能関連の既往歴はなかった。ベースライン時の B 型及び C 型肝炎ウイルス血清検査の結果は陰性であった。アルコールの摂取量は 1 ユニット／週と記録されていたが，アルコール乱用の既往歴はなかった。

2015 年 3 月 26 日（第 1 期）にイブルチニブ 840 mg，2015 年 4 月 2 日（第 2 期）に 1680 mg をそれぞれ単回投与した。最終測定時のイブルチニブ濃度及び血中代謝物濃度は，想定された範囲内であった（投与後 48 時間におけるイブルチニブ濃度：1.11 ng/mL，投与後 72 時間における代

謝物 PCI-45227 濃度：1.80 ng/mL）。試験実施医療機関に入院中，アラニンアミノトランスフェラーゼ（ALT），アスパラギン酸アミノトランスフェラーゼ（AST），アルカリホスファターゼ，及び総ビリルビンに異常は認められなかった。2015 年 4 月 5 日，被験者は，軽度の両腕筋肉痛，低血圧（94/57 mmHg），及び両腕内出血（採血に関連した内出血）を伴い退院した。退院時，凝固検査の結果はすべて基準範囲内であった。

2015 年 4 月 6 日（イブルチニブ 1680 mg 投与後 4 日，退院後 1 日），被験者は，筋肉痛，胸痛，腹痛，悪心，及び頭痛を訴え，入院した。入院時の身体所見では，触診時に心窩部に疼痛が認められた。発熱はなかった。臨床検査の結果，Grade 2 の ALT 増加［156 U/L（基準値 45 U/L 以下）］，Grade 1 の AST 増加［104 U/L（基準値 40 U/L 以下）］，及び C－反応性たん白増加［27 mg/L（基準値 5 mg/L 以下）］が認められた。胸部 X 線，心電図，及び腹部超音波検査は正常であった。心機能検査（クレアチンキナーゼ MB 分画，トロポニン）は陰性であった。入院時に薬物スクリーニング検査は実施しなかった。腹痛に対し pantoprazole による治療が実施され，2015 年 4 月 7 日，被験者は退院した。鑑別診断は，ウイルス症候群又は薬剤による肝酵素増加であった。肝機能検査値上昇の追跡調査は，被験者の担当医が実施した。

2015 年 4 月 10 日（イブルチニブ 1680 mg 投与後 8 日，退院後 3 日），Grade 4 の ALT 増加（3312 U/L）及び Grade 4 の AST 増加（926 U/L）のため，被験者は再入院を薦められた。総ビリルビンは 8 μmol/L（基準値 3～17 μmol/L）であった。被験者は，試験中あるいは試験後に，処方薬，市販薬，生薬のいずれも使用していなかった。入院時には，悪心及び疲労も認められた。身体所見では，触診時に右上腹部痛が認められた。2015 年 4 月 11 日，ALT 値及び AST 値は徐々に低下し始めた。被験者は経過観察のため 2015 年 4 月 13 日まで入院し，退院時には追跡調査のための来院が予定された。入院期間中に実施した腹部超音波検査では，特に異常は認められなかった。最後に報告された追跡調査の時点（2015 年 5 月 6 日）では，AST 値及びビリルビン値は正常（それぞれ 30 U/L 及び 6 μmol/L）であり，ALT 値はほぼ回復した（56 U/L）。2015 年 4 月 6 日から同年 5 月 6 日までに実施した臨床検査結果を以下の表に示す。

追跡期間中，肝酵素増加の他の原因を特定するため，追加の臨床試験を実施した。2015 年 4 月 20 日，A 型，B 型，C 型，及び E 型肝炎ウイルス血清検査，並びにサイトメガロウイルス検査は陰性であった。エプスタイン・バーウイルス血清検査は陽性であったが，陳旧性の感染であることが示唆された。自己免疫誘発性肝炎の臨床検査の結果，抗核抗体陽性（IgG IF 1:80）であり，抗二本鎖 DNA 抗体，可溶性核抗原スクリーニング，抗平滑筋抗体，抗ミトコンドリア抗体，及び抗肝腎ミクロソーム抗体は陰性であった。

被験者は，肝酵素上昇（Grade 4），筋肉痛（Grade 2）及び上腹部痛（Grade 2）のため，試験参加を中止した。これら 3 件の有害事象はいずれも，治験担当医師によりイブルチニブとの因果関係は「可能性小」と判断された。Part 2 で発現した重篤な有害事象は，この 3 件のみであった。

治験依頼者は，肝酵素上昇はイブルチニブと関連性があると判断した。薬物動態解析では，本被験者におけるイブルチニブ及び代謝物 PCI-45227 の全身曝露量は定量下限であったことが示された。肝酵素上昇の追加調査として解析した，他の 5 種類のイブルチニブ代謝物の曝露量も，同様に低かった。しかし，イブルチニブは初回通過効果を大きく受けやすいため，肝臓入口におけるイブルチニブ濃度は，全身濃度に比べ非常に高いことがある。そのため，特にイブルチニブ

1680 mg の投与後では，本被験者の肝臓における曝露量は他の被験者と比較して高かった可能性は否定できない。