ガザイバ点滴静注1000 mg
（オビヌツズマブ（遺伝子組換え））

［CD20陽性の B 細胞性濾胞性リンパ腫］

第2部　（モジュール2）：CTD の概要（サマリー）

2.7.5 参考文献

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2.7.5 参考文献

(1) 2.7.1で引用した文献
該当なし

(2) 2.7.2で引用した文献
「2.7.2.5 参考文献」参照。

(3) 2.7.3で引用した文献
「2.7.3.7 参考文献」参照。

(4) 2.7.4で引用した文献
該当なし。

(5) 2.7.6で引用した文献
該当なし。

ガザイバ点滴静注1000 mg
（オビヌツズマブ（遺伝子組換え））
［CD20陽性の B 細胞性濾胞性リンパ腫］

第2部　（モジュール2）：CTD の概要（サマリー）

2.7.6 個々の試験のまとめ

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2.7.6 個々の試験のまとめ

本項では，ガザイバ点滴静注1000 mg（以下，本剤）に関する臨床試験一覧表（表 2.7.6-1）及び個々の試験の概要（2.7.6.1）を記載した。なお，参考として本項では，本剤の単剤投与時の薬物動態，安全性，有効性の検討を試験目的に含む，海外で実施された試験（YP25623試験）についても記載した。

本項の付録2.7.6.2.1では，すべての評価資料についての因果関係を問わないすべての有害事象と因果関係が否定できない有害事象を，事象名を日本語表記として試験ごとに示した。なお，BO21900試験，BO20999試験，BO21003試験，BO21000試験の総括報告書では，治験薬投与中から投与終了後24時間以内に発現した有害事象の内，因果関係が否定できない事象を，有害事象の集計の際にすべて基本語（以下，PT）の「INFUSION RELATED REACTION」と読替えて集計していたため，本項では読替えを行わずに解析した結果を示した（5.3.5.1-2，5.3.5.3-1及び5.3.5.4-5参照）。

本項の付録2.7.6.2.2では，国内で実施した JO21900試験，JO29737試験で発現した，因果関係を問わない死亡及び重篤な有害事象の叙述を示した。

表 2.7.6-1 臨床試験一覧表

地域	試験番号 (試験略称)	相 (依頼者)	試験 デザイン	対象	登録 例数	治療群	主要評価項目	治験実施期間	CTD 番号 <資料区分>
国内	JO21900	I (中外)	非盲検 用量漸増	再発・治療抵抗性の CD20陽性 NHL	12	本剤群	安全性	2008年[redacted]月[redacted]日～2011年[redacted]月[redacted]日	5.3.3.2-1 <評価>
国内	JO29737 (GATS)	II (中外)	非盲検 単群	未治療の CD20陽性 NHL	36	G–CHOP 療法群	安全性・PK	2015年[redacted]月[redacted]日～2016年[redacted]月[redacted]日	5.3.3.2-2 <評価>
海外・ 国内	BO21223 (GALLIUM)	III (Roche,中外)	ランダム化 非盲検 2群	未治療の CD20陽性 進行期 iNHL	1401	G–化学療法群 R–化学療法群	FL の PFS	2011年7月6日～ (実施中)	5.3.5.1-1 <評価>
海外	GAO4753g (GADOLIN)	III (Roche)	ランダム化 非盲検 2群	リツキシマブ治療抵 抗性の CD20陽性 iNHL	396 [a)]	G–B 療法群 Benda 群	PFS	2010年4月15日～ (実施中)	5.3.5.1-3 <評価>
海外	GAO4915g (GATHER)	II (Roche)	非盲検 単群	未治療の CD20陽性 進行期 DLBCL	100	G–CHOP 療法群	完全奏効率 全奏効率	2011年8月10日～ (実施中)	5.3.5.2-1 <評価>
海外	BO20999 (GAUGUIN)	I/II (Roche)	PI：非盲検 用量漸増 PII：ランダム化 非盲検 2群 [b)] 再投与：非盲検 単群	再発・治療抵抗性の CD20陽性 NHL [b)]	PI：21 [b)] PII：80 [b)] 再投 与：11 [b)]	PI：本剤群 PII： 本剤低用量群 [c)] 本剤高用量群 [d)] 再投与：本剤群	PI：安全性・ 忍容性 PII：全奏効 率・安全性	PI：2007年9月[redacted]日～2012年3月31日 PII：2008年12月[redacted]日～2012年3月31日 再投与：2009年10月12日～2013年11 月25日	5.3.5.4-1 <参考>
海外	BO21003 (GAUSS)	I/II (Roche)	PI：非盲検 用量漸増 PII：ランダム化 非盲検 2群 [b)]	再発・治療抵抗性の CD20陽性 NHL [b), e)]	PI：17 [b)] PII：175	PI：本剤群 PII： 本剤群 リツキシマブ群	PI：安全性・ 忍容性 PII：全奏効 率・安全性	PI：2008年1月[redacted]日～[redacted]年[redacted]月[redacted]日 PII：2009年6月24日～2013年3月14日	5.3.5.4-2 <参考>
海外	BO21000 (GAUDI)	Ib (Roche)	ランダム化 非盲検 6群	再発・治療抵抗性, 未治療の CD20陽性 B 細胞性 FL	56 [f)] 81 [g)]	G–CHOP 療法群 [f), g)] G–FC 療法群 [f)] G–B 療法群 [g)]	安全性	2009年2月[redacted]日～2015年11月[redacted]日	5.3.5.4-3 <参考>
海外・ 国内	BO21005 (GOYA)	III (Roche,中外)	ランダム化 非盲検 2群	未治療の CD20陽性 DLBCL	1418	G–CHOP 療法群 R–CHOP 療法群	PFS	2011年7月25日～ (実施中)	5.3.5.4-4 <参考>
海外	YP25623 (GERSHWIN)	I (Roche)	非盲検 単群	再発・治療抵抗性の CD20陽性 NHL [b)]	36 [b)]	本剤群	PK	2012年9月6日～2014年12月[redacted]日	5.3.5.4-6 <参考>

NHL：非ホジキンリンパ腫，G-CHOP：本剤，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／プレドニゾン／メチルプレドニゾロン併用，PK：薬物動態，iNHL：低

悪性度 NHL，G–化学療法：本剤，化学療法（CHOP 療法，CVP 療法，ベンダムスチン）併用療法 + 本剤維持療法，R–化学療法：リツキシマブ，化学療法（CHOP 療法，CVP 療法，ベンダムスチン）併用療法 + リツキシマブ維持療法，FL：濾胞性リンパ腫，PFS：無増悪生存期間，G–B：本剤，ベンダムスチン併用，Benda：ベンダムスチン単剤療法，DLBCL：びまん性大細胞型 B 細胞性リンパ腫，G-FC：本剤，フルダラビン，シクロホスファミド併用，R-CHOP：リツキシマブ，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／プレドニゾン／メチルプレドニゾロン併用

a) 主要解析時点の登録例数
b) NHL を対象としたパートのみ
c) 本剤400 mg/body，NHL を対象としたパートのみ
d) 本剤1600 mg/body（サイクル1 Day 1及び Day 8），本剤800 mg/body（サイクル2 Day 1以降），NHL を対象としたパートのみ
e) PII は再発・治療抵抗性 CD20陽性 iNHL 対象
f) 再発・治療抵抗性患者対象，本剤400 mg/body の低用量群と本剤1600 mg/body（サイクル1 Day 1及び Day 8），本剤800 mg/body（サイクル2 Day 1以降）の高用量群の2群
g) 未治療患者対象

2.7.6.1　概要

2.7.6.1.1　JO21900試験

(1) 試験の標題

RO5072759の CD20陽性 B 細胞性非ホジキンリンパ腫を対象とした第 I 相臨床試験

(2) フェーズ

第 I 相

(3) 治験依頼者及び治験実施施設

中外製薬株式会社／国内3施設

(4) 公表

なし

(5) 治験実施期間

2008年[redacted]月[redacted]日～2011年[redacted]月[redacted]日

(6) 目的

非ホジキンリンパ腫（NHL）を対象として，RO5072759単剤の静脈投与時における安全性，忍容性，薬物動態（以下，PK）及び有効性を検討する。

(7) 治験方法

多施設非盲検漸増試験

(8) 被験者数

目標被験者数 計12～24例（1群3～6例，最大4群）

登録被験者数 計12例

（コホート1：3例，コホート2：3例，コホート3：3例，コホート4：3例）

(9) 診断及び主な組入れ基準

選択基準

1) 本治験内容について十分な説明を受け，本人の文書による同意が得られている患者。
2) 組織診で悪性リンパ腫と診断され，フローサイトメトリーあるいは免疫組織化学検査により CD20陽性が確認された B 細胞性 NHL で，他に優先すべき治療法がない患者。
3) リツキシマブを含む治療における再発*あるいは抵抗性**の患者。
   *再発：24週間以上の完全奏効（CR），不確定完全奏効（CRu），部分奏効（PR）が認められた場合
   **抵抗性：治療中の病勢進行若しくは治療の最終投与後24週間未満に病勢安定（SD），PR，CRu，CR から病勢進行が認められた場合
4) 少なくとも1つの測定可能病変［コンピュータ断層撮影（CT）にて直交する2方向で計測可能で腫瘍の最大径が1.5 cm を超える］を有する患者。
5) 同意取得時の年齢が満20歳以上75歳未満の患者。
6) Eastern Cooperative Oncology Group（ECOG）Performance Status（PS）が0～1の患者。
7) 登録日から12週間以上の生存が可能と判断された患者。
8) 登録前2週間以内の主要臓器機能について，以下の基準を満たしていることとした。なお，当該期間内に検査結果が複数存在する場合は登録前直近のものを採用した。
   ① クレアチニンクリアランス（Cockcroft-Gault 式）50 mL/分を超える

② アスパラギン酸アミノトランスフェラーゼ（AST），アラニンアミノトランスフェラーゼ（ALT）施設基準値上限の2.5倍以下
③ 血小板数 $7.5 \times 10^4/mm^3$以上
④ 好中球数 $1.5 \times 10^4/mm^3$以上
⑤ ヘモグロビン 10 g/dL 以上

除外基準

1) 登録前24週間以内にモノクローナル抗体療法の治験薬の投与を受けた患者，あるいは登録前4週間以内に他の治験薬にて治療を受けた患者。
2) 何らかの癌治療用ワクチンの投与を受けたことがある患者。
3) 原疾患に対し同種造血幹細胞移植を受けたことがある患者。
4) 登録前8週間以内にリツキシマブの投与を受けた患者，あるいは登録前12週間以内に何らかの放射性免疫療法を受けた患者。
5) 登録前4週間以内に化学療法又は放射線療法を受けた患者。
6) ヒト化，マウスーヒトキメラ型若しくはマウスモノクローナル抗体に対して重篤なアレルギーあるいはアナフィラキシー反応の既往歴のある患者。マウス由来製品に過敏症あるいはアレルギーがあることが分かっている患者。
7) 原疾患による中枢神経系浸潤の症状を有する患者。
8) 無病期間が5年未満の重複癌を有する患者（治癒している皮膚基底細胞癌あるいは子宮頸部上皮内癌の既往のある患者は除く）。
9) 重篤な心疾患（New York Heart Association Class III 若しくは IV 度の心臓系疾患，登録前24週間以内に心筋梗塞，不安定不整脈，不安定狭心症と診断されている）を有する患者。
10) 症候性気管支痙攣（既往も含む），閉塞性肺疾患又は治療を要する肺疾患を有する患者。
11) 治療を要する，あるいは症状のある感染症を有する患者（表在性の真菌感染（白癬等）は除く），あるいは登録前4週間以内に，入院加療又は抗生物質の静脈内投与を必要とした感染歴のある患者。
12) 登録前4週間以内に全身麻酔が必要な外科手術を受けた患者。
13) ヒト免疫不全ウイルス（HIV）抗原陽性，HIV 抗体陽性，HBs 抗原陽性，HBc 抗体陽性，B 型肝炎ウイルス（HBV）-DNA 陽性，あるいは C 型肝炎ウイルス（HCV）抗体陽性の患者。
14) 腫瘍細胞数が$25{,}000/mm^3$を超える患者。ただし，節性病変のみの患者6例が本剤の投与を受け，治験依頼者及び医学専門家により安全性及び忍容性を確認した後，治験責任医師の判断により登録することができる。
15) 妊娠中若しくは授乳中の患者。なお，妊娠検査は過去1年以内に月経のあった女性を対象に実施する。
16) 治験期間中及び RO5072759最終投与後少なくとも48週間にわたり避妊する意思のない患者。
17) その他，治験責任医師又は治験分担医師が本治験への参加が不適当と認めた患者。

(10) 被験薬の用量，投与方法及び投与期間

1) RO5072759（以下，RO5072759又は本剤）

本剤は1バイアル中に RO5072759を50 mg 含有する注射剤（凍結乾燥製剤）である。バイアル中の本剤を注射用水で溶解し，日局生理食塩液に加え最終濃度が0.2～8 mg/mL になるよう希釈した。

2) 用量，投与方法及び投与期間

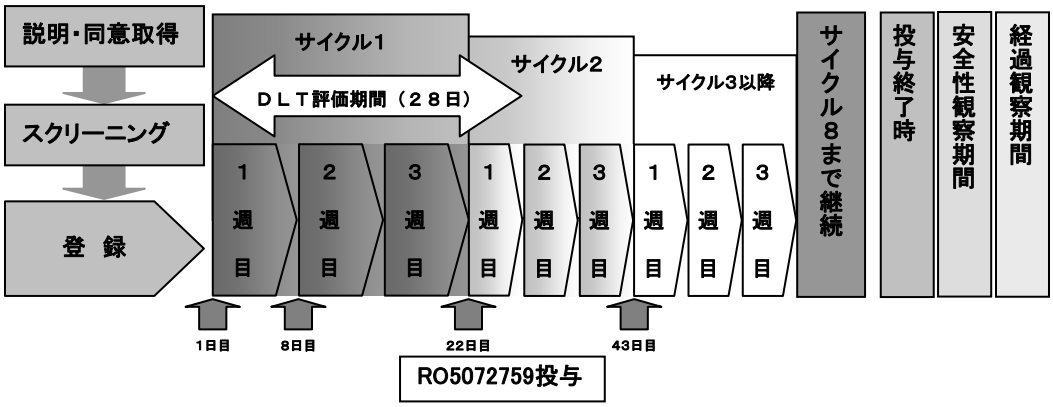
本剤を3週間ごとに8サイクル投与した。ただしサイクル1では Day1及び Day8に本剤を投与した。合計投与回数は9回とした。

本剤の投与量

コホート1：初回投与量 200 mg	2回目以降の投与量　400 mg
コホート2：初回投与量 400 mg	2回目以降の投与量　800 mg
コホート3：初回投与量 800 mg	2回目以降の投与量　1200 mg
コホート4：初回投与量 1200 mg	2回目以降の投与量　2000 mg

すべての被験者において，本剤投与前に解熱鎮痛剤（カロナール®）及び抗ヒスタミン剤（ポララミン®）を投与した。

図 2.7.6.1.1-1　治験スケジュール



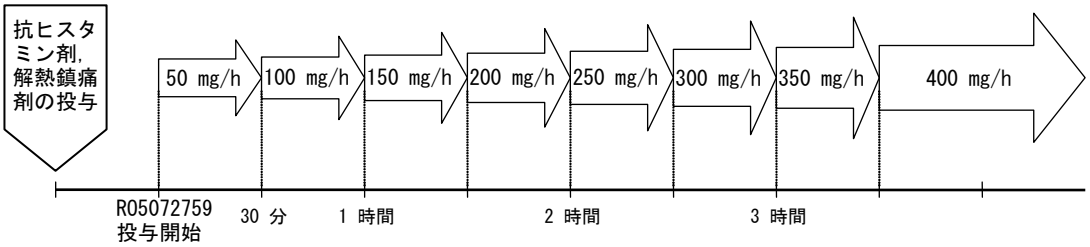
3)　投与時間

初回投与：最初の30分は50 mg/時間の速度で点滴静注を開始し，Infusion reaction（投与開始後に発現するアレルギー反応/過敏症，発熱，疼痛，気管支攣縮，喘鳴，低酸素症等，Infusion-related reaction，以降 IRR）に十分な注意を払った。問題所見がない場合は30分ごとに50 mg/時間ずつ投与速度を上げることができるが，上限は400 mg/時間とした。

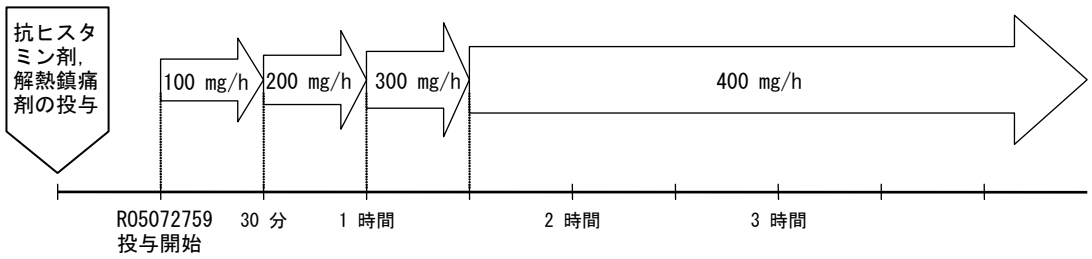
2回目以降：前回投与にて投与中断/処置を要する IRR が発現していない場合は，最初の30分は100 mg/時間の速度で点滴静注を開始し，問題所見がない場合には30分ごとに100 mg/時間ずつ速度を上げることができるが，上限は400 mg/時間とした。前回投与にて投与中断/処置を要する IRR が発現した場合は，初回投与の投与方法に準じて実施することとした。

図 2.7.6.1.1-2　RO5072759点滴速度

初回投与時



2回目以降の投与時



4) コホート移行規定；

コホート移行の可否は，各コホートの本剤初回投与から28日目までに認められた因果関係の否定できない用量制限毒性（DLT）の発現状況を基に最大耐量（MTD）を判定し，決定した。コホート移行に関しては，必要に応じて効果安全性評価委員会の意見を求めることとした。

DLT には，下記に示すとおり初回投与時の IRR に関する DLT_1とそれ以外の DLT_2があり，各々の DLT 発現状況により，初回投与量の MTD1及び2回目以降の投与量の MTD_2を決定するが，コホート移行は DLT_2の発現状況により決定した。すなわち，2例以上に DLT_2が認められた場合のみ，次コホートへの移行は行わないこととした。DLT_1及び DLT_2の発現状況に応じた対応を以下に示した。

なお，各コホート2例目以降は，最初の被験者の初回投与後15日間経過するまで投与できないものとした。また，1例目に DLT が発現した場合には2例目以降の投与は同日には行わないこととした。

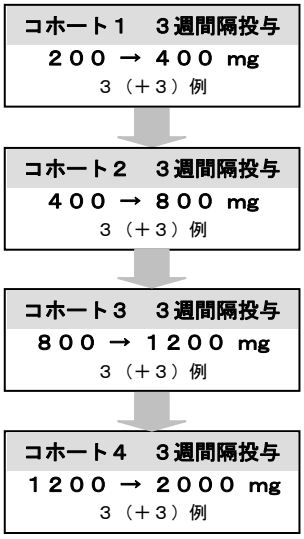
① 3例中 DLT_1及び DLT_2が0例の場合，次コホートに移行し，規定の投与量を投与する。
② 3例中1例に DLT_1あるいは DLT_2が発現した場合は，該当する DLT の評価可能症例が6例になるよう被験者を追加し，検討を行う。

- DLT_1及び DLT_2が各々1例発現した場合は，次コホートに移行し，規定の投与量を投与する。
- DLT_1が2例以上に認められた場合は，前コホートの初回投与量を MTD_1とし，次コホートに移行する。次コホートの初回投与量は MTD_1にて実施し，2回目以降の投与量は計画に従い増量する。なお，次コホート以降の初回投与量は MTD_1にて実施する。
- DLT_2が2例以上に認められた場合は，前コホートの2回目以降の投与量を MTD_2とし，次コホートへの移行は行わない。MTD_2決定後，当該コホートの被験者の投与は MTD_2にて実施する。

③ 3例中2例に DLT が発現し，その内1例は DLT_1で，他の1例は DLT_2であった場合は，各々の評価可能症例が6例になるよう被験者を追加し，検討を行う。追加した被験者に DLT が認められた場合には，その DLT のタイプにより MTD_1あるいは MTD_2であるかを判定する。

なお，DLT_2が2例発現した時点で当該コホートの更なる被験者の登録は行わないこととした。また，コホート1にて DLT が2例発現した場合は，効果安全性評価委員会にて治験実施計画書の変更について検討を行うこととした。

図 2.7.6.1.1-3　治験全体の流れ



- DLT は本剤初回投与から28日目までに発現した因果関係の否定できない有害事象に限定する。
- 各コホートの最初の被験者が DLT を発現せずに15日間経過した後，次の2例の被験者を登録することができる。
- 3例中1例に DLT が発現した場合は更に被験者を3例追加し，DLT が発現していないことを確認後，次のコホートへ移行する。
- 6例中2例以上で DLT が観察された場合には MTD を超えたものとみなす。
- 各コホートの最後の被験者が投与開始後28日間経過し，DLT を発現していないことを確認した後，次のコホートへ移行することができる。

DLT の定義

DLT は投与開始後28日間に発現した有害事象に基づき判定した。初回投与により発現した DLT_1とそれ以外の DLT_2とで定義が異なる。DLT の有害事象 Grade は Common Terminology Criteria for Adverse Events（CTCAE）v3.0により判定し，治験薬との関連が明らかに否定できるもの（因果関係判定「関連なし」）を除いた。DLT の判定に際しては医学専門家と治験依頼者の協議により最終的に決定するものとした。

5) DLT_1の定義

初回投与により発現した IRR を DLT_1と定義し，MTD_1の判定に用いた。

- 初回投与中若しくは投与開始後24時間以内に発現した Grade 4の IRR（アレルギー/過敏反応，発熱，疼痛，気管支痙攣，喘鳴，低酸素症等）
- 初回投与中若しくは投与開始後24時間以内に発現した Grade 3の IRR で，点滴速度を減じ，副腎皮質ステロイド等の対症療法を行っても軽快しないもの

6) DLT_2の定義

初回投与の IRR 以外の DLT を DLT_2と定義し，MTD_2の判定に用いた。

- RO5072759に起因する Grade 4の有害事象。ただし以下のものを除く。
  - Grade 4のリンパ球減少症
  - 発熱性好中球減少症に至らない Grade 4の好中球減少症で，G-CSF の投与を行わずに1週間以内に Grade 3に回復し，更に1週間以内に Grade 2以下に軽快したもの
  - 出血を伴わない Grade 4の血小板減少症で血小板輸血をせずに1週間以内に Grade 3に回復し，更に1週間以内に Grade 2以下に軽快したもの
- RO5072759に起因する Grade 3の有害事象。ただし以下のものを除く。
  - Grade 3のリンパ球減少症
  - 発熱性好中球減少症に至らない Grade 3の好中球減少症で，G-CSF の投与を行わずに1週間以内に Grade 2以下に軽快したもの
  - 出血を伴わない Grade 3の血小板減少症で血小板輸血をせずに1週間以内に Grade 2以下に軽快したもの
  - 投与中若しくは投与開始後24時間以内に発現した Grade 3の IRR（アレルギー/過敏反

応，発熱，疼痛，気管支痙攣，喘鳴，低酸素症等）で，点滴速度を減じ，副腎皮質ステロイド等の対症療法を行って軽快したもの

(11) 治療期間

各被験者の治験期間は，同意取得日から最終観察日までとした。

治験中の期間について以下のとおり定義した。

- スクリーニング期間：同意取得日から本剤投与開始前まで
- 治験薬投与期間：本剤投与開始から本剤最終投与後28日目の検査終了まで
- 安全性観察期間：本剤最終投与後28日目の検査終了後から本剤最終投与後28週まで
- 経過観察期間：本剤最終投与後29週から B 細胞回復後24週間が経過するまで

経過観察は，安全性観察期間終了時（本剤最終投与後28週）に B 細胞数が回復していない，若しくは B 細胞数回復後24週間が経過していない被験者において実施することとした。経過観察期間は B 細胞数回復後24週間が経過するまで，ただし最大本剤最終投与から76週間後までとした。

なお，被験者に対する次の治療を開始する必要が生じた場合には，次の治療開始前日までを各被験者の治験期間とした。

(12) 対照薬の用量及び投与方法

本治験は対照薬を用いなかったため該当しない。

(13) 評価基準

主要評価項目

1) 安全性

CTCAE v3.0を用いて下記項目を評価した。

① 各投与量段階における DLT（DLT_1及び DLT_2）の発現頻度
② DLT 発現頻度によって判断される MTD（MTD_1及び MTD_2）
③ 有害事象の種類，Grade，発現頻度

副次的評価項目

2) PK

- 血清中 RO5072759濃度推移及びその要約統計量（算術平均値，幾何平均，標準偏差，変動係数，中央値，最小値，最大値）
- PK パラメータ及び要約統計量（算術平均値，幾何平均，標準偏差，変動係数，中央値，最小値，最大値）
- PK パラメータに基づく線形性
- 反復投与後の定常状態到達時期と血清中 RO5072759累積性

3) 薬力学

CD19陽性 B 細胞数と初期値からの変化率を算出し，要約統計量を算出した。それぞれの値と患者背景，血清中 RO5072759トラフ濃度，投与量，AUC 等，PK パラメータとの関係について検討した。

4) 有効性

RO5072759投与による抗腫瘍効果の予備データ収集のため，以下の項目を評価した。

① 奏効率
② 完全奏効率

(14) 統計的手法

1) 被験者特性

集計，要約した。

2) 有効性

奏効率及び完全奏効率の点推定値とその95%信頼区間を推定した。

3) 安全性

主要評価項目である DLT に関しては，コホートごとに発現頻度と発現割合を集計し，MTD の推定の根拠とした。DLT を含む他の有害事象のプロファイルに関しても，コホートごと及び全被験者について発現頻度と発現割合を集計した。

4) PK

血清中 RO5072759濃度及びコンパートメントに依存しない方法を用いて PK パラメータを算出し，要約統計量（算術平均値，幾何平均，標準偏差，変動係数，中央値，最小値，最大値）を求めた。また，血清中 RO5072759濃度のトラフ濃度の推移を検討した。PK パラメータについて用量間の線形性並びに反復投与後の定常状態の評価を行い，血清中 RO5072759累積性を検討した。

(15) 中間集計

中間集計は，全症例の DLT 評価期間（初回投与から28日間）が終了した時点，全症例の投与期間（治験薬最終投与から28日後）が終了した時点，全症例の安全性観察期間が終了した時点の計三回，症例検討会（治験総括報告書 付録「16.4 本治験に関わる検討会等の議事録」参照）を開催し，安全性について検討した。

(16) 結果の要約／結論

1) 有効性

- 投与終了時点での奏効例は12例中7例であり，CR が2例，PR が5例で，奏効率は58.3%（95%CI：27.7～84.8%）であった。奏効例の内訳は，コホート1の2例，コホート2の2例，コホート4の3例であった。濾胞性リンパ腫（以下，FL）の被験者8例の内，奏効例は6例であった。
- 投与終了時点での完全奏効例は12例中2例であり，完全奏効率は16.7%（95%CI：2.1～48.4%）であった。完全奏効例の内訳は，コホート2の2例であった。FL の被験者8例の内，投与終了時点での完全奏効例は2例であった。
- リツキシマブ治療抵抗性の患者が2例登録され，その内1例で奏効（PR）がみられた。

2) 安全性

- 本治験では，コホート1（200/400 mg）で3例，コホート2（400/800 mg）で3例，コホート3（800/1200 mg）で3例，コホート4（1200/2000 mg）で3例，計12例の被験者に本剤が投与され，これら12例すべてが安全性評価及び DLT 評価の対象となった。
- DLT 評価期間である投与開始後28日間で，DLT_1及び DLT_2に該当する副作用は認められず，当該試験の最高用量（1200/2000 mg）まで MTD_1及び MTD_2には至らなかった。なお，DLT 評価期間以外で DLT の定義に該当する副作用は2例（コホート2；1例，コホート4；1例）に認められ，それぞれ Grade 4の好中球数減少，Grade 3の好中球数減少であった。
- 投与期間中（初回投与から最終投与後28日目まで）に発現した有害事象は，全12例に81件であり，コホート1では3例中3例に14件，コホート2では3例中3例に19件，コホート3では3例中3例に30件及びコホート4では3例中3例に18件発現した。その内，4例以上に発現した有害事象は，IRR（12/12例），白血球数減少（8/12例），好中球数減少（6/12例），血小板数減少（5/12例），ALT 増加（4/12例）及びヘモグロビン減少（4/12例）

であった。

- 投与期間中に発現した副作用は，全12例に71件であり，コホート1では3例中3例に12件，コホート2では3例中3例に18件，コホート3では3例中3例に25件，コホート4では3例中3例に16件発現した。その内4例以上に発現した副作用は，IRR（12例），白血球数減少（8例），好中球数減少（6例），血小板数減少（5例），ヘモグロビン減少（4例）であった。
- 投与期間中に発現した Grade 3以上の有害事象は，12例中4例に8件であり，この内，Grade 3の有害事象は12例中4例に7件，Grade 4の有害事象は12例中1例に1件であった。Grade 3の有害事象は，IRR（2/12例），白血球数減少（2/12例），好中球数減少（1/12例），血小板数減少（1/12例）及び血中リン減少（1/12例）であり，Grade 4の有害事象は好中球数減少（1/12例）であった。
- 投与期間中に発現した Grade 3以上の因果関係の否定できない有害事象（副作用）は，12例中4例に7件であり，この内，Grade 3の副作用は12例中4例に6件，Grade 4の副作用は12例中1例に1件であり，Grade 5の副作用は認められなかった。Grade 3の副作用は，IRR（2/12例），白血球数減少（2/12例），好中球数減少（1/12例）及び血小板数減少（1/12例）であり，Grade 4の副作用は好中球数減少（1/12例）であった。
- IRR は全12例に発現し，重症度は Grade 1が3例，Grade 2が7例，Grade 3が2例に発現し，Grade 4は認められなかった。IRR の症状は全12例に53件発現し，4例以上に発現した IRR の症状の SOC は，全身障害および投与局所様態（11例21件），血管障害（6例9件），胃腸障害（4例6件），神経系障害（4例5件）であり，4例以上に発現した症状の PT は，発熱（10/12例），悪寒（6/12例）及び潮紅（4/12例）であった。Grade 3以上の症状は認められず，総合的には Grade 3の IRR と判定された2例で発現した各症状は，すべて Grade 2以下と判定された。初回投与時には，IRR は全12例に発現し，症状は45件発現した。主な症状は発熱（10/12例），悪寒（6/12例）及び潮紅（4/12例）であった。全45件の症状の内，37件が Grade 1，8件が Grade 2であった。投与2回目以降は，IRR は12例中5例に発現し，症状は13件発現した。主な症状は高血圧（2/5例）であった。全13件の症状の内，すべてが Grade 1であった。
- 感染症は，全コホートを合わせ，治験期間中に12例中7例に11件発現し，鼻咽頭炎（7例），胃腸炎（1例），上気道感染（1例），帯状疱疹（1例）及び胃不快感（1例）であった。この内，Grade 3の感染症は帯状疱疹（1例）のみであり，他はすべて Grade 1であった。投与期間中では，全コホートを合わせ，12例中3例に3件の感染症が発現し，すべて Grade 1の鼻咽頭炎（3例，コホート1で1件，コホート2で2件）であった。
- 重篤な有害事象は，2例2件であり，帯状疱疹及び左中大脳動脈瘤であった。この内，因果関係が否定できないものは帯状疱疹のみであった。
- 本治験では減量を許容していないため，減量を要する有害事象はなかった。

3) PK

- RO5072759の曝露量（AUC_{last}）は，一部，コホート1からコホート2にかけては用量比以上の増加を示したものの，コホート1からコホート4の用量範囲で総じて用量比例性を示した。
- 体重及び体表面積の増加に応じて，緩やかに分布容積が増加する傾向が認められた。
- 海外臨床試験（BO20999試験）と本治験の AUC_{last} に明確な差異は認められなかったことから，RO5072759の PK は民族差の影響を受ける可能性は低いと考えられた。
- いずれの被験者も，CD19陽性 B 細胞数は初回投与後に速やかに低下し，投与期間中低値を維持した。

(17) 報告書作成日

[redacted]年[redacted]月[redacted]日

2.7.6.1.2　JO29737試験（GATS 試験）

(1) 試験の標題

CD20陽性非ホジキンリンパ腫を対象としたオビヌツズマブ（RO5072759）の投与時間短縮を検討する第 II 相臨床試験

(2) フェーズ

第 II 相

(3) 治験依頼者及び治験実施地域

中外製薬株式会社／国内8施設

(4) 公表

なし

(5) 治験実施期間

2015年[redacted]月[redacted]日～2016年[redacted]月[redacted]日

(6) 目的

主要目的

本治験の主要目的は以下のとおりである。

- サイクル2からオビヌツズマブの投与時間短縮投与（Shorter Duration of Infusion，以下 SDI）を開始した被験者（以下，SDI 移行例）の，サイクル2における Grade 3以上の Infusion reaction（Infusion-related reaction，以降 IRR）の発現割合に基づく忍容性の検討
- SDI 移行例のサイトカイン（TNFα，IFNγ，IL6，IL8，IL10）推移の国内外臨床試験結果との比較
- SDI 移行例のサイクル2 Day 12までに集積された血清中オビヌツズマブ濃度及びオビヌツズマブの薬物動態学的パラメータの国内外臨床試験結果との類似性の検討

副次的目的

本治験の副次的目的は以下のとおりである。

- 投与方法を問わず，オビヌツズマブ投与時に認められた有害事象の発現状況の評価
- オビヌツズマブの SDI 時の IRR 発現状況の評価
- 投与終了時の奏効率及び最良総合効果に基づく奏効率の評価

(7) 治験方法

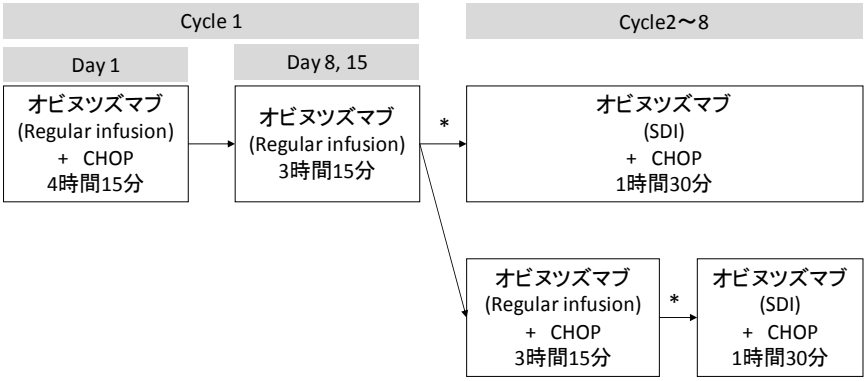
本治験は，未治療の CD20陽性 B 細胞性非ホジキンリンパ腫（NHL）患者に対して，CHOP 療法の併用下においてオビヌツズマブの SDI の忍容性を確認することを目的とした多施設共同第 II 相臨床試験であった。

本治験では，サイクル1の Day 1，Day 8，Day 15に，標準時間点滴投与（regular infusion）の方法でオビヌツズマブ1000 mg の投与を Day 1では約4時間15分，Day 8及び Day 15では約3時間15分で行った。サイクル1を完遂したすべての被験者に対して，サイクル2の Day 1における投与開始前に SDI 実施基準に合致するか否かを評価した。SDI 実施基準に合致した被験者はサイクル2 Day 1に SDI の方法でオビヌツズマブ1000 mg の投与を約1時間30分で行った。SDI に対して忍容性を示した被験者に対しては，以降サイクル8まで SDI を継続した。CHOP 療法はサイクル1から6までの各 Day 1に投与した。CHOP 療法のプレドニゾロンについては Day 2～5に

も投与した。

サイクル2 Day 1における投与開始前に SDI 実施基準に合致しなかった被験者も，その後 SDI 実施基準を満たせば，投与サイクルに係わらず SDI へ移行可能とした。

図 2.7.6.1.2-1　治験デザイン



*SDI実施基準を満たした場合

(8) 被験者数

目標例数：36例

登録例数：36例，投与例数：35例

(9) 診断及び主な組入れ基準

選択基準

下記項目のすべてに該当する被験者を本治験の対象とした。

1) 本治験内容について十分な説明を受け，本人の文書による同意が得られている。
2) 同意取得時の年齢が20歳以上。
3) ECOG PS が0～2。
4) 登録日から12カ月以上の生存が見込める。
5) 組織学的に確認された CD20陽性 B 細胞性非ホジキンリンパ腫（びまん性大細胞型 B 細胞リンパ腫［DLBCL］，FL，辺縁帯リンパ腫［MZL］）であり，前治療歴を有さない。
6) 登録前2週間以内の主要臓器機能が以下の基準を満たしている（異常所見が NHL に起因する場合を除く）。なお，当該期間内に検査結果が複数存在する場合は，登録前直近のものを採用することとする。
   ① 好中球数　1500/μL 以上
   ② 末梢リンパ球数　5000/μL 未満
   ③ 血小板数　75000/μL 以上
   ④ ヘモグロビン　9.0 g/dL 以上
   ⑤ 総ビリルビン　施設基準値上限の1.5倍以下
   ⑥ AST，ALT　施設基準値上限の2.5倍以下
   ⑦ 血清クレアチニン　施設基準値上限の1.5倍以下
   ⑧ PT-INR，APTT　施設基準値上限の1.5倍以下
7) 十分な心機能を有する（心エコー又は MUGA により算出した左室駆出率が50%以上）
8) 登録時に，処置の終了日から少なくとも以下の期間が経過している。
   ① 手術療法　4週間
   開胸・開腹を要する，又は腹腔鏡下で臓器切除を伴うなどの大手術。ただし，大手術を除く切開を伴う処置（ポート留置を含む）は，登録時点で出血のリスクがないと判

断できるまで回復している場合は登録可能とする。

② 免疫抑制療法　4週間
シクロホスファミド，アザチオプリン，メトトレキサート，サリドマイドを含む。ただし，局所的，若しくは低用量の副腎皮質ステロイド等は許容する。

③ モノクローナル抗体　12週間

④ 生ワクチン製剤　4週間

⑤ 他の治験薬　4週間

除外基準

下記項目のいずれかに該当する被験者は，本治験から除外した。

1) オビヌツズマブに含まれる成分（ヒスチジン，トレハロース，ポロキサマー188）や，チャイニーズハムスター卵巣細胞由来の薬剤，又は他の遺伝子組換えモノクローナル抗体に対する過敏症又はアレルギーの既往を有する，又は禁忌である。
2) アントラサイクリン系薬剤，及び CHOP 療法の各薬剤のいずれかに対する過敏症の既往を有する，又は禁忌である。
3) リンパ節生検及び局所放射線照射を除く，NHL に対する治療歴を有する。
4) 原発性中枢神経系リンパ腫及び悪性リンパ腫の二次性中枢神経系浸潤又は軟膜リンパ腫を有する。
5) リンパ腫以外の疾患（関節リウマチ等）に対する細胞傷害性薬剤又はリツキシマブの投与歴，又は抗 CD20抗体の投与歴がある。
6) リンパ腫症状のコントロール以外を目的とした30 mg/日を超えるプレドニゾロン又は同等量の副腎皮質ステロイド剤を投与されている。ただし，30 mg/日以下のプレドニゾロン又は同等量の副腎皮質ステロイド剤が投与されている患者については，初回投与（サイクル 1 Day 1）前の少なくとも4週間の期間にわたって投与量が一定量である場合は許容する。
治験薬投与開始前に，リンパ腫の症状緩和に対して副腎皮質ステロイド剤による緊急治療を要する場合，100 mg/日を上限とするプレドニゾロン単剤又は同等量の副腎皮質ステロイド剤について一時的な使用を許容する。
7) 抗生物質，抗真菌剤又は抗ウイルス剤等の全身投与を要する活動性の感染症を有する。
8) 登録前4週間以内に，入院加療又は抗生物質の静脈内投与を必要とした感染症の病歴がある。
9) 治験結果の解釈に影響を及ぼし得る炎症性自己免疫疾患（関節リウマチ，全身性エリテマトーデス等，治験期間中に免疫抑制剤による治療を要する）を有する。
10) HBs 抗原，HBs 抗体，HBc 抗体又は HCV 抗体陽性である。ただし，HBs 抗体陽性がワクチン接種によるものであることが明らかな場合，HBs 抗体及び／又は HBc 抗体のみ陽性で HBV–DNA が検出されない場合は適格とする。HCV 抗体陽性の場合は PCR 検査で HCV-RNA が検出されない場合は適格とする。
11) HIV 感染が既知である。
12) ヒト T 細胞白血病ウイルス1型（HTLV-1）陽性である。
13) 進行性多巣性白質脳症（PML）の確定診断歴を有する。
14) 重大な心疾患*や肺疾患**等，治験結果の解釈に影響を及ぼし得る重大かつコントロール不良な合併症又は既往を有する。
    * New York Heart Association（NYHA）分類クラス III 以上の心臓系疾患，コントロール不良な不整脈，不安定狭心症等の合併，又は登録前6カ月以内の心筋梗塞の既往及び合併
    **閉塞性肺疾患又は治療を要する肺疾患の合併，症候性気管支痙攣の合併及び既往
15) コントロール不能な糖尿病を有する。
16) 妊婦，授乳中の女性（授乳中の女性については，治験期間中及び治験薬の最終投与後18カ月間，授乳を中止することに同意した患者は除く）。

17) 妊娠検査陽性の女性（登録前12カ月以内に月経があった妊娠する可能性のある女性は妊娠検査を実施する。ただし，12カ月以内に月経がない場合でも化学閉経等の理由により妊娠の可能性が否定できない女性は妊娠検査を実施する）。
18) 男性で，治験期間中及び治験薬の最終投与後3カ月間，適切な避妊法を用いる意思がない。又は妊娠する可能性のある女性で，治験期間中及び治験薬の最終投与後18カ月間，適切な避妊法を用いる意思がない。
19) その他悪性腫瘍の既往又は合併を有する。ただし，内視鏡的粘膜切除術により完全切除した消化器癌，完全切除した子宮頚部の上皮内癌，前立腺切除術を施行した前立腺癌，完全切除した皮膚の基底／扁平上皮癌，及び根治目的で外科的処置のみが施行されその後無治療で2年以上無再発の場合等は除く。
20) その他，治験責任医師又は治験分担医師が本治験への参加を不適切と判断した場合。

(10) 被験薬の用量，投与方法及び投与期間

- 投与方法

一定用量として1000 mg のオビヌツズマブを3週間ごとに8サイクル点滴静注投与した。ただしサイクル1では Day 8，Day 15にもオビヌツズマブを投与し，合計投与回数は10回とした。サイクル1は regular infusion で投与し，以下の SDI 実施基準に合致した患者はサイクル2以降に SDI を実施した。なお，オビヌツズマブの被験者への投与は，緊急時に蘇生設備が直ちに利用できるような臨床環境（入院又は外来）において行い，被験者は常に主治医の密接な管理下においた。

オビヌツズマブの投与中に有害事象が発現した被験者においては，必要に応じ，翌日に続けて投与してもよいこととした。サイクル1 Day 1のオビヌツズマブの投与を2日に分けた場合，必ず両日とも適切なプレメディケーションとともに初回投与時の速度で投与を実施することとした。

- SDI 実施基準

1) Regular infusion による投与が連続3回以上実施され，Grade 3以上の IRR が発現していない。
2) SDI の前の末梢血中リンパ球数が5000/μL 未満である。

SDI 実施後に Grade 3以上の IRR が発現した場合，以降の投与で SDI は実施しない。

- オビヌツズマブの投与中断

投与中に IRR が発現した場合は，回復／軽快するまで，投与を中断するか一時的に投与速度を遅らせる。

(11) 治療期間

各被験者の治験期間は，同意取得日から最終観察日（治験薬最終投与後4～8週の検査・観察日）までとした。

(12) 併用薬，投与量，投与方法

- 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（以下 CHOP 療法）を3週間ごとに6サイクル，各サイクルの Day 1に投与した。プレドニゾロンは Day 2～5にも投与した。患者の状態に合わせて適宜減量可能とした。
  - シクロホスファミド　750 mg/m^2 IV，Day 1
  - ドキソルビシン　50 mg/m^2 IV，Day 1
  - ビンクリスチン　1.4 mg/m^2 IV，Day 1
  - プレドニゾロン　100 mg/day PO/IV，Day 1～5

オビヌツズマブ投与とCHOP療法を同日に実施する場合は，プレドニゾロン（100 mg）投与をオビヌツズマブ投与の前に実施した。またシクロホスファミド，ドキソルビシン，ビンクリスチンを投与する前にオビヌツズマブ投与後30分間は患者の観察を実施した。

(13) 評価基準

以下の評価基準を用いた。

主要評価項目

- サイクル2のGrade 3以上のIRRの発現割合
- サイトカイン（TNFα，IFNγ，IL6，IL8，IL10）の経時推移
- サイクル2 Day 12までに集積された血清中オビヌツズマブ濃度及びオビヌツズマブの薬物動態学的パラメータ

副次的評価項目

- 有害事象の発現状況
- SDI時のIRR発現状況
- 投与終了時の奏効率
- 最良総合効果に基づく奏効率

(14) 統計的手法

以下の統計手法を用いた。

主要解析

本試験の主要評価項目は，SDI移行例におけるサイクル2のGrade 3以上のIRRの発現割合，薬物動態学的パラメータ及びサイトカインである。

- サイクル2のGrade 3以上のIRR発現割合

サイクル2のGrade 3以上のIRR発現割合は，SDI移行例を分母，サイクル2中のGrade 3以上のIRRの発現例数を分子とした割合と定義する。Grade 3以上のIRRの発現数が被験者数nと真のGrade 3以上のIRR発現確率pをパラメータとする二項分布に従うと仮定し，pに共役な事前分布としてベータ分布を仮定すると，pの事後分布は同じくベータ分布としてベイズ流に推定可能である。事前分布としては，投与速度によらず日本人と非日本人でIRR発現確率に差異がないという仮定の下で，GAO4915g試験のSDI移行例におけるサイクル2のGrade 3以上のIRRの発現割合0%（45例中0例）の情報を利用する。すなわち，有効被験者数が45例の事前分布としてBeta（0,45）を設定する。本試験では，Grade 3以上のIRR発現確率の真値が5%以下であればSDIは十分忍容可能であると仮定する。その上で，主要な意思決定は上述の事後分布から推定される「サイクル2中のGrade 3以上のIRR発現確率の真値が5%を超える確率」に基づくこととし，この確率が5%未満であることをもってオビヌツズマブのSDIは忍容可能と判断する。補助的に，事前分布として無情報事前分布を利用した場合に得られる事後分布に基づく推測も実施する。推定された事後分布は事後平均や95%信用区間を推定することで要約し，記述的に頻度論としてのサイクル2のIRR発現割合並びにその95%信頼区間の推定値も報告する。なお，推定精度を向上させる目的で被験者数を追加する場合でも同様の評価を実施する。

- 薬物動態学的パラメータ

SDI移行例のサイクル2 Day 12までの血清中オビヌツズマブ濃度及びコンパートメントに依存しない方法による薬物動態学的パラメータを求め要約統計量（算術平均値，幾何平均，標準偏差，変動係数，中央値，最小値，最大値）を求める。得られた結果を，JO21900試験，BO21005試験及びGAO4915g試験と比較する。

- サイトカイン

SDI移行例のサイクル2までのサイトカイン濃度を求めvisitごとに要約統計量（算術平均値，幾何平均，標準偏差，変動係数，中央値，最小値，最大値）を求める。また，その経時的な推

移を評価する。CRP についても，visit ごとの要約統計量を求め，経時的な推移を評価する。得られた結果を，JO21900試験，BO20999試験，BO21003試験及び BO21000試験と比較する。

(15) 結果の要約

1) 安全性

- 安全性解析対象集団は35例，治験中に SDI を実施した被験者（SDI 実施例）は33例，SDI 移行例は31例であった。
- 本剤の投与を8サイクル完遂したのは28/35例（80%）であった。SDI 実施例で本剤の投与を8サイクル完遂したのは28/33例，SDI 移行例では27/31例であった。本剤の SDI 実施例33例の SDI 開始サイクルはサイクル2が最も多く，31例（93.9%）であり，その他はサイクル3及びサイクル4が各1例（3.0%）であった。本剤の用量強度の中央値は100.00%であり，十分な治療の強度が確保されていた。
- SDI 移行例のサイクル2において Grade 3以上の IRR の発現は認められず，事前分布として GAO4915g 試験の情報を利用して推定した SDI 移行例におけるサイクル2中の Grade 3以上の IRR 発現確率の真値が5%を超える確率は推定不能だった。また，事前分布に無情報事前分布を利用して推定した SDI 移行例におけるサイクル2中の Grade 3以上の IRR 発現確率の真値が5%を超える確率は0.05%であった。
- 有害事象は，35/35例（100%）に認められた。副作用は，35/35例（100%）に認められた。発現率が10%以上の有害事象は，悪心，注入に伴う反応及び末梢性感覚ニューロパチー（各48.6%），便秘（42.9%），好中球減少症（40.0%），発熱（34.3%），味覚異常（31.4%），脱毛症（28.6%），好中球数減少及び食欲減退（各25.7%），不眠症（22.9%），末梢性ニューロパチー（20.0%），血小板数減少，口内炎及び発熱性好中球減少症（各17.1%），倦怠感及び白血球減少症（各14.3%），背部痛（11.4%）であった。背部痛4例，発熱及び不眠症各1例を除き，すべて副作用であった。
- Grade3以上の有害事象は，30/35例（85.7%）に認められた。Grade 3以上の副作用は，29/35例（82.9%）に認められた。Grade3以上の有害事象は蜂巣炎，下痢，誤嚥性肺炎，失神，貧血及び齲歯各1例を除き，すべて副作用であった。発現率が5%以上の Grade3以上の有害事象は，好中球減少症（40.0%），好中球数減少（25.7%），発熱性好中球減少症（17.1%），白血球減少症（14.3%），血小板減少症及び白血球数減少（各8.6%），蜂巣炎（5.7%）であった。
- 注目すべき有害事象を事前に設定した定義に基づき集計したところ，安全性解析対象集団において，IRR は，17/35例（48.6%）に認められた。10%以上に発現した IRR に該当する有害事象は発熱（25.7%）であった。また，サイクル1 Day 1において，15例（42.9%）に38件の IRR 及び IRR に該当する有害事象が認められ，2件が Grade 3以上であった。サイクル1 Day 8以降では，IRR の発現頻度が低下しており，Grade 3以上の IRR 及び IRR に該当する有害事象は認められなかった。
- SDI 実施例及び SDI 移行例においても，IRR の発現頻度はサイクル1 Day 1が最も高く，SDI 実施例では14/33例（42.4%）に36件，SDI 移行例では12/31例（38.7%）に30件の IRR 及び IRR に該当する有害事象が発現した。また，SDI 移行例，SDI 実施例ともに，SDI 開始後のサイクル6，サイクル7及びサイクル8に IRR の発現が各1例に認められたが，いずれも Grade 1であり，Grade 3以上の IRR 及び IRR に該当する有害事象は認められず，IRR による SDI 中止例は認められなかった。
- IRR 以外の注目すべき有害事象では，「感染症」は，15/35例（42.9%）に認められた。2例以上に発現した「感染症」は，帯状疱疹及び鼻咽頭炎が各3例，蜂巣炎，副鼻腔炎及び上気道感染が各2例であった。「好中球減少症」は，26/35例（74.3%）に認められた。その内訳は，好中球減少症が14例，好中球数減少が9例及び発熱性好中球減少症が6例であった。「血小板減少症」は，9/35例（25.7%）に認められた。その内訳は，血小板数

減少が6例及び血小板減少症が3例であった。「心臓障害」は1/35例（2.9%）に認められた。その内訳は動悸が1例であった。「腫瘍崩壊症候群」，「消化管穿孔」，「二次性悪性腫瘍」，「B 型肝炎ウイルスの再活性化」は認められなかった。

- 因果関係を問わない重篤な有害事象は，9/35例（25.7%）に認められた。2例以上に認められた重篤な有害事象は，蜂巣炎及び発熱性好中球減少症が各2例であった。蜂巣炎及び誤嚥性肺炎各1例を除き，すべて副作用であった。なお，治験期間中の死亡は認められなかった。
- 本剤の投与中止に至った有害事象は，3/35例（8.6%）に認められた。その内訳は，感染性皮膚膿腫，細気管支炎及び誤嚥性肺炎が各1例であった。誤嚥性肺炎を除き，すべて副作用であった。
- 治験治療のいずれかの薬剤の投与中止に至った有害事象は，5/35例（14.3%）に認められた。その内訳は，感染性皮膚膿腫，細気管支炎，注入部位血管漏出，誤嚥性肺炎及び末梢性感覚ニューロパチーが各1例であった。誤嚥性肺炎を除き，すべて副作用であった。
- 本剤の減量又は休薬に至った有害事象は，3/35例（8.6%）に認められた。その内訳は，蜂巣炎，好中球減少症，注入に伴う反応及び脳梗塞が各1例であった。すべて副作用であった。
- 治験治療のいずれかの薬剤の減量又は休薬に至った有害事象は，9/35例（25.7%）に認められた。その内訳は，好中球減少症が3例，血小板減少症及び白血球減少症が各2例，脳梗塞，末梢性ニューロパチー，末梢性感覚ニューロパチー，アスパラギン酸アミノトランスフェラーゼ増加，アラニンアミノトランスフェラーゼ増加，血小板数減少，好中球数減少，白血球数減少，蜂巣炎，肺臓炎，注入に伴う反応及びステロイド離脱症候群が各1例であった。すべて副作用であった。
- 本剤の投与延期に至った有害事象は，13/35例（37.1%）に認められた。その内訳は，帯状疱疹及び好中球数減少が各3例，好中球減少症が2例，菌血症，蜂巣炎，肺感染，肺炎，アラニンアミノトランスフェラーゼ増加，アスパラギン酸アミノトランスフェラーゼ増加，白血球減少，便秘，肝障害及び肺臓炎が各1例であった。
- 本剤の投与速度減速に至った有害事象は，4/35例（11.4%）に認められた。その内訳は，注入に伴う反応が4例，発熱が2例，悪寒及び嘔吐が各1例であった。
- 本剤の投与中断に至った有害事象は，10/35例（28.6%）に認められた。その内訳は，注入に伴う反応が10例，発熱が7例，悪寒及び血圧上昇が各2例，悪心，嘔吐，低酸素症，喘鳴及びそう痒症が各1例であった。

2) 薬力学

- 薬力学的解析対象例35例及びその内の SDI 移行例31例のいずれにおいても，CD19陽性細胞は初回投与後に B 細胞の枯渇と定義した0.07×10^9/L 未満に低下し，試験期間を通じて0.07×10^9/L 未満で推移した。
- 薬力学的解析対象例35例及びその内の SDI 移行例31例のいずれにおいても，いずれのサイトカインも投与中に最高値を示した後，投与後2～5時間後にはベースライン値に復した。CRP はサイクル1 Day 15に最高値を示した。サイクル2 Day 1の SDI 投与後のサイトカイン及び CRP ともに明確な変動を示さなかった。
- 日本人を対象に regular infusion で実施した JO21900試験，外国人を対象に regular infusion で実施した BO20999試験，BO21003試験のいずれの試験においても，各サイトカインの推移は，サイクル1 Day 1の投与中に最高値を示した後，速やかにベースライン値に復し，サイクル2 Day 1の投与中には明確な変動を示さず，本試験の SDI 移行例31例のサイトカインと同様の推移が認められた。

3) 薬物動態

- 血清中オビヌツズマブ濃度の推移は，薬物動態解析対象例20例及びその内の SDI 移行例17例のいずれにおいてもサイクル2 Day 1に最高値を示し，以降は同様の推移を示した。
- 本剤の SDI と regular infusion との薬物動態の比較のため，本試験の SDI 移行例17例とJO21900試験及び BO21005試験の日本人被験者の血清中オビヌツズマブ濃度及び薬物濃度パラメータを比較したところ，本試験の SDI 移行例17例の血清中オビヌツズマブ濃度は，JO21900試験の800/1600 mg 群と1200/2000 mg 群の間で推移し，また，BO21005試験と同様の推移を示した。本試験の SDI 移行例17例のサイクル2 Day 1の投与終了直後の血清中オビヌツズマブ濃度は907 ± 246 µg/mL であり，BO21005試験の982 ± 297 µg/mL と同程度であった。
- 本剤の SDI の薬物動態について，民族差の有無を検討するため，本試験の SDI 移行例17例と GAO4915g 試験の血清中オビヌツズマブ濃度の推移及び薬物動態パラメータを比較したところ，本試験の SDI 移行例17例の血清中オビヌツズマブ濃度は，GAO4915g 試験の SDI 移行例と同様の推移を示した。また，本試験の SDI 移行例17例のサイクル2 Day 1の AUC_{last} 及び C_{max} はそれぞれ4770 ± 898 µg•day/mL 及び925 ± 221 µg/mL であり，GAO4915g 試験のそれぞれ3590 ± 1060 µg•day/mL 及び612 ± 184 µg/mL と明確な差異は認められなかった。

4) 有効性

- 有効性の解析対象集団35例における PET を用いない効果判定に基づく投与終了時の総合効果は，CR が21例，PR が4例，SD が2例，PD が6例，欠測又は評価不能が2例であった。奏効例は25例，奏効率は71.4%であった。また，PET 実施例13例における PET を用いた効果判定に基づく投与終了時の総合効果は，CR が11例，PR が1例，SD が0例，PD が1例であった。奏効例は12例，奏効率は92.3%であった。
- 有効性の解析対象集団35例における PET を用いない効果判定に基づく最良総合効果は，CR が22例，PR が7例，SD が3例，PD が1例，欠測又は評価不能が2例であった。奏効例は29例，奏効率は82.9%であった。また，PET 実施例13例における PET を用いた効果判定に基づく最良総合効果は，CR が11例，PR が1例，SD が0例，PD が1例であった。奏効例は12例，奏効率は92.3%であった。

(16) 結論

本治験では，未治療の CD20陽性 B 細胞性 NHL 患者に対して，本剤の SDI の忍容性を，SDI を開始したサイクル2における Grade 3以上の IRR の発現割合を用いて検討した。その結果，本剤の SDI は十分に忍容可能であると考えられた。また，本剤の薬力学及び薬物動態について本剤の投与時間及び民族差の影響を他試験の結果と比較することで検討した。その結果，本剤の薬力学及び薬物動態に本剤の投与時間及び民族差の影響はないと考えられた。

(17) 報告書作成日

[redacted]年[redacted]月[redacted]日

2.7.6.1.3　BO21223試験（GALLIUM 試験）

(1) 試験の標題

BO21223 – A Multicenter, Phase III, Open Label, Randomized Study in Previously Untreated Patients with Advanced Indolent Non Hodgkin's Lymphoma Evaluating the Benefit of GA101 (RO5072759) plus Chemotherapy Compared with Rituximab plus Chemotherapy Followed by GA101 or Rituximab Maintenance Therapy in Responders.

BO21223試験 – 未治療の進行期低悪性度非ホジキンリンパ腫患者を対象とした GA101

（RO5072759） + 化学療法併用後の奏効例に対して GA101維持療法を施行する群とリツキシマブ + 化学療法併用後の奏効例に対してリツキシマブ維持療法を施行する群の有用性を評価する第 III 相多施設共同非盲検ランダム化試験

(2) フェーズ
第 III 相

(3) 治験依頼者及び治験実施施設
F. Hoffmann-La Roche 社／患者は18カ国，177施設から登録された。登録例数が多い国は，英国（293例），ドイツ（237例），カナダ（138例），オーストラリア（136例），日本（129例）であった。

(4) 公表
なし

(5) 治験実施期間
2011年7月6日（1例目登録日）～2016年1月31日（データカットオフ日），試験は実施中。

(6) 目的
BO21223/GALLIUM 試験の主要目的は，未治療の進行期濾胞性リンパ腫（FL）患者を対象として，リツキシマブ + 化学療法併用（R–化学療法）後にリツキシマブ維持療法を行う治療に対する，オビヌツズマブ + 化学療法併用（G–化学療法）後にオビヌツズマブ維持療法を行う治療の有効性を主治医評価の無増悪生存期間（PFS）を用いて検証することである。
以下の副次的目的は，未治療の進行期低悪性度非ホジキンリンパ腫（NHL）患者（ = 全被験者）に対して適応される。
- 2群間の PFS の評価・比較（主治医評価）

以下の副次的目的は，未治療の進行期低悪性度 NHL 患者（ = 全被験者）及び未治療の進行期 FL 患者（ = 濾胞性リンパ腫集団）に対して適応される。
- 2群間の PFS の評価・比較（独立評価委員会［IRC］評価）
  米国では PFS（IRC 評価）に基づき規制当局の決定がなされる。
- 2群間の導入療法終了時の全奏効（OR）及び完全奏効（CR）の評価・比較（主治医評価，FDG PET 所見を含む評価と含まない評価）
- 2群間の導入療法終了時の OR 及び CR の評価・比較（IRC 評価，FDG PET 所見を含む評価と含まない評価）
- 2群間の全生存期間（OS），無イベント生存期間（EFS），無病生存期間（DFS），奏効期間（DOR）及び新たなリンパ腫治療開始までの期間（TTNALT）の評価・比較
  EFS，DFS，DOR は主治医評価を用いる。
- 2群間の導入療法期間及び維持療法期間中の安全性プロファイルの評価・比較
- 両群の患者報告に基づくアウトカム（PROs）の評価

(7) 治験方法
選択/除外基準を満たした適格な FL 患者1202例が G–化学療法後にオビヌツズマブ維持療法を受ける群と R–化学療法後にリツキシマブ維持療法を受ける群の2群に1：1の割合でランダム化された。加えて，195例の MZL 患者も1：1の割合で2つの治療群にランダム化された。その他に4例の非 FL 患者がいた。
リツキシマブ又はオビヌツズマブの投与スケジュールは併用する化学療法に依存した。試験

開始前に，各治験実施施設において，濾胞性リンパ腫の標準療法とみなされている3種類の化学療法レジメン（CHOP 療法，CVP 療法又はベンダムスチン）から1種類を選択し，選択された化学療法レジメンを当該治験実施施設の濾胞性リンパ腫患者全例に対して全試験期間にわたって投与する（新たな科学的なデータが得られた場合は，治験依頼者の承認に基づき，他のレジメンに変更することが可能）。非濾胞性リンパ腫患者に対しては，主治医が患者ごとに3種類の化学療法レジメン（CHOP 療法，CVP 療法又はベンダムスチン）から1種類を選択した。

本試験の対照群（A 群）では，化学療法とともにリツキシマブ375 mg/m^{2}を6～8回，点滴静注した。本試験の試験群（B 群）では，化学療法とともにオビヌツズマブ1000 mg の絶対（一定）用量を8～10回，点滴静注した（サイクル1の Day 8及び Day 15の2回の追加投与を含む）。導入療法終了時に CR 又は PR を達成した被験者に対しては，リツキシマブ375 mg/m^2（A 群）又はオビヌツズマブ1000 mg を2カ月ごとに，病勢進行又は最大2年間のどちらか早い方まで継続投与した。

導入療法期間終了時に病勢安定（SD）の被験者に対しては，維持療法を施行する奏効例（CR 又は PR）と同じスケジュールで病勢進行を確認する追跡調査を最大2年間にわたって実施する（経過観察）。導入療法が毒性又は毒性以外の理由で中止された場合には，試験治療を中止し直ちに追跡調査に移行する。

各被験者について，主治医による診断，臨床検査及びコンピューター断層撮影（CT）又は磁気共鳴画像法（MRI）により奏効及び病勢進行を評価した。FL 及び MZL（脾性 MZL 以外）の奏効／病勢進行は，改変版「悪性リンパ腫効果判定規準（改訂版），Cheson 他，2007」に従い評価した。MZL 患者集団では，パラプロテイン評価に基づく追加の効果判定規準にも従い，脾性 MZL 患者集団では，血液学的パラメータ及び脾臓の大きさに基づく追加の効果判定規準にも従った。導入療法期間中の腫瘍評価は，3サイクル（ベンダムスチン投与例）又は4サイクル（CVP 療法又は CHOP 療法投与例）後（ = 全被験者にとって初回投与後12週時点）及び導入療法終了時に実施した。

導入療法終了後は，維持療法を実施した被験者（CR 又は PR を達成した被験者）又は経過観察を実施した被験者（SD の被験者）に対して臨床的な追跡調査を2カ月ごと2年間にわたって実施した（CT は最初の1年は4カ月ごと，2年目は6カ月ごとに実施した）。維持療法又は経過観察終了時（サイクル8 Day 1［CHOP 療法／CVP 療法投与群］又はサイクル6 Day1［ベンダムスチン投与群］から25カ月時点）に病勢進行が認められなかった被験者は，腫瘍評価を3カ月ごとに3年間（CT は6カ月ごと），その後は6カ月ごとに2年間（CT は1年ごと）実施した（病勢進行確認のための追跡調査）。5年間の追跡調査の後又は病勢進行後（いずれか早い方），治療終了（最初の症例登録から約10.2年）まで，6カ月ごとに OS 及び新たなリンパ腫治療（NALT），又は病勢進行（該当する場合）の追跡調査を実施した。導入療法を PD 以外の理由で早期に中止した被験者は PD，NALT 及び OS の追跡調査を実施した。PD のため導入療法を早期に中止した被験者は直ちに OS 及び NALT の追跡調査に移行した。治験実施計画書に定めた治療方法を中止する被験者及び病勢の進行が認められないまま新たなリンパ腫治療を開始する必要がある被験者（スクリーニング時の診断に誤りがあり，正しい診断により治療方法の変更が必要となった被験者等）は病勢進行及び OS の追跡調査を実施する。

独立データモニタリング委員会（IDMC）は，被験者の安全性の監視及び中間結果の評価のために設置された。IDMC は1例目の登録後1カ月後，それから約2カ月ごとに100例が2サイクルの試験治療を完了するまで開催された。その後，IDMC は約6カ月ごとに開催された。3回の中間解析が計画され，実施された。2回は無益性を目的とした解析であり，1回は有効性を目的とした解析であった。

IRC により，すべての被験者の有効性について，独立した放射線学的見地及び腫瘍学的見地からの評価も実施した。

病理組織型，CD20発現状況，加えてその他の予後に関する特徴を評価するため，病理検体を用いてレトロスペクティブな品質保証のための病理判定を実施した。

(8) 被験者数

予定被験者数：FL 患者1200例，MZL 患者200例

登録，主要解析対象例数：1401例（FL 患者1202例，MZL 患者195例，非 FL 患者4例）

(9) 診断及び主な組入れ基準

18歳以上の男性又は女性の未治療で組織学的に確認された CD20陽性進行低悪性度 B 細胞 NHL（濾胞性リンパ腫（Grade 1-3a），脾性 MZL，節性 MZL，節外性 MZL を含む）患者。

(10) 被験薬の用量，投与方法及び投与期間

導入療法期間中は，化学療法とともにオビヌツズマブ1000 mg を8～10回，点滴静注した。

オビヌツズマブはサイクル1では Day 1，Day 8，Day 15に投与し，以降のサイクル（サイクル2～6又はサイクル2～8，併用する化学療法によって異なる）では Day 1に投与した。

CHOP 療法はサイクル1～6の Day 1に投与した。

CVP 療法はサイクル1～8の Day 1に投与した。

ベンダムスチンはサイクル1～6の Day 1及び Day 2に投与した。

1サイクルは3週間（CHOP 療法又は CVP 療法併用時）又は4週間（ベンダムスチン併用時）とした。

G–化学療法群にランダム化された被験者の内，導入療法終了時に CR 又は PR を達成した被験者には，病勢進行が認められるまで最大2年間にわたり，オビヌツズマブ1000 mg を2カ月ごとに継続投与した。

(11) 対照薬の用量，投与方法及び投与期間

導入療法期間中は，化学療法とともにリツキシマブ375 mg/m^{2}を6～8回，点滴静注した。リツキシマブは各サイクル（サイクル1～6又はサイクル1～8，併用する化学療法のレジメンにより異なる）の Day1に投与した。

CHOP 療法はサイクル1～6の Day 1に投与した。

CVP 療法はサイクル1～8の Day 1に投与した。

ベンダムスチンはサイクル1～6の Day 1及び Day 2に投与した。

1サイクルは3週間（CHOP 療法又は CVP 療法併用時）又は4週間（ベンダムスチン併用時）とした。

R–化学療法群にランダム化された被験者の内，導入療法終了時に CR 又は PR を達成した被験者には，病勢進行が認められるまで最大2年間にわたり，リツキシマブ375 mg/m^{2}を2カ月ごとに継続投与した。

(12) 評価基準

1) 有効性

<u>主要評価項目</u>

濾胞性リンパ腫症例（ = 濾胞性リンパ腫患者の Intent to treat［ITT］［FL ITT］集団）の PFS（主治医評価）

米国では PFS（IRC 評価）に基づき規制当局の決定がなされる。

<u>副次的評価項目</u>

- ランダム化されたすべての症例（ = 濾胞性リンパ腫患者及び MZL 患者，以下，全 ITT 患者集団）の PFS
- PET の所見を含まない評価に基づく導入療法終了時の CR 率（濾胞性リンパ腫患者及び全 ITT 患者集団）
- OS（濾胞性リンパ腫患者及び全 ITT 患者集団）

- PET の所見を含まない評価に基づく導入療法終了時の全奏効率（ORR）（濾胞性リンパ腫患者及び全 ITT 患者集団）

2) 薬物動態

時間経過に伴う血清中オビヌツズマブ濃度の個別値及び平均値（集計及びプロット）を別々に報告する。

3) 薬力学

試験期間を通しての CD19陽性 B 細胞数の絶対数，ベースライン時の B 細胞数に対する割合，最小値，最小値までの期間，B 細胞枯渇の期間及び B 細胞数回復までの期間。

4) 安全性

有害事象（NCI CTCAE Ver.4.0に基づく Grade 判定），標準的な臨床検査（オビヌツズマブ投与例におけるヒト抗ヒト抗体［HAHA］の発現率を含む）及びバイタルサイン。

(13) 統計的手法

有効性：両側層別 Log-rank 検定（有意水準0.05），化学療法レジメン（CHOP 療法，CVP 療法又はベンダムスチン）及び FL 患者では濾胞性リンパ腫国際予後指標（FLIPI）リスクグループ（low，intermediate 又は high），非 FL 患者では国際予後指標（IPI）リスクグループ（low 又は low intermediate vs. high-intermediate 又は high）を用いて層別した。Kaplan-Meier 法を用いて両群の PFS 分布を推定した。治療効果の推定は，層別 Cox 比例ハザード解析（95%信頼区間を含む）により算出されたハザード比を用いて記載した。

(14) 結果の要約

1) 有効性

2016年5月20日（事前に規定した有効性の3回目の中間解析時点）に，事前に規定した主要評価項目である FL 患者集団の PFS（主治医評価）の有意水準を満たしたことから，IDMC は治験依頼者に対して集計した被験者のデータの盲検化を解除し，すべての解析を実施しその結果を公表することを勧告した。[redacted]年[redacted]月[redacted]日に治験依頼者はこの勧告を受け入れ，中間解析を有効性の主要解析として実施した。本項に記載する主要解析は IDMC のために実施した中間解析と同じ2016年1月31日をカットオフ日として実施された。

BO21223試験の有効性の結果を以下に要約する。

- 主要評価項目である FL 患者集団における PFS（主治医評価）において，統計学的に有意で臨床的に意義のある改善が示された。これは治験実施計画書で規定していた，最終解析に必要なイベント数である370件の内245件（66%）が発生した後に実施する有効性の中間解析において示されたものである。G–化学療法により，R–化学療法と比較して，PFS（主治医評価）イベント（病勢の進行／再発又は死亡）のリスクを臨床的に意義があり，統計学的に有意である34%減少させることが示された（ハザード比：0.66［95%CI：0.51～0.85］，層別 Log-rank 検定：P = 0.0012）。PFS（主治医評価）の層別 Log-rank 検定による P 値は事前に規定した有意水準0.012を下回った。Kaplan-Meier 法で推定した PFS 中央値は両群とも未達であった。Kaplan-Meier 法の推定の結果，3年 PFS は R–化学療法群73.3%（95%CI；68.8～77.2），G–化学療法群80.0%（95%CI；75.9～83.6）であった。
- PFS（IRC 評価）は PFS（主治医評価）と同様の結果が得られており，G–化学療法群において，R–化学療法群と比較して PFS（IRC 評価）を延長した。PFS（IRC 評価）のイベント（病勢進行／再発）又は死亡のリスクは G–化学療法群において，R–化学療法群と比較して29%減少した（ハザード比：0.71［95%CI：0.54～0.93］，層別 Log-rank 検

定：P = 0.0138）。
- 主要解析結果の頑健性は以下の方法で示された：
  - 層別しない Log-rank 検定，re-randomization 検定，腫瘍評価欠測の影響，NALT の影響，治療中止の影響，死亡イベントの影響及び最後の腫瘍評価における評価不能による影響を含む感度解析。
  - ベースライン時の被験者背景，予後因子及び層別因子に基づく事前に規定した部分集団解析（FL 患者の FLIPI が low risk の部分集団を除き，全体の10%以上の例数であった部分集団におけるハザード比の点推定値は1を下回った）。
- PET 所見を含まない評価に基づく全奏効率（主治医評価及び IRC 評価）は両群で同等であり，それぞれ G–化学療法群が1.7%，3.2%高かった。PET 所見を含まない評価に基づく CR 率（主治医評価）は R–化学療法群が良好であった（両群の差は-4.3%）が，PET 所見を含まない評価に基づく CR 率（IRC 評価）は G–化学療法群が良好であった（両群の差は2.0%）。
- PET 所見を含む評価に基づく全奏効率（主治医評価及び IRC 評価）は両群で同等であり，それぞれ G–化学療法群が4.3%，3.3%高かった。PET 所見を含む評価に基づく CR 率（主治医評価及び IRC 評価）は G–化学療法群が良好であった（両群の差はそれぞれ 5.6%，11.7%）。
- データカットオフ時点で死亡例は81例のみ（FL 患者集団の6.7%）であり，4年以上の生存追跡調査がなされている被験者は20%未満であった。したがって，OS の評価は現時点ではデータが不十分と考えられた（ハザード比：0.75 ［95% CI：0.49～1.17］，層別 Log-rank 検定：P = 0.21）。
- EFS（病勢進行，再発，死亡又は NALT 開始までの期間）は R–化学療法群と比較して G–化学療法群が長かった（ハザード比：0.65［95% CI：0.51～0.83］，層別 Log-rank 検定：P = 0.0006）。
- R–化学療法群と比較して G–化学療法群では NALT を開始又は理由を問わない死亡に至る可能性が低かった（ハザード比：0.68［95% CI：0.51～0.91］，層別 Log-rank 検定：P = 0.0094）。
- 全体の患者集団の有効性は FL 患者集団の有効性と同様であった。

2) 患者報告アウトカム

全体的に，ベースライン時の FACT-Lym 質問票を用いて測定した HRQOL 及び EQ-5D 質問票を用いて測定した健康状態は，両群で同様であった。原疾患のため，両群の被験者は身体機能，機能的な健康状態，精神的及び社会的機能について，いくつかの障害を有していた。

治療期間全体において，HRQOL は両群で同様であった。試験期間を通じて，G–化学療法群が R–化学療法群よりも臨床的に悪化した時期は認められなかった。両群とも臨床的に意義のある改善がリンパ腫特有の症状及びサブスケール（TOI や Lym-Total）を含むスケールの要約において確認された。

3) 安全性

本試験の主要な患者集団は FL 患者集団であった。したがって，安全性の項では FL 患者集団に主に焦点を当てて記載した。カットオフ時点の FL 患者の試験期間中（導入療法期間，維持療法期間及び追跡調査期間）の全体的な有害事象を要約し，以下に示した（表 2.7.6.1.3-1）。
- G–化学療法群において高い治療完遂率，少ない投与延期の回数及び投与中止数が認められ，G–化学療法が十分に忍容可能であり，有効性に影響を与える可能性があるほど重大な治療不十分に至ることはないことが示された。両群間で曝露状況は同等であること及び投与完遂例が多かったことは，両群を比較した結果の頑健性を支持するものであった。
- 全体的に，両群で報告された有害事象の性質及び重症度は，オビヌツズマブと化学療法

併用やリツキシマブと化学療法併用の既知の安全性プロファイルと一致していた。

- 全体的に G–化学療法群の毒性は臨床的に管理可能であり，両群で有害事象による治療中止や減量の割合は同様であったが，R–化学療法群と比較し，G–化学療法群で有害事象による抗体投与の中断を要した被験者が多かった。投与中断は主にサイクル1で認められ，Day 1で最も多く認められた。投与中断の原因の大部分は IRR であった。これらの投与中断は全体的な治験薬の曝露に影響を与えなかった。
- 両群ともほぼ全例において少なくとも一つの有害事象が認められた。
- R–化学療法群と G–化学療法群で致死的な有害事象（Grade 5），出血系の有害事象又は消化管穿孔系の有害事象の発現率は同様であった。
- R–化学療法群と比較し，G–化学療法群で Grade 3～5の有害事象及び SAE の発現率が高かった。
- R–化学療法群と比較し，G–化学療法群で以下に示す特に注目すべき有害事象（全 Grade 及び Grade 3～5）の発現率が高かった。
  - IRR，好中球減少症，血小板減少症，感染症（PML は報告されなかった）及び二次性悪性腫瘍。
  - 両群とも TLS の報告例数は少なく，G–化学療法群で多く発現した（R–化学療法群3例，G–化学療法群6例）。
- 安全性解析対象集団における死亡例（理由を問わない，病勢進行も含む）は R–化学療法群（46/597例）が G–化学療法群（35/595例）と比較して多かった。有害事象による死亡例は両群で同様であった。

表 2.7.6.1.3-1　有害事象の要約（FL 患者集団）

t_ae_osafe_emerge_foly_223_SE APPROVED Summary of Overall Safety - Treatment-Emergent AEs - Follicular Lymphoma Patients (Safety-Evaluable Patients)

Protocol(s): BO21223 (L21223A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

	R-chemo (N=597)	G-chemo (N=595)
Total number of patients with at least one adverse event	587 (98.3%)	592 (99.5%)
Total number of events	9343	10311
Total number of deaths	46 (7.7%)	35 (5.9%)
Total number of patients with at least one		
AE with fatal outcome	20 (3.4%)	24 (4.0%)
Grade 3-5 AE	405 (67.8%)	444 (74.6%)
Serious AE	238 (39.9%)	274 (46.1%)
Serious AE leading to withdrawal from any treatment	36 (6.0%)	44 (7.4%)
Serious AE leading to any dose reduction	10 (1.7%)	12 (2.0%)
Serious AE leading to any dose interruption	45 (7.5%)	83 (13.9%)
Related Serious AE	122 (20.4%)	152 (25.5%)
AE leading to withdrawal from any treatment	85 (14.2%)	97 (16.3%)
AE leading to any dose reduction	95 (15.9%)	107 (18.0%)
AE leading to any dose interruption	338 (56.6%)	395 (66.4%)
Related AE	547 (91.6%)	564 (94.8%)
Related AE leading to withdrawal from any treatment	65 (10.9%)	75 (12.6%)
Related AE leading to any dose reduction	89 (14.9%)	103 (17.3%)
Related AE leading to any dose interruption	296 (49.6%)	349 (58.7%)

Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Total number of events includes deaths for patients that had no adverse events.
Fatal/withdrawal rows include outcomes that were available in the database as of the snapshot date, for adverse events with onset date on or before the clinical cutoff date.

Program: /opt/BIOSTAT/prod/cdt7159z/k21223d/t_ae_osafe.sas
Output: /opt/BIOSTAT/prod/cdt7159n/l21223a/reports/t_ae_osafe_emerge_foly_223_SE.out
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［5.3.5.1-1-1 Table 40を再掲］

(15) 結論

- 事前に規定した有効性の中間解析において，主要評価項目である FL 患者の PFS（主治医評価）について，事前に規定した有意水準を下回り，臨床的に意義ある結果が得られたと考えられたことから，IDMC はすべての解析を実施することを勧告した。
- G–化学療法及びその後のオビヌツズマブ維持療法は，R–化学療法及びその後のリツキシマブ維持療法と比較して FL 患者の PFS（主治医評価）を統計学的有意に改善することが示された（層別ハザード比：0.66［95%CI：0.51～0.85］，層別 Log-rank 検定：P = 0.0012）（有効性の中間解析における有意水準は0.012）。
- FL 患者の PFS（IRC 評価）は FL 患者の PFS（主治医評価）と一貫した結果が得られた。R–化学療法群と比較し，G–化学療法群で PFS（IRC 評価）は延長した（層別ハザード比：0.71［95%CI：0.54～0.93］，層別 Log-rank 検定：P = 0.0138）。
- OS の中間データ及びその他の副次的評価項目であるイベント発生までの期間に関する項目（EFS，DFS，DOR 及び TTNALT）は，主要評価項目と一貫した結果が得られており，FL 患者に対するオビヌツズマブと化学療法併用レジメンの臨床的有用性を支持するものであった。全患者集団から得られた有効性の知見は FL 患者集団から得られた有効性の知見と一貫していた。
- FL 患者における G–化学療法群の安全性プロファイル（有害事象の性質や重症度）は，IRR，好中球減少症，血小板減少症，感染症及び二次性悪性腫瘍の発現率が高かったことを除き，R–化学療法群と同様であった。R–化学療法群と比較し，G–化学療法群では維持療法期間及び追跡調査期間中の Grade 3～5の感染症がより多く発現した。G–化学療法群の安全性プロファイルは全体患者集団と MZL 患者集団で同様であった。試験全体で新たな安全性のシグナルは特定されなかった。
- 本試験において示された臨床的有用性の大きさ及び忍容可能な安全性プロファイルから，FL 患者における G–化学療法による治療の良好なベネフィット・リスクバランスが確認された。

(16) 報告書作成日

[redacted]年[redacted]月

[redacted]年[redacted]月に2016年9月10日までのデータを取りまとめ，BO21223試験の総括報告書の改訂版が作成された。以下に主な追加情報及び変更点を記載する。

(1) 治験実施期間

2011年7月6日（1例目登録日）～2016年9月10日（データカットオフ日），試験は実施中。

(2) 結果の要約

1) 有効性

- 主要解析時点と比較し，両群とも6カ月以上の追加フォローアップがなされた。FL 患者のデータカットオフ時点の観察期間中央値は，R–化学療法群41.0カ月（範囲：0.1～61.8カ月），G–化学療法群41.1カ月（範囲：0～61.1カ月）だった。
- 全体的に有効性の結果は主要解析時点と一貫した結果が得られた。
- FL 患者集団の PFS（主治医評価）において臨床的に意義のある改善が認められた。R–化学療法群と比較し，G–化学療法群で PFS（主治医評価）イベント（病勢の進行／再発又は死亡）のリスクを32%減少させることが示された（ハザード比：0.68［95%CI：0.54～0.87］，層別 Log-rank 検定：P = 0.0016）。Kaplan-Meier 法で推定した PFS 中央値は両群とも未達であった。Kaplan-Meier 法による推定の結果，3年 PFS は R–化学療法群75.0%（95%CI：71.0～78.5%），G–化学療法群81.5%（95%CI：77.9～84.6%）であった。データカットオフ時点の解析の結果は主要解析時点の結果と一貫していた。

- PFS（IRC 評価）の結果は PFS（主治医評価）と一貫していた。R–化学療法群と比較し，G–化学療法群で PFS（IRC 評価）は延長した。R–化学療法群と比較し，G–化学療法群で PFS（IRC 評価）イベント（病勢の進行／再発又は死亡）のリスクを28%減少させることが示された（ハザード比：0.72［95%CI：0.56～0.93］，層別 Log-rank 検定：P = 0.0118）。
- 追加解析結果の頑健性は以下の方法で示された：
  - 層別しない Log-rank 検定，re-randomization 検定，腫瘍評価欠測の影響，NALT の影響，治療中止の影響，死亡イベントの影響及び最後の腫瘍評価における評価不能による影響を含む感度解析。
  - ベースライン時の被験者背景，予後因子及び層別因子に基づく事前に規定した部分集団解析（FL 患者の FLIPI が low risk の部分集団を除き，全体の10%以上の例数であった部分集団におけるハザード比の点推定値は1を下回った）。
- PET 所見を含まない評価に基づく全奏効率（主治医評価及び IRC 評価）はいずれも両群で同等であり，それぞれ G–化学療法群が1.8%，3.3%高かった。PET 所見を含まない評価に基づく CR 率（主治医評価）は R–化学療法群が良好であった（両群の差は-5.5%）。一方，PET 所見を含まない評価に基づく CR 率（IRC 評価）は G–化学療法群が良好であった（両群の差は1.7%）。
- PET 所見を含む評価に基づく全奏効率（主治医評価及び IRC 評価）は両群で同等であり，それぞれ G–化学療法群が4.3%，3.3%高かった。PET 所見を含む評価に基づく CR 率（主治医評価及び IRC 評価）は G–化学療法群が良好であった（両群の差はそれぞれ 5.2%，11.7%）。
- データカットオフ時点で死亡例は95例（FL 患者の7.9%）であり，4年以上の生存追跡調査がなされている被験者は20%以下であった。したがって，追加解析時点においても OS の評価に必要なデータは不十分と考えられた（ハザード比：0.82 ［95% CI：0.54～1.22］，層別 Log-rank 検定：P = 0.32）。
- EFS（病勢進行，再発，死亡又は NALT 開始までの期間）は R–化学療法群と比較して G–化学療法群が長かった（ハザード比：0.66［95% CI：0.53～0.83］，層別 Log-rank 検定：P = 0.0004）。
- R–化学療法群と比較して G–化学療法群では NALT を開始又は理由を問わない死亡に至る可能性が低かった（ハザード比：0.68［95% CI：0.52～0.90］，層別 Log-rank 検定：P = 0.007）。
- 全体の患者集団の有効性は FL 患者集団の有効性と同様であった。

2) 安全性

以下，FL 患者集団の結果を記載する。

- 全体的に，両群で報告された有害事象の性質及び重症度は，オビヌツズマブと化学療法併用やリツキシマブと化学療法併用の既知の安全性プロファイルと一致していた。
- 全体的に G–化学療法群の毒性は臨床的に管理可能であり，両群で有害事象による治療中止や減量の割合は同様であったが，R–化学療法群と比較し，G–化学療法群で有害事象による抗体投与の中断を要した被験者が多かった。投与中断は主にサイクル1で認められ，Day 1で最も多く認められた。投与中断の原因の大部分は IRR であった。これらの投与中断は全体的な治験薬の曝露に影響を与えなかった。
- R–化学療法群と G–化学療法群で致死的な有害事象（Grade 5），出血系の有害事象又は消化管穿孔系の有害事象の発現率は同様であった。
- R–化学療法群と比較し，G–化学療法群で Grade 3～5の有害事象及び SAE の発現率が高かった。
- R–化学療法群と比較し，G–化学療法群で以下に示す特に注目すべき有害事象（全 Grade

及び Grade 3～5）の発現率が高かった。
- IRR，好中球減少症，血小板減少症，感染症及び二次性悪性腫瘍。
- 両群とも TLS の報告例数は少なく，G–化学療法群で多く発現した（R–化学療法群3例，G–化学療法群6例）。

- 安全性解析対象集団における死亡例（理由を問わない，病勢進行も含む）は R–化学療法群（52/597例［8.7%］）が G–化学療法群（42/595例［7.1%］）と比較して多かった。有害事象による死亡例の割合は両群で同様であった。
- G–化学療法群において高い治療完遂率，少ない投与延期の回数及び投与中止数が認められ，G–化学療法が十分に忍容可能であり，有効性に影響を与える可能性があるほど重大な治療不十分に至ることはないことが示された。両群間で曝露状況は同等であること及び投与完遂例が多かったことは，両群を比較した結果の頑健性を支持するものであった。

(3) 結論

- 追加解析時点（データカットオフ日：2016年9月10日）の安全性と有効性の結果は，観察期間中央値41.1カ月の結果に基づいたものであり，大多数の患者（71.7%）でランダム化から36カ月を超える期間の追跡調査が実施された。
- 追加解析時点の安全性及び有効性の結果は，主要解析時点と一貫していた。
- R–化学療法後にリツキシマブ維持療法を行う治療法と比較し，G–化学療法後にオビヌツズマブ維持療法を行う治療法は FL 患者の PFS（主治医評価）を改善することが示された（ハザード比：0.68［95%CI：0.54～0.87］，層別 Log-rank 検定：P = 0.0016）。
- FL 患者の PFS（IRC 評価）の結果は PFS（主治医評価）と一貫していた。R–化学療法群と比較し，G–化学療法群で PFS（IRC 評価）は延長した（ハザード比：0.72［95%CI：0.56～0.93］，層別 Log-rank 検定：P = 0.0118）。
- 事前に計画された感度解析及び部分集団解析により，PFS の結果の頑健性が確認された。
- OS の中間データ及びその他の副次的評価項目であるイベント発生までの期間に関する項目（EFS，DFS，DOR 及び TTNALT を含む）は，主要評価項目と一貫した結果が得られており，FL 患者に対するオビヌツズマブと化学療法併用レジメンの臨床的有用性を支持するものであった。
- 全患者集団から得られた有効性の知見は FL 患者集団から得られた有効性の知見と一貫していた。
- FL 患者における G–化学療法群の安全性プロファイル（有害事象の性質や重症度）は，IRR，好中球減少症，血小板減少症，感染症及び二次性悪性腫瘍の発現率が高かったことを除き，R–化学療法群と同様であった。G–化学療法群での二次性悪性腫瘍の高い発現率は，非メラノーマ性の皮膚癌及び血液癌によるものであった。Grade 3～5の感染症は，他の試験期間と比較し，維持療法期間（2年間の治療中）に最も多く発現した。R–化学療法群と比較し，G–化学療法群では観察／追跡調査期間中に Grade 3～5の感染症がより多く報告された。
- G–化学療法群の安全性プロファイルは全体患者集団と FL 患者集団で同様であった。試験全体で新たな安全性のシグナルは特定されなかった。
- G–化学療法群において高い治療完遂率，少ない投与延期の回数及び投与中止数が認められ，G–化学療法が十分に忍容可能であり，有効性に影響を与える可能性があるほど重大な治療不十分に至ることはないことが示された。両群間で曝露状況は同等であること及び投与完遂例が多かったことは，両群を比較した結果の頑健性を支持するものであった。
- 本試験において示された臨床的有用性の大きさ及び忍容可能な安全性プロファイルから，FL 患者における G–化学療法の良好なベネフィット・リスクバランスが確認された。

(4) 報告書作成日

[redacted]年[redacted]月

【delayed-entry AEs について】

[redacted]年[redacted]月に[redacted]実施医療機関で確認された有害事象の発現状況とデータベースに入力された有害事象に乖離があることが指摘された。これを受け，Roche 社及び Genentech 社が，モニタリングプロセスの検証の一環として，BO21223試験でも[redacted]年[redacted]月から[redacted]年[redacted]月まで一部の実施医療機関で追加の原資料の直接閲覧（以下，SDV）を実施した。その結果，データカットオフ日以前に発現し，報告されていなかった有害事象（以下，delayed-entry AEs）が確認された。[redacted]年[redacted]月に delayed-entry AEs が主要解析結果（データカットオフ日：2016年1月31日）及び追加解析結果（データカットオフ日：2016年9月10日）に与えた影響を評価した Assessmet report が作成された。以下にその結論を記載する。

(1) 主要解析（データカットオフ日：2016年1月31日）に対する影響の結論

- 177施設中81施設でランダム化された65%にあたる被験者（907例）に対する SDV が追加で実施された。
- 追加の SDV の結果，最近の2017年5月5日のスナップショットで，BO21223試験で報告された有害事象の8.1%にあたる，合計2025件の delayed-entry AEs が確認された。これらの delayed-entry AEs の大多数（66%）は14施設で確認されたものであった。追加の SDV は，幅広いリスクを考慮して大多数の有害事象の情報が得られるよう，FDA と合意した基準を用いて実施された。
- FL 患者の安全性解析対象集団及び全体の安全性解析対象集団における安全性の再解析（delayed-entry AEs と更新された安全性データに基づく解析）の結果，両群ともに全体の有害事象の発現率が1～2%増加した。delayed-entry AEs が未治療の FL 患者に対するオビヌツズマブのリスクプロファイルに影響を与える証拠は認められなかった。

– 全体の安全性解析対象集団では，有害事象発現率の変化は最小限であり，新たに報告された有害事象のほとんどが Grade 1～2であった。全 Grade の有害事象の発現率の変化は主に感染症によるものであり，R–化学療法群で2.9%，G–化学療法群で2.7%の増加が認められた（Grade 3～5の感染症の増加は両群とも1%未満であった）。Grade 3～5の有害事象の発現率の顕著な変化は主に R–化学療法群で1.7%，G–化学療法群で2.1%増加した好中球減少症によるものであった。二次性悪性腫瘍はほとんど報告されておらず，重症度が Grade 3～5の事象は認められなかった。
– 治療群間の発現率の差に顕著な変化は認められなかった。
– 有害事象の性質別及び重症度別の相対分布は，主要解析時点の総括報告書及び申請資料に記載された未治療の FL 患者に対する化学療法と併用した際のオビヌツズマブの既知の安全性プロファイルと一致していた。
– 治療フェーズ別及び併用化学療法別の有害事象の発現率は，主要解析時点で観察された傾向から明らかな変化を認めなかった。
– 2つのスナップショットの日付のデータ間で全体的な発現率（少なくとも1件の有害事象を発現した患者の割合）の数値上のわずかな変化が認められたが，新たな安全性のシグナルや懸念は確認されなかった。

治験依頼者は未治療の FL 患者に対するオビヌツズマブのリスクプロファイルに影響はないと結論付けた。ベネフィット・リスクのバランスが優れているという結論に変更はない。

(2) 追加解析（データカットオフ日：2016年9月10日）に対する影響の結論

- 177施設中81施設でランダム化された65%にあたる被験者（907例）に対する SDV が追加で実施された。
- 追加の SDV の結果，最近の2017年5月5日のスナップショットで，BO21223試験で報告され

た有害事象の7.4%にあたる，合計1873件の delayed-entry AEs が確認された。これらの delayed-entry AEs の大多数（68%）は13施設で確認されたものであった。追加の SDV は，幅広いリスクを考慮して大多数の有害事象の情報が得られるよう，FDA と合意した基準を用いて実施された。

- FL 患者の安全性解析対象集団及び全体の安全性解析対象集団における安全性の再解析（delayed-entry AEs と更新された安全性データに基づく解析）の結果，両群ともに全体の有害事象の発現率が1～3%増加した。delayed-entry AEs が未治療の FL 患者に対するオビヌツズマブのリスクプロファイルに影響を与える証拠は認められなかった。
  - 全体の安全性解析対象集団では，有害事象発現率の変化は最小限であり，新たに報告された有害事象のほとんどが Grade 1～2であった。全 Grade の有害事象の発現率の変化は主に感染症によるものであり，R–化学療法群で2.5%，G–化学療法群で2.7%の増加が認められた。Grade 3～5の有害事象の発現率の顕著な変化は主に好中球減少症と感染症で認められた。Grade 3～5の好中球減少症の発現率は，R–化学療法群で1.7%，G–化学療法群で1.9%増加し，Grade 3～5の感染症は，R–化学療法群で1.0%，G–化学療法群で0.9%増加した。二次性悪性腫瘍はほとんど報告されておらず，重症度が Grade 3～5の事象は認められなかった。
  - 治療群間の発現率の差に顕著な変化は認められなかった。
  - 有害事象の性質別及び重症度別の相対分布は，追加解析時点の総括報告書及び申請資料に記載された未治療の FL 患者に対する化学療法と併用した際のオビヌツズマブの既知の安全性プロファイルと一致していた。
  - 治療フェーズ別及び併用化学療法別の有害事象の発現率は，追加解析時点で観察された傾向から明らかな変化を認めなかった。
  - 2つのスナップショットの日付のデータ間で全体的な発現率（少なくとも1件の有害事象を発現した患者の割合）の数値上のわずかな変化が認められたが，新たな安全性のシグナルや懸念は確認されなかった。

治験依頼者は未治療の FL 患者に対するオビヌツズマブのリスクプロファイルに影響はないと結論付けた。ベネフィット・リスクのバランスが優れているという結論に変更はない。

2.7.6.1.4　GAO4753g/GO01297試験（GADOLIN 試験）

(1) 試験の標題

GAO4753g/GO01297（以下，GAO4753g）– An open-label, multicenter, randomized, Phase III study to investigate the efficacy and safety of bendamustine compared with bendamustine + RO5072759 (GA101) in patients with rituximab-refractory, indolent non-Hodgkin's lymphoma.

GAO04753g/GO01297試験 – リツキシマブ治療抵抗性の低悪性度非ホジキンリンパ腫患者に対するベンダムスチン単剤とベンダムスチン+ RO5072759（GA101）併用の有効性と安全性を比較する第 III 相非盲検多施設共同ランダム化試験

(2) フェーズ

第 III 相

(3) 治験依頼者及び治験実施施設

F. Hoffmann-La Roche 社／患者は14カ国から登録された（83施設：オーストリア2施設，ベルギー2施設，カナダ10施設，チェコ3施設，フランス18施設，ドイツ3施設，イタリア8施設，オランダ3施設，ロシア6施設，スペイン3施設，スウェーデン4施設，スイス1施設，英国5施設，アメリカ15施設）。

(4) 公表

以下の3つの要約が作成されている。

Cheson BD, Chua N, Mayer J, et al. Primary results from the phase III GADOLIN study of obinutuzumab plus bendamustine versus bendamustine alone in rituximabrefractory indolent non-Hodgkin lymphoma [abstract]. 2015 ICML.

Sehn LH, Chua NS, Mayer J, et al. GADOLIN: Primary results from a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma [abstract]. J Clin Oncol. 2015; 33(15), LBA8502.

Sehn LH, Chua NS, Mayer J, et al. GADOLIN: Primary results from a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma [abstract]. 2015 EHA-5767.

(5) 治験実施期間

2010年4月15日（初回患者登録日）～2014年9月1日（データカットオフ日）

(6) 目的

主要目的

- リツキシマブを含む前治療に対して治療抵抗性の低悪性度非ホジキンリンパ腫（iNHL）患者を対象として，独立評価機関（IRF）評価に基づく無増悪生存期間（PFS）の観点から，オビヌツズマブをベンダムスチンと併用した際の臨床的有用性をベンダムスチン単剤と比較することで評価する。

副次的目的

- 主治医評価の PFS を比較する。
- 全生存期間（OS）を両群で比較する。
- 治療終了時／早期治療中止時の全奏効率（ORR）（完全奏効［CR］ + 部分奏効［PR］の割合）及び完全奏効率（CRR），治療期間中又は治療開始後12カ月以内の最良全奏効率，CR 達成患者の無病生存期間（DFS），CR 及び PR 達成患者の奏効期間をそれぞれの試験群で評価し，両群間で比較する。
- 無イベント生存期間（EFS）を両群間で比較する。
- ベンダムスチン + オビヌツズマブ併用療法又はベンダムスチン単剤療法を受けた患者の安全性プロファイルを評価，比較する。
- オビヌツズマブとベンダムスチンを併用した場合の薬物動態特性を明らかにし，ベンダムスチン単剤の薬物動態と比較することで，薬物間相互作用を評価する。
- 本試験の両群の薬剤経済学（医療資源の利用）を分析する。
- 両群の患者報告アウトカム（PROs）を評価する。

(7) 治験方法

患者は，1：1の割合で2つの治療群にランダム化した。最初の20例がサイクル1の試験治療を完了した後に独立データモニタリング委員会（IDMC）が過剰毒性の有無を決定した。IDMC がいずれかの群で過剰毒性が観察されたと決定した場合，ランダム化を中止し，治験実施計画書（特に投与方法）の修正を検討することとした。この最初の中間安全性解析の前に，IDMC は重篤な有害事象の月例評価を実施した。最初の中間安全性解析の後，IDMC は安全性要約の定期中間評価を年に約2回実施した。

ランダム化計画は，1）iNHL サブタイプ（FL vs. その他），2）治療抵抗性の種類（リツキシマブ単剤療法 vs. リツキシマブ + 化学療法），3）前治療（ ≤ 2 vs. > 2），4）地理的地域の4つの層別因子について，2つの試験群において症例数がほぼ均等となるように設計された。ランダム化は双方向音声認識システム（IVRS）を用いて実施した。

Benda 群では，ベンダムスチン単剤を120 mg/m^2/日の用量で各28日サイクルの Day 1及び Day 2に静脈内投与する治療を最大6サイクル実施した。

G–B 療法群では，オビヌツズマブを1000 mg の絶対（一定）用量で，サイクル1の Day 1，Day 8及び Day 15に，サイクル2～6（1サイクルは28日）では Day 1に，その後は2カ月ごとに病勢進行が認められるまで最大2年間静脈内投与した。ベンダムスチンは，本治験の試験（G–B 療法）群に最初に登録された10例において，薬物動態（PK）検査を実施するため，最初の10例に対しては，90 mg/m^2/日の用量でサイクル1の Day2及び Day3に，サイクル2～6では Day 1及び Day 2に静脈内投与し，その他の患者に対しては，90 mg/m^2/日の用量でサイクル1～6の Day 1及び Day 2に静脈内投与した。

すべての被験者について，主治医による診察，一般臨床検査，及びコンピューター断層撮影（CT）に基づき，改訂版 NHL 効果判定規準に従って，サイクル3の約4週間後（サイクル4開始前），サイクル6の約28～42日後，治療開始後6カ月後からは2カ月ごと（CT は3カ月ごと）に24カ月間（病勢の進行が認められない場合は最大で計30カ月）にわたり，治療効果を評価した。

試験来院日はサイクル1の Day 1（初回投与日），Day 8及び Day 15，以降のサイクルは Day 1及び Day 15とした。最終追跡調査日（FU16 + 28日，試験治療開始から約31カ月後）において再発が認められなかった被験者は，更に2年間又は病勢の進行（どちらか早い方）まで6カ月ごとに腫瘍評価を継続した。病勢進行前に新たなリンパ腫治療を開始した被験者は同意を撤回しない限り，治験実施計画書のスケジュールに従い追跡調査を行った。226例の死亡例が発生する（最初の患者が登録されてから約96カ月後）まで全生存期間（OS）の追跡調査を行った。

すべての被験者について，IRF における CT 画像の盲検評価を含む，効果の独立評価も実施した。効果の独立評価は，中間解析及び最終有効性解析の前にそれぞれ実施することとした。病勢進行前にすべての試験治療を中止した被験者（副作用等のため）は，試験を継続し，病勢進行及び OS の追跡調査を行った（その後の新たなリンパ腫治療の施行の有無は問わない）。

(8) 被験者数

カットオフ日までに合計で396例がランダム化された。内訳は Benda 群202例，G–B 療法群194例であった。

(9) 診断及び主な組入れ基準

- 組織学的に確認された CD20陽性 iNHL（FL Grade1～3a，MZL［脾性，節性，節外性］，及びリンパ球の絶対数が5000 × 10^9/L 未満の小リンパ球性リンパ腫を含む）患者。
- リツキシマブを含む治療法に対して治療抵抗性の患者（直近のリツキシマブ療法［単剤療法か化学療法との併用のいずれか］に対して不応，又は治療終了後6カ月以内に病勢の進行が認められると定義する）。
- 過去に最大4回までの化学療法剤含有レジメン（「投与レジメン」とは，化学療法を単独又は抗体療法と併用するレジメンで，予定された治療を少なくとも2サイクル施行する投与レジメンと定義する）が施行された患者。
- 少なくとも1つの直交する2方向で計測可能な病変（CT 画像上の最大径> 1.5 cm の病変）を有する患者。
- Eastern Cooperative Oncology Group (ECOG) Performance Status が0～2である患者。

(10) 被験薬の用量，投与方法及び投与期間

オビヌツズマブ1000 mg をサイクル1の Day 1，Day 8及び Day 15に，サイクル2～6にかけては Day 1に投与し，その後は2カ月ごとに，病勢進行が認められるまで最大2年間投与した。

(11) 対照薬の用量及び投与方法

Benda 群：各28日サイクルの連続する2日間にベンダムスチンを120 mg/m^{2}の用量で60分かけて静脈内投与する治療を単剤療法として最大6サイクル施行した。

G–B 療法群：各28日サイクルの連続する2日間にベンダムスチンを90 mg/m^{2}の用量でオビヌツズマブ（上記参照）とともに60分かけて静脈内投与する治療を最大6サイクル施行した。

(12) 評価基準

1) 有効性

主要変数：主要有効性評価項目は，IRC 評価に基づく PFS とした。PFS の解析には有効性及び無益性の棄却限界値が含まれた。有効性の棄却限界値は，O'Brien-Fleming 型の形状の棄却限界値への Lan-DeMets 近似を用いて算出された。無益性の棄却限界値は，中間解析時に観察されるハザード比が無益性の棄却限界値に正確に一致する場合に，その95%CI（解析時点の順序を用いて中止ルールを調整）が対立仮説のハザード比である0.7を含まないように選択された。

2) 薬力学

ベンダムスチン + オビヌツズマブ投与患者における CD19陽性 B 細胞数の経時的変化。

3) 薬物動態

オビヌツズマブとベンダムスチンの併用療法を受けた最初の10例の薬物動態解析用検体及びベンダムスチン単剤療法を受けた最初の10例の薬物動態解析用検体。

オビヌツズマブのベンダムスチン併用投与時の薬物動態プロファイル（トラフ濃度，クリアランス速度，血中濃度–時間曲線下面積［AUC］）。

4) 安全性

有害事象（NCI-CTCAE Ver.4.0に基づく Grade 判定），B 細胞の枯渇及び回復，IgA，IgG，IgM を含む臨床検査。

(13) 統計的手法

有効性：両側層別 Log-rank 検定，主要解析の確認のため，両側有意水準5%とする層別 Log-rank 検定を実施した。PFS 中央値及び95%信頼限界は Greenwood の公式を用いた Kaplan-Meier 法を用いて推定した。感度解析として非層別 Log-rank 検定も実施した。奏効率はカイ二乗検定を用いて比較した。加えて，両群の差の95%信頼限界を Cochran-Mantel Haenszel 検定を用いて算出した。

(14) 結果の要約

1) 有効性

3回目の中間解析（有効性及び無益性）は，170件の IRC 評価による PFS イベントが起きた後に実施するように計画された。主要評価項目である IRC 評価の PFS を達成したため，IDMC は治験依頼者に対して盲検化の解除，完全な解析の実施，及び結果の公表を勧告した。主要解析は，この計画された3回目の中間解析後に，2014年9月1日をカットオフ日として実施された。

主要評価項目を達成したことから，重要な副次的評価項目を，以下の階層順で検定した。

- 主治医評価による PFS
- IRC 評価による治療開始後12カ月間の BOR
- IRC 評価による治療開始後12カ月間の最良奏効としての CR
- OS

GAO4753g 試験の有効性の結果を以下に要約する。

- 主要評価項目である IRC 評価の PFS は達成された。
  - G–B 療法群において，Benda 群と比較し，IRC 評価の病勢の進行と死亡のリスクを45%と統計学的に有意で臨床的に意義ある減少が認められた（層別ハザード比：0.55［95%CI：0.40～0.74］，層別 Log-rank 検定：P = 0.0001）。
  - Benda 群の PFS 中央値は14.9カ月（95%CI：12.8～16.6カ月），G–B 療法群では未達であった。

- 主要な有効性の結果の頑健性は，以下により証明された。
  - re-randomization 検定，非層別解析，及び PFS の代替定義を評価するために特定の打ち切りルールを適用した様々な探索的解析を含む感度解析（IRC 評価による PFS のハザード比：0.49～0.62）。
  - 患者背景，ベースライン時の要因，及び潜在的な予後マーカーに基づくサブグループにおける，G–B 療法群での IRC 評価による PFS の改善（20例を超えるすべてのサブグループの IRC 評価による PFS のハザード比は1を下回った。）。

- ベンダムスチンにオビヌツズマブを加えることのベネフィットは，主要解析と一致していた副次的有効性評価項目である主治医評価の PFS の結果により更に支持された（ハザード比：0.52，95%CI：0.39～0.70，層別 Log-rank 検定：P < 0.0001）。
- IRC 評価による最良全奏効率（CR／PR）（G–B 療法群：78.6%，Benda 群：76.6%），及び治療開始後12カ月間の最良 CR 率（16.7%，17.3%）では群間で統計学的な有意差は認められなかった。IRC 評価による治療終了時（EOT）の奏効率は Benda 群（63.0%）に比べて G–B 療法群（69.1%）で数字の上では高かった。
- 完全奏効を達成した患者における，CR／PR を達成した患者の奏効期間（DOR）及び無病生存期間（DFS：CR／PR を達成してから病勢進行又は死亡までの期間）は，Benda 群（DOR，DFS ともに中央値13.2カ月）と比べて G–B 療法群（中央値未達）で長かった。DOR のハザード比は0.42（95%CI：0.29～0.61），DFS のハザード比は0.09（95%CI：0.02～0.40）であった。
- 無イベント生存期間（EFS）（病勢進行，再発，死亡又は新たなリンパ腫治療［NALT］開始までの期間）は Benda 群と比べて G–B 療法群で長かった（中央値：26.8カ月 vs. 13.7カ月）（ハザード比：0.57；95%CI：0.43～0.76，層別 Log-rank 検定：P = 0.0001）。
- 主要解析時点で，いずれの治療群も OS 中央値は推定不能であったが，ハザード比は1を下回っていた（層別解析：ハザード比：0.82；95%CI：0.52～1.30，層別 Log-rank 検定：P = 0.4017）。
- 組織型別の有効性評価項目の探索的解析において，FL 患者のサブグループと iNHL 患者群全体（ITT）で一致した結果が示された。
- FACT-Lym 及び EQ-5D 健康指標調査を用いた，患者報告 HRQoL 及び健康状態は，いずれも治療期間中及び追跡調査期間において，Benda 群と G–B 療法群で違いは示されなかった。ベースラインから6ポイントの悪化と定義した FACT-Lym TOI スコアが悪化するまでの期間は，ベンダムスチン群（中央値4.6カ月）と比べて G–B 療法群（中央値8.0カ月）で遅かった（ハザード比：0.74；95%CI：0.56～0.98）。

2) 薬力学

B 細胞の枯渇と回復は G–B 療法群の被験者のみ評価した。B 細胞の結果が得られた121例中116例で最後のオビヌツズマブ投与時に B 細胞が枯渇していた。十分な期間にわたり追跡された被験者数が少ないため，回復の評価はできなかった。オビヌツズマブ最終投与後6～12カ月時点において，26例のみが B 細胞が評価され，B 細胞が回復していたのは26例中1例のみであった。12カ月後の B 細胞評価の結果が得られた被験者数は非常に少なかった。データカット

オフ時点で B 細胞の回復が確認された被験者のみを考えると，抗体最終投与から B 細胞回復までの期間の中央値は660日（約1.8年）（範囲：1～746日）であった。データカットオフ時点で，G–B 療法群の免疫グロブリンが枯渇した被験者の内，免疫グロブリンの回復した被験者はおらず，回復までの期間の算出はできなかった。

3) 薬物動態

以前の母集団 PK 解析モデルは，BO20999試験，BO21003試験，BO21000試験，BO21004試験から確立された（CLL11BAR pop PK report）。今回のモデルでは，GAO4753g 試験及び GAO4915g の2つの新しい試験のデータが追加された。母集団 PK 解析から得られた，組織型別のサイクル6終了時の血清オビヌツズマブ濃度の幾何平均を表 2.7.6.1.4-1に示す。これらの結果は，GAO4753g 試験から得られた追加データが以前の解析結果と一致していることを示している。

表 2.7.6.1.4-1　サイクル6終了時の組織型別の C_{max}，C_{trough}，AUC_{τ} の条件予測の要約

PK Parameter	Static	Disease Type			
		CLL	iNHL	DLBCL	MCL
Number of subjects		342	469	130	20
C_{max} (μg/mL)	Geometric Mean (CV)	466.3 (0.35)	539.1 (0.33)	463.4 (0.33)	340.5 (0.41)
C_{trough} (μg/mL)	Geometric Mean (CV)	192.5 (0.78)	276.9 (0.69)	223.8 (0.57)	73.4 (1.38)
AUCτ (μg/mL•day)	Geometric Mean (CV)	8701 (0.51)	10927 (0.45)	8904 (0.44)	5069 (0.68)

［5.3.5.1-3-1 Table 45を改変］

ベンダムスチンの薬物動態に対するオビヌツズマブの影響を調べるため20例を対象に集中的な PK 測定を実施した。10例はオビヌツズマブが投与された時にベンダムスチンの薬物動態を評価し，ベンダムスチン単剤を投与された10例との比較が行われた。オビヌツズマブの PK に対するベンダムスチンの影響は評価しなかった（BO21000試験で検討したため）。

ベンダムスチンの静脈内投与後，ベンダムスチンの半減期（$t_{1/2}$）は，ベンダムスチン単剤投与，併用投与のそれぞれにおいて24.6分と28.6分と速やかな消失を示していた。併用群（ベンダムスチンの用量：90 mg/m^2）と単剤群（ベンダムスチンの用量：120 mg/m^2）の間にベンダムスチンの AUC_{inf} 及び C_{max}（用量標準化）の差は認められなかった。単回投与後のベンダムスチンのクリアランス（CL）の幾何平均は，オビヌツズマブとの併用時（594 mL/分）と単剤投与時（650 mL/分）で臨床的意義のある差は認められなかった（幾何平均の比の95%CI）。本試験の最初の20例のベンダムスチンの PK 結果の要約を表 2.7.6.1.4-2に示す。

表 2.7.6.1.4-2　ベンダムスチンの血漿中薬物動態（PK）の要約

	Bendamustine	Bendamustine + GA101	Bendamustine/ Bendamustine + GA101	
	Geometric mean (%CV)	Geometric mean (%CV)	Ratio of Geometric Mean	95% CI for Ratio of Geometric Mean
C_{max} (ng/mL/mg)	26.40 (65.3)	23.8 (72.5)	1.11	(0.57, 2.16)
AUC (inf) (min・ng/mL/mg)	1680 (72.6)	1540 (87.7)	1.10	(0.53, 2.26)
$t_{1/2}$ (min)	24.6 (29.0)	28.6 (20.7)		
V_d (mL)	21100 (71.6)	26800 (59.5)		
CL (mL/min)	594 (78.0)	650 (54.2)		

C_{max} and AUC_{inf} were dose normalized.
［5.3.5.1-3-1 Table 46を再掲］

4)　安全性

治療期間において，大多数の患者が予定された投与量の90%以上の用量を投与された。両群でベンダムスチンが異なる予定投与量で投与されたため，導入療法期間において，ベンダムスチンの累積投与量は，G–B 療法群と比べて Benda 群で高かった（表 2.7.6.1.4-3）。

全体として，予測できない安全性所見は認められなかった。両群で治療期間や安全性報告に違いがあるにもかかわらず，有害事象（全 Grade）（Benda 群：98.0% vs. G–B 療法群：98.5%），死亡（20.7% vs. 17.5%），致死的な有害事象（6.1% vs. 6.2%）の発現率は，両群で同様であった。両群ともに，最も発現頻度が高かった致死的な有害事象は，感染症と二次性悪性腫瘍であり，特定の致死的な有害事象の発現率は両群間で著しい不均衡はなかった。

G–B 療法群で発現率が高かった Grade 3～5の有害事象，SAE，投与中止に至った有害事象の大部分は，主に好中球減少症と注入に伴う反応によるものであった。

血小板減少症は G–B 療法群と比べて，Benda 群で頻度が高く報告された。

試験期間中（導入療法期間，維持療法期間，追跡調査期間を含む）の全 Grade の心臓の有害事象の発現率は，G–B 療法群と比べて Benda 群で低かった（11 例［5.6%］vs. 22 例［11.3%］）。心臓の有害事象の3分の1は投与中又は投与後24時間以内に発現し，本試験のために使われた IRR の定義に従い，IRR とみなされた。IRR とみなされた事象を考慮すると，心臓の有害事象は患者の2.1%以下で報告されたため，この差は特定の心臓有害事象によるものではないと考えられた。

本試験の特に注目すべき有害事象の性質，頻度，重症度は，既知のオビヌツズマブの安全性プロファイルと一致していた。

FL 患者集団における安全性解析は，iNHL 患者集団における安全性解析と一致していた。

表 2.7.6.1.4-3　全試験期間の曝露及び有害事象の概要（安全性解析対象集団［SAP］）

	Benda	G-benda
	(N = 198)	(N = 194)
Induction		
Median Cumulative dose bendamustine	2347 mg	1920 mg
Median cumulative dose of obinutuzumab	-	8000 mg
Maintenance		
Median duration of treatment (months)	-	330 days
Median cumulative dose of obinutuzumab	-	6000 mg
Median observation time	20.3 months	21.9 months
Safety Events		
Total number of deaths	41 (20.7%)	34 (17.5%)
Total number of patients with at least one:		
AE	194 (98.0%)	191 (98.5%)
Grade 3-5 AE	123 (62.1%)	132 (68.0%)
Grade 5 AE (fatal outcome)	12 (6.1%)	12 (6.2%)
Serious AE	65 (32.8%)	74 (38.1%)
AE leading to withdrawal from any study treatment	31 (15.7%)	35 (18.0%)
AE leading to withdrawal from assigned study regimen (all study medication)*	31 (15.7%)	22 (11.3%)
AE leading to dose modification (all modifications, including interruptions)	87 (43.9%)	119 (61.3%)
AE leading to dose modification (dose decreased or held)	82 (41.4%)	96 (49.5%)
AE leading to dose interruption	8 (4.0%)	50 (25.8%)
AEs of particular interest		
Neutropenia	63 (31.8%)	73 (37.6%)
Grade 3-5	58 (29.3%)	69 (35.6%)
Infusion related AEs	125 (63.1%)	133 (68.6%)
Grade 3-5	11 (5.6%)	21 (10.8%)
Thrombocytopenia	47 (23.7%)	29 (14.9%)
Grade 3-5	32 (16.2%)	21 (10.8%)
Infections	110 (55.6%)	127 (65.5%)
Grade 3-5	34 (17.2%)	35 (18.0%)
Cardiac events	11 (5.6%)	22 (11.3%)
Grade 3-5	3 (1.5%)	9 (4.6%)
Second malignancy	10 (5.1%)	14 (7.2%)
Grade 3-5	7 (3.5%)	6 (3.1%)

Investigator text for AEs encoded using MedDRA v17.1.

* This shows the number of patients who were withdrawn from all assigned study medication

［5.3.5.1-3-1 Table 47を改変］

注釈：G–B 療法群における投与中断に至った有害事象の高い発現率は，主に IRR によるものであった。ベンダムスチンの用量変更に至った有害事象の発現率は，G–B 療法群に比べて Benda 群で高かった。

(15) 結論

- IRC 評価の PFS（主要有効性評価項目）の主要解析により，G–B 療法群において，Benda 群と比較し，病勢の進行と死亡のリスクを45%と統計学的に有意で臨床的に意義ある減少が認められた（ハザード比：0.55；95%CI：0.40～0.74； P = 0.0001，層別 Log-rank 検定）。Kaplan-Meier 法によって推定された Benda 群の PFS 中央値は14.9カ月，G–B 療法群では未達であった。主治医評価の PFS の結果は，IRC 評価の結果を確認するものであった（ハザード比：0.52，95% CI: 0.39～0.70，P < 0.0001，層別 Log-rank 検定）。Kaplan-Meier 法によって推定された Benda 群の PFS 中央値は14.0カ月，G–B 療法群は29.2カ月であった。
- ITT 集団の81.1%を占める FL 患者集団の結果は，iNHL 患者集団の結果と一致していた。IRC 評価の PFS のハザード比は0.48であった（95% CI：0.34～0.68，P < 0.0001，層別 Log-rank 検定）。Kaplan-Meier 法によって推定された Benda 群の PFS 中央値は13.8カ月，G–B 療法群では未達であった。EFS，DFS，DOR を含むイベントまでの期間（副次的評価項目）は，iNHL 患者集団及び FL 患者集団の双方で主要評価項目を支持した。全生存期間のデータはまだ不十分であった。奏効率（EOI の奏効率，BOR，最初の12カ月間の CR 率）は iNHL 患者集団及び FL 患者集団ともに両群で同様であった。これは，導入療法期間中に異なる用量のベンダムスチンを用いたことを反映したものと考えられた。
- FL 患者集団，iNHL 患者集団の双方で，ランダム化層別因子である患者背景，ベースライン時の疾患特性，及び FLIPI/IPI に基づくリスクグループに基づき事前に設定されたサブグループすべてにおいて，G–B 療法 + G 維持療法による治療ベネフィットは一貫していた。20例を超えるサブグループにおいて，HR は1を下回った。
- オビヌツズマブの用法・用量は，リツキシマブ治療抵抗性の iNHL 患者集団において，治療期間中の速やかな標的の飽和とトラフ濃度の安定をもたらした。本試験の iNHL 患者から得られた PK 所見は，以前の母集団 PK 解析の所見と一致していた。
- G–B 療法群の全体的な安全性プロファイルは，SAE，Grade 3～5の有害事象，用量変更／投与中断に至った有害事象の発現率が高かったことを除き，Benda 群の全体的な安全性プロファイルと同様であった。これらの違いは主に注入に伴う反応によるものであった。感染症は，G–B 療法群において，頻度が高く報告されたが，Grade 3～5の感染症，重篤な感染症，及び致死的な感染症の発現率は両治療群で同様であった。
- 全体的に，大半の有害事象は導入療法期間中に発現した。維持療法期間中の有害事象の性質，頻度は，iNHL 患者集団におけるオビヌツズマブ単剤療法の既知の安全性プロファイルと一致していた。
- iNHL 患者全体と FL 患者における G–B 療法群の安全性プロファイルと Benda 群の安全性プロファイルは同様であった。非 FL の患者数は，iNHL や FL 患者集団と比較するためには少なすぎたと考えられた。
- 本試験の忍容可能な安全性プロファイル及び良好な患者報告アウトカムに加えて，PFS 及び関連する有効性の指標の改善の大きさは，iNHL 及び FL 患者に対するオビヌツズマブとベンダムスチンによる治療の有望なベネフィットとリスクのバランスを示している。

(16) 報告書作成日

2015年7月

2015年12月に主要解析のためのカットオフ以降に更新されたデータについて，2015年5月1日までのデータを取りまとめ，GAO4753g 試験の総括報告書の改訂版が作成された。以下に主な追加情報及び変更点を記載する。

(1) 治験実施期間

2010年4月15日（初回患者登録日）～2015年5月1日（データカットオフ日）

(2) 被験者数

主要解析時点以降に17例（G–B 療法群10例，Benda 群7例）が登録され，カットオフ日までに413例（G–B 療法群204例，Benda 群209例）が登録された。

(3) 結果の要約

1) 有効性

- G–B 療法群において，Benda 群と比較し，IRC 評価の病勢の進行と死亡のリスクを47%と統計学的に有意で臨床的に意義ある減少が認められた（ハザード比：0.53［95%CI：0.40～0.70］，層別解析）。この結果は主要解析の結果（ハザード比：0.55［95%CI：0.40～0.74］，層別 Log-rank 検定：P= 0.0001）と一貫していた。
- Kaplan-Meier 法で推定した PFS 中央値は，Benda 群は14.1カ月（95%CI：11.7～16.6カ月），G–B 療法群は Benda 群の2倍を超える29.2カ月（95%CI：20.5カ月～推定不能）であり，G–B 療法群で15.1カ月の PFS の延長が認められた。
- 副次的評価項目である PFS（主治医評価）は IRC 評価と同様の結果であった（ハザード比：0.52［95%CI：0.40～0.68］）。PFS（主治医評価）中央値は，Benda 群は14.0カ月（95%CI：11.5～16.0カ月），G–B 療法群は25.8カ月（95%CI：20.2～42.7カ月）であった。
- 最良全奏効率（BORR）及び導入療法終了時の奏効率は両群で同様であった。しかしながら，奏効は G–B 療法群がより長続きしており，CR 例又は PR 例の病勢進行・再発・死亡の Benda 群に対する G–B 療法群のハザード比は0.43（95%CI：0.31～0.61）と G–B 療法群が良好であった。DOR 中央値は G–B 療法群が Benda 群と比較して3倍であった（G–B 療法群：38.5カ月，Benda 群：12.7カ月）。これは，G–B 療法群で維持療法を実施したことが原因である可能性があった。
- OS は，本総括報告書アップデート作成時点においても不十分であった。Benda 群と比較し，G–B 療法群で死亡は少なかった（G–B 療法群：42/204例［20.6%］，Benda 群：56/209例［26.8%］）。ITT 患者集団の追加解析時点の死亡のリスクの Benda 群に対する G–B 療法群のハザード比は0.72（95%CI：0.48～1.08）であった（主要解析時点のハザード比は0.82［95%CI：0.52～1.30］）。

2) 安全性

安全性の追加解析は，主要解析のためのカットオフ後にランダム化されたベンダムスチン群7例，G–B 療法群10例を含む，409例（Benda 群205例，G–B 療法群204例）を対象に実施した。

導入療法期間では，G–B 療法群の多く（81.9%）が本剤を6サイクル投与しており，89.7%がオビヌツズマブを予定投与量の90%以上投与していた。また，Benda 群では71.7%，G–B 療法群では78.4%がベンダムスチンを6サイクル投与しており，各群の76.6%及び79.3%が予定投与量の90%以上投与されていた。ベンダムスチンの累積投与量の中央値は，ベンダムスチン群が高かったが（Benda 群2366 mg［範囲：394～3744 mg］，G–B 療法群1920.0 mg［範囲：128～2700 mg］，ベンダムスチンの用量が両群で異なることを反映したものと考えられた（Benda 群120 mg/m^2，G–B 療法群90 mg/m^2）。

追加解析時点で154例が少なくとも1回の維持療法を受けており，維持療法期間では大半（97.4%）が予定投与量の90%以上投与されていた。維持療法の投与回数の中央値は7であった（主要解析時点では6）。

安全性は，主要解析時点と一貫しており，新たな安全性のシグナルは検出されなかった。観察期間の中央値が延びたことにより（Benda 群4.2カ月，G–B 療法群3.4カ月），両群とも有害事象の発現率は主要解析時点と比較し，わずかに増えた。

主要解析時点と同様に，追加解析時点の Grade 3以上の有害事象の発現率は，Benda 群が64.4%，G–B 療法群が69.1%，SAE の発現率は，Benda 群が35.6%，G–B 療法群が41.2%，投与

中止に至った有害事象の発現率は，Benda 群が16.6%，G–B 療法群が19.1%，用量変更に至った有害事象の発現率は，Benda 群が42.0%，G–B 療法群が48.5%と，いずれも G–B 療法群で発現率が高かった。

追加解析時点で，Benda 群56例（27.3%），G–B 療法群42例（20.6%）が死亡していた。最も多い死亡理由は病勢進行であった（Benda 群21.0%，G–B 療法群13.2%）。また，死亡に至った有害事象の発現率は両群で同様であった（13例［6.3%］，15例［7.4%］）。主要解析時点以降に新たに23例（Benda 群15例，G–B 療法群8例）が死亡しており，主な死因は追跡調査期間中の病勢進行（14例，5例）であった。主要解析時点以降に新たに Benda 群1例（追跡調査期間中の虚血性発作），G–B 療法群3例（追跡調査期間中の骨髄異形成症候群と心筋梗塞，維持療法期間中の腸管腺癌）で死亡に至った有害事象が発現した。

追加解析時点で，Benda 群8例，G–B 療法群10例が主要解析時点以降に新たに SAE を発現した。また，Benda 群3例，G–B 療法群4例が主要解析時点以降に新たに投与中止に至った有害事象を発現した。

主要解析時点と同様に，追加解析時点で認められた特に注目すべき有害事象の発現率は Benda 群と比較して G–B 療法群が高かった。G–B 療法群の特に注目すべき有害事象の発現率は，主要解析時点と同様であった。

主要解析時点と同様に，ベンダムスチンの累積投与量が Benda 群で高いことと一貫して，血小板減少症の発現率は Benda 群で高かった（Grade 3以上：50例［24.4%］，30例［14.7%］）。

(4) 結論

- iNHL 患者の ITT 患者集団における PFS（IRC 評価）で一貫したベンダムスチン群に対する G–B 療法群の治療ベネフィットが示された（ハザード比：0.53［95%CI：0.40～0.70］）。追加解析時点で G–B 療法群の PFS 中央値に到達しており（29.2カ月［95%CI：20.5カ月～推定不能］），Benda 群の PFS 中央値（14.1カ月［95%CI：11.7～16.6カ月］）の2倍を超えており，15.1カ月の PFS 中央値の延長が認められた。
- より長い追跡調査に伴い，ITT 患者群の死亡のリスクのハザード比は主要解析時点で0.82（95%CI：0.52～1.30）から0.72（95%CI：0.48～1.08）と改善が認められた。
- 奏効率は両群で同様であったが，奏効は Benda 群と比較し G–B 療法群でより長く続いた（DOR 中央値：G–B 療法群38.5カ月，Benda 群12.7カ月）。
- 全体的に追加解析時の本剤の安全性プロファイルは主要解析時点と比較し，有害事象の発現率，種類，重症度の点で一貫した結果が得られた。より長い経過観察において，新たな安全性のシグナルは観察されなかった。
- ITT 患者集団の81.1%を占める FL 患者の有効性，安全性の結果は iNHL 患者全体の結果と同様であった。

  FL 患者において，G–B 療法群は Benda 群と比較して IRC 評価に基づく病勢進行又は死亡のリスクを53%低下させた（ハザード比：0.47［95%CI：0.34～0.64］）。FL 患者の PFS（IRC 評価）は ITT 患者集団の PFS（IRC 評価）と同様に中央値に到達しており（29.2カ月［95%CI：20.5カ月～推定不能］），Benda 群の PFS 中央値（13.8カ月［95%CI：11.5～15.8カ月］）の2倍を超える15.4カ月の PFS の延長が認められた。より長い追跡調査に伴い，FL 患者の死亡のリスクのハザード比は主要解析時点で0.71（95%CI：0.43～1.19）から0.62（95%CI：0.39～0.98）と改善が認められた。
- 本試験で観察された PFS 中央値の2倍の延長，生存期間の改善及び許容可能な安全性プロファイルは，再発・治療抵抗性の iNHL 患者及び FL 患者に対するオビヌツズマブとベンダムスチンによる治療の明確なベネフィットとリスクのバランスを引き続き支持するものである。

(5) 報告書作成日

2015年12月

[redacted]年[redacted]月に2016年4月1日までのデータを取りまとめ，GAO4753g 試験の総括報告書の改訂版が作成された。以下に主な追加情報及び変更点を記載する。

(1) 公表

GAO4753g 試験の主要な結果は以下の論文で報告されている。

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, openlabel, multicentre, phase 3 trial. Lancet Oncol. 2016;17: 1081-1093.

(2) 治験実施期間

2010年4月15日（初回患者登録日）～2016年4月1日（データカットオフ日）

(3) 結果の要約

1) 有効性

- ITT 患者集団の追加解析のためのデータカットオフ時点の観察期間中央値は，Benda 群30.0カ月（範囲：0～65.1カ月），G–B 療法群34.0カ月（範囲：0.4～65.9カ月）であった。主要解析時点の観察期間中央値と比較し，Benda 群で9.8カ月，G–B 療法群で12.1カ月の追加フォローアップがなされた。
- 2016年4月1日のデータカットオフ時点で G–B 療法群の56.4%及び Benda 群の69.9%の被験者で病勢の進行又は死亡の PFS イベントが認められた。G–B 療法群では，Benda 群と比較して主治医評価に基づく病勢進行及び死亡のリスクを43%減少させた（ハザード比：0.57［95%CI：0.44～0.73］，層別解析）。データカットオフ時点の解析の結果は主要解析時点の結果と一貫していた。Kaplan-Meier 法で推定した PFS 中央値（主治医評価）は Benda 群では14.1カ月（95%CI：12.6～16.0カ月），G–B 療法群では25.8カ月（95%CI：19.5～41.1カ月）と G–B 療法群で11.7カ月の延長が認められた。
- 本追加解析では，探索的に新たなリンパ腫治療開始までの期間を評価した。データカットオフ時点で Benda 群の66.5%，G–B 療法群の49.0%の被験者が新たなリンパ腫治療を開始又は理由を問わない死亡に至っていた。新たなリンパ腫治療開始前に死亡した被験者数は両群で同様であった（Benda 群24例，G–B 療法群23例）。Benda 群と比較すると，G–B 療法群で新たなリンパ腫治療開始又は理由を問わない死亡の頻度は低かった（ハザード比：0.59［95%CI：0.45～0.77］）。PFS 中央値が Benda 群と比較し，G–B 療法群が長いことと関連して，新たなリンパ腫治療開始までの期間の中央値は G–B 療法群で40.8カ月と Benda 群の19.4カ月の2倍以上であった。
- データカットオフ時点で，生存期間のフォローアップ期間の中央値は両群で同様であった（Benda 群41.7カ月，G–B 療法群41.6カ月）。Benda 群と比較して G–B 療法群の死亡は少なかった（Benda 群73/209例［34.9%］，G–B 療法群52/204例［25.5%］）。追加解析時点の ITT 患者集団の死亡のリスクのハザード比は0.67（95% CI: 0.47～0.96）であり，主要解析時点のハザード比0.82（95% CI: 0.52～1.30）と比較すると，より OS を改善する傾向が示された。OS 中央値は両群とも未達であった。
- 治療期間中及び治療開始から12カ月までの，主治医評価に基づく最良奏効率（CR 及び PR）（Benda 群83.3%，G–B 療法群82.4%）と最良 CR 率（Benda 群21.5%，G–B 療法群23.5%）は両群で同様であった。
- 主治医評価に基づく奏効が得られた被験者（CR 又は PR）が病勢進行又は死亡するまでの期間のハザード比は0.49（95%CI：0.37～0.65）であり，G–B 療法群の方が長かった。G–B 療法群では Benda 群と比較し，DOR 中央値が2.5倍以上長かった（Benda 群12.2カ月，G–B 療法群32.4カ月）。G–B 療法群には維持療法期間があることに起因している可能性がある。

- 主治医評価に基づく完全奏効が得られた被験者が病勢進行又は死亡するまでの期間のハザード比は0.49（95%CI：0.28～0.84）であり，G–B 療法群の方が長かった。G–B 療法群の DFS 中央値は33.4カ月，Benda 群の DFS 中央値は20.0カ月であった。
- 導入療法終了時の奏効率（CR 及び PR）は Benda 群と比較して G–B 療法群が高かったが（Benda 群68.9%，G–B 療法群77.5%），導入療法終了時の CR 率は両群で同様であった（Benda 群15.8%，G–B 療法群17.2%）。
- 2016年4月1日のデータカットオフ時点で，FL 患者は335例登録された（Benda 群171例［ITT 患者集団の81.8%］，G–B 療法群164例［80.4%］）。FL 患者のデータカットオフ時点の観察期間中央値は，Benda 群29.3カ月，G–B 療法群32.6カ月であり，主要解析時点と比較し，Benda 群で9.0カ月，G–B 療法群で10.5カ月の追加フォローアップがなされた。
- 追加解析時の FL 患者の PFS（主治医評価）のハザード比は0.52（95%CI：0.39～0.69）であり，主要解析時点（ハザード比：0.48［95%CI：0.34～0.68］）と一貫していた。Kaplan-Meier 法で推定した FL 患者の PFS 中央値（主治医評価）は G–B 療法群では25.3カ月（95%CI：17.4～36.0カ月），Benda 群では14.0カ月（95%CI：11.3～15.3カ月）と G–B 療法群で11.3カ月の延長が認められた。
- データカットオフ時点で Benda 群の70.8%，G–B 療法群の50.0%の被験者（FL）が新たなリンパ腫治療を開始又は理由を問わない死亡に至っていた。Benda 群と比較すると，G–B 療法群で新たなリンパ腫治療開始又は理由を問わない死亡の頻度は低かった（ハザード比：0.57［95%CI：0.43～0.75］）。新たなリンパ腫治療開始までの期間の中央値は，Benda 群の18.0カ月，G–B 療法群33.6カ月であった。
- Benda 群と比較して G–B 療法群の死亡は少なかった（Benda 群64/171例［37.4%］，G–B 療法群39/164例［23.8%］）。追加解析時点の Benda 群に対する G–B 療法群の FL 患者集団の死亡のリスクのハザード比は0.58（95% CI: 0.39～0.86）であった（主要解析時点のハザード比0.71［95% CI: 0.43～1.19］）。

2) 安全性

安全性の追加解析は安全性解析対象集団を対象に実施した。合計409例（Benda 群205例，G–B 療法群204例）が少なくとも1回治験薬を投与された。

治験実施計画書第10版の記載に従い，Benda 群の内2例がベンダムスチンの導入療法後にオビヌツズマブの維持療法を実施することが許可された。これら2例は導入療法期間を除き，安全性の解析から除外された。したがって，本項では Benda 群203例，G–B 療法群204例の安全性データを記載する。

導入療法期間では，G–B 療法群の多く（81.9%）がオビヌツズマブを6サイクル投与しており，89.7%が本剤を予定投与量の90%以上投与していた。また，Benda 群では72.2%，G–B 療法群では78.3%がベンダムスチンを6サイクル投与しており，各群の76.6%及び79.3%が予定投与量の90%以上投与されていた。ベンダムスチンの累積投与量の中央値は，ベンダムスチン群が高かったが（Benda 群2368 mg［範囲：394～3744 mg］，G–B 療法群1920 mg［範囲：128～2700 mg］，ベンダムスチンの用量が両群で異なることを反映したものと考えられた（Benda 群120 mg/m^2，G–B 療法群90 mg/m^2）。オビヌツズマブの維持療法を受けた Benda 群の2例はベンダムスチンの導入療法を6サイクル実施した。

追加解析時点で158例が少なくとも1回の維持療法を受けており，維持療法期間では大半（98.1%）が予定投与量の90%以上投与されていた。維持療法の投与回数の中央値は9であった（主要解析時点では6）。

安全性は，主要解析時点と一貫しており，新たな安全性のシグナルは検出されなかった。両群ともほぼ全例が少なくとも1つの有害事象を発現していた（Benda 群98.5%，G–B 療法群99.0%）。

主要解析時点と同様に，追加解析時点の Grade 3以上の有害事象の発現率は，Benda 群が65.5%，G–B 療法群が72.5%，SAE の発現率は，Benda 群が36.9%，G–B 療法群が43.6%，投与中止に至った有害事象の発現率は，Benda 群が17.2%，G–B 療法群が20.1%と，いずれも G–B 療法群で発現率が高かった。

追加解析時点で，Benda 群73例（34.9%），G–B 療法群52例（25.5%）が死亡していた。最も多い死亡理由は病勢進行であった（Benda 群29.6%，G–B 療法群17.6%）。また，死亡に至った有害事象の発現率は両群で同様であった（13例［6.4%］，16例［7.8%］）。死亡に至った有害事象の内，頻度が高かったのは感染症（7例，6例）と主にフォローアップ期間中に報告された固形癌と血液癌を含む二次性悪性腫瘍（3例，5例）であった。

追加解析時点で，Benda 群と比較し G–B 療法群で SAE 発現率が高かった（Benda 群75/203例［36.9%］に122件，G–B 療法群89/204例［43.6%］に170件）。

追加解析時点の試験薬（オビヌツズマブ又はベンダムスチン）の投与中止に至った有害事象の発現率は，Benda 群17.2%（35例），G–B 療法群20.1%（41例）であった。

主要解析時点と同様に，追加解析時点で認められた特に注目すべき有害事象（好中球減少症，IRR，感染症，心臓関連事象及び二次性悪性腫瘍）の発現率は Benda 群と比較して G–B 療法群が高かった。より長いフォローアップにより，両群とも感染症の発現率が少し増加し，二次性悪性腫瘍及び好中球減少症の発現率は Benda 群と比較し，G–B 療法群で増加した。G–B 療法群での増加は主に被験者がオビヌツズマブの単剤投与を受けた維持療法期間中にこれらの事象が報告されたこと及びフォローアップ期間中にこれらの事象が報告されたことに起因している。追加解析時点における上記以外の特に注目すべき有害事象の発現率（全 Grade 及び Grade 3～5）は主要解析時点と同様であった。

(4) 結論

GAO4753g 試験の改訂版 CSR の有効性及び安全性の解析は，2016年4月1日のデータカットオフ日のデータに基づき実施された。観察期間中央値は Benda 群30.0カ月（範囲：0～65.1カ月），G–B 療法群34.0カ月（範囲：0.4～65.9カ月）であり，主要解析時点（データカットオフ日：2014年9月1日）の観察期間中央値と比較し，Benda 群で9.8カ月，G–B 療法群で12.1カ月の追加フォローアップがなされた。全体的に得られた結果は主要解析時点と同様であった：

- iNHL 患者の ITT 患者集団では，G–B 療法群は Benda 群と比較して病勢進行（主治医評価）又は死亡のリスクを43%減少させた（ハザード比0.57［95%CI：0.44～0.73］）。治療効果は主要解析と同様であった。Kaplan-Meier 法で推定した PFS 中央値は，Benda 群14.1カ月（95%CI：12.6～16.0カ月），G–B 療法群25.8カ月（95%CI：19.5～41.1カ月）であり，G–B 療法群で PFS 中央値が11.7カ月長かった。
- ITT 患者集団では，Benda 群に対する G–B 療法群の生存期間のハザード比は，より長いフォローアップに伴い改善した。すなわち，主要解析時点の ITT 患者集団の死亡のリスクのハザード比0.82（95%CI：0.52～1.30）と比較し，追加解析時点における ITT 患者集団の死亡のリスクのハザード比は0.67（95%CI：0.47～0.96）であった。G–B 療法群と比較し，Benda 群でより多くの死亡例が認められた（Benda 群73例［34.9%］，G–B 療法群52例［25.5%］）。主な死因は病勢進行であった。
- 奏効率は両群で同様であったが，奏効は Benda 群と比較して G–B 療法群で良好であった（DOR 中央値：Benda 群12.2カ月，G–B 療法群32.4カ月，DFS 中央値：Benda 群20.0カ月，G–B 療法群33.4カ月）。
- 新たなリンパ腫治療開始までの期間は，ベンダムスチンの治療（導入療法のみ）後の期間（中央値19.4カ月）と比較し，G–B 療法による導入療法後のオビヌツズマブ維持療法後の期間（中央値40.8カ月）が長かった。
- 全体的に，本改訂版 CSR に示したオビヌツズマブの安全性プロファイルは，主要解析時点と比較し，有害事象の発現率，タイプ及び重症度の面で同様であった。より長いフォローア

ップ期間中に新たな安全性のシグナルは観察されなかった。

- Grade 3～5の有害事象，重篤な有害事象，投与中止に至った有害事象及び特に注目すべき有害事象である好中球減少症，IRR，感染症，心臓関連の有害事象及び二次悪性腫瘍の発現率は，全般的に Benda 群と比較し，G–B 療法群が高かった。GAO4753g 試験の安全性の両群間の比較では，治療期間の違い（Benda 群6カ月，G–B 療法群2.5年）と治療期間の大部分を占める導入療法後の安全性データの収集の両群間での違いを考慮に入れる必要がある。
- G–B 療法群と比較し，Benda 群でより多くの死亡例が認められた（Benda 群73例［36.0%］，G–B 療法群52例［25.5%］）。主な死因は病勢進行であった。病勢進行によらない有害事象による死亡例（最も頻度が高かったのは感染症と二次悪性腫瘍）は両群で同様であった（Benda 群13例［6.4%］，G–B 療法群16例［7.8%］）。
- より長いフォローアップにより，両群とも感染症の発現率が少し増加し，二次性悪性腫瘍及び好中球減少症の発現率は Benda 群と比較し，G–B 療法群でより多く増加した。G–B 療法群での増加は主に被験者がオビヌツズマブの単剤投与を受けた維持療法期間中にこれらの事象が報告されたこと及びフォローアップ期間中にこれらの事象が報告されたことに起因している。
- 胃腸障害は Benda 群で多く報告され（Benda 群82.3%，G–B 療法群74.0%），血小板減少症の発現率は Benda 群が高かった（Benda 群24.6%，G–B 療法群14.7%）。これらは，Benda 群の方がベンダムスチンの用量が多いことに関連していると考えられた。
- G–B 療法群の二次性悪性腫瘍の発現率と性質（10.8%，主に皮膚癌［BCC 及び SCC］，皮膚癌以外の二次性悪性腫瘍では臨床的な傾向は認められなかった）は，FL 患者に対するベンダムスチンの治療に関する文献で報告されたものと同様であった。
- 追加解析時点における上記以外の特に注目すべき有害事象の発現率（全 Grade 及び Grade 3～5）は主要解析時点と同様であった。

- ITT 患者集団の81.1%を占める FL 患者集団における有効性と安全性は iNHL 患者集団と同様であった。FL 患者でも，G–B 療法群と Benda 群を比較し，PFS（主治医評価）で G–B 療法の一貫した治療効果が示された（ハザード比：0.52［95%CI：0.39～0.69］）。FL 患者の PFS 中央値（主治医評価）は，Benda 群14.0カ月（95%CI：11.3～15.3カ月），G–B 療法群25.3カ月（95%CI：17.4～36.0カ月）であり，G–B 療法群で PFS 中央値が11.3カ月長かった。FL 患者では，Benda 群に対する G–B 療法群の生存期間のハザード比は，より長いフォローアップに伴い改善した。すなわち，主要解析時点の FL 患者集団の死亡のリスクのハザード比0.71（95%CI：0.43～1.19）と比較し，追加解析時点における FL 患者集団の死亡のリスクのハザード比は0.58（95%CI：0.39～0.86）であり，新たな生存期間のベネフィットが示された。
- GAO4753g 試験で観察された11カ月を超える PFS 中央値の延長と生存期間の改善，許容可能な安全性プロファイルは，再発・治療抵抗性の iNHL 及び FL に対するオビヌツズマブとベンダムスチンによる治療（G–B）の良好なベネフィットとリスクのバランスを引き続き支持するものである。

(5) 報告書作成日

[redacted]年[redacted]月

2.7.6.1.5　GAO4915g 試験（GATHER 試験）

(1) 試験の標題

GAO4915g – A Phase II, Open-Label, Multicenter Study of Efficacy, Safety, and Biomarkers in Patients With Previously Untreated Advanced Diffuse Large B-Cell Lymphoma Treated With GA101 (RO5072759) in Combination With CHOP Chemotherapy

GAO4915g 試験 – 未治療の進行期びまん性大細胞型 B 細胞リンパ腫患者を対象とした

GA101（RO5072759）と CHOP 療法を併用した際の有効性と安全性及びバイオマーカーを検討する第 II 相非盲検多施設共同試験

(2) フェーズ
第 II 相

(3) 治験依頼者及び治験実施施設
F. Hoffmann-La Roche 社／Genentech 社／アメリカの24施設

(4) 公表
Zelenetz AD, Mobasher M, Costa LJ, et al. Safety and efficacy of obinutuzumab (GA101) plus CHOP chemotherapy in first-line advanced diffuse large B-cell lymphoma: results from the Phase 2 GATHER study (GAO4915g) [abstract]. Proc American Society of Hematology 2013: abstract 1820.

(5) 治験実施期間
2011年8月10日（初回患者登録日）～2013年12月20日（データカットオフ日）

(6) 目的
主要目的
- 未治療の CD20陽性びまん性大細胞型 B 細胞性リンパ腫（DLBCL）患者を対象として，主治医評価に基づく全奏効率（ORR）及び完全奏効（CR）を検討することにより，CHOP（シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾン）療法と併用するときの GA101の有効性を推定する。

副次的目的
安全性に関する目的
- 未治療の CD20陽性 DLBCL 患者を対象として，有害事象及び重篤な有害事象の発現率及び重症度を検討することにより，CHOP 療法と併用するときの GA101の安全性を評価する。
- 投与時間短縮投与（SDI）で GA101投与を受けた患者を対象として，Grade 3又は4の Infusion reaction（Infusion-related reaction，以降 IRR）関連の有害事象の発現率を検討することにより，GA101を SDI で投与するときの安全性及び忍容性を評価する。

有効性に関する目的
- 未治療の CD20陽性 DLBCL 患者を対象として，GA101を CHOP 療法と併用するときの主治医評価に基づく無増悪生存期間（PFS）を推定する。
- 未治療の CD20陽性 DLBCL 患者を対象として，GA101を CHOP 療法と併用するときの独立判定委員会（IRF）の評価に基づく PFS 及び奏効期間を推定する。
- 未治療の CD20陽性 DLBCL 患者を対象として，IRF の評価に基づく ORR 及び CR を検討することにより，CHOP 療法と併用するときの GA101の有効性を推定する。

バイオマーカーに関する目的
- DLBCL サブタイプと DLBCL を分類するための遺伝子発現プロファイルとの相関について，RNA の定量的評価から単独の予後マーカーを探索的に検討する。

薬物動態（PK）及び薬力学に関する目的
- CHOP 療法と併用した場合の GA101の PK 特性を明らかにする。
- 末梢血中の B 細胞の枯渇及び回復を検討する。

CHOP 療法と併用した場合の GA101の PK への相対的影響を評価するために，薬物間相互作用（DDI）のサブ試験を行う。

探索的目的

- 全生存期間（OS）の予備的評価を行う。
- ^{18}F-フルオロデオキシグルコース（^{18}F-FDG）陽電子放射断層撮影（PET）の早期検査結果と ORR，CR 及び PFS との相関を検討する。
- FcγR の遺伝子多型の状態と ORR，CR 及び PFS との相関を検討する。

(7) 治験方法

本治験は，未治療の CD20陽性 DLBCL 患者を対象として，CHOP 療法と併用投与した際の GA101の安全性及び有効性を検討する第 II 相多施設共同非盲検単群試験である。

約80例の適格被験者に対し，GA101と標準 CHOP 療法の併用投与を6サイクル（1サイクル：21日）施行し，GA101の投与は計8サイクル継続することとした。本治験への最初の80例の登録後には，DDI サブ試験に，追加コホートとして約15例を登録することとした。CHOP 療法の各薬剤の PK に対する GA101の相対的影響を評価するために実施するサブ試験には，本治験に参加する実施医療機関の一部が参加した。

患者の負担軽減を目的として，GA101の SDI で投与した際の安全性について評価した。通常の投与速度での安全性が最初の20例の安全性データから確認された後，SDI での投与基準に合致した被験者（サイクル1の Day 1，Day 8及び Day 15の通常速度での GA101の投与中に Grade 3以上の IRR 関連の有害事象が発現せず，サイクル2 Day 1の GA101の投与前に末梢血中リンパ球数が5000/μL 未満であった被験者）に対し SDI で投与し，SDI で投与した際の安全性及び忍容性を評価した。

病勢進行（PD）が認められない被験者に対し，治験終了時，早期治療中止時以降の腫瘍評価は Month 24までは3カ月ごと，その後 Month 36まで（3年間又はそれ以前に PD が認められた場合はその時点まで）は6カ月ごとに行った。Month 36の評価終了後は，治験の終了又は中止に至る時点まで，年に1回，電話にて生存の確認を行った。

本治験の終了時期は，全被験者が最低2年間の投与終了後の追跡調査を受けられる期間を考慮し，最初の被験者の登録から約5年後を想定している。

(8) 被験者数

目標被験者数：80例 ＋DDI サブ試験に約15例

登録被験者数：80例 ＋DDI サブ試験に20例

(9) 診断及び主な組入れ基準

未治療の CD20陽性 DLBCL 患者

(10) 被験薬の用量，投与方法及び投与期間

21日間を1サイクルとし，各サイクル Day 1に GA101 1000 mg を点滴静脈内投与*した（CHOP 療法を開始する少なくとも30分前に投与完了することとした）。最大8サイクル投与した。また，サイクル1では，Day 8及び Day 15にも GA101を投与し，サイクル7及びサイクル8では，GA101を単独投与した。

*DDI サブ試験（各コホート10例）では，以下のとおり投与することとした。

コホート1：CHOP をサイクル1 Day 1に，GA101をサイクル1 Day 2に投与した。

コホート2：GA101をサイクル1 Day 1に，CHOP をサイクル1 Day 2に投与した。

また，サイクル1 Day 8及びサイクル1 Day 15には上記と同様に投与した。更にサイクル2からサイクル6にかけて CHOP を下記の通常投与時と同様に投与した。

(11) 併用薬の用量，投与方法及び投与期間

CHOP を21日サイクルの各 Day 1に6サイクル投与した。なお，各施設で通常行われている薬剤の調整方法，投与方法で投与した。

(12) 対照薬の用量及び投与方法

本治験は対照薬を用いなかったため該当しない。

(13) 評価基準

1) 有効性

主要評価項目

- 主治医評価による ORR 及び CR

副次的評価項目

- IRF 評価による ORR 及び CR
- IRF 評価による PFS
- 主治医評価及び IRF 評価による奏効期間

探索的評価項目

- 全生存期間（OS）
- ^{18}F-FDG PET の早期検査結果（主治医評価による PET と投与終了時の ORR 及び CR 率との相関に関する中間解析。結果は別途報告する。）
- FcγR の遺伝子多型の状態
- DLBCL サブタイプごとの単独な予後マーカー
- 抗腫瘍効果はすべて「悪性リンパ腫効果判定規準（改訂版）」（Cheson et al. 2007）に従って主治医が判定する。

2) PK

- CHOP の各薬剤の PK パラメータ：$t_{1/2}$，t_{max}，C_{max}，AUC_{last}，分布容積（V）及びクリアランス（CL）
- GA101の PK パラメータ：$t_{1/2}$，C_{max}，AUC_{7day}，V 及び CL

母集団薬物動態解析法による結果は別途報告する。

3) 薬力学

- CD19陽性 B 細胞数の枯渇の程度（CD19陽性 B 細胞数 $< 0.07 \times 10^9$/L），最小値までの到達時間及び B 細胞枯渇の持続時間

4) 安全性

- 本剤に起因する特徴的な有害事象を含めた有害事象，重篤な有害事象の発現率及び重症度
- 標準的な臨床検査値，ヒト抗ヒト抗体（HAHA）の発現率，バイタルサイン

(14) 統計的手法

本治験では仮説検定ではなく推定に重点を置いた。

有効性解析

奏効率は Clopper-Pearson 法を用いて求めた95%信頼区間（CI）とともに要約した。

抗腫瘍効果の基準（CR，PR，SD，PD）ごとに比率と95%CI を要約した。

Kaplan-Meier 法を用いて PFS の分布を推定し，Kaplan-Meier 曲線を示した。6カ月時 PFS 及び1年時 PFS を95%CI とともに示した。

FcγR の遺伝子多型の状態を叙述した。

DLBCL のサブタイプごとに単独の予後マーカーの結果を叙述した。FcγR の遺伝子多型ごとに，投与終了時の奏効率は Clopper-Pearson 法を用いて求めた95%CI とともに要約した。

薬力学及び PK 解析

CHOP 及び GA101の PK パラメータは，Phoenix WinNonLin version 6.2を用いてノンコンパートメント法で解析した。

薬力学データの CD19陽性 B 細胞数の枯渇の程度，最小値までの到達時間及び B 細胞枯渇の持続時間は要約統計量（平均値，標準偏差，中央値，変動係数，最小値及び最大値）で記述した。Ig の減少と回復について IgA，IgM 及び IgG の3パラメータの閾値から評価した。

安全性解析

治験薬投与について，曝露状況，用量強度，減量・投与延期状況を要約した。

有害事象及び重篤な有害事象，臨床検査値，HAHA の発現状況，バイタルサインを含む安全性評価，GA101の SDI 投与時の安全性及び忍容性の評価については要約統計量を用いて評価した。有害事象については報告者の有害事象用語を MedDRA シソーラス用語にマッピングし，NCI CTCAE v4.0に基づいて Grade 判定した。また，死亡，Grade 3～5の有害事象，重篤な有害事象，投与中止に至った有害事象，休薬・減量に至った有害事象及び IRR についても要約した。更に，本剤に起因する特徴的な有害事象については，より詳細に解析した。

(15) 結果の要約

1) 有効性

主要解析については，2013年12月20日にデータカットオフして評価した。データが少なかったため，計画していた IRF 評価による PFS，奏効期間，OS，PET と PFS との相関に関する中間解析，PFS と FCγ との相関，PFS とバイオマーカーとの相関に関する探索的解析は現時点で未実施である。

未治療の DLBCL 患者に対する，GA101と CHOP 療法を併用投与した際の有効性については，Cheson らが2007年に発表した判定規準に従って主治医及び IRF が判定した。その結果，主治医評価の ORR は82.0%（95%CI：73.05～88.97%），主治医評価の CR 率は55.0%（95%CI：44.73～64.97%）であり，IRF 評価の ORR は75.0%（95%CI：65.34～83.12%），IRF 評価での CR 率は58.0%（95%CI：47.71～67.80%）であった。Cheson らが2007年に発表した判定規準による投与終了時の主治医評価と IRF 評価の一致率は71%であり，概して一致した。

CT 又は MRI 検査，FDG-PET 検査に基づき，投与終了時に再発又は病勢進行が認められた被験者は，主治医評価では11.0%，IRF 評価では14.0%であった。

データカットオフ時点の解析では，すべての被験者が投与終了後又は投与中止後の直近の来院であったため，病勢進行，再発又は死亡のイベントがみられた被験者は19.0%であった。予備的な PFS の結果から，50%の被験者の PFS は1.5年未満と想定されたものの，明確な結論をつけるに至らなかった。

探索的バイオマーカー

DLBCL のサブタイプごとの病態：ベースラインでは，78例中45例（57.7%）が germinal center B cell（GCB）型の DLBCL であり，78例中19例（24.4%）が activated B cell（ABC）型の DLBCL であった。

ベースラインでは，ABC 様群の被験者の内，85.7%の被験者で節外性標的病変が1個であり，GCB 様群の被験者の内，37.5%の被験者で節外性標的病変が1個であり，37.5%の被験者で標的病変が2個であった。

ABC 型の被験者では，B 症状が認められる，ECOG PS が2である，骨髄リンパ腫が認められ

る，及び血清 LDH レベルが高値であるといった症状が高頻度に認められた。更に，国際予後因子（IPI）では，ABC 型に比べて GCB 型で，より病態が悪く，巨大腫瘤病変を有するようにみられた。

ABC 型の被験者で IPI スコアが3より大きい被験者は認められなかった。

DLBCL のサブタイプごとの投与終了時の奏効率：CR が認められた被験者は，ABC 型の被験者（42.1%，95%CI：20.25～66.50%），又は未分類の被験者（35.7%，95%CI：12.76～64.86%）に比べて，GCB 型の被験者（62.2%，95%CI：46.54～76.23%）で多く認められた。GCB 型の被験者に比べて，ABC 型の被験者及び未分類の被験者で病勢進行が多く認められた結果と一致した。

FCγR 遺伝子多型の状態：遺伝子多型を検査した被験者68例の内，FCγRIIa-131H/R 多型を有する被験者はは29例（42.6%），FCγRIIIa-158 F/V 多型又は F/F 多型を有する被験者は，それぞれ30例（44.1%）及び29例（42.6%）であった。高親和力を有する FCγRIIIa-158V/V 多型は13.2%の被験者に認められた。

FCγRIIa 遺伝子多型ごとの投与終了時の奏効率：FCγRIIa 遺伝子の高親和力多型（131H/H）を有する被験者と低親和力多型（131R/R）を有する被験者間で奏効率に違いはみられなかった。

FCγRIIIa 遺伝子多型ごとの投与終了時の奏効率：FCγRIIIa 遺伝子の高親和力多型（158V/V）を有する被験者（88.9%）と低親和力多型（158F/F）を有する被験者（86.2%）の間で奏効率に明確な違いはみられなかった。

2) 薬物動態

CHOP 療法の PK 解析

CHOP 療法と併用した場合の GA101の PK への相対的影響を評価するために実施した DDI サブ試験で，サイクル1 Day 1の GA101非存在下での CHOP 療法の PK は14例，サイクル1 Day 2 の GA101存在下での CHOP 療法の PK は11例で評価した。CHOP 単独投与時の CHOP 療法及び代謝物の PK パラメータの平均値は，CHOP 療法と GA101併用投与時の PK パラメータの範囲内であった。

GA101の PK 解析

サイクル1では100例，サイクル8では85例が PK データの評価が可能であった。サイクル1～サイクル8にかけての曝露量（平均 C_{max} 及び AUC_{7day}）で想定どおりの増加が認められた。サイクル8の C_{max} はこれまでに観察された1000 mg 投与時の定常状態での C_{max} と同程度であった。$t_{1/2}$，CL 及び V の平均値 ± 標準偏差の結果は想定どおりであった。

投与時間に関する GA101の PK 解析

SDI での投与時の検討として，GA101の投与終了時の薬物濃度を投与時間に従って要約した。通常投与時の安全性が確認された後に，90分間での SDI 投与を検討する前に，計画したとおり，5例の限られた被験者を対象として120分間の SDI 投与を検討した。各サイクルでの GA101の薬物濃度の平均値は，通常投与を受けた被験者と比べて，90分間での SDI 投与を受けた被験者で，わずかに高値を示した。データに変化は認められたものの，投与時間変更時による影響は認められなかった。

3) 薬力学

B 細胞の枯渇及び回復に関する評価は，追跡調査のデータがまだ不十分であるため，別途報告する。評価可能であった100例中，投与終了時に IgA，IgG，IgM の減少が認められた被験者

はそれぞれ8%，8%及び25%であった。Ig の減少が認められた被験者数が少なかったことから，回復に関しては明確に結論づけるに至らなかった。

4) 安全性

- 死亡例は100例中9例（9.0%）にみられたが，いずれも治験薬との関連はみられなかった。致死的な有害事象は2.0%にみられ，発現した事象は感染性脳炎（被験者識別番号3056）と診断名不明の心血管障害（被験者識別番号3098）であったが，いずれも治験薬との関連はみられなかった。
- 重篤な有害事象は39.0%の被験者，投与中止に至った重篤な有害事象は5.0%の被験者，休薬又は用量変更に至った重篤な有害事象は22.0%の被験者にみられた。
- 治験中止に至った有害事象の発現はみられなかった。
- 有害事象はすべての被験者（100.0%）にみられ，GA101に関連した有害事象は76.0%の被験者にみられた。GA101の投与中止に至った有害事象は8.0%の被験者，GA101の休薬に至った有害事象は77.0%の被験者にみられた。CHOP 療法の投与中止に至った有害事象は10.0%の被験者にみられた。
- GA101に関連した休薬に至った有害事象は61.0%の被験者にみられた。
- 治験薬に関連した IRR の徴候や症状は69.0%の被験者にみられ，その内，5.0%の被験者に Grade 3又は4の IRR がみられた。
- Grade 3又は4の好中球減少症は49.0%の被験者にみられたが，Grade 5の好中球減少症の発現はみられなかった。
- 感染症は58.0%の被験者にみられ，110件中84件（76.4%）と多くの事象は Grade 1又は2であった。

(16) 結論

- DLBCL 患者を対象に GA101を CHOP 療法と併用した際の有効性は想定通りであった（Cheson らが2007年に発表した判定規準に従った主治医評価の ORR は82%，CR 率は55%であり，IRF 評価の ORR は75%，CR 率は58%であった）。CT 又は MRI 検査，FDG-PET 検査に基づき，投与終了時に再発又は病勢進行が認められた被験者は，主治医評価では11%，IRF 評価では14%であった。
- PFS 及び OS の結果は試験終了後に評価する。
- GA101を CHOP 療法と併用した際の忍容性は良好であり，これまでの試験結果と比較しても新たな安全性シグナルは認められなかった。
- サイクル1以降に SDI 投与（90分間で投与）した70例で忍容性は良好であり，新たな安全性シグナルは認められなかった。
- 本治験では薬物間相互作用はみられず，CHOP 療法のデータからも結果は支持された。
- 本治験で確認された GA101の PK データは，これまで確認されたデータと同様であった。

(17) 報告書作成日

2014年12月

2.7.6.1.6 BO20999試験（GAUGUIN 試験）

2.7.6.1.6.1 第 I 相臨床試験部分

(1) 試験の標題

BO20999 – An open-label, multicentre, non-randomized, dose-escalating Phase I/II study, with a randomized Phase II part, to investigate the safety and tolerability of RO5072759 given as monotherapy in patients with CD20+ malignant disease.

BO20999試験 - CD20陽性悪性疾患患者に対する RO5072759単剤療法による安全性及び忍容

性を検討するランダム化第 II 相部分を含む，非盲検多施設非ランダム化用量漸増第 I/II 相臨床試験

(2) フェーズ
第 I 相

(3) 治験依頼者及び治験実施施設
F. Hoffmann-La Roche 社／フランスの7施設

(4) 公表
なし

(5) 治験実施期間
2007年9月[redacted]日～2009年10月1日

(6) 目的
本治験の第 I 相部分の主要目的は，CD20陽性悪性固形癌患者及び白血病患者（B 細胞性慢性リンパ性白血病［B-CLL］，非ホジキンリンパ腫（NHL）患者等）を対象として，単剤療法としての RO5072759の用量漸増，静脈内投与による，安全性及び忍容性を検討する。

副次的評価項目：
- RO5072759の薬物動態（PK）特性を明らかにする。
- RO5072759用量増加に伴う末梢血 B 細胞の枯渇及び回復を検討する。
- 全奏効率（ORR）を評価し，再発・治療抵抗性 iNHL，再発・治療抵抗性 aNHL，再発・治療抵抗性 B-CLL に対する RO5072759単剤療法による抗腫瘍効果のデータを収集する。
- 有効性に関するゲノム薬理学パラメータ（FcγRIIa 及び IIIa 多型を含む）及び薬力学パラメータ（ベースライン，投与中及び投与終了後の bcl-2遺伝子再構成を含む）を検討する。

(7) 治験方法
本治験の第 I 相部分は用量漸増のデザインであり，すべての被験者に対して RO5072759を単剤療法として静脈内投与した。各コホート内では，絶対（一定）用量で投与した。コホート1～3では NHL 患者各3例，コホート4～6では各6例（コホート4a～6a として NHL 患者各3例，コホート4b～6b として CLL 患者各3例）を，順次登録するように計画した。各被験者は1つのコホートに割り当て，各コホートで規定された用量の投与を受けた（21日間サイクルで8回投与し，期間は約6カ月間であった）。各コホートの初回投与量は当該コホート用量の50%とした（コホート4まで）。初回投与で忍容性が認められた場合に，次の投与より最大用量で投与した（すなわち，コホート1の初回投与量は50 mg とし，次の投与からは100 mg を投与した）。6例（コホート7a に NHL 患者3例，コホート7b に CLL 患者3例）からなる，コホート7a/b は，コホート1～6の臨床データ及び薬物動態データから用量追加の決定がされた場合にのみ実施する計画であった。コホート7a では，NHL に対する追加用量（コホートの3例に対し，サイクル1の Day 1及び Day 8では1600 mg，Day 22では800 mg，その後は21日おきに800 mg を投与）を検討した。当該用量の安全性及び忍容性を評価して，本試験の第 II 相部分への当該用量の導入について検討した。コホート7b では CLL 患者を対象に第 II 相部分に用いる用量である1000 mg 一定用量を投与した際の安全性及び忍容性を評価した。

以下の表 2.7.6.1.6.1-1に各コホートの用量を示した。

表 2.7.6.1.6.1-1　BO20999試験での RO5072759の用量

Cohort No.	First dose	Subsequent Dose
1	50 mg	100 mg
2	100 mg	200 mg
3	200 mg	400 mg
4a/b*	400 mg	800 mg
5a/b	800 mg	1200 mg
6a/b	1200 mg	2000 mg
7a	1600 mg	1600 mg on Cycle 1 Day 8 and then 800 mg for subsequent infusions
7b	1000 mg	1000 mg

a cohorts – NHL patients; b cohorts – CLL patients
*The B-CLL dose escalation was initiated with cohort 4b (400/800 mg).
［5.3.5.4-1-1 Table 1を改変］

安全性評価はサイクル1の Day 1及び Day 8，その後3週間おきの各サイクルの Day 1，最終投与の28日後に実施した。腫瘍評価は，標準的な NHL/CLL 基準を基に，NHL 患者及び CLL 患者のいずれも RO5072759投与のサイクル4及びサイクル8（それぞれ，登録後12週及び24週時点）で実施し，CLL 患者では，追加評価を RO5072759の最終投与の3カ月後にも実施した。なお，早期に投与中止し，腫瘍評価ができなかった被験者は非奏効例として扱った。

投与期間の終了後，患者は2年間の安全性追跡調査に組み入れられた。

(8)　被験者数

34例（NHL 21例，CLL 13例）

(9)　診断及び主な組入れ基準

再発・治療抵抗性の CD20陽性悪性疾患を有し，他に優先すべき治療法がなく，抗 CD20抗体療法が適当と判断される男女成人患者。

(10) 被験薬の用量及び投与方法

NHL 及び B-CLL 患者に対し，サイクル1は Day 1及び Day 8に，サイクル2からサイクル8（計9回投与）は Day 1にコホートで規定された用量を静脈内投与した。

(11) 対照薬の用量及び投与方法

本治験は対照薬を用いなかったため該当しない。

(12) 評価基準

1)　有効性

- 標準的な NHL 及び CLL 基準による CR 率。
- 標準的な NHL 及び CLL 基準による PR 率。

2)　薬物動態

CD19陽性 B 細胞数及び血清補体値。

3)　薬物動態

最高血漿中濃度（C_{max}）及び血漿中濃度-時間曲線下面積（AUC）を測定する。結果は別途

PK 報告書で報告する。

4) 安全性

National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0を用いて有害事象の重症度を判定する。臨床検査値及び身体検査についても確認する。

(13) 統計的手法

要約統計量を示す。

(14) 結果の要約

1) 有効性

NHL 患者集団では，投与終了時の奏効率は33%，内訳は CR 4例（19%）及び PR 3例（14%）であり，データカットオフ時点での BORR は43%，内訳は CR 5例（24%）及び PR 4例（19%）であった。奏効例の組織型はいずれも濾胞性リンパ腫であった。

CLL 患者集団では，投与終了時の奏効率は62%，内訳は PR 8例であり，その内4例はコホート6の用量が最も多いコホートであった。また，2009年10月1日のデータカットオフ時点では BORR は62%，内訳は PR 8例であった。

2) 薬力学

NHL 患者集団の大多数で，ベースラインの末梢血 CD19陽性 B 細胞数は，前治療の影響から想定どおりの低値であった。CD19陽性 B 細胞数は RO5072759を投与することにより，更に低下し，RO5072759投与時に期待された B 細胞の枯渇という薬理学的効果が認められた。ベースライン時の CD19陽性 B 細胞数の中央値は0.0550 × 10^9/L（範囲：0.002～128.214，主治医の基準範囲：0.080～0.616 × 10^9/L）であった。サイクル1の投与終了までに，2例を除き，NHL コホート全例の B 細胞数が枯渇した（0.04 × 10^9/L 以下）。

NHL 患者と対照的に，病態と一致して，CLL 患者集団の大多数で，ベースラインの末梢血 CD19陽性細胞数が著しく高値であった（中央値：44.699 × 10^9/L，範囲：2.427～113.888，主治医の基準範囲：0.080～0.616 × 10^9/L）。CLL 患者群で RO5072759の投与開始以降を観察したところ，Day 8まで B 細胞数の速やかな低下が認められた。

本総括報告書作成のためのデータカットオフ時点では，B 細胞回復のための安全性追跡調査期間の長さが十分ではなかったため，両患者集団ともに B 細胞回復について結論づけることはできなかった。

3) 薬物動態

薬物動態の結果は別途 PK 報告書で報告する。

4) 安全性

投与した用量範囲で RO5072759は忍容性が良好であり，有害事象の発現頻度に用量依存性は認められず，用量制限毒性（DLT）も認められなかった。新たな安全性の問題は認められず，Grade 4の因果関係が否定できない事象はすべて好中球減少症であり，Grade 3の有害事象の多くは血液毒性や Infusion-related reaction（IRR）であった。好中球減少症は NHL 患者集団に比べ，CLL 患者集団で見かけ上は多く発現したが，両群間で Grade 3及び4の有害事象を発現した被験者の割合に違いがみられたことが第一の原因と考えられた。しかし，例数が少なく明確に結論づけるには至らなかった。投与期間中に，重篤な有害事象は7例（NHL 患者集団3例，CLL 患者集団4例）に発現し，投与中止に至った有害事象（脳血管発作を発現し，転帰は死亡であった）が1例に発現した。

NHL 患者集団で，投与期間中に最も多く発現した有害事象は，IRR（18/21例，86%）及び無

力症（8例，38%）であった。発現した IRR のほとんどが初回投与中に発現し，投与を重ねるにつれて発現頻度及び重症度は低下した。その他の少なくとも3例以上に発現した有害事象は，下痢5例（24%），血小板減少症，気管支炎，体重減少及び食欲不振各4例（19%），疲労，リンパ球減少症，悪心及び不眠症各3例（14%）であった。発現した事象の多くは Grade 1（75/132件）又は Grade 2（39/132件）であり，Grade 3，4及び5の有害事象（残る18件）の発現がみられたのは7/21例であった。投与開始から投与終了24時間後の間に，主治医評価で因果関係ありと判断された Grade 3及び4の有害事象が3例に発現した。発現した事象の内訳は IRR 2例，貧血，好中球減少症，血小板減少症及び腫瘍崩壊症候群（TLS）各1例であった。

投与期間中に，NHL 患者1例が Grade 5の重篤な有害事象である脳血管発作（主治医により治験薬との因果関係はなしと判断された）により死亡し，追跡調査期間中に病勢進行のため NHL 患者2例が死亡した。

投与期間中に CLL 患者集団の13例全例で，少なくとも1件の有害事象が発現し，最も多く発現した有害事象は IRR であり，13例（100%）に発現した。その他の少なくとも3例以上に発現した有害事象は，好中球減少症7例（54%），リンパ球減少症及び血小板減少症各4例（31%），発熱，背部痛，気管支炎，アフタ性口内炎，下痢，咳嗽，トランスアミナーゼ減少及び回転性めまい各3例（23%）であった。NHL 患者集団と同様に，発現した事象の多くは Grade 1（61/113件）又は Grade 2（32/113件）であり，Grade 3及び4の有害事象（残る20件）の発現は少なく，10/13例（77%）に発現した。投与開始から投与終了24時間後の間に，主治医評価で因果関係ありと判断された Grade 3及び4の有害事象が6例に7件発現した。発現した事象の内訳は IRR2例，好中球減少症，リンパ球減少症，血小板減少症，歯肉炎及び TLS 各1例であった。CLL 患者集団では Grade 5の有害事象及び死亡例は認められなかった。

(15) 結論

BO20999試験の第 I 相部分は抗 CD20抗体の RO5072759を NHL 患者及び CLL 患者に投与した最初の臨床試験であった。本治験では，DLT の発現はみられず安全であり，部分奏効及び完全奏効もみられ有効性も良好であった。

第 I 相部分で良好な結果が得られたことから，第 II 相部分の試験実施を決定した。

(16) 報告書作成日

2010年10月

2012年11月に BO20999試験の試験終了に伴い，第 I 相試験部分の総括報告書補遺が作成された。以下に主要解析時に作成した総括報告書からの主な追加情報及び変更点を記載する。

(1) 治験実施期間

2007年9月[redacted]日～2012年3月31日

(2) 被験者数

34例（NHL 21例，CLL 13例），追跡調査対象33例（NHL 20例，CLL 13例）

(3) 結果の要約

1) 有効性

観察期間（投与期間及び追跡調査期間）の中央値は NHL 患者集団では41.3カ月（範囲：2.2～53.4カ月），CLL 患者集団では38.7カ月（範囲：14.4～44.5カ月）であった。奏効が認められた NHL 患者集団9例の奏効期間の中央値は978日（範囲：91～1288日）であり，追跡調査終了時点において4例で奏効の継続が認められた。一方，奏効が認められた CLL 患者集団8例の奏効期間の中央値は318.5日（範囲：257～1126日）であり，追跡調査終了時点において1例で

奏効の継続が認められた。

2) 薬力学

B 細胞数の回復は NHL 患者集団では5例に認められた。B 細胞回復までの期間が最短（14日）であった被験者は投与終了時には病勢進行が認められており信頼できるデータではないが，投与終了後の B 細胞数回復までの期間の範囲は14～860日であった。追跡調査期間中，B 細胞数の回復は CLL 患者集団では8例に認められた。投与終了後の B 細胞回復までの期間の範囲は82～891日であった。B 細胞数回復までの期間が最短であった被験者は，投与終了時には PD であり，回復時には SD であった。病状の変化はおそらく B 細胞数回復までの期間に影響しており，被験者によっては B 細胞数回復前に病勢進行が認められることが想定された。

3) 安全性

追跡調査期間中に，NHL 患者集団，CLL 患者集団のいずれにおいても，因果関係ありと判断された Grade 3及び4の有害事象の発現はみられなかった。また，追跡調査期間中では有害事象による死亡例はみられず，追跡期間中に発現した6例の重篤な有害事象はいずれも治験薬との因果関係なしと判断された。臨床検査値やその他の所見も安全性上の問題は認められなかった。

(4) 結論

- 追跡調査期間（最大2年間）を通して，新たな安全性上の問題点はみられなかった。また，主要評価項目である有効性の結論も変わらなかった。多くの被験者で B 細胞数の回復前に病勢進行が認められた。
- NHL 患者集団及び CLL 患者集団のいずれにおいても400/800 mg 以上の用量群では，C_{max} 及びトラフ濃度は8サイクルの投与期間中に増加した。

2.7.6.1.6.2 第 II 相臨床試験部分

(1) 試験の標題

BO20999 – An open-label, multicentre, non-randomized, dose-escalating Phase I/II study, with a randomized Phase II part, to investigate the safety and tolerability of RO5072759 given as monotherapy in patients with CD20+ malignant disease.

BO20999 - CD20陽性悪性疾患患者に対する RO5072759単剤療法による安全性及び忍容性を検討するランダム化第 II 相部分を含む，非盲検多施設非ランダム化用量漸増第 I/II 相臨床試験

(2) フェーズ

第 II 相

(3) 治験依頼者及び治験実施施設

F. Hoffmann-La Roche 社／ドイツ及びフランスの20施設

(4) 公表

なし

(5) 治験実施期間

2008年12月[redacted]日～2010年5月27日

(6) 目的

本治験の第 II 相部分の主要目的

1) 再発・治療抵抗性の低悪性度非ホジキンリンパ腫（iNHL）（主に濾胞性リンパ腫），再発・治療抵抗性の中高悪性度非ホジキンリンパ腫（aNHL）（マントル細胞リンパ腫（MCL）及びびまん性大細胞型 B 細胞性リンパ腫（DLBCL））を対象に2用量（低用量及び高用量）の RO5072759投与時の有効性及び安全性を検討する。
2) 再発・治療抵抗性の慢性リンパ性白血病に対する RO5072759（1000 mg）投与時の有効性及び安全性を検討する。

本治験の副次的目的

1) RO5072759の薬物動態（PK）特性を明らかにする。
2) RO5072759用量増加に伴う末梢血 B 細胞の枯渇及び回復について検討を行う。
3) 再発・治療抵抗性 iNHL，再発・治療抵抗性 aNHL，再発・治療抵抗性 CLL に対する RO5072759単剤療法による抗腫瘍効果のデータ収集のため，以下の事項について評価する。
   - 全奏効率（ORR）
   - 無増悪生存期間（PFS）
   - 無イベント生存期間（EFS）
4) 有効性に関するゲノム薬理学パラメータ（FcγRIIa 及び IIIa 多型を含む）及び薬力学パラメータ（ベースライン，投与中及び投与終了後の bcl-2遺伝子再構成を含む）を検討する。

(7) 治験方法

第 II 相部分は第 I 相部分で決定した推奨用量を投与した際の有効性及び安全性を評価するデザインであり，CD20陽性の再発・治療抵抗性 iNHL，再発・治療抵抗性 aNHL 及び再発・治療抵抗性 CLL を対象に，該当用量の安全性情報，早期有効性データを更に得るために実施した。

NHL 患者集団では RO5072759単剤療法を以下の2用量で評価した。

- サイクル1の Day 1及び8は400 mg，サイクル2～8の Day 1に400 mg を投与（低用量群）
- サイクル1の Day 1及び8は1600 mg，サイクル2～8の Day 1に800 mg を投与（高用量群）

NHL 患者は高用量群又は低用量群にランダム化され，組織型（iNHL 又は aNHL）に基づき，層別化された。CLL 患者は単一コホートに登録され，RO5072759 1000 mg を投与された。投与サイクル数は8サイクルであり，NHL 患者集団には合計9回投与，CLL 患者集団には合計10回投与した（CLL 患者集団はサイクル1 Day 15にも投与した。）。NHL 及び CLL の両患者は，RO5072759の最終投与28日後に腫瘍評価及び安全性追跡調査をまとめて行った。NHL 患者では腫瘍評価を追跡調査の Day 28に行い，CLL 患者では追跡調査の Day 28の腫瘍評価に加え，投与終了2カ月後，すなわち追跡調査の Day 28の1カ月後に評価の確定を必要とした。

投与終了28日後の追跡調査時点で B 細胞の枯渇がみられた被験者は，B 細胞数が回復した6カ月後まで3カ月おきに追跡調査を行った。更に，CR，CRu，骨髄機能の回復が不完全な完全奏効（CRi），PR，SD と評価された被験者は初回投与から24カ月間，その後は6カ月おきに病勢進行（PD）がみられるまで，新たな治療を開始するまで，又は最終被験者の登録の2年後までは継続して腫瘍評価を行った。

最初の投与時に奏効（CR，CRu，CRi，PR）が認められ，投与完遂後（NHL 患者では9回投与，CLL 患者では10回投与後）に病勢進行がみられた被験者を対象に RO5072759の再投与を可能とした。本報告書のためのカットオフ時点で再投与を開始した被験者はいなかったため，再投与のデータは本報告書には記載しなかった。

(8) 被験者数

100例（iNHL 40例，aNHL 40例，CLL 20例）

(9) 診断及び主な組入れ基準

第 II 相臨床試験：再発・治療抵抗性の CD20陽性悪性疾患（iNHL，aNHL 及び CLL）を有す

る男女成人患者。

(10) 被験薬の用量及び投与方法

- NHL 患者：サイクル1の Day 1及び Day 8，その後サイクル2からサイクル8は Day 1にコホートで定義された投与量を点滴静注した（9回投与）。
- CLL 患者：サイクル1の Day 1，Day 8及び Day 15，その後サイクル2からサイクル8は Day 1に1000 mg の用量で点滴静注した（10回投与）。

(11) 対照薬の用量及び投与方法

本治験は対照薬を用いなかったため該当しない。

(12) 評価基準

1) 有効性

- 標準的な NHL 及び CLL 基準による CR 率
- 標準的な NHL 及び CLL 基準による PR 率
- PFS
- EFS
- 奏効期間

2) 薬力学

CD19陽性 B 細胞数及び血清補体値を確認する。

3) PK

最高血漿中濃度（C_{max}）及び血漿中濃度-時間曲線下面積（AUC）を測定する。

4) 安全性

National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0を用いて有害事象の重症度を判定する。臨床検査値及び身体検査についても確認する。

(13) 統計的手法

要約統計量を示す。

(14) 結果の要約

1) 有効性

iNHL コホートでは，奏効に用量依存性がみられ，投与終了時の奏効率（ETR）は低用量群で16.7%，高用量群で54.5%であり，BOR は低用量群で22.2%，高用量群で63.6%と高用量群でより効果が強くみられた。aNHL コホートでは，想定されたとおり，奏効例は少なかったが，iNHL と同様の傾向がみられ，高用量群でより効果が強くみられた。aNHL コホートでの ETR は低用量群で24%，高用量群で32%であり，BOR は低用量群で23.8%，高用量群で36.8%であった。CLL コホートでは，ETR 率は20%（4/20例）であり，BOR は25%（5/20例）であった。

iNHL 患者集団及び aNHL 患者集団の主な有効性の結果を以下の表 2.7.6.1.6.2-1に，CLL 患者集団の主な有効性の結果を以下の表 2.7.6.1.6.2-2に示す。

表 2.7.6.1.6.2-1　主な有効性結果（iNHL 及び aNHL）

Efficacy Parameter	Low Dose	High Dose	Total
iNHL			
End of treatment response (ETR)	3/18 (16.7%)	12/22 (54.5%)	15/40 (37.5%)
CR	-	2 (9.1%)	2/40 (5%)
PR	3/18 (16.7%)	10/22 (45.5%)	13/40 (32.5%)
FL subset	3/14 (21.4%)	10/20 (50%)	13/34 (38.2%)
Best overall response (BOR)**	4/18 (22.2%)	14/22 (63.6%)	18/40 (45%)
CR	1/18 (5.6%)	3/22 (13.6%)	4/40 (10%)
CRu	-	1/22 (4.5%)	1/40 (2.5%)
PR	3/18 (16.7%)	10/22 (45.5%)	13/40 (32.5%)
FL subset (n = 34)	4/14 (28.6%)	12/20 (60%)	16/34 (47.1%)
PFS (median)	182 days (range 32 -513)	345 days (range 56 - 432)	
PFS (median) FL	182 days (range 32 -513)	361 days (range 56 - 432)	
aNHL			
End of treatment response (ETR)	5/21 (23.8%)	6/19 (31.6%)	11/40 (27.5%)
CR	2/21 (9.5%)	-	2/40 (5%)
CRu	1/21 (4.8)	-	1/40 (2.5%)
PR	2/21 (9.5%)	6/19 (31.6%)	8/40 (20%)
DLBCL subset (n = 25)	3/10 (30%)	4/15 (26.7%)	7/25 (28%)
MCL subset (n = 15)	2/11 (18.2)	2/4 (50%)	4/15 (26.7%)
Best overall response (BOR)**	5/21 (23.8%)	7/19 (36.8%)	12/40 (30%)
CR	2/21 (9.5%)	3/19 (15.8%)	5/40 (12.5%)
CRu	1/21 (4.8%)	-	1/40 (2.5%)
PR	2/21 (9.5%)	4/19 (21.1%)	6/40 (15%)
DLBCL (n = 25)	3/10 (30%)	5/15 (33.3%)	8/25 (32%)
MCL (n = 15)	2/11 (18.2%)	2/4 (50%)	4/15 (26.7%)
PFS (median)	78 days (range 8 - 356)	83 days (range 7 - 428)	

CRu: complete response unconfirmed. **, subject to change with longer follow-up.
［5.3.5.4-1-3 Table 10を改変］

表 2.7.6.1.6.2-2　主な有効性結果（CLL）

Efficacy Parameter	
End of treatment response (ETR)	4/20 (20%)
PR	2/20 (10%)
PRu	2/20 (10%)
Best overall response (BOR)**	5/20 (25%)
PR	5/20 (25%)
PFS	ND*

ND: not done, *: data immature, PRu: partial response unconfirmed; **, subject to change with longer follow-up.
［5.3.5.4-1-3 Table 11を再掲］

2)　薬力学

ベースラインからの CD19陽性細胞数の平均値及び中央値の低下が，すべての組織型で認められた。多くの被験者で B 細胞数の減少が投与中に認められた。B 細胞数の枯渇（ベースラインの B 細胞数から5%以下の減少）は，iNHL では33/38例（87%），aNHL では34/38例（89%），CLL では17/19例（89%）に認められた。B 細胞数の0.04 × 10^9/L 以下への低下は iNHL では37/39例（95%），aNHL では40/40例（100%），CLL では16/19例（84%）に認められた。

B 細胞数の追跡調査期間は，最初に登録された iNHL 患者が一番長かった。B 細胞数の回復（少なくとも0.08 × 10^9/L へ回復）がみられたのは，iNHL で0/37例，aNHL で2/40例（1例は低用量群，1例は高用量群），CLL では1/16例であった。

ベースラインの CD3陽性，CD4陽性，CD8陽性，CD16陽性56陽性の細胞数の平均値及び中央値がベースラインから減少し，次のサイクル1Day 8投与時に回復がみられた。この結果は各組織型で一貫していた。

すべての組織型で，IgA，IgG 及び IgM のベースライン時の平均値及び中央値は，最終観察である追跡調査の28日目まで投与期間中を通して変化が認められた。

C3，C4補体から派生した C3a，C5a 補体値の平均値及び中央値は，いずれの組織型でも，投与期間中を通して，基準値範囲内で相対的に一定であった。Bb ファクターはサイクル1Day 1の初回投与時に平均値及び中央値が若干増加したが，その後は減少し，残りの投与期間中は基準値範囲内であり，一定であった。

測定したすべてのサイトカイン（IL-6，IL-8，IL-10，TNFα 及び IFNγ）は，いずれの組織型でも，同様の遊離傾向がみられ，投与期間中から投与終了時に最大となり，その後はベースライン時に近いレベルへ減少した。

3) 薬物動態

iNHL 及び aNHL の，第 II 相部分の用量コホートは400 mg 及び1600/800 mg であった。いずれの組織型でも，血清中薬物濃度に用量依存性がみられた。高用量群ではサイクル3後に定常状態に到達し，C_{max} 及びトラフ濃度はその後の投与サイクルで一定の値を保った。一方で，400 mg 投与コホートでは，C_{max} 及びトラフ濃度は投与期間中を通して増加した。CLL 患者の第 II 相の1000 mg 投与における血清中薬物濃度は，サイクル2以降 C_{max} 及びトラフ濃度は定常状態に到達し，その後の投与サイクルで一定の値を保った。

4) 安全性

本試験の安全性プロファイルを以下の表 2.7.6.1.6.2-3に示す。

- 投与期間中では，iNHL 患者1例及び aNHL 患者2例を除き，すべての被験者で少なくとも1件の有害事象を発現した。
- いずれの組織型においても，多く発現がみられた有害事象は IRR であり，発現した IRR の重症度の多くが Grade 1又は2であり，初回投与に関連し発現したものであった。しかしながら，重篤な IRR が aNHL 患者の3/40例（7.5%）及び CLL 患者の4/20例（20%）と少数例に発現した。
- 症例数が少なく，多種多様な症状が発現したことから，iNHL 及び aNHL それぞれの低用量群，高用量群の用量ごとの安全性プロファイルの違いに関して明確な結論を見出すことはできなかった。
  - iNHL の低用量群では67件，高用量群では104件の有害事象が発現した。
  - aNHL の低用量群では81件，高用量群では72件の有害事象が発現した。
  - CLL では101件の有害事象が発現した。
- 重篤な有害事象は，iNHL の23%，aNHL の35%，CLL の45%に発現した。
- iNHL 1/40例（3%），aNHL 17/40例（43%），CLL 1/20例（5%）が死亡し，多くの死因は病勢進行であった。aNHL の1例は投与期間中に治験薬との因果関係が否定された心肺

停止により死亡した。投与期間中に因果関係が否定されなかった有害事象による死亡例はみられなかった。

- iNHL 1/40例（3%）及びCLL 3/20例（15%）に投与中止に至った有害事象が発現した。
- 投与期間中では，少なくとも1回以上の感染症が iNHL 13/40例（33%），aNHL 5/40例（13%），CLL 6/20例（30%）に発現した。発現した感染症の多くは1例に発現したものであった。

表 2.7.6.1.6.2-3　安全性の概要（iNHL，aNHL，CLL コホート）

	iNHL			aNHL			CLL
	Low n = 18	High n = 22	All n = 40	Low n = 21	High n = 19	All n = 40	n = 20
Any AE	18 (100%)	21 (95%)	39 (98%)	20 (95%)	18 (95%)	38 (95%)	20 (100%)
Any Grade ≥ 3 AE	4 (22%)	9 (41%)	13 (33%)	13 (62%)	7 (37%)	20 (50%)	15 (75%)
SAE	3 (17%)	6 (27%)	9 (23%)	9 (43%)	5 (26%)	14 (35%)	9 (45%)
Death	1* (6%)	-	1 (3%)	11 (52%)	6 (32%)	17 (43%)	1 (5%)*, [a]
PD				9 (43%)	5 (26%)	14 (35%)	
Other				2 (10%)**	1 (5%)[#]	3 (8%)	
Withdrawal for AE	-	1 (5%)[b]	1 (3%)	-	-	-	3 (15%)[c]
AEs of Special Interest							
IRR	13 (72%)	16 (73%)	29 (73%)	17 (81%)	13 (68%)	30 (75%)	19 (95%)
Grade ≥ 3	-	2 (9%)	2 (5%)	-	-	-	6 (30%)
Infection	5 (28%)	8 (36%)	13 (33%)	4 (19%)	1 (5%)	5 (13%)	6 (30%)
Grade ≥ 3	1 (6%)	3 (14%)	4 (10%)	-	-	-	4 (20%)
Tumor Lysis Syndrome	-	-	-	2 (10%)	1 (5%)	3 (8%)	-
Grade ≥ 3	-	-	-	2 (10%)		2 (5%)	-
Neutropenia	-	3 (14%)	3 (8%)	-	1 (5%)	1 (3%)	4 (20%)
Grade ≥ 3	-	3 (14%)	3 (8%)	-	1 (5%)	1 (3%)	4 (20%)
Febrile Neutropenia	-	1 (5%)	1 (3%)	-	-	-	2 (10%)
Grade ≥ 3	-	1 (5%)	1 (3%)	-	-	-	1 (5%)
Thrombocytopenia	-	1 (5%)	1 (3%)	3 (14%)	-	3 (8%)	3 (15%)
Grade ≥ 3	-	1 (5%)	1 (3%)	3 (14%)	-	3 (8%)	3 (15%)

*, patient died in survival follow-up; PD = Disease progression; **, causes of death were AE and hematotoxicity; [#], cause of death was respiratory distress; [a], cause of death was colon cancer; [b], CTC Grade 2 SAE of Pancreatitis; [c], AEs were interstitial lung disease and 2 IRRs, both CTC Grade 3, with one recorded as a SAE.
［5.3.5.4-1-3 Table 15を再掲］

(15) 結論

治療歴を有するNHL患者及びCLL患者に対するRO5072759単剤投与で良好な結果が認められた。第I相部分及び第II相部分の結果から，CLL患者及びNHL患者に対する第III相臨床試験の用量を1000 mgと決定した。

(16) 報告書作成日

2011年12月

2012年11月に2012年3月31日のデータカットオフ日までの追跡調査期間の情報を取りまとめ，

第 II 相試験部分の総括報告書補遺が作成された。以下に主要解析時に作成した総括報告書からの主な追加情報及び変更点を記載する。

(1) 治験依頼者及び治験実施施設
F. Hoffmann-La Roche 社／ドイツ及びフランスの16施設

(2) 治験実施期間
2008年12月[redacted]日～2012年3月31日（データカットオフ日）

(3) 結果の要約
1) 有効性
追跡調査の結果，観察期間の中央値は iNHL 患者では33.7カ月（範囲：7.4～39.5カ月），aNHL 患者では14.2カ月（範囲：0.3～36.1カ月），CLL 患者では28.8カ月（範囲：8.8～31.3カ月）であった。更新したイベント発現までの期間に関する有効性のデータを以下に示す。

表 2.7.6.1.6.2-4　更新したイベント発現までの期間の要約

	iNHL		aNHL		CLL
	400/400 mg	1600/800 mg	400/400 mg	1600/800 mg	1000 mg
PFS (median, 95% CI)					
	n=18	n=22	n=21	n=19	n=20
Months	6.0 (3.5-17.3)	11.9 (11.3-22.3)	2.6 (1.4-8.6)	2.7 (1.4-11.2)	10.7 (7.1-11.7)
Days	182 (106-526)	361 (343-678)	78 (42-260)	83 (43-339)	324 (217-357)
DOR (median, range)					
	n=20		n=12		n=6
Months	17.2 (0.8-31.3)		9.8 (3.1-30.6)		8.9 (0.8-26.1)
Days	523.0 (23-952)		298 (95-929)		272.5 (23-794)

aNHL: aggressive non-Hodgkin's lymphoma: CLL: chronic lymphocytic leukemia: DOR: duration of response; iNHL: indolent non-Hodgkin's lymphoma; PFS: progression-free survival.
［5.3.5.4-1-4 Table 1を再掲］

2) 薬力学
追跡調査の結果，B 細胞数の回復が iNHL 患者8例（この内，3例は回復時又はそれ以前に病勢進行が認められた），aNHL 患者5例（この内，3例は回復時又はそれ以前に病勢進行が認められた），CLL 患者10例（この内，6例は回復時又はそれ以前に病勢進行が認められた）に認められた。
追跡調査期間中，その他のリンパ球サブセット及び免疫グロブリン値は投与終了時の解析で報告された値からほとんど変化しなかった。4カ月及び12カ月時の HAHA 力価は，iNHL 患者で25例及び14例，aNHL 患者で10例及び5例，CLL 患者で8例及び5例のデータが利用可能であったが，いずれも検出限界以下であった。

3) 薬物動態
薬物動態プロファイルと結果は iNHL 患者と aNHL 患者で非常に似ていた。400 mg コホートと比較し1600/800 mg コホートでより高い血清中薬物濃度が観察された。1600/800 mg コホートでは，サイクル2投与後に定常状態に到達した。定常状態であるサイクル8時点の C_{max} 及びトラフ濃度は，それぞれ iNHL 患者では654 μg/mL 及び350 μg/mL であり，aNHL 患者では601

μg/mL 及び416 μg/mL であった。

400 mg コホートでは，C_{max} 及びトラフ濃度はサイクル2からサイクル8の期間中に増加し続けた。投与量が400 mg から800 mg へ増加しても，iNHL 患者，aNHL 患者のいずれにおいても，サイクル8の投与期間中の総クリアランス低下は認められなかった。同様に，iNHL 患者，aNHL 患者のいずれにおいても，投与量が400 mg から800 mg へ増加しても消失半減期（$t_{1/2}$）の幾何平均，定常状態の分布容積（V_{ss}）の平均値に変化はみられなかった。

1000 mg の用量で投与した CLL 患者では，C_{max} 及びトラフ濃度はサイクル1の投与期間中を通して増加し，サイクル2の投与後に定常状態に到達した。CLL 患者では患者ごとの結果のばらつきが大きく，総クリアランスの幾何平均は105 mL/日，$t_{1/2}$の平均値は21.0日，V_{ss} の平均値は7.20 L であった。

4) 安全性

追跡調査の結果，いずれの組織型でも，多く発現した有害事象は，感染症および寄生虫症に関連する事象であり，すべての組織型を通して，Grade 3又は4の有害事象は16件報告された。発現した有害事象の内，肺感染，敗血性ショック，腸管膿瘍，尿路感染，リンパ球減少症，好中球減少症，発熱及び腎癌が治験薬投与との関連ありと判断された。

追跡調査期間中の死亡例は36例であり，主な死因は病勢進行であった（28例）。病勢進行以外の理由による死亡例の内，2例は有害事象による死亡であった（aNHL 患者1例の因果関係が否定された心肺停止，CLL 患者1例の因果関係ありと判断された敗血性ショック）。すべての組織型を通して，10件の重篤な有害事象が発現し，この内5件は治験薬投与との因果関係ありと判断された（iNHL 患者1例の腸管膿瘍，CLL 患者1例の肺感染及び敗血性ショック，別の CLL 患者の発熱及び腎癌）。

(4) 結論

- 追跡調査で得られたデータは，投与終了後のカットオフ時の解析から導かれた有効性及び安全性の結論を変えるものではなかった。
- iNHL 及び aNHL のいずれにおいても，RO5072759の血清中薬物濃度は400 mg コホートに比べて1600/800 mg コホートで高値であった。
- iNHL 患者及び aNHL 患者のサイクル1 Day 1，サイクル1 Day 8及びサイクル8時点の全身曝露量（C_{max} 及び AUC_{7d}）は用量を400 mg から1600/800 mg に増加するに従い用量に比例して増加した。
- CLL 患者では，サイクル1の Day 1，Day 8及び Day 15に1000 mg の用量で3回投与するに従い，C_{max} 及びトラフ濃度は増加した。
- 薬物動態データから，サイクル1中の追加投与を含む投与スケジュールは，早期の標的の飽和達成と以降のサイクルにおける適切な RO5072759の曝露量を維持することを可能とするのに十分な高さの曝露量に速やかに到達させることが可能であることが示唆された。

2014年8月に再投与期間の結果に基づき，BO20999試験の最終総括報告書が作成された。以下に主な追加情報及び変更点を記載する。

(1) フェーズ

第 I/II 相再投与

(2) 治験依頼者及び治験実施施設

F. Hoffmann-La Roche 社／再投与した患者が含まれるフランスの5施設

(3) 公表

1. Salles G et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. Blood 2012. May 31;119(22): 5126-32.

2. Salles G et al. Obinutuzumab (GA101) in patients with relapsed/refractory indolent non-Hodgkin lymphoma: results from the phase II GAUGUIN study. JCO 2013. Aug10;31(23): 2920-6.

3. Morschhauser F et al. Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large B-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN study. JCO 2013. Aug 10;31(23): 2912-9.

(4) 治験実施期間

2009年10月12日～2013年11月25日（1例目の初回再投与日～最終観察日）

(5) 治験方法

病勢進行が認められた患者で再投与が可能と判断された患者に対して前回と同一用量又は800 mg の用量で合計8サイクル投与した。

再投与された被験者は，最終被験者が試験中止するまで，又は最終被験者の再投与開始の2年後まで腫瘍評価及び生存について追跡調査した。

(6) 被験者数

登録例134例（第 I 相34例，第 II 相100例）の内，PD 症例13例が再投与実施（第 I 相から4例，第 II 相から9例，NHL 11例，CLL 2例）

(7) 診断及び主な組入れ基準

再発・治療抵抗性の CD20陽性悪性疾患を有し，他に優先すべき治療法がなく，抗 CD20抗体療法が適当と判断される男女成人患者。主治医の診察に基づき，患者ごとに治験依頼者が評価し，病勢進行が認められた患者の内，再投与可能と判断された患者。

再投与実施の基準：

- RO5072759を8サイクル投与した（NHL は9回投与，CLL は10回投与）
- RO5072759投与により奏効がみられた（CR/CRu/CRi 又は PR が確認された）
- その後，病勢進行した

(8) 被験薬の用量及び投与方法

NHL 患者：サイクル1の Day 1及び Day 8に，その後は3週間間隔でサイクル2からサイクル8の Day 1にコホートで規定した用量を静脈内投与した（9回投与）。

CLL 患者：サイクル1の Day 1，8，15に，その後は3週間隔でサイクル2からサイクル8の Day 1にコホートで規定した用量を静脈内投与した（10回投与）。

(9) 評価基準

1) 有効性

標準的な NHL 及び CLL 基準による最良総合効果（BOR）

2) 薬力学

本総括報告書では報告しない。

3) 薬物動態

本総括報告書では報告しない。

(10) 結果の要約

1) 有効性

初回投与で奏効がみられ，投与完遂後に病勢進行となった13例（BOR で CR 4例，PR 9例）に対して再投与された。再投与での奏効例は8/13例（いずれも NHL）であり，内訳は CR が3/13例及び PR が5/13例であった。

NHL 患者の再投与期間の BOR は CR 3例及び PR 5例であった。

初回投与で奏効がみられた CLL 患者2例の BOR は PR であった。これらの2例が病勢進行後に再投与を受けた。再投与期間の BOR はいずれも SD であった。

2) 安全性

再投与期間中の安全性プロファイルを以下に要約した。

- 再投与したすべての被験者で少なくとも1件の有害事象が発現した。Grade 3及び4の有害事象は46%（6/13例）に8件発現した。
- 最も多く発現がみられた有害事象は IRR であった。発現した IRR は1件が Grade 3以上であったのを除き，重症度はいずれも Grade 1又は2であった。IRR は，投与期間中を通して85%（11/13例）の被験者に，サイクル1 Day 1には69%（9/13例）の被験者に発現した。より後の投与時には IRR の発現率は23%に減少した。また，重篤な IRR の発現はみられなかった。
- 重篤な有害事象は31%（4/13例）の被験者に発現した（CLL 1例，NHL 3例）。
- 再投与期間中に2例が死亡した。死亡した被験者はいずれも NHL であり，死亡理由は病勢進行であった。

表 2.7.6.1.6.2-5　安全性の概要（再投与された被験者）

	Phase I/II re-treatment Patients with NHL and CLL N=13
Patients with at least one AE	13
Grade 3 and 4 AEs	6 (46%)
SAEs	4 (31%)
Deaths	2 (15%)
Withdrawals due to AEs	0
Most frequently occurring AEs (in > 1 patient)	
IRRs	11 (85%)
Asthenia	6 (46%)
Pyrexia	2 (15%)
Oral Herpes	2 (15%)
Constipation	2 (15%)
Hypotension	2 (15%)

［5.3.5.4-1-5 Table 4を再掲］

(11) 結論

再投与期間から試験終了（データカットオフ日：2013年11月25日）までの結果は，投与終了後の追跡調査期間（データカットオフ日：2012年3月31日）で得られた有効性及び安全性の結論と同様であった。導入療法時に奏効がみられた被験者に対して再投与した場合に，忍容性が

あり，得られた有効性の結果から，再投与によりベネフィットが認められる可能性が示された。

2.7.6.1.7　BO21003試験（GAUSS 試験）

2.7.6.1.7.1　第 I 相臨床試験部分

(1) 試験の標題

Protocol BO21003 - An open-label, multicentre, dose escalating, Phase I / randomized Phase II study to investigate the safety and tolerability of RO5072759 (GA101) given as monotherapy in patients with CD20+ malignant disease.

BO21003試験 – CD20陽性悪性疾患患者に対する RO5072759単剤療法による安全性及び忍容性を検討する非盲検多施設用量漸増第 I 相／ランダム化第 II 相臨床試験

(2) フェーズ

第 I 相

(3) 治験依頼者及び治験実施施設

F. Hoffmann-La Roche 社，Genentech 社／カナダの5施設

(4) 公表

なし

(5) 治験実施期間

2008年1月[redacted]日～[redacted]年[redacted]月[redacted]日（報告日）

(6) 目的

第 I 相試験部分の主要目的

- CD20陽性悪性疾患患者に対する RO5072759単剤・用量漸増・静脈内（IV）投与における安全性及び忍容性について検討を行う。

副次的目的

- RO5072759の薬物動態（PK）特性を明らかにする。
- RO5072759投与に伴う末梢血 B 細胞の枯渇及び回復を検討する。
- 有効性に関連するゲノム薬理学パラメータ（ベースラインにおける FcyRIIa 及び IIIa 多型）及び薬力学パラメータ（ベースライン，投与中及び投与終了後の bcl-2遺伝子再構成を含む）を検討する。
- RO5072759維持療法を評価する。
- ベースラインにおけるヒト抗キメラ抗体（HACA）の発現状況，RO5072759投与に伴うヒト抗ヒト抗体（HAHA）の発現状況を評価する。

(7) 治験方法

本治験の第 I 相部分は非ランダム化・複数コホートの3 × 3の用量漸増デザインであり，CD20陽性悪性疾患患者（リンパ腫又は慢性リンパ性白血病（CLL））を対象に RO5072759を各コホートで絶対（一定）用量で投与した。

各コホートは3～6例の被験者からなり，コホート1～5には各3例，コホート6には6例，時間差をつけて登録し，RO5072759の開始用量は200 mg とした（用量漸増計画は表 2.7.6.1.7.1-1を参照）。コホートに割り付けられた被験者は，各コホート規定用量を導入期間（週1回4週間）で投与した。コホート3までの各コホートでの初回投与量は当該コホートの用量の50%とした（すなわち，開始用量が200 mg であるコホート1での Day 1の初回投与量は100 mg とし，その

後3サイクルの投与量は200 mg とした）。初回投与時に忍容性が認められた場合には，残りの投与は最大用量で投与した。

コホート1の最初の3例で毒性の発現が認められなかった場合は，重大な毒性が認められるまで増加率は上限を100%として投与量を漸増した。重大な毒性とは，対象コホートにて Grade 2 の有害事象が2件又は Grade 3以上の有害事象が1件発現した場合，若しくは主治医が重大と判断する因果関係の否定できない有害事象が発現した場合と定義し，重大な毒性が認められた場合は，増加率は上限50%を許容とした。

用量漸増期間中は，安全性データ，PK データ及び有効性データの内，利用可能な情報は用量漸増の決定に用いた。コホート6は，第 II 相部分を開始する前に1000 mg 一定用量で投与した際の安全性及び忍容性のデータを評価するために追加した。

導入療法終了時に CR，CRu，PR と評価された被験者は，維持療法期間として，更に3カ月おきに最大2年間継続投与した。

安全性は，1サイクル7日として各サイクルの Day 1及び導入部分の投与終了28日後に評価した。維持療法を受けた被験者は，導入部分の投与終了2カ月後～4カ月後の間は1カ月おき，その後の導入部分の投与終了6カ月後～24カ月後の間は3カ月おきに安全性を評価した。

抗腫瘍評価は，標準的な NHL / CLL 基準（1999 Cheson criteria）を用いて，スクリーニング時と導入療法の投与終了28日後に行った。維持療法期間では，導入部分の投与終了の2，6，12及び18カ月後に評価した。有効性解析に際し，導入療法時に早期に投与中止した被験者は非奏効例として取り扱った。

導入療法は完遂したものの，維持療法の実施基準を満たさなかった被験者は，導入療法の投与終了後に追跡調査を行い，維持療法を実施した被験者は維持療法を中止した後，又は2年間の維持療法の完遂後に追跡調査を行った。

表 2.7.6.1.7.1-1　各コホートでの RO5072759の用量

Cohort	First Infusion	Subsequent Infusions
1	100 mg	200 mg
2	200 mg	400 mg
3	400 mg	800 mg
4	800 mg	1200 mg
5	1200 mg	2000 mg
6	1000 mg	1000 mg

［5.3.5.4-2-1 Table 1を再掲］

(8) 被験者数

22例（NHL 17例，CLL 5例）

(9) 診断及び主な組入れ基準

CD20陽性悪性疾患を有する男女成人患者

(10) 被験薬の用量，投与方法及び投与期間

RO5072759を週1回，最大4週間（計4回投与），コホートで規定された用量を単剤で静脈内投与した。更に，導入療法後に CR，CRu，PR が認められ，RO5072759の維持療法が適格と判断される場合は，3カ月おき，最大2年間（計8回投与），コホートで規定された用量を継続投与した。

(11) 対照薬の用量及び投与方法

対象薬を設定しなかったため，該当しない。

(12) 評価基準

1) 有効性

- 導入療法終了時の奏効率及び試験期間中（導入療法中及び継続投与中）の最良総合効果（BOR）
- 導入療法時点の総合効果（主要評価項目）から，以降の試験観察期間中又は維持療法期間を含む投与期間中にみられた最良効果（BR）までの効果改善

奏効率は標準的な NHL / CLL 基準で評価した。

2) 薬力学

- 末梢血 B 細胞の枯渇及び回復（CD19陽性 B 細胞数）
- 血清中の補体値
- 免疫グロブリンの枯渇及び回復
- HAHA

3) 薬物動態

最高血清中濃度（C_{max}）及び濃度–時間曲線下面積（AUC）について評価した。

4) 安全性

National Cancer Institute-Common Toxicity Criteria for Adverse Events（NCI-CTCAE）version 3.0 を用いて有害事象の Grade を判定した。臨床検査値及び身体検査についても評価した。

(13) 統計的手法

要約統計量を算出した。

(14) 結果の要約

1) 有効性

21例の被験者で少なくとも1回の腫瘍評価が導入療法開始後に行われた。残る1例は，サイクル4の腫瘍評価より前に試験を中止したため，腫瘍評価の結果を用いることができなかったことから，有効性解析では非奏効例として取り扱った。

投与終了時の奏効率は22.7%（95%CI：7.8～45.4%），内訳は PR5例，CR0例であり，BOR は31.8%（95%CI：13.9～54.9%），内訳は CR1例（4.5%），PR6例（27.3%）であった。

2) 薬力学

ベースライン（サイクル1の Day 1前）における CD19陽性 B 細胞数は多くの被験者で低値であり，RO5072759投与時に期待された B 細胞数の枯渇という薬力学的効果と矛盾することなく，RO5072759を投与に伴い，更に低下した。ベースライン時の CD19陽性 B 細胞数の中央値は 0.1680×10^9/L（範囲：0.000～119.836，主治医の基準範囲：$0.080～0.616 \times 10^9$/L）であった。導入療法及び維持療法期間中，多くの被験者は B 細胞数が枯渇した（0.04×10^9/L 以下）。最小値までの期間の中央値は7日（範囲：−1～611日）であった。[redacted]年[redacted]月[redacted]日のデータカットオフ時点では，多くの被験者の B 細胞数は，回復していなかった（0.08×10^9/L への回復）。B 細胞数の回復が遅れたのは，RO5072759の投与中止後の追跡調査期間が短いことや B 細胞数の回復を遅らせる他治療に移行したことが理由として考えられた。観察期間の中央値は8.5カ月（範囲：0.8～28.3カ月）であった。少数例の被験者（いずれも CLL 患者）では，投与期間中に B 細胞数が一時的に枯渇し，その後，ある時点で回復した。

3) 安全性

全体的に RO5072759は投与した用量おいて良好な忍容性を示し，用量漸増投与時（コホート

1～5）に，用量制限毒性（DLT）は認められなかった。しかし，コホート6の1例で初回投与時に Grade 4の IRR の DLT が発現し，導入療法中に投与中止に至った。ただし，コホート6は用量漸増部分ではなく，第 II 相部分を開始する前に1000 mg 一定用量で投与した際の安全性及び忍容性のデータを得るために追加したものである。データカットオフ日までに死亡例は2例認められ，重篤な有害事象は7例に発現し，有害事象による投与中止は上述したように1例に発現した。

導入療法期間中に多く発現した有害事象は，IRR が16/22例（73%），発熱及び好中球減少症が各5例（23%）であった。その他の少なくとも3例以上（10%以上）に発現した有害事象は，頭痛及び悪心が各4例（18%），疲労，下痢及び呼吸困難が各3例（14%）であった。

導入療法期間中に発現した有害事象の多くは Grade 1（74/112件）又は Grade 2（26/112件）であり，Grade 3及び Grade 4の有害事象は8/22例（36%）に合計で12件発現した。Grade 3及び Grade 4の有害事象の内訳は，好中球減少症が5例（23%），IRR が4例（18%），発熱性好中球減少症，骨盤骨折及び頭痛が各1例（5%）であった。また，導入療法期間中に，主治医により治験薬投与との因果関係ありと判断された Grade 3及び Grade 4の有害事象は7例であり，その内訳は好中球減少症が3件，IRR が4件，発熱性好中球減少症及び頭痛が各1件であった。

維持療法期間中，有害事象は8例中6例に25件発現し，多く発現した器官別大分類は感染症および寄生虫症（5/8例）であった。この分類の中では，副鼻腔炎及び上気道感染が各2例と多く発現した感染症であった。その他に少なくとも2例以上に発現した有害事象は，IRR，発熱及び咳嗽が各2例であった。維持療法期間中に発現した有害事象の多くは Grade 1（15/25件）又は Grade 2（8/25件）であった。Grade 3の有害事象は1例に2件（副鼻腔炎及び肺炎）発現し，Grade 4の有害事象は認められなかった。

(15) 結論

- RO5072759の導入療法時及び維持療法時の安全性プロファイルは許容可能であり，いずれの用量群でも管理可能であった。発現した有害事象の多くは Grade 1又は Grade 2であり，投与中止に至る有害事象の発現はまれであった。MTD に未達であり，免疫原性も認められなかった。
- 用量設定を目的とした第 I 相部分では，RO5072759単剤療法群の投与終了時の奏効率は23%，BORR は32%であった。リツキシマブ治療抵抗性の被験者を含む，前治療歴を有する不均一な被験者集団から得られた結果であるが，奏効期間の範囲は90～643日であった。
- 2年間の維持療法期間の忍容性は良好であった。
- B 細胞数の枯渇は速やかに認められたが，追跡調査期間が短く，脱落例もみられたことから B 細胞数の回復について十分に評価することができなかった。
- CD20陽性血液腫瘍に対する RO5072759の導入療法は，臨床的に意味のある結果が得られ，ベネフィットとリスクのプロファイルも良く，新たな治療選択肢の一つになると考えられた。

(16) 報告書作成日

2011年4月

[redacted]年[redacted]月に BO21003試験の試験終了に伴い，第 I 相試験部分の総括報告書補遺が作成された。以下に主要解析時に作成した総括報告書からの主な追加情報及び変更点を記載する。

(1) 治験実施期間

2008年1月[redacted]日～[redacted]年[redacted]月[redacted]日（プロトコル既定の試験終了日）

(2) 評価基準

1) 薬力学

- 末梢血 B 細胞の枯渇及び回復（CD19陽性 B 細胞数）
- 免疫グロブリン測定値
- HAHA 及び HACA

(3) 結果の要約

1) 有効性

主要解析時から奏効期間の最長期間に延長がみられ，643日から947日に延長した。

2) 薬力学

投与期間終了時に末梢血の B 細胞数の枯渇（0.08 × 10^9/L 以下と定義）がみられた被験者は20/21例（95%）であり，投与終了12カ月後の追跡調査時にはデータが確認可能であった8例中5例に回復がみられた。最終評価時には，回復が15/21例（71%）にみられた。

更なる追跡調査の結果，CD3陽性，CD8陽性，CD16陽性56陽性細胞数の投与前値への回復や従前から低値の CD4陽性 T 細胞数の回復といった，その他のリンパ球サブセットの全体像に変化はみられなかった。

測定可能な HACA 力価（<5.0 RU/mL）が Day 1に認められたものの，Day 870では検出されなかった患者識別番号129296/1000の被験者を除いて，カットオフ以降に投与継続した被験者の内，HAHA を測定した被験者（3カ月時点で13例，最終投与から少なくとも1年後では5例）のいずれも HAHA の状態変化は認められなかった。

3) 薬物動態

サイクル1の血清中濃度は用量依存的に増加した。サイクル1（導入療法）時点の PK パラメータを以下に示す。

表 2.7.6.1.7.1-2　サイクル1の導入療法後の血清中 PK パラメータの平均値（%CV）

Dose (mg)	C_{max} (µg /mL)	AUC_{last} (µg*day/mL)
100 (n = 3)	39.7 (22.8)	151 (69.4)
200 (n = 3)	73.1 (32.9)	318 (49.8)
400 (n = 3)	102 (58.1)	397 (73.3)
800 PT1	395	1486
800 PT2	267	1027
1000 (n = 3)	338 (30.0)	1457 (64.2)
1200 PT1	332	1688
1200 PT2	432	1364

The following patients were excluded from the analysis due to limited PK sampling: 1002 (800/1200 mg); 1154 (1200/2000 mg); 1053, 1103, 1156 and 1250 (1000 mg).
For 800 mg and 1200 mg dose individual values are provided.
［5.3.5.4-2-2 Table 2を再掲］

サイクル4投与時でも，同様に，血清中濃度は用量依存的に増加した。C_{max} 及びトラフ濃度は4サイクルの投与を続けるに従い増加し，最大用量である2000 mg をサイクル4まで投与した際には，それぞれ1421 µg/mL 及び1222 µg/mL に到達した。

いずれの用量コホートにおいても，サイクル1からサイクル4までの AUC から算出した，おおよその累積係数は3であった。サイクル4時点では，用量を200 mg から2000 mg まで増加するのに伴い，総クリアランスの低下がみられた。

400 mg 又はそれ以上の用量では，1名の外れ値により800 mg の用量コホートを除外すると，用量間でのクリアランスの差異は小さかった。

導入療法（4回投与）の最終投与後には，RO5072759の血清中薬物濃度は速やかに減少し，3カ月おきの維持療法の期間中は RO5072759の血清中薬物濃度に明らかな増加傾向はみられなかった。8例が維持療法を開始し，いずれの投与量群（200～2000 mg）においても，維持療法期間中の RO5072759のトラフ濃度の平均値は同様であり，範囲は15～40 mg/mL であった（1例の血清中薬物濃度は定量検出限界以下であった）。

4) 安全性

主要解析のためのカットオフ時点から試験終了までの期間中に，追跡調査を継続中の5例から1件の有害事象が報告された。この有害事象は治験薬との因果関係はなしと判断された。

(4) 結論

- 主要解析のためのデータカットオフ時点以降に追跡調査を継続中であった5例から得られた結果は，主要解析で得られた結果に基づく有効性及び安全性の結論を変えるものではなかった。
- RO5072759の血清中薬物濃度は，導入療法実施時の用量コホート間で用量依存的な増加傾向が認められた。しかし，限られたデータから得られた結果であるため，明確な結論を付けることはできなかった。
- 第 I 相部分の維持療法期間中の薬物動態プロファイルから，維持療法を開始した被験者全例で3カ月おきの維持療法の最初の2サイクルでは RO5072759が速やかに消失し，血清中薬物濃度の明らかな増加はみられなかった。この結果から，以降の試験におけるより投与頻度の高い2カ月ごとの投与が支持された。

2.7.6.1.7.2　第 II 相臨床試験部分

(1) 試験の標題

An open-label, multi-centre, randomized phase II study to investigate the safety and tolerability of RO5072759 versus rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin's Lymphoma

再発性 CD20陽性 B 細胞性低悪性度非ホジキンリンパ腫に対する RO5072759及びリツキシマブ投与時の安全性及び忍容性を検討した非盲検多施設ランダム化第 II 相臨床試験

(2) フェーズ

第 II 相

(3) 治験依頼者及び治験実施施設

F. Hoffmann-La Roche 社／Genentech 社／15カ国の54施設（多くの施設は1～2例を登録した）。患者が多く登録された3施設はニュージャージー（米国）11例（6%），ヘント（ベルギー）10例（6%），ミラン（イタリア）8例（5%）

(4) 公表

なし

(5) 治験実施期間

2009年7月[redacted]日～2011年9月1日（1例目のスクリーニング日～データカットオフ日）

(6) 目的

第 II 相部分の主要目的

再発 CD20陽性低悪性度非ホジキンリンパ腫患者（iNHL）に対する RO5072759（1000 mg 一

定用量）単剤療法の全奏効率（ORR）及び安全性をリツキシマブ（375 mg/m^2）単剤療法と比較検討する。

副次的目的

- RO5072759の薬物動態（PK）特性を明らかにする。
- RO5072759の投与時間の短縮の可能性を検討する
- RO5072759投与に伴う末梢血 B 細胞の枯渇及び回復を検討する。
- ORR，PFS 及び EFS を評価し，維持療法期間を含め，再発 CD20陽性 iNHL 患者におけるリツキシマブ（375 mg/m^2）単剤療法に対する RO5072759単剤療法の抗腫瘍効果の予備データを収集する。
- 有効性に関連するゲノム薬理学パラメータ（ベースラインにおける FcyRIIa 及び IIIa 多型）及び薬力学パラメータ（ベースライン，投与中及び投与終了後の bcl-2遺伝子再構成を含む）を検討する。
- RO5072759維持療法の実行可能性を評価する。
- ベースラインにおけるヒト抗キメラ抗体（HACA）の発現頻度，RO5072759投与に伴うヒト抗ヒト抗体（HAHA）の発現頻度を評価する。

(7) 治験方法

CD20陽性悪性疾患に対する RO5072759及びリツキシマブ投与時の安全性及び忍容性を検討するための非盲検多施設共同ランダム化臨床試験である。

適格と判断された CD20陽性 iNHL を有する患者を，RO5072759単剤投与群（1000 mg 一定用量）又はリツキシマブ単剤投与群（375 mg/m^2）にランダムに割り付けた。

RO5072759は一定用量を点滴静注し，リツキシマブは患者の実体重から換算した体表面積に基づく用量を点滴静注した。被験者は週1回4週間（Day 1，8，15及び22）に RO5072759又はリツキシマブが投与された。CR，CRu，PR，病勢安定（SD）と評価された被験者は，維持療法期間として，2カ月おきに最大2年間，病勢進行，許容できない毒性の発現，同意の撤回又は新たな抗リンパ腫治療を開始するまで，割り付けられた薬剤を継続投与した。

すべての被験者が投与中止しない限り，最終被験者の登録（最終被験者の登録日は2010年9月7日）された2.5年後に試験終了することを治験実施計画書に定義した。

(8) 被験者数

198例でスクリーニングを実施し，175例が登録された。

(9) 診断及び主な組入れ基準

1) 組織学的に確認された CD20陽性 iNHL（Grade 1～3a）であること。ただし，小リンパ球性リンパ腫及び辺縁体リンパ腫は含むが，B 細胞性慢性リンパ性白血病，マントル細胞リンパ腫，リンパ形質細胞性リンパ腫は含まない。
2) 本治療が臨床的に適切であると主治医により診断されていること。
3) リツキシマブを含む治療により過去に文書で確認可能な6カ月以上の奏効歴（CR，CRu 又は PR）があり，その後再発した病変を有すること。
4) すべての患者は，少なくとも一つの二次元的に測定可能な病変（CT スキャンによる計測可能な長径寸法は1.5 cm より大きいもの）があること。
5) ECOG PS が0～2であること。
6) 試験参加のための文書による同意が可能で，かつ，試験計画を遵守できること。
7) 19歳以上であること。
8) 12週間以上の生存が可能であると判断されていること。

(10) 被験薬の用量，投与方法及び投与期間

RO5072759を1000 mg の用量で週1回，最大4週間（Day 1，8，15，22に投与）に単剤で静脈内投与を行い，投与終了28日後まで観察した。その際に，病勢進行が認められなかった被験者は RO5072759を1000 mg の用量で2カ月おき，最大2年間の継続投与を行った。

(11) 対照薬の用量及び投与方法

リツキシマブを375 mg/m^{2}の用量で週1回，最大4週間（Day 1，8，15，22に投与）に単剤で静脈内投与を行い，投与終了28日後まで観察した。その際に，病勢進行が認められなかった被験者はリツキシマブを375 mg/m^{2}の用量で2カ月おき，最大2年間の継続投与を行った。

(12) 評価基準

1) 有効性

主要評価項目

- 主治医評価に基づく導入療法期間終了時の FL 患者の全奏効率［ORR］（全奏効は完全奏効［CR］，不確定完全奏効［CRu］又は部分奏効［PR］とする）

副次的評価項目

- 導入療法終了時の CR，CRu
- 導入療法終了時の PR
- 試験期間中（導入療法中及び継続投与中）の最良総合効果（BR：CR，CRu 又は PR）
- 試験期間中（導入療法中及び継続投与中）の BORR
- 導入療法時点の総合効果（すなわち，主要評価項目）から，以降の試験観察期間中又は継続投与期間を含む投与期間中にみられた BR までの効果改善
- 主治医評価の PFS
- EFS
- 奏効期間

独立判定委員会（IRF）の評価結果に基づき，以下のパラメータについて感度分析を行った。

- 導入療法終了時点の ORR
- 試験期間中（導入療法中及び継続投与中）の BR
- IRF 評価の PFS（PFS-IRF）

2) 薬力学

治験薬投与に伴う薬力学的マーカー（サイトカイン，補体，T 細胞，B 細胞，免疫グロブリン）の時系列変化を評価した（例：数時間でサイトカインがまず変化し，その後数日でリンパ球値が変化し，その後，数週間から数カ月で免疫グロブリン値が変化する）。薬力学的パラメータについては平均値，標準偏差，中央値，変動係数，最小値及び最大値を記載した。

3) 薬物動態

iNHL 患者77例対象として，サイクル4の投与終了時にノンコンパートメント解析（NCA）を実施し，$T_{1/2}$，C_{max}，AUC_{last}，CL_{ss}，V_{ss}，AUC_{tau} について評価した。また，維持療法の初回サイクル時に投与された58例，維持療法の投与終了時には5例を対象に同様に NCA を実施した。

投与時間短縮投与のサブ試験に参加した5例の PK は別途解析を行った。

4) 安全性

NCI-CTCAE version 3.0を用いて有害事象の Grade を判定した。臨床検査値，バイタルサイン，ECOG PS，心電図検査，血清中抗オビヌツズマブ抗体，特に注目する有害事象（重篤な感染症，IRR，重篤な好中球減少症，腫瘍崩壊症候群）についても評価した。

(13) 統計的手法

有効性の初期仮説は H_0：$ORR_{obinutuzumab} \leq ORR_R$ vs H_1：$ORR_{obinutuzumab} > ORR_R$ とし，ORR は各治療群の CR 率と PR 率を合わせた割合とした。本仮説について濾胞性非ホジキンリンパ腫患者に限定して α 係数が0.2の片側カイ二乗検定（連続補正なし）を用いて評価した。

(14) 結果の要約

1) 有効性

FL 患者へのリツキシマブ又は RO5072759の導入療法終了時点の，主治医評価の奏効率（主要評価項目）をカイ二乗検定で解析した結果，両側検定の P 値は0.1587であり，統計学的有意差は認められなかった。

表 2.7.6.1.7.2-1　有効性の結果（ITT 集団，FL 患者）

Section	Rituximab (n=75)	Obinutuzumab (n=74)	Difference between treatments[a]
Primary Efficacy Endpoint			
Overall Response Rate at End of Induction Treatment (as Determined by the Investigator)			
	33.3%	44.6%	11.3% (80% CI one-tailed: 3.9, ---), p-value=0.1587
Secondary Efficacy Endpoints			
Complete Response Rate at the End of Induction Treatment (as Determined by the Investigator)			
	5.3%	12.2%	6.8% (95% CI: -2.9; 16.6)
Partial Response Rate at the End of Induction Treatment (as Determined by the Investigator)			
	28.0%	32.4%	ND
Best Overall Response Rate (as Determined by the Investigator)			
	64.0%	66.2%	2.2% (95% CI: -13.9; 18.9)
Change in Overall Response during Extended Treatment (n=63 rituximab and n=62 obinutuzumab)			
	30 improved 27 no change 6 worsened	29 improved 27 no change 5 worsened 1 missing	ND
Progression-Free Survival (Median)			
	529 days	527 days	HR=1.06 (95% CI: 0.62, 1.8)
Event-Free Survival (Median)			
	437 days	472 days	HR=1.08 (95% CI: 0.67,1.74)
Duration of Response			
	not yet reached	627 days	ND
Sensitivity Analyses of the Primary Efficacy Endpoint			
Overall Response Rate as Assessed by the IRF (radiological review combined with clinical data)			
	26.7%	44.6%	17.9% (80% CI: one-tailed: 10.7, ---)

[a] P-values are reported in this table for a two-tailed test.

Results are based the clinical data-cut off of 1 September, 2011.

Note: CI: confidence interval; IRF: Independent Review Facility; ITT: intention to treat; ND=not done; HR: hazard ratio

［5.3.5.4-2-3 Table 12を改変］

2) 薬力学

RO5072759投与群のより多くの被験者で，初回投与中に血清中 IFNγ 及び TNFα の増加がみ

られた。RO5072759投与群では，初回投与中にサイトカインの IL6，IL8及び IL10の濃度の中央値の著しい増加がみられたが，急激な変化の理由は明確に分からなかった。両群とも，CD3陽性，CD4陽性，CD8陽性及び CD19陽性細胞の濃度の中央値は初回投与時に急激に減少したが，2回目の投与までに回復した。

データカットオフ日前の B 細胞数最終評価時には，リツキシマブ投与群では81/86例（94%），RO5072759投与群では79/85例（93%）で B 細胞の枯渇が認められた。

3) 薬物動態

C_{max} 及びトラフ濃度は4サイクルの投与を続けるに従い顕著に増加し，C_{max} はサイクル1では274 μg/mL であったが，サイクル4では649 μg/mL であった。導入療法最終投与後（4回目投与後）には，RO5072759の血清中薬物濃度は速やかに減少した。11サイクルの維持療法期間中を通して，RO5072759のトラフ濃度の幾何平均値は同様であり，範囲は133～182 μg/mL であった。RO5072759の最終投与後の CL_{ss} の幾何平均は250 mL/日であり，変動係数は48.7%であったが，1例（被験者識別番号2601）は4150 mL/日のクリアランスが認められ，他の被験者に比べて高値であった。血清中半減期の幾何平均は32.7日であり，分布容積の平均は12.4 L であった。全身曝露量（AUC_{last} 及び AUC_{tau}），総クリアランス及び分布容積は RO5072759を regular infusion で投与した被験者と投与時間を短縮した被験者の間で同様であった

4) 安全性

2011年9月1日のデータカットオフ時点での安全性の概要を以下に示す。本治験では，安全性上問題となる所見はみられなかった。投与期間を通して，導入療法期間中（特に初回投与時）に RO5072759投与群で IRR が多く発現したのを除き，両群間の安全性プロファイルに大きな違いはみられなかった。

表 2.7.6.1.7.2-2　安全性の概要（SAP）

Protocol(s): I21003T
Analysis: SAP　　Center: ALL CENTERS
Snapshot Date: 07OCT2011　　Cutoff Date: 01SEP2011
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

	RITUXIMAB N = 86 No. (%)	RO5072759 N = 87 No. (%)
Total Pts with at Least one AE	72 (84)	82 (94)
Total Number of AEs	327	442
Deaths #	6 (7)	6 (7)
Patients with at least one		
AE leading to Death	3 (3)	2 (2)
Serious AE	14 (16)	15 (17)
Serious AE leading to withdrawal from treatment	4 (5)	5 (6)
Serious AE leading to dose modification/interruption	1 (1)	0 (0)
Related serious AE	6 (7)	7 (8)
AE leading to withdrawal from treatment	9 (10)	7 (8)
AE leading to dose modification/interruption	30 (35)	47 (54)
Related AE	51 (59)	75 (86)
Related AE leading to withdrawal from treatment	3 (3)	6 (7)
Related AE leading to dose modification/interruption	30 (35)	47 (54)
Severe AE	26 (30)	30 (34)

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page.
AE24 11NOV2011:08:40:23　　ae24_sa

［5.3.5.4-2-3 Table 22を再掲］

(15) 結論

- 非盲検多施設共同ランダム化第 II 相臨床試験では，前治療歴を有する FL 患者に対するRO5072759単剤の4サイクルの導入療法は，リツキシマブ単剤の4サイクルの導入療法に比べて，導入療法終了時の全奏効率を改善した。
- 導入療法期間中の初回サイクルでリツキシマブ投与群に比べて，RO5072759投与群で IRR が多く発現したのを除き，両群間の安全性プロファイルに大きな違いはみられなかった。
  しかしながら，発現した IRR の多くが Grade 1又は2で対処可能であり，維持療法期間中では，IRR の発現率に投与群間で違いはみられなかった。Grade 3又は4の IRR の多くは初回投与時に発現した。データカットオフ時には HAHA 陽性の被験者はみられなかった。
- RO5072759の PK プロファイルから，RO5072759を1000 mg の用量で，導入療法として1週間おきの4回投与した際に，全身曝露量の増加がみられた。維持療法期間中では，導入療法期間中と異なり C_{max} の増加傾向はみられず，データカットオフ時点までにデータが得られた維持療法期間中を通して，トラフ濃度の平均値は同様であった。

(16) 報告書作成日

2012年11月

2014年2月に BO21003試験の試験終了に伴い，第 II 相試験部分の総括報告書補遺が作成された。以下に主要解析時に作成した総括報告書からの主な追加情報及び変更点を記載する。

(1) 治験実施期間

2009年6月24日（1例目のスクリーニング日）～2013年3月14日（最終患者の最終観察日）

(2) 評価基準

1) 有効性

PET 検査に基づく IRF 評価の抗腫瘍効果は，別途，CSR 追補で報告することとした。

2) 薬力学

治療群ごとの CD19陽性 B 細胞の枯渇及び回復，投与終了時に B 細胞の枯渇がみられた被験者数と治験薬の最終投与時に B 細胞数の枯渇がみられた被験者数を要約した。

3) 薬物動態

限られたサンプル採取スケジュールであり，投与間隔も1週間おきであることから，サイクル1～3の PK パラメータを評価することができなかった。更に，サイクル4では CL_{ss}，V_{ss}，$T_{1/2}$ のような PK パラメータで頑健性を評価するため，サンプル採取スケジュールの期間をより長くする必要があった。

(3) 統計的手法

有効性について ITT 集団及び ITT 集団の内，濾胞性非ホジキンリンパ腫の患者について分けて評価した。有効性の評価項目として奏効率の両側95%信頼区間（CI）を Pearson-Clopper 法を用いて，可能な限り治療群ごとに算出した。

(4) 結果の要約

1) 有効性

ITT 集団の内，FL 患者の更新時点の有効性結果を以下に示す。

表 2.7.6.1.7.2-3　有効性の結果（更新時点，ITT 集団，FL 患者）

Section	Rituximab (n = 75)	Obinutuzumab (n = 74)	Difference Between Treatments[a]
Secondary Efficacy Endpoints			
Best Overall Response Rate (as Determined by the Investigator)			
	64.0%	66.2%	2.2 [95% CI: -13.9; 18.3]
Change in Overall Response during Extended Treatment (n = 63 rituximab and n = 62 obinutuzumab)			
	31 improved 26 no change 6 worsened	32 improved 22 no change 7 worsened 1 missing	ND
Progression-Free Survival (Median)			
	772 days	536 days	HR: 0.9 [95% CI: 0.6, 1.4]
Event-Free Survival (Median)			
	472 days	472 days	HR: 1.0 [95% CI: 0.7, 1.5]
Duration of Response			
	809 days	not yet reached	ND
Sensitivity Analyses of the BOR			
BOR as Assessed by the IRF (radiological review)			
	49.3%	63.5%	14.2 [95% CI: -2.4; 30.7]
Progression-Free Survival Assessed by IRF			
	52.0%	44.6%	0.8 [95% CI: 0.5, 1.3]

[a] Pearson-Clopper methodology for 95% CIs
Results were based the clinical data cutoff of 07 March 2013
CI = confidence interval; IRF = Independent Review Facility; ITT = intent-to-treat; ND = not done; HR = hazard ratio
［5.3.5.4-2-4 Table 1を改変］

2)　薬力学

維持療法及び追跡調査に参加した被験者の結果から，濾胞性非ホジキンリンパ腫患者の CD3陽性，CD4陽性，CD8陽性及び CD19陽性細胞濃度のベースラインからの変化の中央値は安全性解析対象集団の傾向と同様であった。

最終総括報告書の更新データの結果から，導入療法終了時，安全性解析対象集団の内，リツキシマブ投与群では80/84例（95%），RO5072759投与群では82/85例（96%）の被験者で B 細胞の枯渇が認められた。

3)　薬物動態

サイクル1の C_{max} は292 μg/mL，サイクル4の C_{max} は692 μg/mL であり，サイクル4の投与後のトラフ濃度は418 μg/mL であった。また，12サイクルの維持療法期間中を通して，RO5072759のトラフ濃度の幾何平均値は同様であり，範囲は180～201 μg/mL であった（1例の血清中薬物濃度は定量検出限界以下であった）。

維持療法開始前には58例，サイクル12の維持療法開始時には3例の PK データが評価可能であった。更に，RO5072759 1000 mg の最終投与後の CLss の幾何平均は308 mL/日であり，変動係数は153%であった。血清中半減期の幾何平均は41.0日（CV = 69.8%）であり，分布容積の平均は14.6 L（CV = 67.3%）であった。

4) 安全性

本試験の安全性の概要を以下に示す。維持療法期間中でも，RO5072759投与により新たな安全性上問題となる所見はみられず，忍容性が良好であると考えられた。投与期間を通して，RO5072759投与群で IRR が多く発現したのを除き，両群間の安全性プロファイルに大きな違いはみられなかった。治験薬投与との因果関係ありと判断された IRR は，リツキシマブ投与群で86例中44例（51%）に126件，RO5072759投与群で87例中70例（80%）に233件発現した。

表 2.7.6.1.7.2-4　安全性の概要（SAP，更新データ）

Protocol(s): BO21003 (K21003F) - Phase II
Analysis: SAP　　Center: ALL CENTERS
Snapshot Date: 17JUN2013　　Cutoff Date: 07MAR2013
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

	RITUXIMAB N = 86 No. (%)	RO5072759 N = 87 No. (%)
Total Pts with at Least one AE	74 (86)	83 (95)
Total Number of AEs	387	512
Deaths #	11 (13)	18 (21)
Patients with at least one		
AE leading to Death	3 (3)	4 (5)
Serious AE	17 (20)	21 (24)
Serious AE leading to withdrawal from treatment	5 (6)	6 (7)
Serious AE leading to dose modification/interruption	1 (1)	0 (0)
Related serious AE	7 (8)	8 (9)
AE leading to withdrawal from treatment	10 (12)	10 (11)
AE leading to dose modification/interruption	30 (35)	47 (54)
Related AE	53 (62)	75 (86)
Related AE leading to withdrawal from treatment	3 (3)	9 (10)
Related AE leading to dose modification/interruption	30 (35)	47 (54)
Severe AE	29 (34)	33 (38)

Investigator text for Adverse Events encoded using MedDRA version 16.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page.
AE24 27JUN2013:09:54:33　　ae24_sa
Patient 129301/1203 in the rituximab arm died due to graft versus host disease post transplant but has not been included in this table.
［5.3.5.4-2-4 Table 8を再掲］

(5) 結論

- 試験終了時では，BOR で初回解析時の結果と大きな違いはみられなかった。両群間の差異を評価するには統計的検出力はなかったものの，両群間の PFS に違いはみられなかった。
- 更新データも踏まえた安全性プロファイルの結果は，初回解析時にみられた安全性プロファイルと大きな違いはみられなかった。

2.7.6.1.8　BO21000試験（GAUDI 試験）

2.7.6.1.8.1　再発・治療抵抗性患者対象部分

(1) 試験の標題

An open-label, multi-centre, randomised, phase Ib study to investigate the safety and efficacy of RO5072759 given in combination with CHOP, FC or bendamustine chemotherapy in patients with CD20+ B-cell follicular non-Hodgkin's lymphoma.

CD20陽性 B 細胞濾胞性非ホジキンリンパ腫患者に対する RO5072759を CHOP 療法，FC 療法，ベンダムスチンの化学療法と併用投与した際の安全性及び有効性を検討する第 Ib 相非盲検・多施設・ランダム化臨床試験

(2) フェーズ
第 Ib 相

(3) 治験依頼者及び治験実施施設
F. Hoffmann-La Roche 社／6カ国（オーストラリア，ドイツ，フランス，イタリア，スペイン，英国）の16施設

(4) 公表
なし

(5) 治験実施期間
2009年2月[redacted]日～[redacted]年[redacted]月[redacted]日

(6) 目的
主要目的
- 再発・治療抵抗性の CD20陽性 B 細胞濾胞性リンパ腫（FL）患者に対する，RO5072759（以下，GA101）の静脈内（IV）投与に CHOP 療法又は FC（フルダラビン，シクロホスファミド）療法を併用した際の安全性について検討を行う。
- 未治療の CD20陽性 B 細胞性 FL 患者に対する，GA101の IV 投与に CHOP 療法又はベンダムスチンを併用した際の安全性について検討を行う。

副次的目的
- 再発・治療抵抗性濾胞性リンパ腫患者に対する GA101と CHOP 療法又は FC 療法を併用した際，又は未治療の濾胞性リンパ腫患者に対する GA101と CHOP 療法又はベンダムスチンを併用した際の抗腫瘍効果の予備的なデータを収集する。
- GA101の薬物動態（PK）特性を明らかにする。
- GA101投与に伴う末梢血 B 細胞の枯渇及び回復を検討する。
- 有効性に関するゲノム薬理学パラメータ（特にベースラインの FcγRIIa 及び IIIa 多型）及び薬力学パラメータ（ベースライン，投与中及び投与終了後の bcl-2/IgH 遺伝子再構成を含む）を検討する。
- 維持療法として GA101を投与した際の安全性を評価する。

本中間報告では再発・治療抵抗性の濾胞性リンパ腫患者のデータのみを報告する。また，イベント発生までの期間のデータ（PFS，EFS）は予備的なデータであり，解釈に注意を要する。

(7) 治験方法
再発・治療抵抗性の FL 患者に対する導入療法
FL 患者は，選択基準及び主治医の臨床的判断を基に適格性を判断し，GA101と CHOP 療法の併用投与群（以下，G–CHOP 群）又は GA101と FC 療法の併用投与群（以下，G–FC 群）に割り付けられた。G–CHOP 群，G–FC 群の両群ともに，GA101の投与量は，400 mg 一定用量又は，サイクル1（Day 1及び Day 8）では1600 mg，その後の投与は800 mg のどちらかにランダム化した。

未治療の FL 患者に対する導入療法
治験実施施設単位で G–CHOP 群又は GA101とベンダムスチン療法の併用投与群（以下，G–B 群）に割り付けられた。両群とも被験者には GA101を1000 mg の一定用量で投与した。

維持療法及び追跡調査期間

導入療法を受けたすべての被験者はGA101と化学療法の併用投与終了28日後の安全性追跡調査を行い，引き続き，維持療法を開始する又は試験中止するまで，少なくとも2年間は追跡調査を行うこととした。導入療法完遂時に CR，CRu，又は PR の奏効が認められ，主治医により継続投与のベネフィットがあると判断された被験者を維持療法の適格患者と判断した。維持療法の終了後は，病勢進行が認められるまで，又は新たな抗リンパ腫治療を開始するまで少なくとも2年間は追跡調査を行うこととした。

最終投与から2年後の時点で，CR，CRu，又は PR の奏効継続が認められた被験者は再発状況，すべての被験者は生存状況を，6カ月おきに継続して調査することとした。

(8) 被験者数

56例が登録され，14例ごとに4治療群（GA101低用量 + CHOP 療法併用投与群，GA101低用量 + FC 療法併用投与群，GA101高用量 + CHOP 療法併用投与群，GA101高用量 + FC 療法併用投与群）にランダム化された。

(9) 診断及び主な組入れ基準

主な選択基準

1) 最大2レジメンの前治療歴がある G–CHOP 療法又は G–FC 療法が適格と判断された再発・治療抵抗性の CD20陽性 B 細胞性 FL，又は，前治療歴のない CD20陽性 B 細胞性 FL の19歳以上の男女患者。
2) 少なくとも1つの測定可能病変［コンピューター断層撮影（CT）にて直交する2方向で計測可能で腫瘍の最大径が1.5 cm を超える］を有する患者。
3) 文書により同意取得が可能であり，試験実施計画書を遵守する意思がある患者。

主な除外基準

1) G–CHOP 療法群の再発・治療抵抗性の患者は，アントラサイクリンの前治療歴がある患者。G–FC 療法群の再発・治療抵抗性の患者は，直前の治療でフルダラビン又はフッ化ピリミジン系薬剤を用いた患者。
2) 試験開始の6カ月以内にモノクローナル抗体の治験薬投与を受けた患者。
3) 試験登録の56日以内にリツキシマブの前治療歴を有する患者。又は試験登録3カ月以内に放射線免疫療法を受けた患者。
4) ヒト化又はマウスモノクローナル抗体に対して重篤なアレルギー又はアナフィラキシー反応の既往歴のある患者。マウス由来製品に過敏症又はアレルギーがあることが分かっている患者。
5) 中枢神経系（CNS）のリンパ腫を有する患者
6) 試験登録の2年以内に，試験実施計画書の遵守又は結果の解釈に影響を及ぼす可能性のある悪性疾患の既往歴がある患者。
7) 試験実施計画書の遵守又は結果の解釈に影響を及ぼす可能性のある，症状のある，制御不能な合併症を有する患者。

(10) 被験薬の用量，投与方法及び投与期間

再発・治療抵抗性 FL 患者

GA101低用量群：GA101は一定用量で投与した。G–CHOP 療法群は GA101 400 mg を3週間間隔で6～8サイクル投与，G–FC 療法群は GA101 400 mg を4週間間隔で4～6サイクル投与した。

GA101高用量群：GA101をサイクル1の Day 1及び8に1600 mg，その後は800 mg の用量で投与した。各治療群の投与間隔は低用量群と同様に投与した。

未治療の FL 患者

GA101は1000 mg 一定用量で投与し，G–CHOP 療法群は GA101 1000 mg を3週間間隔で6～8サイクル投与，G–B 療法群は GA101 1000 mg を4週間間隔で4～6サイクル投与した。

維持療法（適格患者のみ）

GA101を400 mg 又は800 mg の用量で，3カ月おきに最長2年間又は病勢進行が認められるまで投与した。

GA101の投与時にはポンプを用いて，ゆっくりと点滴静注を行った。

(11) 併用薬の用量及び投与方法

化学療法（CHOP，FC 又はベンダムスチン）は体表面積（BSA）で投与量を算出し投与した。

(12) 対照薬の用量及び投与方法

本治験は対照薬を用いなかったため該当しない。

(13) 評価基準

1) 有効性

全奏効率，完全奏効（CR/CRu）率，無増悪生存期間，無イベント生存期間

2) 薬力学

末梢血 B 細胞の枯渇及び回復

3) 薬物動態

試験期間を通しての GA101の薬物濃度

4) 安全性

GA101と化学療法併用時の安全性

(14) 統計的手法

有効性解析

再発・治療抵抗性患者に対しては用量及び投与群ごと，未治療患者に対しては投与群ごとに，導入療法時の奏効率及び Pearson-Clopper 法で求めた95%CI を示した。

薬物動態解析

記述要約統計量

薬力学的解析

あらかじめ規定したレベルから CD19陽性の B 細胞数の減少又は回復がみられた被験者を，B 細胞数の枯渇及び回復がみられた被験者数として示した。

安全性解析

再発・治療抵抗性の患者では用量及び投与群ごとに，未治療の患者では投与群ごとに要約した。

なお，本中間報告では，再発・治療抵抗性患者集団の結果のみを報告している。

(15) 結果の要約

1) 有効性

G–CHOP 療法群では，低用量群13例（92.9%），高用量群14例（100%）が導入療法終了時に奏効がみられ，全奏効率は96.4%，CR 率は45%であった。

G–FC 療法群では，低用量群14例（100%），高用量群12例（85.7%）が導入療法終了時に奏効がみられ，全奏効率は92.8%，CR 率は50%であった。

2) 薬力学

すべての被験者で B 細胞数の枯渇（0.04 × 10^9 /L 以下）が認められ，ほとんどの被験者が治療継続中（維持療法中）であったことから，本報告のためのデータカットオフ（[redacted]年[redacted]月[redacted]日）までに回復は認められなかった。

3) 薬物動態

GA101の血清中薬物濃度は，G–CHOP 療法群，G–FC 療法群ともに低用量群に比べて高用量群で高値であった。また，両群ともに，PR 例に比べて CR 例で GA101の血清中薬物濃度は高値であった。

4) 安全性

単剤投与を検討した臨床試験の結果と比べて，新たな安全性上問題は特定されなかった。

G–CHOP 療法群では，GA101の投与量に関係なく，すべての被験者が6～8サイクル投与された。G–FC 療法群では有害事象を理由に28例中5例が投与中止した。

有害事象の発現率を器官別大分類（SOC）で評価した結果，低用量群及び高用量群間に大きな違いはみられなかった。しかし，被験者数が少なく，低用量群及び高用量群の有害事象発現率について明確に結論づけるに至らなかった。

(16) 結論

- 単剤投与を検討した臨床試験の結果と比べて，新たな安全性のシグナルは特定されなかった。
- G–CHOP 療法群では，GA101の投与量に関係なく，すべての患者が6～8サイクルで投与された。
- G–FC 群療法では，有害事象を理由に28例中5例が投与中止し，これらの被験者で原疾患がより長期化していることが原因と考えられた。
- 導入療法により，ほとんどの被験者で CR 又は PR の奏効がみられた。

(17) 報告書作成日

[redacted]年[redacted]月

2.7.6.1.8.2 未治療患者対象部分

(1) 試験の標題

An open-label, multi-centre, randomised, phase Ib study to investigate the safety and efficacy of RO5072759 given in combination with CHOP, FC or bendamustine chemotherapy in patients with CD20+ B-cell follicular non-Hodgkin’s lymphoma.

CD20陽性 B 細胞濾胞性非ホジキンリンパ腫患者に対する RO5072759を CHOP 療法，FC 療法，ベンダムスチンの化学療法と併用投与した際の安全性及び有効性を検討する第 Ib 相非盲検多施設ランダム化臨床試験

(2) フェーズ

第 Ib 相

(3) 治験依頼者及び治験実施施設

F. Hoffmann-La Roche 社／オーストラリアの8施設，ドイツの6施設，イタリアの2施設，スペインの5施設，英国の5施設

(4) 公表

なし

(5) 治験実施期間

2010年8月[redacted]日～[redacted]年[redacted]月[redacted]日（データカットオフ日）

(6) 目的

主要目的（未治療患者対象）

- 未治療の CD20陽性 B 細胞性濾胞性リンパ腫（FL）患者に対する，GA101の IV 投与に CHOP 療法又はベンダムスチンを併用した際の安全性を検討する。

副次的目的

- 未治療の濾胞性リンパ腫患者に対する GA101と CHOP 療法又はベンダムスチンを併用した際の抗腫瘍効果のデータ収集のため，以下の事項について評価する。
  - 全奏効率（ORR）
  - 完全奏効／不確定完全奏効（CR/CRu）
  - 無増悪生存期間（PFS）
  - 無イベント生存期間（EFS）
  - GA101の薬物動態（PK）特性を明らかにする。
  - 未治療の濾胞性リンパ腫患者において GA101の投与に伴う末梢血 B 細胞の枯渇及び回復を検討する。
  - 有効性に関するゲノム薬理学パラメータ（特にベースラインの FcγRIIa 及び IIIa 多型）及び薬力学パラメータ（ベースライン，投与中及び投与終了後の bcl-2/IgH 遺伝子再構成を含む）を探索的に検討する。
- 未治療の濾胞性リンパ腫患者に対して維持療法として GA101を投与した際の安全性を評価する。

(7) 治験方法

本治験は，導入療法期間，適応が確認された被験者に対する追加の維持療法期間，投与後の追跡調査期間，維持療法後の追跡調査期間を既定した第 Ib 相非盲検・多施設・ランダム化臨床試験である。

施設単位で G–CHOP 療法群又は G–B 療法群に割り付けた。未治療の患者を登録開始する前に，各施設は試験期間中，いずれの化学療法を用いて治療するのかを決定した。G–B 療法群では最初の3例の被験者を Day 15まで重大で予期しない毒性が発現しないかを観察した。最初の3例で重大で予期しない毒性がみられなかった場合は，症例登録の継続を可能とした。

導入療法を受けたすべての被験者は GA101と化学療法の併用投与終了28日後の安全性調査を行い，引き続き，維持療法を開始する又は試験を中止するまで，少なくとも2年間は追跡調査を行うこととした。

導入療法完遂時に CR，CRu，又は PR の奏効が認められ，主治医により継続投与のベネフィットがあると判断された被験者を維持療法の適格患者と判断した。維持療法は，導入療法終了の12週後に投与開始し，1000 mg の用量で，最長2年間又は病勢進行が認められるまで，3カ月おきに1回 GA101を投与した。維持療法の終了後は，病勢進行が認められるまで，又は新たな抗リンパ腫治療を開始するまで少なくとも2年間は追跡調査を行うこととした。

試験の終了は最後の被験者が維持療法の終了後2年間の追跡調査終了時点と定義した。

導入療法，維持療法に限らず，最終投与から2年後の時点で，CR，CRu，又は PR の奏効継続が認められた被験者は再発状況，生存が確認されているすべての被験者は生存状況を，6カ月おきに継続して調査することとした。

(8) 被験者数

目標被験者数は80例とし，実際の登録被験者数は81例であった。

(9) 診断及び主な組入れ基準

未治療の CD20陽性 B 細胞性 FL を有する，19歳以上の男女成人患者。

少なくとも1つの2方向測定可能病変（CT にて直交する2方向で計測可能で腫瘍の最大径が 1.5 cm を超える］を有する患者。

測定可能及び評価可能なすべての腫瘍所見を GA101と化学療法の併用投与開始前に評価しなければならない。腫瘍評価は，すべての部位の腫瘍の状態に基づく。

文書により同意取得が可能であり，試験実施計画書を遵守する意思がある患者。

(10) 被験薬の用量，投与方法及び投与期間

GA101は1000 mg 一定用量で投与し，G–CHOP 療法群は3週間間隔で6～8サイクル投与，G–B 療法群は4週間間隔で4～6サイクル投与した。最大投与サイクル数（G–CHOP 療法群：6又は8サイクル，G–B 療法群：4又は6サイクル）は主治医の裁量で決定した。

なお，投与時に用いた GA101は以下の2種類の異なる製剤を用いて投与した。

- 粉末状製剤は，20 mL のガラスバイアルに凍結乾燥した白色粉末を密閉した形で提供した。キット1つにつきバイアル2個（バイアル1個につき50 mg の GA101を含む）が含まれており，1000 mg の用量で投与する際には10キット（400 mg の用量で投与する際には4キット，800 mg の用量で投与する際には8キット）必要となる。
- 液状製剤は，キット1つにつき1000 mg の GA101を含むバイアル1個から構成されており，溶解することなく利用可能である。1000 mg の用量を含むバイアル1個につき40 mL であり，溶液濃度は25 mg/mL である。

(11) 併用薬の用量及び投与方法

化学療法の用量は体表面積（BSA）を基に算出し投与した。CHOP 療法及び FC 療法の投与は，各薬剤の添付文書を参考に各実施医療機関における標準的な調製・投与方法に従い行った。ベンダムスチンは添付文書に従い，保存及び調製を行い投与した。

(12) 対照薬の用量及び投与方法

本治験は対照薬を用いなかったため該当しない。

(13) 評価基準

1) 有効性

以下の有効性パラメータについて副次的項目として評価した。

- 全奏効率（ORR）
- 完全奏効率（CR/CRu）

本治験では2007年改訂の改訂版 NHL 効果判定基準を基に評価した。CRu の評価は改訂版 NHL 効果判定基準には含まれていないため，改訂前の1999年の効果判定基準を基に CRu と判断された被験者は，陽電子放射断層撮影（PET）を効果判定に用いていない場合でも本治験では PR と取り扱うこととした。

- 無増悪生存期間（PFS）
- 無イベント生存期間（EFS）
- 奏効期間（探索的パラメータ）

2) 薬力学

末梢血の B 細胞数の枯渇及び回復を含む薬力学的パラメータを評価した。更に探索的解析として，ベースラインの FcγRIIa 及び FcγRIIIa 受容体の遺伝子多型，ベースライン，試験期間中及び投与終了後の bcl-2/IgH 遺伝子再構成について評価した。

3) 薬物動態

PK 評価のためのサンプル採取スケジュールの遵守を必須とした。

PK サンプルは GA101の投与前後，及び維持療法を行った被験者については，最終投与以降3カ月おきに治療終了後2年間の追跡調査期間又は B 細胞数の回復がみられるまで（つまり，B 細胞数が標準値又はスクリーニング時に戻るまで），にもサンプル採取を行った。

35.0 μL のヒト血清サンプル中の GA101濃度を，酵素免疫測定法（ELISA）を用いて評価した。

4) 安全性

GA101 1000 mg を FL 患者に対する一次治療として CHOP 療法又はベンダムスチンと併用した際の有害事象の発現状況及び臨床検査値を含む安全性について評価した。

(14) 統計的手法

本試験の主要評価項目は GA101と化学療法併用時の安全性の評価である。

有効性解析は，導入療法時の化学療法（CHOP 療法又はベンダムスチン）ごとに，投与終了時の全奏効率及び最良全奏効率（BORR）及び Pearson-Clopper 法で求めた95%CI を示した。

GA101の各サイクル投与時の C_{max}，トラフ濃度，AUC_{inf}，AUC_{last}，$AUC_{0-\tau}$，$t_{1/2}$，CL_{ss} 及び V_{ss} を GA101の血清中薬物濃度から標準的なノンコンパートメント解析（NCA）を用いて算出した。AUC パラメータについては，一次台形法を用いて，実際のサンプル採取時間を基に算出した。RO5072759の用量，濃度，時間データは非線形混合効果モデル（NONMEM）を用いて解析した。すべての PK パラメータは算術的平均，標準偏差，幾何的平均，変動係数（CV），中央値及び範囲を含む記述統計量を用いて要約した。

(15) 結果の要約

1) 有効性

導入療法時に多くの被験者に奏効がみられた。G–B 療法群では，投与終了時に CR は39%，PR は53.7%の被験者にみられた。G–CHOP 療法群では，投与終了時に CR は35%，PR は60%の被験者にみられた。データカットオフ時点（[redacted]年[redacted]月[redacted]日）では，BORR は投与終了時の奏効率と同様であったが，維持療法期間中に PR から CR へ改善した被験者がみられた。データカットオフ時点では，イベントが発生した被験者も少なく，維持療法も継続中であったことから，イベント発生までの期間のデータ（PFS，EFS，奏効期間）の解釈は十分にできなかった。そのため，イベント発生までの期間の中央値は評価しなかった。

2) 薬力学

CD19陽性 B 細胞数の中央値は，両群ともに GA101の初回投与後に速やかに減少した。

初回投与後の B 細胞数の中央値は0.085から0.0×10^9/L（B 細胞数の枯渇は0.07×10^9/L より低下と定義）に減少した。データカットオフ時には，ほとんどの被験者が維持療法を継続中であり，B 細胞数の回復に関するデータは得られていない。

その他，白血球細胞に関するパラメータはフローサイトメトリー（FACS）を用いて評価した。CD3陽性，CD4陽性，CD8陽性及び CD16陽性 B 細胞数の中央値は初回投与後に減少し，追跡調査の Day 8時点で，それぞれベースライン時の27%，45%，78%及び42%まで回復した。

3) 薬物動態

GA101の投与時間に対する薬物濃度は，G–CHOP 療法群及び G–B 療法群間で同様であり，導入療法期間中に C_{max} 及び C_{min} の増加がみられた。全身曝露量（C_{max} 及び AUC_{7days}）は，両群ともにサイクル1（Day 1及び Day 8）から投与終了時まで同様な増加がみられた。更に，総クリアランス及び分布容積も両群間で違いはみられなかった。

サンプル採取スケジュールは本来母集団 PK 解析のため計画された。サンプル採取スケジュールが限られており，投与間隔が1週間間隔と短かったことから，サイクル1 Day 1及びサイクル1 Day 8時点の PK パラメータを正確に評価することができなかった。

$t_{1/2}$の幾何平均は G–B 療法群では37.3日（範囲：22.0～81.9日），G–CHOP 療法群では35.5日（範囲：18.3～66.9日）であった。$t_{1/2}$，総クリアランス，分布容積のような PK パラメータのより頑健な評価のため，投与終了後のサンプリング期間を長くする必要があると考えられた。

4) 安全性

安全性の概要を表 2.7.6.1.8.2-1に示した。データカットオフ時点では，維持療法を実施した被験者数は少なく，導入療法時の結果を主に評価した。

すべての被験者で少なくとも1件の有害事象が発現した。同一被験者に，同一の有害事象が複数回発現した際には，1回として集計し表に要約した。データカットオフ時点で有害事象は G–B 療法群で354件，G–CHOP 療法群で401件発現した。主治医により因果関係ありと判断された有害事象は，G–B 療法群では90%の被験者に162件，G–CHOP 療法群では100%の被験者に229件発現した。なお，治験実施計画書に規定した投与期間及び投与サイクル数は G–B 療法群に比べて，G–CHOP 療法群が長く，結果として G–B 療法群に比べて，G–CHOP 療法群で GA101の曝露量は高かった。データカットオフ時点では死亡は2例にみられ，各治療群1例ずつ死亡例が認められた。また，有害事象による投与中止も各治療群で1例ずつ認められた。

表 2.7.6.1.8.2-1　安全性の概要

Number (%) of patients with	GA101 + Bendamustine N = 41	GA101 + CHOP N = 40
Any AE	41 (100)	40 (100)
Related to treatment	37 (90)	40 (100)
Grade 3/4	22 (54)	32 (80)
Serious	10 (24)	20 (50)
AE leading to withdrawal from treatment	1 (3)	1 (3)
Death due to AE	1[a] (3)	1[b] (3)

[a] Death due to disease progressive disease.

[b] Death occurred during maintenance treatment period.

［5.3.5.4-3-2 Table 20を改変］

Infusion-related reaction（IRR）は，G–B 療法群で59%の被験者，G–CHOP 療法群で58%の被

験者に発現した。発現した IRR のほとんどは重症度が Grade 1又は Grade 2であり，GA101の休薬又は投与速度の変更の主な原因となり，発現期間としては，主にサイクル1の間に発現した。

導入療法期間中に好中球減少症は，G–B 療法群では34%の被験者，G–CHOP 療法群では63%の被験者に発現した。感染症および寄生虫症の SOC に含まれる感染症関連の有害事象は，G–B 療法群では51%の被験者，G–CHOP 療法群では63%の被験者に発現し，Grade 3又は Grade 4の感染症は，G–B 療法群では10%の被験者，G–CHOP 療法群では23%の被験者に発現した。

臨床検査値を評価した結果，ベースライン時の Grade 0，1，2から Grade 3又は Grade 4へ悪化がみられた白血球数減少は，G–CHOP 療法群では35件，G–B 療法群では18件報告された。ヘモグロビン及び血小板数の変化は比較的に穏やかであり，Grade 0，1，2から Grade 3又は Grade 4への悪化がみられた被験者は少数であった。治験薬投与に関連した，臨床的に重大な生化学的パラメータの変化は認められていない。

サイトカインパラメータの変化は主に初回投与時にみられた。免疫グロブリン値の中央値は，試験期間中を通して基準値内であった。バイタルサインや ECOG PS では臨床的に問題となる変化はみられなかった。GA101の最終導入療法後の3カ月時点の追跡調査時（59例を評価），6カ月時点の追跡調査時（38例を評価）した結果，ヒト抗ヒト抗体（HAHA）は認められなかった。

(16) 結論

- 未治療患者に対し，GA101と化学療法を併用投与した際に，新たな安全性のシグナルは特定されなかった。
- 導入療法時及び初回投与時に認められた安全性の所見は，再発・治療抵抗性患者でみられた所見と同様であった。
- データカットオフ時点では，維持療法が実施された被験者数は少なく，維持療法期間中の安全性について明確に結論づけることはできなかった。
- 本治験では，GA101と化学療法の併用投与により，化学療法の投与量を減少させることはなかった。
- GA101の PK プロファイルは両群で違いはみられなかった。
- 導入療法期間中に，ほとんどの被験者で CR 又は PR の奏効がみられた。
- 両群ともに安全性プロファイルは良好であり，第 III 相試験が進行中である。

(17) 報告書作成日

[redacted]年[redacted]月

[redacted]年[redacted]月に BO21000試験の最終症例の最終来院日である2015年11月[redacted]日までのデータを取りまとめ，BO21000試験の最終総括報告書が作成された。以下に主な追加情報及び変更点を記載する。

(1) 治験実施期間

2009年2月[redacted]日～2015年11月[redacted]日（最終症例の最終来院日）

(2) 公表

Carlisle et al, ASH 2011; Radford et al, ASH 2011; Dyer et al, ASH 2012;, Davies et al, ASH 2013; Radford et al, Blood 2013; Cartron et al, Haematologica 2016.

(3) 結果の要約

1) 有効性

① 再発・治療抵抗性患者

再発・治療抵抗性 FL 患者に対して本剤を CHOP 療法又は FC 療法と併用した際の抗腫瘍効果が示された（表 2.7.6.1.8.2-2）。治療終了時の奏効は主要解析時点の総括報告書から変わらず，多くの患者が導入療法後に CR 又は PR を達成し，維持療法期間に本剤単剤投与を継続した。BORR は以下のとおりであった。

- G–CHOP 療法：低用量群：92.9%（CR 42.9%，PR 50.0%），高用量群：100%（CR 71.4%，PR 28.6%）
- G–FC 療法：低用量群：100%（CR 92.9%，PR 7.1%），高用量群：92.9%（CR 50.0%，PR 42.9%）

推定された PFS 中央値は G–CHOP 療法群が約60カ月，G–FC 療法群の高用量群が33カ月であった（低用量群は中央値に未達であった。）。どちらの化学療法併用群においても，本剤の高用量群と低用量群の有効性に明確な違いは認められなかったが，明確な結論を導くには部分集団の例数が少なかった（各群14例）。

表 2.7.6.1.8.2-2　有効性の概要（再発・治療抵抗性 FL 患者）

	G + CHOP N = 28		G + FC N = 28	
	Low Dose	**High Dose**	**Low Dose**	**High Dose**
Response Endpoints				
End of Treatment Response[a]	14	14	14	14
Patients with CR	2 (14.3%)	9 (64.3%)	11 (78.6%)	3 (21.4%)
95% CI for CR	1.8; 42.8	35.1; 87.2	49.2; 95.3	4.7; 50.8
Patients with PR	11 (78.6%)	5 (35.7%)	3 (21.4%)	9 (64.3%)
EOT response rate (95% CI)	92.9% [66.1; 99.8]	100% [76.8;100.0]	100% [76.8;100.0]	85.7% [57.2; 98.2]
BOR	14	14	14	14
Patients with CR	6 (42.9%)	10 (71.4%)	13 (92.9%)	7 (50.0%)
Patients with PR	7 (50.0%)	4 (28.6%)	1 (7.1%)	6 (42.9%)
BOR (95% CI)	92.9% [66.1; 99.8]	100% [76.8;100.0]	100% [76.8; 100.0]	92.9% [66.1; 99.8]
CR at 30 Months (CR30)[b]	14	14	10	14
Patients (%) with response	4 (28.6%)	7 (50.0%)	7 (70.0%)	6 (42.9%)
95% CI	[8.4; 58.1]	[23.0; 77.0]	[34.8; 93.3]	[17.7; 71.1]
Time to Event/Duration Endpoints				
PFS				
Number (%) of pts with event	7 (50.0%)	7 (50.0%)	6 (42.9%)	7 (50.0%)
Median, months [95% CI]	61.7 [15; NE]	59.2 [26;NE]	NE	33.4 [8; NE]
EFS				
Number (%) of pts with event	7 (50.0%)	7 (50.0%)	8 (57.1%)	8 (57.1%)
Median, months [95% CI]	61.7 [15;.NE]	59.2 [26; NE]	45.6 [14; NE]	33.4 [8; NE]
36 month PFS Rate				
Number (%) of pts with event	7 (50.0%)	7 (50.0%)	6 (42.9%)	7 (50.0%)
Event-free rate [95% CI]	0.57 [0.31; 0.83]	0.71 [0.48; 0.95]	0.76 [151; 1.00]	0.49 [0.22; 0.76]
Duration of Response				
Number of pts with response	13	14	14	13
Patients with PD after CR/PR	7 (53.8%)	7 (50.0%)	6 (42.9%)	6 (46.2%)
Median duration, months [95% CI]	59.1 [12; NE]	56.5 [23; NE]	NE	NE
Time to NALT				
Number (%) of pts with NALT	5 (35.7%)	6 (42.9%)	7 (50.0%)	8 (57.1%)
Median, months [95% CI]	NE [19; NE]	NE [44; NE]	NE [15; NE]	49.0 [8, NE]

NE = Not estimable

[a] Based on induction period. No change in results from those reported in the primary CSR.

[b] CR at 30 months was a post-hoc exploratory analysis. All other parameters were pre-specified in the protocol.

［5.3.5.4-3-3 Table 11を再掲］

② 未治療患者

導入療法として本剤をベンダムスチン又は CHOP 療法と併用し，その後本剤の維持療法を行う治療法が未治療の FL 患者に対する一次治療になり得るという有効性の予備的なエビデンスが示された（表 2.7.6.1.8.2-3）。

- 主要解析時の総括報告書から，1例の治療終了時の有効性評価結果が CR から PR に変更された（CR の評価が治験実施計画書で認められない方法により実施されたため。）。そのため，導入療法終了時の奏効率は，G–B 療法群が CR 37%，PR 56%，G–CHOP 療法群が CR 35%，PR 60%となった。
- 最良全奏効率は G–B 療法群が92.7%（CR 68.3%，PR 24.4%），G–CHOP 療法群が95.0%（CR 80.0%，PR 15.0%）であった。
- G–B 療法群の PFS 中央値及び EFS 中央値はいずれも56.0カ月であり，奏効例の奏効期間

中央値は53.6カ月であった。G–CHOP 療法群ではいずれのエンドポイントも中央値に未達であった。

- 探索的な事後解析として治療開始後30カ月時点の CR を評価したところ，G–B 療法群の63.2%，G–CHOP 療法群の58.3%が CR を達成していた。

表 2.7.6.1.8.2-3　有効性の概要（未治療 FL 患者）

	G + benda N = 41	G + CHOP N = 40
Response Endpoints		
End of Treatment Response[a]		
Patients with CR [95%CI]	15 (36.5%) [22.1; 53.1]	14 (35.0%) [20.6; 51.7]
Patients with PR	23 (56.1%)	24 (60.0%)
EOT response rate [95% CI]	92.7% [80.1; 98.5]	95.0% [83.1; 99.4]
BOR		
Patients with CR	28 (68.3%)	32 (80.0%)
Patients with PR	10 (24.4%)	6 (15.0%)
BOR (95% CI)	92.7% [80.1; 98.5]	95.0% [83.1; 99.4]
Complete Response at 30 Months (CR30)[b]		
Patients with response	24 (63.2%)	21 (58.3%)
95% CI	[46.0; 78.2]	[40.8; 74.5]
Time to Event/Duration Endpoints		
Progression-free Survival (PFS)		
Number (%) of patients with event	6 (14.6%)	11 (27.5%)
Median, months [95% CI]	56.0 [NE, NE]	NE
Event-free Survival (EFS)		
Number (%) of patients with event	8 (19.5%)	13 (32.5%)
Median, months [95% CI]	56.0 [NE, NE]	NE
36 month PFS Rate		
Number (%) of patients with event	6 (14.6%)	11 (27.5%)
Median, months [95% CI]	0.90 [0.80; 0.99]	0.84 [0.72; 0.96]
Duration of Response		
Number of patients with response	38	38
Patients with PD after CR/PR	5 (13.2%)	11 (28.9%)
Median duration, months [95% CI]	53.6 [NE, NE]	NE
Time to NALT		
Number (%) of patients with NALT	5 (12.2%)	9 (22.5%)
Median, months [95% CI]	NE [58; NE]	NE [NE; NE]

[a] Updated since primary CSR, on the basis of an update in the response assessment of one patient from CR to PR.
[b] CR30 was a post-hoc exploratory analysis. All other parameters were pre-specified in protocol.
［5.3.5.4-3-3 Table 55を再掲］

2)　薬力学

①　再発・治療抵抗性患者

治療終了時において G–CHOP 療法群の全例で B 細胞の枯渇が認められ，回復までの期間の中央値は低用量群が19.2カ月（95%CI：15～38カ月），高用量群が44.6カ月（95%CI：推定不能）であった。G–FC 療法群ではどちらの用量群においても中央値に未達であった。

②　未治療患者

G–B 療法群の41例全例，G–CHOP 療法群の40例中39例で B 細胞の枯渇が認められた。治療終了時から B 細胞回復までの期間の中央値は，G–B 療法群が23.7カ月（95%CI：20カ月～推定不能），G–CHOP 療法群が28.6カ月（95%CI：22～30カ月）であった。

3) 薬物動態

① 再発・治療抵抗性患者

血清中オビヌツズマブ濃度の平均値はどちらの化学療法併用群においても，高用量群（1600/800 mg）が低用量群（400/400 mg）と比較して高かった。これは，導入療法期間及び維持療法期間の双方で認められた。

② 未治療患者

2つのコホート（G–B 療法群及び G–CHOP 療法群）で同様の PK プロファイル（時間ごとの血清中オビヌツズマブ濃度）が観察され，C_{max} と C_{min} は導入療法期間を通じて増加した。加えて，維持療法期間において，両コホートで C_{max} と C_{min} に違いは認められなかった。

4) 安全性

① 再発・治療抵抗性

再発・治療抵抗性の FL 患者を対象に本剤と化学療法（CHOP 療法又は FC 療法）を導入療法として併用し，その後維持療法として本剤単剤療法を実施する治療法の安全性プロファイルは許容可能であった（表 2.7.6.1.8.2-4）。試験期間中に全例が少なくとも1件の有害事象を発現した。各群の例数が少ないため，明確な結論や比較を導くことは困難であるが，試験期間中に得られた安全性の重要な知見は以下のとおりであった。

G–CHOP 療法群：

- G–CHOP 療法群の低用量群で最も頻度の高い有害事象は悪心，便秘，下痢，IRR 及び疲労であった。高用量では IRR，好中球減少症及び便秘であった。
- Grade 3以上の有害事象，SAE，死亡，投与中止に至った有害事象の発現率は低用量群の方が低かったが，有害事象の PT レベルでは明確な用量依存性の傾向は認められなかった。
- 4例の死亡例が認められた。1例は試験治療と因果関係ありと判断された有害事象（肝脾 T 細胞性リンパ腫）による死亡であった。その他の3例の死亡は生存調査期間中に認められたもので，死因は病勢の進行，肺炎，心停止であった。

G–FC 療法群：

- 低用量群で最も頻度の高い有害事象は，IRR，悪心，好中球減少症，下痢及び発熱であり，高用量群では IRR，悪心及び便秘であった。両用量群間で用量依存性に関する明確な傾向は認められなかった。
- ほぼ全例（90%）が Grade 3以上の有害事象を発現し，最も頻度の高い有害事象は好中球減少症であった。SAE は58%の被験者に認められた。
- Grade 3以上の有害事象，死亡，投与中止に至った有害事象の発現率は低用量群，高用量群で同様であった。
- 10例の死亡例が試験期間を通して認められ，4例は有害事象による死亡であった（COPD，パーキンソン病，腹水，PML）。PML は試験治療と因果関係ありと判断された。その他の6例の内5例は病勢の進行による死亡であり，残り1例は追跡調査期間中の心停止による死亡であった。

維持療法期間中（表 2.7.6.1.8.2-5），本剤の単剤投与を受けていた被験者のほぼ全例が少なくとも1件の有害事象を発現しており，G–CHOP 療法群の低用量群及び高用量群で25%と27%，G–FC 療法群の67%と75%が副作用を発現した。感染症および寄生虫症が維持療法期間中に最も頻度が高く両群で認められた有害事象の SOC であった（G–CHOP 療法群61%，G–FC 療法群76%）。導入療法期間と比較して維持療法期間では副作用，重度の有害事象，減量又は休薬に至った有害事象の発現率は低く，IRR と好中球減少症の発現率はかなり低かった。

特に注目すべき有害事象（AEPI）（表 2.7.6.1.8.2-4）：

大多数の被験者は IRR を発現した（G–CHOP 療法群の両用量群71%，G–FC 療法群の低用量群86%，高用量群93%）。これらの多くは Grade 1又は2であり，導入療法期間中に認められた。同様に，多くの被験者が感染症を発現した（G–CHOP 療法群の低用量群86%，高用量群100%，G–FC 療法群の低用量群86%，高用量群79%）。Grade 3以上の有害事象として最も頻度が高く報告された SOC は血液およびリンパ系障害及び感染症および寄生虫症であった。PT では好中球減少症が最も頻度が高い Grade 3以上の有害事象であった。また，好中球減少症は，最も頻度が高い Grade 3以上の臨床検査値異常であり，好中球減少症（とその関連する有害事象）は最も頻度が高い本剤中止に至った理由であった。

表 2.7.6.1.8.2-4　再発・治療抵抗性 FL 患者の有害事象の概要（試験期間全体）

	G + CHOP Arm		G + FC Arm	
Number (%) of Patients with	**Low Dose G + CHOP N = 14**	**High Dose G + CHOP N = 14**	**Low Dose G + FC N = 14**	**High Dose G + FC N = 14**
Any AE	14 (100%)	14 (100%)	14 (100%)	14 (100%)
Fatal AE	0	1 (7%)	1 (7%)	3 (21%)
Grade ≥ 3 AE	9 (64%)	11 (79%)	13 (93%)	12 (86%)
SAE	4 (29%)	6 (43%)	4 (29%)	9 (64%)
Related AE	14 (100%)	14 (100%)	14 (100%)	14 (100%)
AE leading to Treatment Withdrawal	0	1 (7%)	5 (36%)	4 (29%)
AEs of Particular Interest				
IRRs	10 (71%)	10 (71%)	12 (86%)	13 (93%)
Neutropenia	5 (36%)	9 (64%)	10 (71%)	8 (57%)
Infections	12 (86%)	14 (100%)	12 (86%)	11 (79%)
PML	0	0	1 (7%)	0
Thrombocytopenia	0	1 (7%)	5 (36%)	4 (29%)
Hemorrhages	3 (21%)	3 (21%)	0	0
Tumor Lysis Syndrome	0	0	0	0
GI Perforation	0	0	0	0
Cardiac AEs	4 (36%)	3 (21%)	3 (21%)	4 (36%)
Second Malignancies	2 (14%)	1 (7%)	2 (14%)	3 (21%)

［5.3.5.4-3-3 Table 24を再掲］

表 2.7.6.1.8.2-5　再発・治療抵抗性 FL 患者の有害事象の概要（導入療法期間及び維持療法期間）

	Induction Period				Maintenance Period			
	G + CHOP Arm		G + FC Arm		G + CHOP Arm		G + FC Arm	
Number (%) of Patients with	Low Dose G + CHOP N = 14	High Dose G + CHOP N = 14	Low Dose G + FC N=14	High Dose G + FC N=14	Low Dose G + CHOP N = 12	High Dose G + CHOP N = 11	Low Dose G + FC N = 9	High Dose G + FC N = 8
Any AE	14 (100%)	14 (100%)	14 (100%)	14 (100%)	10 (83%)	8 (73%)	9 (100%)	8 (100%)
- total number of AEs	177	179	122	129	43	57	51	33
Fatal AE	0	0	0	2 (14%)	0	1 (9%)	1 (11%)	1 (13%)
Grade ≥ 3 AE	8 (57%)	11 (79%)	12 (86%)	9 (64%)	1 (8%)	3 (27%)	4 (44%)	5 (63%)
SAE	4 (29%)	4 (29%)	3 (21%)	4 (29%)	0	3 (27%)	2 (22%)	4 (50%)
Related AE	14 (100%)	13 (93%)	14 (100%)	14 (100%)	3 (25%)	3 (27%)	6 (67%)	6 (75%)
AEs leading to Treatment Withdrawal	0	0	2 (14%)	3 (21%)	0	1 (9%)	3 (33%)	1 (13%)
AEs leading to Dose Modification*	10 (71%)	13 (93%)	10 (71%)	12 (86%)	0	3 (27%)	2 (22%)	2 (25%)

Clinical cut-off date is 04 November 2015 for all data.

* Includes infusion interruptions.

［5.3.5.4-3-3 Table 25を再掲］

② 未治療患者

未治療の FL 患者を対象に本剤と化学療法（ベンダムスチン又は CHOP）を導入療法として併用し，その後維持療法として本剤単剤療法を実施する治療法の安全性プロファイルは許容可能であった（表 2.7.6.1.8.2-6）。試験期間中に全例が少なくとも1件の有害事象を発現した。G–B 療法群について，試験期間中（導入療法期間，維持療法期間，追跡調査期間）に得られた安全性の重要な知見は以下のとおりであった。

- G–B 療法群で最も頻度の高い有害事象（25%以上の発現）は，IRR（59%），悪心（59%），疲労（44%），好中球減少症（41%），下痢（41%），頭痛（39%）及び咳嗽（29%）であった。
- 大多数の被験者（76%）が Grade 3以上の有害事象を発現し，最も頻度の高い有害事象の PT は好中球減少症（41%）であった。SAE は32%の被験者に発現した。
- 2例の死亡例が認められ，いずれも有害事象による死亡ではなかった（追跡調査期間中の病勢の進行及び急性骨髄性白血病）。
- 大多数の被験者が本剤と化学療法の併用に対して忍容性を示し，有害事象で治験薬の投与を中止したのは12%の被験者であった。

G–CHOP 療法群について，試験期間中（導入療法期間，維持療法期間，追跡調査期間）に得られた安全性の重要な知見は以下のとおりであった。

- G–CHOP 療法群で最も頻度の高い有害事象は，IRR（58%），好中球減少症（45%），悪心（43%），便秘（35%），咳嗽（35%），疲労（35%），頭痛（33%）及び下痢（28%）であった。
- ほぼ全例（90%）の被験者が Grade 3以上の有害事象を発現し，最も頻度の高い有害事象は好中球減少症（43%）であった。SAE は58%の被験者に発現した。
- 試験期間中に4例の死亡例が認められ，1例は主治医によって試験治療と因果関係ありと判断された維持療法期間中に発現した有害事象（既存の呼吸器感染症に関連した乳酸性アシドーシス）により死亡した。残り3例の死亡理由は，病勢進行が2例，追跡調査期間中に認められた好中球減少症性敗血症が1例であった。
- 大多数の被験者が本剤と化学療法の併用に対して忍容性を示し，有害事象で試験治療を中止したのは13%の被験者であった。

導入療法期間中に，両治療群とも新たな安全性の懸念は同定されなかった。同様に，維持療法期間中の本剤単剤投与時においても，両治療群とも新たな安全性の懸念は同定されなかった（表 2.7.6.1.8.2-7）。維持療法期間中に多くの被験者が少なくとも1件の有害事象を発現し（G–B 療法群100%，G–CHOP 療法群78%），その半数以上は副作用と判断された（両群とも53%）。重度な有害事象，副作用，SAE，減量又は休薬に至った有害事象，IRR 及び好中球減少症の発現率は導入療法期間と比較して維持療法期間が低かった。

AEPI（表 2.7.6.1.8.2-6）：

大多数の被験者は IRR を発現した（G–B 療法群78%，G–CHOP 療法群70%）。これらの多くは Grade 1又は2であり，導入療法期間中の早いサイクルで認められた。同様に，多くの被験者が少なくとも1件の感染症を発現した（G–B 療法群83%，G–CHOP 療法群75%）。Grade 3以上の感染症は G–B 療法群24%，G–CHOP 療法群35%に認められた。感染症は最も頻度の高い本剤中止理由であった。好中球減少症は最も頻度が高い Grade 3以上の AEPI 及び Grade 3，4の臨床検査値異常であった。治療開始後6カ月後に発現した二次悪性腫瘍は7例に発現した（G–B 療法群6例，G–CHOP 療法群1例）。試験期間中に未治療患者において，腫瘍崩壊症候群及び消化管穿孔は認められなかった。

表 2.7.6.1.8.2-6　未治療 FL 患者の有害事象の概要（試験期間全体）

Number (%) of Patients with	G + benda N = 41	G + CHOP N = 40
Any AE	41 (100%)	40 (100%)
Fatal AE	0	1 (3%)
Grade ≥ 3 AE	31 (76%)	36 (90%)
SAE	13 (32%)	23 (58%)
Related AE	38 (93%)	40 (100%)
AE leading to Treatment Withdrawal	5 (12%)	5 (13%)
AEs of Particular Interest		
IRRs	32 (78%)	28 (70%)
Neutropenia	20 (49%)	25 (63%)
Infections	34 (83%)	30 (75%)
PML	0	0
Thrombocytopenia	6 (15%)	1 (3%)
Hemorrhages	4 (10%)	7 (18%)
Tumor Lysis Syndrome	0	0
GI Perforation	0	0
Cardiac AEs	3 (7%)	8 (20%)
Second Malignancies	6 (15%)	1 (3%)

［5.3.5.4-3-3 Table 64を改変］

表 2.7.6.1.8.2-7　未治療 FL 患者の有害事象の概要（導入療法期間及び維持療法期間）

	Induction		Maintenance	
Number (%) of Patients with	G + benda N = 41	G + CHOP N = 40	G + benda N = 36	G + CHOP N = 36
Any AE	41 (100%)	40 (100%)	36 (100%)	28 (78%)
- total number of AEs	346	389	194	130
Fatal AE	0	0	0	1 (3%)
Grade ≥ 3 AE	21 (51%)	31 (78%)	16 (44%)	11 (31%)
SAE	10 (24%)	19 (48%)	6 (17%)	8 (22%)
Related AE	37 (90%)	40 (100%)	19 (53%)	19 (53%)
AE leading to Treatment Withdrawal	0	2 (5%)	5 (12%)	3 (8%)
AE leading to Dose Modification*	24 (59%)	29 (73%)	6 (17%)	2 (6%)

* Includes infusion interruptions
［5.3.5.4-3-3 Table 65を再掲］

ベースライン後の試験期間中に HAHA が検出された被験者は認められなかった（再発・治療抵抗性患者，未治療患者の双方）。アッセイにおける限られた薬物耐性による HAHA 偽陰性の可能性は除外できないが，検体採血時間は HAHA 評価時に血清中オビヌツズマブ濃度が最低になるように設定した。

(4) 結論

- FL 患者を対象に本剤と化学療法を導入療法として併用し，その後維持療法として本剤単剤療法を実施する治療法は許容可能であり，安全性プロファイルは管理可能であった。維持療法期間中の本剤単剤投与における安全性の知見はこれまでに知られていた安全性と一貫しており，より長い維持療法期間において新たな安全性の懸念は同定されなかった。
- 本剤と化学療法を導入療法として併用し，その後維持療法として本剤単剤療法を実施するすべての治療レジメンは，未治療患者，再発・治療抵抗性患者の双方に対して臨床的に意義のある有効性（高い奏効率，奏効の持続）を示した。
- まとめると，症例数が少なく明確な結論は出せないものの，意義のある有効性と試験期間中の忍容可能な安全性プロファイルから，FL 患者に対する一次治療又は再発・治療抵抗性 FL 患者に対する治療としての治療レジメンの一部としての本剤の更なる評価が求められる。

2.7.6.1.9 BO21005試験（GOYA 試験）

(1) 試験の標題

BO21005 – A Phase III, Multicenter, Open-Label, Randomized Trial Comparing the Efficacy of GA101 (RO5072759) in Combination with CHOP (G-CHOP) versus Rituximab and CHOP (R-CHOP) in Previously Untreated Patients with CD20-Positive Diffuse Large B-Cell Lymphoma (DLBCL)

BO21005試験–未治療の CD20陽性びまん性大細胞型 B 細胞リンパ腫（DLBCL）患者を対象とした GA101（RO5072759） + CHOP 併用群（G–CHOP）とリツキシマブ+ CHOP 併用群（R–CHOP）の有効性を比較する第 III 相多施設共同非盲検ランダム化試験

(2) フェーズ

第 III 相

(3) 治験依頼者及び治験実施施設

F. Hoffmann-La Roche 社／患者は29カ国，207施設から登録された。登録例数が多い国は，イタリア（259例），中国（252例），カナダ（120例），日本（111例），米国（96例），タイ（86例），スペイン（79例），チェコ共和国（74例）及びハンガリー（68例）であった。

(4) 公表

なし

(5) 治験実施期間

2011年7月25日（1例目登録日）～2016年4月29日（データカットオフ日），試験は実施中。

(6) 目的

BO21005試験の主要目的は，未治療の CD20陽性びまん性大細胞型 B 細胞リンパ腫（DLBCL）患者を対象として，リツキシマブ + CHOP 併用群（R–CHOP）に対するオビヌツズマブ（GA101） + CHOP 併用群（G–CHOP）の優越性を，主治医評価の PFS を用いて検証することである。

副次的目的

- G–CHOP 群及び R–CHOP 群の2つの併用療法群間での全生存期間（OS）の評価・比較
- 2群間の治療終了時の全奏効率（ORR）及び完全奏効率（CR 率）の評価・比較（フルオロデオキシグルコース陽電子放射断層撮影［FDG-PET］所見を含む評価及び含まない評価）（主治医評価）
- 2群間の PFS の評価・比較（独立評価委員会［IRC］評価）

- 2群間の治療終了時の ORR 及び CR 率の評価・比較（FDG-PET 所見を含む評価及び含まない評価）（IRC 評価）
- 2群間の無イベント生存期間（EFS）の評価・比較（主治医評価）
- 2群間の無病生存期間（DFS），奏効期間（DOR），新たなリンパ腫治療開始までの期間（TTNALT）の評価・比較
  DFS と DOR は主治医評価を用いる
- G–CHOP 群及び R–CHOP 群の2つの併用療法群間における安全性プロファイルの評価・比較
- 両群の患者報告に基づくアウトカム（PROs）の評価
- 両群の医療資源の利用の評価
- 日本人被験者のみ：オビヌツズマブを CHOP 療法と併用した際の薬物動態特性解析

(7) 治験方法

被験者は21日を1サイクルとして，8サイクルのオビヌツズマブ又はリツキシマブを6又は8サイクルの CHOP 療法とともに投与された。G–CHOP 群にランダム化された被験者はサイクル1 Day 8及び Day 15にもオビヌツズマブが投与された。実施医療機関は試験開始前に CHOP 療法のサイクル数を6又は8サイクルのどちらかを選択した。患者は計画された化学療法のサイクル数（CHOP 療法6サイクル又は8サイクル），IPI スコア（low/low-intermediate risk［巨大腫瘤病変のない IPI スコア0は除外］，high-intermediate risk，high risk）及び地域（西欧，東欧，中南米，北米，アジア，その他）を割付因子として，G–CHOP 群及び R–CHOP 群に1：1の割合でランダムに割り付けた。試験群間のクロスオーバーは認めなかった。

(8) 被験者数

予定被験者数：30～40カ国の約300施設から約1400例

29カ国207施設から1418例が登録されランダム化された（R–CHOP 群：712例，G–CHOP 群：706例）。

(9) 診断及び主な組入れ基準

未治療の進行期 DLBCL の男性及び女性患者を対象とした。

(10) 被験薬の用量，投与方法及び投与期間

オビヌツズマブは絶対（一定）用量として1000 mg を21日サイクルの各 Day 1（8サイクル）に点滴静注した。サイクル1のみ Day 8及び Day 15にも点滴静注した。

(11) 対照薬の用量，投与方法及び投与期間

リツキシマブは375 mg/m^{2}を21日サイクルの各 Day 1（8サイクル）に点滴静注した。

(12) 評価基準

1) 有効性

有効性の主要評価項目は主治医評価による PFS とした。PFS はランダム化された日から病勢進行，再発又は理由を問わない死亡までのいずれか早い時期までの期間と定義した。主要有効性評価項目及び主な副次的有効性評価項目の多重性を調整し，全体の第一種の過誤確率を両側有意水準5%未満に制御するために，fixed sequential testing procedure を用いた。これらの評価項目は有意水準を両側0.05として，以下の順序で検定した。

- 治療終了時の CR 率（CT 所見のみ用い，PET 所見は用いない評価）
- OS
- 治療終了時の ORR（CR 又は PR）（CT 所見のみ用い，PET 所見は用いない評価）
- 治療終了時の CR 率（CT 所見及び PET 所見を用いた評価）

- 治療終了時の ORR（CR 又は PR）（CT 所見及び PET 所見を用いた評価）

2) 薬物動態

日本人患者集団のみ，登録され G–CHOP 療法が実施された最大40例を対象に血清中オビヌツズマブ濃度の測定のため採血を実施した（すなわち，G–CHOP 群に登録された日本人患者の最初の40例を対象とした。）。

3) 安全性

安全性評価には，有害事象（SAE，注意すべき有害事象，特に注目すべき有害事象を含む）のモニタリングと記録，及び治験実施計画書で規定した血液学的検査及び血液生化学検査の測定，治験実施計画書で規定したバイタルサインの測定，その他の治験実施計画書で規定した治験薬の安全性評価に重要と考えられる検査が含まれた。

(13) 統計的手法

有効性：IPI スコア（low/low-intermediate risk［巨大腫瘤病変のない IPI スコア0は除外］，high-intermediate risk，high risk），CHOP の計画されたサイクル数（8サイクル又は6サイクル）を層別因子とした，有意水準を両側0.05とする層別ログランク検定を用いた。Kaplan-Meier 法を用いて，各治療群の PFS 分布を推定した。治療効果の推定値は，95%信頼区間を含む層別 Cox 比例ハザード分析を使用してハザード比として表した。

(14) 結果の要約

1) 有効性

2016年4月29日のデータカットオフ日時点で405イベントを超える PFS イベントが認められた。データカットオフ日時点でハザード比（目標ハザード比0.75）に関して，R–CHOP 群に対して G–CHOP 群で主治医評価による PFS が統計学的に有意な改善を示すという BO21005試験の主要評価項目を達成することができなかった。副次的評価項目も主要評価項目と同様に R–CHOP 群に対する G–CHOP 群のベネフィットは示されなかった。

2) 薬物動態

BO21005試験は DLBCL 患者を対象とした第 III 相臨床試験として，各投与日の投与前及び投与後の採血を含む血清検体の採取が計画された。薬物動態測定用の検体は日本人被験者40例からのみ採取された。サイクル1 Day 1，Day 8及び Day15の投与に伴い，投与後の血清中オビヌツズマブ濃度の幾何平均はサイクル1（435 μg/mL）からサイクル2（938 μg/mL）で増加した。サイクル2からサイクル6までは投与後の血清中オビヌツズマブ濃度は，サイクル4の817 μg/mL からサイクル8の881 μg/mL の範囲にあり，治療期間を通じて一定であった。投与前の血清中オビヌツズマブ濃度は，サイクル4の352 μg/mL からサイクル8の477 μg/mL の範囲にあった。

3) 安全性

カットオフ日時点の安全性の結果を以下に示す。

- 全体的には，重症度が重度で重篤な有害事象の発現率は R–CHOP 群と比較して G–CHOP 群で高かったが，毒性は管理可能な範囲であり，予定されていたオビヌツズマブ及び CHOP 投与に影響を与えなかった。曝露は両群で同等であった。
- 各治療群の多くの被験者が少なくとも1件の有害事象を発現した（R–CHOP 群93.5%，G–CHOP 群97.0%）。報告された有害事象の性質及び重症度は，G–CHOP 及び R–CHOP の安全性プロファイルで既知の事象であった。
- 治療中止に至った有害事象の発現率及び減量に至った有害事象の発現率は両群で同様であった。投与中断に至った有害事象の発現率は，R–CHOP 群（26.6%）と比較して G–

CHOP 群（48.0%）が高かった。両群とも投与中断は主にサイクル1で認められ，最も頻度が高かったのは Day 1であった。投与中断の大部分は IRR によるものであった。これらの投与中断は全体的な治験薬の曝露に影響を与えなかった。

- 試験期間中の死亡例は両群で同様であった（R–CHOP 群17.4%，G–CHOP 群17.9%）。有害事象による死亡例は R–CHOP 群30例（4.3%），G–CHOP 群41例（5.8%）であった。
- Grade 3～5の有害事象（R–CHOP 群64.7%，G–CHOP 群73.7%）及び SAE の発現率（R–CHOP 群37.6%，G–CHOP 群42.6%）は R–CHOP 群と比較して G–CHOP 群で高かった。
- 以下の特に注目すべき有害事象の発現率は R–CHOP 群と比較して G–CHOP 群で高かった。IRR（G–CHOP 群45.3%，R–CHOP 群31.7%），好中球数減少症（G–CHOP 群56.5%，R–CHOP 群48.1%），血小板減少症（G–CHOP 群7.8%，R–CHOP 群2.6%），感染症（G–CHOP 群53.8%，R–CHOP 群44.1%），消化管穿孔（G–CHOP 群2.0%，R–CHOP 群1.1%），心臓事象（G–CHOP 群10.7%，R–CHOP 群7.5%），B 型肝炎の再活性化（G–CHOP 群2.2%，R–CHOP 群0.9%）
- 初回投与から6カ月以降に発現した SOC が「良性，悪性および詳細不明な新生物（嚢胞およびポリープを含む）」の事象と定義した二次性悪性腫瘍の発現率は両群で同様であった（各2.1%）。MedDRA SMQ の「悪性および詳細不明な新生物」で定義した場合の二次性悪性腫瘍の発現率も両群で同様であった（R–CHOP 群2.1%，G–CHOP 群1.7%）。
- G–CHOP 群で進行性後白質脳症（Grade 3，重篤）の症例が1例報告された。

表 2.7.6.1.9-1　安全性の要約（安全性解析対象集団）

t_ae_osafe_emerge_005_SE APPROVED Summary Of Overall Safety - Treatment-Emergent AEs (Safety-Evaluable Patients)
Protocol(s): BO21005 (L21005A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

	R-CHOP (N=703)	G-CHOP (N=704)
Total number of patients with at least one event(AE/death without AE)	667 (94.9%)	687 (97.6%)
Total number of events(AE/death without AE)	6119	7360
Total number of deaths	122 (17.4%)	126 (17.9%)
Total number of patients withdrawn from study due to an AE	3 (0.4%)	4 (0.6%)
Total number of patients with at least one		
AE with fatal outcome	30 (4.3%)	41 (5.8%)
Serious AE	264 (37.6%)	300 (42.6%)
Grade 3-5 AE	455 (64.7%)	519 (73.7%)
Serious AE leading to withdrawal from any treatment	37 (5.3%)	54 (7.7%)
Serious AE leading to dose reduction	22 (3.1%)	28 (4.0%)
Serious AE leading to dose interruption	42 (6.0%)	102 (14.5%)
AE leading to withdrawal from any treatment	60 (8.5%)	84 (11.9%)
AE leading to dose reduction	138 (19.6%)	145 (20.6%)
AE leading to dose interruption	187 (26.6%)	338 (48.0%)

Investigator text for AEs encoded using MedDRA v19.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which
multiple occurrences of the same AE are counted separately.
Total number of events includes deaths for patients that had no adverse events.
Fatal/withdrawal rows include outcomes that were available in the database as of the snapshot date, for adverse events with onset
date on or before the clinical cutoff date.

Program: /opt/BIOSTAT/prod/cdt7159z/k21005d/t_ae_osafe.sas
Output: /opt/BIOSTAT/prod/cdt7159u/l21005a/reports/t_ae_osafe_emerge_005_SE.out
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［5.3.5.4-4 Table 25を再掲］

注釈：この表では，有害事象を発現せずに死亡した被験者が少なくとも1件の有害事象を発現した被験者数に含まれている。

(15) 結論

- 統計解析計画書で主要解析のために事前に規定した405イベントを超える PFS イベントが認められた2016年4月29日にカットオフした。データカットオフ日時点でハザード比（目標ハザード比0.75）に関し，R–CHOP 群と比較して G–CHOP 群で主治医評価による PFS が統計学的に有意な改善を示すという BO21005試験の主要評価項目を達成することができなかった。副次的評価項目も主要評価項目と同様に R–CHOP 群に対する G–CHOP 群のベネフィットは示されなかった。
- 本試験で得られた安全性プロファイル（報告された有害事象の発現頻度及び重症度）は本試験の患者集団及び治療レジメンにおいて予期されるものであった。全体的に予期されない安全性所見は認められず，投与完遂率の高さや投与延期や有害事象による中止の少なさから，G–CHOP 群で認められた毒性は臨床的に管理可能と考えられた。全体的に新たな安全性のシグナルは同定されなかった。

(16) 報告書作成日
[redacted]年[redacted]月

2.7.6.1.10　YP25623試験（GERSHWIN 試験）

(1) 試験の標題
YP25623 – A Multi-Center, Open Label, Single Arm, Multiple Dose Study to Assess the Pharmacokinetics of RO5072759 in Chinese Patients with CD20 + Malignant Disease
YP25623試験–中国人の CD20陽性悪性疾患患者に対する RO5072759の薬物動態を検討する多施設共同非盲検単群反復投与試験

(2) フェーズ
第 I 相

(3) 治験依頼者及び治験実施施設
F. Hoffmann-La Roche 社／中国の4施設

(4) 公表
なし

(5) 治験実施期間
2012年9月6日（1例目の登録日）～2014年12月[redacted]日（最終症例の最終来院日）

(6) 目的
主要目的：
中国人の CD20陽性悪性疾患患者に対して反復静脈内投与後のオビヌツズマブの薬物動態（PK）を評価する。

副次的目的：
中国人の CD20陽性悪性疾患患者に対して反復静脈内投与後のオビヌツズマブの安全性，忍容性，有効性及び薬力学を評価する。

(7) 治験方法
本試験は以下の期間から構成される：
- スクリーニング（Day -28～Day -1）
- 24週間の治療期間（サイクル1～8，各サイクルは21日間）。治験薬はサイクル1では Day 1,

Day 8及び Day 15に投与（CLL 患者ではサイクル1 Day 1の初回投与を2日間にわたって投与）し，サイクル2～8では Day 1のみ投与した。

- 最終投与後1年間の追跡調査期間（4週間の安全性及び有効性評価の追跡調査，［CLL 患者のみサイクル8投与2カ月後の追加の有効性評価］，サイクル8投与後3カ月及び6カ月後のヒト抗ヒト抗体［HAHA］及び PK 測定，最終投与後3週間ごとの安全性評価を含む。）。

(8) 被験者数

予定被験者数は24例，登録された被験者数は48例（CLL12例，DLBCL23例，FL13例）。

(9) 診断及び主な組入れ基準

本試験の対象とする患者集団は男性及び女性の再発・治療抵抗性 CD20陽性悪性疾患患者（CLL，FL 及び DLBCL）の内，効果が期待できる他の優先するべき治療法がなく，抗 CD20抗体を用いた治療が適切と判断された患者である。

(10) 被験薬の用量，投与方法及び投与期間

本剤は21日サイクルの Day 1に1000 mg を最大8サイクル静脈内投与した。サイクル1 Day 8及び Day 15に追加投与した。

(11) 対照薬の用量及び投与方法

対照薬を設定しなかったため，該当しない。

(12) 評価基準

1) 有効性

有効性は治療終了時の奏効（サイクル8 Day 1の投与1カ月後又は早期中止の場合はサイクル4の投与1カ月後，CLL 患者はサイクル8終了後2カ月時点にも評価）及び新たなリンパ腫／白血病治療を開始する前の治験中のいかなる時点の最良全奏効を用いて評価した。治療終了時の奏効及び最良全奏効のいずれも完全奏効（CR），不確定完全奏効（CRu），骨髄機能の回復が不完全の完全奏効（CRi，CLL 患者のみ）又は部分奏効（PR）と評価された被験者を奏効例と取り扱い，病勢安定（SD），病勢進行（PD）又は評価欠測となった被験者は非奏効例として取り扱った。

2) 薬物動態

オビヌツズマブ血清濃度測定のため採血を実施した。

3) 薬力学

リンパ球免疫表現型検査により CD19陽性 B 細胞数を測定した。

4) 安全性

安全性及び忍容性はバイタルサイン，臨床検査値，心電図及び有害事象（AE）をモニタリングして評価した。

(13) 統計的手法

本試験では正式な仮説検定は実施せず，被験者数は試験実施上の観点に基づき設定した。オビヌツズマブの PK パラメータはノンコンパートメント PK 解析（Phoenix WinNonlin® Version 6.2）を用いて評価した。この解析には以下のパラメータを含む。

- t_{max}：最高血清中濃度に達するまでの時間
- C_{max}：最高血清中濃度

- $t_{1/2}$：見かけ上の半減期。（ln2）/k_{el} で算出される。k_{el} は見かけ上の消失速度であり，血漿中濃度－時間曲線の見かけ上の消失相における線形回帰曲線の傾きの大きさとして算出される。
- AUC_{7d}：血清中濃度－時間曲線下の0～Day 7までの面積であり，linear trapezoidal 法を用いて算出される。
- AUC_{21d}：血清中濃度－時間曲線下の0～Day 21までの面積であり，linear trapezoidal 法を用いて算出される。

有効性は，奏効率及びその95% Pearson-Clopper 信頼区間を用いて評価した。

(14) 結果の要約

1) 有効性

CLL 患者（12例）の投与終了時の奏効率は58.3%であった（PR 8例）。最良全奏効率は75.0%であった（PR 9例）。

DLBCL 患者（23例）の投与終了時の奏効率は13%であった（Cru 1例［4.3%］，PR 2例［8.7%］）。最良全奏効率は26.1%であった（CRu 1例［4.3%］，PR 5例［21.7%］）。

FL 患者の投与終了時の奏効率は46.2%であった（PR 6例）。最良全奏効率は61.5%であった（PR 8例）。

2) 薬物動態

すべての患者集団（CLL，DLBCL，FL）において，曝露（AUC）等の PK パラメータは同程度であり，C_{max} やトラフ濃度（C_{trough}）の幾何平均はサイクル2で定常状態に達した。

サイクル8において，CLL 患者の C_{max} 及び C_{trough} の幾何平均はそれぞれ1050 μg/ml 及び403 μg/ml であり，DLBCL 患者ではそれぞれ966 μg/ml 及び455 μg/ml，FL 患者ではそれぞれ867 μg/ml 及び352 μg/ml であった。CLL 患者，DLBCL 患者，FL 患者のサイクル8における AUC_{21day} の幾何平均は，それぞれ12289 day•μg/ml，13000 day•μg/ml，11285 day•μg/ml であった。

オビヌツズマブ曝露における PK の個体間のばらつきでは，CLL 患者が DLBCL 患者及び FL 患者よりも一般的に高かった（CLL 患者の両サイクルの変動係数［CV%］は AUC が最大43%，C_{max} が最大33%，DLBCL 患者，FL 患者の両サイクルの CV%は AUC が39%未満，C_{max} が28%未満であった）。

体重とサイクル8における AUC との間に明確な関係は認められなかったが，FL 患者において体重増加に伴い AUC が減少するわずかな傾向が認められた（FL 患者の P 値 = 0.286，CLL 患者の P 値 = 0.897，DLBCL 患者の P 値 = 0.876）。

本試験で中国人患者から得られた PK データは母集団 PK 解析に用いられ，その結果は以前確立された母集団 PK 解析における非アジア人の FL 患者，DLBCL 患者及び CLL 患者のオビヌツズマブの PK 特性と一致していた。

3) 薬力学

ベースライン時の CD19陽性 B 細胞数の平均値は，CLL 患者が$32.0 \pm 43.7 \times 10^9$/L，DLBCL 患者が$0.3 \pm 1.0 \times 10^9$/L，FL 患者が0であった。B 細胞数が$0.07 \times 10^9$/L 未満と定義した B 細胞の枯渇は CLL 患者で9/12例（75.0%），DLBCL 患者で23/23例（100%），FL 患者で13/13例（100%）に認められた。

FL 患者集団が最も B 細胞の枯渇の期間中央値が長く，465.0日であり，DLBCL 患者集団が最も枯渇の期間中央値が短く92.0日であった。

CD19陽性 B 細胞の回復（CD19陽性 B 細胞数が0.07×10^9/L 以上と定義）が認められた被験者の割合は，CLL 患者で4/12例（33.3%），DLBCL 患者で1/23例（4.3%），FL 患者で1/13例（7.7%）であった。

B 細胞の回復が認められた CLL 患者の4例の内の1例及び FL 患者1例は B 細胞回復前又は B

細胞の回復から45日以内に PD となった。PD となった被験者の B 細胞回復までの期間は CLL 患者が419日，FL 患者が331日であった。

CLL 患者の残りの3例は PD となっておらず，B 細胞回復までの期間の中央値は182.0日，DLBCL 患者1例も PD となっておらず，B 細胞回復までの期間は515.0日であった。

4) 安全性

全48例が1回以上のオビヌツズマブの投与を受け，安全性評価対象集団に含まれた。全部で141件の AE が報告され，少なくとも1件以上の有害事象を発現した被験者は35例（35/48，72.9%）であり，その内訳は CLL 10例（10/12，83.3%），DLBCL 18例（18/23，78.3%），FL 7例（7/13，53.8%）であった。

主な安全性の結果を以下に要約する。

報告された多くの AE は NCI-CTC Grade 1又は2であった（141件中116件）。

25件が NCI-CTC Grade 3～5であった。NCI-CTC Grade 3の有害事象は9例（9/48，18.8%）に，NCI-CTC Grade 4の有害事象は5例（5/48，10.4%）に認められた。CLL 患者において NCI-CTC Grade 5の AE が1件報告された（間質性肺疾患，Day 230に発現［オビヌツズマブ最終投与から60日後］。）。

最も頻度の高い AE の PT は注入に伴う反応15例（15/48，31.3%），発熱11例（11/48，22.9%），咳嗽5例（5/48，10.4%）であった。注入に伴う反応の発現率は DLBCL 患者，FL 患者と比較し CLL 患者で高い傾向が認められた。2例の死亡例が生存追跡調査期間中に認められた。1例は CLL 患者であり主治医が因果関係ありと判定した有害事象（Day 252に発現した間質性肺疾患，治験薬最終投与は Day 170）で死亡した。もう1例は FL 患者であり Day 357に病勢進行のため死亡した（治験薬最終投与は Day 148）。

9例（18.8%）に全13件の SAE が報告された。5例は CLL 患者（5/12，41.7%），3例は DLBCL 患者（3/23，13.0%），1例は FL 患者（1/13，7.7%）であった。最も頻度の高い SAE は SOC が感染症および寄生虫症の事象であり，5例であった（10.4%）。

オビヌツズマブの投与中止に至った有害事象が1例に認められ，CLL 患者に発現した肺炎（NCI CTC Grade 3）であり，Day 52に発現し，Day 66のオビヌツズマブ投与後に治験薬投与が中止された。Day 90に被験者は治験を中止した。オビヌツズマブの投与中断に至った有害事象は9例（18.8%）に認められた。最も頻度の高いオビヌツズマブの投与中断に至った有害事象の PT は注入に伴う反応であり5例（5/48，10.4%）に認められた。被験者識別番号9168の IRR 以外は，すべてオビヌツズマブの初回投与時に発現し，1日以内に回復した。被験者識別番号9168は Day 64にオビヌツズマブを投与し，主治医によって本剤と因果関係ありと判断された肺炎が報告された。この有害事象は治験実施計画書の定義に基づき，IRR と分類された。

試験を通して6例（12.5%）に全8件の AESI が報告された。重篤な IRR，重篤な好中球減少症及び重篤な感染症に分類される有害事象が AESI として報告された。TLS は報告されなかった。

バイタルサイン，ECG 又は臨床検査値のパラメータについて，臨床的に重要な変動は観察されなかった。

(15) 結論

オビヌツズマブの反復静脈内投与後の中国人の CD20陽性悪性疾患患者におけるオビヌツズマブの薬物動態及び CLL 患者，DLBCL 患者及び FL 患者における曝露量は組織型間で同程度であった。

中国人の CD20陽性悪性疾患患者に対するオビヌツズマブ単剤療法の忍容性は良好であった。新たな安全性シグナルは検出されなかった。

オビヌツズマブ単剤療法後に中国人の CLL 患者，DLBCL 患者及び FL 患者において奏効が認められた。オビヌツズマブは中国人の再発・治療抵抗性 CLL 及び NHL において，非中国人患者と同様の活性を示した。

(16) 報告書作成日

[redacted]年[redacted]月

2.7.6.2 付録

2.7.6.2.1 有害事象の集計表

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2.7.6.2.1.1　JO21900試験

表 2.7.6.2.1.1-1　因果関係を問わないすべての有害事象（JO21900試験，再発・治療抵抗性 NHL 患者）

ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): JO21900 (J21900E)
Analysis: AS SELECTED　　Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 1(200/400); N = 3

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS											
Total Pts with at Least one AE	3 (100.0)	3	(100.0)	3	(100.0)	-		-		-	
Total Number of AEs	18	11		7		-		-		-	
臨床検査											
Total Pts With at Least one AE	3 (100.0)	2	(66.7)	1	(33.3)	-		-		-	
白血球数減少	2 (66.7)	1	(33.3)	1	(33.3)	-		-		-	
血中ビリルビン増加	1 (33.3)	1	(33.3)	-		-		-		-	
血中リン減少	1 (33.3)	1	(33.3)	-		-		-		-	
白血球数増加	1 (33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	5	4		1		-		-		-	
全身障害および投与局所様態											
Total Pts With at Least one AE	2 (66.7)	-		2	(66.7)	-		-		-	
悪寒	2 (66.7)	-		2	(66.7)	-		-		-	
発熱	2 (66.7)	-		2	(66.7)	-		-		-	
Total Number of AEs	4	-		4		-		-		-	
胃腸障害											
Total Pts With at Least one AE	2 (66.7)	2	(66.7)	-		-		-		-	
腹部膨満	1 (33.3)	1	(33.3)	-		-		-		-	
便秘	1 (33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	2	2		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 16MAR2015:18:10:29　　(1 of 15)

ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 1(200/400); N = 3

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
精神障害						
Total Pts With at Least one AE	2 (66.7)	1 (33.3)	1 (33.3)	-	-	-
不安障害	1 (33.3)	-	1 (33.3)	-	-	-
不眠症	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	2	1	1	-	-	-
感染症および寄生虫症						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
鼻咽頭炎	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
血管障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
高血圧	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
心臓障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
頻脈	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
神経系障害						
Total Pts With at Least one AE	1 (33.3)	-	1 (33.3)	-	-	-
頭痛	1 (33.3)	-	1 (33.3)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 1(200/400); N = 3

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
皮膚および皮下組織障害											
Total Pts With at Least one AE	1 (33.3)	1	(33.3)	-		-		-		-	
発疹	1 (33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 16MAR2015:18:10:29 (3 of 15)

ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 2(400/800); N = 3

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	3 (100.0)	3 (100.0)	3 (100.0)	1 (33.3)	1 (33.3)	-
Total Number of AEs	26	15	9	1	1	-
臨床検査						
Total Pts With at Least one AE	3 (100.0)	2 (66.7)	2 (66.7)	1 (33.3)	1 (33.3)	-
好中球数減少	2 (66.7)	1 (33.3)	-	-	1 (33.3)	-
アスパラギン酸アミノトランスフェラーゼ増加	1 (33.3)	1 (33.3)	-	-	-	-
アラニン・アミノトランスフェラーゼ増加	1 (33.3)	-	1 (33.3)	-	-	-
ビタミンＢ１２減少	1 (33.3)	1 (33.3)	-	-	-	-
血小板数減少	1 (33.3)	1 (33.3)	-	-	-	-
血中アルカリホスファターゼ増加	1 (33.3)	1 (33.3)	-	-	-	-
血中ビリルビン増加	1 (33.3)	1 (33.3)	-	-	-	-
血中リン減少	1 (33.3)	-	1 (33.3)	-	-	-
白血球数減少	1 (33.3)	-	-	1 (33.3)	-	-
Total Number of AEs	10	6	2	1	1	-
全身障害および投与局所様態						
Total Pts With at Least one AE	3 (100.0)	2 (66.7)	1 (33.3)	-	-	-
発熱	2 (66.7)	2 (66.7)	-	-	-	-
悪寒	1 (33.3)	-	1 (33.3)	-	-	-
倦怠感	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	4	3	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 2(400/800); N = 3

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	2 (66.7)	1 (33.3)	2 (66.7)	-	-	-
高血圧	2 (66.7)	1 (33.3)	1 (33.3)	-	-	-
潮紅	1 (33.3)	-	1 (33.3)	-	-	-
Total Number of AEs	3	1	2	-	-	-
感染症および寄生虫症						
Total Pts With at Least one AE	2 (66.7)	2 (66.7)	-	-	-	-
鼻咽頭炎	2 (66.7)	2 (66.7)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
胃腸障害						
Total Pts With at Least one AE	1 (33.3)	-	1 (33.3)	-	-	-
悪心	1 (33.3)	-	1 (33.3)	-	-	-
下痢	1 (33.3)	-	1 (33.3)	-	-	-
嘔吐	1 (33.3)	-	1 (33.3)	-	-	-
Total Number of AEs	3	-	3	-	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	1 (33.3)	-	-	-
筋肉痛	1 (33.3)	-	1 (33.3)	-	-	-
背部痛	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	2	1	1	-	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
鼻閉	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 2(400/800); N = 3

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
神経系障害											
Total Pts With at Least one AE	1 (33.3)	1	(33.3)	-		-		-		-	
頭痛	1 (33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 16MAR2015:18:10:29 (6 of 15)

ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 3(800/1200); N = 3

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	3 (100.0)	3 (100.0)	2 (66.7)	2 (66.7)	-	-
Total Number of AEs	44	20	7	17	-	-
臨床検査						
Total Pts With at Least one AE	3 (100.0)	3 (100.0)	2 (66.7)	1 (33.3)	-	-
ヘモグロビン減少	3 (100.0)	1 (33.3)	2 (66.7)	-	-	-
アスパラギン酸アミノトランスフェラーゼ増加	2 (66.7)	2 (66.7)	-	-	-	-
アラニン・アミノトランスフェラーゼ増加	2 (66.7)	2 (66.7)	-	-	-	-
血小板数減少	2 (66.7)	1 (33.3)	-	1 (33.3)	-	-
好中球数減少	2 (66.7)	1 (33.3)	1 (33.3)	-	-	-
白血球数減少	2 (66.7)	1 (33.3)	1 (33.3)	-	-	-
血中リン減少	1 (33.3)	-	-	1 (33.3)	-	-
血中乳酸脱水素酵素増加	1 (33.3)	-	1 (33.3)	-	-	-
Total Number of AEs	15	8	5	2	-	-
全身障害および投与局所様態						
Total Pts With at Least one AE	3 (100.0)	2 (66.7)	1 (33.3)	2 (66.7)	-	-
発熱	3 (100.0)	-	1 (33.3)	2 (66.7)	-	-
悪寒	1 (33.3)	-	-	1 (33.3)	-	-
倦怠感	1 (33.3)	1 (33.3)	-	-	-	-
熱感	1 (33.3)	1 (33.3)	-	-	-	-
疲労	1 (33.3)	-	-	1 (33.3)	-	-
不快感	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	8	3	1	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 16MAR2015:18:10:29 (7 of 15)

ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 3(800/1200); N = 3

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
胃腸障害											
Total Pts With at Least one AE	2 (66.7)	2	(66.7)	-		2	(66.7)	-		-	
悪心	2 (66.7)	-		-		2	(66.7)	-		-	
消化不良	1 (33.3)	1	(33.3)	-		-		-		-	
腹痛	1 (33.3)	1	(33.3)	-		-		-		-	
嘔吐	1 (33.3)	-		-		1	(33.3)	-		-	
Total Number of AEs	5	2		-		3		-		-	
血管障害											
Total Pts With at Least one AE	2 (66.7)	-		-		2	(66.7)	-		-	
潮紅	2 (66.7)	-		-		2	(66.7)	-		-	
低血圧	2 (66.7)	-		-		2	(66.7)	-		-	
Total Number of AEs	4	-		-		4		-		-	
神経系障害											
Total Pts With at Least one AE	2 (66.7)	2	(66.7)	-		1	(33.3)	-		-	
血管迷走神経性失神	1 (33.3)	-		-		1	(33.3)	-		-	
頭痛	1 (33.3)	1	(33.3)	-		-		-		-	
浮動性めまい	1 (33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	3	2		-		1		-		-	
皮膚および皮下組織障害											
Total Pts With at Least one AE	2 (66.7)	-		1	(33.3)	1	(33.3)	-		-	
そう痒症	1 (33.3)	-		-		1	(33.3)	-		-	
発疹	1 (33.3)	-		1	(33.3)	-		-		-	
蕁麻疹	1 (33.3)	-		-		1	(33.3)	-		-	
Total Number of AEs	3	-		1		2		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 3(800/1200); N = 3

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	2 (66.7)	2 (66.7)	-	-	-	-
筋骨格系胸痛	1 (33.3)	1 (33.3)	-	-	-	-
筋肉痛	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
精神障害						
Total Pts With at Least one AE	2 (66.7)	2 (66.7)	-	-	-	-
不快気分	1 (33.3)	1 (33.3)	-	-	-	-
不眠症	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
眼障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
複視	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
心臓障害						
Total Pts With at Least one AE	1 (33.3)	-	-	1 (33.3)	-	-
洞性徐脈	1 (33.3)	-	-	1 (33.3)	-	-
Total Number of AEs	1	-	-	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 4(1200/2000); N = 3

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	3 (100.0)	3 (100.0)	2 (66.7)	1 (33.3)	-	-
Total Number of AEs	29	20	7	2	-	-
臨床検査						
Total Pts With at Least one AE	3 (100.0)	3 (100.0)	1 (33.3)	1 (33.3)	-	-
白血球数減少	3 (100.0)	1 (33.3)	1 (33.3)	1 (33.3)	-	-
血小板数減少	2 (66.7)	2 (66.7)	-	-	-	-
血中乳酸脱水素酵素増加	2 (66.7)	2 (66.7)	-	-	-	-
好中球数減少	2 (66.7)	-	1 (33.3)	1 (33.3)	-	-
アラニン・アミノトランスフェラーゼ増加	1 (33.3)	1 (33.3)	-	-	-	-
ヘモグロビン減少	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	11	7	2	2	-	-
全身障害および投与局所様態						
Total Pts With at Least one AE	3 (100.0)	1 (33.3)	2 (66.7)	-	-	-
発熱	3 (100.0)	1 (33.3)	2 (66.7)	-	-	-
悪寒	2 (66.7)	1 (33.3)	1 (33.3)	-	-	-
胸部不快感	1 (33.3)	-	1 (33.3)	-	-	-
倦怠感	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	7	3	4	-	-	-
胃腸障害						
Total Pts With at Least one AE	2 (66.7)	2 (66.7)	-	-	-	-
下痢	2 (66.7)	2 (66.7)	-	-	-	-
便秘	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	3	3	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 4(1200/2000); N = 3

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
咽喉刺激感	1 (33.3)	1 (33.3)	-	-	-	-
口腔咽頭痛	1 (33.3)	1 (33.3)	-	-	-	-
喉頭刺激感	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	3	3	-	-	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
関節痛	1 (33.3)	1 (33.3)	-	-	-	-
背部痛	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
眼障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
結膜充血	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
血管障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
潮紅	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
神経系障害						
Total Pts With at Least one AE	1 (33.3)	-	1 (33.3)	-	-	-
頭痛	1 (33.3)	-	1 (33.3)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 16MAR2015:18:10:29 (11 of 15)

ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Total; N = 12

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	12 (100.0)	12 (100.0)	10 (83.3)	4 (33.3)	1 (8.3)	-
Total Number of AEs	117	66	30	20	1	-
臨床検査						
Total Pts With at Least one AE	12 (100.0)	10 (83.3)	6 (50.0)	3 (25.0)	1 (8.3)	-
白血球数減少	8 (66.7)	3 (25.0)	3 (25.0)	2 (16.7)	-	-
好中球数減少	6 (50.0)	2 (16.7)	2 (16.7)	1 (8.3)	1 (8.3)	-
血小板数減少	5 (41.7)	4 (33.3)	-	1 (8.3)	-	-
アラニン・アミノトランスフェラーゼ増加	4 (33.3)	3 (25.0)	1 (8.3)	-	-	-
ヘモグロビン減少	4 (33.3)	2 (16.7)	2 (16.7)	-	-	-
アスパラギン酸アミノトランスフェラーゼ増加	3 (25.0)	3 (25.0)	-	-	-	-
血中リン減少	3 (25.0)	1 (8.3)	1 (8.3)	1 (8.3)	-	-
血中乳酸脱水素酵素増加	3 (25.0)	2 (16.7)	1 (8.3)	-	-	-
血中ビリルビン増加	2 (16.7)	2 (16.7)	-	-	-	-
ビタミンＢ１２減少	1 (8.3)	1 (8.3)	-	-	-	-
血中アルカリホスファターゼ増加	1 (8.3)	1 (8.3)	-	-	-	-
白血球数増加	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	41	25	10	5	1	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Total; N = 12

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
全身障害および投与局所様態						
Total Pts With at Least one AE	11 (91.7)	5 (41.7)	6 (50.0)	2 (16.7)	-	-
発熱	10 (83.3)	3 (25.0)	5 (41.7)	2 (16.7)	-	-
悪寒	6 (50.0)	1 (8.3)	4 (33.3)	1 (8.3)	-	-
倦怠感	3 (25.0)	3 (25.0)	-	-	-	-
胸部不快感	1 (8.3)	-	1 (8.3)	-	-	-
熱感	1 (8.3)	1 (8.3)	-	-	-	-
疲労	1 (8.3)	-	-	1 (8.3)	-	-
不快感	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	23	9	10	4	-	-
胃腸障害						
Total Pts With at Least one AE	7 (58.3)	6 (50.0)	1 (8.3)	2 (16.7)	-	-
悪心	3 (25.0)	-	1 (8.3)	2 (16.7)	-	-
下痢	3 (25.0)	2 (16.7)	1 (8.3)	-	-	-
便秘	2 (16.7)	2 (16.7)	-	-	-	-
嘔吐	2 (16.7)	-	1 (8.3)	1 (8.3)	-	-
消化不良	1 (8.3)	1 (8.3)	-	-	-	-
腹痛	1 (8.3)	1 (8.3)	-	-	-	-
腹部膨満	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	13	7	3	3	-	-
血管障害						
Total Pts With at Least one AE	6 (50.0)	3 (25.0)	2 (16.7)	2 (16.7)	-	-
潮紅	4 (33.3)	1 (8.3)	1 (8.3)	2 (16.7)	-	-
高血圧	3 (25.0)	2 (16.7)	1 (8.3)	-	-	-
低血圧	2 (16.7)	-	-	2 (16.7)	-	-
Total Number of AEs	9	3	2	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Total; N = 12

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	5 (41.7)	3 (25.0)	2 (16.7)	1 (8.3)	-	-
頭痛	4 (33.3)	2 (16.7)	2 (16.7)	-	-	-
血管迷走神経性失神	1 (8.3)	-	-	1 (8.3)	-	-
浮動性めまい	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	6	3	2	1	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	4 (33.3)	4 (33.3)	1 (8.3)	-	-	-
筋肉痛	2 (16.7)	1 (8.3)	1 (8.3)	-	-	-
背部痛	2 (16.7)	2 (16.7)	-	-	-	-
関節痛	1 (8.3)	1 (8.3)	-	-	-	-
筋骨格系胸痛	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	6	5	1	-	-	-
精神障害						
Total Pts With at Least one AE	4 (33.3)	3 (25.0)	1 (8.3)	-	-	-
不眠症	2 (16.7)	2 (16.7)	-	-	-	-
不安障害	1 (8.3)	-	1 (8.3)	-	-	-
不快気分	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	4	3	1	-	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	3 (25.0)	1 (8.3)	1 (8.3)	1 (8.3)	-	-
発疹	2 (16.7)	1 (8.3)	1 (8.3)	-	-	-
そう痒症	1 (8.3)	-	-	1 (8.3)	-	-
蕁麻疹	1 (8.3)	-	-	1 (8.3)	-	-
Total Number of AEs	4	1	1	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17_900_s001 Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Total; N = 12

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	3 (25.0)	3 (25.0)	-	-	-	-
鼻咽頭炎	3 (25.0)	3 (25.0)	-	-	-	-
Total Number of AEs	3	3	-	-	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	2 (16.7)	2 (16.7)	-	-	-	-
咽喉刺激感	1 (8.3)	1 (8.3)	-	-	-	-
口腔咽頭痛	1 (8.3)	1 (8.3)	-	-	-	-
喉頭刺激感	1 (8.3)	1 (8.3)	-	-	-	-
鼻閉	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	4	4	-	-	-	-
眼障害						
Total Pts With at Least one AE	2 (16.7)	2 (16.7)	-	-	-	-
結膜充血	1 (8.3)	1 (8.3)	-	-	-	-
複視	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
心臓障害						
Total Pts With at Least one AE	2 (16.7)	1 (8.3)	-	1 (8.3)	-	-
洞性徐脈	1 (8.3)	-	-	1 (8.3)	-	-
頻脈	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	2	1	-	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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[5.3.5.3-1 ae17_900_s001を再掲]

表 2.7.6.2.1.1-2　因果関係が否定できないすべての有害事象（J021900試験，再発・治療抵抗性 NHL 患者）

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED　　Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 1(200/400); N = 3

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	3 (100.0)	3 (100.0)	3 (100.0)	-	-	-
Total Number of AEs	16	10	6	-	-	-
臨床検査						
Total Pts With at Least one AE	3 (100.0)	2 (66.7)	1 (33.3)	-	-	-
白血球数減少	2 (66.7)	1 (33.3)	1 (33.3)	-	-	-
血中ビリルビン増加	1 (33.3)	1 (33.3)	-	-	-	-
血中リン減少	1 (33.3)	1 (33.3)	-	-	-	-
白血球数増加	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	5	4	1	-	-	-
全身障害および投与局所様態						
Total Pts With at Least one AE	2 (66.7)	-	2 (66.7)	-	-	-
悪寒	2 (66.7)	-	2 (66.7)	-	-	-
発熱	2 (66.7)	-	2 (66.7)	-	-	-
Total Number of AEs	4	-	4	-	-	-
胃腸障害						
Total Pts With at Least one AE	2 (66.7)	2 (66.7)	-	-	-	-
腹部膨満	1 (33.3)	1 (33.3)	-	-	-	-
便秘	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
感染症および寄生虫症						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
鼻咽頭炎	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 1(200/400); N = 3

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
血管障害											
Total Pts With at Least one AE	1 (33.3)	1	(33.3)	-		-		-		-	
高血圧	1 (33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	
心臓障害											
Total Pts With at Least one AE	1 (33.3)	1	(33.3)	-		-		-		-	
頻脈	1 (33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	
神経系障害											
Total Pts With at Least one AE	1 (33.3)	-		1	(33.3)	-		-		-	
頭痛	1 (33.3)	-		1	(33.3)	-		-		-	
Total Number of AEs	1	-		1		-		-		-	
皮膚および皮下組織障害											
Total Pts With at Least one AE	1 (33.3)	1	(33.3)	-		-		-		-	
発疹	1 (33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 26MAY2015:09:19:53 (2 of 14)

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 2(400/800); N = 3

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	3	(100.0)	3	(100.0)	3	(100.0)	1	(33.3)	1	(33.3)	-	
Total Number of AEs	25		14		9		1		1		-	
臨床検査												
Total Pts With at Least one AE	3	(100.0)	2	(66.7)	2	(66.7)	1	(33.3)	1	(33.3)	-	
好中球数減少	2	(66.7)	1	(33.3)	-		-		1	(33.3)	-	
アスパラギン酸アミノトランスフェラーゼ増加	1	(33.3)	1	(33.3)	-		-		-		-	
アラニン・アミノトランスフェラーゼ増加	1	(33.3)	-		1	(33.3)	-		-		-	
ビタミンＢ１２減少	1	(33.3)	1	(33.3)	-		-		-		-	
血小板数減少	1	(33.3)	1	(33.3)	-		-		-		-	
血中アルカリホスファターゼ増加	1	(33.3)	1	(33.3)	-		-		-		-	
血中ビリルビン増加	1	(33.3)	1	(33.3)	-		-		-		-	
血中リン減少	1	(33.3)	-		1	(33.3)	-		-		-	
白血球数減少	1	(33.3)	-		-		1	(33.3)	-		-	
Total Number of AEs	10		6		2		1		1		-	
全身障害および投与局所様態												
Total Pts With at Least one AE	3	(100.0)	2	(66.7)	1	(33.3)	-		-		-	
発熱	2	(66.7)	2	(66.7)	-		-		-		-	
悪寒	1	(33.3)	-		1	(33.3)	-		-		-	
倦怠感	1	(33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	4		3		1		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 26MAY2015:09:19:53 (3 of 14)

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 2(400/800); N = 3

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	2 (66.7)	1 (33.3)	2 (66.7)	-	-	-
高血圧	2 (66.7)	1 (33.3)	1 (33.3)	-	-	-
潮紅	1 (33.3)	-	1 (33.3)	-	-	-
Total Number of AEs	3	1	2	-	-	-
感染症および寄生虫症						
Total Pts With at Least one AE	2 (66.7)	2 (66.7)	-	-	-	-
鼻咽頭炎	2 (66.7)	2 (66.7)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
胃腸障害						
Total Pts With at Least one AE	1 (33.3)	-	1 (33.3)	-	-	-
悪心	1 (33.3)	-	1 (33.3)	-	-	-
下痢	1 (33.3)	-	1 (33.3)	-	-	-
嘔吐	1 (33.3)	-	1 (33.3)	-	-	-
Total Number of AEs	3	-	3	-	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	1 (33.3)	-	1 (33.3)	-	-	-
筋肉痛	1 (33.3)	-	1 (33.3)	-	-	-
Total Number of AEs	1	-	1	-	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
鼻閉	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 26MAY2015:09:19:53 (4 of 14)

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 2(400/800); N = 3

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
神経系障害											
Total Pts With at Least one AE	1 (33.3)	1	(33.3)	-		-		-		-	
頭痛	1 (33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 26MAY2015:09:19:53 (5 of 14)

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 3(800/1200); N = 3

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	3	(100.0)	3	(100.0)	2	(66.7)	2	(66.7)	-		-	
Total Number of AEs	39		16		7		16		-		-	
臨床検査												
Total Pts With at Least one AE	3	(100.0)	3	(100.0)	2	(66.7)	1	(33.3)	-		-	
ヘモグロビン減少	3	(100.0)	1	(33.3)	2	(66.7)	-		-		-	
アスパラギン酸アミノトランスフェラーゼ増加	2	(66.7)	2	(66.7)	-		-		-		-	
アラニン・アミノトランスフェラーゼ増加	2	(66.7)	2	(66.7)	-		-		-		-	
血小板数減少	2	(66.7)	1	(33.3)	-		1	(33.3)	-		-	
好中球数減少	2	(66.7)	1	(33.3)	1	(33.3)	-		-		-	
白血球数減少	2	(66.7)	1	(33.3)	1	(33.3)	-		-		-	
血中乳酸脱水素酵素増加	1	(33.3)	-		1	(33.3)	-		-		-	
Total Number of AEs	14		8		5		1		-		-	
全身障害および投与局所様態												
Total Pts With at Least one AE	3	(100.0)	2	(66.7)	1	(33.3)	2	(66.7)	-		-	
発熱	3	(100.0)	-		1	(33.3)	2	(66.7)	-		-	
悪寒	1	(33.3)	-		-		1	(33.3)	-		-	
倦怠感	1	(33.3)	1	(33.3)	-		-		-		-	
熱感	1	(33.3)	1	(33.3)	-		-		-		-	
疲労	1	(33.3)	-		-		1	(33.3)	-		-	
不快感	1	(33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	8		3		1		4		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 3(800/1200); N = 3

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	2 (66.7)	1 (33.3)	-	2 (66.7)	-	-
悪心	2 (66.7)	-	-	2 (66.7)	-	-
消化不良	1 (33.3)	1 (33.3)	-	-	-	-
嘔吐	1 (33.3)	-	-	1 (33.3)	-	-
Total Number of AEs	4	1	-	3	-	-
血管障害						
Total Pts With at Least one AE	2 (66.7)	-	-	2 (66.7)	-	-
潮紅	2 (66.7)	-	-	2 (66.7)	-	-
低血圧	2 (66.7)	-	-	2 (66.7)	-	-
Total Number of AEs	4	-	-	4	-	-
神経系障害						
Total Pts With at Least one AE	2 (66.7)	2 (66.7)	-	1 (33.3)	-	-
血管迷走神経性失神	1 (33.3)	-	-	1 (33.3)	-	-
頭痛	1 (33.3)	1 (33.3)	-	-	-	-
浮動性めまい	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	3	2	-	1	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	2 (66.7)	-	1 (33.3)	1 (33.3)	-	-
そう痒症	1 (33.3)	-	-	1 (33.3)	-	-
発疹	1 (33.3)	-	1 (33.3)	-	-	-
蕁麻疹	1 (33.3)	-	-	1 (33.3)	-	-
Total Number of AEs	3	-	1	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 26MAY2015:09:19:53 (7 of 14)

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 3(800/1200); N = 3

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
眼障害												
Total Pts With at Least one AE	1	(33.3)	1	(33.3)	-		-		-		-	
複視	1	(33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	1		1		-		-		-		-	
心臓障害												
Total Pts With at Least one AE	1	(33.3)	-		-		1	(33.3)	-		-	
洞性徐脈	1	(33.3)	-		-		1	(33.3)	-		-	
Total Number of AEs	1		-		-		1		-		-	
精神障害												
Total Pts With at Least one AE	1	(33.3)	1	(33.3)	-		-		-		-	
不快気分	1	(33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	1		1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 4(1200/2000); N = 3

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	3	(100.0)	3	(100.0)	2	(66.7)	1	(33.3)	-		-	
Total Number of AEs	27		18		7		2		-		-	
臨床検査												
Total Pts With at Least one AE	3	(100.0)	3	(100.0)	1	(33.3)	1	(33.3)	-		-	
白血球数減少	3	(100.0)	1	(33.3)	1	(33.3)	1	(33.3)	-		-	
血小板数減少	2	(66.7)	2	(66.7)	-		-		-		-	
血中乳酸脱水素酵素増加	2	(66.7)	2	(66.7)	-		-		-		-	
好中球数減少	2	(66.7)	-		1	(33.3)	1	(33.3)	-		-	
ヘモグロビン減少	1	(33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	10		6		2		2		-		-	
全身障害および投与局所様態												
Total Pts With at Least one AE	3	(100.0)	1	(33.3)	2	(66.7)	-		-		-	
発熱	3	(100.0)	1	(33.3)	2	(66.7)	-		-		-	
悪寒	2	(66.7)	1	(33.3)	1	(33.3)	-		-		-	
胸部不快感	1	(33.3)	-		1	(33.3)	-		-		-	
倦怠感	1	(33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	7		3		4		-		-		-	
胃腸障害												
Total Pts With at Least one AE	2	(66.7)	2	(66.7)	-		-		-		-	
下痢	1	(33.3)	1	(33.3)	-		-		-		-	
便秘	1	(33.3)	1	(33.3)	-		-		-		-	
Total Number of AEs	2		2		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Cohort 4(1200/2000); N = 3

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
咽喉刺激感	1 (33.3)	1 (33.3)	-	-	-	-
口腔咽頭痛	1 (33.3)	1 (33.3)	-	-	-	-
喉頭刺激感	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	3	3	-	-	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
関節痛	1 (33.3)	1 (33.3)	-	-	-	-
背部痛	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
眼障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
結膜充血	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
血管障害						
Total Pts With at Least one AE	1 (33.3)	1 (33.3)	-	-	-	-
潮紅	1 (33.3)	1 (33.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
神経系障害						
Total Pts With at Least one AE	1 (33.3)	-	1 (33.3)	-	-	-
頭痛	1 (33.3)	-	1 (33.3)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Total; N = 12

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	12 (100.0)	12 (100.0)	10 (83.3)	4 (33.3)	1 (8.3)	-
Total Number of AEs	107	58	29	19	1	-
臨床検査						
Total Pts With at Least one AE	12 (100.0)	10 (83.3)	6 (50.0)	3 (25.0)	1 (8.3)	-
白血球数減少	8 (66.7)	3 (25.0)	3 (25.0)	2 (16.7)	-	-
好中球数減少	6 (50.0)	2 (16.7)	2 (16.7)	1 (8.3)	1 (8.3)	-
血小板数減少	5 (41.7)	4 (33.3)	-	1 (8.3)	-	-
ヘモグロビン減少	4 (33.3)	2 (16.7)	2 (16.7)	-	-	-
アスパラギン酸アミノトランスフェラーゼ増加	3 (25.0)	3 (25.0)	-	-	-	-
アラニン・アミノトランスフェラーゼ増加	3 (25.0)	2 (16.7)	1 (8.3)	-	-	-
血中乳酸脱水素酵素増加	3 (25.0)	2 (16.7)	1 (8.3)	-	-	-
血中ビリルビン増加	2 (16.7)	2 (16.7)	-	-	-	-
血中リン減少	2 (16.7)	1 (8.3)	1 (8.3)	-	-	-
ビタミンＢ１２減少	1 (8.3)	1 (8.3)	-	-	-	-
血中アルカリホスファターゼ増加	1 (8.3)	1 (8.3)	-	-	-	-
白血球数増加	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	39	24	10	4	1	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 26MAY2015:09:19:53 (11 of 14)

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Total; N = 12

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
全身障害および投与局所様態						
Total Pts With at Least one AE	11 (91.7)	5 (41.7)	6 (50.0)	2 (16.7)	-	-
発熱	10 (83.3)	3 (25.0)	5 (41.7)	2 (16.7)	-	-
悪寒	6 (50.0)	1 (8.3)	4 (33.3)	1 (8.3)	-	-
倦怠感	3 (25.0)	3 (25.0)	-	-	-	-
胸部不快感	1 (8.3)	-	1 (8.3)	-	-	-
熱感	1 (8.3)	1 (8.3)	-	-	-	-
疲労	1 (8.3)	-	-	1 (8.3)	-	-
不快感	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	23	9	10	4	-	-
胃腸障害						
Total Pts With at Least one AE	7 (58.3)	5 (41.7)	1 (8.3)	2 (16.7)	-	-
悪心	3 (25.0)	-	1 (8.3)	2 (16.7)	-	-
下痢	2 (16.7)	1 (8.3)	1 (8.3)	-	-	-
便秘	2 (16.7)	2 (16.7)	-	-	-	-
嘔吐	2 (16.7)	-	1 (8.3)	1 (8.3)	-	-
消化不良	1 (8.3)	1 (8.3)	-	-	-	-
腹部膨満	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	11	5	3	3	-	-
血管障害						
Total Pts With at Least one AE	6 (50.0)	3 (25.0)	2 (16.7)	2 (16.7)	-	-
潮紅	4 (33.3)	1 (8.3)	1 (8.3)	2 (16.7)	-	-
高血圧	3 (25.0)	2 (16.7)	1 (8.3)	-	-	-
低血圧	2 (16.7)	-	-	2 (16.7)	-	-
Total Number of AEs	9	3	2	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
AE17 26MAY2015:09:19:53 (12 of 14)

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Total; N = 12

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	5 (41.7)	3 (25.0)	2 (16.7)	1 (8.3)	-	-
頭痛	4 (33.3)	2 (16.7)	2 (16.7)	-	-	-
血管迷走神経性失神	1 (8.3)	-	-	1 (8.3)	-	-
浮動性めまい	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	6	3	2	1	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	3 (25.0)	1 (8.3)	1 (8.3)	1 (8.3)	-	-
発疹	2 (16.7)	1 (8.3)	1 (8.3)	-	-	-
そう痒症	1 (8.3)	-	-	1 (8.3)	-	-
蕁麻疹	1 (8.3)	-	-	1 (8.3)	-	-
Total Number of AEs	4	1	1	2	-	-
感染症および寄生虫症						
Total Pts With at Least one AE	3 (25.0)	3 (25.0)	-	-	-	-
鼻咽頭炎	3 (25.0)	3 (25.0)	-	-	-	-
Total Number of AEs	3	3	-	-	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	2 (16.7)	2 (16.7)	-	-	-	-
咽喉刺激感	1 (8.3)	1 (8.3)	-	-	-	-
口腔咽頭痛	1 (8.3)	1 (8.3)	-	-	-	-
喉頭刺激感	1 (8.3)	1 (8.3)	-	-	-	-
鼻閉	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	4	4	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake

ae17r_900_s001 Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): J021900 (J21900E)
Analysis: AS SELECTED Center: ALL CENTERS
SAFETY POPULATION
Study cohort Total; N = 12

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	2 (16.7)	1 (8.3)	1 (8.3)	-	-	-
関節痛	1 (8.3)	1 (8.3)	-	-	-	-
筋肉痛	1 (8.3)	-	1 (8.3)	-	-	-
背部痛	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	3	2	1	-	-	-
眼障害						
Total Pts With at Least one AE	2 (16.7)	2 (16.7)	-	-	-	-
結膜充血	1 (8.3)	1 (8.3)	-	-	-	-
複視	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
心臓障害						
Total Pts With at Least one AE	2 (16.7)	1 (8.3)	-	1 (8.3)	-	-
洞性徐脈	1 (8.3)	-	-	1 (8.3)	-	-
頻脈	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	2	1	-	1	-	-
精神障害						
Total Pts With at Least one AE	1 (8.3)	1 (8.3)	-	-	-	-
不快気分	1 (8.3)	1 (8.3)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake
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[5.3.5.3-1 ae17r_900_s001を再掲]

2.7.6.2.1.2　JO29737試験（GATS 試験）

表 2.7.6.2.1.2-1　因果関係を問わないすべての有害事象（JO29737試験，未治療 NHL 患者）

Listing of Adverse Events
Protocol(s): JO29737
Analysis: All Patients Population

Treatment: G-CHOP (N=36)

Site ID/ Subject ID - Age/Sex/Weight yr kg Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	Relation to Study Drug					Serious	Outcome	Treatment for AE		Subject Discon. from Study	Action Taken with Study Drug				
						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Blood pressure increased	血圧上昇	C1D1	3	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Infusion related reaction	注入に伴う反応	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Infusion site extravasation	注入部位血管外漏出	C1D1	2	3		No	No	Yes	No	No	No	2	Yes	Yes	No	2	5	5	5	5
Constipation	便秘	C1D1	1	6	22	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Platelet count decreased	血小板数減少	C1D1	2	7	11	No	Yes	Yes	Yes	No	No	3	No	No	No	2	3	3	2	2
Decreased appetite	食欲不振	C1D1	1	8	6	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
White blood cell count decreased	白血球減少	C1D8	4	11	5	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	3	3	2	2
Neutrophil count decreased	好中球数減少	C1D8	4	13	3	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	3	3	2	2
Cellulitis	蜂窩織炎	C2	3	26	20	No	No	Yes	No	Yes	Yes	3	Yes	Yes	No	4	4	4	4	4
Neutrophil count decreased	好中球数減少	C2	3	31	4	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
White blood cell count decreased	白血球減少	C2	3	31	4	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Diarrhoea	下痢	C2	3	36	8	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2

(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.
G : Obinutuzumab, C : Cyclophosphamide, H : Doxorubicin, O : Vincristine, P : Predonisolone

Listing of Adverse Events
Protocol(s): JO29737
Analysis: All Patients Population

Treatment: G-CHOP (N=36)

Site ID/ Subject ID - Age/Sex/Weight yr kg Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	Relation to Study Drug					Serious	Outcome	Treatment for AE		Subject Discon. from Study	Action Taken with Study Drug				
						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Infusion related reaction	注入に伴う反応	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Wheezing	喘鳴	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C1D1	1	5	187	No	No	No	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C1D1	1	5	8	No	Yes	Yes	No	No	No	3	Yes	No	No	2	2	2	2	2
Anaemia	貧血	C1D8	3	9	5	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Neutrophil count decreased	好中球数減少	C1D8	4	13	5	No	Yes	Yes	No	No	No	3	Yes	No	No	2	2	2	2	2
Platelet count decreased	血小板数減少	C1D8	2	13	4	No	Yes	Yes	No	No	No	3	No	No	No	2	2	2	2	2
White blood cell count decreased	白血球減少	C1D8	4	13	5	No	Yes	Yes	No	No	No	3	Yes	No	No	2	2	2	2	2
Syncope	失神	C2	3	32	1	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
White blood cell count decreased	白血球減少	C2	4	35	5	No	Yes	Yes	No	No	No	3	Yes	No	No	2	2	2	2	2
Febrile neutropenia	発熱性好中球減少症	C2	3	36	4	No	Yes	Yes	No	No	No	3	Yes	No	No	2	2	2	2	2
Pneumonitis	肺臓炎	C2	3	40	17	No	Yes	Yes	Yes	No	Yes	3	Yes	No	No	4	4	4	4	4
Anaemia	貧血	C2	3	42	3	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Vertigo	回転性眩暈	C2	1	42	27	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C2	2	52	13	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2

(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.
G : Obinutuzumab, C : Cyclophosphamide, H : Doxorubicin, O : Vincristine, P : Predonisolone

Listing of Adverse Events
Protocol(s): JO29737
Analysis: All Patients Population

Treatment: G-CHOP (N=36)

Site ID/ Subject ID	- Age/Sex/Weight yr kg					Relation to Study Drug							Treatment for AE			Action Taken with Study Drug				
Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	G	C	H	O	P	Serious	Outcome	Medication	Procedure /Surgery	Subject Discon. from Study	G	C	H	O	P
[redacted]																				
Pollakiuria	頻尿	C3	1	57	21	No	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Osmotic demyelination syndrome	橋中心髄鞘崩壊症	C3	1	58		No	No	No	No	No	No	5	No	No	No	2	2	2	2	2
White blood cell count decreased	白血球減少	C4	3	86	8	No	Yes	Yes	No	No	No	3	Yes	No	No	2	2	2	2	2
Neutrophil count decreased	好中球減少	C4	4	88	6	No	Yes	Yes	No	No	No	3	Yes	No	No	2	2	2	2	2

(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.
G : Obinutuzumab, C : Cyclophosphamide, H : Doxorubicin, O : Vincristine, P : Predonisolone

Listing of Adverse Events
Protocol(s): JO29737
Analysis: All Patients Population

Treatment: G-CHOP (N=36)

Site ID/ Subject ID - Age/Sex/Weight yr kg Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	Relation to Study Drug G	C	H	O	P	Serious	Outcome	Treatment for AE: Medication	Procedure /Surgery	Subject Discon. from Study	Action Taken with Study Drug G	C	H	O	P
[redacted]																				
Dysgeusia	味覚異常	C1D1	1	2	190	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutrophil count decreased	好中球数減少	C1D8	4	10	12	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
White blood cell count decreased	白血球減少	C1D8	3	10	12	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C1D8	1	15		No	No	No	Yes	No	No	2	Yes	No	No	2	2	2	5	2
Alopecia	脱毛症	C1D15	2	19	173	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutrophil count decreased	好中球数減少	C2	4	37	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
White blood cell count decreased	白血球減少	C2	3	37	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutrophil count decreased	好中球数減少	C3	4	58	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
White blood cell count decreased	白血球減少	C3	3	58	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutrophil count decreased	好中球数減少	C7	3	149	8	Yes	No	No	No	No	No	3	Yes	No	No	4	6	6	6	6

(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.
G : Obinutuzumab, C : Cyclophosphamide, H : Doxorubicin, O : Vincristine, P : Predonisolone

Listing of Adverse Events
Protocol(s): JO29737
Analysis: All Patients Population

Treatment: G-CHOP (N=36)

Site ID/ Subject ID	- Age/Sex/Weight yr kg					Relation to Study Drug							Treatment for AE			Action Taken with Study Drug				
Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	G	C	H	O	P	Serious	Outcome	Medication	Procedure /Surgery	Subject Discon. from Study	G	C	H	O	P
[redacted]																				
Blood pressure decreased	血圧低下	C1D1	1	1	1	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Infusion related reaction	注入に伴う反応	C1D1	1	1	1	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Platelet count decreased	血小板数減少	C1D1	1	7	11	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Febrile neutropenia	発熱性好中球減少症	C1D8	3	9	6	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Lung infection	肺感染	C4	2	87	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	4	4	4	4	4
Dysphagia	通過障害	C8	2	173		No	No	No	No	No	No	2	No	No	No	6	6	6	6	6
[redacted]																				
Platelet count decreased	血小板数低下	C1D1	2	6	60	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Dysgeusia	味覚異常	C2	1	25	149	No	No	No	Yes	No	No	3	No	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C7	1	135		No	No	No	Yes	No	No	2	No	No	No	2	6	6	6	6

(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.
G : Obinutuzumab, C : Cyclophosphamide, H : Doxorubicin, O : Vincristine, P : Predonisolone

Listing of Adverse Events
Protocol(s): JO29737
Analysis: All Patients Population

Treatment: G-CHOP (N=36)

Site ID/ Subject ID	- Age/Sex/Weight yr kg					Relation to Study Drug							Treatment for AE			Action Taken with Study Drug				
Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	G	C	H	O	P	Serious	Outcome	Medication	Procedure /Surgery	Subject Discon. from Study	G	C	H	O	P
[redacted]																				
Fluid retention	体液貯留	C1D1	1	2	5	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C1D1	1	7	2	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Platelet count decreased	血小板数減少	C1D1	1	7	16	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C1D8	1	10		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Malaise	倦怠感	C2	1	23	8	No	Yes	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Malaise	倦怠感	C3	1	44	14	No	Yes	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Non-cardiac chest pain	非心臓性胸痛	C3	1	44	14	No	Yes	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Bone pain	骨痛	C3	1	45	8	No	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Bone pain	骨痛	C4	1	68	4	No	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Malaise	倦怠感	C4	2	68	11	No	Yes	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Malaise	倦怠感	C5	2	89	10	No	Yes	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Stomatitis	口腔粘膜炎	C5	2	89	10	No	Yes	Yes	No	No	No	3	Yes	No	No	2	2	2	2	2
Non-cardiac chest pain	非心臓性胸痛	C5	1	90	8	No	Yes	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Febrile neutropenia	発熱性好中球減少症	C6	3	114	5	No	Yes	Yes	No	No	Yes	3	Yes	No	No	2	6	6	6	6
Stomatitis	口腔粘膜炎	C6	2	118	6	No	Yes	Yes	No	No	No	3	Yes	No	No	2	2	2	2	2
[redacted]																				
Headache	頭痛	C1D1	1	1	2	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2

(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.
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Listing of Adverse Events
Protocol(s): JO29737
Analysis: All Patients Population

Treatment: G-CHOP (N=36)

Site ID/ Subject ID - Age/Sex/Weight yr kg Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	Relation to Study Drug					Serious	Outcome	Treatment for AE		Subject Discon. from Study	Action Taken with Study Drug				
						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Infusion related reaction	注入に伴う反応	C1D1	1	1	2	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C1D1	1	3	3	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Headache	頭痛	C1D1	2	4	18	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Alopecia	脱毛	C1D8	2	14	185	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Headache	頭痛	C2	1	24	6	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C2	2	24	6	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Palpitations	動悸	C2	1	24	6	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Headache	頭痛	C3	1	46	10	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C3	2	46	10	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Palpitations	動悸	C3	1	46	10	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Headache	頭痛	C4	1	71	8	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C4	2	71	8	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Palpitations	動悸	C4	1	71	8	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutrophil count decreased	好中球減少	C4	3	91	8	No	Yes	Yes	Yes	No	No	3	No	No	No	4	4	4	4	4
Headache	頭痛	C5	1	102	11	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C5	2	102	11	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Palpitations	動悸	C5	1	102	11	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutrophil count decreased	好中球減少	C5	3	119	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	4	4	4	4	4
Headache	頭痛	C6	1	127	4	No	Yes	Yes	Yes	No	No	3	No	No	No	2	6	6	6	6
Nausea	悪心	C6	2	127	4	No	Yes	Yes	Yes	No	No	3	No	No	No	2	6	6	6	6

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Treatment: G-CHOP (N=36)

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[redacted]																				
Palpitations	動悸	C6	1	127	4	No	Yes	Yes	Yes	No	No	3	No	No	No	2	6	6	6	6
Headache	頭痛	C7	1	147	6	Yes	No	No	No	No	No	3	No	No	No	2	6	6	6	6
Infusion related reaction	注入に伴う反応	C7	1	147	6	Yes	No	No	No	No	No	3	No	No	No	2	6	6	6	6
Palpitations	動悸	C7	1	147	6	Yes	No	No	No	No	No	3	No	No	No	2	6	6	6	6
Headache	頭痛	C8	1	168	3	Yes	No	No	No	No	No	3	No	No	No	6	6	6	6	6
Infusion related reaction	注入に伴う反応	C8	1	168	3	Yes	No	No	No	No	No	3	No	No	No	6	6	6	6	6

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C1D1	1	3		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Decreased appetite	食欲不振	C1D1	1	4	3	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Malaise	倦怠感	C1D1	1	4	3	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Arthralgia	関節痛	C1D1	1	6	4	No	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Alopecia	脱毛	C1D15	2	22	163	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Fatigue	疲労	C2	1	23	8	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Constipation	便秘	C2	2	41	11	No	No	No	Yes	No	No	3	Yes	No	No	4	4	4	4	4
Fatigue	疲労	C3	1	51	7	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Constipation	便秘	C3	2	52	45	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Dysgeusia	味覚異常	C4	1	72	113	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C4	1	75	3	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Nail discolouration	爪変色	C4	1	84		No	Yes	Yes	Yes	No	No	2	No	No	No	2	2	2	2	2
Stomatitis	口腔粘膜炎	C6	1	116	41	No	Yes	Yes	Yes	No	No	3	No	No	No	2	6	6	6	6

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Platelet count decreased	血小板数減少	C1D1	3	7	9	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Dizziness	浮動性めまい	C1D8	1	15	151	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Decreased appetite	食欲不振	C6	2	112	10	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	6	6	6	6
Febrile neutropenia	発熱性好中球減少症	C6	3	115	8	No	Yes	Yes	Yes	No	Yes	3	Yes	No	No	2	6	6	6	6
Bronchitis	気管支炎	C6	2	118	48	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	6	6	6	6
Pneumonia	肺炎	C6	3	126	40	No	Yes	Yes	Yes	No	Yes	3	Yes	No	No	4	6	6	6	6
Compression fracture	圧迫骨折	C7	1	147		No	No	No	No	No	No	2	Yes	No	No	2	6	6	6	6
Neutrophil count decreased	好中球減少	C7	4	158	8	Yes	No	No	No	No	No	3	No	No	No	4	6	6	6	6
[redacted]																				
Nausea	悪心	C1D1	1	1	3	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C1D1	4	8	9	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	3	3	3	2
Neutropenia	好中球減少症	C1D1	4	8	9	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	3	3	3	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C2	1	26		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C2	4	29	5	No	Yes	Yes	Yes	No	No	3	No	No	No	2	3	3	3	2
Neutropenia	好中球減少症	C2	4	29	5	No	Yes	Yes	Yes	No	No	3	No	No	No	2	3	3	3	2
Infected dermal cyst	感染性粉瘤	C3	2	61		Yes	Yes	Yes	Yes	Yes	No	5	Yes	Yes	No	5	5	5	5	5

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Site ID/ Subject ID	- Age/Sex/Weight yr kg					Relation to Study Drug							Treatment for AE			Action Taken with Study Drug				
Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	G	C	H	O	P	Serious	Outcome	Medication	Procedure /Surgery	Subject Discon. from Study	G	C	H	O	P
[redacted]																				
Chills	悪寒	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Infusion related reaction	INFUSION REACTION	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Hiccups	しゃっくり	C1D1	2	2	1	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Insomnia	不眠症	C1D1	1	2	15	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C1D1	1	2	7	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C1D8	4	10	5	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C1D8	4	10	5	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Back pain	腰部痛	C1D8	1	13	1	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Nasopharyngitis	感冒	C1D15	2	20	4	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C1D15	1	21		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Insomnia	不眠	C1D15	1	22	127	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C2	1	24	9	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C2	2	28	4	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C2	4	31	4	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	3	3	3	2
Neutropenia	好中球減少症	C2	4	31	4	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	3	3	3	2
Thrombocytopenia	血小板減少症	C2	3	31	18	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	3	3	3	2
Constipation	便秘	C3	1	52	4	Yes	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Leukopenia	白血球減少症	C3	3	56	4	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C3	3	56	4	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Thrombocytopenia	血小板減少症	C3	3	56	4	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C4	4	80	4	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C4	4	80	4	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Thrombocytopenia	血小板減少症	C4	3	80	4	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Thrombocytopenia	血小板減少症	C5	2	101	18	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C5	2	118	9	Yes	Yes	Yes	Yes	No	No	3	Yes	No	No	4	4	4	4	4
Neutropenia	好中球減少症	C5	2	118	9	Yes	Yes	Yes	Yes	No	No	3	Yes	No	No	4	4	4	4	4
Thrombocytopenia	血小板減少症	C6	3	126	15	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C6	3	128	2	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C6	4	128	2	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Pyrexia	発熱	C1D1	1	6	3	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C1D8	3	10	6	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C1D8	4	10	13	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Dry skin	皮膚乾燥	C1D8	1	12		No	No	No	No	No	No	2	Yes	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C2	3	38	8	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C2	2	38	8	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C2	1	38		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Cataract	白内障の悪化	C3	3	49	15	No	No	No	No	Yes	Yes	3	No	Yes	No	2	2	2	2	2
Glaucoma	緑内障	C3	3	49	15	No	No	No	No	Yes	No	3	Yes	Yes	No	2	2	2	2	2
Cough	咳嗽	C4	1	80	33	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Insomnia	不眠症	C1D1	1	4	17	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C1D8	4	11	4	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C1D8	4	11	4	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C1D8	1	14		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Nausea	悪心	C1D15	1	17	2	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C2	3	31	15	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C2	2	31	15	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Back pain	腰痛	C3	1	49	38	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Stomatitis	口内炎	C4	2	71	58	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Dry skin	皮膚乾燥	C5	1	99	51	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Hepatic function abnormal	肝機能障害	C5	1	106		Yes	Yes	Yes	Yes	Yes	No	5	Yes	No	No	2	2	2	2	2
Cystitis	膀胱炎	C7	2	140	10	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Hepatic function abnormal	肝機能障害	C1D1	3	2	106	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Vomiting	嘔吐	C1D1	1	2	1	No	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Hypercalcaemia	高カルシウム血症	C1D8	1	9	6	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Hyperkalaemia	高カリウム血症	C1D8	2	9	6	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Infusion related reaction	インフュージョンリアクション	C1D8	1	9	6	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Leukopenia	白血球減少症	C1D8	4	9	13	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C1D8	1	9	4	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C1D8	4	9	13	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C1D8	1	9		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Hyperkalaemia	高カリウム血症	C1D15	2	16	6	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Infusion related reaction	インフュージョンリアクション	C1D15	1	16	6	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Dysgeusia	味覚異常	C2	1	30	120	No	No	No	Yes	No	No	3	No	No	No	2	2	2	2	2
Oedema peripheral	下肢浮腫	C7	1	147		No	No	No	No	No	No	2	No	No	No	2	6	6	6	6

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Treatment: G-CHOP (N=36)

Site ID/ Subject ID - Age/Sex/Weight yr kg Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	Relation to Study Drug					Serious	Outcome	Treatment for AE		Subject Discon. from Study	Action Taken with Study Drug				
						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Nausea	悪心	C1D1	2	2	188	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Insomnia	不眠症	C1D1	2	3	57	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Alopecia	脱毛	C1D15	2	23	155	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Infusion site phlebitis	静脈炎（注入部位）	C2	2	23	1	No	No	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Bacteraemia	菌血症	C2	3	28	32	No	No	No	No	No	Yes	3	Yes	No	No	4	4	4	4	4
Cellulitis	蜂窩織炎	C2	3	30	30	No	No	No	No	No	Yes	3	Yes	No	No	4	4	4	4	4
Erythema	紅斑（下腿）	C2	1	30	8	No	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Pruritus	そう痒症	C4	1	90	13	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Bacteraemia	菌血症の再燃	C5	3	113	27	Yes	Yes	Yes	Yes	Yes	Yes	3	Yes	No	No	4	4	4	4	4
Diarrhoea	下痢	C6	1	140	65	No	No	No	No	No	No	3	No	No	No	2	6	6	6	6

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Blood pressure increased	血圧上昇	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Infusion related reaction	INFUSION RELATED REACTION	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Headache	頭痛	C1D1	1	4	11	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C1D1	2	5	10	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C2	4	35	8	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Infusion site phlebitis	血管炎	C4	1	64	1	No	No	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Infusion site phlebitis	血管炎	C5	1	85	1	No	No	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Herpes zoster	帯状疱疹	C5	2	100	27	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	4	4	4	4	4
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C8	1	199		No	No	No	Yes	No	No	2	Yes	No	No	6	6	6	6	6
[redacted]																				
Constipation	便秘	C1D1	1	4	4	No	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C1D1	1	7		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Stomatitis	口内炎	C1D8	1	14	15	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Alopecia	脱毛症	C1D15	2	21		No	Yes	Yes	Yes	No	No	2	No	No	No	2	2	2	2	2
Nausea	悪心	C2	1	27	2	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Alanine aminotransferase increased	ALT上昇	C2	3	28	24	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	4	3	3	4	4
Aspartate aminotransferase increased	AST上昇	C2	3	28	24	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	4	3	3	4	4
Pyrexia	発熱	C2	1	34	3	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Alanine aminotransferase increased	ALT上昇	C3	2	61	17	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	4	4	4	4	4
Aspartate aminotransferase increased	AST上昇	C3	2	61	17	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	4	4	4	4	4
Nausea	悪心	C3	1	73	40	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C4	2	86	8	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Dyspnoea	呼吸困難感	C4	1	96	1	No	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Anaemia	貧血	C4	2	103	22	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C6	2	130	6	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	6	6	6	6
Pyrexia	発熱	C6	1	131	2	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	6	6	6	6
Neutropenia	好中球減少症	C6	4	135	11	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	6	6	6	6
Aspartate aminotransferase increased	AST上昇	C6	2	138	12	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	6	6	6	6
Neutropenia	好中球減少症	C7	3	170	6	Yes	No	No	No	No	No	3	Yes	No	No	4	6	6	6	6

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Infusion related reaction	INFUSION RELATED REACTION	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C1D1	2	4	19	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C1D1	4	8	8	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	4	3	3	2	2
Thrombocytopenia	血小板減少症	C1D1	3	8	8	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	3	3	2	2
Dysgeusia	味覚異常	C1D8	1	15		No	Yes	Yes	Yes	No	No	2	No	No	No	2	2	2	2	2
Upper respiratory tract infection	上気道炎	C1D8	2	15	43	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Decreased appetite	食欲不振	C2	1	33	11	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C3	4	57	8	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C4	1	65	14	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Decreased appetite	食欲不振	C4	1	66	13	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C4	2	66	13	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C4	2	69		No	No	No	Yes	No	No	2	No	No	No	2	2	2	3	2
Bronchiolitis	細気管支炎	C4	2	78		Yes	Yes	Yes	Yes	Yes	No	2	Yes	No	No	5	2	2	2	2
Sinusitis	副鼻腔炎	C4	1	78		Yes	Yes	Yes	Yes	Yes	No	2	No	No	No	2	2	2	2	2
Constipation	便秘	C5	1	86	14	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Febrile neutropenia	発熱性好中球減少症	C6	3	114	7	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Hypoxia	低酸素血症	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Infusion related reaction	INFUSION RELATED REACTION	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C1D15	1	22		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Bladder irritation	膀胱刺激症状	C2	1	36	15	No	Yes	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C2	4	36	8	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C3	4	55	3	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
[redacted]																				
Nausea	悪心	C1D1	2	2	7	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C1D1	2	3	6	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C1D8	4	15	8	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C2	2	26	8	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Upper respiratory tract infection	上気道炎	C2	1	27	7	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C3	2	47	11	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Infection	感染症	C3	2	58	11	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Neutropenia	好中球減少症	C1D8	4	15	10	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C3	1	53	8	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	C4	1	92		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
[redacted]																				
Infusion related reaction	INFUSION REACTION	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Depression	うつ病	C1D1	3	7		No	No	No	No	Yes	Yes	2	Yes	No	No	2	2	2	2	2

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[redacted]																				
Oedema	浮腫	C1D1	1	2	4	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Dysgeusia	味覚異常	C1D1	1	4		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Nausea	悪心	C1D1	2	4	6	No	Yes	Yes	No	No	No	3	No	No	No	2	2	2	2	2
Insomnia	不眠	C2	1	21	106	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Neuropathy peripheral	末梢神経障害	C2	1	21		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Pyrexia	発熱	C4	1	74	4	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Erythema	紅斑	C4	1	77	74	No	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C5	1	87	2	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C5	2	89	4	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C6	1	113	2	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
[redacted]																				
Infusion site phlebitis	静脈炎（注入部位）	C1D1	2	2	3	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Hypertension	高血圧の悪化	C1D8	2	8		No	No	No	No	No	No	2	Yes	No	No	2	2	2	2	2
Alopecia	脱毛	C1D8	2	14		No	Yes	Yes	Yes	No	No	2	No	No	No	2	2	2	2	2
Toothache	歯痛	C2	1	37	7	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Stomatitis	口内炎	C2	1	38	6	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Neuropathy peripheral	末梢神経障害	C3	1	46		No	No	No	Yes	No	No	2	Yes	No	No	2	2	2	3	2
Back pain	背部痛	C3	1	47	27	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Herpes zoster	帯状疱疹	C3	2	63	36	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	4	4	4	4	4

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[redacted]																				
Chills	悪寒	C1D1	1	1	1	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Infusion related reaction	インフュージョンリアクション	C1D1	1	1	1	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Insomnia	不眠	C1D1	1	3		No	No	No	No	Yes	No	2	Yes	No	No	2	2	2	2	2
Liver disorder	肝障害	C1D1	3	3	41	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Dysgeusia	味覚障害	C1D1	1	4		No	Yes	No	No	No	No	2	No	No	No	2	2	2	2	2
Steroid withdrawal syndrome	ステロイド離脱症候群	C1D1	1	5	123	No	No	No	No	Yes	No	3	No	No	No	2	2	2	2	3
Neuropathy peripheral	末梢神経障害	C1D8	1	10		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Abdominal pain upper	心窩部痛	C1D8	1	11	7	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Oedema	浮腫	C2	1	23	2	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Stomatitis	口内炎	C5	1	92	3	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2

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Listing of Adverse Events
Protocol(s): JO29737
Analysis: All Patients Population

Treatment: G-CHOP (N=36)

Site ID/ Subject ID - Age/Sex/Weight yr kg Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	Relation to Study Drug					Serious	Outcome	Treatment for AE		Subject Discon. from Study	Action Taken with Study Drug				
						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Infusion related reaction	インフュージョンリアクション	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Pruritus	掻痒感	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C1D1	1	3	5	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Insomnia	不眠	C1D1	1	5		No	No	No	No	Yes	No	2	Yes	No	No	2	2	2	2	2
Febrile neutropenia	発熱性好中球減少症	C5	3	102	8	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Liver disorder	肝障害	C5	2	109	22	No	Yes	Yes	Yes	Yes	No	3	Yes	No	No	4	4	4	4	4
Haemorrhoids	痔核	C6	2	130	8	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Iron deficiency anaemia	鉄欠乏性貧血	C8	2	183		No	Yes	Yes	Yes	Yes	No	2	Yes	No	No	6	6	6	6	6

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Treatment: G-CHOP (N=36)

Site ID/ Subject ID	- Age/Sex/Weight yr kg					Relation to Study Drug							Treatment for AE			Action Taken with Study Drug				
Adverse Event Preferred Term	Adverse Event Inv. Text	Cycle	Most Extreme Intensity	Study day of Onset	Duration in Days	G	C	H	O	P	Serious	Outcome	Medication	Procedure /Surgery	Subject Discon. from Study	G	C	H	O	P
[redacted]																				
Oedema	浮腫	C1D1	1	3	2	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Dysgeusia	味覚異常	C1D1	1	4		No	Yes	No	No	No	No	2	No	No	No	2	2	2	2	2
Periodontitis	歯周炎	C1D15	2	20	171	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Haemorrhoids	痔核	C3	2	57	134	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Neutrophil count decreased	好中球減少	C3	4	58	7	Yes	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Herpes zoster	汎発性帯状疱疹	C4	3	73	118	Yes	Yes	Yes	Yes	Yes	Yes	3	Yes	No	No	4	4	4	4	4
Gastroenteritis	感染性胃腸炎	C5	3	107	14	Yes	Yes	Yes	Yes	Yes	Yes	3	Yes	No	No	2	2	2	2	2
[redacted]																				
Constipation	便秘	C1D1	1	5	24	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Erythema	皮膚発赤	C1D8	1	15	2	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	2	2	2	2
Cerebral infarction	脳梗塞	C1D15	2	16		Yes	No	No	No	No	Yes	5	Yes	Yes	No	4	4	4	4	4
Infusion related reaction	インフュージョンリアクション	C1D15	2	16		Yes	No	No	No	No	Yes	5	Yes	Yes	No	4	4	4	4	4
Pneumonia aspiration	誤嚥性肺炎	C1D15	3	16		No	No	No	No	No	Yes	2	Yes	Yes	No	5	5	5	5	5
Alopecia	脱毛	C1D15	2	30		No	Yes	Yes	Yes	No	No	2	No	No	No	2	2	2	2	2

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Treatment: G-CHOP (N=36)

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Infusion related reaction	インフュージョンリアクション	C1D1	1	1	1	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Pyrexia	発熱	C1D1	1	1	1	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Decreased appetite	食思不振	C1D1	1	4	61	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Insomnia	不眠症	C1D1	1	5		No	No	No	No	Yes	No	2	Yes	No	No	2	2	2	2	2
Malaise	倦怠感	C1D1	1	8	57	No	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Neuropathy peripheral	末梢神経障害	C1D8	1	9		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Neutrophil count decreased	好中球数減少	C1D8	3	12	4	Yes	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Nasopharyngitis	感冒	C2	1	36	8	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Skin induration	皮膚硬結	C3	1	57	22	Yes	Yes	Yes	Yes	No	No	3	No	Yes	No	2	2	2	2	2
Nail pigmentation	爪色素沈着	C3	1	60		Yes	Yes	Yes	Yes	Yes	No	2	No	No	No	2	2	2	2	2
Breath odour	口臭	C4	1	85	22	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Nasopharyngitis	感冒	C7	1	146	32	Yes	No	No	No	No	No	3	No	No	No	2	6	6	6	6

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Infusion related reaction	インフュージョンリアクション	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Vomiting	嘔吐	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Insomnia	不眠症	C1D1	1	3	41	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C1D1	1	3	125	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C1D1	1	4	145	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Malaise	倦怠感	C1D1	1	4	124	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Dysgeusia	味覚障害	C1D1	2	7	121	No	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Neutrophil count decreased	好中球数減少	C1D8	4	15	8	Yes	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Alopecia	脱毛	C1D15	1	16	163	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neuropathy peripheral	末梢神経障害	C1D15	1	16	168	No	No	No	Yes	No	No	3	No	No	No	2	2	2	2	2
Skin induration	皮膚硬結	C5	2	86		Yes	Yes	Yes	Yes	No	No	2	Yes	No	No	2	2	2	2	2
Infusion related reaction	インフュージョンリアクション	C6	1	107	72	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	6	6	6	6
Nasopharyngitis	感冒	C6	1	107	72	Yes	Yes	Yes	Yes	Yes	No	3	Yes	No	No	2	6	6	6	6

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[redacted]																				
Constipation	便秘	C1D1	1	4	145	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutrophil count decreased	好中球数減少	C1D8	4	10	12	Yes	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Skin exfoliation	皮膚剥離	C1D15	1	16	2	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Neuropathy peripheral	末梢神経障害	C3	1	64	85	No	No	No	Yes	No	No	3	No	No	No	2	2	2	2	2
[redacted]																				
Decreased appetite	食欲不振	C1D1	1	3	181	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Dysgeusia	味覚障害	C1D1	1	5		Yes	Yes	Yes	Yes	Yes	No	2	No	No	No	2	2	2	2	2
Alopecia	脱毛	C1D8	1	15	169	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Dry skin	皮膚乾燥	C1D15	1	20		Yes	Yes	Yes	Yes	Yes	No	2	Yes	No	No	2	2	2	2	2
Chest discomfort	胸部不快感	C2	1	43	141	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Neuropathy peripheral	末梢神経障害	C5	1	102		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Gynaecomastia	女性化乳房	C7	1	145		Yes	Yes	Yes	Yes	Yes	No	2	No	No	No	2	6	6	6	6

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Hyperglycaemia	高血糖	C1D1	2	1	6	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Nausea	悪心	C1D1	1	1	2	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Constipation	便秘	C1D1	1	5	125	No	No	No	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Blood pressure increased	血圧上昇	C1D8	1	8	1	No	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Decreased appetite	食思不振	C1D8	1	9	9	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C1D8	4	11	6	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Bone pain	骨痛	C1D8	1	15	1	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢神経感覚性ニューロパチー	C1D15	1	21		No	No	No	Yes	No	No	5	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C2	3	37	9	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Arthralgia	関節痛	C3	1	49	2	Yes	Yes	Yes	Yes	Yes	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C5	2	100	9	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C6	3	121	9	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
[redacted]																				
Hyperglycaemia	高血糖	C1D1	2	1	6	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C1D1	1	2		No	No	No	Yes	No	No	2	Yes	No	No	2	2	2	2	2
Infusion related reaction	輸注時反応	C1D1	1	2	20	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C1D1	1	2	2	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2

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[redacted]																				
Peripheral sensory neuropathy	末梢神経感覚性ニューロパチー	C1D1	1	2		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Thrombocytopenia	血小板減少症	C1D1	4	2	20	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Dysgeusia	味覚障害	C1D1	1	3	3	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Decreased appetite	食欲不振	C1D8	1	9	4	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Malaise	倦怠感	C1D8	1	9	4	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Nausea	悪心	C1D8	1	9	2	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Bone pain	骨痛	C1D8	1	10	5	No	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C1D8	4	10	9	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Alopecia	脱毛症	C1D15	2	17		No	Yes	Yes	Yes	No	No	2	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C2	4	33	10	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C3	4	56	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Dental caries	齲歯	C4	3	65		No	No	No	No	No	No	5	No	Yes	No	2	2	2	2	2
Neutropenia	好中球減少症	C4	4	75	10	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Thrombocytopenia	血小板減少症	C4	2	75	124	Yes	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Back pain	腰痛	C4	2	84		No	No	No	No	No	No	2	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C5	4	97	9	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C6	4	117	11	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Spinal compression fracture	腰椎圧迫骨折	C7	2	138		No	No	No	No	Yes	No	2	Yes	No	No	2	6	6	6	6

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						G	C	H	O	P			Medication	Procedure /Surgery		G	C	H	O	P
[redacted]																				
Chills	悪寒	C1D1	1	1	1	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Headache	頭痛	C1D1	1	1	1	Yes	No	No	No	No	No	3	No	No	No	2	2	2	2	2
Infusion related reaction	輸注時反応	C1D1	2	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Pyrexia	発熱	C1D1	1	1	1	Yes	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Constipation	便秘	C1D1	1	2		No	No	No	Yes	No	No	2	Yes	No	No	2	2	2	2	2
Hypokalaemia	低カリウム血症	C1D1	1	3	15	No	No	No	No	No	No	3	Yes	No	No	2	2	2	2	2
Decreased appetite	食思不振	C1D1	1	5	5	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C1D8	4	13	5	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Decreased appetite	食欲不振	C2	1	24	9	No	Yes	Yes	Yes	No	No	3	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C2	3	35	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Sinusitis	副鼻腔炎	C2	2	42	169	No	No	No	No	Yes	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C3	3	56	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Peripheral sensory neuropathy	末梢神経感覚性ニューロパチー	C3	1	63		No	No	No	Yes	No	No	2	No	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C4	3	77	8	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C5	2	98	10	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2
Neutropenia	好中球減少症	C6	3	119	14	No	Yes	Yes	Yes	No	No	3	Yes	No	No	2	2	2	2	2

(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose increased; 2 = dose not changed; 3 = dose reduced; 4 = drug interrupted; 5 = drug withdrawn; 6 = not applicable; 7 = unknown.
G : Obinutuzumab, C : Cyclophosphamide, H : Doxorubicin, O : Vincristine, P : Predonisolone

Program: /opt/BIOSTAT/prod/cdpt7159/jo29737/ael02.sas / Output: /opt/BIOSTAT/prod/cdt7159a/j29737a/reports/ael02_ap.out
24JUN2016 12:27

[5.3.3.2-2 Listing 16.2-13を再掲]

2.7.6.2.1.3　BO21223試験（GALLIUM 試験）

表 2.7.6.2.1.3-1　因果関係を問わないすべての有害事象（BO21223試験，未治療 iNHL 患者）

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	678 (98.0%)	24 (3.5%)	175 (25.3%)	254 (36.7%)	199 (28.8%)	26 (3.8%)
胃腸障害						
- Overall -	508 (73.4%)	212 (30.6%)	237 (34.2%)	58 (8.4%)	1 (0.1%)	0
悪心	313 (45.2%)	190 (27.5%)	112 (16.2%)	11 (1.6%)	0	0
便秘	205 (29.6%)	127 (18.4%)	75 (10.8%)	3 (0.4%)	0	0
下痢	154 (22.3%)	98 (14.2%)	46 (6.6%)	10 (1.4%)	0	0
嘔吐	138 (19.9%)	83 (12.0%)	44 (6.4%)	11 (1.6%)	0	0
腹痛	71 (10.3%)	38 (5.5%)	26 (3.8%)	7 (1.0%)	0	0
口内炎	50 (7.2%)	32 (4.6%)	16 (2.3%)	2 (0.3%)	0	0
消化不良	42 (6.1%)	26 (3.8%)	16 (2.3%)	0	0	0
上腹部痛	43 (6.2%)	35 (5.1%)	6 (0.9%)	2 (0.3%)	0	0
胃食道逆流性疾患	23 (3.3%)	11 (1.6%)	12 (1.7%)	0	0	0
口内乾燥	20 (2.9%)	18 (2.6%)	2 (0.3%)	0	0	0
口腔内潰瘍形成	24 (3.5%)	14 (2.0%)	8 (1.2%)	2 (0.3%)	0	0
腹部膨満	17 (2.5%)	13 (1.9%)	4 (0.6%)	0	0	0
腹部不快感	15 (2.2%)	13 (1.9%)	2 (0.3%)	0	0	0
口腔内痛	15 (2.2%)	10 (1.4%)	5 (0.7%)	0	0	0
歯痛	18 (2.6%)	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0
胃炎	13 (1.9%)	4 (0.6%)	8 (1.2%)	1 (0.1%)	0	0
痔核	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
放屁	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0	0
下腹部痛	10 (1.4%)	6 (0.9%)	4 (0.6%)	0	0	0
歯肉痛	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
大腸炎	6 (0.9%)	0	3 (0.4%)	3 (0.4%)	0	0
齲歯	6 (0.9%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

Program: /opt/BIOSTAT/prod/cdt7159z/k21223l/aet04.sas / Output: /opt/BIOSTAT/prod/cdt7159z/k21223l/reports/aet04_223_SE.out
03OCT2016 3:49

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
嚥下障害	8 (1.2%)	4 (0.6%)	4 (0.6%)	0	0	0
口の錯感覚	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
アフタ性潰瘍	8 (1.2%)	7 (1.0%)	1 (0.1%)	0	0	0
直腸出血	4 (0.6%)	3 (0.4%)	0	1 (0.1%)	0	0
消化器痛	5 (0.7%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0	0
心窩部不快感	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
便失禁	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
膵炎	1 (0.1%)	0	0	1 (0.1%)	0	0
食道炎	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
大腸ポリープ	2 (0.3%)	2 (0.3%)	0	0	0	0
腸閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
腹水	3 (0.4%)	1 (0.1%)	0	2 (0.3%)	0	0
嚥下痛	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔そう痒症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
痔出血	1 (0.1%)	0	1 (0.1%)	0	0	0
舌潰瘍	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
裂孔ヘルニア	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
裂肛	1 (0.1%)	0	1 (0.1%)	0	0	0
鼠径ヘルニア	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
クローン病	1 (0.1%)	0	1 (0.1%)	0	0	0
メレナ	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
過敏性腸症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
憩室	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔粘膜水疱形成	2 (0.3%)	0	2 (0.3%)	0	0	0
舌苔	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
舌痛	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肛門周囲痛	1 (0.1%)	1 (0.1%)	0	0	0	0
びらん性胃炎	1 (0.1%)	0	0	1 (0.1%)	0	0
急性膵炎	1 (0.1%)	0	0	0	1 (0.1%)	0
口の感覚鈍麻	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔粘膜紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
歯の知覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
歯周病	1 (0.1%)	1 (0.1%)	0	0	0	0
歯肉出血	1 (0.1%)	1 (0.1%)	0	0	0	0
小腸炎	2 (0.3%)	0	2 (0.3%)	0	0	0
食道痛	1 (0.1%)	1 (0.1%)	0	0	0	0
舌炎	1 (0.1%)	1 (0.1%)	0	0	0	0
腸管拡張症	1 (0.1%)	1 (0.1%)	0	0	0	0
腸膀胱瘻	1 (0.1%)	0	1 (0.1%)	0	0	0
非感染性歯肉炎	1 (0.1%)	1 (0.1%)	0	0	0	0
腹部圧痛	2 (0.3%)	2 (0.3%)	0	0	0	0
糞塊	1 (0.1%)	0	1 (0.1%)	0	0	0
肛門潰瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
セリアック病	1 (0.1%)	1 (0.1%)	0	0	0	0
ミクリッツ症候群	1 (0.1%)	0	0	1 (0.1%)	0	0
レッチング	1 (0.1%)	0	1 (0.1%)	0	0	0
胃拡張	1 (0.1%)	0	1 (0.1%)	0	0	0
胃軸捻転	1 (0.1%)	0	1 (0.1%)	0	0	0
胃腸障害	1 (0.1%)	0	1 (0.1%)	0	0	0
胃排出不全	1 (0.1%)	0	0	1 (0.1%)	0	0
回腸狭窄	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血栓性痔核	1 (0.1%)	0	1 (0.1%)	0	0	0
呼気臭	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
口唇そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
口唇上皮剥脱	1 (0.1%)	1 (0.1%)	0	0	0	0
好酸球性胃腸炎	1 (0.1%)	0	0	1 (0.1%)	0	0
歯の障害	1 (0.1%)	0	1 (0.1%)	0	0	0
歯肉腫	1 (0.1%)	0	1 (0.1%)	0	0	0
歯肉障害	1 (0.1%)	1 (0.1%)	0	0	0	0
歯肉潰瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
痔瘻	1 (0.1%)	0	1 (0.1%)	0	0	0
十二指腸潰瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
食道不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
食道痙攣	1 (0.1%)	0	1 (0.1%)	0	0	0
舌そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
大腸閉塞	1 (0.1%)	0	0	1 (0.1%)	0	0
腸間膜脂肪織炎	1 (0.1%)	0	1 (0.1%)	0	0	0
腸間膜静脈血栓症	1 (0.1%)	0	0	1 (0.1%)	0	0
腸絨毛萎縮	1 (0.1%)	0	1 (0.1%)	0	0	0
直腸脱	1 (0.1%)	0	1 (0.1%)	0	0	0
排便回数増加	1 (0.1%)	1 (0.1%)	0	0	0	0
白色便	1 (0.1%)	1 (0.1%)	0	0	0	0
便意切迫	1 (0.1%)	1 (0.1%)	0	0	0	0
感染症および寄生虫症 - Overall -	481 (69.5%)	100 (14.5%)	271 (39.2%)	100 (14.5%)	6 (0.9%)	4 (0.6%)

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
上気道感染	122 (17.6%)	50 (7.2%)	67 (9.7%)	5 (0.7%)	0	0
鼻咽頭炎	120 (17.3%)	83 (12.0%)	37 (5.3%)	0	0	0
尿路感染	62 (9.0%)	5 (0.7%)	48 (6.9%)	9 (1.3%)	0	0
下気道感染	70 (10.1%)	11 (1.6%)	54 (7.8%)	5 (0.7%)	0	0
帯状疱疹	47 (6.8%)	4 (0.6%)	37 (5.3%)	6 (0.9%)	0	0
肺炎	49 (7.1%)	2 (0.3%)	18 (2.6%)	24 (3.5%)	3 (0.4%)	2 (0.3%)
副鼻腔炎	44 (6.4%)	12 (1.7%)	29 (4.2%)	3 (0.4%)	0	0
気管支炎	37 (5.3%)	5 (0.7%)	29 (4.2%)	3 (0.4%)	0	0
鼻炎	32 (4.6%)	27 (3.9%)	5 (0.7%)	0	0	0
口腔ヘルペス	36 (5.2%)	20 (2.9%)	15 (2.2%)	1 (0.1%)	0	0
気道感染	33 (4.8%)	8 (1.2%)	19 (2.7%)	6 (0.9%)	0	0
結膜炎	24 (3.5%)	10 (1.4%)	13 (1.9%)	1 (0.1%)	0	0
インフルエンザ	21 (3.0%)	13 (1.9%)	8 (1.2%)	0	0	0
感染	21 (3.0%)	4 (0.6%)	9 (1.3%)	8 (1.2%)	0	0
咽頭炎	13 (1.9%)	5 (0.7%)	8 (1.2%)	0	0	0
口腔カンジダ症	16 (2.3%)	7 (1.0%)	9 (1.3%)	0	0	0
膀胱炎	15 (2.2%)	3 (0.4%)	12 (1.7%)	0	0	0
胃腸炎	18 (2.6%)	6 (0.9%)	11 (1.6%)	1 (0.1%)	0	0
肺感染	18 (2.6%)	2 (0.3%)	7 (1.0%)	9 (1.3%)	0	0
耳感染	10 (1.4%)	5 (0.7%)	5 (0.7%)	0	0	0
敗血症	8 (1.2%)	0	1 (0.1%)	5 (0.7%)	2 (0.3%)	0
蜂巣炎	7 (1.0%)	0	5 (0.7%)	2 (0.3%)	0	0
毛包炎	14 (2.0%)	8 (1.2%)	6 (0.9%)	0	0	0
ウイルス感染	11 (1.6%)	5 (0.7%)	4 (0.6%)	2 (0.3%)	0	0
歯肉炎	9 (1.3%)	1 (0.1%)	8 (1.2%)	0	0	0
中耳炎	6 (0.9%)	1 (0.1%)	5 (0.7%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
慢性副鼻腔炎	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
外陰部腟カンジダ症	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
歯感染	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
麦粒腫	3 (0.4%)	3 (0.4%)	0	0	0	0
単純ヘルペス	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
腟感染	5 (0.7%)	2 (0.3%)	2 (0.3%)	1 (0.1%)	0	0
眼感染	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇感染	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
好中球減少性敗血症	6 (0.9%)	0	2 (0.3%)	2 (0.3%)	1 (0.1%)	1 (0.1%)
歯周炎	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
歯膿瘍	4 (0.6%)	0	4 (0.6%)	0	0	0
皮膚真菌感染	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
せつ	3 (0.4%)	3 (0.4%)	0	0	0	0
尿路性敗血症	4 (0.6%)	0	2 (0.3%)	1 (0.1%)	1 (0.1%)	0
皮膚感染	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
医療機器関連感染	4 (0.6%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	0	0
憩室炎	4 (0.6%)	0	4 (0.6%)	0	0	0
消化管感染	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
真菌感染	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
限局性感染	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
喉頭炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
Ｂ型肝炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
ウイルス性胃腸炎	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
ウイルス性上気道感染	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
異型肺炎	5 (0.7%)	0	2 (0.3%)	3 (0.4%)	0	0
扁桃炎	1 (0.1%)	0	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
カンジダ感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
感染性腸炎	1 (0.1%)	0	1 (0.1%)	0	0	0
急性副鼻腔炎	2 (0.3%)	0	2 (0.3%)	0	0	0
虫垂炎	4 (0.6%)	0	0	4 (0.6%)	0	0
爪真菌症	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
熱性感染症	4 (0.6%)	0	2 (0.3%)	2 (0.3%)	0	0
皮下組織膿瘍	4 (0.6%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	0	0
サイトメガロウイルス感染	1 (0.1%)	0	0	1 (0.1%)	0	0
ヘルペスウイルス感染	3 (0.4%)	0	3 (0.4%)	0	0	0
粘膜感染	1 (0.1%)	0	1 (0.1%)	0	0	0
白癬感染	1 (0.1%)	1 (0.1%)	0	0	0	0
ブドウ球菌感染	1 (0.1%)	1 (0.1%)	0	0	0	0
ヘモフィルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
外陰部炎	2 (0.3%)	0	2 (0.3%)	0	0	0
外陰膣真菌感染	1 (0.1%)	1 (0.1%)	0	0	0	0
外耳炎	1 (0.1%)	0	1 (0.1%)	0	0	0
感染性関節炎	1 (0.1%)	0	0	1 (0.1%)	0	0
気管炎	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
菌血症	1 (0.1%)	0	0	1 (0.1%)	0	0
口角口唇炎	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔真菌感染	1 (0.1%)	0	1 (0.1%)	0	0	0
細菌性膣症	1 (0.1%)	0	1 (0.1%)	0	0	0
爪感染	1 (0.1%)	1 (0.1%)	0	0	0	0
尿道炎	1 (0.1%)	1 (0.1%)	0	0	0	0
敗血症性ショック	3 (0.4%)	0	0	2 (0.3%)	0	1 (0.1%)
咬傷感染	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
癜風	1 (0.1%)	1 (0.1%)	0	0	0	0
アデノイド咽頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス血症	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性気道感染	2 (0.3%)	2 (0.3%)	0	0	0	0
カテーテル留置部位感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ノロウイルス性胃腸炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
ヘリコバクター感染	1 (0.1%)	0	1 (0.1%)	0	0	0
陰部ヘルペス	2 (0.3%)	0	2 (0.3%)	0	0	0
気管気管支炎	1 (0.1%)	0	1 (0.1%)	0	0	0
好中球減少性感染	1 (0.1%)	0	1 (0.1%)	0	0	0
細菌感染	2 (0.3%)	2 (0.3%)	0	0	0	0
細菌性肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
処置後感染	1 (0.1%)	0	1 (0.1%)	0	0	0
足部白癬	1 (0.1%)	1 (0.1%)	0	0	0	0
大腸菌性尿路感染	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚カンジダ	1 (0.1%)	0	1 (0.1%)	0	0	0
扁桃周囲膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
ウイルス性肝炎	1 (0.1%)	0	0	1 (0.1%)	0	0
カンジダ性亀頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
カンピロバクター胃腸炎	1 (0.1%)	1 (0.1%)	0	0	0	0
クロストリジウム・ディフィシレ感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ジアルジア症	1 (0.1%)	0	1 (0.1%)	0	0	0
ステノトロフォモナス性敗血症	1 (0.1%)	0	1 (0.1%)	0	0	0
ストーマ部感染	1 (0.1%)	0	0	1 (0.1%)	0	0
ニューモシスチス・イロベチイ感染	1 (0.1%)	0	1 (0.1%)	0	0	0
バルトリン腺膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
パルボウイルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ブドウ球菌性膿痂疹	1 (0.1%)	1 (0.1%)	0	0	0	0
ヘリコバクター性胃炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ヘルペス眼感染	1 (0.1%)	0	1 (0.1%)	0	0	0
レンサ球菌性咽頭炎	1 (0.1%)	1 (0.1%)	0	0	0	0
陰茎感染	1 (0.1%)	0	1 (0.1%)	0	0	0
陰嚢感染	1 (0.1%)	0	1 (0.1%)	0	0	0
眼窩周囲蜂巣炎	1 (0.1%)	0	0	1 (0.1%)	0	0
骨膿瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
細菌性関節炎	1 (0.1%)	0	0	1 (0.1%)	0	0
真菌性舌感染	1 (0.1%)	0	1 (0.1%)	0	0	0
神経ボレリア症	1 (0.1%)	0	0	1 (0.1%)	0	0
神経合併症を伴う帯状疱疹感染	1 (0.1%)	0	0	1 (0.1%)	0	0
精巣上体炎	1 (0.1%)	0	1 (0.1%)	0	0	0
全身性感染	1 (0.1%)	1 (0.1%)	0	0	0	0
創傷感染	1 (0.1%)	0	1 (0.1%)	0	0	0
丹毒	1 (0.1%)	0	1 (0.1%)	0	0	0
中咽頭カンジダ症	1 (0.1%)	0	1 (0.1%)	0	0	0
椎間板炎	1 (0.1%)	0	1 (0.1%)	0	0	0
爪囲炎	1 (0.1%)	1 (0.1%)	0	0	0	0
軟骨膜炎	1 (0.1%)	1 (0.1%)	0	0	0	0
乳様突起炎	1 (0.1%)	0	0	1 (0.1%)	0	0
膿痂疹	1 (0.1%)	1 (0.1%)	0	0	0	0
膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
肺炎球菌性肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
鼻ヘルペス	1 (0.1%)	1 (0.1%)	0	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
迷路炎	1 (0.1%)	0	1 (0.1%)	0	0	0
卵巣細菌感染	1 (0.1%)	0	0	1 (0.1%)	0	0
涙小管炎	1 (0.1%)	1 (0.1%)	0	0	0	0
肛門直腸感染	1 (0.1%)	0	1 (0.1%)	0	0	0
肛門膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	475 (68.6%)	239 (34.5%)	196 (28.3%)	34 (4.9%)	1 (0.1%)	5 (0.7%)
疲労	247 (35.7%)	169 (24.4%)	72 (10.4%)	6 (0.9%)	0	0
発熱	156 (22.5%)	102 (14.7%)	45 (6.5%)	9 (1.3%)	0	0
悪寒	73 (10.5%)	41 (5.9%)	28 (4.0%)	4 (0.6%)	0	0
胸部不快感	37 (5.3%)	24 (3.5%)	12 (1.7%)	1 (0.1%)	0	0
末梢性浮腫	34 (4.9%)	22 (3.2%)	11 (1.6%)	1 (0.1%)	0	0
粘膜の炎症	40 (5.8%)	27 (3.9%)	12 (1.7%)	1 (0.1%)	0	0
無力症	36 (5.2%)	28 (4.0%)	7 (1.0%)	1 (0.1%)	0	0
インフルエンザ様疾患	30 (4.3%)	13 (1.9%)	17 (2.5%)	0	0	0
胸痛	30 (4.3%)	21 (3.0%)	6 (0.9%)	3 (0.4%)	0	0
疼痛	31 (4.5%)	14 (2.0%)	13 (1.9%)	4 (0.6%)	0	0
倦怠感	25 (3.6%)	17 (2.5%)	8 (1.2%)	0	0	0
末梢腫脹	17 (2.5%)	10 (1.4%)	7 (1.0%)	0	0	0
熱感	10 (1.4%)	4 (0.6%)	5 (0.7%)	1 (0.1%)	0	0
浮腫	8 (1.2%)	5 (0.7%)	3 (0.4%)	0	0	0
注入部位血管外漏出	8 (1.2%)	1 (0.1%)	7 (1.0%)	0	0	0
非心臓性胸痛	8 (1.2%)	6 (0.9%)	2 (0.3%)	0	0	0
注射部位疼痛	12 (1.7%)	9 (1.3%)	3 (0.4%)	0	0	0
顔面浮腫	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
カテーテル留置部位疼痛	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
注射部位反応	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
冷感	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
腋窩痛	6 (0.9%)	4 (0.6%)	0	2 (0.3%)	0	0
全身健康状態低下	4 (0.6%)	1 (0.1%)	0	2 (0.3%)	0	1 (0.1%)
溢出	1 (0.1%)	0	1 (0.1%)	0	0	0
注入部位疼痛	2 (0.3%)	2 (0.3%)	0	0	0	0
局所腫脹	4 (0.6%)	4 (0.6%)	0	0	0	0
異物感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
顔面痛	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
粘膜乾燥	1 (0.1%)	1 (0.1%)	0	0	0	0
嚢胞	2 (0.3%)	2 (0.3%)	0	0	0	0
医療機器閉塞	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
歩行障害	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
異常感	1 (0.1%)	1 (0.1%)	0	0	0	0
医薬品副作用	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
苦悶感	1 (0.1%)	0	1 (0.1%)	0	0	0
死亡	2 (0.3%)	0	0	0	0	2 (0.3%)
多臓器不全	3 (0.4%)	0	0	0	1 (0.1%)	2 (0.3%)
カテーテル留置部位紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
カテーテル留置部位内出血	2 (0.3%)	2 (0.3%)	0	0	0	0
ポリープ	1 (0.1%)	0	1 (0.1%)	0	0	0
医療機器関連の血栓症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
医療機器破損	1 (0.1%)	1 (0.1%)	0	0	0	0
温度変化不耐症	1 (0.1%)	1 (0.1%)	0	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
限局性浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
高熱	1 (0.1%)	0	0	1 (0.1%)	0	0
腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
恥骨上痛	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位紅斑	2 (0.3%)	2 (0.3%)	0	0	0	0
低体温	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
不明確な障害	1 (0.1%)	0	1 (0.1%)	0	0	0
薬物不耐性	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
びくびく感	1 (0.1%)	0	1 (0.1%)	0	0	0
ステントグラフトエンドリーク	1 (0.1%)	0	0	1 (0.1%)	0	0
ヘルニア	1 (0.1%)	1 (0.1%)	0	0	0	0
炎症	1 (0.1%)	1 (0.1%)	0	0	0	0
泣き	1 (0.1%)	1 (0.1%)	0	0	0	0
空腹	1 (0.1%)	1 (0.1%)	0	0	0	0
脂肪壊死	1 (0.1%)	1 (0.1%)	0	0	0	0
体温変動感	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位内出血	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位発疹	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
注入部位冷感	1 (0.1%)	0	1 (0.1%)	0	0	0
潰瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
適用部位発疹	1 (0.1%)	1 (0.1%)	0	0	0	0
粘膜出血	1 (0.1%)	1 (0.1%)	0	0	0	0
廃用症候群	1 (0.1%)	1 (0.1%)	0	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
傷害、中毒および処置合併症						
- Overall -	381 (55.1%)	136 (19.7%)	200 (28.9%)	42 (6.1%)	3 (0.4%)	0
注入に伴う反応	339 (49.0%)	128 (18.5%)	178 (25.7%)	31 (4.5%)	2 (0.3%)	0
転倒	15 (2.2%)	6 (0.9%)	6 (0.9%)	3 (0.4%)	0	0
挫傷	12 (1.7%)	9 (1.3%)	2 (0.3%)	1 (0.1%)	0	0
裂傷	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
処置による疼痛	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
節足動物咬傷	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
肋骨骨折	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
上肢骨折	5 (0.7%)	0	2 (0.3%)	3 (0.4%)	0	0
熱傷	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
創傷	4 (0.6%)	4 (0.6%)	0	0	0	0
脊椎圧迫骨折	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
顔面骨骨折	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
歯牙破折	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
皮膚擦過傷	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
漿液腫	1 (0.1%)	1 (0.1%)	0	0	0	0
手首関節骨折	2 (0.3%)	0	2 (0.3%)	0	0	0
肉離れ	1 (0.1%)	1 (0.1%)	0	0	0	0
靱帯捻挫	3 (0.4%)	0	3 (0.4%)	0	0	0
節足動物刺傷	3 (0.4%)	3 (0.4%)	0	0	0	0
造影剤反応	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
足関節部骨折	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
足骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
大腿骨骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
関節損傷	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
眼挫傷	1 (0.1%)	0	1 (0.1%)	0	0	0
骨挫傷	1 (0.1%)	1 (0.1%)	0	0	0	0
骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
事故	1 (0.1%)	1 (0.1%)	0	0	0	0
手骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
脊椎骨折	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
創合併症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
頭部損傷	1 (0.1%)	0	0	1 (0.1%)	0	0
橈骨骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
じん肺症	1 (0.1%)	0	1 (0.1%)	0	0	0
圧迫骨折	1 (0.1%)	0	0	0	1 (0.1%)	0
化学的損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
外傷性肺損傷	1 (0.1%)	0	1 (0.1%)	0	0	0
角膜損傷	1 (0.1%)	0	1 (0.1%)	0	0	0
顎の骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
眼内異物	1 (0.1%)	1 (0.1%)	0	0	0	0
腰椎骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
処置による高血圧	1 (0.1%)	0	1 (0.1%)	0	0	0
多発骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
爪裂離	1 (0.1%)	0	1 (0.1%)	0	0	0
尾骨骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
腹部創離開	1 (0.1%)	1 (0.1%)	0	0	0	0
放射線関連痛	1 (0.1%)	0	1 (0.1%)	0	0	0
有毒性咬傷	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血液およびリンパ系障害						
- Overall -	363 (52.5%)	18 (2.6%)	39 (5.6%)	117 (16.9%)	188 (27.2%)	1 (0.1%)
好中球減少症	298 (43.1%)	9 (1.3%)	27 (3.9%)	97 (14.0%)	165 (23.8%)	0
白血球減少症	81 (11.7%)	7 (1.0%)	15 (2.2%)	42 (6.1%)	17 (2.5%)	0
血小板減少症	50 (7.2%)	17 (2.5%)	14 (2.0%)	14 (2.0%)	5 (0.7%)	0
貧血	65 (9.4%)	18 (2.6%)	32 (4.6%)	15 (2.2%)	0	0
発熱性好中球減少症	39 (5.6%)	0	1 (0.1%)	20 (2.9%)	18 (2.6%)	0
リンパ球減少症	12 (1.7%)	1 (0.1%)	3 (0.4%)	5 (0.7%)	3 (0.4%)	0
骨髄機能不全	5 (0.7%)	0	0	2 (0.3%)	3 (0.4%)	0
汎血球減少症	4 (0.6%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	0	0
顆粒球減少症	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
リンパ節症	2 (0.3%)	2 (0.3%)	0	0	0	0
リンパ節痛	2 (0.3%)	2 (0.3%)	0	0	0	0
鉄欠乏性貧血	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
白血球増加症	1 (0.1%)	1 (0.1%)	0	0	0	0
脾腫	1 (0.1%)	0	1 (0.1%)	0	0	0
リンパ節炎	1 (0.1%)	1 (0.1%)	0	0	0	0
好酸球増加症	1 (0.1%)	1 (0.1%)	0	0	0	0
自己免疫性溶血性貧血	1 (0.1%)	0	0	0	0	1 (0.1%)
ビタミンＢ１２欠乏性貧血	1 (0.1%)	0	1 (0.1%)	0	0	0
ヘモグロビン血症	1 (0.1%)	0	1 (0.1%)	0	0	0
悪性貧血	1 (0.1%)	0	1 (0.1%)	0	0	0
欠乏性貧血	1 (0.1%)	0	1 (0.1%)	0	0	0
血小板増加症	1 (0.1%)	1 (0.1%)	0	0	0	0
小球性貧血	1 (0.1%)	0	1 (0.1%)	0	0	0
赤血球増加症	1 (0.1%)	1 (0.1%)	0	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
低グロブリン血症	1 (0.1%)	1 (0.1%)	0	0	0	0
溶血	1 (0.1%)	0	0	1 (0.1%)	0	0
溶血性貧血	1 (0.1%)	0	0	1 (0.1%)	0	0
貪食細胞性組織球症	1 (0.1%)	0	0	0	1 (0.1%)	0
呼吸器、胸郭および縦隔障害						
- Overall -	360 (52.0%)	167 (24.1%)	154 (22.3%)	32 (4.6%)	6 (0.9%)	1 (0.1%)
咳嗽	165 (23.8%)	99 (14.3%)	65 (9.4%)	1 (0.1%)	0	0
呼吸困難	89 (12.9%)	45 (6.5%)	31 (4.5%)	11 (1.6%)	2 (0.3%)	0
口腔咽頭痛	70 (10.1%)	52 (7.5%)	16 (2.3%)	2 (0.3%)	0	0
湿性咳嗽	27 (3.9%)	14 (2.0%)	11 (1.6%)	1 (0.1%)	1 (0.1%)	0
咽喉刺激感	33 (4.8%)	15 (2.2%)	18 (2.6%)	0	0	0
労作性呼吸困難	23 (3.3%)	16 (2.3%)	7 (1.0%)	0	0	0
鼻漏	12 (1.7%)	9 (1.3%)	3 (0.4%)	0	0	0
鼻出血	15 (2.2%)	12 (1.7%)	2 (0.3%)	1 (0.1%)	0	0
胸水	11 (1.6%)	3 (0.4%)	4 (0.6%)	3 (0.4%)	1 (0.1%)	0
鼻閉	9 (1.3%)	8 (1.2%)	1 (0.1%)	0	0	0
低酸素症	5 (0.7%)	0	5 (0.7%)	0	0	0
肺塞栓症	4 (0.6%)	0	1 (0.1%)	2 (0.3%)	1 (0.1%)	0
発声障害	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
副鼻腔うっ血	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
慢性閉塞性肺疾患	4 (0.6%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
喘息	7 (1.0%)	3 (0.4%)	2 (0.3%)	2 (0.3%)	0	0
上気道咳症候群	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
しゃっくり	8 (1.2%)	6 (0.9%)	2 (0.3%)	0	0	0
胸膜痛	7 (1.0%)	2 (0.3%)	3 (0.4%)	2 (0.3%)	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
喘鳴	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
アレルギー性鼻炎	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
咽喉絞扼感	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
咽喉乾燥	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
口腔咽頭不快感	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
間質性肺疾患	5 (0.7%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	0	0
カタル	2 (0.3%)	0	2 (0.3%)	0	0	0
咽頭異常感覚	3 (0.4%)	3 (0.4%)	0	0	0	0
咽頭浮腫	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
気管支痙攣	3 (0.4%)	0	2 (0.3%)	0	1 (0.1%)	0
肺臓炎	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
咽頭紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
呼吸不全	2 (0.3%)	0	0	0	2 (0.3%)	0
肺気腫	1 (0.1%)	1 (0.1%)	0	0	0	0
肺障害	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
慢性気管支炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
くしゃみ	1 (0.1%)	1 (0.1%)	0	0	0	0
喉頭の炎症	3 (0.4%)	3 (0.4%)	0	0	0	0
上気道の炎症	1 (0.1%)	0	1 (0.1%)	0	0	0
変色痰	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
ラ音	1 (0.1%)	1 (0.1%)	0	0	0	0
誤嚥性肺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
喉頭痛	3 (0.4%)	3 (0.4%)	0	0	0	0
息詰まり感	1 (0.1%)	1 (0.1%)	0	0	0	0
肺硬化	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
肺水腫	1 (0.1%)	0	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
咽頭知覚不全	1 (0.1%)	1 (0.1%)	0	0	0	0
過換気	1 (0.1%)	1 (0.1%)	0	0	0	0
気管支拡張症	1 (0.1%)	0	1 (0.1%)	0	0	0
上気道うっ血	1 (0.1%)	1 (0.1%)	0	0	0	0
睡眠時無呼吸症候群	2 (0.3%)	0	2 (0.3%)	0	0	0
息詰まり	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
頻呼吸	1 (0.1%)	0	0	1 (0.1%)	0	0
無気肺	1 (0.1%)	1 (0.1%)	0	0	0	0
咽頭潰瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
胸膜線維症	1 (0.1%)	1 (0.1%)	0	0	0	0
血管運動性鼻炎	1 (0.1%)	1 (0.1%)	0	0	0	0
呼吸窮迫	1 (0.1%)	0	1 (0.1%)	0	0	0
呼吸障害	1 (0.1%)	0	0	1 (0.1%)	0	0
喉頭不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
上気道性喘鳴	1 (0.1%)	1 (0.1%)	0	0	0	0
声帯肥厚	1 (0.1%)	0	1 (0.1%)	0	0	0
窒息	1 (0.1%)	0	1 (0.1%)	0	0	0
窒息感	1 (0.1%)	0	1 (0.1%)	0	0	0
肺うっ血	1 (0.1%)	0	0	1 (0.1%)	0	0
肺腫瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻乾燥	1 (0.1%)	0	1 (0.1%)	0	0	0
鼻腔内異常感覚	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻部障害	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
閉塞性気道障害	1 (0.1%)	0	1 (0.1%)	0	0	0
喀血	1 (0.1%)	0	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
神経系障害						
- Overall -	351 (50.7%)	204 (29.5%)	112 (16.2%)	28 (4.0%)	2 (0.3%)	5 (0.7%)
頭痛	114 (16.5%)	77 (11.1%)	35 (5.1%)	2 (0.3%)	0	0
浮動性めまい	51 (7.4%)	44 (6.4%)	6 (0.9%)	1 (0.1%)	0	0
味覚異常	55 (7.9%)	50 (7.2%)	5 (0.7%)	0	0	0
末梢性感覚ニューロパチー	47 (6.8%)	36 (5.2%)	10 (1.4%)	1 (0.1%)	0	0
錯感覚	45 (6.5%)	32 (4.6%)	12 (1.7%)	1 (0.1%)	0	0
末梢性ニューロパチー	49 (7.1%)	34 (4.9%)	13 (1.9%)	2 (0.3%)	0	0
嗜眠	26 (3.8%)	21 (3.0%)	5 (0.7%)	0	0	0
感覚鈍麻	24 (3.5%)	15 (2.2%)	9 (1.3%)	0	0	0
多発ニューロパチー	18 (2.6%)	10 (1.4%)	7 (1.0%)	0	0	1 (0.1%)
失神	16 (2.3%)	5 (0.7%)	4 (0.6%)	7 (1.0%)	0	0
振戦	11 (1.6%)	6 (0.9%)	4 (0.6%)	1 (0.1%)	0	0
片頭痛	9 (1.3%)	3 (0.4%)	6 (0.9%)	0	0	0
記憶障害	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0	0
神経痛	10 (1.4%)	2 (0.3%)	7 (1.0%)	1 (0.1%)	0	0
注意力障害	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
失神寸前の状態	7 (1.0%)	1 (0.1%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0
体位性めまい	8 (1.2%)	7 (1.0%)	1 (0.1%)	0	0	0
異常感覚	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
下肢静止不能症候群	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
坐骨神経痛	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
認知障害	8 (1.2%)	6 (0.9%)	2 (0.3%)	0	0	0
一過性脳虚血発作	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
灼熱感	4 (0.6%)	3 (0.4%)	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
ヘルペス後神経痛	2 (0.3%)	0	2 (0.3%)	0	0	0
味覚消失	1 (0.1%)	1 (0.1%)	0	0	0	0
傾眠	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
健忘	1 (0.1%)	1 (0.1%)	0	0	0	0
手根管症候群	4 (0.6%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0	0
知覚過敏	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
嗅覚錯誤	3 (0.4%)	3 (0.4%)	0	0	0	0
てんかん	1 (0.1%)	0	1 (0.1%)	0	0	0
頭部不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
副鼻腔炎に伴う頭痛	1 (0.1%)	0	1 (0.1%)	0	0	0
痙攣発作	3 (0.4%)	0	3 (0.4%)	0	0	0
運動失調	2 (0.3%)	0	2 (0.3%)	0	0	0
平衡障害	2 (0.3%)	2 (0.3%)	0	0	0	0
末梢性運動ニューロパチー	1 (0.1%)	0	1 (0.1%)	0	0	0
ジスキネジア	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
意識レベルの低下	1 (0.1%)	1 (0.1%)	0	0	0	0
感覚消失	1 (0.1%)	1 (0.1%)	0	0	0	0
虚血性脳卒中	1 (0.1%)	0	0	0	0	1 (0.1%)
頚動脈狭窄	1 (0.1%)	0	0	1 (0.1%)	0	0
三叉神経痛	1 (0.1%)	0	1 (0.1%)	0	0	0
第７脳神経麻痺	1 (0.1%)	0	1 (0.1%)	0	0	0
脳虚血	1 (0.1%)	0	0	1 (0.1%)	0	0
不全単麻痺	1 (0.1%)	0	1 (0.1%)	0	0	0
味覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
くも膜下出血	1 (0.1%)	0	0	1 (0.1%)	0	0
アルツハイマー型認知症	1 (0.1%)	0	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
パーキンソン病	1 (0.1%)	1 (0.1%)	0	0	0	0
起立時振戦	1 (0.1%)	0	0	1 (0.1%)	0	0
筋痙直	1 (0.1%)	0	1 (0.1%)	0	0	0
群発頭痛	1 (0.1%)	1 (0.1%)	0	0	0	0
頚動脈閉塞	1 (0.1%)	1 (0.1%)	0	0	0	0
視野欠損	1 (0.1%)	0	1 (0.1%)	0	0	0
失語症	1 (0.1%)	0	1 (0.1%)	0	0	0
出血性卒中	1 (0.1%)	0	0	1 (0.1%)	0	0
小脳症候群	1 (0.1%)	0	0	1 (0.1%)	0	0
神経系障害	1 (0.1%)	0	0	0	1 (0.1%)	0
神経毒性	1 (0.1%)	1 (0.1%)	0	0	0	0
睡眠の質低下	1 (0.1%)	1 (0.1%)	0	0	0	0
頭蓋内出血	1 (0.1%)	0	0	1 (0.1%)	0	0
頭蓋内動脈瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
脳血管発作	1 (0.1%)	0	0	0	0	1 (0.1%)
脳血腫	1 (0.1%)	0	0	0	0	1 (0.1%)
脳症	1 (0.1%)	0	0	0	0	1 (0.1%)
不全対麻痺	1 (0.1%)	0	0	1 (0.1%)	0	0
末梢性感覚運動ニューロパチー	1 (0.1%)	0	1 (0.1%)	0	0	0
末梢性麻痺	1 (0.1%)	0	1 (0.1%)	0	0	0
腕神経叢障害	1 (0.1%)	0	0	1 (0.1%)	0	0
嗅覚減退	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚および皮下組織障害						
- Overall -	348 (50.3%)	172 (24.9%)	156 (22.5%)	20 (2.9%)	0	0
発疹	122 (17.6%)	58 (8.4%)	54 (7.8%)	10 (1.4%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
そう痒症	89 (12.9%)	66 (9.5%)	22 (3.2%)	1 (0.1%)	0	0
脱毛症	75 (10.8%)	38 (5.5%)	36 (5.2%)	1 (0.1%)	0	0
皮膚乾燥	33 (4.8%)	30 (4.3%)	3 (0.4%)	0	0	0
紅斑	32 (4.6%)	21 (3.0%)	11 (1.6%)	0	0	0
寝汗	33 (4.8%)	23 (3.3%)	9 (1.3%)	1 (0.1%)	0	0
多汗症	27 (3.9%)	19 (2.7%)	8 (1.2%)	0	0	0
蕁麻疹	23 (3.3%)	5 (0.7%)	14 (2.0%)	4 (0.6%)	0	0
斑状丘疹状皮疹	18 (2.6%)	4 (0.6%)	11 (1.6%)	3 (0.4%)	0	0
湿疹	12 (1.7%)	10 (1.4%)	2 (0.3%)	0	0	0
そう痒性皮疹	5 (0.7%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0	0
ざ瘡様皮膚炎	5 (0.7%)	5 (0.7%)	0	0	0	0
皮膚剥脱	3 (0.4%)	3 (0.4%)	0	0	0	0
斑状皮疹	6 (0.9%)	1 (0.1%)	5 (0.7%)	0	0	0
顔面腫脹	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
皮膚炎	2 (0.3%)	2 (0.3%)	0	0	0	0
紅斑性皮疹	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
水疱	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
乾癬	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
皮膚嚢腫	2 (0.3%)	2 (0.3%)	0	0	0	0
冷汗	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
薬疹	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚潰瘍	3 (0.4%)	3 (0.4%)	0	0	0	0
脂漏性皮膚炎	1 (0.1%)	1 (0.1%)	0	0	0	0
全身性皮疹	3 (0.4%)	3 (0.4%)	0	0	0	0
多形紅斑	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
爪変色	5 (0.7%)	5 (0.7%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
皮膚腫瘤	2 (0.3%)	2 (0.3%)	0	0	0	0
ざ瘡	2 (0.3%)	2 (0.3%)	0	0	0	0
アレルギー性皮膚炎	2 (0.3%)	0	2 (0.3%)	0	0	0
光線過敏性反応	1 (0.1%)	1 (0.1%)	0	0	0	0
酒さ	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
水疱性皮膚炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
全身性そう痒症	3 (0.4%)	3 (0.4%)	0	0	0	0
爪破損	4 (0.6%)	4 (0.6%)	0	0	0	0
点状出血	2 (0.3%)	2 (0.3%)	0	0	0	0
扁平苔癬	1 (0.1%)	0	1 (0.1%)	0	0	0
貨幣状湿疹	1 (0.1%)	0	1 (0.1%)	0	0	0
汗疹	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
接触性皮膚炎	2 (0.3%)	2 (0.3%)	0	0	0	0
爪の障害	2 (0.3%)	2 (0.3%)	0	0	0	0
爪線状隆起	1 (0.1%)	1 (0.1%)	0	0	0	0
日光角化症	2 (0.3%)	2 (0.3%)	0	0	0	0
剥脱性皮膚炎	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚亀裂	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚色素過剰	3 (0.4%)	3 (0.4%)	0	0	0	0
皮膚疼痛	2 (0.3%)	2 (0.3%)	0	0	0	0
丘疹性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
血管浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
手掌・足底発赤知覚不全症候群	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
色素沈着障害	1 (0.1%)	1 (0.1%)	0	0	0	0
斑状出血	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚硬結	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
皮膚障害	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚反応	2 (0.3%)	2 (0.3%)	0	0	0	0
皮膚病変	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
嵌入爪	1 (0.1%)	0	1 (0.1%)	0	0	0
瘢痕そう痒感	2 (0.3%)	2 (0.3%)	0	0	0	0
亜急性皮膚エリテマトーデス	1 (0.1%)	0	1 (0.1%)	0	0	0
間擦疹	1 (0.1%)	1 (0.1%)	0	0	0	0
硬化性苔癬	1 (0.1%)	0	1 (0.1%)	0	0	0
手掌紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
手皮膚炎	1 (0.1%)	1 (0.1%)	0	0	0	0
掌蹠角皮症	1 (0.1%)	1 (0.1%)	0	0	0	0
全身紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
中毒性皮疹	1 (0.1%)	0	1 (0.1%)	0	0	0
剥脱性発疹	1 (0.1%)	0	1 (0.1%)	0	0	0
皮下出血	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚刺激	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚灼熱感	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚臭異常	1 (0.1%)	1 (0.1%)	0	0	0	0
毛質異常	1 (0.1%)	1 (0.1%)	0	0	0	0
痂皮	1 (0.1%)	1 (0.1%)	0	0	0	0
褥瘡性潰瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
筋骨格系および結合組織障害						
- Overall -	310 (44.8%)	166 (24.0%)	123 (17.8%)	21 (3.0%)	0	0
背部痛	110 (15.9%)	68 (9.8%)	38 (5.5%)	4 (0.6%)	0	0
関節痛	88 (12.7%)	54 (7.8%)	30 (4.3%)	4 (0.6%)	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
四肢痛	57 (8.2%)	38 (5.5%)	15 (2.2%)	4 (0.6%)	0	0
筋肉痛	30 (4.3%)	24 (3.5%)	5 (0.7%)	1 (0.1%)	0	0
筋痙縮	36 (5.2%)	25 (3.6%)	11 (1.6%)	0	0	0
骨痛	37 (5.3%)	23 (3.3%)	11 (1.6%)	3 (0.4%)	0	0
筋骨格痛	32 (4.6%)	24 (3.5%)	8 (1.2%)	0	0	0
頚部痛	17 (2.5%)	11 (1.6%)	6 (0.9%)	0	0	0
肩径部痛	20 (2.9%)	17 (2.5%)	3 (0.4%)	0	0	0
関節腫脹	13 (1.9%)	9 (1.3%)	4 (0.6%)	0	0	0
筋骨格系胸痛	12 (1.7%)	7 (1.0%)	5 (0.7%)	0	0	0
側腹部痛	11 (1.6%)	7 (1.0%)	4 (0.6%)	0	0	0
筋力低下	11 (1.6%)	8 (1.2%)	2 (0.3%)	1 (0.1%)	0	0
変形性関節症	9 (1.3%)	3 (0.4%)	4 (0.6%)	2 (0.3%)	0	0
顎痛	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
関節炎	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
筋骨格硬直	4 (0.6%)	4 (0.6%)	0	0	0	0
筋骨格不快感	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
関節周囲炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
脊椎痛	2 (0.3%)	0	2 (0.3%)	0	0	0
滑液包炎	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
筋緊張	4 (0.6%)	4 (0.6%)	0	0	0	0
関節硬直	3 (0.4%)	3 (0.4%)	0	0	0	0
骨粗鬆症	2 (0.3%)	2 (0.3%)	0	0	0	0
四肢不快感	4 (0.6%)	4 (0.6%)	0	0	0	0
椎間板突出	1 (0.1%)	0	0	1 (0.1%)	0	0
肩回旋筋腱板症候群	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
弾発指	1 (0.1%)	0	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腱炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
デュプイトラン拘縮	1 (0.1%)	0	1 (0.1%)	0	0	0
関節可動域低下	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
筋炎	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
腰部脊柱管狭窄症	2 (0.3%)	0	2 (0.3%)	0	0	0
ミオパチー	1 (0.1%)	0	1 (0.1%)	0	0	0
滑膜炎	1 (0.1%)	0	0	1 (0.1%)	0	0
頚部腫瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
斜頚	1 (0.1%)	1 (0.1%)	0	0	0	0
出血性関節症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
脊柱管狭窄症	2 (0.3%)	0	0	2 (0.3%)	0	0
足底筋膜炎	2 (0.3%)	0	2 (0.3%)	0	0	0
ピロリン酸カルシウム結晶性軟骨石灰化症	1 (0.1%)	0	1 (0.1%)	0	0	0
外骨腫	1 (0.1%)	1 (0.1%)	0	0	0	0
乾癬性関節症	1 (0.1%)	0	1 (0.1%)	0	0	0
筋膜疼痛症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
交感神経性後頚部症候群	1 (0.1%)	0	1 (0.1%)	0	0	0
好酸球性筋膜炎	1 (0.1%)	0	1 (0.1%)	0	0	0
仙腸骨炎	1 (0.1%)	1 (0.1%)	0	0	0	0
線維筋痛	1 (0.1%)	1 (0.1%)	0	0	0	0
全身性エリテマトーデス	1 (0.1%)	1 (0.1%)	0	0	0	0
椎間板変性症	1 (0.1%)	0	1 (0.1%)	0	0	0
閉経後骨粗鬆症	1 (0.1%)	1 (0.1%)	0	0	0	0
変形性骨炎	1 (0.1%)	0	0	1 (0.1%)	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血管障害						
- Overall -	196 (28.3%)	87 (12.6%)	84 (12.1%)	23 (3.3%)	2 (0.3%)	0
高血圧	45 (6.5%)	14 (2.0%)	19 (2.7%)	12 (1.7%)	0	0
潮紅	39 (5.6%)	26 (3.8%)	13 (1.9%)	0	0	0
低血圧	25 (3.6%)	14 (2.0%)	8 (1.2%)	3 (0.4%)	0	0
ほてり	19 (2.7%)	15 (2.2%)	4 (0.6%)	0	0	0
静脈炎	22 (3.2%)	8 (1.2%)	14 (2.0%)	0	0	0
血栓性静脈炎	14 (2.0%)	7 (1.0%)	7 (1.0%)	0	0	0
静脈障害	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
血管炎	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
血管痛	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
深部静脈血栓症	7 (1.0%)	0	4 (0.6%)	3 (0.4%)	0	0
表在性血栓性静脈炎	6 (0.9%)	1 (0.1%)	5 (0.7%)	0	0	0
血腫	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
血栓症	4 (0.6%)	0	4 (0.6%)	0	0	0
起立性低血圧	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
末梢冷感	2 (0.3%)	2 (0.3%)	0	0	0	0
高血圧クリーゼ	1 (0.1%)	0	0	0	1 (0.1%)	0
塞栓症	4 (0.6%)	0	1 (0.1%)	2 (0.3%)	1 (0.1%)	0
循環虚脱	1 (0.1%)	1 (0.1%)	0	0	0	0
鎖骨下静脈血栓症	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
静脈穿刺不良	1 (0.1%)	0	0	1 (0.1%)	0	0
表在性静脈炎	1 (0.1%)	1 (0.1%)	0	0	0	0
血圧変動	2 (0.3%)	2 (0.3%)	0	0	0	0
静脈硬化症	1 (0.1%)	1 (0.1%)	0	0	0	0
大動脈瘤	2 (0.3%)	2 (0.3%)	0	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腋窩静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
リンパ浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
頚静脈血栓症	1 (0.1%)	0	0	1 (0.1%)	0	0
血栓性静脈瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
四肢静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
充血	1 (0.1%)	1 (0.1%)	0	0	0	0
出血	1 (0.1%)	1 (0.1%)	0	0	0	0
静脈瘤	1 (0.1%)	0	1 (0.1%)	0	0	0
静脈瘤性潰瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
大動脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
動脈硬化症	1 (0.1%)	0	1 (0.1%)	0	0	0
末梢循環不良	1 (0.1%)	1 (0.1%)	0	0	0	0
末梢静脈疾患	1 (0.1%)	0	1 (0.1%)	0	0	0
末梢動脈狭窄	1 (0.1%)	0	0	1 (0.1%)	0	0
末梢動脈瘤	1 (0.1%)	0	1 (0.1%)	0	0	0
代謝および栄養障害						
- Overall -	165 (23.8%)	89 (12.9%)	46 (6.6%)	29 (4.2%)	0	1 (0.1%)
食欲減退	77 (11.1%)	61 (8.8%)	14 (2.0%)	2 (0.3%)	0	0
低カリウム血症	26 (3.8%)	17 (2.5%)	4 (0.6%)	5 (0.7%)	0	0
高尿酸血症	16 (2.3%)	13 (1.9%)	3 (0.4%)	0	0	0
高血糖	14 (2.0%)	8 (1.2%)	1 (0.1%)	5 (0.7%)	0	0
脱水	10 (1.4%)	3 (0.4%)	3 (0.4%)	4 (0.6%)	0	0
糖尿病	8 (1.2%)	3 (0.4%)	5 (0.7%)	0	0	0
低リン酸血症	7 (1.0%)	1 (0.1%)	4 (0.6%)	2 (0.3%)	0	0
高カリウム血症	5 (0.7%)	3 (0.4%)	0	2 (0.3%)	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
痛風	6 (0.9%)	1 (0.1%)	5 (0.7%)	0	0	0
低マグネシウム血症	8 (1.2%)	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0
低ナトリウム血症	3 (0.4%)	1 (0.1%)	0	2 (0.3%)	0	0
２型糖尿病	5 (0.7%)	1 (0.1%)	3 (0.4%)	1 (0.1%)	0	0
腫瘍崩壊症候群	3 (0.4%)	0	0	3 (0.4%)	0	0
高脂血症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
高カルシウム血症	4 (0.6%)	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)
低血糖	5 (0.7%)	3 (0.4%)	0	2 (0.3%)	0	0
水分過負荷	1 (0.1%)	1 (0.1%)	0	0	0	0
体液貯留	2 (0.3%)	2 (0.3%)	0	0	0	0
栄養障害	1 (0.1%)	0	1 (0.1%)	0	0	0
鉄欠乏	2 (0.3%)	2 (0.3%)	0	0	0	0
ビタミンＤ欠乏	1 (0.1%)	0	1 (0.1%)	0	0	0
高コレステロール血症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
低アルブミン血症	1 (0.1%)	0	1 (0.1%)	0	0	0
高トリグリセリド血症	1 (0.1%)	0	1 (0.1%)	0	0	0
食欲亢進	1 (0.1%)	1 (0.1%)	0	0	0	0
低カルシウム血症	1 (0.1%)	0	1 (0.1%)	0	0	0
葉酸欠乏	1 (0.1%)	0	1 (0.1%)	0	0	0
アルコール不耐性	1 (0.1%)	0	0	1 (0.1%)	0	0
パントテン酸欠乏	1 (0.1%)	1 (0.1%)	0	0	0	0
ビタミンＢ１２欠乏	1 (0.1%)	1 (0.1%)	0	0	0	0
マグネシウム欠乏	1 (0.1%)	0	1 (0.1%)	0	0	0
高ナトリウム血症	1 (0.1%)	1 (0.1%)	0	0	0	0
食欲障害	1 (0.1%)	1 (0.1%)	0	0	0	0
低尿酸血症	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
精神障害						
- Overall -	154 (22.3%)	82 (11.8%)	64 (9.2%)	6 (0.9%)	2 (0.3%)	0
不眠症	78 (11.3%)	45 (6.5%)	31 (4.5%)	2 (0.3%)	0	0
不安	27 (3.9%)	13 (1.9%)	13 (1.9%)	1 (0.1%)	0	0
うつ病	34 (4.9%)	17 (2.5%)	14 (2.0%)	2 (0.3%)	1 (0.1%)	0
抑うつ気分	8 (1.2%)	3 (0.4%)	4 (0.6%)	1 (0.1%)	0	0
睡眠障害	8 (1.2%)	6 (0.9%)	2 (0.3%)	0	0	0
落ち着きのなさ	3 (0.4%)	3 (0.4%)	0	0	0	0
気分動揺	2 (0.3%)	2 (0.3%)	0	0	0	0
激越	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
錯乱状態	4 (0.6%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0
易刺激性	2 (0.3%)	2 (0.3%)	0	0	0	0
気分変化	2 (0.3%)	2 (0.3%)	0	0	0	0
悪夢	2 (0.3%)	2 (0.3%)	0	0	0	0
譫妄	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
情動障害	1 (0.1%)	0	0	1 (0.1%)	0	0
物質誘発性精神病性障害	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0
パニック障害	1 (0.1%)	1 (0.1%)	0	0	0	0
パニック発作	1 (0.1%)	1 (0.1%)	0	0	0	0
リビドー減退	1 (0.1%)	0	1 (0.1%)	0	0	0
感情的苦悩	1 (0.1%)	1 (0.1%)	0	0	0	0
心身症	1 (0.1%)	0	1 (0.1%)	0	0	0
心的外傷後ストレス障害	1 (0.1%)	0	1 (0.1%)	0	0	0
精神障害	1 (0.1%)	0	1 (0.1%)	0	0	0
大うつ病	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
注意欠陥多動性障害	1 (0.1%)	1 (0.1%)	0	0	0	0
予期不安	1 (0.1%)	1 (0.1%)	0	0	0	0
臨床検査						
- Overall -	130 (18.8%)	70 (10.1%)	42 (6.1%)	17 (2.5%)	1 (0.1%)	0
体重減少	38 (5.5%)	15 (2.2%)	19 (2.7%)	4 (0.6%)	0	0
アラニンアミノトランスフェラーゼ増加	20 (2.9%)	14 (2.0%)	5 (0.7%)	1 (0.1%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	12 (1.7%)	10 (1.4%)	2 (0.3%)	0	0	0
血中クレアチニン増加	10 (1.4%)	8 (1.2%)	2 (0.3%)	0	0	0
血中乳酸脱水素酵素増加	8 (1.2%)	8 (1.2%)	0	0	0	0
体重増加	13 (1.9%)	12 (1.7%)	1 (0.1%)	0	0	0
Ｃ－反応性蛋白増加	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
γ－グルタミルトランスフェラーゼ増加	9 (1.3%)	5 (0.7%)	3 (0.4%)	1 (0.1%)	0	0
血中アルカリホスファターゼ増加	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
血中ビリルビン増加	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
体温上昇	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
血圧上昇	5 (0.7%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	0	0
肝機能検査異常	4 (0.6%)	0	1 (0.1%)	3 (0.4%)	0	0
血中カリウム減少	2 (0.3%)	2 (0.3%)	0	0	0	0
駆出率減少	2 (0.3%)	2 (0.3%)	0	0	0	0
血中コレステロール増加	3 (0.4%)	3 (0.4%)	0	0	0	0
トランスアミナーゼ上昇	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
ビタミンＤ減少	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
酸素飽和度低下	1 (0.1%)	0	0	1 (0.1%)	0	0
レスピロウイルス検査陽性	1 (0.1%)	0	0	1 (0.1%)	0	0
胸部コンピュータ断層撮影異常	1 (0.1%)	1 (0.1%)	0	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血中アルブミン減少	1 (0.1%)	0	1 (0.1%)	0	0	0
血中ブドウ糖増加	1 (0.1%)	0	1 (0.1%)	0	0	0
血中マグネシウム減少	1 (0.1%)	1 (0.1%)	0	0	0	0
細菌検査陽性	1 (0.1%)	0	1 (0.1%)	0	0	0
心雑音	1 (0.1%)	1 (0.1%)	0	0	0	0
心電図ＱＴ延長	1 (0.1%)	1 (0.1%)	0	0	0	0
尿中血陽性	2 (0.3%)	2 (0.3%)	0	0	0	0
尿量減少	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
免疫グロブリン減少	1 (0.1%)	1 (0.1%)	0	0	0	0
ＪＣウイルス検査陽性	1 (0.1%)	0	0	1 (0.1%)	0	0
ＲＳウイルス検査陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
ヘモフィルス検査陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
握力低下	1 (0.1%)	1 (0.1%)	0	0	0	0
肝酵素上昇	1 (0.1%)	0	0	0	1 (0.1%)	0
血圧低下	1 (0.1%)	0	1 (0.1%)	0	0	0
血中リン減少	1 (0.1%)	0	1 (0.1%)	0	0	0
血中甲状腺刺激ホルモン増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中鉄減少	1 (0.1%)	1 (0.1%)	0	0	0	0
血中免疫グロブリンＡ減少	1 (0.1%)	0	1 (0.1%)	0	0	0
血中免疫グロブリンＭ減少	1 (0.1%)	0	1 (0.1%)	0	0	0
好中球数	1 (0.1%)	0	0	1 (0.1%)	0	0
骨密度減少	1 (0.1%)	1 (0.1%)	0	0	0	0
心電図ＳＴ部分上昇	1 (0.1%)	0	1 (0.1%)	0	0	0
心電図Ｔ波逆転	1 (0.1%)	0	1 (0.1%)	0	0	0
心拍数不整	1 (0.1%)	1 (0.1%)	0	0	0	0
前立腺特異性抗原増加	1 (0.1%)	1 (0.1%)	0	0	0	0

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Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
尿中白血球陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
陽電子放出断層撮影異常	1 (0.1%)	1 (0.1%)	0	0	0	0
心臓障害						
- Overall -	67 (9.7%)	29 (4.2%)	20 (2.9%)	12 (1.7%)	4 (0.6%)	2 (0.3%)
動悸	18 (2.6%)	14 (2.0%)	3 (0.4%)	1 (0.1%)	0	0
頻脈	11 (1.6%)	7 (1.0%)	3 (0.4%)	1 (0.1%)	0	0
心房細動	10 (1.4%)	2 (0.3%)	4 (0.6%)	4 (0.6%)	0	0
狭心症	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
洞性頻脈	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
徐脈	2 (0.3%)	0	2 (0.3%)	0	0	0
心不全	3 (0.4%)	0	0	0	3 (0.4%)	0
うっ血性心不全	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
冠動脈疾患	4 (0.6%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	0	0
上室性頻脈	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
心筋虚血	1 (0.1%)	0	1 (0.1%)	0	0	0
心原性ショック	1 (0.1%)	0	0	0	1 (0.1%)	0
大動脈弁狭窄	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
冠動脈狭窄	1 (0.1%)	0	0	0	1 (0.1%)	0
心筋梗塞	1 (0.1%)	0	0	0	0	1 (0.1%)
心室性頻脈	1 (0.1%)	0	1 (0.1%)	0	0	0
心障害	2 (0.3%)	2 (0.3%)	0	0	0	0
心停止	1 (0.1%)	0	0	0	0	1 (0.1%)
うっ血性心筋症	1 (0.1%)	0	1 (0.1%)	0	0	0
冠動脈閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
期外収縮	1 (0.1%)	1 (0.1%)	0	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
左室機能不全	1 (0.1%)	0	1 (0.1%)	0	0	0
心室血栓症	1 (0.1%)	0	0	1 (0.1%)	0	0
心粗動	1 (0.1%)	1 (0.1%)	0	0	0	0
僧帽弁疾患	1 (0.1%)	1 (0.1%)	0	0	0	0
慢性心不全	1 (0.1%)	0	0	1 (0.1%)	0	0
眼障害						
- Overall -	75 (10.8%)	52 (7.5%)	20 (2.9%)	3 (0.4%)	0	0
眼乾燥	11 (1.6%)	10 (1.4%)	1 (0.1%)	0	0	0
霧視	7 (1.0%)	5 (0.7%)	1 (0.1%)	1 (0.1%)	0	0
眼痛	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
白内障	4 (0.6%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	0	0
眼そう痒症	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
流涙増加	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
眼充血	4 (0.6%)	4 (0.6%)	0	0	0	0
結膜出血	9 (1.3%)	9 (1.3%)	0	0	0	0
視力低下	2 (0.3%)	2 (0.3%)	0	0	0	0
眼刺激	2 (0.3%)	2 (0.3%)	0	0	0	0
眼脂	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
眼瞼浮腫	3 (0.4%)	3 (0.4%)	0	0	0	0
眼の異物感	1 (0.1%)	1 (0.1%)	0	0	0	0
眼部腫脹	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
眼窩周囲浮腫	3 (0.4%)	3 (0.4%)	0	0	0	0
視力障害	1 (0.1%)	1 (0.1%)	0	0	0	0
眼瞼炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
緑内障	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
羞明	1 (0.1%)	1 (0.1%)	0	0	0	0
眼瞼痙攣	1 (0.1%)	1 (0.1%)	0	0	0	0
結膜刺激	1 (0.1%)	1 (0.1%)	0	0	0	0
硝子体浮遊物	1 (0.1%)	1 (0.1%)	0	0	0	0
潰瘍性角膜炎	1 (0.1%)	0	1 (0.1%)	0	0	0
角膜症	1 (0.1%)	0	1 (0.1%)	0	0	0
眼のアレルギー	1 (0.1%)	0	1 (0.1%)	0	0	0
眼の障害	1 (0.1%)	1 (0.1%)	0	0	0	0
眼内血腫	1 (0.1%)	1 (0.1%)	0	0	0	0
結膜充血	1 (0.1%)	1 (0.1%)	0	0	0	0
散瞳	1 (0.1%)	0	1 (0.1%)	0	0	0
硝子体出血	1 (0.1%)	0	1 (0.1%)	0	0	0
糖尿病網膜症	1 (0.1%)	1 (0.1%)	0	0	0	0
虹彩炎	1 (0.1%)	0	1 (0.1%)	0	0	0
嚢胞様黄斑浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
複視	1 (0.1%)	1 (0.1%)	0	0	0	0
網膜剥離	1 (0.1%)	0	1 (0.1%)	0	0	0
網膜浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
網膜裂孔	1 (0.1%)	0	1 (0.1%)	0	0	0
霰粒腫	1 (0.1%)	1 (0.1%)	0	0	0	0
腎および尿路障害						
- Overall -	72 (10.4%)	44 (6.4%)	19 (2.7%)	9 (1.3%)	0	0
頻尿	11 (1.6%)	9 (1.3%)	2 (0.3%)	0	0	0
排尿困難	16 (2.3%)	12 (1.7%)	4 (0.6%)	0	0	0
尿失禁	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
夜間頻尿	3 (0.4%)	3 (0.4%)	0	0	0	0
血尿	5 (0.7%)	5 (0.7%)	0	0	0	0
腎不全	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
尿閉	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
急性腎不全	1 (0.1%)	0	1 (0.1%)	0	0	0
腎結石症	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
水腎症	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
尿意切迫	1 (0.1%)	1 (0.1%)	0	0	0	0
腎機能障害	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
腎仙痛	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
多尿	1 (0.1%)	0	1 (0.1%)	0	0	0
尿管結石	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
尿臭異常	1 (0.1%)	1 (0.1%)	0	0	0	0
緊張性膀胱	1 (0.1%)	0	1 (0.1%)	0	0	0
失禁	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
出血性膀胱炎	1 (0.1%)	0	1 (0.1%)	0	0	0
腎臓痛	2 (0.3%)	2 (0.3%)	0	0	0	0
尿管閉塞	1 (0.1%)	0	0	1 (0.1%)	0	0
尿路痛	1 (0.1%)	1 (0.1%)	0	0	0	0
尿路閉塞	1 (0.1%)	0	0	1 (0.1%)	0	0
非感染性膀胱炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
腹圧性尿失禁	1 (0.1%)	0	0	1 (0.1%)	0	0
慢性腎臓病	1 (0.1%)	0	1 (0.1%)	0	0	0
下部尿路症状	1 (0.1%)	0	0	1 (0.1%)	0	0
急性腎前性腎不全	1 (0.1%)	1 (0.1%)	0	0	0	0
腎梗塞	1 (0.1%)	0	0	1 (0.1%)	0	0

Investigator text for AEs encoded using MedDRA version 18.1.
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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腎損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
糖尿	1 (0.1%)	1 (0.1%)	0	0	0	0
排尿躊躇	1 (0.1%)	1 (0.1%)	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）						
- Overall -	60 (8.7%)	17 (2.5%)	18 (2.6%)	16 (2.3%)	2 (0.3%)	7 (1.0%)
基底細胞癌	11 (1.6%)	2 (0.3%)	7 (1.0%)	2 (0.3%)	0	0
扁平上皮癌	7 (1.0%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0
脂漏性角化症	2 (0.3%)	2 (0.3%)	0	0	0	0
メラノサイト性母斑	3 (0.4%)	3 (0.4%)	0	0	0	0
前立腺癌	3 (0.4%)	0	0	2 (0.3%)	1 (0.1%)	0
脂肪腫	2 (0.3%)	2 (0.3%)	0	0	0	0
皮膚乳頭腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
腫瘍フレア	1 (0.1%)	0	0	1 (0.1%)	0	0
ボーエン病	3 (0.4%)	0	3 (0.4%)	0	0	0
悪性黒色腫	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
結腸癌	2 (0.3%)	1 (0.1%)	0	0	0	1 (0.1%)
大腸腺腫	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚有棘細胞癌	1 (0.1%)	0	0	1 (0.1%)	0	0
ケラトアカントーマ	1 (0.1%)	0	0	1 (0.1%)	0	0
腫瘍疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
新生物	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
浸潤性乳管癌	1 (0.1%)	0	0	1 (0.1%)	0	0
腎癌	1 (0.1%)	0	1 (0.1%)	0	0	0
直腸腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
肛門性器疣贅	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
胃癌	1 (0.1%)	0	0	0	0	1 (0.1%)
下垂体の良性腫瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
外陰膣部疣贅	1 (0.1%)	0	0	1 (0.1%)	0	0
眼球内黒色腫	1 (0.1%)	0	0	1 (0.1%)	0	0
結腸直腸癌	1 (0.1%)	0	0	1 (0.1%)	0	0
脂肪線維腫	1 (0.1%)	1 (0.1%)	0	0	0	0
腎細胞癌	1 (0.1%)	0	0	1 (0.1%)	0	0
線維腫	1 (0.1%)	1 (0.1%)	0	0	0	0
腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
乳管内増殖性病変	1 (0.1%)	0	0	1 (0.1%)	0	0
肺の悪性新生物	1 (0.1%)	0	0	0	0	1 (0.1%)
肺腺癌	1 (0.1%)	0	0	0	0	1 (0.1%)
皮膚の新生物	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚神経内分泌癌	1 (0.1%)	0	0	0	0	1 (0.1%)
良性髄膜腫	1 (0.1%)	1 (0.1%)	0	0	0	0
良性腺腫	1 (0.1%)	0	0	1 (0.1%)	0	0
扁桃新生物	1 (0.1%)	1 (0.1%)	0	0	0	0
膵腺管癌	1 (0.1%)	0	0	0	0	1 (0.1%)
耳および迷路障害						
- Overall -	65 (9.4%)	32 (4.6%)	30 (4.3%)	3 (0.4%)	0	0
回転性めまい	21 (3.0%)	16 (2.3%)	5 (0.7%)	0	0	0
耳痛	14 (2.0%)	6 (0.9%)	7 (1.0%)	1 (0.1%)	0	0
耳鳴	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
耳そう痒症	9 (1.3%)	2 (0.3%)	7 (1.0%)	0	0	0
耳不快感	6 (0.9%)	2 (0.3%)	4 (0.6%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
聴力低下	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
難聴	1 (0.1%)	0	1 (0.1%)	0	0	0
聴覚障害	2 (0.3%)	0	2 (0.3%)	0	0	0
頭位性回転性めまい	2 (0.3%)	2 (0.3%)	0	0	0	0
耳閉	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
耳の障害	1 (0.1%)	1 (0.1%)	0	0	0	0
中耳の炎症	2 (0.3%)	0	2 (0.3%)	0	0	0
外耳の炎症	1 (0.1%)	0	0	1 (0.1%)	0	0
乗物酔い	1 (0.1%)	0	1 (0.1%)	0	0	0
中耳滲出液	1 (0.1%)	1 (0.1%)	0	0	0	0
突発性難聴	1 (0.1%)	0	0	1 (0.1%)	0	0
生殖系および乳房障害						
- Overall -	56 (8.1%)	30 (4.3%)	19 (2.7%)	7 (1.0%)	0	0
骨盤痛	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
無月経	3 (0.4%)	3 (0.4%)	0	0	0	0
膣分泌物	1 (0.1%)	1 (0.1%)	0	0	0	0
勃起不全	5 (0.7%)	2 (0.3%)	2 (0.3%)	1 (0.1%)	0	0
外陰膣乾燥	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
女性化乳房	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
乳房痛	2 (0.3%)	2 (0.3%)	0	0	0	0
不規則月経	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
閉経期症状	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
良性前立腺肥大症	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
月経過多	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
外陰膣痛	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
月経困難症	1 (0.1%)	1 (0.1%)	0	0	0	0
前立腺炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
外陰腟そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
性器発疹	1 (0.1%)	1 (0.1%)	0	0	0	0
不正子宮出血	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
陰嚢紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
陰嚢腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
陰部そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
子宮脱	1 (0.1%)	0	0	1 (0.1%)	0	0
子宮痛	1 (0.1%)	0	1 (0.1%)	0	0	0
性器水疱	1 (0.1%)	0	0	1 (0.1%)	0	0
精液瘤	1 (0.1%)	0	1 (0.1%)	0	0	0
精索静脈瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
精巣腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
精巣痛	1 (0.1%)	1 (0.1%)	0	0	0	0
前立腺石灰化	1 (0.1%)	1 (0.1%)	0	0	0	0
多嚢胞性卵巣	1 (0.1%)	1 (0.1%)	0	0	0	0
乳頭障害	1 (0.1%)	1 (0.1%)	0	0	0	0
乳房うっ滞	1 (0.1%)	1 (0.1%)	0	0	0	0
乳房萎縮	1 (0.1%)	1 (0.1%)	0	0	0	0
乳房炎症	1 (0.1%)	1 (0.1%)	0	0	0	0
乳房腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
閉経期障害	1 (0.1%)	1 (0.1%)	0	0	0	0
遊走精巣	1 (0.1%)	1 (0.1%)	0	0	0	0
腟脱	1 (0.1%)	0	1 (0.1%)	0	0	0
腟潰瘍	1 (0.1%)	0	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
免疫系障害						
- Overall -	48 (6.9%)	18 (2.6%)	20 (2.9%)	8 (1.2%)	2 (0.3%)	0
過敏症	14 (2.0%)	5 (0.7%)	6 (0.9%)	2 (0.3%)	1 (0.1%)	0
季節性アレルギー	15 (2.2%)	8 (1.2%)	7 (1.0%)	0	0	0
低γグロブリン血症	9 (1.3%)	1 (0.1%)	6 (0.9%)	2 (0.3%)	0	0
薬物過敏症	7 (1.0%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0
造影剤アレルギー	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
アナフィラキシー反応	1 (0.1%)	0	0	1 (0.1%)	0	0
香料過敏症	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫不全症	1 (0.1%)	0	0	1 (0.1%)	0	0
肝胆道系障害						
- Overall -	27 (3.9%)	7 (1.0%)	8 (1.2%)	11 (1.6%)	1 (0.1%)	0
胆嚢炎	8 (1.2%)	1 (0.1%)	2 (0.3%)	4 (0.6%)	1 (0.1%)	0
胆石症	7 (1.0%)	4 (0.6%)	0	3 (0.4%)	0	0
肝機能異常	5 (0.7%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	0	0
高ビリルビン血症	2 (0.3%)	0	2 (0.3%)	0	0	0
脂肪肝	2 (0.3%)	2 (0.3%)	0	0	0	0
胆道仙痛	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
肝障害	1 (0.1%)	0	1 (0.1%)	0	0	0
黄疸	1 (0.1%)	0	1 (0.1%)	0	0	0
肝腫大	1 (0.1%)	1 (0.1%)	0	0	0	0
肝損傷	1 (0.1%)	0	0	1 (0.1%)	0	0
急性胆嚢炎	1 (0.1%)	0	0	1 (0.1%)	0	0
胆管炎	1 (0.1%)	0	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
胆管狭窄	1 (0.1%)	0	0	1 (0.1%)	0	0
胆汁うっ滞性黄疸	1 (0.1%)	0	0	1 (0.1%)	0	0
門脈圧亢進症	1 (0.1%)	0	1 (0.1%)	0	0	0
内分泌障害						
- Overall -	11 (1.6%)	4 (0.6%)	7 (1.0%)	0	0	0
ステロイド離脱症候群	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
甲状腺機能低下症	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
甲状腺機能亢進症	3 (0.4%)	0	3 (0.4%)	0	0	0
甲状腺腫	2 (0.3%)	2 (0.3%)	0	0	0	0
甲状腺嚢腫	1 (0.1%)	0	1 (0.1%)	0	0	0
外科および内科処置						
- Overall -	14 (2.0%)	6 (0.9%)	4 (0.6%)	4 (0.6%)	0	0
抜歯	4 (0.6%)	4 (0.6%)	0	0	0	0
癌手術	1 (0.1%)	0	0	1 (0.1%)	0	0
白内障手術	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚新生物切除	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
リハビリテーション療法	1 (0.1%)	0	1 (0.1%)	0	0	0
リンパ節切除	1 (0.1%)	1 (0.1%)	0	0	0	0
回腸切除	1 (0.1%)	0	0	1 (0.1%)	0	0
歯修復	1 (0.1%)	1 (0.1%)	0	0	0	0
歯内療法	1 (0.1%)	0	1 (0.1%)	0	0	0
脳室腹腔短絡	1 (0.1%)	0	0	1 (0.1%)	0	0

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To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
先天性、家族性および遺伝性障害						
- Overall -	5 (0.7%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0	0
家族性振戦	1 (0.1%)	1 (0.1%)	0	0	0	0
脊椎奇形	1 (0.1%)	1 (0.1%)	0	0	0	0
表皮融解	1 (0.1%)	1 (0.1%)	0	0	0	0
毛包性角化症	1 (0.1%)	0	1 (0.1%)	0	0	0
腓骨部筋萎縮症	1 (0.1%)	0	0	1 (0.1%)	0	0
社会環境						
- Overall -	1 (0.1%)	1 (0.1%)	0	0	0	0
元タバコ使用者	1 (0.1%)	1 (0.1%)	0	0	0	0
妊娠、産褥および周産期の状態						
- Overall -	1 (0.1%)	0	0	1 (0.1%)	0	0
妊娠糖尿病	1 (0.1%)	0	0	1 (0.1%)	0	0

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To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	695 (99.6%)	17 (2.4%)	150 (21.5%)	253 (36.2%)	239 (34.2%)	36 (5.2%)
胃腸障害						
- Overall -	554 (79.4%)	240 (34.4%)	256 (36.7%)	52 (7.4%)	4 (0.6%)	2 (0.3%)
悪心	330 (47.3%)	206 (29.5%)	115 (16.5%)	8 (1.1%)	1 (0.1%)	0
便秘	240 (34.4%)	173 (24.8%)	64 (9.2%)	3 (0.4%)	0	0
下痢	190 (27.2%)	116 (16.6%)	61 (8.7%)	13 (1.9%)	0	0
嘔吐	164 (23.5%)	97 (13.9%)	59 (8.5%)	8 (1.1%)	0	0
腹痛	71 (10.2%)	45 (6.4%)	18 (2.6%)	8 (1.1%)	0	0
口内炎	54 (7.7%)	36 (5.2%)	16 (2.3%)	1 (0.1%)	1 (0.1%)	0
消化不良	59 (8.5%)	36 (5.2%)	23 (3.3%)	0	0	0
上腹部痛	52 (7.4%)	35 (5.0%)	16 (2.3%)	1 (0.1%)	0	0
胃食道逆流性疾患	28 (4.0%)	15 (2.1%)	13 (1.9%)	0	0	0
口内乾燥	28 (4.0%)	26 (3.7%)	2 (0.3%)	0	0	0
口腔内潰瘍形成	14 (2.0%)	7 (1.0%)	4 (0.6%)	3 (0.4%)	0	0
腹部膨満	21 (3.0%)	16 (2.3%)	4 (0.6%)	1 (0.1%)	0	0
腹部不快感	19 (2.7%)	15 (2.1%)	4 (0.6%)	0	0	0
口腔内痛	18 (2.6%)	14 (2.0%)	4 (0.6%)	0	0	0
歯痛	15 (2.1%)	6 (0.9%)	9 (1.3%)	0	0	0
胃炎	11 (1.6%)	4 (0.6%)	7 (1.0%)	0	0	0
痔核	15 (2.1%)	11 (1.6%)	3 (0.4%)	1 (0.1%)	0	0
放屁	11 (1.6%)	9 (1.3%)	2 (0.3%)	0	0	0
下腹部痛	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
歯肉痛	9 (1.3%)	5 (0.7%)	4 (0.6%)	0	0	0
大腸炎	9 (1.3%)	3 (0.4%)	4 (0.6%)	2 (0.3%)	0	0
齲歯	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
嚥下障害	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
口の錯感覚	6 (0.9%)	6 (0.9%)	0	0	0	0
アフタ性潰瘍	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
直腸出血	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
消化器痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
心窩部不快感	4 (0.6%)	4 (0.6%)	0	0	0	0
便失禁	2 (0.3%)	2 (0.3%)	0	0	0	0
膵炎	5 (0.7%)	0	1 (0.1%)	4 (0.6%)	0	0
血便排泄	5 (0.7%)	5 (0.7%)	0	0	0	0
食道炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
大腸ポリープ	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
腸閉塞	4 (0.6%)	1 (0.1%)	0	2 (0.3%)	1 (0.1%)	0
腹水	2 (0.3%)	0	2 (0.3%)	0	0	0
嚥下痛	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
口腔そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
痔出血	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
舌潰瘍	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
裂孔ヘルニア	1 (0.1%)	1 (0.1%)	0	0	0	0
裂肛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
鼡径ヘルニア	2 (0.3%)	0	2 (0.3%)	0	0	0
クローン病	2 (0.3%)	0	0	2 (0.3%)	0	0
メレナ	1 (0.1%)	0	0	1 (0.1%)	0	0
過敏性腸症候群	2 (0.3%)	0	2 (0.3%)	0	0	0
憩室	2 (0.3%)	2 (0.3%)	0	0	0	0
口腔粘膜水疱形成	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇炎	3 (0.4%)	3 (0.4%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
口唇潰瘍	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
小腸閉塞	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
舌苔	1 (0.1%)	1 (0.1%)	0	0	0	0
舌痛	2 (0.3%)	2 (0.3%)	0	0	0	0
流涎過多	3 (0.4%)	3 (0.4%)	0	0	0	0
肛門周囲痛	2 (0.3%)	0	2 (0.3%)	0	0	0
びらん性胃炎	1 (0.1%)	1 (0.1%)	0	0	0	0
イレウス	2 (0.3%)	0	2 (0.3%)	0	0	0
胃腸出血	2 (0.3%)	2 (0.3%)	0	0	0	0
胃潰瘍	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
急性膵炎	1 (0.1%)	0	0	1 (0.1%)	0	0
口の感覚鈍麻	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔知覚不全	2 (0.3%)	2 (0.3%)	0	0	0	0
口腔粘膜紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
歯の知覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
歯周病	1 (0.1%)	1 (0.1%)	0	0	0	0
歯肉出血	1 (0.1%)	1 (0.1%)	0	0	0	0
食道痛	1 (0.1%)	1 (0.1%)	0	0	0	0
舌炎	1 (0.1%)	1 (0.1%)	0	0	0	0
腸炎	2 (0.3%)	0	2 (0.3%)	0	0	0
腸管拡張症	1 (0.1%)	1 (0.1%)	0	0	0	0
腸膀胱瘻	1 (0.1%)	0	0	0	1 (0.1%)	0
非感染性歯肉炎	1 (0.1%)	1 (0.1%)	0	0	0	0
糞塊	1 (0.1%)	0	0	1 (0.1%)	0	0
肛門出血	2 (0.3%)	2 (0.3%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肛門潰瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
臍ヘルニア	2 (0.3%)	2 (0.3%)	0	0	0	0
胃出血	1 (0.1%)	0	0	0	0	1 (0.1%)
胃障害	1 (0.1%)	1 (0.1%)	0	0	0	0
下部消化管出血	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔粘膜疹	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔瘻	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇乾燥	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇水疱	1 (0.1%)	1 (0.1%)	0	0	0	0
歯の脱落	1 (0.1%)	0	1 (0.1%)	0	0	0
歯周の炎症	1 (0.1%)	0	1 (0.1%)	0	0	0
歯肉腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
十二指腸胃逆流	1 (0.1%)	0	1 (0.1%)	0	0	0
上部消化管出血	1 (0.1%)	0	0	0	0	1 (0.1%)
食中毒	1 (0.1%)	1 (0.1%)	0	0	0	0
舌腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
舌障害	1 (0.1%)	1 (0.1%)	0	0	0	0
唾液腺結石	1 (0.1%)	0	1 (0.1%)	0	0	0
唾液腺痛	1 (0.1%)	0	1 (0.1%)	0	0	0
弛緩歯	1 (0.1%)	1 (0.1%)	0	0	0	0
腸管ポリープ	1 (0.1%)	0	1 (0.1%)	0	0	0
腸管虚血	1 (0.1%)	0	0	1 (0.1%)	0	0
腸出血	1 (0.1%)	1 (0.1%)	0	0	0	0
直腸しぶり	1 (0.1%)	1 (0.1%)	0	0	0	0
吐血	1 (0.1%)	0	0	1 (0.1%)	0	0
粘液便	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
排便痛	1 (0.1%)	1 (0.1%)	0	0	0	0
反応性胃障害	1 (0.1%)	0	1 (0.1%)	0	0	0
腹腔内血腫	1 (0.1%)	1 (0.1%)	0	0	0	0
腹部ヘルニア	1 (0.1%)	0	0	1 (0.1%)	0	0
慢性胃炎	1 (0.1%)	1 (0.1%)	0	0	0	0
肛門そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
肛門直腸不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
膵嚢胞	1 (0.1%)	1 (0.1%)	0	0	0	0
感染症および寄生虫症						
- Overall -	545 (78.1%)	89 (12.8%)	304 (43.6%)	122 (17.5%)	14 (2.0%)	16 (2.3%)
上気道感染	129 (18.5%)	43 (6.2%)	80 (11.5%)	6 (0.9%)	0	0
鼻咽頭炎	117 (16.8%)	71 (10.2%)	45 (6.4%)	1 (0.1%)	0	0
尿路感染	74 (10.6%)	12 (1.7%)	49 (7.0%)	13 (1.9%)	0	0
下気道感染	60 (8.6%)	10 (1.4%)	35 (5.0%)	13 (1.9%)	0	2 (0.3%)
帯状疱疹	71 (10.2%)	8 (1.1%)	55 (7.9%)	8 (1.1%)	0	0
肺炎	69 (9.9%)	2 (0.3%)	28 (4.0%)	34 (4.9%)	0	5 (0.7%)
副鼻腔炎	68 (9.7%)	16 (2.3%)	50 (7.2%)	2 (0.3%)	0	0
気管支炎	48 (6.9%)	5 (0.7%)	35 (5.0%)	7 (1.0%)	1 (0.1%)	0
鼻炎	47 (6.7%)	27 (3.9%)	19 (2.7%)	1 (0.1%)	0	0
口腔ヘルペス	40 (5.7%)	21 (3.0%)	17 (2.4%)	2 (0.3%)	0	0
気道感染	38 (5.4%)	7 (1.0%)	24 (3.4%)	6 (0.9%)	0	1 (0.1%)
結膜炎	31 (4.4%)	10 (1.4%)	21 (3.0%)	0	0	0
インフルエンザ	30 (4.3%)	16 (2.3%)	12 (1.7%)	2 (0.3%)	0	0
感染	24 (3.4%)	6 (0.9%)	11 (1.6%)	7 (1.0%)	0	0
咽頭炎	29 (4.2%)	9 (1.3%)	20 (2.9%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
口腔カンジダ症	22 (3.2%)	10 (1.4%)	12 (1.7%)	0	0	0
膀胱炎	20 (2.9%)	7 (1.0%)	12 (1.7%)	1 (0.1%)	0	0
胃腸炎	15 (2.1%)	8 (1.1%)	1 (0.1%)	6 (0.9%)	0	0
肺感染	15 (2.1%)	1 (0.1%)	4 (0.6%)	7 (1.0%)	1 (0.1%)	2 (0.3%)
耳感染	15 (2.1%)	2 (0.3%)	13 (1.9%)	0	0	0
敗血症	14 (2.0%)	0	1 (0.1%)	5 (0.7%)	6 (0.9%)	2 (0.3%)
蜂巣炎	15 (2.1%)	1 (0.1%)	11 (1.6%)	2 (0.3%)	1 (0.1%)	0
毛包炎	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
ウイルス感染	9 (1.3%)	4 (0.6%)	4 (0.6%)	1 (0.1%)	0	0
歯肉炎	8 (1.1%)	1 (0.1%)	7 (1.0%)	0	0	0
中耳炎	10 (1.4%)	1 (0.1%)	9 (1.3%)	0	0	0
慢性副鼻腔炎	13 (1.9%)	3 (0.4%)	7 (1.0%)	3 (0.4%)	0	0
外陰部腟カンジダ症	10 (1.4%)	5 (0.7%)	5 (0.7%)	0	0	0
歯感染	9 (1.3%)	0	6 (0.9%)	3 (0.4%)	0	0
麦粒腫	10 (1.4%)	7 (1.0%)	3 (0.4%)	0	0	0
単純ヘルペス	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
腟感染	7 (1.0%)	1 (0.1%)	6 (0.9%)	0	0	0
眼感染	10 (1.4%)	4 (0.6%)	6 (0.9%)	0	0	0
口唇感染	7 (1.0%)	3 (0.4%)	4 (0.6%)	0	0	0
好中球減少性敗血症	5 (0.7%)	0	0	2 (0.3%)	3 (0.4%)	0
歯周炎	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
歯膿瘍	7 (1.0%)	1 (0.1%)	6 (0.9%)	0	0	0
皮膚真菌感染	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
せつ	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
尿路性敗血症	5 (0.7%)	0	1 (0.1%)	4 (0.6%)	0	0
皮膚感染	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
医療機器関連感染	4 (0.6%)	0	2 (0.3%)	2 (0.3%)	0	0
憩室炎	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
消化管感染	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
真菌感染	2 (0.3%)	0	2 (0.3%)	0	0	0
限局性感染	4 (0.6%)	0	4 (0.6%)	0	0	0
喉頭炎	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
Ｂ型肝炎	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
ウイルス性胃腸炎	3 (0.4%)	3 (0.4%)	0	0	0	0
ウイルス性上気道感染	1 (0.1%)	1 (0.1%)	0	0	0	0
異型肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
扁桃炎	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
カンジダ感染	3 (0.4%)	0	3 (0.4%)	0	0	0
感染性腸炎	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
急性副鼻腔炎	3 (0.4%)	0	3 (0.4%)	0	0	0
虫垂炎	1 (0.1%)	0	0	1 (0.1%)	0	0
爪真菌症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
熱性感染症	1 (0.1%)	0	1 (0.1%)	0	0	0
皮下組織膿瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
サイトメガロウイルス感染	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
ヘルペスウイルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
感染による慢性閉塞性気道疾患の増悪	4 (0.6%)	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
粘膜感染	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
白癬感染	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
ブドウ球菌感染	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
ヘモフィルス感染	2 (0.3%)	2 (0.3%)	0	0	0	0
外陰部炎	1 (0.1%)	1 (0.1%)	0	0	0	0

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Protocol(s): BO21223 (K21223L)
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外陰腟真菌感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
外耳炎	2 (0.3%)	0	2 (0.3%)	0	0	0
感染性関節炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
感染性嚢腫	3 (0.4%)	0	3 (0.4%)	0	0	0
菌血症	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
口角口唇炎	2 (0.3%)	2 (0.3%)	0	0	0	0
口腔真菌感染	2 (0.3%)	0	2 (0.3%)	0	0	0
細菌性腟症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
爪感染	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
尿道炎	2 (0.3%)	0	2 (0.3%)	0	0	0
咬傷感染	2 (0.3%)	0	2 (0.3%)	0	0	0
癜風	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
アデノイド咽頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス血症	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性筋炎	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
ウイルス性鼻炎	2 (0.3%)	2 (0.3%)	0	0	0	0
カテーテル留置部位感染	1 (0.1%)	0	1 (0.1%)	0	0	0
クロストリジウム・ディフィシレ大腸炎	2 (0.3%)	0	1 (0.1%)	0	0	1 (0.1%)
ニューモシスチス・イロベチイ肺炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
ヘリコバクター感染	1 (0.1%)	0	1 (0.1%)	0	0	0
気管気管支炎	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
好中球減少性感染	1 (0.1%)	0	0	1 (0.1%)	0	0
細気管支炎	2 (0.3%)	0	2 (0.3%)	0	0	0
細菌性肺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
歯肉膿瘍	2 (0.3%)	0	2 (0.3%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
処置後感染	1 (0.1%)	0	1 (0.1%)	0	0	0
食道カンジダ症	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
食道感染	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
水痘帯状疱疹ウイルス感染	2 (0.3%)	0	2 (0.3%)	0	0	0
足部白癬	1 (0.1%)	1 (0.1%)	0	0	0	0
大腸菌性尿路感染	1 (0.1%)	0	0	1 (0.1%)	0	0
播種性帯状疱疹	2 (0.3%)	0	0	2 (0.3%)	0	0
皮膚カンジダ	1 (0.1%)	0	1 (0.1%)	0	0	0
副鼻腔気管支炎	2 (0.3%)	0	2 (0.3%)	0	0	0
扁桃周囲膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
鼻径部感染	2 (0.3%)	0	2 (0.3%)	0	0	0
ＢＫウイルス感染	1 (0.1%)	0	0	1 (0.1%)	0	0
アスペルギルス感染	1 (0.1%)	0	0	1 (0.1%)	0	0
ウイルス性咽頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性気管支炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性消化管感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性迷路炎	1 (0.1%)	1 (0.1%)	0	0	0	0
エンテロウイルス性髄膜炎	1 (0.1%)	0	0	1 (0.1%)	0	0
エンテロウイルス性脳炎	1 (0.1%)	0	0	0	1 (0.1%)	0
カテーテル留置部位蜂巣炎	1 (0.1%)	0	0	1 (0.1%)	0	0
カンピロバクター感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ブドウ球菌性菌血症	1 (0.1%)	0	0	0	0	1 (0.1%)
ブドウ球菌皮膚感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ヘモフィルス性肺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ヘルペス性皮膚炎	1 (0.1%)	1 (0.1%)	0	0	0	0
ライノウイルス感染	1 (0.1%)	0	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
医療機器関連敗血症	1 (0.1%)	0	0	1 (0.1%)	0	0
咽頭膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
会陰膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
外耳蜂巣炎	1 (0.1%)	0	1 (0.1%)	0	0	0
感染性下痢	1 (0.1%)	0	0	1 (0.1%)	0	0
感染性小腸結腸炎	1 (0.1%)	0	1 (0.1%)	0	0	0
感染性舌炎	1 (0.1%)	1 (0.1%)	0	0	0	0
感染性瘻孔	1 (0.1%)	0	1 (0.1%)	0	0	0
汗腺膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
眼帯状疱疹	1 (0.1%)	0	1 (0.1%)	0	0	0
眼内炎	1 (0.1%)	0	0	1 (0.1%)	0	0
眼膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
眼部単純ヘルペス	1 (0.1%)	0	1 (0.1%)	0	0	0
結核	1 (0.1%)	0	0	1 (0.1%)	0	0
股部白癬	1 (0.1%)	1 (0.1%)	0	0	0	0
喉頭蓋炎	1 (0.1%)	0	0	1 (0.1%)	0	0
骨盤膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌性気管炎	1 (0.1%)	0	0	0	1 (0.1%)	0
細菌性上気道感染	1 (0.1%)	1 (0.1%)	0	0	0	0
細菌性副鼻腔炎	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌性扁桃炎	1 (0.1%)	0	1 (0.1%)	0	0	0
歯髄炎	1 (0.1%)	0	1 (0.1%)	0	0	0
耳帯状疱疹	1 (0.1%)	0	0	1 (0.1%)	0	0
術後創感染	1 (0.1%)	0	1 (0.1%)	0	0	0
真菌性耳感染	1 (0.1%)	1 (0.1%)	0	0	0	0
真菌性性器感染	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
真菌性肺炎	1 (0.1%)	0	0	0	0	1 (0.1%)
真菌性副鼻腔炎	1 (0.1%)	0	0	1 (0.1%)	0	0
腎盂腎炎	1 (0.1%)	0	0	1 (0.1%)	0	0
水痘	1 (0.1%)	0	1 (0.1%)	0	0	0
性器カンジダ症	1 (0.1%)	0	1 (0.1%)	0	0	0
性器感染	1 (0.1%)	1 (0.1%)	0	0	0	0
前立腺感染	1 (0.1%)	1 (0.1%)	0	0	0	0
体部白癬	1 (0.1%)	1 (0.1%)	0	0	0	0
大腸菌感染	1 (0.1%)	0	0	1 (0.1%)	0	0
大腸菌性胃腸炎	1 (0.1%)	0	1 (0.1%)	0	0	0
単純ヘルペス性咽頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
注入部位感染	1 (0.1%)	1 (0.1%)	0	0	0	0
腸管膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
腸球菌感染	1 (0.1%)	1 (0.1%)	0	0	0	0
爪の皮膚糸状菌症	1 (0.1%)	1 (0.1%)	0	0	0	0
軟部組織感染	1 (0.1%)	0	1 (0.1%)	0	0	0
乳房膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
膿性痰	1 (0.1%)	1 (0.1%)	0	0	0	0
膿疱性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
肺真菌症	1 (0.1%)	0	1 (0.1%)	0	0	0
肺敗血症	1 (0.1%)	0	0	0	1 (0.1%)	0
百日咳	1 (0.1%)	0	1 (0.1%)	0	0	0
腹部膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
末梢神経感染	1 (0.1%)	0	1 (0.1%)	0	0	0
卵管卵巣膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
卵巣炎	1 (0.1%)	0	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
涙嚢炎	1 (0.1%)	0	1 (0.1%)	0	0	0
臍炎	1 (0.1%)	1 (0.1%)	0	0	0	0
肛径部膿瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	527 (75.5%)	263 (37.7%)	211 (30.2%)	47 (6.7%)	3 (0.4%)	3 (0.4%)
疲労	259 (37.1%)	176 (25.2%)	75 (10.7%)	8 (1.1%)	0	0
発熱	209 (29.9%)	119 (17.0%)	72 (10.3%)	16 (2.3%)	2 (0.3%)	0
悪寒	124 (17.8%)	66 (9.5%)	53 (7.6%)	5 (0.7%)	0	0
胸部不快感	43 (6.2%)	24 (3.4%)	17 (2.4%)	2 (0.3%)	0	0
末梢性浮腫	39 (5.6%)	28 (4.0%)	9 (1.3%)	2 (0.3%)	0	0
粘膜の炎症	31 (4.4%)	22 (3.2%)	7 (1.0%)	2 (0.3%)	0	0
無力症	32 (4.6%)	18 (2.6%)	14 (2.0%)	0	0	0
インフルエンザ様疾患	30 (4.3%)	24 (3.4%)	6 (0.9%)	0	0	0
胸痛	28 (4.0%)	19 (2.7%)	5 (0.7%)	4 (0.6%)	0	0
疼痛	23 (3.3%)	18 (2.6%)	5 (0.7%)	0	0	0
倦怠感	27 (3.9%)	21 (3.0%)	6 (0.9%)	0	0	0
末梢腫脹	17 (2.4%)	15 (2.1%)	2 (0.3%)	0	0	0
熱感	14 (2.0%)	5 (0.7%)	7 (1.0%)	2 (0.3%)	0	0
浮腫	15 (2.1%)	12 (1.7%)	3 (0.4%)	0	0	0
注入部位血管外漏出	10 (1.4%)	4 (0.6%)	6 (0.9%)	0	0	0
非心臓性胸痛	10 (1.4%)	5 (0.7%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0
注射部位疼痛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
顔面浮腫	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
カテーテル留置部位疼痛	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
注射部位反応	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
冷感	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
腋窩痛	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
全身健康状態低下	6 (0.9%)	1 (0.1%)	2 (0.3%)	2 (0.3%)	0	1 (0.1%)
溢出	8 (1.1%)	5 (0.7%)	3 (0.4%)	0	0	0
注入部位疼痛	6 (0.9%)	6 (0.9%)	0	0	0	0
局所腫脹	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
異物感	4 (0.6%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0	0
顔面痛	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
粘膜乾燥	5 (0.7%)	5 (0.7%)	0	0	0	0
嚢胞	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
医療機器閉塞	1 (0.1%)	1 (0.1%)	0	0	0	0
不快感	3 (0.4%)	3 (0.4%)	0	0	0	0
歩行障害	1 (0.1%)	1 (0.1%)	0	0	0	0
異常感	2 (0.3%)	2 (0.3%)	0	0	0	0
医薬品副作用	1 (0.1%)	0	0	1 (0.1%)	0	0
苦悶感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
死亡	1 (0.1%)	0	0	0	0	1 (0.1%)
カテーテル留置部位紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
カテーテル留置部位腫脹	2 (0.3%)	2 (0.3%)	0	0	0	0
カテーテル留置部位分泌物	2 (0.3%)	2 (0.3%)	0	0	0	0
ポリープ	1 (0.1%)	0	0	1 (0.1%)	0	0
医療機器破損	1 (0.1%)	0	0	1 (0.1%)	0	0
温度変化不耐症	1 (0.1%)	1 (0.1%)	0	0	0	0
限局性浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
口渇	2 (0.3%)	2 (0.3%)	0	0	0	0
高熱	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
腫瘤	2 (0.3%)	2 (0.3%)	0	0	0	0
早期満腹	2 (0.3%)	2 (0.3%)	0	0	0	0
恥骨上痛	1 (0.1%)	0	1 (0.1%)	0	0	0
不明確な障害	1 (0.1%)	0	0	0	0	1 (0.1%)
カテーテル留置部位そう痒感	1 (0.1%)	1 (0.1%)	0	0	0	0
カテーテル留置部位静脈炎	1 (0.1%)	1 (0.1%)	0	0	0	0
カテーテル留置部位発疹	1 (0.1%)	1 (0.1%)	0	0	0	0
ヘルニア痛	1 (0.1%)	0	1 (0.1%)	0	0	0
異形成	1 (0.1%)	1 (0.1%)	0	0	0	0
医療機器による疼痛	1 (0.1%)	0	1 (0.1%)	0	0	0
医療機器不具合	1 (0.1%)	1 (0.1%)	0	0	0	0
全身性浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位そう痒感	1 (0.1%)	0	1 (0.1%)	0	0	0
注射部位漏出	1 (0.1%)	0	0	1 (0.1%)	0	0
注入部位反応	1 (0.1%)	0	1 (0.1%)	0	0	0
嚢胞破裂	1 (0.1%)	0	0	1 (0.1%)	0	0
傷害、中毒および処置合併症						
- Overall -	458 (65.6%)	129 (18.5%)	267 (38.3%)	52 (7.4%)	10 (1.4%)	0
注入に伴う反応	426 (61.0%)	129 (18.5%)	249 (35.7%)	39 (5.6%)	9 (1.3%)	0
転倒	13 (1.9%)	8 (1.1%)	5 (0.7%)	0	0	0
挫傷	13 (1.9%)	10 (1.4%)	3 (0.4%)	0	0	0
裂傷	7 (1.0%)	3 (0.4%)	4 (0.6%)	0	0	0
処置による疼痛	6 (0.9%)	1 (0.1%)	5 (0.7%)	0	0	0
節足動物咬傷	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肋骨骨折	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
上肢骨折	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
熱傷	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
創傷	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
脊椎圧迫骨折	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
顔面骨骨折	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
歯牙破折	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
皮膚擦過傷	2 (0.3%)	2 (0.3%)	0	0	0	0
漿液腫	4 (0.6%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0
手首関節骨折	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
肉離れ	3 (0.4%)	3 (0.4%)	0	0	0	0
靱帯捻挫	1 (0.1%)	0	1 (0.1%)	0	0	0
関節脱臼	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
上腕骨骨折	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
足関節部骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
足骨折	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
大腿骨骨折	2 (0.3%)	0	0	2 (0.3%)	0	0
動物咬傷	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
サンバーン	2 (0.3%)	2 (0.3%)	0	0	0	0
引っかき傷	2 (0.3%)	2 (0.3%)	0	0	0	0
眼挫傷	1 (0.1%)	1 (0.1%)	0	0	0	0
交通事故	2 (0.3%)	2 (0.3%)	0	0	0	0
骨挫傷	1 (0.1%)	1 (0.1%)	0	0	0	0
骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
四肢損傷	2 (0.3%)	0	2 (0.3%)	0	0	0
事故	1 (0.1%)	0	0	1 (0.1%)	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
手骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
頭部損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
半月板損傷	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0
皮膚損傷	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
橈骨骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
アルコール中毒	1 (0.1%)	0	0	1 (0.1%)	0	0
下肢骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
外傷後頚部症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
外傷性気胸	1 (0.1%)	0	0	1 (0.1%)	0	0
各種物質毒性	1 (0.1%)	0	1 (0.1%)	0	0	0
眼外傷	1 (0.1%)	1 (0.1%)	0	0	0	0
筋断裂	1 (0.1%)	1 (0.1%)	0	0	0	0
血管確保合併症	1 (0.1%)	1 (0.1%)	0	0	0	0
処置による悪心	1 (0.1%)	0	1 (0.1%)	0	0	0
処置による嘔吐	1 (0.1%)	1 (0.1%)	0	0	0	0
処置後血腫	1 (0.1%)	0	1 (0.1%)	0	0	0
処置後腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
処置後出血	1 (0.1%)	0	0	1 (0.1%)	0	0
上顎炎	1 (0.1%)	1 (0.1%)	0	0	0	0
静脈損傷	1 (0.1%)	0	1 (0.1%)	0	0	0
前腕骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
創部分泌	1 (0.1%)	1 (0.1%)	0	0	0	0
爪損傷	1 (0.1%)	0	1 (0.1%)	0	0	0
低温による損傷	1 (0.1%)	0	1 (0.1%)	0	0	0
投薬過誤	1 (0.1%)	1 (0.1%)	0	0	0	0
軟骨損傷	1 (0.1%)	0	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
軟部組織損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
脳挫傷	1 (0.1%)	0	1 (0.1%)	0	0	0
剥離骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
吻合部狭窄	1 (0.1%)	0	0	1 (0.1%)	0	0
瘢痕ヘルニア	1 (0.1%)	0	0	1 (0.1%)	0	0
靭帯断裂	1 (0.1%)	1 (0.1%)	0	0	0	0
血液およびリンパ系障害						
- Overall -	407 (58.3%)	18 (2.6%)	35 (5.0%)	134 (19.2%)	220 (31.5%)	0
好中球減少症	336 (48.1%)	9 (1.3%)	20 (2.9%)	113 (16.2%)	194 (27.8%)	0
白血球減少症	81 (11.6%)	6 (0.9%)	19 (2.7%)	36 (5.2%)	20 (2.9%)	0
血小板減少症	87 (12.5%)	18 (2.6%)	23 (3.3%)	30 (4.3%)	16 (2.3%)	0
貧血	68 (9.7%)	15 (2.1%)	24 (3.4%)	28 (4.0%)	1 (0.1%)	0
発熱性好中球減少症	48 (6.9%)	0	3 (0.4%)	31 (4.4%)	14 (2.0%)	0
リンパ球減少症	7 (1.0%)	1 (0.1%)	1 (0.1%)	4 (0.6%)	1 (0.1%)	0
骨髄機能不全	8 (1.1%)	0	0	1 (0.1%)	7 (1.0%)	0
汎血球減少症	1 (0.1%)	0	0	1 (0.1%)	0	0
顆粒球減少症	3 (0.4%)	0	0	1 (0.1%)	2 (0.3%)	0
血球減少症	4 (0.6%)	0	1 (0.1%)	3 (0.4%)	0	0
リンパ節症	1 (0.1%)	1 (0.1%)	0	0	0	0
リンパ節痛	1 (0.1%)	1 (0.1%)	0	0	0	0
白血球増加症	2 (0.3%)	0	2 (0.3%)	0	0	0
脾腫	2 (0.3%)	0	0	2 (0.3%)	0	0
リンパ節炎	1 (0.1%)	1 (0.1%)	0	0	0	0
好酸球増加症	1 (0.1%)	1 (0.1%)	0	0	0	0
自己免疫性溶血性貧血	1 (0.1%)	0	0	1 (0.1%)	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
播種性血管内凝固	2 (0.3%)	0	2 (0.3%)	0	0	0
血液毒性	1 (0.1%)	0	1 (0.1%)	0	0	0
無顆粒球症	1 (0.1%)	0	0	1 (0.1%)	0	0
免疫性血小板減少性紫斑病	1 (0.1%)	0	0	0	1 (0.1%)	0
有熱性骨髄無形成	1 (0.1%)	0	0	1 (0.1%)	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	394 (56.4%)	163 (23.4%)	166 (23.8%)	49 (7.0%)	11 (1.6%)	5 (0.7%)
咳嗽	194 (27.8%)	109 (15.6%)	83 (11.9%)	2 (0.3%)	0	0
呼吸困難	116 (16.6%)	44 (6.3%)	48 (6.9%)	21 (3.0%)	2 (0.3%)	1 (0.1%)
口腔咽頭痛	76 (10.9%)	58 (8.3%)	17 (2.4%)	1 (0.1%)	0	0
湿性咳嗽	35 (5.0%)	15 (2.1%)	20 (2.9%)	0	0	0
咽喉刺激感	26 (3.7%)	17 (2.4%)	9 (1.3%)	0	0	0
労作性呼吸困難	13 (1.9%)	9 (1.3%)	4 (0.6%)	0	0	0
鼻漏	21 (3.0%)	19 (2.7%)	2 (0.3%)	0	0	0
鼻出血	13 (1.9%)	12 (1.7%)	0	1 (0.1%)	0	0
胸水	13 (1.9%)	3 (0.4%)	5 (0.7%)	5 (0.7%)	0	0
鼻閉	14 (2.0%)	10 (1.4%)	4 (0.6%)	0	0	0
低酸素症	14 (2.0%)	0	9 (1.3%)	4 (0.6%)	1 (0.1%)	0
肺塞栓症	13 (1.9%)	0	1 (0.1%)	9 (1.3%)	3 (0.4%)	0
発声障害	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0	0
副鼻腔うっ血	8 (1.1%)	4 (0.6%)	4 (0.6%)	0	0	0
慢性閉塞性肺疾患	10 (1.4%)	1 (0.1%)	8 (1.1%)	0	0	1 (0.1%)
喘息	7 (1.0%)	0	6 (0.9%)	1 (0.1%)	0	0
上気道咳症候群	9 (1.3%)	6 (0.9%)	3 (0.4%)	0	0	0
しゃっくり	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
胸膜痛	5 (0.7%)	0	4 (0.6%)	1 (0.1%)	0	0
喘鳴	7 (1.0%)	2 (0.3%)	5 (0.7%)	0	0	0
アレルギー性鼻炎	6 (0.9%)	2 (0.3%)	4 (0.6%)	0	0	0
咽喉絞扼感	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
咽喉乾燥	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
口腔咽頭不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
間質性肺疾患	2 (0.3%)	0	0	2 (0.3%)	0	0
カタル	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
咽頭異常感覚	3 (0.4%)	3 (0.4%)	0	0	0	0
咽頭浮腫	1 (0.1%)	0	0	1 (0.1%)	0	0
気管支痙攣	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
肺臓炎	3 (0.4%)	0	3 (0.4%)	0	0	0
咽頭紅斑	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
呼吸不全	3 (0.4%)	0	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
肺気腫	4 (0.6%)	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0
肺障害	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
慢性気管支炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
くしゃみ	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
喉頭の炎症	1 (0.1%)	0	1 (0.1%)	0	0	0
上気道の炎症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
変色痰	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
ラ音	2 (0.3%)	0	2 (0.3%)	0	0	0
胸膜炎	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
誤嚥性肺炎	2 (0.3%)	0	0	2 (0.3%)	0	0
息詰まり感	2 (0.3%)	2 (0.3%)	0	0	0	0
肺硬化	1 (0.1%)	0	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肺浸潤	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
肺水腫	2 (0.3%)	0	0	2 (0.3%)	0	0
アレルギー性呼吸器疾患	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
咽頭知覚不全	1 (0.1%)	0	1 (0.1%)	0	0	0
過換気	1 (0.1%)	0	1 (0.1%)	0	0	0
気管支拡張症	1 (0.1%)	0	1 (0.1%)	0	0	0
気管支分泌増加	2 (0.3%)	2 (0.3%)	0	0	0	0
急性呼吸窮迫症候群	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
上気道うっ血	1 (0.1%)	0	1 (0.1%)	0	0	0
頻呼吸	1 (0.1%)	1 (0.1%)	0	0	0	0
副鼻腔不快感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
無気肺	1 (0.1%)	1 (0.1%)	0	0	0	0
安静時呼吸困難	1 (0.1%)	0	0	1 (0.1%)	0	0
咽頭の炎症	1 (0.1%)	0	0	0	1 (0.1%)	0
咽頭出血	1 (0.1%)	1 (0.1%)	0	0	0	0
咽頭障害	1 (0.1%)	1 (0.1%)	0	0	0	0
下気道うっ血	1 (0.1%)	0	1 (0.1%)	0	0	0
気胸	1 (0.1%)	0	0	0	1 (0.1%)	0
起坐呼吸	1 (0.1%)	1 (0.1%)	0	0	0	0
逆流性喉頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
急性呼吸不全	1 (0.1%)	0	0	0	1 (0.1%)	0
急性肺損傷	1 (0.1%)	0	0	0	0	1 (0.1%)
呼吸時疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
呼吸停止	1 (0.1%)	0	0	0	1 (0.1%)	0
口腔咽頭水疱形成	1 (0.1%)	1 (0.1%)	0	0	0	0
低音性連続性ラ音	1 (0.1%)	0	1 (0.1%)	0	0	0

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Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
乳び胸	1 (0.1%)	1 (0.1%)	0	0	0	0
肺高血圧症	1 (0.1%)	0	0	1 (0.1%)	0	0
肺線維症	1 (0.1%)	1 (0.1%)	0	0	0	0
肺動脈性肺高血圧症	1 (0.1%)	0	0	0	1 (0.1%)	0
肺嚢胞	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻甲介肥大	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻茸	1 (0.1%)	0	1 (0.1%)	0	0	0
鼻部不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
副鼻腔嚢胞	1 (0.1%)	0	1 (0.1%)	0	0	0
神経系障害						
- Overall -	399 (57.2%)	243 (34.8%)	126 (18.1%)	28 (4.0%)	2 (0.3%)	0
頭痛	138 (19.8%)	102 (14.6%)	35 (5.0%)	1 (0.1%)	0	0
浮動性めまい	66 (9.5%)	50 (7.2%)	15 (2.1%)	1 (0.1%)	0	0
味覚異常	60 (8.6%)	54 (7.7%)	6 (0.9%)	0	0	0
末梢性感覚ニューロパチー	55 (7.9%)	41 (5.9%)	11 (1.6%)	3 (0.4%)	0	0
錯感覚	56 (8.0%)	44 (6.3%)	11 (1.6%)	1 (0.1%)	0	0
末梢性ニューロパチー	49 (7.0%)	40 (5.7%)	9 (1.3%)	0	0	0
嗜眠	27 (3.9%)	19 (2.7%)	7 (1.0%)	1 (0.1%)	0	0
感覚鈍麻	22 (3.2%)	20 (2.9%)	2 (0.3%)	0	0	0
多発ニューロパチー	19 (2.7%)	8 (1.1%)	9 (1.3%)	2 (0.3%)	0	0
失神	18 (2.6%)	2 (0.3%)	7 (1.0%)	9 (1.3%)	0	0
振戦	11 (1.6%)	8 (1.1%)	3 (0.4%)	0	0	0
片頭痛	8 (1.1%)	5 (0.7%)	3 (0.4%)	0	0	0
記憶障害	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
神経痛	5 (0.7%)	0	5 (0.7%)	0	0	0
注意力障害	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
失神寸前の状態	6 (0.9%)	1 (0.1%)	3 (0.4%)	2 (0.3%)	0	0
体位性めまい	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
異常感覚	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
下肢静止不能症候群	7 (1.0%)	7 (1.0%)	0	0	0	0
坐骨神経痛	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
認知障害	1 (0.1%)	1 (0.1%)	0	0	0	0
一過性脳虚血発作	5 (0.7%)	4 (0.6%)	0	1 (0.1%)	0	0
灼熱感	3 (0.4%)	3 (0.4%)	0	0	0	0
ヘルペス後神経痛	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
味覚消失	5 (0.7%)	5 (0.7%)	0	0	0	0
傾眠	1 (0.1%)	1 (0.1%)	0	0	0	0
健忘	4 (0.6%)	4 (0.6%)	0	0	0	0
手根管症候群	1 (0.1%)	0	1 (0.1%)	0	0	0
知覚過敏	2 (0.3%)	2 (0.3%)	0	0	0	0
嗅覚錯誤	2 (0.3%)	2 (0.3%)	0	0	0	0
てんかん	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
感覚障害	4 (0.6%)	4 (0.6%)	0	0	0	0
頭部不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
副鼻腔炎に伴う頭痛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
痙攣発作	1 (0.1%)	0	0	1 (0.1%)	0	0
運動失調	1 (0.1%)	1 (0.1%)	0	0	0	0
筋緊張低下	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
平衡障害	1 (0.1%)	1 (0.1%)	0	0	0	0
末梢性運動ニューロパチー	2 (0.3%)	2 (0.3%)	0	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
意識レベルの低下	1 (0.1%)	0	1 (0.1%)	0	0	0
意識消失	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
感覚消失	1 (0.1%)	0	1 (0.1%)	0	0	0
虚血性脳卒中	1 (0.1%)	0	0	0	1 (0.1%)	0
頚動脈狭窄	1 (0.1%)	0	1 (0.1%)	0	0	0
三叉神経痛	1 (0.1%)	0	1 (0.1%)	0	0	0
神経圧迫	2 (0.3%)	2 (0.3%)	0	0	0	0
第７脳神経麻痺	1 (0.1%)	0	0	1 (0.1%)	0	0
脳虚血	1 (0.1%)	0	0	1 (0.1%)	0	0
不全単麻痺	1 (0.1%)	0	1 (0.1%)	0	0	0
味覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
味覚減退	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
くも膜嚢胞	1 (0.1%)	0	1 (0.1%)	0	0	0
アカシジア	1 (0.1%)	0	1 (0.1%)	0	0	0
パーキンソニズム	1 (0.1%)	0	1 (0.1%)	0	0	0
概日リズム睡眠障害	1 (0.1%)	0	1 (0.1%)	0	0	0
起立不耐性	1 (0.1%)	0	1 (0.1%)	0	0	0
緊張性頭痛	1 (0.1%)	1 (0.1%)	0	0	0	0
頚髄神経根障害	1 (0.1%)	1 (0.1%)	0	0	0	0
頚腕症候群	1 (0.1%)	0	1 (0.1%)	0	0	0
血管性脳症	1 (0.1%)	0	1 (0.1%)	0	0	0
神経根痛	1 (0.1%)	0	1 (0.1%)	0	0	0
脊髄圧迫	1 (0.1%)	0	0	1 (0.1%)	0	0
大脳障害	1 (0.1%)	0	1 (0.1%)	0	0	0
椎骨脳底動脈不全	1 (0.1%)	1 (0.1%)	0	0	0	0
認知症	1 (0.1%)	0	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
脳微小血管症	1 (0.1%)	1 (0.1%)	0	0	0	0
白質脳症	1 (0.1%)	1 (0.1%)	0	0	0	0
半盲	1 (0.1%)	0	1 (0.1%)	0	0	0
不全片麻痺	1 (0.1%)	1 (0.1%)	0	0	0	0
麻痺	1 (0.1%)	1 (0.1%)	0	0	0	0
無嗅覚	1 (0.1%)	1 (0.1%)	0	0	0	0
迷走神経障害	1 (0.1%)	0	1 (0.1%)	0	0	0
労作性めまい	1 (0.1%)	0	1 (0.1%)	0	0	0
肋間神経痛	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚および皮下組織障害						
- Overall -	388 (55.6%)	200 (28.7%)	165 (23.6%)	23 (3.3%)	0	0
発疹	117 (16.8%)	71 (10.2%)	39 (5.6%)	7 (1.0%)	0	0
そう痒症	91 (13.0%)	59 (8.5%)	30 (4.3%)	2 (0.3%)	0	0
脱毛症	88 (12.6%)	45 (6.4%)	43 (6.2%)	0	0	0
皮膚乾燥	38 (5.4%)	33 (4.7%)	5 (0.7%)	0	0	0
紅斑	37 (5.3%)	25 (3.6%)	9 (1.3%)	3 (0.4%)	0	0
寝汗	30 (4.3%)	26 (3.7%)	3 (0.4%)	1 (0.1%)	0	0
多汗症	27 (3.9%)	19 (2.7%)	7 (1.0%)	1 (0.1%)	0	0
蕁麻疹	21 (3.0%)	6 (0.9%)	14 (2.0%)	1 (0.1%)	0	0
斑状丘疹状皮疹	11 (1.6%)	6 (0.9%)	3 (0.4%)	2 (0.3%)	0	0
湿疹	15 (2.1%)	10 (1.4%)	5 (0.7%)	0	0	0
そう痒性皮疹	11 (1.6%)	7 (1.0%)	4 (0.6%)	0	0	0
ざ瘡様皮膚炎	8 (1.1%)	7 (1.0%)	1 (0.1%)	0	0	0
皮膚剥脱	10 (1.4%)	8 (1.1%)	2 (0.3%)	0	0	0
斑状皮疹	6 (0.9%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
顔面腫脹	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
皮膚炎	9 (1.3%)	5 (0.7%)	4 (0.6%)	0	0	0
紅斑性皮疹	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
水疱	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
乾癬	3 (0.4%)	0	3 (0.4%)	0	0	0
皮膚嚢腫	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
冷汗	5 (0.7%)	4 (0.6%)	0	1 (0.1%)	0	0
薬疹	6 (0.9%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0
皮膚潰瘍	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
脂漏性皮膚炎	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
全身性皮疹	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
多形紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚腫瘤	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
ざ瘡	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
アレルギー性皮膚炎	2 (0.3%)	0	2 (0.3%)	0	0	0
光線過敏性反応	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
酒さ	1 (0.1%)	0	1 (0.1%)	0	0	0
水疱性皮膚炎	2 (0.3%)	2 (0.3%)	0	0	0	0
全身性そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
点状出血	2 (0.3%)	2 (0.3%)	0	0	0	0
扁平苔癬	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
貨幣状湿疹	2 (0.3%)	2 (0.3%)	0	0	0	0
接触性皮膚炎	1 (0.1%)	0	0	1 (0.1%)	0	0
爪の障害	1 (0.1%)	1 (0.1%)	0	0	0	0
爪線状隆起	2 (0.3%)	2 (0.3%)	0	0	0	0
日光角化症	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
剥脱性皮膚炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
皮膚亀裂	2 (0.3%)	2 (0.3%)	0	0	0	0
皮膚変色	3 (0.4%)	3 (0.4%)	0	0	0	0
皮膚疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
黄色皮膚	2 (0.3%)	2 (0.3%)	0	0	0	0
丘疹性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
血管浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
色素沈着障害	1 (0.1%)	1 (0.1%)	0	0	0	0
斑状出血	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚腫脹	2 (0.3%)	2 (0.3%)	0	0	0	0
皮膚障害	1 (0.1%)	0	1 (0.1%)	0	0	0
嵌入爪	1 (0.1%)	1 (0.1%)	0	0	0	0
うっ滞性皮膚炎	1 (0.1%)	1 (0.1%)	0	0	0	0
過角化	1 (0.1%)	1 (0.1%)	0	0	0	0
乾皮症	1 (0.1%)	1 (0.1%)	0	0	0	0
丘疹	1 (0.1%)	0	1 (0.1%)	0	0	0
結節性紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
内方発育毛	1 (0.1%)	1 (0.1%)	0	0	0	0
皮脂欠乏性湿疹	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚局面	1 (0.1%)	1 (0.1%)	0	0	0	0
痒疹	1 (0.1%)	1 (0.1%)	0	0	0	0
筋骨格系および結合組織障害						
- Overall -	347 (49.7%)	199 (28.5%)	133 (19.1%)	15 (2.1%)	0	0
背部痛	96 (13.8%)	66 (9.5%)	26 (3.7%)	4 (0.6%)	0	0
関節痛	103 (14.8%)	68 (9.7%)	35 (5.0%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
四肢痛	63 (9.0%)	44 (6.3%)	19 (2.7%)	0	0	0
筋肉痛	47 (6.7%)	38 (5.4%)	9 (1.3%)	0	0	0
筋痙縮	37 (5.3%)	28 (4.0%)	9 (1.3%)	0	0	0
骨痛	36 (5.2%)	20 (2.9%)	15 (2.1%)	1 (0.1%)	0	0
筋骨格痛	26 (3.7%)	21 (3.0%)	5 (0.7%)	0	0	0
頚部痛	23 (3.3%)	15 (2.1%)	7 (1.0%)	1 (0.1%)	0	0
肩径部痛	10 (1.4%)	7 (1.0%)	3 (0.4%)	0	0	0
関節腫脹	13 (1.9%)	7 (1.0%)	6 (0.9%)	0	0	0
筋骨格系胸痛	10 (1.4%)	6 (0.9%)	4 (0.6%)	0	0	0
側腹部痛	11 (1.6%)	7 (1.0%)	4 (0.6%)	0	0	0
筋力低下	9 (1.3%)	8 (1.1%)	1 (0.1%)	0	0	0
変形性関節症	9 (1.3%)	3 (0.4%)	4 (0.6%)	2 (0.3%)	0	0
顎痛	9 (1.3%)	8 (1.1%)	1 (0.1%)	0	0	0
関節炎	7 (1.0%)	4 (0.6%)	3 (0.4%)	0	0	0
筋骨格硬直	8 (1.1%)	7 (1.0%)	0	1 (0.1%)	0	0
筋骨格不快感	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
関節周囲炎	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
脊椎痛	7 (1.0%)	1 (0.1%)	5 (0.7%)	1 (0.1%)	0	0
滑液包炎	3 (0.4%)	0	3 (0.4%)	0	0	0
筋緊張	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
関節硬直	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
骨粗鬆症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
四肢不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
椎間板突出	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
滑液嚢腫	4 (0.6%)	4 (0.6%)	0	0	0	0
肩回旋筋腱板症候群	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
弾発指	3 (0.4%)	3 (0.4%)	0	0	0	0
腱炎	2 (0.3%)	0	2 (0.3%)	0	0	0
デュプイトラン拘縮	2 (0.3%)	2 (0.3%)	0	0	0	0
関節可動域低下	1 (0.1%)	1 (0.1%)	0	0	0	0
関節障害	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
筋炎	1 (0.1%)	0	1 (0.1%)	0	0	0
腰部脊柱管狭窄症	1 (0.1%)	0	0	1 (0.1%)	0	0
シェーグレン症候群	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
ミオパチー	1 (0.1%)	0	1 (0.1%)	0	0	0
顎関節症候群	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
滑膜炎	1 (0.1%)	1 (0.1%)	0	0	0	0
関節滲出液	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
頚部腫瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
骨粗鬆症性骨折	2 (0.3%)	2 (0.3%)	0	0	0	0
斜頚	1 (0.1%)	0	1 (0.1%)	0	0	0
痛風性関節炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
関節不安定	1 (0.1%)	0	0	1 (0.1%)	0	0
筋拘縮	1 (0.1%)	0	1 (0.1%)	0	0	0
筋膜炎	1 (0.1%)	1 (0.1%)	0	0	0	0
筋攣縮	1 (0.1%)	1 (0.1%)	0	0	0	0
血清反応陰性関節炎	1 (0.1%)	0	1 (0.1%)	0	0	0
骨炎	1 (0.1%)	0	1 (0.1%)	0	0	0
骨減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
骨腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
骨折痛	1 (0.1%)	0	1 (0.1%)	0	0	0
脊椎すべり症	1 (0.1%)	0	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
脊椎炎	1 (0.1%)	1 (0.1%)	0	0	0	0
椎間孔狭窄	1 (0.1%)	0	1 (0.1%)	0	0	0
軟骨石灰化症	1 (0.1%)	0	1 (0.1%)	0	0	0
尾骨痛	1 (0.1%)	1 (0.1%)	0	0	0	0
病的骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
変形性脊椎症	1 (0.1%)	0	1 (0.1%)	0	0	0
腱鞘炎	1 (0.1%)	0	1 (0.1%)	0	0	0
腱付着部症	1 (0.1%)	1 (0.1%)	0	0	0	0
血管障害						
- Overall -	229 (32.8%)	108 (15.5%)	87 (12.5%)	30 (4.3%)	4 (0.6%)	0
高血圧	53 (7.6%)	13 (1.9%)	25 (3.6%)	15 (2.1%)	0	0
潮紅	46 (6.6%)	25 (3.6%)	20 (2.9%)	1 (0.1%)	0	0
低血圧	46 (6.6%)	18 (2.6%)	17 (2.4%)	9 (1.3%)	2 (0.3%)	0
ほてり	34 (4.9%)	26 (3.7%)	7 (1.0%)	1 (0.1%)	0	0
静脈炎	17 (2.4%)	10 (1.4%)	7 (1.0%)	0	0	0
血栓性静脈炎	12 (1.7%)	8 (1.1%)	4 (0.6%)	0	0	0
静脈障害	9 (1.3%)	9 (1.3%)	0	0	0	0
血管炎	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
血管痛	6 (0.9%)	6 (0.9%)	0	0	0	0
深部静脈血栓症	3 (0.4%)	0	3 (0.4%)	0	0	0
表在性血栓性静脈炎	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
血腫	4 (0.6%)	4 (0.6%)	0	0	0	0
血栓症	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
起立性低血圧	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
末梢冷感	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
高血圧クリーゼ	3 (0.4%)	0	0	2 (0.3%)	1 (0.1%)	0
循環虚脱	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
鎖骨下静脈血栓症	1 (0.1%)	1 (0.1%)	0	0	0	0
静脈穿刺不良	2 (0.3%)	0	2 (0.3%)	0	0	0
表在性静脈炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
静脈血栓症	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
静脈硬化症	1 (0.1%)	1 (0.1%)	0	0	0	0
腋窩静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
くも状静脈	1 (0.1%)	1 (0.1%)	0	0	0	0
リンパ嚢腫	1 (0.1%)	1 (0.1%)	0	0	0	0
レイノー現象	1 (0.1%)	1 (0.1%)	0	0	0	0
間欠性跛行	1 (0.1%)	1 (0.1%)	0	0	0	0
静脈退色	1 (0.1%)	1 (0.1%)	0	0	0	0
大動脈狭窄	1 (0.1%)	1 (0.1%)	0	0	0	0
末梢血管障害	1 (0.1%)	0	1 (0.1%)	0	0	0
末梢性虚血	1 (0.1%)	0	0	0	1 (0.1%)	0
代謝および栄養障害						
- Overall -	196 (28.1%)	95 (13.6%)	67 (9.6%)	29 (4.2%)	4 (0.6%)	1 (0.1%)
食欲減退	87 (12.5%)	66 (9.5%)	20 (2.9%)	1 (0.1%)	0	0
低カリウム血症	45 (6.4%)	28 (4.0%)	12 (1.7%)	5 (0.7%)	0	0
高尿酸血症	25 (3.6%)	20 (2.9%)	4 (0.6%)	1 (0.1%)	0	0
高血糖	14 (2.0%)	2 (0.3%)	7 (1.0%)	5 (0.7%)	0	0
脱水	13 (1.9%)	3 (0.4%)	7 (1.0%)	2 (0.3%)	0	1 (0.1%)
糖尿病	10 (1.4%)	3 (0.4%)	5 (0.7%)	2 (0.3%)	0	0
低リン酸血症	9 (1.3%)	2 (0.3%)	4 (0.6%)	3 (0.4%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
高カリウム血症	10 (1.4%)	1 (0.1%)	7 (1.0%)	2 (0.3%)	0	0
痛風	9 (1.3%)	1 (0.1%)	8 (1.1%)	0	0	0
低マグネシウム血症	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
低ナトリウム血症	9 (1.3%)	3 (0.4%)	0	4 (0.6%)	2 (0.3%)	0
２型糖尿病	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
腫瘍崩壊症候群	6 (0.9%)	0	0	5 (0.7%)	1 (0.1%)	0
高脂血症	5 (0.7%)	2 (0.3%)	2 (0.3%)	1 (0.1%)	0	0
高カルシウム血症	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
低血糖	1 (0.1%)	1 (0.1%)	0	0	0	0
水分過負荷	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
体液貯留	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
栄養障害	3 (0.4%)	0	3 (0.4%)	0	0	0
鉄欠乏	2 (0.3%)	0	2 (0.3%)	0	0	0
ビタミンＤ欠乏	2 (0.3%)	0	2 (0.3%)	0	0	0
低アルブミン血症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
高トリグリセリド血症	1 (0.1%)	0	1 (0.1%)	0	0	0
食欲亢進	1 (0.1%)	1 (0.1%)	0	0	0	0
低カルシウム血症	1 (0.1%)	1 (0.1%)	0	0	0	0
葉酸欠乏	1 (0.1%)	1 (0.1%)	0	0	0	0
ビタミンＢ６欠乏	1 (0.1%)	1 (0.1%)	0	0	0	0
ラクトース不耐性	1 (0.1%)	0	1 (0.1%)	0	0	0
脂質異常症	1 (0.1%)	1 (0.1%)	0	0	0	0
肥満	1 (0.1%)	1 (0.1%)	0	0	0	0
精神障害						
- Overall -	168 (24.1%)	103 (14.8%)	51 (7.3%)	10 (1.4%)	4 (0.6%)	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
不眠症	104 (14.9%)	66 (9.5%)	35 (5.0%)	3 (0.4%)	0	0
不安	37 (5.3%)	18 (2.6%)	18 (2.6%)	1 (0.1%)	0	0
うつ病	28 (4.0%)	16 (2.3%)	8 (1.1%)	2 (0.3%)	2 (0.3%)	0
抑うつ気分	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
睡眠障害	3 (0.4%)	3 (0.4%)	0	0	0	0
落ち着きのなさ	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
気分動揺	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
激越	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
錯乱状態	4 (0.6%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	0	0
易刺激性	3 (0.4%)	3 (0.4%)	0	0	0	0
気分変化	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
悪夢	1 (0.1%)	1 (0.1%)	0	0	0	0
自殺念慮	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
異常な夢	2 (0.3%)	2 (0.3%)	0	0	0	0
情動障害	1 (0.1%)	1 (0.1%)	0	0	0	0
精神状態変化	2 (0.3%)	0	0	2 (0.3%)	0	0
涙ぐむ	2 (0.3%)	2 (0.3%)	0	0	0	0
アルコールに関連する問題	1 (0.1%)	0	0	1 (0.1%)	0	0
ストレス	1 (0.1%)	1 (0.1%)	0	0	0	0
パーソナリティ障害	1 (0.1%)	0	1 (0.1%)	0	0	0
感情不安定	1 (0.1%)	1 (0.1%)	0	0	0	0
幻覚	1 (0.1%)	1 (0.1%)	0	0	0	0
攻撃性	1 (0.1%)	0	1 (0.1%)	0	0	0
自殺企図	1 (0.1%)	0	0	0	1 (0.1%)	0
失見当識	1 (0.1%)	1 (0.1%)	0	0	0	0
初期不眠症	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
食物嫌悪	1 (0.1%)	1 (0.1%)	0	0	0	0
身体疾患による精神障害	1 (0.1%)	0	0	1 (0.1%)	0	0
精神病性障害	1 (0.1%)	0	0	0	1 (0.1%)	0
適応障害	1 (0.1%)	1 (0.1%)	0	0	0	0
不快気分	1 (0.1%)	1 (0.1%)	0	0	0	0
抑うつ症状	1 (0.1%)	0	1 (0.1%)	0	0	0
離人症	1 (0.1%)	1 (0.1%)	0	0	0	0
躁病	1 (0.1%)	1 (0.1%)	0	0	0	0
臨床検査						
- Overall -	154 (22.1%)	83 (11.9%)	46 (6.6%)	23 (3.3%)	2 (0.3%)	0
体重減少	33 (4.7%)	21 (3.0%)	10 (1.4%)	2 (0.3%)	0	0
アラニンアミノトランスフェラーゼ増加	31 (4.4%)	16 (2.3%)	10 (1.4%)	5 (0.7%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	22 (3.2%)	16 (2.3%)	5 (0.7%)	1 (0.1%)	0	0
血中クレアチニン増加	16 (2.3%)	11 (1.6%)	4 (0.6%)	1 (0.1%)	0	0
血中乳酸脱水素酵素増加	15 (2.1%)	13 (1.9%)	1 (0.1%)	1 (0.1%)	0	0
体重増加	7 (1.0%)	2 (0.3%)	5 (0.7%)	0	0	0
Ｃ－反応性蛋白増加	11 (1.6%)	3 (0.4%)	6 (0.9%)	2 (0.3%)	0	0
γ－グルタミルトランスフェラーゼ増加	6 (0.9%)	2 (0.3%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0
血中アルカリホスファターゼ増加	8 (1.1%)	5 (0.7%)	1 (0.1%)	2 (0.3%)	0	0
血中ビリルビン増加	7 (1.0%)	4 (0.6%)	2 (0.3%)	1 (0.1%)	0	0
体温上昇	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0	0
血圧上昇	5 (0.7%)	2 (0.3%)	2 (0.3%)	1 (0.1%)	0	0
肝機能検査異常	3 (0.4%)	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	0
血中カリウム減少	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
駆出率減少	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血中コレステロール増加	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
トランスアミナーゼ上昇	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
ビタミンＤ減少	2 (0.3%)	2 (0.3%)	0	0	0	0
血中尿酸増加	4 (0.6%)	4 (0.6%)	0	0	0	0
国際標準比増加	4 (0.6%)	3 (0.4%)	0	1 (0.1%)	0	0
酸素飽和度低下	3 (0.4%)	0	3 (0.4%)	0	0	0
血中クレアチンホスホキナーゼ増加	3 (0.4%)	3 (0.4%)	0	0	0	0
レスピロウイルス検査陽性	1 (0.1%)	0	0	1 (0.1%)	0	0
胸部コンピュータ断層撮影異常	1 (0.1%)	1 (0.1%)	0	0	0	0
血中アルブミン減少	1 (0.1%)	0	1 (0.1%)	0	0	0
血中ブドウ糖増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中マグネシウム減少	1 (0.1%)	1 (0.1%)	0	0	0	0
細菌検査陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
心雑音	1 (0.1%)	1 (0.1%)	0	0	0	0
心電図ＱＴ延長	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫グロブリン減少	1 (0.1%)	1 (0.1%)	0	0	0	0
ＥＣＯＧパフォーマンスステータス悪化	1 (0.1%)	0	0	1 (0.1%)	0	0
ＱＲＳ軸異常	1 (0.1%)	1 (0.1%)	0	0	0	0
サイトメガロウイルス検査陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
レンサ球菌検査陽性	1 (0.1%)	0	0	1 (0.1%)	0	0
活性化部分トロンボプラスチン時間延長	1 (0.1%)	1 (0.1%)	0	0	0	0
肝触知	1 (0.1%)	1 (0.1%)	0	0	0	0
眼圧検査	1 (0.1%)	1 (0.1%)	0	0	0	0
眼圧上昇	1 (0.1%)	1 (0.1%)	0	0	0	0
駆出率	1 (0.1%)	0	0	1 (0.1%)	0	0
血清フェリチン増加	1 (0.1%)	0	1 (0.1%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血中カリウム増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中クレアチニン減少	1 (0.1%)	1 (0.1%)	0	0	0	0
血中ブドウ糖減少	1 (0.1%)	1 (0.1%)	0	0	0	0
血中リン増加	1 (0.1%)	0	1 (0.1%)	0	0	0
血中免疫グロブリンG減少	1 (0.1%)	1 (0.1%)	0	0	0	0
血中葉酸減少	1 (0.1%)	0	1 (0.1%)	0	0	0
呼吸音異常	1 (0.1%)	1 (0.1%)	0	0	0	0
好中球数増加	1 (0.1%)	0	0	1 (0.1%)	0	0
収縮期血圧低下	1 (0.1%)	1 (0.1%)	0	0	0	0
腎クレアチニン・クリアランス増加	1 (0.1%)	0	1 (0.1%)	0	0	0
腹腔内圧上昇	1 (0.1%)	1 (0.1%)	0	0	0	0
便潜血	1 (0.1%)	1 (0.1%)	0	0	0	0
便潜血陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫グロブリン増加	1 (0.1%)	0	1 (0.1%)	0	0	0
心臓障害						
- Overall -	102 (14.6%)	37 (5.3%)	29 (4.2%)	27 (3.9%)	6 (0.9%)	3 (0.4%)
動悸	17 (2.4%)	12 (1.7%)	4 (0.6%)	1 (0.1%)	0	0
頻脈	21 (3.0%)	9 (1.3%)	11 (1.6%)	1 (0.1%)	0	0
心房細動	17 (2.4%)	4 (0.6%)	6 (0.9%)	7 (1.0%)	0	0
狭心症	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
洞性頻脈	9 (1.3%)	3 (0.4%)	4 (0.6%)	1 (0.1%)	1 (0.1%)	0
徐脈	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
洞性徐脈	7 (1.0%)	3 (0.4%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0
心不全	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
うっ血性心不全	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
冠動脈疾患	1 (0.1%)	1 (0.1%)	0	0	0	0
上室性頻脈	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
不整脈	5 (0.7%)	3 (0.4%)	0	2 (0.3%)	0	0
急性心筋梗塞	4 (0.6%)	0	0	4 (0.6%)	0	0
心筋虚血	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
心原性ショック	2 (0.3%)	0	0	0	0	2 (0.3%)
右室不全	2 (0.3%)	0	0	2 (0.3%)	0	0
冠動脈狭窄	1 (0.1%)	0	0	1 (0.1%)	0	0
心筋梗塞	1 (0.1%)	0	0	0	1 (0.1%)	0
心室性期外収縮	2 (0.3%)	2 (0.3%)	0	0	0	0
心室性頻脈	1 (0.1%)	0	0	1 (0.1%)	0	0
心停止	1 (0.1%)	0	0	0	1 (0.1%)	0
心房粗動	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
チアノーゼ	1 (0.1%)	1 (0.1%)	0	0	0	0
右脚ブロック	1 (0.1%)	1 (0.1%)	0	0	0	0
上室性期外収縮	1 (0.1%)	1 (0.1%)	0	0	0	0
心筋炎	1 (0.1%)	1 (0.1%)	0	0	0	0
心血管不全	1 (0.1%)	1 (0.1%)	0	0	0	0
心室機能不全	1 (0.1%)	1 (0.1%)	0	0	0	0
心嚢液貯留	1 (0.1%)	1 (0.1%)	0	0	0	0
心肺停止	1 (0.1%)	0	0	0	1 (0.1%)	0
第一度房室ブロック	1 (0.1%)	1 (0.1%)	0	0	0	0
眼障害						
- Overall -	90 (12.9%)	66 (9.5%)	23 (3.3%)	1 (0.1%)	0	0
眼乾燥	15 (2.1%)	12 (1.7%)	3 (0.4%)	0	0	0

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aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
霧視	11 (1.6%)	11 (1.6%)	0	0	0	0
眼痛	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0	0
白内障	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
眼そう痒症	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
流涙増加	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
眼充血	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
視力低下	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
眼刺激	3 (0.4%)	3 (0.4%)	0	0	0	0
眼脂	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
眼瞼浮腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
眼の異物感	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
眼部腫脹	2 (0.3%)	0	2 (0.3%)	0	0	0
眼窩周囲浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
視力障害	3 (0.4%)	3 (0.4%)	0	0	0	0
眼瞼炎	1 (0.1%)	0	1 (0.1%)	0	0	0
緑内障	1 (0.1%)	1 (0.1%)	0	0	0	0
羞明	2 (0.3%)	2 (0.3%)	0	0	0	0
ぶどう膜炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
眼瞼痙攣	1 (0.1%)	1 (0.1%)	0	0	0	0
結膜刺激	1 (0.1%)	1 (0.1%)	0	0	0	0
硝子体浮遊物	1 (0.1%)	1 (0.1%)	0	0	0	0
潰瘍性角膜炎	1 (0.1%)	1 (0.1%)	0	0	0	0
アレルギー性結膜炎	1 (0.1%)	1 (0.1%)	0	0	0	0
加齢黄斑変性	1 (0.1%)	0	1 (0.1%)	0	0	0
角膜混濁	1 (0.1%)	0	0	1 (0.1%)	0	0
眼球乾燥症	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
眼球浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
眼出血	1 (0.1%)	1 (0.1%)	0	0	0	0
眼部不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
眼瞼機能障害	1 (0.1%)	1 (0.1%)	0	0	0	0
虚血性視神経症	1 (0.1%)	0	1 (0.1%)	0	0	0
光視症	1 (0.1%)	1 (0.1%)	0	0	0	0
失明	1 (0.1%)	0	1 (0.1%)	0	0	0
硝子体剥離	1 (0.1%)	1 (0.1%)	0	0	0	0
腎および尿路障害						
- Overall -	90 (12.9%)	55 (7.9%)	29 (4.2%)	5 (0.7%)	1 (0.1%)	0
頻尿	24 (3.4%)	18 (2.6%)	6 (0.9%)	0	0	0
排尿困難	18 (2.6%)	12 (1.7%)	6 (0.9%)	0	0	0
尿失禁	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
夜間頻尿	9 (1.3%)	5 (0.7%)	4 (0.6%)	0	0	0
血尿	6 (0.9%)	6 (0.9%)	0	0	0	0
腎不全	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
尿閉	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
急性腎不全	5 (0.7%)	0	0	4 (0.6%)	1 (0.1%)	0
腎結石症	1 (0.1%)	0	0	1 (0.1%)	0	0
水腎症	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
尿意切迫	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
腎機能障害	3 (0.4%)	0	3 (0.4%)	0	0	0
腎仙痛	1 (0.1%)	1 (0.1%)	0	0	0	0
多尿	2 (0.3%)	2 (0.3%)	0	0	0	0
尿管結石	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
尿臭異常	2 (0.3%)	2 (0.3%)	0	0	0	0
緊張性膀胱	1 (0.1%)	1 (0.1%)	0	0	0	0
出血性膀胱炎	1 (0.1%)	0	1 (0.1%)	0	0	0
蛋白尿	2 (0.3%)	2 (0.3%)	0	0	0	0
着色尿	2 (0.3%)	2 (0.3%)	0	0	0	0
尿管閉塞	1 (0.1%)	1 (0.1%)	0	0	0	0
尿路痛	1 (0.1%)	0	1 (0.1%)	0	0	0
尿路閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
腹圧性尿失禁	1 (0.1%)	1 (0.1%)	0	0	0	0
慢性腎臓病	1 (0.1%)	0	1 (0.1%)	0	0	0
遺尿	1 (0.1%)	1 (0.1%)	0	0	0	0
白血球尿	1 (0.1%)	0	1 (0.1%)	0	0	0
有痛性排尿困難	1 (0.1%)	1 (0.1%)	0	0	0	0
膀胱出口部閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
膀胱障害	1 (0.1%)	1 (0.1%)	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）						
- Overall -	90 (12.9%)	26 (3.7%)	23 (3.3%)	21 (3.0%)	13 (1.9%)	7 (1.0%)
基底細胞癌	14 (2.0%)	3 (0.4%)	8 (1.1%)	1 (0.1%)	2 (0.3%)	0
扁平上皮癌	6 (0.9%)	2 (0.3%)	1 (0.1%)	3 (0.4%)	0	0
脂漏性角化症	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
メラノサイト性母斑	4 (0.6%)	3 (0.4%)	0	1 (0.1%)	0	0
前立腺癌	4 (0.6%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
脂肪腫	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
皮膚乳頭腫	3 (0.4%)	3 (0.4%)	0	0	0	0
骨髄異形成症候群	4 (0.6%)	0	0	0	3 (0.4%)	1 (0.1%)

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腫瘍フレア	3 (0.4%)	3 (0.4%)	0	0	0	0
乳癌	4 (0.6%)	0	0	3 (0.4%)	1 (0.1%)	0
悪性黒色腫	1 (0.1%)	0	0	1 (0.1%)	0	0
結腸癌	1 (0.1%)	0	0	1 (0.1%)	0	0
大腸腺腫	2 (0.3%)	0	2 (0.3%)	0	0	0
皮膚有棘細胞癌	2 (0.3%)	0	0	2 (0.3%)	0	0
ケラトアカントーマ	1 (0.1%)	0	1 (0.1%)	0	0	0
ホジキン病	2 (0.3%)	0	0	0	2 (0.3%)	0
癌疼痛	2 (0.3%)	0	2 (0.3%)	0	0	0
急性骨髄性白血病	2 (0.3%)	0	0	0	1 (0.1%)	1 (0.1%)
腫瘍疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
浸潤性乳管癌	1 (0.1%)	0	0	0	1 (0.1%)	0
腎癌	1 (0.1%)	0	0	1 (0.1%)	0	0
直腸腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
非小細胞肺癌	2 (0.3%)	0	0	0	1 (0.1%)	1 (0.1%)
肛門性器疣贅	1 (0.1%)	0	1 (0.1%)	0	0	0
Ｔ細胞性リンパ腫	1 (0.1%)	0	0	1 (0.1%)	0	0
エストロゲン受容体陽性乳癌	1 (0.1%)	0	0	0	1 (0.1%)	0
シュワン細胞腫	1 (0.1%)	0	0	1 (0.1%)	0	0
移行上皮癌	1 (0.1%)	0	0	1 (0.1%)	0	0
角結膜上皮内腫瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
汗腺腫瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
肝新生物	1 (0.1%)	0	0	0	0	1 (0.1%)
肝臓血管腫	1 (0.1%)	0	1 (0.1%)	0	0	0
眼血管腫	1 (0.1%)	1 (0.1%)	0	0	0	0
急性リンパ性白血病	1 (0.1%)	0	0	0	0	1 (0.1%)

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
結節性硬化型ホジキン病	1 (0.1%)	0	0	0	1 (0.1%)	0
結腸腺癌	1 (0.1%)	0	1 (0.1%)	0	0	0
甲状腺の良性新生物	1 (0.1%)	0	1 (0.1%)	0	0	0
甲状腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
甲状腺新生物	1 (0.1%)	1 (0.1%)	0	0	0	0
子宮平滑筋腫	1 (0.1%)	1 (0.1%)	0	0	0	0
食道癌	1 (0.1%)	0	0	0	0	1 (0.1%)
髄膜腫	1 (0.1%)	0	0	1 (0.1%)	0	0
虫垂腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
聴神経腫	1 (0.1%)	0	1 (0.1%)	0	0	0
乳腺線維腺腫	1 (0.1%)	0	1 (0.1%)	0	0	0
乳頭様甲状腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
肺扁平上皮癌	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚癌	1 (0.1%)	0	0	1 (0.1%)	0	0
皮膚良性新生物	1 (0.1%)	1 (0.1%)	0	0	0	0
非小細胞肺癌第４期	1 (0.1%)	0	0	0	0	1 (0.1%)
鼻新生物	1 (0.1%)	1 (0.1%)	0	0	0	0
平滑筋腫	1 (0.1%)	1 (0.1%)	0	0	0	0
卵巣胚細胞良性奇形腫	1 (0.1%)	1 (0.1%)	0	0	0	0
良性新生物	1 (0.1%)	1 (0.1%)	0	0	0	0
濾胞性甲状腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
耳および迷路障害						
- Overall -	57 (8.2%)	40 (5.7%)	14 (2.0%)	3 (0.4%)	0	0
回転性めまい	18 (2.6%)	13 (1.9%)	5 (0.7%)	0	0	0
耳痛	11 (1.6%)	9 (1.3%)	2 (0.3%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
耳鳴	12 (1.7%)	11 (1.6%)	1 (0.1%)	0	0	0
耳そう痒症	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
耳不快感	1 (0.1%)	0	1 (0.1%)	0	0	0
聴力低下	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
難聴	4 (0.6%)	2 (0.3%)	0	2 (0.3%)	0	0
聴覚障害	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
頭位性回転性めまい	2 (0.3%)	2 (0.3%)	0	0	0	0
耳閉	1 (0.1%)	1 (0.1%)	0	0	0	0
耳の障害	1 (0.1%)	1 (0.1%)	0	0	0	0
鼓膜穿孔	1 (0.1%)	0	1 (0.1%)	0	0	0
聴覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
片耳難聴	1 (0.1%)	0	1 (0.1%)	0	0	0
生殖系および乳房障害						
- Overall -	60 (8.6%)	30 (4.3%)	25 (3.6%)	5 (0.7%)	0	0
骨盤痛	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
無月経	6 (0.9%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0
腟分泌物	8 (1.1%)	4 (0.6%)	4 (0.6%)	0	0	0
勃起不全	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
外陰腟乾燥	4 (0.6%)	0	4 (0.6%)	0	0	0
女性化乳房	3 (0.4%)	3 (0.4%)	0	0	0	0
乳房痛	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
不規則月経	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
閉経期症状	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
良性前立腺肥大症	2 (0.3%)	0	2 (0.3%)	0	0	0
月経過多	2 (0.3%)	2 (0.3%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
外陰腟痛	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
乳頭痛	4 (0.6%)	4 (0.6%)	0	0	0	0
月経困難症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
前立腺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
卵巣嚢胞	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
外陰腟そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
亀頭包皮炎	2 (0.3%)	0	2 (0.3%)	0	0	0
性器発疹	1 (0.1%)	0	1 (0.1%)	0	0	0
陰嚢痛	1 (0.1%)	0	1 (0.1%)	0	0	0
子宮頚管分泌	1 (0.1%)	0	1 (0.1%)	0	0	0
子宮付属器嚢胞	1 (0.1%)	1 (0.1%)	0	0	0	0
女性生殖器瘻	1 (0.1%)	0	1 (0.1%)	0	0	0
性器浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
前立腺痛	1 (0.1%)	1 (0.1%)	0	0	0	0
卵巣腫瘤	1 (0.1%)	0	0	1 (0.1%)	0	0
腟出血	1 (0.1%)	1 (0.1%)	0	0	0	0
腟障害	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫系障害						
- Overall -	43 (6.2%)	22 (3.2%)	15 (2.1%)	4 (0.6%)	2 (0.3%)	0
過敏症	12 (1.7%)	9 (1.3%)	3 (0.4%)	0	0	0
季節性アレルギー	8 (1.1%)	8 (1.1%)	0	0	0	0
低γグロブリン血症	11 (1.6%)	1 (0.1%)	9 (1.3%)	1 (0.1%)	0	0
薬物過敏症	2 (0.3%)	2 (0.3%)	0	0	0	0
造影剤アレルギー	2 (0.3%)	2 (0.3%)	0	0	0	0
アナフィラキシー反応	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
サイトカイン放出症候群	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
サルコイドーシス	2 (0.3%)	2 (0.3%)	0	0	0	0
選択的ＩｇＧサブクラス欠損症	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
ＩｇＡ欠損性免疫不全症	1 (0.1%)	0	1 (0.1%)	0	0	0
ＩｇＭ欠損性免疫不全症	1 (0.1%)	0	1 (0.1%)	0	0	0
アナフィラキシーショック	1 (0.1%)	0	0	0	1 (0.1%)	0
節足動物咬傷アレルギー	1 (0.1%)	0	0	1 (0.1%)	0	0
肝胆道系障害						
- Overall -	29 (4.2%)	9 (1.3%)	8 (1.1%)	10 (1.4%)	2 (0.3%)	0
胆嚢炎	5 (0.7%)	0	1 (0.1%)	4 (0.6%)	0	0
胆石症	4 (0.6%)	3 (0.4%)	0	1 (0.1%)	0	0
肝機能異常	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
高ビリルビン血症	2 (0.3%)	0	2 (0.3%)	0	0	0
脂肪肝	2 (0.3%)	2 (0.3%)	0	0	0	0
胆道仙痛	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
肝障害	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
黄疸	1 (0.1%)	0	0	1 (0.1%)	0	0
薬物性肝障害	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
肝炎	1 (0.1%)	1 (0.1%)	0	0	0	0
肝硬変	1 (0.1%)	0	1 (0.1%)	0	0	0
肝細胞損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
肝臓痛	1 (0.1%)	1 (0.1%)	0	0	0	0
肝毒性	1 (0.1%)	0	1 (0.1%)	0	0	0
急性肝炎	1 (0.1%)	0	0	0	1 (0.1%)	0
胆管結石	1 (0.1%)	0	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
胆嚢痛	1 (0.1%)	1 (0.1%)	0	0	0	0
胆嚢摘出術後症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
内分泌障害						
- Overall -	15 (2.1%)	6 (0.9%)	9 (1.3%)	0	0	0
ステロイド離脱症候群	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
甲状腺機能低下症	4 (0.6%)	0	4 (0.6%)	0	0	0
甲状腺機能亢進症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
甲状腺腫	2 (0.3%)	2 (0.3%)	0	0	0	0
甲状腺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
外科および内科処置						
- Overall -	11 (1.6%)	5 (0.7%)	2 (0.3%)	4 (0.6%)	0	0
癌手術	1 (0.1%)	0	0	1 (0.1%)	0	0
手根管除圧	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
白内障手術	1 (0.1%)	1 (0.1%)	0	0	0	0
甲状腺摘除	1 (0.1%)	0	0	1 (0.1%)	0	0
鼻形成	1 (0.1%)	0	0	1 (0.1%)	0	0
膝手術	1 (0.1%)	1 (0.1%)	0	0	0	0
副鼻腔手術	1 (0.1%)	0	1 (0.1%)	0	0	0
縫合	1 (0.1%)	0	1 (0.1%)	0	0	0
扁桃摘出	1 (0.1%)	1 (0.1%)	0	0	0	0
腱手術	1 (0.1%)	1 (0.1%)	0	0	0	0
先天性、家族性および遺伝性障害						
- Overall -	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_223_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
陰嚢水瘤	1 (0.1%)	0	1 (0.1%)	0	0	0
社会環境						
- Overall -	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
閉経	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
妊娠、産褥および周産期の状態						
- Overall -	1 (0.1%)	0	0	1 (0.1%)	0	0
流産	1 (0.1%)	0	0	1 (0.1%)	0	0

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To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
NCI-CTCAE ver. 4.0

Program: /opt/BIOSTAT/prod/cdt7159z/k21223l/aet04.sas / Output: /opt/BIOSTAT/prod/cdt7159z/k21223l/reports/aet04_223_SE.out
03OCT2016 3:49

[5.3.5.1-2 aet04_223_SE を再掲]

表 2.7.6.2.1.3-2　因果関係が否定できないすべての有害事象（BO21223試験，未治療 iNHL 患者）

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	634 (91.6%)	80 (11.6%)	189 (27.3%)	172 (24.9%)	190 (27.5%)	3 (0.4%)
胃腸障害						
- Overall -	420 (60.7%)	229 (33.1%)	162 (23.4%)	29 (4.2%)	0	0
悪心	276 (39.9%)	175 (25.3%)	92 (13.3%)	9 (1.3%)	0	0
便秘	124 (17.9%)	78 (11.3%)	43 (6.2%)	3 (0.4%)	0	0
嘔吐	99 (14.3%)	56 (8.1%)	35 (5.1%)	8 (1.2%)	0	0
下痢	63 (9.1%)	42 (6.1%)	17 (2.5%)	4 (0.6%)	0	0
口内炎	44 (6.4%)	29 (4.2%)	13 (1.9%)	2 (0.3%)	0	0
腹痛	28 (4.0%)	16 (2.3%)	9 (1.3%)	3 (0.4%)	0	0
消化不良	21 (3.0%)	13 (1.9%)	8 (1.2%)	0	0	0
上腹部痛	15 (2.2%)	12 (1.7%)	3 (0.4%)	0	0	0
口腔内潰瘍形成	18 (2.6%)	12 (1.7%)	5 (0.7%)	1 (0.1%)	0	0
口内乾燥	11 (1.6%)	10 (1.4%)	1 (0.1%)	0	0	0
口腔内痛	12 (1.7%)	8 (1.2%)	4 (0.6%)	0	0	0
腹部不快感	8 (1.2%)	7 (1.0%)	1 (0.1%)	0	0	0
腹部膨満	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0	0
胃食道逆流性疾患	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
胃炎	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
口の錯感覚	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
アフタ性潰瘍	6 (0.9%)	6 (0.9%)	0	0	0	0
歯肉痛	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
歯痛	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
嚥下障害	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
口腔そう痒症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
食道炎	2 (0.3%)	0	2 (0.3%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
舌潰瘍	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
放屁	2 (0.3%)	2 (0.3%)	0	0	0	0
小腸炎	2 (0.3%)	0	2 (0.3%)	0	0	0
消化器痛	1 (0.1%)	1 (0.1%)	0	0	0	0
心窩部不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
舌炎	1 (0.1%)	1 (0.1%)	0	0	0	0
大腸炎	2 (0.3%)	0	0	2 (0.3%)	0	0
ミクリッツ症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
レッチング	1 (0.1%)	0	1 (0.1%)	0	0	0
胃腸障害	1 (0.1%)	0	1 (0.1%)	0	0	0
下腹部痛	1 (0.1%)	1 (0.1%)	0	0	0	0
血栓性痔核	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔粘膜紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
口唇そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
口唇腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
歯の知覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
歯肉障害	1 (0.1%)	1 (0.1%)	0	0	0	0
舌そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
大腸閉塞	1 (0.1%)	0	0	1 (0.1%)	0	0
腸絨毛萎縮	1 (0.1%)	0	1 (0.1%)	0	0	0
直腸出血	1 (0.1%)	1 (0.1%)	0	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	355 (51.3%)	197 (28.5%)	145 (21.0%)	13 (1.9%)	0	0
疲労	188 (27.2%)	130 (18.8%)	55 (7.9%)	3 (0.4%)	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
発熱	95 (13.7%)	63 (9.1%)	29 (4.2%)	3 (0.4%)	0	0
悪寒	61 (8.8%)	31 (4.5%)	26 (3.8%)	4 (0.6%)	0	0
粘膜の炎症	34 (4.9%)	24 (3.5%)	9 (1.3%)	1 (0.1%)	0	0
胸部不快感	24 (3.5%)	12 (1.7%)	11 (1.6%)	1 (0.1%)	0	0
倦怠感	21 (3.0%)	14 (2.0%)	7 (1.0%)	0	0	0
無力症	19 (2.7%)	17 (2.5%)	2 (0.3%)	0	0	0
インフルエンザ様疾患	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
熱感	9 (1.3%)	3 (0.4%)	5 (0.7%)	1 (0.1%)	0	0
末梢性浮腫	9 (1.3%)	8 (1.2%)	1 (0.1%)	0	0	0
末梢腫脹	7 (1.0%)	4 (0.6%)	3 (0.4%)	0	0	0
疼痛	7 (1.0%)	3 (0.4%)	4 (0.6%)	0	0	0
注射部位疼痛	9 (1.3%)	6 (0.9%)	3 (0.4%)	0	0	0
胸痛	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
注射部位反応	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
注入部位血管外漏出	5 (0.7%)	0	5 (0.7%)	0	0	0
非心臓性胸痛	5 (0.7%)	5 (0.7%)	0	0	0	0
浮腫	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
冷感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
注入部位疼痛	2 (0.3%)	2 (0.3%)	0	0	0	0
カテーテル留置部位疼痛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
顔面浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
異物感	1 (0.1%)	0	1 (0.1%)	0	0	0
全身健康状態低下	1 (0.1%)	0	1 (0.1%)	0	0	0
不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
限局性浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
医薬品副作用	1 (0.1%)	0	0	1 (0.1%)	0	0
顔面痛	1 (0.1%)	0	1 (0.1%)	0	0	0
空腹	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位発疹	1 (0.1%)	1 (0.1%)	0	0	0	0
注入部位冷感	1 (0.1%)	0	1 (0.1%)	0	0	0
粘膜出血	1 (0.1%)	1 (0.1%)	0	0	0	0
傷害、中毒および処置合併症						
- Overall -	339 (49.0%)	128 (18.5%)	177 (25.6%)	31 (4.5%)	3 (0.4%)	0
注入に伴う反応	337 (48.7%)	128 (18.5%)	176 (25.4%)	31 (4.5%)	2 (0.3%)	0
挫傷	2 (0.3%)	2 (0.3%)	0	0	0	0
骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
圧迫骨折	1 (0.1%)	0	0	0	1 (0.1%)	0
外傷性肺損傷	1 (0.1%)	0	1 (0.1%)	0	0	0
腰椎骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
腹部創離開	1 (0.1%)	1 (0.1%)	0	0	0	0
裂傷	1 (0.1%)	0	1 (0.1%)	0	0	0
血液およびリンパ系障害						
- Overall -	334 (48.3%)	8 (1.2%)	33 (4.8%)	112 (16.2%)	180 (26.0%)	1 (0.1%)
好中球減少症	282 (40.8%)	9 (1.3%)	24 (3.5%)	92 (13.3%)	157 (22.7%)	0
白血球減少症	78 (11.3%)	7 (1.0%)	15 (2.2%)	40 (5.8%)	16 (2.3%)	0
血小板減少症	46 (6.6%)	14 (2.0%)	14 (2.0%)	13 (1.9%)	5 (0.7%)	0
貧血	47 (6.8%)	10 (1.4%)	24 (3.5%)	13 (1.9%)	0	0

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aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
発熱性好中球減少症	37 (5.3%)	0	1 (0.1%)	19 (2.7%)	17 (2.5%)	0
リンパ球減少症	12 (1.7%)	1 (0.1%)	3 (0.4%)	5 (0.7%)	3 (0.4%)	0
骨髄機能不全	5 (0.7%)	0	0	2 (0.3%)	3 (0.4%)	0
顆粒球減少症	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
汎血球減少症	3 (0.4%)	1 (0.1%)	0	2 (0.3%)	0	0
自己免疫性溶血性貧血	1 (0.1%)	0	0	0	0	1 (0.1%)
リンパ節炎	1 (0.1%)	1 (0.1%)	0	0	0	0
低グロブリン血症	1 (0.1%)	1 (0.1%)	0	0	0	0
貪食細胞性組織球症	1 (0.1%)	0	0	0	1 (0.1%)	0
神経系障害						
- Overall -	226 (32.7%)	149 (21.5%)	65 (9.4%)	11 (1.6%)	0	1 (0.1%)
頭痛	53 (7.7%)	40 (5.8%)	13 (1.9%)	0	0	0
味覚異常	48 (6.9%)	44 (6.4%)	4 (0.6%)	0	0	0
末梢性感覚ニューロパチー	42 (6.1%)	31 (4.5%)	10 (1.4%)	1 (0.1%)	0	0
末梢性ニューロパチー	41 (5.9%)	27 (3.9%)	12 (1.7%)	2 (0.3%)	0	0
錯感覚	33 (4.8%)	24 (3.5%)	8 (1.2%)	1 (0.1%)	0	0
浮動性めまい	17 (2.5%)	13 (1.9%)	4 (0.6%)	0	0	0
嗜眠	14 (2.0%)	10 (1.4%)	4 (0.6%)	0	0	0
感覚鈍麻	16 (2.3%)	11 (1.6%)	5 (0.7%)	0	0	0
多発ニューロパチー	15 (2.2%)	7 (1.0%)	7 (1.0%)	0	0	1 (0.1%)
振戦	5 (0.7%)	1 (0.1%)	3 (0.4%)	1 (0.1%)	0	0
失神	5 (0.7%)	2 (0.3%)	0	3 (0.4%)	0	0
記憶障害	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
異常感覚	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
味覚消失	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
神経痛	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
認知障害	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
嗅覚錯誤	2 (0.3%)	2 (0.3%)	0	0	0	0
意識レベルの低下	1 (0.1%)	1 (0.1%)	0	0	0	0
灼熱感	2 (0.3%)	2 (0.3%)	0	0	0	0
体位性めまい	1 (0.1%)	1 (0.1%)	0	0	0	0
頭部不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
副鼻腔炎に伴う頭痛	1 (0.1%)	0	1 (0.1%)	0	0	0
末梢性運動ニューロパチー	1 (0.1%)	0	1 (0.1%)	0	0	0
味覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
感覚消失	1 (0.1%)	1 (0.1%)	0	0	0	0
起立時振戦	1 (0.1%)	0	0	1 (0.1%)	0	0
神経毒性	1 (0.1%)	1 (0.1%)	0	0	0	0
末梢性感覚運動ニューロパチー	1 (0.1%)	0	1 (0.1%)	0	0	0
腕神経叢障害	1 (0.1%)	0	0	1 (0.1%)	0	0
嗅覚減退	1 (0.1%)	1 (0.1%)	0	0	0	0
感染症および寄生虫症						
- Overall -	226 (32.7%)	39 (5.6%)	139 (20.1%)	44 (6.4%)	4 (0.6%)	0
上気道感染	36 (5.2%)	9 (1.3%)	26 (3.8%)	1 (0.1%)	0	0
帯状疱疹	26 (3.8%)	2 (0.3%)	21 (3.0%)	3 (0.4%)	0	0
鼻咽頭炎	33 (4.8%)	16 (2.3%)	17 (2.5%)	0	0	0
下気道感染	27 (3.9%)	2 (0.3%)	25 (3.6%)	0	0	0
肺炎	18 (2.6%)	1 (0.1%)	5 (0.7%)	10 (1.4%)	2 (0.3%)	0
口腔ヘルペス	18 (2.6%)	11 (1.6%)	6 (0.9%)	1 (0.1%)	0	0
尿路感染	18 (2.6%)	0	16 (2.3%)	2 (0.3%)	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
副鼻腔炎	13 (1.9%)	4 (0.6%)	8 (1.2%)	1 (0.1%)	0	0
気道感染	8 (1.2%)	2 (0.3%)	4 (0.6%)	2 (0.3%)	0	0
気管支炎	8 (1.2%)	2 (0.3%)	6 (0.9%)	0	0	0
口腔カンジダ症	13 (1.9%)	5 (0.7%)	8 (1.2%)	0	0	0
結膜炎	8 (1.2%)	4 (0.6%)	4 (0.6%)	0	0	0
感染	9 (1.3%)	2 (0.3%)	5 (0.7%)	2 (0.3%)	0	0
肺感染	11 (1.6%)	1 (0.1%)	2 (0.3%)	8 (1.2%)	0	0
鼻炎	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
咽頭炎	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
敗血症	4 (0.6%)	0	0	3 (0.4%)	1 (0.1%)	0
膀胱炎	6 (0.9%)	2 (0.3%)	4 (0.6%)	0	0	0
歯肉炎	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
インフルエンザ	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
好中球減少性敗血症	5 (0.7%)	0	2 (0.3%)	2 (0.3%)	1 (0.1%)	0
蜂巣炎	4 (0.6%)	0	3 (0.4%)	1 (0.1%)	0	0
毛包炎	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
外陰部腟カンジダ症	2 (0.3%)	0	2 (0.3%)	0	0	0
単純ヘルペス	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
耳感染	3 (0.4%)	0	3 (0.4%)	0	0	0
胃腸炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
歯感染	1 (0.1%)	1 (0.1%)	0	0	0	0
中耳炎	3 (0.4%)	0	3 (0.4%)	0	0	0
Ｂ型肝炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
口唇感染	2 (0.3%)	0	2 (0.3%)	0	0	0
歯周炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
熱性感染症	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
カンジダ感染	1 (0.1%)	1 (0.1%)	0	0	0	0
異型肺炎	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
急性副鼻腔炎	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔真菌感染	1 (0.1%)	0	1 (0.1%)	0	0	0
真菌感染	2 (0.3%)	2 (0.3%)	0	0	0	0
尿路性敗血症	1 (0.1%)	0	0	0	1 (0.1%)	0
皮膚感染	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚真菌感染	2 (0.3%)	0	2 (0.3%)	0	0	0
アデノイド咽頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
カテーテル留置部位感染	1 (0.1%)	0	1 (0.1%)	0	0	0
陰部ヘルペス	2 (0.3%)	0	2 (0.3%)	0	0	0
外陰部炎	1 (0.1%)	0	1 (0.1%)	0	0	0
感染性腸炎	1 (0.1%)	0	1 (0.1%)	0	0	0
菌血症	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌性肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
歯膿瘍	2 (0.3%)	0	2 (0.3%)	0	0	0
粘膜感染	1 (0.1%)	0	1 (0.1%)	0	0	0
敗血症性ショック	2 (0.3%)	0	0	2 (0.3%)	0	0
白癬感染	1 (0.1%)	1 (0.1%)	0	0	0	0
皮下組織膿瘍	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
扁桃炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性上気道感染	1 (0.1%)	0	1 (0.1%)	0	0	0
カンジダ性亀頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
パルボウイルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ブドウ球菌性膿痂疹	1 (0.1%)	1 (0.1%)	0	0	0	0
ヘモフィルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
ヘルペスウイルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
眼窩周囲蜂巣炎	1 (0.1%)	0	0	1 (0.1%)	0	0
気管気管支炎	1 (0.1%)	0	1 (0.1%)	0	0	0
憩室炎	1 (0.1%)	0	1 (0.1%)	0	0	0
神経ボレリア症	1 (0.1%)	0	0	1 (0.1%)	0	0
神経合併症を伴う帯状疱疹感染	1 (0.1%)	0	0	1 (0.1%)	0	0
足部白癬	1 (0.1%)	1 (0.1%)	0	0	0	0
椎間板炎	1 (0.1%)	0	1 (0.1%)	0	0	0
爪囲炎	1 (0.1%)	1 (0.1%)	0	0	0	0
乳様突起炎	1 (0.1%)	0	0	1 (0.1%)	0	0
尿道炎	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻ヘルペス	1 (0.1%)	1 (0.1%)	0	0	0	0
迷路炎	1 (0.1%)	0	1 (0.1%)	0	0	0
卵巣細菌感染	1 (0.1%)	0	0	1 (0.1%)	0	0
肛門直腸感染	1 (0.1%)	0	1 (0.1%)	0	0	0
肛門膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚および皮下組織障害						
- Overall -	240 (34.7%)	118 (17.1%)	108 (15.6%)	14 (2.0%)	0	0
脱毛症	73 (10.5%)	36 (5.2%)	36 (5.2%)	1 (0.1%)	0	0
発疹	70 (10.1%)	32 (4.6%)	31 (4.5%)	7 (1.0%)	0	0
そう痒症	60 (8.7%)	41 (5.9%)	18 (2.6%)	1 (0.1%)	0	0
紅斑	18 (2.6%)	9 (1.3%)	9 (1.3%)	0	0	0
皮膚乾燥	19 (2.7%)	17 (2.5%)	2 (0.3%)	0	0	0
蕁麻疹	17 (2.5%)	3 (0.4%)	12 (1.7%)	2 (0.3%)	0	0
多汗症	11 (1.6%)	7 (1.0%)	4 (0.6%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
斑状丘疹状皮疹	12 (1.7%)	3 (0.4%)	6 (0.9%)	3 (0.4%)	0	0
ざ瘡様皮膚炎	4 (0.6%)	4 (0.6%)	0	0	0	0
湿疹	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
そう痒性皮疹	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
斑状皮疹	4 (0.6%)	0	4 (0.6%)	0	0	0
冷汗	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
寝汗	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
皮膚剥脱	2 (0.3%)	2 (0.3%)	0	0	0	0
爪変色	5 (0.7%)	5 (0.7%)	0	0	0	0
顔面腫脹	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
紅斑性皮疹	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
光線過敏性反応	1 (0.1%)	1 (0.1%)	0	0	0	0
脂漏性皮膚炎	1 (0.1%)	1 (0.1%)	0	0	0	0
多形紅斑	2 (0.3%)	0	2 (0.3%)	0	0	0
爪の障害	2 (0.3%)	2 (0.3%)	0	0	0	0
皮膚炎	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚色素過剰	3 (0.4%)	3 (0.4%)	0	0	0	0
酒さ	1 (0.1%)	1 (0.1%)	0	0	0	0
色素沈着障害	1 (0.1%)	1 (0.1%)	0	0	0	0
水疱	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
全身性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
点状出血	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
薬疹	1 (0.1%)	0	1 (0.1%)	0	0	0
アレルギー性皮膚炎	1 (0.1%)	0	1 (0.1%)	0	0	0
丘疹性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
手掌・足底発赤知覚不全症候群	1 (0.1%)	0	0	1 (0.1%)	0	0
全身紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
中毒性皮疹	1 (0.1%)	0	1 (0.1%)	0	0	0
爪破損	1 (0.1%)	1 (0.1%)	0	0	0	0
皮下出血	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚刺激	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚障害	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚病変	1 (0.1%)	0	1 (0.1%)	0	0	0
痂皮	1 (0.1%)	1 (0.1%)	0	0	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	182 (26.3%)	84 (12.1%)	80 (11.6%)	17 (2.5%)	1 (0.1%)	0
呼吸困難	47 (6.8%)	21 (3.0%)	18 (2.6%)	8 (1.2%)	0	0
咳嗽	36 (5.2%)	27 (3.9%)	8 (1.2%)	1 (0.1%)	0	0
口腔咽頭痛	39 (5.6%)	28 (4.0%)	9 (1.3%)	2 (0.3%)	0	0
咽喉刺激感	33 (4.8%)	15 (2.2%)	18 (2.6%)	0	0	0
低酸素症	4 (0.6%)	0	4 (0.6%)	0	0	0
湿性咳嗽	7 (1.0%)	4 (0.6%)	2 (0.3%)	1 (0.1%)	0	0
鼻漏	3 (0.4%)	3 (0.4%)	0	0	0	0
咽喉絞扼感	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
鼻閉	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
しゃっくり	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
労作性呼吸困難	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
間質性肺疾患	5 (0.7%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	0	0
口腔咽頭不快感	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
鼻出血	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0

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aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
咽頭異常感覚	3 (0.4%)	3 (0.4%)	0	0	0	0
気管支痙攣	3 (0.4%)	0	2 (0.3%)	0	1 (0.1%)	0
上気道咳症候群	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
喘鳴	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
肺塞栓症	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
発声障害	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
アレルギー性鼻炎	2 (0.3%)	0	2 (0.3%)	0	0	0
咽喉乾燥	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
咽頭浮腫	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
胸膜痛	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
肺臓炎	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
咽頭知覚不全	1 (0.1%)	1 (0.1%)	0	0	0	0
喉頭の炎症	2 (0.3%)	2 (0.3%)	0	0	0	0
喉頭痛	2 (0.3%)	2 (0.3%)	0	0	0	0
頻呼吸	1 (0.1%)	0	0	1 (0.1%)	0	0
副鼻腔うっ血	1 (0.1%)	0	1 (0.1%)	0	0	0
喘息	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
ラ音	1 (0.1%)	1 (0.1%)	0	0	0	0
過換気	1 (0.1%)	1 (0.1%)	0	0	0	0
気管支拡張症	1 (0.1%)	0	1 (0.1%)	0	0	0
呼吸窮迫	1 (0.1%)	0	1 (0.1%)	0	0	0
喉頭不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
上気道性喘鳴	1 (0.1%)	1 (0.1%)	0	0	0	0
息詰まり	1 (0.1%)	0	1 (0.1%)	0	0	0
息詰まり感	1 (0.1%)	1 (0.1%)	0	0	0	0
窒息	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
窒息感	1 (0.1%)	0	1 (0.1%)	0	0	0
鼻閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
血管障害						
- Overall -	105 (15.2%)	54 (7.8%)	41 (5.9%)	10 (1.4%)	0	0
潮紅	30 (4.3%)	18 (2.6%)	12 (1.7%)	0	0	0
低血圧	16 (2.3%)	9 (1.3%)	5 (0.7%)	2 (0.3%)	0	0
高血圧	22 (3.2%)	6 (0.9%)	10 (1.4%)	6 (0.9%)	0	0
ほてり	9 (1.3%)	6 (0.9%)	3 (0.4%)	0	0	0
静脈炎	7 (1.0%)	3 (0.4%)	4 (0.6%)	0	0	0
静脈障害	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
血栓性静脈炎	8 (1.2%)	3 (0.4%)	5 (0.7%)	0	0	0
血管炎	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
血管痛	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
表在性血栓性静脈炎	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
起立性低血圧	1 (0.1%)	0	0	1 (0.1%)	0	0
静脈硬化症	1 (0.1%)	1 (0.1%)	0	0	0	0
表在性静脈炎	1 (0.1%)	1 (0.1%)	0	0	0	0
血圧変動	1 (0.1%)	1 (0.1%)	0	0	0	0
血栓性静脈瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
深部静脈血栓症	1 (0.1%)	0	0	1 (0.1%)	0	0
末梢循環不良	1 (0.1%)	1 (0.1%)	0	0	0	0
代謝および栄養障害						
- Overall -	92 (13.3%)	62 (9.0%)	19 (2.7%)	11 (1.6%)	0	0
食欲減退	63 (9.1%)	51 (7.4%)	11 (1.6%)	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
低カリウム血症	10 (1.4%)	9 (1.3%)	1 (0.1%)	0	0	0
高尿酸血症	8 (1.2%)	8 (1.2%)	0	0	0	0
高血糖	6 (0.9%)	4 (0.6%)	1 (0.1%)	1 (0.1%)	0	0
糖尿病	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
腫瘍崩壊症候群	3 (0.4%)	0	0	3 (0.4%)	0	0
低リン酸血症	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
脱水	4 (0.6%)	0	2 (0.3%)	2 (0.3%)	0	0
低マグネシウム血症	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
高カルシウム血症	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
痛風	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
高カリウム血症	1 (0.1%)	1 (0.1%)	0	0	0	0
パントテン酸欠乏	1 (0.1%)	1 (0.1%)	0	0	0	0
高ナトリウム血症	1 (0.1%)	1 (0.1%)	0	0	0	0
低カルシウム血症	1 (0.1%)	0	1 (0.1%)	0	0	0
低尿酸血症	1 (0.1%)	1 (0.1%)	0	0	0	0
筋骨格系および結合組織障害						
- Overall -	74 (10.7%)	48 (6.9%)	25 (3.6%)	1 (0.1%)	0	0
関節痛	16 (2.3%)	13 (1.9%)	3 (0.4%)	0	0	0
筋肉痛	9 (1.3%)	7 (1.0%)	1 (0.1%)	1 (0.1%)	0	0
背部痛	13 (1.9%)	9 (1.3%)	4 (0.6%)	0	0	0
四肢痛	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
筋痙縮	12 (1.7%)	7 (1.0%)	5 (0.7%)	0	0	0
筋力低下	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
骨痛	8 (1.2%)	4 (0.6%)	4 (0.6%)	0	0	0
頚部痛	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
筋骨格痛	1 (0.1%)	1 (0.1%)	0	0	0	0
関節炎	1 (0.1%)	0	1 (0.1%)	0	0	0
筋骨格系胸痛	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
側腹部痛	2 (0.3%)	2 (0.3%)	0	0	0	0
関節周囲炎	1 (0.1%)	1 (0.1%)	0	0	0	0
筋緊張	1 (0.1%)	1 (0.1%)	0	0	0	0
弾発指	1 (0.1%)	0	1 (0.1%)	0	0	0
好酸球性筋膜炎	1 (0.1%)	0	1 (0.1%)	0	0	0
骨粗鬆症	1 (0.1%)	1 (0.1%)	0	0	0	0
四肢不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
閉経後骨粗鬆症	1 (0.1%)	1 (0.1%)	0	0	0	0
鼡径部痛	1 (0.1%)	1 (0.1%)	0	0	0	0
臨床検査						
- Overall -	59 (8.5%)	27 (3.9%)	24 (3.5%)	8 (1.2%)	0	0
アラニンアミノトランスフェラーゼ増加	10 (1.4%)	10 (1.4%)	0	0	0	0
体重減少	17 (2.5%)	3 (0.4%)	13 (1.9%)	1 (0.1%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	6 (0.9%)	6 (0.9%)	0	0	0	0
γ－グルタミルトランスフェラーゼ増加	6 (0.9%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0
体温上昇	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
血中ビリルビン増加	2 (0.3%)	0	2 (0.3%)	0	0	0
血中アルカリホスファターゼ増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中クレアチニン増加	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
血圧上昇	2 (0.3%)	0	0	2 (0.3%)	0	0
Ｃ－反応性蛋白増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中乳酸脱水素酵素増加	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
酸素飽和度低下	1 (0.1%)	0	0	1 (0.1%)	0	0
体重増加	3 (0.4%)	3 (0.4%)	0	0	0	0
トランスアミナーゼ上昇	1 (0.1%)	0	0	1 (0.1%)	0	0
肝機能検査異常	1 (0.1%)	0	0	1 (0.1%)	0	0
駆出率減少	1 (0.1%)	1 (0.1%)	0	0	0	0
血中コレステロール増加	1 (0.1%)	1 (0.1%)	0	0	0	0
心電図ＱＴ延長	1 (0.1%)	1 (0.1%)	0	0	0	0
尿量減少	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
ＲＳウイルス検査陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
握力低下	1 (0.1%)	1 (0.1%)	0	0	0	0
胸部コンピュータ断層撮影異常	1 (0.1%)	1 (0.1%)	0	0	0	0
血圧低下	1 (0.1%)	0	1 (0.1%)	0	0	0
血中ブドウ糖増加	1 (0.1%)	0	1 (0.1%)	0	0	0
血中免疫グロブリンＡ減少	1 (0.1%)	0	1 (0.1%)	0	0	0
血中免疫グロブリンＭ減少	1 (0.1%)	0	1 (0.1%)	0	0	0
好中球数	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌検査陽性	1 (0.1%)	0	1 (0.1%)	0	0	0
尿中白血球陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
精神障害						
- Overall -	43 (6.2%)	26 (3.8%)	16 (2.3%)	1 (0.1%)	0	0
不眠症	32 (4.6%)	19 (2.7%)	12 (1.7%)	1 (0.1%)	0	0
うつ病	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
易刺激性	2 (0.3%)	2 (0.3%)	0	0	0	0
不安	2 (0.3%)	0	2 (0.3%)	0	0	0
落ち着きのなさ	2 (0.3%)	2 (0.3%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
抑うつ気分	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
睡眠障害	1 (0.1%)	1 (0.1%)	0	0	0	0
心臓障害						
- Overall -	24 (3.5%)	10 (1.4%)	6 (0.9%)	4 (0.6%)	4 (0.6%)	0
頻脈	7 (1.0%)	3 (0.4%)	3 (0.4%)	1 (0.1%)	0	0
動悸	6 (0.9%)	5 (0.7%)	0	1 (0.1%)	0	0
洞性頻脈	2 (0.3%)	2 (0.3%)	0	0	0	0
徐脈	2 (0.3%)	0	2 (0.3%)	0	0	0
心不全	3 (0.4%)	0	0	0	3 (0.4%)	0
狭心症	1 (0.1%)	0	1 (0.1%)	0	0	0
心房細動	1 (0.1%)	0	0	1 (0.1%)	0	0
うっ血性心筋症	1 (0.1%)	0	1 (0.1%)	0	0	0
うっ血性心不全	1 (0.1%)	0	0	1 (0.1%)	0	0
冠動脈狭窄	1 (0.1%)	0	0	0	1 (0.1%)	0
心原性ショック	1 (0.1%)	0	0	0	1 (0.1%)	0
心室血栓症	1 (0.1%)	0	0	1 (0.1%)	0	0
慢性心不全	1 (0.1%)	0	0	1 (0.1%)	0	0
眼障害						
- Overall -	24 (3.5%)	14 (2.0%)	8 (1.2%)	2 (0.3%)	0	0
霧視	5 (0.7%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0	0
眼乾燥	3 (0.4%)	3 (0.4%)	0	0	0	0
眼そう痒症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
流涙増加	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
眼痛	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
眼瞼浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
眼窩周囲浮腫	2 (0.3%)	2 (0.3%)	0	0	0	0
結膜刺激	1 (0.1%)	1 (0.1%)	0	0	0	0
視力低下	1 (0.1%)	1 (0.1%)	0	0	0	0
眼のアレルギー	1 (0.1%)	0	1 (0.1%)	0	0	0
眼部腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
結膜出血	1 (0.1%)	1 (0.1%)	0	0	0	0
虹彩炎	1 (0.1%)	0	1 (0.1%)	0	0	0
白内障	1 (0.1%)	0	0	1 (0.1%)	0	0
免疫系障害						
- Overall -	21 (3.0%)	1 (0.1%)	14 (2.0%)	5 (0.7%)	1 (0.1%)	0
低γグロブリン血症	7 (1.0%)	0	5 (0.7%)	2 (0.3%)	0	0
過敏症	9 (1.3%)	1 (0.1%)	6 (0.9%)	1 (0.1%)	1 (0.1%)	0
アナフィラキシー反応	1 (0.1%)	0	0	1 (0.1%)	0	0
季節性アレルギー	2 (0.3%)	0	2 (0.3%)	0	0	0
免疫不全症	1 (0.1%)	0	0	1 (0.1%)	0	0
薬物過敏症	1 (0.1%)	0	1 (0.1%)	0	0	0
耳および迷路障害						
- Overall -	25 (3.6%)	11 (1.6%)	13 (1.9%)	1 (0.1%)	0	0
耳そう痒症	9 (1.3%)	2 (0.3%)	7 (1.0%)	0	0	0
回転性めまい	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
耳痛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
耳不快感	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
耳鳴	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
聴力低下	1 (0.1%)	0	1 (0.1%)	0	0	0
耳閉	1 (0.1%)	1 (0.1%)	0	0	0	0
乗物酔い	1 (0.1%)	0	1 (0.1%)	0	0	0
突発性難聴	1 (0.1%)	0	0	1 (0.1%)	0	0
腎および尿路障害						
- Overall -	14 (2.0%)	11 (1.6%)	3 (0.4%)	0	0	0
頻尿	2 (0.3%)	2 (0.3%)	0	0	0	0
排尿困難	5 (0.7%)	5 (0.7%)	0	0	0	0
非感染性膀胱炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
腎仙痛	1 (0.1%)	0	1 (0.1%)	0	0	0
腎臓痛	1 (0.1%)	1 (0.1%)	0	0	0	0
腎損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
多尿	1 (0.1%)	0	1 (0.1%)	0	0	0
尿管結石	1 (0.1%)	1 (0.1%)	0	0	0	0
排尿躊躇	1 (0.1%)	1 (0.1%)	0	0	0	0
生殖系および乳房障害						
- Overall -	13 (1.9%)	6 (0.9%)	5 (0.7%)	2 (0.3%)	0	0
無月経	3 (0.4%)	3 (0.4%)	0	0	0	0
不規則月経	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
骨盤痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
閉経期症状	1 (0.1%)	1 (0.1%)	0	0	0	0
外陰腟そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
外陰腟痛	1 (0.1%)	0	1 (0.1%)	0	0	0
女性化乳房	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
勃起不全	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
陰嚢紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
閉経期障害	1 (0.1%)	1 (0.1%)	0	0	0	0
膣潰瘍	1 (0.1%)	0	0	1 (0.1%)	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）						
- Overall -	6 (0.9%)	1 (0.1%)	2 (0.3%)	2 (0.3%)	0	1 (0.1%)
腫瘍フレア	1 (0.1%)	0	0	1 (0.1%)	0	0
基底細胞癌	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
ケラトアカントーマ	1 (0.1%)	0	0	1 (0.1%)	0	0
結腸癌	1 (0.1%)	1 (0.1%)	0	0	0	0
肺腺癌	1 (0.1%)	0	0	0	0	1 (0.1%)
肛門性器疣贅	1 (0.1%)	0	1 (0.1%)	0	0	0
肝胆道系障害						
- Overall -	8 (1.2%)	1 (0.1%)	3 (0.4%)	3 (0.4%)	1 (0.1%)	0
肝機能異常	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
高ビリルビン血症	2 (0.3%)	0	2 (0.3%)	0	0	0
脂肪肝	1 (0.1%)	1 (0.1%)	0	0	0	0
胆嚢炎	1 (0.1%)	0	0	0	1 (0.1%)	0
肝損傷	1 (0.1%)	0	0	1 (0.1%)	0	0
内分泌障害						
- Overall -	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
ステロイド離脱症候群	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
甲状腺機能低下症	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: R-chemo (N=692)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
甲状腺機能亢進症	1 (0.1%)	0	1 (0.1%)	0	0	0
外科および内科処置						
- Overall -	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
歯内療法	1 (0.1%)	0	1 (0.1%)	0	0	0
白内障手術	1 (0.1%)	0	1 (0.1%)	0	0	0
抜歯	1 (0.1%)	1 (0.1%)	0	0	0	0
先天性、家族性および遺伝性障害						
- Overall -	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
毛包性角化症	1 (0.1%)	1 (0.1%)	0	0	0	0
腓骨部筋萎縮症	1 (0.1%)	0	0	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	663 (95.0%)	56 (8.0%)	182 (26.1%)	194 (27.8%)	218 (31.2%)	13 (1.9%)
胃腸障害						
- Overall -	444 (63.6%)	220 (31.5%)	200 (28.7%)	21 (3.0%)	1 (0.1%)	2 (0.3%)
悪心	298 (42.7%)	182 (26.1%)	108 (15.5%)	7 (1.0%)	1 (0.1%)	0
便秘	134 (19.2%)	93 (13.3%)	39 (5.6%)	2 (0.3%)	0	0
嘔吐	118 (16.9%)	68 (9.7%)	45 (6.4%)	5 (0.7%)	0	0
下痢	82 (11.7%)	48 (6.9%)	28 (4.0%)	6 (0.9%)	0	0
口内炎	43 (6.2%)	30 (4.3%)	13 (1.9%)	0	0	0
腹痛	27 (3.9%)	16 (2.3%)	9 (1.3%)	2 (0.3%)	0	0
消化不良	32 (4.6%)	18 (2.6%)	14 (2.0%)	0	0	0
上腹部痛	24 (3.4%)	15 (2.1%)	8 (1.1%)	1 (0.1%)	0	0
口腔内潰瘍形成	12 (1.7%)	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0
口内乾燥	14 (2.0%)	13 (1.9%)	1 (0.1%)	0	0	0
口腔内痛	12 (1.7%)	9 (1.3%)	3 (0.4%)	0	0	0
腹部不快感	14 (2.0%)	10 (1.4%)	4 (0.6%)	0	0	0
腹部膨満	8 (1.1%)	5 (0.7%)	2 (0.3%)	1 (0.1%)	0	0
胃食道逆流性疾患	7 (1.0%)	1 (0.1%)	6 (0.9%)	0	0	0
胃炎	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
口の錯感覚	5 (0.7%)	5 (0.7%)	0	0	0	0
アフタ性潰瘍	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
歯肉痛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
歯痛	1 (0.1%)	0	1 (0.1%)	0	0	0
嚥下障害	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
口腔そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
食道炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
舌潰瘍	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
放屁	1 (0.1%)	0	1 (0.1%)	0	0	0
イレウス	2 (0.3%)	0	2 (0.3%)	0	0	0
口腔知覚不全	2 (0.3%)	2 (0.3%)	0	0	0	0
痔核	2 (0.3%)	2 (0.3%)	0	0	0	0
消化器痛	1 (0.1%)	1 (0.1%)	0	0	0	0
舌炎	1 (0.1%)	1 (0.1%)	0	0	0	0
腸炎	2 (0.3%)	0	2 (0.3%)	0	0	0
流涎過多	2 (0.3%)	2 (0.3%)	0	0	0	0
裂肛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
胃出血	1 (0.1%)	0	0	0	0	1 (0.1%)
胃腸出血	1 (0.1%)	1 (0.1%)	0	0	0	0
血便排泄	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔粘膜疹	1 (0.1%)	0	1 (0.1%)	0	0	0
口唇炎	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇潰瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
歯周の炎症	1 (0.1%)	0	1 (0.1%)	0	0	0
痔出血	1 (0.1%)	0	1 (0.1%)	0	0	0
上部消化管出血	1 (0.1%)	0	0	0	0	1 (0.1%)
舌腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
舌障害	1 (0.1%)	1 (0.1%)	0	0	0	0
舌苔	1 (0.1%)	1 (0.1%)	0	0	0	0
舌痛	1 (0.1%)	1 (0.1%)	0	0	0	0
排便痛	1 (0.1%)	1 (0.1%)	0	0	0	0
嚥下痛	1 (0.1%)	1 (0.1%)	0	0	0	0
膵炎	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
齲歯	1 (0.1%)	1 (0.1%)	0	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	429 (61.5%)	232 (33.2%)	168 (24.1%)	26 (3.7%)	2 (0.3%)	1 (0.1%)
疲労	194 (27.8%)	130 (18.6%)	56 (8.0%)	8 (1.1%)	0	0
発熱	148 (21.2%)	92 (13.2%)	48 (6.9%)	6 (0.9%)	2 (0.3%)	0
悪寒	115 (16.5%)	60 (8.6%)	50 (7.2%)	5 (0.7%)	0	0
粘膜の炎症	28 (4.0%)	19 (2.7%)	7 (1.0%)	2 (0.3%)	0	0
胸部不快感	36 (5.2%)	19 (2.7%)	15 (2.1%)	2 (0.3%)	0	0
倦怠感	21 (3.0%)	17 (2.4%)	4 (0.6%)	0	0	0
無力症	17 (2.4%)	7 (1.0%)	10 (1.4%)	0	0	0
インフルエンザ様疾患	15 (2.1%)	13 (1.9%)	2 (0.3%)	0	0	0
熱感	12 (1.7%)	3 (0.4%)	7 (1.0%)	2 (0.3%)	0	0
末梢性浮腫	11 (1.6%)	8 (1.1%)	3 (0.4%)	0	0	0
末梢腫脹	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
疼痛	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
注射部位疼痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
胸痛	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
注射部位反応	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
注入部位血管外漏出	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
非心臓性胸痛	4 (0.6%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0
浮腫	5 (0.7%)	5 (0.7%)	0	0	0	0
冷感	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
注入部位疼痛	5 (0.7%)	5 (0.7%)	0	0	0	0
カテーテル留置部位疼痛	2 (0.3%)	2 (0.3%)	0	0	0	0
顔面浮腫	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
異物感	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
溢出	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
全身健康状態低下	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
粘膜乾燥	4 (0.6%)	4 (0.6%)	0	0	0	0
不快感	3 (0.4%)	3 (0.4%)	0	0	0	0
異常感	2 (0.3%)	2 (0.3%)	0	0	0	0
苦悶感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
限局性浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
カテーテル留置部位腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
カテーテル留置部位静脈炎	1 (0.1%)	1 (0.1%)	0	0	0	0
口渇	1 (0.1%)	1 (0.1%)	0	0	0	0
高熱	1 (0.1%)	1 (0.1%)	0	0	0	0
死亡	1 (0.1%)	0	0	0	0	1 (0.1%)
早期満腹	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位そう痒感	1 (0.1%)	0	1 (0.1%)	0	0	0
注入部位反応	1 (0.1%)	0	1 (0.1%)	0	0	0
傷害、中毒および処置合併症						
- Overall -	427 (61.2%)	129 (18.5%)	250 (35.8%)	39 (5.6%)	9 (1.3%)	0
注入に伴う反応	426 (61.0%)	129 (18.5%)	249 (35.7%)	39 (5.6%)	9 (1.3%)	0
挫傷	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
静脈損傷	1 (0.1%)	0	1 (0.1%)	0	0	0
創傷	1 (0.1%)	0	1 (0.1%)	0	0	0
転倒	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血液およびリンパ系障害						
- Overall -	377 (54.0%)	15 (2.1%)	27 (3.9%)	130 (18.6%)	205 (29.4%)	0
好中球減少症	317 (45.4%)	9 (1.3%)	16 (2.3%)	107 (15.3%)	185 (26.5%)	0
白血球減少症	72 (10.3%)	6 (0.9%)	15 (2.1%)	33 (4.7%)	18 (2.6%)	0
血小板減少症	74 (10.6%)	12 (1.7%)	20 (2.9%)	28 (4.0%)	14 (2.0%)	0
貧血	51 (7.3%)	10 (1.4%)	16 (2.3%)	24 (3.4%)	1 (0.1%)	0
発熱性好中球減少症	43 (6.2%)	0	2 (0.3%)	28 (4.0%)	13 (1.9%)	0
リンパ球減少症	5 (0.7%)	1 (0.1%)	0	3 (0.4%)	1 (0.1%)	0
骨髄機能不全	7 (1.0%)	0	0	1 (0.1%)	6 (0.9%)	0
顆粒球減少症	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
血球減少症	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
自己免疫性溶血性貧血	1 (0.1%)	0	0	1 (0.1%)	0	0
播種性血管内凝固	2 (0.3%)	0	2 (0.3%)	0	0	0
血液毒性	1 (0.1%)	0	1 (0.1%)	0	0	0
好酸球増加症	1 (0.1%)	1 (0.1%)	0	0	0	0
無顆粒球症	1 (0.1%)	0	0	1 (0.1%)	0	0
神経系障害						
- Overall -	282 (40.4%)	189 (27.1%)	84 (12.0%)	8 (1.1%)	1 (0.1%)	0
頭痛	72 (10.3%)	54 (7.7%)	18 (2.6%)	0	0	0
味覚異常	56 (8.0%)	51 (7.3%)	5 (0.7%)	0	0	0
末梢性感覚ニューロパチー	48 (6.9%)	36 (5.2%)	9 (1.3%)	3 (0.4%)	0	0
末梢性ニューロパチー	45 (6.4%)	36 (5.2%)	9 (1.3%)	0	0	0
錯感覚	34 (4.9%)	24 (3.4%)	9 (1.3%)	1 (0.1%)	0	0
浮動性めまい	29 (4.2%)	20 (2.9%)	9 (1.3%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
嗜眠	19 (2.7%)	12 (1.7%)	6 (0.9%)	1 (0.1%)	0	0
感覚鈍麻	15 (2.1%)	13 (1.9%)	2 (0.3%)	0	0	0
多発ニューロパチー	16 (2.3%)	7 (1.0%)	8 (1.1%)	1 (0.1%)	0	0
振戦	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
失神	4 (0.6%)	0	2 (0.3%)	2 (0.3%)	0	0
記憶障害	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
異常感覚	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
味覚消失	5 (0.7%)	5 (0.7%)	0	0	0	0
神経痛	2 (0.3%)	0	2 (0.3%)	0	0	0
注意力障害	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
認知障害	1 (0.1%)	1 (0.1%)	0	0	0	0
嗅覚錯誤	2 (0.3%)	2 (0.3%)	0	0	0	0
下肢静止不能症候群	3 (0.4%)	3 (0.4%)	0	0	0	0
感覚障害	3 (0.4%)	3 (0.4%)	0	0	0	0
ヘルペス後神経痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
意識レベルの低下	1 (0.1%)	0	1 (0.1%)	0	0	0
体位性めまい	1 (0.1%)	1 (0.1%)	0	0	0	0
頭部不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
副鼻腔炎に伴う頭痛	1 (0.1%)	1 (0.1%)	0	0	0	0
末梢性運動ニューロパチー	1 (0.1%)	1 (0.1%)	0	0	0	0
味覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
味覚減退	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
てんかん	1 (0.1%)	0	0	0	1 (0.1%)	0
意識消失	1 (0.1%)	0	1 (0.1%)	0	0	0
一過性脳虚血発作	1 (0.1%)	1 (0.1%)	0	0	0	0
失神寸前の状態	1 (0.1%)	0	1 (0.1%)	0	0	0

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aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
知覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
半盲	1 (0.1%)	0	1 (0.1%)	0	0	0
平衡障害	1 (0.1%)	1 (0.1%)	0	0	0	0
片頭痛	1 (0.1%)	1 (0.1%)	0	0	0	0
麻痺	1 (0.1%)	1 (0.1%)	0	0	0	0
無嗅覚	1 (0.1%)	1 (0.1%)	0	0	0	0
迷走神経障害	1 (0.1%)	0	1 (0.1%)	0	0	0
労作性めまい	1 (0.1%)	0	1 (0.1%)	0	0	0
肋間神経痛	1 (0.1%)	0	1 (0.1%)	0	0	0
感染症および寄生虫症						
- Overall -	276 (39.5%)	43 (6.2%)	160 (22.9%)	60 (8.6%)	8 (1.1%)	5 (0.7%)
上気道感染	46 (6.6%)	12 (1.7%)	33 (4.7%)	1 (0.1%)	0	0
帯状疱疹	44 (6.3%)	3 (0.4%)	37 (5.3%)	4 (0.6%)	0	0
鼻咽頭炎	33 (4.7%)	12 (1.7%)	20 (2.9%)	1 (0.1%)	0	0
下気道感染	26 (3.7%)	1 (0.1%)	21 (3.0%)	3 (0.4%)	0	1 (0.1%)
肺炎	30 (4.3%)	1 (0.1%)	12 (1.7%)	16 (2.3%)	0	1 (0.1%)
口腔ヘルペス	23 (3.3%)	11 (1.6%)	11 (1.6%)	1 (0.1%)	0	0
尿路感染	21 (3.0%)	4 (0.6%)	13 (1.9%)	4 (0.6%)	0	0
副鼻腔炎	26 (3.7%)	6 (0.9%)	18 (2.6%)	2 (0.3%)	0	0
気道感染	20 (2.9%)	2 (0.3%)	13 (1.9%)	5 (0.7%)	0	0
気管支炎	19 (2.7%)	2 (0.3%)	15 (2.1%)	2 (0.3%)	0	0
口腔カンジダ症	14 (2.0%)	5 (0.7%)	9 (1.3%)	0	0	0
結膜炎	11 (1.6%)	3 (0.4%)	8 (1.1%)	0	0	0
感染	9 (1.3%)	2 (0.3%)	4 (0.6%)	3 (0.4%)	0	0
肺感染	7 (1.0%)	0	1 (0.1%)	5 (0.7%)	0	1 (0.1%)

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
鼻炎	10 (1.4%)	8 (1.1%)	2 (0.3%)	0	0	0
咽頭炎	10 (1.4%)	5 (0.7%)	5 (0.7%)	0	0	0
敗血症	7 (1.0%)	0	0	3 (0.4%)	4 (0.6%)	0
膀胱炎	5 (0.7%)	2 (0.3%)	2 (0.3%)	1 (0.1%)	0	0
歯肉炎	6 (0.9%)	1 (0.1%)	5 (0.7%)	0	0	0
インフルエンザ	5 (0.7%)	4 (0.6%)	0	1 (0.1%)	0	0
好中球減少性敗血症	4 (0.6%)	0	0	2 (0.3%)	2 (0.3%)	0
蜂巣炎	5 (0.7%)	0	4 (0.6%)	1 (0.1%)	0	0
毛包炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
外陰部腟カンジダ症	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
単純ヘルペス	3 (0.4%)	0	3 (0.4%)	0	0	0
耳感染	3 (0.4%)	0	3 (0.4%)	0	0	0
胃腸炎	3 (0.4%)	3 (0.4%)	0	0	0	0
歯感染	4 (0.6%)	0	2 (0.3%)	2 (0.3%)	0	0
中耳炎	2 (0.3%)	0	2 (0.3%)	0	0	0
慢性副鼻腔炎	5 (0.7%)	0	3 (0.4%)	2 (0.3%)	0	0
Ｂ型肝炎	2 (0.3%)	2 (0.3%)	0	0	0	0
口唇感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
歯周炎	2 (0.3%)	0	2 (0.3%)	0	0	0
熱性感染症	1 (0.1%)	0	1 (0.1%)	0	0	0
腟感染	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
カンジダ感染	2 (0.3%)	0	2 (0.3%)	0	0	0
サイトメガロウイルス感染	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
医療機器関連感染	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
急性副鼻腔炎	2 (0.3%)	0	2 (0.3%)	0	0	0
口腔真菌感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
真菌感染	1 (0.1%)	0	1 (0.1%)	0	0	0
尿路性敗血症	2 (0.3%)	0	0	2 (0.3%)	0	0
皮膚感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
皮膚真菌感染	1 (0.1%)	1 (0.1%)	0	0	0	0
せつ	2 (0.3%)	0	2 (0.3%)	0	0	0
アデノイド咽頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性筋炎	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
カテーテル留置部位感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ニューモシスチス・イロベチイ肺炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
ブドウ球菌感染	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0
外陰部炎	1 (0.1%)	1 (0.1%)	0	0	0	0
外陰腟真菌感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
感染性腸炎	1 (0.1%)	1 (0.1%)	0	0	0	0
菌血症	1 (0.1%)	0	0	1 (0.1%)	0	0
口角口唇炎	2 (0.3%)	2 (0.3%)	0	0	0	0
細気管支炎	2 (0.3%)	0	2 (0.3%)	0	0	0
細菌性肺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
消化管感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
食道カンジダ症	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
爪感染	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
粘膜感染	1 (0.1%)	0	1 (0.1%)	0	0	0
白癬感染	1 (0.1%)	0	1 (0.1%)	0	0	0
副鼻腔気管支炎	2 (0.3%)	0	2 (0.3%)	0	0	0
扁桃炎	1 (0.1%)	1 (0.1%)	0	0	0	0
ＢＫウイルス感染	1 (0.1%)	0	0	1 (0.1%)	0	0
ウイルス血症	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
ウイルス性消化管感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性鼻炎	1 (0.1%)	1 (0.1%)	0	0	0	0
エンテロウイルス性脳炎	1 (0.1%)	0	0	0	1 (0.1%)	0
カンピロバクター感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ブドウ球菌性菌血症	1 (0.1%)	0	0	0	0	1 (0.1%)
ヘモフィルス性肺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ライノウイルス感染	1 (0.1%)	0	0	1 (0.1%)	0	0
医療機器関連敗血症	1 (0.1%)	0	0	1 (0.1%)	0	0
感染による慢性閉塞性気道疾患の増悪	1 (0.1%)	0	0	1 (0.1%)	0	0
感染性下痢	1 (0.1%)	0	0	1 (0.1%)	0	0
感染性舌炎	1 (0.1%)	1 (0.1%)	0	0	0	0
眼感染	1 (0.1%)	0	1 (0.1%)	0	0	0
眼内炎	1 (0.1%)	0	0	1 (0.1%)	0	0
眼部単純ヘルペス	1 (0.1%)	0	1 (0.1%)	0	0	0
結核	1 (0.1%)	0	0	1 (0.1%)	0	0
限局性感染	1 (0.1%)	0	1 (0.1%)	0	0	0
股部白癬	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔感染	1 (0.1%)	0	1 (0.1%)	0	0	0
喉頭炎	1 (0.1%)	1 (0.1%)	0	0	0	0
好中球減少性感染	1 (0.1%)	0	0	1 (0.1%)	0	0
骨盤膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌性気管炎	1 (0.1%)	0	0	0	1 (0.1%)	0
細菌性副鼻腔炎	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌性扁桃炎	1 (0.1%)	0	1 (0.1%)	0	0	0
細菌性膣症	1 (0.1%)	1 (0.1%)	0	0	0	0
歯肉膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
真菌性肺炎	1 (0.1%)	0	0	0	0	1 (0.1%)
真菌性副鼻腔炎	1 (0.1%)	0	0	1 (0.1%)	0	0
水痘	1 (0.1%)	0	1 (0.1%)	0	0	0
水痘帯状疱疹ウイルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
大腸菌感染	1 (0.1%)	0	0	1 (0.1%)	0	0
注入部位感染	1 (0.1%)	1 (0.1%)	0	0	0	0
爪真菌症	1 (0.1%)	0	1 (0.1%)	0	0	0
播種性帯状疱疹	1 (0.1%)	0	0	1 (0.1%)	0	0
肺真菌症	1 (0.1%)	0	1 (0.1%)	0	0	0
麦粒腫	1 (0.1%)	1 (0.1%)	0	0	0	0
百日咳	1 (0.1%)	0	1 (0.1%)	0	0	0
末梢神経感染	1 (0.1%)	0	1 (0.1%)	0	0	0
扁桃周囲膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
癜風	1 (0.1%)	0	1 (0.1%)	0	0	0
臍炎	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚および皮下組織障害						
- Overall -	252 (36.1%)	121 (17.3%)	114 (16.3%)	17 (2.4%)	0	0
脱毛症	84 (12.0%)	42 (6.0%)	42 (6.0%)	0	0	0
発疹	66 (9.5%)	37 (5.3%)	25 (3.6%)	4 (0.6%)	0	0
そう痒症	50 (7.2%)	26 (3.7%)	22 (3.2%)	2 (0.3%)	0	0
紅斑	19 (2.7%)	11 (1.6%)	5 (0.7%)	3 (0.4%)	0	0
皮膚乾燥	16 (2.3%)	13 (1.9%)	3 (0.4%)	0	0	0
蕁麻疹	15 (2.1%)	2 (0.3%)	12 (1.7%)	1 (0.1%)	0	0
多汗症	18 (2.6%)	11 (1.6%)	6 (0.9%)	1 (0.1%)	0	0
斑状丘疹状皮疹	7 (1.0%)	4 (0.6%)	1 (0.1%)	2 (0.3%)	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
ざ瘡様皮膚炎	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
湿疹	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
そう痒性皮疹	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
斑状皮疹	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
冷汗	5 (0.7%)	4 (0.6%)	0	1 (0.1%)	0	0
寝汗	3 (0.4%)	3 (0.4%)	0	0	0	0
皮膚剥脱	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
顔面腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
紅斑性皮疹	1 (0.1%)	0	0	1 (0.1%)	0	0
光線過敏性反応	2 (0.3%)	2 (0.3%)	0	0	0	0
脂漏性皮膚炎	2 (0.3%)	0	2 (0.3%)	0	0	0
多形紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
爪の障害	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
黄色皮膚	2 (0.3%)	2 (0.3%)	0	0	0	0
乾癬	2 (0.3%)	0	2 (0.3%)	0	0	0
酒さ	1 (0.1%)	0	1 (0.1%)	0	0	0
色素沈着障害	1 (0.1%)	1 (0.1%)	0	0	0	0
全身性皮疹	1 (0.1%)	0	1 (0.1%)	0	0	0
点状出血	1 (0.1%)	1 (0.1%)	0	0	0	0
剥脱性皮膚炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
皮膚疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
薬疹	1 (0.1%)	0	1 (0.1%)	0	0	0
過角化	1 (0.1%)	1 (0.1%)	0	0	0	0
丘疹	1 (0.1%)	0	1 (0.1%)	0	0	0
結節性紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
全身性そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
爪線状隆起	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚局面	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚嚢腫	1 (0.1%)	1 (0.1%)	0	0	0	0
痒疹	1 (0.1%)	1 (0.1%)	0	0	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	198 (28.4%)	67 (9.6%)	97 (13.9%)	28 (4.0%)	5 (0.7%)	1 (0.1%)
呼吸困難	77 (11.0%)	23 (3.3%)	34 (4.9%)	18 (2.6%)	2 (0.3%)	0
咳嗽	43 (6.2%)	18 (2.6%)	24 (3.4%)	1 (0.1%)	0	0
口腔咽頭痛	31 (4.4%)	19 (2.7%)	11 (1.6%)	1 (0.1%)	0	0
咽喉刺激感	22 (3.2%)	13 (1.9%)	9 (1.3%)	0	0	0
低酸素症	13 (1.9%)	0	9 (1.3%)	4 (0.6%)	0	0
湿性咳嗽	9 (1.3%)	0	9 (1.3%)	0	0	0
鼻漏	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
咽喉絞扼感	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
鼻閉	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
しゃっくり	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
労作性呼吸困難	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
間質性肺疾患	2 (0.3%)	0	0	2 (0.3%)	0	0
口腔咽頭不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻出血	2 (0.3%)	2 (0.3%)	0	0	0	0
咽頭異常感覚	3 (0.4%)	3 (0.4%)	0	0	0	0
気管支痙攣	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
上気道咳症候群	3 (0.4%)	0	3 (0.4%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
喘鳴	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
肺塞栓症	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
発声障害	2 (0.3%)	2 (0.3%)	0	0	0	0
アレルギー性鼻炎	2 (0.3%)	0	2 (0.3%)	0	0	0
咽喉乾燥	1 (0.1%)	0	1 (0.1%)	0	0	0
咽頭浮腫	1 (0.1%)	0	0	1 (0.1%)	0	0
胸膜痛	1 (0.1%)	0	1 (0.1%)	0	0	0
肺臓炎	1 (0.1%)	0	1 (0.1%)	0	0	0
咽頭紅斑	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
咽頭知覚不全	1 (0.1%)	0	1 (0.1%)	0	0	0
胸水	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
上気道の炎症	2 (0.3%)	0	2 (0.3%)	0	0	0
頻呼吸	1 (0.1%)	1 (0.1%)	0	0	0	0
副鼻腔うっ血	1 (0.1%)	0	1 (0.1%)	0	0	0
慢性閉塞性肺疾患	2 (0.3%)	0	2 (0.3%)	0	0	0
くしゃみ	1 (0.1%)	0	1 (0.1%)	0	0	0
咽頭障害	1 (0.1%)	1 (0.1%)	0	0	0	0
急性呼吸窮迫症候群	1 (0.1%)	0	0	1 (0.1%)	0	0
急性肺損傷	1 (0.1%)	0	0	0	0	1 (0.1%)
胸膜炎	1 (0.1%)	0	1 (0.1%)	0	0	0
呼吸停止	1 (0.1%)	0	0	0	1 (0.1%)	0
肺硬化	1 (0.1%)	0	1 (0.1%)	0	0	0
肺障害	1 (0.1%)	1 (0.1%)	0	0	0	0
肺水腫	1 (0.1%)	0	0	1 (0.1%)	0	0
鼻茸	1 (0.1%)	0	1 (0.1%)	0	0	0
副鼻腔不快感	1 (0.1%)	0	1 (0.1%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
変色痰	1 (0.1%)	0	1 (0.1%)	0	0	0
慢性気管支炎	1 (0.1%)	0	1 (0.1%)	0	0	0
無気肺	1 (0.1%)	1 (0.1%)	0	0	0	0
血管障害						
- Overall -	162 (23.2%)	80 (11.5%)	61 (8.7%)	18 (2.6%)	3 (0.4%)	0
潮紅	44 (6.3%)	23 (3.3%)	20 (2.9%)	1 (0.1%)	0	0
低血圧	40 (5.7%)	18 (2.6%)	13 (1.9%)	7 (1.0%)	2 (0.3%)	0
高血圧	25 (3.6%)	6 (0.9%)	11 (1.6%)	8 (1.1%)	0	0
ほてり	23 (3.3%)	15 (2.1%)	7 (1.0%)	1 (0.1%)	0	0
静脈炎	11 (1.6%)	6 (0.9%)	5 (0.7%)	0	0	0
静脈障害	9 (1.3%)	9 (1.3%)	0	0	0	0
血栓性静脈炎	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
血管炎	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
血管痛	5 (0.7%)	5 (0.7%)	0	0	0	0
表在性血栓性静脈炎	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
末梢冷感	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
起立性低血圧	1 (0.1%)	0	1 (0.1%)	0	0	0
循環虚脱	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
静脈硬化症	1 (0.1%)	1 (0.1%)	0	0	0	0
静脈穿刺不良	2 (0.3%)	0	2 (0.3%)	0	0	0
表在性静脈炎	1 (0.1%)	1 (0.1%)	0	0	0	0
高血圧クリーゼ	1 (0.1%)	0	0	0	1 (0.1%)	0
静脈退色	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
代謝および栄養障害						
- Overall -	106 (15.2%)	65 (9.3%)	28 (4.0%)	10 (1.4%)	2 (0.3%)	1 (0.1%)
食欲減退	67 (9.6%)	55 (7.9%)	11 (1.6%)	1 (0.1%)	0	0
低カリウム血症	13 (1.9%)	9 (1.3%)	3 (0.4%)	1 (0.1%)	0	0
高尿酸血症	8 (1.1%)	8 (1.1%)	0	0	0	0
高血糖	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
糖尿病	6 (0.9%)	1 (0.1%)	4 (0.6%)	1 (0.1%)	0	0
腫瘍崩壊症候群	6 (0.9%)	0	0	5 (0.7%)	1 (0.1%)	0
低リン酸血症	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
脱水	4 (0.6%)	0	2 (0.3%)	1 (0.1%)	0	1 (0.1%)
低マグネシウム血症	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
低ナトリウム血症	4 (0.6%)	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0
痛風	1 (0.1%)	0	1 (0.1%)	0	0	0
高カリウム血症	1 (0.1%)	0	1 (0.1%)	0	0	0
体液貯留	2 (0.3%)	2 (0.3%)	0	0	0	0
２型糖尿病	1 (0.1%)	0	1 (0.1%)	0	0	0
高トリグリセリド血症	1 (0.1%)	0	1 (0.1%)	0	0	0
水分過負荷	1 (0.1%)	0	1 (0.1%)	0	0	0
筋骨格系および結合組織障害						
- Overall -	111 (15.9%)	74 (10.6%)	35 (5.0%)	2 (0.3%)	0	0
関節痛	30 (4.3%)	22 (3.2%)	8 (1.1%)	0	0	0
筋肉痛	21 (3.0%)	16 (2.3%)	5 (0.7%)	0	0	0
背部痛	17 (2.4%)	9 (1.3%)	7 (1.0%)	1 (0.1%)	0	0
四肢痛	22 (3.2%)	14 (2.0%)	8 (1.1%)	0	0	0
筋痙縮	9 (1.3%)	6 (0.9%)	3 (0.4%)	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
筋力低下	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
骨痛	1 (0.1%)	1 (0.1%)	0	0	0	0
頚部痛	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
筋骨格痛	5 (0.7%)	5 (0.7%)	0	0	0	0
顎痛	4 (0.6%)	4 (0.6%)	0	0	0	0
関節炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
側腹部痛	1 (0.1%)	0	1 (0.1%)	0	0	0
関節硬直	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
関節腫脹	2 (0.3%)	2 (0.3%)	0	0	0	0
関節周囲炎	1 (0.1%)	1 (0.1%)	0	0	0	0
関節障害	2 (0.3%)	2 (0.3%)	0	0	0	0
筋緊張	1 (0.1%)	0	1 (0.1%)	0	0	0
弾発指	1 (0.1%)	1 (0.1%)	0	0	0	0
痛風性関節炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
ミオパチー	1 (0.1%)	0	1 (0.1%)	0	0	0
関節滲出液	1 (0.1%)	0	0	1 (0.1%)	0	0
筋炎	1 (0.1%)	0	1 (0.1%)	0	0	0
筋骨格硬直	1 (0.1%)	1 (0.1%)	0	0	0	0
筋膜炎	1 (0.1%)	1 (0.1%)	0	0	0	0
血清反応陰性関節炎	1 (0.1%)	0	1 (0.1%)	0	0	0
骨減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
腱炎	1 (0.1%)	0	1 (0.1%)	0	0	0
腱鞘炎	1 (0.1%)	0	1 (0.1%)	0	0	0
臨床検査						
- Overall -	78 (11.2%)	43 (6.2%)	23 (3.3%)	12 (1.7%)	0	0

Investigator text for AEs encoded using MedDRA version 18.1.
All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
アラニンアミノトランスフェラーゼ増加	22 (3.2%)	13 (1.9%)	7 (1.0%)	2 (0.3%)	0	0
体重減少	15 (2.1%)	9 (1.3%)	5 (0.7%)	1 (0.1%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	15 (2.1%)	12 (1.7%)	3 (0.4%)	0	0	0
γ－グルタミルトランスフェラーゼ増加	5 (0.7%)	2 (0.3%)	1 (0.1%)	2 (0.3%)	0	0
体温上昇	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
血中ビリルビン増加	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
血中アルカリホスファターゼ増加	5 (0.7%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0	0
血中クレアチニン増加	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
血圧上昇	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
Ｃ－反応性蛋白増加	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
血中乳酸脱水素酵素増加	3 (0.4%)	3 (0.4%)	0	0	0	0
酸素飽和度低下	3 (0.4%)	0	3 (0.4%)	0	0	0
体重増加	1 (0.1%)	1 (0.1%)	0	0	0	0
トランスアミナーゼ上昇	1 (0.1%)	0	0	1 (0.1%)	0	0
肝機能検査異常	1 (0.1%)	1 (0.1%)	0	0	0	0
駆出率減少	1 (0.1%)	0	0	1 (0.1%)	0	0
血中コレステロール増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中尿酸増加	2 (0.3%)	2 (0.3%)	0	0	0	0
国際標準比増加	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
心電図ＱＴ延長	1 (0.1%)	1 (0.1%)	0	0	0	0
ＥＣＯＧパフォーマンスステータス悪化	1 (0.1%)	0	0	1 (0.1%)	0	0
サイトメガロウイルス検査陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
レスピロウイルス検査陽性	1 (0.1%)	0	0	1 (0.1%)	0	0
レンサ球菌検査陽性	1 (0.1%)	0	0	1 (0.1%)	0	0
血清フェリチン増加	1 (0.1%)	0	1 (0.1%)	0	0	0
血中クレアチニン減少	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血中クレアチンホスホキナーゼ増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中マグネシウム減少	1 (0.1%)	1 (0.1%)	0	0	0	0
好中球数増加	1 (0.1%)	0	0	1 (0.1%)	0	0
腹腔内圧上昇	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫グロブリン増加	1 (0.1%)	0	1 (0.1%)	0	0	0
精神障害						
- Overall -	54 (7.7%)	38 (5.4%)	11 (1.6%)	4 (0.6%)	1 (0.1%)	0
不眠症	41 (5.9%)	28 (4.0%)	11 (1.6%)	2 (0.3%)	0	0
易刺激性	2 (0.3%)	2 (0.3%)	0	0	0	0
不安	2 (0.3%)	2 (0.3%)	0	0	0	0
落ち着きのなさ	2 (0.3%)	2 (0.3%)	0	0	0	0
気分動揺	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
感情不安定	1 (0.1%)	1 (0.1%)	0	0	0	0
気分変化	1 (0.1%)	0	1 (0.1%)	0	0	0
激越	1 (0.1%)	1 (0.1%)	0	0	0	0
攻撃性	1 (0.1%)	0	1 (0.1%)	0	0	0
錯乱状態	1 (0.1%)	0	0	1 (0.1%)	0	0
精神状態変化	1 (0.1%)	0	0	1 (0.1%)	0	0
精神病性障害	1 (0.1%)	0	0	0	1 (0.1%)	0
離人症	1 (0.1%)	1 (0.1%)	0	0	0	0
涙ぐむ	1 (0.1%)	1 (0.1%)	0	0	0	0
心臓障害						
- Overall -	47 (6.7%)	19 (2.7%)	18 (2.6%)	8 (1.1%)	2 (0.3%)	0
頻脈	14 (2.0%)	3 (0.4%)	10 (1.4%)	1 (0.1%)	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
動悸	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
洞性頻脈	5 (0.7%)	1 (0.1%)	3 (0.4%)	0	1 (0.1%)	0
徐脈	4 (0.6%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0	0
心不全	2 (0.3%)	0	0	2 (0.3%)	0	0
洞性徐脈	5 (0.7%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0
狭心症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
心室性期外収縮	2 (0.3%)	2 (0.3%)	0	0	0	0
心房細動	1 (0.1%)	0	0	1 (0.1%)	0	0
チアノーゼ	1 (0.1%)	1 (0.1%)	0	0	0	0
右脚ブロック	1 (0.1%)	1 (0.1%)	0	0	0	0
急性心筋梗塞	1 (0.1%)	0	0	1 (0.1%)	0	0
上室性期外収縮	1 (0.1%)	1 (0.1%)	0	0	0	0
心筋炎	1 (0.1%)	1 (0.1%)	0	0	0	0
心血管不全	1 (0.1%)	1 (0.1%)	0	0	0	0
心室機能不全	1 (0.1%)	1 (0.1%)	0	0	0	0
第一度房室ブロック	1 (0.1%)	1 (0.1%)	0	0	0	0
眼障害						
- Overall -	28 (4.0%)	21 (3.0%)	6 (0.9%)	1 (0.1%)	0	0
霧視	4 (0.6%)	4 (0.6%)	0	0	0	0
眼乾燥	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
眼そう痒症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
流涙増加	2 (0.3%)	2 (0.3%)	0	0	0	0
眼痛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
眼瞼浮腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
眼窩周囲浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
結膜刺激	1 (0.1%)	1 (0.1%)	0	0	0	0
視力低下	1 (0.1%)	1 (0.1%)	0	0	0	0
ぶどう膜炎	1 (0.1%)	1 (0.1%)	0	0	0	0
角膜混濁	1 (0.1%)	0	0	1 (0.1%)	0	0
眼の異物感	1 (0.1%)	0	1 (0.1%)	0	0	0
眼刺激	1 (0.1%)	1 (0.1%)	0	0	0	0
眼脂	1 (0.1%)	1 (0.1%)	0	0	0	0
眼瞼機能障害	1 (0.1%)	1 (0.1%)	0	0	0	0
眼瞼痙攣	1 (0.1%)	1 (0.1%)	0	0	0	0
虚血性視神経症	1 (0.1%)	0	1 (0.1%)	0	0	0
視力障害	1 (0.1%)	1 (0.1%)	0	0	0	0
羞明	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫系障害						
- Overall -	23 (3.3%)	5 (0.7%)	14 (2.0%)	2 (0.3%)	2 (0.3%)	0
低γグロブリン血症	9 (1.3%)	0	8 (1.1%)	1 (0.1%)	0	0
過敏症	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
アナフィラキシー反応	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
サイトカイン放出症候群	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
ＩｇＡ欠損性免疫不全症	1 (0.1%)	0	1 (0.1%)	0	0	0
ＩｇＭ欠損性免疫不全症	1 (0.1%)	0	1 (0.1%)	0	0	0
アナフィラキシーショック	1 (0.1%)	0	0	0	1 (0.1%)	0
サルコイドーシス	1 (0.1%)	1 (0.1%)	0	0	0	0
選択的ＩｇＧサブクラス欠損症	1 (0.1%)	0	1 (0.1%)	0	0	0
造影剤アレルギー	1 (0.1%)	1 (0.1%)	0	0	0	0

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NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
耳および迷路障害						
- Overall -	16 (2.3%)	11 (1.6%)	4 (0.6%)	1 (0.1%)	0	0
耳そう痒症	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
回転性めまい	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
耳痛	1 (0.1%)	1 (0.1%)	0	0	0	0
耳鳴	1 (0.1%)	0	1 (0.1%)	0	0	0
聴力低下	1 (0.1%)	1 (0.1%)	0	0	0	0
聴覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
頭位性回転性めまい	1 (0.1%)	1 (0.1%)	0	0	0	0
難聴	1 (0.1%)	0	0	1 (0.1%)	0	0
腎および尿路障害						
- Overall -	20 (2.9%)	13 (1.9%)	7 (1.0%)	0	0	0
頻尿	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
排尿困難	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
尿意切迫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
夜間頻尿	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
遺尿	1 (0.1%)	1 (0.1%)	0	0	0	0
血尿	1 (0.1%)	1 (0.1%)	0	0	0	0
出血性膀胱炎	1 (0.1%)	0	1 (0.1%)	0	0	0
尿失禁	1 (0.1%)	1 (0.1%)	0	0	0	0
尿閉	1 (0.1%)	0	1 (0.1%)	0	0	0
腹圧性尿失禁	1 (0.1%)	1 (0.1%)	0	0	0	0
生殖系および乳房障害						
- Overall -	17 (2.4%)	7 (1.0%)	8 (1.1%)	2 (0.3%)	0	0

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To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
無月経	4 (0.6%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0
不規則月経	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
骨盤痛	1 (0.1%)	1 (0.1%)	0	0	0	0
閉経期症状	2 (0.3%)	0	2 (0.3%)	0	0	0
外陰腟そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
外陰腟痛	1 (0.1%)	1 (0.1%)	0	0	0	0
女性化乳房	1 (0.1%)	1 (0.1%)	0	0	0	0
外陰腟乾燥	1 (0.1%)	0	1 (0.1%)	0	0	0
亀頭包皮炎	1 (0.1%)	0	1 (0.1%)	0	0	0
月経困難症	1 (0.1%)	1 (0.1%)	0	0	0	0
子宮頚管分泌	1 (0.1%)	0	1 (0.1%)	0	0	0
乳頭痛	1 (0.1%)	1 (0.1%)	0	0	0	0
良性前立腺肥大症	1 (0.1%)	0	1 (0.1%)	0	0	0
腟分泌物	1 (0.1%)	0	1 (0.1%)	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）						
- Overall -	19 (2.7%)	6 (0.9%)	2 (0.3%)	2 (0.3%)	6 (0.9%)	3 (0.4%)
骨髄異形成症候群	4 (0.6%)	0	0	0	3 (0.4%)	1 (0.1%)
腫瘍フレア	3 (0.4%)	3 (0.4%)	0	0	0	0
基底細胞癌	1 (0.1%)	0	1 (0.1%)	0	0	0
急性骨髄性白血病	2 (0.3%)	0	0	0	1 (0.1%)	1 (0.1%)
Ｔ細胞性リンパ腫	1 (0.1%)	0	0	1 (0.1%)	0	0
ホジキン病	1 (0.1%)	0	0	0	1 (0.1%)	0
急性リンパ性白血病	1 (0.1%)	0	0	0	0	1 (0.1%)
結腸腺癌	1 (0.1%)	0	1 (0.1%)	0	0	0
脂漏性角化症	1 (0.1%)	0	1 (0.1%)	0	0	0

Investigator text for AEs encoded using MedDRA version 18.1.
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To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
NCI-CTCAE ver. 4.0

aet04_rel_223_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity (Safety-Evaluable Patients)

Protocol(s): BO21223 (K21223L)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 29APR2016 Cutoff Date: 31JAN2016:23:59:59

Treatment: G-chemo (N=698)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腫瘍疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
乳癌	1 (0.1%)	0	0	1 (0.1%)	0	0
皮膚良性新生物	1 (0.1%)	1 (0.1%)	0	0	0	0
非小細胞肺癌	1 (0.1%)	0	0	0	1 (0.1%)	0
良性新生物	1 (0.1%)	1 (0.1%)	0	0	0	0
肝胆道系障害						
- Overall -	10 (1.4%)	3 (0.4%)	3 (0.4%)	2 (0.3%)	2 (0.3%)	0
肝機能異常	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
高ビリルビン血症	1 (0.1%)	1 (0.1%)	0	0	0	0
肝障害	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
脂肪肝	1 (0.1%)	1 (0.1%)	0	0	0	0
胆嚢炎	1 (0.1%)	0	1 (0.1%)	0	0	0
薬物性肝障害	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
急性肝炎	1 (0.1%)	0	0	0	1 (0.1%)	0
内分泌障害						
- Overall -	7 (1.0%)	3 (0.4%)	4 (0.6%)	0	0	0
ステロイド離脱症候群	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
甲状腺機能低下症	1 (0.1%)	0	1 (0.1%)	0	0	0

Investigator text for AEs encoded using MedDRA version 18.1.
All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
NCI-CTCAE ver. 4.0

Program: /opt/BIOSTAT/prod/cdt7159z/k21223l/aet04_rel.sas / Output: /opt/BIOSTAT/prod/cdt7159z/k21223l/reports/aet04_rel_223_SE.out
03OCT2016 3:55

[5.3.5.1-2 aet04_rel_223_SE を再掲]

2.7.6.2.1.4　GAO4753g 試験（GADOLIN 試験）

表 2.7.6.2.1.4-1　因果関係を問わないすべての有害事象（GAO4753g 試験，リツキシマブ治療抵抗性 iNHL 患者）

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GAO4753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	194 (98.0%)	10 (5.1%)	61 (30.8%)	73 (36.9%)	38 (19.2%)	12 (6.1%)
胃腸障害						
- Overall -	163 (82.3%)	74 (37.4%)	73 (36.9%)	15 (7.6%)	1 (0.5%)	0
悪心	121 (61.1%)	76 (38.4%)	39 (19.7%)	6 (3.0%)	0	0
下痢	60 (30.3%)	38 (19.2%)	17 (8.6%)	4 (2.0%)	1 (0.5%)	0
嘔吐	54 (27.3%)	29 (14.6%)	23 (11.6%)	2 (1.0%)	0	0
便秘	38 (19.2%)	28 (14.1%)	10 (5.1%)	0	0	0
腹痛	18 (9.1%)	13 (6.6%)	4 (2.0%)	1 (0.5%)	0	0
上腹部痛	16 (8.1%)	11 (5.6%)	4 (2.0%)	1 (0.5%)	0	0
消化不良	8 (4.0%)	5 (2.5%)	3 (1.5%)	0	0	0
口内乾燥	11 (5.6%)	10 (5.1%)	1 (0.5%)	0	0	0
腹部膨満	11 (5.6%)	8 (4.0%)	2 (1.0%)	1 (0.5%)	0	0
口内炎	9 (4.5%)	3 (1.5%)	6 (3.0%)	0	0	0
胃食道逆流性疾患	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
下腹部痛	4 (2.0%)	4 (2.0%)	0	0	0	0
口腔内潰瘍形成	2 (1.0%)	0	2 (1.0%)	0	0	0
嚥下障害	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
放屁	3 (1.5%)	3 (1.5%)	0	0	0	0
歯痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
消化器痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
腹部不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
アフタ性口内炎	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
胃炎	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
口腔内痛	1 (0.5%)	1 (0.5%)	0	0	0	0
肛門潰瘍	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
レッチング	1 (0.5%)	1 (0.5%)	0	0	0	0
血便排泄	1 (0.5%)	0	0	1 (0.5%)	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159v/n01297a/ae17.sas / Output: /opt/BIOSTAT/prod/cdt7159v/n01297a/reports/ae17_297_SE.out
09SEP2016 9:00

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
嚥下痛	1 (0.5%)	1 (0.5%)	0	0	0	0
メレナ	1 (0.5%)	0	0	1 (0.5%)	0	0
胃拡張	1 (0.5%)	0	1 (0.5%)	0	0	0
歯肉痛	1 (0.5%)	1 (0.5%)	0	0	0	0
痔出血	1 (0.5%)	1 (0.5%)	0	0	0	0
心窩部不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
舌痛	1 (0.5%)	1 (0.5%)	0	0	0	0
唾液腺結石	1 (0.5%)	0	1 (0.5%)	0	0	0
大腸閉塞	1 (0.5%)	0	0	1 (0.5%)	0	0
直腸炎	1 (0.5%)	0	0	1 (0.5%)	0	0
排便回数増加	1 (0.5%)	1 (0.5%)	0	0	0	0
腹水	1 (0.5%)	1 (0.5%)	0	0	0	0
腹部硬直	1 (0.5%)	1 (0.5%)	0	0	0	0
肛門出血	1 (0.5%)	1 (0.5%)	0	0	0	0
膵機能不全	1 (0.5%)	1 (0.5%)	0	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	131 (66.2%)	70 (35.4%)	52 (26.3%)	9 (4.5%)	0	0
疲労	66 (33.3%)	32 (16.2%)	29 (14.6%)	5 (2.5%)	0	0
発熱	36 (18.2%)	26 (13.1%)	10 (5.1%)	0	0	0
無力症	23 (11.6%)	15 (7.6%)	7 (3.5%)	1 (0.5%)	0	0
悪寒	20 (10.1%)	18 (9.1%)	2 (1.0%)	0	0	0
末梢性浮腫	14 (7.1%)	10 (5.1%)	4 (2.0%)	0	0	0
インフルエンザ様疾患	8 (4.0%)	5 (2.5%)	3 (1.5%)	0	0	0
粘膜の炎症	8 (4.0%)	5 (2.5%)	3 (1.5%)	0	0	0
胸痛	5 (2.5%)	1 (0.5%)	3 (1.5%)	1 (0.5%)	0	0
疼痛	10 (5.1%)	7 (3.5%)	2 (1.0%)	1 (0.5%)	0	0
末梢腫脹	7 (3.5%)	4 (2.0%)	3 (1.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159v/n01297a/ae17.sas / Output: /opt/BIOSTAT/prod/cdt7159v/n01297a/reports/ae17_297_SE.out
09SEP2016 9:00

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
倦怠感	1 (0.5%)	1 (0.5%)	0	0	0	0
注入部位疼痛	5 (2.5%)	4 (2.0%)	1 (0.5%)	0	0	0
注射部位疼痛	2 (1.0%)	2 (1.0%)	0	0	0	0
浮腫	1 (0.5%)	0	1 (0.5%)	0	0	0
カテーテル留置部位疼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
口渇	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
腫脹	1 (0.5%)	0	1 (0.5%)	0	0	0
注射部位反応	2 (1.0%)	2 (1.0%)	0	0	0	0
顔面浮腫	1 (0.5%)	1 (0.5%)	0	0	0	0
胸部不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
血管穿刺部位血腫	2 (1.0%)	2 (1.0%)	0	0	0	0
硬結	1 (0.5%)	1 (0.5%)	0	0	0	0
高熱	1 (0.5%)	0	0	1 (0.5%)	0	0
注入部位血管外漏出	1 (0.5%)	0	1 (0.5%)	0	0	0
非心臓性胸痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
腋窩痛	1 (0.5%)	1 (0.5%)	0	0	0	0
温度変化不耐症	1 (0.5%)	1 (0.5%)	0	0	0	0
乾燥症	1 (0.5%)	0	1 (0.5%)	0	0	0
顔面痛	1 (0.5%)	1 (0.5%)	0	0	0	0
泣き	1 (0.5%)	1 (0.5%)	0	0	0	0
早期満腹	1 (0.5%)	1 (0.5%)	0	0	0	0
注射部位腫脹	1 (0.5%)	1 (0.5%)	0	0	0	0
注入部位炎症	1 (0.5%)	1 (0.5%)	0	0	0	0
注入部位静脈炎	1 (0.5%)	0	1 (0.5%)	0	0	0
低体温	1 (0.5%)	1 (0.5%)	0	0	0	0
歩行障害	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
傷害、中毒および処置合併症						
- Overall -	118 (59.6%)	54 (27.3%)	55 (27.8%)	8 (4.0%)	1 (0.5%)	0
注入に伴う反応	115 (58.1%)	53 (26.8%)	55 (27.8%)	7 (3.5%)	0	0
転倒	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
挫傷	2 (1.0%)	2 (1.0%)	0	0	0	0
手骨折	1 (0.5%)	0	1 (0.5%)	0	0	0
顎の骨折	1 (0.5%)	0	1 (0.5%)	0	0	0
骨亀裂	1 (0.5%)	1 (0.5%)	0	0	0	0
刺創	1 (0.5%)	0	0	1 (0.5%)	0	0
処置による疼痛	1 (0.5%)	0	1 (0.5%)	0	0	0
処置後胆汁漏出	1 (0.5%)	0	0	1 (0.5%)	0	0
食道熱傷	1 (0.5%)	1 (0.5%)	0	0	0	0
頭部損傷	1 (0.5%)	0	0	0	1 (0.5%)	0
感染症および寄生虫症						
- Overall -	110 (55.6%)	20 (10.1%)	56 (28.3%)	24 (12.1%)	3 (1.5%)	7 (3.5%)
上気道感染	16 (8.1%)	7 (3.5%)	8 (4.0%)	1 (0.5%)	0	0
気管支炎	19 (9.6%)	3 (1.5%)	14 (7.1%)	2 (1.0%)	0	0
副鼻腔炎	10 (5.1%)	4 (2.0%)	6 (3.0%)	0	0	0
尿路感染	11 (5.6%)	2 (1.0%)	9 (4.5%)	0	0	0
鼻咽頭炎	8 (4.0%)	6 (3.0%)	2 (1.0%)	0	0	0
帯状疱疹	16 (8.1%)	4 (2.0%)	9 (4.5%)	3 (1.5%)	0	0
肺炎	13 (6.6%)	0	2 (1.0%)	9 (4.5%)	1 (0.5%)	1 (0.5%)
口腔ヘルペス	8 (4.0%)	6 (3.0%)	2 (1.0%)	0	0	0
敗血症	7 (3.5%)	0	0	1 (0.5%)	3 (1.5%)	3 (1.5%)
下気道感染	7 (3.5%)	2 (1.0%)	3 (1.5%)	1 (0.5%)	1 (0.5%)	0
結膜炎	7 (3.5%)	3 (1.5%)	4 (2.0%)	0	0	0
鼻炎	6 (3.0%)	5 (2.5%)	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
咽頭炎	1 (0.5%)	1 (0.5%)	0	0	0	0
肺感染	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
気道感染	3 (1.5%)	0	3 (1.5%)	0	0	0
口腔カンジダ症	4 (2.0%)	1 (0.5%)	3 (1.5%)	0	0	0
蜂巣炎	4 (2.0%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	0	0
胃腸炎	4 (2.0%)	3 (1.5%)	1 (0.5%)	0	0	0
中耳炎	2 (1.0%)	0	2 (1.0%)	0	0	0
ウイルス性気道感染	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
感染	4 (2.0%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	0	0
歯感染	3 (1.5%)	0	2 (1.0%)	1 (0.5%)	0	0
毛包炎	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	0	0
眼感染	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
皮膚感染	2 (1.0%)	0	2 (1.0%)	0	0	0
ニューモシスチス・イロベチイ肺炎	2 (1.0%)	0	0	0	0	2 (1.0%)
気管支肺炎	1 (0.5%)	0	1 (0.5%)	0	0	0
口腔真菌感染	1 (0.5%)	0	1 (0.5%)	0	0	0
単純ヘルペス	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
せつ	1 (0.5%)	0	1 (0.5%)	0	0	0
ウイルス性下気道感染	1 (0.5%)	0	1 (0.5%)	0	0	0
ウイルス性上気道感染	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
サイトメガロウイルス性脈絡網膜炎	1 (0.5%)	0	0	1 (0.5%)	0	0
ブドウ球菌皮膚感染	1 (0.5%)	0	0	1 (0.5%)	0	0
異型肺炎	1 (0.5%)	0	0	1 (0.5%)	0	0
外陰部腟カンジダ症	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
外陰腟真菌感染	1 (0.5%)	0	1 (0.5%)	0	0	0
憩室炎	1 (0.5%)	0	1 (0.5%)	0	0	0
喉頭炎	1 (0.5%)	1 (0.5%)	0	0	0	0
歯膿瘍	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
副鼻腔気管支炎	1 (0.5%)	0	1 (0.5%)	0	0	0
Ｂ型肝炎	1 (0.5%)	0	0	1 (0.5%)	0	0
ウイルス性下痢	1 (0.5%)	0	1 (0.5%)	0	0	0
ウイルス性気管支炎	1 (0.5%)	1 (0.5%)	0	0	0	0
ウイルス性鼻炎	1 (0.5%)	1 (0.5%)	0	0	0	0
サイトメガロウイルス感染	1 (0.5%)	0	0	1 (0.5%)	0	0
サイトメガロウイルス性肺炎	1 (0.5%)	0	1 (0.5%)	0	0	0
ノロウイルス性胃腸炎	1 (0.5%)	0	0	1 (0.5%)	0	0
ヘルペスウイルス感染	1 (0.5%)	1 (0.5%)	0	0	0	0
リンパ節感染	1 (0.5%)	0	0	1 (0.5%)	0	0
外陰部炎	1 (0.5%)	1 (0.5%)	0	0	0	0
感染性静脈炎	1 (0.5%)	0	1 (0.5%)	0	0	0
好中球減少性敗血症	1 (0.5%)	0	0	0	0	1 (0.5%)
歯周炎	1 (0.5%)	0	1 (0.5%)	0	0	0
心内膜炎	1 (0.5%)	0	0	1 (0.5%)	0	0
真菌性上気道感染	1 (0.5%)	0	1 (0.5%)	0	0	0
腸球菌性尿路感染	1 (0.5%)	0	1 (0.5%)	0	0	0
爪真菌症	1 (0.5%)	0	1 (0.5%)	0	0	0
伝染性紅斑	1 (0.5%)	0	0	1 (0.5%)	0	0
皮膚カンジダ	1 (0.5%)	1 (0.5%)	0	0	0	0
肛径部膿瘍	1 (0.5%)	0	1 (0.5%)	0	0	0
血液およびリンパ系障害						
- Overall -	88 (44.4%)	3 (1.5%)	7 (3.5%)	41 (20.7%)	37 (18.7%)	0
好中球減少症	57 (28.8%)	0	5 (2.5%)	26 (13.1%)	26 (13.1%)	0
血小板減少症	47 (23.7%)	2 (1.0%)	13 (6.6%)	23 (11.6%)	9 (4.5%)	0
貧血	30 (15.2%)	2 (1.0%)	8 (4.0%)	18 (9.1%)	2 (1.0%)	0
発熱性好中球減少症	7 (3.5%)	0	0	6 (3.0%)	1 (0.5%)	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
白血球減少症	4 (2.0%)	0	1 (0.5%)	3 (1.5%)	0	0
リンパ球減少症	1 (0.5%)	0	0	1 (0.5%)	0	0
自己免疫性溶血性貧血	1 (0.5%)	0	0	1 (0.5%)	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	76 (38.4%)	40 (20.2%)	29 (14.6%)	6 (3.0%)	1 (0.5%)	0
咳嗽	34 (17.2%)	23 (11.6%)	11 (5.6%)	0	0	0
呼吸困難	21 (10.6%)	13 (6.6%)	7 (3.5%)	1 (0.5%)	0	0
鼻閉	5 (2.5%)	3 (1.5%)	2 (1.0%)	0	0	0
口腔咽頭痛	7 (3.5%)	5 (2.5%)	2 (1.0%)	0	0	0
鼻漏	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
労作性呼吸困難	7 (3.5%)	6 (3.0%)	1 (0.5%)	0	0	0
湿性咳嗽	5 (2.5%)	4 (2.0%)	1 (0.5%)	0	0	0
鼻出血	5 (2.5%)	3 (1.5%)	2 (1.0%)	0	0	0
胸水	4 (2.0%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0
肺塞栓症	4 (2.0%)	0	0	3 (1.5%)	1 (0.5%)	0
しゃっくり	3 (1.5%)	3 (1.5%)	0	0	0	0
発声障害	3 (1.5%)	3 (1.5%)	0	0	0	0
上気道咳症候群	2 (1.0%)	2 (1.0%)	0	0	0	0
喘鳴	1 (0.5%)	0	1 (0.5%)	0	0	0
アレルギー性鼻炎	1 (0.5%)	1 (0.5%)	0	0	0	0
咽喉刺激感	1 (0.5%)	1 (0.5%)	0	0	0	0
間質性肺疾患	1 (0.5%)	1 (0.5%)	0	0	0	0
胸膜痛	1 (0.5%)	0	1 (0.5%)	0	0	0
変色痰	1 (0.5%)	1 (0.5%)	0	0	0	0
喀血	1 (0.5%)	1 (0.5%)	0	0	0	0
喘息	1 (0.5%)	1 (0.5%)	0	0	0	0
ラ音	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
胸膜炎	1 (0.5%)	1 (0.5%)	0	0	0	0
上気道の炎症	1 (0.5%)	1 (0.5%)	0	0	0	0
乳び胸	1 (0.5%)	0	1 (0.5%)	0	0	0
肺気腫	1 (0.5%)	0	0	1 (0.5%)	0	0
肺浸潤	1 (0.5%)	0	1 (0.5%)	0	0	0
副鼻腔うっ血	1 (0.5%)	1 (0.5%)	0	0	0	0
無気肺	1 (0.5%)	0	1 (0.5%)	0	0	0
神経系障害						
- Overall -	76 (38.4%)	46 (23.2%)	21 (10.6%)	7 (3.5%)	1 (0.5%)	1 (0.5%)
頭痛	33 (16.7%)	21 (10.6%)	10 (5.1%)	2 (1.0%)	0	0
味覚異常	16 (8.1%)	13 (6.6%)	3 (1.5%)	0	0	0
浮動性めまい	17 (8.6%)	14 (7.1%)	3 (1.5%)	0	0	0
錯感覚	2 (1.0%)	0	2 (1.0%)	0	0	0
感覚鈍麻	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
失神	5 (2.5%)	1 (0.5%)	0	4 (2.0%)	0	0
嗜眠	6 (3.0%)	4 (2.0%)	2 (1.0%)	0	0	0
記憶障害	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
末梢性ニューロパチー	1 (0.5%)	0	1 (0.5%)	0	0	0
失神寸前の状態	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
末梢性感覚ニューロパチー	3 (1.5%)	3 (1.5%)	0	0	0	0
ヘルペス後神経痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
神経痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
認知障害	1 (0.5%)	1 (0.5%)	0	0	0	0
異常感覚	1 (0.5%)	1 (0.5%)	0	0	0	0
坐骨神経痛	2 (1.0%)	2 (1.0%)	0	0	0	0
振戦	1 (0.5%)	1 (0.5%)	0	0	0	0
くも膜下出血	1 (0.5%)	0	0	0	1 (0.5%)	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
虚血性脳卒中	1 (0.5%)	0	0	0	0	1 (0.5%)
失声症	1 (0.5%)	1 (0.5%)	0	0	0	0
多発ニューロパチー	1 (0.5%)	1 (0.5%)	0	0	0	0
中枢神経系病変	1 (0.5%)	0	0	1 (0.5%)	0	0
脳梗塞	1 (0.5%)	1 (0.5%)	0	0	0	0
味覚消失	1 (0.5%)	1 (0.5%)	0	0	0	0
筋骨格系および結合組織障害						
- Overall -	57 (28.8%)	31 (15.7%)	26 (13.1%)	0	0	0
関節痛	9 (4.5%)	7 (3.5%)	2 (1.0%)	0	0	0
背部痛	18 (9.1%)	10 (5.1%)	8 (4.0%)	0	0	0
四肢痛	10 (5.1%)	10 (5.1%)	0	0	0	0
筋肉痛	15 (7.6%)	7 (3.5%)	8 (4.0%)	0	0	0
筋痙縮	8 (4.0%)	5 (2.5%)	3 (1.5%)	0	0	0
頚部痛	5 (2.5%)	3 (1.5%)	2 (1.0%)	0	0	0
骨痛	3 (1.5%)	3 (1.5%)	0	0	0	0
筋骨格系胸痛	2 (1.0%)	2 (1.0%)	0	0	0	0
関節腫脹	2 (1.0%)	2 (1.0%)	0	0	0	0
筋骨格痛	1 (0.5%)	1 (0.5%)	0	0	0	0
筋力低下	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
鼡径部痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
顎痛	2 (1.0%)	2 (1.0%)	0	0	0	0
側腹部痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
変形性関節症	1 (0.5%)	0	1 (0.5%)	0	0	0
腱痛	1 (0.5%)	0	1 (0.5%)	0	0	0
滑液包炎	1 (0.5%)	0	1 (0.5%)	0	0	0
関節リウマチ	1 (0.5%)	1 (0.5%)	0	0	0	0
筋骨格硬直	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
骨粗鬆症	1 (0.5%)	0	1 (0.5%)	0	0	0
四肢不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
脛骨内側過労性症候群	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚および皮下組織障害						
- Overall -	62 (31.3%)	37 (18.7%)	23 (11.6%)	2 (1.0%)	0	0
発疹	23 (11.6%)	17 (8.6%)	6 (3.0%)	0	0	0
そう痒症	12 (6.1%)	9 (4.5%)	3 (1.5%)	0	0	0
紅斑	4 (2.0%)	2 (1.0%)	2 (1.0%)	0	0	0
皮膚乾燥	9 (4.5%)	7 (3.5%)	2 (1.0%)	0	0	0
寝汗	4 (2.0%)	4 (2.0%)	0	0	0	0
多汗症	4 (2.0%)	1 (0.5%)	3 (1.5%)	0	0	0
脱毛症	4 (2.0%)	4 (2.0%)	0	0	0	0
湿疹	1 (0.5%)	1 (0.5%)	0	0	0	0
蕁麻疹	1 (0.5%)	0	1 (0.5%)	0	0	0
そう痒性皮疹	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
薬疹	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
水疱	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
全身性そう痒症	1 (0.5%)	0	1 (0.5%)	0	0	0
皮膚炎	1 (0.5%)	1 (0.5%)	0	0	0	0
丘疹性皮疹	1 (0.5%)	0	0	1 (0.5%)	0	0
紅色症	1 (0.5%)	1 (0.5%)	0	0	0	0
全身性皮疹	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
日光角化症	2 (1.0%)	0	2 (1.0%)	0	0	0
斑状皮疹	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
皮膚疼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
顔面腫脹	1 (0.5%)	1 (0.5%)	0	0	0	0
爪の障害	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
斑状丘疹状皮疹	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚嚢腫	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚変色	1 (0.5%)	1 (0.5%)	0	0	0	0
毛髪成長異常	1 (0.5%)	1 (0.5%)	0	0	0	0
代謝および栄養障害						
- Overall -	64 (32.3%)	29 (14.6%)	23 (11.6%)	10 (5.1%)	1 (0.5%)	1 (0.5%)
食欲減退	35 (17.7%)	20 (10.1%)	13 (6.6%)	2 (1.0%)	0	0
低カリウム血症	13 (6.6%)	1 (0.5%)	7 (3.5%)	4 (2.0%)	1 (0.5%)	0
高尿酸血症	5 (2.5%)	4 (2.0%)	1 (0.5%)	0	0	0
低マグネシウム血症	5 (2.5%)	4 (2.0%)	1 (0.5%)	0	0	0
脱水	6 (3.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	0	0
低リン酸血症	2 (1.0%)	0	0	2 (1.0%)	0	0
体液貯留	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
低ナトリウム血症	2 (1.0%)	0	0	2 (1.0%)	0	0
高血糖	1 (0.5%)	0	1 (0.5%)	0	0	0
腫瘍崩壊症候群	2 (1.0%)	0	0	1 (0.5%)	0	1 (0.5%)
痛風	2 (1.0%)	2 (1.0%)	0	0	0	0
ビタミンD欠乏	1 (0.5%)	0	1 (0.5%)	0	0	0
葉酸欠乏	1 (0.5%)	1 (0.5%)	0	0	0	0
血管障害						
- Overall -	41 (20.7%)	10 (5.1%)	24 (12.1%)	7 (3.5%)	0	0
低血圧	3 (1.5%)	0	1 (0.5%)	2 (1.0%)	0	0
静脈炎	13 (6.6%)	3 (1.5%)	10 (5.1%)	0	0	0
高血圧	7 (3.5%)	0	5 (2.5%)	2 (1.0%)	0	0
深部静脈血栓症	5 (2.5%)	0	4 (2.0%)	1 (0.5%)	0	0
ほてり	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
起立性低血圧	2 (1.0%)	2 (1.0%)	0	0	0	0
表在性静脈炎	3 (1.5%)	0	3 (1.5%)	0	0	0
血管痛	1 (0.5%)	1 (0.5%)	0	0	0	0
血腫	2 (1.0%)	2 (1.0%)	0	0	0	0
表在性血栓性静脈炎	1 (0.5%)	0	1 (0.5%)	0	0	0
間欠性跛行	1 (0.5%)	0	1 (0.5%)	0	0	0
頚静脈血栓症	1 (0.5%)	0	0	1 (0.5%)	0	0
血栓症	1 (0.5%)	0	1 (0.5%)	0	0	0
血栓性静脈炎	1 (0.5%)	1 (0.5%)	0	0	0	0
四肢静脈血栓症	1 (0.5%)	0	1 (0.5%)	0	0	0
静脈血栓症	1 (0.5%)	0	0	1 (0.5%)	0	0
精神障害						
- Overall -	35 (17.7%)	21 (10.6%)	12 (6.1%)	1 (0.5%)	1 (0.5%)	0
不眠症	21 (10.6%)	13 (6.6%)	8 (4.0%)	0	0	0
不安	8 (4.0%)	3 (1.5%)	4 (2.0%)	0	1 (0.5%)	0
うつ病	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
錯乱状態	1 (0.5%)	1 (0.5%)	0	0	0	0
抑うつ気分	1 (0.5%)	1 (0.5%)	0	0	0	0
気分変化	2 (1.0%)	2 (1.0%)	0	0	0	0
激越	1 (0.5%)	0	1 (0.5%)	0	0	0
アルコール離脱症候群	1 (0.5%)	0	0	1 (0.5%)	0	0
自殺念慮	1 (0.5%)	0	0	1 (0.5%)	0	0
神経過敏	1 (0.5%)	1 (0.5%)	0	0	0	0
睡眠障害	1 (0.5%)	1 (0.5%)	0	0	0	0
統合失調症、妄想型	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
臨床検査						
- Overall -	28 (14.1%)	12 (6.1%)	12 (6.1%)	3 (1.5%)	1 (0.5%)	0
体重減少	17 (8.6%)	11 (5.6%)	6 (3.0%)	0	0	0
血中クレアチニン増加	4 (2.0%)	2 (1.0%)	2 (1.0%)	0	0	0
アスパラギン酸アミノトランスフェラーゼ増加	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
アラニンアミノトランスフェラーゼ増加	2 (1.0%)	0	2 (1.0%)	0	0	0
血中アルカリホスファターゼ増加	1 (0.5%)	0	1 (0.5%)	0	0	0
エプスタイン・バーウイルス抗原陽性	1 (0.5%)	1 (0.5%)	0	0	0	0
サイトメガロウイルス検査陽性	1 (0.5%)	1 (0.5%)	0	0	0	0
セラチア検査陽性	1 (0.5%)	0	1 (0.5%)	0	0	0
駆出率減少	1 (0.5%)	0	0	1 (0.5%)	0	0
血中尿酸増加	1 (0.5%)	0	0	0	1 (0.5%)	0
収縮期血圧上昇	1 (0.5%)	1 (0.5%)	0	0	0	0
心電図Ｔ波逆転	1 (0.5%)	0	0	1 (0.5%)	0	0
心拍数不整	1 (0.5%)	1 (0.5%)	0	0	0	0
腎クレアチニン・クリアランス減少	1 (0.5%)	1 (0.5%)	0	0	0	0
前立腺生検	1 (0.5%)	0	1 (0.5%)	0	0	0
超音波スキャン	1 (0.5%)	0	1 (0.5%)	0	0	0
眼障害						
- Overall -	13 (6.6%)	10 (5.1%)	3 (1.5%)	0	0	0
霧視	3 (1.5%)	3 (1.5%)	0	0	0	0
眼乾燥	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
視力障害	1 (0.5%)	1 (0.5%)	0	0	0	0
視力低下	1 (0.5%)	1 (0.5%)	0	0	0	0
流涙増加	1 (0.5%)	1 (0.5%)	0	0	0	0
霰粒腫	1 (0.5%)	1 (0.5%)	0	0	0	0
黄斑変性	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
壊死性網膜炎	1 (0.5%)	0	1 (0.5%)	0	0	0
角膜瘢痕	1 (0.5%)	0	1 (0.5%)	0	0	0
眼部不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
網膜剥離	1 (0.5%)	0	1 (0.5%)	0	0	0
羞明	1 (0.5%)	1 (0.5%)	0	0	0	0
腎および尿路障害						
- Overall -	18 (9.1%)	13 (6.6%)	3 (1.5%)	1 (0.5%)	1 (0.5%)	0
頻尿	8 (4.0%)	8 (4.0%)	0	0	0	0
排尿困難	1 (0.5%)	1 (0.5%)	0	0	0	0
急性腎不全	2 (1.0%)	1 (0.5%)	0	0	1 (0.5%)	0
夜間頻尿	2 (1.0%)	2 (1.0%)	0	0	0	0
血尿	1 (0.5%)	0	0	1 (0.5%)	0	0
水腎症	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
多尿	1 (0.5%)	1 (0.5%)	0	0	0	0
慢性腎不全	1 (0.5%)	0	1 (0.5%)	0	0	0
腎損傷	1 (0.5%)	0	1 (0.5%)	0	0	0
着色尿	1 (0.5%)	1 (0.5%)	0	0	0	0
尿異常	1 (0.5%)	1 (0.5%)	0	0	0	0
心臓障害						
- Overall -	11 (5.6%)	6 (3.0%)	2 (1.0%)	2 (1.0%)	1 (0.5%)	0
心房細動	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
頻脈	2 (1.0%)	2 (1.0%)	0	0	0	0
動悸	2 (1.0%)	2 (1.0%)	0	0	0	0
狭心症	1 (0.5%)	1 (0.5%)	0	0	0	0
心筋梗塞	1 (0.5%)	0	0	0	1 (0.5%)	0
リバウンド頻脈	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
冠動脈硬化症	1 (0.5%)	1 (0.5%)	0	0	0	0
僧帽弁閉鎖不全症	1 (0.5%)	0	1 (0.5%)	0	0	0
発作性不整脈	1 (0.5%)	0	0	1 (0.5%)	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）						
- Overall -	15 (7.6%)	0	6 (3.0%)	4 (2.0%)	2 (1.0%)	3 (1.5%)
基底細胞癌	1 (0.5%)	0	0	1 (0.5%)	0	0
扁平上皮癌	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
骨髄異形成症候群	1 (0.5%)	0	0	0	1 (0.5%)	0
皮膚有棘細胞癌	1 (0.5%)	0	1 (0.5%)	0	0	0
悪性黒色腫	1 (0.5%)	0	1 (0.5%)	0	0	0
急性骨髄性白血病	1 (0.5%)	0	0	0	0	1 (0.5%)
白血病	2 (1.0%)	0	1 (0.5%)	0	0	1 (0.5%)
汗孔癌	1 (0.5%)	0	1 (0.5%)	0	0	0
肝内胆管癌	1 (0.5%)	0	0	1 (0.5%)	0	0
甲状腺新生物	1 (0.5%)	0	1 (0.5%)	0	0	0
子宮平滑筋腫	1 (0.5%)	0	0	1 (0.5%)	0	0
腫瘍随伴性天疱瘡	1 (0.5%)	0	0	1 (0.5%)	0	0
腺癌	1 (0.5%)	0	0	0	0	1 (0.5%)
平滑筋肉腫	1 (0.5%)	0	0	0	1 (0.5%)	0
耳および迷路障害						
- Overall -	10 (5.1%)	9 (4.5%)	1 (0.5%)	0	0	0
回転性めまい	6 (3.0%)	5 (2.5%)	1 (0.5%)	0	0	0
耳痛	2 (1.0%)	2 (1.0%)	0	0	0	0
聴力低下	2 (1.0%)	2 (1.0%)	0	0	0	0
耳鳴	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
生殖系および乳房障害						
- Overall -	9 (4.5%)	5 (2.5%)	3 (1.5%)	1 (0.5%)	0	0
良性前立腺肥大症	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
勃起不全	1 (0.5%)	1 (0.5%)	0	0	0	0
膣出血	1 (0.5%)	0	1 (0.5%)	0	0	0
外陰膣障害	1 (0.5%)	1 (0.5%)	0	0	0	0
子宮出血	1 (0.5%)	0	0	1 (0.5%)	0	0
前立腺腫大	1 (0.5%)	0	1 (0.5%)	0	0	0
前立腺症	1 (0.5%)	1 (0.5%)	0	0	0	0
前立腺痛	1 (0.5%)	1 (0.5%)	0	0	0	0
肝胆道系障害						
- Overall -	8 (4.0%)	2 (1.0%)	3 (1.5%)	2 (1.0%)	1 (0.5%)	0
胆汁うっ滞	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
胆嚢炎	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
脂肪肝	1 (0.5%)	0	0	1 (0.5%)	0	0
肝毒性	1 (0.5%)	0	0	0	1 (0.5%)	0
胆道仙痛	1 (0.5%)	0	1 (0.5%)	0	0	0
免疫系障害						
- Overall -	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
過敏症	1 (0.5%)	1 (0.5%)	0	0	0	0
低γグロブリン血症	1 (0.5%)	0	1 (0.5%)	0	0	0
社会環境						
- Overall -	1 (0.5%)	1 (0.5%)	0	0	0	0
社会問題	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
外科および内科処置						
- Overall -	1 (0.5%)	0	1 (0.5%)	0	0	0
静脈カテーテル留置	1 (0.5%)	0	1 (0.5%)	0	0	0
内分泌障害						
- Overall -	1 (0.5%)	1 (0.5%)	0	0	0	0
クッシング様症状	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159v/n01297a/ae17.sas / Output: /opt/BIOSTAT/prod/cdt7159v/n01297a/reports/ae17_297_SE.out
09SEP2016 9:00

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	191 (98.5%)	10 (5.2%)	49 (25.3%)	60 (30.9%)	60 (30.9%)	12 (6.2%)
胃腸障害						
- Overall -	145 (74.7%)	68 (35.1%)	55 (28.4%)	19 (9.8%)	3 (1.5%)	0
悪心	104 (53.6%)	70 (36.1%)	32 (16.5%)	2 (1.0%)	0	0
下痢	53 (27.3%)	31 (16.0%)	20 (10.3%)	2 (1.0%)	0	0
嘔吐	43 (22.2%)	25 (12.9%)	14 (7.2%)	4 (2.1%)	0	0
便秘	41 (21.1%)	32 (16.5%)	9 (4.6%)	0	0	0
腹痛	12 (6.2%)	8 (4.1%)	2 (1.0%)	2 (1.0%)	0	0
上腹部痛	10 (5.2%)	8 (4.1%)	1 (0.5%)	1 (0.5%)	0	0
消化不良	12 (6.2%)	11 (5.7%)	1 (0.5%)	0	0	0
口内乾燥	8 (4.1%)	8 (4.1%)	0	0	0	0
腹部膨満	7 (3.6%)	5 (2.6%)	2 (1.0%)	0	0	0
口内炎	8 (4.1%)	5 (2.6%)	3 (1.5%)	0	0	0
胃食道逆流性疾患	6 (3.1%)	2 (1.0%)	4 (2.1%)	0	0	0
下腹部痛	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
口腔内潰瘍形成	5 (2.6%)	3 (1.5%)	1 (0.5%)	1 (0.5%)	0	0
嚥下障害	4 (2.1%)	3 (1.5%)	1 (0.5%)	0	0	0
放屁	3 (1.5%)	3 (1.5%)	0	0	0	0
歯痛	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
痔核	4 (2.1%)	2 (1.0%)	2 (1.0%)	0	0	0
消化器痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
大腸炎	4 (2.1%)	0	2 (1.0%)	2 (1.0%)	0	0
腹部不快感	3 (1.5%)	3 (1.5%)	0	0	0	0
アフタ性口内炎	1 (0.5%)	1 (0.5%)	0	0	0	0
胃炎	1 (0.5%)	1 (0.5%)	0	0	0	0
口腔内痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
直腸出血	3 (1.5%)	1 (0.5%)	0	1 (0.5%)	1 (0.5%)	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肛門潰瘍	1 (0.5%)	0	1 (0.5%)	0	0	0
レッチング	1 (0.5%)	1 (0.5%)	0	0	0	0
胃腸音異常	2 (1.0%)	2 (1.0%)	0	0	0	0
胃腸出血	2 (1.0%)	0	0	2 (1.0%)	0	0
胃腸障害	2 (1.0%)	2 (1.0%)	0	0	0	0
血便排泄	1 (0.5%)	1 (0.5%)	0	0	0	0
上部消化管出血	2 (1.0%)	0	0	1 (0.5%)	1 (0.5%)	0
嚥下痛	1 (0.5%)	0	1 (0.5%)	0	0	0
肛門周囲痛	2 (1.0%)	2 (1.0%)	0	0	0	0
イレウス	1 (0.5%)	0	1 (0.5%)	0	0	0
血性下痢	1 (0.5%)	0	1 (0.5%)	0	0	0
呼気臭	1 (0.5%)	1 (0.5%)	0	0	0	0
口蓋浮腫	1 (0.5%)	0	0	0	1 (0.5%)	0
口腔腫脹	1 (0.5%)	1 (0.5%)	0	0	0	0
口腔粘膜紅斑	1 (0.5%)	1 (0.5%)	0	0	0	0
口唇のひび割れ	1 (0.5%)	1 (0.5%)	0	0	0	0
口唇潰瘍	1 (0.5%)	1 (0.5%)	0	0	0	0
歯の知覚過敏	1 (0.5%)	1 (0.5%)	0	0	0	0
耳下腺腫大	1 (0.5%)	1 (0.5%)	0	0	0	0
食中毒	1 (0.5%)	1 (0.5%)	0	0	0	0
舌苔	1 (0.5%)	1 (0.5%)	0	0	0	0
舌潰瘍	1 (0.5%)	1 (0.5%)	0	0	0	0
腸管穿孔	1 (0.5%)	0	0	1 (0.5%)	0	0
腹部ヘルニア	1 (0.5%)	1 (0.5%)	0	0	0	0
変色便	1 (0.5%)	1 (0.5%)	0	0	0	0
慢性胃炎	1 (0.5%)	0	1 (0.5%)	0	0	0
裂肛	1 (0.5%)	0	0	1 (0.5%)	0	0
膵炎	1 (0.5%)	0	0	0	1 (0.5%)	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
臍径ヘルニア	1 (0.5%)	1 (0.5%)	0	0	0	0
齲歯	1 (0.5%)	0	0	1 (0.5%)	0	0
一般・全身障害および投与部位の状態						
- Overall -	139 (71.6%)	64 (33.0%)	62 (32.0%)	12 (6.2%)	1 (0.5%)	0
疲労	76 (39.2%)	46 (23.7%)	27 (13.9%)	3 (1.5%)	0	0
発熱	54 (27.8%)	33 (17.0%)	19 (9.8%)	2 (1.0%)	0	0
無力症	29 (14.9%)	20 (10.3%)	6 (3.1%)	3 (1.5%)	0	0
悪寒	24 (12.4%)	15 (7.7%)	8 (4.1%)	1 (0.5%)	0	0
末梢性浮腫	12 (6.2%)	8 (4.1%)	4 (2.1%)	0	0	0
インフルエンザ様疾患	10 (5.2%)	9 (4.6%)	1 (0.5%)	0	0	0
粘膜の炎症	9 (4.6%)	6 (3.1%)	1 (0.5%)	2 (1.0%)	0	0
胸痛	10 (5.2%)	7 (3.6%)	3 (1.5%)	0	0	0
疼痛	5 (2.6%)	3 (1.5%)	2 (1.0%)	0	0	0
末梢腫脹	4 (2.1%)	3 (1.5%)	1 (0.5%)	0	0	0
倦怠感	5 (2.6%)	3 (1.5%)	1 (0.5%)	1 (0.5%)	0	0
注入部位疼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
注射部位疼痛	3 (1.5%)	3 (1.5%)	0	0	0	0
浮腫	4 (2.1%)	4 (2.1%)	0	0	0	0
カテーテル留置部位疼痛	3 (1.5%)	3 (1.5%)	0	0	0	0
口渇	1 (0.5%)	1 (0.5%)	0	0	0	0
腫脹	2 (1.0%)	2 (1.0%)	0	0	0	0
注射部位反応	1 (0.5%)	1 (0.5%)	0	0	0	0
カテーテル留置部位紅斑	2 (1.0%)	2 (1.0%)	0	0	0	0
顔面浮腫	1 (0.5%)	1 (0.5%)	0	0	0	0
胸部不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
硬結	1 (0.5%)	1 (0.5%)	0	0	0	0
高熱	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
全身健康状態低下	2 (1.0%)	0	0	1 (0.5%)	1 (0.5%)	0
注入部位血管外漏出	1 (0.5%)	1 (0.5%)	0	0	0	0
不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
腋窩痛	1 (0.5%)	1 (0.5%)	0	0	0	0
カテーテル留置部位血腫	1 (0.5%)	1 (0.5%)	0	0	0	0
カテーテル留置部位腫脹	1 (0.5%)	1 (0.5%)	0	0	0	0
圧痛	1 (0.5%)	0	1 (0.5%)	0	0	0
異物感	1 (0.5%)	1 (0.5%)	0	0	0	0
注射部位過敏反応	1 (0.5%)	1 (0.5%)	0	0	0	0
注射部位硬結	1 (0.5%)	1 (0.5%)	0	0	0	0
注射部位線維症	1 (0.5%)	1 (0.5%)	0	0	0	0
薬物不耐性	1 (0.5%)	1 (0.5%)	0	0	0	0
冷感	1 (0.5%)	1 (0.5%)	0	0	0	0
傷害、中毒および処置合併症						
- Overall -	130 (67.0%)	54 (27.8%)	54 (27.8%)	17 (8.8%)	4 (2.1%)	1 (0.5%)
注入に伴う反応	125 (64.4%)	57 (29.4%)	51 (26.3%)	13 (6.7%)	4 (2.1%)	0
転倒	4 (2.1%)	3 (1.5%)	1 (0.5%)	0	0	0
挫傷	1 (0.5%)	1 (0.5%)	0	0	0	0
手首関節骨折	3 (1.5%)	0	2 (1.0%)	1 (0.5%)	0	0
筋断裂	2 (1.0%)	0	2 (1.0%)	0	0	0
四肢損傷	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
手骨折	1 (0.5%)	1 (0.5%)	0	0	0	0
創傷	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
大腿骨骨折	2 (1.0%)	0	0	2 (1.0%)	0	0
裂傷	2 (1.0%)	2 (1.0%)	0	0	0	0
靱帯捻挫	2 (1.0%)	2 (1.0%)	0	0	0	0
サンバーン	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
滑膜断裂	1 (0.5%)	1 (0.5%)	0	0	0	0
顔面骨骨折	1 (0.5%)	0	1 (0.5%)	0	0	0
血管偽動脈瘤	1 (0.5%)	0	0	0	0	1 (0.5%)
股関節部骨折	1 (0.5%)	0	0	1 (0.5%)	0	0
歯牙破折	1 (0.5%)	1 (0.5%)	0	0	0	0
尺骨骨折	1 (0.5%)	0	1 (0.5%)	0	0	0
節足動物咬傷	1 (0.5%)	1 (0.5%)	0	0	0	0
造影剤反応	1 (0.5%)	0	1 (0.5%)	0	0	0
爪損傷	1 (0.5%)	0	1 (0.5%)	0	0	0
熱傷	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚擦過傷	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚創傷	1 (0.5%)	1 (0.5%)	0	0	0	0
橈骨骨折	1 (0.5%)	0	1 (0.5%)	0	0	0
漿液腫	1 (0.5%)	0	0	1 (0.5%)	0	0
感染症および寄生虫症						
- Overall -	127 (65.5%)	29 (14.9%)	63 (32.5%)	22 (11.3%)	8 (4.1%)	5 (2.6%)
上気道感染	25 (12.9%)	5 (2.6%)	16 (8.2%)	4 (2.1%)	0	0
気管支炎	18 (9.3%)	5 (2.6%)	13 (6.7%)	0	0	0
副鼻腔炎	23 (11.9%)	6 (3.1%)	15 (7.7%)	2 (1.0%)	0	0
尿路感染	19 (9.8%)	2 (1.0%)	11 (5.7%)	6 (3.1%)	0	0
鼻咽頭炎	17 (8.8%)	13 (6.7%)	4 (2.1%)	0	0	0
帯状疱疹	7 (3.6%)	1 (0.5%)	5 (2.6%)	1 (0.5%)	0	0
肺炎	10 (5.2%)	1 (0.5%)	4 (2.1%)	4 (2.1%)	1 (0.5%)	0
口腔ヘルペス	8 (4.1%)	6 (3.1%)	2 (1.0%)	0	0	0
敗血症	6 (3.1%)	0	0	1 (0.5%)	4 (2.1%)	1 (0.5%)
下気道感染	5 (2.6%)	1 (0.5%)	1 (0.5%)	3 (1.5%)	0	0
結膜炎	5 (2.6%)	2 (1.0%)	3 (1.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
鼻炎	6 (3.1%)	3 (1.5%)	3 (1.5%)	0	0	0
咽頭炎	8 (4.1%)	5 (2.6%)	3 (1.5%)	0	0	0
肺感染	6 (3.1%)	1 (0.5%)	3 (1.5%)	1 (0.5%)	1 (0.5%)	0
気道感染	4 (2.1%)	1 (0.5%)	3 (1.5%)	0	0	0
口腔カンジダ症	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
蜂巣炎	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
インフルエンザ	6 (3.1%)	4 (2.1%)	2 (1.0%)	0	0	0
胃腸炎	2 (1.0%)	1 (0.5%)	0	0	0	1 (0.5%)
中耳炎	4 (2.1%)	3 (1.5%)	1 (0.5%)	0	0	0
ウイルス性気道感染	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
感染	1 (0.5%)	1 (0.5%)	0	0	0	0
歯感染	2 (1.0%)	0	2 (1.0%)	0	0	0
毛包炎	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
眼感染	1 (0.5%)	0	1 (0.5%)	0	0	0
皮膚感染	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
ニューモシスチス・イロベチイ肺炎	1 (0.5%)	0	0	1 (0.5%)	0	0
気管支肺炎	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
口腔真菌感染	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
単純ヘルペス	1 (0.5%)	1 (0.5%)	0	0	0	0
せつ	1 (0.5%)	0	1 (0.5%)	0	0	0
ウイルス性下気道感染	1 (0.5%)	1 (0.5%)	0	0	0	0
ウイルス性副鼻腔炎	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
サイトメガロウイルス性脈絡網膜炎	1 (0.5%)	0	0	1 (0.5%)	0	0
ブドウ球菌皮膚感染	1 (0.5%)	0	1 (0.5%)	0	0	0
異型肺炎	1 (0.5%)	0	0	1 (0.5%)	0	0
医療機器関連感染	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
外陰膣真菌感染	1 (0.5%)	0	1 (0.5%)	0	0	0
菌血症	2 (1.0%)	0	2 (1.0%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
憩室炎	1 (0.5%)	0	1 (0.5%)	0	0	0
喉頭炎	1 (0.5%)	0	1 (0.5%)	0	0	0
歯膿瘍	1 (0.5%)	0	1 (0.5%)	0	0	0
耳感染	2 (1.0%)	0	2 (1.0%)	0	0	0
大腸菌性敗血症	2 (1.0%)	0	0	0	1 (0.5%)	1 (0.5%)
膿疱性皮疹	2 (1.0%)	2 (1.0%)	0	0	0	0
皮膚真菌感染	2 (1.0%)	2 (1.0%)	0	0	0	0
副鼻腔気管支炎	1 (0.5%)	0	1 (0.5%)	0	0	0
膣感染	2 (1.0%)	0	2 (1.0%)	0	0	0
ウイルス性胃腸炎	1 (0.5%)	1 (0.5%)	0	0	0	0
カンジダ感染	1 (0.5%)	1 (0.5%)	0	0	0	0
カンピロバクター感染	1 (0.5%)	0	0	1 (0.5%)	0	0
サルモネラ菌性胃腸炎	1 (0.5%)	0	1 (0.5%)	0	0	0
サルモネラ症	1 (0.5%)	0	1 (0.5%)	0	0	0
シュードモナス菌性肺感染	1 (0.5%)	0	1 (0.5%)	0	0	0
シュードモナス性敗血症	1 (0.5%)	0	0	0	0	1 (0.5%)
ダニ皮膚炎	1 (0.5%)	0	1 (0.5%)	0	0	0
ブドウ球菌性敗血症	1 (0.5%)	0	0	0	1 (0.5%)	0
ライム病	1 (0.5%)	0	1 (0.5%)	0	0	0
陰茎感染	1 (0.5%)	0	1 (0.5%)	0	0	0
陰部ヘルペス	1 (0.5%)	1 (0.5%)	0	0	0	0
急性副鼻腔炎	1 (0.5%)	0	1 (0.5%)	0	0	0
口唇感染	1 (0.5%)	0	1 (0.5%)	0	0	0
細気管支炎	1 (0.5%)	0	1 (0.5%)	0	0	0
細菌感染	1 (0.5%)	0	1 (0.5%)	0	0	0
細菌性下気道感染	1 (0.5%)	0	1 (0.5%)	0	0	0
細菌性尿路感染	1 (0.5%)	0	1 (0.5%)	0	0	0
四肢膿瘍	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
真菌性敗血症	1 (0.5%)	0	0	0	0	1 (0.5%)
舌膿瘍	1 (0.5%)	0	1 (0.5%)	0	0	0
創傷感染	1 (0.5%)	0	1 (0.5%)	0	0	0
大腸菌性膀胱炎	1 (0.5%)	0	1 (0.5%)	0	0	0
丹毒	1 (0.5%)	0	1 (0.5%)	0	0	0
爪床感染	1 (0.5%)	0	1 (0.5%)	0	0	0
尿路性敗血症	1 (0.5%)	0	0	1 (0.5%)	0	0
膿性痰	1 (0.5%)	1 (0.5%)	0	0	0	0
鼻膿瘍	1 (0.5%)	0	1 (0.5%)	0	0	0
腹部膿瘍	1 (0.5%)	0	1 (0.5%)	0	0	0
慢性副鼻腔炎	1 (0.5%)	0	1 (0.5%)	0	0	0
迷路炎	1 (0.5%)	0	1 (0.5%)	0	0	0
扁桃炎	1 (0.5%)	0	1 (0.5%)	0	0	0
膀胱炎	1 (0.5%)	0	1 (0.5%)	0	0	0
鼠径部感染	1 (0.5%)	0	1 (0.5%)	0	0	0
血液およびリンパ系障害						
- Overall -	102 (52.6%)	3 (1.5%)	8 (4.1%)	43 (22.2%)	47 (24.2%)	1 (0.5%)
好中球減少症	68 (35.1%)	0	4 (2.1%)	27 (13.9%)	37 (19.1%)	0
血小板減少症	29 (14.9%)	4 (2.1%)	4 (2.1%)	11 (5.7%)	10 (5.2%)	0
貧血	24 (12.4%)	0	9 (4.6%)	12 (6.2%)	3 (1.5%)	0
発熱性好中球減少症	9 (4.6%)	0	0	7 (3.6%)	2 (1.0%)	0
白血球減少症	3 (1.5%)	1 (0.5%)	0	2 (1.0%)	0	0
リンパ節痛	4 (2.1%)	3 (1.5%)	1 (0.5%)	0	0	0
汎血球減少症	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	0	0
リンパ節症	1 (0.5%)	1 (0.5%)	0	0	0	0
血小板減少性紫斑病	1 (0.5%)	0	0	1 (0.5%)	0	0
低グロブリン血症	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
無顆粒球症	1 (0.5%)	0	0	0	0	1 (0.5%)
呼吸器、胸郭および縦隔障害						
- Overall -	101 (52.1%)	60 (30.9%)	29 (14.9%)	8 (4.1%)	4 (2.1%)	0
咳嗽	54 (27.8%)	39 (20.1%)	15 (7.7%)	0	0	0
呼吸困難	22 (11.3%)	14 (7.2%)	6 (3.1%)	2 (1.0%)	0	0
鼻閉	16 (8.2%)	15 (7.7%)	1 (0.5%)	0	0	0
口腔咽頭痛	11 (5.7%)	8 (4.1%)	2 (1.0%)	1 (0.5%)	0	0
鼻漏	11 (5.7%)	11 (5.7%)	0	0	0	0
労作性呼吸困難	5 (2.6%)	5 (2.6%)	0	0	0	0
湿性咳嗽	6 (3.1%)	4 (2.1%)	1 (0.5%)	1 (0.5%)	0	0
鼻出血	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
低酸素症	7 (3.6%)	0	4 (2.1%)	3 (1.5%)	0	0
胸水	2 (1.0%)	0	1 (0.5%)	0	1 (0.5%)	0
肺塞栓症	1 (0.5%)	0	0	0	1 (0.5%)	0
しゃっくり	1 (0.5%)	1 (0.5%)	0	0	0	0
発声障害	1 (0.5%)	1 (0.5%)	0	0	0	0
上気道咳症候群	1 (0.5%)	1 (0.5%)	0	0	0	0
喘鳴	2 (1.0%)	0	2 (1.0%)	0	0	0
アレルギー性鼻炎	1 (0.5%)	1 (0.5%)	0	0	0	0
咽喉絞扼感	2 (1.0%)	0	1 (0.5%)	0	1 (0.5%)	0
咽喉刺激感	1 (0.5%)	1 (0.5%)	0	0	0	0
間質性肺疾患	1 (0.5%)	0	0	1 (0.5%)	0	0
気道うっ血	2 (1.0%)	2 (1.0%)	0	0	0	0
胸膜痛	1 (0.5%)	1 (0.5%)	0	0	0	0
肺障害	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
変色痰	1 (0.5%)	1 (0.5%)	0	0	0	0
喀血	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
喘息	1 (0.5%)	0	1 (0.5%)	0	0	0
気管支痙攣	1 (0.5%)	0	0	0	1 (0.5%)	0
気胸	1 (0.5%)	0	0	1 (0.5%)	0	0
誤嚥性肺炎	1 (0.5%)	0	0	1 (0.5%)	0	0
喉頭不快感	1 (0.5%)	0	1 (0.5%)	0	0	0
喉頭浮腫	1 (0.5%)	0	0	0	1 (0.5%)	0
睡眠時無呼吸症候群	1 (0.5%)	0	1 (0.5%)	0	0	0
鼻閉塞	1 (0.5%)	0	1 (0.5%)	0	0	0
副鼻腔障害	1 (0.5%)	1 (0.5%)	0	0	0	0
副鼻腔分泌過多	1 (0.5%)	0	1 (0.5%)	0	0	0
慢性気管支炎	1 (0.5%)	1 (0.5%)	0	0	0	0
神経系障害						
- Overall -	67 (34.5%)	48 (24.7%)	13 (6.7%)	6 (3.1%)	0	0
頭痛	26 (13.4%)	20 (10.3%)	5 (2.6%)	1 (0.5%)	0	0
味覚異常	15 (7.7%)	14 (7.2%)	1 (0.5%)	0	0	0
浮動性めまい	13 (6.7%)	12 (6.2%)	1 (0.5%)	0	0	0
錯感覚	8 (4.1%)	7 (3.6%)	1 (0.5%)	0	0	0
感覚鈍麻	6 (3.1%)	5 (2.6%)	1 (0.5%)	0	0	0
失神	2 (1.0%)	0	0	2 (1.0%)	0	0
嗜眠	1 (0.5%)	1 (0.5%)	0	0	0	0
記憶障害	3 (1.5%)	3 (1.5%)	0	0	0	0
末梢性ニューロパチー	5 (2.6%)	5 (2.6%)	0	0	0	0
失神寸前の状態	3 (1.5%)	0	1 (0.5%)	2 (1.0%)	0	0
末梢性感覚ニューロパチー	1 (0.5%)	1 (0.5%)	0	0	0	0
ヘルペス後神経痛	1 (0.5%)	1 (0.5%)	0	0	0	0
神経痛	1 (0.5%)	0	1 (0.5%)	0	0	0
認知障害	2 (1.0%)	2 (1.0%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
片頭痛	3 (1.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0
異常感覚	1 (0.5%)	1 (0.5%)	0	0	0	0
灼熱感	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
振戦	1 (0.5%)	1 (0.5%)	0	0	0	0
注意力障害	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
下肢静止不能症候群	1 (0.5%)	1 (0.5%)	0	0	0	0
傾眠	1 (0.5%)	0	1 (0.5%)	0	0	0
血管原性脳浮腫	1 (0.5%)	0	0	1 (0.5%)	0	0
手根管症候群	1 (0.5%)	0	1 (0.5%)	0	0	0
知覚過敏	1 (0.5%)	1 (0.5%)	0	0	0	0
鎮静	1 (0.5%)	1 (0.5%)	0	0	0	0
副鼻腔炎に伴う頭痛	1 (0.5%)	1 (0.5%)	0	0	0	0
末梢性運動ニューロパチー	1 (0.5%)	0	1 (0.5%)	0	0	0
嗅覚錯誤	1 (0.5%)	1 (0.5%)	0	0	0	0
筋骨格系および結合組織障害						
- Overall -	80 (41.2%)	47 (24.2%)	28 (14.4%)	5 (2.6%)	0	0
関節痛	23 (11.9%)	17 (8.8%)	6 (3.1%)	0	0	0
背部痛	13 (6.7%)	5 (2.6%)	7 (3.6%)	1 (0.5%)	0	0
四肢痛	18 (9.3%)	12 (6.2%)	4 (2.1%)	2 (1.0%)	0	0
筋肉痛	12 (6.2%)	10 (5.2%)	2 (1.0%)	0	0	0
筋痙縮	8 (4.1%)	5 (2.6%)	3 (1.5%)	0	0	0
頚部痛	5 (2.6%)	2 (1.0%)	3 (1.5%)	0	0	0
骨痛	7 (3.6%)	4 (2.1%)	3 (1.5%)	0	0	0
筋骨格系胸痛	6 (3.1%)	4 (2.1%)	2 (1.0%)	0	0	0
関節腫脹	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
筋骨格痛	4 (2.1%)	2 (1.0%)	2 (1.0%)	0	0	0
筋力低下	2 (1.0%)	2 (1.0%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
鼡径部痛	3 (1.5%)	3 (1.5%)	0	0	0	0
顎痛	2 (1.0%)	2 (1.0%)	0	0	0	0
側腹部痛	1 (0.5%)	1 (0.5%)	0	0	0	0
変形性関節症	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	0	0
腱痛	1 (0.5%)	1 (0.5%)	0	0	0	0
リウマチ性障害	1 (0.5%)	1 (0.5%)	0	0	0	0
リウマチ性多発筋痛	1 (0.5%)	0	1 (0.5%)	0	0	0
滑液嚢腫	1 (0.5%)	1 (0.5%)	0	0	0	0
関節炎	1 (0.5%)	1 (0.5%)	0	0	0	0
筋骨格不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
筋肉内出血	1 (0.5%)	0	0	1 (0.5%)	0	0
骨炎	1 (0.5%)	0	1 (0.5%)	0	0	0
上肢腫瘤	1 (0.5%)	1 (0.5%)	0	0	0	0
腱炎	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚および皮下組織障害						
- Overall -	74 (38.1%)	44 (22.7%)	26 (13.4%)	3 (1.5%)	1 (0.5%)	0
発疹	24 (12.4%)	15 (7.7%)	7 (3.6%)	1 (0.5%)	1 (0.5%)	0
そう痒症	25 (12.9%)	15 (7.7%)	9 (4.6%)	1 (0.5%)	0	0
紅斑	10 (5.2%)	9 (4.6%)	1 (0.5%)	0	0	0
皮膚乾燥	5 (2.6%)	4 (2.1%)	1 (0.5%)	0	0	0
寝汗	8 (4.1%)	8 (4.1%)	0	0	0	0
多汗症	6 (3.1%)	5 (2.6%)	1 (0.5%)	0	0	0
脱毛症	5 (2.6%)	5 (2.6%)	0	0	0	0
湿疹	5 (2.6%)	3 (1.5%)	2 (1.0%)	0	0	0
蕁麻疹	5 (2.6%)	1 (0.5%)	4 (2.1%)	0	0	0
そう痒性皮疹	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	0	0
薬疹	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159v/n01297a/ae17.sas / Output: /opt/BIOSTAT/prod/cdt7159v/n01297a/reports/ae17_297_SE.out
09SEP2016 9:00

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
ざ瘡様皮膚炎	3 (1.5%)	0	3 (1.5%)	0	0	0
水疱	1 (0.5%)	1 (0.5%)	0	0	0	0
全身性そう痒症	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
皮膚炎	2 (1.0%)	2 (1.0%)	0	0	0	0
丘疹性皮疹	1 (0.5%)	1 (0.5%)	0	0	0	0
紅色症	1 (0.5%)	1 (0.5%)	0	0	0	0
斑状出血	2 (1.0%)	2 (1.0%)	0	0	0	0
皮膚疼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
ざ瘡	1 (0.5%)	1 (0.5%)	0	0	0	0
アレルギー性皮膚炎	1 (0.5%)	0	1 (0.5%)	0	0	0
過角化	1 (0.5%)	1 (0.5%)	0	0	0	0
乾癬	1 (0.5%)	0	1 (0.5%)	0	0	0
光線過敏性反応	1 (0.5%)	1 (0.5%)	0	0	0	0
紅斑性皮疹	1 (0.5%)	1 (0.5%)	0	0	0	0
酒さ	1 (0.5%)	1 (0.5%)	0	0	0	0
中毒性皮疹	1 (0.5%)	1 (0.5%)	0	0	0	0
点状出血	1 (0.5%)	1 (0.5%)	0	0	0	0
日光皮膚炎	1 (0.5%)	0	1 (0.5%)	0	0	0
皮膚腫瘤	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚剥脱	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚反応	1 (0.5%)	1 (0.5%)	0	0	0	0
代謝および栄養障害						
- Overall -	65 (33.5%)	29 (14.9%)	19 (9.8%)	14 (7.2%)	3 (1.5%)	0
食欲減退	34 (17.5%)	22 (11.3%)	9 (4.6%)	3 (1.5%)	0	0
低カリウム血症	14 (7.2%)	6 (3.1%)	6 (3.1%)	2 (1.0%)	0	0
高尿酸血症	5 (2.6%)	2 (1.0%)	2 (1.0%)	0	1 (0.5%)	0
低マグネシウム血症	5 (2.6%)	3 (1.5%)	1 (0.5%)	1 (0.5%)	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
脱水	3 (1.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0
低リン酸血症	4 (2.1%)	0	3 (1.5%)	1 (0.5%)	0	0
体液貯留	2 (1.0%)	2 (1.0%)	0	0	0	0
低ナトリウム血症	2 (1.0%)	0	0	2 (1.0%)	0	0
高血糖	2 (1.0%)	0	0	1 (0.5%)	1 (0.5%)	0
腫瘍崩壊症候群	1 (0.5%)	0	0	1 (0.5%)	0	0
痛風	1 (0.5%)	0	1 (0.5%)	0	0	0
食欲亢進	2 (1.0%)	2 (1.0%)	0	0	0	0
低血糖症	2 (1.0%)	0	0	1 (0.5%)	1 (0.5%)	0
糖尿病	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
２型糖尿病	1 (0.5%)	0	1 (0.5%)	0	0	0
高脂血症	1 (0.5%)	0	1 (0.5%)	0	0	0
耐糖能障害	1 (0.5%)	0	0	1 (0.5%)	0	0
低アルブミン血症	1 (0.5%)	0	1 (0.5%)	0	0	0
低カルシウム血症	1 (0.5%)	1 (0.5%)	0	0	0	0
低蛋白血症	1 (0.5%)	0	0	1 (0.5%)	0	0
電解質失調	1 (0.5%)	0	1 (0.5%)	0	0	0
血管障害						
- Overall -	54 (27.8%)	23 (11.9%)	23 (11.9%)	8 (4.1%)	0	0
低血圧	23 (11.9%)	7 (3.6%)	13 (6.7%)	3 (1.5%)	0	0
静脈炎	11 (5.7%)	6 (3.1%)	5 (2.6%)	0	0	0
高血圧	9 (4.6%)	2 (1.0%)	4 (2.1%)	3 (1.5%)	0	0
深部静脈血栓症	1 (0.5%)	0	1 (0.5%)	0	0	0
潮紅	6 (3.1%)	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0
ほてり	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
起立性低血圧	1 (0.5%)	1 (0.5%)	0	0	0	0
血管痛	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
表在性血栓性静脈炎	1 (0.5%)	1 (0.5%)	0	0	0	0
リンパ浮腫	1 (0.5%)	0	1 (0.5%)	0	0	0
血行不全	1 (0.5%)	1 (0.5%)	0	0	0	0
高血圧クリーゼ	1 (0.5%)	0	0	1 (0.5%)	0	0
鎖骨下静脈血栓症	1 (0.5%)	0	1 (0.5%)	0	0	0
静脈狭窄	1 (0.5%)	1 (0.5%)	0	0	0	0
静脈障害	1 (0.5%)	1 (0.5%)	0	0	0	0
末梢血管障害	1 (0.5%)	1 (0.5%)	0	0	0	0
末梢静脈疾患	1 (0.5%)	1 (0.5%)	0	0	0	0
精神障害						
- Overall -	34 (17.5%)	22 (11.3%)	10 (5.2%)	1 (0.5%)	1 (0.5%)	0
不眠症	21 (10.8%)	18 (9.3%)	3 (1.5%)	0	0	0
不安	5 (2.6%)	3 (1.5%)	2 (1.0%)	0	0	0
うつ病	7 (3.6%)	3 (1.5%)	4 (2.1%)	0	0	0
錯乱状態	3 (1.5%)	0	2 (1.0%)	1 (0.5%)	0	0
抑うつ気分	2 (1.0%)	2 (1.0%)	0	0	0	0
激越	1 (0.5%)	1 (0.5%)	0	0	0	0
リビドー減退	1 (0.5%)	1 (0.5%)	0	0	0	0
無感情	1 (0.5%)	1 (0.5%)	0	0	0	0
落ち着きのなさ	1 (0.5%)	1 (0.5%)	0	0	0	0
譫妄	1 (0.5%)	1 (0.5%)	0	0	0	0
躁病	1 (0.5%)	0	0	0	1 (0.5%)	0
臨床検査						
- Overall -	29 (14.9%)	11 (5.7%)	14 (7.2%)	4 (2.1%)	0	0
体重減少	9 (4.6%)	4 (2.1%)	5 (2.6%)	0	0	0
血中クレアチニン増加	1 (0.5%)	0	0	1 (0.5%)	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
体温上昇	4 (2.1%)	2 (1.0%)	2 (1.0%)	0	0	0
アスパラギン酸アミノトランスフェラーゼ増加	1 (0.5%)	0	1 (0.5%)	0	0	0
アラニンアミノトランスフェラーゼ増加	1 (0.5%)	0	0	1 (0.5%)	0	0
血中ビリルビン増加	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
体重増加	3 (1.5%)	3 (1.5%)	0	0	0	0
Ｃ－反応性蛋白増加	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
血中アルカリホスファターゼ増加	1 (0.5%)	0	1 (0.5%)	0	0	0
心雑音	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
Ｂリンパ球数減少	1 (0.5%)	0	1 (0.5%)	0	0	0
ＱＲＳ軸異常	1 (0.5%)	1 (0.5%)	0	0	0	0
ウエスト周囲径増加	1 (0.5%)	1 (0.5%)	0	0	0	0
血小板数減少	1 (0.5%)	1 (0.5%)	0	0	0	0
血中カルシウム減少	1 (0.5%)	1 (0.5%)	0	0	0	0
血中ブドウ糖増加	1 (0.5%)	0	0	1 (0.5%)	0	0
血中甲状腺刺激ホルモン増加	1 (0.5%)	0	1 (0.5%)	0	0	0
血中鉄減少	1 (0.5%)	1 (0.5%)	0	0	0	0
血中免疫グロブリンＧ減少	1 (0.5%)	0	1 (0.5%)	0	0	0
腎クレアチニン・クリアランス増加	1 (0.5%)	0	1 (0.5%)	0	0	0
尿量増加	1 (0.5%)	1 (0.5%)	0	0	0	0
免疫グロブリン減少	1 (0.5%)	0	1 (0.5%)	0	0	0
眼障害						
- Overall -	25 (12.9%)	20 (10.3%)	4 (2.1%)	1 (0.5%)	0	0
霧視	7 (3.6%)	7 (3.6%)	0	0	0	0
眼乾燥	4 (2.1%)	4 (2.1%)	0	0	0	0
眼充血	4 (2.1%)	4 (2.1%)	0	0	0	0
視力障害	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
視力低下	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
流涙増加	1 (0.5%)	1 (0.5%)	0	0	0	0
霰粒腫	1 (0.5%)	0	1 (0.5%)	0	0	0
ぶどう膜炎	1 (0.5%)	0	1 (0.5%)	0	0	0
眼そう痒症	1 (0.5%)	1 (0.5%)	0	0	0	0
眼刺激	1 (0.5%)	1 (0.5%)	0	0	0	0
眼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
眼部腫脹	1 (0.5%)	1 (0.5%)	0	0	0	0
眼瞼血腫	1 (0.5%)	1 (0.5%)	0	0	0	0
眼窩周囲浮腫	1 (0.5%)	1 (0.5%)	0	0	0	0
結膜出血	1 (0.5%)	0	1 (0.5%)	0	0	0
白内障	1 (0.5%)	0	0	1 (0.5%)	0	0
緑内障	1 (0.5%)	1 (0.5%)	0	0	0	0
腎および尿路障害						
- Overall -	19 (9.8%)	11 (5.7%)	5 (2.6%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
頻尿	6 (3.1%)	5 (2.6%)	0	1 (0.5%)	0	0
排尿困難	6 (3.1%)	5 (2.6%)	0	1 (0.5%)	0	0
尿失禁	5 (2.6%)	1 (0.5%)	3 (1.5%)	1 (0.5%)	0	0
急性腎不全	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
夜間頻尿	2 (1.0%)	2 (1.0%)	0	0	0	0
血尿	1 (0.5%)	0	0	1 (0.5%)	0	0
多尿	1 (0.5%)	1 (0.5%)	0	0	0	0
慢性腎不全	1 (0.5%)	0	0	0	0	1 (0.5%)
腎結石症	1 (0.5%)	1 (0.5%)	0	0	0	0
尿管閉塞	1 (0.5%)	0	0	0	1 (0.5%)	0
尿路痛	1 (0.5%)	1 (0.5%)	0	0	0	0
排尿回数減少	1 (0.5%)	1 (0.5%)	0	0	0	0
有痛性排尿困難	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
膀胱痙縮	1 (0.5%)	0	1 (0.5%)	0	0	0
心臓障害						
- Overall -	22 (11.3%)	7 (3.6%)	6 (3.1%)	6 (3.1%)	3 (1.5%)	0
心房細動	4 (2.1%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	0	0
頻脈	4 (2.1%)	2 (1.0%)	2 (1.0%)	0	0	0
動悸	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
心不全	4 (2.1%)	0	2 (1.0%)	0	2 (1.0%)	0
洞性徐脈	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
狭心症	1 (0.5%)	1 (0.5%)	0	0	0	0
心筋梗塞	1 (0.5%)	0	0	0	1 (0.5%)	0
冠動脈疾患	1 (0.5%)	0	0	1 (0.5%)	0	0
急性冠動脈症候群	1 (0.5%)	0	0	1 (0.5%)	0	0
心臓内血栓	1 (0.5%)	0	0	1 (0.5%)	0	0
心房粗動	1 (0.5%)	0	0	1 (0.5%)	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）						
- Overall -	16 (8.2%)	4 (2.1%)	4 (2.1%)	1 (0.5%)	4 (2.1%)	3 (1.5%)
基底細胞癌	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
扁平上皮癌	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
骨髄異形成症候群	2 (1.0%)	0	0	0	2 (1.0%)	0
皮膚有棘細胞癌	2 (1.0%)	0	2 (1.0%)	0	0	0
悪性黒色腫	1 (0.5%)	0	0	0	1 (0.5%)	0
急性骨髄性白血病	1 (0.5%)	0	0	0	0	1 (0.5%)
Ｔ細胞性リンパ腫	1 (0.5%)	0	0	0	0	1 (0.5%)
ボーエン病	1 (0.5%)	0	1 (0.5%)	0	0	0
結腸直腸癌	1 (0.5%)	0	0	0	0	1 (0.5%)
脂漏性角化症	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
真性多血症	1 (0.5%)	0	1 (0.5%)	0	0	0
腎癌	1 (0.5%)	0	0	0	1 (0.5%)	0
髄膜腫	1 (0.5%)	1 (0.5%)	0	0	0	0
聴神経腫	1 (0.5%)	1 (0.5%)	0	0	0	0
膀胱癌	1 (0.5%)	0	0	1 (0.5%)	0	0
耳および迷路障害						
- Overall -	14 (7.2%)	12 (6.2%)	2 (1.0%)	0	0	0
回転性めまい	4 (2.1%)	4 (2.1%)	0	0	0	0
耳痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
聴力低下	1 (0.5%)	1 (0.5%)	0	0	0	0
難聴	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
耳鳴	1 (0.5%)	1 (0.5%)	0	0	0	0
聴覚障害	2 (1.0%)	2 (1.0%)	0	0	0	0
耳垢栓塞	1 (0.5%)	1 (0.5%)	0	0	0	0
耳不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
片耳難聴	1 (0.5%)	1 (0.5%)	0	0	0	0
生殖系および乳房障害						
- Overall -	10 (5.2%)	5 (2.6%)	5 (2.6%)	0	0	0
良性前立腺肥大症	2 (1.0%)	0	2 (1.0%)	0	0	0
勃起不全	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
膣出血	1 (0.5%)	1 (0.5%)	0	0	0	0
外陰膣乾燥	1 (0.5%)	1 (0.5%)	0	0	0	0
子宮の炎症	1 (0.5%)	0	1 (0.5%)	0	0	0
女性化乳房	1 (0.5%)	1 (0.5%)	0	0	0	0
前立腺炎	1 (0.5%)	0	1 (0.5%)	0	0	0
乳房痛	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_297_SE APPROVED Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肝胆道系障害						
- Overall -	5 (2.6%)	2 (1.0%)	1 (0.5%)	2 (1.0%)	0	0
胆汁うっ滞	1 (0.5%)	0	0	1 (0.5%)	0	0
胆嚢炎	1 (0.5%)	0	0	1 (0.5%)	0	0
脂肪肝	1 (0.5%)	1 (0.5%)	0	0	0	0
肝障害	1 (0.5%)	0	1 (0.5%)	0	0	0
肝不全	1 (0.5%)	1 (0.5%)	0	0	0	0
免疫系障害						
- Overall -	9 (4.6%)	4 (2.1%)	4 (2.1%)	0	0	1 (0.5%)
過敏症	5 (2.6%)	3 (1.5%)	2 (1.0%)	0	0	0
低γグロブリン血症	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
移植片対宿主病	1 (0.5%)	0	0	0	0	1 (0.5%)
造影剤アレルギー	1 (0.5%)	0	1 (0.5%)	0	0	0
社会環境						
- Overall -	1 (0.5%)	1 (0.5%)	0	0	0	0
社会的入院	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159v/n01297a/ae17.sas / Output: /opt/BIOSTAT/prod/cdt7159v/n01297a/reports/ae17_297_SE.out
09SEP2016 9:00

[5.3.5.3-1 ae17_297_SE を再掲]

表 2.7.6.2.1.4-2　因果関係が否定できないすべての有害事象（GAO4753g 試験，リツキシマブ治療抵抗性 iNHL 患者）

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GAO4753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	183 (92.4%)	30 (15.2%)	59 (29.8%)	55 (27.8%)	34 (17.2%)	5 (2.5%)
胃腸障害						
- Overall -	145 (73.2%)	73 (36.9%)	65 (32.8%)	7 (3.5%)	0	0
悪心	116 (58.6%)	73 (36.9%)	37 (18.7%)	6 (3.0%)	0	0
嘔吐	45 (22.7%)	21 (10.6%)	24 (12.1%)	0	0	0
下痢	43 (21.7%)	28 (14.1%)	13 (6.6%)	2 (1.0%)	0	0
便秘	18 (9.1%)	13 (6.6%)	5 (2.5%)	0	0	0
口内炎	8 (4.0%)	2 (1.0%)	6 (3.0%)	0	0	0
口内乾燥	9 (4.5%)	8 (4.0%)	1 (0.5%)	0	0	0
上腹部痛	8 (4.0%)	6 (3.0%)	2 (1.0%)	0	0	0
消化不良	6 (3.0%)	3 (1.5%)	3 (1.5%)	0	0	0
腹痛	6 (3.0%)	4 (2.0%)	2 (1.0%)	0	0	0
腹部膨満	6 (3.0%)	5 (2.5%)	1 (0.5%)	0	0	0
口腔内潰瘍形成	1 (0.5%)	0	1 (0.5%)	0	0	0
口腔内痛	1 (0.5%)	1 (0.5%)	0	0	0	0
アフタ性口内炎	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
下腹部痛	1 (0.5%)	1 (0.5%)	0	0	0	0
放屁	1 (0.5%)	1 (0.5%)	0	0	0	0
嚥下障害	1 (0.5%)	1 (0.5%)	0	0	0	0
胃炎	1 (0.5%)	1 (0.5%)	0	0	0	0
胃拡張	1 (0.5%)	0	1 (0.5%)	0	0	0
歯肉痛	1 (0.5%)	1 (0.5%)	0	0	0	0
痔出血	1 (0.5%)	1 (0.5%)	0	0	0	0
消化器痛	1 (0.5%)	0	1 (0.5%)	0	0	0
心窩部不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
舌痛	1 (0.5%)	1 (0.5%)	0	0	0	0
大腸閉塞	1 (0.5%)	0	0	1 (0.5%)	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
排便回数増加	1 (0.5%)	1 (0.5%)	0	0	0	0
傷害、中毒および処置合併症						
- Overall -	116 (58.6%)	54 (27.3%)	55 (27.8%)	7 (3.5%)	0	0
注入に伴う反応	115 (58.1%)	53 (26.8%)	55 (27.8%)	7 (3.5%)	0	0
食道熱傷	1 (0.5%)	1 (0.5%)	0	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	102 (51.5%)	57 (28.8%)	40 (20.2%)	5 (2.5%)	0	0
疲労	54 (27.3%)	27 (13.6%)	23 (11.6%)	4 (2.0%)	0	0
発熱	24 (12.1%)	18 (9.1%)	6 (3.0%)	0	0	0
無力症	18 (9.1%)	11 (5.6%)	6 (3.0%)	1 (0.5%)	0	0
悪寒	17 (8.6%)	15 (7.6%)	2 (1.0%)	0	0	0
粘膜の炎症	6 (3.0%)	3 (1.5%)	3 (1.5%)	0	0	0
末梢性浮腫	6 (3.0%)	5 (2.5%)	1 (0.5%)	0	0	0
倦怠感	1 (0.5%)	1 (0.5%)	0	0	0	0
注射部位疼痛	2 (1.0%)	2 (1.0%)	0	0	0	0
注入部位疼痛	4 (2.0%)	3 (1.5%)	1 (0.5%)	0	0	0
胸痛	1 (0.5%)	0	1 (0.5%)	0	0	0
腫脹	1 (0.5%)	0	1 (0.5%)	0	0	0
注射部位反応	2 (1.0%)	2 (1.0%)	0	0	0	0
浮腫	1 (0.5%)	0	1 (0.5%)	0	0	0
末梢腫脹	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
顔面浮腫	1 (0.5%)	1 (0.5%)	0	0	0	0
胸部不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
注入部位血管外漏出	1 (0.5%)	0	1 (0.5%)	0	0	0
疼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
インフルエンザ様疾患	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血管穿刺部位血腫	1 (0.5%)	1 (0.5%)	0	0	0	0
早期満腹	1 (0.5%)	1 (0.5%)	0	0	0	0
注射部位腫脹	1 (0.5%)	1 (0.5%)	0	0	0	0
注入部位炎症	1 (0.5%)	1 (0.5%)	0	0	0	0
注入部位静脈炎	1 (0.5%)	0	1 (0.5%)	0	0	0
非心臓性胸痛	1 (0.5%)	0	1 (0.5%)	0	0	0
血液およびリンパ系障害						
- Overall -	83 (41.9%)	3 (1.5%)	12 (6.1%)	37 (18.7%)	31 (15.7%)	0
好中球減少症	53 (26.8%)	0	5 (2.5%)	24 (12.1%)	24 (12.1%)	0
血小板減少症	41 (20.7%)	2 (1.0%)	14 (7.1%)	20 (10.1%)	5 (2.5%)	0
貧血	19 (9.6%)	1 (0.5%)	6 (3.0%)	11 (5.6%)	1 (0.5%)	0
発熱性好中球減少症	7 (3.5%)	0	0	6 (3.0%)	1 (0.5%)	0
白血球減少症	2 (1.0%)	0	0	2 (1.0%)	0	0
リンパ球減少症	1 (0.5%)	0	0	1 (0.5%)	0	0
自己免疫性溶血性貧血	1 (0.5%)	0	0	1 (0.5%)	0	0
感染症および寄生虫症						
- Overall -	53 (26.8%)	10 (5.1%)	25 (12.6%)	13 (6.6%)	2 (1.0%)	3 (1.5%)
帯状疱疹	10 (5.1%)	2 (1.0%)	5 (2.5%)	3 (1.5%)	0	0
気管支炎	7 (3.5%)	0	7 (3.5%)	0	0	0
副鼻腔炎	4 (2.0%)	0	4 (2.0%)	0	0	0
肺炎	6 (3.0%)	0	0	5 (2.5%)	1 (0.5%)	0
口腔ヘルペス	5 (2.5%)	4 (2.0%)	1 (0.5%)	0	0	0
上気道感染	4 (2.0%)	1 (0.5%)	3 (1.5%)	0	0	0
尿路感染	1 (0.5%)	0	1 (0.5%)	0	0	0
敗血症	4 (2.0%)	0	0	1 (0.5%)	2 (1.0%)	1 (0.5%)
下気道感染	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
口腔カンジダ症	3 (1.5%)	0	3 (1.5%)	0	0	0
鼻炎	2 (1.0%)	2 (1.0%)	0	0	0	0
肺感染	1 (0.5%)	0	0	1 (0.5%)	0	0
鼻咽頭炎	2 (1.0%)	0	2 (1.0%)	0	0	0
感染	3 (1.5%)	1 (0.5%)	0	2 (1.0%)	0	0
蜂巣炎	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
サイトメガロウイルス性脈絡網膜炎	1 (0.5%)	0	0	1 (0.5%)	0	0
ニューモシスチス・イロベチイ肺炎	2 (1.0%)	0	0	0	0	2 (1.0%)
ブドウ球菌皮膚感染	1 (0.5%)	0	0	1 (0.5%)	0	0
気管支肺炎	1 (0.5%)	0	1 (0.5%)	0	0	0
憩室炎	1 (0.5%)	0	1 (0.5%)	0	0	0
Ｂ型肝炎	1 (0.5%)	0	0	1 (0.5%)	0	0
ウイルス性下気道感染	1 (0.5%)	0	1 (0.5%)	0	0	0
ウイルス性下痢	1 (0.5%)	0	1 (0.5%)	0	0	0
ウイルス性気管支炎	1 (0.5%)	1 (0.5%)	0	0	0	0
ウイルス性上気道感染	1 (0.5%)	0	1 (0.5%)	0	0	0
サイトメガロウイルス性肺炎	1 (0.5%)	0	1 (0.5%)	0	0	0
ノロウイルス性胃腸炎	1 (0.5%)	0	0	1 (0.5%)	0	0
胃腸炎	1 (0.5%)	1 (0.5%)	0	0	0	0
外陰部腟カンジダ症	1 (0.5%)	1 (0.5%)	0	0	0	0
感染性静脈炎	1 (0.5%)	0	1 (0.5%)	0	0	0
眼感染	1 (0.5%)	0	1 (0.5%)	0	0	0
結膜炎	1 (0.5%)	0	1 (0.5%)	0	0	0
口腔真菌感染	1 (0.5%)	0	1 (0.5%)	0	0	0
真菌性上気道感染	1 (0.5%)	0	1 (0.5%)	0	0	0
単純ヘルペス	1 (0.5%)	0	1 (0.5%)	0	0	0
中耳炎	1 (0.5%)	0	1 (0.5%)	0	0	0
爪真菌症	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
毛包炎	1 (0.5%)	0	0	1 (0.5%)	0	0
神経系障害						
- Overall -	46 (23.2%)	29 (14.6%)	13 (6.6%)	4 (2.0%)	0	0
頭痛	17 (8.6%)	11 (5.6%)	5 (2.5%)	1 (0.5%)	0	0
味覚異常	14 (7.1%)	11 (5.6%)	3 (1.5%)	0	0	0
浮動性めまい	13 (6.6%)	10 (5.1%)	3 (1.5%)	0	0	0
錯感覚	1 (0.5%)	0	1 (0.5%)	0	0	0
感覚鈍麻	1 (0.5%)	0	1 (0.5%)	0	0	0
記憶障害	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
嗜眠	4 (2.0%)	2 (1.0%)	2 (1.0%)	0	0	0
失神寸前の状態	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
末梢性ニューロパチー	1 (0.5%)	0	1 (0.5%)	0	0	0
末梢性感覚ニューロパチー	3 (1.5%)	3 (1.5%)	0	0	0	0
失神	2 (1.0%)	0	0	2 (1.0%)	0	0
異常感覚	1 (0.5%)	1 (0.5%)	0	0	0	0
中枢神経系病変	1 (0.5%)	0	0	1 (0.5%)	0	0
味覚消失	1 (0.5%)	1 (0.5%)	0	0	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	27 (13.6%)	14 (7.1%)	13 (6.6%)	0	0	0
咳嗽	9 (4.5%)	5 (2.5%)	4 (2.0%)	0	0	0
呼吸困難	8 (4.0%)	5 (2.5%)	3 (1.5%)	0	0	0
鼻閉	2 (1.0%)	0	2 (1.0%)	0	0	0
口腔咽頭痛	4 (2.0%)	2 (1.0%)	2 (1.0%)	0	0	0
湿性咳嗽	2 (1.0%)	2 (1.0%)	0	0	0	0
労作性呼吸困難	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
鼻出血	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
鼻漏	1 (0.5%)	0	1 (0.5%)	0	0	0
上気道咳症候群	1 (0.5%)	1 (0.5%)	0	0	0	0
変色痰	1 (0.5%)	1 (0.5%)	0	0	0	0
しゃっくり	1 (0.5%)	1 (0.5%)	0	0	0	0
胸膜炎	1 (0.5%)	1 (0.5%)	0	0	0	0
胸膜痛	1 (0.5%)	0	1 (0.5%)	0	0	0
発声障害	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚および皮下組織障害						
- Overall -	35 (17.7%)	22 (11.1%)	12 (6.1%)	1 (0.5%)	0	0
発疹	13 (6.6%)	9 (4.5%)	4 (2.0%)	0	0	0
そう痒症	6 (3.0%)	5 (2.5%)	1 (0.5%)	0	0	0
紅斑	2 (1.0%)	0	2 (1.0%)	0	0	0
皮膚乾燥	5 (2.5%)	4 (2.0%)	1 (0.5%)	0	0	0
脱毛症	3 (1.5%)	3 (1.5%)	0	0	0	0
そう痒性皮疹	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
湿疹	1 (0.5%)	1 (0.5%)	0	0	0	0
寝汗	2 (1.0%)	2 (1.0%)	0	0	0	0
蕁麻疹	1 (0.5%)	0	1 (0.5%)	0	0	0
全身性皮疹	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
皮膚炎	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚疼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
薬疹	2 (1.0%)	2 (1.0%)	0	0	0	0
全身性そう痒症	1 (0.5%)	0	1 (0.5%)	0	0	0
爪の障害	1 (0.5%)	1 (0.5%)	0	0	0	0
斑状丘疹状皮疹	1 (0.5%)	1 (0.5%)	0	0	0	0
斑状皮疹	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
代謝および栄養障害						
- Overall -	39 (19.7%)	14 (7.1%)	19 (9.6%)	5 (2.5%)	1 (0.5%)	0
食欲減退	28 (14.1%)	14 (7.1%)	12 (6.1%)	2 (1.0%)	0	0
低カリウム血症	7 (3.5%)	0	4 (2.0%)	2 (1.0%)	1 (0.5%)	0
低リン酸血症	2 (1.0%)	0	0	2 (1.0%)	0	0
低マグネシウム血症	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
脱水	3 (1.5%)	0	2 (1.0%)	1 (0.5%)	0	0
腫瘍崩壊症候群	1 (0.5%)	0	0	1 (0.5%)	0	0
血管障害						
- Overall -	21 (10.6%)	4 (2.0%)	16 (8.1%)	1 (0.5%)	0	0
低血圧	1 (0.5%)	1 (0.5%)	0	0	0	0
静脈炎	10 (5.1%)	1 (0.5%)	9 (4.5%)	0	0	0
表在性静脈炎	3 (1.5%)	0	3 (1.5%)	0	0	0
血管痛	1 (0.5%)	1 (0.5%)	0	0	0	0
高血圧	1 (0.5%)	0	0	1 (0.5%)	0	0
深部静脈血栓症	1 (0.5%)	0	1 (0.5%)	0	0	0
表在性血栓性静脈炎	1 (0.5%)	0	1 (0.5%)	0	0	0
間欠性跛行	1 (0.5%)	0	1 (0.5%)	0	0	0
血栓症	1 (0.5%)	0	1 (0.5%)	0	0	0
血栓性静脈炎	1 (0.5%)	1 (0.5%)	0	0	0	0
筋骨格系および結合組織障害						
- Overall -	20 (10.1%)	13 (6.6%)	7 (3.5%)	0	0	0
筋肉痛	9 (4.5%)	4 (2.0%)	5 (2.5%)	0	0	0
四肢痛	5 (2.5%)	5 (2.5%)	0	0	0	0
関節痛	2 (1.0%)	2 (1.0%)	0	0	0	0
顎痛	1 (0.5%)	1 (0.5%)	0	0	0	0

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Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
筋痙縮	1 (0.5%)	0	1 (0.5%)	0	0	0
背部痛	1 (0.5%)	1 (0.5%)	0	0	0	0
筋力低下	1 (0.5%)	0	1 (0.5%)	0	0	0
筋骨格硬直	1 (0.5%)	1 (0.5%)	0	0	0	0
骨痛	1 (0.5%)	1 (0.5%)	0	0	0	0
四肢不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
臨床検査						
- Overall -	17 (8.6%)	11 (5.6%)	6 (3.0%)	0	0	0
体重減少	13 (6.6%)	8 (4.0%)	5 (2.5%)	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 (0.5%)	0	1 (0.5%)	0	0	0
アラニンアミノトランスフェラーゼ増加	1 (0.5%)	0	1 (0.5%)	0	0	0
血中アルカリホスファターゼ増加	1 (0.5%)	0	1 (0.5%)	0	0	0
血中クレアチニン増加	2 (1.0%)	2 (1.0%)	0	0	0	0
サイトメガロウイルス検査陽性	1 (0.5%)	1 (0.5%)	0	0	0	0
心拍数不整	1 (0.5%)	1 (0.5%)	0	0	0	0
腎クレアチニン・クリアランス減少	1 (0.5%)	1 (0.5%)	0	0	0	0
精神障害						
- Overall -	9 (4.5%)	7 (3.5%)	2 (1.0%)	0	0	0
不眠症	7 (3.5%)	5 (2.5%)	2 (1.0%)	0	0	0
うつ病	1 (0.5%)	1 (0.5%)	0	0	0	0
気分変化	1 (0.5%)	1 (0.5%)	0	0	0	0
心臓障害						
- Overall -	3 (1.5%)	2 (1.0%)	0	1 (0.5%)	0	0
頻脈	1 (0.5%)	1 (0.5%)	0	0	0	0
冠動脈硬化症	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
心房細動	1 (0.5%)	0	0	1 (0.5%)	0	0
眼障害						
- Overall -	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
眼乾燥	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
視力低下	1 (0.5%)	1 (0.5%)	0	0	0	0
流涙増加	1 (0.5%)	1 (0.5%)	0	0	0	0
腎および尿路障害						
- Overall -	4 (2.0%)	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	0
頻尿	1 (0.5%)	1 (0.5%)	0	0	0	0
急性腎不全	1 (0.5%)	0	0	0	1 (0.5%)	0
腎損傷	1 (0.5%)	0	1 (0.5%)	0	0	0
多尿	1 (0.5%)	1 (0.5%)	0	0	0	0
免疫系障害						
- Overall -	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
過敏症	1 (0.5%)	1 (0.5%)	0	0	0	0
低γグロブリン血症	1 (0.5%)	0	1 (0.5%)	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）						
- Overall -	4 (2.0%)	0	0	0	2 (1.0%)	2 (1.0%)
骨髄異形成症候群	1 (0.5%)	0	0	0	1 (0.5%)	0
急性骨髄性白血病	1 (0.5%)	0	0	0	0	1 (0.5%)
白血病	1 (0.5%)	0	0	0	0	1 (0.5%)
平滑筋肉腫	1 (0.5%)	0	0	0	1 (0.5%)	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: B (N=198)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肝胆道系障害						
- Overall -	4 (2.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
胆汁うっ滞	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
脂肪肝	1 (0.5%)	0	0	1 (0.5%)	0	0
肝毒性	1 (0.5%)	0	0	0	1 (0.5%)	0
耳および迷路障害						
- Overall -	5 (2.5%)	5 (2.5%)	0	0	0	0
回転性めまい	3 (1.5%)	3 (1.5%)	0	0	0	0
聴力低下	1 (0.5%)	1 (0.5%)	0	0	0	0
耳痛	1 (0.5%)	1 (0.5%)	0	0	0	0
耳鳴	1 (0.5%)	1 (0.5%)	0	0	0	0
生殖系および乳房障害						
- Overall -	1 (0.5%)	1 (0.5%)	0	0	0	0
外陰腟障害	1 (0.5%)	1 (0.5%)	0	0	0	0
社会環境						
- Overall -	1 (0.5%)	1 (0.5%)	0	0	0	0
社会問題	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	184 (94.8%)	29 (14.9%)	52 (26.8%)	45 (23.2%)	55 (28.4%)	3 (1.5%)
胃腸障害						
- Overall -	120 (61.9%)	62 (32.0%)	48 (24.7%)	8 (4.1%)	2 (1.0%)	0
悪心	92 (47.4%)	59 (30.4%)	31 (16.0%)	2 (1.0%)	0	0
嘔吐	33 (17.0%)	18 (9.3%)	13 (6.7%)	2 (1.0%)	0	0
下痢	32 (16.5%)	20 (10.3%)	11 (5.7%)	1 (0.5%)	0	0
便秘	18 (9.3%)	15 (7.7%)	3 (1.5%)	0	0	0
口内炎	6 (3.1%)	4 (2.1%)	2 (1.0%)	0	0	0
口内乾燥	4 (2.1%)	4 (2.1%)	0	0	0	0
上腹部痛	4 (2.1%)	4 (2.1%)	0	0	0	0
消化不良	4 (2.1%)	4 (2.1%)	0	0	0	0
腹痛	3 (1.5%)	3 (1.5%)	0	0	0	0
口腔内潰瘍形成	4 (2.1%)	3 (1.5%)	0	1 (0.5%)	0	0
口腔内痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
胃腸障害	2 (1.0%)	2 (1.0%)	0	0	0	0
下腹部痛	1 (0.5%)	1 (0.5%)	0	0	0	0
歯痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
腹部不快感	2 (1.0%)	2 (1.0%)	0	0	0	0
放屁	1 (0.5%)	1 (0.5%)	0	0	0	0
嚥下障害	1 (0.5%)	0	1 (0.5%)	0	0	0
胃食道逆流性疾患	1 (0.5%)	0	1 (0.5%)	0	0	0
胃腸音異常	1 (0.5%)	1 (0.5%)	0	0	0	0
胃腸出血	1 (0.5%)	0	0	1 (0.5%)	0	0
呼気臭	1 (0.5%)	1 (0.5%)	0	0	0	0
口蓋浮腫	1 (0.5%)	0	0	0	1 (0.5%)	0
口腔腫脹	1 (0.5%)	1 (0.5%)	0	0	0	0
口腔粘膜紅斑	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
口唇潰瘍	1 (0.5%)	1 (0.5%)	0	0	0	0
歯の知覚過敏	1 (0.5%)	1 (0.5%)	0	0	0	0
痔核	1 (0.5%)	1 (0.5%)	0	0	0	0
腸管穿孔	1 (0.5%)	0	0	1 (0.5%)	0	0
嚥下痛	1 (0.5%)	0	1 (0.5%)	0	0	0
肛門周囲痛	1 (0.5%)	1 (0.5%)	0	0	0	0
肛門潰瘍	1 (0.5%)	0	1 (0.5%)	0	0	0
膵炎	1 (0.5%)	0	0	0	1 (0.5%)	0
傷害、中毒および処置合併症						
- Overall -	125 (64.4%)	57 (29.4%)	51 (26.3%)	12 (6.2%)	4 (2.1%)	1 (0.5%)
注入に伴う反応	125 (64.4%)	57 (29.4%)	51 (26.3%)	13 (6.7%)	4 (2.1%)	0
血管偽動脈瘤	1 (0.5%)	0	0	0	0	1 (0.5%)
爪損傷	1 (0.5%)	0	1 (0.5%)	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	111 (57.2%)	56 (28.9%)	47 (24.2%)	8 (4.1%)	0	0
疲労	68 (35.1%)	40 (20.6%)	26 (13.4%)	2 (1.0%)	0	0
発熱	34 (17.5%)	23 (11.9%)	10 (5.2%)	1 (0.5%)	0	0
無力症	20 (10.3%)	14 (7.2%)	4 (2.1%)	2 (1.0%)	0	0
悪寒	19 (9.8%)	11 (5.7%)	7 (3.6%)	1 (0.5%)	0	0
粘膜の炎症	8 (4.1%)	5 (2.6%)	2 (1.0%)	1 (0.5%)	0	0
末梢性浮腫	4 (2.1%)	3 (1.5%)	1 (0.5%)	0	0	0
倦怠感	4 (2.1%)	3 (1.5%)	1 (0.5%)	0	0	0
注射部位疼痛	3 (1.5%)	3 (1.5%)	0	0	0	0
注入部位疼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
胸痛	3 (1.5%)	3 (1.5%)	0	0	0	0
腫脹	2 (1.0%)	2 (1.0%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
注射部位反応	1 (0.5%)	1 (0.5%)	0	0	0	0
浮腫	2 (1.0%)	2 (1.0%)	0	0	0	0
顔面浮腫	1 (0.5%)	1 (0.5%)	0	0	0	0
胸部不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
注入部位血管外漏出	1 (0.5%)	1 (0.5%)	0	0	0	0
疼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
カテーテル留置部位紅斑	1 (0.5%)	1 (0.5%)	0	0	0	0
圧痛	1 (0.5%)	0	1 (0.5%)	0	0	0
口渇	1 (0.5%)	1 (0.5%)	0	0	0	0
高熱	1 (0.5%)	0	1 (0.5%)	0	0	0
全身健康状態低下	1 (0.5%)	0	0	1 (0.5%)	0	0
注射部位硬結	1 (0.5%)	1 (0.5%)	0	0	0	0
注射部位線維症	1 (0.5%)	1 (0.5%)	0	0	0	0
不快感	1 (0.5%)	1 (0.5%)	0	0	0	0
冷感	1 (0.5%)	1 (0.5%)	0	0	0	0
血液およびリンパ系障害						
- Overall -	90 (46.4%)	2 (1.0%)	7 (3.6%)	37 (19.1%)	44 (22.7%)	0
好中球減少症	63 (32.5%)	0	4 (2.1%)	25 (12.9%)	34 (17.5%)	0
血小板減少症	27 (13.9%)	3 (1.5%)	4 (2.1%)	11 (5.7%)	9 (4.6%)	0
貧血	15 (7.7%)	1 (0.5%)	7 (3.6%)	6 (3.1%)	1 (0.5%)	0
発熱性好中球減少症	7 (3.6%)	0	0	5 (2.6%)	2 (1.0%)	0
白血球減少症	2 (1.0%)	0	0	2 (1.0%)	0	0
低グロブリン血症	1 (0.5%)	0	1 (0.5%)	0	0	0
感染症および寄生虫症						
- Overall -	53 (27.3%)	9 (4.6%)	32 (16.5%)	7 (3.6%)	4 (2.1%)	1 (0.5%)
帯状疱疹	6 (3.1%)	1 (0.5%)	4 (2.1%)	1 (0.5%)	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
気管支炎	7 (3.6%)	1 (0.5%)	6 (3.1%)	0	0	0
副鼻腔炎	8 (4.1%)	1 (0.5%)	7 (3.6%)	0	0	0
肺炎	5 (2.6%)	0	3 (1.5%)	2 (1.0%)	0	0
口腔ヘルペス	4 (2.1%)	3 (1.5%)	1 (0.5%)	0	0	0
上気道感染	4 (2.1%)	0	3 (1.5%)	1 (0.5%)	0	0
尿路感染	7 (3.6%)	0	6 (3.1%)	1 (0.5%)	0	0
敗血症	3 (1.5%)	0	0	0	3 (1.5%)	0
下気道感染	3 (1.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0
口腔カンジダ症	2 (1.0%)	0	2 (1.0%)	0	0	0
鼻炎	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
肺感染	3 (1.5%)	0	2 (1.0%)	0	1 (0.5%)	0
鼻咽頭炎	2 (1.0%)	2 (1.0%)	0	0	0	0
蜂巣炎	1 (0.5%)	0	1 (0.5%)	0	0	0
サイトメガロウイルス性脈絡網膜炎	1 (0.5%)	0	0	1 (0.5%)	0	0
ブドウ球菌皮膚感染	1 (0.5%)	0	1 (0.5%)	0	0	0
気管支肺炎	1 (0.5%)	0	1 (0.5%)	0	0	0
気道感染	2 (1.0%)	0	2 (1.0%)	0	0	0
憩室炎	1 (0.5%)	0	1 (0.5%)	0	0	0
膣感染	2 (1.0%)	0	2 (1.0%)	0	0	0
シュードモナス菌性肺感染	1 (0.5%)	0	1 (0.5%)	0	0	0
シュードモナス性敗血症	1 (0.5%)	0	0	0	0	1 (0.5%)
ダニ皮膚炎	1 (0.5%)	0	1 (0.5%)	0	0	0
医療機器関連感染	1 (0.5%)	0	1 (0.5%)	0	0	0
咽頭炎	1 (0.5%)	1 (0.5%)	0	0	0	0
陰部ヘルペス	1 (0.5%)	1 (0.5%)	0	0	0	0
細菌感染	1 (0.5%)	0	1 (0.5%)	0	0	0
耳感染	1 (0.5%)	0	1 (0.5%)	0	0	0
舌膿瘍	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
尿路性敗血症	1 (0.5%)	0	0	1 (0.5%)	0	0
鼻膿瘍	1 (0.5%)	0	1 (0.5%)	0	0	0
腹部膿瘍	1 (0.5%)	0	1 (0.5%)	0	0	0
膀胱炎	1 (0.5%)	0	1 (0.5%)	0	0	0
鼠径部感染	1 (0.5%)	0	1 (0.5%)	0	0	0
神経系障害						
- Overall -	45 (23.2%)	38 (19.6%)	5 (2.6%)	2 (1.0%)	0	0
頭痛	14 (7.2%)	11 (5.7%)	2 (1.0%)	1 (0.5%)	0	0
味覚異常	15 (7.7%)	14 (7.2%)	1 (0.5%)	0	0	0
浮動性めまい	9 (4.6%)	9 (4.6%)	0	0	0	0
錯感覚	5 (2.6%)	5 (2.6%)	0	0	0	0
感覚鈍麻	4 (2.1%)	4 (2.1%)	0	0	0	0
記憶障害	3 (1.5%)	3 (1.5%)	0	0	0	0
嗜眠	1 (0.5%)	1 (0.5%)	0	0	0	0
失神寸前の状態	2 (1.0%)	0	1 (0.5%)	1 (0.5%)	0	0
末梢性ニューロパチー	3 (1.5%)	3 (1.5%)	0	0	0	0
末梢性感覚ニューロパチー	1 (0.5%)	1 (0.5%)	0	0	0	0
失神	1 (0.5%)	0	0	1 (0.5%)	0	0
異常感覚	1 (0.5%)	1 (0.5%)	0	0	0	0
灼熱感	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
認知障害	2 (1.0%)	2 (1.0%)	0	0	0	0
振戦	1 (0.5%)	1 (0.5%)	0	0	0	0
嗅覚錯誤	1 (0.5%)	1 (0.5%)	0	0	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	54 (27.8%)	29 (14.9%)	16 (8.2%)	5 (2.6%)	4 (2.1%)	0
咳嗽	16 (8.2%)	11 (5.7%)	5 (2.6%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
呼吸困難	15 (7.7%)	9 (4.6%)	5 (2.6%)	1 (0.5%)	0	0
鼻閉	10 (5.2%)	10 (5.2%)	0	0	0	0
口腔咽頭痛	4 (2.1%)	4 (2.1%)	0	0	0	0
低酸素症	7 (3.6%)	0	4 (2.1%)	3 (1.5%)	0	0
湿性咳嗽	3 (1.5%)	2 (1.0%)	0	1 (0.5%)	0	0
労作性呼吸困難	2 (1.0%)	2 (1.0%)	0	0	0	0
鼻出血	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
鼻漏	3 (1.5%)	3 (1.5%)	0	0	0	0
咽喉絞扼感	2 (1.0%)	0	1 (0.5%)	0	1 (0.5%)	0
上気道咳症候群	1 (0.5%)	1 (0.5%)	0	0	0	0
肺障害	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
変色痰	1 (0.5%)	1 (0.5%)	0	0	0	0
喘鳴	2 (1.0%)	0	2 (1.0%)	0	0	0
咽喉刺激感	1 (0.5%)	1 (0.5%)	0	0	0	0
間質性肺疾患	1 (0.5%)	0	0	1 (0.5%)	0	0
気管支痙攣	1 (0.5%)	0	0	0	1 (0.5%)	0
胸水	1 (0.5%)	0	0	0	1 (0.5%)	0
喉頭不快感	1 (0.5%)	0	1 (0.5%)	0	0	0
喉頭浮腫	1 (0.5%)	0	0	0	1 (0.5%)	0
肺塞栓症	1 (0.5%)	0	0	0	1 (0.5%)	0
鼻閉塞	1 (0.5%)	0	1 (0.5%)	0	0	0
皮膚および皮下組織障害						
- Overall -	43 (22.2%)	29 (14.9%)	10 (5.2%)	3 (1.5%)	1 (0.5%)	0
発疹	16 (8.2%)	11 (5.7%)	3 (1.5%)	1 (0.5%)	1 (0.5%)	0
そう痒症	16 (8.2%)	9 (4.6%)	6 (3.1%)	1 (0.5%)	0	0
紅斑	7 (3.6%)	6 (3.1%)	1 (0.5%)	0	0	0
皮膚乾燥	2 (1.0%)	2 (1.0%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
脱毛症	3 (1.5%)	3 (1.5%)	0	0	0	0
そう痒性皮疹	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	0	0
湿疹	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
寝汗	1 (0.5%)	1 (0.5%)	0	0	0	0
多汗症	3 (1.5%)	3 (1.5%)	0	0	0	0
蕁麻疹	2 (1.0%)	0	2 (1.0%)	0	0	0
皮膚炎	1 (0.5%)	1 (0.5%)	0	0	0	0
皮膚疼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
ざ瘡	1 (0.5%)	1 (0.5%)	0	0	0	0
ざ瘡様皮膚炎	1 (0.5%)	0	1 (0.5%)	0	0	0
過角化	1 (0.5%)	1 (0.5%)	0	0	0	0
丘疹性皮疹	1 (0.5%)	1 (0.5%)	0	0	0	0
光線過敏性反応	1 (0.5%)	1 (0.5%)	0	0	0	0
代謝および栄養障害						
- Overall -	35 (18.0%)	21 (10.8%)	9 (4.6%)	4 (2.1%)	1 (0.5%)	0
食欲減退	22 (11.3%)	17 (8.8%)	5 (2.6%)	0	0	0
低カリウム血症	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
低リン酸血症	3 (1.5%)	0	2 (1.0%)	1 (0.5%)	0	0
高尿酸血症	4 (2.1%)	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	0
低マグネシウム血症	1 (0.5%)	1 (0.5%)	0	0	0	0
腫瘍崩壊症候群	1 (0.5%)	0	0	1 (0.5%)	0	0
低血糖症	1 (0.5%)	0	0	1 (0.5%)	0	0
低蛋白血症	1 (0.5%)	0	0	1 (0.5%)	0	0
糖尿病	1 (0.5%)	0	1 (0.5%)	0	0	0
血管障害						
- Overall -	37 (19.1%)	17 (8.8%)	16 (8.2%)	4 (2.1%)	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/G001297 (N01297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
低血圧	19 (9.8%)	7 (3.6%)	11 (5.7%)	1 (0.5%)	0	0
静脈炎	7 (3.6%)	4 (2.1%)	3 (1.5%)	0	0	0
潮紅	6 (3.1%)	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0
ほてり	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
血管痛	1 (0.5%)	1 (0.5%)	0	0	0	0
高血圧	1 (0.5%)	0	0	1 (0.5%)	0	0
深部静脈血栓症	1 (0.5%)	0	1 (0.5%)	0	0	0
表在性血栓性静脈炎	1 (0.5%)	1 (0.5%)	0	0	0	0
起立性低血圧	1 (0.5%)	1 (0.5%)	0	0	0	0
高血圧クリーゼ	1 (0.5%)	0	0	1 (0.5%)	0	0
静脈狭窄	1 (0.5%)	1 (0.5%)	0	0	0	0
筋骨格系および結合組織障害						
- Overall -	25 (12.9%)	18 (9.3%)	7 (3.6%)	0	0	0
筋肉痛	5 (2.6%)	5 (2.6%)	0	0	0	0
四肢痛	8 (4.1%)	7 (3.6%)	1 (0.5%)	0	0	0
関節痛	5 (2.6%)	4 (2.1%)	1 (0.5%)	0	0	0
顎痛	2 (1.0%)	2 (1.0%)	0	0	0	0
筋痙縮	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
背部痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
筋骨格系胸痛	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
筋力低下	1 (0.5%)	1 (0.5%)	0	0	0	0
リウマチ性多発筋痛	1 (0.5%)	0	1 (0.5%)	0	0	0
関節腫脹	1 (0.5%)	1 (0.5%)	0	0	0	0
筋骨格痛	1 (0.5%)	1 (0.5%)	0	0	0	0
頚部痛	1 (0.5%)	0	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
臨床検査						
- Overall -	11 (5.7%)	4 (2.1%)	6 (3.1%)	1 (0.5%)	0	0
体重減少	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
体温上昇	4 (2.1%)	2 (1.0%)	2 (1.0%)	0	0	0
血中ビリルビン増加	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0
アスパラギン酸アミノトランスフェラーゼ増加	1 (0.5%)	0	1 (0.5%)	0	0	0
アラニンアミノトランスフェラーゼ増加	1 (0.5%)	0	0	1 (0.5%)	0	0
血中アルカリホスファターゼ増加	1 (0.5%)	0	1 (0.5%)	0	0	0
Ｂリンパ球数減少	1 (0.5%)	0	1 (0.5%)	0	0	0
血中甲状腺刺激ホルモン増加	1 (0.5%)	0	1 (0.5%)	0	0	0
精神障害						
- Overall -	6 (3.1%)	4 (2.1%)	2 (1.0%)	0	0	0
不眠症	3 (1.5%)	2 (1.0%)	1 (0.5%)	0	0	0
うつ病	1 (0.5%)	0	1 (0.5%)	0	0	0
リビドー減退	1 (0.5%)	1 (0.5%)	0	0	0	0
激越	1 (0.5%)	1 (0.5%)	0	0	0	0
不安	1 (0.5%)	0	1 (0.5%)	0	0	0
無感情	1 (0.5%)	1 (0.5%)	0	0	0	0
心臓障害						
- Overall -	9 (4.6%)	2 (1.0%)	4 (2.1%)	1 (0.5%)	2 (1.0%)	0
頻脈	2 (1.0%)	0	2 (1.0%)	0	0	0
動悸	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
洞性徐脈	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
狭心症	1 (0.5%)	1 (0.5%)	0	0	0	0
心筋梗塞	1 (0.5%)	0	0	0	1 (0.5%)	0
心不全	1 (0.5%)	0	0	0	1 (0.5%)	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
心房粗動	1 (0.5%)	0	0	1 (0.5%)	0	0
眼障害						
- Overall -	8 (4.1%)	7 (3.6%)	0	1 (0.5%)	0	0
眼乾燥	2 (1.0%)	2 (1.0%)	0	0	0	0
霧視	3 (1.5%)	3 (1.5%)	0	0	0	0
視力低下	1 (0.5%)	1 (0.5%)	0	0	0	0
流涙増加	1 (0.5%)	1 (0.5%)	0	0	0	0
眼痛	1 (0.5%)	1 (0.5%)	0	0	0	0
眼部腫脹	1 (0.5%)	1 (0.5%)	0	0	0	0
白内障	1 (0.5%)	0	0	1 (0.5%)	0	0
腎および尿路障害						
- Overall -	7 (3.6%)	4 (2.1%)	3 (1.5%)	0	0	0
頻尿	2 (1.0%)	2 (1.0%)	0	0	0	0
急性腎不全	1 (0.5%)	0	1 (0.5%)	0	0	0
尿失禁	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
排尿困難	2 (1.0%)	2 (1.0%)	0	0	0	0
尿路痛	1 (0.5%)	1 (0.5%)	0	0	0	0
夜間頻尿	1 (0.5%)	1 (0.5%)	0	0	0	0
有痛性排尿困難	1 (0.5%)	0	1 (0.5%)	0	0	0
免疫系障害						
- Overall -	6 (3.1%)	3 (1.5%)	3 (1.5%)	0	0	0
過敏症	4 (2.1%)	2 (1.0%)	2 (1.0%)	0	0	0
低γグロブリン血症	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_297_SE APPROVED Related Adverse Events by Intensity (NCI-CTC Grades 1-5) (Safety-Evaluable Patients)

Protocol(s): GA04753g/GO01297 (NO1297A)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 19DEC2014 Cutoff Date: 01SEP2014:23:59:59

Treatment: G-B (N=194)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	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）						
- Overall -	4 (2.1%)	0	0	1 (0.5%)	2 (1.0%)	1 (0.5%)
骨髄異形成症候群	2 (1.0%)	0	0	0	2 (1.0%)	0
急性骨髄性白血病	1 (0.5%)	0	0	0	0	1 (0.5%)
膀胱癌	1 (0.5%)	0	0	1 (0.5%)	0	0
肝胆道系障害						
- Overall -	3 (1.5%)	2 (1.0%)	0	1 (0.5%)	0	0
胆汁うっ滞	1 (0.5%)	0	0	1 (0.5%)	0	0
脂肪肝	1 (0.5%)	1 (0.5%)	0	0	0	0
肝不全	1 (0.5%)	1 (0.5%)	0	0	0	0
耳および迷路障害						
- Overall -	1 (0.5%)	1 (0.5%)	0	0	0	0
聴力低下	1 (0.5%)	1 (0.5%)	0	0	0	0
生殖系および乳房障害						
- Overall -	4 (2.1%)	2 (1.0%)	2 (1.0%)	0	0	0
勃起不全	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	0	0
前立腺炎	1 (0.5%)	0	1 (0.5%)	0	0	0
腟出血	1 (0.5%)	1 (0.5%)	0	0	0	0

NCI-CTCAE ver. 4.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159v/n01297a/ae17r.sas / Output: /opt/BIOSTAT/prod/cdt7159v/n01297a/reports/ae17r_297_SE.out
09SEP2016 9:02

[5.3.5.3-1 ae17r_297_SE を再掲]

2.7.6.2.1.5　GAO4915g 試験（GATHER 試験）

表 2.7.6.2.1.5-1　因果関係を問わないすべての有害事象（GAO4915g 試験，未治療 DLBCL 患者）

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GAO4915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	100 (100.0%)	5 (5.0%)	31 (31.0%)	23 (23.0%)	39 (39.0%)	2 (2.0%)
一般・全身障害および投与部位の状態						
- Overall -	89 (89.0%)	30 (30.0%)	55 (55.0%)	4 (4.0%)	0	0
疲労	48 (48.0%)	25 (25.0%)	22 (22.0%)	1 (1.0%)	0	0
悪寒	41 (41.0%)	14 (14.0%)	26 (26.0%)	1 (1.0%)	0	0
発熱	26 (26.0%)	18 (18.0%)	6 (6.0%)	2 (2.0%)	0	0
粘膜の炎症	10 (10.0%)	6 (6.0%)	4 (4.0%)	0	0	0
末梢性浮腫	9 (9.0%)	8 (8.0%)	1 (1.0%)	0	0	0
胸痛	7 (7.0%)	4 (4.0%)	2 (2.0%)	1 (1.0%)	0	0
疼痛	7 (7.0%)	7 (7.0%)	0	0	0	0
無力症	6 (6.0%)	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0
胸部不快感	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0
局所腫脹	2 (2.0%)	2 (2.0%)	0	0	0	0
注射部位反応	2 (2.0%)	0	2 (2.0%)	0	0	0
浮腫	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
びくびく感	1 (1.0%)	0	1 (1.0%)	0	0	0
カテーテル留置部位疼痛	1 (1.0%)	1 (1.0%)	0	0	0	0
異物感	1 (1.0%)	0	1 (1.0%)	0	0	0
顔面浮腫	1 (1.0%)	1 (1.0%)	0	0	0	0
倦怠感	1 (1.0%)	1 (1.0%)	0	0	0	0
全身健康状態低下	1 (1.0%)	0	1 (1.0%)	0	0	0
注射部位内出血	1 (1.0%)	1 (1.0%)	0	0	0	0
潰瘍性出血	1 (1.0%)	1 (1.0%)	0	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159z/t25324h/ae17.sas / Output: /opt/BIOSTAT/prod/cdt7159z/t25324h/reports/ae17_915_SE.out
30MAR2015 2:55

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
熱感	1 (1.0%)	1 (1.0%)	0	0	0	0
胃腸障害						
- Overall -	86 (86.0%)	36 (36.0%)	36 (36.0%)	13 (13.0%)	1 (1.0%)	0
悪心	58 (58.0%)	39 (39.0%)	17 (17.0%)	2 (2.0%)	0	0
下痢	38 (38.0%)	26 (26.0%)	8 (8.0%)	4 (4.0%)	0	0
嘔吐	31 (31.0%)	21 (21.0%)	9 (9.0%)	1 (1.0%)	0	0
便秘	29 (29.0%)	20 (20.0%)	9 (9.0%)	0	0	0
口内炎	14 (14.0%)	9 (9.0%)	3 (3.0%)	2 (2.0%)	0	0
腹痛	13 (13.0%)	4 (4.0%)	7 (7.0%)	2 (2.0%)	0	0
口内乾燥	9 (9.0%)	7 (7.0%)	2 (2.0%)	0	0	0
胃食道逆流性疾患	8 (8.0%)	5 (5.0%)	3 (3.0%)	0	0	0
口腔内痛	6 (6.0%)	4 (4.0%)	2 (2.0%)	0	0	0
消化不良	6 (6.0%)	6 (6.0%)	0	0	0	0
痔核	5 (5.0%)	2 (2.0%)	3 (3.0%)	0	0	0
鼓腸	4 (4.0%)	4 (4.0%)	0	0	0	0
口腔内潰瘍形成	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0
直腸出血	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0
腹部不快感	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
腹部膨満	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
おくび	2 (2.0%)	2 (2.0%)	0	0	0	0
下腹部痛	2 (2.0%)	1 (1.0%)	0	1 (1.0%)	0	0
血便排泄	2 (2.0%)	2 (2.0%)	0	0	0	0
口の錯感覚	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
嚥下障害	2 (2.0%)	2 (2.0%)	0	0	0	0
胃炎	1 (1.0%)	1 (1.0%)	0	0	0	0
胃腸出血	1 (1.0%)	1 (1.0%)	0	0	0	0
胃潰瘍	1 (1.0%)	0	1 (1.0%)	0	0	0
口の感覚鈍麻	1 (1.0%)	1 (1.0%)	0	0	0	0
口腔内不快感	1 (1.0%)	1 (1.0%)	0	0	0	0
歯の知覚過敏	1 (1.0%)	1 (1.0%)	0	0	0	0
歯周病	1 (1.0%)	1 (1.0%)	0	0	0	0
歯痛	1 (1.0%)	1 (1.0%)	0	0	0	0
歯肉紅斑	1 (1.0%)	1 (1.0%)	0	0	0	0
歯肉障害	1 (1.0%)	1 (1.0%)	0	0	0	0
歯肉退縮	1 (1.0%)	1 (1.0%)	0	0	0	0
痔出血	1 (1.0%)	1 (1.0%)	0	0	0	0
小腸閉塞	1 (1.0%)	0	0	1 (1.0%)	0	0
上部消化管出血	1 (1.0%)	0	0	1 (1.0%)	0	0
上腹部痛	1 (1.0%)	1 (1.0%)	0	0	0	0
食道炎	1 (1.0%)	1 (1.0%)	0	0	0	0
舌障害	1 (1.0%)	1 (1.0%)	0	0	0	0
舌痛	1 (1.0%)	1 (1.0%)	0	0	0	0
大腸穿孔	1 (1.0%)	0	0	1 (1.0%)	0	0
腸管穿孔	1 (1.0%)	0	0	1 (1.0%)	0	0
腸憩室	1 (1.0%)	0	1 (1.0%)	0	0	0
腹腔内出血	1 (1.0%)	0	0	0	1 (1.0%)	0
腹部ヘルニア	1 (1.0%)	0	1 (1.0%)	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腹部圧痛	1 (1.0%)	1 (1.0%)	0	0	0	0
嚥下痛	1 (1.0%)	0	0	1 (1.0%)	0	0
肛門周囲痛	1 (1.0%)	1 (1.0%)	0	0	0	0
膵炎	1 (1.0%)	0	1 (1.0%)	0	0	0
鼠径ヘルニア	1 (1.0%)	0	1 (1.0%)	0	0	0
齲歯	1 (1.0%)	0	1 (1.0%)	0	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	65 (65.0%)	36 (36.0%)	24 (24.0%)	5 (5.0%)	0	0
呼吸困難	29 (29.0%)	15 (15.0%)	13 (13.0%)	1 (1.0%)	0	0
咳嗽	19 (19.0%)	11 (11.0%)	8 (8.0%)	0	0	0
口腔咽頭痛	15 (15.0%)	14 (14.0%)	1 (1.0%)	0	0	0
しゃっくり	6 (6.0%)	5 (5.0%)	1 (1.0%)	0	0	0
湿性咳嗽	4 (4.0%)	2 (2.0%)	2 (2.0%)	0	0	0
鼻出血	4 (4.0%)	4 (4.0%)	0	0	0	0
鼻閉	4 (4.0%)	3 (3.0%)	1 (1.0%)	0	0	0
鼻漏	4 (4.0%)	4 (4.0%)	0	0	0	0
副鼻腔うっ血	4 (4.0%)	2 (2.0%)	2 (2.0%)	0	0	0
喘鳴	4 (4.0%)	2 (2.0%)	2 (2.0%)	0	0	0
低酸素症	3 (3.0%)	0	1 (1.0%)	2 (2.0%)	0	0
肺塞栓症	3 (3.0%)	0	0	3 (3.0%)	0	0
咽喉刺激感	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
上気道咳症候群	2 (2.0%)	2 (2.0%)	0	0	0	0
発声障害	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
くしゃみ	1 (1.0%)	1 (1.0%)	0	0	0	0
間質性肺疾患	1 (1.0%)	0	1 (1.0%)	0	0	0
急性呼吸不全	1 (1.0%)	0	1 (1.0%)	0	0	0
胸膜痛	1 (1.0%)	1 (1.0%)	0	0	0	0
肺高血圧症	1 (1.0%)	1 (1.0%)	0	0	0	0
副鼻腔分泌過多	1 (1.0%)	0	1 (1.0%)	0	0	0
慢性閉塞性肺疾患	1 (1.0%)	0	0	1 (1.0%)	0	0
神経系障害						
- Overall -	65 (65.0%)	41 (41.0%)	18 (18.0%)	5 (5.0%)	1 (1.0%)	0
末梢性ニューロパチー	24 (24.0%)	20 (20.0%)	4 (4.0%)	0	0	0
頭痛	20 (20.0%)	13 (13.0%)	7 (7.0%)	0	0	0
浮動性めまい	18 (18.0%)	15 (15.0%)	3 (3.0%)	0	0	0
味覚異常	7 (7.0%)	6 (6.0%)	1 (1.0%)	0	0	0
錯感覚	5 (5.0%)	5 (5.0%)	0	0	0	0
失神	5 (5.0%)	1 (1.0%)	0	4 (4.0%)	0	0
末梢性感覚ニューロパチー	5 (5.0%)	0	5 (5.0%)	0	0	0
感覚鈍麻	4 (4.0%)	4 (4.0%)	0	0	0	0
振戦	4 (4.0%)	2 (2.0%)	2 (2.0%)	0	0	0
片頭痛	2 (2.0%)	0	2 (2.0%)	0	0	0
ヘルペス後神経痛	1 (1.0%)	1 (1.0%)	0	0	0	0
下肢静止不能症候群	1 (1.0%)	1 (1.0%)	0	0	0	0
傾眠	1 (1.0%)	0	1 (1.0%)	0	0	0
失神寸前の状態	1 (1.0%)	0	0	1 (1.0%)	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
脊椎炎性脊髄症	1 (1.0%)	0	0	1 (1.0%)	0	0
大発作痙攣	1 (1.0%)	0	1 (1.0%)	0	0	0
知覚過敏	1 (1.0%)	1 (1.0%)	0	0	0	0
注意力障害	1 (1.0%)	1 (1.0%)	0	0	0	0
認知障害	1 (1.0%)	1 (1.0%)	0	0	0	0
脳血管発作	1 (1.0%)	0	0	0	1 (1.0%)	0
不全片麻痺	1 (1.0%)	1 (1.0%)	0	0	0	0
味覚減退	1 (1.0%)	1 (1.0%)	0	0	0	0
嗅覚錯誤	1 (1.0%)	1 (1.0%)	0	0	0	0
嗜眠	1 (1.0%)	1 (1.0%)	0	0	0	0
傷害、中毒および処置合併症						
- Overall -	63 (63.0%)	21 (21.0%)	37 (37.0%)	5 (5.0%)	0	0
注入に伴う反応	56 (56.0%)	18 (18.0%)	36 (36.0%)	2 (2.0%)	0	0
擦過傷	5 (5.0%)	5 (5.0%)	0	0	0	0
転倒	2 (2.0%)	2 (2.0%)	0	0	0	0
股関節部骨折	1 (1.0%)	0	0	1 (1.0%)	0	0
歯牙破折	1 (1.0%)	1 (1.0%)	0	0	0	0
処置による疼痛	1 (1.0%)	0	1 (1.0%)	0	0	0
節足動物咬傷	1 (1.0%)	0	1 (1.0%)	0	0	0
創傷	1 (1.0%)	0	0	1 (1.0%)	0	0
大腿骨骨折	1 (1.0%)	0	0	1 (1.0%)	0	0
頭部損傷	1 (1.0%)	0	1 (1.0%)	0	0	0
熱傷	1 (1.0%)	1 (1.0%)	0	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
裂傷	1 (1.0%)	1 (1.0%)	0	0	0	0
皮膚および皮下組織障害						
- Overall -	59 (59.0%)	28 (28.0%)	31 (31.0%)	0	0	0
脱毛症	42 (42.0%)	15 (15.0%)	27 (27.0%)	0	0	0
発疹	9 (9.0%)	8 (8.0%)	1 (1.0%)	0	0	0
そう痒症	7 (7.0%)	5 (5.0%)	2 (2.0%)	0	0	0
寝汗	6 (6.0%)	6 (6.0%)	0	0	0	0
多汗症	4 (4.0%)	4 (4.0%)	0	0	0	0
爪変色	4 (4.0%)	4 (4.0%)	0	0	0	0
皮膚色素過剰	4 (4.0%)	4 (4.0%)	0	0	0	0
紅斑	3 (3.0%)	3 (3.0%)	0	0	0	0
ざ瘡	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
爪の障害	2 (2.0%)	2 (2.0%)	0	0	0	0
斑状出血	2 (2.0%)	2 (2.0%)	0	0	0	0
丘疹性皮疹	1 (1.0%)	1 (1.0%)	0	0	0	0
光線過敏性反応	1 (1.0%)	1 (1.0%)	0	0	0	0
紅斑性皮疹	1 (1.0%)	1 (1.0%)	0	0	0	0
脂漏性皮膚炎	1 (1.0%)	1 (1.0%)	0	0	0	0
水疱	1 (1.0%)	1 (1.0%)	0	0	0	0
爪甲脱落症	1 (1.0%)	1 (1.0%)	0	0	0	0
爪甲離床症	1 (1.0%)	1 (1.0%)	0	0	0	0
点状出血	1 (1.0%)	1 (1.0%)	0	0	0	0
斑	1 (1.0%)	1 (1.0%)	0	0	0	0

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159z/t25324h/ae17.sas / Output: /opt/BIOSTAT/prod/cdt7159z/t25324h/reports/ae17_915_SE.out
30MAR2015 2:55

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
斑状皮疹	1 (1.0%)	1 (1.0%)	0	0	0	0
皮膚炎	1 (1.0%)	1 (1.0%)	0	0	0	0
皮膚乾燥	1 (1.0%)	1 (1.0%)	0	0	0	0
皮膚灼熱感	1 (1.0%)	1 (1.0%)	0	0	0	0
皮膚変色	1 (1.0%)	1 (1.0%)	0	0	0	0
皮膚疼痛	1 (1.0%)	1 (1.0%)	0	0	0	0
感染症および寄生虫症						
- Overall -	58 (58.0%)	13 (13.0%)	27 (27.0%)	14 (14.0%)	3 (3.0%)	1 (1.0%)
尿路感染	9 (9.0%)	1 (1.0%)	7 (7.0%)	1 (1.0%)	0	0
肺炎	8 (8.0%)	0	4 (4.0%)	4 (4.0%)	0	0
副鼻腔炎	6 (6.0%)	2 (2.0%)	4 (4.0%)	0	0	0
カンジダ感染	5 (5.0%)	2 (2.0%)	3 (3.0%)	0	0	0
上気道感染	5 (5.0%)	1 (1.0%)	4 (4.0%)	0	0	0
口腔ヘルペス	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0
帯状疱疹	3 (3.0%)	0	2 (2.0%)	1 (1.0%)	0	0
鼻咽頭炎	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
蜂巣炎	3 (3.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0	0
毛包炎	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
気管支炎	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
真菌感染	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
足部白癬	2 (2.0%)	0	2 (2.0%)	0	0	0
大葉性肺炎	2 (2.0%)	1 (1.0%)	0	1 (1.0%)	0	0
粘膜感染	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
敗血症	2 (2.0%)	0	0	0	2 (2.0%)	0
皮膚真菌感染	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
ウイルス感染	1 (1.0%)	1 (1.0%)	0	0	0	0
ウイルス性胃腸炎	1 (1.0%)	0	1 (1.0%)	0	0	0
カテーテル留置部位感染	1 (1.0%)	0	1 (1.0%)	0	0	0
カテーテル留置部位蜂巣炎	1 (1.0%)	0	0	1 (1.0%)	0	0
クロストリジウム・ディフィシレ感染	1 (1.0%)	0	0	1 (1.0%)	0	0
サイトメガロウイルス感染	1 (1.0%)	0	1 (1.0%)	0	0	0
ブドウ球菌性菌血症	1 (1.0%)	0	0	1 (1.0%)	0	0
ブドウ球菌性膿瘍	1 (1.0%)	0	1 (1.0%)	0	0	0
レジオネラ菌性肺炎	1 (1.0%)	0	0	1 (1.0%)	0	0
医療機器関連感染	1 (1.0%)	0	0	1 (1.0%)	0	0
咽頭炎	1 (1.0%)	0	1 (1.0%)	0	0	0
外陰部腟カンジダ症	1 (1.0%)	0	1 (1.0%)	0	0	0
感染性脳炎	1 (1.0%)	0	0	0	0	1 (1.0%)
感染性皮膚嚢腫	1 (1.0%)	1 (1.0%)	0	0	0	0
憩室炎	1 (1.0%)	0	0	1 (1.0%)	0	0
頚部膿瘍	1 (1.0%)	1 (1.0%)	0	0	0	0
限局性感染	1 (1.0%)	0	0	1 (1.0%)	0	0
口腔カンジダ症	1 (1.0%)	0	1 (1.0%)	0	0	0
細菌性肺炎	1 (1.0%)	0	0	1 (1.0%)	0	0
歯膿瘍	1 (1.0%)	0	1 (1.0%)	0	0	0
創傷感染	1 (1.0%)	0	1 (1.0%)	0	0	0
腸管膿瘍	1 (1.0%)	0	0	1 (1.0%)	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腸球菌感染	1 (1.0%)	0	0	1 (1.0%)	0	0
爪真菌症	1 (1.0%)	1 (1.0%)	0	0	0	0
膿痂疹	1 (1.0%)	0	1 (1.0%)	0	0	0
膿疱性皮疹	1 (1.0%)	0	1 (1.0%)	0	0	0
播種性帯状疱疹	1 (1.0%)	0	0	1 (1.0%)	0	0
敗血症性ショック	1 (1.0%)	0	0	0	1 (1.0%)	0
皮膚カンジダ	1 (1.0%)	1 (1.0%)	0	0	0	0
腹膜炎	1 (1.0%)	0	1 (1.0%)	0	0	0
無症候性細菌尿	1 (1.0%)	0	0	1 (1.0%)	0	0
膀胱炎	1 (1.0%)	0	1 (1.0%)	0	0	0
膣感染	1 (1.0%)	0	1 (1.0%)	0	0	0
血液およびリンパ系障害						
- Overall -	56 (56.0%)	1 (1.0%)	3 (3.0%)	16 (16.0%)	36 (36.0%)	0
好中球減少症	41 (41.0%)	1 (1.0%)	2 (2.0%)	11 (11.0%)	27 (27.0%)	0
貧血	19 (19.0%)	1 (1.0%)	9 (9.0%)	8 (8.0%)	1 (1.0%)	0
発熱性好中球減少症	16 (16.0%)	0	0	9 (9.0%)	7 (7.0%)	0
血小板減少症	6 (6.0%)	1 (1.0%)	0	1 (1.0%)	4 (4.0%)	0
鉄欠乏性貧血	1 (1.0%)	0	0	1 (1.0%)	0	0
白血球減少症	1 (1.0%)	0	0	0	1 (1.0%)	0
白血球増加症	1 (1.0%)	0	0	0	1 (1.0%)	0
汎血球減少症	1 (1.0%)	0	0	0	1 (1.0%)	0
脾腫	1 (1.0%)	1 (1.0%)	0	0	0	0

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
筋骨格系および結合組織障害						
- Overall -	51 (51.0%)	22 (22.0%)	23 (23.0%)	6 (6.0%)	0	0
骨痛	14 (14.0%)	6 (6.0%)	7 (7.0%)	1 (1.0%)	0	0
背部痛	14 (14.0%)	8 (8.0%)	6 (6.0%)	0	0	0
関節痛	11 (11.0%)	8 (8.0%)	1 (1.0%)	2 (2.0%)	0	0
筋肉痛	8 (8.0%)	5 (5.0%)	3 (3.0%)	0	0	0
筋力低下	5 (5.0%)	3 (3.0%)	1 (1.0%)	1 (1.0%)	0	0
四肢痛	5 (5.0%)	3 (3.0%)	1 (1.0%)	1 (1.0%)	0	0
側腹部痛	4 (4.0%)	1 (1.0%)	2 (2.0%)	1 (1.0%)	0	0
顎痛	3 (3.0%)	3 (3.0%)	0	0	0	0
筋骨格痛	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
筋痙縮	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
外骨腫	1 (1.0%)	1 (1.0%)	0	0	0	0
滑液嚢腫	1 (1.0%)	0	1 (1.0%)	0	0	0
関節障害	1 (1.0%)	1 (1.0%)	0	0	0	0
筋緊張	1 (1.0%)	0	1 (1.0%)	0	0	0
筋骨格系胸痛	1 (1.0%)	1 (1.0%)	0	0	0	0
脊椎障害	1 (1.0%)	1 (1.0%)	0	0	0	0
脊椎痛	1 (1.0%)	0	1 (1.0%)	0	0	0
病的骨折	1 (1.0%)	0	0	1 (1.0%)	0	0
鼡径部痛	1 (1.0%)	1 (1.0%)	0	0	0	0
代謝および栄養障害						
- Overall -	41 (41.0%)	14 (14.0%)	15 (15.0%)	11 (11.0%)	1 (1.0%)	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
食欲減退	19 (19.0%)	12 (12.0%)	7 (7.0%)	0	0	0
脱水	16 (16.0%)	3 (3.0%)	10 (10.0%)	3 (3.0%)	0	0
低カリウム血症	10 (10.0%)	2 (2.0%)	2 (2.0%)	5 (5.0%)	1 (1.0%)	0
低ナトリウム血症	5 (5.0%)	1 (1.0%)	1 (1.0%)	3 (3.0%)	0	0
低マグネシウム血症	5 (5.0%)	4 (4.0%)	1 (1.0%)	0	0	0
高血糖	4 (4.0%)	0	1 (1.0%)	3 (3.0%)	0	0
低カルシウム血症	4 (4.0%)	0	1 (1.0%)	2 (2.0%)	1 (1.0%)	0
低リン酸血症	4 (4.0%)	0	1 (1.0%)	3 (3.0%)	0	0
ビタミンD欠乏	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
栄養障害	1 (1.0%)	0	0	1 (1.0%)	0	0
高リン酸塩血症	1 (1.0%)	1 (1.0%)	0	0	0	0
水分過負荷	1 (1.0%)	1 (1.0%)	0	0	0	0
精神障害						
- Overall -	25 (25.0%)	8 (8.0%)	13 (13.0%)	4 (4.0%)	0	0
不眠症	14 (14.0%)	8 (8.0%)	6 (6.0%)	0	0	0
不安	10 (10.0%)	5 (5.0%)	4 (4.0%)	1 (1.0%)	0	0
うつ病	4 (4.0%)	1 (1.0%)	3 (3.0%)	0	0	0
錯乱状態	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
精神状態変化	2 (2.0%)	0	0	2 (2.0%)	0	0
譫妄	2 (2.0%)	1 (1.0%)	0	1 (1.0%)	0	0
激越	1 (1.0%)	0	1 (1.0%)	0	0	0
自殺企図	1 (1.0%)	0	0	1 (1.0%)	0	0
抑うつ気分	1 (1.0%)	1 (1.0%)	0	0	0	0

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
落ち着きのなさ	1 (1.0%)	0	1 (1.0%)	0	0	0
血管障害						
- Overall -	24 (24.0%)	16 (16.0%)	7 (7.0%)	1 (1.0%)	0	0
低血圧	15 (15.0%)	10 (10.0%)	4 (4.0%)	1 (1.0%)	0	0
潮紅	4 (4.0%)	3 (3.0%)	1 (1.0%)	0	0	0
高血圧	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0
深部静脈血栓症	2 (2.0%)	0	2 (2.0%)	0	0	0
ほてり	1 (1.0%)	1 (1.0%)	0	0	0	0
静脈退色	1 (1.0%)	1 (1.0%)	0	0	0	0
臨床検査						
- Overall -	23 (23.0%)	11 (11.0%)	10 (10.0%)	2 (2.0%)	0	0
体重減少	12 (12.0%)	9 (9.0%)	3 (3.0%)	0	0	0
駆出率減少	5 (5.0%)	0	3 (3.0%)	2 (2.0%)	0	0
体重増加	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
アスパラギン酸アミノトランスフェラーゼ増加	1 (1.0%)	0	1 (1.0%)	0	0	0
アラニンアミノトランスフェラーゼ増加	1 (1.0%)	0	1 (1.0%)	0	0	0
トロポニンＩ増加	1 (1.0%)	0	0	1 (1.0%)	0	0
血中クレアチニン増加	1 (1.0%)	0	1 (1.0%)	0	0	0
血中尿酸増加	1 (1.0%)	1 (1.0%)	0	0	0	0
心雑音	1 (1.0%)	0	1 (1.0%)	0	0	0
心拍数増加	1 (1.0%)	0	1 (1.0%)	0	0	0
尿量減少	1 (1.0%)	1 (1.0%)	0	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
心臓障害						
- Overall -	17 (17.0%)	6 (6.0%)	5 (5.0%)	5 (5.0%)	0	1 (1.0%)
頻脈	9 (9.0%)	6 (6.0%)	3 (3.0%)	0	0	0
うっ血性心不全	3 (3.0%)	0	0	3 (3.0%)	0	0
左室機能不全	2 (2.0%)	0	0	2 (2.0%)	0	0
急性心不全	1 (1.0%)	0	0	1 (1.0%)	0	0
狭心症	1 (1.0%)	0	1 (1.0%)	0	0	0
収縮機能障害	1 (1.0%)	0	0	1 (1.0%)	0	0
徐脈	1 (1.0%)	1 (1.0%)	0	0	0	0
心血管障害	1 (1.0%)	0	0	0	0	1 (1.0%)
洞性徐脈	1 (1.0%)	1 (1.0%)	0	0	0	0
洞性頻脈	1 (1.0%)	0	1 (1.0%)	0	0	0
腎および尿路障害						
- Overall -	17 (17.0%)	15 (15.0%)	2 (2.0%)	0	0	0
排尿困難	5 (5.0%)	5 (5.0%)	0	0	0	0
急性腎不全	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
尿失禁	3 (3.0%)	3 (3.0%)	0	0	0	0
頻尿	3 (3.0%)	3 (3.0%)	0	0	0	0
着色尿	2 (2.0%)	2 (2.0%)	0	0	0	0
血尿	1 (1.0%)	1 (1.0%)	0	0	0	0
水尿管症	1 (1.0%)	0	1 (1.0%)	0	0	0
尿閉	1 (1.0%)	1 (1.0%)	0	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
眼障害						
- Overall -	9 (9.0%)	5 (5.0%)	4 (4.0%)	0	0	0
霧視	5 (5.0%)	5 (5.0%)	0	0	0	0
流涙増加	5 (5.0%)	4 (4.0%)	1 (1.0%)	0	0	0
眼乾燥	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
結膜炎	2 (2.0%)	0	2 (2.0%)	0	0	0
視力障害	2 (2.0%)	2 (2.0%)	0	0	0	0
眼球浮腫	1 (1.0%)	1 (1.0%)	0	0	0	0
眼充血	1 (1.0%)	1 (1.0%)	0	0	0	0
耳および迷路障害						
- Overall -	4 (4.0%)	4 (4.0%)	0	0	0	0
難聴	2 (2.0%)	2 (2.0%)	0	0	0	0
聴覚過敏	1 (1.0%)	1 (1.0%)	0	0	0	0
両耳難聴	1 (1.0%)	1 (1.0%)	0	0	0	0
生殖系および乳房障害						
- Overall -	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
外陰膣そう痒症	1 (1.0%)	1 (1.0%)	0	0	0	0
外陰膣紅斑	1 (1.0%)	1 (1.0%)	0	0	0	0
子宮脱	1 (1.0%)	0	1 (1.0%)	0	0	0
性器発疹	1 (1.0%)	1 (1.0%)	0	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17_915_SE Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
免疫系障害						
- Overall -	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
サルコイドーシス	1 (1.0%)	1 (1.0%)	0	0	0	0
過敏症	1 (1.0%)	1 (1.0%)	0	0	0	0
薬物過敏症	1 (1.0%)	0	1 (1.0%)	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）						
- Overall -	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
基底細胞癌	1 (1.0%)	0	1 (1.0%)	0	0	0
血管腫	1 (1.0%)	1 (1.0%)	0	0	0	0
脂漏性角化症	1 (1.0%)	1 (1.0%)	0	0	0	0
外科および内科処置						
- Overall -	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
創傷治療	1 (1.0%)	0	1 (1.0%)	0	0	0
抜歯	1 (1.0%)	1 (1.0%)	0	0	0	0
内分泌障害						
- Overall -	1 (1.0%)	0	1 (1.0%)	0	0	0
副腎機能不全	1 (1.0%)	0	1 (1.0%)	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159z/t25324h/ae17.sas / Output: /opt/BIOSTAT/prod/cdt7159z/t25324h/reports/ae17_915_SE.out
30MAR2015 2:55

[5.3.5.3-1 ae17_915_SE を再掲]

表 2.7.6.2.1.5-2　因果関係が否定できないすべての有害事象（GA04915g 試験，未治療 DLBCL 患者）

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	96 (96.0%)	6 (6.0%)	37 (37.0%)	19 (19.0%)	34 (34.0%)	0
一般・全身障害および投与部位の状態						
- Overall -	72 (72.0%)	21 (21.0%)	49 (49.0%)	2 (2.0%)	0	0
悪寒	38 (38.0%)	11 (11.0%)	26 (26.0%)	1 (1.0%)	0	0
疲労	37 (37.0%)	16 (16.0%)	21 (21.0%)	0	0	0
発熱	15 (15.0%)	12 (12.0%)	2 (2.0%)	1 (1.0%)	0	0
粘膜の炎症	6 (6.0%)	3 (3.0%)	3 (3.0%)	0	0	0
胸痛	3 (3.0%)	2 (2.0%)	1 (1.0%)	0	0	0
胸部不快感	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0
疼痛	3 (3.0%)	3 (3.0%)	0	0	0	0
局所腫脹	2 (2.0%)	2 (2.0%)	0	0	0	0
末梢性浮腫	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
無力症	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
びくびく感	1 (1.0%)	0	1 (1.0%)	0	0	0
異物感	1 (1.0%)	0	1 (1.0%)	0	0	0
倦怠感	1 (1.0%)	1 (1.0%)	0	0	0	0
注射部位反応	1 (1.0%)	0	1 (1.0%)	0	0	0
浮腫	1 (1.0%)	0	1 (1.0%)	0	0	0
胃腸障害						
- Overall -	65 (65.0%)	36 (36.0%)	24 (24.0%)	5 (5.0%)	0	0
悪心	42 (42.0%)	30 (30.0%)	11 (11.0%)	1 (1.0%)	0	0
下痢	23 (23.0%)	19 (19.0%)	3 (3.0%)	1 (1.0%)	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159z/t25324h/ae17r.sas / Output: /opt/BIOSTAT/prod/cdt7159z/t25324h/reports/ae17r_915_SE.out
03JUN2015 9:01

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
嘔吐	23 (23.0%)	16 (16.0%)	6 (6.0%)	1 (1.0%)	0	0
便秘	13 (13.0%)	7 (7.0%)	6 (6.0%)	0	0	0
口内炎	12 (12.0%)	7 (7.0%)	3 (3.0%)	2 (2.0%)	0	0
口内乾燥	5 (5.0%)	4 (4.0%)	1 (1.0%)	0	0	0
口腔内痛	4 (4.0%)	2 (2.0%)	2 (2.0%)	0	0	0
腹痛	4 (4.0%)	2 (2.0%)	2 (2.0%)	0	0	0
消化不良	3 (3.0%)	3 (3.0%)	0	0	0	0
胃食道逆流性疾患	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
鼓腸	2 (2.0%)	2 (2.0%)	0	0	0	0
痔核	2 (2.0%)	0	2 (2.0%)	0	0	0
口の感覚鈍麻	1 (1.0%)	1 (1.0%)	0	0	0	0
口の錯感覚	1 (1.0%)	0	1 (1.0%)	0	0	0
口腔内潰瘍形成	1 (1.0%)	0	1 (1.0%)	0	0	0
歯の知覚過敏	1 (1.0%)	1 (1.0%)	0	0	0	0
歯周病	1 (1.0%)	1 (1.0%)	0	0	0	0
歯肉紅斑	1 (1.0%)	1 (1.0%)	0	0	0	0
歯肉障害	1 (1.0%)	1 (1.0%)	0	0	0	0
歯肉退縮	1 (1.0%)	1 (1.0%)	0	0	0	0
直腸出血	1 (1.0%)	1 (1.0%)	0	0	0	0
腹部不快感	1 (1.0%)	1 (1.0%)	0	0	0	0
腹部膨満	1 (1.0%)	1 (1.0%)	0	0	0	0
嚥下障害	1 (1.0%)	1 (1.0%)	0	0	0	0
嚥下痛	1 (1.0%)	0	0	1 (1.0%)	0	0
膵炎	1 (1.0%)	0	1 (1.0%)	0	0	0

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
傷害、中毒および処置合併症						
- Overall -	55 (55.0%)	18 (18.0%)	36 (36.0%)	1 (1.0%)	0	0
注入に伴う反応	55 (55.0%)	18 (18.0%)	36 (36.0%)	1 (1.0%)	0	0
皮膚および皮下組織障害						
- Overall -	48 (48.0%)	19 (19.0%)	29 (29.0%)	0	0	0
脱毛症	41 (41.0%)	14 (14.0%)	27 (27.0%)	0	0	0
そう痒症	5 (5.0%)	4 (4.0%)	1 (1.0%)	0	0	0
紅斑	3 (3.0%)	3 (3.0%)	0	0	0	0
爪変色	3 (3.0%)	3 (3.0%)	0	0	0	0
皮膚色素過剰	3 (3.0%)	3 (3.0%)	0	0	0	0
爪の障害	2 (2.0%)	2 (2.0%)	0	0	0	0
発疹	2 (2.0%)	2 (2.0%)	0	0	0	0
ざ瘡	1 (1.0%)	0	1 (1.0%)	0	0	0
丘疹性皮疹	1 (1.0%)	1 (1.0%)	0	0	0	0
紅斑性皮疹	1 (1.0%)	1 (1.0%)	0	0	0	0
寝汗	1 (1.0%)	1 (1.0%)	0	0	0	0
爪甲離床症	1 (1.0%)	1 (1.0%)	0	0	0	0
点状出血	1 (1.0%)	1 (1.0%)	0	0	0	0
斑	1 (1.0%)	1 (1.0%)	0	0	0	0
斑状皮疹	1 (1.0%)	1 (1.0%)	0	0	0	0
皮膚乾燥	1 (1.0%)	1 (1.0%)	0	0	0	0

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血液およびリンパ系障害						
- Overall -	46 (46.0%)	1 (1.0%)	2 (2.0%)	11 (11.0%)	32 (32.0%)	0
好中球減少症	36 (36.0%)	1 (1.0%)	2 (2.0%)	10 (10.0%)	23 (23.0%)	0
貧血	15 (15.0%)	1 (1.0%)	7 (7.0%)	6 (6.0%)	1 (1.0%)	0
発熱性好中球減少症	12 (12.0%)	0	0	6 (6.0%)	6 (6.0%)	0
血小板減少症	6 (6.0%)	1 (1.0%)	0	1 (1.0%)	4 (4.0%)	0
白血球減少症	1 (1.0%)	0	0	0	1 (1.0%)	0
白血球増加症	1 (1.0%)	0	0	0	1 (1.0%)	0
汎血球減少症	1 (1.0%)	0	0	0	1 (1.0%)	0
神経系障害						
- Overall -	43 (43.0%)	28 (28.0%)	14 (14.0%)	1 (1.0%)	0	0
末梢性ニューロパチー	21 (21.0%)	17 (17.0%)	4 (4.0%)	0	0	0
頭痛	7 (7.0%)	6 (6.0%)	1 (1.0%)	0	0	0
浮動性めまい	7 (7.0%)	5 (5.0%)	2 (2.0%)	0	0	0
味覚異常	6 (6.0%)	5 (5.0%)	1 (1.0%)	0	0	0
末梢性感覚ニューロパチー	5 (5.0%)	0	5 (5.0%)	0	0	0
感覚鈍麻	4 (4.0%)	4 (4.0%)	0	0	0	0
錯感覚	4 (4.0%)	4 (4.0%)	0	0	0	0
振戦	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0
傾眠	1 (1.0%)	0	1 (1.0%)	0	0	0
失神	1 (1.0%)	0	0	1 (1.0%)	0	0
片頭痛	1 (1.0%)	0	1 (1.0%)	0	0	0
嗅覚錯誤	1 (1.0%)	1 (1.0%)	0	0	0	0

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
嗜眠	1 (1.0%)	1 (1.0%)	0	0	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	33 (33.0%)	17 (17.0%)	13 (13.0%)	3 (3.0%)	0	0
呼吸困難	14 (14.0%)	6 (6.0%)	8 (8.0%)	0	0	0
咳嗽	7 (7.0%)	3 (3.0%)	4 (4.0%)	0	0	0
口腔咽頭痛	6 (6.0%)	5 (5.0%)	1 (1.0%)	0	0	0
肺塞栓症	3 (3.0%)	0	0	3 (3.0%)	0	0
鼻出血	3 (3.0%)	3 (3.0%)	0	0	0	0
しゃっくり	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
咽喉刺激感	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
湿性咳嗽	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
発声障害	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
副鼻腔うっ血	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
喘鳴	2 (2.0%)	0	2 (2.0%)	0	0	0
くしゃみ	1 (1.0%)	1 (1.0%)	0	0	0	0
上気道咳症候群	1 (1.0%)	1 (1.0%)	0	0	0	0
低酸素症	1 (1.0%)	0	1 (1.0%)	0	0	0
鼻漏	1 (1.0%)	1 (1.0%)	0	0	0	0
副鼻腔分泌過多	1 (1.0%)	0	1 (1.0%)	0	0	0
感染症および寄生虫症						
- Overall -	26 (26.0%)	4 (4.0%)	12 (12.0%)	8 (8.0%)	2 (2.0%)	0
カンジダ感染	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
口腔ヘルペス	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0
上気道感染	2 (2.0%)	0	2 (2.0%)	0	0	0
帯状疱疹	2 (2.0%)	0	1 (1.0%)	1 (1.0%)	0	0
尿路感染	2 (2.0%)	0	1 (1.0%)	1 (1.0%)	0	0
粘膜感染	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
敗血症	2 (2.0%)	0	0	0	2 (2.0%)	0
カテーテル留置部位蜂巣炎	1 (1.0%)	0	0	1 (1.0%)	0	0
クロストリジウム・ディフィシレ感染	1 (1.0%)	0	0	1 (1.0%)	0	0
レジオネラ菌性肺炎	1 (1.0%)	0	0	1 (1.0%)	0	0
医療機器関連感染	1 (1.0%)	0	0	1 (1.0%)	0	0
外陰部腟カンジダ症	1 (1.0%)	0	1 (1.0%)	0	0	0
口腔カンジダ症	1 (1.0%)	0	1 (1.0%)	0	0	0
真菌感染	1 (1.0%)	0	1 (1.0%)	0	0	0
足部白癬	1 (1.0%)	0	1 (1.0%)	0	0	0
大葉性肺炎	1 (1.0%)	0	0	1 (1.0%)	0	0
膿疱性皮疹	1 (1.0%)	0	1 (1.0%)	0	0	0
播種性帯状疱疹	1 (1.0%)	0	0	1 (1.0%)	0	0
肺炎	1 (1.0%)	0	0	1 (1.0%)	0	0
鼻咽頭炎	1 (1.0%)	1 (1.0%)	0	0	0	0
無症候性細菌尿	1 (1.0%)	0	0	1 (1.0%)	0	0
毛包炎	1 (1.0%)	1 (1.0%)	0	0	0	0
腟感染	1 (1.0%)	0	1 (1.0%)	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
代謝および栄養障害						
- Overall -	26 (26.0%)	10 (10.0%)	10 (10.0%)	5 (5.0%)	1 (1.0%)	0
食欲減退	14 (14.0%)	9 (9.0%)	5 (5.0%)	0	0	0
脱水	10 (10.0%)	2 (2.0%)	6 (6.0%)	2 (2.0%)	0	0
高血糖	3 (3.0%)	0	1 (1.0%)	2 (2.0%)	0	0
低ナトリウム血症	3 (3.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0	0
低カリウム血症	2 (2.0%)	0	0	1 (1.0%)	1 (1.0%)	0
低カルシウム血症	2 (2.0%)	0	1 (1.0%)	0	1 (1.0%)	0
低リン酸血症	2 (2.0%)	0	1 (1.0%)	1 (1.0%)	0	0
高リン酸塩血症	1 (1.0%)	1 (1.0%)	0	0	0	0
低マグネシウム血症	1 (1.0%)	1 (1.0%)	0	0	0	0
血管障害						
- Overall -	17 (17.0%)	11 (11.0%)	5 (5.0%)	1 (1.0%)	0	0
低血圧	9 (9.0%)	6 (6.0%)	2 (2.0%)	1 (1.0%)	0	0
潮紅	4 (4.0%)	3 (3.0%)	1 (1.0%)	0	0	0
高血圧	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
深部静脈血栓症	1 (1.0%)	0	1 (1.0%)	0	0	0
静脈退色	1 (1.0%)	1 (1.0%)	0	0	0	0
臨床検査						
- Overall -	16 (16.0%)	9 (9.0%)	5 (5.0%)	2 (2.0%)	0	0
体重減少	9 (9.0%)	8 (8.0%)	1 (1.0%)	0	0	0
駆出率減少	5 (5.0%)	0	3 (3.0%)	2 (2.0%)	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
アスパラギン酸アミノトランスフェラーゼ増加	1 (1.0%)	0	1 (1.0%)	0	0	0
アラニンアミノトランスフェラーゼ増加	1 (1.0%)	0	1 (1.0%)	0	0	0
体重増加	1 (1.0%)	1 (1.0%)	0	0	0	0
筋骨格系および結合組織障害						
- Overall -	14 (14.0%)	7 (7.0%)	5 (5.0%)	2 (2.0%)	0	0
筋肉痛	4 (4.0%)	3 (3.0%)	1 (1.0%)	0	0	0
顎痛	3 (3.0%)	3 (3.0%)	0	0	0	0
関節痛	2 (2.0%)	2 (2.0%)	0	0	0	0
筋力低下	2 (2.0%)	1 (1.0%)	0	1 (1.0%)	0	0
筋痙縮	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
側腹部痛	2 (2.0%)	0	1 (1.0%)	1 (1.0%)	0	0
背部痛	2 (2.0%)	0	2 (2.0%)	0	0	0
四肢痛	1 (1.0%)	1 (1.0%)	0	0	0	0
心臓障害						
- Overall -	9 (9.0%)	1 (1.0%)	3 (3.0%)	5 (5.0%)	0	0
うっ血性心不全	3 (3.0%)	0	0	3 (3.0%)	0	0
頻脈	3 (3.0%)	1 (1.0%)	2 (2.0%)	0	0	0
左室機能不全	2 (2.0%)	0	0	2 (2.0%)	0	0
収縮機能障害	1 (1.0%)	0	0	1 (1.0%)	0	0
洞性頻脈	1 (1.0%)	0	1 (1.0%)	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
精神障害						
- Overall -	7 (7.0%)	3 (3.0%)	4 (4.0%)	0	0	0
不眠症	6 (6.0%)	4 (4.0%)	2 (2.0%)	0	0	0
不安	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
激越	1 (1.0%)	0	1 (1.0%)	0	0	0
落ち着きのなさ	1 (1.0%)	0	1 (1.0%)	0	0	0
眼障害						
- Overall -	4 (4.0%)	2 (2.0%)	2 (2.0%)	0	0	0
霧視	3 (3.0%)	3 (3.0%)	0	0	0	0
眼乾燥	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
流涙増加	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	0	0
眼球浮腫	1 (1.0%)	1 (1.0%)	0	0	0	0
腎および尿路障害						
- Overall -	4 (4.0%)	4 (4.0%)	0	0	0	0
血尿	1 (1.0%)	1 (1.0%)	0	0	0	0
着色尿	1 (1.0%)	1 (1.0%)	0	0	0	0
尿失禁	1 (1.0%)	1 (1.0%)	0	0	0	0
頻尿	1 (1.0%)	1 (1.0%)	0	0	0	0
生殖系および乳房障害						
- Overall -	1 (1.0%)	1 (1.0%)	0	0	0	0
性器発疹	1 (1.0%)	1 (1.0%)	0	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

ae17r_915_SE Related Adverse Events by Intensity (NCI-CTC Grades 1-5)

Protocol: bo25324/GA04915g (t25324h)
Population: Safety-Evaluable Patients
Cutoff Date: 20DEC2013

Treatment: GA101 + CHOP (N=100)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
内分泌障害						
- Overall -	1 (1.0%)	0	1 (1.0%)	0	0	0
副腎機能不全	1 (1.0%)	0	1 (1.0%)	0	0	0

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days

Program: /opt/BIOSTAT/prod/cdt7159z/t25324h/ae17r.sas / Output: /opt/BIOSTAT/prod/cdt7159z/t25324h/reports/ae17r_915_SE.out
03JUN2015 9:01

[5.3.5.3-1 ae17r_915_SE を再掲]

2.7.6.2.1.6　BO20999試験（GAUGUIN 試験）

表 2.7.6.2.1.6-1　因果関係を問わないすべての有害事象（BO20999試験, Phase II, 再発・治療抵抗性 iNHL 患者）

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 400/400; N = 18

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	18 (100.0)	18 (100.0)	12 (66.7)	3 (16.7)	1 (5.6)	-
Total Number of AEs	87	44	38	4	1	-
全身障害および投与局所様態						
Total Pts With at Least one AE	11 (61.1)	5 (27.8)	7 (38.9)	-	-	-
発熱	5 (27.8)	2 (11.1)	3 (16.7)	-	-	-
無力症	5 (27.8)	2 (11.1)	3 (16.7)	-	-	-
悪寒	4 (22.2)	1 (5.6)	3 (16.7)	-	-	-
低体温	1 (5.6)	-	1 (5.6)	-	-	-
末梢性浮腫	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	16	6	10	-	-	-
血管障害						
Total Pts With at Least one AE	11 (61.1)	7 (38.9)	5 (27.8)	-	-	-
低血圧	7 (38.9)	2 (11.1)	5 (27.8)	-	-	-
高血圧	5 (27.8)	5 (27.8)	-	-	-	-
静脈不全	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	13	8	5	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.
AE17 26MAY2015:08:39:04 (1 of 21)

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 400/400; N = 18

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	8 (44.4)	6 (33.3)	3 (16.7)	1 (5.6)	-	-
咽喉刺激感	2 (11.1)	1 (5.6)	1 (5.6)	-	-	-
咳嗽	2 (11.1)	2 (11.1)	-	-	-	-
呼吸困難	2 (11.1)	1 (5.6)	1 (5.6)	-	-	-
鼻漏	2 (11.1)	2 (11.1)	-	-	-	-
気胸	1 (5.6)	-	-	1 (5.6)	-	-
胸水	1 (5.6)	-	-	1 (5.6)	-	-
扁桃肥大	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	11	6	3	2	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	7 (38.9)	4 (22.2)	3 (16.7)	-	-	-
関節炎	1 (5.6)	1 (5.6)	-	-	-	-
筋骨格痛	1 (5.6)	-	1 (5.6)	-	-	-
筋痙縮	1 (5.6)	1 (5.6)	-	-	-	-
頚部痛	1 (5.6)	-	1 (5.6)	-	-	-
骨腫脹	1 (5.6)	1 (5.6)	-	-	-	-
四肢痛	1 (5.6)	-	1 (5.6)	-	-	-
末梢部痛	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	7	4	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 400/400; N = 18

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	6 (33.3)	3 (16.7)	2 (11.1)	-	1 (5.6)	-
鼻咽頭炎	2 (11.1)	1 (5.6)	1 (5.6)	-	-	-
副鼻腔炎	2 (11.1)	-	2 (11.1)	-	-	-
胃腸炎	1 (5.6)	1 (5.6)	-	-	-	-
眼瞼毛包炎	1 (5.6)	1 (5.6)	-	-	-	-
気管支炎	1 (5.6)	-	1 (5.6)	-	-	-
肺炎球菌感染	1 (5.6)	-	-	-	1 (5.6)	-
鼻炎	1 (5.6)	1 (5.6)	-	-	-	-
膀胱炎	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	10	5	4	-	1	-
胃腸障害						
Total Pts With at Least one AE	6 (33.3)	3 (16.7)	4 (22.2)	-	-	-
腹痛	3 (16.7)	1 (5.6)	2 (11.1)	-	-	-
嘔吐	3 (16.7)	1 (5.6)	2 (11.1)	-	-	-
下痢	2 (11.1)	2 (11.1)	-	-	-	-
Total Number of AEs	8	4	4	-	-	-
神経系障害						
Total Pts With at Least one AE	4 (22.2)	3 (16.7)	2 (11.1)	-	-	-
頭痛	4 (22.2)	2 (11.1)	2 (11.1)	-	-	-
浮動性めまい	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	5	3	2	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 400/400; N = 18

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	3 (16.7)	2 (11.1)	2 (11.1)	-	-	-
発疹	2 (11.1)	-	2 (11.1)	-	-	-
そう痒症	1 (5.6)	1 (5.6)	-	-	-	-
湿疹	1 (5.6)	1 (5.6)	-	-	-	-
蕁麻疹	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	5	2	3	-	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	2 (11.1)	-	1 (5.6)	1 (5.6)	-	-
リンパ球減少症	1 (5.6)	-	-	1 (5.6)	-	-
貧血	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	2	-	1	1	-	-
心臓障害						
Total Pts With at Least one AE	2 (11.1)	1 (5.6)	1 (5.6)	-	-	-
動悸	1 (5.6)	1 (5.6)	-	-	-	-
頻脈	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	2	1	1	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	2 (11.1)	1 (5.6)	-	1 (5.6)	-	-
腎不全	1 (5.6)	-	-	1 (5.6)	-	-
排尿困難	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	2	1	-	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 400/400; N = 18

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
精神障害						
Total Pts With at Least one AE	1 (5.6)	1 (5.6)	-	-	-	-
不眠症	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	1 (5.6)	1 (5.6)	-	-	-	-
高カルシウム血症	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
内分泌障害						
Total Pts With at Least one AE	1 (5.6)	-	1 (5.6)	-	-	-
自己免疫性甲状腺炎	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	1	-	1	-	-	-
免疫系障害						
Total Pts With at Least one AE	1 (5.6)	-	1 (5.6)	-	-	-
過敏症	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	1	-	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)						
Total Pts With at Least one AE	1 (5.6)	1 (5.6)	-	-	-	-
皮膚乳頭腫	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 400/400; N = 18

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
臨床検査												
Total Pts With at Least one AE	1	(5.6)	1	(5.6)	-		-		-		-	
体重減少	1	(5.6)	1	(5.6)	-		-		-		-	
Total Number of AEs	1		1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.
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ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	21 (95.5)	19 (86.4)	16 (72.7)	9 (40.9)	2 (9.1)	-
Total Number of AEs	144	69	50	23	2	-
全身障害および投与局所様態						
Total Pts With at Least one AE	16 (72.7)	11 (50.0)	6 (27.3)	2 (9.1)	-	-
無力症	8 (36.4)	5 (22.7)	2 (9.1)	1 (4.5)	-	-
発熱	7 (31.8)	3 (13.6)	3 (13.6)	1 (4.5)	-	-
悪寒	6 (27.3)	2 (9.1)	3 (13.6)	1 (4.5)	-	-
末梢性浮腫	3 (13.6)	1 (4.5)	2 (9.1)	-	-	-
胸痛	1 (4.5)	-	-	1 (4.5)	-	-
苦悶感	1 (4.5)	-	1 (4.5)	-	-	-
疼痛	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	27	12	11	4	-	-
血管障害						
Total Pts With at Least one AE	15 (68.2)	11 (50.0)	4 (18.2)	2 (9.1)	-	-
低血圧	10 (45.5)	8 (36.4)	1 (4.5)	1 (4.5)	-	-
高血圧	7 (31.8)	4 (18.2)	2 (9.1)	1 (4.5)	-	-
ほてり	1 (4.5)	1 (4.5)	-	-	-	-
血栓症	1 (4.5)	-	1 (4.5)	-	-	-
潮紅	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	20	13	5	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	11 (50.0)	6 (27.3)	4 (18.2)	3 (13.6)	-	-
気管支炎	3 (13.6)	2 (9.1)	1 (4.5)	-	-	-
尿路感染	3 (13.6)	2 (9.1)	1 (4.5)	-	-	-
鼻咽頭炎	3 (13.6)	2 (9.1)	1 (4.5)	-	-	-
インフルエンザ	1 (4.5)	1 (4.5)	-	-	-	-
クロストリジウム感染	1 (4.5)	-	-	1 (4.5)	-	-
ヘモフィルス感染	1 (4.5)	-	-	1 (4.5)	-	-
医療機器関連感染	1 (4.5)	-	1 (4.5)	-	-	-
急性副鼻腔炎	1 (4.5)	1 (4.5)	-	-	-	-
真菌性消化管感染	1 (4.5)	-	1 (4.5)	-	-	-
帯状疱疹	1 (4.5)	-	-	1 (4.5)	-	-
肺感染	1 (4.5)	-	-	1 (4.5)	-	-
鼻炎	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	18	8	6	4	-	-
胃腸障害						
Total Pts With at Least one AE	10 (45.5)	5 (22.7)	6 (27.3)	1 (4.5)	-	-
悪心	7 (31.8)	4 (18.2)	3 (13.6)	-	-	-
下痢	2 (9.1)	2 (9.1)	-	-	-	-
消化不良	2 (9.1)	2 (9.1)	-	-	-	-
嘔吐	2 (9.1)	-	1 (4.5)	1 (4.5)	-	-
腹痛	1 (4.5)	-	1 (4.5)	-	-	-
便秘	1 (4.5)	-	1 (4.5)	-	-	-
膵炎	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	16	8	7	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	10 (45.5)	4 (18.2)	6 (27.3)	-	-	-
頭痛	6 (27.3)	2 (9.1)	4 (18.2)	-	-	-
ヘルペス後神経痛	1 (4.5)	-	1 (4.5)	-	-	-
頚動脈狭窄	1 (4.5)	-	1 (4.5)	-	-	-
振戦	1 (4.5)	1 (4.5)	-	-	-	-
浮動性めまい	1 (4.5)	1 (4.5)	-	-	-	-
味覚異常	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	11	5	6	-	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	9 (40.9)	4 (18.2)	5 (22.7)	-	-	-
筋肉痛	2 (9.1)	1 (4.5)	1 (4.5)	-	-	-
四肢痛	2 (9.1)	1 (4.5)	1 (4.5)	-	-	-
背部痛	2 (9.1)	-	2 (9.1)	-	-	-
関節痛	1 (4.5)	1 (4.5)	-	-	-	-
筋骨格痛	1 (4.5)	-	1 (4.5)	-	-	-
筋痙縮	1 (4.5)	1 (4.5)	-	-	-	-
骨痛	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	10	4	6	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	8 (36.4)	5 (22.7)	3 (13.6)	2 (9.1)	-	-
呼吸困難	5 (22.7)	2 (9.1)	1 (4.5)	2 (9.1)	-	-
喉頭刺激感	2 (9.1)	2 (9.1)	-	-	-	-
咽喉刺激感	1 (4.5)	-	1 (4.5)	-	-	-
咳嗽	1 (4.5)	-	1 (4.5)	-	-	-
気管支痙攣	1 (4.5)	-	-	1 (4.5)	-	-
上気道閉塞	1 (4.5)	1 (4.5)	-	-	-	-
発声障害	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	12	6	3	3	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	7 (31.8)	2 (9.1)	-	5 (22.7)	2 (9.1)	-
好中球減少症	3 (13.6)	-	-	1 (4.5)	2 (9.1)	-
リンパ球減少症	2 (9.1)	-	-	2 (9.1)	-	-
貧血	2 (9.1)	1 (4.5)	-	1 (4.5)	-	-
血小板減少症	1 (4.5)	-	-	1 (4.5)	-	-
特発性血小板減少性紫斑病	1 (4.5)	1 (4.5)	-	-	-	-
発熱性好中球減少症	1 (4.5)	-	-	1 (4.5)	-	-
Total Number of AEs	10	2	-	6	2	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.
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ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	6 (27.3)	4 (18.2)	1 (4.5)	1 (4.5)	-	-
そう痒症	2 (9.1)	2 (9.1)	-	-	-	-
紅斑	2 (9.1)	1 (4.5)	1 (4.5)	-	-	-
多汗症	1 (4.5)	-	-	1 (4.5)	-	-
皮膚刺激	1 (4.5)	1 (4.5)	-	-	-	-
皮膚病変	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	7	5	1	1	-	-
精神障害						
Total Pts With at Least one AE	3 (13.6)	2 (9.1)	-	1 (4.5)	-	-
自殺企図	1 (4.5)	-	-	1 (4.5)	-	-
睡眠障害	1 (4.5)	1 (4.5)	-	-	-	-
不眠症	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	3	2	-	1	-	-
臨床検査						
Total Pts With at Least one AE	3 (13.6)	1 (4.5)	2 (9.1)	-	-	-
体重減少	2 (9.1)	-	2 (9.1)	-	-	-
トランスアミナーゼ上昇	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	3	1	2	-	-	-
肝胆道系障害						
Total Pts With at Least one AE	1 (4.5)	-	-	1 (4.5)	-	-
肝細胞融解性肝炎	1 (4.5)	-	-	1 (4.5)	-	-
Total Number of AEs	1	-	-	1	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800: N = 22

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
眼障害						
Total Pts With at Least one AE	1 (4.5)	-	1 (4.5)	-	-	-
結膜炎	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	1 (4.5)	1 (4.5)	-	-	-	-
聴力低下	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	1 (4.5)	1 (4.5)	-	-	-	-
動物咬傷	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	1 (4.5)	-	1 (4.5)	-	-	-
腎不全	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	1 (4.5)	-	1 (4.5)	-	-	-
食欲減退	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
免疫系障害											
Total Pts With at Least one AE	1 (4.5)	1	(4.5)	-		-		-		-	
季節性アレルギー	1 (4.5)	1	(4.5)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 13.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.
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ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	39 (97.5)	37 (92.5)	28 (70.0)	12 (30.0)	3 (7.5)	-
Total Number of AEs	231	113	88	27	3	-
全身障害および投与局所様態						
Total Pts With at Least one AE	27 (67.5)	16 (40.0)	13 (32.5)	2 (5.0)	-	-
無力症	13 (32.5)	7 (17.5)	5 (12.5)	1 (2.5)	-	-
発熱	12 (30.0)	5 (12.5)	6 (15.0)	1 (2.5)	-	-
悪寒	10 (25.0)	3 (7.5)	6 (15.0)	1 (2.5)	-	-
末梢性浮腫	4 (10.0)	2 (5.0)	2 (5.0)	-	-	-
胸痛	1 (2.5)	-	-	1 (2.5)	-	-
苦悶感	1 (2.5)	-	1 (2.5)	-	-	-
低体温	1 (2.5)	-	1 (2.5)	-	-	-
疼痛	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	43	18	21	4	-	-
血管障害						
Total Pts With at Least one AE	26 (65.0)	18 (45.0)	9 (22.5)	2 (5.0)	-	-
低血圧	17 (42.5)	10 (25.0)	6 (15.0)	1 (2.5)	-	-
高血圧	12 (30.0)	9 (22.5)	2 (5.0)	1 (2.5)	-	-
ほてり	1 (2.5)	1 (2.5)	-	-	-	-
血栓症	1 (2.5)	-	1 (2.5)	-	-	-
静脈不全	1 (2.5)	1 (2.5)	-	-	-	-
潮紅	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	33	21	10	2	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	17 (42.5)	9 (22.5)	6 (15.0)	3 (7.5)	1 (2.5)	-
鼻咽頭炎	5 (12.5)	3 (7.5)	2 (5.0)	-	-	-
気管支炎	4 (10.0)	2 (5.0)	2 (5.0)	-	-	-
尿路感染	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
鼻炎	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
副鼻腔炎	2 (5.0)	-	2 (5.0)	-	-	-
インフルエンザ	1 (2.5)	1 (2.5)	-	-	-	-
クロストリジウム感染	1 (2.5)	-	-	1 (2.5)	-	-
ヘモフィルス感染	1 (2.5)	-	-	1 (2.5)	-	-
胃腸炎	1 (2.5)	1 (2.5)	-	-	-	-
医療機器関連感染	1 (2.5)	-	1 (2.5)	-	-	-
眼瞼毛包炎	1 (2.5)	1 (2.5)	-	-	-	-
急性副鼻腔炎	1 (2.5)	1 (2.5)	-	-	-	-
真菌性消化管感染	1 (2.5)	-	1 (2.5)	-	-	-
帯状疱疹	1 (2.5)	-	-	1 (2.5)	-	-
肺炎球菌感染	1 (2.5)	-	-	-	1 (2.5)	-
肺感染	1 (2.5)	-	-	1 (2.5)	-	-
膀胱炎	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	28	13	10	4	1	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	16 (40.0)	8 (20.0)	10 (25.0)	1 (2.5)	-	-
悪心	7 (17.5)	4 (10.0)	3 (7.5)	-	-	-
嘔吐	5 (12.5)	1 (2.5)	3 (7.5)	1 (2.5)	-	-
下痢	4 (10.0)	4 (10.0)	-	-	-	-
腹痛	4 (10.0)	1 (2.5)	3 (7.5)	-	-	-
消化不良	2 (5.0)	2 (5.0)	-	-	-	-
便秘	1 (2.5)	-	1 (2.5)	-	-	-
膵炎	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	24	12	11	1	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	16 (40.0)	11 (27.5)	6 (15.0)	3 (7.5)	-	-
呼吸困難	7 (17.5)	3 (7.5)	2 (5.0)	2 (5.0)	-	-
咽喉刺激感	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
咳嗽	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
喉頭刺激感	2 (5.0)	2 (5.0)	-	-	-	-
鼻漏	2 (5.0)	2 (5.0)	-	-	-	-
気管支痙攣	1 (2.5)	-	-	1 (2.5)	-	-
気胸	1 (2.5)	-	-	1 (2.5)	-	-
胸水	1 (2.5)	-	-	1 (2.5)	-	-
上気道閉塞	1 (2.5)	1 (2.5)	-	-	-	-
発声障害	1 (2.5)	1 (2.5)	-	-	-	-
扁桃肥大	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	23	12	6	5	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	16 (40.0)	8 (20.0)	8 (20.0)	-	-	-
四肢痛	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
筋骨格痛	2 (5.0)	-	2 (5.0)	-	-	-
筋肉痛	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
筋痙縮	2 (5.0)	2 (5.0)	-	-	-	-
背部痛	2 (5.0)	-	2 (5.0)	-	-	-
関節炎	1 (2.5)	1 (2.5)	-	-	-	-
関節痛	1 (2.5)	1 (2.5)	-	-	-	-
頚部痛	1 (2.5)	-	1 (2.5)	-	-	-
骨腫脹	1 (2.5)	1 (2.5)	-	-	-	-
骨痛	1 (2.5)	-	1 (2.5)	-	-	-
鼠径部痛	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	17	8	9	-	-	-
神経系障害						
Total Pts With at Least one AE	14 (35.0)	7 (17.5)	8 (20.0)	-	-	-
頭痛	10 (25.0)	4 (10.0)	6 (15.0)	-	-	-
浮動性めまい	2 (5.0)	2 (5.0)	-	-	-	-
ヘルペス後神経痛	1 (2.5)	-	1 (2.5)	-	-	-
頚動脈狭窄	1 (2.5)	-	1 (2.5)	-	-	-
振戦	1 (2.5)	1 (2.5)	-	-	-	-
味覚異常	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	16	8	8	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	9 (22.5)	2 (5.0)	1 (2.5)	6 (15.0)	2 (5.0)	-
リンパ球減少症	3 (7.5)	-	-	3 (7.5)	-	-
好中球減少症	3 (7.5)	-	-	1 (2.5)	2 (5.0)	-
貧血	3 (7.5)	1 (2.5)	1 (2.5)	1 (2.5)	-	-
血小板減少症	1 (2.5)	-	-	1 (2.5)	-	-
特発性血小板減少性紫斑病	1 (2.5)	1 (2.5)	-	-	-	-
発熱性好中球減少症	1 (2.5)	-	-	1 (2.5)	-	-
Total Number of AEs	12	2	1	7	2	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	9 (22.5)	6 (15.0)	3 (7.5)	1 (2.5)	-	-
そう痒症	3 (7.5)	3 (7.5)	-	-	-	-
紅斑	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
発疹	2 (5.0)	-	2 (5.0)	-	-	-
湿疹	1 (2.5)	1 (2.5)	-	-	-	-
多汗症	1 (2.5)	-	-	1 (2.5)	-	-
皮膚刺激	1 (2.5)	1 (2.5)	-	-	-	-
皮膚病変	1 (2.5)	1 (2.5)	-	-	-	-
蕁麻疹	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	12	7	4	1	-	-
精神障害						
Total Pts With at Least one AE	4 (10.0)	3 (7.5)	-	1 (2.5)	-	-
不眠症	2 (5.0)	2 (5.0)	-	-	-	-
自殺企図	1 (2.5)	-	-	1 (2.5)	-	-
睡眠障害	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	4	3	-	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
臨床検査						
Total Pts With at Least one AE	4 (10.0)	2 (5.0)	2 (5.0)	-	-	-
体重減少	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
トランスアミナーゼ上昇	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	4	2	2	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	3 (7.5)	1 (2.5)	1 (2.5)	1 (2.5)	-	-
腎不全	2 (5.0)	-	1 (2.5)	1 (2.5)	-	-
排尿困難	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	3	1	1	1	-	-
心臓障害						
Total Pts With at Least one AE	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
動悸	1 (2.5)	1 (2.5)	-	-	-	-
頻脈	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	2	1	1	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
高カルシウム血症	1 (2.5)	1 (2.5)	-	-	-	-
食欲減退	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	2	1	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
免疫系障害						
Total Pts With at Least one AE	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
過敏症	1 (2.5)	-	1 (2.5)	-	-	-
季節性アレルギー	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	2	1	1	-	-	-
肝胆道系障害						
Total Pts With at Least one AE	1 (2.5)	-	-	1 (2.5)	-	-
肝細胞融解性肝炎	1 (2.5)	-	-	1 (2.5)	-	-
Total Number of AEs	1	-	-	1	-	-
眼障害						
Total Pts With at Least one AE	1 (2.5)	-	1 (2.5)	-	-	-
結膜炎	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	1 (2.5)	1 (2.5)	-	-	-	-
聴力低下	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	1 (2.5)	1 (2.5)	-	-	-	-
動物咬傷	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17_9992p_si Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
内分泌障害						
Total Pts With at Least one AE	1 (2.5)	-	1 (2.5)	-	-	-
自己免疫性甲状腺炎	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	1	-	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）						
Total Pts With at Least one AE	1 (2.5)	1 (2.5)	-	-	-	-
皮膚乳頭腫	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.
AE17 26MAY2015:08:39:04 (21 of 21)

[5.3.5.3-1 ae17_9992p_si を再掲]

表 2.7.6.2.1.6-2 因果関係が否定できないすべての有害事象（BO20999試験, Phase II, 再発・治療抵抗性 iNHL 患者）

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 400/400; N = 18

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	14 (77.8)	12 (66.7)	10 (55.6)	1 (5.6)	-	-
Total Number of AEs	51	20	30	1	-	-
血管障害						
Total Pts With at Least one AE	11 (61.1)	7 (38.9)	5 (27.8)	-	-	-
低血圧	7 (38.9)	2 (11.1)	5 (27.8)	-	-	-
高血圧	5 (27.8)	5 (27.8)	-	-	-	-
Total Number of AEs	12	7	5	-	-	-
全身障害および投与局所様態						
Total Pts With at Least one AE	10 (55.6)	5 (27.8)	6 (33.3)	-	-	-
発熱	5 (27.8)	2 (11.1)	3 (16.7)	-	-	-
悪寒	4 (22.2)	1 (5.6)	3 (16.7)	-	-	-
無力症	4 (22.2)	2 (11.1)	2 (11.1)	-	-	-
低体温	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	14	5	9	-	-	-
胃腸障害						
Total Pts With at Least one AE	5 (27.8)	2 (11.1)	3 (16.7)	-	-	-
嘔吐	3 (16.7)	1 (5.6)	2 (11.1)	-	-	-
腹痛	2 (11.1)	1 (5.6)	1 (5.6)	-	-	-
下痢	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	6	3	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 400/400; N = 18

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	4 (22.2)	2 (11.1)	2 (11.1)	-	-	-
咽喉刺激感	2 (11.1)	1 (5.6)	1 (5.6)	-	-	-
咳嗽	1 (5.6)	1 (5.6)	-	-	-	-
呼吸困難	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	4	2	2	-	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	3 (16.7)	1 (5.6)	2 (11.1)	-	-	-
頚部痛	1 (5.6)	-	1 (5.6)	-	-	-
骨腫脹	1 (5.6)	1 (5.6)	-	-	-	-
四肢痛	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	3	1	2	-	-	-
神経系障害						
Total Pts With at Least one AE	3 (16.7)	1 (5.6)	2 (11.1)	-	-	-
頭痛	3 (16.7)	1 (5.6)	2 (11.1)	-	-	-
Total Number of AEs	3	1	2	-	-	-
感染症および寄生虫症						
Total Pts With at Least one AE	2 (11.1)	-	2 (11.1)	-	-	-
副鼻腔炎	2 (11.1)	-	2 (11.1)	-	-	-
気管支炎	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	3	-	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 400/400; N = 18

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	2 (11.1)	-	1 (5.6)	1 (5.6)	-	-
リンパ球減少症	1 (5.6)	-	-	1 (5.6)	-	-
貧血	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	2	-	1	1	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	1 (5.6)	-	1 (5.6)	-	-	-
発疹	1 (5.6)	-	1 (5.6)	-	-	-
蕁麻疹	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	2	-	2	-	-	-
精神障害						
Total Pts With at Least one AE	1 (5.6)	1 (5.6)	-	-	-	-
不眠症	1 (5.6)	1 (5.6)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
免疫系障害						
Total Pts With at Least one AE	1 (5.6)	-	1 (5.6)	-	-	-
過敏症	1 (5.6)	-	1 (5.6)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	20 (90.9)	18 (81.8)	12 (54.5)	8 (36.4)	2 (9.1)	-
Total Number of AEs	92	44	28	18	2	-
血管障害						
Total Pts With at Least one AE	15 (68.2)	11 (50.0)	3 (13.6)	2 (9.1)	-	-
低血圧	10 (45.5)	8 (36.4)	1 (4.5)	1 (4.5)	-	-
高血圧	7 (31.8)	4 (18.2)	2 (9.1)	1 (4.5)	-	-
ほてり	1 (4.5)	1 (4.5)	-	-	-	-
潮紅	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	19	13	4	2	-	-
全身障害および投与局所様態						
Total Pts With at Least one AE	13 (59.1)	8 (36.4)	5 (22.7)	2 (9.1)	-	-
悪寒	6 (27.3)	2 (9.1)	3 (13.6)	1 (4.5)	-	-
発熱	6 (27.3)	3 (13.6)	2 (9.1)	1 (4.5)	-	-
無力症	6 (27.3)	3 (13.6)	2 (9.1)	1 (4.5)	-	-
胸痛	1 (4.5)	-	-	1 (4.5)	-	-
苦悶感	1 (4.5)	-	1 (4.5)	-	-	-
疼痛	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	21	9	8	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	9 (40.9)	4 (18.2)	6 (27.3)	1 (4.5)	-	-
悪心	6 (27.3)	3 (13.6)	3 (13.6)	-	-	-
嘔吐	2 (9.1)	-	1 (4.5)	1 (4.5)	-	-
下痢	1 (4.5)	1 (4.5)	-	-	-	-
消化不良	1 (4.5)	1 (4.5)	-	-	-	-
腹痛	1 (4.5)	-	1 (4.5)	-	-	-
便秘	1 (4.5)	-	1 (4.5)	-	-	-
膵炎	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	13	5	7	1	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	7 (31.8)	1 (4.5)	-	5 (22.7)	2 (9.1)	-
好中球減少症	3 (13.6)	-	-	1 (4.5)	2 (9.1)	-
リンパ球減少症	2 (9.1)	-	-	2 (9.1)	-	-
血小板減少症	1 (4.5)	-	-	1 (4.5)	-	-
発熱性好中球減少症	1 (4.5)	-	-	1 (4.5)	-	-
貧血	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	8	1	-	5	2	-
神経系障害						
Total Pts With at Least one AE	7 (31.8)	4 (18.2)	3 (13.6)	-	-	-
頭痛	5 (22.7)	2 (9.1)	3 (13.6)	-	-	-
振戦	1 (4.5)	1 (4.5)	-	-	-	-
浮動性めまい	1 (4.5)	1 (4.5)	-	-	-	-
味覚異常	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	8	5	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	6 (27.3)	3 (13.6)	2 (9.1)	2 (9.1)	-	-
呼吸困難	4 (18.2)	2 (9.1)	-	2 (9.1)	-	-
喉頭刺激感	2 (9.1)	2 (9.1)	-	-	-	-
咽喉刺激感	1 (4.5)	-	1 (4.5)	-	-	-
咳嗽	1 (4.5)	-	1 (4.5)	-	-	-
気管支痙攣	1 (4.5)	-	-	1 (4.5)	-	-
Total Number of AEs	9	4	2	3	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	5 (22.7)	3 (13.6)	1 (4.5)	1 (4.5)	-	-
そう痒症	2 (9.1)	2 (9.1)	-	-	-	-
紅斑	2 (9.1)	1 (4.5)	1 (4.5)	-	-	-
多汗症	1 (4.5)	-	-	1 (4.5)	-	-
Total Number of AEs	5	3	1	1	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	3 (13.6)	2 (9.1)	1 (4.5)	-	-	-
関節痛	1 (4.5)	1 (4.5)	-	-	-	-
筋骨格痛	1 (4.5)	-	1 (4.5)	-	-	-
筋肉痛	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	3	2	1	-	-	-
感染症および寄生虫症						
Total Pts With at Least one AE	2 (9.1)	1 (4.5)	-	1 (4.5)	-	-
気管支炎	1 (4.5)	1 (4.5)	-	-	-	-
帯状疱疹	1 (4.5)	-	-	1 (4.5)	-	-
Total Number of AEs	2	1	-	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: RO5072759 1600/800; N = 22

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
肝胆道系障害						
Total Pts With at Least one AE	1 (4.5)	-	-	1 (4.5)	-	-
肝細胞融解性肝炎	1 (4.5)	-	-	1 (4.5)	-	-
Total Number of AEs	1	-	-	1	-	-
眼障害						
Total Pts With at Least one AE	1 (4.5)	-	1 (4.5)	-	-	-
結膜炎	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	1 (4.5)	1 (4.5)	-	-	-	-
聴力低下	1 (4.5)	1 (4.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	1 (4.5)	-	1 (4.5)	-	-	-
腎不全	1 (4.5)	-	1 (4.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	34 (85.0)	30 (75.0)	22 (55.0)	9 (22.5)	2 (5.0)	-
Total Number of AEs	143	64	58	19	2	-
血管障害						
Total Pts With at Least one AE	26 (65.0)	18 (45.0)	8 (20.0)	2 (5.0)	-	-
低血圧	17 (42.5)	10 (25.0)	6 (15.0)	1 (2.5)	-	-
高血圧	12 (30.0)	9 (22.5)	2 (5.0)	1 (2.5)	-	-
ほてり	1 (2.5)	1 (2.5)	-	-	-	-
潮紅	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	31	20	9	2	-	-
全身障害および投与局所様態						
Total Pts With at Least one AE	23 (57.5)	13 (32.5)	11 (27.5)	2 (5.0)	-	-
発熱	11 (27.5)	5 (12.5)	5 (12.5)	1 (2.5)	-	-
悪寒	10 (25.0)	3 (7.5)	6 (15.0)	1 (2.5)	-	-
無力症	10 (25.0)	5 (12.5)	4 (10.0)	1 (2.5)	-	-
胸痛	1 (2.5)	-	-	1 (2.5)	-	-
苦悶感	1 (2.5)	-	1 (2.5)	-	-	-
低体温	1 (2.5)	-	1 (2.5)	-	-	-
疼痛	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	35	14	17	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	14 (35.0)	6 (15.0)	9 (22.5)	1 (2.5)	-	-
悪心	6 (15.0)	3 (7.5)	3 (7.5)	-	-	-
嘔吐	5 (12.5)	1 (2.5)	3 (7.5)	1 (2.5)	-	-
腹痛	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
下痢	2 (5.0)	2 (5.0)	-	-	-	-
消化不良	1 (2.5)	1 (2.5)	-	-	-	-
便秘	1 (2.5)	-	1 (2.5)	-	-	-
膵炎	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	19	8	10	1	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	10 (25.0)	5 (12.5)	4 (10.0)	2 (5.0)	-	-
呼吸困難	5 (12.5)	2 (5.0)	1 (2.5)	2 (5.0)	-	-
咽喉刺激感	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
咳嗽	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
喉頭刺激感	2 (5.0)	2 (5.0)	-	-	-	-
気管支痙攣	1 (2.5)	-	-	1 (2.5)	-	-
Total Number of AEs	13	6	4	3	-	-
神経系障害						
Total Pts With at Least one AE	10 (25.0)	5 (12.5)	5 (12.5)	-	-	-
頭痛	8 (20.0)	3 (7.5)	5 (12.5)	-	-	-
振戦	1 (2.5)	1 (2.5)	-	-	-	-
浮動性めまい	1 (2.5)	1 (2.5)	-	-	-	-
味覚異常	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	11	6	5	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	9 (22.5)	1 (2.5)	1 (2.5)	6 (15.0)	2 (5.0)	-
リンパ球減少症	3 (7.5)	-	-	3 (7.5)	-	-
好中球減少症	3 (7.5)	-	-	1 (2.5)	2 (5.0)	-
貧血	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
血小板減少症	1 (2.5)	-	-	1 (2.5)	-	-
発熱性好中球減少症	1 (2.5)	-	-	1 (2.5)	-	-
Total Number of AEs	10	1	1	6	2	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	6 (15.0)	3 (7.5)	2 (5.0)	1 (2.5)	-	-
そう痒症	2 (5.0)	2 (5.0)	-	-	-	-
紅斑	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
多汗症	1 (2.5)	-	-	1 (2.5)	-	-
発疹	1 (2.5)	-	1 (2.5)	-	-	-
蕁麻疹	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	7	3	3	1	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	6 (15.0)	3 (7.5)	3 (7.5)	-	-	-
関節痛	1 (2.5)	1 (2.5)	-	-	-	-
筋骨格痛	1 (2.5)	-	1 (2.5)	-	-	-
筋肉痛	1 (2.5)	1 (2.5)	-	-	-	-
頚部痛	1 (2.5)	-	1 (2.5)	-	-	-
骨腫脹	1 (2.5)	1 (2.5)	-	-	-	-
四肢痛	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	6	3	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	4 (10.0)	1 (2.5)	2 (5.0)	1 (2.5)	-	-
気管支炎	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
副鼻腔炎	2 (5.0)	-	2 (5.0)	-	-	-
帯状疱疹	1 (2.5)	-	-	1 (2.5)	-	-
Total Number of AEs	5	1	3	1	-	-
肝胆道系障害						
Total Pts With at Least one AE	1 (2.5)	-	-	1 (2.5)	-	-
肝細胞融解性肝炎	1 (2.5)	-	-	1 (2.5)	-	-
Total Number of AEs	1	-	-	1	-	-
眼障害						
Total Pts With at Least one AE	1 (2.5)	-	1 (2.5)	-	-	-
結膜炎	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	1 (2.5)	1 (2.5)	-	-	-	-
聴力低下	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	1 (2.5)	-	1 (2.5)	-	-	-
腎不全	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.

ae17r_9992p_si Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO20999 (T20999N) Phase II Primary
Analysis: SAP, iNHL Center: ALL CENTERS
Snapshot Date: 20JUL2010 Cutoff Date: 27MAY2010
Treatment: Total; N = 40

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
精神障害						
Total Pts With at Least one AE	1 (2.5)	1 (2.5)	-	-	-	-
不眠症	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
免疫系障害						
Total Pts With at Least one AE	1 (2.5)	-	1 (2.5)	-	-	-
過敏症	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset Between Very First Drug Intake And Last Drug Intake Plus 28 Days Or Crossover To The High Dose.
AE17 26MAY2015:08:13:45 (12 of 12)

[5.3.5.3-1 ae17r_9992p_si を再掲]

2.7.6.2.1.7　BO21003試験（GAUSS 試験）

表 2.7.6.2.1.7-1　因果関係を問わないすべての有害事象（BO21003試験，再発・治療抵抗性 NHL 患者）

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	74 (86.0)	53 (61.6)	53 (61.6)	20 (23.3)	4 (4.7)	3 (3.5)
Total Number of AEs	439	221	173	37	5	3
傷害、中毒および処置合併症						
Total Pts With at Least one AE	47 (54.7)	24 (27.9)	21 (24.4)	5 (5.8)	-	-
注入に伴う反応	44 (51.2)	23 (26.7)	17 (19.8)	4 (4.7)	-	-
関節捻挫	1 (1.2)	-	1 (1.2)	-	-	-
処置後合併症	1 (1.2)	-	1 (1.2)	-	-	-
上肢骨折	1 (1.2)	-	1 (1.2)	-	-	-
転倒	1 (1.2)	1 (1.2)	-	-	-	-
頭部損傷	1 (1.2)	-	-	1 (1.2)	-	-
橈骨骨折	1 (1.2)	-	1 (1.2)	-	-	-
腓骨骨折	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	51	24	21	6	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	44 (51.2)	31 (36.0)	18 (20.9)	3 (3.5)	-	-
疲労	19 (22.1)	14 (16.3)	5 (5.8)	-	-	-
発熱	15 (17.4)	8 (9.3)	6 (7.0)	1 (1.2)	-	-
悪寒	13 (15.1)	8 (9.3)	3 (3.5)	2 (2.3)	-	-
無力症	4 (4.7)	4 (4.7)	-	-	-	-
インフルエンザ様疾患	3 (3.5)	2 (2.3)	1 (1.2)	-	-	-
末梢性浮腫	3 (3.5)	1 (1.2)	2 (2.3)	-	-	-
顔面浮腫	2 (2.3)	-	2 (2.3)	-	-	-
胸痛	2 (2.3)	-	2 (2.3)	-	-	-
胸部不快感	1 (1.2)	-	1 (1.2)	-	-	-
倦怠感	1 (1.2)	1 (1.2)	-	-	-	-
腫脹	1 (1.2)	-	-	1 (1.2)	-	-
注射部位静脈炎	1 (1.2)	1 (1.2)	-	-	-	-
浮腫	1 (1.2)	1 (1.2)	-	-	-	-
疼痛	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	67	40	23	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21 (2 of 26)

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	36 (41.9)	17 (19.8)	21 (24.4)	3 (3.5)	-	1 (1.2)
上気道感染	9 (10.5)	5 (5.8)	4 (4.7)	-	-	-
インフルエンザ	4 (4.7)	4 (4.7)	-	-	-	-
気管支炎	4 (4.7)	-	4 (4.7)	-	-	-
副鼻腔炎	4 (4.7)	1 (1.2)	3 (3.5)	-	-	-
咽頭炎	3 (3.5)	1 (1.2)	2 (2.3)	-	-	-
帯状疱疹	3 (3.5)	1 (1.2)	2 (2.3)	-	-	-
肺炎	3 (3.5)	-	1 (1.2)	1 (1.2)	-	1 (1.2)
鼻咽頭炎	3 (3.5)	3 (3.5)	-	-	-	-
鼻炎	3 (3.5)	2 (2.3)	1 (1.2)	-	-	-
気道感染	2 (2.3)	-	2 (2.3)	-	-	-
尿路感染	2 (2.3)	-	1 (1.2)	1 (1.2)	-	-
膀胱炎	2 (2.3)	2 (2.3)	-	-	-	-
胃腸炎	1 (1.2)	1 (1.2)	-	-	-	-
眼感染	1 (1.2)	-	1 (1.2)	-	-	-
憩室炎	1 (1.2)	-	1 (1.2)	-	-	-
口腔ヘルペス	1 (1.2)	-	1 (1.2)	-	-	-
喉頭炎	1 (1.2)	1 (1.2)	-	-	-	-
歯感染	1 (1.2)	-	1 (1.2)	-	-	-
耳感染	1 (1.2)	-	1 (1.2)	-	-	-
創傷感染	1 (1.2)	1 (1.2)	-	-	-	-
単純ヘルペス	1 (1.2)	-	1 (1.2)	-	-	-
肺感染	1 (1.2)	-	1 (1.2)	-	-	-
蜂巣炎	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	53	22	27	3	-	1

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	33 (38.4)	23 (26.7)	15 (17.4)	1 (1.2)	-	-
悪心	12 (14.0)	6 (7.0)	6 (7.0)	-	-	-
下痢	8 (9.3)	7 (8.1)	1 (1.2)	-	-	-
嘔吐	6 (7.0)	4 (4.7)	2 (2.3)	-	-	-
上腹部痛	5 (5.8)	4 (4.7)	1 (1.2)	-	-	-
便秘	4 (4.7)	4 (4.7)	-	-	-	-
下腹部痛	2 (2.3)	1 (1.2)	1 (1.2)	-	-	-
歯痛	2 (2.3)	2 (2.3)	-	-	-	-
歯肉炎	2 (2.3)	2 (2.3)	-	-	-	-
腹痛	2 (2.3)	-	2 (2.3)	-	-	-
胃炎	1 (1.2)	-	1 (1.2)	-	-	-
結腸ポリープ	1 (1.2)	-	-	1 (1.2)	-	-
鼓腸	1 (1.2)	1 (1.2)	-	-	-	-
口の錯感覚	1 (1.2)	-	1 (1.2)	-	-	-
口内炎	1 (1.2)	1 (1.2)	-	-	-	-
歯肉腫脹	1 (1.2)	1 (1.2)	-	-	-	-
歯肉障害	1 (1.2)	1 (1.2)	-	-	-	-
消化不良	1 (1.2)	-	1 (1.2)	-	-	-
食道炎	1 (1.2)	-	1 (1.2)	-	-	-
舌腫脹	1 (1.2)	1 (1.2)	-	-	-	-
腹部膨満	1 (1.2)	-	1 (1.2)	-	-	-
嚥下痛	1 (1.2)	1 (1.2)	-	-	-	-
齲歯	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	56	36	19	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	28 (32.6)	15 (17.4)	12 (14.0)	3 (3.5)	-	-
咳嗽	8 (9.3)	3 (3.5)	5 (5.8)	-	-	-
咽喉刺激感	7 (8.1)	5 (5.8)	2 (2.3)	-	-	-
口腔咽頭痛	6 (7.0)	4 (4.7)	2 (2.3)	-	-	-
呼吸困難	4 (4.7)	1 (1.2)	3 (3.5)	-	-	-
喉頭刺激感	3 (3.5)	1 (1.2)	2 (2.3)	-	-	-
咽頭浮腫	2 (2.3)	-	1 (1.2)	1 (1.2)	-	-
アレルギー性鼻炎	1 (1.2)	1 (1.2)	-	-	-	-
咽喉絞扼感	1 (1.2)	1 (1.2)	-	-	-	-
気管支拡張症	1 (1.2)	-	1 (1.2)	-	-	-
気管支痙攣	1 (1.2)	-	1 (1.2)	-	-	-
胸水	1 (1.2)	-	-	1 (1.2)	-	-
胸水症	1 (1.2)	-	-	1 (1.2)	-	-
鼻閉	1 (1.2)	1 (1.2)	-	-	-	-
鼻閉塞	1 (1.2)	-	1 (1.2)	-	-	-
副鼻腔うっ血	1 (1.2)	1 (1.2)	-	-	-	-
喘息	1 (1.2)	-	1 (1.2)	-	-	-
喘鳴	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	41	18	20	3	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	22 (25.6)	11 (12.8)	12 (14.0)	1 (1.2)	-	-
そう痒症	8 (9.3)	5 (5.8)	3 (3.5)	-	-	-
発疹	7 (8.1)	2 (2.3)	4 (4.7)	1 (1.2)	-	-
湿疹	2 (2.3)	1 (1.2)	1 (1.2)	-	-	-
多汗症	2 (2.3)	1 (1.2)	1 (1.2)	-	-	-
蕁麻疹	2 (2.3)	-	2 (2.3)	-	-	-
そう痒性皮疹	1 (1.2)	-	1 (1.2)	-	-	-
顔面腫脹	1 (1.2)	1 (1.2)	-	-	-	-
丘疹	1 (1.2)	1 (1.2)	-	-	-	-
紅斑	1 (1.2)	1 (1.2)	-	-	-	-
酒さ	1 (1.2)	-	1 (1.2)	-	-	-
寝汗	1 (1.2)	1 (1.2)	-	-	-	-
水疱性皮膚炎	1 (1.2)	1 (1.2)	-	-	-	-
接触性皮膚炎	1 (1.2)	1 (1.2)	-	-	-	-
脱毛症	1 (1.2)	1 (1.2)	-	-	-	-
斑状丘疹状皮疹	1 (1.2)	1 (1.2)	-	-	-	-
冷汗	1 (1.2)	1 (1.2)	-	-	-	-
嵌入爪	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	33	19	13	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	22 (25.6)	15 (17.4)	6 (7.0)	3 (3.5)	-	1 (1.2)
頭痛	7 (8.1)	5 (5.8)	2 (2.3)	-	-	-
浮動性めまい	6 (7.0)	5 (5.8)	1 (1.2)	-	-	-
錯感覚	2 (2.3)	2 (2.3)	-	-	-	-
失神	2 (2.3)	-	-	2 (2.3)	-	-
失神寸前の状態	2 (2.3)	-	2 (2.3)	-	-	-
副鼻腔炎に伴う頭痛	2 (2.3)	1 (1.2)	-	1 (1.2)	-	-
坐骨神経痛	1 (1.2)	1 (1.2)	-	-	-	-
失語症	1 (1.2)	1 (1.2)	-	-	-	-
出血性卒中	1 (1.2)	-	-	-	-	1 (1.2)
認知障害	1 (1.2)	-	1 (1.2)	-	-	-
末梢性感覚ニューロパチー	1 (1.2)	1 (1.2)	-	-	-	-
末梢性感覚運動ニューロパチー	1 (1.2)	1 (1.2)	-	-	-	-
嗅覚錯誤	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	28	18	6	3	-	1
血管障害						
Total Pts With at Least one AE	21 (24.4)	9 (10.5)	9 (10.5)	3 (3.5)	-	-
潮紅	8 (9.3)	3 (3.5)	4 (4.7)	1 (1.2)	-	-
高血圧	7 (8.1)	4 (4.7)	3 (3.5)	-	-	-
低血圧	6 (7.0)	1 (1.2)	3 (3.5)	2 (2.3)	-	-
静脈痛	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	22	9	10	3	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
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ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	20 (23.3)	13 (15.1)	8 (9.3)	1 (1.2)	-	-
関節痛	5 (5.8)	4 (4.7)	1 (1.2)	-	-	-
背部痛	5 (5.8)	3 (3.5)	1 (1.2)	1 (1.2)	-	-
筋骨格痛	3 (3.5)	1 (1.2)	2 (2.3)	-	-	-
筋肉痛	2 (2.3)	2 (2.3)	-	-	-	-
腱炎	2 (2.3)	1 (1.2)	1 (1.2)	-	-	-
筋痙縮	1 (1.2)	-	1 (1.2)	-	-	-
頚部痛	1 (1.2)	1 (1.2)	-	-	-	-
四肢痛	1 (1.2)	1 (1.2)	-	-	-	-
重感	1 (1.2)	1 (1.2)	-	-	-	-
側腹部痛	1 (1.2)	1 (1.2)	-	-	-	-
椎間板突出	1 (1.2)	-	1 (1.2)	-	-	-
半月板変性	1 (1.2)	-	1 (1.2)	-	-	-
変形性関節症	1 (1.2)	-	1 (1.2)	-	-	-
肩径部痛	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	26	15	9	2	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	9 (10.5)	1 (1.2)	3 (3.5)	3 (3.5)	4 (4.7)	-
好中球減少症	6 (7.0)	-	1 (1.2)	1 (1.2)	4 (4.7)	-
発熱性好中球減少症	3 (3.5)	-	1 (1.2)	1 (1.2)	1 (1.2)	-
リンパ節症	1 (1.2)	-	1 (1.2)	-	-	-
血小板減少症	1 (1.2)	1 (1.2)	-	-	-	-
貧血	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	12	1	3	3	5	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
代謝および栄養障害						
Total Pts With at Least one AE	9 (10.5)	5 (5.8)	3 (3.5)	1 (1.2)	-	-
食欲減退	3 (3.5)	2 (2.3)	1 (1.2)	-	-	-
２型糖尿病	1 (1.2)	-	1 (1.2)	-	-	-
ポダグラ	1 (1.2)	-	1 (1.2)	-	-	-
高血糖	1 (1.2)	1 (1.2)	-	-	-	-
高尿酸血症	1 (1.2)	-	-	1 (1.2)	-	-
低カリウム血症	1 (1.2)	1 (1.2)	-	-	-	-
低マグネシウム血症	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	9	5	3	1	-	-
眼障害						
Total Pts With at Least one AE	7 (8.1)	3 (3.5)	4 (4.7)	-	-	-
結膜炎	4 (4.7)	1 (1.2)	3 (3.5)	-	-	-
黄斑症	1 (1.2)	1 (1.2)	-	-	-	-
眼の炎症	1 (1.2)	1 (1.2)	-	-	-	-
緑内障	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	7	3	4	-	-	-
精神障害						
Total Pts With at Least one AE	7 (8.1)	3 (3.5)	3 (3.5)	1 (1.2)	-	-
うつ病	2 (2.3)	-	2 (2.3)	-	-	-
不眠症	2 (2.3)	2 (2.3)	-	-	-	-
気分変化	1 (1.2)	1 (1.2)	-	-	-	-
錯乱状態	1 (1.2)	-	-	1 (1.2)	-	-
不安	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	7	3	3	1	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
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ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
耳および迷路障害						
Total Pts With at Least one AE	5 (5.8)	2 (2.3)	3 (3.5)	-	-	-
回転性めまい	2 (2.3)	2 (2.3)	-	-	-	-
耳鳴	2 (2.3)	-	2 (2.3)	-	-	-
メニエール病	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	5	2	3	-	-	-
心臓障害						
Total Pts With at Least one AE	4 (4.7)	2 (2.3)	-	1 (1.2)	-	1 (1.2)
頻脈	2 (2.3)	1 (1.2)	-	1 (1.2)	-	-
心肺停止	1 (1.2)	-	-	-	-	1 (1.2)
動悸	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	4	2	-	1	-	1
腎および尿路障害						
Total Pts With at Least one AE	3 (3.5)	-	3 (3.5)	-	-	-
腎仙痛	1 (1.2)	-	1 (1.2)	-	-	-
水腎症	1 (1.2)	-	1 (1.2)	-	-	-
頻尿	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	3	-	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）						
Total Pts With at Least one AE	3 (3.5)	-	-	3 (3.5)	-	-
基底細胞癌	1 (1.2)	-	-	1 (1.2)	-	-
皮膚癌	1 (1.2)	-	-	1 (1.2)	-	-
卵巣癌	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	3	-	-	3	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
外科および内科処置						
Total Pts With at Least one AE	2 (2.3)	1 (1.2)	2 (2.3)	-	-	-
デンタルケア	1 (1.2)	-	1 (1.2)	-	-	-
舌切除	1 (1.2)	-	1 (1.2)	-	-	-
白内障手術	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	3	1	2	-	-	-
生殖系および乳房障害						
Total Pts With at Least one AE	2 (2.3)	2 (2.3)	-	-	-	-
萎縮性外陰膣炎	1 (1.2)	1 (1.2)	-	-	-	-
子宮ポリープ	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
免疫系障害						
Total Pts With at Least one AE	2 (2.3)	1 (1.2)	1 (1.2)	-	-	-
過敏症	1 (1.2)	-	1 (1.2)	-	-	-
季節性アレルギー	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	2	1	1	-	-	-
臨床検査						
Total Pts With at Least one AE	2 (2.3)	-	1 (1.2)	1 (1.2)	-	-
好中球数減少	1 (1.2)	-	-	1 (1.2)	-	-
体重減少	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	2	-	1	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
肝胆道系障害						
Total Pts With at Least one AE	1 (1.2)	-	1 (1.2)	1 (1.2)	-	-
肝障害	1 (1.2)	-	-	1 (1.2)	-	-
胆汁うっ滞性肝炎	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	2	-	1	1	-	-
内分泌障害						
Total Pts With at Least one AE	1 (1.2)	-	1 (1.2)	-	-	-
甲状腺腫	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	1	-	1	-	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21 (12 of 26)

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	82 (94.3)	66 (75.9)	55 (63.2)	25 (28.7)	4 (4.6)	2 (2.3)
Total Number of AEs	644	343	214	77	7	2
傷害、中毒および処置合併症						
Total Pts With at Least one AE	66 (75.9)	31 (35.6)	26 (29.9)	10 (11.5)	1 (1.1)	-
注入に伴う反応	64 (73.6)	28 (32.2)	26 (29.9)	9 (10.3)	1 (1.1)	-
口腔内損傷	1 (1.1)	1 (1.1)	-	-	-	-
創傷	1 (1.1)	-	-	1 (1.1)	-	-
転倒	1 (1.1)	1 (1.1)	-	-	-	-
軟骨損傷	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	68	31	26	10	1	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21 (13 of 26)

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	65 (74.7)	43 (49.4)	32 (36.8)	8 (9.2)	-	-
悪寒	27 (31.0)	9 (10.3)	13 (14.9)	5 (5.7)	-	-
発熱	25 (28.7)	13 (14.9)	9 (10.3)	3 (3.4)	-	-
疲労	22 (25.3)	15 (17.2)	7 (8.0)	-	-	-
末梢性浮腫	7 (8.0)	5 (5.7)	2 (2.3)	-	-	-
無力症	6 (6.9)	5 (5.7)	1 (1.1)	-	-	-
胸痛	4 (4.6)	1 (1.1)	3 (3.4)	-	-	-
胸部不快感	4 (4.6)	2 (2.3)	-	2 (2.3)	-	-
倦怠感	4 (4.6)	3 (3.4)	1 (1.1)	-	-	-
疼痛	2 (2.3)	2 (2.3)	-	-	-	-
易刺激性	1 (1.1)	1 (1.1)	-	-	-	-
医療機器閉塞	1 (1.1)	1 (1.1)	-	-	-	-
腫脹	1 (1.1)	1 (1.1)	-	-	-	-
注射部位血腫	1 (1.1)	1 (1.1)	-	-	-	-
腋窩痛	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	106	60	36	10	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21 (14 of 26)

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	40 (46.0)	26 (29.9)	15 (17.2)	2 (2.3)	1 (1.1)	1 (1.1)
悪心	21 (24.1)	14 (16.1)	4 (4.6)	2 (2.3)	1 (1.1)	-
嘔吐	11 (12.6)	7 (8.0)	4 (4.6)	-	-	-
下痢	7 (8.0)	6 (6.9)	1 (1.1)	-	-	-
便秘	4 (4.6)	3 (3.4)	1 (1.1)	-	-	-
腹痛	3 (3.4)	-	3 (3.4)	-	-	-
口腔内痛	2 (2.3)	2 (2.3)	-	-	-	-
口内炎	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
消化不良	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
下腹部痛	1 (1.1)	1 (1.1)	-	-	-	-
鼓腸	1 (1.1)	1 (1.1)	-	-	-	-
歯肉炎	1 (1.1)	-	1 (1.1)	-	-	-
痔核	1 (1.1)	-	1 (1.1)	-	-	-
十二指腸穿孔	1 (1.1)	-	-	-	-	1 (1.1)
上腹部痛	1 (1.1)	1 (1.1)	-	-	-	-
舌痛	1 (1.1)	1 (1.1)	-	-	-	-
直腸出血	1 (1.1)	1 (1.1)	-	-	-	-
腹部不快感	1 (1.1)	-	1 (1.1)	-	-	-
腹部膨満	1 (1.1)	1 (1.1)	-	-	-	-
嚥下障害	1 (1.1)	1 (1.1)	-	-	-	-
嚥下痛	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	64	41	19	2	1	1

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21 (15 of 26)

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	39 (44.8)	23 (26.4)	16 (18.4)	5 (5.7)	-	-
咳嗽	20 (23.0)	13 (14.9)	6 (6.9)	1 (1.1)	-	-
呼吸困難	13 (14.9)	3 (3.4)	5 (5.7)	5 (5.7)	-	-
咽喉刺激感	4 (4.6)	2 (2.3)	2 (2.3)	-	-	-
気管支痙攣	4 (4.6)	1 (1.1)	1 (1.1)	2 (2.3)	-	-
口腔咽頭痛	3 (3.4)	2 (2.3)	1 (1.1)	-	-	-
胸水	2 (2.3)	-	2 (2.3)	-	-	-
喉頭浮腫	2 (2.3)	-	-	2 (2.3)	-	-
湿性咳嗽	2 (2.3)	2 (2.3)	-	-	-	-
上気道咳症候群	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
上気道分泌増加	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
低酸素症	2 (2.3)	-	-	2 (2.3)	-	-
鼻漏	2 (2.3)	2 (2.3)	-	-	-	-
労作性呼吸困難	2 (2.3)	2 (2.3)	-	-	-	-
くしゃみ	1 (1.1)	1 (1.1)	-	-	-	-
気管支拡張症	1 (1.1)	1 (1.1)	-	-	-	-
気道うっ血	1 (1.1)	1 (1.1)	-	-	-	-
喉頭刺激感	1 (1.1)	1 (1.1)	-	-	-	-
鼻出血	1 (1.1)	-	1 (1.1)	-	-	-
鼻痛	1 (1.1)	1 (1.1)	-	-	-	-
鼻閉	1 (1.1)	1 (1.1)	-	-	-	-
慢性閉塞性肺疾患	1 (1.1)	1 (1.1)	-	-	-	-
喘息	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	69	37	20	12	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21 (16 of 26)

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	38 (43.7)	14 (16.1)	26 (29.9)	4 (4.6)	-	1 (1.1)
副鼻腔炎	8 (9.2)	1 (1.1)	7 (8.0)	-	-	-
上気道感染	7 (8.0)	2 (2.3)	5 (5.7)	-	-	-
気管支炎	6 (6.9)	-	6 (6.9)	-	-	-
鼻咽頭炎	5 (5.7)	4 (4.6)	1 (1.1)	-	-	-
帯状疱疹	4 (4.6)	1 (1.1)	2 (2.3)	1 (1.1)	-	-
鼻炎	4 (4.6)	3 (3.4)	1 (1.1)	-	-	-
インフルエンザ	3 (3.4)	1 (1.1)	2 (2.3)	-	-	-
ヘルペスウイルス感染	2 (2.3)	2 (2.3)	-	-	-	-
感染	2 (2.3)	-	2 (2.3)	-	-	-
気道感染	2 (2.3)	-	1 (1.1)	1 (1.1)	-	-
口腔ヘルペス	2 (2.3)	2 (2.3)	-	-	-	-
尿路感染	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
肺炎	2 (2.3)	-	-	2 (2.3)	-	-
ウイルス感染	1 (1.1)	-	1 (1.1)	-	-	-
胃腸炎	1 (1.1)	1 (1.1)	-	-	-	-
医療機器関連感染	1 (1.1)	-	1 (1.1)	-	-	-
急性副鼻腔炎	1 (1.1)	-	1 (1.1)	-	-	-
細気管支炎	1 (1.1)	-	1 (1.1)	-	-	-
真菌性肺炎	1 (1.1)	-	-	-	-	1 (1.1)
丹毒	1 (1.1)	-	1 (1.1)	-	-	-
単純ヘルペス	1 (1.1)	1 (1.1)	-	-	-	-
播種性帯状疱疹	1 (1.1)	-	1 (1.1)	-	-	-
泌尿生殖器感染	1 (1.1)	1 (1.1)	-	-	-	-
皮膚感染	1 (1.1)	1 (1.1)	-	-	-	-
皮膚真菌感染	1 (1.1)	-	1 (1.1)	-	-	-

(body system continuing ...)

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
(... body system continuing)						
慢性副鼻腔炎	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	62	21	36	4	-	1
血管障害						
Total Pts With at Least one AE	35 (40.2)	14 (16.1)	16 (18.4)	5 (5.7)	1 (1.1)	-
低血圧	18 (20.7)	8 (9.2)	4 (4.6)	5 (5.7)	1 (1.1)	-
高血圧	10 (11.5)	2 (2.3)	8 (9.2)	-	-	-
潮紅	10 (11.5)	3 (3.4)	5 (5.7)	2 (2.3)	-	-
ほてり	1 (1.1)	1 (1.1)	-	-	-	-
起立性低血圧	1 (1.1)	-	1 (1.1)	-	-	-
血腫	1 (1.1)	1 (1.1)	-	-	-	-
静脈瘤	1 (1.1)	-	1 (1.1)	-	-	-
蒼白	1 (1.1)	-	-	1 (1.1)	-	-
Total Number of AEs	43	15	19	8	1	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21 (18 of 26)

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	32 (36.8)	19 (21.8)	12 (13.8)	4 (4.6)	1 (1.1)	-
頭痛	16 (18.4)	9 (10.3)	6 (6.9)	1 (1.1)	-	-
浮動性めまい	10 (11.5)	3 (3.4)	5 (5.7)	2 (2.3)	-	-
錯感覚	5 (5.7)	5 (5.7)	-	-	-	-
失神	2 (2.3)	2 (2.3)	-	-	-	-
意識消失	1 (1.1)	-	-	-	1 (1.1)	-
一過性脳虚血発作	1 (1.1)	-	-	1 (1.1)	-	-
感覚鈍麻	1 (1.1)	1 (1.1)	-	-	-	-
平衡障害	1 (1.1)	1 (1.1)	-	-	-	-
末梢性ニューロパチー	1 (1.1)	1 (1.1)	-	-	-	-
末梢性運動ニューロパチー	1 (1.1)	-	-	1 (1.1)	-	-
末梢性感覚ニューロパチー	1 (1.1)	-	1 (1.1)	-	-	-
末梢性感覚運動ニューロパチー	1 (1.1)	-	1 (1.1)	-	-	-
味覚消失	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	42	23	13	5	1	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21 (19 of 26)

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	28 (32.2)	20 (23.0)	6 (6.9)	4 (4.6)	-	-
発疹	12 (13.8)	7 (8.0)	3 (3.4)	2 (2.3)	-	-
多汗症	5 (5.7)	2 (2.3)	1 (1.1)	2 (2.3)	-	-
そう痒症	4 (4.6)	3 (3.4)	-	1 (1.1)	-	-
そう痒性皮疹	2 (2.3)	-	2 (2.3)	-	-	-
寝汗	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
斑状皮疹	2 (2.3)	2 (2.3)	-	-	-	-
蕁麻疹	2 (2.3)	2 (2.3)	-	-	-	-
間擦疹	1 (1.1)	1 (1.1)	-	-	-	-
丘疹	1 (1.1)	1 (1.1)	-	-	-	-
丘疹性皮疹	1 (1.1)	1 (1.1)	-	-	-	-
酒さ	1 (1.1)	1 (1.1)	-	-	-	-
接触性皮膚炎	1 (1.1)	1 (1.1)	-	-	-	-
全身性そう痒症	1 (1.1)	-	1 (1.1)	-	-	-
脱毛症	1 (1.1)	1 (1.1)	-	-	-	-
斑状丘疹状皮疹	1 (1.1)	1 (1.1)	-	-	-	-
皮膚潰瘍	1 (1.1)	-	1 (1.1)	-	-	-
皮膚剥脱	1 (1.1)	1 (1.1)	-	-	-	-
皮膚反応	1 (1.1)	1 (1.1)	-	-	-	-
皮膚病変	1 (1.1)	1 (1.1)	-	-	-	-
冷汗	1 (1.1)	-	-	1 (1.1)	-	-
Total Number of AEs	42	27	9	6	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	28 (32.2)	19 (21.8)	9 (10.3)	2 (2.3)	-	-
背部痛	8 (9.2)	4 (4.6)	3 (3.4)	1 (1.1)	-	-
筋肉痛	7 (8.0)	4 (4.6)	3 (3.4)	-	-	-
関節痛	4 (4.6)	3 (3.4)	1 (1.1)	-	-	-
筋骨格痛	4 (4.6)	2 (2.3)	2 (2.3)	-	-	-
四肢痛	4 (4.6)	3 (3.4)	1 (1.1)	-	-	-
頚部痛	2 (2.3)	-	1 (1.1)	1 (1.1)	-	-
外骨腫	1 (1.1)	1 (1.1)	-	-	-	-
筋骨格系胸痛	1 (1.1)	1 (1.1)	-	-	-	-
筋痙縮	1 (1.1)	1 (1.1)	-	-	-	-
肩回旋筋腱板症候群	1 (1.1)	-	1 (1.1)	-	-	-
骨痛	1 (1.1)	-	-	1 (1.1)	-	-
重感	1 (1.1)	1 (1.1)	-	-	-	-
椎間板障害	1 (1.1)	1 (1.1)	-	-	-	-
変形性関節症	1 (1.1)	1 (1.1)	-	-	-	-
腋窩腫瘤	1 (1.1)	1 (1.1)	-	-	-	-
腱痛	1 (1.1)	1 (1.1)	-	-	-	-
巣径部痛	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	40	25	12	3	-	-

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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
心臓障害						
Total Pts With at Least one AE	16 (18.4)	6 (6.9)	6 (6.9)	4 (4.6)	-	-
頻脈	8 (9.2)	2 (2.3)	3 (3.4)	3 (3.4)	-	-
徐脈	2 (2.3)	2 (2.3)	-	-	-	-
心房細動	2 (2.3)	-	1 (1.1)	1 (1.1)	-	-
動悸	2 (2.3)	2 (2.3)	-	-	-	-
冠動脈疾患	1 (1.1)	-	1 (1.1)	-	-	-
狭心症	1 (1.1)	-	-	1 (1.1)	-	-
上室性不整脈	1 (1.1)	-	1 (1.1)	-	-	-
不整脈	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	18	6	7	5	-	-
眼障害						
Total Pts With at Least one AE	12 (13.8)	9 (10.3)	3 (3.4)	-	-	-
眼充血	2 (2.3)	2 (2.3)	-	-	-	-
結膜炎	2 (2.3)	-	2 (2.3)	-	-	-
白内障	2 (2.3)	2 (2.3)	-	-	-	-
一過性視力低下	1 (1.1)	1 (1.1)	-	-	-	-
眼運動障害	1 (1.1)	1 (1.1)	-	-	-	-
眼乾燥	1 (1.1)	1 (1.1)	-	-	-	-
眼刺激	1 (1.1)	1 (1.1)	-	-	-	-
眼出血	1 (1.1)	1 (1.1)	-	-	-	-
眼痛	1 (1.1)	-	1 (1.1)	-	-	-
強膜炎	1 (1.1)	-	1 (1.1)	-	-	-
結膜充血	1 (1.1)	1 (1.1)	-	-	-	-
視力障害	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	15	11	4	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
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ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
代謝および栄養障害						
Total Pts With at Least one AE	12 (13.8)	12 (13.8)	-	2 (2.3)	-	-
食欲減退	8 (9.2)	8 (9.2)	-	-	-	-
低マグネシウム血症	2 (2.3)	2 (2.3)	-	-	-	-
ビタミンＢ１２欠乏	1 (1.1)	1 (1.1)	-	-	-	-
高カルシウム血症	1 (1.1)	-	-	1 (1.1)	-	-
高血糖	1 (1.1)	1 (1.1)	-	-	-	-
水分過負荷	1 (1.1)	1 (1.1)	-	-	-	-
低カリウム血症	1 (1.1)	-	-	1 (1.1)	-	-
Total Number of AEs	15	13	-	2	-	-
精神障害						
Total Pts With at Least one AE	12 (13.8)	9 (10.3)	2 (2.3)	1 (1.1)	-	-
不眠症	6 (6.9)	5 (5.7)	1 (1.1)	-	-	-
不安	3 (3.4)	3 (3.4)	-	-	-	-
うつ病	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
アルコール症	1 (1.1)	1 (1.1)	-	-	-	-
落ち着きのなさ	1 (1.1)	-	-	1 (1.1)	-	-
Total Number of AEs	13	10	2	1	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	9 (10.3)	-	2 (2.3)	4 (4.6)	3 (3.4)	-
好中球減少症	3 (3.4)	-	-	2 (2.3)	1 (1.1)	-
発熱性好中球減少症	3 (3.4)	-	-	2 (2.3)	1 (1.1)	-
血小板減少症	1 (1.1)	-	1 (1.1)	-	-	-
好酸球増加症	1 (1.1)	-	-	-	1 (1.1)	-
貧血	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	9	-	2	4	3	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
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）						
Total Pts With at Least one AE	8 (9.2)	6 (6.9)	1 (1.1)	1 (1.1)	-	-
基底細胞癌	2 (2.3)	1 (1.1)	-	1 (1.1)	-	-
喉頭の良性新生物	1 (1.1)	-	1 (1.1)	-	-	-
子宮平滑筋腫	1 (1.1)	1 (1.1)	-	-	-	-
脂肪腫	1 (1.1)	1 (1.1)	-	-	-	-
唾液腺腫	1 (1.1)	1 (1.1)	-	-	-	-
皮膚癌	1 (1.1)	1 (1.1)	-	-	-	-
皮膚乳頭腫	1 (1.1)	1 (1.1)	-	-	-	-
良性腺腫	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	9	7	1	1	-	-
臨床検査						
Total Pts With at Least one AE	8 (9.2)	5 (5.7)	1 (1.1)	3 (3.4)	-	-
体重減少	2 (2.3)	2 (2.3)	-	-	-	-
ヘモグロビン減少	1 (1.1)	-	-	1 (1.1)	-	-
β２ミクログロブリン増加	1 (1.1)	-	1 (1.1)	-	-	-
一酸化炭素拡散能減少	1 (1.1)	-	-	1 (1.1)	-	-
血中ブドウ糖増加	1 (1.1)	1 (1.1)	-	-	-	-
血中尿酸増加	1 (1.1)	1 (1.1)	-	-	-	-
好中球数減少	1 (1.1)	-	-	1 (1.1)	-	-
酸素飽和度低下	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	9	5	1	3	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:59:21

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
免疫系障害						
Total Pts With at Least one AE	6 (6.9)	3 (3.4)	3 (3.4)	-	-	-
低γグロブリン血症	3 (3.4)	1 (1.1)	2 (2.3)	-	-	-
過敏症	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
季節性アレルギー	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	6	3	3	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	4 (4.6)	3 (3.4)	1 (1.1)	-	-	-
回転性めまい	1 (1.1)	1 (1.1)	-	-	-	-
耳の障害	1 (1.1)	-	1 (1.1)	-	-	-
耳痛	1 (1.1)	1 (1.1)	-	-	-	-
聴力低下	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	4	3	1	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	4 (4.6)	1 (1.1)	2 (2.3)	1 (1.1)	-	-
腎結石症	1 (1.1)	-	-	1 (1.1)	-	-
腎仙痛	1 (1.1)	-	1 (1.1)	-	-	-
腎不全	1 (1.1)	1 (1.1)	-	-	-	-
頻尿	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	4	1	2	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0032p_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
生殖系および乳房障害						
Total Pts With at Least one AE	3 (3.4)	2 (2.3)	-	-	-	-
骨盤静脈瘤	1 (1.1)	1 (1.1)	-	-	-	-
子宮ポリープ	1 (1.1)	-	-	-	-	-
卵巣腫瘤	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	3	2	-	-	-	-
Body System NOT DEFINED						
Total Pts With at Least one AE	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
<NO INFORMATION PROVIDED>	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
Total Number of AEs	2	1	1	-	-	-
内分泌障害						
Total Pts With at Least one AE	1 (1.1)	1 (1.1)	-	-	-	-
甲状腺腫	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
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[5.3.5.3-1 ae17_0032p_sa を再掲]

表 2.7.6.2.1.7-2　因果関係が否定できないすべての有害事象（BO21003試験，Phase II，再発・治療抵抗性 NHL 患者）

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	51 (59.3)	35 (40.7)	26 (30.2)	8 (9.3)	3 (3.5)	-
Total Number of AEs	215	103	85	24	3	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	44 (51.2)	23 (26.7)	17 (19.8)	4 (4.7)	-	-
注入に伴う反応	44 (51.2)	23 (26.7)	17 (19.8)	4 (4.7)	-	-
頭部損傷	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	45	23	17	5	-	-
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	29 (33.7)	19 (22.1)	11 (12.8)	3 (3.5)	-	-
悪寒	13 (15.1)	8 (9.3)	3 (3.5)	2 (2.3)	-	-
発熱	11 (12.8)	7 (8.1)	3 (3.5)	1 (1.2)	-	-
疲労	7 (8.1)	4 (4.7)	3 (3.5)	-	-	-
インフルエンザ様疾患	2 (2.3)	2 (2.3)	-	-	-	-
顔面浮腫	2 (2.3)	-	2 (2.3)	-	-	-
胸痛	2 (2.3)	-	2 (2.3)	-	-	-
胸部不快感	1 (1.2)	-	1 (1.2)	-	-	-
倦怠感	1 (1.2)	1 (1.2)	-	-	-	-
腫脹	1 (1.2)	-	-	1 (1.2)	-	-
浮腫	1 (1.2)	1 (1.2)	-	-	-	-
無力症	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	42	24	14	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	17 (19.8)	9 (10.5)	9 (10.5)	1 (1.2)	-	-
咽喉刺激感	7 (8.1)	5 (5.8)	2 (2.3)	-	-	-
咳嗽	4 (4.7)	1 (1.2)	3 (3.5)	-	-	-
呼吸困難	3 (3.5)	1 (1.2)	2 (2.3)	-	-	-
喉頭刺激感	3 (3.5)	1 (1.2)	2 (2.3)	-	-	-
咽頭浮腫	2 (2.3)	-	1 (1.2)	1 (1.2)	-	-
咽喉絞扼感	1 (1.2)	1 (1.2)	-	-	-	-
気管支痙攣	1 (1.2)	-	1 (1.2)	-	-	-
口腔咽頭痛	1 (1.2)	-	1 (1.2)	-	-	-
鼻閉塞	1 (1.2)	-	1 (1.2)	-	-	-
喘鳴	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	24	9	14	1	-	-
胃腸障害						
Total Pts With at Least one AE	16 (18.6)	11 (12.8)	6 (7.0)	-	-	-
悪心	9 (10.5)	5 (5.8)	4 (4.7)	-	-	-
嘔吐	4 (4.7)	2 (2.3)	2 (2.3)	-	-	-
下痢	3 (3.5)	3 (3.5)	-	-	-	-
下腹部痛	1 (1.2)	-	1 (1.2)	-	-	-
鼓腸	1 (1.2)	1 (1.2)	-	-	-	-
口の錯感覚	1 (1.2)	-	1 (1.2)	-	-	-
口内炎	1 (1.2)	1 (1.2)	-	-	-	-
歯肉炎	1 (1.2)	1 (1.2)	-	-	-	-
腹痛	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	22	14	8	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	15 (17.4)	7 (8.1)	6 (7.0)	2 (2.3)	-	-
潮紅	8 (9.3)	3 (3.5)	4 (4.7)	1 (1.2)	-	-
低血圧	4 (4.7)	1 (1.2)	2 (2.3)	1 (1.2)	-	-
高血圧	3 (3.5)	2 (2.3)	1 (1.2)	-	-	-
静脈痛	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	16	7	7	2	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	11 (12.8)	6 (7.0)	5 (5.8)	1 (1.2)	-	-
そう痒症	6 (7.0)	5 (5.8)	1 (1.2)	-	-	-
発疹	4 (4.7)	1 (1.2)	2 (2.3)	1 (1.2)	-	-
蕁麻疹	2 (2.3)	-	2 (2.3)	-	-	-
接触性皮膚炎	1 (1.2)	1 (1.2)	-	-	-	-
多汗症	1 (1.2)	-	1 (1.2)	-	-	-
斑状丘疹状皮疹	1 (1.2)	1 (1.2)	-	-	-	-
冷汗	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	16	9	6	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49 (3 of 13)

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	11 (12.8)	7 (8.1)	2 (2.3)	3 (3.5)	-	-
浮動性めまい	3 (3.5)	3 (3.5)	-	-	-	-
失神	2 (2.3)	-	-	2 (2.3)	-	-
頭痛	2 (2.3)	1 (1.2)	1 (1.2)	-	-	-
副鼻腔炎に伴う頭痛	2 (2.3)	1 (1.2)	-	1 (1.2)	-	-
錯感覚	1 (1.2)	1 (1.2)	-	-	-	-
失神寸前の状態	1 (1.2)	-	1 (1.2)	-	-	-
末梢性感覚ニューロパチー	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	12	7	2	3	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	8 (9.3)	1 (1.2)	3 (3.5)	2 (2.3)	3 (3.5)	-
好中球減少症	5 (5.8)	-	1 (1.2)	1 (1.2)	3 (3.5)	-
発熱性好中球減少症	2 (2.3)	-	1 (1.2)	1 (1.2)	-	-
リンパ節症	1 (1.2)	-	1 (1.2)	-	-	-
血小板減少症	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	9	1	3	2	3	-
感染症および寄生虫症						
Total Pts With at Least one AE	7 (8.1)	3 (3.5)	3 (3.5)	1 (1.2)	-	-
上気道感染	3 (3.5)	2 (2.3)	1 (1.2)	-	-	-
帯状疱疹	2 (2.3)	-	2 (2.3)	-	-	-
気管支炎	1 (1.2)	-	1 (1.2)	-	-	-
鼻炎	1 (1.2)	1 (1.2)	-	-	-	-
副鼻腔炎	1 (1.2)	1 (1.2)	-	-	-	-
蜂巣炎	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	9	4	4	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49 (4 of 13)

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	5 (5.8)	2 (2.3)	2 (2.3)	1 (1.2)	-	-
背部痛	3 (3.5)	1 (1.2)	1 (1.2)	1 (1.2)	-	-
関節痛	1 (1.2)	-	1 (1.2)	-	-	-
筋肉痛	1 (1.2)	1 (1.2)	-	-	-	-
筋痙縮	1 (1.2)	-	1 (1.2)	-	-	-
肛径部痛	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	7	2	3	2	-	-
心臓障害						
Total Pts With at Least one AE	3 (3.5)	2 (2.3)	-	1 (1.2)	-	-
頻脈	2 (2.3)	1 (1.2)	-	1 (1.2)	-	-
動悸	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	3	2	-	1	-	-
代謝および栄養障害						
Total Pts With at Least one AE	3 (3.5)	1 (1.2)	1 (1.2)	1 (1.2)	-	-
食欲減退	2 (2.3)	1 (1.2)	1 (1.2)	-	-	-
高尿酸血症	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	3	1	1	1	-	-
眼障害						
Total Pts With at Least one AE	2 (2.3)	-	2 (2.3)	-	-	-
結膜炎	2 (2.3)	-	2 (2.3)	-	-	-
Total Number of AEs	2	-	2	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49 (5 of 13)

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RITUXIMAB; N = 86

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
肝胆道系障害						
Total Pts With at Least one AE	1 (1.2)	-	1 (1.2)	1 (1.2)	-	-
肝障害	1 (1.2)	-	-	1 (1.2)	-	-
胆汁うっ滞性肝炎	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	2	-	1	1	-	-
外科および内科処置						
Total Pts With at Least one AE	1 (1.2)	-	1 (1.2)	-	-	-
デンタルケア	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	1	-	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	1 (1.2)	-	1 (1.2)	-	-	-
耳鳴	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	1	-	1	-	-	-
臨床検査						
Total Pts With at Least one AE	1 (1.2)	-	1 (1.2)	-	-	-
体重減少	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	75 (86.2)	46 (52.9)	38 (43.7)	16 (18.4)	2 (2.3)	-
Total Number of AEs	349	148	132	64	5	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	64 (73.6)	28 (32.2)	26 (29.9)	9 (10.3)	1 (1.1)	-
注入に伴う反応	64 (73.6)	28 (32.2)	26 (29.9)	9 (10.3)	1 (1.1)	-
Total Number of AEs	64	28	26	9	1	-
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	55 (63.2)	27 (31.0)	25 (28.7)	8 (9.2)	-	-
悪寒	27 (31.0)	9 (10.3)	13 (14.9)	5 (5.7)	-	-
発熱	24 (27.6)	13 (14.9)	8 (9.2)	3 (3.4)	-	-
疲労	12 (13.8)	7 (8.0)	5 (5.7)	-	-	-
胸部不快感	3 (3.4)	1 (1.1)	-	2 (2.3)	-	-
倦怠感	3 (3.4)	2 (2.3)	1 (1.1)	-	-	-
無力症	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
胸痛	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	72	33	29	10	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49 (7 of 13)

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	31 (35.6)	13 (14.9)	13 (14.9)	5 (5.7)	1 (1.1)	-
低血圧	18 (20.7)	9 (10.3)	3 (3.4)	5 (5.7)	1 (1.1)	-
潮紅	10 (11.5)	3 (3.4)	5 (5.7)	2 (2.3)	-	-
高血圧	8 (9.2)	2 (2.3)	6 (6.9)	-	-	-
起立性低血圧	1 (1.1)	-	1 (1.1)	-	-	-
蒼白	1 (1.1)	-	-	1 (1.1)	-	-
Total Number of AEs	38	14	15	8	1	-
胃腸障害						
Total Pts With at Least one AE	25 (28.7)	15 (17.2)	9 (10.3)	2 (2.3)	1 (1.1)	-
悪心	16 (18.4)	10 (11.5)	3 (3.4)	2 (2.3)	1 (1.1)	-
嘔吐	7 (8.0)	3 (3.4)	4 (4.6)	-	-	-
便秘	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
下痢	1 (1.1)	1 (1.1)	-	-	-	-
鼓腸	1 (1.1)	1 (1.1)	-	-	-	-
口内炎	1 (1.1)	-	1 (1.1)	-	-	-
上腹部痛	1 (1.1)	1 (1.1)	-	-	-	-
腹痛	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	30	17	10	2	1	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49 (8 of 13)

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	21 (24.1)	8 (9.2)	9 (10.3)	5 (5.7)	-	-
呼吸困難	13 (14.9)	3 (3.4)	5 (5.7)	5 (5.7)	-	-
咳嗽	6 (6.9)	4 (4.6)	1 (1.1)	1 (1.1)	-	-
咽喉刺激感	4 (4.6)	2 (2.3)	2 (2.3)	-	-	-
気管支痙攣	4 (4.6)	1 (1.1)	1 (1.1)	2 (2.3)	-	-
喉頭浮腫	2 (2.3)	-	-	2 (2.3)	-	-
上気道分泌増加	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
低酸素症	2 (2.3)	-	-	2 (2.3)	-	-
気管支拡張症	1 (1.1)	1 (1.1)	-	-	-	-
口腔咽頭痛	1 (1.1)	-	1 (1.1)	-	-	-
喉頭刺激感	1 (1.1)	1 (1.1)	-	-	-	-
上気道咳症候群	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	37	14	11	12	-	-
神経系障害						
Total Pts With at Least one AE	19 (21.8)	7 (8.0)	10 (11.5)	3 (3.4)	1 (1.1)	-
頭痛	11 (12.6)	4 (4.6)	6 (6.9)	1 (1.1)	-	-
浮動性めまい	7 (8.0)	1 (1.1)	4 (4.6)	2 (2.3)	-	-
意識消失	1 (1.1)	-	-	-	1 (1.1)	-
錯感覚	1 (1.1)	1 (1.1)	-	-	-	-
平衡障害	1 (1.1)	1 (1.1)	-	-	-	-
末梢性運動ニューロパチー	1 (1.1)	-	-	1 (1.1)	-	-
Total Number of AEs	22	7	10	4	1	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49 (9 of 13)

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	14 (16.1)	6 (6.9)	6 (6.9)	2 (2.3)	-	-
筋肉痛	4 (4.6)	1 (1.1)	3 (3.4)	-	-	-
関節痛	3 (3.4)	2 (2.3)	1 (1.1)	-	-	-
筋骨格痛	3 (3.4)	2 (2.3)	1 (1.1)	-	-	-
背部痛	3 (3.4)	-	2 (2.3)	1 (1.1)	-	-
頚部痛	2 (2.3)	-	1 (1.1)	1 (1.1)	-	-
四肢痛	2 (2.3)	2 (2.3)	-	-	-	-
筋骨格系胸痛	1 (1.1)	1 (1.1)	-	-	-	-
筋痙縮	1 (1.1)	1 (1.1)	-	-	-	-
骨痛	1 (1.1)	-	-	1 (1.1)	-	-
腱痛	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	21	10	8	3	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	13 (14.9)	8 (9.2)	2 (2.3)	4 (4.6)	-	-
発疹	7 (8.0)	4 (4.6)	1 (1.1)	2 (2.3)	-	-
多汗症	4 (4.6)	1 (1.1)	1 (1.1)	2 (2.3)	-	-
そう痒症	2 (2.3)	1 (1.1)	-	1 (1.1)	-	-
全身性そう痒症	1 (1.1)	-	1 (1.1)	-	-	-
斑状丘疹状皮疹	1 (1.1)	1 (1.1)	-	-	-	-
斑状皮疹	1 (1.1)	1 (1.1)	-	-	-	-
冷汗	1 (1.1)	-	-	1 (1.1)	-	-
蕁麻疹	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	18	9	3	6	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49 (10 of 13)

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	10 (11.5)	3 (3.4)	7 (8.0)	2 (2.3)	-	-
上気道感染	3 (3.4)	-	3 (3.4)	-	-	-
帯状疱疹	2 (2.3)	-	1 (1.1)	1 (1.1)	-	-
鼻咽頭炎	2 (2.3)	2 (2.3)	-	-	-	-
副鼻腔炎	2 (2.3)	-	2 (2.3)	-	-	-
ヘルペスウイルス感染	1 (1.1)	1 (1.1)	-	-	-	-
気管支炎	1 (1.1)	-	1 (1.1)	-	-	-
気道感染	1 (1.1)	-	-	1 (1.1)	-	-
細気管支炎	1 (1.1)	-	1 (1.1)	-	-	-
播種性帯状疱疹	1 (1.1)	-	1 (1.1)	-	-	-
鼻炎	1 (1.1)	-	1 (1.1)	-	-	-
慢性副鼻腔炎	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	16	3	11	2	-	-
心臓障害						
Total Pts With at Least one AE	9 (10.3)	3 (3.4)	3 (3.4)	3 (3.4)	-	-
頻脈	8 (9.2)	2 (2.3)	3 (3.4)	3 (3.4)	-	-
徐脈	1 (1.1)	1 (1.1)	-	-	-	-
不整脈	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	10	3	4	3	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	5 (5.7)	-	1 (1.1)	3 (3.4)	1 (1.1)	-
好中球減少症	3 (3.4)	-	-	2 (2.3)	1 (1.1)	-
血小板減少症	1 (1.1)	-	1 (1.1)	-	-	-
発熱性好中球減少症	1 (1.1)	-	-	1 (1.1)	-	-
Total Number of AEs	5	-	1	3	1	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49 (11 of 13)

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
眼障害						
Total Pts With at Least one AE	3 (3.4)	2 (2.3)	1 (1.1)	-	-	-
眼刺激	1 (1.1)	1 (1.1)	-	-	-	-
強膜炎	1 (1.1)	-	1 (1.1)	-	-	-
視力障害	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	3	2	1	-	-	-
精神障害						
Total Pts With at Least one AE	3 (3.4)	2 (2.3)	-	1 (1.1)	-	-
不安	2 (2.3)	2 (2.3)	-	-	-	-
落ち着きのなさ	1 (1.1)	-	-	1 (1.1)	-	-
Total Number of AEs	3	2	-	1	-	-
Body System NOT DEFINED						
Total Pts With at Least one AE	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
<NO INFORMATION PROVIDED>	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
Total Number of AEs	2	1	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
回転性めまい	1 (1.1)	1 (1.1)	-	-	-	-
耳の障害	1 (1.1)	-	1 (1.1)	-	-	-
Total Number of AEs	2	1	1	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	2 (2.3)	2 (2.3)	-	-	-	-
食欲減退	2 (2.3)	2 (2.3)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:53:49

ae17r_0032p_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21003 (T21003M) Phase II Primary
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 07OCT2011 Cutoff Date: 01SEP2011
Treatment: RO5072759; N = 87

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
免疫系障害						
Total Pts With at Least one AE	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
低γグロブリン血症	2 (2.3)	1 (1.1)	1 (1.1)	-	-	-
Total Number of AEs	2	1	1	-	-	-
臨床検査						
Total Pts With at Least one AE	2 (2.3)	1 (1.1)	-	1 (1.1)	-	-
好中球数減少	1 (1.1)	-	-	1 (1.1)	-	-
酸素飽和度低下	1 (1.1)	1 (1.1)	-	-	-	-
Total Number of AEs	2	1	-	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
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[5.3.5.3-1 ae17r_0032p_sa を再掲]

2.7.6.2.1.8　BO21000試験（GAUDI 試験）

(1)　再発・治療抵抗性患者対象部分

表 2.7.6.2.1.8-1　因果関係を問わないすべての有害事象（BO21000試験，再発・治療抵抗性 FL 患者，FC 療法群）

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC　　Center: ALL CENTERS
Snapshot Date: [redacted]　　Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC: N = 14

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	14 (100.0)	14 (100.0)	14 (100.0)	9 (64.3)	5 (35.7)	-
Total Number of AEs	158	64	69	20	5	-
胃腸障害						
Total Pts With at Least one AE	13 (92.9)	10 (71.4)	8 (57.1)	2 (14.3)	-	-
悪心	13 (92.9)	6 (42.9)	6 (42.9)	1 (7.1)	-	-
下痢	7 (50.0)	4 (28.6)	3 (21.4)	-	-	-
嘔吐	5 (35.7)	1 (7.1)	4 (28.6)	-	-	-
便秘	4 (28.6)	4 (28.6)	-	-	-	-
胃炎	1 (7.1)	1 (7.1)	-	-	-	-
壊死性口内炎	1 (7.1)	-	-	1 (7.1)	-	-
口腔内痛	1 (7.1)	-	-	1 (7.1)	-	-
嚥下障害	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	33	16	14	3	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41　　(1 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	11 (78.6)	5 (35.7)	11 (78.6)	-	-	-
発熱	8 (57.1)	4 (28.6)	4 (28.6)	-	-	-
悪寒	4 (28.6)	-	4 (28.6)	-	-	-
無力症	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
疲労	2 (14.3)	2 (14.3)	-	-	-	-
インフルエンザ様疾患	1 (7.1)	-	1 (7.1)	-	-	-
カテーテル留置部位炎症	1 (7.1)	-	1 (7.1)	-	-	-
胸痛	1 (7.1)	-	1 (7.1)	-	-	-
熱感	1 (7.1)	-	1 (7.1)	-	-	-
粘膜の炎症	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	22	7	15	-	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	10 (71.4)	-	1 (7.1)	7 (50.0)	5 (35.7)	-
好中球減少症	9 (64.3)	-	-	4 (28.6)	5 (35.7)	-
血小板減少症	3 (21.4)	-	-	3 (21.4)	-	-
貧血	2 (14.3)	-	-	2 (14.3)	-	-
汎血球減少症	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	15	-	1	9	5	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (2 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	9 (64.3)	4 (28.6)	8 (57.1)	3 (21.4)	-	-
下気道感染	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
上気道感染	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
インフルエンザ	1 (7.1)	-	1 (7.1)	-	-	-
ウイルス性胃腸炎	1 (7.1)	-	1 (7.1)	-	-	-
カンジダ症	1 (7.1)	-	1 (7.1)	-	-	-
胃腸炎	1 (7.1)	-	1 (7.1)	-	-	-
咽頭炎	1 (7.1)	1 (7.1)	-	-	-	-
気管支炎	1 (7.1)	-	-	1 (7.1)	-	-
限局性感染	1 (7.1)	1 (7.1)	-	-	-	-
好中球減少性敗血症	1 (7.1)	-	-	1 (7.1)	-	-
歯膿瘍	1 (7.1)	-	1 (7.1)	-	-	-
尿路感染	1 (7.1)	-	1 (7.1)	-	-	-
敗血症	1 (7.1)	-	-	1 (7.1)	-	-
鼻炎	1 (7.1)	-	1 (7.1)	-	-	-
膀胱炎	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	17	5	9	3	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	9 (64.3)	6 (42.9)	5 (35.7)	1 (7.1)	-	-
咳嗽	6 (42.9)	3 (21.4)	3 (21.4)	-	-	-
呼吸困難	4 (28.6)	3 (21.4)	-	1 (7.1)	-	-
口腔咽頭痛	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
喉頭刺激感	1 (7.1)	1 (7.1)	-	-	-	-
発声障害	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	15	9	5	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (3 of 23)

ae17_000rr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	9 (64.3)	5 (35.7)	3 (21.4)	2 (14.3)	-	-
頭痛	5 (35.7)	4 (28.6)	1 (7.1)	-	-	-
浮動性めまい	2 (14.3)	1 (7.1)	-	1 (7.1)	-	-
嗜眠	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
異常感覚	1 (7.1)	1 (7.1)	-	-	-	-
感覚鈍麻	1 (7.1)	1 (7.1)	-	-	-	-
小脳症候群	1 (7.1)	-	1 (7.1)	-	-	-
振戦	1 (7.1)	-	1 (7.1)	-	-	-
味覚異常	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	14	8	4	2	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	7 (50.0)	4 (28.6)	5 (35.7)	-	-	-
骨痛	2 (14.3)	-	2 (14.3)	-	-	-
筋骨格痛	1 (7.1)	-	1 (7.1)	-	-	-
筋力低下	1 (7.1)	1 (7.1)	-	-	-	-
筋痙縮	1 (7.1)	1 (7.1)	-	-	-	-
頚部痛	1 (7.1)	1 (7.1)	-	-	-	-
骨粗鬆症	1 (7.1)	-	1 (7.1)	-	-	-
四肢痛	1 (7.1)	-	1 (7.1)	-	-	-
脊椎炎	1 (7.1)	1 (7.1)	-	-	-	-
椎間板突出	1 (7.1)	-	1 (7.1)	-	-	-
背部痛	1 (7.1)	-	1 (7.1)	-	-	-
変形性関節症	1 (7.1)	1 (7.1)	-	-	-	-
変形性脊椎症	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	13	5	8	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (4 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
ほてり	1 (7.1)	-	1 (7.1)	-	-	-
起立性低血圧	1 (7.1)	1 (7.1)	-	-	-	-
静脈炎	1 (7.1)	-	1 (7.1)	-	-	-
低血圧	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	4	1	3	-	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
そう痒症	2 (14.3)	2 (14.3)	-	-	-	-
紅斑	2 (14.3)	2 (14.3)	-	-	-	-
発疹	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	5	4	1	-	-	-
精神障害						
Total Pts With at Least one AE	3 (21.4)	3 (21.4)	1 (7.1)	-	-	-
不安	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
不眠症	2 (14.3)	2 (14.3)	-	-	-	-
Total Number of AEs	4	3	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
臨床検査						
Total Pts With at Least one AE	3 (21.4)	2 (14.3)	1 (7.1)	1 (7.1)	-	-
γ－グルタミルトランスフェラーゼ増加	1 (7.1)	-	-	1 (7.1)	-	-
心雑音	1 (7.1)	1 (7.1)	-	-	-	-
体重減少	1 (7.1)	-	1 (7.1)	-	-	-
体重増加	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	4	2	1	1	-	-
心臓障害						
Total Pts With at Least one AE	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
徐脈	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
動悸	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	3	1	2	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
血液量減少症	1 (7.1)	-	1 (7.1)	-	-	-
食欲減退	1 (7.1)	1 (7.1)	-	-	-	-
食欲障害	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	3	1	2	-	-	-
眼障害						
Total Pts With at Least one AE	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
アレルギー性結膜炎	1 (7.1)	-	1 (7.1)	-	-	-
オキュラーサーフェス疾患	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	2	1	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (6 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
腎および尿路障害						
Total Pts With at Least one AE	1 (7.1)	-	1 (7.1)	1 (7.1)	-	-
腎結石症	1 (7.1)	-	-	1 (7.1)	-	-
排尿困難	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	2	-	1	1	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	1 (7.1)	1 (7.1)	-	-	-	-
半月板障害	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
免疫系障害						
Total Pts With at Least one AE	1 (7.1)	-	1 (7.1)	-	-	-
季節性アレルギー	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (7 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	14 (100.0)	14 (100.0)	14 (100.0)	9 (64.3)	6 (42.9)	2 (14.3)
Total Number of AEs	159	60	68	21	8	2
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	13 (92.9)	8 (57.1)	10 (71.4)	2 (14.3)	-	-
発熱	7 (50.0)	1 (7.1)	5 (35.7)	1 (7.1)	-	-
悪寒	5 (35.7)	1 (7.1)	3 (21.4)	1 (7.1)	-	-
疲労	5 (35.7)	2 (14.3)	3 (21.4)	-	-	-
無力症	4 (28.6)	3 (21.4)	1 (7.1)	-	-	-
胸痛	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
カテーテル留置部位紅斑	1 (7.1)	1 (7.1)	-	-	-	-
粘膜の炎症	1 (7.1)	-	1 (7.1)	-	-	-
浮腫	1 (7.1)	-	1 (7.1)	-	-	-
疼痛	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	28	9	16	3	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (8 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	10 (71.4)	9 (64.3)	5 (35.7)	1 (7.1)	-	-
悪心	10 (71.4)	7 (50.0)	3 (21.4)	-	-	-
便秘	6 (42.9)	3 (21.4)	3 (21.4)	-	-	-
下痢	2 (14.3)	2 (14.3)	-	-	-	-
アフタ性口内炎	1 (7.1)	-	1 (7.1)	-	-	-
痔核	1 (7.1)	-	-	1 (7.1)	-	-
上腹部痛	1 (7.1)	-	1 (7.1)	-	-	-
腹痛	1 (7.1)	-	1 (7.1)	-	-	-
嘔吐	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	23	12	10	1	-	-
神経系障害						
Total Pts With at Least one AE	10 (71.4)	7 (50.0)	4 (28.6)	1 (7.1)	-	1 (7.1)
頭痛	8 (57.1)	4 (28.6)	4 (28.6)	-	-	-
パーキンソン病	1 (7.1)	-	-	-	-	1 (7.1)
錯感覚	1 (7.1)	1 (7.1)	-	-	-	-
失神	1 (7.1)	-	-	1 (7.1)	-	-
多発ニューロパチー	1 (7.1)	1 (7.1)	-	-	-	-
体位性めまい	1 (7.1)	1 (7.1)	-	-	-	-
浮動性めまい	1 (7.1)	1 (7.1)	-	-	-	-
片側頭痛	1 (7.1)	-	1 (7.1)	-	-	-
末梢性ニューロパチー	1 (7.1)	1 (7.1)	-	-	-	-
味覚異常	1 (7.1)	1 (7.1)	-	-	-	-
嗜眠	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	18	11	5	1	-	1

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (9 of 23)

ae17_000rr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	8 (57.1)	2 (14.3)	5 (35.7)	5 (35.7)	-	-
気管支炎	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
カンジダ症	1 (7.1)	-	1 (7.1)	-	-	-
ノロウイルス性胃腸炎	1 (7.1)	-	1 (7.1)	-	-	-
下気道感染	1 (7.1)	-	-	1 (7.1)	-	-
感染	1 (7.1)	-	-	1 (7.1)	-	-
気道感染	1 (7.1)	1 (7.1)	-	-	-	-
好中球減少性敗血症	1 (7.1)	-	-	1 (7.1)	-	-
歯膿瘍	1 (7.1)	-	1 (7.1)	-	-	-
上気道感染	1 (7.1)	-	-	1 (7.1)	-	-
帯状疱疹	1 (7.1)	-	1 (7.1)	-	-	-
皮膚感染	1 (7.1)	-	1 (7.1)	-	-	-
鼻咽頭炎	1 (7.1)	1 (7.1)	-	-	-	-
副鼻腔炎	1 (7.1)	-	1 (7.1)	-	-	-
膀胱炎	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	15	2	7	6	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	8 (57.1)	-	1 (7.1)	4 (28.6)	5 (35.7)	-
好中球減少症	5 (35.7)	-	-	1 (7.1)	4 (28.6)	-
血小板減少症	4 (28.6)	-	-	3 (21.4)	1 (7.1)	-
発熱性好中球減少症	3 (21.4)	-	-	1 (7.1)	2 (14.3)	-
白血球減少症	1 (7.1)	-	-	1 (7.1)	-	-
貧血	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	14	-	1	6	7	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (10 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	7 (50.0)	5 (35.7)	4 (28.6)	1 (7.1)	1 (7.1)	1 (7.1)
咳嗽	4 (28.6)	3 (21.4)	1 (7.1)	-	-	-
呼吸困難	4 (28.6)	-	2 (14.3)	1 (7.1)	1 (7.1)	-
喉頭刺激感	2 (14.3)	-	2 (14.3)	-	-	-
咽喉刺激感	1 (7.1)	-	1 (7.1)	-	-	-
気管支痙攣	1 (7.1)	-	1 (7.1)	-	-	-
胸水	1 (7.1)	1 (7.1)	-	-	-	-
口腔咽頭痛	1 (7.1)	1 (7.1)	-	-	-	-
湿性咳嗽	1 (7.1)	-	1 (7.1)	-	-	-
非感染性副鼻腔炎	1 (7.1)	1 (7.1)	-	-	-	-
慢性閉塞性肺疾患	1 (7.1)	-	-	-	-	1 (7.1)
Total Number of AEs	17	6	8	1	1	1
筋骨格系および結合組織障害						
Total Pts With at Least one AE	6 (42.9)	3 (21.4)	3 (21.4)	-	-	-
関節痛	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
筋肉痛	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
四肢痛	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
筋骨格痛	1 (7.1)	1 (7.1)	-	-	-	-
筋痙縮	1 (7.1)	1 (7.1)	-	-	-	-
背部痛	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	10	6	4	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (11 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	6 (42.9)	2 (14.3)	4 (28.6)	-	-	-
高血圧	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
低血圧	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
Total Number of AEs	6	2	4	-	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	4 (28.6)	2 (14.3)	2 (14.3)	-	-	-
そう痒症	2 (14.3)	2 (14.3)	-	-	-	-
寝汗	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
発疹	1 (7.1)	1 (7.1)	-	-	-	-
皮膚亀裂	1 (7.1)	1 (7.1)	-	-	-	-
皮膚嚢腫	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	7	5	2	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	4 (28.6)	2 (14.3)	2 (14.3)	-	-	-
食欲減退	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
高コレステロール血症	1 (7.1)	1 (7.1)	-	-	-	-
体液貯留	1 (7.1)	-	1 (7.1)	-	-	-
痛風	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	5	2	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (12 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
心臓障害						
Total Pts With at Least one AE	4 (28.6)	1 (7.1)	2 (14.3)	1 (7.1)	-	-
頻脈	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
徐脈	1 (7.1)	-	1 (7.1)	-	-	-
不整脈	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	4	1	2	1	-	-
精神障害						
Total Pts With at Least one AE	3 (21.4)	2 (14.3)	2 (14.3)	-	-	-
不眠症	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
錯乱状態	1 (7.1)	1 (7.1)	-	-	-	-
睡眠障害	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	4	2	2	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	2 (14.3)	1 (7.1)	1 (7.1)	1 (7.1)	-	-
排尿困難	1 (7.1)	-	1 (7.1)	-	-	-
頻尿	1 (7.1)	-	-	1 (7.1)	-	-
夜間頻尿	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	3	1	1	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）						
Total Pts With at Least one AE	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
ボーエン病	1 (7.1)	-	1 (7.1)	-	-	-
扁平上皮癌	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	2	-	1	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (13 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
傷害、中毒および処置合併症						
Total Pts With at Least one AE	1 (7.1)	1 (7.1)	-	-	-	-
節足動物咬傷	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
免疫系障害						
Total Pts With at Least one AE	1 (7.1)	-	1 (7.1)	-	-	-
低γグロブリン血症	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	1	-	1	-	-	-
臨床検査						
Total Pts With at Least one AE	1 (7.1)	-	1 (7.1)	-	-	-
体重減少	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	28	(100.0)	28	(100.0)	28	(100.0)	18	(64.3)	11	(39.3)	2	(7.1)
Total Number of AEs	317		124		137		41		13		2	
一般・全身障害および投与部位の状態												
Total Pts With at Least one AE	24	(85.7)	13	(46.4)	21	(75.0)	2	(7.1)	-		-	
発熱	15	(53.6)	5	(17.9)	9	(32.1)	1	(3.6)	-		-	
悪寒	9	(32.1)	1	(3.6)	7	(25.0)	1	(3.6)	-		-	
疲労	7	(25.0)	4	(14.3)	3	(10.7)	-		-		-	
無力症	7	(25.0)	4	(14.3)	3	(10.7)	-		-		-	
胸痛	4	(14.3)	1	(3.6)	3	(10.7)	-		-		-	
粘膜の炎症	2	(7.1)	-		2	(7.1)	-		-		-	
インフルエンザ様疾患	1	(3.6)	-		1	(3.6)	-		-		-	
カテーテル留置部位炎症	1	(3.6)	-		1	(3.6)	-		-		-	
カテーテル留置部位紅斑	1	(3.6)	1	(3.6)	-		-		-		-	
熱感	1	(3.6)	-		1	(3.6)	-		-		-	
浮腫	1	(3.6)	-		1	(3.6)	-		-		-	
疼痛	1	(3.6)	-		-		1	(3.6)	-		-	
Total Number of AEs	50		16		31		3		-		-	

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	23 (82.1)	19 (67.9)	13 (46.4)	3 (10.7)	-	-
悪心	23 (82.1)	13 (46.4)	9 (32.1)	1 (3.6)	-	-
便秘	10 (35.7)	7 (25.0)	3 (10.7)	-	-	-
下痢	9 (32.1)	6 (21.4)	3 (10.7)	-	-	-
嘔吐	6 (21.4)	1 (3.6)	5 (17.9)	-	-	-
アフタ性口内炎	1 (3.6)	-	1 (3.6)	-	-	-
胃炎	1 (3.6)	1 (3.6)	-	-	-	-
壊死性口内炎	1 (3.6)	-	-	1 (3.6)	-	-
口腔内痛	1 (3.6)	-	-	1 (3.6)	-	-
痔核	1 (3.6)	-	-	1 (3.6)	-	-
上腹部痛	1 (3.6)	-	1 (3.6)	-	-	-
腹痛	1 (3.6)	-	1 (3.6)	-	-	-
嚥下障害	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	56	28	24	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (16 of 23)

ae17_000rr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	19 (67.9)	12 (42.9)	7 (25.0)	3 (10.7)	-	1 (3.6)
頭痛	13 (46.4)	8 (28.6)	5 (17.9)	-	-	-
浮動性めまい	3 (10.7)	2 (7.1)	-	1 (3.6)	-	-
嗜眠	3 (10.7)	1 (3.6)	1 (3.6)	1 (3.6)	-	-
味覚異常	2 (7.1)	2 (7.1)	-	-	-	-
パーキンソン病	1 (3.6)	-	-	-	-	1 (3.6)
異常感覚	1 (3.6)	1 (3.6)	-	-	-	-
感覚鈍麻	1 (3.6)	1 (3.6)	-	-	-	-
錯感覚	1 (3.6)	1 (3.6)	-	-	-	-
失神	1 (3.6)	-	-	1 (3.6)	-	-
小脳症候群	1 (3.6)	-	1 (3.6)	-	-	-
振戦	1 (3.6)	-	1 (3.6)	-	-	-
多発ニューロパチー	1 (3.6)	1 (3.6)	-	-	-	-
体位性めまい	1 (3.6)	1 (3.6)	-	-	-	-
片側頭痛	1 (3.6)	-	1 (3.6)	-	-	-
末梢性ニューロパチー	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	32	19	9	3	-	1
血液およびリンパ系障害						
Total Pts With at Least one AE	18 (64.3)	-	2 (7.1)	11 (39.3)	10 (35.7)	-
好中球減少症	14 (50.0)	-	-	5 (17.9)	9 (32.1)	-
血小板減少症	7 (25.0)	-	-	6 (21.4)	1 (3.6)	-
発熱性好中球減少症	3 (10.7)	-	-	1 (3.6)	2 (7.1)	-
貧血	3 (10.7)	-	1 (3.6)	2 (7.1)	-	-
白血球減少症	1 (3.6)	-	-	1 (3.6)	-	-
汎血球減少症	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	29	-	2	15	12	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (17 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	17 (60.7)	6 (21.4)	13 (46.4)	8 (28.6)	-	-
下気道感染	3 (10.7)	1 (3.6)	1 (3.6)	1 (3.6)	-	-
気管支炎	3 (10.7)	-	1 (3.6)	2 (7.1)	-	-
上気道感染	3 (10.7)	1 (3.6)	1 (3.6)	1 (3.6)	-	-
カンジダ症	2 (7.1)	-	2 (7.1)	-	-	-
好中球減少性敗血症	2 (7.1)	-	-	2 (7.1)	-	-
歯膿瘍	2 (7.1)	-	2 (7.1)	-	-	-
膀胱炎	2 (7.1)	1 (3.6)	-	1 (3.6)	-	-
インフルエンザ	1 (3.6)	-	1 (3.6)	-	-	-
ウイルス性胃腸炎	1 (3.6)	-	1 (3.6)	-	-	-
ノロウイルス性胃腸炎	1 (3.6)	-	1 (3.6)	-	-	-
胃腸炎	1 (3.6)	-	1 (3.6)	-	-	-
咽頭炎	1 (3.6)	1 (3.6)	-	-	-	-
感染	1 (3.6)	-	-	1 (3.6)	-	-
気道感染	1 (3.6)	1 (3.6)	-	-	-	-
限局性感染	1 (3.6)	1 (3.6)	-	-	-	-
帯状疱疹	1 (3.6)	-	1 (3.6)	-	-	-
尿路感染	1 (3.6)	-	1 (3.6)	-	-	-
敗血症	1 (3.6)	-	-	1 (3.6)	-	-
皮膚感染	1 (3.6)	-	1 (3.6)	-	-	-
鼻咽頭炎	1 (3.6)	1 (3.6)	-	-	-	-
鼻炎	1 (3.6)	-	1 (3.6)	-	-	-
副鼻腔炎	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	32	7	16	9	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (18 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	16 (57.1)	11 (39.3)	9 (32.1)	2 (7.1)	1 (3.6)	1 (3.6)
咳嗽	10 (35.7)	6 (21.4)	4 (14.3)	-	-	-
呼吸困難	8 (28.6)	3 (10.7)	2 (7.1)	2 (7.1)	1 (3.6)	-
口腔咽頭痛	4 (14.3)	2 (7.1)	2 (7.1)	-	-	-
喉頭刺激感	3 (10.7)	1 (3.6)	2 (7.1)	-	-	-
咽喉刺激感	1 (3.6)	-	1 (3.6)	-	-	-
気管支痙攣	1 (3.6)	-	1 (3.6)	-	-	-
胸水	1 (3.6)	1 (3.6)	-	-	-	-
湿性咳嗽	1 (3.6)	-	1 (3.6)	-	-	-
発声障害	1 (3.6)	1 (3.6)	-	-	-	-
非感染性副鼻腔炎	1 (3.6)	1 (3.6)	-	-	-	-
慢性閉塞性肺疾患	1 (3.6)	-	-	-	-	1 (3.6)
Total Number of AEs	32	15	13	2	1	1

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (19 of 23)

ae17_000rr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	13 (46.4)	7 (25.0)	8 (28.6)	-	-	-
関節痛	3 (10.7)	1 (3.6)	2 (7.1)	-	-	-
四肢痛	3 (10.7)	1 (3.6)	2 (7.1)	-	-	-
筋骨格痛	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
筋肉痛	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
筋痙縮	2 (7.1)	2 (7.1)	-	-	-	-
骨痛	2 (7.1)	-	2 (7.1)	-	-	-
背部痛	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
筋力低下	1 (3.6)	1 (3.6)	-	-	-	-
頚部痛	1 (3.6)	1 (3.6)	-	-	-	-
骨粗鬆症	1 (3.6)	-	1 (3.6)	-	-	-
脊椎炎	1 (3.6)	1 (3.6)	-	-	-	-
椎間板突出	1 (3.6)	-	1 (3.6)	-	-	-
変形性関節症	1 (3.6)	1 (3.6)	-	-	-	-
変形性脊椎症	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	23	11	12	-	-	-
血管障害						
Total Pts With at Least one AE	10 (35.7)	3 (10.7)	7 (25.0)	-	-	-
低血圧	4 (14.3)	1 (3.6)	3 (10.7)	-	-	-
高血圧	3 (10.7)	1 (3.6)	2 (7.1)	-	-	-
ほてり	1 (3.6)	-	1 (3.6)	-	-	-
起立性低血圧	1 (3.6)	1 (3.6)	-	-	-	-
静脈炎	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	10	3	7	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (20 of 23)

ae17_000rr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	7 (25.0)	4 (14.3)	3 (10.7)	-	-	-
そう痒症	4 (14.3)	4 (14.3)	-	-	-	-
紅斑	2 (7.1)	2 (7.1)	-	-	-	-
寝汗	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
発疹	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
皮膚亀裂	1 (3.6)	1 (3.6)	-	-	-	-
皮膚嚢腫	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	12	9	3	-	-	-
心臓障害						
Total Pts With at Least one AE	7 (25.0)	2 (7.1)	4 (14.3)	1 (3.6)	-	-
徐脈	3 (10.7)	1 (3.6)	2 (7.1)	-	-	-
頻脈	2 (7.1)	-	1 (3.6)	1 (3.6)	-	-
動悸	1 (3.6)	-	1 (3.6)	-	-	-
不整脈	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	7	2	4	1	-	-
精神障害						
Total Pts With at Least one AE	6 (21.4)	5 (17.9)	3 (10.7)	-	-	-
不眠症	4 (14.3)	3 (10.7)	1 (3.6)	-	-	-
不安	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
錯乱状態	1 (3.6)	1 (3.6)	-	-	-	-
睡眠障害	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	8	5	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (21 of 23)

ae17_OOOrr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
代謝および栄養障害						
Total Pts With at Least one AE	6 (21.4)	3 (10.7)	3 (10.7)	-	-	-
食欲減退	3 (10.7)	2 (7.1)	1 (3.6)	-	-	-
血液量減少症	1 (3.6)	-	1 (3.6)	-	-	-
高コレステロール血症	1 (3.6)	1 (3.6)	-	-	-	-
食欲障害	1 (3.6)	-	1 (3.6)	-	-	-
体液貯留	1 (3.6)	-	1 (3.6)	-	-	-
痛風	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	8	3	5	-	-	-
臨床検査						
Total Pts With at Least one AE	4 (14.3)	2 (7.1)	2 (7.1)	1 (3.6)	-	-
体重減少	2 (7.1)	-	2 (7.1)	-	-	-
γ－グルタミルトランスフェラーゼ増加	1 (3.6)	-	-	1 (3.6)	-	-
心雑音	1 (3.6)	1 (3.6)	-	-	-	-
体重増加	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	5	2	2	1	-	-
腎および尿路障害						
Total Pts With at Least one AE	3 (10.7)	1 (3.6)	2 (7.1)	2 (7.1)	-	-
排尿困難	2 (7.1)	-	2 (7.1)	-	-	-
腎結石症	1 (3.6)	-	-	1 (3.6)	-	-
頻尿	1 (3.6)	-	-	1 (3.6)	-	-
夜間頻尿	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	5	1	2	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (22 of 23)

ae17_000rr_sj Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
眼障害						
Total Pts With at Least one AE	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
アレルギー性結膜炎	1 (3.6)	-	1 (3.6)	-	-	-
オキュラーサーフェス疾患	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	2	1	1	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	2 (7.1)	2 (7.1)	-	-	-	-
節足動物咬傷	1 (3.6)	1 (3.6)	-	-	-	-
半月板障害	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
免疫系障害						
Total Pts With at Least one AE	2 (7.1)	-	2 (7.1)	-	-	-
季節性アレルギー	1 (3.6)	-	1 (3.6)	-	-	-
低γグロブリン血症	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	2	-	2	-	-	-
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）						
Total Pts With at Least one AE	2 (7.1)	-	1 (3.6)	1 (3.6)	-	-
ボーエン病	1 (3.6)	-	1 (3.6)	-	-	-
扁平上皮癌	1 (3.6)	-	-	1 (3.6)	-	-
Total Number of AEs	2	-	1	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:55:41 (23 of 23)

[5.3.5.3-1 ae17_000rr_sj を再掲]

表 2.7.6.2.1.8-2 因果関係が否定できないすべての有害事象（B021000試験，再発・治療抵抗性FL患者，FC療法群）

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	14 (100.0)	11 (78.6)	13 (92.9)	9 (64.3)	5 (35.7)	-
Total Number of AEs	85	25	41	14	5	-
胃腸障害						
Total Pts With at Least one AE	11 (78.6)	6 (42.9)	6 (42.9)	2 (14.3)	-	-
悪心	9 (64.3)	2 (14.3)	6 (42.9)	1 (7.1)	-	-
嘔吐	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
下痢	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
便秘	3 (21.4)	3 (21.4)	-	-	-	-
胃炎	1 (7.1)	1 (7.1)	-	-	-	-
壊死性口内炎	1 (7.1)	-	-	1 (7.1)	-	-
口腔内痛	1 (7.1)	-	-	1 (7.1)	-	-
嚥下障害	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	23	9	11	3	-	-
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	10 (71.4)	3 (21.4)	10 (71.4)	-	-	-
発熱	5 (35.7)	3 (21.4)	2 (14.3)	-	-	-
悪寒	4 (28.6)	-	4 (28.6)	-	-	-
無力症	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
インフルエンザ様疾患	1 (7.1)	-	1 (7.1)	-	-	-
胸痛	1 (7.1)	-	1 (7.1)	-	-	-
熱感	1 (7.1)	-	1 (7.1)	-	-	-
粘膜の炎症	1 (7.1)	-	1 (7.1)	-	-	-
疲労	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	17	5	12	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46

ae17r_000rr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	10 (71.4)	-	1 (7.1)	7 (50.0)	5 (35.7)	-
好中球減少症	9 (64.3)	-	-	4 (28.6)	5 (35.7)	-
血小板減少症	2 (14.3)	-	-	2 (14.3)	-	-
汎血球減少症	1 (7.1)	-	1 (7.1)	-	-	-
貧血	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	13	-	1	7	5	-
神経系障害						
Total Pts With at Least one AE	7 (50.0)	3 (21.4)	3 (21.4)	2 (14.3)	-	-
頭痛	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
浮動性めまい	2 (14.3)	1 (7.1)	-	1 (7.1)	-	-
嗜眠	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
振戦	1 (7.1)	-	1 (7.1)	-	-	-
味覚異常	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	9	4	3	2	-	-
感染症および寄生虫症						
Total Pts With at Least one AE	7 (50.0)	2 (14.3)	5 (35.7)	1 (7.1)	-	-
下気道感染	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
ウイルス性胃腸炎	1 (7.1)	-	1 (7.1)	-	-	-
カンジダ症	1 (7.1)	-	1 (7.1)	-	-	-
咽頭炎	1 (7.1)	1 (7.1)	-	-	-	-
気管支炎	1 (7.1)	-	-	1 (7.1)	-	-
上気道感染	1 (7.1)	-	1 (7.1)	-	-	-
鼻炎	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	8	2	5	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (2 of 14)

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
ほてり	1 (7.1)	-	1 (7.1)	-	-	-
起立性低血圧	1 (7.1)	1 (7.1)	-	-	-	-
静脈炎	1 (7.1)	-	1 (7.1)	-	-	-
低血圧	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	4	1	3	-	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
口腔咽頭痛	2 (14.3)	-	2 (14.3)	-	-	-
喉頭刺激感	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	3	1	2	-	-	-
心臓障害						
Total Pts With at Least one AE	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
徐脈	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
動悸	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	3	1	2	-	-	-
臨床検査						
Total Pts With at Least one AE	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
γ－グルタミルトランスフェラーゼ増加	1 (7.1)	-	-	1 (7.1)	-	-
体重減少	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	2	-	1	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (3 of 14)

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
眼障害						
Total Pts With at Least one AE	1 (7.1)	1 (7.1)	-	-	-	-
オキュラーサーフェス疾患	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	1 (7.1)	-	1 (7.1)	-	-	-
背部痛	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	1	-	1	-	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	1 (7.1)	1 (7.1)	-	-	-	-
紅斑	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (4 of 14)

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	14 (100.0)	12 (85.7)	12 (85.7)	6 (42.9)	5 (35.7)	-
Total Number of AEs	93	24	48	14	7	-
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	9 (64.3)	4 (28.6)	7 (50.0)	1 (7.1)	-	-
発熱	7 (50.0)	1 (7.1)	5 (35.7)	1 (7.1)	-	-
悪寒	5 (35.7)	1 (7.1)	3 (21.4)	1 (7.1)	-	-
無力症	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
疲労	2 (14.3)	-	2 (14.3)	-	-	-
胸痛	1 (7.1)	-	1 (7.1)	-	-	-
粘膜の炎症	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	19	4	13	2	-	-
胃腸障害						
Total Pts With at Least one AE	9 (64.3)	6 (42.9)	4 (28.6)	-	-	-
悪心	9 (64.3)	6 (42.9)	3 (21.4)	-	-	-
便秘	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
アフタ性口内炎	1 (7.1)	-	1 (7.1)	-	-	-
上腹部痛	1 (7.1)	-	1 (7.1)	-	-	-
腹痛	1 (7.1)	-	1 (7.1)	-	-	-
嘔吐	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	15	7	8	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (5 of 14)

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	7 (50.0)	4 (28.6)	4 (28.6)	-	-	-
頭痛	6 (42.9)	2 (14.3)	4 (28.6)	-	-	-
錯感覚	1 (7.1)	1 (7.1)	-	-	-	-
末梢性ニューロパチー	1 (7.1)	1 (7.1)	-	-	-	-
嗜眠	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	9	5	4	-	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	6 (42.9)	-	-	3 (21.4)	5 (35.7)	-
好中球減少症	5 (35.7)	-	-	1 (7.1)	4 (28.6)	-
血小板減少症	4 (28.6)	-	-	3 (21.4)	1 (7.1)	-
発熱性好中球減少症	2 (14.3)	-	-	-	2 (14.3)	-
白血球減少症	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	12	-	-	5	7	-
感染症および寄生虫症						
Total Pts With at Least one AE	6 (42.9)	-	4 (28.6)	4 (28.6)	-	-
気管支炎	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
感染	1 (7.1)	-	-	1 (7.1)	-	-
好中球減少性敗血症	1 (7.1)	-	-	1 (7.1)	-	-
歯膿瘍	1 (7.1)	-	1 (7.1)	-	-	-
上気道感染	1 (7.1)	-	-	1 (7.1)	-	-
帯状疱疹	1 (7.1)	-	1 (7.1)	-	-	-
皮膚感染	1 (7.1)	-	1 (7.1)	-	-	-
副鼻腔炎	1 (7.1)	-	1 (7.1)	-	-	-
膀胱炎	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	10	-	5	5	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (6 of 14)

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	5 (35.7)	1 (7.1)	4 (28.6)	1 (7.1)	-	-
呼吸困難	3 (21.4)	-	2 (14.3)	1 (7.1)	-	-
喉頭刺激感	2 (14.3)	-	2 (14.3)	-	-	-
咽喉刺激感	1 (7.1)	-	1 (7.1)	-	-	-
気管支痙攣	1 (7.1)	-	1 (7.1)	-	-	-
口腔咽頭痛	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	8	1	6	1	-	-
血管障害						
Total Pts With at Least one AE	5 (35.7)	2 (14.3)	3 (21.4)	-	-	-
低血圧	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
高血圧	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
Total Number of AEs	5	2	3	-	-	-
心臓障害						
Total Pts With at Least one AE	4 (28.6)	1 (7.1)	2 (14.3)	1 (7.1)	-	-
頻脈	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
徐脈	1 (7.1)	-	1 (7.1)	-	-	-
不整脈	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	4	1	2	1	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	3 (21.4)	-	3 (21.4)	-	-	-
関節痛	2 (14.3)	-	2 (14.3)	-	-	-
筋肉痛	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	3	-	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + FC; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
代謝および栄養障害						
Total Pts With at Least one AE	2 (14.3)	-	2 (14.3)	-	-	-
食欲減退	1 (7.1)	-	1 (7.1)	-	-	-
痛風	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	2	-	2	-	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	1 (7.1)	1 (7.1)	-	-	-	-
そう痒症	1 (7.1)	1 (7.1)	-	-	-	-
寝汗	1 (7.1)	1 (7.1)	-	-	-	-
発疹	1 (7.1)	1 (7.1)	-	-	-	-
皮膚亀裂	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	4	4	-	-	-	-
精神障害						
Total Pts With at Least one AE	1 (7.1)	-	1 (7.1)	-	-	-
不眠症	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	1	-	1	-	-	-
免疫系障害						
Total Pts With at Least one AE	1 (7.1)	-	1 (7.1)	-	-	-
低γグロブリン血症	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (8 of 14)

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	28 (100.0)	23 (82.1)	25 (89.3)	15 (53.6)	10 (35.7)	-
Total Number of AEs	178	49	89	28	12	-
胃腸障害						
Total Pts With at Least one AE	20 (71.4)	12 (42.9)	10 (35.7)	2 (7.1)	-	-
悪心	18 (64.3)	8 (28.6)	9 (32.1)	1 (3.6)	-	-
便秘	5 (17.9)	4 (14.3)	1 (3.6)	-	-	-
嘔吐	5 (17.9)	1 (3.6)	4 (14.3)	-	-	-
下痢	3 (10.7)	2 (7.1)	1 (3.6)	-	-	-
アフタ性口内炎	1 (3.6)	-	1 (3.6)	-	-	-
胃炎	1 (3.6)	1 (3.6)	-	-	-	-
壊死性口内炎	1 (3.6)	-	-	1 (3.6)	-	-
口腔内痛	1 (3.6)	-	-	1 (3.6)	-	-
上腹部痛	1 (3.6)	-	1 (3.6)	-	-	-
腹痛	1 (3.6)	-	1 (3.6)	-	-	-
嚥下障害	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	38	16	19	3	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (9 of 14)

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	19 (67.9)	7 (25.0)	17 (60.7)	1 (3.6)	-	-
発熱	12 (42.9)	4 (14.3)	7 (25.0)	1 (3.6)	-	-
悪寒	9 (32.1)	1 (3.6)	7 (25.0)	1 (3.6)	-	-
無力症	6 (21.4)	3 (10.7)	3 (10.7)	-	-	-
疲労	3 (10.7)	1 (3.6)	2 (7.1)	-	-	-
胸痛	2 (7.1)	-	2 (7.1)	-	-	-
粘膜の炎症	2 (7.1)	-	2 (7.1)	-	-	-
インフルエンザ様疾患	1 (3.6)	-	1 (3.6)	-	-	-
熱感	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	36	9	25	2	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	16 (57.1)	-	1 (3.6)	10 (35.7)	10 (35.7)	-
好中球減少症	14 (50.0)	-	-	5 (17.9)	9 (32.1)	-
血小板減少症	6 (21.4)	-	-	5 (17.9)	1 (3.6)	-
発熱性好中球減少症	2 (7.1)	-	-	-	2 (7.1)	-
白血球減少症	1 (3.6)	-	-	1 (3.6)	-	-
汎血球減少症	1 (3.6)	-	1 (3.6)	-	-	-
貧血	1 (3.6)	-	-	1 (3.6)	-	-
Total Number of AEs	25	-	1	12	12	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (10 of 14)

ae17r_000rr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	14 (50.0)	7 (25.0)	7 (25.0)	2 (7.1)	-	-
頭痛	9 (32.1)	4 (14.3)	5 (17.9)	-	-	-
嗜眠	3 (10.7)	1 (3.6)	1 (3.6)	1 (3.6)	-	-
浮動性めまい	2 (7.1)	1 (3.6)	-	1 (3.6)	-	-
錯感覚	1 (3.6)	1 (3.6)	-	-	-	-
振戦	1 (3.6)	-	1 (3.6)	-	-	-
末梢性ニューロパチー	1 (3.6)	1 (3.6)	-	-	-	-
味覚異常	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	18	9	7	2	-	-
感染症および寄生虫症						
Total Pts With at Least one AE	13 (46.4)	2 (7.1)	9 (32.1)	5 (17.9)	-	-
気管支炎	3 (10.7)	-	1 (3.6)	2 (7.1)	-	-
下気道感染	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
上気道感染	2 (7.1)	-	1 (3.6)	1 (3.6)	-	-
ウイルス性胃腸炎	1 (3.6)	-	1 (3.6)	-	-	-
カンジダ症	1 (3.6)	-	1 (3.6)	-	-	-
咽頭炎	1 (3.6)	1 (3.6)	-	-	-	-
感染	1 (3.6)	-	-	1 (3.6)	-	-
好中球減少性敗血症	1 (3.6)	-	-	1 (3.6)	-	-
歯膿瘍	1 (3.6)	-	1 (3.6)	-	-	-
帯状疱疹	1 (3.6)	-	1 (3.6)	-	-	-
皮膚感染	1 (3.6)	-	1 (3.6)	-	-	-
鼻炎	1 (3.6)	-	1 (3.6)	-	-	-
副鼻腔炎	1 (3.6)	-	1 (3.6)	-	-	-
膀胱炎	1 (3.6)	-	-	1 (3.6)	-	-
Total Number of AEs	18	2	10	6	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	9 (32.1)	3 (10.7)	6 (21.4)	-	-	-
低血圧	4 (14.3)	1 (3.6)	3 (10.7)	-	-	-
高血圧	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
ほてり	1 (3.6)	-	1 (3.6)	-	-	-
起立性低血圧	1 (3.6)	1 (3.6)	-	-	-	-
静脈炎	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	9	3	6	-	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	8 (28.6)	2 (7.1)	6 (21.4)	1 (3.6)	-	-
呼吸困難	3 (10.7)	-	2 (7.1)	1 (3.6)	-	-
口腔咽頭痛	3 (10.7)	1 (3.6)	2 (7.1)	-	-	-
喉頭刺激感	3 (10.7)	1 (3.6)	2 (7.1)	-	-	-
咽喉刺激感	1 (3.6)	-	1 (3.6)	-	-	-
気管支痙攣	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	11	2	8	1	-	-
心臓障害						
Total Pts With at Least one AE	7 (25.0)	2 (7.1)	4 (14.3)	1 (3.6)	-	-
徐脈	3 (10.7)	1 (3.6)	2 (7.1)	-	-	-
頻脈	2 (7.1)	-	1 (3.6)	1 (3.6)	-	-
動悸	1 (3.6)	-	1 (3.6)	-	-	-
不整脈	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	7	2	4	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46

ae17r_OOOrr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	4 (14.3)	-	4 (14.3)	-	-	-
関節痛	2 (7.1)	-	2 (7.1)	-	-	-
筋肉痛	1 (3.6)	-	1 (3.6)	-	-	-
背部痛	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	4	-	4	-	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	2 (7.1)	2 (7.1)	-	-	-	-
そう痒症	1 (3.6)	1 (3.6)	-	-	-	-
紅斑	1 (3.6)	1 (3.6)	-	-	-	-
寝汗	1 (3.6)	1 (3.6)	-	-	-	-
発疹	1 (3.6)	1 (3.6)	-	-	-	-
皮膚亀裂	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	5	5	-	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	2 (7.1)	-	2 (7.1)	-	-	-
食欲減退	1 (3.6)	-	1 (3.6)	-	-	-
痛風	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	2	-	2	-	-	-
臨床検査						
Total Pts With at Least one AE	2 (7.1)	-	1 (3.6)	1 (3.6)	-	-
γ－グルタミルトランスフェラーゼ増加	1 (3.6)	-	-	1 (3.6)	-	-
体重減少	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	2	-	1	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (13 of 14)

ae17r_000rr_sj Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, FC Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
眼障害						
Total Pts With at Least one AE	1 (3.6)	1 (3.6)	-	-	-	-
オキュラーサーフェス疾患	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
精神障害						
Total Pts With at Least one AE	1 (3.6)	-	1 (3.6)	-	-	-
不眠症	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	1	-	1	-	-	-
免疫系障害						
Total Pts With at Least one AE	1 (3.6)	-	1 (3.6)	-	-	-
低γグロブリン血症	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:45:46 (14 of 14)

[5.3.5.3-1 ae17r_000rr_sj を再掲]

表 2.7.6.2.1.8-3 因果関係を問わないすべての有害事象（BO21000試験，再発・治療抵抗性 FL 患者，CHOP 療法群）

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	14 (100.0)	14 (100.0)	14 (100.0)	6 (42.9)	4 (28.6)	-
Total Number of AEs	194	110	71	9	4	-
胃腸障害						
Total Pts With at Least one AE	14 (100.0)	13 (92.9)	11 (78.6)	1 (7.1)	-	-
悪心	11 (78.6)	4 (28.6)	6 (42.9)	1 (7.1)	-	-
便秘	9 (64.3)	7 (50.0)	2 (14.3)	-	-	-
下痢	8 (57.1)	4 (28.6)	4 (28.6)	-	-	-
嘔吐	7 (50.0)	2 (14.3)	4 (28.6)	1 (7.1)	-	-
消化不良	5 (35.7)	-	5 (35.7)	-	-	-
鼓腸	2 (14.3)	2 (14.3)	-	-	-	-
口内乾燥	2 (14.3)	-	2 (14.3)	-	-	-
アフタ性口内炎	1 (7.1)	1 (7.1)	-	-	-	-
過敏性腸症候群	1 (7.1)	-	1 (7.1)	-	-	-
口腔内出血	1 (7.1)	1 (7.1)	-	-	-	-
口腔内痛	1 (7.1)	1 (7.1)	-	-	-	-
痔核	1 (7.1)	1 (7.1)	-	-	-	-
上腹部痛	1 (7.1)	-	1 (7.1)	-	-	-
食道痛	1 (7.1)	1 (7.1)	-	-	-	-
腹部膨満	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	52	25	25	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (1 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	13 (92.9)	10 (71.4)	3 (21.4)	2 (14.3)	-	-
疲労	8 (57.1)	7 (50.0)	-	1 (7.1)	-	-
悪寒	5 (35.7)	2 (14.3)	3 (21.4)	-	-	-
発熱	4 (28.6)	1 (7.1)	2 (14.3)	1 (7.1)	-	-
粘膜の炎症	2 (14.3)	2 (14.3)	-	-	-	-
カテーテル留置部位疼痛	1 (7.1)	1 (7.1)	-	-	-	-
胸痛	1 (7.1)	1 (7.1)	-	-	-	-
倦怠感	1 (7.1)	1 (7.1)	-	-	-	-
無力症	1 (7.1)	1 (7.1)	-	-	-	-
疼痛	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	24	16	6	2	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	11 (78.6)	10 (71.4)	2 (14.3)	-	-	-
関節痛	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
筋痙縮	3 (21.4)	3 (21.4)	-	-	-	-
背部痛	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
顎痛	1 (7.1)	1 (7.1)	-	-	-	-
筋骨格痛	1 (7.1)	1 (7.1)	-	-	-	-
筋肉痛	1 (7.1)	1 (7.1)	-	-	-	-
筋攣縮	1 (7.1)	1 (7.1)	-	-	-	-
頚部痛	1 (7.1)	1 (7.1)	-	-	-	-
骨痛	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	15	13	2	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	10 (71.4)	9 (64.3)	5 (35.7)	-	-	-
末梢性ニューロパチー	5 (35.7)	3 (21.4)	2 (14.3)	-	-	-
味覚異常	4 (28.6)	4 (28.6)	-	-	-	-
浮動性めまい	3 (21.4)	3 (21.4)	-	-	-	-
末梢性感覚ニューロパチー	3 (21.4)	3 (21.4)	-	-	-	-
嗜眠	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
頭痛	2 (14.3)	-	2 (14.3)	-	-	-
失声症	1 (7.1)	-	1 (7.1)	-	-	-
振戦	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	22	16	6	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (3 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	9 (64.3)	5 (35.7)	6 (42.9)	3 (21.4)	-	-
上気道感染	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
下気道感染	2 (14.3)	-	2 (14.3)	-	-	-
口腔ヘルペス	2 (14.3)	-	2 (14.3)	-	-	-
鼻咽頭炎	2 (14.3)	2 (14.3)	-	-	-	-
インフルエンザ	1 (7.1)	1 (7.1)	-	-	-	-
胃腸炎	1 (7.1)	-	-	1 (7.1)	-	-
感染	1 (7.1)	-	1 (7.1)	-	-	-
眼感染	1 (7.1)	-	1 (7.1)	-	-	-
気道感染	1 (7.1)	-	1 (7.1)	-	-	-
口腔カンジダ症	1 (7.1)	1 (7.1)	-	-	-	-
口腔感染	1 (7.1)	-	1 (7.1)	-	-	-
好中球減少性感染	1 (7.1)	-	1 (7.1)	-	-	-
好中球減少性敗血症	1 (7.1)	-	-	1 (7.1)	-	-
耳感染	1 (7.1)	-	1 (7.1)	-	-	-
帯状疱疹	1 (7.1)	-	-	1 (7.1)	-	-
尿路感染	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	21	7	11	3	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	7 (50.0)	5 (35.7)	3 (21.4)	-	-	-
脱毛症	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
皮膚乾燥	2 (14.3)	2 (14.3)	-	-	-	-
そう痒症	1 (7.1)	1 (7.1)	-	-	-	-
紅斑	1 (7.1)	1 (7.1)	-	-	-	-
皮膚疼痛	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	9	6	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	7 (50.0)	-	2 (14.3)	1 (7.1)	4 (28.6)	-
好中球減少症	4 (28.6)	-	-	-	4 (28.6)	-
貧血	3 (21.4)	-	2 (14.3)	1 (7.1)	-	-
Total Number of AEs	7	-	2	1	4	-
血管障害						
Total Pts With at Least one AE	6 (42.9)	3 (21.4)	3 (21.4)	1 (7.1)	-	-
低血圧	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
ほてり	2 (14.3)	2 (14.3)	-	-	-	-
潮紅	2 (14.3)	1 (7.1)	-	1 (7.1)	-	-
血栓症	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	9	4	4	1	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	5 (35.7)	4 (28.6)	1 (7.1)	-	-	-
咳嗽	3 (21.4)	3 (21.4)	-	-	-	-
咽喉刺激感	1 (7.1)	-	1 (7.1)	-	-	-
咽頭の炎症	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	5	4	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (5 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
精神障害						
Total Pts With at Least one AE	4 (28.6)	3 (21.4)	1 (7.1)	-	-	-
不眠症	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
リビドー減退	1 (7.1)	1 (7.1)	-	-	-	-
気分変化	1 (7.1)	1 (7.1)	-	-	-	-
激越	1 (7.1)	1 (7.1)	-	-	-	-
不安	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	6	5	1	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	4 (28.6)	3 (21.4)	1 (7.1)	-	-	-
食欲減退	4 (28.6)	3 (21.4)	1 (7.1)	-	-	-
脱水	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	5	4	1	-	-	-
心臓障害						
Total Pts With at Least one AE	4 (28.6)	3 (21.4)	1 (7.1)	-	-	-
動悸	2 (14.3)	2 (14.3)	-	-	-	-
心房細動	1 (7.1)	1 (7.1)	-	-	-	-
頻脈	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	4	3	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (6 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
臨床検査						
Total Pts With at Least one AE	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
血中カルシウム減少	1 (7.1)	-	1 (7.1)	-	-	-
血中リン増加	1 (7.1)	-	1 (7.1)	-	-	-
血中乳酸脱水素酵素増加	1 (7.1)	-	1 (7.1)	-	-	-
血中尿酸増加	1 (7.1)	-	1 (7.1)	-	-	-
血中尿素増加	1 (7.1)	-	1 (7.1)	-	-	-
体重減少	1 (7.1)	-	1 (7.1)	-	-	-
体重増加	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	7	1	6	-	-	-
眼障害						
Total Pts With at Least one AE	2 (14.3)	2 (14.3)	-	-	-	-
眼そう痒症	1 (7.1)	1 (7.1)	-	-	-	-
結膜出血	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	2 (14.3)	2 (14.3)	-	-	-	-
挫傷	1 (7.1)	1 (7.1)	-	-	-	-
転倒	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (7 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
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）						
Total Pts With at Least one AE	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
腫瘍疼痛	1 (7.1)	1 (7.1)	-	-	-	-
皮膚有棘細胞癌	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	2	1	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	1 (7.1)	1 (7.1)	-	-	-	-
耳不快感	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	1 (7.1)	-	1 (7.1)	-	-	-
頻尿	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (8 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	14 (100.0)	13 (92.9)	14 (100.0)	7 (50.0)	7 (50.0)	-
Total Number of AEs	190	92	75	14	9	-
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	13 (92.9)	9 (64.3)	10 (71.4)	1 (7.1)	-	-
悪寒	7 (50.0)	-	6 (42.9)	1 (7.1)	-	-
疲労	6 (42.9)	-	6 (42.9)	-	-	-
粘膜の炎症	5 (35.7)	4 (28.6)	1 (7.1)	-	-	-
無力症	4 (28.6)	4 (28.6)	-	-	-	-
末梢性浮腫	3 (21.4)	3 (21.4)	-	-	-	-
発熱	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
腋窩痛	2 (14.3)	2 (14.3)	-	-	-	-
胸痛	1 (7.1)	-	1 (7.1)	-	-	-
胸部不快感	1 (7.1)	-	1 (7.1)	-	-	-
不明確な障害	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	32	14	16	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (9 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	13 (92.9)	6 (42.9)	7 (50.0)	1 (7.1)	2 (14.3)	-
鼻咽頭炎	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
気管支炎	2 (14.3)	-	2 (14.3)	-	-	-
歯感染	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
上気道感染	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
膀胱炎	2 (14.3)	2 (14.3)	-	-	-	-
ウイルス性胃腸炎	1 (7.1)	-	1 (7.1)	-	-	-
エンテロウイルス性脳炎	1 (7.1)	-	-	-	1 (7.1)	-
胃腸炎	1 (7.1)	-	1 (7.1)	-	-	-
咽頭炎	1 (7.1)	1 (7.1)	-	-	-	-
下気道感染	1 (7.1)	-	1 (7.1)	-	-	-
外陰部腟カンジダ症	1 (7.1)	-	1 (7.1)	-	-	-
眼感染	1 (7.1)	1 (7.1)	-	-	-	-
気管支肺アスペルギルス症	1 (7.1)	-	-	-	1 (7.1)	-
好中球減少性敗血症	1 (7.1)	-	-	-	1 (7.1)	-
中咽頭カンジダ症	1 (7.1)	-	1 (7.1)	-	-	-
鼻炎	1 (7.1)	1 (7.1)	-	-	-	-
副鼻腔炎	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	23	9	10	1	3	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (10 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	11 (78.6)	9 (64.3)	9 (64.3)	1 (7.1)	-	-
便秘	7 (50.0)	5 (35.7)	2 (14.3)	-	-	-
悪心	6 (42.9)	1 (7.1)	5 (35.7)	-	-	-
下痢	5 (35.7)	3 (21.4)	2 (14.3)	-	-	-
嘔吐	4 (28.6)	2 (14.3)	1 (7.1)	1 (7.1)	-	-
消化不良	3 (21.4)	3 (21.4)	-	-	-	-
口腔内潰瘍形成	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
腹痛	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
口腔内不快感	1 (7.1)	1 (7.1)	-	-	-	-
口内炎	1 (7.1)	1 (7.1)	-	-	-	-
歯肉痛	1 (7.1)	1 (7.1)	-	-	-	-
痔核	1 (7.1)	-	1 (7.1)	-	-	-
上腹部痛	1 (7.1)	1 (7.1)	-	-	-	-
舌炎	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	35	21	13	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (11 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	10 (71.4)	7 (50.0)	6 (42.9)	2 (14.3)	-	-
頭痛	6 (42.9)	3 (21.4)	3 (21.4)	-	-	-
錯感覚	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
神経痛	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
浮動性めまい	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
運動失調	1 (7.1)	-	-	1 (7.1)	-	-
傾眠	1 (7.1)	1 (7.1)	-	-	-	-
坐骨神経痛	1 (7.1)	-	1 (7.1)	-	-	-
失神	1 (7.1)	-	-	1 (7.1)	-	-
振戦	1 (7.1)	1 (7.1)	-	-	-	-
末梢性ニューロパチー	1 (7.1)	1 (7.1)	-	-	-	-
嗜眠	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	19	10	7	2	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	9 (64.3)	6 (42.9)	3 (21.4)	2 (14.3)	-	-
骨痛	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
筋痙縮	2 (14.3)	2 (14.3)	-	-	-	-
背部痛	2 (14.3)	1 (7.1)	-	1 (7.1)	-	-
関節腫脹	1 (7.1)	1 (7.1)	-	-	-	-
関節痛	1 (7.1)	1 (7.1)	-	-	-	-
筋骨格痛	1 (7.1)	1 (7.1)	-	-	-	-
筋肉痛	1 (7.1)	1 (7.1)	-	-	-	-
四肢痛	1 (7.1)	1 (7.1)	-	-	-	-
四肢不快感	1 (7.1)	1 (7.1)	-	-	-	-
腋窩腫瘤	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	15	10	3	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (12 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	9 (64.3)	2 (14.3)	3 (21.4)	3 (21.4)	6 (42.9)	-
好中球減少症	8 (57.1)	1 (7.1)	-	2 (14.3)	5 (35.7)	-
貧血	3 (21.4)	-	3 (21.4)	-	-	-
血小板減少症	1 (7.1)	-	-	1 (7.1)	-	-
白血球減少症	1 (7.1)	-	-	1 (7.1)	-	-
発熱性好中球減少症	1 (7.1)	-	-	-	1 (7.1)	-
脾臓障害	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	15	2	3	4	6	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	7 (50.0)	4 (28.6)	3 (21.4)	1 (7.1)	-	-
咳嗽	2 (14.3)	2 (14.3)	-	-	-	-
口腔咽頭痛	2 (14.3)	2 (14.3)	-	-	-	-
湿性咳嗽	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
アレルギー性鼻炎	1 (7.1)	-	1 (7.1)	-	-	-
咽喉刺激感	1 (7.1)	-	-	1 (7.1)	-	-
気管支痙攣	1 (7.1)	-	1 (7.1)	-	-	-
呼吸困難	1 (7.1)	-	1 (7.1)	-	-	-
鼻出血	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	11	6	4	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (13 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	7 (50.0)	4 (28.6)	5 (35.7)	-	-	-
低血圧	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
高血圧	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
ほてり	1 (7.1)	1 (7.1)	-	-	-	-
潮紅	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	9	4	5	-	-	-
精神障害						
Total Pts With at Least one AE	6 (42.9)	3 (21.4)	3 (21.4)	-	-	-
うつ病	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
不眠症	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
悪夢	1 (7.1)	1 (7.1)	-	-	-	-
激越	1 (7.1)	1 (7.1)	-	-	-	-
身体疾患による精神障害	1 (7.1)	-	1 (7.1)	-	-	-
不安	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	11	5	6	-	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	6 (42.9)	4 (28.6)	3 (21.4)	1 (7.1)	-	-
脱毛症	4 (28.6)	-	3 (21.4)	1 (7.1)	-	-
寝汗	1 (7.1)	1 (7.1)	-	-	-	-
多汗症	1 (7.1)	1 (7.1)	-	-	-	-
発疹	1 (7.1)	1 (7.1)	-	-	-	-
皮膚疼痛	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	8	4	3	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
心臓障害						
Total Pts With at Least one AE	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
左室機能不全	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
頻脈	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	3	1	2	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	2 (14.3)	2 (14.3)	-	-	-	-
耳鳴	1 (7.1)	1 (7.1)	-	-	-	-
聴力低下	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	2 (14.3)	-	2 (14.3)	-	-	-
排尿困難	1 (7.1)	-	1 (7.1)	-	-	-
頻尿	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	2	-	2	-	-	-
眼障害						
Total Pts With at Least one AE	1 (7.1)	1 (7.1)	1 (7.1)	-	-	-
眼痛	1 (7.1)	1 (7.1)	-	-	-	-
霰粒腫	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	2	1	1	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	1 (7.1)	1 (7.1)	-	-	-	-
挫傷	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (15 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
代謝および栄養障害											
Total Pts With at Least one AE	1 (7.1)	1	(7.1)	-		-		-		-	
食欲減退	1 (7.1)	1	(7.1)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	
臨床検査											
Total Pts With at Least one AE	1 (7.1)	1	(7.1)	-		-		-		-	
体重減少	1 (7.1)	1	(7.1)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (16 of 26)

ae17_000rr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	28	(100.0)	27	(96.4)	28	(100.0)	13	(46.4)	11	(39.3)	-	
Total Number of AEs	384		202		146		23		13		-	
一般・全身障害および投与部位の状態												
Total Pts With at Least one AE	26	(92.9)	19	(67.9)	13	(46.4)	3	(10.7)	-		-	
疲労	14	(50.0)	7	(25.0)	6	(21.4)	1	(3.6)	-		-	
悪寒	12	(42.9)	2	(7.1)	9	(32.1)	1	(3.6)	-		-	
粘膜の炎症	7	(25.0)	6	(21.4)	1	(3.6)	-		-		-	
発熱	6	(21.4)	2	(7.1)	3	(10.7)	1	(3.6)	-		-	
無力症	5	(17.9)	5	(17.9)	-		-		-		-	
末梢性浮腫	3	(10.7)	3	(10.7)	-		-		-		-	
胸痛	2	(7.1)	1	(3.6)	1	(3.6)	-		-		-	
腋窩痛	2	(7.1)	2	(7.1)	-		-		-		-	
カテーテル留置部位疼痛	1	(3.6)	1	(3.6)	-		-		-		-	
胸部不快感	1	(3.6)	-		1	(3.6)	-		-		-	
倦怠感	1	(3.6)	1	(3.6)	-		-		-		-	
不明確な障害	1	(3.6)	-		-		1	(3.6)	-		-	
疼痛	1	(3.6)	-		1	(3.6)	-		-		-	
Total Number of AEs	56		30		22		4		-		-	

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (17 of 26)

ae17_000rr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	25 (89.3)	22 (78.6)	20 (71.4)	2 (7.1)	-	-
悪心	17 (60.7)	5 (17.9)	11 (39.3)	1 (3.6)	-	-
便秘	16 (57.1)	12 (42.9)	4 (14.3)	-	-	-
下痢	13 (46.4)	7 (25.0)	6 (21.4)	-	-	-
嘔吐	11 (39.3)	4 (14.3)	5 (17.9)	2 (7.1)	-	-
消化不良	8 (28.6)	3 (10.7)	5 (17.9)	-	-	-
鼓腸	2 (7.1)	2 (7.1)	-	-	-	-
口腔内潰瘍形成	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
口内乾燥	2 (7.1)	-	2 (7.1)	-	-	-
痔核	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
上腹部痛	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
腹痛	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
アフタ性口内炎	1 (3.6)	1 (3.6)	-	-	-	-
過敏性腸症候群	1 (3.6)	-	1 (3.6)	-	-	-
口腔内出血	1 (3.6)	1 (3.6)	-	-	-	-
口腔内痛	1 (3.6)	1 (3.6)	-	-	-	-
口腔内不快感	1 (3.6)	1 (3.6)	-	-	-	-
口内炎	1 (3.6)	1 (3.6)	-	-	-	-
歯肉痛	1 (3.6)	1 (3.6)	-	-	-	-
食道痛	1 (3.6)	1 (3.6)	-	-	-	-
舌炎	1 (3.6)	1 (3.6)	-	-	-	-
腹部膨満	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	87	46	38	3	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (18 of 26)

ae17_000rr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	22 (78.6)	11 (39.3)	13 (46.4)	4 (14.3)	2 (7.1)	-
上気道感染	5 (17.9)	3 (10.7)	2 (7.1)	-	-	-
鼻咽頭炎	5 (17.9)	4 (14.3)	1 (3.6)	-	-	-
下気道感染	3 (10.7)	-	3 (10.7)	-	-	-
胃腸炎	2 (7.1)	-	1 (3.6)	1 (3.6)	-	-
眼感染	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
気管支炎	2 (7.1)	-	2 (7.1)	-	-	-
口腔ヘルペス	2 (7.1)	-	2 (7.1)	-	-	-
好中球減少性敗血症	2 (7.1)	-	-	1 (3.6)	1 (3.6)	-
歯感染	2 (7.1)	-	1 (3.6)	1 (3.6)	-	-
膀胱炎	2 (7.1)	2 (7.1)	-	-	-	-
インフルエンザ	1 (3.6)	1 (3.6)	-	-	-	-
ウイルス性胃腸炎	1 (3.6)	-	1 (3.6)	-	-	-
エンテロウイルス性脳炎	1 (3.6)	-	-	-	1 (3.6)	-
咽頭炎	1 (3.6)	1 (3.6)	-	-	-	-
外陰部腟カンジダ症	1 (3.6)	-	1 (3.6)	-	-	-
感染	1 (3.6)	-	1 (3.6)	-	-	-
気管支肺アスペルギルス症	1 (3.6)	-	-	-	1 (3.6)	-
気道感染	1 (3.6)	-	1 (3.6)	-	-	-
口腔カンジダ症	1 (3.6)	1 (3.6)	-	-	-	-
口腔感染	1 (3.6)	-	1 (3.6)	-	-	-
好中球減少性感染	1 (3.6)	-	1 (3.6)	-	-	-
耳感染	1 (3.6)	-	1 (3.6)	-	-	-
帯状疱疹	1 (3.6)	-	-	1 (3.6)	-	-
中咽頭カンジダ症	1 (3.6)	-	1 (3.6)	-	-	-
尿路感染	1 (3.6)	1 (3.6)	-	-	-	-
鼻炎	1 (3.6)	1 (3.6)	-	-	-	-

(body system continuing ...)

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
(... body system continuing)						
副鼻腔炎	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	44	16	21	4	3	-
神経系障害						
Total Pts With at Least one AE	20 (71.4)	16 (57.1)	11 (39.3)	2 (7.1)	-	-
頭痛	8 (28.6)	3 (10.7)	5 (17.9)	-	-	-
末梢性ニューロパチー	6 (21.4)	4 (14.3)	2 (7.1)	-	-	-
浮動性めまい	5 (17.9)	4 (14.3)	1 (3.6)	-	-	-
味覚異常	4 (14.3)	4 (14.3)	-	-	-	-
嗜眠	4 (14.3)	3 (10.7)	1 (3.6)	-	-	-
末梢性感覚ニューロパチー	3 (10.7)	3 (10.7)	-	-	-	-
錯感覚	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
振戦	2 (7.1)	2 (7.1)	-	-	-	-
神経痛	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
運動失調	1 (3.6)	-	-	1 (3.6)	-	-
傾眠	1 (3.6)	1 (3.6)	-	-	-	-
坐骨神経痛	1 (3.6)	-	1 (3.6)	-	-	-
失神	1 (3.6)	-	-	1 (3.6)	-	-
失声症	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	41	26	13	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (20 of 26)

ae17_000rr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	20 (71.4)	16 (57.1)	5 (17.9)	2 (7.1)	-	-
筋痙縮	5 (17.9)	5 (17.9)	-	-	-	-
骨痛	5 (17.9)	2 (7.1)	3 (10.7)	-	-	-
背部痛	5 (17.9)	3 (10.7)	1 (3.6)	1 (3.6)	-	-
関節痛	4 (14.3)	3 (10.7)	1 (3.6)	-	-	-
筋骨格痛	2 (7.1)	2 (7.1)	-	-	-	-
筋肉痛	2 (7.1)	2 (7.1)	-	-	-	-
顎痛	1 (3.6)	1 (3.6)	-	-	-	-
関節腫脹	1 (3.6)	1 (3.6)	-	-	-	-
筋攣縮	1 (3.6)	1 (3.6)	-	-	-	-
頚部痛	1 (3.6)	1 (3.6)	-	-	-	-
四肢痛	1 (3.6)	1 (3.6)	-	-	-	-
四肢不快感	1 (3.6)	1 (3.6)	-	-	-	-
腋窩腫瘤	1 (3.6)	-	-	1 (3.6)	-	-
Total Number of AEs	30	23	5	2	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	16 (57.1)	2 (7.1)	5 (17.9)	4 (14.3)	10 (35.7)	-
好中球減少症	12 (42.9)	1 (3.6)	-	2 (7.1)	9 (32.1)	-
貧血	6 (21.4)	-	5 (17.9)	1 (3.6)	-	-
血小板減少症	1 (3.6)	-	-	1 (3.6)	-	-
白血球減少症	1 (3.6)	-	-	1 (3.6)	-	-
発熱性好中球減少症	1 (3.6)	-	-	-	1 (3.6)	-
脾臓障害	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	22	2	5	5	10	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (21 of 26)

ae17_000rr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	13 (46.4)	7 (25.0)	8 (28.6)	1 (3.6)	-	-
低血圧	8 (28.6)	2 (7.1)	6 (21.4)	-	-	-
ほてり	3 (10.7)	3 (10.7)	-	-	-	-
高血圧	3 (10.7)	2 (7.1)	1 (3.6)	-	-	-
潮紅	3 (10.7)	1 (3.6)	1 (3.6)	1 (3.6)	-	-
血栓症	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	18	8	9	1	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	13 (46.4)	9 (32.1)	6 (21.4)	1 (3.6)	-	-
脱毛症	8 (28.6)	1 (3.6)	6 (21.4)	1 (3.6)	-	-
皮膚乾燥	2 (7.1)	2 (7.1)	-	-	-	-
皮膚疼痛	2 (7.1)	2 (7.1)	-	-	-	-
そう痒症	1 (3.6)	1 (3.6)	-	-	-	-
紅斑	1 (3.6)	1 (3.6)	-	-	-	-
寝汗	1 (3.6)	1 (3.6)	-	-	-	-
多汗症	1 (3.6)	1 (3.6)	-	-	-	-
発疹	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	17	10	6	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (22 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	12 (42.9)	8 (28.6)	4 (14.3)	1 (3.6)	-	-
咳嗽	5 (17.9)	5 (17.9)	-	-	-	-
咽喉刺激感	2 (7.1)	-	1 (3.6)	1 (3.6)	-	-
口腔咽頭痛	2 (7.1)	2 (7.1)	-	-	-	-
湿性咳嗽	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
アレルギー性鼻炎	1 (3.6)	-	1 (3.6)	-	-	-
咽頭の炎症	1 (3.6)	1 (3.6)	-	-	-	-
気管支痙攣	1 (3.6)	-	1 (3.6)	-	-	-
呼吸困難	1 (3.6)	-	1 (3.6)	-	-	-
鼻出血	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	16	10	5	1	-	-
精神障害						
Total Pts With at Least one AE	10 (35.7)	6 (21.4)	4 (14.3)	-	-	-
不眠症	5 (17.9)	3 (10.7)	2 (7.1)	-	-	-
うつ病	4 (14.3)	1 (3.6)	3 (10.7)	-	-	-
激越	2 (7.1)	2 (7.1)	-	-	-	-
不安	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
リビドー減退	1 (3.6)	1 (3.6)	-	-	-	-
悪夢	1 (3.6)	1 (3.6)	-	-	-	-
気分変化	1 (3.6)	1 (3.6)	-	-	-	-
身体疾患による精神障害	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	17	10	7	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52

ae17_000rr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
心臓障害						
Total Pts With at Least one AE	7 (25.0)	4 (14.3)	3 (10.7)	-	-	-
左室機能不全	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
動悸	2 (7.1)	2 (7.1)	-	-	-	-
頻脈	2 (7.1)	-	2 (7.1)	-	-	-
心房細動	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	7	4	3	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	5 (17.9)	4 (14.3)	1 (3.6)	-	-	-
食欲減退	5 (17.9)	4 (14.3)	1 (3.6)	-	-	-
脱水	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	6	5	1	-	-	-
臨床検査						
Total Pts With at Least one AE	4 (14.3)	2 (7.1)	2 (7.1)	-	-	-
体重減少	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
血中カルシウム減少	1 (3.6)	-	1 (3.6)	-	-	-
血中リン増加	1 (3.6)	-	1 (3.6)	-	-	-
血中乳酸脱水素酵素増加	1 (3.6)	-	1 (3.6)	-	-	-
血中尿酸増加	1 (3.6)	-	1 (3.6)	-	-	-
血中尿素増加	1 (3.6)	-	1 (3.6)	-	-	-
体重増加	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	8	2	6	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (24 of 26)

ae17_OOOrr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
眼障害						
Total Pts With at Least one AE	3 (10.7)	3 (10.7)	1 (3.6)	-	-	-
眼そう痒症	1 (3.6)	1 (3.6)	-	-	-	-
眼痛	1 (3.6)	1 (3.6)	-	-	-	-
結膜出血	1 (3.6)	1 (3.6)	-	-	-	-
霰粒腫	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	4	3	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	3 (10.7)	3 (10.7)	-	-	-	-
耳不快感	1 (3.6)	1 (3.6)	-	-	-	-
耳鳴	1 (3.6)	1 (3.6)	-	-	-	-
聴力低下	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	3	3	-	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	3 (10.7)	3 (10.7)	-	-	-	-
挫傷	2 (7.1)	2 (7.1)	-	-	-	-
転倒	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	3	3	-	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	3 (10.7)	-	3 (10.7)	-	-	-
頻尿	2 (7.1)	-	2 (7.1)	-	-	-
排尿困難	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	3	-	3	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (25 of 26)

ae17_000rr_sh Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
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）						
Total Pts With at Least one AE	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
腫瘍疼痛	1 (3.6)	1 (3.6)	-	-	-	-
皮膚有棘細胞癌	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	2	1	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:44:52 (26 of 26)

[5.3.5.3-1 ae17_000rr_sh を再掲]

表 2.7.6.2.1.8-4 因果関係が否定できないすべての有害事象（BO21000試験，再発・治療抵抗性 FL 患者，CHOP 療法群）

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	14 (100.0)	12 (85.7)	12 (85.7)	5 (35.7)	4 (28.6)	-
Total Number of AEs	103	47	45	7	4	-
胃腸障害						
Total Pts With at Least one AE	12 (85.7)	10 (71.4)	7 (50.0)	1 (7.1)	-	-
悪心	7 (50.0)	2 (14.3)	4 (28.6)	1 (7.1)	-	-
下痢	7 (50.0)	5 (35.7)	2 (14.3)	-	-	-
嘔吐	6 (42.9)	2 (14.3)	3 (21.4)	1 (7.1)	-	-
便秘	4 (28.6)	3 (21.4)	1 (7.1)	-	-	-
消化不良	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
アフタ性口内炎	1 (7.1)	1 (7.1)	-	-	-	-
口腔内痛	1 (7.1)	1 (7.1)	-	-	-	-
口内乾燥	1 (7.1)	-	1 (7.1)	-	-	-
上腹部痛	1 (7.1)	-	1 (7.1)	-	-	-
食道痛	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	32	16	14	2	-	-
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	7 (50.0)	5 (35.7)	3 (21.4)	1 (7.1)	-	-
悪寒	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
発熱	4 (28.6)	1 (7.1)	2 (14.3)	1 (7.1)	-	-
疲労	2 (14.3)	2 (14.3)	-	-	-	-
胸痛	1 (7.1)	1 (7.1)	-	-	-	-
粘膜の炎症	1 (7.1)	1 (7.1)	-	-	-	-
疼痛	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	13	6	6	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (1 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	7 (50.0)	-	2 (14.3)	1 (7.1)	4 (28.6)	-
好中球減少症	4 (28.6)	-	-	-	4 (28.6)	-
貧血	3 (21.4)	-	2 (14.3)	1 (7.1)	-	-
Total Number of AEs	7	-	2	1	4	-
神経系障害						
Total Pts With at Least one AE	6 (42.9)	6 (42.9)	2 (14.3)	-	-	-
頭痛	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
末梢性ニューロパチー	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
末梢性感覚ニューロパチー	2 (14.3)	2 (14.3)	-	-	-	-
味覚異常	2 (14.3)	2 (14.3)	-	-	-	-
嗜眠	2 (14.3)	2 (14.3)	-	-	-	-
浮動性めまい	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	11	9	2	-	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	6 (42.9)	4 (28.6)	3 (21.4)	-	-	-
脱毛症	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
皮膚乾燥	2 (14.3)	2 (14.3)	-	-	-	-
そう痒症	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	7	4	3	-	-	-
血管障害						
Total Pts With at Least one AE	5 (35.7)	1 (7.1)	3 (21.4)	1 (7.1)	-	-
低血圧	4 (28.6)	1 (7.1)	3 (21.4)	-	-	-
潮紅	2 (14.3)	1 (7.1)	-	1 (7.1)	-	-
Total Number of AEs	6	2	3	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	4 (28.6)	1 (7.1)	2 (14.3)	2 (14.3)	-	-
眼感染	1 (7.1)	-	1 (7.1)	-	-	-
口腔ヘルペス	1 (7.1)	-	1 (7.1)	-	-	-
口腔感染	1 (7.1)	-	1 (7.1)	-	-	-
好中球減少性感染	1 (7.1)	-	1 (7.1)	-	-	-
好中球減少性敗血症	1 (7.1)	-	-	1 (7.1)	-	-
耳感染	1 (7.1)	-	1 (7.1)	-	-	-
帯状疱疹	1 (7.1)	-	-	1 (7.1)	-	-
尿路感染	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	8	1	5	2	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	4 (28.6)	3 (21.4)	1 (7.1)	-	-	-
関節痛	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
筋痙縮	1 (7.1)	1 (7.1)	-	-	-	-
頚部痛	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	4	3	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (3 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
臨床検査						
Total Pts With at Least one AE	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
血中カルシウム減少	1 (7.1)	-	1 (7.1)	-	-	-
血中リン増加	1 (7.1)	-	1 (7.1)	-	-	-
血中乳酸脱水素酵素増加	1 (7.1)	-	1 (7.1)	-	-	-
血中尿酸増加	1 (7.1)	-	1 (7.1)	-	-	-
血中尿素増加	1 (7.1)	-	1 (7.1)	-	-	-
体重減少	1 (7.1)	-	1 (7.1)	-	-	-
体重増加	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	7	1	6	-	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
咽喉刺激感	1 (7.1)	-	1 (7.1)	-	-	-
咽頭の炎症	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	2	1	1	-	-	-
心臓障害						
Total Pts With at Least one AE	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
心房細動	1 (7.1)	1 (7.1)	-	-	-	-
頻脈	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	2	1	1	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
食欲減退	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
Total Number of AEs	2	1	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 Low Dose + CHOP: N = 14

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
精神障害											
Total Pts With at Least one AE	1 (7.1)	1	(7.1)	-		-		-		-	
不眠症	1 (7.1)	1	(7.1)	-		-		-		-	
Total Number of AEs	1	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）											
Total Pts With at Least one AE	1 (7.1)	1	(7.1)	-		-		-		-	
腫瘍疼痛	1 (7.1)	1	(7.1)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (5 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	13 (92.9)	12 (85.7)	11 (78.6)	6 (42.9)	7 (50.0)	-
Total Number of AEs	89	31	39	10	9	-
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	9 (64.3)	5 (35.7)	7 (50.0)	1 (7.1)	-	-
悪寒	5 (35.7)	-	4 (28.6)	1 (7.1)	-	-
粘膜の炎症	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
疲労	3 (21.4)	-	3 (21.4)	-	-	-
無力症	3 (21.4)	3 (21.4)	-	-	-	-
発熱	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
胸痛	1 (7.1)	-	1 (7.1)	-	-	-
胸部不快感	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	18	6	11	1	-	-
胃腸障害						
Total Pts With at Least one AE	9 (64.3)	6 (42.9)	5 (35.7)	1 (7.1)	-	-
悪心	5 (35.7)	1 (7.1)	4 (28.6)	-	-	-
下痢	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
消化不良	2 (14.3)	2 (14.3)	-	-	-	-
便秘	2 (14.3)	2 (14.3)	-	-	-	-
口腔内不快感	1 (7.1)	1 (7.1)	-	-	-	-
痔核	1 (7.1)	1 (7.1)	-	-	-	-
嘔吐	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	15	8	6	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (6 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	9 (64.3)	2 (14.3)	3 (21.4)	3 (21.4)	6 (42.9)	-
好中球減少症	8 (57.1)	1 (7.1)	-	2 (14.3)	5 (35.7)	-
貧血	3 (21.4)	-	3 (21.4)	-	-	-
血小板減少症	1 (7.1)	-	-	1 (7.1)	-	-
白血球減少症	1 (7.1)	-	-	1 (7.1)	-	-
発熱性好中球減少症	1 (7.1)	-	-	-	1 (7.1)	-
脾臓障害	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	15	2	3	4	6	-
感染症および寄生虫症						
Total Pts With at Least one AE	8 (57.1)	1 (7.1)	5 (35.7)	-	2 (14.3)	-
気管支炎	2 (14.3)	-	2 (14.3)	-	-	-
エンテロウイルス性脳炎	1 (7.1)	-	-	-	1 (7.1)	-
咽頭炎	1 (7.1)	1 (7.1)	-	-	-	-
外陰部腟カンジダ症	1 (7.1)	-	1 (7.1)	-	-	-
気管支肺アスペルギルス症	1 (7.1)	-	-	-	1 (7.1)	-
好中球減少性敗血症	1 (7.1)	-	-	-	1 (7.1)	-
上気道感染	1 (7.1)	-	1 (7.1)	-	-	-
中咽頭カンジダ症	1 (7.1)	-	1 (7.1)	-	-	-
鼻咽頭炎	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	10	1	6	-	3	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (7 of 17)

ae17r_000rr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	6 (42.9)	3 (21.4)	3 (21.4)	1 (7.1)	-	-
錯感覚	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
頭痛	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
運動失調	1 (7.1)	-	-	1 (7.1)	-	-
神経痛	1 (7.1)	-	1 (7.1)	-	-	-
末梢性ニューロパチー	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	7	3	3	1	-	-
血管障害						
Total Pts With at Least one AE	5 (35.7)	1 (7.1)	4 (28.6)	-	-	-
低血圧	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
高血圧	1 (7.1)	-	1 (7.1)	-	-	-
潮紅	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	5	1	4	-	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	4 (28.6)	2 (14.3)	2 (14.3)	1 (7.1)	-	-
脱毛症	3 (21.4)	-	2 (14.3)	1 (7.1)	-	-
発疹	1 (7.1)	1 (7.1)	-	-	-	-
皮膚疼痛	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	5	2	2	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (8 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
精神障害						
Total Pts With at Least one AE	3 (21.4)	2 (14.3)	1 (7.1)	-	-	-
うつ病	1 (7.1)	1 (7.1)	-	-	-	-
激越	1 (7.1)	1 (7.1)	-	-	-	-
身体疾患による精神障害	1 (7.1)	-	1 (7.1)	-	-	-
不眠症	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	4	3	1	-	-	-
心臓障害						
Total Pts With at Least one AE	3 (21.4)	1 (7.1)	2 (14.3)	-	-	-
左室機能不全	2 (14.3)	1 (7.1)	1 (7.1)	-	-	-
頻脈	1 (7.1)	-	1 (7.1)	-	-	-
Total Number of AEs	3	1	2	-	-	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	2 (14.3)	1 (7.1)	-	1 (7.1)	-	-
咽喉刺激感	1 (7.1)	-	-	1 (7.1)	-	-
咳嗽	1 (7.1)	1 (7.1)	-	-	-	-
口腔咽頭痛	1 (7.1)	1 (7.1)	-	-	-	-
Total Number of AEs	3	2	-	1	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	2 (14.3)	-	1 (7.1)	1 (7.1)	-	-
骨痛	1 (7.1)	-	1 (7.1)	-	-	-
背部痛	1 (7.1)	-	-	1 (7.1)	-	-
Total Number of AEs	2	-	1	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group RO5072759 High Dose + CHOP; N = 14

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
耳および迷路障害											
Total Pts With at Least one AE	1 (7.1)	1	(7.1)	-		-		-		-	
耳鳴	1 (7.1)	1	(7.1)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	
臨床検査											
Total Pts With at Least one AE	1 (7.1)	1	(7.1)	-		-		-		-	
体重減少	1 (7.1)	1	(7.1)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (10 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	27	(96.4)	24	(85.7)	23	(82.1)	11	(39.3)	11	(39.3)	-	
Total Number of AEs	192		78		84		17		13		-	
胃腸障害												
Total Pts With at Least one AE	21	(75.0)	16	(57.1)	12	(42.9)	2	(7.1)	-		-	
悪心	12	(42.9)	3	(10.7)	8	(28.6)	1	(3.6)	-		-	
下痢	10	(35.7)	6	(21.4)	4	(14.3)	-		-		-	
嘔吐	7	(25.0)	2	(7.1)	3	(10.7)	2	(7.1)	-		-	
便秘	6	(21.4)	5	(17.9)	1	(3.6)	-		-		-	
消化不良	5	(17.9)	3	(10.7)	2	(7.1)	-		-		-	
アフタ性口内炎	1	(3.6)	1	(3.6)	-		-		-		-	
口腔内痛	1	(3.6)	1	(3.6)	-		-		-		-	
口腔内不快感	1	(3.6)	1	(3.6)	-		-		-		-	
口内乾燥	1	(3.6)	-		1	(3.6)	-		-		-	
痔核	1	(3.6)	1	(3.6)	-		-		-		-	
上腹部痛	1	(3.6)	-		1	(3.6)	-		-		-	
食道痛	1	(3.6)	1	(3.6)	-		-		-		-	
Total Number of AEs	47		24		20		3		-		-	

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (11 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	16 (57.1)	10 (35.7)	10 (35.7)	2 (7.1)	-	-
悪寒	9 (32.1)	1 (3.6)	7 (25.0)	1 (3.6)	-	-
発熱	6 (21.4)	2 (7.1)	3 (10.7)	1 (3.6)	-	-
疲労	5 (17.9)	2 (7.1)	3 (10.7)	-	-	-
粘膜の炎症	4 (14.3)	3 (10.7)	1 (3.6)	-	-	-
無力症	3 (10.7)	3 (10.7)	-	-	-	-
胸痛	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
胸部不快感	1 (3.6)	-	1 (3.6)	-	-	-
疼痛	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	31	12	17	2	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	16 (57.1)	2 (7.1)	5 (17.9)	4 (14.3)	10 (35.7)	-
好中球減少症	12 (42.9)	1 (3.6)	-	2 (7.1)	9 (32.1)	-
貧血	6 (21.4)	-	5 (17.9)	1 (3.6)	-	-
血小板減少症	1 (3.6)	-	-	1 (3.6)	-	-
白血球減少症	1 (3.6)	-	-	1 (3.6)	-	-
発熱性好中球減少症	1 (3.6)	-	-	-	1 (3.6)	-
脾臓障害	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	22	2	5	5	10	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (12 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	12 (42.9)	2 (7.1)	7 (25.0)	2 (7.1)	2 (7.1)	-
気管支炎	2 (7.1)	-	2 (7.1)	-	-	-
好中球減少性敗血症	2 (7.1)	-	-	1 (3.6)	1 (3.6)	-
エンテロウイルス性脳炎	1 (3.6)	-	-	-	1 (3.6)	-
咽頭炎	1 (3.6)	1 (3.6)	-	-	-	-
外陰部腟カンジダ症	1 (3.6)	-	1 (3.6)	-	-	-
眼感染	1 (3.6)	-	1 (3.6)	-	-	-
気管支肺アスペルギルス症	1 (3.6)	-	-	-	1 (3.6)	-
口腔ヘルペス	1 (3.6)	-	1 (3.6)	-	-	-
口腔感染	1 (3.6)	-	1 (3.6)	-	-	-
好中球減少性感染	1 (3.6)	-	1 (3.6)	-	-	-
耳感染	1 (3.6)	-	1 (3.6)	-	-	-
上気道感染	1 (3.6)	-	1 (3.6)	-	-	-
帯状疱疹	1 (3.6)	-	-	1 (3.6)	-	-
中咽頭カンジダ症	1 (3.6)	-	1 (3.6)	-	-	-
尿路感染	1 (3.6)	1 (3.6)	-	-	-	-
鼻咽頭炎	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	18	2	11	2	3	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (13 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	12 (42.9)	9 (32.1)	5 (17.9)	1 (3.6)	-	-
頭痛	4 (14.3)	2 (7.1)	2 (7.1)	-	-	-
末梢性ニューロパチー	3 (10.7)	2 (7.1)	1 (3.6)	-	-	-
錯感覚	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
末梢性感覚ニューロパチー	2 (7.1)	2 (7.1)	-	-	-	-
味覚異常	2 (7.1)	2 (7.1)	-	-	-	-
嗜眠	2 (7.1)	2 (7.1)	-	-	-	-
運動失調	1 (3.6)	-	-	1 (3.6)	-	-
神経痛	1 (3.6)	-	1 (3.6)	-	-	-
浮動性めまい	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	18	12	5	1	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	10 (35.7)	6 (21.4)	5 (17.9)	1 (3.6)	-	-
脱毛症	7 (25.0)	1 (3.6)	5 (17.9)	1 (3.6)	-	-
皮膚乾燥	2 (7.1)	2 (7.1)	-	-	-	-
そう痒症	1 (3.6)	1 (3.6)	-	-	-	-
発疹	1 (3.6)	1 (3.6)	-	-	-	-
皮膚疼痛	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	12	6	5	1	-	-
血管障害						
Total Pts With at Least one AE	10 (35.7)	2 (7.1)	7 (25.0)	1 (3.6)	-	-
低血圧	7 (25.0)	2 (7.1)	5 (17.9)	-	-	-
潮紅	3 (10.7)	1 (3.6)	1 (3.6)	1 (3.6)	-	-
高血圧	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	11	3	7	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (14 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	6 (21.4)	3 (10.7)	2 (7.1)	1 (3.6)	-	-
関節痛	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
筋痙縮	1 (3.6)	1 (3.6)	-	-	-	-
頚部痛	1 (3.6)	1 (3.6)	-	-	-	-
骨痛	1 (3.6)	-	1 (3.6)	-	-	-
背部痛	1 (3.6)	-	-	1 (3.6)	-	-
Total Number of AEs	6	3	2	1	-	-
心臓障害						
Total Pts With at Least one AE	5 (17.9)	2 (7.1)	3 (10.7)	-	-	-
左室機能不全	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
頻脈	2 (7.1)	-	2 (7.1)	-	-	-
心房細動	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	5	2	3	-	-	-
臨床検査						
Total Pts With at Least one AE	4 (14.3)	2 (7.1)	2 (7.1)	-	-	-
体重減少	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
血中カルシウム減少	1 (3.6)	-	1 (3.6)	-	-	-
血中リン増加	1 (3.6)	-	1 (3.6)	-	-	-
血中乳酸脱水素酵素増加	1 (3.6)	-	1 (3.6)	-	-	-
血中尿酸増加	1 (3.6)	-	1 (3.6)	-	-	-
血中尿素増加	1 (3.6)	-	1 (3.6)	-	-	-
体重増加	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	8	2	6	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (15 of 17)

ae17r_OOOrr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	4 (14.3)	2 (7.1)	1 (3.6)	1 (3.6)	-	-
咽喉刺激感	2 (7.1)	-	1 (3.6)	1 (3.6)	-	-
咽頭の炎症	1 (3.6)	1 (3.6)	-	-	-	-
咳嗽	1 (3.6)	1 (3.6)	-	-	-	-
口腔咽頭痛	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	5	3	1	1	-	-
精神障害						
Total Pts With at Least one AE	4 (14.3)	3 (10.7)	1 (3.6)	-	-	-
不眠症	2 (7.1)	2 (7.1)	-	-	-	-
うつ病	1 (3.6)	1 (3.6)	-	-	-	-
激越	1 (3.6)	1 (3.6)	-	-	-	-
身体疾患による精神障害	1 (3.6)	-	1 (3.6)	-	-	-
Total Number of AEs	5	4	1	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
食欲減退	2 (7.1)	1 (3.6)	1 (3.6)	-	-	-
Total Number of AEs	2	1	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	1 (3.6)	1 (3.6)	-	-	-	-
耳鳴	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (16 of 17)

ae17r_000rr_sh Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000F) Relapse, Refractory
Analysis: SAP, CHOP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
Treatment Group Total: N = 28

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
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）						
Total Pts With at Least one AE	1 (3.6)	1 (3.6)	-	-	-	-
腫瘍疼痛	1 (3.6)	1 (3.6)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:42:13 (17 of 17)

[5.3.5.3-1 ae17r_000rr_sh を再掲]

(2) 未治療患者対象部分

表 2.7.6.2.1.8-5 因果関係を問わないすべての有害事象（B021000試験，未治療 FL 患者）

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total		CTC Grading 1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	41	(100.0)	39	(95.1)	37	(90.2)	17	(41.5)	8	(19.5)	-	
Total Number of AEs	401		200		141		50		10		-	
胃腸障害												
Total Pts With at Least one AE	35	(85.4)	33	(80.5)	17	(41.5)	5	(12.2)	-		-	
悪心	26	(63.4)	13	(31.7)	10	(24.4)	3	(7.3)	-		-	
下痢	14	(34.1)	11	(26.8)	1	(2.4)	2	(4.9)	-		-	
嘔吐	10	(24.4)	3	(7.3)	5	(12.2)	2	(4.9)	-		-	
便秘	8	(19.5)	7	(17.1)	1	(2.4)	-		-		-	
消化不良	5	(12.2)	4	(9.8)	1	(2.4)	-		-		-	
上腹部痛	3	(7.3)	3	(7.3)	-		-		-		-	
腹痛	2	(4.9)	2	(4.9)	-		-		-		-	
レッチング	1	(2.4)	-		1	(2.4)	-		-		-	
下腹部痛	1	(2.4)	1	(2.4)	-		-		-		-	
鼓腸	1	(2.4)	1	(2.4)	-		-		-		-	
口腔そう痒症	1	(2.4)	-		1	(2.4)	-		-		-	
口唇潰瘍	1	(2.4)	1	(2.4)	-		-		-		-	
口内炎	1	(2.4)	-		1	(2.4)	-		-		-	
歯痛	1	(2.4)	1	(2.4)	-		-		-		-	
直腸出血	1	(2.4)	1	(2.4)	-		-		-		-	
腹部不快感	1	(2.4)	1	(2.4)	-		-		-		-	
腹部膨満	1	(2.4)	1	(2.4)	-		-		-		-	
Total Number of AEs	78		50		21		7		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (1 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	35 (85.4)	21 (51.2)	20 (48.8)	4 (9.8)	-	-
発熱	20 (48.8)	6 (14.6)	11 (26.8)	3 (7.3)	-	-
悪寒	18 (43.9)	3 (7.3)	12 (29.3)	3 (7.3)	-	-
疲労	15 (36.6)	11 (26.8)	3 (7.3)	1 (2.4)	-	-
無力症	4 (9.8)	2 (4.9)	2 (4.9)	-	-	-
胸部不快感	3 (7.3)	-	2 (4.9)	1 (2.4)	-	-
末梢性浮腫	3 (7.3)	3 (7.3)	-	-	-	-
倦怠感	2 (4.9)	2 (4.9)	-	-	-	-
疼痛	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
カテーテル留置部位静脈炎	1 (2.4)	1 (2.4)	-	-	-	-
胸痛	1 (2.4)	1 (2.4)	-	-	-	-
注射部位紅斑	1 (2.4)	1 (2.4)	-	-	-	-
粘膜の炎症	1 (2.4)	-	1 (2.4)	-	-	-
浮腫	1 (2.4)	1 (2.4)	-	-	-	-
冷感	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	73	33	32	8	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (2 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	22 (53.7)	13 (31.7)	15 (36.6)	4 (9.8)	2 (4.9)	-
感染	7 (17.1)	1 (2.4)	5 (12.2)	1 (2.4)	-	-
好中球減少性感染	4 (9.8)	-	-	2 (4.9)	2 (4.9)	-
上気道感染	3 (7.3)	-	3 (7.3)	-	-	-
下気道感染	2 (4.9)	-	2 (4.9)	-	-	-
気道感染	2 (4.9)	2 (4.9)	-	-	-	-
尿路感染	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
皮膚感染	2 (4.9)	-	1 (2.4)	1 (2.4)	-	-
鼻咽頭炎	2 (4.9)	2 (4.9)	-	-	-	-
鼻炎	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
せつ	1 (2.4)	1 (2.4)	-	-	-	-
カテーテル留置部位感染	1 (2.4)	-	1 (2.4)	-	-	-
クロストリジウム・ディフィシレ大腸炎	1 (2.4)	1 (2.4)	-	-	-	-
胃腸炎	1 (2.4)	-	1 (2.4)	-	-	-
眼感染	1 (2.4)	1 (2.4)	-	-	-	-
気管支炎	1 (2.4)	1 (2.4)	-	-	-	-
限局性感染	1 (2.4)	-	1 (2.4)	-	-	-
口腔カンジダ症	1 (2.4)	1 (2.4)	-	-	-	-
口腔ヘルペス	1 (2.4)	-	-	1 (2.4)	-	-
口腔感染	1 (2.4)	-	1 (2.4)	-	-	-
口腔真菌感染	1 (2.4)	1 (2.4)	-	-	-	-
口唇感染	1 (2.4)	-	1 (2.4)	-	-	-
帯状疱疹	1 (2.4)	-	1 (2.4)	-	-	-
単純ヘルペス	1 (2.4)	1 (2.4)	-	-	-	-
中耳炎	1 (2.4)	-	1 (2.4)	-	-	-
粘膜感染	1 (2.4)	1 (2.4)	-	-	-	-

(body system continuing ...)

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
(... body system continuing)						
肺感染	1 (2.4)	1 (2.4)	-	-	-	-
副鼻腔炎	1 (2.4)	-	1 (2.4)	-	-	-
膣感染	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	45	17	21	5	2	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	21 (51.2)	16 (39.0)	8 (19.5)	1 (2.4)	-	-
発疹	8 (19.5)	2 (4.9)	5 (12.2)	1 (2.4)	-	-
多汗症	6 (14.6)	6 (14.6)	-	-	-	-
そう痒症	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
顔面腫脹	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
紅斑	2 (4.9)	2 (4.9)	-	-	-	-
丘疹	1 (2.4)	1 (2.4)	-	-	-	-
脂漏	1 (2.4)	1 (2.4)	-	-	-	-
湿疹	1 (2.4)	1 (2.4)	-	-	-	-
水疱	1 (2.4)	1 (2.4)	-	-	-	-
多形紅斑	1 (2.4)	-	1 (2.4)	-	-	-
脱毛症	1 (2.4)	1 (2.4)	-	-	-	-
皮脂欠乏性湿疹	1 (2.4)	-	1 (2.4)	-	-	-
皮膚乾燥	1 (2.4)	1 (2.4)	-	-	-	-
瘢痕	1 (2.4)	1 (2.4)	-	-	-	-
蕁麻疹	1 (2.4)	-	1 (2.4)	-	-	-
Total Number of AEs	30	19	10	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (4 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	20 (48.8)	14 (34.1)	7 (17.1)	1 (2.4)	-	-
頭痛	16 (39.0)	9 (22.0)	6 (14.6)	1 (2.4)	-	-
浮動性めまい	3 (7.3)	1 (2.4)	2 (4.9)	-	-	-
味覚異常	3 (7.3)	3 (7.3)	-	-	-	-
感覚運動障害	1 (2.4)	1 (2.4)	-	-	-	-
記憶障害	1 (2.4)	1 (2.4)	-	-	-	-
振戦	1 (2.4)	1 (2.4)	-	-	-	-
末梢性感覚ニューロパチー	1 (2.4)	1 (2.4)	-	-	-	-
嗜眠	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	27	18	8	1	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	19 (46.3)	13 (31.7)	7 (17.1)	1 (2.4)	-	-
背部痛	5 (12.2)	3 (7.3)	2 (4.9)	-	-	-
関節痛	4 (9.8)	3 (7.3)	-	1 (2.4)	-	-
筋骨格痛	4 (9.8)	3 (7.3)	1 (2.4)	-	-	-
筋肉痛	3 (7.3)	2 (4.9)	1 (2.4)	-	-	-
筋痙縮	2 (4.9)	2 (4.9)	-	-	-	-
骨痛	2 (4.9)	-	1 (2.4)	1 (2.4)	-	-
四肢痛	2 (4.9)	2 (4.9)	-	-	-	-
筋炎	1 (2.4)	-	1 (2.4)	-	-	-
筋緊張	1 (2.4)	-	1 (2.4)	-	-	-
筋骨格不快感	1 (2.4)	-	1 (2.4)	-	-	-
頚部痛	1 (2.4)	1 (2.4)	-	-	-	-
変形性関節症	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	27	17	8	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (5 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	19 (46.3)	12 (29.3)	7 (17.1)	2 (4.9)	-	-
咳嗽	10 (24.4)	8 (19.5)	2 (4.9)	-	-	-
呼吸困難	5 (12.2)	1 (2.4)	3 (7.3)	1 (2.4)	-	-
口腔咽頭痛	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
しゃっくり	1 (2.4)	1 (2.4)	-	-	-	-
咽喉刺激感	1 (2.4)	-	1 (2.4)	-	-	-
胸水	1 (2.4)	-	1 (2.4)	-	-	-
喉頭浮腫	1 (2.4)	-	1 (2.4)	-	-	-
低酸素症	1 (2.4)	-	-	1 (2.4)	-	-
発声障害	1 (2.4)	1 (2.4)	-	-	-	-
労作性呼吸困難	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	24	13	9	2	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	18 (43.9)	1 (2.4)	3 (7.3)	12 (29.3)	7 (17.1)	-
好中球減少症	14 (34.1)	1 (2.4)	-	7 (17.1)	6 (14.6)	-
血小板減少症	5 (12.2)	-	2 (4.9)	2 (4.9)	1 (2.4)	-
貧血	4 (9.8)	-	1 (2.4)	3 (7.3)	-	-
白血球減少症	1 (2.4)	-	-	-	1 (2.4)	-
Total Number of AEs	24	1	3	12	8	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (6 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine; N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	15 (36.6)	5 (12.2)	9 (22.0)	3 (7.3)	-	-
潮紅	7 (17.1)	1 (2.4)	4 (9.8)	2 (4.9)	-	-
低血圧	6 (14.6)	1 (2.4)	3 (7.3)	2 (4.9)	-	-
静脈炎	4 (9.8)	1 (2.4)	3 (7.3)	-	-	-
高血圧	2 (4.9)	-	1 (2.4)	1 (2.4)	-	-
血腫	1 (2.4)	1 (2.4)	-	-	-	-
血栓性静脈炎	1 (2.4)	1 (2.4)	-	-	-	-
塞栓症	1 (2.4)	-	-	1 (2.4)	-	-
四肢静脈血栓症	1 (2.4)	-	1 (2.4)	-	-	-
Total Number of AEs	23	5	12	6	-	-
精神障害						
Total Pts With at Least one AE	9 (22.0)	6 (14.6)	3 (7.3)	1 (2.4)	-	-
不眠症	4 (9.8)	3 (7.3)	1 (2.4)	-	-	-
不安	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
うつ病	1 (2.4)	-	-	1 (2.4)	-	-
錯乱状態	1 (2.4)	1 (2.4)	-	-	-	-
人格障害	1 (2.4)	1 (2.4)	-	-	-	-
睡眠障害	1 (2.4)	1 (2.4)	-	-	-	-
精神病性障害	1 (2.4)	-	1 (2.4)	-	-	-
不安障害	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	12	8	3	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
臨床検査						
Total Pts With at Least one AE	6 (14.6)	5 (12.2)	-	1 (2.4)	-	-
アスパラギン酸アミノトランスフェラーゼ増加	1 (2.4)	-	-	1 (2.4)	-	-
アラニンアミノトランスフェラーゼ増加	1 (2.4)	-	-	1 (2.4)	-	-
血中クレアチニン増加	1 (2.4)	1 (2.4)	-	-	-	-
血中尿酸増加	1 (2.4)	1 (2.4)	-	-	-	-
総蛋白減少	1 (2.4)	1 (2.4)	-	-	-	-
体重減少	1 (2.4)	1 (2.4)	-	-	-	-
体重増加	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	7	5	-	2	-	-
代謝および栄養障害						
Total Pts With at Least one AE	5 (12.2)	3 (7.3)	1 (2.4)	3 (7.3)	-	-
低カリウム血症	3 (7.3)	2 (4.9)	1 (2.4)	-	-	-
食欲減退	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
脱水	2 (4.9)	-	1 (2.4)	1 (2.4)	-	-
体液貯留	1 (2.4)	-	-	1 (2.4)	-	-
低マグネシウム血症	1 (2.4)	-	-	1 (2.4)	-	-
Total Number of AEs	9	3	3	3	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
眼障害						
Total Pts With at Least one AE	5 (12.2)	4 (9.8)	1 (2.4)	-	-	-
角膜炎	1 (2.4)	-	1 (2.4)	-	-	-
眼乾燥	1 (2.4)	1 (2.4)	-	-	-	-
視力障害	1 (2.4)	1 (2.4)	-	-	-	-
硝子体出血	1 (2.4)	1 (2.4)	-	-	-	-
流涙増加	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	5	4	1	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	3 (7.3)	3 (7.3)	1 (2.4)	-	-	-
サンバーン	1 (2.4)	1 (2.4)	-	-	-	-
擦過傷	1 (2.4)	1 (2.4)	-	-	-	-
転倒	1 (2.4)	-	1 (2.4)	-	-	-
熱傷	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	4	3	1	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	3 (7.3)	1 (2.4)	2 (4.9)	-	-	-
回転性めまい	1 (2.4)	-	1 (2.4)	-	-	-
外耳痛	1 (2.4)	1 (2.4)	-	-	-	-
耳痛	1 (2.4)	-	1 (2.4)	-	-	-
Total Number of AEs	3	1	2	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (9 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
腎および尿路障害						
Total Pts With at Least one AE	3 (7.3)	2 (4.9)	1 (2.4)	-	-	-
尿失禁	1 (2.4)	1 (2.4)	-	-	-	-
排尿困難	1 (2.4)	-	1 (2.4)	-	-	-
夜間頻尿	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	3	2	1	-	-	-
心臓障害						
Total Pts With at Least one AE	2 (4.9)	-	2 (4.9)	-	-	-
頻脈	2 (4.9)	-	2 (4.9)	-	-	-
Total Number of AEs	2	-	2	-	-	-
免疫系障害						
Total Pts With at Least one AE	2 (4.9)	-	2 (4.9)	-	-	-
過敏症	2 (4.9)	-	2 (4.9)	-	-	-
Total Number of AEs	2	-	2	-	-	-
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）						
Total Pts With at Least one AE	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
汗腺腫瘍	1 (2.4)	1 (2.4)	-	-	-	-
腫瘍フレア	1 (2.4)	-	1 (2.4)	-	-	-
Total Number of AEs	2	1	1	-	-	-
生殖系および乳房障害						
Total Pts With at Least one AE	1 (2.4)	-	1 (2.4)	-	-	-
外陰腟そう痒症	1 (2.4)	-	1 (2.4)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (10 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	40 (100.0)	39 (97.5)	34 (85.0)	25 (62.5)	13 (32.5)	1 (2.5)
Total Number of AEs	447	209	172	49	16	1
胃腸障害						
Total Pts With at Least one AE	37 (92.5)	29 (72.5)	21 (52.5)	5 (12.5)	-	-
悪心	21 (52.5)	9 (22.5)	10 (25.0)	2 (5.0)	-	-
嘔吐	15 (37.5)	2 (5.0)	11 (27.5)	2 (5.0)	-	-
便秘	13 (32.5)	8 (20.0)	5 (12.5)	-	-	-
下痢	7 (17.5)	5 (12.5)	2 (5.0)	-	-	-
消化不良	6 (15.0)	4 (10.0)	1 (2.5)	1 (2.5)	-	-
腹痛	4 (10.0)	3 (7.5)	1 (2.5)	-	-	-
口腔内潰瘍形成	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
口内乾燥	3 (7.5)	3 (7.5)	-	-	-	-
腹部膨満	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
アフタ性口内炎	2 (5.0)	2 (5.0)	-	-	-	-
口内炎	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
嚥下障害	2 (5.0)	2 (5.0)	-	-	-	-
イレウス	1 (2.5)	-	-	1 (2.5)	-	-
胃炎	1 (2.5)	1 (2.5)	-	-	-	-
下腹部痛	1 (2.5)	-	1 (2.5)	-	-	-
口の錯感覚	1 (2.5)	-	1 (2.5)	-	-	-
口腔内出血	1 (2.5)	1 (2.5)	-	-	-	-
歯痛	1 (2.5)	1 (2.5)	-	-	-	-
歯肉出血	1 (2.5)	1 (2.5)	-	-	-	-
歯肉痛	1 (2.5)	1 (2.5)	-	-	-	-
痔核	1 (2.5)	1 (2.5)	-	-	-	-
食中毒	1 (2.5)	-	1 (2.5)	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
(... body system continuing)						
舌痛	1 (2.5)	1 (2.5)	-	-	-	-
舌潰瘍	1 (2.5)	-	1 (2.5)	-	-	-
大腸炎	1 (2.5)	1 (2.5)	-	-	-	-
腹水	1 (2.5)	-	-	1 (2.5)	-	-
Total Number of AEs	95	50	38	7	-	-
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	28 (70.0)	14 (35.0)	18 (45.0)	3 (7.5)	1 (2.5)	-
発熱	14 (35.0)	3 (7.5)	10 (25.0)	1 (2.5)	-	-
疲労	13 (32.5)	6 (15.0)	5 (12.5)	1 (2.5)	1 (2.5)	-
悪寒	9 (22.5)	-	9 (22.5)	-	-	-
粘膜の炎症	7 (17.5)	6 (15.0)	1 (2.5)	-	-	-
胸部不快感	4 (10.0)	-	3 (7.5)	1 (2.5)	-	-
末梢性浮腫	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
インフルエンザ様疾患	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
胸痛	2 (5.0)	1 (2.5)	-	1 (2.5)	-	-
医療機器損傷	1 (2.5)	1 (2.5)	-	-	-	-
溢出	1 (2.5)	1 (2.5)	-	-	-	-
体温変動感	1 (2.5)	-	1 (2.5)	-	-	-
浮腫	1 (2.5)	1 (2.5)	-	-	-	-
無力症	1 (2.5)	1 (2.5)	-	-	-	-
疼痛	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	60	24	31	4	1	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (12 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	27 (67.5)	13 (32.5)	18 (45.0)	11 (27.5)	1 (2.5)	-
感染	4 (10.0)	-	3 (7.5)	1 (2.5)	-	-
上気道感染	4 (10.0)	2 (5.0)	2 (5.0)	-	-	-
下気道感染	3 (7.5)	-	1 (2.5)	2 (5.0)	-	-
好中球減少性敗血症	3 (7.5)	-	-	2 (5.0)	1 (2.5)	-
歯肉感染	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
尿路感染	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
肺炎	3 (7.5)	-	2 (5.0)	1 (2.5)	-	-
インフルエンザ	2 (5.0)	-	-	2 (5.0)	-	-
ウイルス性上気道感染	2 (5.0)	2 (5.0)	-	-	-	-
眼感染	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
気管支炎	2 (5.0)	-	2 (5.0)	-	-	-
口腔カンジダ症	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
耳感染	2 (5.0)	-	2 (5.0)	-	-	-
帯状疱疹	2 (5.0)	-	2 (5.0)	-	-	-
敗血症	2 (5.0)	-	-	2 (5.0)	-	-
鼻咽頭炎	2 (5.0)	2 (5.0)	-	-	-	-
ウイルス感染	1 (2.5)	-	1 (2.5)	-	-	-
ニューモシスティスジロヴェシ肺炎	1 (2.5)	-	-	1 (2.5)	-	-
医療機器関連感染	1 (2.5)	-	-	1 (2.5)	-	-
外陰部腟カンジダ症	1 (2.5)	-	1 (2.5)	-	-	-
気管支肺炎	1 (2.5)	-	1 (2.5)	-	-	-
気道感染	1 (2.5)	-	-	1 (2.5)	-	-
急性中耳炎	1 (2.5)	-	1 (2.5)	-	-	-
口腔ウイルス感染	1 (2.5)	-	1 (2.5)	-	-	-
口腔感染	1 (2.5)	1 (2.5)	-	-	-	-

(body system continuing ...)

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
(... body system continuing)						
好中球減少性感染	1 (2.5)	-	-	1 (2.5)	-	-
処置後感染	1 (2.5)	-	1 (2.5)	-	-	-
皮膚カンジダ	1 (2.5)	-	1 (2.5)	-	-	-
副鼻腔炎	1 (2.5)	-	-	1 (2.5)	-	-
毛包炎	1 (2.5)	1 (2.5)	-	-	-	-
膀胱炎	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	56	14	26	15	1	-
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	26 (65.0)	18 (45.0)	11 (27.5)	3 (7.5)	-	-
咳嗽	10 (25.0)	7 (17.5)	2 (5.0)	1 (2.5)	-	-
呼吸困難	7 (17.5)	1 (2.5)	4 (10.0)	2 (5.0)	-	-
咽喉刺激感	4 (10.0)	-	4 (10.0)	-	-	-
鼻漏	3 (7.5)	3 (7.5)	-	-	-	-
咽頭の炎症	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
気管支痙攣	2 (5.0)	-	1 (2.5)	1 (2.5)	-	-
口腔咽頭痛	2 (5.0)	2 (5.0)	-	-	-	-
喉頭刺激感	2 (5.0)	-	2 (5.0)	-	-	-
発声障害	2 (5.0)	2 (5.0)	-	-	-	-
労作性呼吸困難	2 (5.0)	2 (5.0)	-	-	-	-
胸水	1 (2.5)	1 (2.5)	-	-	-	-
湿性咳嗽	1 (2.5)	1 (2.5)	-	-	-	-
鼻閉	1 (2.5)	1 (2.5)	-	-	-	-
副鼻腔うっ血	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	40	21	15	4	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (14 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	24 (60.0)	21 (52.5)	9 (22.5)	2 (5.0)	-	-
頭痛	14 (35.0)	9 (22.5)	4 (10.0)	1 (2.5)	-	-
浮動性めまい	7 (17.5)	6 (15.0)	1 (2.5)	-	-	-
錯感覚	5 (12.5)	3 (7.5)	2 (5.0)	-	-	-
末梢性ニューロパチー	5 (12.5)	4 (10.0)	1 (2.5)	-	-	-
末梢性感覚ニューロパチー	5 (12.5)	3 (7.5)	2 (5.0)	-	-	-
嗜眠	4 (10.0)	4 (10.0)	-	-	-	-
失神	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
味覚異常	3 (7.5)	3 (7.5)	-	-	-	-
感覚鈍麻	1 (2.5)	1 (2.5)	-	-	-	-
失神寸前の状態	1 (2.5)	-	-	1 (2.5)	-	-
失声症	1 (2.5)	1 (2.5)	-	-	-	-
神経痛	1 (2.5)	-	1 (2.5)	-	-	-
片頭痛	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	51	36	13	2	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	23 (57.5)	-	3 (7.5)	10 (25.0)	12 (30.0)	-
好中球減少症	18 (45.0)	-	1 (2.5)	6 (15.0)	11 (27.5)	-
発熱性好中球減少症	4 (10.0)	-	-	3 (7.5)	1 (2.5)	-
白血球減少症	2 (5.0)	-	-	2 (5.0)	-	-
貧血	2 (5.0)	-	1 (2.5)	1 (2.5)	-	-
血小板減少症	1 (2.5)	-	-	-	1 (2.5)	-
播種性血管内凝固	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	28	-	3	12	13	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (15 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	22 (55.0)	18 (45.0)	5 (12.5)	-	-	-
関節痛	5 (12.5)	4 (10.0)	1 (2.5)	-	-	-
筋痙縮	4 (10.0)	4 (10.0)	-	-	-	-
四肢痛	4 (10.0)	3 (7.5)	1 (2.5)	-	-	-
骨痛	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
背部痛	3 (7.5)	3 (7.5)	-	-	-	-
筋骨格系胸痛	2 (5.0)	2 (5.0)	-	-	-	-
筋骨格痛	2 (5.0)	2 (5.0)	-	-	-	-
顎痛	1 (2.5)	1 (2.5)	-	-	-	-
関節硬直	1 (2.5)	1 (2.5)	-	-	-	-
筋拘縮	1 (2.5)	1 (2.5)	-	-	-	-
筋硬化症	1 (2.5)	1 (2.5)	-	-	-	-
筋肉痛	1 (2.5)	-	1 (2.5)	-	-	-
変形性関節症	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	29	24	5	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (16 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	16 (40.0)	11 (27.5)	10 (25.0)	-	-	-
脱毛症	8 (20.0)	1 (2.5)	7 (17.5)	-	-	-
そう痒症	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
発疹	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
多汗症	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
皮膚乾燥	2 (5.0)	2 (5.0)	-	-	-	-
皮膚疼痛	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
顔面腫脹	1 (2.5)	1 (2.5)	-	-	-	-
丘疹	1 (2.5)	1 (2.5)	-	-	-	-
接触性皮膚炎	1 (2.5)	-	1 (2.5)	-	-	-
爪の障害	1 (2.5)	1 (2.5)	-	-	-	-
冷汗	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	25	12	13	-	-	-
精神障害						
Total Pts With at Least one AE	10 (25.0)	7 (17.5)	5 (12.5)	-	-	-
不眠症	5 (12.5)	4 (10.0)	1 (2.5)	-	-	-
うつ病	2 (5.0)	-	2 (5.0)	-	-	-
激越	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
感情不安定	1 (2.5)	1 (2.5)	-	-	-	-
気分変化	1 (2.5)	-	1 (2.5)	-	-	-
失見当識	1 (2.5)	-	1 (2.5)	-	-	-
不安	1 (2.5)	1 (2.5)	-	-	-	-
不安障害	1 (2.5)	1 (2.5)	-	-	-	-
抑うつ気分	1 (2.5)	1 (2.5)	-	-	-	-
落ち着きのなさ	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	16	10	6	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	9 (22.5)	-	8 (20.0)	2 (5.0)	-	-
潮紅	4 (10.0)	-	3 (7.5)	1 (2.5)	-	-
低血圧	3 (7.5)	-	2 (5.0)	1 (2.5)	-	-
蒼白	2 (5.0)	-	1 (2.5)	1 (2.5)	-	-
高血圧	1 (2.5)	-	1 (2.5)	-	-	-
静脈炎	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	11	-	8	3	-	-
代謝および栄養障害						
Total Pts With at Least one AE	8 (20.0)	4 (10.0)	1 (2.5)	1 (2.5)	1 (2.5)	1 (2.5)
高血糖	1 (2.5)	-	-	-	1 (2.5)	-
食欲減退	1 (2.5)	1 (2.5)	-	-	-	-
体液貯留	1 (2.5)	-	1 (2.5)	-	-	-
脱水	1 (2.5)	1 (2.5)	-	-	-	-
痛風	1 (2.5)	-	-	1 (2.5)	-	-
低カリウム血症	1 (2.5)	1 (2.5)	-	-	-	-
低カルシウム血症	1 (2.5)	1 (2.5)	-	-	-	-
乳酸アシドーシス	1 (2.5)	-	-	-	-	1 (2.5)
Total Number of AEs	8	4	1	1	1	1
心臓障害						
Total Pts With at Least one AE	7 (17.5)	2 (5.0)	5 (12.5)	-	-	-
頻脈	6 (15.0)	1 (2.5)	5 (12.5)	-	-	-
動悸	2 (5.0)	2 (5.0)	-	-	-	-
Total Number of AEs	8	3	5	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
眼障害						
Total Pts With at Least one AE	6 (15.0)	3 (7.5)	3 (7.5)	-	-	-
結膜炎	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
眼乾燥	1 (2.5)	1 (2.5)	-	-	-	-
眼瞼機能障害	1 (2.5)	-	1 (2.5)	-	-	-
視力障害	1 (2.5)	1 (2.5)	-	-	-	-
霧視	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	6	3	3	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	5 (12.5)	4 (10.0)	1 (2.5)	-	-	-
サンバーン	1 (2.5)	1 (2.5)	-	-	-	-
引っかき傷	1 (2.5)	1 (2.5)	-	-	-	-
処置による疼痛	1 (2.5)	-	1 (2.5)	-	-	-
足関節部骨折	1 (2.5)	1 (2.5)	-	-	-	-
爪損傷	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	5	4	1	-	-	-
腎および尿路障害						
Total Pts With at Least one AE	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
血尿	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
頻尿	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	3	2	1	-	-	-
肝胆道系障害						
Total Pts With at Least one AE	2 (5.0)	-	2 (5.0)	-	-	-
胆道仙痛	2 (5.0)	-	2 (5.0)	-	-	-
Total Number of AEs	2	-	2	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
外科および内科処置						
Total Pts With at Least one AE	1 (2.5)	-	-	1 (2.5)	-	-
腸管ステント挿入	1 (2.5)	-	-	1 (2.5)	-	-
Total Number of AEs	1	-	-	1	-	-
耳および迷路障害						
Total Pts With at Least one AE	1 (2.5)	1 (2.5)	-	-	-	-
耳介腫脹	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	1	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）						
Total Pts With at Least one AE	1 (2.5)	1 (2.5)	-	-	-	-
腫瘍フレア	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-
臨床検査						
Total Pts With at Least one AE	1 (2.5)	-	1 (2.5)	-	-	-
Ｃ－反応性蛋白増加	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	1	-	1	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	81 (100.0)	78 (96.3)	71 (87.7)	42 (51.9)	21 (25.9)	1 (1.2)
Total Number of AEs	848	409	313	99	26	1
胃腸障害						
Total Pts With at Least one AE	72 (88.9)	62 (76.5)	38 (46.9)	10 (12.3)	-	-
悪心	47 (58.0)	22 (27.2)	20 (24.7)	5 (6.2)	-	-
嘔吐	25 (30.9)	5 (6.2)	16 (19.8)	4 (4.9)	-	-
下痢	21 (25.9)	16 (19.8)	3 (3.7)	2 (2.5)	-	-
便秘	21 (25.9)	15 (18.5)	6 (7.4)	-	-	-
消化不良	11 (13.6)	8 (9.9)	2 (2.5)	1 (1.2)	-	-
腹痛	6 (7.4)	5 (6.2)	1 (1.2)	-	-	-
腹部膨満	4 (4.9)	3 (3.7)	1 (1.2)	-	-	-
口腔内潰瘍形成	3 (3.7)	1 (1.2)	2 (2.5)	-	-	-
口内炎	3 (3.7)	1 (1.2)	2 (2.5)	-	-	-
口内乾燥	3 (3.7)	3 (3.7)	-	-	-	-
上腹部痛	3 (3.7)	3 (3.7)	-	-	-	-
アフタ性口内炎	2 (2.5)	2 (2.5)	-	-	-	-
下腹部痛	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
歯痛	2 (2.5)	2 (2.5)	-	-	-	-
嚥下障害	2 (2.5)	2 (2.5)	-	-	-	-
イレウス	1 (1.2)	-	-	1 (1.2)	-	-
レッチング	1 (1.2)	-	1 (1.2)	-	-	-
胃炎	1 (1.2)	1 (1.2)	-	-	-	-
鼓腸	1 (1.2)	1 (1.2)	-	-	-	-
口の錯感覚	1 (1.2)	-	1 (1.2)	-	-	-
口腔そう痒症	1 (1.2)	-	1 (1.2)	-	-	-
口腔内出血	1 (1.2)	1 (1.2)	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (21 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
(... body system continuing)												
口唇潰瘍	1	(1.2)	1	(1.2)	-		-		-		-	
歯肉出血	1	(1.2)	1	(1.2)	-		-		-		-	
歯肉痛	1	(1.2)	1	(1.2)	-		-		-		-	
痔核	1	(1.2)	1	(1.2)	-		-		-		-	
食中毒	1	(1.2)	-		1	(1.2)	-		-		-	
舌痛	1	(1.2)	1	(1.2)	-		-		-		-	
舌潰瘍	1	(1.2)	-		1	(1.2)	-		-		-	
大腸炎	1	(1.2)	1	(1.2)	-		-		-		-	
直腸出血	1	(1.2)	1	(1.2)	-		-		-		-	
腹水	1	(1.2)	-		-		1	(1.2)	-		-	
腹部不快感	1	(1.2)	1	(1.2)	-		-		-		-	
Total Number of AEs	173		100		59		14		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	63 (77.8)	35 (43.2)	38 (46.9)	7 (8.6)	1 (1.2)	-
発熱	34 (42.0)	9 (11.1)	21 (25.9)	4 (4.9)	-	-
疲労	28 (34.6)	17 (21.0)	8 (9.9)	2 (2.5)	1 (1.2)	-
悪寒	27 (33.3)	3 (3.7)	21 (25.9)	3 (3.7)	-	-
粘膜の炎症	8 (9.9)	6 (7.4)	2 (2.5)	-	-	-
胸部不快感	7 (8.6)	-	5 (6.2)	2 (2.5)	-	-
末梢性浮腫	6 (7.4)	5 (6.2)	1 (1.2)	-	-	-
無力症	5 (6.2)	3 (3.7)	2 (2.5)	-	-	-
胸痛	3 (3.7)	2 (2.5)	-	1 (1.2)	-	-
疼痛	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
インフルエンザ様疾患	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
倦怠感	2 (2.5)	2 (2.5)	-	-	-	-
浮腫	2 (2.5)	2 (2.5)	-	-	-	-
カテーテル留置部位静脈炎	1 (1.2)	1 (1.2)	-	-	-	-
医療機器損傷	1 (1.2)	1 (1.2)	-	-	-	-
溢出	1 (1.2)	1 (1.2)	-	-	-	-
体温変動感	1 (1.2)	-	1 (1.2)	-	-	-
注射部位紅斑	1 (1.2)	1 (1.2)	-	-	-	-
冷感	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	133	57	63	12	1	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (23 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	49 (60.5)	26 (32.1)	33 (40.7)	15 (18.5)	3 (3.7)	-
感染	11 (13.6)	1 (1.2)	8 (9.9)	2 (2.5)	-	-
上気道感染	7 (8.6)	2 (2.5)	5 (6.2)	-	-	-
下気道感染	5 (6.2)	-	3 (3.7)	2 (2.5)	-	-
好中球減少性感染	5 (6.2)	-	-	3 (3.7)	2 (2.5)	-
尿路感染	5 (6.2)	3 (3.7)	2 (2.5)	-	-	-
鼻咽頭炎	4 (4.9)	4 (4.9)	-	-	-	-
眼感染	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
気管支炎	3 (3.7)	1 (1.2)	2 (2.5)	-	-	-
気道感染	3 (3.7)	2 (2.5)	-	1 (1.2)	-	-
口腔カンジダ症	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
好中球減少性敗血症	3 (3.7)	-	-	2 (2.5)	1 (1.2)	-
歯肉感染	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
帯状疱疹	3 (3.7)	-	3 (3.7)	-	-	-
肺炎	3 (3.7)	-	2 (2.5)	1 (1.2)	-	-
インフルエンザ	2 (2.5)	-	-	2 (2.5)	-	-
ウイルス性上気道感染	2 (2.5)	2 (2.5)	-	-	-	-
口腔感染	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
耳感染	2 (2.5)	-	2 (2.5)	-	-	-
敗血症	2 (2.5)	-	-	2 (2.5)	-	-
皮膚感染	2 (2.5)	-	1 (1.2)	1 (1.2)	-	-
鼻炎	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
副鼻腔炎	2 (2.5)	-	1 (1.2)	1 (1.2)	-	-
せつ	1 (1.2)	1 (1.2)	-	-	-	-
ウイルス感染	1 (1.2)	-	1 (1.2)	-	-	-
カテーテル留置部位感染	1 (1.2)	-	1 (1.2)	-	-	-

(body system continuing ...)

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
(... body system continuing)												
クロストリジウム・ディフィシレ大腸炎	1	(1.2)	1	(1.2)	-		-		-		-	
ニューモシスティスジロヴェシ肺炎	1	(1.2)	-		-		1	(1.2)	-		-	
胃腸炎	1	(1.2)	-		1	(1.2)	-		-		-	
医療機器関連感染	1	(1.2)	-		-		1	(1.2)	-		-	
外陰部膣カンジダ症	1	(1.2)	-		1	(1.2)	-		-		-	
気管支肺炎	1	(1.2)	-		1	(1.2)	-		-		-	
急性中耳炎	1	(1.2)	-		1	(1.2)	-		-		-	
限局性感染	1	(1.2)	-		1	(1.2)	-		-		-	
口腔ウイルス感染	1	(1.2)	-		1	(1.2)	-		-		-	
口腔ヘルペス	1	(1.2)	-		-		1	(1.2)	-		-	
口腔真菌感染	1	(1.2)	1	(1.2)	-		-		-		-	
口唇感染	1	(1.2)	-		1	(1.2)	-		-		-	
処置後感染	1	(1.2)	-		1	(1.2)	-		-		-	
単純ヘルペス	1	(1.2)	1	(1.2)	-		-		-		-	
中耳炎	1	(1.2)	-		1	(1.2)	-		-		-	
粘膜感染	1	(1.2)	1	(1.2)	-		-		-		-	
肺感染	1	(1.2)	1	(1.2)	-		-		-		-	
皮膚カンジダ	1	(1.2)	-		1	(1.2)	-		-		-	
毛包炎	1	(1.2)	1	(1.2)	-		-		-		-	
膀胱炎	1	(1.2)	-		1	(1.2)	-		-		-	
膣感染	1	(1.2)	1	(1.2)	-		-		-		-	
Total Number of AEs	101		31		47		20		3		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (25 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	45 (55.6)	30 (37.0)	18 (22.2)	5 (6.2)	-	-
咳嗽	20 (24.7)	15 (18.5)	4 (4.9)	1 (1.2)	-	-
呼吸困難	12 (14.8)	2 (2.5)	7 (8.6)	3 (3.7)	-	-
咽喉刺激感	5 (6.2)	-	5 (6.2)	-	-	-
口腔咽頭痛	4 (4.9)	3 (3.7)	1 (1.2)	-	-	-
発声障害	3 (3.7)	3 (3.7)	-	-	-	-
鼻漏	3 (3.7)	3 (3.7)	-	-	-	-
労作性呼吸困難	3 (3.7)	3 (3.7)	-	-	-	-
咽頭の炎症	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
気管支痙攣	2 (2.5)	-	1 (1.2)	1 (1.2)	-	-
胸水	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
喉頭刺激感	2 (2.5)	-	2 (2.5)	-	-	-
しゃっくり	1 (1.2)	1 (1.2)	-	-	-	-
喉頭浮腫	1 (1.2)	-	1 (1.2)	-	-	-
湿性咳嗽	1 (1.2)	1 (1.2)	-	-	-	-
低酸素症	1 (1.2)	-	-	1 (1.2)	-	-
鼻閉	1 (1.2)	1 (1.2)	-	-	-	-
副鼻腔うっ血	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	64	34	24	6	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	44 (54.3)	35 (43.2)	16 (19.8)	3 (3.7)	-	-
頭痛	30 (37.0)	18 (22.2)	10 (12.3)	2 (2.5)	-	-
浮動性めまい	10 (12.3)	7 (8.6)	3 (3.7)	-	-	-
末梢性感覚ニューロパチー	6 (7.4)	4 (4.9)	2 (2.5)	-	-	-
味覚異常	6 (7.4)	6 (7.4)	-	-	-	-
錯感覚	5 (6.2)	3 (3.7)	2 (2.5)	-	-	-
末梢性ニューロパチー	5 (6.2)	4 (4.9)	1 (1.2)	-	-	-
嗜眠	5 (6.2)	5 (6.2)	-	-	-	-
失神	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
感覚運動障害	1 (1.2)	1 (1.2)	-	-	-	-
感覚鈍麻	1 (1.2)	1 (1.2)	-	-	-	-
記憶障害	1 (1.2)	1 (1.2)	-	-	-	-
失神寸前の状態	1 (1.2)	-	-	1 (1.2)	-	-
失声症	1 (1.2)	1 (1.2)	-	-	-	-
振戦	1 (1.2)	1 (1.2)	-	-	-	-
神経痛	1 (1.2)	-	1 (1.2)	-	-	-
片頭痛	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	78	54	21	3	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (27 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	41 (50.6)	31 (38.3)	12 (14.8)	1 (1.2)	-	-
関節痛	9 (11.1)	7 (8.6)	1 (1.2)	1 (1.2)	-	-
背部痛	8 (9.9)	6 (7.4)	2 (2.5)	-	-	-
筋骨格痛	6 (7.4)	5 (6.2)	1 (1.2)	-	-	-
筋痙縮	6 (7.4)	6 (7.4)	-	-	-	-
四肢痛	6 (7.4)	5 (6.2)	1 (1.2)	-	-	-
骨痛	5 (6.2)	1 (1.2)	3 (3.7)	1 (1.2)	-	-
筋肉痛	4 (4.9)	2 (2.5)	2 (2.5)	-	-	-
筋骨格系胸痛	2 (2.5)	2 (2.5)	-	-	-	-
変形性関節症	2 (2.5)	2 (2.5)	-	-	-	-
顎痛	1 (1.2)	1 (1.2)	-	-	-	-
関節硬直	1 (1.2)	1 (1.2)	-	-	-	-
筋炎	1 (1.2)	-	1 (1.2)	-	-	-
筋緊張	1 (1.2)	-	1 (1.2)	-	-	-
筋拘縮	1 (1.2)	1 (1.2)	-	-	-	-
筋硬化症	1 (1.2)	1 (1.2)	-	-	-	-
筋骨格不快感	1 (1.2)	-	1 (1.2)	-	-	-
頚部痛	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	56	41	13	2	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (28 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	41 (50.6)	1 (1.2)	6 (7.4)	22 (27.2)	19 (23.5)	-
好中球減少症	32 (39.5)	1 (1.2)	1 (1.2)	13 (16.0)	17 (21.0)	-
血小板減少症	6 (7.4)	-	2 (2.5)	2 (2.5)	2 (2.5)	-
貧血	6 (7.4)	-	2 (2.5)	4 (4.9)	-	-
発熱性好中球減少症	4 (4.9)	-	-	3 (3.7)	1 (1.2)	-
白血球減少症	3 (3.7)	-	-	2 (2.5)	1 (1.2)	-
播種性血管内凝固	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	52	1	6	24	21	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (29 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
皮膚および皮下組織障害												
Total Pts With at Least one AE	37	(45.7)	27	(33.3)	18	(22.2)	1	(1.2)	-		-	
発疹	11	(13.6)	3	(3.7)	7	(8.6)	1	(1.2)	-		-	
脱毛症	9	(11.1)	2	(2.5)	7	(8.6)	-		-		-	
多汗症	8	(9.9)	7	(8.6)	1	(1.2)	-		-		-	
そう痒症	5	(6.2)	3	(3.7)	2	(2.5)	-		-		-	
顔面腫脹	3	(3.7)	2	(2.5)	1	(1.2)	-		-		-	
皮膚乾燥	3	(3.7)	3	(3.7)	-		-		-		-	
丘疹	2	(2.5)	2	(2.5)	-		-		-		-	
紅斑	2	(2.5)	2	(2.5)	-		-		-		-	
皮膚疼痛	2	(2.5)	1	(1.2)	1	(1.2)	-		-		-	
脂漏	1	(1.2)	1	(1.2)	-		-		-		-	
湿疹	1	(1.2)	1	(1.2)	-		-		-		-	
水疱	1	(1.2)	1	(1.2)	-		-		-		-	
接触性皮膚炎	1	(1.2)	-		1	(1.2)	-		-		-	
多形紅斑	1	(1.2)	-		1	(1.2)	-		-		-	
爪の障害	1	(1.2)	1	(1.2)	-		-		-		-	
皮脂欠乏性湿疹	1	(1.2)	-		1	(1.2)	-		-		-	
冷汗	1	(1.2)	1	(1.2)	-		-		-		-	
瘢痕	1	(1.2)	1	(1.2)	-		-		-		-	
蕁麻疹	1	(1.2)	-		1	(1.2)	-		-		-	
Total Number of AEs	55		31		23		1		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
血管障害												
Total Pts With at Least one AE	24	(29.6)	5	(6.2)	17	(21.0)	5	(6.2)	-		-	
潮紅	11	(13.6)	1	(1.2)	7	(8.6)	3	(3.7)	-		-	
低血圧	9	(11.1)	1	(1.2)	5	(6.2)	3	(3.7)	-		-	
静脈炎	5	(6.2)	1	(1.2)	4	(4.9)	-		-		-	
高血圧	3	(3.7)	-		2	(2.5)	1	(1.2)	-		-	
蒼白	2	(2.5)	-		1	(1.2)	1	(1.2)	-		-	
血腫	1	(1.2)	1	(1.2)	-		-		-		-	
血栓性静脈炎	1	(1.2)	1	(1.2)	-		-		-		-	
塞栓症	1	(1.2)	-		-		1	(1.2)	-		-	
四肢静脈血栓症	1	(1.2)	-		1	(1.2)	-		-		-	
Total Number of AEs	34		5		20		9		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (31 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
精神障害												
Total Pts With at Least one AE	19	(23.5)	13	(16.0)	8	(9.9)	1	(1.2)	-		-	
不眠症	9	(11.1)	7	(8.6)	2	(2.5)	-		-		-	
うつ病	3	(3.7)	-		2	(2.5)	1	(1.2)	-		-	
不安	3	(3.7)	2	(2.5)	1	(1.2)	-		-		-	
激越	2	(2.5)	1	(1.2)	1	(1.2)	-		-		-	
不安障害	2	(2.5)	2	(2.5)	-		-		-		-	
感情不安定	1	(1.2)	1	(1.2)	-		-		-		-	
気分変化	1	(1.2)	-		1	(1.2)	-		-		-	
錯乱状態	1	(1.2)	1	(1.2)	-		-		-		-	
失見当識	1	(1.2)	-		1	(1.2)	-		-		-	
人格障害	1	(1.2)	1	(1.2)	-		-		-		-	
睡眠障害	1	(1.2)	1	(1.2)	-		-		-		-	
精神病性障害	1	(1.2)	-		1	(1.2)	-		-		-	
抑うつ気分	1	(1.2)	1	(1.2)	-		-		-		-	
落ち着きのなさ	1	(1.2)	1	(1.2)	-		-		-		-	
Total Number of AEs	28		18		9		1		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (32 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
代謝および栄養障害						
Total Pts With at Least one AE	13 (16.0)	7 (8.6)	2 (2.5)	4 (4.9)	1 (1.2)	1 (1.2)
低カリウム血症	4 (4.9)	3 (3.7)	1 (1.2)	-	-	-
食欲減退	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
脱水	3 (3.7)	1 (1.2)	1 (1.2)	1 (1.2)	-	-
体液貯留	2 (2.5)	-	1 (1.2)	1 (1.2)	-	-
高血糖	1 (1.2)	-	-	-	1 (1.2)	-
痛風	1 (1.2)	-	-	1 (1.2)	-	-
低カルシウム血症	1 (1.2)	1 (1.2)	-	-	-	-
低マグネシウム血症	1 (1.2)	-	-	1 (1.2)	-	-
乳酸アシドーシス	1 (1.2)	-	-	-	-	1 (1.2)
Total Number of AEs	17	7	4	4	1	1
眼障害						
Total Pts With at Least one AE	11 (13.6)	7 (8.6)	4 (4.9)	-	-	-
眼乾燥	2 (2.5)	2 (2.5)	-	-	-	-
結膜炎	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
視力障害	2 (2.5)	2 (2.5)	-	-	-	-
角膜炎	1 (1.2)	-	1 (1.2)	-	-	-
眼瞼機能障害	1 (1.2)	-	1 (1.2)	-	-	-
硝子体出血	1 (1.2)	1 (1.2)	-	-	-	-
霧視	1 (1.2)	-	1 (1.2)	-	-	-
流涙増加	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	11	7	4	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (33 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
心臓障害												
Total Pts With at Least one AE	9	(11.1)	2	(2.5)	7	(8.6)	-		-		-	
頻脈	8	(9.9)	1	(1.2)	7	(8.6)	-		-		-	
動悸	2	(2.5)	2	(2.5)	-		-		-		-	
Total Number of AEs	10		3		7		-		-		-	
傷害、中毒および処置合併症												
Total Pts With at Least one AE	8	(9.9)	7	(8.6)	2	(2.5)	-		-		-	
サンバーン	2	(2.5)	2	(2.5)	-		-		-		-	
引っかき傷	1	(1.2)	1	(1.2)	-		-		-		-	
擦過傷	1	(1.2)	1	(1.2)	-		-		-		-	
処置による疼痛	1	(1.2)	-		1	(1.2)	-		-		-	
足関節部骨折	1	(1.2)	1	(1.2)	-		-		-		-	
爪損傷	1	(1.2)	1	(1.2)	-		-		-		-	
転倒	1	(1.2)	-		1	(1.2)	-		-		-	
熱傷	1	(1.2)	1	(1.2)	-		-		-		-	
Total Number of AEs	9		7		2		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (34 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
臨床検査												
Total Pts With at Least one AE	7	(8.6)	5	(6.2)	1	(1.2)	1	(1.2)	-		-	
Ｃ－反応性蛋白増加	1	(1.2)	-		1	(1.2)	-		-		-	
アスパラギン酸アミノトランスフェラーゼ増加	1	(1.2)	-		-		1	(1.2)	-		-	
アラニンアミノトランスフェラーゼ増加	1	(1.2)	-		-		1	(1.2)	-		-	
血中クレアチニン増加	1	(1.2)	1	(1.2)	-		-		-		-	
血中尿酸増加	1	(1.2)	1	(1.2)	-		-		-		-	
総蛋白減少	1	(1.2)	1	(1.2)	-		-		-		-	
体重減少	1	(1.2)	1	(1.2)	-		-		-		-	
体重増加	1	(1.2)	1	(1.2)	-		-		-		-	
Total Number of AEs	8		5		1		2		-		-	
腎および尿路障害												
Total Pts With at Least one AE	6	(7.4)	4	(4.9)	2	(2.5)	-		-		-	
血尿	2	(2.5)	1	(1.2)	1	(1.2)	-		-		-	
尿失禁	1	(1.2)	1	(1.2)	-		-		-		-	
排尿困難	1	(1.2)	-		1	(1.2)	-		-		-	
頻尿	1	(1.2)	1	(1.2)	-		-		-		-	
夜間頻尿	1	(1.2)	1	(1.2)	-		-		-		-	
Total Number of AEs	6		4		2		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (35 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
耳および迷路障害						
Total Pts With at Least one AE	4 (4.9)	2 (2.5)	2 (2.5)	-	-	-
回転性めまい	1 (1.2)	-	1 (1.2)	-	-	-
外耳痛	1 (1.2)	1 (1.2)	-	-	-	-
耳介腫脹	1 (1.2)	1 (1.2)	-	-	-	-
耳痛	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	4	2	2	-	-	-
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）						
Total Pts With at Least one AE	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
腫瘍フレア	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
汗腺腫瘍	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	3	2	1	-	-	-
肝胆道系障害						
Total Pts With at Least one AE	2 (2.5)	-	2 (2.5)	-	-	-
胆道仙痛	2 (2.5)	-	2 (2.5)	-	-	-
Total Number of AEs	2	-	2	-	-	-
免疫系障害						
Total Pts With at Least one AE	2 (2.5)	-	2 (2.5)	-	-	-
過敏症	2 (2.5)	-	2 (2.5)	-	-	-
Total Number of AEs	2	-	2	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (36 of 37)

ae17_0001l_sa Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
外科および内科処置												
Total Pts With at Least one AE	1	(1.2)	-		-		1	(1.2)	-		-	
腸管ステント挿入	1	(1.2)	-		-		1	(1.2)	-		-	
Total Number of AEs	1		-		-		1		-		-	
生殖系および乳房障害												
Total Pts With at Least one AE	1	(1.2)	-		1	(1.2)	-		-		-	
外陰腟そう痒症	1	(1.2)	-		1	(1.2)	-		-		-	
Total Number of AEs	1		-		1		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 28MAY2015:12:52:02 (37 of 37)

[5.3.5.3-1 ae17_0001l_sa を再掲]

表 2.7.6.2.1.8-6 因果関係が否定できないすべての有害事象（B021000試験，未治療FL患者）

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine; N = 41

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	37	(90.2)	30	(73.2)	30	(73.2)	13	(31.7)	6	(14.6)	-	
Total Number of AEs	213		76		94		35		8		-	
一般・全身障害および投与部位の状態												
Total Pts With at Least one AE	30	(73.2)	15	(36.6)	17	(41.5)	4	(9.8)	-		-	
発熱	17	(41.5)	4	(9.8)	10	(24.4)	3	(7.3)	-		-	
悪寒	16	(39.0)	1	(2.4)	12	(29.3)	3	(7.3)	-		-	
疲労	9	(22.0)	7	(17.1)	2	(4.9)	-		-		-	
無力症	3	(7.3)	2	(4.9)	1	(2.4)	-		-		-	
胸部不快感	2	(4.9)	-		1	(2.4)	1	(2.4)	-		-	
倦怠感	2	(4.9)	2	(4.9)	-		-		-		-	
注射部位紅斑	1	(2.4)	1	(2.4)	-		-		-		-	
粘膜の炎症	1	(2.4)	-		1	(2.4)	-		-		-	
疼痛	1	(2.4)	1	(2.4)	-		-		-		-	
Total Number of AEs	52		18		27		7		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (1 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
胃腸障害						
Total Pts With at Least one AE	26 (63.4)	19 (46.3)	15 (36.6)	4 (9.8)	-	-
悪心	23 (56.1)	11 (26.8)	9 (22.0)	3 (7.3)	-	-
嘔吐	8 (19.5)	2 (4.9)	4 (9.8)	2 (4.9)	-	-
下痢	5 (12.2)	3 (7.3)	1 (2.4)	1 (2.4)	-	-
レッチング	1 (2.4)	-	1 (2.4)	-	-	-
下腹部痛	1 (2.4)	1 (2.4)	-	-	-	-
口腔そう痒症	1 (2.4)	-	1 (2.4)	-	-	-
口内炎	1 (2.4)	-	1 (2.4)	-	-	-
消化不良	1 (2.4)	1 (2.4)	-	-	-	-
腹痛	1 (2.4)	1 (2.4)	-	-	-	-
腹部不快感	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	43	20	17	6	-	-
血液およびリンパ系障害						
Total Pts With at Least one AE	13 (31.7)	1 (2.4)	2 (4.9)	9 (22.0)	5 (12.2)	-
好中球減少症	10 (24.4)	1 (2.4)	-	5 (12.2)	4 (9.8)	-
貧血	4 (9.8)	-	1 (2.4)	3 (7.3)	-	-
血小板減少症	3 (7.3)	-	1 (2.4)	1 (2.4)	1 (2.4)	-
白血球減少症	1 (2.4)	-	-	-	1 (2.4)	-
Total Number of AEs	18	1	2	9	6	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (2 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine; N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	12 (29.3)	6 (14.6)	6 (14.6)	2 (4.9)	2 (4.9)	-
感染	4 (9.8)	1 (2.4)	3 (7.3)	-	-	-
下気道感染	2 (4.9)	-	2 (4.9)	-	-	-
好中球減少性感染	2 (4.9)	-	-	-	2 (4.9)	-
上気道感染	2 (4.9)	-	2 (4.9)	-	-	-
皮膚感染	2 (4.9)	-	1 (2.4)	1 (2.4)	-	-
せつ	1 (2.4)	1 (2.4)	-	-	-	-
気道感染	1 (2.4)	1 (2.4)	-	-	-	-
口腔カンジダ症	1 (2.4)	1 (2.4)	-	-	-	-
口腔ヘルペス	1 (2.4)	-	-	1 (2.4)	-	-
口腔感染	1 (2.4)	-	1 (2.4)	-	-	-
口腔真菌感染	1 (2.4)	1 (2.4)	-	-	-	-
帯状疱疹	1 (2.4)	-	1 (2.4)	-	-	-
粘膜感染	1 (2.4)	1 (2.4)	-	-	-	-
鼻炎	1 (2.4)	-	1 (2.4)	-	-	-
Total Number of AEs	21	6	11	2	2	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (3 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
皮膚および皮下組織障害						
Total Pts With at Least one AE	12 (29.3)	8 (19.5)	6 (14.6)	1 (2.4)	-	-
発疹	6 (14.6)	2 (4.9)	3 (7.3)	1 (2.4)	-	-
多汗症	3 (7.3)	3 (7.3)	-	-	-	-
顔面腫脹	2 (4.9)	1 (2.4)	1 (2.4)	-	-	-
紅斑	2 (4.9)	2 (4.9)	-	-	-	-
そう痒症	1 (2.4)	-	1 (2.4)	-	-	-
脂漏	1 (2.4)	1 (2.4)	-	-	-	-
多形紅斑	1 (2.4)	-	1 (2.4)	-	-	-
皮脂欠乏性湿疹	1 (2.4)	-	1 (2.4)	-	-	-
蕁麻疹	1 (2.4)	-	1 (2.4)	-	-	-
Total Number of AEs	18	9	8	1	-	-
神経系障害						
Total Pts With at Least one AE	12 (29.3)	7 (17.1)	5 (12.2)	1 (2.4)	-	-
頭痛	8 (19.5)	3 (7.3)	4 (9.8)	1 (2.4)	-	-
味覚異常	3 (7.3)	3 (7.3)	-	-	-	-
浮動性めまい	2 (4.9)	-	2 (4.9)	-	-	-
感覚運動障害	1 (2.4)	1 (2.4)	-	-	-	-
振戦	1 (2.4)	1 (2.4)	-	-	-	-
嗜眠	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	16	9	6	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (4 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
血管障害												
Total Pts With at Least one AE	10	(24.4)	2	(4.9)	6	(14.6)	2	(4.9)	-		-	
潮紅	5	(12.2)	-		3	(7.3)	2	(4.9)	-		-	
低血圧	5	(12.2)	1	(2.4)	2	(4.9)	2	(4.9)	-		-	
静脈炎	3	(7.3)	-		3	(7.3)	-		-		-	
血栓性静脈炎	1	(2.4)	1	(2.4)	-		-		-		-	
高血圧	1	(2.4)	-		-		1	(2.4)	-		-	
Total Number of AEs	15		2		8		5		-		-	
筋骨格系および結合組織障害												
Total Pts With at Least one AE	8	(19.5)	6	(14.6)	3	(7.3)	-		-		-	
関節痛	2	(4.9)	2	(4.9)	-		-		-		-	
筋肉痛	2	(4.9)	1	(2.4)	1	(2.4)	-		-		-	
筋痙縮	2	(4.9)	2	(4.9)	-		-		-		-	
筋緊張	1	(2.4)	-		1	(2.4)	-		-		-	
筋骨格不快感	1	(2.4)	-		1	(2.4)	-		-		-	
四肢痛	1	(2.4)	1	(2.4)	-		-		-		-	
Total Number of AEs	9		6		3		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (5 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	7 (17.1)	2 (4.9)	4 (9.8)	2 (4.9)	-	-
呼吸困難	4 (9.8)	-	3 (7.3)	1 (2.4)	-	-
咽喉刺激感	1 (2.4)	-	1 (2.4)	-	-	-
咳嗽	1 (2.4)	-	1 (2.4)	-	-	-
口腔咽頭痛	1 (2.4)	1 (2.4)	-	-	-	-
喉頭浮腫	1 (2.4)	-	1 (2.4)	-	-	-
低酸素症	1 (2.4)	-	-	1 (2.4)	-	-
発声障害	1 (2.4)	1 (2.4)	-	-	-	-
Total Number of AEs	10	2	6	2	-	-
代謝および栄養障害						
Total Pts With at Least one AE	3 (7.3)	-	1 (2.4)	2 (4.9)	-	-
体液貯留	1 (2.4)	-	-	1 (2.4)	-	-
脱水	1 (2.4)	-	-	1 (2.4)	-	-
低カリウム血症	1 (2.4)	-	1 (2.4)	-	-	-
Total Number of AEs	3	-	1	2	-	-
耳および迷路障害						
Total Pts With at Least one AE	2 (4.9)	-	2 (4.9)	-	-	-
回転性めまい	1 (2.4)	-	1 (2.4)	-	-	-
耳痛	1 (2.4)	-	1 (2.4)	-	-	-
Total Number of AEs	2	-	2	-	-	-
心臓障害						
Total Pts With at Least one AE	2 (4.9)	-	2 (4.9)	-	-	-
頻脈	2 (4.9)	-	2 (4.9)	-	-	-
Total Number of AEs	2	-	2	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+Bendamustine: N = 41

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
傷害、中毒および処置合併症											
Total Pts With at Least one AE	1 (2.4)	1	(2.4)	-		-		-		-	
熱傷	1 (2.4)	1	(2.4)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	
生殖系および乳房障害											
Total Pts With at Least one AE	1 (2.4)	-		1	(2.4)	-		-		-	
外陰腟そう痒症	1 (2.4)	-		1	(2.4)	-		-		-	
Total Number of AEs	1	-		1		-		-		-	
精神障害											
Total Pts With at Least one AE	1 (2.4)	1	(2.4)	-		-		-		-	
不眠症	1 (2.4)	1	(2.4)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	
臨床検査											
Total Pts With at Least one AE	1 (2.4)	1	(2.4)	-		-		-		-	
体重増加	1 (2.4)	1	(2.4)	-		-		-		-	
Total Number of AEs	1	1		-		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (7 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
ALL BODY SYSTEMS						
Total Pts with at Least one AE	40 (100.0)	29 (72.5)	29 (72.5)	18 (45.0)	13 (32.5)	1 (2.5)
Total Number of AEs	279	97	130	35	16	1
胃腸障害						
Total Pts With at Least one AE	32 (80.0)	22 (55.0)	18 (45.0)	5 (12.5)	-	-
悪心	19 (47.5)	7 (17.5)	10 (25.0)	2 (5.0)	-	-
嘔吐	15 (37.5)	2 (5.0)	11 (27.5)	2 (5.0)	-	-
便秘	10 (25.0)	6 (15.0)	4 (10.0)	-	-	-
消化不良	4 (10.0)	3 (7.5)	-	1 (2.5)	-	-
口腔内潰瘍形成	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
アフタ性口内炎	2 (5.0)	2 (5.0)	-	-	-	-
下痢	2 (5.0)	2 (5.0)	-	-	-	-
口内炎	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
腹痛	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
嚥下障害	2 (5.0)	2 (5.0)	-	-	-	-
イレウス	1 (2.5)	-	-	1 (2.5)	-	-
口の錯感覚	1 (2.5)	-	1 (2.5)	-	-	-
口腔内出血	1 (2.5)	1 (2.5)	-	-	-	-
口内乾燥	1 (2.5)	1 (2.5)	-	-	-	-
歯肉出血	1 (2.5)	1 (2.5)	-	-	-	-
歯肉痛	1 (2.5)	1 (2.5)	-	-	-	-
痔核	1 (2.5)	1 (2.5)	-	-	-	-
舌潰瘍	1 (2.5)	-	1 (2.5)	-	-	-
腹水	1 (2.5)	-	-	1 (2.5)	-	-
腹部膨満	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	71	33	31	7	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	25 (62.5)	9 (22.5)	17 (42.5)	2 (5.0)	1 (2.5)	-
発熱	13 (32.5)	2 (5.0)	10 (25.0)	1 (2.5)	-	-
疲労	12 (30.0)	5 (12.5)	5 (12.5)	1 (2.5)	1 (2.5)	-
悪寒	9 (22.5)	-	9 (22.5)	-	-	-
粘膜の炎症	6 (15.0)	5 (12.5)	1 (2.5)	-	-	-
胸部不快感	4 (10.0)	-	3 (7.5)	1 (2.5)	-	-
胸痛	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	45	12	29	3	1	-
血液およびリンパ系障害						
Total Pts With at Least one AE	22 (55.0)	-	3 (7.5)	9 (22.5)	12 (30.0)	-
好中球減少症	17 (42.5)	-	1 (2.5)	5 (12.5)	11 (27.5)	-
発熱性好中球減少症	4 (10.0)	-	-	3 (7.5)	1 (2.5)	-
白血球減少症	2 (5.0)	-	-	2 (5.0)	-	-
貧血	2 (5.0)	-	1 (2.5)	1 (2.5)	-	-
血小板減少症	1 (2.5)	-	-	-	1 (2.5)	-
播種性血管内凝固	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	27	-	3	11	13	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (9 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading				
		1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
神経系障害						
Total Pts With at Least one AE	20 (50.0)	16 (40.0)	9 (22.5)	-	-	-
頭痛	8 (20.0)	3 (7.5)	5 (12.5)	-	-	-
末梢性感覚ニューロパチー	5 (12.5)	3 (7.5)	2 (5.0)	-	-	-
浮動性めまい	4 (10.0)	3 (7.5)	1 (2.5)	-	-	-
末梢性ニューロパチー	4 (10.0)	3 (7.5)	1 (2.5)	-	-	-
嗜眠	4 (10.0)	4 (10.0)	-	-	-	-
錯感覚	3 (7.5)	1 (2.5)	2 (5.0)	-	-	-
味覚異常	3 (7.5)	3 (7.5)	-	-	-	-
感覚鈍麻	1 (2.5)	1 (2.5)	-	-	-	-
神経痛	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	33	21	12	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (10 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	15 (37.5)	4 (10.0)	8 (20.0)	6 (15.0)	1 (2.5)	-
感染	3 (7.5)	-	2 (5.0)	1 (2.5)	-	-
肺炎	3 (7.5)	-	2 (5.0)	1 (2.5)	-	-
口腔カンジダ症	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
好中球減少性敗血症	2 (5.0)	-	-	1 (2.5)	1 (2.5)	-
ニューモシスティスジロヴェシ肺炎	1 (2.5)	-	-	1 (2.5)	-	-
外陰部腟カンジダ症	1 (2.5)	-	1 (2.5)	-	-	-
眼感染	1 (2.5)	1 (2.5)	-	-	-	-
気管支炎	1 (2.5)	-	1 (2.5)	-	-	-
気管支肺炎	1 (2.5)	-	1 (2.5)	-	-	-
気道感染	1 (2.5)	-	-	1 (2.5)	-	-
急性中耳炎	1 (2.5)	-	1 (2.5)	-	-	-
口腔感染	1 (2.5)	1 (2.5)	-	-	-	-
好中球減少性感染	1 (2.5)	-	-	1 (2.5)	-	-
歯肉感染	1 (2.5)	1 (2.5)	-	-	-	-
耳感染	1 (2.5)	-	1 (2.5)	-	-	-
帯状疱疹	1 (2.5)	-	1 (2.5)	-	-	-
敗血症	1 (2.5)	-	-	1 (2.5)	-	-
副鼻腔炎	1 (2.5)	-	-	1 (2.5)	-	-
Total Number of AEs	24	4	11	8	1	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (11 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
呼吸器、胸郭および縦隔障害						
Total Pts With at Least one AE	14 (35.0)	5 (12.5)	9 (22.5)	2 (5.0)	-	-
呼吸困難	7 (17.5)	1 (2.5)	4 (10.0)	2 (5.0)	-	-
咽喉刺激感	4 (10.0)	-	4 (10.0)	-	-	-
咽頭の炎症	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
気管支痙攣	2 (5.0)	-	1 (2.5)	1 (2.5)	-	-
喉頭刺激感	2 (5.0)	-	2 (5.0)	-	-	-
咳嗽	1 (2.5)	1 (2.5)	-	-	-	-
口腔咽頭痛	1 (2.5)	1 (2.5)	-	-	-	-
発声障害	1 (2.5)	1 (2.5)	-	-	-	-
鼻閉	1 (2.5)	1 (2.5)	-	-	-	-
副鼻腔うっ血	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	22	6	13	3	-	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	11 (27.5)	5 (12.5)	8 (20.0)	-	-	-
脱毛症	7 (17.5)	1 (2.5)	6 (15.0)	-	-	-
発疹	3 (7.5)	2 (5.0)	1 (2.5)	-	-	-
皮膚乾燥	2 (5.0)	2 (5.0)	-	-	-	-
そう痒症	1 (2.5)	-	1 (2.5)	-	-	-
多汗症	1 (2.5)	-	1 (2.5)	-	-	-
爪の障害	1 (2.5)	1 (2.5)	-	-	-	-
皮膚疼痛	1 (2.5)	-	1 (2.5)	-	-	-
冷汗	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	17	7	10	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血管障害						
Total Pts With at Least one AE	9 (22.5)	-	8 (20.0)	2 (5.0)	-	-
潮紅	4 (10.0)	-	3 (7.5)	1 (2.5)	-	-
低血圧	3 (7.5)	-	2 (5.0)	1 (2.5)	-	-
蒼白	2 (5.0)	-	1 (2.5)	1 (2.5)	-	-
高血圧	1 (2.5)	-	1 (2.5)	-	-	-
静脈炎	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	11	-	8	3	-	-
筋骨格系および結合組織障害						
Total Pts With at Least one AE	7 (17.5)	6 (15.0)	2 (5.0)	-	-	-
関節痛	2 (5.0)	2 (5.0)	-	-	-	-
筋痙縮	2 (5.0)	2 (5.0)	-	-	-	-
四肢痛	2 (5.0)	1 (2.5)	1 (2.5)	-	-	-
関節硬直	1 (2.5)	1 (2.5)	-	-	-	-
筋肉痛	1 (2.5)	-	1 (2.5)	-	-	-
背部痛	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	9	7	2	-	-	-
心臓障害						
Total Pts With at Least one AE	6 (15.0)	1 (2.5)	5 (12.5)	-	-	-
頻脈	6 (15.0)	1 (2.5)	5 (12.5)	-	-	-
Total Number of AEs	6	1	5	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (13 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
代謝および栄養障害						
Total Pts With at Least one AE	5 (12.5)	2 (5.0)	1 (2.5)	-	1 (2.5)	1 (2.5)
高血糖	1 (2.5)	-	-	-	1 (2.5)	-
食欲減退	1 (2.5)	1 (2.5)	-	-	-	-
体液貯留	1 (2.5)	-	1 (2.5)	-	-	-
低カリウム血症	1 (2.5)	1 (2.5)	-	-	-	-
乳酸アシドーシス	1 (2.5)	-	-	-	-	1 (2.5)
Total Number of AEs	5	2	1	-	1	1
精神障害						
Total Pts With at Least one AE	4 (10.0)	2 (5.0)	2 (5.0)	-	-	-
不眠症	2 (5.0)	2 (5.0)	-	-	-	-
うつ病	1 (2.5)	-	1 (2.5)	-	-	-
感情不安定	1 (2.5)	1 (2.5)	-	-	-	-
気分変化	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	5	3	2	-	-	-
眼障害						
Total Pts With at Least one AE	2 (5.0)	-	2 (5.0)	-	-	-
眼瞼機能障害	1 (2.5)	-	1 (2.5)	-	-	-
霧視	1 (2.5)	-	1 (2.5)	-	-	-
Total Number of AEs	2	-	2	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	1 (2.5)	1 (2.5)	-	-	-	-
サンバーン	1 (2.5)	1 (2.5)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): BO21000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: 1000mg RO5072759+CHOP: N = 40

Body System/ Adverse Event	Total	CTC Grading									
		1		2		3		4		5	
	No. (%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
腎および尿路障害											
Total Pts With at Least one AE	1 (2.5)	-		1 (2.5)		-		-		-	
血尿	1 (2.5)	-		1 (2.5)		-		-		-	
Total Number of AEs	1	-		1		-		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (15 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading									
			1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
ALL BODY SYSTEMS												
Total Pts with at Least one AE	77	(95.1)	59	(72.8)	59	(72.8)	31	(38.3)	19	(23.5)	1	(1.2)
Total Number of AEs	492		173		224		70		24		1	
胃腸障害												
Total Pts With at Least one AE	58	(71.6)	41	(50.6)	33	(40.7)	9	(11.1)	-		-	
悪心	42	(51.9)	18	(22.2)	19	(23.5)	5	(6.2)	-		-	
嘔吐	23	(28.4)	4	(4.9)	15	(18.5)	4	(4.9)	-		-	
便秘	10	(12.3)	6	(7.4)	4	(4.9)	-		-		-	
下痢	7	(8.6)	5	(6.2)	1	(1.2)	1	(1.2)	-		-	
消化不良	5	(6.2)	4	(4.9)	-		1	(1.2)	-		-	
口腔内潰瘍形成	3	(3.7)	1	(1.2)	2	(2.5)	-		-		-	
口内炎	3	(3.7)	1	(1.2)	2	(2.5)	-		-		-	
腹痛	3	(3.7)	2	(2.5)	1	(1.2)	-		-		-	
アフタ性口内炎	2	(2.5)	2	(2.5)	-		-		-		-	
嚥下障害	2	(2.5)	2	(2.5)	-		-		-		-	
イレウス	1	(1.2)	-		-		1	(1.2)	-		-	
レッチング	1	(1.2)	-		1	(1.2)	-		-		-	
下腹部痛	1	(1.2)	1	(1.2)	-		-		-		-	
口の錯感覚	1	(1.2)	-		1	(1.2)	-		-		-	
口腔そう痒症	1	(1.2)	-		1	(1.2)	-		-		-	
口腔内出血	1	(1.2)	1	(1.2)	-		-		-		-	
口内乾燥	1	(1.2)	1	(1.2)	-		-		-		-	
歯肉出血	1	(1.2)	1	(1.2)	-		-		-		-	
歯肉痛	1	(1.2)	1	(1.2)	-		-		-		-	
痔核	1	(1.2)	1	(1.2)	-		-		-		-	
舌潰瘍	1	(1.2)	-		1	(1.2)	-		-		-	
腹水	1	(1.2)	-		-		1	(1.2)	-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
(... body system continuing)						
腹部不快感	1 (1.2)	1 (1.2)	-	-	-	-
腹部膨満	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	114	53	48	13	-	-
一般・全身障害および投与部位の状態						
Total Pts With at Least one AE	55 (67.9)	24 (29.6)	34 (42.0)	6 (7.4)	1 (1.2)	-
発熱	30 (37.0)	6 (7.4)	20 (24.7)	4 (4.9)	-	-
悪寒	25 (30.9)	1 (1.2)	21 (25.9)	3 (3.7)	-	-
疲労	21 (25.9)	12 (14.8)	7 (8.6)	1 (1.2)	1 (1.2)	-
粘膜の炎症	7 (8.6)	5 (6.2)	2 (2.5)	-	-	-
胸部不快感	6 (7.4)	-	4 (4.9)	2 (2.5)	-	-
無力症	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
倦怠感	2 (2.5)	2 (2.5)	-	-	-	-
胸痛	1 (1.2)	-	1 (1.2)	-	-	-
注射部位紅斑	1 (1.2)	1 (1.2)	-	-	-	-
疼痛	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	97	30	56	10	1	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (17 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
血液およびリンパ系障害						
Total Pts With at Least one AE	35 (43.2)	1 (1.2)	5 (6.2)	18 (22.2)	17 (21.0)	-
好中球減少症	27 (33.3)	1 (1.2)	1 (1.2)	10 (12.3)	15 (18.5)	-
貧血	6 (7.4)	-	2 (2.5)	4 (4.9)	-	-
血小板減少症	4 (4.9)	-	1 (1.2)	1 (1.2)	2 (2.5)	-
発熱性好中球減少症	4 (4.9)	-	-	3 (3.7)	1 (1.2)	-
白血球減少症	3 (3.7)	-	-	2 (2.5)	1 (1.2)	-
播種性血管内凝固	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	45	1	5	20	19	-
神経系障害						
Total Pts With at Least one AE	32 (39.5)	23 (28.4)	14 (17.3)	1 (1.2)	-	-
頭痛	16 (19.8)	6 (7.4)	9 (11.1)	1 (1.2)	-	-
浮動性めまい	6 (7.4)	3 (3.7)	3 (3.7)	-	-	-
味覚異常	6 (7.4)	6 (7.4)	-	-	-	-
末梢性感覚ニューロパチー	5 (6.2)	3 (3.7)	2 (2.5)	-	-	-
嗜眠	5 (6.2)	5 (6.2)	-	-	-	-
末梢性ニューロパチー	4 (4.9)	3 (3.7)	1 (1.2)	-	-	-
錯感覚	3 (3.7)	1 (1.2)	2 (2.5)	-	-	-
感覚運動障害	1 (1.2)	1 (1.2)	-	-	-	-
感覚鈍麻	1 (1.2)	1 (1.2)	-	-	-	-
振戦	1 (1.2)	1 (1.2)	-	-	-	-
神経痛	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	49	30	18	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
感染症および寄生虫症						
Total Pts With at Least one AE	27 (33.3)	10 (12.3)	14 (17.3)	8 (9.9)	3 (3.7)	-
感染	7 (8.6)	1 (1.2)	5 (6.2)	1 (1.2)	-	-
口腔カンジダ症	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
好中球減少性感染	3 (3.7)	-	-	1 (1.2)	2 (2.5)	-
肺炎	3 (3.7)	-	2 (2.5)	1 (1.2)	-	-
下気道感染	2 (2.5)	-	2 (2.5)	-	-	-
気道感染	2 (2.5)	1 (1.2)	-	1 (1.2)	-	-
口腔感染	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
好中球減少性敗血症	2 (2.5)	-	-	1 (1.2)	1 (1.2)	-
上気道感染	2 (2.5)	-	2 (2.5)	-	-	-
帯状疱疹	2 (2.5)	-	2 (2.5)	-	-	-
皮膚感染	2 (2.5)	-	1 (1.2)	1 (1.2)	-	-
せつ	1 (1.2)	1 (1.2)	-	-	-	-
ニューモシスティスジロヴェシ肺炎	1 (1.2)	-	-	1 (1.2)	-	-
外陰部腟カンジダ症	1 (1.2)	-	1 (1.2)	-	-	-
眼感染	1 (1.2)	1 (1.2)	-	-	-	-
気管支炎	1 (1.2)	-	1 (1.2)	-	-	-
気管支肺炎	1 (1.2)	-	1 (1.2)	-	-	-
急性中耳炎	1 (1.2)	-	1 (1.2)	-	-	-
口腔ヘルペス	1 (1.2)	-	-	1 (1.2)	-	-
口腔真菌感染	1 (1.2)	1 (1.2)	-	-	-	-
歯肉感染	1 (1.2)	1 (1.2)	-	-	-	-
耳感染	1 (1.2)	-	1 (1.2)	-	-	-
粘膜感染	1 (1.2)	1 (1.2)	-	-	-	-
敗血症	1 (1.2)	-	-	1 (1.2)	-	-
鼻炎	1 (1.2)	-	1 (1.2)	-	-	-

(body system continuing ...)

Investigator text for Adverse Events encoded using MedDRA version 15.0.
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NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
(... body system continuing)						
副鼻腔炎	1 (1.2)	-	-	1 (1.2)	-	-
Total Number of AEs	45	10	22	10	3	-
皮膚および皮下組織障害						
Total Pts With at Least one AE	23 (28.4)	13 (16.0)	14 (17.3)	1 (1.2)	-	-
発疹	9 (11.1)	4 (4.9)	4 (4.9)	1 (1.2)	-	-
脱毛症	7 (8.6)	1 (1.2)	6 (7.4)	-	-	-
多汗症	4 (4.9)	3 (3.7)	1 (1.2)	-	-	-
そう痒症	2 (2.5)	-	2 (2.5)	-	-	-
顔面腫脹	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
紅斑	2 (2.5)	2 (2.5)	-	-	-	-
皮膚乾燥	2 (2.5)	2 (2.5)	-	-	-	-
脂漏	1 (1.2)	1 (1.2)	-	-	-	-
多形紅斑	1 (1.2)	-	1 (1.2)	-	-	-
爪の障害	1 (1.2)	1 (1.2)	-	-	-	-
皮脂欠乏性湿疹	1 (1.2)	-	1 (1.2)	-	-	-
皮膚疼痛	1 (1.2)	-	1 (1.2)	-	-	-
冷汗	1 (1.2)	1 (1.2)	-	-	-	-
蕁麻疹	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	35	16	18	1	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (20 of 24)

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total		CTC Grading 1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
呼吸器、胸郭および縦隔障害												
Total Pts With at Least one AE	21	(25.9)	7	(8.6)	13	(16.0)	4	(4.9)	-		-	
呼吸困難	11	(13.6)	1	(1.2)	7	(8.6)	3	(3.7)	-		-	
咽喉刺激感	5	(6.2)	-		5	(6.2)	-		-		-	
咽頭の炎症	2	(2.5)	1	(1.2)	1	(1.2)	-		-		-	
咳嗽	2	(2.5)	1	(1.2)	1	(1.2)	-		-		-	
気管支痙攣	2	(2.5)	-		1	(1.2)	1	(1.2)	-		-	
口腔咽頭痛	2	(2.5)	2	(2.5)	-		-		-		-	
喉頭刺激感	2	(2.5)	-		2	(2.5)	-		-		-	
発声障害	2	(2.5)	2	(2.5)	-		-		-		-	
喉頭浮腫	1	(1.2)	-		1	(1.2)	-		-		-	
低酸素症	1	(1.2)	-		-		1	(1.2)	-		-	
鼻閉	1	(1.2)	1	(1.2)	-		-		-		-	
副鼻腔うっ血	1	(1.2)	-		1	(1.2)	-		-		-	
Total Number of AEs	32		8		19		5		-		-	
血管障害												
Total Pts With at Least one AE	19	(23.5)	2	(2.5)	14	(17.3)	4	(4.9)	-		-	
潮紅	9	(11.1)	-		6	(7.4)	3	(3.7)	-		-	
低血圧	8	(9.9)	1	(1.2)	4	(4.9)	3	(3.7)	-		-	
静脈炎	4	(4.9)	-		4	(4.9)	-		-		-	
高血圧	2	(2.5)	-		1	(1.2)	1	(1.2)	-		-	
蒼白	2	(2.5)	-		1	(1.2)	1	(1.2)	-		-	
血栓性静脈炎	1	(1.2)	1	(1.2)	-		-		-		-	
Total Number of AEs	26		2		16		8		-		-	

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
筋骨格系および結合組織障害						
Total Pts With at Least one AE	15 (18.5)	12 (14.8)	5 (6.2)	-	-	-
関節痛	4 (4.9)	4 (4.9)	-	-	-	-
筋痙縮	4 (4.9)	4 (4.9)	-	-	-	-
筋肉痛	3 (3.7)	1 (1.2)	2 (2.5)	-	-	-
四肢痛	3 (3.7)	2 (2.5)	1 (1.2)	-	-	-
関節硬直	1 (1.2)	1 (1.2)	-	-	-	-
筋緊張	1 (1.2)	-	1 (1.2)	-	-	-
筋骨格不快感	1 (1.2)	-	1 (1.2)	-	-	-
背部痛	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	18	13	5	-	-	-
心臓障害						
Total Pts With at Least one AE	8 (9.9)	1 (1.2)	7 (8.6)	-	-	-
頻脈	8 (9.9)	1 (1.2)	7 (8.6)	-	-	-
Total Number of AEs	8	1	7	-	-	-
代謝および栄養障害						
Total Pts With at Least one AE	8 (9.9)	2 (2.5)	2 (2.5)	2 (2.5)	1 (1.2)	1 (1.2)
体液貯留	2 (2.5)	-	1 (1.2)	1 (1.2)	-	-
低カリウム血症	2 (2.5)	1 (1.2)	1 (1.2)	-	-	-
高血糖	1 (1.2)	-	-	-	1 (1.2)	-
食欲減退	1 (1.2)	1 (1.2)	-	-	-	-
脱水	1 (1.2)	-	-	1 (1.2)	-	-
乳酸アシドーシス	1 (1.2)	-	-	-	-	1 (1.2)
Total Number of AEs	8	2	2	2	1	1

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
精神障害						
Total Pts With at Least one AE	5 (6.2)	3 (3.7)	2 (2.5)	-	-	-
不眠症	3 (3.7)	3 (3.7)	-	-	-	-
うつ病	1 (1.2)	-	1 (1.2)	-	-	-
感情不安定	1 (1.2)	1 (1.2)	-	-	-	-
気分変化	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	6	4	2	-	-	-
眼障害						
Total Pts With at Least one AE	2 (2.5)	-	2 (2.5)	-	-	-
眼瞼機能障害	1 (1.2)	-	1 (1.2)	-	-	-
霧視	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	2	-	2	-	-	-
耳および迷路障害						
Total Pts With at Least one AE	2 (2.5)	-	2 (2.5)	-	-	-
回転性めまい	1 (1.2)	-	1 (1.2)	-	-	-
耳痛	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	2	-	2	-	-	-
傷害、中毒および処置合併症						
Total Pts With at Least one AE	2 (2.5)	2 (2.5)	-	-	-	-
サンバーン	1 (1.2)	1 (1.2)	-	-	-	-
熱傷	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	2	2	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00

ae17r_0001l_sa Related Adverse Events by Intensity (NCI-CTC Grades 1-5)
Protocol(s): B021000 (T21000K) 1st line
Analysis: SAP Center: ALL CENTERS
Snapshot Date: [redacted] Cutoff Date: [redacted]
TT Group: Total; N = 81

Body System/ Adverse Event	Total	CTC Grading 1	2	3	4	5
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
腎および尿路障害						
Total Pts With at Least one AE	1 (1.2)	-	1 (1.2)	-	-	-
血尿	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	1	-	1	-	-	-
生殖系および乳房障害						
Total Pts With at Least one AE	1 (1.2)	-	1 (1.2)	-	-	-
外陰腟そう痒症	1 (1.2)	-	1 (1.2)	-	-	-
Total Number of AEs	1	-	1	-	-	-
臨床検査						
Total Pts With at Least one AE	1 (1.2)	1 (1.2)	-	-	-	-
体重増加	1 (1.2)	1 (1.2)	-	-	-	-
Total Number of AEs	1	1	-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
NCI-CTCAE ver. 3.0
Adverse Event Onset After Very First Drug Intake
AE17 29MAY2015:00:49:00 (24 of 24)

[5.3.5.3-1 ae17r_0001l_sa を再掲]

2.7.6.2.1.9　BO21005試験（GOYA 試験）

表 2.7.6.2.1.9-1　因果関係を問わないすべての有害事象（BO21005試験，未治療 DLBCL 患者）

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	657 (93.5%)	52 (7.4%)	150 (21.3%)	171 (24.3%)	254 (36.1%)	30 (4.3%)
血液およびリンパ系障害						
- Overall -	389 (55.3%)	7 (1.0%)	34 (4.8%)	114 (16.2%)	234 (33.3%)	0
好中球減少症	286 (40.7%)	2 (0.3%)	16 (2.3%)	68 (9.7%)	200 (28.4%)	0
発熱性好中球減少症	108 (15.4%)	1 (0.1%)	0	69 (9.8%)	38 (5.4%)	0
白血球減少症	87 (12.4%)	1 (0.1%)	15 (2.1%)	39 (5.5%)	32 (4.6%)	0
貧血	99 (14.1%)	5 (0.7%)	41 (5.8%)	51 (7.3%)	2 (0.3%)	0
血小板減少症	18 (2.6%)	3 (0.4%)	5 (0.7%)	3 (0.4%)	7 (1.0%)	0
リンパ球減少症	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
低グロブリン血症	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
リンパ節症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
高γグロブリン血症	1 (0.1%)	0	1 (0.1%)	0	0	0
高色素血	1 (0.1%)	1 (0.1%)	0	0	0	0
出血性貧血	1 (0.1%)	1 (0.1%)	0	0	0	0
鉄欠乏性貧血	1 (0.1%)	0	1 (0.1%)	0	0	0
内出血発生の増加傾向	1 (0.1%)	1 (0.1%)	0	0	0	0
溶血	1 (0.1%)	0	1 (0.1%)	0	0	0
溶血性貧血	1 (0.1%)	0	0	0	1 (0.1%)	0
胃腸障害						
- Overall -	410 (58.3%)	171 (24.3%)	187 (26.6%)	41 (5.8%)	7 (1.0%)	4 (0.6%)
悪心	199 (28.3%)	128 (18.2%)	69 (9.8%)	2 (0.3%)	0	0
便秘	172 (24.5%)	105 (14.9%)	61 (8.7%)	6 (0.9%)	0	0
下痢	92 (13.1%)	49 (7.0%)	34 (4.8%)	8 (1.1%)	1 (0.1%)	0
嘔吐	74 (10.5%)	48 (6.8%)	24 (3.4%)	1 (0.1%)	1 (0.1%)	0
口内炎	63 (9.0%)	37 (5.3%)	22 (3.1%)	4 (0.6%)	0	0
腹痛	52 (7.4%)	27 (3.8%)	19 (2.7%)	6 (0.9%)	0	0
消化不良	42 (6.0%)	21 (3.0%)	21 (3.0%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

Program: /opt/BIOSTAT/prod/cdt7159z/k21005n/aet04_all.sas / Output: /opt/BIOSTAT/prod/cdt7159z/k21005n/reports/aet04_all_005_SE.out
11JAN2017 7:13

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
上腹部痛	39 (5.5%)	29 (4.1%)	9 (1.3%)	1 (0.1%)	0	0
痔核	18 (2.6%)	8 (1.1%)	10 (1.4%)	0	0	0
口腔内潰瘍形成	21 (3.0%)	12 (1.7%)	8 (1.1%)	1 (0.1%)	0	0
口内乾燥	13 (1.8%)	12 (1.7%)	1 (0.1%)	0	0	0
胃食道逆流性疾患	12 (1.7%)	5 (0.7%)	7 (1.0%)	0	0	0
腹部膨満	18 (2.6%)	12 (1.7%)	6 (0.9%)	0	0	0
嚥下障害	7 (1.0%)	4 (0.6%)	3 (0.4%)	0	0	0
歯痛	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0	0
胃炎	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
口腔内痛	6 (0.9%)	2 (0.3%)	4 (0.6%)	0	0	0
腹部不快感	8 (1.1%)	4 (0.6%)	4 (0.6%)	0	0	0
歯肉痛	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
肛門周囲痛	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
アフタ性潰瘍	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
鼓腸	2 (0.3%)	2 (0.3%)	0	0	0	0
イレウス	4 (0.6%)	0	2 (0.3%)	1 (0.1%)	1 (0.1%)	0
胃腸出血	3 (0.4%)	0	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
下腹部痛	3 (0.4%)	3 (0.4%)	0	0	0	0
血便排泄	4 (0.6%)	3 (0.4%)	0	1 (0.1%)	0	0
腸閉塞	4 (0.6%)	0	1 (0.1%)	2 (0.3%)	0	1 (0.1%)
嚥下痛	1 (0.1%)	1 (0.1%)	0	0	0	0
痔出血	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
上部消化管出血	1 (0.1%)	0	0	1 (0.1%)	0	0
舌潰瘍	4 (0.6%)	4 (0.6%)	0	0	0	0
大腸炎	2 (0.3%)	0	0	2 (0.3%)	0	0
腸管穿孔	2 (0.3%)	0	0	0	1 (0.1%)	1 (0.1%)
胃出血	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
胃穿孔	3 (0.4%)	0	0	2 (0.3%)	1 (0.1%)	0
口唇炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
歯肉出血	2 (0.3%)	2 (0.3%)	0	0	0	0
小腸炎	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
消化器痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
大腸ポリープ	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
裂肛	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
肛門出血	3 (0.4%)	3 (0.4%)	0	0	0	0
小腸閉塞	1 (0.1%)	0	0	1 (0.1%)	0	0
舌痛	1 (0.1%)	1 (0.1%)	0	0	0	0
直腸出血	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
腹水	1 (0.1%)	0	1 (0.1%)	0	0	0
おくび	2 (0.3%)	2 (0.3%)	0	0	0	0
メレナ	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
亜イレウス	1 (0.1%)	0	0	0	1 (0.1%)	0
異常便	1 (0.1%)	1 (0.1%)	0	0	0	0
下部消化管出血	1 (0.1%)	0	0	1 (0.1%)	0	0
口の感覚鈍麻	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔内出血	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
口唇潰瘍	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
痔瘻	1 (0.1%)	0	0	1 (0.1%)	0	0
小腸穿孔	1 (0.1%)	0	0	1 (0.1%)	0	0
食道炎	1 (0.1%)	1 (0.1%)	0	0	0	0
心窩部不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
麻痺性イレウス	1 (0.1%)	0	0	1 (0.1%)	0	0
鼠径ヘルニア	1 (0.1%)	0	0	1 (0.1%)	0	0
胃拡張	1 (0.1%)	1 (0.1%)	0	0	0	0
胃排出不全	1 (0.1%)	0	0	0	0	1 (0.1%)
憩室	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血栓性痔核	1 (0.1%)	0	1 (0.1%)	0	0	0
口の錯感覚	1 (0.1%)	1 (0.1%)	0	0	0	0
口蓋腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔灼熱感症候群	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔内不快感	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔内分泌物	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇乾燥	1 (0.1%)	1 (0.1%)	0	0	0	0
根尖肉芽腫	1 (0.1%)	0	1 (0.1%)	0	0	0
歯の知覚過敏	1 (0.1%)	0	1 (0.1%)	0	0	0
歯の磨耗	1 (0.1%)	1 (0.1%)	0	0	0	0
直腸分泌物	1 (0.1%)	1 (0.1%)	0	0	0	0
軟便	1 (0.1%)	1 (0.1%)	0	0	0	0
変色便	1 (0.1%)	1 (0.1%)	0	0	0	0
肛門の炎症	1 (0.1%)	0	1 (0.1%)	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	323 (45.9%)	166 (23.6%)	124 (17.6%)	26 (3.7%)	4 (0.6%)	3 (0.4%)
疲労	123 (17.5%)	80 (11.4%)	32 (4.6%)	10 (1.4%)	1 (0.1%)	0
発熱	83 (11.8%)	52 (7.4%)	22 (3.1%)	7 (1.0%)	2 (0.3%)	0
悪寒	37 (5.3%)	19 (2.7%)	16 (2.3%)	1 (0.1%)	1 (0.1%)	0
無力症	76 (10.8%)	41 (5.8%)	27 (3.8%)	8 (1.1%)	0	0
粘膜の炎症	37 (5.3%)	19 (2.7%)	12 (1.7%)	4 (0.6%)	2 (0.3%)	0
末梢性浮腫	40 (5.7%)	29 (4.1%)	11 (1.6%)	0	0	0
倦怠感	21 (3.0%)	15 (2.1%)	5 (0.7%)	1 (0.1%)	0	0
胸部不快感	11 (1.6%)	8 (1.1%)	3 (0.4%)	0	0	0
疼痛	12 (1.7%)	8 (1.1%)	4 (0.6%)	0	0	0
非心臓性胸痛	11 (1.6%)	6 (0.9%)	4 (0.6%)	1 (0.1%)	0	0
浮腫	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
胸痛	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
冷感	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
インフルエンザ様疾患	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
末梢腫脹	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
注入部位血管外漏出	6 (0.9%)	1 (0.1%)	5 (0.7%)	0	0	0
顔面浮腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
死亡	2 (0.3%)	0	0	0	0	2 (0.3%)
熱感	2 (0.3%)	2 (0.3%)	0	0	0	0
注射部位反応	1 (0.1%)	1 (0.1%)	0	0	0	0
活動状態低下	1 (0.1%)	0	1 (0.1%)	0	0	0
全身健康状態低下	1 (0.1%)	0	0	1 (0.1%)	0	0
全身性浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位疼痛	2 (0.3%)	2 (0.3%)	0	0	0	0
不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
腋窩痛	2 (0.3%)	2 (0.3%)	0	0	0	0
カテーテル留置部位疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
顔面痛	1 (0.1%)	0	1 (0.1%)	0	0	0
注入部位腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
注入部位疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
突然死	1 (0.1%)	0	0	0	0	1 (0.1%)
歩行障害	1 (0.1%)	1 (0.1%)	0	0	0	0
異常感	1 (0.1%)	1 (0.1%)	0	0	0	0
溢出	1 (0.1%)	0	1 (0.1%)	0	0	0
乾燥症	1 (0.1%)	1 (0.1%)	0	0	0	0
限局性浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
硬結	1 (0.1%)	1 (0.1%)	0	0	0	0
高熱	1 (0.1%)	0	1 (0.1%)	0	0	0
腫瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
体温調節障害	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位局面	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
注入部位紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
低体温	1 (0.1%)	0	1 (0.1%)	0	0	0
評価不能の事象	1 (0.1%)	0	1 (0.1%)	0	0	0
感染症および寄生虫症						
- Overall -	310 (44.1%)	60 (8.5%)	141 (20.1%)	76 (10.8%)	21 (3.0%)	12 (1.7%)
肺炎	56 (8.0%)	1 (0.1%)	20 (2.8%)	26 (3.7%)	3 (0.4%)	6 (0.9%)
上気道感染	47 (6.7%)	19 (2.7%)	23 (3.3%)	5 (0.7%)	0	0
帯状疱疹	20 (2.8%)	1 (0.1%)	16 (2.3%)	3 (0.4%)	0	0
鼻咽頭炎	24 (3.4%)	13 (1.8%)	9 (1.3%)	2 (0.3%)	0	0
尿路感染	19 (2.7%)	0	15 (2.1%)	4 (0.6%)	0	0
口腔ヘルペス	17 (2.4%)	8 (1.1%)	9 (1.3%)	0	0	0
口腔カンジダ症	18 (2.6%)	3 (0.4%)	14 (2.0%)	1 (0.1%)	0	0
気管支炎	18 (2.6%)	4 (0.6%)	11 (1.6%)	3 (0.4%)	0	0
敗血症	11 (1.6%)	0	1 (0.1%)	3 (0.4%)	4 (0.6%)	3 (0.4%)
肺感染	9 (1.3%)	1 (0.1%)	3 (0.4%)	5 (0.7%)	0	0
Ｂ型肝炎	5 (0.7%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	0	0
結膜炎	11 (1.6%)	5 (0.7%)	6 (0.9%)	0	0	0
胃腸炎	9 (1.3%)	3 (0.4%)	2 (0.3%)	4 (0.6%)	0	0
蜂巣炎	11 (1.6%)	2 (0.3%)	4 (0.6%)	4 (0.6%)	1 (0.1%)	0
膀胱炎	7 (1.0%)	3 (0.4%)	4 (0.6%)	0	0	0
咽頭炎	8 (1.1%)	3 (0.4%)	4 (0.6%)	1 (0.1%)	0	0
副鼻腔炎	10 (1.4%)	4 (0.6%)	6 (0.9%)	0	0	0
カンジダ感染	5 (0.7%)	0	5 (0.7%)	0	0	0
単純ヘルペス	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
敗血症性ショック	3 (0.4%)	0	0	0	3 (0.4%)	0
インフルエンザ	7 (1.0%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0
下気道感染	4 (0.6%)	0	3 (0.4%)	1 (0.1%)	0	0
歯肉炎	4 (0.6%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
鼻炎	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
気道感染	2 (0.3%)	0	2 (0.3%)	0	0	0
口腔感染	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
毛包炎	7 (1.0%)	2 (0.3%)	5 (0.7%)	0	0	0
医療機器関連感染	4 (0.6%)	0	2 (0.3%)	2 (0.3%)	0	0
皮膚感染	6 (0.9%)	2 (0.3%)	1 (0.1%)	3 (0.4%)	0	0
感染	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
腟感染	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
好中球減少性敗血症	3 (0.4%)	0	0	0	3 (0.4%)	0
耳感染	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
ウイルス感染	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
サイトメガロウイルス性脈絡網膜炎	2 (0.3%)	0	0	2 (0.3%)	0	0
ニューモシスチス・イロベチイ肺炎	4 (0.6%)	0	1 (0.1%)	1 (0.1%)	2 (0.3%)	0
外陰部腟カンジダ症	2 (0.3%)	0	2 (0.3%)	0	0	0
外陰腟真菌感染	1 (0.1%)	0	1 (0.1%)	0	0	0
限局性感染	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
口角口唇炎	2 (0.3%)	2 (0.3%)	0	0	0	0
口腔真菌感染	3 (0.4%)	0	3 (0.4%)	0	0	0
歯感染	1 (0.1%)	0	0	1 (0.1%)	0	0
歯周炎	3 (0.4%)	3 (0.4%)	0	0	0	0
歯膿瘍	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
真菌感染	2 (0.3%)	0	2 (0.3%)	0	0	0
爪真菌症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
クロストリジウム・ディフィシレ大腸炎	1 (0.1%)	0	0	1 (0.1%)	0	0
サイトメガロウイルス感染	2 (0.3%)	0	0	0	2 (0.3%)	0
感染性腸炎	1 (0.1%)	0	0	1 (0.1%)	0	0
喉頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
食道カンジダ症	1 (0.1%)	1 (0.1%)	0	0	0	0
水痘	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
虫垂炎	3 (0.4%)	0	0	2 (0.3%)	1 (0.1%)	0
粘膜感染	2 (0.3%)	0	2 (0.3%)	0	0	0
麦粒腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
皮膚真菌感染	1 (0.1%)	1 (0.1%)	0	0	0	0
ウイルス性気道感染	1 (0.1%)	1 (0.1%)	0	0	0	0
クロストリジウム・ディフィシレ感染	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
異型肺炎	2 (0.3%)	0	0	2 (0.3%)	0	0
気管支肺アスペルギルス症	2 (0.3%)	0	1 (0.1%)	0	0	1 (0.1%)
口唇感染	1 (0.1%)	0	1 (0.1%)	0	0	0
骨髄炎	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
消化管感染	1 (0.1%)	0	1 (0.1%)	0	0	0
腹膜炎	1 (0.1%)	0	0	0	0	1 (0.1%)
せつ	1 (0.1%)	1 (0.1%)	0	0	0	0
ウイルス性胃腸炎	1 (0.1%)	1 (0.1%)	0	0	0	0
クレブシエラ性敗血症	1 (0.1%)	0	0	1 (0.1%)	0	0
ヘリコバクター感染	1 (0.1%)	0	1 (0.1%)	0	0	0
外陰部膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
憩室炎	1 (0.1%)	0	1 (0.1%)	0	0	0
結核	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
好中球減少性感染	1 (0.1%)	0	1 (0.1%)	0	0	0
水痘帯状疱疹ウイルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
体部白癬	2 (0.3%)	0	2 (0.3%)	0	0	0
腸球菌感染	1 (0.1%)	0	1 (0.1%)	0	0	0
直腸膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
軟部組織感染	2 (0.3%)	0	0	2 (0.3%)	0	0
尿路性敗血症	1 (0.1%)	0	0	1 (0.1%)	0	0
膿疱性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
白癬感染	1 (0.1%)	1 (0.1%)	0	0	0	0
ウイルス性咽頭炎	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
ウイルス性結膜炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性上気道感染	1 (0.1%)	0	1 (0.1%)	0	0	0
カテーテル留置部位感染	1 (0.1%)	0	0	1 (0.1%)	0	0
カンジダ性敗血症	1 (0.1%)	0	0	0	0	1 (0.1%)
クリプトコッカス性髄膜炎	1 (0.1%)	0	0	0	1 (0.1%)	0
シュードモナス性敗血症	1 (0.1%)	0	0	1 (0.1%)	0	0
ブドウ球菌感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ブドウ球菌性創感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ヘルペス眼感染	1 (0.1%)	0	1 (0.1%)	0	0	0
陰嚢膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
陰部ヘルペス	1 (0.1%)	0	1 (0.1%)	0	0	0
壊死性筋膜炎	1 (0.1%)	0	0	0	1 (0.1%)	0
眼瞼感染	1 (0.1%)	0	1 (0.1%)	0	0	0
眼窩周囲感染	1 (0.1%)	0	1 (0.1%)	0	0	0
頚部膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
細菌感染	1 (0.1%)	0	1 (0.1%)	0	0	0
真菌性気道感染	1 (0.1%)	0	1 (0.1%)	0	0	0
真菌性食道炎	1 (0.1%)	0	1 (0.1%)	0	0	0
精巣炎	1 (0.1%)	0	0	1 (0.1%)	0	0
切開部位膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
前立腺膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
全身性感染	1 (0.1%)	0	1 (0.1%)	0	0	0
大腸菌性尿路感染	1 (0.1%)	1 (0.1%)	0	0	0	0
大腸菌性敗血症	1 (0.1%)	0	0	0	0	1 (0.1%)
中咽頭カンジダ症	1 (0.1%)	0	1 (0.1%)	0	0	0
中耳炎	1 (0.1%)	1 (0.1%)	0	0	0	0
中枢神経系結核	1 (0.1%)	0	0	0	1 (0.1%)	0
糖尿病性足感染	1 (0.1%)	0	1 (0.1%)	0	0	0
膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肺敗血症	1 (0.1%)	0	0	0	1 (0.1%)	0
糞線虫症	1 (0.1%)	0	1 (0.1%)	0	0	0
涙嚢炎	1 (0.1%)	0	1 (0.1%)	0	0	0
神経系障害						
- Overall -	299 (42.5%)	195 (27.7%)	80 (11.4%)	18 (2.6%)	3 (0.4%)	3 (0.4%)
末梢性ニューロパチー	89 (12.7%)	70 (10.0%)	16 (2.3%)	3 (0.4%)	0	0
頭痛	57 (8.1%)	36 (5.1%)	20 (2.8%)	1 (0.1%)	0	0
末梢性感覚ニューロパチー	57 (8.1%)	41 (5.8%)	13 (1.8%)	2 (0.3%)	1 (0.1%)	0
錯感覚	51 (7.3%)	44 (6.3%)	7 (1.0%)	0	0	0
味覚異常	37 (5.3%)	32 (4.6%)	5 (0.7%)	0	0	0
浮動性めまい	27 (3.8%)	19 (2.7%)	6 (0.9%)	2 (0.3%)	0	0
感覚鈍麻	22 (3.1%)	21 (3.0%)	1 (0.1%)	0	0	0
多発ニューロパチー	12 (1.7%)	9 (1.3%)	3 (0.4%)	0	0	0
失神	13 (1.8%)	4 (0.6%)	2 (0.3%)	7 (1.0%)	0	0
振戦	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
失神寸前の状態	5 (0.7%)	3 (0.4%)	1 (0.1%)	1 (0.1%)	0	0
神経痛	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
傾眠	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
末梢性運動ニューロパチー	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
脳血管発作	2 (0.3%)	0	0	0	0	2 (0.3%)
下肢静止不能症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
感覚障害	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
失声症	1 (0.1%)	0	0	1 (0.1%)	0	0
神経毒性	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
体位性めまい	3 (0.4%)	3 (0.4%)	0	0	0	0
味覚消失	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
注意力障害	2 (0.3%)	2 (0.3%)	0	0	0	0
脳虚血	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
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Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
くも膜炎	2 (0.3%)	0	2 (0.3%)	0	0	0
くも膜下出血	1 (0.1%)	0	1 (0.1%)	0	0	0
ヘルペス後神経痛	1 (0.1%)	0	1 (0.1%)	0	0	0
ミオクローヌス	1 (0.1%)	1 (0.1%)	0	0	0	0
意識消失	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
記憶障害	1 (0.1%)	0	1 (0.1%)	0	0	0
灼熱感	1 (0.1%)	1 (0.1%)	0	0	0	0
精神運動亢進	1 (0.1%)	1 (0.1%)	0	0	0	0
声帯麻痺	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0
副鼻腔炎に伴う頭痛	2 (0.3%)	2 (0.3%)	0	0	0	0
片頭痛	2 (0.3%)	2 (0.3%)	0	0	0	0
嗅覚錯誤	1 (0.1%)	0	1 (0.1%)	0	0	0
てんかん	1 (0.1%)	0	0	1 (0.1%)	0	0
レヴィ小体型認知症	1 (0.1%)	0	1 (0.1%)	0	0	0
一過性脳虚血発作	1 (0.1%)	1 (0.1%)	0	0	0	0
運動低下	1 (0.1%)	1 (0.1%)	0	0	0	0
感覚異常性大腿神経痛	1 (0.1%)	1 (0.1%)	0	0	0	0
顔面麻痺	1 (0.1%)	1 (0.1%)	0	0	0	0
蟻走感	1 (0.1%)	1 (0.1%)	0	0	0	0
筋緊張低下	1 (0.1%)	0	1 (0.1%)	0	0	0
頚動脈狭窄	1 (0.1%)	0	0	1 (0.1%)	0	0
塞栓性脳卒中	1 (0.1%)	0	0	1 (0.1%)	0	0
中毒性脳症	1 (0.1%)	0	0	0	0	1 (0.1%)
脳梗塞	1 (0.1%)	0	1 (0.1%)	0	0	0
不全麻痺	1 (0.1%)	1 (0.1%)	0	0	0	0
無感覚	1 (0.1%)	0	1 (0.1%)	0	0	0
傷害、中毒および処置合併症 - Overall -	204 (29.0%)	81 (11.5%)	105 (14.9%)	15 (2.1%)	2 (0.3%)	1 (0.1%)

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
注入に伴う反応	165 (23.5%)	64 (9.1%)	97 (13.8%)	3 (0.4%)	1 (0.1%)	0
転倒	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
挫傷	2 (0.3%)	2 (0.3%)	0	0	0	0
脊椎圧迫骨折	4 (0.6%)	0	3 (0.4%)	1 (0.1%)	0	0
処置による疼痛	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
血管確保合併症	1 (0.1%)	0	0	0	1 (0.1%)	0
裂傷	2 (0.3%)	2 (0.3%)	0	0	0	0
節足動物咬傷	2 (0.3%)	2 (0.3%)	0	0	0	0
創傷	1 (0.1%)	1 (0.1%)	0	0	0	0
大腿骨骨折	2 (0.3%)	0	0	2 (0.3%)	0	0
皮膚擦過傷	1 (0.1%)	1 (0.1%)	0	0	0	0
輸血反応	1 (0.1%)	0	1 (0.1%)	0	0	0
靱帯捻挫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
関節損傷	2 (0.3%)	2 (0.3%)	0	0	0	0
胸椎骨折	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
股関節部骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
擦過傷	1 (0.1%)	1 (0.1%)	0	0	0	0
四肢損傷	1 (0.1%)	0	1 (0.1%)	0	0	0
歯牙破折	1 (0.1%)	1 (0.1%)	0	0	0	0
上肢骨折	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
脊椎骨折	2 (0.3%)	0	2 (0.3%)	0	0	0
足関節部骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
大腿骨頚部骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
過量投与	1 (0.1%)	0	0	1 (0.1%)	0	0
外傷性血胸	1 (0.1%)	0	0	1 (0.1%)	0	0
関節脱臼	1 (0.1%)	1 (0.1%)	0	0	0	0
顔面骨骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
胸骨骨折	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
血管偽動脈瘤	1 (0.1%)	0	0	1 (0.1%)	0	0
肩甲骨骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
口唇損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
腰椎骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
腰椎穿刺後症候群	1 (0.1%)	0	1 (0.1%)	0	0	0
処置後合併症	1 (0.1%)	0	1 (0.1%)	0	0	0
上顎炎	1 (0.1%)	1 (0.1%)	0	0	0	0
人工関節周囲骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
腎臓破裂	1 (0.1%)	0	1 (0.1%)	0	0	0
切開部位痛	1 (0.1%)	1 (0.1%)	0	0	0	0
節足動物刺傷	1 (0.1%)	1 (0.1%)	0	0	0	0
爪損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
腹部創離開	1 (0.1%)	0	0	0	0	1 (0.1%)
放射線性肺臓炎	1 (0.1%)	0	1 (0.1%)	0	0	0
肋骨骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚および皮下組織障害						
- Overall -	226 (32.1%)	98 (13.9%)	120 (17.1%)	8 (1.1%)	0	0
脱毛症	142 (20.2%)	51 (7.3%)	88 (12.5%)	3 (0.4%)	0	0
発疹	45 (6.4%)	30 (4.3%)	15 (2.1%)	0	0	0
そう痒症	35 (5.0%)	27 (3.8%)	8 (1.1%)	0	0	0
紅斑	8 (1.1%)	5 (0.7%)	3 (0.4%)	0	0	0
蕁麻疹	10 (1.4%)	4 (0.6%)	5 (0.7%)	1 (0.1%)	0	0
多汗症	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
皮膚乾燥	10 (1.4%)	10 (1.4%)	0	0	0	0
爪変色	6 (0.9%)	6 (0.9%)	0	0	0	0
寝汗	2 (0.3%)	2 (0.3%)	0	0	0	0
斑状丘疹状皮疹	3 (0.4%)	3 (0.4%)	0	0	0	0
湿疹	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
皮膚潰瘍	4 (0.6%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0
皮膚炎	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
爪の障害	1 (0.1%)	1 (0.1%)	0	0	0	0
ざ瘡様皮膚炎	2 (0.3%)	2 (0.3%)	0	0	0	0
皮膚色素過剰	2 (0.3%)	2 (0.3%)	0	0	0	0
ざ瘡	1 (0.1%)	1 (0.1%)	0	0	0	0
接触性皮膚炎	2 (0.3%)	2 (0.3%)	0	0	0	0
褥瘡性潰瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
過角化	1 (0.1%)	1 (0.1%)	0	0	0	0
丘疹	1 (0.1%)	1 (0.1%)	0	0	0	0
丘疹性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
水疱	1 (0.1%)	0	1 (0.1%)	0	0	0
斑状皮疹	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚病変	2 (0.3%)	2 (0.3%)	0	0	0	0
薬疹	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
そう痒性皮疹	1 (0.1%)	0	1 (0.1%)	0	0	0
壊疽性膿皮症	1 (0.1%)	0	1 (0.1%)	0	0	0
乾皮症	1 (0.1%)	1 (0.1%)	0	0	0	0
顔面腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
色素沈着障害	1 (0.1%)	1 (0.1%)	0	0	0	0
全身性そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
全身性皮疹	1 (0.1%)	0	0	1 (0.1%)	0	0
糖尿病性足病変	1 (0.1%)	0	0	1 (0.1%)	0	0
皮膚亀裂	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚症	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚変色	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
呼吸器、胸郭および縦隔障害						
- Overall -	197 (28.0%)	115 (16.4%)	60 (8.5%)	16 (2.3%)	3 (0.4%)	3 (0.4%)
咳嗽	60 (8.5%)	40 (5.7%)	19 (2.7%)	1 (0.1%)	0	0
呼吸困難	32 (4.6%)	16 (2.3%)	14 (2.0%)	2 (0.3%)	0	0
口腔咽頭痛	37 (5.3%)	29 (4.1%)	6 (0.9%)	2 (0.3%)	0	0
鼻漏	19 (2.7%)	18 (2.6%)	1 (0.1%)	0	0	0
湿性咳嗽	12 (1.7%)	12 (1.7%)	0	0	0	0
しゃっくり	15 (2.1%)	9 (1.3%)	6 (0.9%)	0	0	0
発声障害	10 (1.4%)	10 (1.4%)	0	0	0	0
労作性呼吸困難	10 (1.4%)	9 (1.3%)	1 (0.1%)	0	0	0
肺塞栓症	8 (1.1%)	0	5 (0.7%)	2 (0.3%)	1 (0.1%)	0
胸水	5 (0.7%)	1 (0.1%)	3 (0.4%)	1 (0.1%)	0	0
咽喉刺激感	12 (1.7%)	7 (1.0%)	5 (0.7%)	0	0	0
肺臓炎	3 (0.4%)	1 (0.1%)	0	2 (0.3%)	0	0
間質性肺疾患	5 (0.7%)	1 (0.1%)	0	2 (0.3%)	1 (0.1%)	1 (0.1%)
鼻出血	5 (0.7%)	5 (0.7%)	0	0	0	0
鼻閉	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
低酸素症	1 (0.1%)	0	0	1 (0.1%)	0	0
気管支痙攣	4 (0.6%)	0	3 (0.4%)	1 (0.1%)	0	0
喀血	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔咽頭不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
アレルギー性鼻炎	3 (0.4%)	3 (0.4%)	0	0	0	0
咽喉乾燥	2 (0.3%)	2 (0.3%)	0	0	0	0
急性呼吸不全	3 (0.4%)	0	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
肺水腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
副鼻腔うっ血	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
咽喉絞扼感	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
肺気腫	1 (0.1%)	1 (0.1%)	0	0	0	0
慢性閉塞性肺疾患	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
喘息	1 (0.1%)	1 (0.1%)	0	0	0	0
喘鳴	1 (0.1%)	1 (0.1%)	0	0	0	0
ラ音	1 (0.1%)	1 (0.1%)	0	0	0	0
咽頭浮腫	2 (0.3%)	2 (0.3%)	0	0	0	0
気胸	1 (0.1%)	0	1 (0.1%)	0	0	0
急性呼吸窮迫症候群	1 (0.1%)	0	0	0	1 (0.1%)	0
胸膜痛	1 (0.1%)	0	0	1 (0.1%)	0	0
呼吸不全	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
誤嚥性肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
鼻閉塞	1 (0.1%)	1 (0.1%)	0	0	0	0
無気肺	1 (0.1%)	0	1 (0.1%)	0	0	0
くしゃみ	1 (0.1%)	0	1 (0.1%)	0	0	0
咽頭の炎症	1 (0.1%)	1 (0.1%)	0	0	0	0
咽頭知覚不全	1 (0.1%)	0	1 (0.1%)	0	0	0
器質化肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
気管支閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
気道出血	1 (0.1%)	1 (0.1%)	0	0	0	0
喉頭刺激感	1 (0.1%)	0	1 (0.1%)	0	0	0
喉頭痙攣	1 (0.1%)	0	1 (0.1%)	0	0	0
上気道咳症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
息詰まり感	1 (0.1%)	0	1 (0.1%)	0	0	0
肺うっ血	1 (0.1%)	0	1 (0.1%)	0	0	0
肺嚢胞	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻の炎症	1 (0.1%)	1 (0.1%)	0	0	0	0
副鼻腔不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
代謝および栄養障害						
- Overall -	170 (24.2%)	59 (8.4%)	62 (8.8%)	38 (5.4%)	10 (1.4%)	1 (0.1%)
食欲減退	71 (10.1%)	35 (5.0%)	31 (4.4%)	5 (0.7%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
低カリウム血症	50 (7.1%)	20 (2.8%)	16 (2.3%)	11 (1.6%)	3 (0.4%)	0
高血糖	21 (3.0%)	3 (0.4%)	11 (1.6%)	6 (0.9%)	1 (0.1%)	0
脱水	14 (2.0%)	4 (0.6%)	7 (1.0%)	2 (0.3%)	1 (0.1%)	0
低マグネシウム血症	10 (1.4%)	7 (1.0%)	2 (0.3%)	1 (0.1%)	0	0
低カルシウム血症	8 (1.1%)	3 (0.4%)	3 (0.4%)	2 (0.3%)	0	0
低リン酸血症	9 (1.3%)	3 (0.4%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0
低ナトリウム血症	11 (1.6%)	1 (0.1%)	0	8 (1.1%)	2 (0.3%)	0
高尿酸血症	6 (0.9%)	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0
低アルブミン血症	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
糖尿病	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
栄養障害	4 (0.6%)	1 (0.1%)	2 (0.3%)	0	1 (0.1%)	0
腫瘍崩壊症候群	4 (0.6%)	0	0	3 (0.4%)	1 (0.1%)	0
高カリウム血症	2 (0.3%)	0	2 (0.3%)	0	0	0
高カルシウム血症	1 (0.1%)	1 (0.1%)	0	0	0	0
高トリグリセリド血症	1 (0.1%)	0	0	1 (0.1%)	0	0
水分過負荷	1 (0.1%)	0	1 (0.1%)	0	0	0
成長障害	4 (0.6%)	0	1 (0.1%)	2 (0.3%)	0	1 (0.1%)
２型糖尿病	1 (0.1%)	0	1 (0.1%)	0	0	0
高コレステロール血症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
高脂血症	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
体液貯留	1 (0.1%)	0	1 (0.1%)	0	0	0
鉄欠乏	1 (0.1%)	0	1 (0.1%)	0	0	0
マグネシウム欠乏	1 (0.1%)	0	1 (0.1%)	0	0	0
脂質異常症	1 (0.1%)	0	1 (0.1%)	0	0	0
食欲亢進	1 (0.1%)	1 (0.1%)	0	0	0	0
耐糖能障害	1 (0.1%)	0	1 (0.1%)	0	0	0
痛風	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
筋骨格系および結合組織障害						
- Overall -	162 (23.0%)	97 (13.8%)	54 (7.7%)	10 (1.4%)	1 (0.1%)	0
背部痛	43 (6.1%)	24 (3.4%)	18 (2.6%)	1 (0.1%)	0	0
関節痛	28 (4.0%)	18 (2.6%)	7 (1.0%)	3 (0.4%)	0	0
筋肉痛	31 (4.4%)	23 (3.3%)	8 (1.1%)	0	0	0
骨痛	34 (4.8%)	23 (3.3%)	10 (1.4%)	1 (0.1%)	0	0
四肢痛	18 (2.6%)	11 (1.6%)	5 (0.7%)	2 (0.3%)	0	0
筋力低下	7 (1.0%)	5 (0.7%)	1 (0.1%)	0	1 (0.1%)	0
筋骨格痛	9 (1.3%)	4 (0.6%)	5 (0.7%)	0	0	0
筋痙縮	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
頚部痛	8 (1.1%)	5 (0.7%)	3 (0.4%)	0	0	0
筋骨格系胸痛	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
顎痛	1 (0.1%)	0	1 (0.1%)	0	0	0
肩径部痛	3 (0.4%)	3 (0.4%)	0	0	0	0
関節腫脹	5 (0.7%)	3 (0.4%)	0	2 (0.3%)	0	0
側腹部痛	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
骨粗鬆症	4 (0.6%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	0	0
関節炎	1 (0.1%)	1 (0.1%)	0	0	0	0
四肢不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
脊椎痛	2 (0.3%)	2 (0.3%)	0	0	0	0
変形性関節症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
滑液包炎	1 (0.1%)	0	1 (0.1%)	0	0	0
骨減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
運動性低下	1 (0.1%)	0	0	1 (0.1%)	0	0
滑液嚢腫	1 (0.1%)	1 (0.1%)	0	0	0	0
関節硬直	1 (0.1%)	1 (0.1%)	0	0	0	0
関節障害	1 (0.1%)	1 (0.1%)	0	0	0	0
筋骨格硬直	1 (0.1%)	0	1 (0.1%)	0	0	0
筋肉疲労	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
筋膜疼痛症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
後天性ミトコンドリアミオパチー	1 (0.1%)	1 (0.1%)	0	0	0	0
肋軟骨炎	1 (0.1%)	0	0	1 (0.1%)	0	0
臨床検査						
- Overall -	98 (13.9%)	43 (6.1%)	29 (4.1%)	23 (3.3%)	3 (0.4%)	0
体重減少	27 (3.8%)	12 (1.7%)	10 (1.4%)	5 (0.7%)	0	0
アラニンアミノトランスフェラーゼ増加	26 (3.7%)	15 (2.1%)	5 (0.7%)	6 (0.9%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	17 (2.4%)	10 (1.4%)	5 (0.7%)	2 (0.3%)	0	0
駆出率減少	12 (1.7%)	1 (0.1%)	5 (0.7%)	6 (0.9%)	0	0
体重増加	10 (1.4%)	6 (0.9%)	4 (0.6%)	0	0	0
トランスアミナーゼ上昇	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
リンパ球数減少	1 (0.1%)	0	0	1 (0.1%)	0	0
血中アルカリホスファターゼ増加	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
血中コレステロール増加	1 (0.1%)	1 (0.1%)	0	0	0	0
Ｃ－反応性蛋白増加	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
γ－グルタミルトランスフェラーゼ増加	3 (0.4%)	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	0
血圧上昇	1 (0.1%)	0	0	1 (0.1%)	0	0
血中クレアチニン増加	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
血中ブドウ糖増加	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
血圧低下	1 (0.1%)	1 (0.1%)	0	0	0	0
血中尿酸増加	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0
Ｂ型肝炎ＤＮＡ増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中カリウム増加	1 (0.1%)	0	1 (0.1%)	0	0	0
血中ビリルビン増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中乳酸脱水素酵素増加	2 (0.3%)	2 (0.3%)	0	0	0	0
酸素飽和度低下	1 (0.1%)	0	0	0	1 (0.1%)	0
Ｃ型肝炎ウイルス検査陽性	1 (0.1%)	0	1 (0.1%)	0	0	0
ＱＯＬ低下	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
サイトメガロウイルス検査陽性	1 (0.1%)	0	0	1 (0.1%)	0	0
トロポニン増加	1 (0.1%)	1 (0.1%)	0	0	0	0
活性化部分トロンボプラスチン時間延長	1 (0.1%)	1 (0.1%)	0	0	0	0
血中リン増加	1 (0.1%)	0	1 (0.1%)	0	0	0
血中副甲状腺ホルモン増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血管障害						
- Overall -	93 (13.2%)	31 (4.4%)	45 (6.4%)	17 (2.4%)	0	0
高血圧	27 (3.8%)	5 (0.7%)	12 (1.7%)	10 (1.4%)	0	0
低血圧	26 (3.7%)	12 (1.7%)	13 (1.8%)	1 (0.1%)	0	0
深部静脈血栓症	8 (1.1%)	0	5 (0.7%)	3 (0.4%)	0	0
静脈炎	8 (1.1%)	2 (0.3%)	6 (0.9%)	0	0	0
ほてり	2 (0.3%)	2 (0.3%)	0	0	0	0
血管炎	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
潮紅	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
起立性低血圧	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
血栓性静脈炎	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
血栓症	2 (0.3%)	2 (0.3%)	0	0	0	0
四肢静脈血栓症	2 (0.3%)	0	2 (0.3%)	0	0	0
末梢冷感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
塞栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
進行性高血圧	1 (0.1%)	0	0	1 (0.1%)	0	0
末梢静脈疾患	1 (0.1%)	0	1 (0.1%)	0	0	0
精神障害						
- Overall -	83 (11.8%)	49 (7.0%)	30 (4.3%)	4 (0.6%)	0	0
不眠症	58 (8.3%)	38 (5.4%)	19 (2.7%)	1 (0.1%)	0	0
不安	10 (1.4%)	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
うつ病	14 (2.0%)	6 (0.9%)	6 (0.9%)	2 (0.3%)	0	0
激越	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
譫妄	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
気分変化	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
抑うつ気分	3 (0.4%)	3 (0.4%)	0	0	0	0
落ち着きのなさ	1 (0.1%)	1 (0.1%)	0	0	0	0
易刺激性	1 (0.1%)	0	1 (0.1%)	0	0	0
異常行動	1 (0.1%)	1 (0.1%)	0	0	0	0
強迫性障害	1 (0.1%)	1 (0.1%)	0	0	0	0
食物嫌悪	1 (0.1%)	1 (0.1%)	0	0	0	0
精神運動制止遅滞	1 (0.1%)	1 (0.1%)	0	0	0	0
無感情	1 (0.1%)	1 (0.1%)	0	0	0	0
心臓障害						
- Overall -	53 (7.5%)	16 (2.3%)	17 (2.4%)	16 (2.3%)	1 (0.1%)	3 (0.4%)
心房細動	9 (1.3%)	1 (0.1%)	5 (0.7%)	3 (0.4%)	0	0
心不全	6 (0.9%)	1 (0.1%)	2 (0.3%)	2 (0.3%)	0	1 (0.1%)
頻脈	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
動悸	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0	0
洞性頻脈	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
急性心筋梗塞	5 (0.7%)	0	0	5 (0.7%)	0	0
うっ血性心不全	2 (0.3%)	0	2 (0.3%)	0	0	0
心筋梗塞	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
狭心症	2 (0.3%)	0	0	2 (0.3%)	0	0
左室機能不全	2 (0.3%)	0	2 (0.3%)	0	0	0
上室性頻脈	1 (0.1%)	0	0	1 (0.1%)	0	0
心室性期外収縮	1 (0.1%)	1 (0.1%)	0	0	0	0
心房粗動	2 (0.3%)	0	2 (0.3%)	0	0	0
うっ血性心筋症	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
心筋虚血	1 (0.1%)	0	0	1 (0.1%)	0	0
心室性不整脈	1 (0.1%)	0	1 (0.1%)	0	0	0
心停止	1 (0.1%)	0	0	0	0	1 (0.1%)
冠動脈疾患	1 (0.1%)	0	0	1 (0.1%)	0	0
左房拡張	1 (0.1%)	1 (0.1%)	0	0	0	0
心血管不全	1 (0.1%)	0	1 (0.1%)	0	0	0
心室壁運動低下	1 (0.1%)	1 (0.1%)	0	0	0	0
心肺不全	1 (0.1%)	0	0	0	0	1 (0.1%)
心膜炎	1 (0.1%)	0	1 (0.1%)	0	0	0
発作性頻脈	1 (0.1%)	1 (0.1%)	0	0	0	0
腎および尿路障害						
- Overall -	42 (6.0%)	26 (3.7%)	9 (1.3%)	5 (0.7%)	2 (0.3%)	0
排尿困難	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
頻尿	9 (1.3%)	8 (1.1%)	0	1 (0.1%)	0	0
血尿	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
急性腎障害	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
尿失禁	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
尿閉	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
腎不全	3 (0.4%)	0	0	1 (0.1%)	2 (0.3%)	0
緊張性膀胱	1 (0.1%)	0	1 (0.1%)	0	0	0
腎仙痛	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
非感染性膀胱炎	1 (0.1%)	1 (0.1%)	0	0	0	0
夜間頻尿	2 (0.3%)	2 (0.3%)	0	0	0	0
腎機能障害	1 (0.1%)	1 (0.1%)	0	0	0	0
腎結石症	1 (0.1%)	0	1 (0.1%)	0	0	0
急性腎前性腎不全	1 (0.1%)	0	0	1 (0.1%)	0	0
腎硬化症	1 (0.1%)	1 (0.1%)	0	0	0	0
低張尿	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
尿異常	1 (0.1%)	1 (0.1%)	0	0	0	0
腹圧性尿失禁	1 (0.1%)	0	1 (0.1%)	0	0	0
眼障害						
- Overall -	36 (5.1%)	27 (3.8%)	7 (1.0%)	2 (0.3%)	0	0
流涙増加	7 (1.0%)	7 (1.0%)	0	0	0	0
眼乾燥	5 (0.7%)	5 (0.7%)	0	0	0	0
眼刺激	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
白内障	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
霧視	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
視力低下	2 (0.3%)	2 (0.3%)	0	0	0	0
眼そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
眼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
眼部不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
眼瞼下垂	1 (0.1%)	0	1 (0.1%)	0	0	0
眼窩周囲浮腫	2 (0.3%)	2 (0.3%)	0	0	0	0
視力障害	1 (0.1%)	0	1 (0.1%)	0	0	0
複視	1 (0.1%)	1 (0.1%)	0	0	0	0
アレルギー性結膜炎	1 (0.1%)	1 (0.1%)	0	0	0	0
一過性視力低下	1 (0.1%)	1 (0.1%)	0	0	0	0
角膜炎	1 (0.1%)	0	1 (0.1%)	0	0	0
眼の異常感覚	1 (0.1%)	1 (0.1%)	0	0	0	0
眼球乾燥症	1 (0.1%)	1 (0.1%)	0	0	0	0
眼充血	1 (0.1%)	1 (0.1%)	0	0	0	0
眼部腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
強膜障害	1 (0.1%)	0	1 (0.1%)	0	0	0
網膜出血	1 (0.1%)	1 (0.1%)	0	0	0	0
緑内障	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肝胆道系障害						
- Overall -	17 (2.4%)	4 (0.6%)	6 (0.9%)	5 (0.7%)	2 (0.3%)	0
肝機能異常	5 (0.7%)	1 (0.1%)	3 (0.4%)	1 (0.1%)	0	0
肝障害	1 (0.1%)	0	0	0	1 (0.1%)	0
肝損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
胆石症	3 (0.4%)	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	0
胆嚢炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
急性胆嚢炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
高ビリルビン血症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
脂肪肝	1 (0.1%)	0	0	1 (0.1%)	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）						
- Overall -	19 (2.7%)	4 (0.6%)	1 (0.1%)	10 (1.4%)	1 (0.1%)	3 (0.4%)
前立腺癌	2 (0.3%)	0	0	2 (0.3%)	0	0
肺腺癌	1 (0.1%)	0	0	0	0	1 (0.1%)
急性骨髄性白血病	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
乳癌	2 (0.3%)	0	0	2 (0.3%)	0	0
結腸癌	2 (0.3%)	0	0	0	1 (0.1%)	1 (0.1%)
結腸腺癌	2 (0.3%)	0	0	2 (0.3%)	0	0
脂漏性角化症	1 (0.1%)	1 (0.1%)	0	0	0	0
Ｂ細胞性リンパ腫	1 (0.1%)	1 (0.1%)	0	0	0	0
化膿性肉芽腫	1 (0.1%)	1 (0.1%)	0	0	0	0
筋の良性新生物	1 (0.1%)	1 (0.1%)	0	0	0	0
結腸直腸癌	1 (0.1%)	0	1 (0.1%)	0	0	0
食道癌	1 (0.1%)	0	0	1 (0.1%)	0	0
乳頭様甲状腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
辺縁帯リンパ腫	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
耳および迷路障害						
- Overall -	15 (2.1%)	11 (1.6%)	4 (0.6%)	0	0	0
耳鳴	5 (0.7%)	5 (0.7%)	0	0	0	0
回転性めまい	3 (0.4%)	3 (0.4%)	0	0	0	0
耳痛	2 (0.3%)	2 (0.3%)	0	0	0	0
耳不快感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
難聴	3 (0.4%)	0	3 (0.4%)	0	0	0
耳そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
耳垢栓塞	1 (0.1%)	1 (0.1%)	0	0	0	0
生殖系および乳房障害						
- Overall -	13 (1.8%)	8 (1.1%)	3 (0.4%)	2 (0.3%)	0	0
無月経	1 (0.1%)	1 (0.1%)	0	0	0	0
骨盤痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
精巣痛	2 (0.3%)	2 (0.3%)	0	0	0	0
不規則月経	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
腟出血	1 (0.1%)	1 (0.1%)	0	0	0	0
陰茎水疱	1 (0.1%)	1 (0.1%)	0	0	0	0
陰嚢紅斑	1 (0.1%)	0	0	1 (0.1%)	0	0
陰部そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
精巣障害	1 (0.1%)	0	1 (0.1%)	0	0	0
精巣上体嚢胞	1 (0.1%)	1 (0.1%)	0	0	0	0
乳房痛	1 (0.1%)	1 (0.1%)	0	0	0	0
勃起不全	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫系障害						
- Overall -	12 (1.7%)	3 (0.4%)	9 (1.3%)	0	0	0
過敏症	8 (1.1%)	3 (0.4%)	5 (0.7%)	0	0	0
季節性アレルギー	2 (0.3%)	0	2 (0.3%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
造影剤アレルギー	2 (0.3%)	0	2 (0.3%)	0	0	0
内分泌障害						
- Overall -	5 (0.7%)	0	3 (0.4%)	1 (0.1%)	1 (0.1%)	0
ステロイド離脱症候群	1 (0.1%)	0	1 (0.1%)	0	0	0
甲状腺機能低下症	1 (0.1%)	0	1 (0.1%)	0	0	0
抗利尿ホルモン不適合分泌	1 (0.1%)	0	0	1 (0.1%)	0	0
甲状腺腫	1 (0.1%)	0	0	0	1 (0.1%)	0
続発性副腎皮質機能不全	1 (0.1%)	0	1 (0.1%)	0	0	0
先天性、家族性および遺伝性障害						
- Overall -	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
陰嚢水瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
心房中隔欠損症	1 (0.1%)	0	1 (0.1%)	0	0	0
製品の問題						
- Overall -	1 (0.1%)	0	1 (0.1%)	0	0	0
医療機器閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	683 (97.0%)	37 (5.3%)	127 (18.0%)	161 (22.9%)	317 (45.0%)	41 (5.8%)
血液およびリンパ系障害						
- Overall -	451 (64.1%)	4 (0.6%)	32 (4.5%)	107 (15.2%)	306 (43.5%)	2 (0.3%)
好中球減少症	340 (48.3%)	0	15 (2.1%)	80 (11.4%)	245 (34.8%)	0
発熱性好中球減少症	127 (18.0%)	3 (0.4%)	1 (0.1%)	63 (8.9%)	59 (8.4%)	1 (0.1%)
白血球減少症	115 (16.3%)	2 (0.3%)	17 (2.4%)	43 (6.1%)	53 (7.5%)	0
貧血	95 (13.5%)	5 (0.7%)	39 (5.5%)	48 (6.8%)	3 (0.4%)	0
血小板減少症	55 (7.8%)	6 (0.9%)	18 (2.6%)	16 (2.3%)	15 (2.1%)	0
リンパ球減少症	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
血小板増加症	1 (0.1%)	0	1 (0.1%)	0	0	0
播種性血管内凝固	1 (0.1%)	0	1 (0.1%)	0	0	0
白血球増加症	1 (0.1%)	0	0	1 (0.1%)	0	0
汎血球減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
慢性疾患の貧血	1 (0.1%)	0	0	1 (0.1%)	0	0
免疫性血小板減少性紫斑病	1 (0.1%)	0	0	0	1 (0.1%)	0
脾血腫	1 (0.1%)	0	0	0	1 (0.1%)	0
脾静脈血栓症	1 (0.1%)	0	0	1 (0.1%)	0	0
貪食細胞性組織球症	1 (0.1%)	0	0	0	0	1 (0.1%)
胃腸障害						
- Overall -	428 (60.8%)	183 (26.0%)	184 (26.1%)	49 (7.0%)	11 (1.6%)	1 (0.1%)
悪心	207 (29.4%)	117 (16.6%)	77 (10.9%)	13 (1.8%)	0	0
便秘	165 (23.4%)	118 (16.8%)	43 (6.1%)	4 (0.6%)	0	0
下痢	112 (15.9%)	53 (7.5%)	44 (6.3%)	14 (2.0%)	1 (0.1%)	0
嘔吐	103 (14.6%)	68 (9.7%)	28 (4.0%)	7 (1.0%)	0	0
口内炎	45 (6.4%)	27 (3.8%)	16 (2.3%)	2 (0.3%)	0	0
腹痛	49 (7.0%)	25 (3.6%)	19 (2.7%)	5 (0.7%)	0	0
消化不良	44 (6.3%)	21 (3.0%)	23 (3.3%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
上腹部痛	37 (5.3%)	24 (3.4%)	11 (1.6%)	2 (0.3%)	0	0
痔核	17 (2.4%)	6 (0.9%)	10 (1.4%)	1 (0.1%)	0	0
口腔内潰瘍形成	10 (1.4%)	6 (0.9%)	4 (0.6%)	0	0	0
口内乾燥	15 (2.1%)	15 (2.1%)	0	0	0	0
胃食道逆流性疾患	15 (2.1%)	4 (0.6%)	11 (1.6%)	0	0	0
腹部膨満	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
嚥下障害	8 (1.1%)	6 (0.9%)	0	1 (0.1%)	1 (0.1%)	0
歯痛	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
胃炎	10 (1.4%)	4 (0.6%)	5 (0.7%)	1 (0.1%)	0	0
口腔内痛	6 (0.9%)	5 (0.7%)	0	1 (0.1%)	0	0
腹部不快感	4 (0.6%)	4 (0.6%)	0	0	0	0
歯肉痛	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
肛門周囲痛	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
アフタ性潰瘍	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
鼓腸	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
イレウス	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
胃腸出血	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
下腹部痛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
血便排泄	2 (0.3%)	2 (0.3%)	0	0	0	0
腸閉塞	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
嚥下痛	5 (0.7%)	2 (0.3%)	2 (0.3%)	1 (0.1%)	0	0
痔出血	1 (0.1%)	1 (0.1%)	0	0	0	0
上部消化管出血	4 (0.6%)	1 (0.1%)	0	3 (0.4%)	0	0
舌潰瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
大腸炎	3 (0.4%)	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	0
腸管穿孔	3 (0.4%)	0	0	0	3 (0.4%)	0
胃出血	2 (0.3%)	0	0	2 (0.3%)	0	0
胃穿孔	1 (0.1%)	0	0	0	1 (0.1%)	0
口腔知覚不全	4 (0.6%)	4 (0.6%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
口唇炎	1 (0.1%)	1 (0.1%)	0	0	0	0
歯肉出血	2 (0.3%)	2 (0.3%)	0	0	0	0
小腸炎	1 (0.1%)	1 (0.1%)	0	0	0	0
消化器痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
大腸ポリープ	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
裂肛	1 (0.1%)	1 (0.1%)	0	0	0	0
肛門出血	1 (0.1%)	0	1 (0.1%)	0	0	0
胃潰瘍	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
小腸閉塞	2 (0.3%)	0	0	2 (0.3%)	0	0
舌痛	2 (0.3%)	2 (0.3%)	0	0	0	0
直腸出血	1 (0.1%)	0	1 (0.1%)	0	0	0
腹水	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
齲歯	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
亜イレウス	1 (0.1%)	0	0	1 (0.1%)	0	0
異常便	1 (0.1%)	0	1 (0.1%)	0	0	0
下部消化管出血	1 (0.1%)	0	1 (0.1%)	0	0	0
急性膵炎	2 (0.3%)	0	0	2 (0.3%)	0	0
口の感覚鈍麻	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔内出血	1 (0.1%)	1 (0.1%)	0	0	0	0
歯周病	2 (0.3%)	2 (0.3%)	0	0	0	0
痔瘻	1 (0.1%)	0	1 (0.1%)	0	0	0
小腸穿孔	1 (0.1%)	0	0	1 (0.1%)	0	0
食道炎	1 (0.1%)	0	1 (0.1%)	0	0	0
舌浮腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
麻痺性イレウス	1 (0.1%)	0	1 (0.1%)	0	0	0
臍ヘルニア	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
鼠径ヘルニア	1 (0.1%)	0	0	0	1 (0.1%)	0
レッチング	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
胃障害	1 (0.1%)	0	1 (0.1%)	0	0	0
回腸穿孔	1 (0.1%)	0	0	0	1 (0.1%)	0
気腹	1 (0.1%)	0	0	0	1 (0.1%)	0
血性下痢	1 (0.1%)	1 (0.1%)	0	0	0	0
口蓋垂炎	1 (0.1%)	0	1 (0.1%)	0	0	0
口蓋潰瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
口蓋浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
歯状態不良	1 (0.1%)	0	1 (0.1%)	0	0	0
歯肉腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
歯肉退縮	1 (0.1%)	1 (0.1%)	0	0	0	0
歯肉潰瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
出血性胃炎	1 (0.1%)	0	0	1 (0.1%)	0	0
出血性腸炎	1 (0.1%)	0	1 (0.1%)	0	0	0
食道痛	1 (0.1%)	1 (0.1%)	0	0	0	0
舌そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
舌腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
舌苔	1 (0.1%)	1 (0.1%)	0	0	0	0
唾液変性	1 (0.1%)	1 (0.1%)	0	0	0	0
腸炎	1 (0.1%)	0	1 (0.1%)	0	0	0
腸管虚血	1 (0.1%)	0	0	0	0	1 (0.1%)
腸間膜静脈血栓症	1 (0.1%)	1 (0.1%)	0	0	0	0
腸出血	1 (0.1%)	1 (0.1%)	0	0	0	0
直腸しぶり	1 (0.1%)	1 (0.1%)	0	0	0	0
吐血	1 (0.1%)	0	0	1 (0.1%)	0	0
排便障害	1 (0.1%)	1 (0.1%)	0	0	0	0
慢性膵炎	1 (0.1%)	0	0	1 (0.1%)	0	0
肛門失禁	1 (0.1%)	1 (0.1%)	0	0	0	0
肛門潰瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
膵炎	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
一般・全身障害および投与部位の状態						
- Overall -	420 (59.7%)	197 (28.0%)	174 (24.7%)	40 (5.7%)	4 (0.6%)	5 (0.7%)
疲労	137 (19.5%)	86 (12.2%)	36 (5.1%)	15 (2.1%)	0	0
発熱	142 (20.2%)	92 (13.1%)	40 (5.7%)	8 (1.1%)	2 (0.3%)	0
悪寒	133 (18.9%)	62 (8.8%)	64 (9.1%)	7 (1.0%)	0	0
無力症	71 (10.1%)	43 (6.1%)	21 (3.0%)	7 (1.0%)	0	0
粘膜の炎症	46 (6.5%)	23 (3.3%)	20 (2.8%)	3 (0.4%)	0	0
末梢性浮腫	36 (5.1%)	19 (2.7%)	13 (1.8%)	4 (0.6%)	0	0
倦怠感	21 (3.0%)	15 (2.1%)	5 (0.7%)	1 (0.1%)	0	0
胸部不快感	23 (3.3%)	16 (2.3%)	7 (1.0%)	0	0	0
疼痛	16 (2.3%)	10 (1.4%)	4 (0.6%)	2 (0.3%)	0	0
非心臓性胸痛	12 (1.7%)	7 (1.0%)	5 (0.7%)	0	0	0
浮腫	10 (1.4%)	7 (1.0%)	3 (0.4%)	0	0	0
胸痛	10 (1.4%)	7 (1.0%)	3 (0.4%)	0	0	0
冷感	9 (1.3%)	7 (1.0%)	2 (0.3%)	0	0	0
インフルエンザ様疾患	7 (1.0%)	2 (0.3%)	4 (0.6%)	1 (0.1%)	0	0
末梢腫脹	3 (0.4%)	3 (0.4%)	0	0	0	0
注入部位血管外漏出	2 (0.3%)	0	2 (0.3%)	0	0	0
顔面浮腫	3 (0.4%)	3 (0.4%)	0	0	0	0
死亡	3 (0.4%)	0	0	0	0	3 (0.4%)
熱感	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
注射部位反応	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
活動状態低下	2 (0.3%)	2 (0.3%)	0	0	0	0
口渇	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
全身健康状態低下	2 (0.3%)	0	1 (0.1%)	0	0	1 (0.1%)
全身性浮腫	2 (0.3%)	0	2 (0.3%)	0	0	0
注射部位疼痛	1 (0.1%)	0	1 (0.1%)	0	0	0
不快感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腋窩痛	1 (0.1%)	1 (0.1%)	0	0	0	0
カテーテル留置部位疼痛	1 (0.1%)	0	1 (0.1%)	0	0	0
顔面痛	1 (0.1%)	0	0	1 (0.1%)	0	0
恥骨上痛	2 (0.3%)	2 (0.3%)	0	0	0	0
注入部位腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
注入部位疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
突然死	1 (0.1%)	0	0	0	0	1 (0.1%)
歩行障害	1 (0.1%)	1 (0.1%)	0	0	0	0
カテーテル留置部位そう痒感	1 (0.1%)	1 (0.1%)	0	0	0	0
ヘルニア	1 (0.1%)	0	1 (0.1%)	0	0	0
異常高熱	1 (0.1%)	0	0	0	1 (0.1%)	0
医療機器関連血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
局所腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
全身性炎症反応症候群	1 (0.1%)	0	0	0	1 (0.1%)	0
注射部位静脈炎	1 (0.1%)	0	1 (0.1%)	0	0	0
注射部位漏出	1 (0.1%)	1 (0.1%)	0	0	0	0
粘膜乾燥	1 (0.1%)	1 (0.1%)	0	0	0	0
嵌頓ヘルニア	1 (0.1%)	0	0	1 (0.1%)	0	0
感染症および寄生虫症						
- Overall -	379 (53.8%)	83 (11.8%)	161 (22.9%)	88 (12.5%)	31 (4.4%)	16 (2.3%)
肺炎	57 (8.1%)	2 (0.3%)	15 (2.1%)	28 (4.0%)	7 (1.0%)	5 (0.7%)
上気道感染	43 (6.1%)	14 (2.0%)	27 (3.8%)	2 (0.3%)	0	0
帯状疱疹	31 (4.4%)	6 (0.9%)	20 (2.8%)	4 (0.6%)	1 (0.1%)	0
鼻咽頭炎	26 (3.7%)	19 (2.7%)	7 (1.0%)	0	0	0
尿路感染	27 (3.8%)	4 (0.6%)	17 (2.4%)	5 (0.7%)	1 (0.1%)	0
口腔ヘルペス	23 (3.3%)	13 (1.8%)	10 (1.4%)	0	0	0
口腔カンジダ症	20 (2.8%)	4 (0.6%)	15 (2.1%)	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
気管支炎	17 (2.4%)	4 (0.6%)	11 (1.6%)	2 (0.3%)	0	0
敗血症	16 (2.3%)	0	0	6 (0.9%)	9 (1.3%)	1 (0.1%)
肺感染	15 (2.1%)	1 (0.1%)	4 (0.6%)	10 (1.4%)	0	0
Ｂ型肝炎	15 (2.1%)	3 (0.4%)	9 (1.3%)	3 (0.4%)	0	0
結膜炎	9 (1.3%)	6 (0.9%)	3 (0.4%)	0	0	0
胃腸炎	9 (1.3%)	5 (0.7%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0
蜂巣炎	7 (1.0%)	1 (0.1%)	3 (0.4%)	3 (0.4%)	0	0
膀胱炎	11 (1.6%)	3 (0.4%)	8 (1.1%)	0	0	0
咽頭炎	9 (1.3%)	4 (0.6%)	5 (0.7%)	0	0	0
副鼻腔炎	7 (1.0%)	1 (0.1%)	6 (0.9%)	0	0	0
カンジダ感染	11 (1.6%)	5 (0.7%)	6 (0.9%)	0	0	0
単純ヘルペス	10 (1.4%)	2 (0.3%)	7 (1.0%)	1 (0.1%)	0	0
敗血症性ショック	12 (1.7%)	0	0	2 (0.3%)	4 (0.6%)	6 (0.9%)
インフルエンザ	5 (0.7%)	1 (0.1%)	3 (0.4%)	1 (0.1%)	0	0
下気道感染	7 (1.0%)	1 (0.1%)	6 (0.9%)	0	0	0
歯肉炎	7 (1.0%)	5 (0.7%)	1 (0.1%)	1 (0.1%)	0	0
鼻炎	7 (1.0%)	4 (0.6%)	3 (0.4%)	0	0	0
気道感染	8 (1.1%)	2 (0.3%)	4 (0.6%)	0	2 (0.3%)	0
口腔感染	7 (1.0%)	3 (0.4%)	3 (0.4%)	1 (0.1%)	0	0
毛包炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
医療機器関連感染	5 (0.7%)	2 (0.3%)	2 (0.3%)	1 (0.1%)	0	0
皮膚感染	3 (0.4%)	3 (0.4%)	0	0	0	0
ヘルペスウイルス感染	7 (1.0%)	2 (0.3%)	3 (0.4%)	2 (0.3%)	0	0
感染	4 (0.6%)	0	2 (0.3%)	1 (0.1%)	0	1 (0.1%)
腟感染	3 (0.4%)	0	3 (0.4%)	0	0	0
好中球減少性敗血症	3 (0.4%)	0	0	2 (0.3%)	1 (0.1%)	0
耳感染	2 (0.3%)	0	2 (0.3%)	0	0	0
ウイルス感染	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
サイトメガロウイルス性脈絡網膜炎	3 (0.4%)	0	0	1 (0.1%)	2 (0.3%)	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
ニューモシスチス・イロベチイ肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
外陰部腟カンジダ症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
外陰腟真菌感染	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
限局性感染	2 (0.3%)	2 (0.3%)	0	0	0	0
口角口唇炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
口腔真菌感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
歯感染	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
歯周炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
歯膿瘍	2 (0.3%)	0	2 (0.3%)	0	0	0
真菌感染	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
爪真菌症	3 (0.4%)	3 (0.4%)	0	0	0	0
クロストリジウム・ディフィシレ大腸炎	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
サイトメガロウイルス感染	2 (0.3%)	0	2 (0.3%)	0	0	0
感染性腸炎	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
喉頭炎	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
食道カンジダ症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
水痘	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
虫垂炎	1 (0.1%)	0	0	1 (0.1%)	0	0
粘膜感染	2 (0.3%)	0	2 (0.3%)	0	0	0
麦粒腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
皮膚真菌感染	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
ウイルス性気道感染	2 (0.3%)	0	2 (0.3%)	0	0	0
クロストリジウム・ディフィシレ感染	1 (0.1%)	0	0	1 (0.1%)	0	0
異型肺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
気管支肺アスペルギルス症	1 (0.1%)	0	0	0	0	1 (0.1%)
口唇感染	2 (0.3%)	0	2 (0.3%)	0	0	0
骨髄炎	1 (0.1%)	0	0	0	0	1 (0.1%)
消化管感染	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
創傷感染	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腹膜炎	2 (0.3%)	0	0	2 (0.3%)	0	0
肛門膿瘍	3 (0.4%)	1 (0.1%)	0	2 (0.3%)	0	0
せつ	1 (0.1%)	1 (0.1%)	0	0	0	0
ウイルス性胃腸炎	1 (0.1%)	1 (0.1%)	0	0	0	0
クレブシエラ性敗血症	1 (0.1%)	0	0	0	1 (0.1%)	0
ヘリコバクター感染	1 (0.1%)	0	1 (0.1%)	0	0	0
外陰部膿瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
感染性下痢	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
感染性胸水	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
感染性小腸結腸炎	2 (0.3%)	0	0	2 (0.3%)	0	0
憩室炎	1 (0.1%)	0	0	1 (0.1%)	0	0
好中球減少性感染	1 (0.1%)	0	0	0	1 (0.1%)	0
水痘帯状疱疹ウイルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
足部白癬	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
腸球菌感染	1 (0.1%)	1 (0.1%)	0	0	0	0
直腸膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
尿路性敗血症	1 (0.1%)	0	0	0	1 (0.1%)	0
膿疱性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
白癬感染	1 (0.1%)	0	1 (0.1%)	0	0	0
皮下組織膿瘍	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0
鼻ヘルペス	2 (0.3%)	0	2 (0.3%)	0	0	0
扁桃炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
Ｈ１Ｎ１インフルエンザ	1 (0.1%)	0	0	1 (0.1%)	0	0
ウイルス性気管支炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性髄膜炎	1 (0.1%)	0	0	0	0	1 (0.1%)
ウイルス性肺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
カンジダ尿	1 (0.1%)	0	1 (0.1%)	0	0	0
サイトメガロウイルス血症	1 (0.1%)	0	0	1 (0.1%)	0	0
サイトメガロウイルス性大腸炎	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
マイコバクテリア感染	1 (0.1%)	1 (0.1%)	0	0	0	0
レンサ球菌性咽頭炎	1 (0.1%)	0	0	1 (0.1%)	0	0
医療機器関連敗血症	1 (0.1%)	0	0	0	1 (0.1%)	0
外耳炎	1 (0.1%)	0	1 (0.1%)	0	0	0
感染性リンパ嚢腫	1 (0.1%)	0	0	1 (0.1%)	0	0
感染性舌炎	1 (0.1%)	0	0	1 (0.1%)	0	0
感染性胆嚢炎	1 (0.1%)	0	0	0	1 (0.1%)	0
肝蛭症	1 (0.1%)	1 (0.1%)	0	0	0	0
眼感染	1 (0.1%)	0	1 (0.1%)	0	0	0
眼帯状疱疹	1 (0.1%)	0	1 (0.1%)	0	0	0
気管炎	1 (0.1%)	0	1 (0.1%)	0	0	0
急性中耳炎	1 (0.1%)	0	1 (0.1%)	0	0	0
急性副鼻腔炎	1 (0.1%)	0	1 (0.1%)	0	0	0
細菌性疾患キャリアー	1 (0.1%)	1 (0.1%)	0	0	0	0
細菌性腸炎	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌性敗血症	1 (0.1%)	0	0	0	1 (0.1%)	0
細菌性肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌性膀胱炎	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌性膣症	1 (0.1%)	0	1 (0.1%)	0	0	0
耳下腺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
術後創感染	1 (0.1%)	0	1 (0.1%)	0	0	0
真菌性乳腺炎	1 (0.1%)	1 (0.1%)	0	0	0	0
真菌性副鼻腔炎	1 (0.1%)	0	0	1 (0.1%)	0	0
神経合併症を伴う帯状疱疹感染	1 (0.1%)	0	1 (0.1%)	0	0	0
進行性多巣性白質脳症	1 (0.1%)	0	0	1 (0.1%)	0	0
髄膜炎	1 (0.1%)	0	0	0	1 (0.1%)	0
切開部位感染	1 (0.1%)	0	1 (0.1%)	0	0	0
唾液腺炎	1 (0.1%)	1 (0.1%)	0	0	0	0
丹毒	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
蓄膿	1 (0.1%)	0	0	1 (0.1%)	0	0
虫垂膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
腸球菌性敗血症	1 (0.1%)	1 (0.1%)	0	0	0	0
直腸周囲膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
爪囲炎	1 (0.1%)	1 (0.1%)	0	0	0	0
爪床感染	1 (0.1%)	1 (0.1%)	0	0	0	0
膿尿	1 (0.1%)	1 (0.1%)	0	0	0	0
播種性帯状疱疹	1 (0.1%)	0	0	1 (0.1%)	0	0
敗血症症候群	1 (0.1%)	0	0	0	1 (0.1%)	0
肺結核	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚カンジダ	1 (0.1%)	0	1 (0.1%)	0	0	0
麻疹	1 (0.1%)	0	0	1 (0.1%)	0	0
類丹毒	1 (0.1%)	0	1 (0.1%)	0	0	0
神経系障害						
- Overall -	336 (47.7%)	207 (29.4%)	103 (14.6%)	22 (3.1%)	1 (0.1%)	3 (0.4%)
末梢性ニューロパチー	88 (12.5%)	68 (9.7%)	17 (2.4%)	3 (0.4%)	0	0
頭痛	75 (10.7%)	46 (6.5%)	26 (3.7%)	3 (0.4%)	0	0
末梢性感覚ニューロパチー	54 (7.7%)	41 (5.8%)	13 (1.8%)	0	0	0
錯感覚	55 (7.8%)	37 (5.3%)	18 (2.6%)	0	0	0
味覚異常	44 (6.3%)	38 (5.4%)	6 (0.9%)	0	0	0
浮動性めまい	49 (7.0%)	36 (5.1%)	9 (1.3%)	4 (0.6%)	0	0
感覚鈍麻	30 (4.3%)	22 (3.1%)	8 (1.1%)	0	0	0
多発ニューロパチー	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
失神	4 (0.6%)	0	1 (0.1%)	3 (0.4%)	0	0
振戦	12 (1.7%)	4 (0.6%)	7 (1.0%)	1 (0.1%)	0	0
失神寸前の状態	5 (0.7%)	0	4 (0.6%)	1 (0.1%)	0	0
神経痛	7 (1.0%)	4 (0.6%)	2 (0.3%)	1 (0.1%)	0	0
傾眠	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
末梢性運動ニューロパチー	4 (0.6%)	4 (0.6%)	0	0	0	0
脳血管発作	3 (0.4%)	0	0	0	1 (0.1%)	2 (0.3%)
下肢静止不能症候群	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
坐骨神経痛	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
失声症	3 (0.4%)	3 (0.4%)	0	0	0	0
神経毒性	2 (0.3%)	2 (0.3%)	0	0	0	0
体位性めまい	1 (0.1%)	1 (0.1%)	0	0	0	0
平衡障害	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
味覚消失	1 (0.1%)	1 (0.1%)	0	0	0	0
嗜眠	4 (0.6%)	4 (0.6%)	0	0	0	0
注意力障害	1 (0.1%)	1 (0.1%)	0	0	0	0
脳虚血	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
くも膜下出血	1 (0.1%)	0	0	0	0	1 (0.1%)
ヘルペス後神経痛	1 (0.1%)	1 (0.1%)	0	0	0	0
ミオクローヌス	1 (0.1%)	1 (0.1%)	0	0	0	0
運動失調	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
記憶障害	1 (0.1%)	1 (0.1%)	0	0	0	0
灼熱感	1 (0.1%)	1 (0.1%)	0	0	0	0
精神運動亢進	1 (0.1%)	0	1 (0.1%)	0	0	0
嗅覚錯誤	1 (0.1%)	1 (0.1%)	0	0	0	0
ラクナ梗塞	1 (0.1%)	0	1 (0.1%)	0	0	0
意識レベルの低下	1 (0.1%)	0	1 (0.1%)	0	0	0
過眠症	1 (0.1%)	1 (0.1%)	0	0	0	0
感覚消失	1 (0.1%)	1 (0.1%)	0	0	0	0
虚血性脳卒中	1 (0.1%)	0	0	1 (0.1%)	0	0
筋萎縮性側索硬化症	1 (0.1%)	0	0	1 (0.1%)	0	0
頚腕症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
健忘	1 (0.1%)	1 (0.1%)	0	0	0	0
塞栓性脳梗塞	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
三叉神経痛	1 (0.1%)	1 (0.1%)	0	0	0	0
失語症	1 (0.1%)	1 (0.1%)	0	0	0	0
尺骨神経炎	1 (0.1%)	1 (0.1%)	0	0	0	0
神経根障害	1 (0.1%)	1 (0.1%)	0	0	0	0
進行性脳卒中	1 (0.1%)	0	0	1 (0.1%)	0	0
第３脳神経障害	1 (0.1%)	0	1 (0.1%)	0	0	0
第３脳神経麻痺	1 (0.1%)	0	0	1 (0.1%)	0	0
第６脳神経障害	1 (0.1%)	1 (0.1%)	0	0	0	0
第６脳神経麻痺	1 (0.1%)	0	0	1 (0.1%)	0	0
知覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
頭部不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
認知障害	1 (0.1%)	1 (0.1%)	0	0	0	0
脳出血	1 (0.1%)	0	1 (0.1%)	0	0	0
微細運動機能障害	1 (0.1%)	0	1 (0.1%)	0	0	0
不全片麻痺	1 (0.1%)	0	0	1 (0.1%)	0	0
味覚減退	1 (0.1%)	1 (0.1%)	0	0	0	0
痙攣発作	1 (0.1%)	0	1 (0.1%)	0	0	0
傷害、中毒および処置合併症						
- Overall -	281 (39.9%)	104 (14.8%)	144 (20.5%)	28 (4.0%)	4 (0.6%)	1 (0.1%)
注入に伴う反応	254 (36.1%)	95 (13.5%)	139 (19.7%)	19 (2.7%)	1 (0.1%)	0
転倒	4 (0.6%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0
挫傷	4 (0.6%)	4 (0.6%)	0	0	0	0
脊椎圧迫骨折	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
処置による疼痛	1 (0.1%)	0	1 (0.1%)	0	0	0
血管確保合併症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
裂傷	2 (0.3%)	0	2 (0.3%)	0	0	0
硬膜下血腫	3 (0.4%)	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
節足動物咬傷	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
創傷	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
大腿骨骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
皮膚擦過傷	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
輸血反応	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
靭帯捻挫	1 (0.1%)	0	1 (0.1%)	0	0	0
各種物質毒性	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
股関節部骨折	1 (0.1%)	0	0	0	1 (0.1%)	0
骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
擦過傷	1 (0.1%)	1 (0.1%)	0	0	0	0
四肢損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
歯牙破折	1 (0.1%)	0	1 (0.1%)	0	0	0
神経損傷	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
足関節部骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
大腿骨頚部骨折	1 (0.1%)	0	0	1 (0.1%)	0	0
腓骨骨折	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
圧迫骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
外傷性血腫	1 (0.1%)	1 (0.1%)	0	0	0	0
眼窩周囲出血	1 (0.1%)	1 (0.1%)	0	0	0	0
顔面損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
気圧性外傷	1 (0.1%)	1 (0.1%)	0	0	0	0
交通事故	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔内損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
骨盤骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
鎖骨骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
術後呼吸不全	1 (0.1%)	0	0	0	1 (0.1%)	0
処置後出血	1 (0.1%)	0	1 (0.1%)	0	0	0
処置合併症	1 (0.1%)	0	0	1 (0.1%)	0	0
創傷血腫	1 (0.1%)	0	1 (0.1%)	0	0	0
創傷出血	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
足骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
頭部損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚損傷	1 (0.1%)	1 (0.1%)	0	0	0	0
漿液腫	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚および皮下組織障害						
- Overall -	226 (32.1%)	98 (13.9%)	123 (17.5%)	5 (0.7%)	0	0
脱毛症	145 (20.6%)	56 (8.0%)	89 (12.6%)	0	0	0
発疹	16 (2.3%)	10 (1.4%)	6 (0.9%)	0	0	0
そう痒症	18 (2.6%)	14 (2.0%)	3 (0.4%)	1 (0.1%)	0	0
紅斑	15 (2.1%)	11 (1.6%)	4 (0.6%)	0	0	0
蕁麻疹	10 (1.4%)	2 (0.3%)	7 (1.0%)	1 (0.1%)	0	0
多汗症	12 (1.7%)	7 (1.0%)	5 (0.7%)	0	0	0
皮膚乾燥	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
爪変色	7 (1.0%)	7 (1.0%)	0	0	0	0
寝汗	10 (1.4%)	9 (1.3%)	1 (0.1%)	0	0	0
斑状丘疹状皮疹	8 (1.1%)	7 (1.0%)	1 (0.1%)	0	0	0
湿疹	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
皮膚潰瘍	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
皮膚炎	3 (0.4%)	3 (0.4%)	0	0	0	0
爪の障害	4 (0.6%)	4 (0.6%)	0	0	0	0
ざ瘡様皮膚炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
皮膚色素過剰	2 (0.3%)	2 (0.3%)	0	0	0	0
ざ瘡	2 (0.3%)	2 (0.3%)	0	0	0	0
乾癬	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
接触性皮膚炎	1 (0.1%)	0	1 (0.1%)	0	0	0
冷汗	3 (0.4%)	3 (0.4%)	0	0	0	0
嵌入爪	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
褥瘡性潰瘍	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
アレルギー性皮膚炎	2 (0.3%)	0	2 (0.3%)	0	0	0
過角化	1 (0.1%)	0	1 (0.1%)	0	0	0
丘疹	1 (0.1%)	1 (0.1%)	0	0	0	0
丘疹性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
紫斑	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
水疱	1 (0.1%)	0	0	1 (0.1%)	0	0
斑状皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
うっ滞性皮膚炎	1 (0.1%)	1 (0.1%)	0	0	0	0
ばら色粃糠疹	1 (0.1%)	0	1 (0.1%)	0	0	0
アトピー性皮膚炎	1 (0.1%)	0	1 (0.1%)	0	0	0
間擦疹	1 (0.1%)	0	1 (0.1%)	0	0	0
手掌紅斑	1 (0.1%)	0	0	1 (0.1%)	0	0
全身紅斑	1 (0.1%)	0	0	1 (0.1%)	0	0
爪ジストロフィー	1 (0.1%)	1 (0.1%)	0	0	0	0
爪甲脱落症	1 (0.1%)	0	1 (0.1%)	0	0	0
爪甲離床症	1 (0.1%)	0	1 (0.1%)	0	0	0
爪床出血	1 (0.1%)	1 (0.1%)	0	0	0	0
爪色素沈着	1 (0.1%)	1 (0.1%)	0	0	0	0
爪痛	1 (0.1%)	0	1 (0.1%)	0	0	0
斑状出血	1 (0.1%)	1 (0.1%)	0	0	0	0
皮脂欠乏性湿疹	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚灼熱感	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚軟化	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚剥脱	1 (0.1%)	0	1 (0.1%)	0	0	0
痂皮	1 (0.1%)	1 (0.1%)	0	0	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	232 (33.0%)	110 (15.6%)	80 (11.4%)	27 (3.8%)	9 (1.3%)	6 (0.9%)
咳嗽	83 (11.8%)	58 (8.2%)	24 (3.4%)	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
呼吸困難	53 (7.5%)	18 (2.6%)	26 (3.7%)	6 (0.9%)	2 (0.3%)	1 (0.1%)
口腔咽頭痛	41 (5.8%)	29 (4.1%)	11 (1.6%)	1 (0.1%)	0	0
鼻漏	18 (2.6%)	15 (2.1%)	3 (0.4%)	0	0	0
湿性咳嗽	17 (2.4%)	14 (2.0%)	3 (0.4%)	0	0	0
しゃっくり	7 (1.0%)	4 (0.6%)	3 (0.4%)	0	0	0
発声障害	10 (1.4%)	10 (1.4%)	0	0	0	0
労作性呼吸困難	10 (1.4%)	7 (1.0%)	2 (0.3%)	1 (0.1%)	0	0
肺塞栓症	10 (1.4%)	1 (0.1%)	2 (0.3%)	4 (0.6%)	1 (0.1%)	2 (0.3%)
胸水	11 (1.6%)	3 (0.4%)	5 (0.7%)	3 (0.4%)	0	0
咽喉刺激感	3 (0.4%)	3 (0.4%)	0	0	0	0
肺臓炎	11 (1.6%)	4 (0.6%)	5 (0.7%)	1 (0.1%)	1 (0.1%)	0
間質性肺疾患	8 (1.1%)	2 (0.3%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0
鼻出血	6 (0.9%)	4 (0.6%)	1 (0.1%)	0	1 (0.1%)	0
鼻閉	7 (1.0%)	3 (0.4%)	4 (0.6%)	0	0	0
低酸素症	6 (0.9%)	1 (0.1%)	3 (0.4%)	2 (0.3%)	0	0
気管支痙攣	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
喀血	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
口腔咽頭不快感	3 (0.4%)	3 (0.4%)	0	0	0	0
アレルギー性鼻炎	1 (0.1%)	1 (0.1%)	0	0	0	0
咽喉乾燥	2 (0.3%)	2 (0.3%)	0	0	0	0
急性呼吸不全	1 (0.1%)	0	0	0	0	1 (0.1%)
肺水腫	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
副鼻腔うっ血	1 (0.1%)	0	1 (0.1%)	0	0	0
喉頭痛	3 (0.4%)	3 (0.4%)	0	0	0	0
肺気腫	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
慢性閉塞性肺疾患	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
喘息	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
喘鳴	2 (0.3%)	0	2 (0.3%)	0	0	0
カタル	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
ラ音	1 (0.1%)	1 (0.1%)	0	0	0	0
咽頭紅斑	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
気胸	1 (0.1%)	0	0	0	1 (0.1%)	0
急性呼吸窮迫症候群	1 (0.1%)	0	0	0	0	1 (0.1%)
胸膜痛	1 (0.1%)	1 (0.1%)	0	0	0	0
誤嚥性肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
肺浸潤	2 (0.3%)	0	0	2 (0.3%)	0	0
鼻閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
頻呼吸	2 (0.3%)	2 (0.3%)	0	0	0	0
無気肺	1 (0.1%)	1 (0.1%)	0	0	0	0
気管の炎症	1 (0.1%)	0	1 (0.1%)	0	0	0
急性肺水腫	1 (0.1%)	0	0	0	1 (0.1%)	0
血胸	1 (0.1%)	0	0	1 (0.1%)	0	0
呼吸器症状	1 (0.1%)	1 (0.1%)	0	0	0	0
呼吸時疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
呼吸障害	1 (0.1%)	0	0	1 (0.1%)	0	0
後天性気管食道瘻	1 (0.1%)	0	0	1 (0.1%)	0	0
肺硬化	1 (0.1%)	1 (0.1%)	0	0	0	0
肺線維症	1 (0.1%)	0	1 (0.1%)	0	0	0
肺胞疾患	1 (0.1%)	0	1 (0.1%)	0	0	0
副鼻腔障害	1 (0.1%)	0	1 (0.1%)	0	0	0
変色痰	1 (0.1%)	1 (0.1%)	0	0	0	0
胞隔炎	1 (0.1%)	0	0	1 (0.1%)	0	0
無酸素症	1 (0.1%)	0	0	0	1 (0.1%)	0
扁桃肥大	1 (0.1%)	1 (0.1%)	0	0	0	0
代謝および栄養障害						
- Overall -	202 (28.7%)	93 (13.2%)	56 (8.0%)	46 (6.5%)	7 (1.0%)	0
食欲減退	97 (13.8%)	61 (8.7%)	27 (3.8%)	9 (1.3%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
低カリウム血症	61 (8.7%)	26 (3.7%)	15 (2.1%)	17 (2.4%)	3 (0.4%)	0
高血糖	16 (2.3%)	4 (0.6%)	7 (1.0%)	5 (0.7%)	0	0
脱水	18 (2.6%)	2 (0.3%)	8 (1.1%)	8 (1.1%)	0	0
低マグネシウム血症	14 (2.0%)	11 (1.6%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
低カルシウム血症	11 (1.6%)	4 (0.6%)	6 (0.9%)	1 (0.1%)	0	0
低リン酸血症	8 (1.1%)	1 (0.1%)	2 (0.3%)	5 (0.7%)	0	0
低ナトリウム血症	4 (0.6%)	1 (0.1%)	0	3 (0.4%)	0	0
高尿酸血症	6 (0.9%)	6 (0.9%)	0	0	0	0
低アルブミン血症	8 (1.1%)	2 (0.3%)	3 (0.4%)	2 (0.3%)	1 (0.1%)	0
糖尿病	6 (0.9%)	1 (0.1%)	2 (0.3%)	3 (0.4%)	0	0
栄養障害	4 (0.6%)	1 (0.1%)	0	3 (0.4%)	0	0
腫瘍崩壊症候群	4 (0.6%)	0	0	3 (0.4%)	1 (0.1%)	0
高カリウム血症	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
高カルシウム血症	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
高トリグリセリド血症	3 (0.4%)	3 (0.4%)	0	0	0	0
水分過負荷	3 (0.4%)	1 (0.1%)	0	2 (0.3%)	0	0
２型糖尿病	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
高コレステロール血症	1 (0.1%)	0	1 (0.1%)	0	0	0
高脂血症	1 (0.1%)	1 (0.1%)	0	0	0	0
体液貯留	2 (0.3%)	2 (0.3%)	0	0	0	0
低蛋白血症	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
低血糖	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
鉄欠乏	1 (0.1%)	0	1 (0.1%)	0	0	0
アシドーシス	1 (0.1%)	0	0	1 (0.1%)	0	0
ビタミンＤ欠乏	1 (0.1%)	1 (0.1%)	0	0	0	0
悪液質	1 (0.1%)	0	0	0	1 (0.1%)	0
過小食	1 (0.1%)	1 (0.1%)	0	0	0	0
血液量減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
高ナトリウム血症	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
多飲症	1 (0.1%)	0	1 (0.1%)	0	0	0
体液平衡失調	1 (0.1%)	0	0	1 (0.1%)	0	0
代謝性アルカローシス	1 (0.1%)	1 (0.1%)	0	0	0	0
葉酸欠乏	1 (0.1%)	0	1 (0.1%)	0	0	0
筋骨格系および結合組織障害						
- Overall -	188 (26.7%)	112 (15.9%)	62 (8.8%)	14 (2.0%)	0	0
背部痛	59 (8.4%)	38 (5.4%)	17 (2.4%)	4 (0.6%)	0	0
関節痛	34 (4.8%)	21 (3.0%)	11 (1.6%)	2 (0.3%)	0	0
筋肉痛	28 (4.0%)	21 (3.0%)	6 (0.9%)	1 (0.1%)	0	0
骨痛	25 (3.6%)	16 (2.3%)	9 (1.3%)	0	0	0
四肢痛	16 (2.3%)	13 (1.8%)	2 (0.3%)	1 (0.1%)	0	0
筋力低下	21 (3.0%)	9 (1.3%)	8 (1.1%)	4 (0.6%)	0	0
筋骨格痛	14 (2.0%)	12 (1.7%)	2 (0.3%)	0	0	0
筋痙縮	14 (2.0%)	7 (1.0%)	7 (1.0%)	0	0	0
頚部痛	9 (1.3%)	8 (1.1%)	1 (0.1%)	0	0	0
筋骨格系胸痛	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
顎痛	8 (1.1%)	7 (1.0%)	1 (0.1%)	0	0	0
鼡径部痛	4 (0.6%)	4 (0.6%)	0	0	0	0
関節腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
側腹部痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
筋拘縮	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
関節炎	2 (0.3%)	2 (0.3%)	0	0	0	0
筋骨格不快感	3 (0.4%)	3 (0.4%)	0	0	0	0
四肢不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
脊椎痛	1 (0.1%)	1 (0.1%)	0	0	0	0
変形性関節症	1 (0.1%)	0	0	1 (0.1%)	0	0
ミオパチー	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
滑液包炎	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
骨減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
椎間板突出	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
痛風性関節炎	2 (0.3%)	2 (0.3%)	0	0	0	0
腱炎	2 (0.3%)	2 (0.3%)	0	0	0	0
下肢腫瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
筋硬化症	1 (0.1%)	1 (0.1%)	0	0	0	0
椎間孔狭窄	1 (0.1%)	0	1 (0.1%)	0	0	0
変形性脊椎症	1 (0.1%)	1 (0.1%)	0	0	0	0
腱痛	1 (0.1%)	1 (0.1%)	0	0	0	0
臨床検査						
- Overall -	124 (17.6%)	51 (7.2%)	45 (6.4%)	26 (3.7%)	2 (0.3%)	0
体重減少	33 (4.7%)	12 (1.7%)	15 (2.1%)	6 (0.9%)	0	0
アラニンアミノトランスフェラーゼ増加	32 (4.5%)	18 (2.6%)	8 (1.1%)	6 (0.9%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	19 (2.7%)	13 (1.8%)	3 (0.4%)	3 (0.4%)	0	0
駆出率減少	13 (1.8%)	2 (0.3%)	6 (0.9%)	5 (0.7%)	0	0
体重増加	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
トランスアミナーゼ上昇	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
リンパ球数減少	5 (0.7%)	0	0	4 (0.6%)	1 (0.1%)	0
血中アルカリホスファターゼ増加	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
血中コレステロール増加	5 (0.7%)	5 (0.7%)	0	0	0	0
Ｃ－反応性蛋白増加	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
γ－グルタミルトランスフェラーゼ増加	1 (0.1%)	0	0	1 (0.1%)	0	0
血圧上昇	3 (0.4%)	1 (0.1%)	0	2 (0.3%)	0	0
血中クレアチニン増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中ブドウ糖増加	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
血圧低下	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
血中カリウム減少	3 (0.4%)	0	3 (0.4%)	0	0	0
血中尿酸増加	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
Ｂ型肝炎ＤＮＡ増加	1 (0.1%)	0	1 (0.1%)	0	0	0
血中アルブミン減少	2 (0.3%)	0	2 (0.3%)	0	0	0
血中カリウム増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中ビリルビン増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中葉酸減少	2 (0.3%)	2 (0.3%)	0	0	0	0
国際標準比増加	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
酸素飽和度低下	1 (0.1%)	1 (0.1%)	0	0	0	0
心拍数増加	2 (0.3%)	0	2 (0.3%)	0	0	0
Ａ型インフルエンザウイルス検査陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
ＨＩＶ抗体陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
クロストリジウム検査陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
リパーゼ増加	1 (0.1%)	0	0	0	1 (0.1%)	0
肝機能検査値上昇	1 (0.1%)	1 (0.1%)	0	0	0	0
肝酵素異常	1 (0.1%)	1 (0.1%)	0	0	0	0
好酸球数増加	1 (0.1%)	0	1 (0.1%)	0	0	0
心拍数不整	1 (0.1%)	0	1 (0.1%)	0	0	0
精液量減少	1 (0.1%)	1 (0.1%)	0	0	0	0
尿中血陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫グロブリン減少	1 (0.1%)	0	1 (0.1%)	0	0	0
血管障害						
- Overall -	119 (16.9%)	36 (5.1%)	46 (6.5%)	33 (4.7%)	3 (0.4%)	1 (0.1%)
高血圧	40 (5.7%)	7 (1.0%)	10 (1.4%)	22 (3.1%)	1 (0.1%)	0
低血圧	36 (5.1%)	15 (2.1%)	15 (2.1%)	6 (0.9%)	0	0
深部静脈血栓症	9 (1.3%)	0	7 (1.0%)	2 (0.3%)	0	0
静脈炎	8 (1.1%)	3 (0.4%)	5 (0.7%)	0	0	0
ほてり	9 (1.3%)	7 (1.0%)	1 (0.1%)	1 (0.1%)	0	0
血管炎	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
潮紅	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
起立性低血圧	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
血栓性静脈炎	1 (0.1%)	1 (0.1%)	0	0	0	0
表在性血栓性静脈炎	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
四肢静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
末梢冷感	1 (0.1%)	1 (0.1%)	0	0	0	0
頚静脈血栓症	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
塞栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
血腫	1 (0.1%)	1 (0.1%)	0	0	0	0
骨盤静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
出血	1 (0.1%)	0	0	0	0	1 (0.1%)
出血性ショック	1 (0.1%)	0	0	1 (0.1%)	0	0
静脈閉塞	1 (0.1%)	0	0	0	1 (0.1%)	0
静脈瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
蒼白	1 (0.1%)	1 (0.1%)	0	0	0	0
大静脈血栓症	1 (0.1%)	0	0	1 (0.1%)	0	0
大動脈硬化症	1 (0.1%)	1 (0.1%)	0	0	0	0
表在性静脈炎	1 (0.1%)	1 (0.1%)	0	0	0	0
精神障害						
- Overall -	107 (15.2%)	61 (8.7%)	39 (5.5%)	6 (0.9%)	0	1 (0.1%)
不眠症	76 (10.8%)	51 (7.2%)	25 (3.6%)	0	0	0
不安	16 (2.3%)	5 (0.7%)	11 (1.6%)	0	0	0
うつ病	11 (1.6%)	5 (0.7%)	5 (0.7%)	1 (0.1%)	0	0
激越	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
譫妄	3 (0.4%)	1 (0.1%)	0	2 (0.3%)	0	0
気分変化	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
抑うつ気分	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
落ち着きのなさ	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
易刺激性	1 (0.1%)	0	0	1 (0.1%)	0	0
気分動揺	2 (0.3%)	2 (0.3%)	0	0	0	0
錯乱状態	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
感情的苦悩	1 (0.1%)	0	0	1 (0.1%)	0	0
感情不安定	1 (0.1%)	0	1 (0.1%)	0	0	0
緊張	1 (0.1%)	1 (0.1%)	0	0	0	0
自殺既遂	1 (0.1%)	0	0	0	0	1 (0.1%)
精神状態変化	1 (0.1%)	0	0	1 (0.1%)	0	0
心臓障害						
- Overall -	75 (10.7%)	24 (3.4%)	18 (2.6%)	22 (3.1%)	7 (1.0%)	4 (0.6%)
心房細動	17 (2.4%)	3 (0.4%)	9 (1.3%)	4 (0.6%)	1 (0.1%)	0
心不全	8 (1.1%)	1 (0.1%)	0	6 (0.9%)	1 (0.1%)	0
頻脈	10 (1.4%)	6 (0.9%)	4 (0.6%)	0	0	0
動悸	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
洞性頻脈	9 (1.3%)	3 (0.4%)	4 (0.6%)	2 (0.3%)	0	0
急性心筋梗塞	1 (0.1%)	0	1 (0.1%)	0	0	0
うっ血性心不全	3 (0.4%)	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
心筋梗塞	3 (0.4%)	0	0	0	2 (0.3%)	1 (0.1%)
狭心症	1 (0.1%)	1 (0.1%)	0	0	0	0
左室機能不全	1 (0.1%)	0	0	1 (0.1%)	0	0
上室性頻脈	2 (0.3%)	0	0	2 (0.3%)	0	0
心筋症	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
心室性期外収縮	2 (0.3%)	2 (0.3%)	0	0	0	0
心房粗動	1 (0.1%)	0	0	1 (0.1%)	0	0
徐脈	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0
心筋虚血	1 (0.1%)	1 (0.1%)	0	0	0	0
心室性不整脈	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
心停止	1 (0.1%)	0	0	0	0	1 (0.1%)
洞性徐脈	2 (0.3%)	2 (0.3%)	0	0	0	0
不整脈	2 (0.3%)	0	0	2 (0.3%)	0	0
ストレス心筋症	1 (0.1%)	0	0	1 (0.1%)	0	0
チアノーゼ	1 (0.1%)	0	1 (0.1%)	0	0	0
冠動脈血栓症	1 (0.1%)	0	0	0	0	1 (0.1%)
期外収縮	1 (0.1%)	1 (0.1%)	0	0	0	0
急性冠動脈症候群	1 (0.1%)	0	1 (0.1%)	0	0	0
上室性期外収縮	1 (0.1%)	1 (0.1%)	0	0	0	0
心拡大	1 (0.1%)	1 (0.1%)	0	0	0	0
心室細動	1 (0.1%)	0	1 (0.1%)	0	0	0
心室粗動	1 (0.1%)	0	0	1 (0.1%)	0	0
心穿孔	1 (0.1%)	0	0	1 (0.1%)	0	0
心毒性	1 (0.1%)	0	0	1 (0.1%)	0	0
心嚢液貯留	1 (0.1%)	0	0	0	1 (0.1%)	0
僧帽弁疾患	1 (0.1%)	0	0	1 (0.1%)	0	0
僧帽弁閉鎖不全症	1 (0.1%)	0	1 (0.1%)	0	0	0
腎および尿路障害						
- Overall -	57 (8.1%)	27 (3.8%)	22 (3.1%)	6 (0.9%)	1 (0.1%)	1 (0.1%)
排尿困難	16 (2.3%)	12 (1.7%)	4 (0.6%)	0	0	0
頻尿	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
血尿	8 (1.1%)	5 (0.7%)	2 (0.3%)	1 (0.1%)	0	0
急性腎障害	6 (0.9%)	0	2 (0.3%)	2 (0.3%)	1 (0.1%)	1 (0.1%)
尿失禁	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
尿閉	4 (0.6%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0
腎不全	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
緊張性膀胱	2 (0.3%)	2 (0.3%)	0	0	0	0
腎仙痛	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
非感染性膀胱炎	2 (0.3%)	2 (0.3%)	0	0	0	0
夜間頻尿	1 (0.1%)	1 (0.1%)	0	0	0	0
腎機能障害	1 (0.1%)	0	1 (0.1%)	0	0	0
腎結石症	1 (0.1%)	0	1 (0.1%)	0	0	0
多尿	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
蛋白尿	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
腎臓痛	1 (0.1%)	0	1 (0.1%)	0	0	0
切迫性尿失禁	1 (0.1%)	0	1 (0.1%)	0	0	0
腺性膀胱炎	1 (0.1%)	0	0	1 (0.1%)	0	0
尿意切迫	1 (0.1%)	0	1 (0.1%)	0	0	0
尿道痛	1 (0.1%)	0	0	1 (0.1%)	0	0
尿路痛	1 (0.1%)	1 (0.1%)	0	0	0	0
排尿躊躇	1 (0.1%)	0	1 (0.1%)	0	0	0
有痛性排尿困難	1 (0.1%)	0	1 (0.1%)	0	0	0
膀胱痛	1 (0.1%)	0	1 (0.1%)	0	0	0
眼障害						
- Overall -	37 (5.3%)	28 (4.0%)	6 (0.9%)	3 (0.4%)	0	0
流涙増加	6 (0.9%)	5 (0.7%)	0	1 (0.1%)	0	0
眼乾燥	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
眼刺激	2 (0.3%)	2 (0.3%)	0	0	0	0
白内障	2 (0.3%)	0	0	2 (0.3%)	0	0
霧視	3 (0.4%)	3 (0.4%)	0	0	0	0
視力低下	2 (0.3%)	2 (0.3%)	0	0	0	0
眼そう痒症	2 (0.3%)	2 (0.3%)	0	0	0	0
眼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
眼部不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
眼瞼下垂	1 (0.1%)	1 (0.1%)	0	0	0	0
結膜出血	2 (0.3%)	2 (0.3%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
視力障害	1 (0.1%)	0	1 (0.1%)	0	0	0
複視	1 (0.1%)	0	1 (0.1%)	0	0	0
眼運動障害	1 (0.1%)	0	1 (0.1%)	0	0	0
眼瞼機能障害	1 (0.1%)	0	1 (0.1%)	0	0	0
眼瞼浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
眼窩嚢胞	1 (0.1%)	1 (0.1%)	0	0	0	0
結膜充血	1 (0.1%)	1 (0.1%)	0	0	0	0
失明	1 (0.1%)	1 (0.1%)	0	0	0	0
硝子体剥離	1 (0.1%)	1 (0.1%)	0	0	0	0
硝子体浮遊物	1 (0.1%)	1 (0.1%)	0	0	0	0
羞明	1 (0.1%)	1 (0.1%)	0	0	0	0
霰粒腫	1 (0.1%)	1 (0.1%)	0	0	0	0
肝胆道系障害						
- Overall -	23 (3.3%)	7 (1.0%)	9 (1.3%)	6 (0.9%)	1 (0.1%)	0
肝機能異常	7 (1.0%)	1 (0.1%)	4 (0.6%)	2 (0.3%)	0	0
肝障害	3 (0.4%)	3 (0.4%)	0	0	0	0
肝損傷	3 (0.4%)	0	2 (0.3%)	0	1 (0.1%)	0
胆石症	1 (0.1%)	0	1 (0.1%)	0	0	0
胆嚢炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
急性胆嚢炎	1 (0.1%)	0	0	1 (0.1%)	0	0
高ビリルビン血症	1 (0.1%)	0	1 (0.1%)	0	0	0
高トランスアミナーゼ血症	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
肝臓痛	1 (0.1%)	1 (0.1%)	0	0	0	0
胆管炎	1 (0.1%)	0	0	1 (0.1%)	0	0
胆管閉塞	1 (0.1%)	0	0	1 (0.1%)	0	0
門脈血栓症	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	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）						
- Overall -	18 (2.6%)	3 (0.4%)	2 (0.3%)	8 (1.1%)	3 (0.4%)	2 (0.3%)
前立腺癌	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
肺腺癌	3 (0.4%)	0	0	3 (0.4%)	0	0
急性骨髄性白血病	1 (0.1%)	0	0	0	1 (0.1%)	0
乳癌	1 (0.1%)	0	0	1 (0.1%)	0	0
脂漏性角化症	1 (0.1%)	1 (0.1%)	0	0	0	0
リンパ腫性乳頭状嚢胞腺腫	1 (0.1%)	1 (0.1%)	0	0	0	0
リンパ性白血病	1 (0.1%)	0	0	1 (0.1%)	0	0
遠隔転移を伴う小細胞肺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
肝新生物	1 (0.1%)	0	0	0	0	1 (0.1%)
脂肪肉腫	1 (0.1%)	0	0	0	1 (0.1%)	0
腫瘍穿孔	1 (0.1%)	0	0	0	1 (0.1%)	0
新生物	1 (0.1%)	1 (0.1%)	0	0	0	0
神経内分泌腫瘍	1 (0.1%)	0	0	0	0	1 (0.1%)
大腸腺腫	1 (0.1%)	0	1 (0.1%)	0	0	0
良性上衣腫	1 (0.1%)	1 (0.1%)	0	0	0	0
膀胱乳頭腫	1 (0.1%)	0	0	1 (0.1%)	0	0
耳および迷路障害						
- Overall -	19 (2.7%)	14 (2.0%)	4 (0.6%)	1 (0.1%)	0	0
耳鳴	6 (0.9%)	6 (0.9%)	0	0	0	0
回転性めまい	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
耳痛	2 (0.3%)	2 (0.3%)	0	0	0	0
耳不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
耳閉	1 (0.1%)	1 (0.1%)	0	0	0	0
聴力低下	1 (0.1%)	0	1 (0.1%)	0	0	0
頭位性回転性めまい	1 (0.1%)	0	0	1 (0.1%)	0	0
両耳難聴	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
生殖系および乳房障害						
- Overall -	18 (2.6%)	10 (1.4%)	6 (0.9%)	2 (0.3%)	0	0
無月経	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
腟出血	1 (0.1%)	1 (0.1%)	0	0	0	0
萎縮性外陰腟炎	1 (0.1%)	1 (0.1%)	0	0	0	0
会陰痛	1 (0.1%)	0	1 (0.1%)	0	0	0
会陰潰瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
外陰腟そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
外陰腟乾燥	1 (0.1%)	0	1 (0.1%)	0	0	0
外陰腟紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
亀頭包皮炎	1 (0.1%)	1 (0.1%)	0	0	0	0
子宮出血	1 (0.1%)	0	0	1 (0.1%)	0	0
子宮内膜肥厚	1 (0.1%)	1 (0.1%)	0	0	0	0
女性化乳房	1 (0.1%)	1 (0.1%)	0	0	0	0
精巣浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
乳頭痛	1 (0.1%)	1 (0.1%)	0	0	0	0
不妊症	1 (0.1%)	0	1 (0.1%)	0	0	0
閉経期症状	1 (0.1%)	1 (0.1%)	0	0	0	0
良性前立腺肥大症	1 (0.1%)	0	1 (0.1%)	0	0	0
免疫系障害						
- Overall -	14 (2.0%)	8 (1.1%)	5 (0.7%)	1 (0.1%)	0	0
過敏症	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
季節性アレルギー	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
低γグロブリン血症	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
アレルギー性浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_all_005_SE APPROVED Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
内分泌障害						
- Overall -	15 (2.1%)	7 (1.0%)	6 (0.9%)	2 (0.3%)	0	0
ステロイド離脱症候群	10 (1.4%)	5 (0.7%)	5 (0.7%)	0	0	0
甲状腺機能低下症	1 (0.1%)	1 (0.1%)	0	0	0	0
副腎機能不全	2 (0.3%)	0	0	2 (0.3%)	0	0
アジソン病	1 (0.1%)	0	0	1 (0.1%)	0	0
甲状腺機能亢進症	1 (0.1%)	0	1 (0.1%)	0	0	0
副甲状腺機能亢進症	1 (0.1%)	1 (0.1%)	0	0	0	0
先天性、家族性および遺伝性障害						
- Overall -	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
陰嚢水瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
気管食道瘻	1 (0.1%)	0	1 (0.1%)	0	0	0
製品の問題						
- Overall -	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
医療機器閉塞	1 (0.1%)	1 (0.1%)	0	0	0	0
医療機器内血栓	1 (0.1%)	0	1 (0.1%)	0	0	0
社会環境						
- Overall -	2 (0.3%)	2 (0.3%)	0	0	0	0
閉経	2 (0.3%)	2 (0.3%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

Program: /opt/BIOSTAT/prod/cdt7159z/k21005n/aet04_all.sas / Output: /opt/BIOSTAT/prod/cdt7159z/k21005n/reports/aet04_all_005_SE.out
11JAN2017 7:13

[5.3.5.4-5 aet04_all_005_SE を再掲]

表 2.7.6.2.1.9-2　因果関係が否定できないすべての有害事象（BO21005試験，未治療 DLBCL 患者）

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	596 (84.8%)	69 (9.8%)	143 (20.3%)	134 (19.1%)	235 (33.4%)	15 (2.1%)
血液およびリンパ系障害						
- Overall -	360 (51.2%)	6 (0.9%)	26 (3.7%)	102 (14.5%)	226 (32.1%)	0
好中球減少症	269 (38.3%)	2 (0.3%)	14 (2.0%)	61 (8.7%)	192 (27.3%)	0
発熱性好中球減少症	104 (14.8%)	1 (0.1%)	0	65 (9.2%)	38 (5.4%)	0
白血球減少症	79 (11.2%)	0	11 (1.6%)	38 (5.4%)	30 (4.3%)	0
貧血	80 (11.4%)	4 (0.6%)	36 (5.1%)	39 (5.5%)	1 (0.1%)	0
血小板減少症	17 (2.4%)	2 (0.3%)	5 (0.7%)	3 (0.4%)	7 (1.0%)	0
リンパ球減少症	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
低グロブリン血症	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
リンパ節症	1 (0.1%)	1 (0.1%)	0	0	0	0
高γグロブリン血症	1 (0.1%)	0	1 (0.1%)	0	0	0
高色素血	1 (0.1%)	1 (0.1%)	0	0	0	0
出血性貧血	1 (0.1%)	1 (0.1%)	0	0	0	0
鉄欠乏性貧血	1 (0.1%)	0	1 (0.1%)	0	0	0
内出血発生の増加傾向	1 (0.1%)	1 (0.1%)	0	0	0	0
胃腸障害						
- Overall -	340 (48.4%)	155 (22.0%)	154 (21.9%)	25 (3.6%)	4 (0.6%)	2 (0.3%)
悪心	178 (25.3%)	116 (16.5%)	61 (8.7%)	1 (0.1%)	0	0
便秘	123 (17.5%)	71 (10.1%)	46 (6.5%)	6 (0.9%)	0	0
嘔吐	56 (8.0%)	37 (5.3%)	17 (2.4%)	1 (0.1%)	1 (0.1%)	0
下痢	45 (6.4%)	26 (3.7%)	16 (2.3%)	3 (0.4%)	0	0
口内炎	58 (8.3%)	34 (4.8%)	21 (3.0%)	3 (0.4%)	0	0
消化不良	19 (2.7%)	7 (1.0%)	12 (1.7%)	0	0	0
上腹部痛	23 (3.3%)	17 (2.4%)	6 (0.9%)	0	0	0
腹痛	24 (3.4%)	13 (1.8%)	8 (1.1%)	3 (0.4%)	0	0
口腔内潰瘍形成	17 (2.4%)	9 (1.3%)	7 (1.0%)	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
口内乾燥	9 (1.3%)	8 (1.1%)	1 (0.1%)	0	0	0
胃食道逆流性疾患	7 (1.0%)	3 (0.4%)	4 (0.6%)	0	0	0
腹部膨満	14 (2.0%)	9 (1.3%)	5 (0.7%)	0	0	0
胃炎	2 (0.3%)	0	2 (0.3%)	0	0	0
痔核	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
口腔内痛	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
歯肉痛	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
腹部不快感	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
アフタ性潰瘍	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
嚥下障害	2 (0.3%)	2 (0.3%)	0	0	0	0
肛門周囲痛	2 (0.3%)	2 (0.3%)	0	0	0	0
胃腸出血	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
鼓腸	1 (0.1%)	1 (0.1%)	0	0	0	0
大腸炎	2 (0.3%)	0	0	2 (0.3%)	0	0
腸管穿孔	2 (0.3%)	0	0	0	1 (0.1%)	1 (0.1%)
腸閉塞	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
胃出血	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
胃穿孔	3 (0.4%)	0	0	2 (0.3%)	1 (0.1%)	0
血便排泄	2 (0.3%)	2 (0.3%)	0	0	0	0
口唇炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
歯痛	1 (0.1%)	1 (0.1%)	0	0	0	0
歯肉出血	2 (0.3%)	2 (0.3%)	0	0	0	0
上部消化管出血	1 (0.1%)	0	0	1 (0.1%)	0	0
舌潰瘍	3 (0.4%)	3 (0.4%)	0	0	0	0
嚥下痛	1 (0.1%)	1 (0.1%)	0	0	0	0
肛門出血	2 (0.3%)	2 (0.3%)	0	0	0	0
イレウス	1 (0.1%)	0	1 (0.1%)	0	0	0
異常便	1 (0.1%)	1 (0.1%)	0	0	0	0
下部消化管出血	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
下腹部痛	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
痔出血	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
小腸炎	2 (0.3%)	0	2 (0.3%)	0	0	0
小腸穿孔	1 (0.1%)	0	0	1 (0.1%)	0	0
小腸閉塞	1 (0.1%)	0	0	1 (0.1%)	0	0
食道炎	1 (0.1%)	1 (0.1%)	0	0	0	0
心窩部不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
麻痺性イレウス	1 (0.1%)	0	0	1 (0.1%)	0	0
おくび	1 (0.1%)	1 (0.1%)	0	0	0	0
メレナ	1 (0.1%)	0	1 (0.1%)	0	0	0
口の感覚鈍麻	1 (0.1%)	1 (0.1%)	0	0	0	0
口の錯感覚	1 (0.1%)	1 (0.1%)	0	0	0	0
口蓋腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔灼熱感症候群	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔内不快感	1 (0.1%)	0	1 (0.1%)	0	0	0
口腔内分泌物	1 (0.1%)	1 (0.1%)	0	0	0	0
口唇痛	1 (0.1%)	0	1 (0.1%)	0	0	0
口唇潰瘍	1 (0.1%)	0	1 (0.1%)	0	0	0
歯の知覚過敏	1 (0.1%)	0	1 (0.1%)	0	0	0
痔瘻	1 (0.1%)	0	0	1 (0.1%)	0	0
舌痛	1 (0.1%)	1 (0.1%)	0	0	0	0
腹水	1 (0.1%)	0	1 (0.1%)	0	0	0
肛門の炎症	1 (0.1%)	0	1 (0.1%)	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	242 (34.4%)	125 (17.8%)	92 (13.1%)	19 (2.7%)	3 (0.4%)	3 (0.4%)
疲労	98 (13.9%)	60 (8.5%)	28 (4.0%)	9 (1.3%)	1 (0.1%)	0
悪寒	31 (4.4%)	16 (2.3%)	13 (1.8%)	1 (0.1%)	1 (0.1%)	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
発熱	37 (5.3%)	21 (3.0%)	11 (1.6%)	3 (0.4%)	2 (0.3%)	0
無力症	60 (8.5%)	32 (4.6%)	22 (3.1%)	6 (0.9%)	0	0
粘膜の炎症	29 (4.1%)	17 (2.4%)	8 (1.1%)	3 (0.4%)	1 (0.1%)	0
倦怠感	21 (3.0%)	15 (2.1%)	5 (0.7%)	1 (0.1%)	0	0
末梢性浮腫	16 (2.3%)	11 (1.6%)	5 (0.7%)	0	0	0
胸部不快感	9 (1.3%)	6 (0.9%)	3 (0.4%)	0	0	0
冷感	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
疼痛	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
注入部位血管外漏出	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
浮腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
顔面浮腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
非心臓性胸痛	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
胸痛	1 (0.1%)	0	1 (0.1%)	0	0	0
注射部位反応	1 (0.1%)	1 (0.1%)	0	0	0	0
熱感	1 (0.1%)	1 (0.1%)	0	0	0	0
死亡	2 (0.3%)	0	0	0	0	2 (0.3%)
突然死	1 (0.1%)	0	0	0	0	1 (0.1%)
異常感	1 (0.1%)	1 (0.1%)	0	0	0	0
溢出	1 (0.1%)	0	1 (0.1%)	0	0	0
高熱	1 (0.1%)	0	1 (0.1%)	0	0	0
腫瘤	1 (0.1%)	1 (0.1%)	0	0	0	0
全身健康状態低下	1 (0.1%)	0	0	1 (0.1%)	0	0
体温調節障害	1 (0.1%)	1 (0.1%)	0	0	0	0
注入部位紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
注入部位腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
低体温	1 (0.1%)	0	1 (0.1%)	0	0	0
評価不能の事象	1 (0.1%)	0	1 (0.1%)	0	0	0
末梢腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
神経系障害						
- Overall -	238 (33.9%)	172 (24.5%)	56 (8.0%)	6 (0.9%)	2 (0.3%)	2 (0.3%)
末梢性ニューロパチー	77 (11.0%)	61 (8.7%)	13 (1.8%)	3 (0.4%)	0	0
末梢性感覚ニューロパチー	57 (8.1%)	42 (6.0%)	13 (1.8%)	1 (0.1%)	1 (0.1%)	0
錯感覚	40 (5.7%)	34 (4.8%)	6 (0.9%)	0	0	0
味覚異常	35 (5.0%)	30 (4.3%)	5 (0.7%)	0	0	0
頭痛	24 (3.4%)	17 (2.4%)	7 (1.0%)	0	0	0
感覚鈍麻	17 (2.4%)	17 (2.4%)	0	0	0	0
浮動性めまい	12 (1.7%)	9 (1.3%)	2 (0.3%)	1 (0.1%)	0	0
多発ニューロパチー	11 (1.6%)	9 (1.3%)	2 (0.3%)	0	0	0
振戦	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
末梢性運動ニューロパチー	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
失神	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0
感覚障害	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
失神寸前の状態	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
神経痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
神経毒性	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
味覚消失	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
下肢静止不能症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
記憶障害	1 (0.1%)	0	1 (0.1%)	0	0	0
精神運動亢進	1 (0.1%)	1 (0.1%)	0	0	0	0
嗅覚錯誤	1 (0.1%)	0	1 (0.1%)	0	0	0
くも膜下出血	1 (0.1%)	0	1 (0.1%)	0	0	0
感覚異常性大腿神経痛	1 (0.1%)	1 (0.1%)	0	0	0	0
顔面麻痺	1 (0.1%)	1 (0.1%)	0	0	0	0
蟻走感	1 (0.1%)	1 (0.1%)	0	0	0	0
筋緊張低下	1 (0.1%)	0	1 (0.1%)	0	0	0
声帯麻痺	1 (0.1%)	0	0	0	1 (0.1%)	0
中毒性脳症	1 (0.1%)	0	0	0	0	1 (0.1%)

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
脳血管発作	1 (0.1%)	0	0	0	0	1 (0.1%)
副鼻腔炎に伴う頭痛	1 (0.1%)	1 (0.1%)	0	0	0	0
無感覚	1 (0.1%)	0	1 (0.1%)	0	0	0
傷害、中毒および処置合併症						
- Overall -	170 (24.2%)	67 (9.5%)	99 (14.1%)	3 (0.4%)	1 (0.1%)	0
注入に伴う反応	164 (23.3%)	64 (9.1%)	96 (13.7%)	3 (0.4%)	1 (0.1%)	0
胸椎骨折	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
転倒	1 (0.1%)	0	1 (0.1%)	0	0	0
肩甲骨骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
足関節部骨折	1 (0.1%)	1 (0.1%)	0	0	0	0
感染症および寄生虫症						
- Overall -	159 (22.6%)	22 (3.1%)	73 (10.4%)	46 (6.5%)	12 (1.7%)	6 (0.9%)
肺炎	33 (4.7%)	0	12 (1.7%)	15 (2.1%)	2 (0.3%)	4 (0.6%)
帯状疱疹	16 (2.3%)	1 (0.1%)	12 (1.7%)	3 (0.4%)	0	0
上気道感染	14 (2.0%)	3 (0.4%)	9 (1.3%)	2 (0.3%)	0	0
口腔カンジダ症	10 (1.4%)	2 (0.3%)	7 (1.0%)	1 (0.1%)	0	0
尿路感染	11 (1.6%)	0	10 (1.4%)	1 (0.1%)	0	0
口腔ヘルペス	9 (1.3%)	4 (0.6%)	5 (0.7%)	0	0	0
Ｂ型肝炎	5 (0.7%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	0	0
敗血症	8 (1.1%)	0	0	3 (0.4%)	3 (0.4%)	2 (0.3%)
肺感染	5 (0.7%)	0	3 (0.4%)	2 (0.3%)	0	0
カンジダ感染	4 (0.6%)	0	4 (0.6%)	0	0	0
鼻咽頭炎	7 (1.0%)	3 (0.4%)	3 (0.4%)	1 (0.1%)	0	0
気管支炎	7 (1.0%)	2 (0.3%)	3 (0.4%)	2 (0.3%)	0	0
胃腸炎	5 (0.7%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	0	0
膀胱炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
咽頭炎	5 (0.7%)	1 (0.1%)	3 (0.4%)	1 (0.1%)	0	0
歯肉炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
敗血症性ショック	2 (0.3%)	0	0	0	2 (0.3%)	0
口腔感染	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
単純ヘルペス	1 (0.1%)	0	1 (0.1%)	0	0	0
下気道感染	1 (0.1%)	0	1 (0.1%)	0	0	0
好中球減少性敗血症	3 (0.4%)	0	0	0	3 (0.4%)	0
インフルエンザ	3 (0.4%)	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	0
サイトメガロウイルス性脈絡網膜炎	2 (0.3%)	0	0	2 (0.3%)	0	0
感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
結膜炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
口腔真菌感染	3 (0.4%)	0	3 (0.4%)	0	0	0
副鼻腔炎	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
毛包炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
口角口唇炎	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
蜂巣炎	3 (0.4%)	0	1 (0.1%)	2 (0.3%)	0	0
膣感染	2 (0.3%)	0	2 (0.3%)	0	0	0
ニューモシスチス・イロベチイ肺炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
口唇感染	1 (0.1%)	0	1 (0.1%)	0	0	0
歯周炎	2 (0.3%)	2 (0.3%)	0	0	0	0
耳感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
食道カンジダ症	1 (0.1%)	1 (0.1%)	0	0	0	0
粘膜感染	2 (0.3%)	0	2 (0.3%)	0	0	0
クロストリジウム・ディフィシレ感染	1 (0.1%)	0	0	1 (0.1%)	0	0
医療機器関連感染	1 (0.1%)	0	0	1 (0.1%)	0	0
結核	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
限局性感染	1 (0.1%)	1 (0.1%)	0	0	0	0
好中球減少性感染	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
水痘	1 (0.1%)	0	0	1 (0.1%)	0	0
水痘帯状疱疹ウイルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
爪真菌症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
軟部組織感染	2 (0.3%)	0	0	2 (0.3%)	0	0
麦粒腫	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚感染	2 (0.3%)	0	0	2 (0.3%)	0	0
ウイルス性咽頭炎	1 (0.1%)	0	0	1 (0.1%)	0	0
ウイルス性上気道感染	1 (0.1%)	0	1 (0.1%)	0	0	0
クリプトコッカス性髄膜炎	1 (0.1%)	0	0	0	1 (0.1%)	0
クロストリジウム・ディフィシレ大腸炎	1 (0.1%)	0	0	1 (0.1%)	0	0
ヘルペス眼感染	1 (0.1%)	0	1 (0.1%)	0	0	0
陰嚢膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
壊死性筋膜炎	1 (0.1%)	0	0	0	1 (0.1%)	0
眼窩周囲感染	1 (0.1%)	0	1 (0.1%)	0	0	0
喉頭炎	1 (0.1%)	0	1 (0.1%)	0	0	0
真菌性食道炎	1 (0.1%)	0	1 (0.1%)	0	0	0
精巣炎	1 (0.1%)	0	0	1 (0.1%)	0	0
前立腺膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
全身性感染	1 (0.1%)	0	1 (0.1%)	0	0	0
中枢神経系結核	1 (0.1%)	0	0	0	1 (0.1%)	0
尿路性敗血症	1 (0.1%)	0	0	1 (0.1%)	0	0
腹膜炎	1 (0.1%)	0	0	0	0	1 (0.1%)
皮膚および皮下組織障害						
- Overall -	188 (26.7%)	75 (10.7%)	108 (15.4%)	5 (0.7%)	0	0
脱毛症	139 (19.8%)	50 (7.1%)	86 (12.2%)	3 (0.4%)	0	0
発疹	28 (4.0%)	18 (2.6%)	10 (1.4%)	0	0	0
そう痒症	25 (3.6%)	18 (2.6%)	7 (1.0%)	0	0	0
紅斑	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
蕁麻疹	6 (0.9%)	2 (0.3%)	4 (0.6%)	0	0	0
爪変色	6 (0.9%)	6 (0.9%)	0	0	0	0
多汗症	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
皮膚乾燥	5 (0.7%)	5 (0.7%)	0	0	0	0
斑状丘疹状皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚色素過剰	2 (0.3%)	2 (0.3%)	0	0	0	0
ざ瘡	1 (0.1%)	1 (0.1%)	0	0	0	0
皮膚炎	1 (0.1%)	0	0	1 (0.1%)	0	0
丘疹	1 (0.1%)	1 (0.1%)	0	0	0	0
丘疹性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
湿疹	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
皮膚潰瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
そう痒性皮疹	1 (0.1%)	0	1 (0.1%)	0	0	0
過角化	1 (0.1%)	1 (0.1%)	0	0	0	0
色素沈着障害	1 (0.1%)	1 (0.1%)	0	0	0	0
全身性そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
全身性皮疹	1 (0.1%)	0	0	1 (0.1%)	0	0
斑状皮疹	1 (0.1%)	0	1 (0.1%)	0	0	0
薬疹	1 (0.1%)	1 (0.1%)	0	0	0	0
代謝および栄養障害						
- Overall -	108 (15.4%)	46 (6.5%)	35 (5.0%)	24 (3.4%)	3 (0.4%)	0
食欲減退	55 (7.8%)	31 (4.4%)	19 (2.7%)	5 (0.7%)	0	0
低カリウム血症	23 (3.3%)	14 (2.0%)	6 (0.9%)	2 (0.3%)	1 (0.1%)	0
高血糖	16 (2.3%)	2 (0.3%)	8 (1.1%)	5 (0.7%)	1 (0.1%)	0
脱水	9 (1.3%)	2 (0.3%)	6 (0.9%)	1 (0.1%)	0	0
低マグネシウム血症	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
高尿酸血症	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
低カルシウム血症	3 (0.4%)	2 (0.3%)	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腫瘍崩壊症候群	3 (0.4%)	0	0	3 (0.4%)	0	0
低ナトリウム血症	6 (0.9%)	0	0	6 (0.9%)	0	0
糖尿病	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
低リン酸血症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
高トリグリセリド血症	1 (0.1%)	0	0	1 (0.1%)	0	0
体液貯留	1 (0.1%)	0	1 (0.1%)	0	0	0
低アルブミン血症	1 (0.1%)	1 (0.1%)	0	0	0	0
２型糖尿病	1 (0.1%)	0	1 (0.1%)	0	0	0
高脂血症	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
栄養障害	1 (0.1%)	0	0	0	1 (0.1%)	0
成長障害	1 (0.1%)	0	0	1 (0.1%)	0	0
耐糖能障害	1 (0.1%)	0	1 (0.1%)	0	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	91 (12.9%)	52 (7.4%)	30 (4.3%)	7 (1.0%)	1 (0.1%)	1 (0.1%)
呼吸困難	14 (2.0%)	7 (1.0%)	6 (0.9%)	1 (0.1%)	0	0
咳嗽	16 (2.3%)	12 (1.7%)	3 (0.4%)	1 (0.1%)	0	0
口腔咽頭痛	19 (2.7%)	12 (1.7%)	6 (0.9%)	1 (0.1%)	0	0
咽喉刺激感	12 (1.7%)	7 (1.0%)	5 (0.7%)	0	0	0
鼻漏	7 (1.0%)	7 (1.0%)	0	0	0	0
しゃっくり	8 (1.1%)	3 (0.4%)	5 (0.7%)	0	0	0
肺臓炎	3 (0.4%)	1 (0.1%)	0	2 (0.3%)	0	0
労作性呼吸困難	4 (0.6%)	4 (0.6%)	0	0	0	0
間質性肺疾患	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
気管支痙攣	4 (0.6%)	0	4 (0.6%)	0	0	0
発声障害	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻出血	3 (0.4%)	3 (0.4%)	0	0	0	0
咽喉乾燥	2 (0.3%)	2 (0.3%)	0	0	0	0
胸水	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
口腔咽頭不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
湿性咳嗽	2 (0.3%)	2 (0.3%)	0	0	0	0
副鼻腔うっ血	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
咽喉絞扼感	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
肺水腫	1 (0.1%)	1 (0.1%)	0	0	0	0
鼻閉	1 (0.1%)	1 (0.1%)	0	0	0	0
アレルギー性鼻炎	2 (0.3%)	2 (0.3%)	0	0	0	0
急性呼吸窮迫症候群	1 (0.1%)	0	0	0	1 (0.1%)	0
肺塞栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
咽頭の炎症	1 (0.1%)	1 (0.1%)	0	0	0	0
咽頭浮腫	1 (0.1%)	1 (0.1%)	0	0	0	0
器質化肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
気道出血	1 (0.1%)	1 (0.1%)	0	0	0	0
急性呼吸不全	1 (0.1%)	0	0	0	0	1 (0.1%)
喉頭刺激感	1 (0.1%)	0	1 (0.1%)	0	0	0
喉頭痙攣	1 (0.1%)	0	1 (0.1%)	0	0	0
息詰まり感	1 (0.1%)	0	1 (0.1%)	0	0	0
副鼻腔不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
慢性閉塞性肺疾患	1 (0.1%)	0	0	1 (0.1%)	0	0
喘息	1 (0.1%)	1 (0.1%)	0	0	0	0
臨床検査						
- Overall -	60 (8.5%)	28 (4.0%)	17 (2.4%)	14 (2.0%)	1 (0.1%)	0
アラニンアミノトランスフェラーゼ増加	18 (2.6%)	13 (1.8%)	3 (0.4%)	2 (0.3%)	0	0
体重減少	19 (2.7%)	9 (1.3%)	7 (1.0%)	3 (0.4%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	11 (1.6%)	8 (1.1%)	3 (0.4%)	0	0	0
駆出率減少	8 (1.1%)	0	3 (0.4%)	5 (0.7%)	0	0
体重増加	6 (0.9%)	4 (0.6%)	2 (0.3%)	0	0	0
血中コレステロール増加	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
トランスアミナーゼ上昇	1 (0.1%)	0	0	1 (0.1%)	0	0
リンパ球数減少	1 (0.1%)	0	0	1 (0.1%)	0	0
血圧低下	1 (0.1%)	1 (0.1%)	0	0	0	0
血中ブドウ糖増加	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
Ｂ型肝炎ＤＮＡ増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血圧上昇	1 (0.1%)	0	0	1 (0.1%)	0	0
血中クレアチニン増加	1 (0.1%)	1 (0.1%)	0	0	0	0
Ｃ型肝炎ウイルス検査陽性	1 (0.1%)	0	1 (0.1%)	0	0	0
活性化部分トロンボプラスチン時間延長	1 (0.1%)	1 (0.1%)	0	0	0	0
血中リン増加	1 (0.1%)	0	1 (0.1%)	0	0	0
酸素飽和度低下	1 (0.1%)	0	0	0	1 (0.1%)	0
血管障害						
- Overall -	49 (7.0%)	21 (3.0%)	21 (3.0%)	7 (1.0%)	0	0
高血圧	16 (2.3%)	4 (0.6%)	6 (0.9%)	6 (0.9%)	0	0
低血圧	13 (1.8%)	7 (1.0%)	6 (0.9%)	0	0	0
潮紅	6 (0.9%)	5 (0.7%)	1 (0.1%)	0	0	0
血管炎	5 (0.7%)	3 (0.4%)	2 (0.3%)	0	0	0
静脈炎	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
起立性低血圧	1 (0.1%)	1 (0.1%)	0	0	0	0
静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
末梢冷感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
血栓症	1 (0.1%)	1 (0.1%)	0	0	0	0
深部静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
進行性高血圧	1 (0.1%)	0	0	1 (0.1%)	0	0
筋骨格系および結合組織障害						
- Overall -	45 (6.4%)	26 (3.7%)	16 (2.3%)	3 (0.4%)	0	0
筋肉痛	9 (1.3%)	5 (0.7%)	4 (0.6%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
関節痛	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
筋力低下	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
筋痙縮	3 (0.4%)	3 (0.4%)	0	0	0	0
背部痛	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
四肢痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
骨痛	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
骨粗鬆症	4 (0.6%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	0	0
筋骨格痛	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
筋骨格系胸痛	1 (0.1%)	1 (0.1%)	0	0	0	0
頚部痛	1 (0.1%)	0	1 (0.1%)	0	0	0
骨減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
四肢不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
運動性低下	1 (0.1%)	0	0	1 (0.1%)	0	0
関節硬直	1 (0.1%)	1 (0.1%)	0	0	0	0
関節腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
関節障害	1 (0.1%)	1 (0.1%)	0	0	0	0
筋肉疲労	1 (0.1%)	1 (0.1%)	0	0	0	0
側腹部痛	1 (0.1%)	1 (0.1%)	0	0	0	0
変形性関節症	1 (0.1%)	1 (0.1%)	0	0	0	0
精神障害						
- Overall -	37 (5.3%)	27 (3.8%)	8 (1.1%)	2 (0.3%)	0	0
不眠症	32 (4.6%)	25 (3.6%)	7 (1.0%)	0	0	0
不安	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
気分変化	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
落ち着きのなさ	1 (0.1%)	1 (0.1%)	0	0	0	0
うつ病	1 (0.1%)	1 (0.1%)	0	0	0	0
食物嫌悪	1 (0.1%)	1 (0.1%)	0	0	0	0
精神運動制止遅滞	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
抑うつ気分	1 (0.1%)	1 (0.1%)	0	0	0	0
譫妄	1 (0.1%)	0	0	1 (0.1%)	0	0
心臓障害						
- Overall -	23 (3.3%)	10 (1.4%)	7 (1.0%)	4 (0.6%)	1 (0.1%)	1 (0.1%)
動悸	4 (0.6%)	4 (0.6%)	0	0	0	0
心不全	4 (0.6%)	1 (0.1%)	1 (0.1%)	2 (0.3%)	0	0
心房細動	2 (0.3%)	0	2 (0.3%)	0	0	0
洞性頻脈	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
頻脈	2 (0.3%)	2 (0.3%)	0	0	0	0
左室機能不全	2 (0.3%)	0	2 (0.3%)	0	0	0
うっ血性心筋症	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
急性心筋梗塞	2 (0.3%)	0	0	2 (0.3%)	0	0
心室性期外収縮	1 (0.1%)	1 (0.1%)	0	0	0	0
心血管不全	1 (0.1%)	0	1 (0.1%)	0	0	0
心室壁運動低下	1 (0.1%)	1 (0.1%)	0	0	0	0
心停止	1 (0.1%)	0	0	0	0	1 (0.1%)
心膜炎	1 (0.1%)	0	1 (0.1%)	0	0	0
発作性頻脈	1 (0.1%)	1 (0.1%)	0	0	0	0
腎および尿路障害						
- Overall -	13 (1.8%)	9 (1.3%)	2 (0.3%)	2 (0.3%)	0	0
頻尿	6 (0.9%)	5 (0.7%)	0	1 (0.1%)	0	0
排尿困難	1 (0.1%)	1 (0.1%)	0	0	0	0
急性腎障害	1 (0.1%)	1 (0.1%)	0	0	0	0
腎不全	1 (0.1%)	0	0	1 (0.1%)	0	0
尿閉	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
非感染性膀胱炎	1 (0.1%)	1 (0.1%)	0	0	0	0
尿失禁	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
眼障害						
- Overall -	20 (2.8%)	16 (2.3%)	3 (0.4%)	1 (0.1%)	0	0
流涙増加	5 (0.7%)	5 (0.7%)	0	0	0	0
眼刺激	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
眼乾燥	1 (0.1%)	1 (0.1%)	0	0	0	0
霧視	1 (0.1%)	0	1 (0.1%)	0	0	0
眼そう痒症	1 (0.1%)	0	1 (0.1%)	0	0	0
眼窩周囲浮腫	2 (0.3%)	2 (0.3%)	0	0	0	0
一過性視力低下	1 (0.1%)	1 (0.1%)	0	0	0	0
眼球乾燥症	1 (0.1%)	1 (0.1%)	0	0	0	0
眼部腫脹	1 (0.1%)	1 (0.1%)	0	0	0	0
視力低下	1 (0.1%)	1 (0.1%)	0	0	0	0
白内障	1 (0.1%)	0	0	1 (0.1%)	0	0
複視	1 (0.1%)	1 (0.1%)	0	0	0	0
網膜出血	1 (0.1%)	1 (0.1%)	0	0	0	0
肝胆道系障害						
- Overall -	10 (1.4%)	1 (0.1%)	5 (0.7%)	4 (0.6%)	0	0
肝機能異常	5 (0.7%)	1 (0.1%)	3 (0.4%)	1 (0.1%)	0	0
高ビリルビン血症	1 (0.1%)	0	1 (0.1%)	0	0	0
胆嚢炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
脂肪肝	1 (0.1%)	0	0	1 (0.1%)	0	0
胆石症	1 (0.1%)	0	0	1 (0.1%)	0	0
内分泌障害						
- Overall -	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
ステロイド離脱症候群	1 (0.1%)	0	1 (0.1%)	0	0	0
抗利尿ホルモン不適合分泌	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: R-CHOP (N=703)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
生殖系および乳房障害						
- Overall -	4 (0.6%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0	0
不規則月経	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
無月経	1 (0.1%)	1 (0.1%)	0	0	0	0
骨盤痛	1 (0.1%)	0	1 (0.1%)	0	0	0
免疫系障害						
- Overall -	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
過敏症	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
耳および迷路障害						
- Overall -	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
耳鳴	3 (0.4%)	3 (0.4%)	0	0	0	0
回転性めまい	1 (0.1%)	1 (0.1%)	0	0	0	0
耳不快感	1 (0.1%)	0	1 (0.1%)	0	0	0
難聴	2 (0.3%)	0	2 (0.3%)	0	0	0
耳そう痒症	1 (0.1%)	0	1 (0.1%)	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）						
- Overall -	4 (0.6%)	0	0	2 (0.3%)	0	2 (0.3%)
急性骨髄性白血病	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
結腸癌	1 (0.1%)	0	0	0	0	1 (0.1%)
前立腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
- Any adverse events -	639 (90.8%)	42 (6.0%)	135 (19.2%)	143 (20.3%)	304 (43.2%)	15 (2.1%)
血液およびリンパ系障害						
- Overall -	429 (60.9%)	5 (0.7%)	28 (4.0%)	101 (14.3%)	293 (41.6%)	2 (0.3%)
好中球減少症	323 (45.9%)	0	15 (2.1%)	73 (10.4%)	235 (33.4%)	0
発熱性好中球減少症	119 (16.9%)	2 (0.3%)	1 (0.1%)	59 (8.4%)	56 (8.0%)	1 (0.1%)
白血球減少症	105 (14.9%)	1 (0.1%)	15 (2.1%)	37 (5.3%)	52 (7.4%)	0
貧血	72 (10.2%)	5 (0.7%)	32 (4.5%)	32 (4.5%)	3 (0.4%)	0
血小板減少症	44 (6.3%)	3 (0.4%)	16 (2.3%)	13 (1.8%)	12 (1.7%)	0
リンパ球減少症	1 (0.1%)	0	0	1 (0.1%)	0	0
播種性血管内凝固	1 (0.1%)	0	1 (0.1%)	0	0	0
汎血球減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
慢性疾患の貧血	1 (0.1%)	0	0	1 (0.1%)	0	0
免疫性血小板減少性紫斑病	1 (0.1%)	0	0	0	1 (0.1%)	0
貪食細胞性組織球症	1 (0.1%)	0	0	0	0	1 (0.1%)
胃腸障害						
- Overall -	328 (46.6%)	147 (20.9%)	141 (20.0%)	33 (4.7%)	7 (1.0%)	0
悪心	183 (26.0%)	103 (14.6%)	67 (9.5%)	13 (1.8%)	0	0
便秘	107 (15.2%)	76 (10.8%)	28 (4.0%)	3 (0.4%)	0	0
嘔吐	86 (12.2%)	55 (7.8%)	24 (3.4%)	7 (1.0%)	0	0
下痢	62 (8.8%)	23 (3.3%)	28 (4.0%)	10 (1.4%)	1 (0.1%)	0
口内炎	39 (5.5%)	25 (3.6%)	13 (1.8%)	1 (0.1%)	0	0
消化不良	25 (3.6%)	10 (1.4%)	15 (2.1%)	0	0	0
上腹部痛	21 (3.0%)	13 (1.8%)	8 (1.1%)	0	0	0
腹痛	20 (2.8%)	11 (1.6%)	8 (1.1%)	1 (0.1%)	0	0
口腔内潰瘍形成	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
口内乾燥	11 (1.6%)	11 (1.6%)	0	0	0	0
胃食道逆流性疾患	11 (1.6%)	3 (0.4%)	8 (1.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腹部膨満	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
胃炎	7 (1.0%)	3 (0.4%)	3 (0.4%)	1 (0.1%)	0	0
痔核	4 (0.6%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	0	0
口腔内痛	4 (0.6%)	4 (0.6%)	0	0	0	0
歯肉痛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
腹部不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
アフタ性潰瘍	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
嚥下障害	3 (0.4%)	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	0
肛門周囲痛	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
胃腸出血	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
鼓腸	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
大腸炎	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0
腸管穿孔	2 (0.3%)	0	0	0	2 (0.3%)	0
腸閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
胃出血	1 (0.1%)	0	0	1 (0.1%)	0	0
血便排泄	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔知覚不全	3 (0.4%)	3 (0.4%)	0	0	0	0
口唇炎	1 (0.1%)	1 (0.1%)	0	0	0	0
歯痛	2 (0.3%)	2 (0.3%)	0	0	0	0
歯肉出血	1 (0.1%)	1 (0.1%)	0	0	0	0
上部消化管出血	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
嚥下痛	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
肛門出血	1 (0.1%)	0	1 (0.1%)	0	0	0
イレウス	1 (0.1%)	0	1 (0.1%)	0	0	0
異常便	1 (0.1%)	0	1 (0.1%)	0	0	0
下部消化管出血	1 (0.1%)	0	1 (0.1%)	0	0	0
下腹部痛	1 (0.1%)	1 (0.1%)	0	0	0	0
口腔そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
小腸穿孔	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
小腸閉塞	1 (0.1%)	0	0	1 (0.1%)	0	0
食道炎	1 (0.1%)	0	1 (0.1%)	0	0	0
舌浮腫	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
麻痺性イレウス	1 (0.1%)	0	1 (0.1%)	0	0	0
レッチング	1 (0.1%)	1 (0.1%)	0	0	0	0
亜イレウス	1 (0.1%)	0	0	1 (0.1%)	0	0
回腸穿孔	1 (0.1%)	0	0	0	1 (0.1%)	0
気腹	1 (0.1%)	0	0	0	1 (0.1%)	0
血性下痢	1 (0.1%)	1 (0.1%)	0	0	0	0
口蓋潰瘍	1 (0.1%)	1 (0.1%)	0	0	0	0
歯周病	1 (0.1%)	1 (0.1%)	0	0	0	0
歯状態不良	1 (0.1%)	0	1 (0.1%)	0	0	0
歯肉腫脹	1 (0.1%)	0	1 (0.1%)	0	0	0
食道痛	1 (0.1%)	1 (0.1%)	0	0	0	0
舌そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
唾液変性	1 (0.1%)	1 (0.1%)	0	0	0	0
腸炎	1 (0.1%)	0	1 (0.1%)	0	0	0
膵炎	1 (0.1%)	0	1 (0.1%)	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	336 (47.7%)	166 (23.6%)	143 (20.3%)	25 (3.6%)	1 (0.1%)	1 (0.1%)
疲労	105 (14.9%)	68 (9.7%)	29 (4.1%)	8 (1.1%)	0	0
悪寒	127 (18.0%)	56 (8.0%)	64 (9.1%)	7 (1.0%)	0	0
発熱	99 (14.1%)	70 (9.9%)	26 (3.7%)	2 (0.3%)	1 (0.1%)	0
無力症	49 (7.0%)	29 (4.1%)	16 (2.3%)	4 (0.6%)	0	0
粘膜の炎症	36 (5.1%)	15 (2.1%)	18 (2.6%)	3 (0.4%)	0	0
倦怠感	21 (3.0%)	15 (2.1%)	5 (0.7%)	1 (0.1%)	0	0
末梢性浮腫	14 (2.0%)	6 (0.9%)	6 (0.9%)	2 (0.3%)	0	0
胸部不快感	17 (2.4%)	10 (1.4%)	7 (1.0%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
冷感	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
疼痛	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
注入部位血管外漏出	2 (0.3%)	0	2 (0.3%)	0	0	0
浮腫	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
顔面浮腫	3 (0.4%)	3 (0.4%)	0	0	0	0
非心臓性胸痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
胸痛	2 (0.3%)	2 (0.3%)	0	0	0	0
注射部位反応	2 (0.3%)	2 (0.3%)	0	0	0	0
熱感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
インフルエンザ様疾患	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
突然死	1 (0.1%)	0	0	0	0	1 (0.1%)
不快感	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
全身性浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
恥骨上痛	1 (0.1%)	1 (0.1%)	0	0	0	0
注射部位静脈炎	1 (0.1%)	0	1 (0.1%)	0	0	0
注射部位漏出	1 (0.1%)	1 (0.1%)	0	0	0	0
注入部位疼痛	1 (0.1%)	1 (0.1%)	0	0	0	0
神経系障害						
- Overall -	263 (37.4%)	181 (25.7%)	73 (10.4%)	9 (1.3%)	0	0
末梢性ニューロパチー	81 (11.5%)	64 (9.1%)	15 (2.1%)	2 (0.3%)	0	0
末梢性感覚ニューロパチー	51 (7.2%)	39 (5.5%)	12 (1.7%)	0	0	0
錯感覚	42 (6.0%)	27 (3.8%)	15 (2.1%)	0	0	0
味覚異常	41 (5.8%)	35 (5.0%)	6 (0.9%)	0	0	0
頭痛	22 (3.1%)	15 (2.1%)	6 (0.9%)	1 (0.1%)	0	0
感覚鈍麻	26 (3.7%)	19 (2.7%)	7 (1.0%)	0	0	0
浮動性めまい	23 (3.3%)	14 (2.0%)	7 (1.0%)	2 (0.3%)	0	0
多発ニューロパチー	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
振戦	10 (1.4%)	2 (0.3%)	7 (1.0%)	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
末梢性運動ニューロパチー	4 (0.6%)	4 (0.6%)	0	0	0	0
失神	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
失神寸前の状態	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
神経痛	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
神経毒性	2 (0.3%)	2 (0.3%)	0	0	0	0
味覚消失	1 (0.1%)	1 (0.1%)	0	0	0	0
嗜眠	3 (0.4%)	3 (0.4%)	0	0	0	0
下肢静止不能症候群	1 (0.1%)	1 (0.1%)	0	0	0	0
記憶障害	1 (0.1%)	1 (0.1%)	0	0	0	0
精神運動亢進	1 (0.1%)	0	1 (0.1%)	0	0	0
嗅覚錯誤	1 (0.1%)	1 (0.1%)	0	0	0	0
ラクナ梗塞	1 (0.1%)	0	1 (0.1%)	0	0	0
過眠症	1 (0.1%)	1 (0.1%)	0	0	0	0
感覚消失	1 (0.1%)	1 (0.1%)	0	0	0	0
傾眠	1 (0.1%)	1 (0.1%)	0	0	0	0
健忘	1 (0.1%)	1 (0.1%)	0	0	0	0
失声症	1 (0.1%)	1 (0.1%)	0	0	0	0
尺骨神経炎	1 (0.1%)	1 (0.1%)	0	0	0	0
灼熱感	1 (0.1%)	1 (0.1%)	0	0	0	0
進行性脳卒中	1 (0.1%)	0	0	1 (0.1%)	0	0
体位性めまい	1 (0.1%)	1 (0.1%)	0	0	0	0
第３脳神経障害	1 (0.1%)	0	1 (0.1%)	0	0	0
第３脳神経麻痺	1 (0.1%)	0	0	1 (0.1%)	0	0
第６脳神経障害	1 (0.1%)	1 (0.1%)	0	0	0	0
知覚過敏	1 (0.1%)	1 (0.1%)	0	0	0	0
注意力障害	1 (0.1%)	1 (0.1%)	0	0	0	0
認知障害	1 (0.1%)	1 (0.1%)	0	0	0	0
微細運動機能障害	1 (0.1%)	0	1 (0.1%)	0	0	0
平衡障害	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
味覚減退	1 (0.1%)	1 (0.1%)	0	0	0	0
傷害、中毒および処置合併症						
- Overall -	256 (36.4%)	93 (13.2%)	142 (20.2%)	20 (2.8%)	1 (0.1%)	0
注入に伴う反応	252 (35.8%)	93 (13.2%)	139 (19.7%)	19 (2.7%)	1 (0.1%)	0
脊椎圧迫骨折	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
転倒	1 (0.1%)	0	0	1 (0.1%)	0	0
圧迫骨折	1 (0.1%)	0	1 (0.1%)	0	0	0
各種物質毒性	1 (0.1%)	0	1 (0.1%)	0	0	0
処置後出血	1 (0.1%)	0	1 (0.1%)	0	0	0
神経損傷	1 (0.1%)	0	1 (0.1%)	0	0	0
創傷出血	1 (0.1%)	0	0	1 (0.1%)	0	0
輸血反応	1 (0.1%)	0	1 (0.1%)	0	0	0
感染症および寄生虫症						
- Overall -	227 (32.2%)	45 (6.4%)	97 (13.8%)	57 (8.1%)	19 (2.7%)	9 (1.3%)
肺炎	37 (5.3%)	1 (0.1%)	12 (1.7%)	19 (2.7%)	3 (0.4%)	2 (0.3%)
帯状疱疹	23 (3.3%)	4 (0.6%)	15 (2.1%)	3 (0.4%)	1 (0.1%)	0
上気道感染	22 (3.1%)	5 (0.7%)	16 (2.3%)	1 (0.1%)	0	0
口腔カンジダ症	15 (2.1%)	2 (0.3%)	13 (1.8%)	0	0	0
尿路感染	12 (1.7%)	2 (0.3%)	8 (1.1%)	2 (0.3%)	0	0
口腔ヘルペス	13 (1.8%)	7 (1.0%)	6 (0.9%)	0	0	0
Ｂ型肝炎	14 (2.0%)	3 (0.4%)	8 (1.1%)	3 (0.4%)	0	0
敗血症	9 (1.3%)	0	0	3 (0.4%)	5 (0.7%)	1 (0.1%)
肺感染	10 (1.4%)	0	2 (0.3%)	8 (1.1%)	0	0
カンジダ感染	10 (1.4%)	4 (0.6%)	6 (0.9%)	0	0	0
鼻咽頭炎	7 (1.0%)	5 (0.7%)	2 (0.3%)	0	0	0
気管支炎	4 (0.6%)	1 (0.1%)	3 (0.4%)	0	0	0
胃腸炎	4 (0.6%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
膀胱炎	6 (0.9%)	2 (0.3%)	4 (0.6%)	0	0	0
咽頭炎	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
歯肉炎	6 (0.9%)	4 (0.6%)	1 (0.1%)	1 (0.1%)	0	0
敗血症性ショック	6 (0.9%)	0	0	0	3 (0.4%)	3 (0.4%)
口腔感染	4 (0.6%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0
単純ヘルペス	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
ヘルペスウイルス感染	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
下気道感染	5 (0.7%)	1 (0.1%)	4 (0.6%)	0	0	0
好中球減少性敗血症	3 (0.4%)	0	0	2 (0.3%)	1 (0.1%)	0
インフルエンザ	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
サイトメガロウイルス性脈絡網膜炎	3 (0.4%)	0	0	1 (0.1%)	2 (0.3%)	0
感染	3 (0.4%)	0	1 (0.1%)	1 (0.1%)	0	1 (0.1%)
結膜炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
口腔真菌感染	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
副鼻腔炎	2 (0.3%)	0	2 (0.3%)	0	0	0
毛包炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
口角口唇炎	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
鼻炎	2 (0.3%)	0	2 (0.3%)	0	0	0
蜂巣炎	1 (0.1%)	0	0	1 (0.1%)	0	0
膣感染	2 (0.3%)	0	2 (0.3%)	0	0	0
ニューモシスチス・イロベチイ肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
口唇感染	2 (0.3%)	0	2 (0.3%)	0	0	0
歯周炎	1 (0.1%)	0	1 (0.1%)	0	0	0
耳感染	1 (0.1%)	0	1 (0.1%)	0	0	0
食道カンジダ症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
粘膜感染	1 (0.1%)	0	1 (0.1%)	0	0	0
クロストリジウム・ディフィシレ感染	1 (0.1%)	0	0	1 (0.1%)	0	0
サイトメガロウイルス感染	2 (0.3%)	0	2 (0.3%)	0	0	0
医療機器関連感染	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
外陰膣真菌感染	2 (0.3%)	0	2 (0.3%)	0	0	0
感染性腸炎	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
気道感染	2 (0.3%)	0	1 (0.1%)	0	1 (0.1%)	0
限局性感染	1 (0.1%)	1 (0.1%)	0	0	0	0
好中球減少性感染	1 (0.1%)	0	0	0	1 (0.1%)	0
歯感染	2 (0.3%)	0	2 (0.3%)	0	0	0
水痘	1 (0.1%)	0	0	0	1 (0.1%)	0
水痘帯状疱疹ウイルス感染	1 (0.1%)	0	1 (0.1%)	0	0	0
麦粒腫	1 (0.1%)	1 (0.1%)	0	0	0	0
扁桃炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
肛門膿瘍	2 (0.3%)	0	0	2 (0.3%)	0	0
ウイルス性気管支炎	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性気道感染	1 (0.1%)	0	1 (0.1%)	0	0	0
ウイルス性髄膜炎	1 (0.1%)	0	0	0	0	1 (0.1%)
ウイルス性肺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
サイトメガロウイルス血症	1 (0.1%)	0	0	1 (0.1%)	0	0
マイコバクテリア感染	1 (0.1%)	1 (0.1%)	0	0	0	0
外陰部膣カンジダ症	1 (0.1%)	0	1 (0.1%)	0	0	0
外耳炎	1 (0.1%)	0	1 (0.1%)	0	0	0
感染性下痢	1 (0.1%)	0	0	0	1 (0.1%)	0
感染性小腸結腸炎	1 (0.1%)	0	0	1 (0.1%)	0	0
感染性舌炎	1 (0.1%)	0	0	1 (0.1%)	0	0
気管炎	1 (0.1%)	0	1 (0.1%)	0	0	0
骨髄炎	1 (0.1%)	0	0	0	0	1 (0.1%)
細菌性肺炎	1 (0.1%)	0	0	1 (0.1%)	0	0
細菌性膣症	1 (0.1%)	0	1 (0.1%)	0	0	0
耳下腺炎	1 (0.1%)	0	1 (0.1%)	0	0	0
消化管感染	1 (0.1%)	0	0	1 (0.1%)	0	0
真菌感染	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
真菌性副鼻腔炎	1 (0.1%)	0	0	1 (0.1%)	0	0
神経合併症を伴う帯状疱疹感染	1 (0.1%)	0	1 (0.1%)	0	0	0
進行性多巣性白質脳症	1 (0.1%)	0	0	1 (0.1%)	0	0
髄膜炎	1 (0.1%)	0	0	0	1 (0.1%)	0
切開部位感染	1 (0.1%)	0	1 (0.1%)	0	0	0
虫垂膿瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
腸球菌性敗血症	1 (0.1%)	1 (0.1%)	0	0	0	0
爪囲炎	1 (0.1%)	1 (0.1%)	0	0	0	0
膿疱性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
播種性帯状疱疹	1 (0.1%)	0	0	1 (0.1%)	0	0
肺結核	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚カンジダ	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚真菌感染	1 (0.1%)	0	1 (0.1%)	0	0	0
麻疹	1 (0.1%)	0	0	1 (0.1%)	0	0
皮膚および皮下組織障害						
- Overall -	187 (26.6%)	83 (11.8%)	101 (14.3%)	3 (0.4%)	0	0
脱毛症	143 (20.3%)	56 (8.0%)	87 (12.4%)	0	0	0
発疹	10 (1.4%)	6 (0.9%)	4 (0.6%)	0	0	0
そう痒症	7 (1.0%)	6 (0.9%)	0	1 (0.1%)	0	0
紅斑	11 (1.6%)	8 (1.1%)	3 (0.4%)	0	0	0
蕁麻疹	5 (0.7%)	1 (0.1%)	3 (0.4%)	1 (0.1%)	0	0
爪変色	4 (0.6%)	4 (0.6%)	0	0	0	0
多汗症	6 (0.9%)	2 (0.3%)	4 (0.6%)	0	0	0
皮膚乾燥	1 (0.1%)	1 (0.1%)	0	0	0	0
斑状丘疹状皮疹	4 (0.6%)	4 (0.6%)	0	0	0	0
皮膚色素過剰	2 (0.3%)	2 (0.3%)	0	0	0	0
ざ瘡	2 (0.3%)	2 (0.3%)	0	0	0	0
爪の障害	3 (0.4%)	3 (0.4%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
皮膚炎	2 (0.3%)	2 (0.3%)	0	0	0	0
ざ瘡様皮膚炎	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
丘疹	1 (0.1%)	1 (0.1%)	0	0	0	0
丘疹性皮疹	1 (0.1%)	1 (0.1%)	0	0	0	0
寝汗	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
皮膚潰瘍	1 (0.1%)	0	0	1 (0.1%)	0	0
冷汗	2 (0.3%)	2 (0.3%)	0	0	0	0
うっ滞性皮膚炎	1 (0.1%)	1 (0.1%)	0	0	0	0
乾癬	1 (0.1%)	1 (0.1%)	0	0	0	0
紫斑	1 (0.1%)	1 (0.1%)	0	0	0	0
手掌紅斑	1 (0.1%)	0	0	1 (0.1%)	0	0
全身紅斑	1 (0.1%)	0	0	1 (0.1%)	0	0
爪甲脱落症	1 (0.1%)	0	1 (0.1%)	0	0	0
爪床出血	1 (0.1%)	1 (0.1%)	0	0	0	0
爪色素沈着	1 (0.1%)	1 (0.1%)	0	0	0	0
皮脂欠乏性湿疹	1 (0.1%)	0	1 (0.1%)	0	0	0
皮膚灼熱感	1 (0.1%)	1 (0.1%)	0	0	0	0
嵌入爪	1 (0.1%)	1 (0.1%)	0	0	0	0
代謝および栄養障害						
- Overall -	128 (18.2%)	59 (8.4%)	35 (5.0%)	32 (4.5%)	2 (0.3%)	0
食欲減退	72 (10.2%)	41 (5.8%)	23 (3.3%)	8 (1.1%)	0	0
低カリウム血症	23 (3.3%)	9 (1.3%)	5 (0.7%)	9 (1.3%)	0	0
高血糖	15 (2.1%)	4 (0.6%)	6 (0.9%)	5 (0.7%)	0	0
脱水	10 (1.4%)	2 (0.3%)	2 (0.3%)	6 (0.9%)	0	0
低マグネシウム血症	6 (0.9%)	4 (0.6%)	1 (0.1%)	1 (0.1%)	0	0
高尿酸血症	6 (0.9%)	6 (0.9%)	0	0	0	0
低カルシウム血症	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
腫瘍崩壊症候群	4 (0.6%)	0	0	3 (0.4%)	1 (0.1%)	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
糖尿病	4 (0.6%)	0	2 (0.3%)	2 (0.3%)	0	0
低リン酸血症	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
高トリグリセリド血症	3 (0.4%)	3 (0.4%)	0	0	0	0
体液貯留	2 (0.3%)	2 (0.3%)	0	0	0	0
低アルブミン血症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
２型糖尿病	1 (0.1%)	0	0	1 (0.1%)	0	0
低蛋白血症	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
アシドーシス	1 (0.1%)	0	0	1 (0.1%)	0	0
悪液質	1 (0.1%)	0	0	0	1 (0.1%)	0
血液量減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
高コレステロール血症	1 (0.1%)	0	1 (0.1%)	0	0	0
多飲症	1 (0.1%)	0	1 (0.1%)	0	0	0
低血糖	1 (0.1%)	0	1 (0.1%)	0	0	0
呼吸器、胸郭および縦隔障害						
- Overall -	110 (15.6%)	49 (7.0%)	45 (6.4%)	10 (1.4%)	4 (0.6%)	2 (0.3%)
呼吸困難	29 (4.1%)	7 (1.0%)	20 (2.8%)	2 (0.3%)	0	0
咳嗽	22 (3.1%)	16 (2.3%)	6 (0.9%)	0	0	0
口腔咽頭痛	16 (2.3%)	9 (1.3%)	6 (0.9%)	1 (0.1%)	0	0
咽喉刺激感	3 (0.4%)	3 (0.4%)	0	0	0	0
鼻漏	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
しゃっくり	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
肺臓炎	9 (1.3%)	4 (0.6%)	4 (0.6%)	1 (0.1%)	0	0
労作性呼吸困難	5 (0.7%)	4 (0.6%)	0	1 (0.1%)	0	0
間質性肺疾患	5 (0.7%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	1 (0.1%)	0
気管支痙攣	2 (0.3%)	0	2 (0.3%)	0	0	0
低酸素症	5 (0.7%)	1 (0.1%)	3 (0.4%)	1 (0.1%)	0	0
発声障害	4 (0.6%)	4 (0.6%)	0	0	0	0
鼻出血	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
咽喉乾燥	2 (0.3%)	2 (0.3%)	0	0	0	0
胸水	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
口腔咽頭不快感	2 (0.3%)	2 (0.3%)	0	0	0	0
湿性咳嗽	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
副鼻腔うっ血	1 (0.1%)	1 (0.1%)	0	0	0	0
肺水腫	2 (0.3%)	0	0	1 (0.1%)	0	1 (0.1%)
鼻閉	2 (0.3%)	0	2 (0.3%)	0	0	0
急性呼吸窮迫症候群	1 (0.1%)	0	0	0	0	1 (0.1%)
肺塞栓症	1 (0.1%)	0	1 (0.1%)	0	0	0
喘鳴	2 (0.3%)	0	2 (0.3%)	0	0	0
咽頭紅斑	1 (0.1%)	0	1 (0.1%)	0	0	0
気管の炎症	1 (0.1%)	0	1 (0.1%)	0	0	0
急性肺水腫	1 (0.1%)	0	0	0	1 (0.1%)	0
胸膜痛	1 (0.1%)	1 (0.1%)	0	0	0	0
後天性気管食道瘻	1 (0.1%)	0	0	1 (0.1%)	0	0
喉頭痛	1 (0.1%)	1 (0.1%)	0	0	0	0
肺浸潤	1 (0.1%)	0	0	1 (0.1%)	0	0
肺線維症	1 (0.1%)	0	1 (0.1%)	0	0	0
鼻閉塞	1 (0.1%)	0	1 (0.1%)	0	0	0
頻呼吸	1 (0.1%)	1 (0.1%)	0	0	0	0
変色痰	1 (0.1%)	1 (0.1%)	0	0	0	0
無酸素症	1 (0.1%)	0	0	0	1 (0.1%)	0
臨床検査						
- Overall -	89 (12.6%)	39 (5.5%)	32 (4.5%)	17 (2.4%)	1 (0.1%)	0
アラニンアミノトランスフェラーゼ増加	30 (4.3%)	18 (2.6%)	6 (0.9%)	6 (0.9%)	0	0
体重減少	22 (3.1%)	8 (1.1%)	10 (1.4%)	4 (0.6%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	17 (2.4%)	12 (1.7%)	3 (0.4%)	2 (0.3%)	0	0
駆出率減少	12 (1.7%)	2 (0.3%)	6 (0.9%)	4 (0.6%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
体重増加	2 (0.3%)	0	2 (0.3%)	0	0	0
血中コレステロール増加	4 (0.6%)	4 (0.6%)	0	0	0	0
トランスアミナーゼ上昇	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
リンパ球数減少	3 (0.4%)	0	0	2 (0.3%)	1 (0.1%)	0
血圧低下	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
血中ブドウ糖増加	1 (0.1%)	1 (0.1%)	0	0	0	0
Ｂ型肝炎ＤＮＡ増加	1 (0.1%)	0	1 (0.1%)	0	0	0
血圧上昇	1 (0.1%)	0	0	1 (0.1%)	0	0
血中アルカリホスファターゼ増加	2 (0.3%)	0	2 (0.3%)	0	0	0
血中アルブミン減少	2 (0.3%)	0	2 (0.3%)	0	0	0
血中クレアチニン増加	1 (0.1%)	1 (0.1%)	0	0	0	0
心拍数増加	2 (0.3%)	0	2 (0.3%)	0	0	0
Ｃ－反応性蛋白増加	1 (0.1%)	1 (0.1%)	0	0	0	0
肝機能検査値上昇	1 (0.1%)	1 (0.1%)	0	0	0	0
血中ビリルビン増加	1 (0.1%)	1 (0.1%)	0	0	0	0
血中葉酸減少	1 (0.1%)	1 (0.1%)	0	0	0	0
尿中血陽性	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫グロブリン減少	1 (0.1%)	0	1 (0.1%)	0	0	0
血管障害						
- Overall -	69 (9.8%)	22 (3.1%)	27 (3.8%)	19 (2.7%)	0	1 (0.1%)
高血圧	28 (4.0%)	6 (0.9%)	7 (1.0%)	15 (2.1%)	0	0
低血圧	21 (3.0%)	8 (1.1%)	10 (1.4%)	3 (0.4%)	0	0
潮紅	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
ほてり	9 (1.3%)	7 (1.0%)	1 (0.1%)	1 (0.1%)	0	0
血管炎	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
静脈炎	4 (0.6%)	0	4 (0.6%)	0	0	0
起立性低血圧	1 (0.1%)	1 (0.1%)	0	0	0	0
静脈血栓症	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
出血	1 (0.1%)	0	0	0	0	1 (0.1%)
表在性静脈炎	1 (0.1%)	1 (0.1%)	0	0	0	0
筋骨格系および結合組織障害						
- Overall -	50 (7.1%)	29 (4.1%)	16 (2.3%)	5 (0.7%)	0	0
筋肉痛	11 (1.6%)	8 (1.1%)	2 (0.3%)	1 (0.1%)	0	0
関節痛	12 (1.7%)	8 (1.1%)	4 (0.6%)	0	0	0
筋力低下	10 (1.4%)	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0
筋痙縮	8 (1.1%)	6 (0.9%)	2 (0.3%)	0	0	0
背部痛	8 (1.1%)	5 (0.7%)	2 (0.3%)	1 (0.1%)	0	0
四肢痛	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
骨痛	1 (0.1%)	0	1 (0.1%)	0	0	0
顎痛	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0
ミオパチー	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
筋骨格系胸痛	1 (0.1%)	1 (0.1%)	0	0	0	0
頚部痛	1 (0.1%)	1 (0.1%)	0	0	0	0
骨減少症	1 (0.1%)	0	1 (0.1%)	0	0	0
四肢不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
関節炎	1 (0.1%)	1 (0.1%)	0	0	0	0
精神障害						
- Overall -	55 (7.8%)	37 (5.3%)	16 (2.3%)	2 (0.3%)	0	0
不眠症	43 (6.1%)	31 (4.4%)	12 (1.7%)	0	0	0
不安	3 (0.4%)	0	3 (0.4%)	0	0	0
気分変化	2 (0.3%)	1 (0.1%)	1 (0.1%)	0	0	0
激越	4 (0.6%)	4 (0.6%)	0	0	0	0
落ち着きのなさ	3 (0.4%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
気分動揺	2 (0.3%)	2 (0.3%)	0	0	0	0
易刺激性	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
感情不安定	1 (0.1%)	0	1 (0.1%)	0	0	0
緊張	1 (0.1%)	1 (0.1%)	0	0	0	0
心臓障害						
- Overall -	41 (5.8%)	16 (2.3%)	11 (1.6%)	10 (1.4%)	3 (0.4%)	1 (0.1%)
動悸	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
心不全	4 (0.6%)	1 (0.1%)	0	2 (0.3%)	1 (0.1%)	0
心房細動	6 (0.9%)	2 (0.3%)	3 (0.4%)	1 (0.1%)	0	0
洞性頻脈	5 (0.7%)	2 (0.3%)	3 (0.4%)	0	0	0
頻脈	4 (0.6%)	2 (0.3%)	2 (0.3%)	0	0	0
左室機能不全	1 (0.1%)	0	0	1 (0.1%)	0	0
心筋症	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
徐脈	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)	0
心筋梗塞	2 (0.3%)	0	0	0	1 (0.1%)	1 (0.1%)
心室性期外収縮	1 (0.1%)	1 (0.1%)	0	0	0	0
うっ血性心不全	1 (0.1%)	0	0	1 (0.1%)	0	0
ストレス心筋症	1 (0.1%)	0	0	1 (0.1%)	0	0
チアノーゼ	1 (0.1%)	0	1 (0.1%)	0	0	0
期外収縮	1 (0.1%)	1 (0.1%)	0	0	0	0
狭心症	1 (0.1%)	1 (0.1%)	0	0	0	0
心筋虚血	1 (0.1%)	1 (0.1%)	0	0	0	0
心室細動	1 (0.1%)	0	1 (0.1%)	0	0	0
心室粗動	1 (0.1%)	0	0	1 (0.1%)	0	0
心毒性	1 (0.1%)	0	0	1 (0.1%)	0	0
僧帽弁閉鎖不全症	1 (0.1%)	0	1 (0.1%)	0	0	0
洞性徐脈	1 (0.1%)	1 (0.1%)	0	0	0	0
不整脈	1 (0.1%)	0	0	1 (0.1%)	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
腎および尿路障害						
- Overall -	25 (3.6%)	11 (1.6%)	12 (1.7%)	1 (0.1%)	0	1 (0.1%)
頻尿	3 (0.4%)	1 (0.1%)	2 (0.3%)	0	0	0
排尿困難	6 (0.9%)	3 (0.4%)	3 (0.4%)	0	0	0
急性腎障害	2 (0.3%)	0	1 (0.1%)	0	0	1 (0.1%)
血尿	3 (0.4%)	2 (0.3%)	1 (0.1%)	0	0	0
腎不全	2 (0.3%)	0	1 (0.1%)	1 (0.1%)	0	0
尿閉	1 (0.1%)	1 (0.1%)	0	0	0	0
非感染性膀胱炎	2 (0.3%)	2 (0.3%)	0	0	0	0
尿失禁	1 (0.1%)	0	1 (0.1%)	0	0	0
緊張性膀胱	1 (0.1%)	1 (0.1%)	0	0	0	0
腎機能障害	1 (0.1%)	0	1 (0.1%)	0	0	0
蛋白尿	1 (0.1%)	0	1 (0.1%)	0	0	0
尿路痛	1 (0.1%)	1 (0.1%)	0	0	0	0
夜間頻尿	1 (0.1%)	1 (0.1%)	0	0	0	0
有痛性排尿困難	1 (0.1%)	0	1 (0.1%)	0	0	0
膀胱痛	1 (0.1%)	0	1 (0.1%)	0	0	0
眼障害						
- Overall -	11 (1.6%)	8 (1.1%)	3 (0.4%)	0	0	0
流涙増加	3 (0.4%)	3 (0.4%)	0	0	0	0
眼刺激	2 (0.3%)	2 (0.3%)	0	0	0	0
眼乾燥	2 (0.3%)	2 (0.3%)	0	0	0	0
霧視	2 (0.3%)	2 (0.3%)	0	0	0	0
眼そう痒症	1 (0.1%)	1 (0.1%)	0	0	0	0
眼運動障害	1 (0.1%)	0	1 (0.1%)	0	0	0
眼瞼機能障害	1 (0.1%)	0	1 (0.1%)	0	0	0
視力障害	1 (0.1%)	0	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): B021005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
肝胆道系障害						
- Overall -	12 (1.7%)	3 (0.4%)	5 (0.7%)	3 (0.4%)	1 (0.1%)	0
肝機能異常	5 (0.7%)	1 (0.1%)	2 (0.3%)	2 (0.3%)	0	0
肝損傷	3 (0.4%)	0	2 (0.3%)	0	1 (0.1%)	0
高トランスアミナーゼ血症	2 (0.3%)	1 (0.1%)	0	1 (0.1%)	0	0
高ビリルビン血症	1 (0.1%)	0	1 (0.1%)	0	0	0
肝障害	1 (0.1%)	1 (0.1%)	0	0	0	0
内分泌障害						
- Overall -	11 (1.6%)	5 (0.7%)	4 (0.6%)	2 (0.3%)	0	0
ステロイド離脱症候群	9 (1.3%)	5 (0.7%)	4 (0.6%)	0	0	0
アジソン病	1 (0.1%)	0	0	1 (0.1%)	0	0
副腎機能不全	1 (0.1%)	0	0	1 (0.1%)	0	0
生殖系および乳房障害						
- Overall -	8 (1.1%)	6 (0.9%)	1 (0.1%)	1 (0.1%)	0	0
無月経	1 (0.1%)	1 (0.1%)	0	0	0	0
萎縮性外陰腟炎	1 (0.1%)	1 (0.1%)	0	0	0	0
外陰腟紅斑	1 (0.1%)	1 (0.1%)	0	0	0	0
亀頭包皮炎	1 (0.1%)	1 (0.1%)	0	0	0	0
子宮出血	1 (0.1%)	0	0	1 (0.1%)	0	0
子宮内膜肥厚	1 (0.1%)	1 (0.1%)	0	0	0	0
女性化乳房	1 (0.1%)	1 (0.1%)	0	0	0	0
不妊症	1 (0.1%)	0	1 (0.1%)	0	0	0
閉経期症状	1 (0.1%)	1 (0.1%)	0	0	0	0
免疫系障害						
- Overall -	7 (1.0%)	3 (0.4%)	3 (0.4%)	1 (0.1%)	0	0
過敏症	4 (0.6%)	3 (0.4%)	1 (0.1%)	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

aet04_rel_005_SE APPROVED Related Adverse Events by Trial Treatment, Body System and Intensity
Protocol(s): BO21005 (K21005N)
Analysis Population: Safety-Evaluable Patients - Phase III
Snapshot Date: 12JUL2016 Cutoff Date: 29APR2016

Treatment: G-CHOP (N=704)

MedDRA System Organ Class MedDRA Preferred Term	Any Grade / Grade:	1	2	3	4	5
低γグロブリン血症	3 (0.4%)	0	2 (0.3%)	1 (0.1%)	0	0
アレルギー性浮腫	1 (0.1%)	0	1 (0.1%)	0	0	0
耳および迷路障害						
- Overall -	5 (0.7%)	4 (0.6%)	1 (0.1%)	0	0	0
耳鳴	1 (0.1%)	1 (0.1%)	0	0	0	0
回転性めまい	1 (0.1%)	1 (0.1%)	0	0	0	0
耳不快感	1 (0.1%)	1 (0.1%)	0	0	0	0
耳閉	1 (0.1%)	1 (0.1%)	0	0	0	0
聴力低下	1 (0.1%)	0	1 (0.1%)	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）						
- Overall -	2 (0.3%)	0	0	2 (0.3%)	0	0
肺腺癌	1 (0.1%)	0	0	1 (0.1%)	0	0
膀胱乳頭腫	1 (0.1%)	0	0	1 (0.1%)	0	0
社会環境						
- Overall -	1 (0.1%)	1 (0.1%)	0	0	0	0
閉経	1 (0.1%)	1 (0.1%)	0	0	0	0

事象名：MedDRA ver. 19.0
重症度判定：NCI-CTCAE ver. 4.0

Program: /opt/BIOSTAT/prod/cdt7159z/k21005n/aet04_rel.sas / Output: /opt/BIOSTAT/prod/cdt7159z/k21005n/reports/aet04_rel_005_SE.out
11JAN2017 7:15

[5.3.5.4-5 aet04_rel_005_SE を再掲]

2.7.6.2.2　個別症例の詳細

本項では，国内で実施した JO21900試験，JO29737試験で発現した，因果関係を問わない死亡及び重篤な有害事象の叙述を以降に示す。

また，上記2試験以外の因果関係を問わない死亡及び重篤な有害事象の叙述は，各試験の総括報告書（BO21223：5.3.5.1-1 p305～p2582，GAO4753g：5.3.5.1-3-1 p302～p882，GAO4915g：5.3.5.2-1 p129～p298，BO20999 (Phase II)：5.3.5.4-1-3 p114～p185，BO21003 (Phase II)：5.3.5.4-2-3 p177～p296，BO21000（再発・治療抵抗性患者）：5.3.5.4-3-1 p144～p199，BO21000（未治療患者）：5.3.5.4-3-2 p5718～p5793，BO21005：5.3.5.4-4 p199～p2369，YP25623：5.3.5.4-6 p78～p98）に示した。

2.7.6.2.2.1　JO21900試験

(1) 死亡例

治験期間中の死亡は認められなかった。

(2) 重篤な有害事象発現例

1) 症例番号：[redacted]

報告事象名	帯状疱疹
発現日	*Day 74
重篤区分	入院・入院期間の延長
転帰	回復
転帰日	*Day 95
因果関係	否定できない

性別：	[redacted]
年齢：	[redacted]歳
原疾患：	悪性リンパ腫 CD20陽性 B 細胞性 NHL，Ann Arbor stage II
合併症：	左乳腺良性腫瘍，右肩痛
既往症：	皮疹

【経過】

*Day 1	RO5072759の初回投与（サイクル1，Day1：投与量1200 mg）を実施。
*Day 22	RO5072759のサイクル2投与（投与量：2000 mg）を実施。
*Day 43	好中球数減少 Grade 3（好中球数：756）のため，サイクル3投与を延期。
*Day 59	好中球数減少 Grade 3が回復せず（好中球数：653），RO5072759の投与中止を決定。
*Day 74	左膝に痛みを伴う水疱状の発疹が出現。
*Day 77	痛みを伴う発疹が左大腿部～左膝に広がる。 皮膚科を受診し，臨床症状より，帯状疱疹との診断が下る。 加療目的で入院となる。 ゾビラックス注（250 mg × 3回/日），バクタ錠，アラセナ A 軟膏，カロナール（頓用）による治療を開始。
*Day 79	股関節の疼痛が悪化傾向にあるが，カロナールにて軽快。
*Day 81	水疱は初発部位のみであるが，左大腿，膝，下腿に紅斑として拡大。 紅斑にも疼痛あり，坐骨領域の疼痛も改善せず。 皮膚科と協議し，IgG 779であり，献血グロベニン I を開始。

*新薬承認情報提供時に置き換え

*Day 82	左膝外側の皮疹が一部痂皮化し，紅斑，熱感も前日より改善。
*Day 84	皮膚科を再診，帯状疱疹の活動性はかなり収束との診断。
*Day 85	大部分の皮疹が痂皮化傾向にあるも腰部から下腿への神経痛は残存。
*Day 88	皮膚科を受診し，ウィルスの活性は無いとの診断。
*Day 89	退院。 ゾビラックス注は終了し，退院時処方としてバルトレックス錠（6 T/日）を新たに開始。
*Day 95	皮疹はすべて痂皮化，疼痛は軽快傾向にあり，バルトレックス錠を予防量（2 T/日）とする。 皮疹がすべて痂皮化したことから，帯状疱疹は回復したと判断。

- 治験責任医師のコメント：
  前治療の SyB L-0501投与により，CD4陽性リンパ球数が減少しており，治験薬投与開始前の検査，帯状疱疹発現の直近の検査でも低値であることから，前治療による影響も考えられるが，本剤投与中に発現した有害事象（白血球減少症，好中球減少症）継続中に発現した事象であることから，治験薬との因果関係は否定できないと判断する。

2) 症例番号：[redacted]

報告事象名	左中大脳動脈瘤
発現日	*Day 186
重篤区分	入院・入院期間の延長
転帰	回復
転帰日	*Day 234
因果関係	否定できる

性別：	[redacted]
年齢：	[redacted]歳
原疾患：	悪性リンパ腫 CD20陽性 B 細胞性 NHL，Ann Arbor stage IV
合併症：	外傷性瘢痕（右肩），関節違和感（手指），便通異常，慢性胃炎
既往症：	なし

【経過】

*Day -11	スクリーニング時検査として頭頸部 CT を実施。
*Day 1	RO5072759のサイクル1，Day1投与を実施（投与量：800 mg）。
*Day 147	RO5072759のサイクル8投与を実施（投与量：1200 mg）。
*Day 175	投与終了時検査として，頭頸部 CT を実施。 所見にて，「左中大脳動脈に脳動脈瘤の疑い」との指摘あり。
*Day 176	検査のため，当院脳神経外科に紹介。
*Day 183	三次元脳血管造影を実施する。
*Day 186	「左中大脳動脈に10 mm 以上のやや不整形で wide neck の動脈瘤あり」との診断確定。
*Day 210	処置として，9/28にクリッピング術実施することを決定。
*Day 220	入院。
*Day 221	脳血管造影を実施。
*Day 224	クリッピング術を実施。
*Day 232	三次元脳血管造影を実施し，脳動脈瘤の消失を確認。

*Day 234　退院

- 治験責任医師のコメント：

*Day 175　の頭頸部 CT にて，脳動脈瘤の疑いが指摘された後に，スクリーニング時検査として実施した　*Day -10　の頭頸部 CT を確認し，比較したところ，同様の所見が認められ，治験薬投与後に特に悪化傾向は認められておらず，治験薬投与と脳動脈瘤発症との因果関係は無いと判断する。

左中大脳動脈瘤については，合併症であり，有害事象ではないと判断しているが，脳神経外科にて，手術を勧められ，*Day 224に入院手術を実施することを*Day 210に決定したため，重篤な事象として報告する。

なお，適格性に問題は無かったと判断している。

クリッピング術実施後の経過は良好であった。

2.7.6.2.2.2　JO29737試験（GATS 試験）

(1) 死亡例

治験期間中の死亡は認められなかった。

(2) 重篤な有害事象発現例

1) Patient No. [redacted]　SAE：蜂巣炎

Protocol No. JO29737 Patient No. [redacted] Region: Japan	
Age: [redacted] Years Height: [redacted] cm ECOG PS: 0	Gender: [redacted] Weight: [redacted] kg
Trial Drug: オビヌツズマブ，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	
First Dose: [redacted]/[redacted]/[redacted]（Day 1）	Last Dose: Cycle 2（[redacted]/[redacted]/[redacted]，Day 21）
PT: 蜂巣炎 Event Onset: Day 26 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係なし Outcome: 回復 Confirmed Date: Day 45	Verbatim: 蜂窩織炎 Trial Drug Adjustment Obinutuzumab: drug interrupted Cyclophosphamide: drug interrupted Doxorubicin: drug interrupted Vincristine: drug interrupted Prednisone: drug interrupted

本[redacted]歳[redacted]性患者は[redacted]/[redacted]/[redacted]に DLBCL と診断されている。
オビヌツズマブの投与開始日は　*Day 1　であった。シクロホスファミド，ドキソルビシン、ビンクリスチンの投与開始日は　*Day 3　，プレドニゾロンの投与開始日は　*Day 1　であった。
ベースライン時の Ann Arbor 分類による悪性度はステージ II であった。
ECOG PS は0であった。
IPI のリスク因子数は1であった。
B 症状は認められなかった。
標的病変の SPD は844であった。
骨髄検査の結果，骨髄浸潤は認められなかった。
脾臓，肝臓は触知不可能であった。
既往症はなかった。
合併症は心身症，めまい，高血圧，狭心症，脂質異常症，不眠症，慢性歯周炎，逆流性食道炎，大腸線腫であった。

プレメディケーションはフェブリク錠（開始日: Day -1，投与期間: 8 days，投与経路: ORAL），カロナール錠（開始日: Day 1，投与期間: 21 days，投与経路: ORAL），ポラミン錠（開始日: Day 1，投与期間: 21 days，投与経路: ORAL）であった。
合併症に対する併用療法はエチゾラム錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），セファドール錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），メリスロン錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），アムロジピン（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），エナラプリルマレイン酸（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），アトルバスタチン OD（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），アーチスト錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），ゾルピデム酒石酸塩 OD 錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），メインテート錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），ラベプラゾール NA 塩錠（開始日: Before Start of Treatment，投与期間: 53 days，投与経路: ORAL），ブロチゾラム錠（開始日: Day 3，終了日: After End of Treatment，投与経路: ORAL），カロナール錠（開始日: Day 6，終了日: After End of Treatment，投与経路: ORAL）であった。
蜂巣炎（報告事象名：蜂窩織炎）は Day 26に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「なし」，ビンクリスチンとの因果関係は「なし」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「あり」と判断された。本事象発現前の治験薬最終投与日は Day 21であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は休薬された。本事象に対して治療を要した。転帰は「回復」，回復日は Day 45であった。

本事象の詳細な経過を以下に示す。
*Day -22 ， 文書にて同意取得。
*Day -1 ， 治験薬 G-CHOP 投与管理目的にて入院。
*Day 1 ， Cycle 1投与開始。RO5072759（GA101）初回投与。
*Day 3 ， ドキソルビシン投与時に血管外漏出あり。形成外科フォローのもと軟膏処置にて経過観察。
*Day 17 ， CV ポート造設。
*Day 21 ， Cycle 2投与開始。
*Day 23 ， Cycle 2 G-CHOP 点滴投与終了し，経過良好にて退院となる。ドキソルビシン血管外漏出部位は潰瘍化等なく軟膏処置のみで経過中，今後は外来フォロー可能となった。
*Day 27 ， ドキソルビシン血管外漏出部位の腫脹と疼痛が増強したため当院休日外来受診。「蜂窩織炎」と診断され抗生剤点滴投与。翌日再診予定となり帰宅。
*Day 28 ， 外来受診。症状増悪を認めたため精査加療のために緊急入院となった。
*Day 45 ， 補液，抗生剤投与による全身管理及び切開排膿，デブリードマン，軟膏処置による局所的処置により創部感染は沈静化した。ドキソルビシン血管外漏出部位に対する処置は今後も継続必要だが，蜂窩織炎としては回復と判断。今後は外来フォローとなり退院。

「蜂巣炎」に対する担当医のコメント
本事象はドキソルビシンの血管外漏出による損傷部位を侵入経路として細菌感染を発症したと考える。CHOP 療法との因果関係は否定できないが，治験薬 RO5072759（GA101）との直接的な因果関係は否定的と考える。

同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は血圧上昇（Day 1），注入に伴う反応（Day 1），注入部位血管外漏出（Day 3），便秘（Day 6），血小板数減少（Day 7），食欲不振（Day 8），白血球数減少（Day 11），好中球数減少（Day 13），好中球数減少（Day 31），白血球数減少（Day 31），下痢（Day 36）であった。
本患者はオビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プ

レドニゾロンの投与を完了しなかった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチンの最終投与日は *Day 21 ，プレドニゾロンの最終投与日は *Day 25 で，中止理由は「主治医判断」であった。

2) Patient No. [redacted]　SAE：肺臓炎

Protocol No. JO29737 Patient No. [redacted] Region: Japan	
Age: [redacted] Years Height: [redacted] cm ECOG PS: 2	Gender: [redacted] Weight: [redacted] kg
Trial Drug: オビヌツズマブ，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	
First Dose: [redacted]/[redacted]/[redacted]（Day 1）	Last Dose: Cycle 8（[redacted]/[redacted]/[redacted], Day 163）
PT: 肺臓炎 Event Onset: Day 40 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係なし Outcome: 回復 Confirmed Date: Day 56	Verbatim: 肺臓炎 Trial Drug Adjustment Obinutuzumab: drug interrupted Cyclophosphamide: drug interrupted Doxorubicin: drug interrupted Vincristine: drug interrupted Prednisone: drug interrupted

本[redacted]歳[redacted]性患者は[redacted]/[redacted]/[redacted]に DLBCL と診断されている。
オビヌツズマブの投与開始日は *Day 1 であった。シクロホスファミド，ドキソルビシン、ビンクリスチンの投与開始日は *Day 3 ，プレドニゾロンの投与開始日は *Day 1 であった。
ベースライン時の Ann Arbor 分類による悪性度はステージ IV であった。
ECOG PS は2であった。
IPI のリスク因子数は5であった。
B 症状は体重減少，発熱，寝汗が認められていた。
標的病変の SPD は7528.939であった。
骨髄検査の結果，骨髄浸潤は認められなかった。
脾臓，肝臓は触知不可能であった。
既往症はなかった。
合併症は高血圧，糖尿病，両糖尿病網膜症，腰椎すべり症であった。
プレメディケーションはフェブリク錠（開始日: Day -5，投与期間: 39 days，投与経路: ORAL），カロナール錠（開始日: Day 1，投与期間: 163 days，投与経路: ORAL），ポララミン錠（開始日: Day 1，投与期間: 163 days，投与経路: ORAL），水溶性プレドニン（開始日: Day 1, 8, 15，57，投与期間: 1 day，投与経路: INTRAVENOUS），ソル・コーテフ注射用（開始日: Day 2, 8, 15, 22，投与期間: 1 day，投与経路: INTRAVENOUS），ソリューゲン F 注（開始日: Day 78, 99，投与期間: 1 day，投与経路: INTRAVENOUS）であった。
合併症に対する併用療法はコディオ配合錠 EX（開始日: Before Start of Treatment，終了日:–，投与経路: ORAL），グラクティブ錠（開始日: Before Start of Treatment，終了日: –，投与経路: ），ランタス注（開始日: Before Start of Treatment，終了日: –，投与経路: OTHER），メトグルコ錠（開始日: Before Start of Treatment，終了日: –，投与経路: ORAL），プレミネント配合錠 LD（開始日: Day -5，投与期間: 12 days，投与経路: ORAL），ヒューマリン R 注（開始日: Day -5，投与期間: 33 days，投与経路: ORAL），モーラスパップ（開始日: Day -4，投与期間: 65 days，投与経路: TRANSDERMAL），ジャヌビア錠（開始日: Day -2，投与期間: 42 days，投与経路: ORAL），プロプレス錠（開始日: Day 7，投与期間: 6 days，投与経路: ORAL），フルイトラン（開始日: Day 7，投与期間: 27 days，投与経路: ORAL），オルメテック錠（開始日: Day 13，投与期間: 21 days，投与経路: ORAL），アマリール錠（開始日: Day 23，投与期間: 17 days，投与経路:

ORAL），ノボラピット注（開始日: Day 29，投与期間: 11 days，投与経路: OHTER），プロプレス（開始日: Day 34，投与期間: 6 days，投与経路: ORAL），ヒューマリン R（開始日: Day 41，投与期間: 1 day，投与経路: OHTER），テネリア錠（開始日: Day 47，投与期間: 6 days，投与経路: ORAL），ヒューマリン R（開始日: Day 53，投与期間: 16 day，投与経路: OHTER），アマリール錠（開始日: Day 62，終了日: After End of Treatment，投与経路: ORAL），テネリア錠（開始日: Day 62，終了日: After End of Treatment，投与経路: ORAL），ノボラピット注（開始日: Day 69，投与期間: 122 days，投与経路: OHTER），カプトリル錠（開始日: Day 86，終了日: After End of Treatment，投与経路: ORAL）であった。
肺臓炎（報告事象名：肺臓炎）は Day 40に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「あり」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「なし」と判断された。本事象発現前の治験薬最終投与日は Day 22であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は休薬された。本事象に対して治療を要した。転帰は「回復」，回復日は Day 56であった。

本事象の詳細な経過を以下に示す。
*Day -6 ，原疾患の精査加療目的にて当院初診。症状コントロールのため当日入院された。
*Day -3 ，文書にて同意取得。
*Day 1 ，Cycle 1（G-CHOP 療法）投与開始。RO5072759（GA101）初回投与。
*Day 13 ，好中球減少症（Grade 4）発現。G-CSF 及び抗生剤投与にて回復。
*Day 22 ，Cycle 2（G-CHOP 療法）投与。
*Day 26 ，Cycle 2の CHOP 投与時に末梢ルート確保できず，CV ポート造設。
*Day 32 ，Cycle 2 Day 11，迷走神経反射と思われる一過性の意識消失あり。頭部 CT，心電図等諸検査するが，特に異常指摘されなかった。
*Day 34 ，意識状態は明瞭かつ症状安定して経過。予防処置として G-CSF，抗生剤投与開始。
*Day 35 ，白血球減少及び好中球数減少に伴い，発熱が出現。CRP 上昇傾向あり。
*Day 39 ，白血球減少及び好中球数減少は回復したが，CRP はさらに上昇し，発熱も断続的にあり。
*Day 40 ，夜中にトイレで意識消失し，転倒。39.9°C の発熱あり。全身管理及び精査施行し，CT 検査にて肺臓炎（Grade 3）と診断された。
*Day 56 ，DRPM，TEIC，MCFG，ST 合剤及び免疫グロブリン製剤，輸液，酸素送付等，全身管理にて症状及び臨床検査値は改善した。CT 及び PET による画像検査にて本事象の回復を確認した。今後も原疾患に対する治療管理のため入院は継続するが，本事象に対しては第2報をもって最終報告とする。

「肺臓炎」に対する担当医のコメント
本事象は G-CHOP 療法による骨髄抑制期に感染を生じたと考えられる。骨髄抑制の起因となった薬剤としてはシクロホスファミド，ドキソルビシン，オンコビンが最も考えられる。治験薬 RO5072759（GA101）との直接的な因果関係は否定的と考える。

同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は注入に伴う反応（Day 1），悪心（Day 1），発熱（Day 1），喘鳴（Day 1），便秘（Day 5），悪心（Day 5），貧血（Day 9），好中球数減少（Day 13），血小板数減少（Day 13），白血球数減少（Day 13），失神（Day 32），白血球数減少（Day 35），発熱性好中球減少症（Day 36），貧血（Day 42），回転性めまい（Day 42），悪心（Day 52），頻尿（Day 57），橋中心髄鞘崩壊症（Day 58），白血球数減少（Day 86），好中球数減少（Day 88）であった。
本患者はオビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与を完了した。

3) Patient No. [redacted]　SAE：発熱性好中球減少症

Protocol No. JO29737 Patient No. [redacted] Region: Japan	
Age: [redacted] Years Height: [redacted] cm ECOG PS: 0	Gender: [redacted] Weight: [redacted] kg
Trial Drug: オビヌツズマブ，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	
First Dose: [redacted]/[redacted]/[redacted]	Last Dose: Cycle 8（[redacted]/[redacted]/[redacted], Day 146）
PT: 発熱性好中球減少症 Event Onset: Day 114 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係なし Outcome: 回復 Confirmed Date: Day 118	Verbatim: 発熱性好中球減少症 Trial Drug Adjustment Obinutuzumab: dose not changed Cyclophosphamide: not applicable Doxorubicin: not applicable Vincristine: not applicable Prednisone: not applicable

本[redacted]歳[redacted]性患者は[redacted]/[redacted]/[redacted]に DLBCL と診断されている。
オビヌツズマブの投与開始日は *Day 1 であった。シクロホスファミド，ドキソルビシン、ビンクリスチンの投与開始日は *Day 2 ，プレドニゾロンの投与開始日は *Day 1 であった。
ベースライン時の Ann Arbor 分類による悪性度はステージ III であった。
ECOG PS は0であった。
IPI のリスク因子数は2であった。
B 症状は認められなかった。
標的病変の SPD は3086.96であった。
骨髄検査の結果，骨髄浸潤は認められなかった。
脾臓，肝臓は触知不可能であった。
ベースライン時（Day -2）の血液学的検査の結果，白血球数：4.0 × 10^9/L ，好中球数：2.47 × 10^9/L であった。
既往症は湿疹であった。
合併症は糖尿病，前立腺肥大症，高脂血症，ドライアイ，慢性胃炎，脂肪腫，大腸憩室であった。
プレメディケーションはカロナール細粒（開始日: Day 1，投与期間: 146 days，投与経路: ORAL），ポララミン錠（開始日: Day 1，投与期間: 146 days，投与経路: ORAL），水溶性プレドニン注（開始日: Day 8, 15，投与期間: 1 day，投与経路: INTRAVENOUS）であった。
合併症に対する併用療法はノボラピッド注（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: OTHER），レベミル注（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: OTHER），ジャヌビア錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），ティアバランス点眼液（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: OTHER），ガスコン錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），パリエット錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），メバロチン錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），ハルナール D 錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），セルニルトン錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL）であった。
発熱性好中球減少症（報告事象名：発熱性好中球減少症）は Day 114に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「なし」，ドキ

ソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「なし」と判断された。本事象発現前の治験薬最終投与日は Day 105であった。オビヌツズマブの休薬・用量変更は要さなかった。また，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンは投与は完遂していた。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 118であった。

本事象の詳細な経過を以下に示す。
*Day -5 ，本治験の同意取得。
*Day 1 ，Cycle 1 Day 1 GA101：1000 mg，P：100 mg/day（Day1-5）投与。
*Day 2 ，Cycle 1 Day 2 C：1160 mg，H：77 mg，O：2 mg 投与。
*Day 105，Cycle 6 Day 1 GA101：1000 mg，P：100 mg/day（Day1-5）投与。
*Day 106，Cycle 6 Day 2 C：1160 mg，H：77 mg，O：2 mg 投与。
*Day 107，ジーラスタ皮下注を発熱性好中球減少症予防目的にて投与。
*Day 114，15:00頃 38.3°C の発熱にて電話連絡あり。カロナール内服で様子見るよう指示。16:00と22:00に200 mg/回内服。その後も解熱せず，23:00に39.5°C まで上昇。
*Day 115，4:30にカロナール200 mg 内服。6:30に39.8°C まで上昇したため電話連絡あり，来院指示。来院時体温：37.9°C。インフルエンザ検査実施し陰性。精査目的で採血，尿検査，胸部 X 線，血液培養実施。尿検査，胸部 X 線異常なく明らかな感染源特定できず。好中球数：108 /μL であることから，発熱性好中球減少症 Grade 3と判断し，入院加療とする。セフェピム注1 g，ビーフリード輸液投与開始。19:15の検温時，36.9°C まで解熱。
*Day 116，好中球数：352 /μL，体温36°C 台～37°C 前半で解熱し経過。
*Day 118，好中球数：1342 /μL，体温36°C と解熱し経過。全身状態も良好であるため，セフェピム注1 g，ビーフリード輸液終了し，本日退院とする。好中球数 > 1000 /μL かつ解熱しているため当該事象について回復と判断。

「発熱性好中球減少症」に対する担当医のコメント
当該事象は，入院加療が必要な事象であることから重篤と判断。因果関係について，シクロホスファミド，ドキソルビシンについては骨髄抑制が明らかに既知のため否定できないと判断。GA101，ビンクリスチン及びプレドニゾロンについては否定できると判断。
事象発現日について，*Day 114から発熱しており，かつ*Day 115の好中球数から*Day 114時点で好中球数 < 1000 μL であったと推測される為，再考により発現日を*Day 114と判断し，第2報にて変更。

同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は体液貯留（Day 2），便秘（Day 7），血小板数減少（Day 7），末梢性感覚ニューロパチー（Day 10），倦怠感（Day 23），倦怠感（Day 44），非心臓性胸痛（Day 44），骨痛（Day 45），骨痛（Day 68），倦怠感（Day 68），倦怠感（Day 89），口腔粘膜炎（Day 89），非心臓性胸痛（Day 90），口腔粘膜炎（Day 118）であった。
本患者はオビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与を完了した。

4) Patient No. [redacted]　SAE：発熱性好中球減少症，肺炎

Protocol No. JO29737 Patient No. [redacted] Region: Japan	
Age: [redacted] Years Height: [redacted] cm ECOG PS: 0	Gender: [redacted] Weight: [redacted] kg
Trial Drug: オビヌツズマブ，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	
First Dose: [redacted]/[redacted]/[redacted]（Day 1）	Last Dose: Cycle 8（[redacted]/[redacted]/[redacted], Day 165）
PT: 発熱性好中球減少症 Event Onset: Day 115	Verbatim: 発熱性好中球減少症 Trial Drug Adjustment

Seriousness: 重篤	Obinutuzumab: dose not changed
AESI: －	Cyclophosphamide: not applicable
Drug Relatedness: 因果関係なし	Doxorubicin: not applicable
Outcome: 回復	Vincristine: not applicable
Confirmed Date: Day 122	Prednisone: not applicable
PT: 肺炎	Verbatim: 肺炎
Event Onset: Day 126	Trial Drug Adjustment
Seriousness: 重篤	Obinutuzumab: drug interrupted
AESI: －	Cyclophosphamide: not applicable
Drug Relatedness: 因果関係なし	Doxorubicin: not applicable
Outcome: 回復	Vincristine: not applicable
Confirmed Date: Day 165	Prednisone: not applicable

本[redacted]歳[redacted]性患者は[redacted]に FOLLICULAR LYMPHOMA と診断されている。
オビヌツズマブの投与開始日は *Day 1 であった。シクロホスファミド，ドキソルビシン、ビンクリスチンの投与開始日は *Day 2 ，プレドニゾロンの投与開始日は *Day 1 であった。
ベースライン時の Ann Arbor 分類による悪性度はステージ IV であった。
ECOG PS は0であった。
FLIPI のリスク因子数は3であった。
B 症状は認められなかった。
標的病変の SPD は2215であった。
骨髄検査の結果，骨髄浸潤が認められた。
脾臓，肝臓は触知不可能であった。
ベースライン時（Day -1）の血液学的検査の結果，白血球数：5.4 × 10^9/L ，好中球数：3.76 × 10^9/L であった。
既往症はなかった。
合併症は糖尿病，腰痛症，高脂血症，逆流性食道炎，便秘症，花粉症であった。
プレメディケーションはカロナール錠（開始日: Day 1，投与期間: 165 days，投与経路: ORAL），ポララミン錠（開始日: Day 1，投与期間: 165 days，投与経路: ORAL），プレドニン注（開始日: Day 8, 16，投与期間: 1 day，投与経路: INTRAVENOUS）であった。
合併症に対する併用療法はアマリール錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），リピトール錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），メトグルコ錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL）ジャヌビア錠（開始日: Before Start of Treatment，終了日: –，投与経路: ORAL），グルコバイ錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），テベルサ錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），モーラステープ L（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: TRANSDERMAL），タケプロン OD 錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），マグラックス錠（開始日: Day 2，投与期間: 1 day，投与経路: ORAL），ピコスルファート NA 内服液（開始日: Day 4，投与期間: 1 day，投与経路: ORAL）であった。
発熱性好中球減少症（報告事象名：発熱性好中球減少症）は Day 115に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「あり」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「なし」と判断された。本事象発現前の治験薬最終投与日は Day 107であった。オビヌツズマブの休薬・用量変更は要さなかった。また，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンは投与は完遂していた。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 122であった。
肺炎（報告事象名：肺炎）は Day 126に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「あり」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「なし」と判断された。本事象発現前の治験

薬最終投与日は Day 137であった。オビヌツズマブの投与は休薬された。また，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンは投与は完遂していた。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 165であった。

事象の詳細な経過を以下に示す。
*Day -25，本治験の同意取得。
*Day 1 ，Cycle 1 Day 1 GA101：1000 mg，P：100 mg/day（Day1-5）投与。
*Day 2 ，Cycle 1 Day 2 C：1425 mg，H：95 mg，O：2 mg 投与。
*Day 22 ，Cycle 2 Day 1 高齢のため Cycle 2より CHOP 減量（5/6 dose）にて投与とする。GA101：1000 mg，P：80 mg/day（Day1-5）投与。
*Day 23 ，Cycle 1 Day 2 C：1150 mg，H：77 mg，O：2 mg 投与。
*Day 107，Cycle 6 Day 1 GA101：1000 mg，P：80 mg/day（Day1-5）投与。
*Day 108，Cycle 6 Day 2 C：1150 mg，H：77 mg，O：2 mg 投与。事象発現前直近投与。
*Day 109，ジーラスタ皮下注を発熱性好中球減少症予防目的にて投与。
*Day 115，数日前より食欲不振等の症状が出ていたが，病院へは連絡せず様子を見ていた。本日になり動けなくなったため電話連絡し，時間外で外来受診。来院時バイタル：BT 39.2°C，Bp 126/60 mmHg，PR 116 bpm，RR 20回／分，SpO2 98%，痰貯留と咳嗽も認める。インフルエンザ検査実施したが陰性。精査目的で採血，胸部 X 線検査，血液培養実施。胸部 X 線に異常陰影認めないが，呼吸器症状伴っており今後陰影出現する可能性も否定できない。好中球数：22.2 /μL（白血球数：300 /μL，好中球：7.4%）であることから，発熱性好中球減少症 Grade 3と判断し，入院加療とする。21:00入院し，セフェピム注1 g，アセリオ注，ソルデム3A 投与開始。
*Day 116，朝の検温時，36.5°C，好中球数：67.5 /μL（白血球数：300 /μL，好中球：22.5%）。ビタメジン注，ソリューゲン F 注開始。本日の胸部 X 線検査でも異常を認めないが，咳嗽続いており，引き続き慎重に経過観察。アセリオ注投与終了。
*Day 117，解熱と共に食欲も回復してきたため，本日より補液減量。ビタメジン注，ソリューゲン F 注については，1/22で終了とした。
*Day 118，湿性咳嗽，喀痰排出継続しており，気管支炎も併発していると判断し，ボソルボン錠及びカルボシステイン DS50%を処方。気管支炎については内服治療のみで入院加療を必要とする状態ではない為，非重篤と判断。
*Day 119，血液検査にて好中球数：1304 /μL（白血球数：2000 /μL，好中球：65.2%）。好中球数 > 1000 /μL を確認したが，37°C 台の微熱続いている為，数日経過観察とする。セフェピム注，ソルデム3A については本日で終了とする。
*Day 122，咳嗽は残るもののその他所見に問題なく，退院可能な状態と判断したため，本日をもって発熱性好中球減少症は回復とした。気管支炎については未回復のため治療継続とする。
*Day 126，退院後より食事，水分がほとんど摂れず，家族より電話連絡あった為来院指示。精査目的で，採血と単純 CT 実施。単純 CT にて両側肺野に多発する浸潤影を認めるが，CRP が前回退院前（1/27）より低下しており，治癒過程か増悪過程かの鑑別は現段階ではつかず。入院にて詳細な検査と点滴治療を開始の上，経過観察が必要と判断。
入院時バイタル：体温 36.8°C，Bp 125/92 mmHg，HR 107bpm，SpO2 90%。
気管支炎が継続中であるが，本件は気管支炎の増悪ではなく，肺炎 Grade 3とし別事象と考える。ロセフィン注，ソリューゲン F 注，KN3号輸液投与開始。
食欲不振については，肺炎の軽快に伴い改善があるかを確認していく方針。
胸部 X 線検査を追加実施。右下肺に僅かに浸潤影を指摘。
肺炎球菌尿中抗原検査陰性。プロカルシトニン（–），β–D グルカン 2.84 pg/ml であることから，真菌感染も否定的。結核疑いにて痰培養と塗抹検査実施。蛍光法（–）。
*Day 127，食事ほぼ全量摂取可能となる。
*Day 128，結核の可能性について，呼吸器内科 Dr.に相談。現時点の CT で積極的に結核を疑う所見はないとの判断。T–spot 実施，痰培養及び塗抹検査再検とする。蛍光法（–）。
本日の採血で CRP 低下傾向であり，臨床所見も改善傾向。
*Day 133，T–spot 陰性（2/3採取），喀痰塗抹検査陰性であり，現時点で少なくとも結核菌の排菌はないと判断し，経過観察とする。本日の採血で CRP はさらに低下。SpO2

95%，胸部 X 線検査にて浸潤影消失，その他臨床所見も改善傾向。本日でロセフィン注，KN3号輸液投与終了し，退院可能とした。湿性咳嗽と喀痰排出はまだ継続しているため，現時点では軽快と判断。
*Day 137，Cycle 7 Day 1 GA101：1000 mg 投与。肺炎については，湿性咳嗽と喀痰排出は軽快傾向だが継続しているため Grade 1と判断。投与基準は満たしているため，Cycle 7開始とした。
*Day 158，Cycle 8開始予定だったが，好中球数減少 Grade 4のため投与基準を満たさず延期。肺炎は喀痰排出継続のため Grade 1継続と判断。
*Day 165，Cycle 8 Day 1 GA101：1000 mg 投与。好中球数回復したため，Cycle 8開始とした。喀痰排出無く状態も安定した為，肺炎は本日回復と判断。

「発熱性好中球減少症」に対する担当医のコメント
当該事象は，入院加療が必要な事象であることから重篤と判断。因果関係については，CHOP 療法において既知の事象であり，シクロホスファミド，ドキソルビシン，ビンクリスチンについては否定できないと判断。GA101，プレドニゾロンについては否定できると判断。

「肺炎」に対する担当医のコメント
当該事象は，入院加療が必要な事象であることから重篤と判断。因果関係については，CHOP 療法において既知の事象であり，シクロホスファミド，ドキソルビシン，ビンクリスチンについては否定できないと判断。GA101，プレドニゾロンについては否定できると判断。

同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は血小板数減少（Day 7），浮動性めまい（Day 15），食欲不振（Day 112），気管支炎（Day 118），圧迫骨折（Day 147），好中球数減少（Day 158）であった。
本患者はオビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与を完了した。

5) Patient No.[redacted]　SAE：白内障

Protocol No. JO29737 Patient No. [redacted] Region: Japan	
Age: [redacted] Years Height: [redacted] cm ECOG PS: 0	Gender: [redacted] Weight: [redacted]
Trial Drug: オビヌツズマブ，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	
First Dose: [redacted]（Day 1）	Last Dose: Cycle 8（[redacted], Day 148）
PT: 白内障 Event Onset: Day 49 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係なし Outcome: 回復 Confirmed Date: Day 63	Verbatim: 白内障の悪化 Trial Drug Adjustment Obinutuzumab: dose not changed Cyclophosphamide: dose not changed Doxorubicin: dose not changed Vincristine: dose not changed Prednisone: dose not changed

本[redacted]歳[redacted]性患者は *Day -28 に DLBCL と診断されている。
オビヌツズマブ，シクロホスファミド，ドキソルビシン、ビンクリスチン，プレドニゾロンの投与開始日は *Day 1 であった。
ベースライン時の Ann Arbor 分類による悪性度はステージ IV であった。
ECOG PS は0であった。
IPI のリスク因子数は3であった。

B 症状は体重減少が認められた。
標的病変の SPD は2847.93であった。
骨髄検査の結果，骨髄浸潤は認められなかった。
脾臓，肝臓は触知不可能であった。
既往症は発作性心房細動，せん妄であった。
合併症は不眠症，尋常性白斑，肺気腫，白内障，胆石症，便秘症，腹部大動脈瘤，寒冷じん麻疹であった。
プレメディケーションはカロナール錠（開始日: Day 1，投与期間: 148 days，投与経路: ORAL），ポララミン錠（開始日: Day 1，投与期間: 148 days，投与経路: ORAL）であった。
合併症に対する併用療法はリスパダール内服液（開始日: Before Start of Treatment，終了日: –，投与経路: ORAL），ロゼレム錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），マグラックス錠（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL）ロヒプノール錠（開始日: Before Start of Treatment，終了日: –，投与経路: ORAL），ゾルピデム酒石酸塩 OD 錠5MG「FE」（開始日: Day -3，投与期間: 7 days，投与経路: ORAL），センノシド錠（開始日: Day -2，投与期間: 15 days，投与経路: ORAL），デジレル錠（開始日: Day 4，投与期間: 13 days，投与経路: ORAL），レシカルボン坐剤（開始日: Day 5，投与期間: 1 days，投与経路: OTHER），ピコスルファートナトリウム内用液0.75%「JG」（開始日: Day 6，投与期間: 3 day，投与経路: ORAL）であった。
白内障（報告事象名：白内障の悪化）は Day 49に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「なし」，ビンクリスチンとの因果関係は「なし」，ドキソルビシンとの因果関係は「なし」，プレドニゾロンとの因果関係は「あり」と判断された。本事象発現前の治験薬最終投与日は Day 45であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの休薬・用量変更は要さなかった。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 63であった。

本事象の詳細な経過を以下に示す。
*Day -3 ，本治験の同意取得。
*Day 1 ，治験薬，CHOP 療法開始（Cycle 1）。
*Day 45 ，治験薬，CHOP 療法投与（Cycle 3）。カロナール錠600 mg + ポララミン錠2 mg 内服。プレドニゾロン錠100 mg（*Day 49まで）1日1回内服。グラニセトロン注3 mg，アドリアシン注73.5 mg，オンコビン注2 mg，エンドキサン注1102.5 mg 静脈内投与する。体調変わりなく問題なく治療終了する。 *Day 52 ，3日前から眼痛みられた。血圧の上昇（183/106），頭痛みられるため救急外来受診。右眼球の疼痛と充血・流涙あり。頭部 CT 等実施するが問題なし。アダラートカプセル，ロキソプロフェン内服する。角結膜炎が疑われ眼科受診進められる。
*Day 53 ，近医眼科受診し右眼緑内障と診断される。ダイアモックス錠，タプロス点眼液0.001，フルメトロン点眼液0.1%，サンピロ点眼液2%処方され帰宅。
*Day 54 ，上記治療で眼圧の低下みられず緑内障発作の治療ができる病院へ紹介される。紹介された病院受診し，マンニットール S 注射液施行し，右眼への減圧のため虹彩光凝固術実施する。診察し白内障の悪化を指摘される。レボフロキサシン点眼液1.5%，サンベタゾン眼耳鼻科用液0.1%処方される。
*Day 57 ，白内障手術のため入院する。
*Day 58 ，右眼右水晶体再建術 + 硝子体切除術施行する。クラビット点眼液1.5 mg，リンデロン点眼液0.1%，ブロナック点眼液0.1%点眼開始。
*Day 63 ，退院をもって回復とする。

「白内障」に対する担当医のコメント
治験薬，CHOP 療法開始後のためすべての薬剤の完全な否定は難しいが，プレドニゾロンとの関与が疑われるためその他の薬剤は関連なしと判断する。

同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は発熱（Day 6），白血球減少症（Day 10），好中球減少症（Day 10），皮膚乾燥（Day 12），白血球減少症（Day 38），好中球減少症（Day 38），末梢性感覚ニューロパチー（Day

38），緑内障（Day 49），咳嗽（Day 80）であった。
本患者はオビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与を完了した。

6) Patient No. [redacted]　SAE：菌血症，蜂巣炎，菌血症，菌血症，菌血症

Protocol No. JO29737 Patient No. [redacted] Region: Japan	
Age: [redacted] Years Height: [redacted] cm ECOG PS: 0	Gender: [redacted] Weight: [redacted] kg
Trial Drug: オビヌツズマブ，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 First Dose: [redacted]（Day 1）	Last Dose: Cycle 8（[redacted], Day 177）
PT: 菌血症 Event Onset: Day 28 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係なし Outcome: 回復 Confirmed Date: Day 59	Verbatim: 菌血症 Trial Drug Adjustment Obinutuzumab: drug interrupted Cyclophosphamide: drug interrupted Doxorubicin: drug interrupted Vincristine: drug interrupted Prednisone: drug interrupted
PT: 蜂巣炎 Event Onset: Day 30 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係なし Outcome: 回復 Confirmed Date: Day 59	Verbatim: 蜂窩織炎 Trial Drug Adjustment Obinutuzumab: drug interrupted Cyclophosphamide: drug interrupted Doxorubicin: drug interrupted Vincristine: drug interrupted Prednisone: drug interrupted
PT: 菌血症 Event Onset: Day 113 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係あり Outcome: 回復 Confirmed Date: Day 139	Verbatim: 菌血症の再燃 Trial Drug Adjustment Obinutuzumab: drug interrupted Cyclophosphamide: drug interrupted Doxorubicin: drug interrupted Vincristine: drug interrupted Prednisone: drug interrupted
PT: 菌血症 Event Onset: Day 232 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係あり Outcome: 回復 Confirmed Date: Day 272	Verbatim: 菌血症の再燃 Trial Drug Adjustment Obinutuzumab: not applicable Cyclophosphamide: not applicable Doxorubicin: not applicable Vincristine: not applicable Prednisone: not applicable
PT: 菌血症 Event Onset: Day 304 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係あり Outcome: 回復 Confirmed Date: Day 355	Verbatim: 菌血症の再燃 Trial Drug Adjustment Obinutuzumab: not applicable Cyclophosphamide: not applicable Doxorubicin: not applicable Vincristine: not applicable Prednisone: not applicable

本[redacted]歳[redacted]性患者は *Day -56 に DLBCL と診断されている。
オビヌツズマブの投与開始日は *Day 1 であった。シクロホスファミド，ドキソルビシン、ビンクリスチンの投与開始日は *Day 2 ，プレドニゾロンの投与開始日は *Day 1 であった。

ベースライン時の Ann Arbor 分類による悪性度はステージ I であった。
ECOG PS は0であった。
IPI のリスク因子数は0であった。
B 症状は認められなかった。
標的病変の SPD は190.8であった。
骨髄検査の結果，骨髄浸潤は認められなかった。
脾臓，肝臓は触知不可能であった。
ベースライン時（Day -1）の血液学的検査の結果，白血球数：5.4 × 10^9/L ，好中球数：3.76 × 10^9/L であった。
既往症はなかった。
合併症は頭痛，便秘であった。
プレメディケーションはカロナール（開始日: Day 1，投与期間: 177 days，投与経路: ORAL），ポララミン（開始日: Day 1，投与期間: 177 days，投与経路: ORAL）であった。
合併症に対する併用療法はイブクイック（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），コーラック（開始日: Before Start of Treatment，終了日: After End of Treatment，投与経路: ORAL），カロナール（開始日: Day -7，投与期間: 1 day，投与経路: ORAL），ロキソプロフェン（開始日: Day -7，投与期間: 17 days，投与経路: ORAL），プリンペラン（開始日: Day -7，投与期間: 2 days，投与経路: ORAL），アローゼン（開始日: Day 3，投与期間: 132 days，投与経路: ORAL）であった。
菌血症（報告事象名：菌血症）は Day 28に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「なし」，ビンクリスチンとの因果関係は「なし」，ドキソルビシンとの因果関係は「なし」，プレドニゾロンとの因果関係は「なし」と判断された。本事象発現前の治験薬最終投与日は Day 23であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は休薬された。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 59であった。
蜂巣炎（報告事象名：蜂窩織炎）は Day 30に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「なし」，ビンクリスチンとの因果関係は「なし」，ドキソルビシンとの因果関係は「なし」，プレドニゾロンとの因果関係は「なし」と判断された。本事象発現前の治験薬最終投与日は Day 23であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は休薬された。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 59であった。
菌血症（報告事象名：菌血症の再燃）は Day 113に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「あり」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「あり」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「あり」と判断された。本事象発現前の治験薬最終投与日は Day 100であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は休薬された。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 139であった。
菌血症（報告事象名：菌血症の再燃）は Day 232に発現が報告された。重篤度は重篤，オビヌツズマブとの因果関係は「あり」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「あり」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「あり」と判断された。本事象発現前の治験薬最終投与日は[redacted]（Day 177）であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は完遂していた。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 272であった。
菌血症（報告事象名：菌血症の再燃）は Day 304に発現が報告された。重篤度は重篤，オビヌツズマブとの因果関係は「あり」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「あり」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「あり」と判断された。本事象発現前の治験薬最終投与日は[redacted]（Day 177）であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は完遂していた。本事象に対し

て治療を要した。転帰（確認日）は「回復」，回復日は Day 355であった。

事象の詳細な経過を以下に示す。
*Day 1 ，サイクル1 Day1として治験薬オビヌツズマブ ＋CHOP 開始。
サイクル1 Day8まで入院で治験薬投与し特に問題なく，Day 15以降外来にて投与継続。
*Day 23 ，サイクル2 Day1の治験薬オビヌツズマブ + CHOP 実施。ドキソルビシン点滴時に静脈炎あり，血管外漏出は無かったため，ルーと差し替えのみで対応しそのまま点滴終了した。
*Day 28 ，白血球減少予防のため，ジーラスタ皮下注射実施。夕方から発熱38.7°C あり。
*Day 29 ，状態確認のため採血，血液培養実施。カロナール内服にて解熱しているため様子観察。
*Day 30 ，左前腕（*Day 23静脈炎部分）に発赤，腫脹，熱感あり，蜂窩織炎疑われセファゾリン点滴後ケフラール内服開始。
*Day 32 ，左前腕の発赤，血液データとも改善傾向であり，ケフラール内服継続とした。
*Day 34 ，38.5°C の発熱を認め救急外来受診。6/23の血液培養にてグラム陰性ラセン状桿菌の中間報告あり，白血球の再上昇も認めたため，菌血症に対する点滴（スルバシリン1.5 g × 4/日）治療目的で入院となる。
*Day 43 ，入院後発熱なく，蜂窩織炎も改善傾向。点滴（スルバシリン1.5 g × 4/日）継続中。
*Day 45 ，*Day 39の血液培養にて菌検出されたため，スルバジリン→メロペネム0.5 g × 4/日に変更。
*Day 57 ，*Day 46，*Day 49の血液培養にて陰性となったため，菌血症 G1に改善と判断し，サイクル3の治験薬オビヌツズマブ ＋CHOP 実施。
*Day 59 ，メロペネムの投与終了し，退院となった。
サイクル4 Day 1を*Day 69，サイクル5 Day 1を*Day 100に実施。
*Day 115 ，*Day 113に37.5°C の発熱あり，カロナールで解熱した。*Day 114左前腕（前回蜂窩織炎部位）発赤あり当日中に治まったが，右前腕にも発赤出現したため受診。菌血症を疑い血液培養採血後，ファロムトカナマイシン内服開始。
*Day 122 ，*Day 115の血液培養にてグラム陰性ラセン状桿菌検出したこと，本日右下腿にも発赤出現していることからファロム→メロペネム点滴へ変更。
*Day 123 ，入院にてメロペネム点滴継続となった。
*Day 134 ，*Day 126の血液培養にて陰性を確認したため，菌血症 G1に改善と判断し，サイクル6 Day 1の験薬オビヌツズマブ ＋CHOP 実施。
*Day 139 ，メロペネムの投与終了し，退院となった。
*Day 187 ，サイクル8 Day1の治験薬オビヌツズマブ投与し，
*Day 211 ，治験終了時の観察を実施し，治験期間終了となる。
*Day 221 ，発赤が出現。
*Day 225 ，発熱は無いが，発赤が続くため受診。ファロム内服開始。
*Day 232 ，*Day 225の血液培養が陰性だったため，ファロム中止。
*Day 239 ，*Day 232の血液培養陽性のため，サワシリン・オーグメンチン内服開始。
*Day 248 ，*Day 241の血液培養も陽性であり，内服抗菌剤抵抗性のため入院治療となる。
*Day 249 ，メロペネム点滴開始。*Day 250便よりグラム陰性ラセン状桿菌検出したため，*Day 263よりカナマイシン内服追加。
*Day 272 ，*Day 253以降の静脈血培養は陰性となるが，菌血症を繰り返しているため抗菌剤点滴を3週間実施し*Day 272退院。
*Day 304 ，右下腿に発赤が出現したため受診。
*Day 311，*Day 304の血液培養陽性であり，菌血症再燃のため入院治療となる。*Day 311～メロペネム，*Day 312～ゲンタシン点滴開始し予定通り6週間投与。
*Day 355，退院となる。

「蜂巣炎」，「菌血症」に対する担当医のコメント
蜂窩織炎と菌血症は，静脈穿刺によるものであり白血球減少を伴わないため，治験薬及び CHOP 療法との因果関係はないと考える。 *Day 34 に入院による治療が必要となったため，この時点で重篤と判断した。 *Day 59　退院日を以って回復と判断する。

「菌血炎」に対する担当医のコメント
今回の菌血症については，菌の侵入門戸がはっきりせず明らかな感染巣が認められないため，治験薬及び CHOP 療法による免疫不全を背景とした菌血症の再燃と考え，因果関係は否定できない。 *Day 123 に入院による治療が必要となったため，この時点で重篤と判断した。 *Day 139　退院日を以って回復と判断する。

「菌血症」に対する担当医のコメント
今回は2回目の菌血症再燃となる。前回同様，菌の侵入門戸がはっきりせず明らかな感染巣が認められないため，治験薬及び CHOP 療法による免疫不全を背景とした菌血症の再燃と考え，因果関係は否定できない。 *Day 248 ，入院による治療が必要となったため，この時点で重篤と判断した。退院を以って回復と判断した。

「菌血症」に対する担当医のコメント
今回は3回目の菌血症再燃となる。前回同様，菌の侵入門戸がはっきりせず明らかな感染巣が認められないため，治験薬及び CHOP 療法による免疫不全を背景とした菌血症の再燃と考え，因果関係は否定できない。 *Day 311 ，入院による治療が必要となったため，この時点で重篤と判断した。 *Day 355 退院を以って回復とする。

同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は悪心（Day 2），不眠症（Day 3），脱毛（Day 23），注入部静脈炎（Day 23），紅斑（Day 30），そう痒症（Day 90），下痢（Day 140）であった。
本患者はオビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与を完了した。

7)　Patient No. [redacted]　　SAE：細気管支炎

Protocol No. JO29737 Patient No. [redacted] Region: Japan	
Age: [redacted] Years Height: [redacted] cm ECOG PS: 0	Gender: [redacted] Weight: [redacted] kg
Trial Drug: オビヌツズマブ，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 First Dose: [redacted]（Day 1）	Last Dose: Cycle 6（[redacted], Day 106）
PT: 細気管支炎 Event Onset: Day 78 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係あり Outcome: 軽快 Confirmed Date: Day 249	Verbatim: 細気管支炎 Trial Drug Adjustment Obinutuzumab: drug withdrawn Cyclophosphamide: dose not changed Doxorubicin: dose not changed Vincristine: dose not changed Prednisone: dose not changed

本[redacted]歳[redacted]性患者は *Day -32 に DLBCL と診断されている。
オビヌツズマブの投与開始日は *Day 1 であった。シクロホスファミド，ドキソルビシン、ビンクリスチンの投与開始日は *Day 2 ，プレドニゾロンの投与開始日は *Day 1 であった。
ベースライン時の Ann Arbor 分類による悪性度はステージ IV であった。
ECOG PS は0であった。
IPI のリスク因子数は4であった。
B 症状は認められなかった。
標的病変の SPD は7039であった。
骨髄検査の結果，骨髄浸潤は認められなかった。

脾臓，肝臓は触知不可能であった。
既往症はなかった。
合併症は胃炎，子宮筋腫，左甲状腺腫，変形性脊椎症，肺気腫であった。
プレメディケーションはカロナール錠（開始日: Day 1, 15, 22, 43, 64, 85, 106，投与期間: 1 day，投与経路: ORAL），ネオマレルミン錠（開始日: Day 1, 15, 22, 43, 64, 85, 106，投与期間: 1 day，投与経路: ORAL）であった。
合併症に対する併用療法はなかった。
細気管支炎（報告事象名：細気管支炎）は Day 78に発現が報告された。重篤度は重篤，重症度は Grade 2，オビヌツズマブとの因果関係は「あり」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「あり」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「あり」と判断された。本事象発現前の治験薬最終投与日は Day 106であった。オビヌツズマブの投与は中止，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの休薬・用量変更は要さなかった。本事象に対して治療を要した。転帰（確認日）は「軽快」，転帰確認日は Day 249であった。

本事象の詳細な経過を以下に示す。
*Day -3 ，CT 検査において，肺気腫を認める以外に異常なし。
*Day 1 ，G-CHOP_ Cycle 1開始。
*Day 22 ，G-CHOP_ Cycle 2開始。
*Day 43 ，G-CHOP_ Cycle 3開始。
*Day 64 ，G-CHOP_ Cycle 4開始。
*Day 78 ，CT 検査で右中葉に気管支炎，両側下葉の気管支肥厚，喀痰の貯留を認めた。
*Day 85 ，G-CHOP_ Cycle 5開始。
*Day 106 ，G-CHOP_ Cycle 6開始。
*Day 130 ，CT 検査で病巣は拡大しており，一部結節様陰影あり。
*Day 137 ，[illegible]頃から発現した呼吸器症状（咳，痰，呼吸困難感等）及び画像所見の悪化を認め，治験薬との関連を疑い，治験薬の投与中止を決定した。
～ *Day 227 ，
＜細気管支炎に対する治療経過＞
クラリス錠： *Day 138 - *Day 144
グレースビット錠： *Day 145 - *Day 214
クラリスロマイシン錠： *Day 145 - *Day 207
アストミン錠： *Day 152 - *Day 235
クリアナール錠： *Day 152 - *Day 165
ビソルボン錠： *Day 178 - *Day 235
サワシリンカプセル： *Day 178 - *Day 184
オーグメンチン配合錠： *Day 178 - *Day 184
アモキシシリンカプセル： *Day 185 - *Day 193
クラリス錠： *Day 208 - *Day 227
*Day 228 ，*本剤投与後2カ月目以降，抗生剤（経口）等を投与しているが症状（CRP 高値，咳嗽／喀痰等）改善せず，精査加療目的で入院となった。同日，気管支鏡施行。右 B8a 及び B9より気管支肺生検を行った。
*Day 228 ，細気管支炎に対し，クラリスロマイシン錠に加え，ゾシンの点滴静脈内投与を開始した。
*Day 248 ，咳嗽／喀痰量減少し，CRP 及び画像所見も改善したため，ゾシンの投与を中止した。
*Day 249 ，症状軽快し退院。

「細気管支炎」に対する担当医のコメント
喫煙歴及び治験前の CT で肺気腫を認めていたが，呼吸器疾患での受診歴は無く，治療前に呼吸器症状は認められなかった。被験者は，抗 CD20抗体を含む化学療法に関連した，B 細胞リンパ球の枯渇，免疫低下から易感染状態にあり，細気管支炎を発症したと考える（治験薬との因果関係あり）。この細気管支炎を発症した背景として喫煙歴や肺気腫も関連していたと考える。

*新薬承認情報提供時に置き換え

同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は注入に伴う反応（Day 1），発熱（Day 1），便秘（Day 4），好中球減少症（Day 8），血小板減少症（Day 8），味覚異常（Day 15），上気道炎（Day 15），食欲不振（Day 33），好中球減少症（Day 57），便秘（Day 65），食欲不振（Day 66），悪心（Day 66），末梢性感覚ニューロパチー（Day 69），副鼻腔炎（Day 78），便秘（Day 86），発熱性好中球減少症（Day 114）であった。
本患者はシクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与を完了した。オビヌツズマブは投与を完了しなかった。オビヌツズマブの最終投与日は *Day 106 で中止理由は有害事象（細気管支炎）であった。

8) Patient No. [redacted]　SAE：うつ病

Protocol No. JO29737 Patient No. [redacted] Region: Japan	
Age: [redacted] Years Height: [redacted] cm ECOG PS: 0	Gender: [redacted] Weight: [redacted] kg
Trial Drug: オビヌツズマブ，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 First Dose: [redacted]（Day 1）	Last Dose: Cycle 1（[redacted], Day 1）
PT: うつ病 Event Onset: Day 7 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係なし Outcome: 軽快 Confirmed Date: Day 350	Verbatim: うつ病 Trial Drug Adjustment Obinutuzumab: dose not changed Cyclophosphamide: dose not changed Doxorubicin: dose not changed Vincristine: dose not changed Prednisone: dose not changed

本[redacted]歳[redacted]性患者は *Day -35 に DLBCL と診断されている。
オビヌツズマブの投与開始日は *Day 1 であった。シクロホスファミド，ドキソルビシン、ビンクリスチンの投与開始日は *Day 2 ，プレドニゾロンの投与開始日は *Day 1 であった。
ベースライン時の Ann Arbor 分類による悪性度はステージ IV であった。
ECOG PS は0であった。
IPI のリスク因子数は3であった。
B 症状は認められなかった。
標的病変の SPD は2585であった。
骨髄検査の結果，骨髄浸潤は認められなかった。
脾臓，肝臓は触知不可能であった。
既往症はうつ病であった。
合併症は尿閉，不安，便秘，アレルギー性鼻炎であった。
プレメディケーションはフェブリク（開始日：Day -1，投与期間：3 days，投与経路: ORAL），カロナール錠（開始日: Day 1，投与期間: 1 day，投与経路: ORAL），タジベール錠（開始日: Day 1，投与期間: 1 day，投与経路: ORAL），ソルコーテフ（開始日: Day 1，投与期間: 1 day，投与経路: INTRAVENOUS）であった。
合併症に対する併用療法はアルプラゾラム錠（開始日：Before Start of Treatment，終了日：After End of Treatment，投与経路：ORAL），酸化マグネシウム錠（開始日：Before Start of Treatment，終了日：After End of Treatment，投与経路：ORAL），パンテチン錠（開始日：Before Start of Treatment，終了日：After End of Treatment，投与経路：ORAL），プルゼニド錠（開始日：Day 6，終了日：After End of Treatment，投与経路：ORAL）であった。
うつ病（報告事象名：うつ病）は Day 7に発現が報告された。重篤度は重篤，重症度は

Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「なし」，ビンクリスチンとの因果関係は「なし」，ドキソルビシンとの因果関係は「なし」，プレドニゾロンとの因果関係は「あり」と判断された。本事象発現前の治験薬最終投与日は Day 1であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの休薬・用量変更は要さなかった。本事象に対して治療を要した。転帰（確認日）は「軽快」，転帰確認日は Day 350であった。

本事象の詳細な経過を以下に示す。
*Day -17 ，他院より紹介受診。不安症状が認められたためソラナックス処方。
*Day -15 ，骨盤内腫瘤により尿閉きたし緊急入院。膀胱留置カテーテル挿入。表情乏しく口数少ない。
*Day -2 ，DLBCL と診断され，当治験参加のため文書同意取得。立会人を要したものの，被験者本人の理解力は十分あった。
*Day 1 ，Day 1オビヌツズマブ投与。オビヌツズマブ投与前も不安は著変なく，投与に問題ないと判断し投与開始。投与中インフュージョンリアクション発現したためステロイドにて対応し，その後の再発現はなく投与終了。
*Day 2 ，Day 2 CHOP 投与。
*Day 5 ，Day 5プレドニゾロン投与終了。
*Day 6 ，Day 6膀胱留置カテーテル抜去。自尿あり排尿状況良好。表情明るく活動性あがっている。
*Day 7 ，昼より「死にたい」，「殺してほしい」と繰り返される。うつ病の既往があることを家族から聴取。精神科医の介入を依頼し，ステロイドによって誘発されたうつ病再発であり，精神科病棟のある総合病院への転院を検討する必要があると判断された。ジプレキササイディス錠，ジェイゾロフト錠開始。治療拒否あり治験継続は困難であるため治験中止。
*Day 8 ，セルフケア放棄しほぼ臥床状態。介助にて行うことは拒否なく受け入れあり。
*Day 13 ，抑うつ状態続いている。
*Day 21 ，うつ病治療のため転院。
*Day 125 ，症状軽快したため転院先より他院へ転院。

「うつ病」に対する担当医のコメント
当該被験者は，登録ならびに治験薬開始時に不安症状が認められていたものの，DLBCL に対する不安症状だと考えていた。しかし，本事象発症後に，過去にうつ病の診断がなされていたことが家族からの申告で発覚した。今回うつ病が再発した最も強く疑われる要因として，治験開始に伴う投与を開始したプレドニゾロンと考える。一方，オビヌツズマブに関しては，これまで提供されたガイダンスにはうつ病ならびに精神障害の報告はないため，否定できると考えている。うつ病のための精神科医の介入や薬物療法などを行うことが入院又は入院期間の延長に該当すると判断したため SAE 報告とした。うつ病は軽快しており，因果関係も否定できるため今後のフォローアップは不要と判断した。
同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は注入に伴う反応（Day 1），発熱（Day 1）であった。
本患者はオビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与を完了しなかった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチンの最終投与日は *Day 1 ，プレドニゾロンの最終投与日は *Day 5 で，中止理由は「主治医判断」であった。

9) Patient No. [redacted]　SAE：帯状疱疹，胃腸炎

Protocol No. JO29737 Patient No. [redacted] Region: Japan	
Age: [redacted] Years	Gender: [redacted]
Height: [redacted] cm	Weight: [redacted] kg
ECOG PS: 1	

Trial Drug: オビヌツズマブ，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	
First Dose: [redacted]（Day 1）	Last Dose: Cycle 8（[redacted], Day 162）
PT: 帯状疱疹 Event Onset: Day 73 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係あり Outcome: 回復 Confirmed Date: Day 190	Verbatim: 汎発性帯状疱疹 Trial Drug Adjustment Obinutuzumab: drug interrupted Cyclophosphamide: drug interrupted Doxorubicin: drug interrupted Vincristine: drug interrupted Prednisone: drug interrupted
PT: 胃腸炎 Event Onset: Day 107 Seriousness: 重篤 AESI: － Drug Relatedness: 因果関係あり Outcome: 回復 Confirmed Date: Day 120	Verbatim: 感染性胃腸炎 Trial Drug Adjustment Obinutuzumab: dose not changed Cyclophosphamide: dose not changed Doxorubicin: dose not changed Vincristine: dose not changed Prednisone: dose not changed

本[redacted]歳[redacted]性患者は*Day -398 に FOLLICULAR LYMPHOMA と診断されている。
オビヌツズマブの投与開始日は *Day 1 であった。シクロホスファミド，ドキソルビシン、ビンクリスチンの投与開始日は *Day 2 ，プレドニゾロンの投与開始日は *Day 1 であった。
ベースライン時の Ann Arbor 分類による悪性度はステージ III であった。
ECOG PS は1であった。
FLIPI のリスク因子数は3であった。
B 症状は認められなかった。
標的病変の SPD は2260.4565であった。
骨髄検査の結果，骨髄浸潤は認められなかった。
脾臓，肝臓は触知不可能であった。
既往症はなかった。
合併症は薬剤アレルギー（ピリン系），びらん性胃炎であった。
プレメディケーションはフェブリク錠（開始日: Day 1，投与期間: 5 days，投与経路: ORAL），カロナール錠（開始日: Day 1, 8, 15, 22, 43, 64, 99, 120, 141, 162，投与期間: 1 day，投与経路: ORAL），タベジール錠（開始日: Day 1, 8, 15, 22, 43, 64, 99, 120, 141, 162，投与期間: 1 day，投与経路: ORAL），ソルコーテフ（開始日 : Day 8, 15, 22, 43, 64, 99, 120, 141, 162，投与期間: 1 day，投与経路: INTRAVENOUS）であった。
合併症に対する併用療法はなかった。
帯状疱疹（報告事象名：汎発性帯状疱疹）は Day 73に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「あり」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「あり」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「あり」と判断された。本事象発現前の治験薬最終投与日は Day 64であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は休薬された。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 190であった。
胃腸炎（報告事象名：感染性胃腸炎）は Day 107に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「あり」，シクロホスファミドとの因果関係は「あり」，ビンクリスチンとの因果関係は「あり」，ドキソルビシンとの因果関係は「あり」，プレドニゾロンとの因果関係は「あり」と判断された。本事象発現前の治験薬最終投与日は Day 99であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの休薬・用量変更は要さなかった。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 120であった。

事象の詳細な経過を以下に示す。
*Day -27 ，当治験参加のため文書同意取得。

*Day 1 ，C1 Day 1オビヌツズマブ投与 Day 2 CHOP 投与。
*Day 8 ， Day 8オビヌツズマブ投与
*Day 15 ， Day 15オビヌツズマブ投与。
*Day 22 ， C2オビヌツズマブ ＋CHOP 投与。
*Day 43 ， C3オビヌツズマブ ＋CHOP 投与。
*Day 64 ， C4オビヌツズマブ ＋CHOP 投与。
*Day 72 ， *Day 71より全身に皮疹出現のため近医受診。毛包炎，単純ヘルペスと診断。
*Day 73 ，左下肢痛を伴うため当院受診。頭部，左耳介，右前胸部，右鼠径部，左殿部，左足，背部に紅暈を伴う水疱散在あり。水疱部細胞診（Tzanck test）：陽性。汎発性帯状疱疹と診断され、入院治療が必要と判断。アシクロビル点滴，疼痛コントロール開始。
*Day 75 ，帯状疱疹に変化なし。
*Day 77 ，頭部，左耳介，左足趾，足背は水腫～膿疱。左殿部，左下肢は膿疱～痂皮。アシクロビル点滴継続。
*Day 79 ，全体的に水庖は膿疱化。新生する水疱なく改善傾向。アシクロビル点滴終了（*Day 73～*Day 79）。
*Day 80 ，バルトレックス内服開始。
*Day 84 ，痂皮化不完全な部分はあるが，全体的に痂皮化。バルトレックス内服終了。ビクロックス内服へ切り替え（*Day 86）
*Day 88 ，退院。
*Day 99 ，帯状疱疹ほぼ痂皮化しており，軽快（G1）と判断。C5オビヌツズマブ ＋CHOP 投与実施。
*Day 107，嘔気，嘔吐出現。
*Day 108，嘔気が強く内服薬服用困難のため当院へ電話連絡。軟便～下痢あり。
*Day 109，嘔気続き食事摂取不良。食事摂取不良，PS 低下（PS：2）のため緊急入院とし補液開始。嘔気，嘔吐，下痢あり感染性腸炎を疑う。発熱なし。
*Day 111，嘔気なし。下痢1回。水分摂取できており食事摂取も少量できているため補液減量。
*Day 112，食事摂取後に嘔吐あり。嘔気なし。排便なし。骨髄機能回復傾向。
*Day 113，制吐剤使用しコントロール図れている。
*Day 114，状態安定してきたため退院。
*Day 120，退院後，嘔吐・下痢なく，骨髄機能回復している。感染性胃腸炎は回復と判断。C6オビヌツズマブ ＋CHOP 投与実施。
*Day 131，頭部の痂皮残る。
*Day 190，頭部の痂皮消失し，帯状疱疹は回復と判断。

「帯状疱疹」に対する担当医のコメント
本事象はオビヌツズマブ併用 CHOP 療法による免疫抑制により発現したと考えられ，治験薬との因果関係は否定できないと判断した。

「胃腸炎」に対する担当医のコメント
発熱は認めないが，好中球減少期に嘔気，嘔吐，下痢が発現しているため感染性胃腸炎と考えた。経口摂取不良状態により持続点滴が必要であり入院治療を要するとの判断したため SAE 報告となった。本事象はオビヌツズマブ併用 CHOP 療法による免疫抑制により発現したと考えられ，治験薬との因果関係は否定できないと判断した。

同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は浮腫（Day 3），味覚異常（Day 4），歯周炎（Day 20），痔核（Day 57），好中球数減少（Day 58）であった。
本患者はオビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与を完了した。

10) Patient No. [redacted]　SAE：脳梗塞，注入に伴う反応，誤嚥性肺炎

Protocol No. JO29737 Patient No. [redacted] Region: Japan

Age: [redacted] Years	Gender: [redacted]
Height: [redacted] cm	Weight: [redacted] kg
ECOG PS: 0	
Trial Drug: オビヌツズマブ，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	
First Dose: [redacted]（Day 1）	Last Dose: Cycle 1（[redacted], Day 15）
PT: 脳梗塞	Verbatim: 脳梗塞
Event Onset: Day 16	Trial Drug Adjustment
Seriousness: 重篤	Obinutuzumab: drug interrupted
AESI: －	Cyclophosphamide: drug interrupted
Drug Relatedness: 因果関係あり	Doxorubicin: drug interrupted
Outcome: 回復	Vincristine: drug interrupted
Confirmed Date: Day 118	Prednisone: drug interrupted
PT: 注入に伴う反応	Verbatim: インフュージョンリアクション
Event Onset: Day 16	Trial Drug Adjustment
Seriousness: 重篤	Obinutuzumab: drug interrupted
AESI: －	Cyclophosphamide: drug interrupted
Drug Relatedness: 因果関係あり	Doxorubicin: drug interrupted
Outcome: 回復	Vincristine: drug interrupted
Confirmed Date: Day 118	Prednisone: drug interrupted
PT: 誤嚥性肺炎	Verbatim: 誤嚥性肺炎
Event Onset: Day 16	Trial Drug Adjustment
Seriousness: 重篤	Obinutuzumab: drug withdrawn
AESI: －	Cyclophosphamide: drug withdrawn
Drug Relatedness: 因果関係なし	Doxorubicin: drug withdrawn
Outcome: 回復	Vincristine: drug withdrawn
Confirmed Date: Day 40	Prednisone: drug withdrawn

本[redacted]歳[redacted]性患者は *Day -30 に DLBCL と診断されている。
オビヌツズマブの投与開始日は *Day 1 であった。シクロホスファミド，ドキソルビシン、ビンクリスチンの投与開始日は *Day 2 ，プレドニゾロンの投与開始日は *Day 1 であった。
ベースライン時の Ann Arbor 分類による悪性度はステージ II であった。
ECOG PS は0であった。
IPI のリスク因子数は1であった。
B 症状は認められなかった。
標的病変の SPD は255であった。
骨髄検査の結果，骨髄浸潤は認められなかった。
脾臓，肝臓は触知不可能であった。
既往症はなかった。
合併症は糖尿病，高血圧，花粉症，ワルチン腫瘍，陳旧性脳梗塞であった。
プレメディケーションはカロナール（開始日: Day 1，投与期間: 15 days，投与経路: ORAL），ポララミン（開始日: Day 1，投与期間: 15 days，投与経路: INTRAVENOUS），メイロン84（開始日: Day 1，投与期間: 15 days，投与経路: INTRAVENOUS）であった。
合併症に対する併用療法はノルバスク OD（開始日：Before Start of Treatment，投与期間：–，投与経路：ORAL），グリメピリド（開始日：Before Start of Treatment，終了日：–，投与経路：ORAL），ノボラピッド（開始日: Day 1，投与期間: 16 days，投与経路: OTHER），ノボリン R（開始日: Day 16，投与期間: 7 days，投与経路: OTHER），アマリール（開始日: Day 26，終了日: After End of Treatment，投与経路: ORAL），ノボラピッド（開始日: Day 26，終了日: After End of Treatment，投与経路: OTHER）なかった。
脳梗塞（報告事象名：脳梗塞）は Day 16に発現が報告された。重篤度は重篤，重症度は Grade 2，オビヌツズマブとの因果関係は「あり」，シクロホスファミドとの因果関係は「なし」，ビンクリスチンとの因果関係は「なし」，ドキソルビシンとの因果関係は

「なし」，プレドニゾロンとの因果関係は「なし」と判断された。本事象発現前の治験薬最終投与日は Day 15であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は休薬された。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 118であった。
注入に伴う反応（報告事象名：インフュージョンリアクション）は Day 16に発現が報告された。重篤度は重篤，重症度は Grade 2，オビヌツズマブとの因果関係は「あり」，シクロホスファミドとの因果関係は「なし」，ビンクリスチンとの因果関係は「なし」，ドキソルビシンとの因果関係は「なし」，プレドニゾロンとの因果関係は「なし」と判断された。本事象発現前の治験薬最終投与日は Day 15であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は休薬された。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 118であった。
誤嚥性肺炎（報告事象名：誤嚥性肺炎）は Day 16に発現が報告された。重篤度は重篤，重症度は Grade 3，オビヌツズマブとの因果関係は「なし」，シクロホスファミドとの因果関係は「なし」，ビンクリスチンとの因果関係は「なし」，ドキソルビシンとの因果関係は「なし」，プレドニゾロンとの因果関係は「なし」と判断された。本事象発現前の治験薬最終投与日は Day 15であった。オビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与は中止された。本事象に対して治療を要した。転帰（確認日）は「回復」，回復日は Day 40であった。

事象（脳梗塞，注入に伴う反応）の詳細な経過を以下に示す。
*Day 1 ，悪性リンパ腫に対する化学療法（治験薬 GA101・CHOP 療法）のため入院し、1サイクル目の投与を開始した。
*Day 8 ，1サイクル目 Day 8 治験薬 GA101投与。
*Day 15 ，1サイクル目 Day 15 治験薬 GA101投与。
*Day 16 ，11時 20分に左前頭部頭痛，嘔気気，ふらつき，構音障害，顔面神経麻痺が出現，意識は清明。頭部 CT･ MRI 施行し、左延髄外側梗塞と診断される。陳旧性脳梗塞の所見もみられた。脳梗塞に対しアルテプラーゼ静注療法（tPA）が施行された。
*Day 16 ，Wallenberg 症候群が認められ，嚥下障害あり。絶飲食にて経鼻的に投薬管理とした。同日より，ベッドサイドでの理学療法等のリハビリも開始した。
*Day 17 ，バイアスピリンの投薬を開始した。
*Day 18 ，経管栄養を開始した。
*Day 26 ，嚥下障害は幾分改善しているが，飲み込みにくさはあり，絶飲食は継続中である。室内歩行等のリハビリも進んでいるが，複視，右上下肢，体幹の失調，感覚障害（しびれ感等）は認めており，立位バランスの低下，歩行障害を認める。神経内科医師と相談の上，バイアスピリン投与中であり，脳梗塞の再発の可能性は低いと考え，有害事象が落ち着いていれば，治験薬の再投与は可能と判断した。
*Day 33 ，誤嚥性肺炎の炎症所見が改善せず，サイクル2 Day 1の投与開始の許容範囲内には投与開始できないと判断し，治験中止とした。嚥下障害は回復していないが，歩行状態は安定し，病院内は自力歩行が可能であることより，脳梗塞は軽快と判断する。
*Day 36 ，治験の早期中止時の検査がすべて完了したため，治験は終了した。
*Day 68 ，退院前評価：介護度判定「要介護3」，独歩は安定しているが，左へのふらつきは残存している。嚥下障害は回復せず，リハビリ病院へ転院のため，退院した。脳梗塞は軽快である。
*Day 90 ，R-CHOP4コース目投与のため来院。リハビリ病院にて，経管栄養継続中であるが，むせは軽減している。
*Day 98 ，リハビリ病院より，NG チューブ抜去して経過観察中と，FAX にて経過報告あり。
*Day 118 ，R-CHOP5コース目投与のため来院。2週間前から食事を経口摂取しているが，むせなく，血液データ上，炎症反応なく，リハビリ病院の退院も今月末で決定しており，脳梗塞は回復と判断した。

事象（嚥下性肺炎）の詳細な経過を以下に示す。
*Day 16 ，脳梗塞発症し，アクチバシン投与。水分摂取にて咳込みが見られ，誤嚥の恐れがあるため絶飲食とした。喀痰も多く，SpO2の低下もみられ酸素投与開始。体温 38.8℃ まで上昇し，カロナールを投与した。
*Day 17 ，その後39.2℃ まで体温の上昇がみられた。脳梗塞による嚥下障害のため喀

痰も多く，胸部 X-P にて浸潤影あり，誤嚥性肺炎と診断。抗生剤の点滴を開始した。
*Day 20 ，睡眠などで SpO2の低下と喀痰の貯留がみられ，適宜吸引も施行した。酸素3～10 L の投与を継続，発熱もあり抗生剤の投与も継続していることから，重篤と判断した。
*Day 27 ，誤嚥の恐れはあるため，絶飲食は継続しているが，喀痰の喀出を自身でしっかりおこなえるようになり，吸引と酸素は不要となった。
*Day 30 ，抗生剤の投与を終了し，経過観察とした。
*Day 32 ，体温38.0°C あり。。
*Day 33 ，血液検査結果，炎症所見の再燃がみられ，抗生剤の投与を再開した。サイクル2Day 1の投与を，許容範囲内に再開できる見込みがなく，治験中止の判断をした。嚥下造影（VF）の結果，水分の誤嚥は回復しておらず，間接・直接訓練をすすめていくこととなった。絶飲食は継続。
*Day 36 ，治験の早期中止時検査はすべて終了した。発熱はないが，抗生剤点滴は継続しており，誤嚥性肺炎は未回復である。
*Day 40 ，CRP 改善，胸部 X-P も改善が認められ，誤嚥性肺炎は回復した。抗生剤は再発予防として投与を継続している。

「脳梗塞」，「注入に伴う反応」に対する担当医のコメント
合併症に糖尿病，高血圧，陳旧性脳梗塞があり，動脈硬化が脳梗塞発症の要因として考えられ，治験薬との関連性は低いと考えるが，前日に投与しており否定はできないと考える。脳梗塞の病態意義から重要な医学的事象と判断し，重篤な有害事象と判断した。

「誤嚥性肺炎」に対する担当医のコメント
脳梗塞による嚥下障害によって発症しており，治験薬との因果関係はないと考える。発熱が*Day 16から見られているため，再考の結果，発現日を*Day 17から*Day 16に変更した。

同患者で発現した重篤及び投与中止のいずれにも該当しない有害事象（発現日）は便秘（Day 5），皮膚発赤（Day 15），脱毛（Day 30）であった。
本患者はオビヌツズマブ，シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロンの投与を完了しなかった。オビヌツズマブの最終投与日は *Day 15 ，シクロホスファミド，ドキソルビシン，ビンクリスチンの最終投与日は *Day 2 ，プレドニゾロンの最終投与日は *Day 5 ，中止理由は有害事象（誤嚥性肺炎）であった。