目次

略号一覧表 4
2.7.4 臨床的安全性 5
2.7.4.1 医薬品への曝露 5
2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述 5
2.7.4.1.2 全般的な曝露状況 11
2.7.4.2 有害事象 22
2.7.4.2.1 有害事象の解析 22
2.7.4.2.2 個別有害事象の文章による説明 51
2.7.4.3 臨床検査値の評価 52
2.7.4.4 バイタルサイン、身体的所見及び安全性に関連する他の観察項目 52
2.7.4.5 特別な患者集団及び状況下における安全性 54
2.7.4.5.1 内因性要因 54
2.7.4.5.2 外因性要因 56
2.7.4.5.3 薬物相互作用 56
2.7.4.5.4 妊娠及び授乳時の使用 56
2.7.4.5.5 過量投与 57
2.7.4.5.6 薬物乱用 57
2.7.4.5.7 離脱症状及び反跳現象 57
2.7.4.5.8 自動車運転及び機械操作に対する影響又は精神機能の障害 57
2.7.4.6 市販後データ 57
2.7.4.7 参考文献 57
2.7.4.8 付録 58

表

表 2.7.4.1-1　安全性評価に用いた臨床試験の一覧 5
表 2.7.4.1-2　治験薬の投与変更の定義 8
表 2.7.4.1-3　主な重要な有害事象の定義 9
表 2.7.4.1-4　治験薬の曝露（C25001 試験、安全性解析対象集団） 12
表 2.7.4.1-5　治験薬の投与変更（C25001 試験、安全性解析対象集団） 13
表 2.7.4.1-6　治験薬への曝露（SGN-35-OU 試験、安全性解析対象集団） 14
表 2.7.4.1-7　投与変更（SGN-35-OU 試験、安全性解析対象集団） 15
表 2.7.4.1-8　人口統計学的特性及びその他のベースライン時の特性 （C25001 試験、ITT 解析対象集団） 15
表 2.7.4.1-9　ベースライン時の疾患特性及び病期分類（C25001 試験、ITT 解析対象集団） 17

表 2.7.4.1-10　人口統計学的及び他の基準値の特性（SGN-35-OU 試験、安全性解析対象集団） 20
表 2.7.4.2-1　有害事象の概要（C25001 試験、安全性解析対象集団、最終解析時点） 22
表 2.7.4.2-2　治験薬の曝露あたりの有害事象の発現頻度　（C25001 試験、安全性解析対象集団、最終解析時点） 23
表 2.7.4.2-3　有害事象の概要（SGN-35-OU 試験、安全性解析対象集団） 24
表 2.7.4.2-4　10%以上の被験者に発現した有害事象　（C25001 試験、安全性解析対象集団、最終解析時点） 25
表 2.7.4.2-5　2 例以上の被験者に発現した因果関係が否定できない有害事象　（C25001 試験、安全性解析対象集団、最終解析時点） 25
表 2.7.4.2-6　2 例以上の被験者に発現した Grade 3 以上の有害事象　（C25001 試験、安全性解析対象集団、最終解析時点） 27
表 2.7.4.2-7　2 例以上の被験者に発現した有害事象　（SGN-35-OU 試験、安全性解析対象集団） 28
表 2.7.4.2-8　2 例以上の被験者に発現した因果関係が否定できない有害事象（SGN-35-OU 試験、安全性解析対象集団） 29
表 2.7.4.2-9　Grade 3 以上の有害事象（SGN-35-OU 試験、安全性解析対象集団） 30
表 2.7.4.2-10　治験薬の最終投与後 30 日以内の死亡の一覧（C25001 試験） 31
表 2.7.4.2-11　重篤な有害事象（C25001 試験、安全性解析対象集団、最終解析時点） 33
表 2.7.4.2-12　重篤な有害事象（SGN-35-OU 試験、安全性解析対象集団） 34
表 2.7.4.2-13　治験薬の投与中止に至った有害事象　（C25001 試験、安全性解析対象集団、最終解析時点） 35
表 2.7.4.2-14　治験薬の投与中止に至った有害事象（SGN-35-OU 試験、安全性解析対象集団） 36
表 2.7.4.2-15　重症度別の末梢性ニューロパチー（SMQ）　（C25001 試験、安全性解析対象集団、最終解析時点） 37
表 2.7.4.2-16　末梢性ニューロパチー（SMQ）の発現までの期間　（C25001 試験、安全性解析対象集団、最終解析時点） 39
表 2.7.4.2-17　末梢性ニューロパチー（SMQ）に伴う投与中止及び投与変更　（C25001 試験、安全性解析対象集団、最終解析時点） 40
表 2.7.4.2-18　末梢性ニューロパチー（SMQ）の転帰　（C25001 試験、安全性解析対象集団、最終解析時点） 42
表 2.7.4.2-19　末梢性ニューロパチー（SMQ）の回復又は改善までの期間　（C25001 試験、安全性解析対象集団の本剤群、最終解析時点） 43
表 2.7.4.2-20　末梢性ニューロパチー（SMQ）（SGN-35-OU 試験、安全性解析対象集団） 45
表 2.7.4.2-21　用量変更を要した好中球減少症関連事象の発現頻度　（C25001 試験、安全性解析対象集団、最終解析時点） 46
表 2.7.4.2-22　血液毒性（SGN-35-OU 試験、安全性解析対象集団） 47

表 2.7.4.2-23　Grade 3 又は 4 の好中球減少症関連事象を有する被験者に発現した 感染症および寄生虫症（SOC）の有害事象 （C25001 試験、安全性解析対象集団、最終解析時点） 48
表 2.7.4.2-24　感染症および寄生虫症（SOC）（SGN-35-OU 試験、安全性解析対象集団） 49
表 2.7.4.2-25　注入に伴う反応の概要 （C25001 試験、安全性解析対象集団、最終解析時点） 50
表 2.7.4.4-1　ADA 発現状況別の注入に伴う反応の概要 （C25001 試験、免疫原性評価可能集団(e)、最終解析時点） 53
表 2.7.4.5-1　年齢別の有害事象の概要（C25001 試験、安全性解析対象集団、最終解析時点） 55

略号一覧表

略号	略していない表現又は説明	
ADA	antidrug antibody	抗薬物抗体
ALT	alanine aminotransferase	アラニンアミノトランスフェラーゼ
AST	aspartate aminotransferase	アスパラビン酸アミノトランスフェラーゼ
CR	complete response	完全奏効
CTCL	cutaneous T-cell lymphoma	皮膚 T 細胞リンパ腫
ECOG	Eastern Cooperative Oncology Group	―
EOT	end of treatment	投与終了（時）
HDACI	histone deacetylase inhibitor	ヒストン脱アセチル化酵素阻害剤
HLT	high level term	高位語
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	医薬品規制調和国際会議
ITT	intent-to-treat	―
MedDRA	Medical Dictionary for Regulatory Activities	ICH 国際医薬用語集
MF	mycosis fungoides	菌状息肉症
Nab	neutralizing antibody (neutralizing antitherapeutic antibodies against brentuximab vedotin)	中和抗体（ブレンツキシマブ　ベドチンに対する中和活性を有する ADA）
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events	米国国立がん研究所の有害事象共通用語規準
PBRER	periodic benefit-risk evaluation report	定期的ベネフィットリスク評価報告
pcALCL	primary cutaneous anaplastic large cell lymphoma	原発性皮膚未分化大細胞リンパ腫
PD	progressive disease	進行
PML	progressive multifocal leukoencephalopathy	進行性多巣性白質脳症
PR	partial response	部分奏効
PT	preferred term	基本語
SAF	safety data set	（SGN-35-OU 試験の安全性解析対象集団）
SD	stable disease	安定
SDT	skin-directed therapies	皮膚局所療法
SMQ	standardized MedDRA query	MedDRA 標準検索式
SOC	system organ class	器官別大分類
SS	Sézary syndrome	セザリー症候群
TEAE	treatment-emergent adverse event	試験治療下で発現した有害事象
ULN	upper limit of the normal range	（施設）基準値上限

2.7.4 臨床的安全性

2.7.4.1 医薬品への曝露

2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述

本臨床的安全性では、CD30 を発現する皮膚 T 細胞リンパ腫（CTCL）に対するブレンツキシマブ　ベドチン（以下、本剤）の安全性を、海外第 3 相国際共同治験（以下、C25001 試験）及び国内第 2 相医師主導治験（以下、SGN-35-OU 試験）の 2 試験の結果に基づき評価した。

CD30 を発現する CTCL に対する本剤の安全性評価に用いた臨床試験の一覧を表 2.7.4.1-1 に示した。

表 2.7.4.1-1　安全性評価に用いた臨床試験の一覧

試験番号 （開発相） 実施地域	対象疾患／試験デザイン 本剤の用法・用量／ 本剤の投与期間(a)	安全性評価項目	登録例数 試験期間 実施状況	添付資料 番号 資料区分
C25001 （第 3 相） 海外	CD30 陽性 CTCL 患者（MF 又は pcALCL）(b)／ 本剤の有効性、安全性及び QOL の評価を目的とする 2 群ランダム化非盲検試験（本剤 vs メトトレキサート又はベキサロテン）／ 本剤 1.8 mg/kg 3 週に 1 回静脈内投与／ 16 サイクル	・NCI CTCAE（第 4.03 版）に基づく有害事象及び重篤な有害事象並びに臨床検査値の評価 ・バイタルサイン ・ECOG performance status	ブレンツキシマブ ベドチン群：66 例 治験責任医師が選択した化学療法群：65 例 メトトレキサート：27 例 ベキサロテン：38 例 2012 年 6 月～2018 年 7 月（最後の被験者の最終来院／交信日） 試験終了	5.3.5.1-1 評価
SGN-35-OU （第 2 相） 国内、医師主導	再発又は難治性の CD30 陽性の CTCL 患者(c)／ 本剤の有効性及び安全性の評価を目的とする単群非盲検試験／ 本剤 1.8 mg/kg 3 週に 1 回静脈内投与／ 16 サイクル	・有害事象 ・臨床検査 ・バイタルサイン、体重 ・ECOG performance status ・免疫再構築評価	16 例 コホート 1：13 例 コホート 2：3 例 2019 年 2 月～2021 年 12 月（最後の被験者の追跡終了日） 試験終了	5.3.5.2-1 評価

CTCL：皮膚 T 細胞リンパ腫、ECOG：Eastern Cooperative Oncology Group、IRF：中央判定委員会、MF：菌状息肉症、NCI CTCAE：米国国立がん研究所の有害事象共通用語規準、pcALCL：原発性皮膚未分化大細胞リンパ腫、QOL：quality of life
(a) 最長の投与期間を投与サイクル数として示した。
(b) 過去に 1 回以上の全身療法を受けた MF、若しくは過去に放射線療法又は 1 回以上の全身療法を受けた pcALCL。
(c) コホート 1：CD30 陽性の MF 又は pcALCL、コホート 2：コホート 1 以外の CD30 陽性リンパ増殖性疾患

2.7.4.1.1.1 C25001 試験

C25001 試験は、組織学的に CD30 陽性の菌状息肉症（MF）又は原発性皮膚未分化大細胞リンパ腫（pcALCL）が確認された患者を対象とした非盲検、ランダム化、多施設共同試験である。被験者を診断疾患（MF 又は pcALCL）で層別化し、本剤群又は治験責任医師が選択した化学療法群（治験責任医師の選択によりメトトレキサート又はベキサロテンいずれかの投与を受ける）にランダムに 1 対 1 で割り付けた。

本剤群では、本剤 1.8 mg/kg を各サイクル（1 サイクルを 21 日とする）の Day 1 に約 30 分かけて最大 16 サイクル静脈内投与した。治験責任医師が選択した化学療法群では、メトトレキサート 5～50 mg を週 1 回又はベキサロテン 300 mg/m^2 を 1 日 1 回、最大 48 週間経口投与した。治験責任医師が選択した化学療法群に割り付けられた被験者が受ける治療レジメンは、治験責任医師が前治療を考慮して選択することとした。メトトレキサートによる治療歴のある被験者にはベキサロテンを、ベキサロテンによる治療歴のある被験者にはメトトレキサートを選択することが推奨された。

ランダム化された被験者は、投与終了時（EOT）来院後少なくとも 24 ヵ月間は 12 週ごと、その後は試験中止、死亡又は試験の終了まで 6 ヵ月ごとに生存調査を実施することとした。

なお、C25001 試験では、最終被験者登録の 10 ヵ月後に治験総括報告書のための最終解析を実施し（データカットオフ日：2016 年 5 月 31 日）、試験終了時（全ての被験者が約 24 ヵ月の追跡調査を完了後）に有効性データの更新を行った（データカットオフ日：2018 年 9 月 28 日）。

本文書では、特に断りのない限り、最終解析時点の安全性データについて言及する。

最終解析時点で、本剤群で 3 例（5%）が治験薬の投与を継続していた。治験責任医師が選択した化学療法群は全例が投与を完了又は中止していた。

2.7.4.1.1.2 SGN-35-OU 試験

SGN-35-OU 試験は、CD30 陽性 MF 又は pcALCL を有する被験者群（コホート 1）、並びに、CD30 陽性 MF 及び pcALCL（コホート 1）以外の CD30 陽性リンパ増殖性疾患を有する被験者群（コホート 2）を対象として、本剤の有効性及び安全性を検討する単群、非盲検、多施設共同、医師主導治験である。

SGN-35-OU 試験は、スクリーニング期、治療期及び後観察期からなる。

スクリーニング期には、全ての被験者の皮膚検体の CD30 を実施医療機関で測定し、CD30 陽性と判定された被験者を本治験に登録した。コホート 1 には pcALCL 被験者 3 例を含む計 12 例、コホート 2 には 3 例以上（最大 5 例）を登録する計画とした〔計 15 例以上（最大 17 例）〕。

被験者に対し、本剤 1.8 mg/kg を各サイクル（1 サイクルを 21 日とする）の Day 1 に約 30 分かけて最大 16 サイクル静脈内投与した。

EOT 時に進行（PD）が認められない被験者は、後観察を実施した。また、全ての被験者は EOT 来院後の最長 12 ヵ月間は 12 週ごとに、その後は治験からの脱落、死亡又は治験終了まで、6 ヵ月ごとに生存を確認することとした。

2.7.4.1.1.3 CTCL 患者における本剤の安全性評価

C25001 試験及び SGN-35-OU 試験では、試験対象集団における本剤の安全性プロファイルを、有害事象、臨床検査値、及びその他の安全性関連観察項目〔バイタルサイン、Eastern Cooperative Oncology Group（ECOG）performance status、心電図及び免疫再構築評価など〕により評価した。

（1）対象被験者

C25001 試験では、CTCL のうち CD30 陽性の MF 患者及び pcALCL 患者を対象とした。

SGN-35-OU 試験では、コホート 1 は CD30 陽性の MF 患者及び pcALCL 患者を、コホート 2 は MF 及び pcALCL 以外の CD30 陽性リンパ増殖性疾患を有する患者を対象とした。

両試験の選択／除外基準は、試験デザイン及び評価項目に関連する一部の基準を除いて同様であり、MF 患者は過去に 1 回以上の全身療法を、pcALCL 患者は過去に 1 回以上の全身療法又は放射線療法を受けていること、ECOG performance status が 2 以下であり、十分な血液（SGN-35-OU 試験のみ）、腎臓及び肝機能を有している患者を適格とした。一方、sALCL、セザリー症候群（SS）又は B2 疾患を合併している患者は除外した。また、本剤の既知のリスクから、膵炎の既往や膵炎のリスクファクターのある患者、スクリーニング時にリパーゼ値が基準値上限（ULN）の 3 倍以上かつアミラーゼ値が ULN を超える患者、進行性多巣性白質脳症（PML）の既往を含む既知の脳／髄膜疾患がある患者、治験薬の初回投与前 1 週間以内に重度の活動性感染がある患者も除外した。

対象及び組入れ基準の概要を 2.7.6.1（C25001 試験）及び 2.7.6.2（SGN-35-OU 試験）に、全ての選択／除外基準を各試験の治験総括報告書に記載した（C25001 試験　治験総括報告書 9.3、SGN-35-OU 試験　治験総括報告書　9.3）。

（2）試験治療

C25001 試験の本剤群及び SGN-35-OU 試験では、本剤 1.8 mg/kg を各サイクル（1 サイクルを 21 日とする）の Day 1 に約 30 分かけて最大 16 サイクル静脈内投与した。投与量はスクリーニング時の被験者の体重に基づいて算出し、スクリーニング時から 10%以上の体重変化があった場合は投与量を再計算して調整することとした。体重が 100 kg を超える被験者については 100 kg として投与量を計算した。

C25001 試験の治験責任医師が選択した化学療法群では、メトトレキサート 5～50 mg を週 1 回又はベキサロテン 300 mg/m^2 を 1 日 1 回、最大 48 週間経口投与した。

CTCL の初期の全身療法では、一般に免疫抑制作用が軽度で、蓄積毒性プロファイルが最小限である薬剤が選択される[1]。メトトレキサートは骨髄、肝臓、肺及び腎臓などの重篤な毒性反応が生じる可能性がある[2][3]。また、ベキサロテンはヒトの先天異常と関連するレチノイドであり、主に脂質異常、膵炎、肝機能検査値異常、甲状腺機能検査値異常、白血球減少症や白内障を引き起こす可能性がある[4][5]。

メトトレキサートの用量は至適な臨床反応を達成するよう段階的に調整されるが、50 mg/週を超えないこととした。また、その後は治験責任医師の評価に基づき最低の有効用量まで下げることができた。

ベキサロテンの用量は、毒性が発現した場合は 200 mg/m^2 若しくは 100 mg/m^2 に減量又は一次的に投与を中断（休薬）することができた。毒性が管理可能であれば、投与を再開又は増量することもできた。また、ベキサロテンが投与される被験者では、脂質異常症（高トリグリセリド血症）の予防としてフェノフィブラートを 7 日間（サイクル 1 の 1～7 日目）前投与した。

各治療サイクルの投与開始前、治験責任医師は事前に規定した安全性基準に従って被験者を評価し、必要に応じて表 2.7.4.1-2 に示す投与変更を行った（C25001 試験　治験総括報告書 9.4.5 及び SGN-35-OU 試験　治験実施計画書　10.6）。この安全性基準を満たしていない場合、サイクルの開始を最長 3 週間延期できることとした。治験依頼者の承認なく 3 週間を超えてサイクル開始を延期することは禁止した。本剤の増量は禁止されており、減量後の再増量は認められなかった。一方、C25001 試験では、メトトレキサート又はベキサロテンは添付文書に記載されているガイダンスに従い、治療担当医師の判断で増量を可能とした。

表 2.7.4.1-2　治験薬の投与変更の定義

投与変更	定義
休薬（dose held）	治験責任医師の判断により、予定された治験薬の投与が行われなかった場合。 予定された治験薬は全く投与されていない。
減量（dose reduced）	投与量を減量して投与を継続した場合。
増量（dose increased）	投与量を増量して投与を継続した場合。 本剤では増量は認められていなかった（該当しない）。
投与漏れ（dose missed）	治験責任医師の介入以外の理由により、予定された治験薬の投与が行われなった場合。
投与延期（dose delayed）	予定された治験薬の投与は行われたが、治験実施計画書で規定された投与日／サイクルではなかった場合。 ベキサロテンでは該当しない。
点滴中断（dose interruption）	治験薬の点滴投与を一時的に中断した場合。 メトトレキサート及びベキサロテンは経口投与のため該当しない。

（3）安全性の評価

C25001 試験では、その他の副次評価項目として、米国国立がん研究所の有害事象共通用語規準（NCI CTCAE）（第 4.03 版）に基づく有害事象及び重篤な有害事象並びに臨床検査値の評価を設定した。試験治療下で発現した有害事象（TEAE）の発現頻度、TEAE の重症度及び種類、並びにバイタルサイン、ECOG performance status 及び臨床検査値のベースラインからの変化によって治験薬の安全性及び忍容性を評価した。また、治験薬への曝露及び中止理由を集計した。

C25001 試験では、独立データモニタリング委員会を設置し、事前に規定されたチャーターに基づき安全性データを精査することとした。

SGN-35-OU 試験の安全性の評価項目は、有害事象、臨床検査〔血液学的検査、生化学的検査、膵機能検査（ヘモグロビン A1c）、尿検査、バイタルサイン（収縮期血圧／拡張期血圧、脈拍数、体温）〕、体重及び ECOG performance status であった。

安全性解析の詳細は、各試験の統計解析計画書に記載している（C25001 試験　治験総括報告書　16.1.9 及び SGN-35-OU 試験　治験総括報告書　16.1.9）。

（4）有害事象

C25001 試験及び SGN-35-OU 試験では、TEAE の発現頻度、重症度及び種類について評価した。TEAE は、試験治療の初回投与から試験治療の最終投与後 30 日までに発現した事象と定義した。末梢性ニューロパチー関連事象は、重症度にかかわらずベースライン値に回復するまで追跡することとした。

なお、本概要では特に断りのない限り TEAE を「有害事象」と表記する。

有害事象は、医薬品規制調和国際会議（ICH）国際医薬用語集（MedDRA）を用いて読み替え、器官別大分類（SOC）及び基本語（PT）で分類し、有害事象（全ての有害事象及び治験薬との因果関係が否定できない有害事象）、Grade 3 以上の有害事象（全ての有害事象及び治験薬との因果関係が否定できない有害事象）、重篤な有害事象及び治験薬の投与中止に至った有害事象等を集計した。MedDRA は、C25001 試験の最終解析時は第 19.0 版、試験終了時は第 21.0 を、SGN-35-OU 試験では第 24.1 版を使用した。

因果関係

有害事象と試験治療との因果関係を「関連なし」又は「関連あり」の 2 分類で判定し、治験責任（分担）医師により「関連あり」と判定された場合、「試験治療との因果関係が否定できない有害事象」（SGN-35-OU 試験では「副作用」と表示）として評価した。

重症度

有害事象の重症度を NCI CTCAE を用いて Grade 1～5 の 5 段階で評価した。C25001 試験では第 4.03 版（2010 年 6 月 14 日発効）、SGN-35-OU 試験では第 5.0 版（2017 年 11 月 27 日発効）を使用した。

重要な有害事象

重要な有害事象の定義（評価に含める有害事象）を表 2.7.4.1-3 に示した。

C25001 試験では、特に末梢性ニューロパチー関連事象、血液毒性（好中球減少症関連事象）及び注入に伴う反応に焦点を当てて評価した。また、感染についても血液毒性との関係を精査した。これまでに本剤投与後の少数例で報告されているその他の重要な有害事象についても、発現状況を確認した。

SGN-35-OU 試験では、末梢性ニューロパチー、血液毒性、感染、注入に伴う反応、PML、スティーブン・ジョンソン症候群、中毒性表皮壊死融解症、腫瘍崩壊症候群、急性膵炎、肺毒性、肝毒性、高血糖及び消化管障害を重要な有害事象として検討した。SGN-35-OU 試験では、治験責任医師の報告に基づく注入に伴う反応の事象の収集を行わなかった。

表 2.7.4.1-3　主な重要な有害事象の定義

重要な有害事象	定義
末梢性ニューロパチー関連事象	MedDRA SMQ「末梢性ニューロパチー」（広域）に含まれる PT。
血液毒性（好中球減少症関連事象）	（C25001 試験）MedDRA PT「好中球減少症」又は「好中球数減少」。有害事象として報告されていない臨床検査値異常は含めなかった。
血液毒性	（SGN-35-OU 試験）MedDRA SMQ「造血障害による血球減少症」（広域）に含まれる PT。
注入に伴う反応	（C25001 試験）治験責任医師が本剤の点滴投与に関連する事象と判断した場合に、注入に伴う反応として有害事象を報告することとした。

MedDRA：ICH 国際医薬用語集、PT：基本語、SMQ：MedDRA 標準検索式

（5）臨床検査値

C25001 試験及び SGN-35-OU 試験では、臨床検査値〔血液学的検査、生化学的検査及びヘモグロビン A1c〕はスクリーニング時、各サイクル 1 日目の投薬前及び EOT／早期中止時に測定した。尿検査はスクリーニング時のみ評価した。C25001 試験では、それに加えて甲状腺機能検査、脂質プロファイルも評価した。該当する場合は、臨床検査結果も NCI CTCAE（第 4.03 版）に従って重症度を判定した。いずれの試験も、臨床検査値異常は、ベースラインからの変化が臨床的に有意であると判断された場合、並びに試験治療の中止、投与変更又はその他の治療介入を要した場合に、有害事象として報告された。

臨床検査値は、実測値及びベースラインからの変化量の記述統計量を経時的に示した。

（6）バイタルサイン、身体所見、心電図及び ECOG performance status

C25001 試験及び SGN-35-OU 試験では、バイタルサイン（収縮期血圧／拡張期血圧，脈拍数，体温）、体重及び EGOC performance status をスクリーニング時、各サイクル 1 日目の投薬前及び EOT／早期中止時に測定した。心電図はスクリーニング時及びサイクル 1 の治験薬投与前のみ測定した。さらに、免疫能再構築評価のため治験実施計画書に規定されたスケジュールでリンパ球数、T 細胞／B 細胞サブセット及び NK 細胞（C25001 試験のみ）を測定した。

バイタルサインは、実測値及びベースラインからの変化量の記述統計量を経時的に示した。ECOG performance status 及びそのベースラインからの変化量を要約し、投与群別に集計した。治験責任医師による心電図モニタリングの評価（正常、臨床的に意味のある異常又は臨床的に意味のない異常）は、規定外又は再検査された測定値を含めて一覧表に提示した。

（7）免疫原性

C25001 試験では、本剤投与前又は投与後の血清中抗薬物抗体（ADA）を評価し、ADA 陽性の患者について抗体価を評価した。ベースラインにおける ADA 及び中和抗体（Nab）は本剤投与前検体を用いて評価した。本剤投与後の 1 又は 2 時点で ADA 陽性の場合を一時的陽性、3 時点以上で陽性の場合を持続的陽性と評価した。ADA 陽性の検体について Nab を評価した。

SGN-35-OU 試験では、免疫原性の検討は行わなかった。

（8）解析対象集団

C25001 試験及び SGN-35-OU 試験では、試験治療の投与を 1 回以上受けた全ての被験者を安全性解析対象集団として定義し、治験薬投与時の安全性を評価した。

SGN-35-OU 試験では、コホート 1 の安全性解析対象集団を SAF1、コホート 1＋2 の安全性解析対象集団を SAF2 と表示する。本臨床的安全性では、特に断りのない限り SAF2 のデータについて言及する。

2.7.4.1.2 全般的な曝露状況

2.7.4.1.2.1 被験者の内訳及び曝露状況

（1）C25001 試験

被験者の内訳

被験者 131 例が登録され、本剤群に 66 例、治験責任医師が選択した化学療法群に 65 例がランダムに割り付けられた。診断疾患の内訳は、MF が 100 例、pcALCL が 31 例であった。

本剤群の 23 例（35%）及び治験責任医師が選択した化学療法群の 5 例（8%）が、治験実施計画書で規定された最大投与（16 サイクル／48 週間）を完遂した。治験薬投与を中止した理由の内訳は、疾患進行〔本剤群 13 例（20%）及び治験責任医師が選択した化学療法群 40 例（62%）、以降同順〕、有害事象〔17 例（26%）及び 5 例（8%）〕、同意撤回〔6 例（9%）及び 9 例（14%）〕、効果不十分〔2 例（3%）及び 4 例（6%）〕、治験実施計画書逸脱及びその他〔それぞれ 1 例（2%）及び 1 例（2%）〕であった（C25001 試験　治験総括報告書 Table 14.1.1.1）。

治験薬への曝露

ランダム化された 131 例のうち、128 例が 1 回以上治験薬の投与を受け、治験責任医師が選択した化学療法群にランダム化された被験者 3 例が治験薬の投与を受けなかった。安全性解析対象集団は 128 例であり、その内訳は本剤群 66 例、治験責任医師が選択した化学療法群 62 例（ベキサロテン 37 例及びメトトレキサート 25 例）であった。

治験薬の曝露の概要を表 2.7.4.1-4 に示した。

安全性解析対象集団における本剤群の被験者ごとの投与期間の中央値は 268.5 日（範囲：21～420 日）であり、サイクル数の中央値は 12 サイクル（範囲：1～16 サイクル）であった。治験責任医師が選択した化学療法群のうちベキサロテン投与被験者の投与期間の中央値は 114 日（範囲：7～378 日）であり、5.5 サイクル（範囲：1～16 サイクル）に相当した。また、メトトレキサート投与被験者の投与期間の中央値は 77 日（範囲：7～336 日）であり、3 サイクル（範囲：1～16 サイクル）に相当した（C25001 試験　治験総括報告書　Table 14.1.1.5）。

相対用量強度（予定用量に対する実際に投与されたの割合）の中央値は、本剤群で 99.63%（範囲：68.1%～106.4%）、治験責任医師が選択した化学療法群のうちベキサロテン投与被験者で 94.26%（範囲：27.1%～152.1%）であった（C25001 試験　治験総括報告書 Table 14.1.1.5）。メトトレキサート投与被験者では、治験実施計画書でメトトレキサートの用量変更が認められており週当たりの予定総用量を特定できなかったため、用量強度を算出しなかった（C25001 試験　治験総括報告書　9.4.1.2）。

表 2.7.4.1-4　治験薬の曝露（C25001 試験、安全性解析対象集団）

		Bexarotene (f) N=37		
	Brentuximab Vedotin N=66	Pre-treatment of Fenofibrate N=36	Bexarotene N=36	Methotrexate N=25
Duration of Treatment (days) (a)				
n	66	36	36	25
Mean (std dev)	229.1 (123.39)	6.7 (1.11)	140.0 (111.64)	98.6 (90.24)
Median	268.5	7.0	114.0	77.0
Min, Max	21, 420	1, 7	7, 378	7, 336
Number of Treated Cycles (b)				
n	66	36	36	25
Mean (std dev)	10.3 (5.58)	1.0 (0.00)	6.8 (4.77)	4.8 (4.26)
Median	12.0	1.0	5.5	3.0
Min, Max	1, 16	1, 1	1, 16	1, 16
Total Amount of Dose Taken (c) (mg)				
n	66	36	36	25
Mean (std dev)	1301.33 (738.410)	1099.94 (334.962)	53895.83 (47646.430)	360.36 (361.443)
Median	1351.50	1015.00	33787.50	275.00
Min, Max	100.0, 2880.0	145.0, 2100.0	2100.0, 191100.0	25.0, 1536.0
Total Number of Dose Taken				
n	66	36	36	25
Mean (std dev)	10.4 (5.55)	6.7 (1.11)	130.9 (106.88)	14.0 (12.95)
Median	12.0	7.0	97.0	11.0
Min, Max	1, 16	1, 7	7, 378	1, 48
Dose Intensity (mg/week) (d)				
n	66		36	25
Mean (std dev)	43.60 (9.688)		2695.30 (908.550)	23.44 (10.385)
Median	43.04		2857.82	21.67
Min, Max	20.9, 60.0		1050.0, 4200.0	5.8, 50.0
Relative Dose Intensity (%) (e)				
n	66		36	
Mean (std dev)	95.01 (8.853)		90.31 (29.085)	
Median	99.63		94.26	
Min, Max	68.1, 106.4		27.1, 152.1	

出典：C25001 試験　治験総括報告書　Table 14.1.1.5

BSA: body surface area; C: Cycle; D: Day; eCRF: electronic case report form; Max: maximum; Min: minimum

One subject received pre-treatment of fenofibrate but did not receive any dose of bexarotene.

One subject only received bexarotene but did not receive any dose of pre-treatment of fenofibrate.

(a) Duration of treatment is defined as (last dose date + 21 – first dose date) of brentuximab vedotin or (last dose date + 7 – first dose date) of methotrexate or (last dose date + 1 – first dose date) of bexarotene.

(b) A treated cycle is defined as a 21-day period, during which the patient received any amount of brentuximab vedotin (scheduled for single dose in 21-day), methotrexate (single weekly dose), or bexarotene (single oral daily dose).

(c) Total amount of dose taken for brentuximab vedotin arm is calculated as sum of (prepared dose amount in mg*volume/prepared volume) over each dosing eCRF record.

(d) Dose intensity is calculated as total amount of dose taken (mg)/(3*number of treated cycles). For bexarotene, divided by 3*number of treated cycles - 1.

(e) Relative dose intensity is defined as 100*(Total amount of dose taken (mg)/ Total dose expected (mg)):
- For brentuximab vedotin arm,
  - Total dose expected = sum of expected dose at each cycle over treated cycles, where expected dose = prescribed dose level at C1D1* actual weight used for the prescribed dose calculation derived as:
    - weight at current cycle if the box for question "Check if this weight was used in dose preparation calculation" on the vital sign eCRF is checked "Yes".
    - actual weight used for the prescribed dose calculation at previous cycle if the box is not checked. If the box is not checked at C1D1, use the weight at screening.
    - For patients weighing greater than 100kg, 100 kg should be used for the above calculation.
- For methotrexate arm, it is not calculated; per protocol there is a range of permitted doses, therefore there is no expected dose.
- For bexarotene arm, total dose expected = sum of expected dose each day from date of first dose to date of last dose, where expected dose each day = (prescribed dose level for the first dose (mg/m^2)*baseline BSA (m^2)) rounded to the nearest 75 mg.

(f) This column is separated into two columns representing pre-treatment of fenofibrate from C1D1 to C1D7 and treatment of bexarotene starting from C1D8 for the same set of patients randomized to the bexarotene arm.

治験薬の投与変更の概要を表 2.7.4.1-5 に示した。

投与延期（dose delayed）は本剤群で 40 例（61%）、治験責任医師が選択した化学療法群で 11 例（18%）に報告された。休薬（dose held）は本剤群で 1 例（2%）、治験責任医師が選択した化学療法群で 16 例（26%）に報告された。減量（dose reduced）は本剤群で 17 例（26%）、治験責任医師が選択した化学療法群で 21 例（34%）に報告された。本剤の点滴中断（dose interrupted）は 5 例（8%）に報告された。なお、メトトレキサート及びベキサロテンは、減量後に再増量した可能性もあり、「増量」は必ずしもベースラインを超えた用量が投与されていることを示すものではない。

表 2.7.4.1-5　治験薬の投与変更（C25001 試験、安全性解析対象集団）

		Bexarotene (a) N=37		
	Brentuximab Vedotin N=66	Pre-treatment of Fenofibrate N=36	Bexarotene N=36	Methotrexate N=25
All Cycles				
Action on Study Drug n (%)	48 (73)	2 (6)	31 (86)	13 (52)
Dose reduced	17 (26)	0	16 (44)	5 (20)
Dose increased (b)	0	0	13 (36)	7 (28)
Dose held (c)	1 (2)	0	12 (33)	4 (16)
Dose missed (d)	0	1 (3)	8 (22)	0
Dose interrupted	5 (8)	0	0	1 (4)(f)
Dose delayed (e)	40 (61)	0	7 (19)	4 (16)
Dose discontinued permanently	11 (17)	1 (3)	7 (19)	5 (20)

出典：C25001 試験　治験総括報告書　Table 14.1.1.6

Patient with multiple actions is counted only once.

One subject received pre-treatment of fenofibrate but did not receive any dose of bexarotene.

One subject only received bexarotene but did not receive any dose of pre-treatment of fenofibrate.

(a) This column is separated into two columns representing pre-treatment of fenofibrate from C1D1 to C1D7 and treatment of bexarotene starting from C1D8 for the same set of patients randomized to the bexarotene arm.

(b) Note for methotrexate or bexarotene, it is possible that the dose is reduced first and then increased. The action of dose increased does not necessarily mean the increased dose is higher than baseline dose.

(c) Dose Held: The planned or scheduled dose was not given as a result of an intentional physician intervention. No drug was administered.

(d) Dose Missed: The dose was not administered for reason(s) other than physician intervention.

(e) Dose Delayed: The scheduled dose was given but not within the timeframe specified by the protocol for that particular scheduled dosing day/cycle. Note: Not applicable for bexarotene daily dosing.

(f) メトトレキサートは経口投与のため点滴中断（dose interrupted）は該当しないが、1 例で Cycle 5 Day 1 に同日 2 回に分けて投与された。投与変更の理由は「その他（other）」であった。

（2）SGN-35-OU 試験

被験者の内訳

被験者 16 例（コホート 1：13 例、コホート 2：3 例）が登録された。登録された被験者の診断疾患の内訳は、コホート 1 では MF が 8 例、pcALCL が 5 例、コホート 2 ではリンパ腫様丘疹症が 2 例、原発性皮膚 γδT 細胞リンパ腫が 1 例であった（表 2.7.4.1-10）。

登録された被験者 16 例のうち、全例が治験薬の投与を受け、10 例が治験実施計画書で規定された最大投与（16 サイクル）を完遂した。治験薬投与を中止した理由の内訳は、有害事象が 3 例（コホート 1：2 例及びコホート 2：1 例。以降同順）、疾患進行が 2 例（1 例及び 1 例）、同意撤回が 1 例（1 例及び 0 例）であった。また、投与を完了した 10 例のうち 8 例が

後観察を完了した。後観察を中止した理由の内訳は、疾患進行が 1 例（1 例及び 0 例）、同意撤回が 1 例（1 例及び 0 例）であった（SGN-35-OU 試験　治験総括報告書　表 10.1-1 及び図 10.1-1）。

治験薬への曝露

登録された 16 例（コホート 1：13 例及びコホート 2：3 例）全例が 1 回以上治験薬の投与を受け、SAF1（コホート 1：13 例）及び SAF2（コホート 1 及びコホート 2：16 例）に組み入れられた。

治験薬への曝露を表 2.7.4.1-6 に示した。

SAF2 における被験者ごとの投与期間の中央値は 344.0 日（範囲：44～483 日）であり、サイクル数の中央値は 16 サイクル（範囲：2～16 サイクル）であった。相対用量強度（予定用量に対する実際に投与されたの割合）の中央値は 100.00%（範囲：75.0%～100.0%）であった。

表 2.7.4.1-6　治験薬への曝露（SGN-35-OU 試験、安全性解析対象集団）

解析対象例数	SAF1 N=13	SAF2 N=16
治療期間（日）		
平均値（標準偏差）	324.2 (93.16)	291.6 (124.84)
中央値	346.0	344.0
最小値, 最大値	127, 483	44, 483
治療サイクル数		
平均値（標準偏差）	14.2 (3.29)	12.8 (5.01)
中央値	16.0	16.0
最小値, 最大値	6, 16	2, 16
総投与量（mg）		
平均値（標準偏差）	1466.77 (455.306)	1329.63 (565.349)
中央値	1418.00	1411.00
最小値, 最大値	504.0, 2494.0	294.0, 2494.0
用量強度（mg/週）		
平均値（標準偏差）	34.84 (8.957)	36.12 (10.265)
中央値	30.33	31.33
最小値, 最大値	27.8, 52.0	27.8, 60.0
相対用量強度（%）		
平均値（標準偏差）	93.86 (9.445)	95.01 (8.803)
中央値	100.00	100.00
最小値, 最大値	75.0, 100.0	75.0, 100.0

出典：SGN-35-OU 試験　治験総括報告書　表 14.1-8
SAF: safety data set

治験薬の投与変更の概要を表 2.7.4.1-7 に示した。

SAF2 では、試験期間を通じて投与延期は 8 例（50%）、休薬は 7 例（44%）、減量は 5 例（31%）で報告された。投与（点滴）の中断は報告されなかった。

表 2.7.4.1-7　投与変更（SGN-35-OU 試験、安全性解析対象集団）

	SAF1	SAF2
全サイクル　n (%)		
投与延期	8 (62)	8 (50)
減量	5 (38)	5 (31)
休薬	7 (54)	7 (44)
中断(a)	0	0
投与中止(b)	0	0

出典：SGN-35-OU 試験　治験総括報告書　表 14.1-5 及び表 14.1-6
SAF: safety data set
(a) 治験薬の投与中に一時的に投与を中断した場合
(b) 治験薬の投与中に一時的に中断後、投与を中止した場合

2.7.4.1.2.2 治験対象集団の人口統計学的特性及びその他の特性

（1）C25001 試験

人口統計学的特性

Intent-to-treat（ITT）解析対象集団における人口統計学的特性を表 2.7.4.1-8 に示した。

被験者の人口統計学的特性は、投与群間で概ね均衡がとれていた。ITT 解析対象集団全体の年齢の中央値は 60.0 歳（範囲：22～83 歳）であり、本剤群（62.0 歳）では治験責任医師が選択した化学療法群（58.5 歳）よりもわずかに高かった。男性が多く（55%）、本剤群の 52%、治験責任医師が選択した化学療法群の 58%であった。被験者の多くは白人（85%）であった。この試験対象集団は、概して全身療法を必要とする CD30 陽性 CTCL 患者の集団を代表するものであった。

表 2.7.4.1-8　人口統計学的特性及びその他のベースライン時の特性
（C25001 試験、ITT 解析対象集団）

	Brentuximab Vedotin N=64	Physician's Choice		
		Total N=64	Methotrexate N=26	Bexarotene N=38
Age, years (a)				
Mean (SD)	59.5 (13.99)	56.6 (14.30)	55.8 (12.33)	57.1 (15.64)
Median	62.0	58.5	53.0	62.5
Min, max	22, 83	22, 83	32, 80	22, 83
Sex, n (%)				
Male	33 (52)	37 (58)	17 (65)	20 (53)
Female	31 (48)	27 (42)	9 (35)	18 (47)
Race n (%)				
White	56 (88)	53 (83)	20 (77)	33 (87)
Black or African American	3 (5)	3 (5)	2 (8)	1 (3)
Asian (b)	1 (2)	5 (8)	2 (8)	3 (8)
Not reported	3 (5)	1 (2)	1 (4)	0
Other	1 (2)	2 (3)	1 (4)	1 (3)

出典：C25001 試験　治験総括報告書　Table 14.1.1.2
ITT: intent-to-treat; Max: maximum; min: minimum; SD: standard deviation.
Percentages are based on non-missing values.
(a) Age on date of signed informed consent.
(b) Includes subgroups of Asian Indian, Chinese, Not Reported, and Other.

ベースライン時の疾患特性

ITT 解析対象集団におけるベースライン時の疾患特性を表 2.7.4.1-9 に示した。

ECOG performance status 及び試験登録時の骨髄病変の有無は、投与群間で類似していた。ITT 解析対象集団全体では、ほとんどの被験者の ECOG performance status は 0（70%）又は 1（27%）であり、ECOG performance status が 2 の被験者は 5 例（4%）であった。また、いずれの投与群でもほとんどの被験者（97%）で、試験登録時に骨髄病変の所見がなかった。

本剤群の被験者は、治験責任医師が選択した化学療法群の被験者よりも初回診断からの期間が長く、疾患が進行しており、疾病負荷（腫瘍量）が高く、内臓病変が多かった。初回診断からの期間の中央値は、本剤群で 42.17 ヵ月（範囲：2.6～763.9 ヵ月）、治験責任医師が選択した化学療法群で 36.99 ヵ月（範囲：3.1～273.2 ヵ月）であった。

MF 被験者で試験登録時の病期分類が IV B であった被験者は、本剤群及び治験責任医師が選択した化学療法群でそれぞれ 7 例（15%）及び 0 例であった。また、pcALCL 被験者で試験登録時の皮膚病変が T3 であった被験者はぞれぞれ 12 例（75%）及び 6 例（40%）、内臓病変を有している被験者はそれぞれ 4 例（25%）及び 1 例（7%）であった。

表 2.7.4.1-9　ベースライン時の疾患特性及び病期分類（C25001 試験、ITT 解析対象集団）

	ITT Population			
	Brentuximab Vedotin	Physician's Choice		
		Total	Methotrexate	Bexarotene
	N=64	N=64	N=26	N=38
ECOG performance status, n (%)				
0	43 (67)	46 (72)	19 (73)	27 (71)
1	18 (28)	16 (25)	6 (23)	10 (26)
2	3 (5)	2 (3)	1 (4)	1 (3)
Time since initial diagnosis, months (a)				
N	64	61	24	37
Mean (SD)	75.30 (118.704)	62.23 (65.080)	58.48 (44.999)	64.66 (75.828)
Median	42.17	36.99	48.28	30.69
Min, max	2.6, 763.9	3.1, 273.2	3.9, 141.9	3.1, 273.2
TNM stages at study entry for patients with pcALCL, n (%) (b)				
N	16	15	4	11
Skin				
T1	1 (6)	4 (27)	1 (25)	3 (27)
T2	3 (19)	5 (33)	0	5 (45)
T3	12 (75)	6 (40)	3 (75)	3 (27)
Node				
N0	10 (63)	11 (73)	3 (75)	8 (73)
N1	2 (13)	1 (7)	1 (25)	0
N2	2 (13)	1 (7)	0	1 (9)
N3	2 (13)	2 (13)	0	2 (18)
Visceral				
M0	12 (75)	14 (93)	4 (100)	10 (91)
M1	4 (25)	1 (7)	0	1 (9)
Overall staging at study entry for patients with MF, n (%)				
N	48	49	22	27
IA	4 (8)	1 (2)	1 (5)	0
IB	6 (13)	12 (24)	2 (9)	10 (37)
IIA	5 (10)	5 (10)	2 (9)	3 (11)
IIB	19 (40)	19 (39)	10 (45)	9 (33)
IIIA	4 (8)	2 (4)	1 (5)	1 (4)
IIIB	0	0	0	0
IVA_1	0	1 (2)	0	1 (4)
IVA_2	2 (4)	8 (16)	6 (27)	2 (7)
IVB	7 (15)	0	0	0
Unknown	1 (2)	1 (2)	0	1 (4)
Evidence of bone marrow involvement at study entry, n (%)				
Yes	2 (3)	2 (3)	1 (4)	1 (3)
No	62 (97)	62 (97)	25 (96)	37 (97)

出典：C25001 試験　治験総括報告書　Table 14.1.1.3

ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; max: maximum; MF: mycosis fungoides; min: minimum; pcALCL: primary cutaneous anaplastic large cell lymphoma; SD: standard deviation; TNM: Tumor-Node-Metastasis; TNMB: Tumor-Node-Metastasis-Blood.

Percentages are based on nonmissing values in the ITT population in each column. First dose date of study drug for patients randomized to bexarotene arm was first dose of fenofibrate.

(a) Time since initial diagnosis = (first dose date of study drug – date of initial diagnosis)/30.4375.

(b) TNMB staging components are presented for all patients in the ITT population (MF and pcALCL).

17

前治療

前治療数の中央値は本剤群で 4.0 回（範囲：0~13 回）、治験責任医師が選択した化学療法群で 3.5 回（範囲：1~15 回）であった（C25001 試験　治験総括報告書　Table 14.1.1.4）。前治療の数、種類及び前治療に対する奏効は、投与群間で概ね均衡がとれていた。ITT 解析対象集団全体で、1 回以上の前治療を受けた被験者 127 例全例（100%）が全身療法を、ほとんどの被験者（81%）が皮膚局所療法（SDT）を受けていた。全身療法を受けた回数の中央値は 2.0 回、SDT を受けた回数の中央値は 1.0 回であった（C25001 試験　治験総括報告書　Table 14.1.1.4）。全身療法の前治療を受けた回数は、本剤群で 0～11 回、治験責任医師が選択した化学療法群で 1～8 回と同程度であり、SDT を受けた回数は本剤群で 0～6 回、治験責任医師が選択した化学療法群で 0～9 回であった。

前治療として受けた主な SDT は、放射線療法（64%）及び光線療法（48%）であり、ステロイド外用薬を受けた被験者は 17%であった。

前治療として受けた主な全身療法は、化学療法（71%）、免疫療法（43%）及びベキサロテン（38%）であった。また、がんの手術歴は 9 例（本剤群 3 例、治験責任医師が選択した化学療法群 6 例）、骨髄移植又は幹細胞移植の治療歴は 4 例（本剤群 3 例、治験責任医師が選択した化学療法群 1 例）で報告された（C25001 試験　治験総括報告書　Table 14.1.1.4）。

治験責任医師が選択した化学療法群のうち、3 例（8%）は過去に CTCL に対してベキサロテンの投与を受けており PD は報告されていなかったため、治験責任医師によりベキサロテンに割り付けられた。また、2 例（8%）は過去にメトトレキサートの投与を受けており PD は報告されていなかったため、治験責任医師によりメトトレキサートに割り付けられた（C25001 試験　治験総括報告書　Listing 16.2.4.10）。本剤群にランダム化された pcALCL 被験者 1 例は、過去に放射線療法又は全身療法を受けておらず、治験実施計画書からの重大な逸脱と判断された（C25001 試験　治験総括報告書　Table 10.b）。

放射線療法を含む直近の前治療に対する最良効果は、完全奏効（CR）が 12 例（本剤群 6 例及び治験責任医師が選択した化学療法群 6 例。以降同順）、部分奏効（PR）が 20 例（11 例及び 9 例）、安定（SD）が 18 例（13 例及び 5 例）、PD が 32 例（13 例及び 19 例）であった（C25001 試験　治験総括報告書　Table 14.1.1.4）。また、直近の全身療法で PD であった被験者は 78 例（61%）であった（2.7.3.7　Table ADT14.1.1.4）。

併用薬

併用可能薬及び併用禁止薬は治験実施計画書に規定した（C25001 試験　治験総括報告書 9.4.7）。

安全性解析対象集団で併用薬の投与を 1 回以上受けた被験者は、本剤群 66 例のうち 65 例（98%）、治験責任医師が選択した化学療法群 62 例全例（100%）であった（C25001 試験　治験総括報告書　Table 14.4.4.15）。

本剤群で投与された主な併用薬は、パラセタモール 30 例（45%）、オンダンセトロン 15 例（23%）、アロプリノール及びレボチロキシン各 13 例（20%）であった。脂質低下薬は 19 例（29%）に投与され、その内訳はアトルバスタチン及びシンバスタチン各 6 例（9%）、ロスバスタチン 4 例（6%）、プラバスタチン 2 例（3%）、ピタバスタチン 1 例（2%）であった（C25001 試験　治験総括報告書　Listing 16.2.8.9）。

メトトレキサートを投与された被験者で投与された主な併用薬は、葉酸 13 例（52%）、パラセタモール 11 例（44%）、ヒドロキシジン 7 例（28%）、レボチロキシン及びセチリジン各 6 例（24%）及びフロセミド 5 例（20%）であった。脂質低下薬は 4 例（16%）に投与され、その内訳はアトルバスタチン 2 例（8%）、シンバスタチン及びロスバスタチン各 1 例（4%）であった（C25001 試験　治験総括報告書　Listing 16.2.8.9）。

ベキサロテンを投与された被験者で投与された主な併用薬は、レボチロキシン 33 例（89%）、フェノフィブラート 27 例（73%）、ヒドロキシジン 10 例（27%）、パラセタモール 9 例（24%）、フルクロキサシン及びアセチルサリチル酸各 8 例（22%）であった。脂質低下薬は 27 例（73%）に投与され、その内訳はアトルバスタチンが 11 例（30%）、ロスバスタチン 10 例（27%）、シンバスタチン 6 例（16%）であった（C25001 試験　治験総括報告書　Listing 16.2.8.9）。

（2）SGN-35-OU 試験

人口統計学的特性

安全性解析対象集団における人口統計学的特性を表 2.7.4.1-10 に示した。

SAF2 の年齢の中央値は 52.5 歳（範囲：32～78 歳）であり、男性（63%）が多かった。この試験対象集団の人口統計学的特性は C25001 試験の ITT 解析対象集団と同様であり、概して全身療法を必要とする CD30 陽性 CTCL 患者の集団を代表するものであった。

ベースライン時の疾患特性

安全性解析対象集団におけるベースライン時の疾患特性を表 2.7.4.1-10 に示した。

SAF2 の診断疾患は、MF が 8 例（50%）、pcALCL が 5 例（31%）、リンパ腫様丘疹症 2 例（13%）、原発性皮膚 γδT 細胞リンパ腫 1 例（6%）であった。

ほとんどの被験者の ECOG performance status は 0 又は 1 であり〔それぞれ 12 例（75%）及び 2 例（13%）〕、ECOG performance status が 2 の被験者は 2 例（13%）であった。

MF 被験者のほとんどは試験登録時の病期が II B（6 例）であり、III A が 1 例、IV A2 が 1 例であった。病期 IV B であった被験者はいなかった。pcALCL 被験者の試験登録時の皮膚病変は、T3a（1 例）又は T3b（4 例）であった。その他の診断疾患の被験者の試験登録時の皮膚病変は、T3b（2 例）又は T2a（1 例）であった。pcALCL 被験者及びその他の診断疾患の被験者で内臓病変を有している被験者はいなかった。

SAF2 で試験中の中央病理判定で病理組織学的に CD30 陽性と判定された被験者は 11 例（69%）であった。

表 2.7.4.1-10　人口統計学的及び他の基準値の特性（SGN-35-OU 試験、安全性解析対象集団）

解析対象例数	SAF1 N=13	SAF2 N=16
性別– n (%)		
男性	8 (62%)	10 (63%)
女性	5 (38%)	6 (38%)
年齢（歳）		
平均値（標準偏差）	52.8 (13.15)	54.1 (13.40)
中央値	54.0	52.5
最小値, 最大値	32, 76	32, 78
年齢 – n (%)		
64 歳以下	11 (85%)	13 (81%)
65 歳以上	2 (15%)	3 (19%)
身長（cm）		
平均値（標準偏差）	165.2 (7.34)	165.4 (8.14)
中央値	163.5	163.5
最小値, 最大値	152, 177	152, 181
体重（kg）		
平均値（標準偏差）	62.07 (15.774)	63.73 (17.832)
中央値	55.90	55.25
最小値, 最大値	47.6, 96.9	47.6, 103.5
合計 mSWAT スコア		
平均値（標準偏差）	43.05 (40.344)	36.18 (39.026)
中央値	38.20	27.40
最小値, 最大値	1.4, 146.0	1.3, 146.0
原疾患名 – n (%)		
CD30 陽性菌状息肉症（MF）	8 (62%)	8 (50%)
原発性皮膚未分化大細胞リンパ腫（pcALCL）	5 (38%)	5 (31%)
成人 T 細胞白血病・リンパ腫	0	0
リンパ腫様丘疹症（LyP）	0	2 (13%)
皮下脂肪織炎様 T 細胞リンパ腫	0	0
節外性 NK/T 細胞リンパ腫、鼻型	0	0
種痘様水疱症様リンパ腫	0	0
原発性皮膚 γδT 細胞リンパ腫（PCGDTCL）	0	1 (6%)
原発性皮膚 CD8 陽性進行性表皮向性細胞傷害性 T 細胞リンパ腫	0	0
原発性皮膚 CD4 陽性小・中細胞型 T 細胞リンパ腫	0	0
末梢性 T 細胞リンパ腫、非特異	0	0
病期分類（MF）– n (%)		
IA	0	0
IB	0	0
IIA	0	0
IIB	6 (75%)	6 (75%)
IIIA	1 (13%)	1 (13%)
IIIB	0	0
IVA1	0	0
IVA2	1 (13%)	1 (13%)
IVB	0	0
不明	0	0

表 2.7.4.1-10　人口統計学的及び他の基準値の特性（SGN-35-OU 試験、安全性解析対象集団）（続き）

解析対象例数	SAF1 N=13	SAF2 N=16
原疾患 TNM 分類（pcALCL、その他の診断疾患）– n (%)		
T		
T1a	0	0
T1b	0	0
T2a	0	1 (13%)
T2b	0	0
T2c	0	0
T3a	1 (20%)	1 (13%)
T3b	4 (80%)	6 (75%)
不明	0	0
N		
N0	3 (60%)	5 (63%)
N1	0	0
N2	2 (40%)	3 (38%)
N3	0	0
不明	0	0
M		
M0	5 (100%)	8 (100%)
M1	0	0
不明	0	0
ECOG Performance Status – n (%)		
0	9 (69%)	12 (75%)
1	2 (15%)	2 (13%)
2	2 (15%)	2 (13%)
病理組織学的検査（中央病理判定）CD30 – n (%)		
陽性発現	9 (69%)	11 (69%)
陽性非発現	4 (31%)	5 (31%)
不明	0	0

出典：SGN-35-OU 試験　治験総括報告書　表 14.1-2

ECOG: Eastern Cooperative Oncology Group; mSWAT: modified severity-weighted assessment tool; SAF: safety data set; TNM: Tumor-Node-Metastasis.

前治療

SAF2 の全被験者（100%）が前治療歴を有していた。全身療法としてベキサロテン 9 例（56%）、メトトレキサート 4 例（25%）、その他の化学療法 12 例（75%）、レチノイド 4 例（25%）、免疫療法 3 例（19%）及びヒストン脱アセチル化酵素阻害剤（HDACI）1 例（6%）が報告された。また、手術の治療歴を有する被験者は 2 例（13%）であった（SGN-35-OU 試験　治験総括報告書　表 14.1-2）。

併用薬

SAF2 の全被験者（100%）が併用薬の投与を受けた。主な併用薬は、パラセタモール 10 例（63%）、ムコ多糖体多硫酸エステル 9 例（56%）、ヒドロコルチゾン酪酸エステル及び白色ワセリン各 8 例（50%）、塩酸ロキソプロフェン及びレバミピド各 7 例（44%）であった。また、5 例（31%）が併用療法を受けた（SGN-35-OU 試験　治験総括報告書　表 14.1-2）。

2.7.4.2 有害事象

2.7.4.2.1 有害事象の解析

（1）C25001 試験

安全性解析対象集団で発現した有害事象の概要を表 2.7.4.2-1 に示した。

最終解析時点で、安全性解析対象集団では、有害事象は本剤群で 63 例（95%）、治験責任医師が選択した化学療法群で 56 例（90%）に報告され、治験薬との因果関係が否定できない有害事象はそれぞれ 57 例（86%）及び 44 例（71%）に報告された。Grade 3 以上の有害事象は本剤群で 27 例（41%）、治験責任医師が選択した化学療法群で 29 例（47%）に報告され、治験薬との因果関係が否定できない Grade 3 以上の有害事象はそれぞれ 19 例（29%）及び 18 例（29%）に報告された。重篤な有害事象は本剤群で 19 例（29%）、治験責任医師が選択した化学療法群で 18 例（29%）に報告され、治験薬との因果関係が否定できない重篤な有害事象はそれぞれ 9 例（14%）及び 3 例（5%）で報告された。

治験薬の投与中止に至った有害事象は本剤群で 16 例（24%）、治験責任医師が選択した化学療法群で 5 例（8%）に報告された。治験薬の投与期間は本剤群で長かった〔2.7.4.1.2.1（1）〕。

試験期間中の死亡は、本剤群で 4 例（6%）報告され、治験責任医師が選択した化学療法群では報告されなかった。死亡の 4 例のうち 3 例は被験者の原疾患に起因するものと報告され、残りの 1 例は治験責任医師により原疾患及び内臓リンパ節転移部位に対する本剤の治療効果の両方に起因するものと判断された〔2.7.4.2.1.3（1）〕。

表 2.7.4.2-1　有害事象の概要（C25001 試験、安全性解析対象集団、最終解析時点）

	Brentuximab Vedotin N=66 n (%)	Physician's Choice		
		Total N=62 n (%)	Methotrexate N=25 n (%)	Bexarotene N=37 n (%)
Any AE	63 (95)	56 (90)	23 (92)	33 (89)
Grade 3 or higher AE	27 (41)	29 (47)	9 (36)	20 (54)
Drug-related AE	57 (86)	44 (71)	14 (56)	30 (81)
Drug-related Grade 3 or higher AE	19 (29)	18 (29)	3 (12)	15 (41)
SAE	19 (29) (a)	18 (29)	9 (36)	9 (24)
Drug-related SAE	9 (14) (b)	3 (5)	2 (8)	1 (3)
AEs resulting in study drug discontinuation	16 (24) (c)	5 (8)	1 (4)	4 (11)
Deaths that occurred within 30 days of last dose study drug	4 (6)	0	0	0

出典：C25001 試験　治験総括報告書　Table 14.4.1.1

AE: adverse event; EDC: electronic data capture, EOT: end of treatment, SAE: serious adverse event.

A patient was counted once for each type of event.

(a) 最終解析後、1 例に発現した重篤な有害事象の発現時期が収集期間外であったため EDC から削除され、18 例（27%）に修正された。

(b) 最終解析後、1 例に発現した重篤な有害事象の発現時期が収集期間外であったため EDC から削除され、8 例（12%）に修正された。

(c) この他に、誤って EOT 用紙を用いて報告された有害事象により治験薬の投与を中止した被験者が 1 例報告された。この有害事象（リンパ腫）は、その後死亡に至った。

安全性の追加解析として、各投与群の治験薬の曝露あたりの有害事象の発現頻度を表 2.7.4.2-2 に示した。曝露あたりの発現頻度は有害事象数を総人年で割って算出した。また、個々の人年は被験者の EOT 日から初回投与日を引いて+1 日を 365.25 で除して算出した。総人年は、投与群の全被験者の人年の合計とした。

22

全体的に、本剤群では治験責任医師が選択した化学療法群よりも治験薬の投与期間が長く、本剤群は治験責任医師が選択した化学療法群と比較して総人年が多かった（本剤群 44.48 人年、治験責任医師が選択した化学療法群 25.90 人年）。総人年曝露量あたりの有害事象の発現頻度は、本剤群で 13.15 件／人年、治験責任医師が選択した化学療法群で 14.90 件／人年であり、本剤群で数値上低く、各薬剤（ベキサロテン 14.78 件／人年、メトトレキサート 15.17 件／人年）と比較しても低かった。

表 2.7.4.2-2　治験薬の曝露あたりの有害事象の発現頻度
（C25001 試験、安全性解析対象集団、最終解析時点）

	Brentuximab Vedotin	Physician's Choice		
		Total	Methotrexate	Bexarotene
	N=66	N=62	N=25	N=37
Total person-year	44.48	25.90	8.31	17.60
Number of treatment-emergent adverse events (a)	585	386	126	260
Incidence density	13.15	14.90	15.17	14.78

出典：C25001 試験　治験総括報告書　Table 14.4.1.28

Person years is defined as (end of treatment date - first dose date + 1)/365.25. For patients with end of treatment date missing, impute the missing date as the earlier date of last dose date + 30 days or date of death.

Incidence density: number of events/total person years

(a) number of events are calculated as sum of event count from each preferred term.

（2）SGN-35-OU 試験

安全性解析対象集団で発現した有害事象の概要を表 2.7.4.2-3 に示した。

SAF2 では、有害事象は 16 例全例（100%）に報告され、治験薬との因果関係が否定できない有害事象も 16 例全例（100%）に報告された。Grade 3 以上の有害事象は 9 例（56%）に報告され、治験薬との因果関係が否定できない Grade 3 以上の有害事象は 8 例（50%）に報告された。重篤な有害事象は 5 例（31%）に報告され、治験薬との因果関係が否定できない重篤な有害事象も 5 例（31%）に報告された。コホート 2 に登録された 3 例には重篤な有害事象は発現しなかった。

治験薬の投与中止に至った有害事象は 3 例（19%）に報告され、いずれも本剤との因果関係が否定されなかった。

試験期間中の死亡は報告されなかった。

23

表 2.7.4.2-3　有害事象の概要（SGN-35-OU 試験、安全性解析対象集団）

	SAF1 N=13		SAF2 N=16	
	発現例数（%）	発現件数	発現例数（%）	発現件数
有害事象	13 (100)	127	16 (100)	138
Grade 3 以上の有害事象	8 (62)	19	9 (56)	20
副作用	13 (100)	75	16 (100)	82
Grade 3 以上の副作用	7 (54)	17	8 (50)	18
重篤な有害事象	5 (38)	7	5 (31)	7
重篤な副作用	5 (38)	7	5 (31)	7
重要な有害事象	13 (100)	46	15 (94)	49
重要な副作用	13 (100)	29	15 (94)	31
投与中止に至った有害事象	2 (15)	2	3 (19)	5
投与中止に至った副作用	2 (15)	2	3 (19)	5
試験期間中の死亡	0	0	0	0

出典：SGN-35-OU 試験　治験総括報告書　表 12.2.1.1-1、表 12.2.1.1-2、表 12.2.3.2-1、表 12.2.3.2-2、表 12.2.3.2-3 及び表 12.2.3.2-4
SAF: safety data set

2.7.4.2.1.2 比較的よく見られる有害事象

（1）C25001 試験

安全性解析対象集団の 10%以上の被験者に発現した有害事象を表 2.7.4.2-4 に要約した。

安全性解析対象集団では、有害事象は本剤群で 63 例（95%）、治験責任医師が選択した化学療法群で 56 例（90%）に 1 件以上報告された。20%以上の被験者で報告された有害事象は、本剤群では末梢性感覚ニューロパチー（45%）、悪心（36%）、疲労及び下痢（各 29%）であった。治験責任医師が選択した化学療法群では疲労（27%）のみであった。

表 2.7.4.2-4　10%以上の被験者に発現した有害事象
（C25001 試験、安全性解析対象集団、最終解析時点）

PT	基本語	Brentuximab Vedotin N=66 n (%)	Physician's Choice Total N=62 n (%)	Methotrexate N=25 n (%)	Bexarotene N=37 n (%)
Patients with at least 1 AE (a)		63 (95)	56 (90)	23 (92)	33 (89)
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	30 (45)	1 (2)	1 (4)	0
Nausea	悪心	24 (36)	8 (13)	4 (16)	4 (11)
Fatigue	疲労	19 (29)	17 (27)	5 (20)	12 (32)
Diarrhoea	下痢	19 (29)	4 (6)	1 (4)	3 (8)
Pyrexia	発熱	11 (17)	11 (18)	7 (28)	4 (11)
Pruritus	そう痒症	11 (17)	8 (13)	2 (8)	6 (16)
Vomiting	嘔吐	11 (17)	3 (5)	2 (8)	1 (3)
Alopecia	脱毛症	10 (15)	2 (3)	1 (4)	1 (3)
Decreased appetite	食欲減退	10 (15)	3 (5)	1 (4)	2 (5)
Arthralgia	関節痛	8 (12)	4 (6)	2 (8)	2 (5)
Myalgia	筋肉痛	8 (12)	2 (3)	0	2 (5)
Asthenia	無力症	7 (11)	5 (8)	3 (12)	2 (5)
Oedema peripheral	末梢性浮腫	7 (11)	6 (10)	4 (16)	2 (5)
Pruritus generalised	全身性そう痒症	7 (11)	1 (2)	0	1 (3)
Rash maculo-papular	斑状丘疹状皮疹	7 (11)	3 (5)	1 (4)	2 (5)
Dyspnoea	呼吸困難	7 (11)	0	0	0
Headache	頭痛	5 (8)	6 (10)	1 (4)	5 (14)
Anaemia	貧血	3 (5)	6 (10)	0	6 (16)
Skin infection	皮膚感染	2 (3)	7 (11)	3 (12)	4 (11)
Hypertriglyceridaemia	高トリグリセリド血症	1 (2)	11 (18)	0	11 (30)

出典：C25001 試験　治験総括報告書　Table 14.4.1.3E

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term.

AEs were coded using the MedDRA dictionary Version 19.0.

(a) A patient was counted once for each PT. Percentages were calculated using the number of treated patients as the denominator.

安全性解析対象集団の 2 例以上の被験者に発現した因果関係が否定できない有害事象を表 2.7.4.2-5 に要約した。

治験薬との因果関係が否定できない有害事象は、本剤群で 57 例（86%）、治験責任医師が選択した化学療法群で 44 例（71%）に 1 件以上報告された。20%以上の被験者に認められた因果関係が否定できない有害事象は、本剤群では末梢性感覚ニューロパチー（44%）、悪心（32%）、疲労（27%）、治験責任医師が選択する化学療法群では疲労（23%）であった。

表 2.7.4.2-5　2 例以上の被験者に発現した因果関係が否定できない有害事象
（C25001 試験、安全性解析対象集団、最終解析時点）

PT	基本語	Brentuximab Vedotin N=66 n (%)	Physician's Choice Total N=62 n (%)	Methotrexate N=25 n (%)	Bexarotene N=37 n (%)
Patients with at least 1 drug-related AE (a)		57 (86)	44 (71)	14 (56)	30 (81)
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	29 (44)	0	0	0
Nausea	悪心	21 (32)	5 (8)	1 (4)	4 (11)
Fatigue	疲労	18 (27)	14 (23)	3 (12)	11 (30)
Diarrhoea	下痢	12 (18)	3 (5)	1 (4)	2 (5)
Alopecia	脱毛症	8 (12)	1 (2)	0	1 (3)

表 2.7.4.2-5　2 例以上の被験者に発現した因果関係が否定できない有害事象
（C25001 試験、安全性解析対象集団、最終解析時点）（続き）

PT	基本語	Brentuximab Vedotin N=66 n (%)	Physician's Choice Total N=62 n (%)	Physician's Choice Methotrexate N=25 n (%)	Physician's Choice Bexarotene N=37 n (%)
Vomiting	嘔吐	8 (12)	1 (2)	0	1 (3)
Decreased appetite	食欲減退	7 (11)	1 (2)	0	1 (3)
Pruritus	そう痒症	7 (11)	4 (6)	0	4 (11)
Myalgia	筋肉痛	6 (9)	1 (2)	0	1 (3)
Arthralgia	関節痛	5 (8)	1 (2)	0	1 (3)
Asthenia	無力症	5 (8)	5 (8)	3 (12)	2 (5)
Neutropenia	好中球減少症	5 (8)	4 (6)	0	4 (11)
Pyrexia	発熱	5 (8)	2 (3)	2 (8)	0
Chills	悪寒	4 (6)	0	0	0
Dyspnoea	呼吸困難	4 (6)	0	0	0
Paraesthesia	錯感覚	4 (6)	0	0	0
Peripheral motor neuropathy	末梢性運動ニューロパチー	4 (6)	0	0	0
Pruritus generalised	全身性そう痒症	4 (6)	1 (2)	0	1 (3)
Rash maculo-papular	斑状丘疹状皮疹	4 (6)	1 (2)	0	1 (3)
Constipation	便秘	3 (5)	2 (3)	0	2 (5)
Dysgeusia	味覚異常	3 (5)	0	0	0
Hyperuricaemia	高尿酸血症	3 (5)	0	0	0
Neuropathy peripheral	末梢性ニューロパチー	3 (5)	0	0	0
Urticaria	蕁麻疹	3 (5)	1 (2)	0	1 (3)
Weight decreased	体重減少	3 (5)	1 (2)	0	1 (3)
Dermatitis acneiform	ざ瘡様皮膚炎	2 (3)	0	0	0
Drug hypersensitivity	薬物過敏症	2 (3)	0	0	0
Headache	頭痛	2 (3)	6 (10)	1 (4)	5 (14)
Hot flush	ほてり	2 (3)	0	0	0
Hypertension	高血圧	2 (3)	0	0	0
Hypoaesthesia	感覚鈍麻	2 (3)	0	0	0
Insomnia	不眠症	2 (3)	3 (5)	0	3 (8)
Leukopenia	白血球減少症	2 (3)	1 (2)	0	1 (3)
Neuralgia	神経痛	2 (3)	0	0	0
Tachycardia	頻脈	2 (3)	0	0	0
Vision blurred	霧視	2 (3)	0	0	0
Alanine aminotransferase increased	アラニンアミノトランスフェラーゼ増加	1 (2)	5 (8)	3 (12)	2 (5)
Anaemia	貧血	1 (2)	4 (6)	0	4 (11)
Skin exfoliation	皮膚剥脱	1 (2)	2 (3)	0	2 (5)
Aspartate aminotransferase increased	アスパラギン酸アミノトランスフェラーゼ増加	0	4 (6)	2 (8)	2 (5)
Blood cholesterol increased	血中コレステロール増加	0	4 (6)	0	4 (11)
Blood triglycerides increased	血中トリグリセリド増加	0	5 (8)	0	5 (14)
Dry eye	眼乾燥	0	2 (3)	0	2 (5)
Dry skin	皮膚乾燥	0	3 (5)	1 (4)	2 (5)
Hypercholesterolaemia	高コレステロール血症	0	4 (6)	0	4 (11)
Hypertriglyceridaemia	高トリグリセリド血症	0	11 (18)	0	11 (30)
Hypothyroidism	甲状腺機能低下症	0	5 (8)	0	5 (14)
Secondary hypothyroidism	続発性甲状腺機能低下症	0	2 (3)	0	2 (5)
Skin infection	皮膚感染	0	2 (3)	1 (4)	1 (3)

出典：C25001 試験　治験総括報告書　Table 14.4.1.6B

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term.

AEs were coded using the MedDRA dictionary Version 19.0.

(a) A patient was counted once for each PT. Percentages use the number of treated patients as the denominator.

26

安全性解析対象集団の 2 例以上の被験者に発現した Grade 3 以上の有害事象を表 2.7.4.2-6 に要約した。

Grade 3 以上の有害事象は本剤群で 27 例（41%）、治験責任医師が選択した化学療法群で 29 例（47%）に報告された。5%以上の被験者で認められた Grade 3 以上の有害事象は、本剤群では疲労、高血糖、好中球減少症及び末梢性感覚ニューロパチー（各 5%）であり、治験責任医師が選択した化学療法群では高トリグリセリド血症（13%）、敗血症及び貧血（各 5%）であった。重症度別の有害事象の発現頻度は 2.7.4.8　Table 14.4.1.4B に示した。

表 2.7.4.2-6　2 例以上の被験者に発現した Grade 3 以上の有害事象
（C25001 試験、安全性解析対象集団、最終解析時点）

PT	基本語	Brentuximab Vedotin N=66 n (%)	Physician's Choice Total N=62 n (%)	Physician's Choice Methotrexate N=25 n (%)	Physician's Choice Bexarotene N=37 n (%)
Patients with at least 1 AE ≥Grade 3 (a)		27 (41)	29 (47)	9 (36)	20 (54)
Fatigue	疲労	3 (5)	1 (2)	1 (4)	0
Hyperglycaemia	高血糖	3 (5)	0	0	0
Neutropenia	好中球減少症	3 (5)	2 (3)	0	2 (5)
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	3 (5)	0	0	0
Cellulitis	蜂巣炎	2 (3)	0	0	0
Diarrhoea	下痢	2 (3)	0	0	0
Dizziness	浮動性めまい	2 (3)	0	0	0
Drug hypersensitivity	薬物過敏症	2 (3)	0	0	0
Hypertension	高血圧	2 (3)	0	0	0
Peripheral motor neuropathy	末梢性運動ニューロパチー	2 (3)	0	0	0
Skin infection	皮膚感染	2 (3)	1 (2)	1 (4)	0
Pruritus	そう痒症	1 (2)	2 (3)	0	2 (5)
Sepsis	敗血症	1 (2)	3 (5)	1 (4)	2 (5)
Alanine aminotransferase increased	アラニンアミノトランスフェラーゼ増加	0	2 (3)	2 (8)	0
Anaemia	貧血	0	3 (5)	0	3 (8)
Blood triglycerides increased	血中トリグリセリド増加	0	2 (3)	0	2 (5)
Hypertriglyceridaemia	高トリグリセリド血症	0	8 (13)	0	8 (22)
Hyperuricaemia	高尿酸血症	0	2 (3)	2 (8)	0
Parotitis	耳下腺炎	0	2 (3)	1 (4)	1 (3)

出典：C25001 試験　治験総括報告書　Table 14.4.1.5B

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term.

AEs were coded using the MedDRA dictionary Version 19.0.

(a) A patient was counted once for each PT. Percentages use the number of treated patients as the denominator.

（2）SGN-35-OU 試験

安全性解析対象集団の 2 例以上の被験者に発現した有害事象を表 2.7.4.2-7 に要約した。

SAF2 では、有害事象は 16 例全例（100%）に報告された。20%以上の被験者で報告された有害事象は、末梢性ニューロパチー（56%）、下痢及び発熱（各 31%）、薬疹及び好酸球増加症（各 25%）であった。

表 2.7.4.2-7　2 例以上の被験者に発現した有害事象
（SGN-35-OU 試験、安全性解析対象集団）

SOC PT	SAF1 N=13		SAF2 N=16	
	発現例数 (%)	発現件数	発現例数 (%)	発現件数
全体	13 (100)	127	16 (100)	138
神経系障害	12 (92)	16	13 (81)	17
末梢性ニューロパチー	8 (62)	8	9 (56)	9
感覚鈍麻	2 (15)	3	2 (13)	3
末梢性感覚ニューロパチー	2 (15)	2	2 (13)	2
感染症および寄生虫症	8 (62)	17	9 (56)	18
上咽頭炎	3 (23)	3	3 (19)	3
足部白癬	2 (15)	3	2 (13)	3
上気道感染	2 (15)	3	2 (13)	3
胃腸障害	7 (54)	13	9 (56)	16
下痢	4 (31)	4	5 (31)	5
悪心	2 (15)	2	2 (13)	2
腹痛	1 (8)	1	2 (13)	2
一般・全身障害および投与部位の状態	7 (54)	18	7 (44)	18
発熱	5 (38)	13	5 (31)	13
倦怠感	3 (23)	3	3 (19)	3
末梢性浮腫	2 (15)	2	2 (13)	2
皮膚および皮下組織障害	7 (54)	11	9 (56)	13
薬疹	3 (23)	3	4 (25)	4
発疹	1 (8)	1	2 (13)	2
臨床検査	5 (38)	17	5 (31)	17
Ｃ－反応性蛋白増加	2 (15)	3	2 (13)	3
γ－グルタミルトランスフェラーゼ増加	2 (15)	3	2 (13)	3
血液およびリンパ系障害	4 (31)	4	4 (25)	4
好酸球増加症	4 (31)	4	4 (25)	4
代謝および栄養障害	4 (31)	5	5 (31)	6
高尿酸血症	2 (15)	2	3 (19)	3
筋骨格系および結合組織障害	4 (31)	8	4 (25)	8
関節痛	3 (23)	4	3 (19)	4
呼吸器、胸郭および縦隔障害	4 (31)	4	5 (31)	5
アレルギー性鼻炎	2 (15)	2	2 (13)	2
肝胆道系障害	2 (15)	3	3 (19)	4
肝機能異常	2 (15)	3	3 (19)	4

出典：SGN-35-OU 試験　治験総括報告書　表 12.2.2-1 及び表 12.2.2-2
MedDRA：ICH 国際医薬用語集、PT：基本語、SAF：safety data set、SOC：器官別大分類
MedDRA/J 第 24.1 版を用いて読み替えた。

安全性解析対象集団の 2 例以上の被験者に発現した治験薬との因果関係が否定できない有害事象を表 2.7.4.2-8 に要約した。

SAF2 では、治験薬との因果関係が否定できない有害事象は 16 例全例（100%）に報告された。20%以上の被験者で報告された治験薬との因果関係が否定できない有害事象は、末梢性ニューロパチー（56%）、発熱及び好酸球増加症（各 25%）であった。

表 2.7.4.2-8　2 例以上の被験者に発現した因果関係が否定できない有害事象
（SGN-35-OU 試験、安全性解析対象集団）

SOC	SAF1 N=13		SAF2 N=16	
PT	発現例数（%）	発現件数	発現例数（%）	発現件数
全体	13 (100)	75	16 (100)	82
神経系障害	12 (92)	16	13 (81)	17
末梢性ニューロパチー	8 (62)	8	9 (56)	9
感覚鈍麻	2 (15)	3	2 (13)	3
末梢性感覚ニューロパチー	2 (15)	2	2 (13)	2
一般・全身障害および投与部位の状態	7 (54)	14	7 (44)	14
発熱	4 (31)	9	4 (25)	9
倦怠感	3 (23)	3	3 (19)	3
末梢性浮腫	2 (15)	2	2 (13)	2
胃腸障害	6 (46)	10	7 (44)	12
下痢	2 (15)	2	3 (19)	3
悪心	2 (15)	2	2 (13)	2
皮膚および皮下組織障害	6 (46)	6	8 (50)	8
薬疹	2 (15)	2	3 (19)	3
発疹	1 (8)	1	2 (13)	2
血液およびリンパ系障害	4 (31)	4	4 (25)	4
好酸球増加症	4 (31)	4	4 (25)	4
臨床検査	4 (31)	14	4 (25)	14
Ｃ－反応性蛋白増加	2 (15)	2	2 (13)	2
γ－グルタミルトランスフェラーゼ増加	2 (15)	2	2 (13)	2
代謝および栄養障害	3 (23)	3	4 (25)	4
高尿酸血症	1 (8)	1	2 (13)	2
肝胆道系障害	2 (15)	2	3 (19)	3
肝機能異常	2 (15)	2	3 (19)	3

出典：SGN-35-OU 試験　治験総括報告書　表 12.2.2-3 及び表 12.2.2-4
MedDRA：ICH 国際医薬用語集、PT：基本語、SAF：safety data set、SOC：器官別大分類
MedDRA/J 第 24.1 版を用いて読み替えた。

安全性解析対象集団で発現した Grade 3 以上の有害事象を表 2.7.4.2-9 に要約した。

SAF2 では、Grade 3 以上の有害事象は 9 例（56%）に報告された。10%（2 例）以上の被験者で報告された Grade3 以上の有害事象は、末梢性ニューロパチー（19%）、発熱、好酸球増加症及び肝機能異常（各 13%）であった。

29

表 2.7.4.2-9　Grade 3 以上の有害事象（SGN-35-OU 試験、安全性解析対象集団）

SOC	SAF1 N=13		SAF2 N=16	
PT	発現例数（%）	発現件数	発現例数（%）	発現件数
全体	8 (62)	19	9 (56)	20
神経系障害	3 (23)	3	3 (19)	3
末梢性ニューロパチー	3 (23)	3	3 (19)	3
感染症および寄生虫症	1 (8)	1	1 (6)	1
骨髄炎	1 (8)	1	1 (6)	1
胃腸障害	1 (8)	1	1 (6)	1
鼠径ヘルニア	1 (8)	1	1 (6)	1
一般・全身障害および投与部位の状態	2 (15)	3	2 (13)	3
発熱	2 (15)	3	2 (13)	3
臨床検査	1 (8)	5	1 (6)	5
好中球数減少	1 (8)	3	1 (6)	3
白血球数減少	1 (8)	2	1 (6)	2
血液およびリンパ系障害	2 (15)	2	2 (13)	2
好酸球増加症	2 (15)	2	2 (13)	2
代謝および栄養障害	1 (8)	1	1 (6)	1
高トリグリセリド血症	1 (8)	1	1 (6)	1
呼吸器、胸郭および縦隔障害	1 (8)	1	1 (6)	1
肺毒性	1 (8)	1	1 (6)	1
肝胆道系障害	1 (8)	1	2 (13)	2
肝機能異常	1 (8)	1	2 (13)	2
腎および尿路障害	1 (8)	1	1 (6)	1
急性腎障害	1 (8)	1	1 (6)	1

出典：SGN-35-OU 試験　治験総括報告書　表 12.2.3.2-1 及び表 12.2.3.2-2
MedDRA：ICH 国際医薬用語集、PT：基本語、SAF：safety data set、SOC：器官別大分類
MedDRA/J 第 24.1 版を用いて読み替えた。

2.7.4.2.1.3 死亡

（1）C25001 試験

最終解析のデータカットオフ時点で、報告された死亡数は本剤群で 16 例（24%）、治験責任医師が選択した化学療法群で 14 例（23%）あり、投与群間で同程度であった。

本剤群の死亡のうち、4 例は本剤の最終投与後 30 日以内に、残りの 12 例（死亡被験者の 75%）は本剤の最終投与後 120 日以降に死亡した。治験責任医師が選択した化学療法群の死亡のうち、治験薬の最終投与後 30 日以内の死亡はなく、31～60 日以内の死亡が 3 例、61～90 日以内の死亡が 3 例、91～120 日以内の死亡が 1 例報告され、残りの 7 例（死亡被験者の 50%）は治験薬の最終投与後 120 日以降に死亡した。

全体として、死亡の大部分は原疾患に起因し（本剤群で死亡被験者の 75%、治験責任医師が選択した化学療法群で死亡被験者の 71%）、治験薬との因果関係は否定された（C25001 試験　治験総括報告書　Table 12.j）。

安全性解析対象集団における治験薬の最終投与後 30 日以内の死亡の一覧を表 2.7.4.2-10 に示した。

本剤群で治験薬の最終投与後 30 日以内に死亡した 4 例のうち、3 例の死亡は本剤との因果関係が否定された。残りの 1 例の死因は多臓器機能不全症候群であり、治験責任医師により原疾患及び内臓リンパ節転移部位に対する本剤の治療効果の両方に起因するものと判断され

た。なお、この被験者はベースライン時に適格性基準を満たしておらず（肝機能検査値が基準値以上）、治験実施計画書からの重大な逸脱と判断された（C25001 試験　治験総括報告書 Listing 16.2.2.4）。

本剤との因果関係が否定できない試験期間中の死亡の叙述を 2.7.6.1.5 に示した。

表 2.7.4.2-10　治験薬の最終投与後 30 日以内の死亡の一覧（C25001 試験）

Patient No/Diagnosis	MedDRA PT	Days From First Dose (a)/Days From Last Dose (b)	Cycle and Day of AE That Resulted in Death (c)	Relationship (Assessed by Investigator)
Treatment Arm: Brentuximab Vedotin				
[redacted]/MF	Sepsis 敗血症	43/8	Cycle 2 Day 9	Not related
[redacted]/MF	Lymphoma リンパ腫	68/5	Cycle 4 Day 6	Not related
[redacted]/pcALCL	Multiple organ dysfunction syndrome (d) 多臓器機能不全症候群	28/28	Cycle 1 Day 29	Related
[redacted]/MF	Pulmonary embolism 肺塞栓症	14/14	Cycle 1 Day 15	Not related

出典：C25001 試験　治験総括報告書　Table 14.4.2.1 及び Listing 16.2.4.4

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; MF: mycosis fungoides; pcALCL: primary cutaneous anaplastic large cell lymphoma; PT: preferred term

(a) Number of days from first dose was defined as (date of death−first dose date of Day 1 of Cycle 1).

(b) Number of days from last dose was defined (date of death−date of last dose).

(c) AE that resulted in death was defined as an AE with the same PT as the AE with outcome of death and AE end date before the date of death.

(d) Patient had not met protocol eligibility criteria at study baseline (Study C25001 CSR Listing 16.2.2.4).

（2）SGN-35-OU 試験

SGN-35-OU 試験で、試験期間中に死亡した被験者はいなかった。

MF 被験者の 1 例が投与中止の約 3 ヵ月後に疾患進行により死亡した（SGN-35-OU 試験　治験総括報告書　14.3.3 及び表 12.3.1.1-1）。

当該死亡被験者の叙述を 2.7.6.2.5 に示した。

2.7.4.2.1.4 その他の重篤な有害事象

（1）C25001 試験

安全性解析対象集団における重篤な有害事象を表 2.7.4.2-11 に示した。

重篤な有害事象は、本剤群 19 例（29%）及び治験責任医師が選択した化学療法群 18 例（29%）に計 60 件発現した。本剤群の 2 例以上に報告された重篤な有害事象は、蜂巣炎及び発熱〔各 2 例（3%）〕であった。治験責任医師が選択した化学療法群の 2 例以上に報告された重篤な有害事象は、発熱〔4 例（6%）〕及び敗血症〔3 例（5%）〕であった。

重篤な有害事象の一覧を 2.7.6.1.6 に示した。

治験薬との因果関係の否定できない重篤な有害事象は、本剤群 9 例（14%）及び治験責任医師が選択した化学療法群 3 例（5%）に計 20 件発現した。各投与群で 2 例以上に報告された因果関係の否定できない重篤な有害事象はなかった（C25001 試験　治験総括報告書

Table 14.4.1.10B）。最終解析のデータカットオフ時点で、16 件の事象は回復しており、2 件〔本剤群の Grade 3 の末梢性ニューロパチー及び治験責任医師が選択した化学療法群（メトトレキサート）の Grade1 の皮膚びらん〕は継続していた（2.7.6.1.6　表 2.7.6.1-2）。本剤群の Grade 4 の膵炎は後遺症を残して回復したが、その後、当該被験者は多臓器機能不全症候群で死亡した〔2.7.4.2.1.3（1）〕。

本剤群で治験薬との因果関係が否定できない重篤な有害事象を発現した 9 例のうち、3 例で Grade 3 の感染症および寄生虫症（SOC）に含まれる事象（蜂巣炎、憩室炎、膿痂疹が各 1 例）が発現した。いずれの事象も回復した。このうち重篤な膿痂疹は本剤の投与中止に至った〔2.7.4.2.1.5（1）1）〕。

治験責任医師が選択した化学療法群（メトトレキサート）では、1 例に感染症および寄生虫症（SOC）に含まれる因果関係が否定できない重篤な有害事象（Grade 4 の敗血症）が発現したが、その後疾患進行により投与を中止し、本事象は薬剤投与により回復した。

前述の本剤群の 1 例（Grade 3 の膿痂疹）に加え、その他の治験薬の投与中止に至った因果関係が否定できない重篤な有害事象は、本剤群で 2 例（Grade 4 の薬疹及び Grade 3 の末梢性ニューロパチー）、治験責任医師が選択した化学療法群（ベキサロテン）で 1 例（Grade 3 の血尿）に報告された。

表 2.7.4.2-11　重篤な有害事象（C25001 試験、安全性解析対象集団、最終解析時点）

PT	基本語	Brentuximab Vedotin N=66 n (%)	Physician's Choice Total N=62 n (%)	Physician's Choice Methotrexate N=25 n (%)	Physician's Choice Bexarotene N=37 n (%)
Patients with at least 1 SAE (a)		19 (29)	18 (29)	9 (36)	9 (24)
Cellulitis	蜂巣炎	2 (3)	0	0	0
Pyrexia	発熱	2 (3)	4 (6)	3 (12)	1 (3)
Demyelinating polyneuropathy	脱髄性多発ニューロパチー	1 (2)(b)	0	0	0
Diarrhoea	下痢	1 (2)	0	0	0
Diverticulitis	憩室炎	1 (2)	0	0	0
Dizziness	浮動性めまい	1 (2)	0	0	0
Drug eruption	薬疹	1 (2)	0	0	0
Extravasation	溢出	1 (2)	0	0	0
Fatigue	疲労	1 (2)	0	0	0
Fracture	骨折	1 (2)	0	0	0
General physical health deterioration	全身健康状態低下	1 (2)	0	0	0
Haemolytic uraemic syndrome	溶血性尿毒症症候群	1 (2)	0	0	0
Hepatocellular injury	肝細胞損傷	1 (2)	0	0	0
Hyperglycaemia	高血糖	1 (2)	0	0	0
Hypotension	低血圧	1 (2)	0	0	0
Impetigo	膿痂疹	1 (2)	0	0	0
Intestinal perforation	腸管穿孔	1 (2)	0	0	0
Lower respiratory tract infection	下気道感染	1 (2)	0	0	0
Lymphoma	リンパ腫	1 (2)	0	0	0
Multiple organ dysfunction syndrome	多臓器機能不全症候群	1 (2)	0	0	0
Musculoskeletal chest pain	筋骨格系胸痛	1 (2)	0	0	0
Neck pain	頚部痛	1 (2)	0	0	0
Neuropathy peripheral	末梢性ニューロパチー	1 (2)	0	0	0
Pancreatitis	膵炎	1 (2)	0	0	0
Pulmonary embolism	肺塞栓症	1 (2)	0	0	0
Rash maculo-papular	斑状丘疹状皮疹	1 (2)	0	0	0
Sepsis	敗血症	1 (2)	3 (5)	1 (4)	2 (5)
Sinusitis	副鼻腔炎	1 (2)	0	0	0
Stress	ストレス	1 (2)	0	0	0
Urinary retention	尿閉	1 (2)	0	0	0
Urinary tract infection	尿路感染	1 (2)	0	0	0
Crystal arthropathy	結晶性関節障害	0	1 (2)	1 (4)	0
Dermatitis bullous	水疱性皮膚炎	0	1 (2)	1 (4)	0
Erysipelas	丹毒	0	1 (2)	1 (4)	0
Haematuria	血尿	0	1 (2)	0	1 (3)
Hypernatraemia	高ナトリウム血症	0	1 (2)	0	1 (3)
Neuralgia	神経痛	0	1 (2)	1 (4)	0
Parotitis	耳下腺炎	0	1 (2)	1 (4)	0
Periorbital infection	眼窩周囲感染	0	1 (2)	0	1 (3)
Peripheral ischaemia	末梢性虚血	0	1 (2)	0	1 (3)
Peripheral vascular disorder	末梢血管障害	0	1 (2)	0	1 (3)
Skin erosion	皮膚びらん	0	1 (2)	1 (4)	0
Skin infection	皮膚感染	0	1 (2)	1 (4)	0
Squamous cell carcinoma of skin	皮膚有棘細胞癌	0	1 (2)	0	1 (3)
Superinfection bacterial	細菌重複感染	0	1 (2)	0	1 (3)
Urosepsis	尿路性敗血症	0	1 (2)	0	1 (3)

出典：C25001 試験　治験総括報告書　Table 14.4.1.7B
AE: adverse event; EDC: electronic data capture; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAE: serious adverse event.
AEs were coded using the MedDRA dictionary Version 19.0.
(a) A patient was counted once for each PT. Percentages use the number of treated patients as the denominator.
(b) 最終解析後、発現時期が有害事象の収集期間外であったため EDC から削除された。

（2）SGN-35-OU 試験

安全性解析対象集団で発現した重篤な有害事象を表 2.7.4.2-12 に要約した。

SAF2 では、重篤な有害事象は 5 例（31%）に 7 件報告され、いずれも因果関係が否定できなかった（SGN-35-OU 試験　治験総括報告書　表 12.3.1.2-4）。いずれの事象も 1 例のみに報告された。

表 2.7.4.2-12　重篤な有害事象（SGN-35-OU 試験、安全性解析対象集団）

SOC PT	SAF1 N=13		SAF2 N=16	
	発現例数 (%)	発現件数	発現例数 (%)	発現件数
全体	5 (38)	7	5 (31)	7
血液およびリンパ系障害	1 (8)	1	1 (6)	1
好酸球増加症	1 (8)	1	1 (6)	1
胃腸障害	1 (8)	1	1 (6)	1
鼠径ヘルニア	1 (8)	1	1 (6)	1
一般・全身障害および投与部位の状態	1 (8)	1	1 (6)	1
発熱	1 (8)	1	1 (6)	1
臨床検査	1 (8)	1	1 (6)	1
好中球数減少	1 (8)	1	1 (6)	1
代謝および栄養障害	1 (8)	1	1 (6)	1
高尿酸血症	1 (8)	1	1 (6)	1
腎および尿路障害	1 (8)	1	1 (6)	1
急性腎障害	1 (8)	1	1 (6)	1
呼吸器、胸郭および縦隔障害	1 (8)	1	1 (6)	1
肺毒性	1 (8)	1	1 (6)	1

出典：SGN-35-OU 試験　治験総括報告書　表 12.3.1.2-1 及び表 12.3.1.2-2
MedDRA：ICH 国際医薬用語集、PT：基本語、SAF：safety data set、SOC：器官別大分類
MedDRA/J 第 24.1 版を用いて読み替えた。

2.7.4.2.1.5 その他の重要な有害事象

（1）治験薬の投与中止に至った有害事象

1）C25001 試験

安全性解析対象集団における治験薬の投与中止に至った有害事象を表 2.7.4.2-13 に示した。

治験薬の投与中止に至った有害事象は、本剤群で 16 例（24%）、治験責任医師が選択した化学療法群で 5 例（8%）に報告された。複数の被験者で報告された治験薬の投与中止に至った有害事象は、本剤群では末梢性感覚ニューロパチー5 例（8%）及び末梢性ニューロパチー2 例（3%）であり、治験責任医師が選択した化学療法群では認められなかった。

本剤群では、治験薬の投与を中止した被験者の半数以上（9 例）が末梢性ニューロパチー〔MedDRA 標準検索式（SMQ）〕の事象により投与を中止した。その内訳は、末梢性感覚ニューロパチー5 例（8%）、末梢性ニューロパチー2 例（3%）、末梢性運動ニューロパチー及び感覚鈍麻各 1 例（2%）であった。その他の治験薬の投与中止に至った有害事象は、いずれも 1 例のみに報告された。

表 2.7.4.2-13　治験薬の投与中止に至った有害事象
（C25001 試験、安全性解析対象集団、最終解析時点）

PT	基本語	Brentuximab Vedotin N=66 n (%)	Physician's Choice Total N=62 n (%)	Physician's Choice Methotrexate N=25 n (%)	Physician's Choice Bexarotene N=37 n (%)
Patients with at least 1 AE resulting in study drug discontinuation (a)		16 (24)	5 (8)	1 (4)	4 (11)
Peripheral sensory neuropathy	末梢性感覚ニューロパチー	5 (8)	0	0	0
Neuropathy peripheral	末梢性ニューロパチー	2 (3)	0	0	0
Drug eruption	薬疹	1 (2)	0	0	0
Drug hypersensitivity	薬物過敏症	1 (2)	0	0	0
Escherichia infection	大腸菌感染	1 (2)	0	0	0
Hypoaesthesia	感覚鈍麻	1 (2)	0	0	0
Impetigo	膿痂疹	1 (2)	0	0	0
Peripheral motor neuropathy	末梢性運動ニューロパチー	1 (2)	0	0	0
Pulmonary embolism	肺塞栓症	1 (2)	0	0	0
Rash maculo-papular	斑状丘疹状皮疹	1 (2)	1 (2)	1 (4)	
Urticaria	蕁麻疹	1 (2)	0	0	0
Vertigo	回転性めまい	1 (2)	0	0	0
Asthenia	無力症	0	1 (2)	0	1 (3)
Haematuria	血尿	0	1 (2)	0	1 (3)
Hypernatraemia	高ナトリウム血症	0	1 (2)	0	1 (3)
Neutropenia	好中球減少症	0	1 (2)	0	1 (3)
Periorbital infection	眼窩周囲感染	0	1 (2)	0	1 (3)
Somnolence	傾眠	0	1 (2)	0	1 (3)

出典：C25001 試験　治験総括報告書　Table 14.4.1.9B

AE: adverse event; CSR: clinical study report; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term.

One additional patient in the brentuximab vedotin arm is reported as discontinuing study drug because of an AE in Study C25001 CSR Table 14.1.1.1, Overall Disposition. This patient experienced a fatal TEAE of lymphoma progression. The recorded action for this AE was "discontinued from the study" instead of "study drug discontinued".

AEs were coded using the MedDRA dictionary Version 19.0.

(a) A patient was counted once for each PT. Percentages use the number of treated patients as the denominator.

2）SGN-35-OU 試験

安全性解析対象集団で発現した治験薬の投与の中止に至った有害事象を表 2.7.4.2-14 に要約した。

SAF2 では、治験薬の投与中止に至った有害事象は 3 例（19%）に 5 件報告され、いずれも因果関係が否定できなかった（SGN-35-OU 試験　治験総括報告書　表 14.3.1.1-4）。いずれの事象も 1 例のみに報告された。治験薬の投与中止に至った末梢性ニューロパチー（SMQ）の有害事象は 1 件であった。

表 2.7.4.2-14　治験薬の投与中止に至った有害事象（SGN-35-OU 試験、安全性解析対象集団）

SOC	SAF1 N=13		SAF2 N=16	
PT	発現例数（%）	発現件数	発現例数（%）	発現件数
全体	2 (15)	2	3 (19)	5
神経系障害	1 (8)	1	1 (6)	1
末梢性ニューロパチー	1 (8)	1	1 (6)	1
胃腸障害	0	0	1 (6)	2
下痢	0	0	1 (6)	1
腹痛	0	0	1 (6)	1
呼吸器、胸郭および縦隔障害	1 (8)	1	1 (6)	1
肺毒性	1 (8)	1	1 (6)	1
肝胆道系障害	0	0	1 (6)	1
肝機能異常	0	0	1 (6)	1

出典：SGN-35-OU 試験　治験総括報告書　表 14.3.1.1-1 及び表 14.3.1.1-2
MedDRA：ICH 国際医薬用語集、PT：基本語、SAF：safety data set、SOC：器官別大分類
MedDRA/J 第 24.1 版を用いて読み替えた。

（2）末梢性ニューロパチー関連事象

1）C25001 試験

安全性解析対象集団における末梢性ニューロパチー（SMQ）の重症度別の発現状況を表 2.7.4.2-15 に示した。

末梢性ニューロパチー（SMQ）の有害事象は、本剤群で 44 例（67%）、治験責任医師が選択した化学療法群で 4 例（6%）で報告された。本剤群で報告された主な末梢性ニューロパチー（SMQ）の有害事象は、末梢性感覚ニューロパチー30 例（45%）、錯感覚 6 例（9%）及び末梢性運動ニューロパチー4 例（6%）であった。治験責任医師が選択した化学療法群では複数の被験者で報告された事象はなく、筋力低下、神経痛、錯感覚、末梢性感覚ニューロパチーがそれぞれ 1 例（2%）に報告された。いずれの投与群でも Grade 4 の末梢性ニューロパチー（SMQ）は報告されなかった。

治験薬との因果関係が否定できない末梢性ニューロパチー（SMQ）は、本剤群で 41 例（62%）に報告され、治験責任医師が選択した化学療法群では報告されなかった（C25001 試験　治験総括報告書　Table 14.4.1.17）。

表 2.7.4.2-15　重症度別の末梢性ニューロパチー（SMQ）
（C25001 試験、安全性解析対象集団、最終解析時点）

PN (SMQ) TEAE	基本語	Brentuximab Vedotin (N=66)	Physician's Choice Total N=62	Physician's Choice Methotrexate N=25	Physician's Choice Bexarotene N=37
			n (%)	n (%)	n (%)
Any PN (SMQ) TEAE		44 (67)	4 (6)	2 (8)	2 (5)
Grade 1		17 (26)	1 (2)	0	1 (3)
Grade 2		21 (32)	3 (5)	2 (8)	1 (3)
Grade 3		6 (9)	0	0	0
Grade 4		0	0	0	0
Peripheral motor neuropathy (a)	末梢性運動ニューロパチー (a)				
Grade 2		2 (3)	0	0	0
Grade 3		2 (3)	0	0	0
Demyelinating polyneuropathy	脱髄性多発ニューロパチー				
Grade 2		1 (2)	0	0	0
Dysaesthesia	異常感覚				
Grade 1		1 (2)	0	0	0
Hypoaesthesia	感覚鈍麻				
Grade 1		1 (2)	0	0	0
Grade 2		2 (3)	0	0	0
Muscle atrophy	筋萎縮				
Grade 1		1 (2)	0	0	0
Muscular weakness	筋力低下				
Grade 2		1 (2)	1 (2)	0	1 (3)
Neuralgia	神経痛				
Grade 1		1 (2)	0	0	0
Grade 2		1 (2)	1 (2)	1 (4)	0
Neuropathy peripheral	末梢性ニューロパチー				
Grade 2		2 (3)	0	0	0
Grade 3		1 (2)	0	0	0
Paraesthesia	錯感覚				
Grade 1		4 (6)	1 (2)	0	1 (3)
Grade 2		2 (3)	0	0	0
Peripheral motor neuropathy	末梢性運動ニューロパチー				
Grade 2		2 (3)	0	0	0
Grade 3		2 (3)	0	0	0
Peripheral sensory neuropathy	末梢性感覚ニューロパチー				
Grade 1		12 (18)	0	0	0
Grade 2		14 (21)	1 (2)	1 (4)	0
Grade 3		4 (6)	0	0	0
Polyneuropathy	多発ニューロパチー				
Grade 2		1 (2)	0	0	0
Sensory loss	感覚消失				
Grade 1		1 (2)	0	0	0

出典：C25001 試験　治験総括報告書　Table 14.4.1.16

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PN: peripheral neuropathy; PT: preferred term; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event.

A patient counts once for the highest intensity of each event category. Percentages use the number of treated patients as the denominator.

AEs were coded using the MedDRA dictionary Version 19.0.

(a) Peripheral neuropathy (SMQ) with PT peripheral motor neuropathy, peripheral sensorimotor neuropathy, or peroneal nerve palsy.

末梢性ニューロパチー（SMQ）の発現までの時間

末梢性ニューロパチー（SMQ）の発現までの時間を表 2.7.4.2-16 に示した。

末梢性ニューロパチー（SMQ）の発現までの時間の中央値は、本剤群で 12.0 週間（範囲：0～48 週間）、治験責任医師が選択した化学療法群で 2.5 週間（範囲 : 0～10 週間）であった。また、本剤群における Grade 3 の末梢性ニューロパチー（SMQ）の発現までの時間の中央値は、19.5 週間（範囲：6～25 週間）であった。

表 2.7.4.2-16　末梢性ニューロパチー（SMQ）の発現までの期間
（C25001 試験、安全性解析対象集団、最終解析時点）

		Physician's Choice		
	Brentuximab Vedotin	Total	Methotrexate	Bexarotene
	N=66	N=62	N=25	N=37
Time to Onset (Weeks)	n (%)	n (%)	n (%)	n (%)
Kaplan-Meier estimate of time to onset of any PN SMQ TEAE (a)				
Patients with PN events	44	4	2	2
Median	16.0	NE	NE	NE
95% CI	12.0, 21.0	NE, NE	NE, NE	NE, NE
25th-75th percentile	10.0, 28.0	NE, NE	NE, NE	NE, NE
Time to onset of PN SMQ TEAE among patients with ≥1 event				
Number of patients	44	4	2	2
Mean (SD)	15.0 (11.60)	3.8 (4.35)	6.5 (4.95)	1.0 (1.41)
Median	12.0	2.5	6.5	1.0
Minimum, maximum	0, 48	0, 10	3, 10	0, 2
Time to first onset of Gr 1 PN SMQ TEAE among patients with ≥1 Gr 1 event (b)				
Number of patients	35	1	0	1
Mean (SD)	13.6 (10.28)	2.0		2.0
Median	12.0	2.0		2.0
Minimum, maximum	0, 47	2, 2		2, 2
Time to first onset of Gr 2 PN SMQ TEAE among patients with ≥1 Gr 2 event (b)				
Number of patients	25	3	2	1
Mean (SD)	23.1 (10.82)	4.3 (5.13)	6.5 (4.95)	0.0
Median	22.0	3.0	6.5	0.0
Minimum, maximum	5, 48	0, 10	3, 10	0, 0
Time to first onset of Gr 3 PN SMQ TEAE among patients with ≥1 Gr 3 event (b)				
Number of patients	6	0	0	0
Mean (SD)	16.7 (7.84)			
Median	19.5			
Minimum, maximum	6, 25			
Time to first onset of worst grade PN SMQ TEAE among patients with ≥1 event (c)				
Number of patients	44	4	2	2
Mean (SD)	20.7 (11.69)	3.8 (4.35)	6.5 (4.95)	1.0 (1.41)
Median	20.0	2.5	6.5	1.0
Minimum, maximum	0, 48	0, 10	3, 10	0, 2

出典：C25001 試験　治験総括報告書　Table 14.4.1.21

EOT: end of treatment; Gr: Grade; NE: not estimated/estimable; PN: peripheral neuropathy; SD: standard deviation; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event.

No Grade 4 PN (SMQ) events were reported in either treatment arm.

(a) Time from first dose to event or the time of censoring. Subjects without an event were censored at the EOT visit.

(b) Time to first onset of Grade x event was defined from the date of first dose to first onset date of any Grade x event with no prior higher grade for any event. For example, if a patient experienced a burning sensation with grade fluctuation of Grade 1 to Grade 3 to Grade 2 to resolved, and subsequently the patient experienced a Grade 2 peripheral sensory neuropathy, this patient had a time to first onset of Grade 1 and Grade 3 event, but not a time to first onset of Grade 2 event.

(c) Time to first onset of Grade x event was defined from the date of first dose to first onset date of Grade x event provided that the Grade x did not represent improvement from a higher grade. For example, if a patient experienced an event of burning sensation with a fluctuation of Grade 1 to Grade 3 to Grade 2 to resolved, there is no time to first onset of Grade 2 event for this event.

治験薬の投与中止及び投与変更に至った末梢性ニューロパチー（SMQ）

末梢性ニューロパチー（SMQ）に伴う投与中止及び投与変更を表 2.7.4.2-17 に示した。

治験薬の投与中止に至った末梢性ニューロパチー（SMQ）は本剤群で 9 例〔14%、末梢性ニューロパチー（SMQ）を発現した被験者の 20%〕に発現した。これらの被験者は、投与中止前に中央値で 11 サイクル（範囲：4～15 サイクル）の投与を受けた。治験責任医師で選択された化学療法群で治験薬の投与中止に至った末梢性ニューロパチー（SMQ）は報告されなかった。

また、本剤群で末梢性ニューロパチー（SMQ）を発現した被験者 44 例のうち、投与を延期した被験者は 16 例（36%）であった。治験責任医師で選択された化学療法群で末梢性ニューロパチー（SMQ）により投与を延期した被験者は報告されなかった。

表 2.7.4.2-17　末梢性ニューロパチー（SMQ）に伴う投与中止及び投与変更
（C25001 試験、安全性解析対象集団、最終解析時点）

	Brentuximab Vedotin	Physician's Choice		
		Total	Methotrexate	Bexarotene
	N=66	N=62	N=25	N=37
	N (%)	n (%)	n (%)	n (%)
Patients with ≥1 PN SMQ TEAE, n (%)	44 (67)	4 (6)	2 (8)	2 (5)
Discontinuations due to PN SMQ TEAEs	9 (20)	0	0	0
Treatment cycles received for patients who discontinued because of PN SMQs, median (range)	11 (4, 15)	-	-	-
Category of number of dose delays due to any peripheral neuropathy (SMQ) event				
0 delay	28 (64)	4 (100)	2 (100)	2 (100)
Any delay	16 (36)	0	0	0
1 delay	13 (81)	0	0	0
2 delays	3 (19)	0	0	0
≥3 delays	0	0	0	0

出典：C25001 試験　治験総括報告書　Table 14.4.1.14 及び Table 14.4.1.15

MedDRA: Medical Dictionary for Regulatory Activities; PN: peripheral neuropathy; PT: preferred term SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event.

Only those patients who experienced ≥1 PN SMQ TEAE(s) are included. Note: SMQ search results were conducted using the MedDRA version listed in each clinical study report; therefore, the PTs included in the various searches may differ among studies, and results

末梢性ニューロパチー（SMQ）の回復又は改善

末梢性ニューロパチー（SMQ）の転帰を表 2.7.4.2-18 に示した。

C25001 試験では、EOT 時又は最終追跡調査時点までに報告された転帰が「回復」「回復したが後遺症あり」の転帰であった場合を「回復」と定義した。未回復の末梢性ニューロパチー（SMQ）のうち、直近の評価時点で最大グレードから 1 グレード以上改善した場合を、「改善」と定義した。なお、全ての事象が回復した被験者は「改善」の集計から除外した。

最終解析時点で、本剤群で末梢性ニューロパチー（SMQ）を発現した被験者 44 例のうち、EOT 来院までに 23 例（52%）で事象の回復又は改善が認められた。EOT 時に未回復であった末梢性ニューロパチー（SMQ）事象の最大重症度は、21 例で Grade 1、11 例で Grade 2、3 例で Grade 3 であった。治験責任医師が選択した化学療法群で末梢性ニューロパチー（SMQ）を発現した被験者 4 例のうち、EOT 来院までに 1 例（25%）で事象の回復が認められた。EOT

時に未回復であった末梢性ニューロパチー（SMQ）事象の最大重症度は、1 例で Grade 1、2 例で Grade 2 であった。

最終解析時点（試験全体の追跡期間の中央値：22.9 ヵ月）で、本剤群で末梢性ニューロパチー（SMQ）を発現した被験者 44 例のうち、最終追跡調査時点までに 36 例（82%）で事象の回復又は改善が認められた〔回復 22 例（50%）、改善 14 例（32%）〕。最終追跡調査時点に未回復であった末梢性ニューロパチー（SMQ）事象の最大重症度は、17 例で Grade 1、5 例で Grade 2 であり、Grade 3 の事象は報告されなかった。治験責任医師が選択した化学療法群で末梢性ニューロパチー（SMQ）を発現した被験者 4 例のうち、最終追跡調査時点までに 1 例（25%）で事象の回復が認められた。最終追跡調査時点に未回復であった末梢性ニューロパチー（SMQ）事象の最大重症度は、1 例で Grade 1、2 例で Grade 2 であった。

試験終了時点の末梢性ニューロパチー（SMQ）の転帰も同様の結果であった。

表 2.7.4.2-18　末梢性ニューロパチー（SMQ）の転帰
（C25001 試験、安全性解析対象集団、最終解析時点）

	Brentuximab Vedotin N=44	Physician's Choice Total N=4	Methotrexate N=2	Bexarotene N=2
Patients With ≥1 PN SMQ TEAE	n (%)	n (%)	n (%)	n (%)
最終解析時点				
At the EOT visit (a)				
Resolution (b) or improvement (c) in PN SMQ TEAEs	23 (52)	1 (25)	1 (50)	0
Resolution (b) of all PN SMQ TEAEs	7 (16)	1 (25)	1 (50)	0
Improvement (c) in PN SMQ TEAEs	16 (36)	0	0	0
No resolution or improvement of any PN SMQ TEAEs	21 (48)	3 (75)	1 (50)	2 (100)
Ongoing PN SMQ TEAEs (maximum severity) (d) (e)	35 (80)	3 (75)	1 (50)	2 (100)
Grade 1	21 (48)	1 (25)	0	1 (50)
Grade 2	11 (25)	2 (50)	1 (50)	1 (50)
Grade 3	3 (7)	0	0	0
At last follow-up			0	0
Resolution (b) or improvement (c) in PN SMQ TEAEs	36 (82)	1 (25)	1 (50)	0
Resolution (b) of all PN SMQ TEAEs	22 (50)	1 (25)	1 (50)	0
Improvement (c) in PN SMQ TEAEs	14 (32)	0	0	0
No resolution or improvement of any PN SMQ TEAEs	8 (18)	3 (75)	1 (50)	2 (100)
Ongoing PN SMQ TEAEs (maximum severity) (e) (f)	22 (50)	3 (75)	1 (50)	2 (100)
Grade 1	17 (39)	1 (25)	0	1 (50)
Grade 2	5 (11)	2 (50)	1 (50)	1 (50)
試験終了時点				
At the EOT visit (a)				
Resolution (b) or improvement (c) in PN SMQ TEAEs	24 (55)	1 (25)	1 (50)	0
Resolution (b) of all PN SMQ TEAEs	7 (16)	1 (25)	1 (50)	0
Improvement (c) in PN SMQ TEAEs	17 (39)	0	0	0
No resolution or improvement of any PN SMQ TEAEs	20 (45)	3 (75)	1 (50)	2 (100)
Ongoing PN SMQ TEAEs (maximum severity) (d) (e)	37 (84)	3 (75)	1 (50)	2 (100)
Grade 1	24 (55)	1 (25)	0	1 (50)
Grade 2	10 (23)	2 (50)	1 (50)	1 (50)
Grade 3	3 (7)	0	0	0
At last follow-up	0	0	0	0
Resolution (b) or improvement (c) in PN SMQ TEAEs	38 (86)	2 (50)	2 (100)	0
Resolution (b) of all PN SMQ TEAEs	26 (59)	2 (50)	2 (100)	0
Improvement (c) in PN SMQ TEAEs	12 (27)	0	0	0
No resolution or improvement of any PN SMQ TEAEs	6 (14)	2 (50)	0	2 (100)
Ongoing PN SMQ TEAEs (maximum severity) (e) (f)	18 (41)	2 (50)	0	2 (100)
Grade 1	15 (34)	1 (25)	0	1 (50)
Grade 2	3 (7)	1 (25)	0	1 (50)

出典：C25001 試験　治験総括報告書　Table 14.4.1.18 及び治験総括報告書補遺 1　Table 15.4.1.18

EOT: end of treatment; PN: peripheral neuropathy; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event.
Only those patients who experienced any PN SMQ TEAEs are included.

(a) For patients without an EOT date, the date was imputed as the last dose +30 days.

(b) Resolution is defined as events reported as "resolved" or "resolved with sequelae." Subjects with resolution of all PN events at EOT (or last follow-up) are subjects with all PN resolved and all resolution dates on or before EOT date (or last follow-up date).

(c) Resolution implies improvement. In addition, for events that were not resolved, improvement was defined as a decrease by ≥1 grade from the worst grade, with no higher grade thereafter. Patients with improvement in any event at EOT (or at last follow-up) were those with ≥1 improved event and date of improvement before the EOT (or last follow-up) date. Subjects with all events resolved were excluded.

(d) An ongoing event at EOT is defined as an event with an end date after the EOT date if the event end date was not missing, or last follow-up date on or after the EOT date if the event end date was missing.

(e) Maximum severity was the maximum among grades that were occurring at EOT, not grades that occurred over time.

(f) Ongoing event at last follow-up is defined as event outcome of "unresolved" or "unknown" or events without an end date.

末梢性ニューロパチー（SMQ）の回復又は改善までの期間

本剤群で末梢性ニューロパチー（SMQ）を発現した 44 例（48 件）における末梢性ニューロパチー（SMQ）の回復又は改善までの期間の要約を表 2.7.4.2-19 に示した。

最終解析時点で、本剤群で発現した末梢性ニューロパチー（SMQ）48 件のうち、35 件が回復、13 件が改善した。回復までの期間の中央値は 27.0 週間（範囲：0～111 週間）、改善までの期間の中央値は 8.0 週間（範囲：1～35 週間）であった。

治験責任医師が選択した化学療法群では、末梢性ニューロパチー（SMQ）を発現した 4 例のうち 3 例は未回復であり、1 例に発現した 1 件の末梢性ニューロパチー（SMQ）の事象は 2.0 週間で回復した（C25001 試験　治験総括報告書　Table 14.4.1.20）。

表 2.7.4.2-19　末梢性ニューロパチー（SMQ）の回復又は改善までの期間
（C25001 試験、安全性解析対象集団の本剤群、最終解析時点）

	Brentuximab Vedotin (N=44)	
Time (Weeks)	最終解析時点	試験終了時点
Time to resolution (a) for resolved events		
Number of events	35	41
Mean (SD)	32.4 (30.59)	45.3 (49.45)
Median	27.0	33.0
Minimum, maximum	0, 111	0, 233
Time to improvement (b) for unresolved but improved events		
Number of events	13	10
Mean (SD)	13.6 (12.47)	15.9 (13.46)
Median	8.0	15.0
Minimum, maximum	1, 35	1, 35
Time to resolution or improvement (c) for resolved or improved events		
Number of events	48	51
Mean (SD)	27.3 (28.06)	39.5 (46.12)
Median	19.0	29.0
Minimum, maximum	0, 111	0, 233
Time to resolution for resolved maximum Grade 1 events		
Number of events	14	17
Mean (SD)	28.9 (33.36)	44.4 (58.59)
Median	18.0	22.0
Minimum, maximum	0, 111	0, 233
Time to resolution for resolved maximum Grade 2 events		
Number of events	15	18
Mean (SD)	32.9 (25.46)	48.1 (45.19)
Median	33.0	35.5
Minimum, maximum	1, 99	1, 168
Time to improvement for unresolved but improved maximum Grade 2 events		
Number of events	11	8
Mean (SD)	11.5 (12.09)	13.6 (13.76)
Median	6.0	9.0
Minimum, maximum	1, 35	1, 35
Time to resolution or improvement for resolved or improved maximum Grade 2 events		
Number of events	26	26
Mean (SD)	23.8 (23.17)	37.5 (41.29)
Median	17.0	31.0
Minimum, maximum	1, 99	1, 168

表 2.7.4.2-19　末梢性ニューロパチー（SMQ）の回復又は改善までの期間
（C25001 試験、安全性解析対象集団の本剤群、最終解析時点）（続き）

	Brentuximab Vedotin (N=44)	
Time (Weeks)	最終解析時点	試験終了時点
Time to resolution for resolved maximum Grade 3 events		
Number of events	6	6
Mean (SD)	39.3 (39.48)	39.3 (39.48)
Median	33.0	33.0
Minimum, maximum	2, 109	2, 109
Time to improvement for unresolved but improved maximum Grade 3 events		
Number of events	2	2
Mean (SD)	25.0 (9.90)	25.0 (9.90)
Median	25.0	25.0
Minimum, maximum	18, 32	18, 32
Time to resolution or improvement for resolved or improved maximum Grade 3 events		
Number of events	8	8
Mean (SD)	35.8 (34.23)	35.8 (34.23)
Median	29.5	29.5
Minimum, maximum	2, 109	2, 109

出典：C25001 試験　治験総括報告書　Table 14.4.1.20 及び治験総括報告書補遺 1　Table 15.4.1.20

PN: peripheral neuropathy; SD: standard deviation; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event.
Only those patients who experienced any PN SMQ TEAEs are included.
This table presents event-level analyses and includes only PN SMQ TEAEs.
(a) Resolution was defined as an event outcome of “resolved” or “resolved with sequelae.” Time to resolution was calculated from the initial onset date to the resolution date.
(b) For unresolved but improved events, improvement was defined as a decrease by ≥1 grade from worst grade, with no higher grade thereafter. “Time to improvement” for unresolved but improved events was calculated from the onset date of the maximum grade to the first onset date on which the grade was below the maximum grade, with no higher grade thereafter.
(c) “Time to resolution” was used for resolved events. “Time to improvement” was used for unresolved but improved events.

2）SGN-35-OU 試験

安全性解析対象集団の末梢性ニューロパチー（SMQ）の発現状況を表 2.7.4.2-20 に示した。

SAF2 では、末梢性ニューロパチー（SMQ）は 13 例（81%）に 14 件報告された。その内訳は、末梢性ニューロパチーが 9 例（56%）に 9 件、感覚鈍麻が 2 例（13%）に 3 件、末梢性感覚ニューロパチーが 2 例（13%）に 2 件であった。いずれも治験薬との因果関係が否定できなかった（SGN-35-OU 試験　治験総括報告書　表 12.3.1.3-4）。

SAF2 では、末梢性ニューロパチー（SMQ）のほとんど（12 件）はサイクル 4 までに発現しており、残りはそれぞれサイクル 5～8 及びサイクル 13～16 に 1 件ずつ発現した（SGN-35-OU 試験　治験総括報告書　表 14.3.1.4-2）。末梢性ニューロパチー（SMQ）の 1 件で本剤の投与中止、2 件で休薬、3 件で減量した（SGN-35-OU 試験　治験総括報告書　表 14.3.1.2-2）。末梢性ニューロパチー（SMQ）の大半は試験終了までに回復（4 件）又は軽快（5 件）したが、5 件は未回復であった（SGN-35-OU 試験　治験総括報告書　表 14.3.1.3-2）。未回復の 4 件は本剤の投与を継続し、1 件は減量して継続していた（SGN-35-OU 試験　治験総括報告書　一覧 16.2.7-2）。

44

表 2.7.4.2-20　末梢性ニューロパチー（SMQ）（SGN-35-OU 試験、安全性解析対象集団）

重要な有害事象	SAF1 N=13		SAF2 N=16	
PT	発現例数（%）	発現件数	発現例数（%）	発現件数
末梢性ニューロパチー	12 (92)	13	13 (81)	14
末梢性ニューロパチー	8 (62)	8	9 (56)	9
感覚鈍麻	2 (15)	3	2 (13)	3
末梢性感覚ニューロパチー	2 (15)	2	2 (13)	2

出典：SGN-35-OU 試験　治験総括報告書　表 12.3.1.3-1 及び表 12.3.1.3-2
MedDRA：ICH 国際医薬用語集、PT：基本語、SAF：safety data set、SOC：器官別大分類
MedDRA/J 第 24.1 版を用いて読み替えた。

Grade 3 の末梢性ニューロパチー（SMQ）は SAF2 で 3 例（19%）に 3 件報告され（いずれも末梢性ニューロパチー）、Grade 4 の事象は報告されなかった（SGN-35-OU 試験　治験総括報告書　表 12.2.3.1-2）。Grade 3 の事象はいずれもサイクル 1～3 の間に発現し、本剤の投与中止又は休薬により回復又は軽快した（SGN-35-OU 試験　治験総括報告書　一覧 16.2.7-2）。

（3）血液毒性

1）C25001 試験

C25001 試験では、血液毒性として好中球減少症関連事象について評価した。好中球減少症関連事象の発現状況及び投与変更を要した好中球減少症関連事象の概要を表 2.7.4.2-21 に示した。

好中球減少症関連事象は、本剤群で 6 例（9%）、治験責任医師が選択した化学療法群で 4 例（6%、全てベキサロテン投与被験者）に報告された。本剤群では 3 例（5%）で最大で Grade 3 の事象が、1 例（2%）で Grade 4 の事象が報告された。治験責任医師が選択した化学療法群では 2 例（3%）で Grade 3 の事象が報告され、Grade 4 の事象は報告されなかった。

投与変更を要した好中球減少症関連事象は、本剤群で 4 例（6%）、治験責任医師が選択した化学療法群で 2 例（3%）に報告された。その内訳は、本剤群では投与延期が 4 例（6%）、治験責任医師が選択した化学療法群では減量が 2 例（3%、うち 1 例は投与延期も実施）、投与延期、投与中止及び休薬が各 1 例（2%）であった。本剤群では減量、投与中止及び休薬は行われなかった。

発熱性好中球減少症はいずれの投与群でも報告されなかった。

45

表 2.7.4.2-21　用量変更を要した好中球減少症関連事象の発現頻度
（C25001 試験、安全性解析対象集団、最終解析時点）

	Brentuximab Vedotin (N=66)	Physician's Choice		
		Total N=62 n (%)	Methotrexate N=25 n (%)	Bexarotene N=37 n (%)
Any neutropenia (a) event, n (%)	6 (9)	4 (6)	0	4 (11)
Grade 1	1 (2)	0	0	0
Grade 2	4 (6)	4 (6)	0	4 (11)
Grade 3	3 (5)	2 (3)	0	2 (5)
Grade 4	1 (2)	0	0	0
Grade 5	0	0	0	0
Any dose modification	4 (6)	2 (3)	0	2 (5)
Any dose delay or dose reduction	4 (6)	2 (3)	0	2 (5)
Dose delay	4 (6)	1 (2)	0	1 (3)
Dose reduction	0	2 (3)	0	2 (5)
Both dose delay and dose reduction	0	1 (2)	0	1 (3)
Dose discontinued permanently	0	1 (2)	0	1 (3)
Dose held (b)	0	1 (2)	0	1 (3)
Dose interrupted	0	0	0	0

出典：C25001 試験　治験総括報告書　Table 14.4.1.25

PT: preferred term.

A patient was counted once for each category.

(a) Includes events with the PTs neutropenia and neutrophil count decreased; does not include treatment-emergent laboratory abnormalities.

(b) Dose held: The planned or scheduled dose was not given as a result of an intentional physician intervention. No drug was administered.

2）SGN-35-OU 試験

安全性解析対象集団の血液毒性の発現状況を表 2.7.4.2-22 に示した。

SAF2 では、血液毒性は 2 例（13%）に 7 件報告された。その内訳は、好中球数減少、血小板数減少及び白血球数減少が各 1 例（6%）であった。血小板数減少の 1 件は、サイクル 16 に播種性帯状疱疹が発現した後に発現していることから、本剤との因果関係は否定された（SGN-35-OU 試験　治験総括報告書　一覧 16.2.7-2）。

好中球数減少及び白血球数減少（各 3 件）は同一被験者で発現し、サイクル 2、サイクル 3 及びサイクル 5 の時点で好中球数減少及び白血球数減少が同時に報告された（SGN-35-OU 試験　治験総括報告書　一覧 16.2.7-2）。好中球数減少の重症度は Grade 3 又は 4、白血球数減少の重症度は Grade 2 又は 3 であり、Grade 4 の好中球数減少のみ重篤な有害事象と判断された。好中球数減少及び白血球数減少の 1 回目はサイクル 2 に発現して休薬、2 回目はサイクル 3 に発現して減量、3 回目はサイクル 5 に発現して投与を継続し、いずれの事象も回復した。いずれも治験薬との因果関係が否定できなかった。

表 2.7.4.2-22　血液毒性（SGN-35-OU 試験、安全性解析対象集団）

重要な有害事象	SAF1 N=13		SAF2 N=16	
PT	発現例数（%）	発現件数	発現例数（%）	発現件数
血液毒性	2 (15)	7	2 (13)	7
好中球数減少	1 (8)	3	1 (6)	3
血小板数減少	1 (8)	1	1 (6)	1
白血球数減少	1 (8)	3	1 (6)	3

出典：SGN-35-OU 試験　治験総括報告書　表 12.3.1.3-1 及び表 12.3.1.3-2
MedDRA：ICH 国際医薬用語集、PT：基本語、SAF：safety data set、SOC：器官別大分類
MedDRA/J 第 24.1 版を用いて読み替えた。

（4）感染

1）C25001 試験

感染症および寄生虫症（SOC）の因果関係が否定できない重篤な有害事象は、本剤群で 3 例（5%）に報告された（C25001 試験　治験総括報告書　Table 14.4.1.10A）。その内訳は、Grade 3 の蜂巣炎、Grade 3 の膿痂疹及び Grade 3 の憩室炎が各 1 例であった。これらの重篤な有害事象はいずれも回復又は後遺症はあるが回復した。Grade 3 の膿痂疹は治験薬の投与中止に至った。また、感染症および寄生虫症（SOC）に含まれる非重篤の Grade 1 の大腸菌感染（1 件）は、治験薬との因果関係は否定されたものの本剤の投与を中止して回復した。

治験責任医師が選択した化学療法群では、1 例（2%）に因果関係が否定できない重篤な敗血症が報告された。

Grade 3 又は 4 の好中球減少症関連事象を発現した被験者で報告された感染症および寄生虫症（SOC）

Grade 3 又は 4 の好中球減少症関連事象を有する被験者に発現した感染症および寄生虫症（SOC）の有害事象の概要を表 2.7.4.2-23 に示した。

Grade 3 又は 4 の好中球減少症関連事象は、本剤群で 3 例（5%）、治験責任医師が選択した化学療法群では 2 例（3%）に報告された。このうち各投与群で 1 例ずつに感染症および寄生虫症（SOC）の有害事象が報告された。その内訳は、本剤群の 1 例では蜂巣炎、下気道感染及び上気道感染、治験責任医師が選択した化学療法群の 1 例では切開部位感染、外耳炎、皮膚感染及び股部白癬であった。

表 2.7.4.2-23　Grade 3 又は 4 の好中球減少症関連事象を有する被験者に発現した感染症および寄生虫症（SOC）の有害事象
（C25001 試験、安全性解析対象集団、最終解析時点）

PT	基本語	Brentuximab Vedotin N=66 n (%)	Physician's Choice Total N=62 n (%)	Methotrexate N=25 n (%)	Bexarotene N=37 n (%)
Number of patients with Grade 3 or 4 low neutrophils or Grade 3 or 4 neutropenia (a)		3 (5)	2 (3)	0	2 (5)
Any treatment-emergent infections and infestations (SOC) event (b)		1 (2)	1 (2)	0	1 (3)
Cellulitis	蜂巣炎	1 (2)	0	0	0
Incision site infection	切開部位感染	0	1 (2)	0	1 (3)
Lower respiratory tract infection	下気道感染	1 (2)	0	0	0
Otitis externa	外耳炎	0	1 (2)	0	1 (3)
Skin infection	皮膚感染	0	1 (2)	0	1 (3)
Tinea cruris	股部白癬	0	1 (2)	0	1 (3)
Upper respiratory tract infection	上気道感染	1 (2)	0	0	0

出典：C25001 試験　治験総括報告書　Table 14.4.1.26

AE: adverse event; MedDRA: MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class. AEs were coded using the MedDRA dictionary Version 19.0.

(a) Patients with Grade 3 or 4 low neutrophils at baseline or post-baseline or treatment–emergent Grade 3 or 4 neutropenia.

(b) Patients with treatment-emergent infection that started within 7 days after the lab assessment, or with treatment emergent infection that started during the duration of the Grade 3 or 4 neutropenia.

2）SGN-35-OU 試験

安全性解析対象集団の感染症および寄生虫症（SOC）の発現状況を表 2.7.4.2-24 に示した。

SAF2 では、感染症および寄生虫症（SOC）の事象は 9 例（56%）に 18 件報告された。そのうち、治験薬との因果関係が否定できない事象は 3 例（19%）に 3 件報告され、その内訳は、帯状疱疹、サルモネラ症及び播種性帯状疱疹が各 1 例（6%）であった（SGN-35-OU 試験　治験総括報告書　表 12.3.1.3-4）。Grade 3 以上の感染症および寄生虫症（SOC）の事象は骨髄炎が 1 例（6%）に報告されたが、本剤との因果関係は否定された（SGN-35-OU 試験　治験総括報告書　表 12.2.3.2-2 及び表 12.3.1.3-4）。

感染症および寄生虫症（SOC）に含まれる事象のうち、重篤な有害事象又は投与中止に至った有害事象は報告されなかった。

Grade 3 の好中球数減少を発現した被験者 1 例は、感染症および寄生虫症（SOC）に含まれる結膜炎、足部白癬及び毛包炎を発現した。いずれも Grade 3 の好中球数減少が回復した後に報告された事象であり、本剤との因果関係は否定され、本剤の投与を継続したまま回復した（SGN-35-OU 試験　治験総括報告書　一覧 16.2.7-2）。

表 2.7.4.2-24　感染症および寄生虫症（SOC）（SGN-35-OU 試験、安全性解析対象集団）

重要な有害事象	SAF1 N=13		SAF2 N=16	
PT	発現例数（%）	発現件数	発現例数（%）	発現件数
感染	8 (62)	17	9 (56)	18
上咽頭炎	3 (23)	3	3 (19)	3
足部白癬	2 (15)	3	2 (13)	3
上気道感染	2 (15)	3	2 (13)	3
蜂巣炎	1 (8)	1	1 (6)	1
結膜炎	1 (8)	1	1 (6)	1
毛包炎	1 (8)	1	1 (6)	1
帯状疱疹	1 (8)	1	1 (6)	1
骨髄炎	1 (8)	1	1 (6)	1
中耳炎	1 (8)	1	1 (6)	1
サルモネラ症	1 (8)	1	1 (6)	1
外陰部腟カンジダ症	0	0	1 (6)	1
播種性帯状疱疹	1 (8)	1	1 (6)	1

出典：SGN-35-OU 試験　治験総括報告書　表 12.3.1.3-1 及び表 12.3.1.3-2
MedDRA：ICH 国際医薬用語集、PT：基本語、SAF：safety data set、SOC：器官別大分類
MedDRA/J 第 24.1 版を用いて読み替えた。

（5）注入に伴う反応

1）C25001 試験

治験責任医師が選択した化学療法群で使用したメトトレキサート及びベキサロテンは経口剤であることから、注入に伴う反応は本剤群のみで報告された。治験責任医師が本剤の点滴投与に関連する事象と判断した場合に、注入に伴う反応として有害事象を報告することとした。

注入に伴う反応の概要を表 2.7.4.2-25 に示した。

注入に伴う反応は、本剤群で 9 例（14%）に報告された。Grade 3 以上の注入に伴う反応は、2 例（3%）に報告された。その内訳は、Grade3 の蕁麻疹及び薬物過敏症各 1 例であり、Grade 3 の蕁麻疹は治験薬の投与中止に至った。注入に伴う反応は、そう痒症（3 例、いずれも Grade 1）及び呼吸困難（2 例、Grade 1 及び Grade 2）を除き、いずれも各 1 例に報告された。いずれも重篤な有害事象とはみなされず、Grade 4 の事象やアナフィラキシーは報告されなかった（C25001 試験　治験総括報告書　Table 14.4.1.13）。注入に伴う反応は、サイクル 2 では 8 例、サイクル 3 では 2 例に発現した（C25001 試験　治験総括報告書　Table 14.4.1.22）。

49

表 2.7.4.2-25　注入に伴う反応の概要
（C25001 試験、安全性解析対象集団、最終解析時点）

	Brentuximab Vedotin N=66 n (%)
Any IRR	9 (14)
Drug-related IRRs	9 (14)
Grade 3 or higher IRRs	2 (3)
Drug-related Grade 3 or higher IRRs	2 (3)
Serious IRRs	0
IRRs resulting in study drug discontinuation	1 (2)

出典：C25001 試験　治験総括報告書　Table 14.4.1.12A
AE: adverse event; IRR: infusion-related reaction.
IRRs are AEs related to the infusion of brentuximab vedotin.
A patient was counted once for each type of event.

本剤群で注入に伴う反応を発現した被験者 9 例の ADA 発現状況を検討した。ベースライン時に ADA 陽性であった 1 例は、試験期間中も一時的 ADA 陽性であり、ADA 抗体価は一貫して低かった。ベースライン時に ADA 陰性であった 8 例のうち、5 例は試験期間中に ADA 陽性となった（3 例は持続的 ADA 陽性、2 例は一時的 ADA 陽性）。残りの 3 例は試験期間を通して ADA 陰性であった。ADA 発現状況を 2.7.4.4（1）に示した。

2）SGN-35-OU 試験

SGN-35-OU 試験の SAF2 では、注入に伴う反応は報告されなかった（SGN-35-OU 試験　治験総括報告書　表 12.3.1.3-2）。なお、SGN-35-OU 試験では、治験責任医師が本剤の点滴投与に関連する事象と判断した場合に注入に伴う反応として有害事象を報告することは規定されていなかった。

（6）その他

1）C25001 試験

過去に本剤投与により観察された比較的頻度の低い有害事象である肺毒性、スティーブンス・ジョンソン症候群、中毒性表皮壊死融解症、腫瘍崩壊症候群及び PML は報告されなかった。

本剤群の 1 例に、重篤な有害事象として Grade 2 の肝細胞損傷が報告された。本剤の初回投与の 3 週間後に発現したが、その 1 週間後には回復し、その後再発することなく残りの 15 サイクルの投与を完了した（C25001 試験　治験総括報告書　12.3.4.5）。

2）SGN-35-OU 試験

過去に本剤投与により観察された比較的頻度の低い有害事象であるスティーブンス・ジョンソン症候群、中毒性表皮壊死融解症、腫瘍崩壊症候群及び PML は報告されなかった。また、急性膵炎、高血糖及び消化管障害も報告されなかった。

SAF2 では、肺毒性は Grade 3 の肺毒性が 1 例（6%）に 1 件報告され、重篤な有害事象と判断された。本剤の投与を中止後に軽快し、本剤との因果関係は否定できなかった（SGN-35-OU 試験　治験総括報告書　表 12.3.1.3-2 及び一覧 16.2.7-2）。

また、肝毒性は 6 例（38%）に 9 件報告された。その内訳は、肝機能異常が 3 例（19%）に 4 件、γ－グルタミルトランスフェラーゼ増加が 2 例（13%）に 3 件、アラニンアミノトランスフェラーゼ（ALT）増加及びアスパラギン酸アミノトランスフェラーゼ（AST）増加が各 1 例（6%）（同一被験者）に 1 件報告された（SGN-35-OU 試験　治験総括報告書　表 12.3.1.3-2 及び一覧 16.2.7-2）。いずれも非重篤であり、ほとんどの事象で治験薬との因果関係が否定されなかった。Grade 3 の肝機能異常の 1 例が治験薬の投与を中止し、別の Grade 3 の肝機能異常の 1 例及び Grade 2 のγ－グルタミルトランスフェラーゼ増加の 1 例で休薬した（SGN-35-OU 試験　治験総括報告書　表 14.3.1.2-2）。いずれの事象も回復した（SGN-35-OU 試験　治験総括報告書　表 14.3.1.3-2）。

2.7.4.2.1.6 器官別又は症候群別有害事象の解析

（1）C25001 試験

C25001 試験で報告された有害事象を SOC、高位語（HLT）及び PT ごとに集計した。本剤群で PT が多く報告された SOC は、神経系障害（71%）、胃腸障害（61%）、一般・全身障害および投与部位の状態（59%）、皮膚および皮下組織障害（52%）、感染症および寄生虫症（44%）、筋骨格系および結合組織障害（33%）及び代謝および栄養障害（32%）であった。治験責任医師が選択した化学療法群で PT が多く報告された SOC は、一般・全身障害および投与部位の状態（58%）、感染症および寄生虫症（52%）、胃腸障害（37%）、臨床検査（34%）及び皮膚および皮下組織障害（32%）であった（C25001 試験　治験総括報告書 Table 14.4.1.2A）。

（2）SGN-35-OU 試験

SGN-35-OU 試験で報告された有害事象を SOC、HLT 及び PT ごとに集計した。SAF2 で PT が多く報告された SOC は、神経系障害（81%）、感染症および寄生虫症（56%）、胃腸障害（56%）、皮膚および皮下組織障害（56%）、一般・全身障害および投与部位の状態（44%）、臨床検査（31%）、代謝および栄養障害（31%）及び呼吸器、胸郭および縦隔障害（31%）であった（表 2.7.4.2-7）。

2.7.4.2.2 個別有害事象の文章による説明

C25001 試験において、外国人被験者で認められた因果関係が否定できない死亡の叙述を 2.7.6.1.5 に示した。また、最終解析時点で報告された全ての試験期間中の死亡及び重篤な有害事象の叙述を治験総括報告書に記載した（C25001 試験　治験総括報告書　15.3.3）。

SGN-35-OU 試験において、日本人被験者で認められた全ての死亡及び重篤な有害事象の叙述を 2.7.6.2.5 に示した。

2.7.4.3 臨床検査値の評価

（1）C25001 試験

C25001 試験では、臨床検査値異常は、ベースラインからの変化が臨床的に有意であると判断された場合、並びに試験治療の中止、投与変更又はその他の治療介入を要した場合に、有害事象として報告された。

有害事象として報告された臨床検査値異常は 2.7.4.2 の各表に含まれる。また、臨床検査値の詳細は治験総括報告書に記載した（C25001 試験　治験総括報告書　12.4）。

（2）SGN-35-OU 試験

SGN-35-OU 試験では、臨床検査値異常及びその異常変動は、臨床上問題があると治験責任医師が判断した場合、及び新たな治療や治療方法の変更を要した場合に、有害事象として報告された。

臨床検査値の異常変動は 2.7.4.2 の各表に含まれる。臨床検査値の詳細は治験総括報告書に記載した（SGN-35-OU 試験　治験総括報告書　12.4）。

2.7.4.4 バイタルサイン、身体的所見及び安全性に関連する他の観察項目

（1）C25001 試験

定期的にバイタルサイン、身体的所見及び ECOG performance status のデータを収集し、臨床的に意味のある所見は有害事象として報告した。全体として特記すべき所見及び傾向は認められなかった。

ECOG performance status のベースラインからの最大変化は、両投与群のほとんどの被験者で 1 以内であった〔本剤群 58 例（88%）、治験責任医師が選択した化学療法群 57 例（92%）〕（C25001 試験　治験総括報告書　Table 14.4.4.14B）。

免疫再構築評価の要約を C25001 試験　治験総括報告書　Table 14.4.4.5 に、ベースライン時からの変化を C25001 試験　治験総括報告書　Table 14.4.4.10 に示した。

これら項目の詳細を治験総括報告書に記載した（C25001 試験　治験総括報告書　12.5）。

免疫原性

本剤群の被験者の ADA 及び Nab の発現状況を 2.7.2.2.1.2 に示した。母集団薬物動態解析の結果、ブレンツキシマブ　ベドチンに対する免疫原性は ADC の薬物動態に対して臨床的に意味のある影響を及ぼさないと考えられた〔2.7.2.3.1.1（2）〕。

被験者の ADA 及び Nab の発現状況と有害事象の発現に相関は示されていない（C25001 試験　治験総括報告書　Table 12.dd）。

ADA の発現状況と注入に伴う反応の関係

本剤群で注入に伴う反応を発現した被験者 9 例のうち、ベースライン時に ADA 陽性であった 1 例は、試験期間中も一時的 ADA 陽性であり、ADA 抗体価は一貫して低かった。ベースライン時に ADA 陰性であった 8 例のうち、5 例は試験期間中に ADA 陽性となった（3 例は持続的 ADA 陽性、2 例は一時的 ADA 陽性）。残りの 3 例は試験期間を通して ADA 陰性であった〔2.7.4.2.1.5（5）1）〕。

最終解析時点で、免疫原性の評価が可能であった被験者 60 例における注入に伴う反応の発現状況を ADA 発現状況別に表 2.7.4.4-1 に示した。

試験期間を通して ADA 陰性のままであった 31 例のうち 3 例（10%）で 1 回以上の注入に伴う反応が発現した。ベースライン時に ADA 陰性であったが試験期間中に一時的又は持続的 ADA 陽性となった 25 例のうち、20 例（80%）では、全てのサイクルで注入に伴う反応は発現しなかった。ベースライン時に ADA 陽性であった 4 例のうち、試験期間中に一時的 ADA 陽性となった 1 例で 1 回以上の注入に伴う反応が認められた。残りの 3 例では注入に伴う反応は報告されなかった。

表 2.7.4.4-1　ADA 発現状況別の注入に伴う反応の概要
（C25001 試験、免疫原性評価可能集団(e)、最終解析時点）

Patients Treated With Brentuximab Vedotin, n (%)	ADA Baseline Positive (n=4)	ADA Baseline Negative (n=56)	Overall (N=60)
With IRRs in Cycle 1	0	0	0
ADA negative	1 (25)	31 (55)	32 (53)
IRRs in any cycle (a)	0	3 (10)	3 (9)
ADA transiently positive	3 (75)	13 (23)	16 (27)
IRRs in any cycle (b)	1 (33)	2 (15)	3 (19)
ADA persistently positive	0	12 (21)	12 (20)
IRRs in any cycle (c)	0	3 (25)	3 (25)
ADA transiently or persistently positive	3 (75)	25 (45)	28 (47)
No IRRs in any cycle (d)	2 (67)	20 (80)	22 (79)

出典：C25001 試験　治験総括報告書　Table 14.4.1.12B
ADA: antitherapeutic antibody(ies); IRR: infusion-related reaction; TEAE: treatment-emergent adverse event.
Table includes only those patients who received brentuximab vedotin who had an immunogenicity sample at baseline and ≥1 postbaseline visit. IRRs were defined as TEAEs related to the infusion of brentuximab vedotin.
ADA baseline positive was defined as patients with confirmed ADA-positive response at baseline.
ADA baseline negative was defined as ADA response negative (ie, not confirmed positive) at the baseline visit.
Transiently positive was defined as 1 or 2 postbaseline-confirmed ADA-positive responses.
Persistently positive was defined as >2 postbaseline-confirmed ADA positive responses.
Negative was defined as ADA response negative (ie, not confirmed positive) at all postbaseline time points.
(a) Number of patients with ADA negative status was used as denominator.
(b) Number of patients with transiently positive ADA status was used as denominator.
(c) Number of patients with persistently positive ADA status was used as denominator.
(d) Number of patients with transiently or persistently positive ADA status was used as denominator.
(e) Patients with a sample at baseline and at least one post-baseline visit.

（2）SGN-35-OU 試験

定期的にバイタルサイン、身体的所見及び ECOG performance status のデータを収集し、臨床的に意味のある所見は有害事象として報告した。全体として特記すべき所見及び傾向は認められなかった。

FAS2 の被験者の EGOC performance status は概ね維持されていた。ECOG performance status のベースラインからの最大変化は、両投与群のほとんどの被験者で変化はなく（0 から変化なしが 10 例、1 から変化なしが 4 例）、1 例は 0 から 1 へ、1 例は 2 から 1 へ変化した（SGN-35-OU 試験　治験総括報告書　表 14.3.7-4）。

免疫再構築評価の要約は治験総括報告書に記載した（SGN-35-OU 試験　治験総括報告書 12.5.4）。

SGN-35-OU 試験では、免疫原性は評価しなかった。

2.7.4.5 特別な患者集団及び状況下における安全性

2.7.4.5.1 内因性要因

2.7.4.5.1.1 年齢

C25001 試験の本剤群における年齢別の有害事象の要約を表 2.7.4.5-1 に示した。安全性解析対象集団の本剤群では、60 歳以上は 35 例、65 歳以上は 28 例、70 歳以上は 16 例、75 歳以上は 9 例であり、これら全ての高齢カテゴリにおける有害事象全体の発現頻度は本剤群全体と比較して概ね同様であった。また、発現した事象の種類並びに発現頻度も、各高齢カテゴリ及び本剤群全体で臨床的に意味のある違いは認められなかった（2.7.4.8　ADT14.4.1.3B）。

表 2.7.4.5-1　年齢別の有害事象の概要（C25001 試験、安全性解析対象集団、最終解析時点）

	Brentuximab Vedotin					Methotrexate or Bexarotene
Patients, n (%)	≥60 Years (N=35)	≥65 Years (N=28)	≥70 Years (N=16)	≥75 Years (N=9)	All Patients (N=66)	All Patients (N=62)
Any TEAE	33 (94)	26 (93)	15 (94)	8 (89)	63 (95)	56 (90)
Any ≥Grade 3 TEAE	15 (43)	12 (43)	6 (38)	4 (44)	27 (41)	29 (47)
Treatment-related TEAE	29 (83)	23 (82)	13 (81)	6 (67)	57 (86)	44 (71)
Treatment-related ≥Grade 3 TEAE	9 (26)	7 (25)	2 (13)	1 (11)	19 (29)	18 (29)
Serious TEAE	9 (26)	8 (29)	5 (31)	4 (44)	19 (29)	18 (29)
Treatment-related SAE	3 (9)	2 (7)	1 (6)	1 (11)	9 (14)	3 (5)
TEAE resulting in treatment discontinuation	11 (31)	10 (36)	5 (31)	2 (22)	16 (24) (a)	5 (8)
Deaths ≤30 days after last dose	2 (6)	2 (7)	1 (6)	1 (11)	4 (6)	0

出典：2.7.4.8　Table ADT14.4.1.1

AE: adverse event; EOT: end of treatment; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Treatment-emergent is defined as newly occurring (not present at baseline) or worsening after first dose of study drug and up through 30 days after the last study drug dose. A patient was counted only once for each type of event. Relatedness (causality) to study drug was assessed by the investigator.

(a) Study drug was discontinued because of an AE in 1 additional patient in the brentuximab vedotin arm, but the event was erroneously reported on the patient's EOT form. The AE (lymphoma) subsequently became fatal

55

2.7.4.5.1.2 肝及び腎機能不全

C25001 試験及び SGN-35-OU 試験では、肝機能障害又は腎機能障害を有する患者を試験から除外した。スクリーニング時に肝機能（総ビリルビン、AST 又は ALT）及び腎機能（クレアチニンクリアランス）が基準を満たした患者のみがこれら試験に登録された。

2.7.4.5.1.3 日本人 CTCL 患者における本剤の安全性

SGN-35-OU 試験では、日本人 CTCL 患者を対象に本剤 1.8 mg/kg を 3 週に 1 回、最大 16 サイクル投与した。SGN-35-OU 試験の SAF2 でみられた安全性の結果は、海外第 3 相国際共同治験である C25001 試験で外国人 CTCL 患者に本剤 1.8 mg/kg を 3 週に 1 回、最大 16 サイクル投与したときの安全性プロファイルと概ね一致していた。また、SGN-35-OU 試験の結果は、国内で承認されている適応で本剤を単剤投与した臨床試験の安全性の結果と大きな違いはなく、日本人 CTCL 患者で新たな安全性シグナルは認められなかった。

本剤を日本人 CTCL 患者に投与したときの安全性結果の詳細を 2.7.4.2、2.7.4.3 及び 2.7.4.4 に示した。

このように、本剤 1.8 mg/kg を 3 週に 1 回、最大 16 サイクル投与は、日本人の再発又は難治性の CD30 陽性の CTCL 患者に対して忍容可能かつ管理可能な安全性プロファイルを示した。

2.7.4.5.2 外因性要因

C25001 試験では、地理的地域などの外因性要因による部分集団解析は行わなかった。

2.7.4.5.3 薬物相互作用

C25001 試験及び SGN-35-OU 試験では、薬物相互作用の評価は行わなかった。

2.7.4.5.4 妊娠及び授乳時の使用

C25001 試験及び SGN-35-OU 試験では妊娠例は報告されていない。

C25001 試験では、妊娠可能な女性は、スクリーニング時の血清妊娠検査及び各治療サイクル 1 日目の尿妊娠検査が陰性であることとしており、同意取得時から試験治療の最終投与後 30 日間は効果的な避妊法を二重に用いる又は完全な禁欲に合意することとした。また、男性は、試験期間及び試験治療の最終投与後 6 ヵ月間は効果的な避妊法を用いる又は完全な禁欲に合意することとした。

また、SGN-35-OU 試験では、女性患者はスクリーニング期間中の血清妊娠検査及び各治療サイクル 1 日目の尿妊娠検査が陰性であることとしており、妊娠の可能性のある閉経前の女性患者は同意取得時から治験薬の最終投与後 6 ヵ月まで、又は、妊娠能力を有する男性患者の場合には治験薬投与期間及び治験薬の最終投与後 6 ヵ月まで医学的に承認された方法により避妊することに同意することとした。

現在、本剤の乳汁中への移行、乳汁を介した幼児への影響又は乳汁産生への影響に関する利用可能な情報はない。授乳中の幼児に重篤な有害反応が生じる可能性があるため、本剤投与中の授乳は推奨しない。

2.7.4.5.5 過量投与

ブレンツキシマブ　ベドチンには、過剰摂取に対する既知の解毒剤はない。

C25001 試験及び SGN-35-OU 試験では、過量投与は認められなかった。

2.7.4.5.6 薬物乱用

該当せず

2.7.4.5.7 離脱症状及び反跳現象

該当せず

2.7.4.5.8 自動車運転及び機械操作に対する影響又は精神機能の障害

本剤が自動車運転及び機械操作に軽微な影響を及ぼす可能性が示唆されているが、C25001 試験及び SGN-35-OU 試験からは追加すべき新たなデータは得られなかった。

2.7.4.6 市販後データ

本剤の国際誕生日は 2011 年 8 月 19 日（米国）であり、2022 年 8 月 18 日時点で 77 の国と地域で承認されている。

最新の定期的ベネフィットリスク評価報告（PBRER）では、2022 年 8 月 18 日時点で、本剤の製造販売後の世界累積推定曝露人数は 1 年あたり約 108,981 人であった（5.3.6-1 PBRER）。

当該調査単位期間中に入手した安全性情報及び累積されたデータを評価した結果、本剤のベネフィット・リスク評価に影響を及ぼすような重大な情報はなく、本剤のベネフィット・リスクプロファイルは引き続き良好であると考える。

2.7.4.7 参考文献

[1] Horwitz SM, Olsen EA, Duvic M, Porcu P, Kim YH. Review of the treatment of mycosis fungoides and sézary syndrome: a stage-based Approach. J Natl Compr Canc Netw 2008;6(4):436-42.

[2] Methotrexate (prescribing information) - 2016. Huntsville, AL, USA: DAVA Pharmaceuticals, Inc., 2016.

[3] Methotrexate (Summary of Product Characteristics). UK: Hospira UK Ltd, 2016.

[4] Targretin (bexarotene) [US Package Insert]. San Diego, CA 92121: Ligand Pharmaceuticals Incorporated, 2016.

[5] Targretin (bexarotene) [Summary of Product Characteristics]. Hertfordshire, UK: Eisai Ltd, 2015.

2.7.4.8 付録

LIST OF APPENDIX TABLES

Table ADT14.4.1.1 Overall Summary of Treatment-Emergent Adverse Events (Safety Population)....1
Table ADT14.4.1.3B Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events (Safety Population)....3
Table 14.3.1.7 Summary of Overall Survival (OS) (ITT Population)....31
Table 14.4.1.2B Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term (Safety Population)....33
Table 14.4.1.4B Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity (Safety Population)....73

Table ADT14.4.1.1
Overall Summary of Treatment-Emergent Adverse Events
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Any adverse event	33 (94)	26 (93)	15 (94)	8 (89)	63 (95)	27 (90)	21 (91)	11 (92)	4 (100)	56 (90)
Grade 3 or higher adverse event	15 (43)	12 (43)	6 (38)	4 (44)	27 (41)	13 (43)	11 (48)	5 (42)	2 (50)	29 (47)
Drug-related adverse event	29 (83)	23 (82)	13 (81)	6 (67)	57 (86)	22 (73)	17 (74)	8 (67)	3 (75)	44 (71)
Drug-related Grade 3 or higher adverse event	9 (26)	7 (25)	2 (13)	1 (11)	19 (29)	10 (33)	8 (35)	3 (25)	1 (25)	18 (29)
Serious adverse event	9 (26)	8 (29)	5 (31)	4 (44)	19 (29)	9 (30)	7 (30)	4 (33)	3 (75)	18 (29)
Drug-related serious adverse event	3 (9)	2 (7)	1 (6)	1 (11)	9 (14)	2 (7)	2 (9)	2 (17)	2 (50)	3 (5)
Adverse events resulting in study drug discontinuation	11 (31)	10 (36)	5 (31)	2 (22)	16 (24)	4 (13)	4 (17)	2 (17)	1 (25)	5 (8)
On-study deaths	2 (6)	2 (7)	1 (6)	1 (11)	4 (6)	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
A patient counts once for each type of event.
On-study deaths are defined as deaths that occur within 30 days of the last dose of study drug.
AEs will be coded using the MedDRA dictionary Version 19.0.

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\ADT14.4.1.1-ov_teae_agegroup.sas 09JAN2017: 15:26

Table ADT14.4.1.1
Overall Summary of Treatment-Emergent Adverse Events
Safety Population

	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Any adverse event	17 (89)	15 (88)	7 (88)	2 (100)	33 (89)	10 (91)	6 (100)	4 (100)	2 (100)	23 (92)
Grade 3 or higher adverse event	10 (53)	9 (53)	3 (38)	1 (50)	20 (54)	3 (27)	2 (33)	2 (50)	1 (50)	9 (36)
Drug-related adverse event	15 (79)	13 (76)	5 (63)	2 (100)	30 (81)	7 (64)	4 (67)	3 (75)	1 (50)	14 (56)
Drug-related Grade 3 or higher adverse event	9 (47)	8 (47)	3 (38)	1 (50)	15 (41)	1 (9)	0	0	0	3 (12)
Serious adverse event	6 (32)	5 (29)	2 (25)	1 (50)	9 (24)	3 (27)	2 (33)	2 (50)	2 (100)	9 (36)
Drug-related serious adverse event	1 (5)	1 (6)	1 (13)	1 (50)	1 (3)	1 (9)	1 (17)	1 (25)	1 (50)	2 (8)
Adverse events resulting in study drug discontinuation	3 (16)	3 (18)	1 (13)	1 (50)	4 (11)	1 (9)	1 (17)	1 (25)	0	1 (4)
On-study deaths	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
A patient counts once for each type of event.
On-study deaths are defined as deaths that occur within 30 days of the last dose of study drug.
AEs will be coded using the MedDRA dictionary Version 19.0.

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\ADT14.4.1.1-ov_teae_agegroup.sas 09JAN2017: 15:26

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Patients with At least 1 Adverse Event[a]	33 (94)	26 (93)	15 (94)	8 (89)	63 (95)	27 (90)	21 (91)	11 (92)	4 (100)	56 (90)
Nervous system disorders	24 (69)	20 (71)	11 (69)	6 (67)	47 (71)	5 (17)	3 (13)	0	0	12 (19)
Peripheral neuropathies NEC	19 (54)	17 (61)	9 (56)	5 (56)	35 (53)	0	0	0	0	1 (2)
Peripheral sensory neuropathy	17 (49)	15 (54)	7 (44)	4 (44)	30 (45)	0	0	0	0	1 (2)
Peripheral motor neuropathy	3 (9)	2 (7)	1 (6)	0	4 (6)	0	0	0	0	0
Neuropathy peripheral	1 (3)	1 (4)	1 (6)	0	3 (5)	0	0	0	0	0
Paraesthesias and dysaesthesias	5 (14)	3 (11)	1 (6)	0	9 (14)	1 (3)	0	0	0	1 (2)
Paraesthesia	3 (9)	1 (4)	1 (6)	0	6 (9)	1 (3)	0	0	0	1 (2)
Hypoaesthesia	2 (6)	2 (7)	0	0	3 (5)	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Patients with At least 1 Adverse Event[a]	17 (89)	15 (88)	7 (88)	2 (100)	33 (89)	10 (91)	6 (100)	4 (100)	2 (100)	23 (92)
Nervous system disorders	4 (21)	3 (18)	0	0	9 (24)	1 (9)	0	0	0	3 (12)
Peripheral neuropathies NEC	0	0	0	0	0	0	0	0	0	1 (4)
Peripheral sensory neuropathy	0	0	0	0	0	0	0	0	0	1 (4)
Peripheral motor neuropathy	0	0	0	0	0	0	0	0	0	0
Neuropathy peripheral	0	0	0	0	0	0	0	0	0	0
Paraesthesias and dysaesthesias	1 (5)	0	0	0	1 (3)	0	0	0	0	0
Paraesthesia	1 (5)	0	0	0	1 (3)	0	0	0	0	0
Hypoaesthesia	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Nervous system disorders										
Sensory abnormalities NEC	6 (17)	6 (21)	3 (19)	2 (22)	9 (14)	1 (3)	0	0	0	1 (2)
Dysgeusia	4 (11)	4 (14)	2 (13)	2 (22)	5 (8)	0	0	0	0	0
Headaches NEC	3 (9)	2 (7)	0	0	6 (9)	1 (3)	1 (4)	0	0	6 (10)
Headache	2 (6)	1 (4)	0	0	5 (8)	1 (3)	1 (4)	0	0	6 (10)
Neurological signs and symptoms NEC	4 (11)	3 (11)	2 (13)	2 (22)	5 (8)	0	0	0	0	1 (2)
Dizziness	4 (11)	3 (11)	2 (13)	2 (22)	5 (8)	0	0	0	0	1 (2)
Gastrointestinal disorders	22 (63)	18 (64)	8 (50)	3 (33)	40 (61)	10 (33)	7 (30)	4 (33)	2 (50)	23 (37)
Nausea and vomiting symptoms	16 (46)	13 (46)	6 (38)	3 (33)	27 (41)	4 (13)	3 (13)	3 (25)	2 (50)	10 (16)
Nausea	15 (43)	12 (43)	5 (31)	3 (33)	24 (36)	4 (13)	3 (13)	3 (25)	2 (50)	8 (13)
Vomiting	6 (17)	6 (21)	4 (25)	2 (22)	11 (17)	0	0	0	0	3 (5)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Nervous system disorders										
Sensory abnormalities NEC	0	0	0	0	0	1 (9)	0	0	0	1 (4)
Dysgeusia	0	0	0	0	0	0	0	0	0	0
Headaches NEC	1 (5)	1 (6)	0	0	5 (14)	0	0	0	0	1 (4)
Headache	1 (5)	1 (6)	0	0	5 (14)	0	0	0	0	1 (4)
Neurological signs and symptoms NEC	0	0	0	0	1 (3)	0	0	0	0	0
Dizziness	0	0	0	0	1 (3)	0	0	0	0	0
Gastrointestinal disorders	5 (26)	4 (24)	1 (13)	0	12 (32)	5 (45)	3 (50)	3 (75)	2 (100)	11 (44)
Nausea and vomiting symptoms	0	0	0	0	4 (11)	4 (36)	3 (50)	3 (75)	2 (100)	6 (24)
Nausea	0	0	0	0	4 (11)	4 (36)	3 (50)	3 (75)	2 (100)	4 (16)
Vomiting	0	0	0	0	1 (3)	0	0	0	0	2 (8)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Gastrointestinal disorders										
Diarrhoea (excl infective)	9 (26)	8 (29)	3 (19)	2 (22)	19 (29)	2 (7)	1 (4)	0	0	4 (6)
Diarrhoea	9 (26)	8 (29)	3 (19)	2 (22)	19 (29)	2 (7)	1 (4)	0	0	4 (6)
Gastrointestinal atonic and hypomotility disorders NEC	4 (11)	4 (14)	1 (6)	0	4 (6)	2 (7)	2 (9)	1 (8)	0	6 (10)
Constipation	3 (9)	3 (11)	1 (6)	0	3 (5)	2 (7)	2 (9)	1 (8)	0	4 (6)
Gastrointestinal and abdominal pains (excl oral and throat)	2 (6)	2 (7)	0	0	3 (5)	1 (3)	1 (4)	1 (8)	0	3 (5)
Abdominal pain upper	1 (3)	1 (4)	0	0	1 (2)	1 (3)	1 (4)	1 (8)	0	3 (5)
General disorders and administration site conditions	23 (66)	17 (61)	11 (69)	5 (56)	39 (59)	16 (53)	12 (52)	6 (50)	3 (75)	36 (58)
Asthenic conditions	17 (49)	13 (46)	9 (56)	5 (56)	26 (39)	13 (43)	10 (43)	5 (42)	2 (50)	22 (35)
Fatigue	12 (34)	10 (36)	6 (38)	3 (33)	19 (29)	9 (30)	7 (30)	4 (33)	2 (50)	17 (27)
Asthenia	5 (14)	3 (11)	3 (19)	2 (22)	7 (11)	4 (13)	3 (13)	1 (8)	0	5 (8)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\ADT14.4.1.3B-teae_comn5_agegroup.sas 10JAN2017: 10:16

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Gastrointestinal disorders										
Diarrhoea (excl infective)	2 (11)	1 (6)	0	0	3 (8)	0	0	0	0	1 (4)
Diarrhoea	2 (11)	1 (6)	0	0	3 (8)	0	0	0	0	1 (4)
Gastrointestinal atonic and hypomotility disorders NEC	2 (11)	2 (12)	1 (13)	0	4 (11)	0	0	0	0	2 (8)
Constipation	2 (11)	2 (12)	1 (13)	0	4 (11)	0	0	0	0	0
Gastrointestinal and abdominal pains (excl oral and throat)	0	0	0	0	0	1 (9)	1 (17)	1 (25)	0	3 (12)
Abdominal pain upper	0	0	0	0	0	1 (9)	1 (17)	1 (25)	0	3 (12)
General disorders and administration site conditions	9 (47)	8 (47)	2 (25)	1 (50)	19 (51)	7 (64)	4 (67)	4 (100)	2 (100)	17 (68)
Asthenic conditions	8 (42)	7 (41)	2 (25)	1 (50)	14 (38)	5 (45)	3 (50)	3 (75)	1 (50)	8 (32)
Fatigue	6 (32)	5 (29)	2 (25)	1 (50)	12 (32)	3 (27)	2 (33)	2 (50)	1 (50)	5 (20)
Asthenia	2 (11)	2 (12)	0	0	2 (5)	2 (18)	1 (17)	1 (25)	0	3 (12)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
General disorders and administration site conditions										
Febrile disorders	4 (11)	2 (7)	2 (13)	1 (11)	11 (17)	3 (10)	3 (13)	1 (8)	1 (25)	11 (18)
Pyrexia	4 (11)	2 (7)	2 (13)	1 (11)	11 (17)	3 (10)	3 (13)	1 (8)	1 (25)	11 (18)
Oedema NEC	4 (11)	2 (7)	1 (6)	0	7 (11)	3 (10)	2 (9)	2 (17)	1 (25)	7 (11)
Oedema peripheral	4 (11)	2 (7)	1 (6)	0	7 (11)	3 (10)	2 (9)	2 (17)	1 (25)	6 (10)
Feelings and sensations NEC	4 (11)	4 (14)	2 (13)	0	5 (8)	1 (3)	0	0	0	2 (3)
Chills	3 (9)	3 (11)	2 (13)	0	4 (6)	1 (3)	0	0	0	2 (3)
General signs and symptoms NEC	3 (9)	2 (7)	1 (6)	1 (11)	5 (8)	2 (7)	2 (9)	2 (17)	1 (25)	6 (10)
Peripheral swelling	1 (3)	0	0	0	1 (2)	2 (7)	2 (9)	2 (17)	1 (25)	4 (6)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\ADT14.4.1.3B-teae_comn5_agegroup.sas 10JAN2017: 10:16

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
General disorders and administration site conditions										
Febrile disorders	2 (11)	2 (12)	0	0	4 (11)	1 (9)	1 (17)	1 (25)	1 (50)	7 (28)
Pyrexia	2 (11)	2 (12)	0	0	4 (11)	1 (9)	1 (17)	1 (25)	1 (50)	7 (28)
Oedema NEC	1 (5)	1 (6)	1 (13)	1 (50)	2 (5)	2 (18)	1 (17)	1 (25)	0	5 (20)
Oedema peripheral	1 (5)	1 (6)	1 (13)	1 (50)	2 (5)	2 (18)	1 (17)	1 (25)	0	4 (16)
Feelings and sensations NEC	0	0	0	0	0	1 (9)	0	0	0	2 (8)
Chills	0	0	0	0	0	1 (9)	0	0	0	2 (8)
General signs and symptoms NEC	1 (5)	1 (6)	1 (13)	0	3 (8)	1 (9)	1 (17)	1 (25)	1 (50)	3 (12)
Peripheral swelling	1 (5)	1 (6)	1 (13)	0	3 (8)	1 (9)	1 (17)	1 (25)	1 (50)	1 (4)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Skin and subcutaneous tissue disorders	20 (57)	14 (50)	8 (50)	3 (33)	34 (52)	8 (27)	7 (30)	4 (33)	1 (25)	20 (32)
Pruritus NEC	13 (37)	8 (29)	5 (31)	1 (11)	18 (27)	4 (13)	4 (17)	2 (17)	0	9 (15)
Pruritus	8 (23)	5 (18)	3 (19)	1 (11)	11 (17)	4 (13)	4 (17)	2 (17)	0	8 (13)
Pruritus generalised	5 (14)	3 (11)	2 (13)	0	7 (11)	0	0	0	0	1 (2)
Alopecias	8 (23)	8 (29)	4 (25)	1 (11)	10 (15)	0	0	0	0	2 (3)
Alopecia	8 (23)	8 (29)	4 (25)	1 (11)	10 (15)	0	0	0	0	2 (3)
Rashes, eruptions and exanthems NEC	4 (11)	3 (11)	2 (13)	1 (11)	8 (12)	1 (3)	1 (4)	1 (8)	0	3 (5)
Rash maculo-papular	3 (9)	2 (7)	1 (6)	0	7 (11)	1 (3)	1 (4)	1 (8)	0	3 (5)
Urticarias	1 (3)	0	0	0	5 (8)	1 (3)	0	0	0	1 (2)
Urticaria	1 (3)	0	0	0	5 (8)	1 (3)	0	0	0	1 (2)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\ADT14.4.1.3B-teae_comn5_agegroup.sas 10JAN2017: 10:16

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Skin and subcutaneous tissue disorders	6 (32)	5 (29)	2 (25)	0	14 (38)	2 (18)	2 (33)	2 (50)	1 (50)	6 (24)
Pruritus NEC	4 (21)	4 (24)	2 (25)	0	7 (19)	0	0	0	0	2 (8)
Pruritus	4 (21)	4 (24)	2 (25)	0	6 (16)	0	0	0	0	2 (8)
Pruritus generalised	0	0	0	0	1 (3)	0	0	0	0	0
Alopecias	0	0	0	0	1 (3)	0	0	0	0	1 (4)
Alopecia	0	0	0	0	1 (3)	0	0	0	0	1 (4)
Rashes, eruptions and exanthems NEC	0	0	0	0	2 (5)	1 (9)	1 (17)	1 (25)	0	1 (4)
Rash maculo-papular	0	0	0	0	2 (5)	1 (9)	1 (17)	1 (25)	0	1 (4)
Urticarias	1 (5)	0	0	0	1 (3)	0	0	0	0	0
Urticaria	1 (5)	0	0	0	1 (3)	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Skin and subcutaneous tissue disorders										
Acnes	2 (6)	0	0	0	3 (5)	0	0	0	0	0
Dermatitis acneiform	2 (6)	0	0	0	3 (5)	0	0	0	0	0
Dermal and epidermal conditions NEC	2 (6)	1 (4)	0	0	2 (3)	2 (7)	2 (9)	1 (8)	0	5 (8)
Dry skin	1 (3)	0	0	0	1 (2)	1 (3)	1 (4)	0	0	4 (6)
Infections and infestations	13 (37)	10 (36)	5 (31)	2 (22)	29 (44)	18 (60)	15 (65)	8 (67)	3 (75)	32 (52)
Upper respiratory tract infections	5 (14)	5 (18)	2 (13)	1 (11)	10 (15)	2 (7)	2 (9)	2 (17)	2 (50)	4 (6)
Upper respiratory tract infection	3 (9)	3 (11)	1 (6)	1 (11)	4 (6)	0	0	0	0	2 (3)
Nasopharyngitis	0	0	0	0	3 (5)	1 (3)	1 (4)	1 (8)	1 (25)	1 (2)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Skin and subcutaneous tissue disorders										
Acnes	0	0	0	0	0	0	0	0	0	0
Dermatitis acneiform	0	0	0	0	0	0	0	0	0	0
Dermal and epidermal conditions NEC	2 (11)	2 (12)	1 (13)	0	4 (11)	0	0	0	0	1 (4)
Dry skin	1 (5)	1 (6)	0	0	3 (8)	0	0	0	0	1 (4)
Infections and infestations	10 (53)	9 (53)	4 (50)	1 (50)	17 (46)	8 (73)	6 (100)	4 (100)	2 (100)	15 (60)
Upper respiratory tract infections	0	0	0	0	2 (5)	2 (18)	2 (33)	2 (50)	2 (100)	2 (8)
Upper respiratory tract infection	0	0	0	0	2 (5)	0	0	0	0	0
Nasopharyngitis	0	0	0	0	0	1 (9)	1 (17)	1 (25)	1 (50)	1 (4)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Infections and infestations										
Skin structures and soft tissue infections	3 (9)	2 (7)	0	0	6 (9)	5 (17)	4 (17)	0	0	7 (11)
Impetigo	1 (3)	1 (4)	0	0	3 (5)	0	0	0	0	0
Skin infection	1 (3)	1 (4)	0	0	2 (3)	5 (17)	4 (17)	0	0	7 (11)
Urinary tract infections	3 (9)	3 (11)	2 (13)	1 (11)	5 (8)	3 (10)	3 (13)	2 (17)	1 (25)	4 (6)
Urinary tract infection	3 (9)	3 (11)	2 (13)	1 (11)	5 (8)	3 (10)	3 (13)	2 (17)	1 (25)	4 (6)
Bacterial infections NEC	1 (3)	1 (4)	1 (6)	0	3 (5)	1 (3)	0	0	0	3 (5)
Cellulitis	1 (3)	1 (4)	1 (6)	0	3 (5)	0	0	0	0	2 (3)
Sepsis, bacteraemia, viraemia and fungaemia NEC	0	0	0	0	1 (2)	1 (3)	1 (4)	0	0	4 (6)
Sepsis	0	0	0	0	1 (2)	0	0	0	0	3 (5)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\ADT14.4.1.3B-teae_comn5_agegroup.sas 10JAN2017: 10:16

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Infections and infestations										
Skin structures and soft tissue infections	3 (16)	3 (18)	0	0	4 (11)	2 (18)	1 (17)	0	0	3 (12)
Impetigo	0	0	0	0	0	0	0	0	0	0
Skin infection	3 (16)	3 (18)	0	0	4 (11)	2 (18)	1 (17)	0	0	3 (12)
Urinary tract infections	1 (5)	1 (6)	0	0	1 (3)	2 (18)	2 (33)	2 (50)	1 (50)	3 (12)
Urinary tract infection	1 (5)	1 (6)	0	0	1 (3)	2 (18)	2 (33)	2 (50)	1 (50)	3 (12)
Bacterial infections NEC	1 (5)	0	0	0	3 (8)	0	0	0	0	0
Cellulitis	0	0	0	0	2 (5)	0	0	0	0	0
Sepsis, bacteraemia, viraemia and fungaemia NEC	1 (5)	1 (6)	0	0	3 (8)	0	0	0	0	1 (4)
Sepsis	0	0	0	0	2 (5)	0	0	0	0	1 (4)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Infections and infestations										
Staphylococcal infections	1 (3)	0	0	0	1 (2)	4 (13)	3 (13)	2 (17)	0	6 (10)
Staphylococcal skin infection	1 (3)	0	0	0	1 (2)	4 (13)	3 (13)	2 (17)	0	5 (8)
Musculoskeletal and connective tissue disorders	10 (29)	8 (29)	5 (31)	3 (33)	22 (33)	7 (23)	6 (26)	2 (17)	1 (25)	14 (23)
Musculoskeletal and connective tissue pain and discomfort	6 (17)	4 (14)	2 (13)	1 (11)	9 (14)	4 (13)	3 (13)	0	0	6 (10)
Pain in extremity	4 (11)	2 (7)	2 (13)	1 (11)	6 (9)	2 (7)	1 (4)	0	0	4 (6)
Joint related signs and symptoms	3 (9)	2 (7)	1 (6)	0	8 (12)	2 (7)	2 (9)	2 (17)	1 (25)	4 (6)
Arthralgia	3 (9)	2 (7)	1 (6)	0	8 (12)	2 (7)	2 (9)	2 (17)	1 (25)	4 (6)
Muscle pains	4 (11)	4 (14)	3 (19)	2 (22)	8 (12)	2 (7)	2 (9)	0	0	2 (3)
Myalgia	4 (11)	4 (14)	3 (19)	2 (22)	8 (12)	2 (7)	2 (9)	0	0	2 (3)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Infections and infestations										
Staphylococcal infections	2 (11)	2 (12)	2 (25)	0	3 (8)	2 (18)	1 (17)	0	0	3 (12)
Staphylococcal skin infection	2 (11)	2 (12)	2 (25)	0	3 (8)	2 (18)	1 (17)	0	0	2 (8)
Musculoskeletal and connective tissue disorders	6 (32)	5 (29)	1 (13)	0	12 (32)	1 (9)	1 (17)	1 (25)	1 (50)	2 (8)
Musculoskeletal and connective tissue pain and discomfort	4 (21)	3 (18)	0	0	6 (16)	0	0	0	0	0
Pain in extremity	2 (11)	1 (6)	0	0	4 (11)	0	0	0	0	0
Joint related signs and symptoms	1 (5)	1 (6)	1 (13)	0	2 (5)	1 (9)	1 (17)	1 (25)	1 (50)	2 (8)
Arthralgia	1 (5)	1 (6)	1 (13)	0	2 (5)	1 (9)	1 (17)	1 (25)	1 (50)	2 (8)
Muscle pains	2 (11)	2 (12)	0	0	2 (5)	0	0	0	0	0
Myalgia	2 (11)	2 (12)	0	0	2 (5)	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Musculoskeletal and connective tissue disorders										
Muscle related signs and symptoms NEC	3 (9)	3 (11)	1 (6)	1 (11)	5 (8)	0	0	0	0	3 (5)
Muscle spasms	2 (6)	2 (7)	1 (6)	1 (11)	4 (6)	0	0	0	0	3 (5)
Metabolism and nutrition disorders	13 (37)	11 (39)	5 (31)	4 (44)	21 (32)	10 (33)	9 (39)	6 (50)	2 (50)	18 (29)
Appetite disorders	7 (20)	6 (21)	2 (13)	1 (11)	10 (15)	3 (10)	3 (13)	2 (17)	2 (50)	3 (5)
Decreased appetite	7 (20)	6 (21)	2 (13)	1 (11)	10 (15)	3 (10)	3 (13)	2 (17)	2 (50)	3 (5)
Hyperglycaemic conditions NEC	3 (9)	2 (7)	1 (6)	1 (11)	6 (9)	0	0	0	0	0
Hyperglycaemia	3 (9)	2 (7)	1 (6)	1 (11)	6 (9)	0	0	0	0	0
Disorders of purine metabolism	3 (9)	2 (7)	1 (6)	1 (11)	4 (6)	1 (3)	1 (4)	1 (8)	0	2 (3)
Hyperuricaemia	3 (9)	2 (7)	1 (6)	1 (11)	4 (6)	1 (3)	1 (4)	1 (8)	0	2 (3)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Musculoskeletal and connective tissue disorders										
Muscle related signs and symptoms NEC	0	0	0	0	3 (8)	0	0	0	0	0
Muscle spasms	0	0	0	0	3 (8)	0	0	0	0	0
Metabolism and nutrition disorders	8 (42)	7 (41)	4 (50)	1 (50)	14 (38)	2 (18)	2 (33)	2 (50)	1 (50)	4 (16)
Appetite disorders	2 (11)	2 (12)	1 (13)	1 (50)	2 (5)	1 (9)	1 (17)	1 (25)	1 (50)	1 (4)
Decreased appetite	2 (11)	2 (12)	1 (13)	1 (50)	2 (5)	1 (9)	1 (17)	1 (25)	1 (50)	1 (4)
Hyperglycaemic conditions NEC	0	0	0	0	0	0	0	0	0	0
Hyperglycaemia	0	0	0	0	0	0	0	0	0	0
Disorders of purine metabolism	0	0	0	0	0	1 (9)	1 (17)	1 (25)	0	2 (8)
Hyperuricaemia	0	0	0	0	0	1 (9)	1 (17)	1 (25)	0	2 (8)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Metabolism and nutrition disorders										
Elevated triglycerides	0	0	0	0	1 (2)	7 (23)	6 (26)	4 (33)	1 (25)	11 (18)
Hypertriglyceridaemia	0	0	0	0	1 (2)	7 (23)	6 (26)	4 (33)	1 (25)	11 (18)
Elevated cholesterol	0	0	0	0	0	2 (7)	2 (9)	1 (8)	0	4 (6)
Hypercholesterolaemia	0	0	0	0	0	2 (7)	2 (9)	1 (8)	0	4 (6)
Investigations	6 (17)	5 (18)	1 (6)	0	15 (23)	10 (33)	9 (39)	4 (33)	0	21 (34)
Physical examination procedures and organ system status	2 (6)	2 (7)	0	0	7 (11)	2 (7)	2 (9)	1 (8)	0	2 (3)
Weight decreased	2 (6)	2 (7)	0	0	6 (9)	2 (7)	2 (9)	1 (8)	0	2 (3)
Liver function analyses	2 (6)	1 (4)	0	0	5 (8)	2 (7)	1 (4)	0	0	5 (8)
Alanine aminotransferase increased	1 (3)	0	0	0	3 (5)	2 (7)	1 (4)	0	0	5 (8)
Aspartate aminotransferase increased	0	0	0	0	1 (2)	2 (7)	1 (4)	0	0	4 (6)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Metabolism and nutrition disorders										
Elevated triglycerides	7 (37)	6 (35)	4 (50)	1 (50)	11 (30)	0	0	0	0	0
Hypertriglyceridaemia	7 (37)	6 (35)	4 (50)	1 (50)	11 (30)	0	0	0	0	0
Elevated cholesterol	2 (11)	2 (12)	1 (13)	0	4 (11)	0	0	0	0	0
Hypercholesterolaemia	2 (11)	2 (12)	1 (13)	0	4 (11)	0	0	0	0	0
Investigations	9 (47)	9 (53)	4 (50)	0	16 (43)	1 (9)	0	0	0	5 (20)
Physical examination procedures and organ system status	2 (11)	2 (12)	1 (13)	0	2 (5)	0	0	0	0	0
Weight decreased	2 (11)	2 (12)	1 (13)	0	2 (5)	0	0	0	0	0
Liver function analyses	1 (5)	1 (6)	0	0	2 (5)	1 (9)	0	0	0	3 (12)
Alanine aminotransferase increased	1 (5)	1 (6)	0	0	2 (5)	1 (9)	0	0	0	3 (12)
Aspartate aminotransferase increased	1 (5)	1 (6)	0	0	2 (5)	1 (9)	0	0	0	2 (8)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Investigations										
Cholesterol analyses	0	0	0	0	0	1 (3)	1 (4)	0	0	5 (8)
Blood cholesterol increased	0	0	0	0	0	1 (3)	1 (4)	0	0	4 (6)
Triglyceride analyses	0	0	0	0	0	3 (10)	3 (13)	0	0	5 (8)
Blood triglycerides increased	0	0	0	0	0	3 (10)	3 (13)	0	0	5 (8)
Respiratory, thoracic and mediastinal disorders	7 (20)	5 (18)	2 (13)	2 (22)	13 (20)	2 (7)	2 (9)	1 (8)	0	7 (11)
Breathing abnormalities	4 (11)	2 (7)	0	0	7 (11)	0	0	0	0	0
Dyspnoea	4 (11)	2 (7)	0	0	7 (11)	0	0	0	0	0
Coughing and associated symptoms	1 (3)	1 (4)	0	0	3 (5)	1 (3)	1 (4)	0	0	4 (6)
Cough	1 (3)	1 (4)	0	0	2 (3)	1 (3)	1 (4)	0	0	4 (6)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Investigations										
Cholesterol analyses	1 (5)	1 (6)	0	0	5 (14)	0	0	0	0	0
Blood cholesterol increased	1 (5)	1 (6)	0	0	4 (11)	0	0	0	0	0
Triglyceride analyses	3 (16)	3 (18)	0	0	5 (14)	0	0	0	0	0
Blood triglycerides increased	3 (16)	3 (18)	0	0	5 (14)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (5)	1 (6)	0	0	1 (3)	1 (9)	1 (17)	1 (25)	0	6 (24)
Breathing abnormalities	0	0	0	0	0	0	0	0	0	0
Dyspnoea	0	0	0	0	0	0	0	0	0	0
Coughing and associated symptoms	1 (5)	1 (6)	0	0	1 (3)	0	0	0	0	3 (12)
Cough	1 (5)	1 (6)	0	0	1 (3)	0	0	0	0	3 (12)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Blood and lymphatic system disorders	4 (11)	4 (14)	2 (13)	1 (11)	10 (15)	7 (23)	6 (26)	2 (17)	0	12 (19)
Neutropenias	2 (6)	2 (7)	0	0	5 (8)	2 (7)	2 (9)	1 (8)	0	4 (6)
Neutropenia	2 (6)	2 (7)	0	0	5 (8)	2 (7)	2 (9)	1 (8)	0	4 (6)
Anaemias NEC	1 (3)	1 (4)	1 (6)	0	3 (5)	4 (13)	4 (17)	1 (8)	0	6 (10)
Anaemia	1 (3)	1 (4)	1 (6)	0	3 (5)	4 (13)	4 (17)	1 (8)	0	6 (10)
Vascular disorders	6 (17)	4 (14)	1 (6)	0	10 (15)	2 (7)	2 (9)	1 (8)	0	3 (5)
Vascular hypertensive disorders NEC	4 (11)	2 (7)	1 (6)	0	6 (9)	0	0	0	0	0
Hypertension	4 (11)	2 (7)	1 (6)	0	6 (9)	0	0	0	0	0
Peripheral vascular disorders NEC	2 (6)	2 (7)	0	0	3 (5)	1 (3)	1 (4)	1 (8)	0	1 (2)
Hot flush	2 (6)	2 (7)	0	0	3 (5)	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Blood and lymphatic system disorders	6 (32)	5 (29)	1 (13)	0	10 (27)	1 (9)	1 (17)	1 (25)	0	2 (8)
Neutropenias	2 (11)	2 (12)	1 (13)	0	4 (11)	0	0	0	0	0
Neutropenia	2 (11)	2 (12)	1 (13)	0	4 (11)	0	0	0	0	0
Anaemias NEC	4 (21)	4 (24)	1 (13)	0	6 (16)	0	0	0	0	0
Anaemia	4 (21)	4 (24)	1 (13)	0	6 (16)	0	0	0	0	0
Vascular disorders	2 (11)	2 (12)	1 (13)	0	3 (8)	0	0	0	0	0
Vascular hypertensive disorders NEC	0	0	0	0	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0	0	0	0	0
Peripheral vascular disorders NEC	1 (5)	1 (6)	1 (13)	0	1 (3)	0	0	0	0	0
Hot flush	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Eye disorders	1 (3)	1 (4)	0	0	6 (9)	3 (10)	3 (13)	2 (17)	1 (25)	6 (10)
Visual disorders NEC	1 (3)	1 (4)	0	0	3 (5)	0	0	0	0	0
Vision blurred	1 (3)	1 (4)	0	0	3 (5)	0	0	0	0	0
Lacrimation disorders	0	0	0	0	0	2 (7)	2 (9)	1 (8)	1 (25)	4 (6)
Dry eye	0	0	0	0	0	2 (7)	2 (9)	1 (8)	1 (25)	4 (6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (9)	3 (11)	2 (13)	0	4 (6)	6 (20)	5 (22)	0	0	9 (15)
Oncologic complications and emergencies	1 (3)	1 (4)	0	0	2 (3)	3 (10)	3 (13)	0	0	6 (10)
Cancer pain	0	0	0	0	1 (2)	2 (7)	2 (9)	0	0	5 (8)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Eye disorders	2 (11)	2 (12)	1 (13)	1 (50)	5 (14)	1 (9)	1 (17)	1 (25)	0	1 (4)
Visual disorders NEC	0	0	0	0	0	0	0	0	0	0
Vision blurred	0	0	0	0	0	0	0	0	0	0
Lacrimation disorders	2 (11)	2 (12)	1 (13)	1 (50)	4 (11)	0	0	0	0	0
Dry eye	2 (11)	2 (12)	1 (13)	1 (50)	4 (11)	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (26)	5 (29)	0	0	6 (16)	1 (9)	0	0	0	3 (12)
Oncologic complications and emergencies	3 (16)	3 (18)	0	0	4 (11)	0	0	0	0	2 (8)
Cancer pain	2 (11)	2 (12)	0	0	3 (8)	0	0	0	0	2 (8)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	35 (53)	28 (42)	16 (24)	9 (14)	66 (100)	30 (48)	23 (37)	12 (19)	4 (6)	62 (100)
Psychiatric disorders	2 (6)	2 (7)	0	0	3 (5)	6 (20)	5 (22)	3 (25)	0	10 (16)
Disturbances in initiating and maintaining sleep	2 (6)	2 (7)	0	0	2 (3)	3 (10)	2 (9)	0	0	5 (8)
Insomnia	2 (6)	2 (7)	0	0	2 (3)	3 (10)	2 (9)	0	0	5 (8)
Anxiety symptoms	0	0	0	0	1 (2)	2 (7)	2 (9)	2 (17)	0	4 (6)
Anxiety	0	0	0	0	0	2 (7)	2 (9)	2 (17)	0	4 (6)
Mood alterations with depressive symptoms	0	0	0	0	0	2 (7)	2 (9)	2 (17)	0	3 (5)
Depressed mood	0	0	0	0	0	2 (7)	2 (9)	2 (17)	0	3 (5)
Endocrine disorders	0	0	0	0	0	5 (17)	4 (17)	0	0	7 (11)
Thyroid hypofunction disorders	0	0	0	0	0	5 (17)	4 (17)	0	0	7 (11)
Hypothyroidism	0	0	0	0	0	4 (13)	3 (13)	0	0	5 (8)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table ADT14.4.1.3B
Most Common (At Least 5% in Either BV or the Combined Comparator Arm) Treatment-Emergent Adverse Events
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	>=60	>=65	>=70	>=75	All patients	>=60	>=65	>=70	>=75	All patients
	19 (51)	17 (46)	8 (22)	2 (5)	37 (100)	11 (44)	6 (24)	4 (16)	2 (8)	25 (100)
Psychiatric disorders	5 (26)	4 (24)	2 (25)	0	8 (22)	1 (9)	1 (17)	1 (25)	0	2 (8)
Disturbances in initiating and maintaining sleep	3 (16)	2 (12)	0	0	5 (14)	0	0	0	0	0
Insomnia	3 (16)	2 (12)	0	0	5 (14)	0	0	0	0	0
Anxiety symptoms	2 (11)	2 (12)	2 (25)	0	3 (8)	0	0	0	0	1 (4)
Anxiety	2 (11)	2 (12)	2 (25)	0	3 (8)	0	0	0	0	1 (4)
Mood alterations with depressive symptoms	1 (5)	1 (6)	1 (13)	0	2 (5)	1 (9)	1 (17)	1 (25)	0	1 (4)
Depressed mood	1 (5)	1 (6)	1 (13)	0	2 (5)	1 (9)	1 (17)	1 (25)	0	1 (4)
Endocrine disorders	5 (26)	4 (24)	0	0	7 (19)	0	0	0	0	0
Thyroid hypofunction disorders	5 (26)	4 (24)	0	0	7 (19)	0	0	0	0	0
Hypothyroidism	4 (21)	3 (18)	0	0	5 (14)	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.

Table 14.3.1.7
Summary of Overall Survival (OS)
ITT Population

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64	Bexarotene N=38	Methotrexate N=26	Total N=128	Hazard Ratio[a] (95% CI)	P-value[b]
OS (months)							
Number with Events (%)	15 (23)	14 (22)	6 (16)	8 (31)	29 (23)	0.885	0.742
Number Censored (%)	49 (77)	50 (78)	32 (84)	18 (69)	99 (77)	(0.426, 1.838)	
25th Percentile (95% CI)	20.8(14.3, NE)	21.1(6.0, NE)	NE(5.9, NE)	7.5(2.3, NE)	21.1(12.2, NE)		
Median (95% CI)	NE(30.4, NE)	NE(NE, NE)	NE(NE, NE)	NE(8.2, NE)	NE(NE, NE)		
75th Percentile (95% CI)	NE(NE, NE)	NE(NE, NE)	NE(NE, NE)	NE(NE, NE)	NE(NE, NE)		
Min, Max	0.6, 40.8*	0.1*, 37.1*	0.2*, 37.1*	0.1*, 33.2*	0.1*, 40.8*		
Kaplan-Meier Estimates[c] (95% CI)							
6 Months	93.6(83.8, 97.5) [n=58]	87.6(75.7, 93.9) [n=47]	90.8(74.1, 96.9) [n=29]	83.1(61.0, 93.3) [n=18]	90.8(84.0, 94.8) [n=105]		
1 Year	90.3(79.7, 95.5) [n=46]	76.1(62.4, 85.4) [n=36]	80.9(62.3, 91.0) [n=22]	69.3(46.0, 84.1) [n=14]	83.8(75.7, 89.3) [n=82]		
1.5 Years	79.8(66.1, 88.4) [n=33]	76.1(62.4, 85.4) [n=28]	80.9(62.3, 91.0) [n=18]	69.3(46.0, 84.1) [n=10]	78.1(69.0, 84.8) [n=61]		
2 Years	72.0(56.8, 82.7) [n=23]	72.9(58.1, 83.2) [n=17]	80.9(62.3, 91.0) [n=12]	60.6(34.3, 79.1) [n=5]	72.4(62.2, 80.3) [n=40]		

OS is defined as the time from randomization to the date of subject death due to any cause.
* indicates a censored observation
NE = Not Estimable CI = Confidence Interval
a Hazard Ratio Brentuximab Vedotin/Comparator (Methotrexate or Bexarotene) with the 95% CI from a stratified Cox regression model with treatment as the explanatory variable and baseline disease diagnosis (MF or pcALCL) as stratification factor. A less than 1 hazard ratio favors Brentuximab Vedotin arm.
b P-value is calculated using Log-Rank test stratified by baseline disease diagnosis (MF or pcALCL).
c Percent of patients alive [n=number of patients at risk].
d Median OS Follow-up is calculated from the Kaplan-Meier method switching the OS event/censored status, i.e. OS event as censored and censored as OS event.

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.3.1.7-os.sas 19SEP2016: 21:22

Table 14.3.1.7
Summary of Overall Survival (OS)
ITT Population

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64	Bexarotene N=38	Methotrexate N=26	Total N=128	Hazard Ratio[a] (95% CI)	P-value[b]
Median OS follow-up[d] (months) (95% CI)	23.2(19.1, 28.1)	20.8(14.6, 23.9)	21.2(14.6, 27.4)	18.4(12.0, 24.8)	22.9(18.4, 26.1)		
Reason for Censoring							
End of Study due to	9 (14)	12 (19)	7 (18)	5 (19)	21 (16)		
Withdrawal by Subject	8 (13)	10 (16)	5 (13)	5 (19)	18 (14)		
Lost to Follow-Up	1 (2)	1 (2)	1 (3)	0	2 (2)		
Other	0	1 (2)	1 (3)	0	1 (1)		
Alive at Last Contact	40 (63)	38 (59)	25 (66)	13 (50)	78 (61)		

OS is defined as the time from randomization to the date of subject death due to any cause.
* indicates a censored observation
NE = Not Estimable CI = Confidence Interval
a Hazard Ratio Brentuximab Vedotin/Comparator (Methotrexate or Bexarotene) with the 95% CI from a stratified Cox regression model with treatment as the explanatory variable and baseline disease diagnosis (MF or pcALCL) as stratification factor. A less than 1 hazard ratio favors Brentuximab Vedotin arm.
b P-value is calculated using Log-Rank test stratified by baseline disease diagnosis (MF or pcALCL).
c Percent of patients alive [n=number of patients at risk].
d Median OS Follow-up is calculated from the Kaplan-Meier method switching the OS event/censored status, i.e. OS event as censored and censored as OS event.

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.3.1.7-os.sas 19SEP2016: 21:22

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Patients with at Least 1 Adverse Event[a]	65 (98)	59 (95)	35 (95)	24 (96)	124 (97)
Nervous system disorders	47 (71)	12 (19)	9 (24)	3 (12)	59 (46)
Peripheral neuropathies NEC	35 (53)	1 (2)	0	1 (4)	36 (28)
Peripheral sensory neuropathy	30 (45)	1 (2)	0	1 (4)	31 (24)
Peripheral motor neuropathy	4 (6)	0	0	0	4 (3)
Neuropathy peripheral	3 (5)	0	0	0	3 (2)
Polyneuropathy	1 (2)	0	0	0	1 (< 1)
Paraesthesias and dysaesthesias	9 (14)	1 (2)	1 (3)	0	10 (8)
Paraesthesia	6 (9)	1 (2)	1 (3)	0	7 (5)
Hypoaesthesia	3 (5)	0	0	0	3 (2)
Dysaesthesia	1 (2)	0	0	0	1 (< 1)
Hyperaesthesia	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Nervous system disorders					
Sensory abnormalities NEC	9 (14)	1 (2)	0	1 (4)	10 (8)
Dysgeusia	5 (8)	0	0	0	5 (4)
Neuralgia	2 (3)	1 (2)	0	1 (4)	3 (2)
Ageusia	1 (2)	0	0	0	1 (< 1)
Sensory loss	1 (2)	0	0	0	1 (< 1)
Headaches NEC	6 (9)	6 (10)	5 (14)	1 (4)	12 (9)
Headache	5 (8)	6 (10)	5 (14)	1 (4)	11 (9)
Cluster headache	1 (2)	0	0	0	1 (< 1)
Neurological signs and symptoms NEC	5 (8)	1 (2)	1 (3)	0	6 (5)
Dizziness	5 (8)	1 (2)	1 (3)	0	6 (5)
Disturbances in consciousness NEC	2 (3)	2 (3)	2 (5)	0	4 (3)
Lethargy	1 (2)	1 (2)	1 (3)	0	2 (2)
Somnolence	1 (2)	1 (2)	1 (3)	0	2 (2)
Syncope	0	1 (2)	1 (3)	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Nervous system disorders					
Olfactory nerve disorders	2 (3)	0	0	0	2 (2)
Anosmia	2 (3)	0	0	0	2 (2)
Chronic polyneuropathies	1 (2)	0	0	0	1 (< 1)
Demyelinating polyneuropathy	1 (2)	0	0	0	1 (< 1)
Coordination and balance disturbances	1 (2)	0	0	0	1 (< 1)
Balance disorder	1 (2)	0	0	0	1 (< 1)
Migraine headaches	1 (2)	0	0	0	1 (< 1)
Migraine	1 (2)	0	0	0	1 (< 1)
Facial cranial nerve disorders	0	1 (2)	1 (3)	0	1 (< 1)
Facial paresis	0	1 (2)	1 (3)	0	1 (< 1)
Lumbar spinal cord and nerve root disorders	0	1 (2)	1 (3)	0	1 (< 1)
Sciatica	0	1 (2)	1 (3)	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Blood and lymphatic system disorders	45 (68)	48 (77)	31 (84)	17 (68)	93 (73)
Anaemias NEC	41 (62)	40 (65)	24 (65)	16 (64)	81 (63)
Anaemia[b]	41 (62)	40 (65)	24 (65)	16 (64)	81 (63)
Neutropenias	14 (21)	15 (24)	14 (38)	1 (4)	29 (23)
Neutropenia[c]	14 (21)	15 (24)	14 (38)	1 (4)	29 (23)
Thrombocytopenias	10 (15)	1 (2)	1 (3)	0	11 (9)
Thrombocytopenia[d]	10 (15)	1 (2)	1 (3)	0	11 (9)
Leukopenias NEC	2 (3)	2 (3)	1 (3)	1 (4)	4 (3)
Leukopenia	2 (3)	1 (2)	1 (3)	0	3 (2)
Lymphopenia	0	1 (2)	0	1 (4)	1 (< 1)
Anaemias haemolytic mechanical factor	1 (2)	0	0	0	1 (< 1)
Haemolytic uraemic syndrome	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Blood and lymphatic system disorders					
Eosinophilic disorders	0	1 (2)	1 (3)	0	1 (< 1)
Eosinophilia	0	1 (2)	1 (3)	0	1 (< 1)
Lymphatic system disorders NEC	0	1 (2)	0	1 (4)	1 (< 1)
Lymphadenopathy	0	1 (2)	0	1 (4)	1 (< 1)
Gastrointestinal disorders	40 (61)	23 (37)	12 (32)	11 (44)	63 (49)
Nausea and vomiting symptoms	27 (41)	10 (16)	4 (11)	6 (24)	37 (29)
Nausea	24 (36)	8 (13)	4 (11)	4 (16)	32 (25)
Vomiting	11 (17)	3 (5)	1 (3)	2 (8)	14 (11)
Diarrhoea (excl infective)	19 (29)	4 (6)	3 (8)	1 (4)	23 (18)
Diarrhoea	19 (29)	4 (6)	3 (8)	1 (4)	23 (18)
Gastrointestinal atonic and hypomotility disorders NEC	4 (6)	6 (10)	4 (11)	2 (8)	10 (8)
Constipation	3 (5)	4 (6)	4 (11)	0	7 (5)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Gastrointestinal disorders					
Gastrointestinal atonic and hypomotility disorders NEC					
Gastrooesophageal reflux disease	1 (2)	2 (3)	0	2 (8)	3 (2)
Gastrointestinal and abdominal pains (excl oral and throat)	3 (5)	3 (5)	0	3 (12)	6 (5)
Abdominal pain	2 (3)	0	0	0	2 (2)
Abdominal pain upper	1 (2)	3 (5)	0	3 (12)	4 (3)
Gastrointestinal signs and symptoms NEC	2 (3)	1 (2)	0	1 (4)	3 (2)
Dysphagia	2 (3)	1 (2)	0	1 (4)	3 (2)
Stomatitis and ulceration	2 (3)	1 (2)	1 (3)	0	3 (2)
Mouth ulceration	1 (2)	1 (2)	1 (3)	0	2 (2)
Stomatitis	1 (2)	0	0	0	1 (< 1)
Acute and chronic pancreatitis	1 (2)	0	0	0	1 (< 1)
Pancreatitis	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Gastrointestinal disorders					
Diverticula	1 (2)	0	0	0	1 (< 1)
Diverticulum	1 (2)	0	0	0	1 (< 1)
Dyspeptic signs and symptoms	1 (2)	0	0	0	1 (< 1)
Dyspepsia	1 (2)	0	0	0	1 (< 1)
Gastrointestinal inflammatory disorders NEC	1 (2)	0	0	0	1 (< 1)
Epiploic appendagitis	1 (2)	0	0	0	1 (< 1)
Haemorrhoids and gastrointestinal varices (excl oesophageal)	1 (2)	1 (2)	0	1 (4)	2 (2)
Haemorrhoidal haemorrhage	1 (2)	1 (2)	0	1 (4)	2 (2)
Intestinal ulcers and perforation NEC	1 (2)	0	0	0	1 (< 1)
Intestinal perforation	1 (2)	0	0	0	1 (< 1)
Non-site specific gastrointestinal haemorrhages	1 (2)	0	0	0	1 (< 1)
Melaena	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Gastrointestinal disorders					
Oral dryness and saliva altered	1 (2)	2 (3)	1 (3)	1 (4)	3 (2)
Dry mouth	1 (2)	1 (2)	1 (3)	0	2 (2)
Aptyalism	0	1 (2)	0	1 (4)	1 (< 1)
Oral soft tissue disorders NEC	1 (2)	1 (2)	0	1 (4)	2 (2)
Cheilitis	1 (2)	0	0	0	1 (< 1)
Lip ulceration	0	1 (2)	0	1 (4)	1 (< 1)
Tongue signs and symptoms	1 (2)	0	0	0	1 (< 1)
Swollen tongue	1 (2)	0	0	0	1 (< 1)
Flatulence, bloating and distension	0	1 (2)	1 (3)	0	1 (< 1)
Abdominal distension	0	1 (2)	1 (3)	0	1 (< 1)
Oral soft tissue pain and paraesthesia	0	1 (2)	1 (3)	0	1 (< 1)
Odynophagia	0	1 (2)	1 (3)	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Gastrointestinal disorders					
Salivary gland disorders NEC	0	1 (2)	1 (3)	0	1 (< 1)
Salivary gland calculus	0	1 (2)	1 (3)	0	1 (< 1)
General disorders and administration site conditions	39 (59)	36 (58)	19 (51)	17 (68)	75 (59)
Asthenic conditions	26 (39)	22 (35)	14 (38)	8 (32)	48 (38)
Fatigue	19 (29)	17 (27)	12 (32)	5 (20)	36 (28)
Asthenia	7 (11)	5 (8)	2 (5)	3 (12)	12 (9)
Febrile disorders	11 (17)	11 (18)	4 (11)	7 (28)	22 (17)
Pyrexia	11 (17)	11 (18)	4 (11)	7 (28)	22 (17)
Oedema NEC	7 (11)	7 (11)	2 (5)	5 (20)	14 (11)
Oedema peripheral	7 (11)	6 (10)	2 (5)	4 (16)	13 (10)
Face oedema	0	1 (2)	0	1 (4)	1 (< 1)
Feelings and sensations NEC	5 (8)	2 (3)	0	2 (8)	7 (5)
Chills	4 (6)	2 (3)	0	2 (8)	6 (5)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
General disorders and administration site conditions					
Feelings and sensations NEC					
Feeling cold	1 (2)	0	0	0	1 (< 1)
General signs and symptoms NEC	5 (8)	6 (10)	3 (8)	3 (12)	11 (9)
Extravasation	1 (2)	0	0	0	1 (< 1)
General physical health deterioration	1 (2)	0	0	0	1 (< 1)
Influenza like illness	1 (2)	0	0	0	1 (< 1)
Local swelling	1 (2)	1 (2)	0	1 (4)	2 (2)
Multiple organ dysfunction syndrome	1 (2)	0	0	0	1 (< 1)
Peripheral swelling	1 (2)	4 (6)	3 (8)	1 (4)	5 (4)
Xerosis	0	1 (2)	0	1 (4)	1 (< 1)
Pain and discomfort NEC	1 (2)	0	0	0	1 (< 1)
Pain	1 (2)	0	0	0	1 (< 1)
Healing abnormal NEC	0	1 (2)	0	1 (4)	1 (< 1)
Impaired healing	0	1 (2)	0	1 (4)	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Skin and subcutaneous tissue disorders	34 (52)	20 (32)	14 (38)	6 (24)	54 (42)
Pruritus NEC	18 (27)	9 (15)	7 (19)	2 (8)	27 (21)
Pruritus	11 (17)	8 (13)	6 (16)	2 (8)	19 (15)
Pruritus generalised	7 (11)	1 (2)	1 (3)	0	8 (6)
Rash pruritic	1 (2)	0	0	0	1 (< 1)
Alopecias	10 (15)	2 (3)	1 (3)	1 (4)	12 (9)
Alopecia	10 (15)	2 (3)	1 (3)	1 (4)	12 (9)
Rashes, eruptions and exanthems NEC	8 (12)	3 (5)	2 (5)	1 (4)	11 (9)
Rash maculo-papular	7 (11)	3 (5)	2 (5)	1 (4)	10 (8)
Rash macular	1 (2)	0	0	0	1 (< 1)
Urticarias	5 (8)	1 (2)	1 (3)	0	6 (5)
Urticaria	5 (8)	1 (2)	1 (3)	0	6 (5)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Skin and subcutaneous tissue disorders					
Acnes	3 (5)	0	0	0	3 (2)
Dermatitis acneiform	3 (5)	0	0	0	3 (2)
Apocrine and eccrine gland disorders	2 (3)	0	0	0	2 (2)
Miliaria	1 (2)	0	0	0	1 (< 1)
Night sweats	1 (2)	0	0	0	1 (< 1)
Dermal and epidermal conditions NEC	2 (3)	5 (8)	4 (11)	1 (4)	7 (5)
Dry skin	1 (2)	4 (6)	3 (8)	1 (4)	5 (4)
Skin discolouration	1 (2)	0	0	0	1 (< 1)
Skin fissures	1 (2)	0	0	0	1 (< 1)
Skin lesion	1 (2)	1 (2)	1 (3)	0	2 (2)
Dermatitis ascribed to specific agent	2 (3)	0	0	0	2 (2)
Drug eruption	2 (3)	0	0	0	2 (2)
Erythemas	2 (3)	2 (3)	1 (3)	1 (4)	4 (3)
Erythema	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Skin and subcutaneous tissue disorders					
Erythemas					
Rash erythematous	1 (2)	2 (3)	1 (3)	1 (4)	3 (2)
Exfoliative conditions	2 (3)	2 (3)	2 (5)	0	4 (3)
Skin exfoliation	2 (3)	2 (3)	2 (5)	0	4 (3)
Angioedemas	1 (2)	1 (2)	0	1 (4)	2 (2)
Swelling face	1 (2)	1 (2)	0	1 (4)	2 (2)
Dermatitis and eczema	1 (2)	1 (2)	1 (3)	0	2 (2)
Eczema	1 (2)	0	0	0	1 (< 1)
Intertrigo	0	1 (2)	1 (3)	0	1 (< 1)
Purpura and related conditions	1 (2)	0	0	0	1 (< 1)
Vascular purpura	1 (2)	0	0	0	1 (< 1)
Skin preneoplastic conditions NEC	1 (2)	0	0	0	1 (< 1)
Actinic keratosis	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Skin and subcutaneous tissue disorders					
Bullous conditions	0	1 (2)	0	1 (4)	1 (< 1)
Dermatitis bullous	0	1 (2)	0	1 (4)	1 (< 1)
Ichthyoses	0	1 (2)	1 (3)	0	1 (< 1)
Xeroderma	0	1 (2)	1 (3)	0	1 (< 1)
Papulosquamous conditions	0	1 (2)	1 (3)	0	1 (< 1)
Lymphomatoid papulosis	0	1 (2)	1 (3)	0	1 (< 1)
Pilar disorders NEC	0	1 (2)	1 (3)	0	1 (< 1)
Hair growth abnormal	0	1 (2)	1 (3)	0	1 (< 1)
Skin and subcutaneous tissue ulcerations	0	1 (2)	0	1 (4)	1 (< 1)
Skin erosion	0	1 (2)	0	1 (4)	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Infections and infestations	29 (44)	32 (52)	17 (46)	15 (60)	61 (48)
Upper respiratory tract infections	10 (15)	4 (6)	2 (5)	2 (8)	14 (11)
Upper respiratory tract infection	4 (6)	2 (3)	2 (5)	0	6 (5)
Nasopharyngitis	3 (5)	1 (2)	0	1 (4)	4 (3)
Sinusitis	2 (3)	0	0	0	2 (2)
Acute sinusitis	1 (2)	0	0	0	1 (< 1)
Pharyngitis	1 (2)	0	0	0	1 (< 1)
Rhinitis	1 (2)	1 (2)	0	1 (4)	2 (2)
Skin structures and soft tissue infections	6 (9)	7 (11)	4 (11)	3 (12)	13 (10)
Impetigo	3 (5)	0	0	0	3 (2)
Skin infection	2 (3)	7 (11)	4 (11)	3 (12)	9 (7)
Paronychia	1 (2)	0	0	0	1 (< 1)
Urinary tract infections	5 (8)	4 (6)	1 (3)	3 (12)	9 (7)
Urinary tract infection	5 (8)	4 (6)	1 (3)	3 (12)	9 (7)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Infections and infestations					
Bacterial infections NEC	3 (5)	3 (5)	3 (8)	0	6 (5)
Cellulitis	3 (5)	2 (3)	2 (5)	0	5 (4)
Superinfection bacterial	0	1 (2)	1 (3)	0	1 (< 1)
Infections NEC	2 (3)	2 (3)	1 (3)	1 (4)	4 (3)
Respiratory tract infection	2 (3)	0	0	0	2 (2)
Incision site infection	0	1 (2)	1 (3)	0	1 (< 1)
Wound infection	0	1 (2)	0	1 (4)	1 (< 1)
Influenza viral infections	2 (3)	0	0	0	2 (2)
Influenza	2 (3)	0	0	0	2 (2)
Abdominal and gastrointestinal infections	1 (2)	0	0	0	1 (< 1)
Diverticulitis	1 (2)	0	0	0	1 (< 1)
Borrelial infections	1 (2)	0	0	0	1 (< 1)
Lyme disease	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Infections and infestations					
Candida infections	1 (2)	1 (2)	1 (3)	0	2 (2)
Oropharyngeal candidiasis	1 (2)	0	0	0	1 (< 1)
Oral candidiasis	0	1 (2)	1 (3)	0	1 (< 1)
Dental and oral soft tissue infections	1 (2)	2 (3)	1 (3)	1 (4)	3 (2)
Angular cheilitis	1 (2)	0	0	0	1 (< 1)
Parotitis	0	2 (3)	1 (3)	1 (4)	2 (2)
Ear infections	1 (2)	2 (3)	2 (5)	0	3 (2)
Ear infection	1 (2)	1 (2)	1 (3)	0	2 (2)
Otitis externa	0	1 (2)	1 (3)	0	1 (< 1)
Escherichia infections	1 (2)	0	0	0	1 (< 1)
Escherichia infection	1 (2)	0	0	0	1 (< 1)
Eye and eyelid infections	1 (2)	1 (2)	1 (3)	0	2 (2)
Hordeolum	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Infections and infestations					
Eye and eyelid infections					
Periorbital infection	0	1 (2)	1 (3)	0	1 (< 1)
Gardnerella infections	1 (2)	0	0	0	1 (< 1)
Gardnerella infection	1 (2)	0	0	0	1 (< 1)
Herpes viral infections	1 (2)	3 (5)	2 (5)	1 (4)	4 (3)
Herpes dermatitis	1 (2)	0	0	0	1 (< 1)
Herpes virus infection	0	1 (2)	1 (3)	0	1 (< 1)
Herpes zoster	0	1 (2)	0	1 (4)	1 (< 1)
Oral herpes	0	1 (2)	1 (3)	0	1 (< 1)
Klebsiella infections	1 (2)	0	0	0	1 (< 1)
Klebsiella infection	1 (2)	0	0	0	1 (< 1)
Lower respiratory tract and lung infections	1 (2)	2 (3)	1 (3)	1 (4)	3 (2)
Lower respiratory tract infection	1 (2)	0	0	0	1 (< 1)
Pneumonia	0	2 (3)	1 (3)	1 (4)	2 (2)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Infections and infestations					
Muscle and soft tissue infections	1 (2)	0	0	0	1 (< 1)
Perineal infection	1 (2)	0	0	0	1 (< 1)
Pseudomonal infections	1 (2)	0	0	0	1 (< 1)
Urinary tract infection pseudomonal	1 (2)	0	0	0	1 (< 1)
Rhinoviral infections	1 (2)	0	0	0	1 (< 1)
Rhinovirus infection	1 (2)	0	0	0	1 (< 1)
Sepsis, bacteraemia, viraemia and fungaemia NEC	1 (2)	4 (6)	3 (8)	1 (4)	5 (4)
Sepsis	1 (2)	3 (5)	2 (5)	1 (4)	4 (3)
Urosepsis	0	1 (2)	1 (3)	0	1 (< 1)
Staphylococcal infections	1 (2)	6 (10)	3 (8)	3 (12)	7 (5)
Staphylococcal skin infection	1 (2)	5 (8)	3 (8)	2 (8)	6 (5)
Staphylococcal abscess	0	1 (2)	0	1 (4)	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Infections and infestations					
Bone and joint infections	0	1 (2)	0	1 (4)	1 (< 1)
Abscess jaw	0	1 (2)	0	1 (4)	1 (< 1)
Fungal infections NEC	0	1 (2)	0	1 (4)	1 (< 1)
Fungal skin infection	0	1 (2)	0	1 (4)	1 (< 1)
Streptococcal infections	0	1 (2)	0	1 (4)	1 (< 1)
Erysipelas	0	1 (2)	0	1 (4)	1 (< 1)
Tinea infections	0	1 (2)	1 (3)	0	1 (< 1)
Tinea cruris	0	1 (2)	1 (3)	0	1 (< 1)
Musculoskeletal and connective tissue disorders	22 (33)	14 (23)	12 (32)	2 (8)	36 (28)
Musculoskeletal and connective tissue pain and discomfort	9 (14)	6 (10)	6 (16)	0	15 (12)
Pain in extremity	6 (9)	4 (6)	4 (11)	0	10 (8)
Back pain	2 (3)	1 (2)	1 (3)	0	3 (2)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Musculoskeletal and connective tissue disorders					
Musculoskeletal and connective tissue pain and discomfort					
Musculoskeletal chest pain	2 (3)	0	0	0	2 (2)
Musculoskeletal pain	1 (2)	1 (2)	1 (3)	0	2 (2)
Neck pain	1 (2)	0	0	0	1 (< 1)
Joint related signs and symptoms	8 (12)	4 (6)	2 (5)	2 (8)	12 (9)
Arthralgia	8 (12)	4 (6)	2 (5)	2 (8)	12 (9)
Joint swelling	1 (2)	0	0	0	1 (< 1)
Muscle pains	8 (12)	2 (3)	2 (5)	0	10 (8)
Myalgia	8 (12)	2 (3)	2 (5)	0	10 (8)
Muscle related signs and symptoms NEC	5 (8)	3 (5)	3 (8)	0	8 (6)
Muscle spasms	4 (6)	3 (5)	3 (8)	0	7 (5)
Muscle atrophy	1 (2)	0	0	0	1 (< 1)
Bursal disorders	1 (2)	0	0	0	1 (< 1)
Bursitis	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Musculoskeletal and connective tissue disorders					
Muscle weakness conditions	1 (2)	1 (2)	1 (3)	0	2 (2)
Muscular weakness	1 (2)	1 (2)	1 (3)	0	2 (2)
Osteoarthropathies	1 (2)	0	0	0	1 (< 1)
Osteoarthritis	1 (2)	0	0	0	1 (< 1)
Crystal arthropathic disorders	0	1 (2)	0	1 (4)	1 (< 1)
Crystal arthropathy	0	1 (2)	0	1 (4)	1 (< 1)
Intervertebral disc disorders NEC	0	1 (2)	1 (3)	0	1 (< 1)
Intervertebral disc protrusion	0	1 (2)	1 (3)	0	1 (< 1)
Muscle infections and inflammations	0	1 (2)	1 (3)	0	1 (< 1)
Myositis	0	1 (2)	1 (3)	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Musculoskeletal and connective tissue disorders					
Spine and neck deformities	0	1 (2)	1 (3)	0	1 (< 1)
Lumbar spinal stenosis	0	1 (2)	1 (3)	0	1 (< 1)
Synovial disorders	0	1 (2)	1 (3)	0	1 (< 1)
Synovial cyst	0	1 (2)	1 (3)	0	1 (< 1)
Metabolism and nutrition disorders	21 (32)	18 (29)	14 (38)	4 (16)	39 (30)
Appetite disorders	10 (15)	3 (5)	2 (5)	1 (4)	13 (10)
Decreased appetite	10 (15)	3 (5)	2 (5)	1 (4)	13 (10)
Hyperglycaemic conditions NEC	6 (9)	0	0	0	6 (5)
Hyperglycaemia	6 (9)	0	0	0	6 (5)
Disorders of purine metabolism	4 (6)	2 (3)	0	2 (8)	6 (5)
Hyperuricaemia	4 (6)	2 (3)	0	2 (8)	6 (5)
Calcium metabolism disorders	2 (3)	0	0	0	2 (2)
Hypocalcaemia	2 (3)	0	0	0	2 (2)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Metabolism and nutrition disorders					
Magnesium metabolism disorders	2 (3)	1 (2)	1 (3)	0	3 (2)
Hypomagnesaemia	2 (3)	1 (2)	1 (3)	0	3 (2)
Potassium imbalance	2 (3)	0	0	0	2 (2)
Hypokalaemia	2 (3)	0	0	0	2 (2)
Total fluid volume decreased	2 (3)	0	0	0	2 (2)
Dehydration	2 (3)	0	0	0	2 (2)
Elevated triglycerides	1 (2)	11 (18)	11 (30)	0	12 (9)
Hypertriglyceridaemia	1 (2)	11 (18)	11 (30)	0	12 (9)
Iron deficiencies	1 (2)	0	0	0	1 (< 1)
Iron deficiency	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Metabolism and nutrition disorders					
Protein metabolism disorders NEC	1 (2)	0	0	0	1 (< 1)
Hypoalbuminaemia	1 (2)	0	0	0	1 (< 1)
Elevated cholesterol	0	4 (6)	4 (11)	0	4 (3)
Hypercholesterolaemia	0	4 (6)	4 (11)	0	4 (3)
Hyperlipidaemias NEC	0	1 (2)	1 (3)	0	1 (< 1)
Hyperlipidaemia	0	1 (2)	1 (3)	0	1 (< 1)
Lipid metabolism and deposit disorders NEC	0	1 (2)	0	1 (4)	1 (< 1)
Dyslipidaemia	0	1 (2)	0	1 (4)	1 (< 1)
Metabolic acidoses (excl diabetic acidoses)	0	1 (2)	1 (3)	0	1 (< 1)
Metabolic acidosis	0	1 (2)	1 (3)	0	1 (< 1)
Sodium imbalance	0	1 (2)	1 (3)	0	1 (< 1)
Hypernatraemia	0	1 (2)	1 (3)	0	1 (< 1)
Hyponatraemia	0	1 (2)	1 (3)	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Investigations	15 (23)	21 (34)	16 (43)	5 (20)	36 (28)
Physical examination procedures and organ system status	7 (11)	2 (3)	2 (5)	0	9 (7)
Weight decreased	6 (9)	2 (3)	2 (5)	0	8 (6)
Breath sounds abnormal	1 (2)	0	0	0	1 (< 1)
Liver function analyses	5 (8)	5 (8)	2 (5)	3 (12)	10 (8)
Alanine aminotransferase increased	3 (5)	5 (8)	2 (5)	3 (12)	8 (6)
Aspartate aminotransferase increased	1 (2)	4 (6)	2 (5)	2 (8)	5 (4)
Gamma-glutamyltransferase increased	1 (2)	1 (2)	0	1 (4)	2 (2)
Transaminases increased	1 (2)	0	0	0	1 (< 1)
White blood cell analyses	2 (3)	1 (2)	0	1 (4)	3 (2)
White blood cell count decreased	2 (3)	0	0	0	2 (2)
Neutrophil count decreased	1 (2)	0	0	0	1 (< 1)
White blood cell count increased	1 (2)	0	0	0	1 (< 1)
Lymphocyte count decreased	0	1 (2)	0	1 (4)	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Investigations					
Bacteria identification and serology (excl mycobacteria)	1 (2)	0	0	0	1 (< 1)
Staphylococcus test positive	1 (2)	0	0	0	1 (< 1)
Coagulation and bleeding analyses	1 (2)	0	0	0	1 (< 1)
Activated partial thromboplastin time prolonged	1 (2)	0	0	0	1 (< 1)
International normalised ratio increased	1 (2)	0	0	0	1 (< 1)
Thyroid analyses	1 (2)	4 (6)	4 (11)	0	5 (4)
Thyroxine increased	1 (2)	0	0	0	1 (< 1)
Thyroxine decreased	0	2 (3)	2 (5)	0	2 (2)
Thyroxine free decreased	0	1 (2)	1 (3)	0	1 (< 1)
Tri-iodothyronine free decreased	0	1 (2)	1 (3)	0	1 (< 1)
Urinalysis NEC	1 (2)	0	0	0	1 (< 1)
Urine leukocyte esterase positive	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Investigations					
Cholesterol analyses	0	5 (8)	5 (14)	0	5 (4)
Blood cholesterol increased	0	4 (6)	4 (11)	0	4 (3)
High density lipoprotein decreased	0	1 (2)	1 (3)	0	1 (< 1)
Low density lipoprotein increased	0	1 (2)	1 (3)	0	1 (< 1)
Metabolism tests NEC	0	1 (2)	1 (3)	0	1 (< 1)
Blood uric acid increased	0	1 (2)	1 (3)	0	1 (< 1)
Pituitary analyses anterior	0	1 (2)	1 (3)	0	1 (< 1)
Blood thyroid stimulating hormone decreased	0	1 (2)	1 (3)	0	1 (< 1)
Renal function analyses	0	2 (3)	2 (5)	0	2 (2)
Blood creatinine increased	0	2 (3)	2 (5)	0	2 (2)
Triglyceride analyses	0	5 (8)	5 (14)	0	5 (4)
Blood triglycerides increased	0	5 (8)	5 (14)	0	5 (4)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Investigations					
Virus identification and serology	0	1 (2)	0	1 (4)	1 (< 1)
Cytomegalovirus test positive	0	1 (2)	0	1 (4)	1 (< 1)
Respiratory, thoracic and mediastinal disorders	13 (20)	7 (11)	1 (3)	6 (24)	20 (16)
Breathing abnormalities	7 (11)	0	0	0	7 (5)
Dyspnoea	7 (11)	0	0	0	7 (5)
Coughing and associated symptoms	3 (5)	4 (6)	1 (3)	3 (12)	7 (5)
Cough	2 (3)	4 (6)	1 (3)	3 (12)	6 (5)
Productive cough	1 (2)	0	0	0	1 (< 1)
Upper respiratory tract signs and symptoms	3 (5)	2 (3)	0	2 (8)	5 (4)
Dysphonia	1 (2)	0	0	0	1 (< 1)
Oropharyngeal pain	1 (2)	1 (2)	0	1 (4)	2 (2)
Rhinorrhoea	1 (2)	1 (2)	0	1 (4)	2 (2)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Respiratory, thoracic and mediastinal disorders					
Lower respiratory tract signs and symptoms	1 (2)	0	0	0	1 (< 1)
Increased bronchial secretion	1 (2)	0	0	0	1 (< 1)
Pulmonary thrombotic and embolic conditions	1 (2)	0	0	0	1 (< 1)
Pulmonary embolism	1 (2)	0	0	0	1 (< 1)
Bronchospasm and obstruction	0	1 (2)	0	1 (4)	1 (< 1)
Obstructive airways disorder	0	1 (2)	0	1 (4)	1 (< 1)
Nasal congestion and inflammations	0	1 (2)	0	1 (4)	1 (< 1)
Rhinitis allergic	0	1 (2)	0	1 (4)	1 (< 1)
Nasal disorders NEC	0	1 (2)	0	1 (4)	1 (< 1)
Epistaxis	0	1 (2)	0	1 (4)	1 (< 1)
Vascular disorders	10 (15)	3 (5)	3 (8)	0	13 (10)
Vascular hypertensive disorders NEC	6 (9)	0	0	0	6 (5)
Hypertension	6 (9)	0	0	0	6 (5)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Vascular disorders					
Peripheral vascular disorders NEC	3 (5)	1 (2)	1 (3)	0	4 (3)
Hot flush	3 (5)	0	0	0	3 (2)
Peripheral vascular disorder	0	1 (2)	1 (3)	0	1 (< 1)
Vascular hypotensive disorders	2 (3)	1 (2)	1 (3)	0	3 (2)
Hypotension	2 (3)	1 (2)	1 (3)	0	3 (2)
Non-site specific vascular disorders NEC	1 (2)	0	0	0	1 (< 1)
Poor venous access	1 (2)	0	0	0	1 (< 1)
Peripheral vasoconstriction, necrosis and vascular insufficiency	0	1 (2)	1 (3)	0	1 (< 1)
Peripheral ischaemia	0	1 (2)	1 (3)	0	1 (< 1)
Eye disorders	6 (9)	6 (10)	5 (14)	1 (4)	12 (9)
Visual disorders NEC	3 (5)	0	0	0	3 (2)
Vision blurred	3 (5)	0	0	0	3 (2)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Eye disorders					
Visual disorders NEC					
Diplopia	1 (2)	0	0	0	1 (< 1)
Conjunctival infections, irritations and inflammations	1 (2)	0	0	0	1 (< 1)
Conjunctival hyperaemia	1 (2)	0	0	0	1 (< 1)
Ocular disorders NEC	1 (2)	1 (2)	1 (3)	0	2 (2)
Periorbital oedema	1 (2)	0	0	0	1 (< 1)
Eye swelling	0	1 (2)	1 (3)	0	1 (< 1)
Ocular infections, inflammations and associated manifestations	1 (2)	2 (3)	1 (3)	1 (4)	3 (2)
Eye irritation	1 (2)	0	0	0	1 (< 1)
Eye pruritus	0	1 (2)	1 (3)	0	1 (< 1)
Ocular hyperaemia	0	1 (2)	0	1 (4)	1 (< 1)
Lacrimation disorders	0	4 (6)	4 (11)	0	4 (3)
Dry eye	0	4 (6)	4 (11)	0	4 (3)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Eye disorders					
Lid, lash and lacrimal infections, irritations and inflammations	0	1 (2)	1 (3)	0	1 (< 1)
Eczema eyelids	0	1 (2)	1 (3)	0	1 (< 1)
Lid, lash and lacrimal structural disorders	0	1 (2)	1 (3)	0	1 (< 1)
Ectropion	0	1 (2)	1 (3)	0	1 (< 1)
Cardiac disorders	4 (6)	3 (5)	2 (5)	1 (4)	7 (5)
Rate and rhythm disorders NEC	3 (5)	1 (2)	0	1 (4)	4 (3)
Tachycardia	2 (3)	1 (2)	0	1 (4)	3 (2)
Bradycardia	1 (2)	0	0	0	1 (< 1)
Supraventricular arrhythmias	1 (2)	0	0	0	1 (< 1)
Sinus tachycardia	1 (2)	0	0	0	1 (< 1)
Cardiac signs and symptoms NEC	0	1 (2)	1 (3)	0	1 (< 1)
Palpitations	0	1 (2)	1 (3)	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Cardiac disorders					
Heart failures NEC	0	1 (2)	1 (3)	0	1 (< 1)
Cardiac failure congestive	0	1 (2)	1 (3)	0	1 (< 1)
Ear and labyrinth disorders	4 (6)	2 (3)	2 (5)	0	6 (5)
Inner ear signs and symptoms	2 (3)	0	0	0	2 (2)
Tinnitus	1 (2)	0	0	0	1 (< 1)
Vertigo	1 (2)	0	0	0	1 (< 1)
Ear disorders NEC	1 (2)	2 (3)	2 (5)	0	3 (2)
Otorrhoea	1 (2)	0	0	0	1 (< 1)
Ear haemorrhage	0	1 (2)	1 (3)	0	1 (< 1)
Ear pain	0	1 (2)	1 (3)	0	1 (< 1)
Hearing losses	1 (2)	0	0	0	1 (< 1)
Deafness unilateral	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Injury, poisoning and procedural complications	4 (6)	4 (6)	4 (11)	0	8 (6)
Non-site specific injuries NEC	2 (3)	3 (5)	3 (8)	0	5 (4)
Fall	1 (2)	2 (3)	2 (5)	0	3 (2)
Wound	1 (2)	0	0	0	1 (< 1)
Wound secretion	0	1 (2)	1 (3)	0	1 (< 1)
Fractures and dislocations NEC	1 (2)	0	0	0	1 (< 1)
Fracture	1 (2)	0	0	0	1 (< 1)
Thoracic cage fractures and dislocations	1 (2)	0	0	0	1 (< 1)
Rib fracture	1 (2)	0	0	0	1 (< 1)
Limb fractures and dislocations	0	1 (2)	1 (3)	0	1 (< 1)
Foot fracture	0	1 (2)	1 (3)	0	1 (< 1)
Muscle, tendon and ligament injuries	0	1 (2)	1 (3)	0	1 (< 1)
Ligament sprain	0	1 (2)	1 (3)	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Injury, poisoning and procedural complications					
Non-site specific procedural complications	0	1 (2)	1 (3)	0	1 (< 1)
Incision site complication	0	1 (2)	1 (3)	0	1 (< 1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (6)	9 (15)	6 (16)	3 (12)	13 (10)
Oncologic complications and emergencies	2 (3)	6 (10)	4 (11)	2 (8)	8 (6)
Cancer pain	1 (2)	5 (8)	3 (8)	2 (8)	6 (5)
Tumour associated fever	1 (2)	0	0	0	1 (< 1)
Infected neoplasm	0	1 (2)	1 (3)	0	1 (< 1)
Lymphomas unspecified NEC	1 (2)	0	0	0	1 (< 1)
Lymphoma	1 (2)	0	0	0	1 (< 1)
Mycoses fungoides	1 (2)	2 (3)	1 (3)	1 (4)	3 (2)
Mycosis fungoides	1 (2)	2 (3)	1 (3)	1 (4)	3 (2)
Neoplasms malignant site unspecified NEC	1 (2)	0	0	0	1 (< 1)
Squamous cell carcinoma	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Skin neoplasms malignant and unspecified (excl melanoma)	0	1 (2)	1 (3)	0	1 (< 1)
Squamous cell carcinoma of skin	0	1 (2)	1 (3)	0	1 (< 1)
Immune system disorders	3 (5)	0	0	0	3 (2)
Allergies to foods, food additives, drugs and other chemicals	2 (3)	0	0	0	2 (2)
Drug hypersensitivity	2 (3)	0	0	0	2 (2)
Atopic disorders	1 (2)	0	0	0	1 (< 1)
Seasonal allergy	1 (2)	0	0	0	1 (< 1)
Psychiatric disorders	3 (5)	10 (16)	8 (22)	2 (8)	13 (10)
Disturbances in initiating and maintaining sleep	2 (3)	5 (8)	5 (14)	0	7 (5)
Insomnia	2 (3)	5 (8)	5 (14)	0	7 (5)
Anxiety symptoms	1 (2)	4 (6)	3 (8)	1 (4)	5 (4)
Stress	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Psychiatric disorders					
Anxiety symptoms					
Anxiety	0	4 (6)	3 (8)	1 (4)	4 (3)
Mood alterations with depressive symptoms	0	3 (5)	2 (5)	1 (4)	3 (2)
Depressed mood	0	3 (5)	2 (5)	1 (4)	3 (2)
Parasomnias	0	1 (2)	1 (3)	0	1 (< 1)
Nightmare	0	1 (2)	1 (3)	0	1 (< 1)
Renal and urinary disorders	3 (5)	8 (13)	6 (16)	2 (8)	11 (9)
Bladder and urethral symptoms	2 (3)	4 (6)	2 (5)	2 (8)	6 (5)
Dysuria	1 (2)	1 (2)	0	1 (4)	2 (2)
Urinary retention	1 (2)	0	0	0	1 (< 1)
Micturition urgency	0	1 (2)	0	1 (4)	1 (< 1)
Pollakiuria	0	2 (3)	2 (5)	0	2 (2)
Urinary abnormalities	1 (2)	1 (2)	1 (3)	0	2 (2)
Haematuria	1 (2)	1 (2)	1 (3)	0	2 (2)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Renal and urinary disorders					
Renal failure and impairment	0	3 (5)	3 (8)	0	3 (2)
Chronic kidney disease	0	1 (2)	1 (3)	0	1 (< 1)
Oliguria	0	1 (2)	1 (3)	0	1 (< 1)
Renal impairment	0	1 (2)	1 (3)	0	1 (< 1)
Hepatobiliary disorders	2 (3)	0	0	0	2 (2)
Hepatocellular damage and hepatitis NEC	2 (3)	0	0	0	2 (2)
Hepatocellular injury	1 (2)	0	0	0	1 (< 1)
Hepatotoxicity	1 (2)	0	0	0	1 (< 1)
Reproductive system and breast disorders	2 (3)	2 (3)	0	2 (8)	4 (3)
Breast disorders NEC	1 (2)	0	0	0	1 (< 1)
Nipple disorder	1 (2)	0	0	0	1 (< 1)
Penile disorders NEC (excl erection and ejaculation)	1 (2)	0	0	0	1 (< 1)
Penile pain	1 (2)	0	0	0	1 (< 1)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.2B
Treatment-Emergent Adverse Events including Lab Toxicities by MedDRA Primary System Organ Class, High Level Term and Preferred Term
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Bexarotene N=37 n (%)	Methotrexate N=25 n (%)	Total N=128 n (%)
Reproductive system and breast disorders					
Menstruation and uterine bleeding NEC	0	1 (2)	0	1 (4)	1 (< 1)
Dysmenorrhoea	0	1 (2)	0	1 (4)	1 (< 1)
Prostate and seminal vesicles infections and inflammations	0	1 (2)	0	1 (4)	1 (< 1)
Prostatitis	0	1 (2)	0	1 (4)	1 (< 1)
Congenital, familial and genetic disorders	1 (2)	0	0	0	1 (< 1)
Vascular anomalies congenital NEC	1 (2)	0	0	0	1 (< 1)
Vertebral artery hypoplasia	1 (2)	0	0	0	1 (< 1)
Endocrine disorders	0	7 (11)	7 (19)	0	7 (5)
Thyroid hypofunction disorders	0	7 (11)	7 (19)	0	7 (5)
Hypothyroidism	0	5 (8)	5 (14)	0	5 (4)
Secondary hypothyroidism	0	2 (3)	2 (5)	0	2 (2)

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.2B-teae_socpt_lbtox.sas 20SEP2016: 00:49

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Patients with at Least 1 Adverse Event[a]	9 (14)	28 (42)	21 (32)	3 (5)	4 (6)	6 (10)	23 (37)	20 (32)	9 (15)	0
Nervous system disorders	17 (26)	23 (35)	7 (11)	0	0	5 (8)	7 (11)	0	0	0
Peripheral neuropathies NEC	11 (17)	19 (29)	5 (8)	0	0	0	1 (2)	0	0	0
Peripheral sensory neuropathy	12 (18)	15 (23)	3 (5)	0	0	0	1 (2)	0	0	0
Peripheral motor neuropathy	0	2 (3)	2 (3)	0	0	0	0	0	0	0
Neuropathy peripheral	0	2 (3)	1 (2)	0	0	0	0	0	0	0
Polyneuropathy	0	1 (2)	0	0	0	0	0	0	0	0
Paraesthesias and dysaesthesias	5 (8)	4 (6)	0	0	0	1 (2)	0	0	0	0
Paraesthesia	4 (6)	2 (3)	0	0	0	1 (2)	0	0	0	0
Hypoaesthesia	1 (2)	2 (3)	0	0	0	0	0	0	0	0
Dysaesthesia	1 (2)	0	0	0	0	0	0	0	0	0
Hyperaesthesia	1 (2)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%) Gr1	Gr2	Gr3	Gr4	Gr5	Methotrexate N=25 n (%) Gr1	Gr2	Gr3	Gr4	Gr5
Patients with at Least 1 Adverse Event[a]	4 (11)	11 (30)	14 (38)	6 (16)	0	2 (8)	12 (48)	6 (24)	3 (12)	0
Nervous system disorders	4 (11)	5 (14)	0	0	0	1 (4)	2 (8)	0	0	0
Peripheral neuropathies NEC	0	0	0	0	0	0	1 (4)	0	0	0
Peripheral sensory neuropathy	0	0	0	0	0	0	1 (4)	0	0	0
Peripheral motor neuropathy	0	0	0	0	0	0	0	0	0	0
Neuropathy peripheral	0	0	0	0	0	0	0	0	0	0
Polyneuropathy	0	0	0	0	0	0	0	0	0	0
Paraesthesias and dysaesthesias	1 (3)	0	0	0	0	0	0	0	0	0
Paraesthesia	1 (3)	0	0	0	0	0	0	0	0	0
Hypoaesthesia	0	0	0	0	0	0	0	0	0	0
Dysaesthesia	0	0	0	0	0	0	0	0	0	0
Hyperaesthesia	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Patients with at Least 1 Adverse Event[a]	15 (12)	51 (40)	41 (32)	12 (9)	4 (3)	
Nervous system disorders	22 (17)	30 (23)	7 (5)	0	0	
Peripheral neuropathies NEC	11 (9)	20 (16)	5 (4)	0	0	
Peripheral sensory neuropathy	12 (9)	16 (13)	3 (2)	0	0	
Peripheral motor neuropathy	0	2 (2)	2 (2)	0	0	
Neuropathy peripheral	0	2 (2)	1 (< 1)	0	0	
Polyneuropathy	0	1 (< 1)	0	0	0	
Paraesthesias and dysaesthesias	6 (5)	4 (3)	0	0	0	
Paraesthesia	5 (4)	2 (2)	0	0	0	
Hypoaesthesia	1 (< 1)	2 (2)	0	0	0	
Dysaesthesia	1 (< 1)	0	0	0	0	
Hyperaesthesia	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Nervous system disorders										
Sensory abnormalities NEC	6 (9)	3 (5)	0	0	0	0	1 (2)	0	0	0
Dysgeusia	3 (5)	2 (3)	0	0	0	0	0	0	0	0
Neuralgia	1 (2)	1 (2)	0	0	0	0	1 (2)	0	0	0
Ageusia	1 (2)	0	0	0	0	0	0	0	0	0
Sensory loss	1 (2)	0	0	0	0	0	0	0	0	0
Headaches NEC	4 (6)	2 (3)	0	0	0	5 (8)	1 (2)	0	0	0
Headache	3 (5)	2 (3)	0	0	0	5 (8)	1 (2)	0	0	0
Cluster headache	1 (2)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Nervous system disorders										
Sensory abnormalities NEC	0	0	0	0	0	0	1 (4)	0	0	0
Dysgeusia	0	0	0	0	0	0	0	0	0	0
Neuralgia	0	0	0	0	0	0	1 (4)	0	0	0
Ageusia	0	0	0	0	0	0	0	0	0	0
Sensory loss	0	0	0	0	0	0	0	0	0	0
Headaches NEC	4 (11)	1 (3)	0	0	0	1 (4)	0	0	0	0
Headache	4 (11)	1 (3)	0	0	0	1 (4)	0	0	0	0
Cluster headache	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Nervous system disorders						
Sensory abnormalities NEC	6 (5)	4 (3)	0	0	0	
Dysgeusia	3 (2)	2 (2)	0	0	0	
Neuralgia	1 (< 1)	2 (2)	0	0	0	
Ageusia	1 (< 1)	0	0	0	0	
Sensory loss	1 (< 1)	0	0	0	0	
Headaches NEC	9 (7)	3 (2)	0	0	0	
Headache	8 (6)	3 (2)	0	0	0	
Cluster headache	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Nervous system disorders										
Neurological signs and symptoms NEC	3 (5)	0	2 (3)	0	0	1 (2)	0	0	0	0
Dizziness	3 (5)	0	2 (3)	0	0	1 (2)	0	0	0	0
Disturbances in consciousness NEC	1 (2)	1 (2)	0	0	0	0	2 (3)	0	0	0
Lethargy	0	1 (2)	0	0	0	1 (2)	0	0	0	0
Somnolence	1 (2)	0	0	0	0	0	1 (2)	0	0	0
Syncope	0	0	0	0	0	0	1 (2)	0	0	0
Olfactory nerve disorders	2 (3)	0	0	0	0	0	0	0	0	0
Anosmia	2 (3)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Nervous system disorders										
Neurological signs and symptoms NEC	1 (3)	0	0	0	0	0	0	0	0	0
Dizziness	1 (3)	0	0	0	0	0	0	0	0	0
Disturbances in consciousness NEC	0	2 (5)	0	0	0	0	0	0	0	0
Lethargy	1 (3)	0	0	0	0	0	0	0	0	0
Somnolence	0	1 (3)	0	0	0	0	0	0	0	0
Syncope	0	1 (3)	0	0	0	0	0	0	0	0
Olfactory nerve disorders	0	0	0	0	0	0	0	0	0	0
Anosmia	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Nervous system disorders						
Neurological signs and symptoms NEC	4 (3)	0	2 (2)	0	0	
Dizziness	4 (3)	0	2 (2)	0	0	
Disturbances in consciousness NEC	1 (< 1)	3 (2)	0	0	0	
Lethargy	1 (< 1)	1 (< 1)	0	0	0	
Somnolence	1 (< 1)	1 (< 1)	0	0	0	
Syncope	0	1 (< 1)	0	0	0	
Olfactory nerve disorders	2 (2)	0	0	0	0	
Anosmia	2 (2)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Nervous system disorders										
Chronic polyneuropathies	0	1 (2)	0	0	0	0	0	0	0	0
Demyelinating polyneuropathy	0	1 (2)	0	0	0	0	0	0	0	0
Coordination and balance disturbances	0	1 (2)	0	0	0	0	0	0	0	0
Balance disorder	0	1 (2)	0	0	0	0	0	0	0	0
Migraine headaches	1 (2)	0	0	0	0	0	0	0	0	0
Migraine	1 (2)	0	0	0	0	0	0	0	0	0
Facial cranial nerve disorders	0	0	0	0	0	0	1 (2)	0	0	0
Facial paresis	0	0	0	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%) Gr1	Gr2	Gr3	Gr4	Gr5	Methotrexate N=25 n (%) Gr1	Gr2	Gr3	Gr4	Gr5
Nervous system disorders										
Chronic polyneuropathies	0	0	0	0	0	0	0	0	0	0
Demyelinating polyneuropathy	0	0	0	0	0	0	0	0	0	0
Coordination and balance disturbances	0	0	0	0	0	0	0	0	0	0
Balance disorder	0	0	0	0	0	0	0	0	0	0
Migraine headaches	0	0	0	0	0	0	0	0	0	0
Migraine	0	0	0	0	0	0	0	0	0	0
Facial cranial nerve disorders	0	1 (3)	0	0	0	0	0	0	0	0
Facial paresis	0	1 (3)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Nervous system disorders						
Chronic polyneuropathies	0	1 (< 1)	0	0	0	
Demyelinating polyneuropathy	0	1 (< 1)	0	0	0	
Coordination and balance disturbances	0	1 (< 1)	0	0	0	
Balance disorder	0	1 (< 1)	0	0	0	
Migraine headaches	1 (< 1)	0	0	0	0	
Migraine	1 (< 1)	0	0	0	0	
Facial cranial nerve disorders	0	1 (< 1)	0	0	0	
Facial paresis	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Nervous system disorders										
Lumbar spinal cord and nerve root disorders	0	0	0	0	0	0	1 (2)	0	0	0
Sciatica	0	0	0	0	0	0	1 (2)	0	0	0
Blood and lymphatic system disorders	33 (50)	7 (11)	2 (3)	3 (5)	0	31 (50)	11 (18)	6 (10)	0	0
Anaemias NEC	37 (56)	4 (6)	0	0	0	32 (52)	5 (8)	3 (5)	0	0
Anaemia[b]	37 (56)	4 (6)	0	0	0	32 (52)	5 (8)	3 (5)	0	0
Neutropenias	6 (9)	5 (8)	2 (3)	1 (2)	0	5 (8)	7 (11)	3 (5)	0	0
Neutropenia[c]	6 (9)	5 (8)	2 (3)	1 (2)	0	5 (8)	7 (11)	3 (5)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Nervous system disorders										
Lumbar spinal cord and nerve root disorders	0	1 (3)	0	0	0	0	0	0	0	0
Sciatica	0	1 (3)	0	0	0	0	0	0	0	0
Blood and lymphatic system disorders	17 (46)	8 (22)	6 (16)	0	0	14 (56)	3 (12)	0	0	0
Anaemias NEC	19 (51)	2 (5)	3 (8)	0	0	13 (52)	3 (12)	0	0	0
Anaemia[b]	19 (51)	2 (5)	3 (8)	0	0	13 (52)	3 (12)	0	0	0
Neutropenias	4 (11)	7 (19)	3 (8)	0	0	1 (4)	0	0	0	0
Neutropenia[c]	4 (11)	7 (19)	3 (8)	0	0	1 (4)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Nervous system disorders						
Lumbar spinal cord and nerve root disorders	0	1 (< 1)	0	0	0	
Sciatica	0	1 (< 1)	0	0	0	
Blood and lymphatic system disorders	64 (50)	18 (14)	8 (6)	3 (2)	0	
Anaemias NEC	69 (54)	9 (7)	3 (2)	0	0	
Anaemia[b]	69 (54)	9 (7)	3 (2)	0	0	
Neutropenias	11 (9)	12 (9)	5 (4)	1 (< 1)	0	
Neutropenia[c]	11 (9)	12 (9)	5 (4)	1 (< 1)	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Blood and lymphatic system disorders										
Thrombocytopenias	8 (12)	0	1 (2)	1 (2)	0	1 (2)	0	0	0	0
Thrombocytopenia[d]	8 (12)	0	1 (2)	1 (2)	0	1 (2)	0	0	0	0
Leukopenias NEC	0	2 (3)	0	0	0	1 (2)	1 (2)	0	0	0
Leukopenia	0	2 (3)	0	0	0	0	1 (2)	0	0	0
Lymphopenia	0	0	0	0	0	1 (2)	0	0	0	0
Anaemias haemolytic mechanical factor	0	0	0	1 (2)	0	0	0	0	0	0
Haemolytic uraemic syndrome	0	0	0	1 (2)	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%) Gr1	Gr2	Gr3	Gr4	Gr5	Methotrexate N=25 n (%) Gr1	Gr2	Gr3	Gr4	Gr5
Blood and lymphatic system disorders										
Thrombocytopenias	1 (3)	0	0	0	0	0	0	0	0	0
Thrombocytopenia[d]	1 (3)	0	0	0	0	0	0	0	0	0
Leukopenias NEC	0	1 (3)	0	0	0	1 (4)	0	0	0	0
Leukopenia	0	1 (3)	0	0	0	0	0	0	0	0
Lymphopenia	0	0	0	0	0	1 (4)	0	0	0	0
Anaemias haemolytic mechanical factor	0	0	0	0	0	0	0	0	0	0
Haemolytic uraemic syndrome	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Blood and lymphatic system disorders						
Thrombocytopenias	9 (7)	0	1 (< 1)	1 (< 1)	0	
Thrombocytopenia[d]	9 (7)	0	1 (< 1)	1 (< 1)	0	
Leukopenias NEC	1 (< 1)	3 (2)	0	0	0	
Leukopenia	0	3 (2)	0	0	0	
Lymphopenia	1 (< 1)	0	0	0	0	
Anaemias haemolytic mechanical factor	0	0	0	1 (< 1)	0	
Haemolytic uraemic syndrome	0	0	0	1 (< 1)	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Blood and lymphatic system disorders										
Eosinophilic disorders	0	0	0	0	0	1 (2)	0	0	0	0
Eosinophilia	0	0	0	0	0	1 (2)	0	0	0	0
Lymphatic system disorders NEC	0	0	0	0	0	0	1 (2)	0	0	0
Lymphadenopathy	0	0	0	0	0	0	1 (2)	0	0	0
Gastrointestinal disorders	21 (32)	14 (21)	4 (6)	1 (2)	0	13 (21)	8 (13)	0	1 (2)	0
Nausea and vomiting symptoms	18 (27)	8 (12)	1 (2)	0	0	10 (16)	0	0	0	0
Nausea	16 (24)	7 (11)	1 (2)	0	0	8 (13)	0	0	0	0
Vomiting	8 (12)	2 (3)	1 (2)	0	0	3 (5)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Blood and lymphatic system disorders										
Eosinophilic disorders	1 (3)	0	0	0	0	0	0	0	0	0
Eosinophilia	1 (3)	0	0	0	0	0	0	0	0	0
Lymphatic system disorders NEC	0	0	0	0	0	0	1 (4)	0	0	0
Lymphadenopathy	0	0	0	0	0	0	1 (4)	0	0	0
Gastrointestinal disorders	7 (19)	5 (14)	0	0	0	6 (24)	3 (12)	0	1 (4)	0
Nausea and vomiting symptoms	4 (11)	0	0	0	0	6 (24)	0	0	0	0
Nausea	4 (11)	0	0	0	0	4 (16)	0	0	0	0
Vomiting	1 (3)	0	0	0	0	2 (8)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Blood and lymphatic system disorders						
Eosinophilic disorders	1 (< 1)	0	0	0	0	
Eosinophilia	1 (< 1)	0	0	0	0	
Lymphatic system disorders NEC	0	1 (< 1)	0	0	0	
Lymphadenopathy	0	1 (< 1)	0	0	0	
Gastrointestinal disorders	34 (27)	22 (17)	4 (3)	2 (2)	0	
Nausea and vomiting symptoms	28 (22)	8 (6)	1 (< 1)	0	0	
Nausea	24 (19)	7 (5)	1 (< 1)	0	0	
Vomiting	11 (9)	2 (2)	1 (< 1)	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Diarrhoea (excl infective)	8 (12)	9 (14)	2 (3)	0	0	2 (3)	2 (3)	0	0	0
Diarrhoea	8 (12)	9 (14)	2 (3)	0	0	2 (3)	2 (3)	0	0	0
Gastrointestinal atonic and hypomotility disorders NEC	2 (3)	1 (2)	1 (2)	0	0	2 (3)	4 (6)	0	0	0
Constipation	2 (3)	0	1 (2)	0	0	2 (3)	2 (3)	0	0	0
Gastrooesophageal reflux disease	0	1 (2)	0	0	0	0	2 (3)	0	0	0
Gastrointestinal and abdominal pains (excl oral and throat)	2 (3)	1 (2)	0	0	0	1 (2)	2 (3)	0	0	0
Abdominal pain	1 (2)	1 (2)	0	0	0	0	0	0	0	0
Abdominal pain upper	1 (2)	0	0	0	0	1 (2)	2 (3)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Diarrhoea (excl infective)	1 (3)	2 (5)	0	0	0	1 (4)	0	0	0	0
Diarrhoea	1 (3)	2 (5)	0	0	0	1 (4)	0	0	0	0
Gastrointestinal atonic and hypomotility disorders NEC	2 (5)	2 (5)	0	0	0	0	2 (8)	0	0	0
Constipation	2 (5)	2 (5)	0	0	0	0	0	0	0	0
Gastrooesophageal reflux disease	0	0	0	0	0	0	2 (8)	0	0	0
Gastrointestinal and abdominal pains (excl oral and throat)	0	0	0	0	0	1 (4)	2 (8)	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0	0	0
Abdominal pain upper	0	0	0	0	0	1 (4)	2 (8)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Gastrointestinal disorders						
Diarrhoea (excl infective)	10 (8)	11 (9)	2 (2)	0	0	
Diarrhoea	10 (8)	11 (9)	2 (2)	0	0	
Gastrointestinal atonic and hypomotility disorders NEC	4 (3)	5 (4)	1 (< 1)	0	0	
Constipation	4 (3)	2 (2)	1 (< 1)	0	0	
Gastrooesophageal reflux disease	0	3 (2)	0	0	0	
Gastrointestinal and abdominal pains (excl oral and throat)	3 (2)	3 (2)	0	0	0	
Abdominal pain	1 (< 1)	1 (< 1)	0	0	0	
Abdominal pain upper	2 (2)	2 (2)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Gastrointestinal signs and symptoms NEC	1 (2)	1 (2)	0	0	0	0	1 (2)	0	0	0
Dysphagia	1 (2)	1 (2)	0	0	0	0	1 (2)	0	0	0
Stomatitis and ulceration	0	2 (3)	0	0	0	1 (2)	0	0	0	0
Mouth ulceration	0	1 (2)	0	0	0	1 (2)	0	0	0	0
Stomatitis	0	1 (2)	0	0	0	0	0	0	0	0
Acute and chronic pancreatitis	0	0	0	1 (2)	0	0	0	0	0	0
Pancreatitis	0	0	0	1 (2)	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Gastrointestinal signs and symptoms NEC	0	0	0	0	0	0	1 (4)	0	0	0
Dysphagia	0	0	0	0	0	0	1 (4)	0	0	0
Stomatitis and ulceration	1 (3)	0	0	0	0	0	0	0	0	0
Mouth ulceration	1 (3)	0	0	0	0	0	0	0	0	0
Stomatitis	0	0	0	0	0	0	0	0	0	0
Acute and chronic pancreatitis	0	0	0	0	0	0	0	0	0	0
Pancreatitis	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Gastrointestinal disorders						
Gastrointestinal signs and symptoms NEC	1 (< 1)	2 (2)	0	0	0	
Dysphagia	1 (< 1)	2 (2)	0	0	0	
Stomatitis and ulceration	1 (< 1)	2 (2)	0	0	0	
Mouth ulceration	1 (< 1)	1 (< 1)	0	0	0	
Stomatitis	0	1 (< 1)	0	0	0	
Acute and chronic pancreatitis	0	0	0	1 (< 1)	0	
Pancreatitis	0	0	0	1 (< 1)	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Diverticula	0	1 (2)	0	0	0	0	0	0	0	0
Diverticulum	0	1 (2)	0	0	0	0	0	0	0	0
Dyspeptic signs and symptoms	1 (2)	0	0	0	0	0	0	0	0	0
Dyspepsia	1 (2)	0	0	0	0	0	0	0	0	0
Gastrointestinal inflammatory disorders NEC	0	1 (2)	0	0	0	0	0	0	0	0
Epiploic appendagitis	0	1 (2)	0	0	0	0	0	0	0	0
Haemorrhoids and gastrointestinal varices (excl oesophageal)	1 (2)	0	0	0	0	1 (2)	0	0	0	0
Haemorrhoidal haemorrhage	1 (2)	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Diverticula	0	0	0	0	0	0	0	0	0	0
Diverticulum	0	0	0	0	0	0	0	0	0	0
Dyspeptic signs and symptoms	0	0	0	0	0	0	0	0	0	0
Dyspepsia	0	0	0	0	0	0	0	0	0	0
Gastrointestinal inflammatory disorders NEC	0	0	0	0	0	0	0	0	0	0
Epiploic appendagitis	0	0	0	0	0	0	0	0	0	0
Haemorrhoids and gastrointestinal varices (excl oesophageal)	0	0	0	0	0	1 (4)	0	0	0	0
Haemorrhoidal haemorrhage	0	0	0	0	0	1 (4)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Gastrointestinal disorders						
Diverticula	0	1 (< 1)	0	0	0	
Diverticulum	0	1 (< 1)	0	0	0	
Dyspeptic signs and symptoms	1 (< 1)	0	0	0	0	
Dyspepsia	1 (< 1)	0	0	0	0	
Gastrointestinal inflammatory disorders NEC	0	1 (< 1)	0	0	0	
Epiploic appendagitis	0	1 (< 1)	0	0	0	
Haemorrhoids and gastrointestinal varices (excl oesophageal)	2 (2)	0	0	0	0	
Haemorrhoidal haemorrhage	2 (2)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Intestinal ulcers and perforation NEC	0	0	0	1 (2)	0	0	0	0	0	0
Intestinal perforation	0	0	0	1 (2)	0	0	0	0	0	0
Non-site specific gastrointestinal haemorrhages	0	0	0	1 (2)	0	0	0	0	0	0
Melaena	0	0	0	1 (2)	0	0	0	0	0	0
Oral dryness and saliva altered	1 (2)	0	0	0	0	0	1 (2)	0	0	0
Dry mouth	1 (2)	0	0	0	0	0	1 (2)	0	0	0
Oral soft tissue disorders NEC	1 (2)	0	0	0	0	0	0	0	1 (2)	0
Cheilitis	1 (2)	0	0	0	0	0	0	0	0	0
Lip ulceration	0	0	0	0	0	0	0	0	1 (2)	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Intestinal ulcers and perforation NEC	0	0	0	0	0	0	0	0	0	0
Intestinal perforation	0	0	0	0	0	0	0	0	0	0
Non-site specific gastrointestinal haemorrhages	0	0	0	0	0	0	0	0	0	0
Melaena	0	0	0	0	0	0	0	0	0	0
Oral dryness and saliva altered	0	1 (3)	0	0	0	0	0	0	0	0
Dry mouth	0	1 (3)	0	0	0	0	0	0	0	0
Oral soft tissue disorders NEC	0	0	0	0	0	0	0	0	1 (4)	0
Cheilitis	0	0	0	0	0	0	0	0	0	0
Lip ulceration	0	0	0	0	0	0	0	0	1 (4)	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Gastrointestinal disorders						
Intestinal ulcers and perforation NEC	0	0	0	1 (< 1)	0	
Intestinal perforation	0	0	0	1 (< 1)	0	
Non-site specific gastrointestinal haemorrhages	0	0	0	1 (< 1)	0	
Melaena	0	0	0	1 (< 1)	0	
Oral dryness and saliva altered	1 (< 1)	1 (< 1)	0	0	0	
Dry mouth	1 (< 1)	1 (< 1)	0	0	0	
Oral soft tissue disorders NEC	1 (< 1)	0	0	1 (< 1)	0	
Cheilitis	1 (< 1)	0	0	0	0	
Lip ulceration	0	0	0	1 (< 1)	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Tongue signs and symptoms	0	1 (2)	0	0	0	0	0	0	0	0
Swollen tongue	0	1 (2)	0	0	0	0	0	0	0	0
Flatulence, bloating and distension	0	0	0	0	0	1 (2)	0	0	0	0
Abdominal distension	0	0	0	0	0	1 (2)	0	0	0	0
Oral soft tissue pain and paraesthesia	0	0	0	0	0	1 (2)	0	0	0	0
Odynophagia	0	0	0	0	0	1 (2)	0	0	0	0
Salivary gland disorders NEC	0	0	0	0	0	1 (2)	0	0	0	0
Salivary gland calculus	0	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%) Gr1	Gr2	Gr3	Gr4	Gr5	Methotrexate N=25 n (%) Gr1	Gr2	Gr3	Gr4	Gr5
Gastrointestinal disorders										
Tongue signs and symptoms	0	0	0	0	0	0	0	0	0	0
Swollen tongue	0	0	0	0	0	0	0	0	0	0
Flatulence, bloating and distension	1 (3)	0	0	0	0	0	0	0	0	0
Abdominal distension	1 (3)	0	0	0	0	0	0	0	0	0
Oral soft tissue pain and paraesthesia	1 (3)	0	0	0	0	0	0	0	0	0
Odynophagia	1 (3)	0	0	0	0	0	0	0	0	0
Salivary gland disorders NEC	1 (3)	0	0	0	0	0	0	0	0	0
Salivary gland calculus	1 (3)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5
			Total N=128 n (%)		
Gastrointestinal disorders					
Tongue signs and symptoms	0	1 (< 1)	0	0	0
Swollen tongue	0	1 (< 1)	0	0	0
Flatulence, bloating and distension	1 (< 1)	0	0	0	0
Abdominal distension	1 (< 1)	0	0	0	0
Oral soft tissue pain and paraesthesia	1 (< 1)	0	0	0	0
Odynophagia	1 (< 1)	0	0	0	0
Salivary gland disorders NEC	1 (< 1)	0	0	0	0
Salivary gland calculus	1 (< 1)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
General disorders and administration site conditions	23 (35)	11 (17)	4 (6)	0	1 (2)	20 (32)	12 (19)	3 (5)	1 (2)	0
Asthenic conditions	17 (26)	5 (8)	4 (6)	0	0	16 (26)	4 (6)	1 (2)	1 (2)	0
Fatigue	11 (17)	5 (8)	3 (5)	0	0	13 (21)	3 (5)	1 (2)	0	0
Asthenia	6 (9)	0	1 (2)	0	0	3 (5)	1 (2)	0	1 (2)	0
Febrile disorders	8 (12)	3 (5)	0	0	0	7 (11)	3 (5)	1 (2)	0	0
Pyrexia	8 (12)	3 (5)	0	0	0	7 (11)	3 (5)	1 (2)	0	0
Oedema NEC	6 (9)	1 (2)	0	0	0	3 (5)	3 (5)	1 (2)	0	0
Oedema peripheral	6 (9)	1 (2)	0	0	0	3 (5)	3 (5)	0	0	0
Face oedema	0	0	0	0	0	0	0	1 (2)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
General disorders and administration site conditions	13 (35)	5 (14)	0	1 (3)	0	7 (28)	7 (28)	3 (12)	0	0
Asthenic conditions	12 (32)	1 (3)	0	1 (3)	0	4 (16)	3 (12)	1 (4)	0	0
Fatigue	11 (30)	1 (3)	0	0	0	2 (8)	2 (8)	1 (4)	0	0
Asthenia	1 (3)	0	0	1 (3)	0	2 (8)	1 (4)	0	0	0
Febrile disorders	3 (8)	1 (3)	0	0	0	4 (16)	2 (8)	1 (4)	0	0
Pyrexia	3 (8)	1 (3)	0	0	0	4 (16)	2 (8)	1 (4)	0	0
Oedema NEC	0	2 (5)	0	0	0	3 (12)	1 (4)	1 (4)	0	0
Oedema peripheral	0	2 (5)	0	0	0	3 (12)	1 (4)	0	0	0
Face oedema	0	0	0	0	0	0	0	1 (4)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
General disorders and administration site conditions	43 (34)	23 (18)	7 (5)	1 (< 1)	1 (< 1)	
Asthenic conditions	33 (26)	9 (7)	5 (4)	1 (< 1)	0	
Fatigue	24 (19)	8 (6)	4 (3)	0	0	
Asthenia	9 (7)	1 (< 1)	1 (< 1)	1 (< 1)	0	
Febrile disorders	15 (12)	6 (5)	1 (< 1)	0	0	
Pyrexia	15 (12)	6 (5)	1 (< 1)	0	0	
Oedema NEC	9 (7)	4 (3)	1 (< 1)	0	0	
Oedema peripheral	9 (7)	4 (3)	0	0	0	
Face oedema	0	0	1 (< 1)	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
General disorders and administration site conditions										
Feelings and sensations NEC	3 (5)	2 (3)	0	0	0	1 (2)	1 (2)	0	0	0
Chills	2 (3)	2 (3)	0	0	0	1 (2)	1 (2)	0	0	0
Feeling cold	1 (2)	0	0	0	0	0	0	0	0	0
General signs and symptoms NEC	2 (3)	1 (2)	1 (2)	0	1 (2)	3 (5)	3 (5)	0	0	0
Extravasation	0	0	1 (2)	0	0	0	0	0	0	0
General physical health deterioration	0	0	1 (2)	0	0	0	0	0	0	0
Influenza like illness	1 (2)	0	0	0	0	0	0	0	0	0
Local swelling	1 (2)	0	0	0	0	1 (2)	0	0	0	0
Multiple organ dysfunction syndrome	0	0	0	0	1 (2)	0	0	0	0	0
Peripheral swelling	0	1 (2)	0	0	0	2 (3)	2 (3)	0	0	0
Xerosis	0	0	0	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
General disorders and administration site conditions										
Feelings and sensations NEC	0	0	0	0	0	1 (4)	1 (4)	0	0	0
Chills	0	0	0	0	0	1 (4)	1 (4)	0	0	0
Feeling cold	0	0	0	0	0	0	0	0	0	0
General signs and symptoms NEC	2 (5)	1 (3)	0	0	0	1 (4)	2 (8)	0	0	0
Extravasation	0	0	0	0	0	0	0	0	0	0
General physical health deterioration	0	0	0	0	0	0	0	0	0	0
Influenza like illness	0	0	0	0	0	0	0	0	0	0
Local swelling	0	0	0	0	0	1 (4)	0	0	0	0
Multiple organ dysfunction syndrome	0	0	0	0	0	0	0	0	0	0
Peripheral swelling	2 (5)	1 (3)	0	0	0	0	1 (4)	0	0	0
Xerosis	0	0	0	0	0	0	1 (4)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
General disorders and administration site conditions						
Feelings and sensations NEC	4 (3)	3 (2)	0	0	0	
Chills	3 (2)	3 (2)	0	0	0	
Feeling cold	1 (< 1)	0	0	0	0	
General signs and symptoms NEC	5 (4)	4 (3)	1 (< 1)	0	1 (< 1)	
Extravasation	0	0	1 (< 1)	0	0	
General physical health deterioration	0	0	1 (< 1)	0	0	
Influenza like illness	1 (< 1)	0	0	0	0	
Local swelling	2 (2)	0	0	0	0	
Multiple organ dysfunction syndrome	0	0	0	0	1 (< 1)	
Peripheral swelling	2 (2)	3 (2)	0	0	0	
Xerosis	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
General disorders and administration site conditions										
Pain and discomfort NEC	1 (2)	0	0	0	0	0	0	0	0	0
Pain	1 (2)	0	0	0	0	0	0	0	0	0
Healing abnormal NEC	0	0	0	0	0	1 (2)	0	0	0	0
Impaired healing	0	0	0	0	0	1 (2)	0	0	0	0
Skin and subcutaneous tissue disorders	17 (26)	13 (20)	3 (5)	1 (2)	0	6 (10)	12 (19)	2 (3)	0	0
Pruritus NEC	8 (12)	8 (12)	2 (3)	0	0	2 (3)	5 (8)	2 (3)	0	0
Pruritus	8 (12)	2 (3)	1 (2)	0	0	2 (3)	4 (6)	2 (3)	0	0
Pruritus generalised	0	6 (9)	1 (2)	0	0	0	1 (2)	0	0	0
Rash pruritic	1 (2)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
General disorders and administration site conditions										
Pain and discomfort NEC	0	0	0	0	0	0	0	0	0	0
Pain	0	0	0	0	0	0	0	0	0	0
Healing abnormal NEC	0	0	0	0	0	1 (4)	0	0	0	0
Impaired healing	0	0	0	0	0	1 (4)	0	0	0	0
Skin and subcutaneous tissue disorders	3 (8)	9 (24)	2 (5)	0	0	3 (12)	3 (12)	0	0	0
Pruritus NEC	1 (3)	4 (11)	2 (5)	0	0	1 (4)	1 (4)	0	0	0
Pruritus	1 (3)	3 (8)	2 (5)	0	0	1 (4)	1 (4)	0	0	0
Pruritus generalised	0	1 (3)	0	0	0	0	0	0	0	0
Rash pruritic	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
General disorders and administration site conditions						
Pain and discomfort NEC	1 (< 1)	0	0	0	0	
Pain	1 (< 1)	0	0	0	0	
Healing abnormal NEC	1 (< 1)	0	0	0	0	
Impaired healing	1 (< 1)	0	0	0	0	
Skin and subcutaneous tissue disorders	23 (18)	25 (20)	5 (4)	1 (< 1)	0	
Pruritus NEC	10 (8)	13 (10)	4 (3)	0	0	
Pruritus	10 (8)	6 (5)	3 (2)	0	0	
Pruritus generalised	0	7 (5)	1 (< 1)	0	0	
Rash pruritic	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Alopecias	9 (14)	1 (2)	0	0	0	2 (3)	0	0	0	0
Alopecia	9 (14)	1 (2)	0	0	0	2 (3)	0	0	0	0
Rashes, eruptions and exanthems NEC	5 (8)	2 (3)	1 (2)	0	0	1 (2)	2 (3)	0	0	0
Rash maculo-papular	4 (6)	2 (3)	1 (2)	0	0	1 (2)	2 (3)	0	0	0
Rash macular	1 (2)	0	0	0	0	0	0	0	0	0
Urticarias	3 (5)	1 (2)	1 (2)	0	0	0	1 (2)	0	0	0
Urticaria	3 (5)	1 (2)	1 (2)	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%) Gr1	Gr2	Gr3	Gr4	Gr5	Methotrexate N=25 n (%) Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Alopecias	1 (3)	0	0	0	0	1 (4)	0	0	0	0
Alopecia	1 (3)	0	0	0	0	1 (4)	0	0	0	0
Rashes, eruptions and exanthems NEC	1 (3)	1 (3)	0	0	0	0	1 (4)	0	0	0
Rash maculo-papular	1 (3)	1 (3)	0	0	0	0	1 (4)	0	0	0
Rash macular	0	0	0	0	0	0	0	0	0	0
Urticarias	0	1 (3)	0	0	0	0	0	0	0	0
Urticaria	0	1 (3)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Skin and subcutaneous tissue disorders						
Alopecias	11 (9)	1 (< 1)	0	0	0	
Alopecia	11 (9)	1 (< 1)	0	0	0	
Rashes, eruptions and exanthems NEC	6 (5)	4 (3)	1 (< 1)	0	0	
Rash maculo-papular	5 (4)	4 (3)	1 (< 1)	0	0	
Rash macular	1 (< 1)	0	0	0	0	
Urticarias	3 (2)	2 (2)	1 (< 1)	0	0	
Urticaria	3 (2)	2 (2)	1 (< 1)	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Acnes	3 (5)	0	0	0	0	0	0	0	0	0
Dermatitis acneiform	3 (5)	0	0	0	0	0	0	0	0	0
Apocrine and eccrine gland disorders	1 (2)	1 (2)	0	0	0	0	0	0	0	0
Miliaria	1 (2)	0	0	0	0	0	0	0	0	0
Night sweats	0	1 (2)	0	0	0	0	0	0	0	0
Dermal and epidermal conditions NEC	1 (2)	1 (2)	0	0	0	2 (3)	3 (5)	0	0	0
Dry skin	1 (2)	0	0	0	0	2 (3)	2 (3)	0	0	0
Skin discolouration	1 (2)	0	0	0	0	0	0	0	0	0
Skin fissures	0	1 (2)	0	0	0	0	0	0	0	0
Skin lesion	1 (2)	0	0	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Acnes	0	0	0	0	0	0	0	0	0	0
Dermatitis acneiform	0	0	0	0	0	0	0	0	0	0
Apocrine and eccrine gland disorders	0	0	0	0	0	0	0	0	0	0
Miliaria	0	0	0	0	0	0	0	0	0	0
Night sweats	0	0	0	0	0	0	0	0	0	0
Dermal and epidermal conditions NEC	1 (3)	3 (8)	0	0	0	1 (4)	0	0	0	0
Dry skin	1 (3)	2 (5)	0	0	0	1 (4)	0	0	0	0
Skin discolouration	0	0	0	0	0	0	0	0	0	0
Skin fissures	0	0	0	0	0	0	0	0	0	0
Skin lesion	0	1 (3)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Skin and subcutaneous tissue disorders						
Acnes	3 (2)	0	0	0	0	
Dermatitis acneiform	3 (2)	0	0	0	0	
Apocrine and eccrine gland disorders	1 (< 1)	1 (< 1)	0	0	0	
Miliaria	1 (< 1)	0	0	0	0	
Night sweats	0	1 (< 1)	0	0	0	
Dermal and epidermal conditions NEC	3 (2)	4 (3)	0	0	0	
Dry skin	3 (2)	2 (2)	0	0	0	
Skin discolouration	1 (< 1)	0	0	0	0	
Skin fissures	0	1 (< 1)	0	0	0	
Skin lesion	1 (< 1)	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Dermatitis ascribed to specific agent	1 (2)	0	0	1 (2)	0	0	0	0	0	0
Drug eruption	1 (2)	0	0	1 (2)	0	0	0	0	0	0
Erythemas	1 (2)	1 (2)	0	0	0	1 (2)	1 (2)	0	0	0
Erythema	1 (2)	0	0	0	0	0	0	0	0	0
Rash erythematous	0	1 (2)	0	0	0	1 (2)	1 (2)	0	0	0
Exfoliative conditions	0	2 (3)	0	0	0	2 (3)	0	0	0	0
Skin exfoliation	0	2 (3)	0	0	0	2 (3)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Dermatitis ascribed to specific agent	0	0	0	0	0	0	0	0	0	0
Drug eruption	0	0	0	0	0	0	0	0	0	0
Erythemas	1 (3)	0	0	0	0	0	1 (4)	0	0	0
Erythema	0	0	0	0	0	0	0	0	0	0
Rash erythematous	1 (3)	0	0	0	0	0	1 (4)	0	0	0
Exfoliative conditions	2 (5)	0	0	0	0	0	0	0	0	0
Skin exfoliation	2 (5)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Skin and subcutaneous tissue disorders						
Dermatitis ascribed to specific agent	1 (< 1)	0	0	1 (< 1)	0	
Drug eruption	1 (< 1)	0	0	1 (< 1)	0	
Erythemas	2 (2)	2 (2)	0	0	0	
Erythema	1 (< 1)	0	0	0	0	
Rash erythematous	1 (< 1)	2 (2)	0	0	0	
Exfoliative conditions	2 (2)	2 (2)	0	0	0	
Skin exfoliation	2 (2)	2 (2)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Angioedemas	0	1 (2)	0	0	0	1 (2)	0	0	0	0
Swelling face	0	1 (2)	0	0	0	1 (2)	0	0	0	0
Dermatitis and eczema	1 (2)	0	0	0	0	0	1 (2)	0	0	0
Eczema	1 (2)	0	0	0	0	0	0	0	0	0
Intertrigo	0	0	0	0	0	0	1 (2)	0	0	0
Purpura and related conditions	1 (2)	0	0	0	0	0	0	0	0	0
Vascular purpura	1 (2)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Angioedemas	0	0	0	0	0	1 (4)	0	0	0	0
Swelling face	0	0	0	0	0	1 (4)	0	0	0	0
Dermatitis and eczema	0	1 (3)	0	0	0	0	0	0	0	0
Eczema	0	0	0	0	0	0	0	0	0	0
Intertrigo	0	1 (3)	0	0	0	0	0	0	0	0
Purpura and related conditions	0	0	0	0	0	0	0	0	0	0
Vascular purpura	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Skin and subcutaneous tissue disorders						
Angioedemas	1 (< 1)	1 (< 1)	0	0	0	
Swelling face	1 (< 1)	1 (< 1)	0	0	0	
Dermatitis and eczema	1 (< 1)	1 (< 1)	0	0	0	
Eczema	1 (< 1)	0	0	0	0	
Intertrigo	0	1 (< 1)	0	0	0	
Purpura and related conditions	1 (< 1)	0	0	0	0	
Vascular purpura	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Skin preneoplastic conditions NEC	0	1 (2)	0	0	0	0	0	0	0	0
Actinic keratosis	0	1 (2)	0	0	0	0	0	0	0	0
Bullous conditions	0	0	0	0	0	0	1 (2)	0	0	0
Dermatitis bullous	0	0	0	0	0	0	1 (2)	0	0	0
Ichthyoses	0	0	0	0	0	1 (2)	0	0	0	0
Xeroderma	0	0	0	0	0	1 (2)	0	0	0	0
Papulosquamous conditions	0	0	0	0	0	0	1 (2)	0	0	0
Lymphomatoid papulosis	0	0	0	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Skin preneoplastic conditions NEC	0	0	0	0	0	0	0	0	0	0
Actinic keratosis	0	0	0	0	0	0	0	0	0	0
Bullous conditions	0	0	0	0	0	0	1 (4)	0	0	0
Dermatitis bullous	0	0	0	0	0	0	1 (4)	0	0	0
Ichthyoses	1 (3)	0	0	0	0	0	0	0	0	0
Xeroderma	1 (3)	0	0	0	0	0	0	0	0	0
Papulosquamous conditions	0	1 (3)	0	0	0	0	0	0	0	0
Lymphomatoid papulosis	0	1 (3)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Skin and subcutaneous tissue disorders						
Skin preneoplastic conditions NEC	0	1 (< 1)	0	0	0	
Actinic keratosis	0	1 (< 1)	0	0	0	
Bullous conditions	0	1 (< 1)	0	0	0	
Dermatitis bullous	0	1 (< 1)	0	0	0	
Ichthyoses	1 (< 1)	0	0	0	0	
Xeroderma	1 (< 1)	0	0	0	0	
Papulosquamous conditions	0	1 (< 1)	0	0	0	
Lymphomatoid papulosis	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Pilar disorders NEC	0	0	0	0	0	1 (2)	0	0	0	0
Hair growth abnormal	0	0	0	0	0	1 (2)	0	0	0	0
Skin and subcutaneous tissue ulcerations	0	0	0	0	0	1 (2)	0	0	0	0
Skin erosion	0	0	0	0	0	1 (2)	0	0	0	0
Infections and infestations	8 (12)	11 (17)	9 (14)	0	1 (2)	4 (6)	16 (26)	9 (15)	3 (5)	0
Upper respiratory tract infections	5 (8)	4 (6)	1 (2)	0	0	2 (3)	2 (3)	0	0	0
Upper respiratory tract infection	1 (2)	3 (5)	0	0	0	1 (2)	1 (2)	0	0	0
Nasopharyngitis	3 (5)	0	0	0	0	1 (2)	0	0	0	0
Sinusitis	0	1 (2)	1 (2)	0	0	0	0	0	0	0
Acute sinusitis	0	0	1 (2)	0	0	0	0	0	0	0
Pharyngitis	0	1 (2)	0	0	0	0	0	0	0	0
Rhinitis	1 (2)	0	0	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Skin and subcutaneous tissue disorders										
Pilar disorders NEC	1 (3)	0	0	0	0	0	0	0	0	0
Hair growth abnormal	1 (3)	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue ulcerations	0	0	0	0	0	1 (4)	0	0	0	0
Skin erosion	0	0	0	0	0	1 (4)	0	0	0	0
Infections and infestations	2 (5)	9 (24)	4 (11)	2 (5)	0	2 (8)	7 (28)	5 (20)	1 (4)	0
Upper respiratory tract infections	1 (3)	1 (3)	0	0	0	1 (4)	1 (4)	0	0	0
Upper respiratory tract infection	1 (3)	1 (3)	0	0	0	0	0	0	0	0
Nasopharyngitis	0	0	0	0	0	1 (4)	0	0	0	0
Sinusitis	0	0	0	0	0	0	0	0	0	0
Acute sinusitis	0	0	0	0	0	0	0	0	0	0
Pharyngitis	0	0	0	0	0	0	0	0	0	0
Rhinitis	0	0	0	0	0	0	1 (4)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Skin and subcutaneous tissue disorders						
Pilar disorders NEC	1 (< 1)	0	0	0	0	
Hair growth abnormal	1 (< 1)	0	0	0	0	
Skin and subcutaneous tissue ulcerations	1 (< 1)	0	0	0	0	
Skin erosion	1 (< 1)	0	0	0	0	
Infections and infestations	12 (9)	27 (21)	18 (14)	3 (2)	1 (< 1)	
Upper respiratory tract infections	7 (5)	6 (5)	1 (< 1)	0	0	
Upper respiratory tract infection	2 (2)	4 (3)	0	0	0	
Nasopharyngitis	4 (3)	0	0	0	0	
Sinusitis	0	1 (< 1)	1 (< 1)	0	0	
Acute sinusitis	0	0	1 (< 1)	0	0	
Pharyngitis	0	1 (< 1)	0	0	0	
Rhinitis	1 (< 1)	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Skin structures and soft tissue infections	2 (3)	1 (2)	3 (5)	0	0	1 (2)	5 (8)	1 (2)	0	0
Impetigo	2 (3)	0	1 (2)	0	0	0	0	0	0	0
Skin infection	0	0	2 (3)	0	0	1 (2)	5 (8)	1 (2)	0	0
Paronychia	0	1 (2)	0	0	0	0	0	0	0	0
Urinary tract infections	0	4 (6)	1 (2)	0	0	1 (2)	2 (3)	1 (2)	0	0
Urinary tract infection	0	4 (6)	1 (2)	0	0	1 (2)	2 (3)	1 (2)	0	0
Bacterial infections NEC	0	1 (2)	2 (3)	0	0	0	2 (3)	1 (2)	0	0
Cellulitis	0	1 (2)	2 (3)	0	0	0	2 (3)	0	0	0
Superinfection bacterial	0	0	0	0	0	0	0	1 (2)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Skin structures and soft tissue infections	1 (3)	3 (8)	0	0	0	0	2 (8)	1 (4)	0	0
Impetigo	0	0	0	0	0	0	0	0	0	0
Skin infection	1 (3)	3 (8)	0	0	0	0	2 (8)	1 (4)	0	0
Paronychia	0	0	0	0	0	0	0	0	0	0
Urinary tract infections	0	1 (3)	0	0	0	1 (4)	1 (4)	1 (4)	0	0
Urinary tract infection	0	1 (3)	0	0	0	1 (4)	1 (4)	1 (4)	0	0
Bacterial infections NEC	0	2 (5)	1 (3)	0	0	0	0	0	0	0
Cellulitis	0	2 (5)	0	0	0	0	0	0	0	0
Superinfection bacterial	0	0	1 (3)	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5
			Total N=128 n (%)		
Infections and infestations					
Skin structures and soft tissue infections	3 (2)	6 (5)	4 (3)	0	0
Impetigo	2 (2)	0	1 (< 1)	0	0
Skin infection	1 (< 1)	5 (4)	3 (2)	0	0
Paronychia	0	1 (< 1)	0	0	0
Urinary tract infections	1 (< 1)	6 (5)	2 (2)	0	0
Urinary tract infection	1 (< 1)	6 (5)	2 (2)	0	0
Bacterial infections NEC	0	3 (2)	3 (2)	0	0
Cellulitis	0	3 (2)	2 (2)	0	0
Superinfection bacterial	0	0	1 (< 1)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Infections NEC	1 (2)	1 (2)	0	0	0	0	0	2 (3)	0	0
Respiratory tract infection	1 (2)	1 (2)	0	0	0	0	0	0	0	0
Incision site infection	0	0	0	0	0	0	0	1 (2)	0	0
Wound infection	0	0	0	0	0	0	0	1 (2)	0	0
Influenza viral infections	1 (2)	1 (2)	0	0	0	0	0	0	0	0
Influenza	1 (2)	1 (2)	0	0	0	0	0	0	0	0
Abdominal and gastrointestinal infections	0	0	1 (2)	0	0	0	0	0	0	0
Diverticulitis	0	0	1 (2)	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Infections NEC	0	0	1 (3)	0	0	0	0	1 (4)	0	0
Respiratory tract infection	0	0	0	0	0	0	0	0	0	0
Incision site infection	0	0	1 (3)	0	0	0	0	0	0	0
Wound infection	0	0	0	0	0	0	0	1 (4)	0	0
Influenza viral infections	0	0	0	0	0	0	0	0	0	0
Influenza	0	0	0	0	0	0	0	0	0	0
Abdominal and gastrointestinal infections	0	0	0	0	0	0	0	0	0	0
Diverticulitis	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5
			Total N=128 n (%)		
Infections and infestations					
Infections NEC	1 (< 1)	1 (< 1)	2 (2)	0	0
Respiratory tract infection	1 (< 1)	1 (< 1)	0	0	0
Incision site infection	0	0	1 (< 1)	0	0
Wound infection	0	0	1 (< 1)	0	0
Influenza viral infections	1 (< 1)	1 (< 1)	0	0	0
Influenza	1 (< 1)	1 (< 1)	0	0	0
Abdominal and gastrointestinal infections	0	0	1 (< 1)	0	0
Diverticulitis	0	0	1 (< 1)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Borrelial infections	0	1 (2)	0	0	0	0	0	0	0	0
Lyme disease	0	1 (2)	0	0	0	0	0	0	0	0
Candida infections	1 (2)	0	0	0	0	0	1 (2)	0	0	0
Oropharyngeal candidiasis	1 (2)	0	0	0	0	0	0	0	0	0
Oral candidiasis	0	0	0	0	0	0	1 (2)	0	0	0
Dental and oral soft tissue infections	1 (2)	0	0	0	0	0	0	2 (3)	0	0
Angular cheilitis	1 (2)	0	0	0	0	0	0	0	0	0
Parotitis	0	0	0	0	0	0	0	2 (3)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Borrelial infections	0	0	0	0	0	0	0	0	0	0
Lyme disease	0	0	0	0	0	0	0	0	0	0
Candida infections	0	1 (3)	0	0	0	0	0	0	0	0
Oropharyngeal candidiasis	0	0	0	0	0	0	0	0	0	0
Oral candidiasis	0	1 (3)	0	0	0	0	0	0	0	0
Dental and oral soft tissue infections	0	0	1 (3)	0	0	0	0	1 (4)	0	0
Angular cheilitis	0	0	0	0	0	0	0	0	0	0
Parotitis	0	0	1 (3)	0	0	0	0	1 (4)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5
			Total N=128 n (%)		
Infections and infestations					
Borrelial infections	0	1 (< 1)	0	0	0
Lyme disease	0	1 (< 1)	0	0	0
Candida infections	1 (< 1)	1 (< 1)	0	0	0
Oropharyngeal candidiasis	1 (< 1)	0	0	0	0
Oral candidiasis	0	1 (< 1)	0	0	0
Dental and oral soft tissue infections	1 (< 1)	0	2 (2)	0	0
Angular cheilitis	1 (< 1)	0	0	0	0
Parotitis	0	0	2 (2)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Ear infections	0	1 (2)	0	0	0	0	2 (3)	0	0	0
Ear infection	0	1 (2)	0	0	0	0	1 (2)	0	0	0
Otitis externa	0	0	0	0	0	0	1 (2)	0	0	0
Escherichia infections	1 (2)	0	0	0	0	0	0	0	0	0
Escherichia infection	1 (2)	0	0	0	0	0	0	0	0	0
Eye and eyelid infections	1 (2)	0	0	0	0	0	0	1 (2)	0	0
Hordeolum	1 (2)	0	0	0	0	0	0	0	0	0
Periorbital infection	0	0	0	0	0	0	0	1 (2)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Ear infections	0	2 (5)	0	0	0	0	0	0	0	0
Ear infection	0	1 (3)	0	0	0	0	0	0	0	0
Otitis externa	0	1 (3)	0	0	0	0	0	0	0	0
Escherichia infections	0	0	0	0	0	0	0	0	0	0
Escherichia infection	0	0	0	0	0	0	0	0	0	0
Eye and eyelid infections	0	0	1 (3)	0	0	0	0	0	0	0
Hordeolum	0	0	0	0	0	0	0	0	0	0
Periorbital infection	0	0	1 (3)	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Infections and infestations						
Ear infections	0	3 (2)	0	0	0	
Ear infection	0	2 (2)	0	0	0	
Otitis externa	0	1 (< 1)	0	0	0	
Escherichia infections	1 (< 1)	0	0	0	0	
Escherichia infection	1 (< 1)	0	0	0	0	
Eye and eyelid infections	1 (< 1)	0	1 (< 1)	0	0	
Hordeolum	1 (< 1)	0	0	0	0	
Periorbital infection	0	0	1 (< 1)	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Gardnerella infections	0	1 (2)	0	0	0	0	0	0	0	0
Gardnerella infection	0	1 (2)	0	0	0	0	0	0	0	0
Herpes viral infections	1 (2)	0	0	0	0	1 (2)	2 (3)	0	0	0
Herpes dermatitis	1 (2)	0	0	0	0	0	0	0	0	0
Herpes virus infection	0	0	0	0	0	0	1 (2)	0	0	0
Herpes zoster	0	0	0	0	0	0	1 (2)	0	0	0
Oral herpes	0	0	0	0	0	1 (2)	0	0	0	0
Klebsiella infections	1 (2)	0	0	0	0	0	0	0	0	0
Klebsiella infection	1 (2)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Gardnerella infections	0	0	0	0	0	0	0	0	0	0
Gardnerella infection	0	0	0	0	0	0	0	0	0	0
Herpes viral infections	1 (3)	1 (3)	0	0	0	0	1 (4)	0	0	0
Herpes dermatitis	0	0	0	0	0	0	0	0	0	0
Herpes virus infection	0	1 (3)	0	0	0	0	0	0	0	0
Herpes zoster	0	0	0	0	0	0	1 (4)	0	0	0
Oral herpes	1 (3)	0	0	0	0	0	0	0	0	0
Klebsiella infections	0	0	0	0	0	0	0	0	0	0
Klebsiella infection	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Infections and infestations						
Gardnerella infections	0	1 (< 1)	0	0	0	
Gardnerella infection	0	1 (< 1)	0	0	0	
Herpes viral infections	2 (2)	2 (2)	0	0	0	
Herpes dermatitis	1 (< 1)	0	0	0	0	
Herpes virus infection	0	1 (< 1)	0	0	0	
Herpes zoster	0	1 (< 1)	0	0	0	
Oral herpes	1 (< 1)	0	0	0	0	
Klebsiella infections	1 (< 1)	0	0	0	0	
Klebsiella infection	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Lower respiratory tract and lung infections	0	0	1 (2)	0	0	0	2 (3)	0	0	0
Lower respiratory tract infection	0	0	1 (2)	0	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0	2 (3)	0	0	0
Muscle and soft tissue infections	0	1 (2)	0	0	0	0	0	0	0	0
Perineal infection	0	1 (2)	0	0	0	0	0	0	0	0
Pseudomonal infections	0	1 (2)	0	0	0	0	0	0	0	0
Urinary tract infection pseudomonal	0	1 (2)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Lower respiratory tract and lung infections	0	1 (3)	0	0	0	0	1 (4)	0	0	0
Lower respiratory tract infection	0	0	0	0	0	0	0	0	0	0
Pneumonia	0	1 (3)	0	0	0	0	1 (4)	0	0	0
Muscle and soft tissue infections	0	0	0	0	0	0	0	0	0	0
Perineal infection	0	0	0	0	0	0	0	0	0	0
Pseudomonal infections	0	0	0	0	0	0	0	0	0	0
Urinary tract infection pseudomonal	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Infections and infestations						
Lower respiratory tract and lung infections	0	2 (2)	1 (< 1)	0	0	
Lower respiratory tract infection	0	0	1 (< 1)	0	0	
Pneumonia	0	2 (2)	0	0	0	
Muscle and soft tissue infections	0	1 (< 1)	0	0	0	
Perineal infection	0	1 (< 1)	0	0	0	
Pseudomonal infections	0	1 (< 1)	0	0	0	
Urinary tract infection pseudomonal	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Rhinoviral infections	0	1 (2)	0	0	0	0	0	0	0	0
Rhinovirus infection	0	1 (2)	0	0	0	0	0	0	0	0
Sepsis, bacteraemia, viraemia and fungaemia NEC	0	0	0	0	1 (2)	0	0	1 (2)	3 (5)	0
Sepsis	0	0	0	0	1 (2)	0	0	0	3 (5)	0
Urosepsis	0	0	0	0	0	0	0	1 (2)	0	0
Staphylococcal infections	0	0	1 (2)	0	0	0	5 (8)	1 (2)	0	0
Staphylococcal skin infection	0	0	1 (2)	0	0	0	5 (8)	0	0	0
Staphylococcal abscess	0	0	0	0	0	0	0	1 (2)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Rhinoviral infections	0	0	0	0	0	0	0	0	0	0
Rhinovirus infection	0	0	0	0	0	0	0	0	0	0
Sepsis, bacteraemia, viraemia and fungaemia NEC	0	0	1 (3)	2 (5)	0	0	0	0	1 (4)	0
Sepsis	0	0	0	2 (5)	0	0	0	0	1 (4)	0
Urosepsis	0	0	1 (3)	0	0	0	0	0	0	0
Staphylococcal infections	0	3 (8)	0	0	0	0	2 (8)	1 (4)	0	0
Staphylococcal skin infection	0	3 (8)	0	0	0	0	2 (8)	0	0	0
Staphylococcal abscess	0	0	0	0	0	0	0	1 (4)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Infections and infestations						
Rhinoviral infections	0	1 (< 1)	0	0	0	
Rhinovirus infection	0	1 (< 1)	0	0	0	
Sepsis, bacteraemia, viraemia and fungaemia NEC	0	0	1 (< 1)	3 (2)	1 (< 1)	
Sepsis	0	0	0	3 (2)	1 (< 1)	
Urosepsis	0	0	1 (< 1)	0	0	
Staphylococcal infections	0	5 (4)	2 (2)	0	0	
Staphylococcal skin infection	0	5 (4)	1 (< 1)	0	0	
Staphylococcal abscess	0	0	1 (< 1)	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Bone and joint infections	0	0	0	0	0	0	0	1 (2)	0	0
Abscess jaw	0	0	0	0	0	0	0	1 (2)	0	0
Fungal infections NEC	0	0	0	0	0	1 (2)	0	0	0	0
Fungal skin infection	0	0	0	0	0	1 (2)	0	0	0	0
Streptococcal infections	0	0	0	0	0	0	0	1 (2)	0	0
Erysipelas	0	0	0	0	0	0	0	1 (2)	0	0
Tinea infections	0	0	0	0	0	1 (2)	0	0	0	0
Tinea cruris	0	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Infections and infestations										
Bone and joint infections	0	0	0	0	0	0	0	1 (4)	0	0
Abscess jaw	0	0	0	0	0	0	0	1 (4)	0	0
Fungal infections NEC	0	0	0	0	0	1 (4)	0	0	0	0
Fungal skin infection	0	0	0	0	0	1 (4)	0	0	0	0
Streptococcal infections	0	0	0	0	0	0	0	1 (4)	0	0
Erysipelas	0	0	0	0	0	0	0	1 (4)	0	0
Tinea infections	1 (3)	0	0	0	0	0	0	0	0	0
Tinea cruris	1 (3)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Total N=128 n (%) Gr3	Gr4	Gr5
Infections and infestations					
Bone and joint infections	0	0	1 (< 1)	0	0
Abscess jaw	0	0	1 (< 1)	0	0
Fungal infections NEC	1 (< 1)	0	0	0	0
Fungal skin infection	1 (< 1)	0	0	0	0
Streptococcal infections	0	0	1 (< 1)	0	0
Erysipelas	0	0	1 (< 1)	0	0
Tinea infections	1 (< 1)	0	0	0	0
Tinea cruris	1 (< 1)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Musculoskeletal and connective tissue disorders	11 (17)	9 (14)	2 (3)	0	0	8 (13)	6 (10)	0	0	0
Musculoskeletal and connective tissue pain and discomfort	4 (6)	3 (5)	2 (3)	0	0	4 (6)	2 (3)	0	0	0
Pain in extremity	3 (5)	2 (3)	1 (2)	0	0	2 (3)	2 (3)	0	0	0
Back pain	2 (3)	0	0	0	0	1 (2)	0	0	0	0
Musculoskeletal chest pain	1 (2)	0	1 (2)	0	0	0	0	0	0	0
Musculoskeletal pain	0	1 (2)	0	0	0	1 (2)	0	0	0	0
Neck pain	0	0	1 (2)	0	0	0	0	0	0	0
Joint related signs and symptoms	6 (9)	2 (3)	0	0	0	2 (3)	2 (3)	0	0	0
Arthralgia	6 (9)	2 (3)	0	0	0	2 (3)	2 (3)	0	0	0
Joint swelling	1 (2)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Musculoskeletal and connective tissue disorders	8 (22)	4 (11)	0	0	0	0	2 (8)	0	0	0
Musculoskeletal and connective tissue pain and discomfort	4 (11)	2 (5)	0	0	0	0	0	0	0	0
Pain in extremity	2 (5)	2 (5)	0	0	0	0	0	0	0	0
Back pain	1 (3)	0	0	0	0	0	0	0	0	0
Musculoskeletal chest pain	0	0	0	0	0	0	0	0	0	0
Musculoskeletal pain	1 (3)	0	0	0	0	0	0	0	0	0
Neck pain	0	0	0	0	0	0	0	0	0	0
Joint related signs and symptoms	2 (5)	0	0	0	0	0	2 (8)	0	0	0
Arthralgia	2 (5)	0	0	0	0	0	2 (8)	0	0	0
Joint swelling	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Musculoskeletal and connective tissue disorders	19 (15)	15 (12)	2 (2)	0	0	
Musculoskeletal and connective tissue pain and discomfort	8 (6)	5 (4)	2 (2)	0	0	
Pain in extremity	5 (4)	4 (3)	1 (< 1)	0	0	
Back pain	3 (2)	0	0	0	0	
Musculoskeletal chest pain	1 (< 1)	0	1 (< 1)	0	0	
Musculoskeletal pain	1 (< 1)	1 (< 1)	0	0	0	
Neck pain	0	0	1 (< 1)	0	0	
Joint related signs and symptoms	8 (6)	4 (3)	0	0	0	
Arthralgia	8 (6)	4 (3)	0	0	0	
Joint swelling	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Musculoskeletal and connective tissue disorders										
Muscle pains	5 (8)	3 (5)	0	0	0	1 (2)	1 (2)	0	0	0
Myalgia	5 (8)	3 (5)	0	0	0	1 (2)	1 (2)	0	0	0
Muscle related signs and symptoms NEC	4 (6)	1 (2)	0	0	0	2 (3)	1 (2)	0	0	0
Muscle spasms	3 (5)	1 (2)	0	0	0	2 (3)	1 (2)	0	0	0
Muscle atrophy	1 (2)	0	0	0	0	0	0	0	0	0
Bursal disorders	0	1 (2)	0	0	0	0	0	0	0	0
Bursitis	0	1 (2)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Musculoskeletal and connective tissue disorders										
Muscle pains	1 (3)	1 (3)	0	0	0	0	0	0	0	0
Myalgia	1 (3)	1 (3)	0	0	0	0	0	0	0	0
Muscle related signs and symptoms NEC	2 (5)	1 (3)	0	0	0	0	0	0	0	0
Muscle spasms	2 (5)	1 (3)	0	0	0	0	0	0	0	0
Muscle atrophy	0	0	0	0	0	0	0	0	0	0
Bursal disorders	0	0	0	0	0	0	0	0	0	0
Bursitis	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Musculoskeletal and connective tissue disorders						
Muscle pains	6 (5)	4 (3)	0	0	0	
Myalgia	6 (5)	4 (3)	0	0	0	
Muscle related signs and symptoms NEC	6 (5)	2 (2)	0	0	0	
Muscle spasms	5 (4)	2 (2)	0	0	0	
Muscle atrophy	1 (< 1)	0	0	0	0	
Bursal disorders	0	1 (< 1)	0	0	0	
Bursitis	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Musculoskeletal and connective tissue disorders										
Muscle weakness conditions	0	1 (2)	0	0	0	0	1 (2)	0	0	0
Muscular weakness	0	1 (2)	0	0	0	0	1 (2)	0	0	0
Osteoarthropathies	0	1 (2)	0	0	0	0	0	0	0	0
Osteoarthritis	0	1 (2)	0	0	0	0	0	0	0	0
Crystal arthropathic disorders	0	0	0	0	0	0	1 (2)	0	0	0
Crystal arthropathy	0	0	0	0	0	0	1 (2)	0	0	0
Intervertebral disc disorders NEC	0	0	0	0	0	0	1 (2)	0	0	0
Intervertebral disc protrusion	0	0	0	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Musculoskeletal and connective tissue disorders										
Muscle weakness conditions	0	1 (3)	0	0	0	0	0	0	0	0
Muscular weakness	0	1 (3)	0	0	0	0	0	0	0	0
Osteoarthropathies	0	0	0	0	0	0	0	0	0	0
Osteoarthritis	0	0	0	0	0	0	0	0	0	0
Crystal arthropathic disorders	0	0	0	0	0	0	1 (4)	0	0	0
Crystal arthropathy	0	0	0	0	0	0	1 (4)	0	0	0
Intervertebral disc disorders NEC	0	1 (3)	0	0	0	0	0	0	0	0
Intervertebral disc protrusion	0	1 (3)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Musculoskeletal and connective tissue disorders						
Muscle weakness conditions	0	2 (2)	0	0	0	
Muscular weakness	0	2 (2)	0	0	0	
Osteoarthropathies	0	1 (< 1)	0	0	0	
Osteoarthritis	0	1 (< 1)	0	0	0	
Crystal arthropathic disorders	0	1 (< 1)	0	0	0	
Crystal arthropathy	0	1 (< 1)	0	0	0	
Intervertebral disc disorders NEC	0	1 (< 1)	0	0	0	
Intervertebral disc protrusion	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Musculoskeletal and connective tissue disorders										
Muscle infections and inflammations	0	0	0	0	0	0	1 (2)	0	0	0
Myositis	0	0	0	0	0	0	1 (2)	0	0	0
Spine and neck deformities	0	0	0	0	0	0	1 (2)	0	0	0
Lumbar spinal stenosis	0	0	0	0	0	0	1 (2)	0	0	0
Synovial disorders	0	0	0	0	0	0	1 (2)	0	0	0
Synovial cyst	0	0	0	0	0	0	1 (2)	0	0	0
Metabolism and nutrition disorders	7 (11)	10 (15)	4 (6)	0	0	4 (6)	4 (6)	6 (10)	4 (6)	0
Appetite disorders	6 (9)	4 (6)	0	0	0	2 (3)	1 (2)	0	0	0
Decreased appetite	6 (9)	4 (6)	0	0	0	2 (3)	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Musculoskeletal and connective tissue disorders										
Muscle infections and inflammations	0	1 (3)	0	0	0	0	0	0	0	0
Myositis	0	1 (3)	0	0	0	0	0	0	0	0
Spine and neck deformities	0	1 (3)	0	0	0	0	0	0	0	0
Lumbar spinal stenosis	0	1 (3)	0	0	0	0	0	0	0	0
Synovial disorders	0	1 (3)	0	0	0	0	0	0	0	0
Synovial cyst	0	1 (3)	0	0	0	0	0	0	0	0
Metabolism and nutrition disorders	3 (8)	3 (8)	5 (14)	3 (8)	0	1 (4)	1 (4)	1 (4)	1 (4)	0
Appetite disorders	2 (5)	0	0	0	0	0	1 (4)	0	0	0
Decreased appetite	2 (5)	0	0	0	0	0	1 (4)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Musculoskeletal and connective tissue disorders						
Muscle infections and inflammations	0	1 (< 1)	0	0	0	
Myositis	0	1 (< 1)	0	0	0	
Spine and neck deformities	0	1 (< 1)	0	0	0	
Lumbar spinal stenosis	0	1 (< 1)	0	0	0	
Synovial disorders	0	1 (< 1)	0	0	0	
Synovial cyst	0	1 (< 1)	0	0	0	
Metabolism and nutrition disorders	11 (9)	14 (11)	10 (8)	4 (3)	0	
Appetite disorders	8 (6)	5 (4)	0	0	0	
Decreased appetite	8 (6)	5 (4)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Metabolism and nutrition disorders										
Hyperglycaemic conditions NEC	1 (2)	2 (3)	3 (5)	0	0	0	0	0	0	0
Hyperglycaemia	1 (2)	2 (3)	3 (5)	0	0	0	0	0	0	0
Disorders of purine metabolism	4 (6)	0	0	0	0	0	0	1 (2)	1 (2)	0
Hyperuricaemia	4 (6)	0	0	0	0	0	0	1 (2)	1 (2)	0
Calcium metabolism disorders	0	1 (2)	1 (2)	0	0	0	0	0	0	0
Hypocalcaemia	0	1 (2)	1 (2)	0	0	0	0	0	0	0
Magnesium metabolism disorders	2 (3)	0	0	0	0	1 (2)	0	0	0	0
Hypomagnesaemia	2 (3)	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Metabolism and nutrition disorders										
Hyperglycaemic conditions NEC	0	0	0	0	0	0	0	0	0	0
Hyperglycaemia	0	0	0	0	0	0	0	0	0	0
Disorders of purine metabolism	0	0	0	0	0	0	0	1 (4)	1 (4)	0
Hyperuricaemia	0	0	0	0	0	0	0	1 (4)	1 (4)	0
Calcium metabolism disorders	0	0	0	0	0	0	0	0	0	0
Hypocalcaemia	0	0	0	0	0	0	0	0	0	0
Magnesium metabolism disorders	1 (3)	0	0	0	0	0	0	0	0	0
Hypomagnesaemia	1 (3)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Metabolism and nutrition disorders						
Hyperglycaemic conditions NEC	1 (< 1)	2 (2)	3 (2)	0	0	
Hyperglycaemia	1 (< 1)	2 (2)	3 (2)	0	0	
Disorders of purine metabolism	4 (3)	0	1 (< 1)	1 (< 1)	0	
Hyperuricaemia	4 (3)	0	1 (< 1)	1 (< 1)	0	
Calcium metabolism disorders	0	1 (< 1)	1 (< 1)	0	0	
Hypocalcaemia	0	1 (< 1)	1 (< 1)	0	0	
Magnesium metabolism disorders	3 (2)	0	0	0	0	
Hypomagnesaemia	3 (2)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Metabolism and nutrition disorders										
Potassium imbalance	1 (2)	1 (2)	0	0	0	0	0	0	0	0
Hypokalaemia	1 (2)	1 (2)	0	0	0	0	0	0	0	0
Total fluid volume decreased	0	2 (3)	0	0	0	0	0	0	0	0
Dehydration	0	2 (3)	0	0	0	0	0	0	0	0
Elevated triglycerides	1 (2)	0	0	0	0	1 (2)	2 (3)	5 (8)	3 (5)	0
Hypertriglyceridaemia	1 (2)	0	0	0	0	1 (2)	2 (3)	5 (8)	3 (5)	0
Iron deficiencies	0	1 (2)	0	0	0	0	0	0	0	0
Iron deficiency	0	1 (2)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Metabolism and nutrition disorders										
Potassium imbalance	0	0	0	0	0	0	0	0	0	0
Hypokalaemia	0	0	0	0	0	0	0	0	0	0
Total fluid volume decreased	0	0	0	0	0	0	0	0	0	0
Dehydration	0	0	0	0	0	0	0	0	0	0
Elevated triglycerides	1 (3)	2 (5)	5 (14)	3 (8)	0	0	0	0	0	0
Hypertriglyceridaemia	1 (3)	2 (5)	5 (14)	3 (8)	0	0	0	0	0	0
Iron deficiencies	0	0	0	0	0	0	0	0	0	0
Iron deficiency	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Metabolism and nutrition disorders						
Potassium imbalance	1 (< 1)	1 (< 1)	0	0	0	
Hypokalaemia	1 (< 1)	1 (< 1)	0	0	0	
Total fluid volume decreased	0	2 (2)	0	0	0	
Dehydration	0	2 (2)	0	0	0	
Elevated triglycerides	2 (2)	2 (2)	5 (4)	3 (2)	0	
Hypertriglyceridaemia	2 (2)	2 (2)	5 (4)	3 (2)	0	
Iron deficiencies	0	1 (< 1)	0	0	0	
Iron deficiency	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Metabolism and nutrition disorders										
Protein metabolism disorders NEC	1 (2)	0	0	0	0	0	0	0	0	0
Hypoalbuminaemia	1 (2)	0	0	0	0	0	0	0	0	0
Elevated cholesterol	0	0	0	0	0	3 (5)	1 (2)	0	0	0
Hypercholesterolaemia	0	0	0	0	0	3 (5)	1 (2)	0	0	0
Hyperlipidaemias NEC	0	0	0	0	0	0	1 (2)	0	0	0
Hyperlipidaemia	0	0	0	0	0	0	1 (2)	0	0	0
Lipid metabolism and deposit disorders NEC	0	0	0	0	0	1 (2)	0	0	0	0
Dyslipidaemia	0	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Metabolism and nutrition disorders										
Protein metabolism disorders NEC	0	0	0	0	0	0	0	0	0	0
Hypoalbuminaemia	0	0	0	0	0	0	0	0	0	0
Elevated cholesterol	3 (8)	1 (3)	0	0	0	0	0	0	0	0
Hypercholesterolaemia	3 (8)	1 (3)	0	0	0	0	0	0	0	0
Hyperlipidaemias NEC	0	1 (3)	0	0	0	0	0	0	0	0
Hyperlipidaemia	0	1 (3)	0	0	0	0	0	0	0	0
Lipid metabolism and deposit disorders NEC	0	0	0	0	0	1 (4)	0	0	0	0
Dyslipidaemia	0	0	0	0	0	1 (4)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Metabolism and nutrition disorders						
Protein metabolism disorders NEC	1 (< 1)	0	0	0	0	
Hypoalbuminaemia	1 (< 1)	0	0	0	0	
Elevated cholesterol	3 (2)	1 (< 1)	0	0	0	
Hypercholesterolaemia	3 (2)	1 (< 1)	0	0	0	
Hyperlipidaemias NEC	0	1 (< 1)	0	0	0	
Hyperlipidaemia	0	1 (< 1)	0	0	0	
Lipid metabolism and deposit disorders NEC	1 (< 1)	0	0	0	0	
Dyslipidaemia	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Metabolism and nutrition disorders										
Metabolic acidoses (excl diabetic acidoses)	0	0	0	0	0	1 (2)	0	0	0	0
Metabolic acidosis	0	0	0	0	0	1 (2)	0	0	0	0
Sodium imbalance	0	0	0	0	0	0	1 (2)	0	0	0
Hypernatraemia	0	0	0	0	0	0	1 (2)	0	0	0
Hyponatraemia	0	0	0	0	0	1 (2)	0	0	0	0
Investigations	7 (11)	8 (12)	0	0	0	5 (8)	11 (18)	5 (8)	0	0
Physical examination procedures and organ system status	2 (3)	5 (8)	0	0	0	0	2 (3)	0	0	0
Weight decreased	1 (2)	5 (8)	0	0	0	0	2 (3)	0	0	0
Breath sounds abnormal	1 (2)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Metabolism and nutrition disorders										
Metabolic acidoses (excl diabetic acidoses)	1 (3)	0	0	0	0	0	0	0	0	0
Metabolic acidosis	1 (3)	0	0	0	0	0	0	0	0	0
Sodium imbalance	0	1 (3)	0	0	0	0	0	0	0	0
Hypernatraemia	0	1 (3)	0	0	0	0	0	0	0	0
Hyponatraemia	1 (3)	0	0	0	0	0	0	0	0	0
Investigations	4 (11)	10 (27)	2 (5)	0	0	1 (4)	1 (4)	3 (12)	0	0
Physical examination procedures and organ system status	0	2 (5)	0	0	0	0	0	0	0	0
Weight decreased	0	2 (5)	0	0	0	0	0	0	0	0
Breath sounds abnormal	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Metabolism and nutrition disorders						
Metabolic acidoses (excl diabetic acidoses)	1 (< 1)	0	0	0	0	
Metabolic acidosis	1 (< 1)	0	0	0	0	
Sodium imbalance	0	1 (< 1)	0	0	0	
Hypernatraemia	0	1 (< 1)	0	0	0	
Hyponatraemia	1 (< 1)	0	0	0	0	
Investigations	12 (9)	19 (15)	5 (4)	0	0	
Physical examination procedures and organ system status	2 (2)	7 (5)	0	0	0	
Weight decreased	1 (< 1)	7 (5)	0	0	0	
Breath sounds abnormal	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Investigations										
Liver function analyses	2 (3)	3 (5)	0	0	0	3 (5)	0	2 (3)	0	0
Alanine aminotransferase increased	1 (2)	2 (3)	0	0	0	3 (5)	0	2 (3)	0	0
Aspartate aminotransferase increased	1 (2)	0	0	0	0	2 (3)	1 (2)	1 (2)	0	0
Gamma-glutamyltransferase increased	0	1 (2)	0	0	0	1 (2)	0	0	0	0
Transaminases increased	1 (2)	0	0	0	0	0	0	0	0	0
White blood cell analyses	1 (2)	1 (2)	0	0	0	0	0	1 (2)	0	0
White blood cell count decreased	1 (2)	1 (2)	0	0	0	0	0	0	0	0
Neutrophil count decreased	0	1 (2)	0	0	0	0	0	0	0	0
White blood cell count increased	1 (2)	0	0	0	0	0	0	0	0	0
Lymphocyte count decreased	0	0	0	0	0	0	0	1 (2)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Investigations										
Liver function analyses	2 (5)	0	0	0	0	1 (4)	0	2 (8)	0	0
Alanine aminotransferase increased	2 (5)	0	0	0	0	1 (4)	0	2 (8)	0	0
Aspartate aminotransferase increased	2 (5)	0	0	0	0	0	1 (4)	1 (4)	0	0
Gamma-glutamyltransferase increased	0	0	0	0	0	1 (4)	0	0	0	0
Transaminases increased	0	0	0	0	0	0	0	0	0	0
White blood cell analyses	0	0	0	0	0	0	0	1 (4)	0	0
White blood cell count decreased	0	0	0	0	0	0	0	0	0	0
Neutrophil count decreased	0	0	0	0	0	0	0	0	0	0
White blood cell count increased	0	0	0	0	0	0	0	0	0	0
Lymphocyte count decreased	0	0	0	0	0	0	0	1 (4)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5
			Total N=128 n (%)		
Investigations					
Liver function analyses	5 (4)	3 (2)	2 (2)	0	0
Alanine aminotransferase increased	4 (3)	2 (2)	2 (2)	0	0
Aspartate aminotransferase increased	3 (2)	1 (< 1)	1 (< 1)	0	0
Gamma-glutamyltransferase increased	1 (< 1)	1 (< 1)	0	0	0
Transaminases increased	1 (< 1)	0	0	0	0
White blood cell analyses	1 (< 1)	1 (< 1)	1 (< 1)	0	0
White blood cell count decreased	1 (< 1)	1 (< 1)	0	0	0
Neutrophil count decreased	0	1 (< 1)	0	0	0
White blood cell count increased	1 (< 1)	0	0	0	0
Lymphocyte count decreased	0	0	1 (< 1)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Investigations										
Bacteria identification and serology (excl mycobacteria)	1 (2)	0	0	0	0	0	0	0	0	0
Staphylococcus test positive	1 (2)	0	0	0	0	0	0	0	0	0
Coagulation and bleeding analyses	1 (2)	0	0	0	0	0	0	0	0	0
Activated partial thromboplastin time prolonged	1 (2)	0	0	0	0	0	0	0	0	0
International normalised ratio increased	1 (2)	0	0	0	0	0	0	0	0	0
Thyroid analyses	1 (2)	0	0	0	0	4 (6)	0	0	0	0
Thyroxine increased	1 (2)	0	0	0	0	0	0	0	0	0
Thyroxine decreased	0	0	0	0	0	2 (3)	0	0	0	0
Thyroxine free decreased	0	0	0	0	0	1 (2)	0	0	0	0
Tri-iodothyronine free decreased	0	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Investigations										
Bacteria identification and serology (excl mycobacteria)	0	0	0	0	0	0	0	0	0	0
Staphylococcus test positive	0	0	0	0	0	0	0	0	0	0
Coagulation and bleeding analyses	0	0	0	0	0	0	0	0	0	0
Activated partial thromboplastin time prolonged	0	0	0	0	0	0	0	0	0	0
International normalised ratio increased	0	0	0	0	0	0	0	0	0	0
Thyroid analyses	0	4 (11)	0	0	0	0	0	0	0	0
Thyroxine increased	0	0	0	0	0	0	0	0	0	0
Thyroxine decreased	0	2 (5)	0	0	0	0	0	0	0	0
Thyroxine free decreased	0	1 (3)	0	0	0	0	0	0	0	0
Tri-iodothyronine free decreased	0	1 (3)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Investigations						
Bacteria identification and serology (excl mycobacteria)	1 (< 1)	0	0	0	0	
Staphylococcus test positive	1 (< 1)	0	0	0	0	
Coagulation and bleeding analyses	1 (< 1)	0	0	0	0	
Activated partial thromboplastin time prolonged	1 (< 1)	0	0	0	0	
International normalised ratio increased	1 (< 1)	0	0	0	0	
Thyroid analyses	1 (< 1)	4 (3)	0	0	0	
Thyroxine increased	1 (< 1)	0	0	0	0	
Thyroxine decreased	0	2 (2)	0	0	0	
Thyroxine free decreased	0	1 (< 1)	0	0	0	
Tri-iodothyronine free decreased	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Investigations										
Urinalysis NEC	1 (2)	0	0	0	0	0	0	0	0	0
Urine leukocyte esterase positive	1 (2)	0	0	0	0	0	0	0	0	0
Cholesterol analyses	0	0	0	0	0	1 (2)	4 (6)	0	0	0
Blood cholesterol increased	0	0	0	0	0	0	4 (6)	0	0	0
High density lipoprotein decreased	0	0	0	0	0	1 (2)	0	0	0	0
Low density lipoprotein increased	0	0	0	0	0	0	1 (2)	0	0	0
Metabolism tests NEC	0	0	0	0	0	1 (2)	0	0	0	0
Blood uric acid increased	0	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Investigations										
Urinalysis NEC	0	0	0	0	0	0	0	0	0	0
Urine leukocyte esterase positive	0	0	0	0	0	0	0	0	0	0
Cholesterol analyses	1 (3)	4 (11)	0	0	0	0	0	0	0	0
Blood cholesterol increased	0	4 (11)	0	0	0	0	0	0	0	0
High density lipoprotein decreased	1 (3)	0	0	0	0	0	0	0	0	0
Low density lipoprotein increased	0	1 (3)	0	0	0	0	0	0	0	0
Metabolism tests NEC	1 (3)	0	0	0	0	0	0	0	0	0
Blood uric acid increased	1 (3)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Investigations						
Urinalysis NEC	1 (< 1)	0	0	0	0	
Urine leukocyte esterase positive	1 (< 1)	0	0	0	0	
Cholesterol analyses	1 (< 1)	4 (3)	0	0	0	
Blood cholesterol increased	0	4 (3)	0	0	0	
High density lipoprotein decreased	1 (< 1)	0	0	0	0	
Low density lipoprotein increased	0	1 (< 1)	0	0	0	
Metabolism tests NEC	1 (< 1)	0	0	0	0	
Blood uric acid increased	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Investigations										
Pituitary analyses anterior	0	0	0	0	0	0	1 (2)	0	0	0
Blood thyroid stimulating hormone decreased	0	0	0	0	0	0	1 (2)	0	0	0
Renal function analyses	0	0	0	0	0	1 (2)	1 (2)	0	0	0
Blood creatinine increased	0	0	0	0	0	1 (2)	1 (2)	0	0	0
Triglyceride analyses	0	0	0	0	0	0	3 (5)	2 (3)	0	0
Blood triglycerides increased	0	0	0	0	0	0	3 (5)	2 (3)	0	0
Virus identification and serology	0	0	0	0	0	0	1 (2)	0	0	0
Cytomegalovirus test positive	0	0	0	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Investigations										
Pituitary analyses anterior	0	1 (3)	0	0	0	0	0	0	0	0
Blood thyroid stimulating hormone decreased	0	1 (3)	0	0	0	0	0	0	0	0
Renal function analyses	1 (3)	1 (3)	0	0	0	0	0	0	0	0
Blood creatinine increased	1 (3)	1 (3)	0	0	0	0	0	0	0	0
Triglyceride analyses	0	3 (8)	2 (5)	0	0	0	0	0	0	0
Blood triglycerides increased	0	3 (8)	2 (5)	0	0	0	0	0	0	0
Virus identification and serology	0	0	0	0	0	0	1 (4)	0	0	0
Cytomegalovirus test positive	0	0	0	0	0	0	1 (4)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5
			Total N=128 n (%)		
Investigations					
Pituitary analyses anterior	0	1 (< 1)	0	0	0
Blood thyroid stimulating hormone decreased	0	1 (< 1)	0	0	0
Renal function analyses	1 (< 1)	1 (< 1)	0	0	0
Blood creatinine increased	1 (< 1)	1 (< 1)	0	0	0
Triglyceride analyses	0	3 (2)	2 (2)	0	0
Blood triglycerides increased	0	3 (2)	2 (2)	0	0
Virus identification and serology	0	1 (< 1)	0	0	0
Cytomegalovirus test positive	0	1 (< 1)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Respiratory, thoracic and mediastinal disorders	10 (15)	1 (2)	1 (2)	0	1 (2)	4 (6)	3 (5)	0	0	0
Breathing abnormalities	6 (9)	1 (2)	0	0	0	0	0	0	0	0
Dyspnoea	6 (9)	1 (2)	0	0	0	0	0	0	0	0
Coughing and associated symptoms	3 (5)	0	0	0	0	2 (3)	2 (3)	0	0	0
Cough	2 (3)	0	0	0	0	2 (3)	2 (3)	0	0	0
Productive cough	1 (2)	0	0	0	0	0	0	0	0	0
Upper respiratory tract signs and symptoms	3 (5)	0	0	0	0	2 (3)	0	0	0	0
Dysphonia	1 (2)	0	0	0	0	0	0	0	0	0
Oropharyngeal pain	1 (2)	0	0	0	0	1 (2)	0	0	0	0
Rhinorrhoea	1 (2)	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Respiratory, thoracic and mediastinal disorders	0	1 (3)	0	0	0	4 (16)	2 (8)	0	0	0
Breathing abnormalities	0	0	0	0	0	0	0	0	0	0
Dyspnoea	0	0	0	0	0	0	0	0	0	0
Coughing and associated symptoms	0	1 (3)	0	0	0	2 (8)	1 (4)	0	0	0
Cough	0	1 (3)	0	0	0	2 (8)	1 (4)	0	0	0
Productive cough	0	0	0	0	0	0	0	0	0	0
Upper respiratory tract signs and symptoms	0	0	0	0	0	2 (8)	0	0	0	0
Dysphonia	0	0	0	0	0	0	0	0	0	0
Oropharyngeal pain	0	0	0	0	0	1 (4)	0	0	0	0
Rhinorrhoea	0	0	0	0	0	1 (4)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Respiratory, thoracic and mediastinal disorders	14 (11)	4 (3)	1 (< 1)	0	1 (< 1)	
Breathing abnormalities	6 (5)	1 (< 1)	0	0	0	
Dyspnoea	6 (5)	1 (< 1)	0	0	0	
Coughing and associated symptoms	5 (4)	2 (2)	0	0	0	
Cough	4 (3)	2 (2)	0	0	0	
Productive cough	1 (< 1)	0	0	0	0	
Upper respiratory tract signs and symptoms	5 (4)	0	0	0	0	
Dysphonia	1 (< 1)	0	0	0	0	
Oropharyngeal pain	2 (2)	0	0	0	0	
Rhinorrhoea	2 (2)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Respiratory, thoracic and mediastinal disorders										
Lower respiratory tract signs and symptoms	0	0	1 (2)	0	0	0	0	0	0	0
Increased bronchial secretion	0	0	1 (2)	0	0	0	0	0	0	0
Pulmonary thrombotic and embolic conditions	0	0	0	0	1 (2)	0	0	0	0	0
Pulmonary embolism	0	0	0	0	1 (2)	0	0	0	0	0
Bronchospasm and obstruction	0	0	0	0	0	0	1 (2)	0	0	0
Obstructive airways disorder	0	0	0	0	0	0	1 (2)	0	0	0
Nasal congestion and inflammations	0	0	0	0	0	1 (2)	0	0	0	0
Rhinitis allergic	0	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Respiratory, thoracic and mediastinal disorders										
Lower respiratory tract signs and symptoms	0	0	0	0	0	0	0	0	0	0
Increased bronchial secretion	0	0	0	0	0	0	0	0	0	0
Pulmonary thrombotic and embolic conditions	0	0	0	0	0	0	0	0	0	0
Pulmonary embolism	0	0	0	0	0	0	0	0	0	0
Bronchospasm and obstruction	0	0	0	0	0	0	1 (4)	0	0	0
Obstructive airways disorder	0	0	0	0	0	0	1 (4)	0	0	0
Nasal congestion and inflammations	0	0	0	0	0	1 (4)	0	0	0	0
Rhinitis allergic	0	0	0	0	0	1 (4)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Total N=128 n (%) Gr3	Gr4	Gr5
Respiratory, thoracic and mediastinal disorders					
Lower respiratory tract signs and symptoms	0	0	1 (< 1)	0	0
Increased bronchial secretion	0	0	1 (< 1)	0	0
Pulmonary thrombotic and embolic conditions	0	0	0	0	1 (< 1)
Pulmonary embolism	0	0	0	0	1 (< 1)
Bronchospasm and obstruction	0	1 (< 1)	0	0	0
Obstructive airways disorder	0	1 (< 1)	0	0	0
Nasal congestion and inflammations	1 (< 1)	0	0	0	0
Rhinitis allergic	1 (< 1)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Respiratory, thoracic and mediastinal disorders										
Nasal disorders NEC	0	0	0	0	0	1 (2)	0	0	0	0
Epistaxis	0	0	0	0	0	1 (2)	0	0	0	0
Vascular disorders	7 (11)	0	3 (5)	0	0	0	2 (3)	1 (2)	0	0
Vascular hypertensive disorders NEC	4 (6)	0	2 (3)	0	0	0	0	0	0	0
Hypertension	4 (6)	0	2 (3)	0	0	0	0	0	0	0
Peripheral vascular disorders NEC	3 (5)	0	0	0	0	0	1 (2)	0	0	0
Hot flush	3 (5)	0	0	0	0	0	0	0	0	0
Peripheral vascular disorder	0	0	0	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Respiratory, thoracic and mediastinal disorders										
Nasal disorders NEC	0	0	0	0	0	1 (4)	0	0	0	0
Epistaxis	0	0	0	0	0	1 (4)	0	0	0	0
Vascular disorders	0	2 (5)	1 (3)	0	0	0	0	0	0	0
Vascular hypertensive disorders NEC	0	0	0	0	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0	0	0	0	0
Peripheral vascular disorders NEC	0	1 (3)	0	0	0	0	0	0	0	0
Hot flush	0	0	0	0	0	0	0	0	0	0
Peripheral vascular disorder	0	1 (3)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Respiratory, thoracic and mediastinal disorders						
Nasal disorders NEC	1 (< 1)	0	0	0	0	
Epistaxis	1 (< 1)	0	0	0	0	
Vascular disorders	7 (5)	2 (2)	4 (3)	0	0	
Vascular hypertensive disorders NEC	4 (3)	0	2 (2)	0	0	
Hypertension	4 (3)	0	2 (2)	0	0	
Peripheral vascular disorders NEC	3 (2)	1 (< 1)	0	0	0	
Hot flush	3 (2)	0	0	0	0	
Peripheral vascular disorder	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Vascular disorders										
Vascular hypotensive disorders	1 (2)	0	1 (2)	0	0	0	1 (2)	0	0	0
Hypotension	1 (2)	0	1 (2)	0	0	0	1 (2)	0	0	0
Non-site specific vascular disorders NEC	0	0	1 (2)	0	0	0	0	0	0	0
Poor venous access	0	0	1 (2)	0	0	0	0	0	0	0
Peripheral vasoconstriction, necrosis and vascular insufficiency	0	0	0	0	0	0	0	1 (2)	0	0
Peripheral ischaemia	0	0	0	0	0	0	0	1 (2)	0	0
Eye disorders	5 (8)	1 (2)	0	0	0	4 (6)	2 (3)	0	0	0
Visual disorders NEC	2 (3)	1 (2)	0	0	0	0	0	0	0	0
Vision blurred	2 (3)	1 (2)	0	0	0	0	0	0	0	0
Diplopia	0	1 (2)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%) Gr1	Gr2	Gr3	Gr4	Gr5	Methotrexate N=25 n (%) Gr1	Gr2	Gr3	Gr4	Gr5
Vascular disorders										
Vascular hypotensive disorders	0	1 (3)	0	0	0	0	0	0	0	0
Hypotension	0	1 (3)	0	0	0	0	0	0	0	0
Non-site specific vascular disorders NEC	0	0	0	0	0	0	0	0	0	0
Poor venous access	0	0	0	0	0	0	0	0	0	0
Peripheral vasoconstriction, necrosis and vascular insufficiency	0	0	1 (3)	0	0	0	0	0	0	0
Peripheral ischaemia	0	0	1 (3)	0	0	0	0	0	0	0
Eye disorders	3 (8)	2 (5)	0	0	0	1 (4)	0	0	0	0
Visual disorders NEC	0	0	0	0	0	0	0	0	0	0
Vision blurred	0	0	0	0	0	0	0	0	0	0
Diplopia	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5
			Total N=128 n (%)		
Vascular disorders					
Vascular hypotensive disorders	1 (< 1)	1 (< 1)	1 (< 1)	0	0
Hypotension	1 (< 1)	1 (< 1)	1 (< 1)	0	0
Non-site specific vascular disorders NEC	0	0	1 (< 1)	0	0
Poor venous access	0	0	1 (< 1)	0	0
Peripheral vasoconstriction, necrosis and vascular insufficiency	0	0	1 (< 1)	0	0
Peripheral ischaemia	0	0	1 (< 1)	0	0
Eye disorders	9 (7)	3 (2)	0	0	0
Visual disorders NEC	2 (2)	1 (< 1)	0	0	0
Vision blurred	2 (2)	1 (< 1)	0	0	0
Diplopia	0	1 (< 1)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Eye disorders										
Conjunctival infections, irritations and inflammations	1 (2)	0	0	0	0	0	0	0	0	0
Conjunctival hyperaemia	1 (2)	0	0	0	0	0	0	0	0	0
Ocular disorders NEC	1 (2)	0	0	0	0	1 (2)	0	0	0	0
Periorbital oedema	1 (2)	0	0	0	0	0	0	0	0	0
Eye swelling	0	0	0	0	0	1 (2)	0	0	0	0
Ocular infections, inflammations and associated manifestations	1 (2)	0	0	0	0	1 (2)	1 (2)	0	0	0
Eye irritation	1 (2)	0	0	0	0	0	0	0	0	0
Eye pruritus	0	0	0	0	0	0	1 (2)	0	0	0
Ocular hyperaemia	0	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Eye disorders										
Conjunctival infections, irritations and inflammations	0	0	0	0	0	0	0	0	0	0
Conjunctival hyperaemia	0	0	0	0	0	0	0	0	0	0
Ocular disorders NEC	1 (3)	0	0	0	0	0	0	0	0	0
Periorbital oedema	0	0	0	0	0	0	0	0	0	0
Eye swelling	1 (3)	0	0	0	0	0	0	0	0	0
Ocular infections, inflammations and associated manifestations	0	1 (3)	0	0	0	1 (4)	0	0	0	0
Eye irritation	0	0	0	0	0	0	0	0	0	0
Eye pruritus	0	1 (3)	0	0	0	0	0	0	0	0
Ocular hyperaemia	0	0	0	0	0	1 (4)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Eye disorders						
Conjunctival infections, irritations and inflammations	1 (< 1)	0	0	0	0	
Conjunctival hyperaemia	1 (< 1)	0	0	0	0	
Ocular disorders NEC	2 (2)	0	0	0	0	
Periorbital oedema	1 (< 1)	0	0	0	0	
Eye swelling	1 (< 1)	0	0	0	0	
Ocular infections, inflammations and associated manifestations	2 (2)	1 (< 1)	0	0	0	
Eye irritation	1 (< 1)	0	0	0	0	
Eye pruritus	0	1 (< 1)	0	0	0	
Ocular hyperaemia	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Eye disorders										
Lacrimation disorders	0	0	0	0	0	4 (6)	0	0	0	0
Dry eye	0	0	0	0	0	4 (6)	0	0	0	0
Lid, lash and lacrimal infections, irritations and inflammations	0	0	0	0	0	1 (2)	0	0	0	0
Eczema eyelids	0	0	0	0	0	1 (2)	0	0	0	0
Lid, lash and lacrimal structural disorders	0	0	0	0	0	0	1 (2)	0	0	0
Ectropion	0	0	0	0	0	0	1 (2)	0	0	0
Cardiac disorders	3 (5)	1 (2)	0	0	0	2 (3)	0	1 (2)	0	0
Rate and rhythm disorders NEC	2 (3)	1 (2)	0	0	0	1 (2)	0	0	0	0
Tachycardia	2 (3)	0	0	0	0	1 (2)	0	0	0	0
Bradycardia	0	1 (2)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Eye disorders										
Lacrimation disorders	4 (11)	0	0	0	0	0	0	0	0	0
Dry eye	4 (11)	0	0	0	0	0	0	0	0	0
Lid, lash and lacrimal infections, irritations and inflammations	1 (3)	0	0	0	0	0	0	0	0	0
Eczema eyelids	1 (3)	0	0	0	0	0	0	0	0	0
Lid, lash and lacrimal structural disorders	0	1 (3)	0	0	0	0	0	0	0	0
Ectropion	0	1 (3)	0	0	0	0	0	0	0	0
Cardiac disorders	1 (3)	0	1 (3)	0	0	1 (4)	0	0	0	0
Rate and rhythm disorders NEC	0	0	0	0	0	1 (4)	0	0	0	0
Tachycardia	0	0	0	0	0	1 (4)	0	0	0	0
Bradycardia	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Eye disorders						
Lacrimation disorders	4 (3)	0	0	0	0	
Dry eye	4 (3)	0	0	0	0	
Lid, lash and lacrimal infections, irritations and inflammations	1 (< 1)	0	0	0	0	
Eczema eyelids	1 (< 1)	0	0	0	0	
Lid, lash and lacrimal structural disorders	0	1 (< 1)	0	0	0	
Ectropion	0	1 (< 1)	0	0	0	
Cardiac disorders	5 (4)	1 (< 1)	1 (< 1)	0	0	
Rate and rhythm disorders NEC	3 (2)	1 (< 1)	0	0	0	
Tachycardia	3 (2)	0	0	0	0	
Bradycardia	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Cardiac disorders										
Supraventricular arrhythmias	1 (2)	0	0	0	0	0	0	0	0	0
Sinus tachycardia	1 (2)	0	0	0	0	0	0	0	0	0
Cardiac signs and symptoms NEC	0	0	0	0	0	1 (2)	0	0	0	0
Palpitations	0	0	0	0	0	1 (2)	0	0	0	0
Heart failures NEC	0	0	0	0	0	0	0	1 (2)	0	0
Cardiac failure congestive	0	0	0	0	0	0	0	1 (2)	0	0
Ear and labyrinth disorders	1 (2)	3 (5)	0	0	0	2 (3)	0	0	0	0
Inner ear signs and symptoms	1 (2)	1 (2)	0	0	0	0	0	0	0	0
Tinnitus	1 (2)	0	0	0	0	0	0	0	0	0
Vertigo	0	1 (2)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Cardiac disorders										
Supraventricular arrhythmias	0	0	0	0	0	0	0	0	0	0
Sinus tachycardia	0	0	0	0	0	0	0	0	0	0
Cardiac signs and symptoms NEC	1 (3)	0	0	0	0	0	0	0	0	0
Palpitations	1 (3)	0	0	0	0	0	0	0	0	0
Heart failures NEC	0	0	1 (3)	0	0	0	0	0	0	0
Cardiac failure congestive	0	0	1 (3)	0	0	0	0	0	0	0
Ear and labyrinth disorders	2 (5)	0	0	0	0	0	0	0	0	0
Inner ear signs and symptoms	0	0	0	0	0	0	0	0	0	0
Tinnitus	0	0	0	0	0	0	0	0	0	0
Vertigo	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5
			Total N=128 n (%)		
Cardiac disorders					
Supraventricular arrhythmias	1 (< 1)	0	0	0	0
Sinus tachycardia	1 (< 1)	0	0	0	0
Cardiac signs and symptoms NEC	1 (< 1)	0	0	0	0
Palpitations	1 (< 1)	0	0	0	0
Heart failures NEC	0	0	1 (< 1)	0	0
Cardiac failure congestive	0	0	1 (< 1)	0	0
Ear and labyrinth disorders	3 (2)	3 (2)	0	0	0
Inner ear signs and symptoms	1 (< 1)	1 (< 1)	0	0	0
Tinnitus	1 (< 1)	0	0	0	0
Vertigo	0	1 (< 1)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Ear and labyrinth disorders										
Ear disorders NEC	0	1 (2)	0	0	0	2 (3)	0	0	0	0
Otorrhoea	0	1 (2)	0	0	0	0	0	0	0	0
Ear haemorrhage	0	0	0	0	0	1 (2)	0	0	0	0
Ear pain	0	0	0	0	0	1 (2)	0	0	0	0
Hearing losses	0	1 (2)	0	0	0	0	0	0	0	0
Deafness unilateral	0	1 (2)	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	2 (3)	2 (3)	0	0	0	3 (5)	1 (2)	0	0	0
Non-site specific injuries NEC	1 (2)	1 (2)	0	0	0	3 (5)	0	0	0	0
Fall	1 (2)	0	0	0	0	2 (3)	0	0	0	0
Wound	0	1 (2)	0	0	0	0	0	0	0	0
Wound secretion	0	0	0	0	0	1 (2)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%) Gr1	Gr2	Gr3	Gr4	Gr5	Methotrexate N=25 n (%) Gr1	Gr2	Gr3	Gr4	Gr5
Ear and labyrinth disorders										
Ear disorders NEC	2 (5)	0	0	0	0	0	0	0	0	0
Otorrhoea	0	0	0	0	0	0	0	0	0	0
Ear haemorrhage	1 (3)	0	0	0	0	0	0	0	0	0
Ear pain	1 (3)	0	0	0	0	0	0	0	0	0
Hearing losses	0	0	0	0	0	0	0	0	0	0
Deafness unilateral	0	0	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	3 (8)	1 (3)	0	0	0	0	0	0	0	0
Non-site specific injuries NEC	3 (8)	0	0	0	0	0	0	0	0	0
Fall	2 (5)	0	0	0	0	0	0	0	0	0
Wound	0	0	0	0	0	0	0	0	0	0
Wound secretion	1 (3)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Ear and labyrinth disorders						
Ear disorders NEC	2 (2)	1 (< 1)	0	0	0	
Otorrhoea	0	1 (< 1)	0	0	0	
Ear haemorrhage	1 (< 1)	0	0	0	0	
Ear pain	1 (< 1)	0	0	0	0	
Hearing losses	0	1 (< 1)	0	0	0	
Deafness unilateral	0	1 (< 1)	0	0	0	
Injury, poisoning and procedural complications	5 (4)	3 (2)	0	0	0	
Non-site specific injuries NEC	4 (3)	1 (< 1)	0	0	0	
Fall	3 (2)	0	0	0	0	
Wound	0	1 (< 1)	0	0	0	
Wound secretion	1 (< 1)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Injury, poisoning and procedural complications										
Fractures and dislocations NEC	0	1 (2)	0	0	0	0	0	0	0	0
Fracture	0	1 (2)	0	0	0	0	0	0	0	0
Thoracic cage fractures and dislocations	1 (2)	0	0	0	0	0	0	0	0	0
Rib fracture	1 (2)	0	0	0	0	0	0	0	0	0
Limb fractures and dislocations	0	0	0	0	0	0	1 (2)	0	0	0
Foot fracture	0	0	0	0	0	0	1 (2)	0	0	0
Muscle, tendon and ligament injuries	0	0	0	0	0	0	1 (2)	0	0	0
Ligament sprain	0	0	0	0	0	0	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Injury, poisoning and procedural complications										
Fractures and dislocations NEC	0	0	0	0	0	0	0	0	0	0
Fracture	0	0	0	0	0	0	0	0	0	0
Thoracic cage fractures and dislocations	0	0	0	0	0	0	0	0	0	0
Rib fracture	0	0	0	0	0	0	0	0	0	0
Limb fractures and dislocations	0	1 (3)	0	0	0	0	0	0	0	0
Foot fracture	0	1 (3)	0	0	0	0	0	0	0	0
Muscle, tendon and ligament injuries	0	1 (3)	0	0	0	0	0	0	0	0
Ligament sprain	0	1 (3)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Injury, poisoning and procedural complications						
Fractures and dislocations NEC	0	1 (< 1)	0	0	0	
Fracture	0	1 (< 1)	0	0	0	
Thoracic cage fractures and dislocations	1 (< 1)	0	0	0	0	
Rib fracture	1 (< 1)	0	0	0	0	
Limb fractures and dislocations	0	1 (< 1)	0	0	0	
Foot fracture	0	1 (< 1)	0	0	0	
Muscle, tendon and ligament injuries	0	1 (< 1)	0	0	0	
Ligament sprain	0	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Injury, poisoning and procedural complications										
Non-site specific procedural complications	0	0	0	0	0	1 (2)	0	0	0	0
Incision site complication	0	0	0	0	0	1 (2)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (3)	1 (2)	0	1 (2)	3 (5)	4 (6)	1 (2)	0	0
Oncologic complications and emergencies	1 (2)	0	1 (2)	0	0	1 (2)	3 (5)	1 (2)	0	0
Cancer pain	0	0	1 (2)	0	0	1 (2)	2 (3)	1 (2)	0	0
Tumour associated fever	1 (2)	0	0	0	0	0	0	0	0	0
Infected neoplasm	0	0	0	0	0	0	1 (2)	0	0	0
Lymphomas unspecified NEC	0	0	0	0	1 (2)	0	0	0	0	0
Lymphoma	0	0	0	0	1 (2)	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%) Gr1	Gr2	Gr3	Gr4	Gr5	Methotrexate N=25 n (%) Gr1	Gr2	Gr3	Gr4	Gr5
Injury, poisoning and procedural complications										
Non-site specific procedural complications	1 (3)	0	0	0	0	0	0	0	0	0
Incision site complication	1 (3)	0	0	0	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3)	3 (8)	1 (3)	0	0	2 (8)	1 (4)	0	0	0
Oncologic complications and emergencies	0	2 (5)	1 (3)	0	0	1 (4)	1 (4)	0	0	0
Cancer pain	0	1 (3)	1 (3)	0	0	1 (4)	1 (4)	0	0	0
Tumour associated fever	0	0	0	0	0	0	0	0	0	0
Infected neoplasm	0	1 (3)	0	0	0	0	0	0	0	0
Lymphomas unspecified NEC	0	0	0	0	0	0	0	0	0	0
Lymphoma	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Injury, poisoning and procedural complications						
Non-site specific procedural complications	1 (< 1)	0	0	0	0	
Incision site complication	1 (< 1)	0	0	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2)	6 (5)	2 (2)	0	1 (< 1)	
Oncologic complications and emergencies	2 (2)	3 (2)	2 (2)	0	0	
Cancer pain	1 (< 1)	2 (2)	2 (2)	0	0	
Tumour associated fever	1 (< 1)	0	0	0	0	
Infected neoplasm	0	1 (< 1)	0	0	0	
Lymphomas unspecified NEC	0	0	0	0	1 (< 1)	
Lymphoma	0	0	0	0	1 (< 1)	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
Mycoses fungoides	0	1 (2)	0	0	0	2 (3)	0	0	0	0
Mycosis fungoides	0	1 (2)	0	0	0	2 (3)	0	0	0	0
Neoplasms malignant site unspecified NEC	0	1 (2)	0	0	0	0	0	0	0	0
Squamous cell carcinoma	0	1 (2)	0	0	0	0	0	0	0	0
Skin neoplasms malignant and unspecified (excl melanoma)	0	0	0	0	0	0	1 (2)	0	0	0
Squamous cell carcinoma of skin	0	0	0	0	0	0	1 (2)	0	0	0
Immune system disorders	1 (2)	0	2 (3)	0	0	0	0	0	0	0
Allergies to foods, food additives, drugs and other chemicals	0	0	2 (3)	0	0	0	0	0	0	0
Drug hypersensitivity	0	0	2 (3)	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
Mycoses fungoides	1 (3)	0	0	0	0	1 (4)	0	0	0	0
Mycosis fungoides	1 (3)	0	0	0	0	1 (4)	0	0	0	0
Neoplasms malignant site unspecified NEC	0	0	0	0	0	0	0	0	0	0
Squamous cell carcinoma	0	0	0	0	0	0	0	0	0	0
Skin neoplasms malignant and unspecified (excl melanoma)	0	1 (3)	0	0	0	0	0	0	0	0
Squamous cell carcinoma of skin	0	1 (3)	0	0	0	0	0	0	0	0
Immune system disorders	0	0	0	0	0	0	0	0	0	0
Allergies to foods, food additives, drugs and other chemicals	0	0	0	0	0	0	0	0	0	0
Drug hypersensitivity	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Mycoses fungoides	2 (2)	1 (< 1)	0	0	0	
Mycosis fungoides	2 (2)	1 (< 1)	0	0	0	
Neoplasms malignant site unspecified NEC	0	1 (< 1)	0	0	0	
Squamous cell carcinoma	0	1 (< 1)	0	0	0	
Skin neoplasms malignant and unspecified (excl melanoma)	0	1 (< 1)	0	0	0	
Squamous cell carcinoma of skin	0	1 (< 1)	0	0	0	
Immune system disorders	1 (< 1)	0	2 (2)	0	0	
Allergies to foods, food additives, drugs and other chemicals	0	0	2 (2)	0	0	
Drug hypersensitivity	0	0	2 (2)	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Immune system disorders										
Atopic disorders	1 (2)	0	0	0	0	0	0	0	0	0
Seasonal allergy	1 (2)	0	0	0	0	0	0	0	0	0
Psychiatric disorders	1 (2)	2 (3)	0	0	0	7 (11)	3 (5)	0	0	0
Disturbances in initiating and maintaining sleep	1 (2)	1 (2)	0	0	0	3 (5)	2 (3)	0	0	0
Insomnia	1 (2)	1 (2)	0	0	0	3 (5)	2 (3)	0	0	0
Anxiety symptoms	0	1 (2)	0	0	0	2 (3)	2 (3)	0	0	0
Stress	0	1 (2)	0	0	0	0	0	0	0	0
Anxiety	0	0	0	0	0	2 (3)	2 (3)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Immune system disorders										
Atopic disorders	0	0	0	0	0	0	0	0	0	0
Seasonal allergy	0	0	0	0	0	0	0	0	0	0
Psychiatric disorders	5 (14)	3 (8)	0	0	0	2 (8)	0	0	0	0
Disturbances in initiating and maintaining sleep	3 (8)	2 (5)	0	0	0	0	0	0	0	0
Insomnia	3 (8)	2 (5)	0	0	0	0	0	0	0	0
Anxiety symptoms	1 (3)	2 (5)	0	0	0	1 (4)	0	0	0	0
Stress	0	0	0	0	0	0	0	0	0	0
Anxiety	1 (3)	2 (5)	0	0	0	1 (4)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Immune system disorders						
Atopic disorders	1 (< 1)	0	0	0	0	
Seasonal allergy	1 (< 1)	0	0	0	0	
Psychiatric disorders	8 (6)	5 (4)	0	0	0	
Disturbances in initiating and maintaining sleep	4 (3)	3 (2)	0	0	0	
Insomnia	4 (3)	3 (2)	0	0	0	
Anxiety symptoms	2 (2)	3 (2)	0	0	0	
Stress	0	1 (< 1)	0	0	0	
Anxiety	2 (2)	2 (2)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Psychiatric disorders										
Mood alterations with depressive symptoms	0	0	0	0	0	3 (5)	0	0	0	0
Depressed mood	0	0	0	0	0	3 (5)	0	0	0	0
Parasomnias	0	0	0	0	0	1 (2)	0	0	0	0
Nightmare	0	0	0	0	0	1 (2)	0	0	0	0
Renal and urinary disorders	2 (3)	0	1 (2)	0	0	5 (8)	2 (3)	1 (2)	0	0
Bladder and urethral symptoms	1 (2)	0	1 (2)	0	0	3 (5)	1 (2)	0	0	0
Dysuria	1 (2)	0	0	0	0	0	1 (2)	0	0	0
Urinary retention	0	0	1 (2)	0	0	0	0	0	0	0
Micturition urgency	0	0	0	0	0	1 (2)	0	0	0	0
Pollakiuria	0	0	0	0	0	2 (3)	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%) Gr1	Gr2	Gr3	Gr4	Gr5	Methotrexate N=25 n (%) Gr1	Gr2	Gr3	Gr4	Gr5
Psychiatric disorders										
Mood alterations with depressive symptoms	2 (5)	0	0	0	0	1 (4)	0	0	0	0
Depressed mood	2 (5)	0	0	0	0	1 (4)	0	0	0	0
Parasomnias	1 (3)	0	0	0	0	0	0	0	0	0
Nightmare	1 (3)	0	0	0	0	0	0	0	0	0
Renal and urinary disorders	4 (11)	1 (3)	1 (3)	0	0	1 (4)	1 (4)	0	0	0
Bladder and urethral symptoms	2 (5)	0	0	0	0	1 (4)	1 (4)	0	0	0
Dysuria	0	0	0	0	0	0	1 (4)	0	0	0
Urinary retention	0	0	0	0	0	0	0	0	0	0
Micturition urgency	0	0	0	0	0	1 (4)	0	0	0	0
Pollakiuria	2 (5)	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Psychiatric disorders						
Mood alterations with depressive symptoms	3 (2)	0	0	0	0	
Depressed mood	3 (2)	0	0	0	0	
Parasomnias	1 (< 1)	0	0	0	0	
Nightmare	1 (< 1)	0	0	0	0	
Renal and urinary disorders	7 (5)	2 (2)	2 (2)	0	0	
Bladder and urethral symptoms	4 (3)	1 (< 1)	1 (< 1)	0	0	
Dysuria	1 (< 1)	1 (< 1)	0	0	0	
Urinary retention	0	0	1 (< 1)	0	0	
Micturition urgency	1 (< 1)	0	0	0	0	
Pollakiuria	2 (2)	0	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Renal and urinary disorders										
Urinary abnormalities	1 (2)	0	0	0	0	0	0	1 (2)	0	0
Haematuria	1 (2)	0	0	0	0	0	0	1 (2)	0	0
Renal failure and impairment	0	0	0	0	0	2 (3)	1 (2)	0	0	0
Chronic kidney disease	0	0	0	0	0	0	1 (2)	0	0	0
Oliguria	0	0	0	0	0	1 (2)	0	0	0	0
Renal impairment	0	0	0	0	0	1 (2)	0	0	0	0
Hepatobiliary disorders	0	0	2 (3)	0	0	0	0	0	0	0
Hepatocellular damage and hepatitis NEC	0	0	2 (3)	0	0	0	0	0	0	0
Hepatocellular injury	0	0	1 (2)	0	0	0	0	0	0	0
Hepatotoxicity	0	0	1 (2)	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Renal and urinary disorders										
Urinary abnormalities	0	0	1 (3)	0	0	0	0	0	0	0
Haematuria	0	0	1 (3)	0	0	0	0	0	0	0
Renal failure and impairment	2 (5)	1 (3)	0	0	0	0	0	0	0	0
Chronic kidney disease	0	1 (3)	0	0	0	0	0	0	0	0
Oliguria	1 (3)	0	0	0	0	0	0	0	0	0
Renal impairment	1 (3)	0	0	0	0	0	0	0	0	0
Hepatobiliary disorders	0	0	0	0	0	0	0	0	0	0
Hepatocellular damage and hepatitis NEC	0	0	0	0	0	0	0	0	0	0
Hepatocellular injury	0	0	0	0	0	0	0	0	0	0
Hepatotoxicity	0	0	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Total N=128 n (%) Gr3	Gr4	Gr5
Renal and urinary disorders					
Urinary abnormalities	1 (< 1)	0	1 (< 1)	0	0
Haematuria	1 (< 1)	0	1 (< 1)	0	0
Renal failure and impairment	2 (2)	1 (< 1)	0	0	0
Chronic kidney disease	0	1 (< 1)	0	0	0
Oliguria	1 (< 1)	0	0	0	0
Renal impairment	1 (< 1)	0	0	0	0
Hepatobiliary disorders	0	0	2 (2)	0	0
Hepatocellular damage and hepatitis NEC	0	0	2 (2)	0	0
Hepatocellular injury	0	0	1 (< 1)	0	0
Hepatotoxicity	0	0	1 (< 1)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Reproductive system and breast disorders	1 (2)	0	1 (2)	0	0	0	1 (2)	1 (2)	0	0
Breast disorders NEC	1 (2)	0	0	0	0	0	0	0	0	0
Nipple disorder	1 (2)	0	0	0	0	0	0	0	0	0
Penile disorders NEC (excl erection and ejaculation)	0	0	1 (2)	0	0	0	0	0	0	0
Penile pain	0	0	1 (2)	0	0	0	0	0	0	0
Menstruation and uterine bleeding NEC	0	0	0	0	0	0	0	1 (2)	0	0
Dysmenorrhoea	0	0	0	0	0	0	0	1 (2)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Reproductive system and breast disorders	0	0	0	0	0	0	1 (4)	1 (4)	0	0
Breast disorders NEC	0	0	0	0	0	0	0	0	0	0
Nipple disorder	0	0	0	0	0	0	0	0	0	0
Penile disorders NEC (excl erection and ejaculation)	0	0	0	0	0	0	0	0	0	0
Penile pain	0	0	0	0	0	0	0	0	0	0
Menstruation and uterine bleeding NEC	0	0	0	0	0	0	0	1 (4)	0	0
Dysmenorrhoea	0	0	0	0	0	0	0	1 (4)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Total N=128 n (%) Gr3	Gr4	Gr5
Reproductive system and breast disorders	1 (< 1)	1 (< 1)	2 (2)	0	0
Breast disorders NEC	1 (< 1)	0	0	0	0
Nipple disorder	1 (< 1)	0	0	0	0
Penile disorders NEC (excl erection and ejaculation)	0	0	1 (< 1)	0	0
Penile pain	0	0	1 (< 1)	0	0
Menstruation and uterine bleeding NEC	0	0	1 (< 1)	0	0
Dysmenorrhoea	0	0	1 (< 1)	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

0114\mpiunbl\0046\ICR_BIO\dev\primary\programs\tables\t14.4.1.4B-teae_sev_lbtox.sas 19DEC2016: 14:19

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Brentuximab Vedotin N=66 n (%)					Methotrexate or Bexarotene N=62 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Reproductive system and breast disorders										
Prostate and seminal vesicles infections and inflammations	0	0	0	0	0	0	1 (2)	0	0	0
Prostatitis	0	0	0	0	0	0	1 (2)	0	0	0
Congenital, familial and genetic disorders	1 (2)	0	0	0	0	0	0	0	0	0
Vascular anomalies congenital NEC	1 (2)	0	0	0	0	0	0	0	0	0
Vertebral artery hypoplasia	1 (2)	0	0	0	0	0	0	0	0	0
Endocrine disorders	0	0	0	0	0	3 (5)	4 (6)	0	0	0
Thyroid hypofunction disorders	0	0	0	0	0	3 (5)	4 (6)	0	0	0
Hypothyroidism	0	0	0	0	0	2 (3)	3 (5)	0	0	0
Secondary hypothyroidism	0	0	0	0	0	1 (2)	1 (2)	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Bexarotene N=37 n (%)					Methotrexate N=25 n (%)				
	Gr1	Gr2	Gr3	Gr4	Gr5	Gr1	Gr2	Gr3	Gr4	Gr5
Reproductive system and breast disorders										
Prostate and seminal vesicles infections and inflammations	0	0	0	0	0	0	1 (4)	0	0	0
Prostatitis	0	0	0	0	0	0	1 (4)	0	0	0
Congenital, familial and genetic disorders	0	0	0	0	0	0	0	0	0	0
Vascular anomalies congenital NEC	0	0	0	0	0	0	0	0	0	0
Vertebral artery hypoplasia	0	0	0	0	0	0	0	0	0	0
Endocrine disorders	3 (8)	4 (11)	0	0	0	0	0	0	0	0
Thyroid hypofunction disorders	3 (8)	4 (11)	0	0	0	0	0	0	0	0
Hypothyroidism	2 (5)	3 (8)	0	0	0	0	0	0	0	0
Secondary hypothyroidism	1 (3)	1 (3)	0	0	0	0	0	0	0	0

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

Table 14.4.1.4B
Treatment-Emergent Adverse Events including Lab Toxicities by Maximum Severity
Safety Population

Primary System Organ Class High Level Term Preferred Term	Gr1	Gr2	Gr3	Gr4	Gr5	Total N=128 n (%)
Reproductive system and breast disorders						
Prostate and seminal vesicles infections and inflammations	0	1 (< 1)	0	0	0	
Prostatitis	0	1 (< 1)	0	0	0	
Congenital, familial and genetic disorders	1 (< 1)	0	0	0	0	
Vascular anomalies congenital NEC	1 (< 1)	0	0	0	0	
Vertebral artery hypoplasia	1 (< 1)	0	0	0	0	
Endocrine disorders	3 (2)	4 (3)	0	0	0	
Thyroid hypofunction disorders	3 (2)	4 (3)	0	0	0	
Hypothyroidism	2 (2)	3 (2)	0	0	0	
Secondary hypothyroidism	1 (< 1)	1 (< 1)	0	0	0	

Treatment-emergent adverse event is defined as any adverse event that occurs after study drug administration of the first dose of study drug and up through 30 days after the last dose of study medication.
AEs will be coded using the MedDRA dictionary Version 19.0.
a Patient Incidence: A patient counts once for the highest intensity of each preferred term, high level term and system organ class. Percentages use the number of treated patients as the denominator.
b Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher hemoglobin).
c Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher ANC).
d Incidence was defined as TEAE of the preferred term, or the treatment-emergent laboratory abnormality (G1 or higher platelets).

目次

2.7.5 参考文献 2
2.7.5.1 「2.7.1 生物薬剤学試験及び関連する分析法」で使用した参考文献 2
2.7.5.2 「2.7.2 臨床薬理試験」で使用した参考文献 2
2.7.5.3 「2.7.3 臨床的有効性」で使用した参考文献 2
2.7.5.4 「2.7.4 臨床的安全性」で使用した参考文献 2

2.7.5 参考文献

2.7.5.1 「2.7.1 生物薬剤学試験及び関連する分析法」で使用した参考文献

該当せず

2.7.5.2 「2.7.2 臨床薬理試験」で使用した参考文献

2.7.2.6 参考文献に記載

2.7.5.3 「2.7.3 臨床的有効性」で使用した参考文献

2.7.3.6 参考文献に記載

2.7.5.4 「2.7.4 臨床的安全性」で使用した参考文献

2.7.4.7 参考文献に記載

目次

略号一覧表 2
2.7.6 個々の試験のまとめ 4
2.7.6.1 海外第 3 相国際共同治験（C25001 試験） 2.7.6.1-1
2.7.6.2 国内第 2 相医師主導治験（SGN-35-OU 試験） 2.7.6.2-1

略号一覧表

略号	略していない表現又は説明	
	英語	日本語
ACNU	nimustine hydrochloride	ニムスチン塩酸塩
ADA	antidrug antibody	抗薬物抗体
ADC	antibody-drug conjugate	抗体薬物複合体
ALT	alanine aminotransferase	アスパラギン酸アミノトランスフェラーゼ
AST	aspartate aminotransferase	アラニンアミノトランスフェラーゼ
CI	confidence interval	信頼区間
CR	complete response	完全奏効（寛解）
CT	computed tomography	コンピュータ断層撮影
CTACK	cutaneous T-cell–attracting chemokine	皮膚 T 細胞誘引ケモカイン
CTCAE	Common Terminology Criteria for Adverse Events	有害事象共通用語規準
CTCL	cutaneous T-cell lymphoma	皮膚 T 細胞リンパ腫
DLQI	Dermatology Life Quality Index	—
DOR	duration of response	奏効期間
ECOG	Eastern Cooperative Oncology Group	—
EFS	event-free survival	無イベント生存期間
EORTC	Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer	—
EOT	end of treatment	投与終了時／治療の終了
EQ-5D-3L	European Quality of Life 5-Dimension Three Level Version	—
FACT-G	Functional Assessment of Cancer Therapy-General	—
FAS	full analysis set	最大の解析対象集団
GRS	global response score	—
HIV	human immunodeficiency virus	ヒト免疫不全ウイルス
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	医薬品規制調和国際会議
IFN	interferon	インターフェロン
IRB	institutional review board	治験審査委員会
IRF	independent review facility	独立評価委員会
ISCL	International Society for Cutaneous Lymphoma	—
ITT	intent-to-treat	—
MedDRA	Medical Dictionary for Regulatory Activities	国際医薬用語集
MF	mycosis fungoides	菌状息肉症
mFAS	modified full analysis set	調整された最大の解析対象集団
MMAE	monomethyl auristatin E	モノメチルアウリスタチン E

略号一覧表（続き）

略号	略していない表現又は説明	
	英語	日本語
mSWAT	modified severity-weighted assessment tool	—
NB-UVB	narrow band-ultraviolet light B	狭帯域紫外線 B
NCI	National Cancer Institute	米国国立がん研究所
NYHA	New York Heart Association	ニューヨーク心臓協会
OPDREC	Objective Primary Disease Response Evaluation Criteria	客観的な原疾患の治療効果判定基準
ORR1	objective response rate lasting at least 4 weeks	少なくとも 4 週間／4 週間以上持続する客観的奏効
ORR4	objective response rate lasting at least 4 months	少なくとも 4 ヵ月／4 ヵ月以上持続する客観的奏効
OS	overall survival	全生存期間
pcALCL	primary cutaneous anaplastic large cell lymphoma	原発性皮膚未分化大細胞リンパ腫
PD	progressive disease	進行
PFS	progression-free survival	無増悪生存期間
PML	progressive multifocal leukoencephalopathy	進行性多巣性白質脳症
PP	per protocol	—
PR	partial response	部分奏効（寛解）
PT	preferred term	基本語
PTFU	post treatment follow up	後観察期
PUVA	psoralen with ultraviolet light A	ソラレンと紫外線 A
QOL	quality of life	—
SAF	safety data set	安全性データの解析対象集団
sALCL	systemic anaplastic large cell lymphoma	全身性未分化大細胞リンパ腫
sCD30	soluble CD30	可溶性 CD30
SD	stable disease	安定（状態）
SDT	skin directed therapy	皮膚指向療法
SMQ	standardized MedDRA query	MedDRA 標準検索式
SOC	system organ class	器官別大分類
TAb	total antibody	全抗体
TARC	thymus and activation regulated chemokine	胸腺及び活性化調節ケモカイン
TEAE	treatment-emergent adverse event	試験治療下で発現した有害事象
ULN	upper limit of the normal range	正常範囲の上限
USCLC	the United States Cutaneous Lymphoma Consortium	—

2.7.6 個々の試験のまとめ

番号	実施地域	相	試験番号（評価･参考）	試験目的	対象	試験デザイン	用法・用量	症例数	投与期間	施設数	試験期間（年･月）	添付資料番号
2.7.6.1	海外	3	C25001（評価）	有効性、安全性、QOL、PK、免疫原性	CD30 陽性 CTCL 患者（MF 又は pcALCL）	非盲検、2 群、ランダム化、多施設共同試験	本剤 1.8 mg/kg 21 日サイクルの 1 日目に静脈内投与 メトトレキサート 5～50 mg 1 週間に 1 回経口投与 ベキサロテン 300 mg/m^2 1 日 1 回経口投与	合計 131 例 本剤 66 例 メトトレキサート：27 例 ベキサロテン：38 例	48 週間（16 サイクル）	34	2012 年 6 月～2018 年 7 月（最後の被験者の最終来院／交信日）	5.3.5.1-1
2.7.6.2	日本	2	SGN-35-OU（評価）	有効性、安全性	コホート 1 再発又は難治性の CD30 陽性 MF 又は pcALCL 患者 コホート 2 コホート 1 以外の CD30 陽性リンパ増殖異常症患者	非盲検、単群、多施設共同、医師主導治験	本剤 1.8 mg/kg 21 日サイクルの 1 日目に静脈内投与	16 例	48 週間（16 サイクル）	6	2019 年 2 月～2021 年 12 月（最後の被験者の追跡終了日）	5.3.5.2-1

CTCL：皮膚 T 細胞リンパ腫、MF：菌状息肉症、pcALCL：原発性皮膚未分化大細胞リンパ腫、PK：薬物動態、QOL：quality of life

4

2.7.6.1 第 3 相国際共同試験（C25001 試験）

：添付資料番号 5.3.5.1-1（評価）

試験の標題

A Randomized, Open-Label, Phase 3 Trial of Brentuximab Vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma

実施医療機関

34 医療機関（欧州連合、米国、オーストラリア、スイス及びブラジル）

公表文献

Horwitz, SM., Scarisbrick JJ, Dummer R, Whittaker S, Duvic M, Kim YH, et al. Randomized phase 3 ALCANZA study of brentuximab vedotin vs physician's choice in cutaneous T-cell lymphoma: final data. Blood Adv. 2021;5(23):5098-106.

Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017;390(10094):555-66.

試験期間

2012 年 6 月 11 日（最初の被験者の同意取得日）～2018 年 7 月 6 日（最後の被験者の最終来院／交信日）

治験総括報告書のための最終解析のデータカットオフ日：2016 年 5 月 31 日

試験終了時の有効性及びその他の試験評価項目の更新のデータカットオフ日：2018 年 9 月 28 日

試験の種類

第 3 相

2.7.6.1.1 試験方法

2.7.6.1.1.1 試験の目的

［主目的］

CD30 陽性の菌状息肉症（MF）又は原発性皮膚未分化大細胞リンパ腫（pcALCL）患者を対象に、ブレンツキシマブ　ベドチン（SGN-35、アドセトリス。以下、本剤）により 4 ヵ月以上の客観的奏効が得られた被験者の割合（ORR4）を特定し、対照治療と比較する。

［重要な副目的］

- 本剤の完全奏効（CR）が得られた被験者の割合（CR 率）を特定し、対照治療と比較評価する。
- 本剤の無増悪生存期間（PFS）を特定し、対照治療と比較評価する。
- 本剤の投与期間中の症状負荷を特定し、対照治療と比較評価する。

［その他の副目的］
· 本剤の奏効期間（DOR）を評価する。
· 本剤の皮膚反応の持続期間（皮膚奏効期間）を評価する。
· 本剤の無イベント生存期間（EFS）を特定し対照治療と比較評価する。
· 血液中の本剤及びモノメチルアウリスタチン E（MMAE）の薬物動態を評価する。
· 本剤の免疫原性を特定する。
· Quality of life（QOL）の患者報告による転帰を評価する。
· 本剤の安全性を評価する。

2.7.6.1.1.2 試験デザイン

本試験は、組織学的に CD30 陽性の MF 又は pcALCL が確認された患者を対象とした非盲検、ランダム化、多施設共同試験である。被験者を診断疾患（MF 又は pcALCL）で層別化し、本剤群又は治験責任医師が選択した化学療法群（治験責任医師の選択によりメトトレキサート又はベキサロテンいずれかの投与を受ける）にランダムに割り付けた。本剤群では、本剤 1.8 mg/kg を各サイクル（1 サイクルを 21 日とする）の Day 1 に約 30 分かけて最大 16 サイクル静脈内投与した。治験責任医師が選択した化学療法群では、メトトレキサート 5～50 mg を週 1 回又はベキサロテン 300 mg/m^2 を 1 日 1 回、最大 48 週間経口投与した。3 つの治療レジメンに用量調整ガイドラインを設定した。治験責任医師が選択した化学療法群に割り付けられた被験者が受ける治療レジメンは、治験責任医師が前治療を考慮して選択することとし、メトトレキサートによる治療歴のある被験者にはベキサロテンを、ベキサロテンによる治療歴のある被験者にはメトトレキサートを選択することが推奨された。

独立評価委員会（IRF）による客観的奏効の評価に基づく ORR4 は、global response score（GRS）により判定された。GRS は、治験責任医師による modified severity-weighted assessment tool（mSWAT）を用いた皮膚評価、IRF によるリンパ節及び内臓の画像評価、及び IRF による循環セザリー細胞の検出（MF 被験者のみ）で構成される。治験責任医師による客観的奏効は、サイクル 3、6、9、12、15 及び投与終了（EOT）時に、IRF による客観的奏効は、各サイクル及び EOT 時に評価した。本剤の投与を受け、EOT 時又は早期中止時に疾患進行が認められなかった全ての被験者は、少なくとも 24 ヵ月間は 12 週ごと、その後は疾患進行又は治験終了まで 6 ヵ月ごとに客観的奏効を追跡することとした。CR 又は部分奏効（PR）は、次サイクルの mSWAT 評価により皮膚反応が継続していることを確認することとした。規定外の GRS 評価は、皮膚反応の変化後又はコンピュータ断層撮影（CT）時に実施できることとした。

サイクル 3 終了時及びその後の疾患評価時に CR 又は PR が確認された場合、本剤の投与を受けた被験者は最大 16 サイクル、ベキサロテン又はメトトレキサートの投与を受けた被験者は最大 48 週間の継続投与が認められた。安定（SD）の場合、被験者は治験責任医師の判断で治療を継続することができた。試験期間中の任意の時点で進行（PD）と判定された場合、被験者は試験治療を中止することとした。サイクル 3 終了時の評価前までに mSWAT が増加した被験者は、それが疾患進行ではなく腫瘍フレアによるものであると治験責任医師が判断した場合、サイクル 3 の評価まで治療を継続することが認められた。

疾患進行は、International Society for Cutaneous Lymphoma（ISCL）、the United States Cutaneous Lymphoma Consortium（USCLC）及び Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer（EORTC）で合意された効果判定基準に従って評価した。ベースラインでリンパ節／内臓病変が確認され、直近の CT スキャンが EOT の 8 週間以上前であった被験者には、EOT 時に CT スキャンを実施した。

本剤の安全性及び忍容性は、試験治療下で発現した有害事象（TEAE）の発現頻度、有害事象の重症度及び種類、並びにバイタルサイン、Eastern Cooperative Oncology Group（ECOG）performance status 及び臨床検査値のベースラインからの変化によって評価した。毒性は、米国国立がん研究所（NCI）による有害事象共通用語規準（CTCAE）（第 4.03 版）に従って評価した。

本剤の濃度と、可溶性 CD30（sCD30）及び皮膚生検、腫瘍生検及び／又は血液細胞由来のリンパ腫細胞における CD30 発現の関係性を評価した。健康関連 QOL は、患者自身が報告する質問票である Skindex-29、Functional Assessment of Cancer Therapy-General（FACT-G）及び European Quality of Life 5-Dimension Three Level Version（EQ-5D-3L）を用いて評価した。

ランダム化された被験者は、EOT 来院後少なくとも 24 ヵ月間は 12 週ごと、その後は試験中止、死亡又は試験の終了まで 6 ヵ月ごとに生存調査を実施することとした。

本治験では、独立データモニタリング委員会を設立し、治験の実施を監視し（安全性データの定期的なレビューを含む）、治験の完全性及び信頼性を維持しながら被験者の利益を保護するために治験依頼者に勧告を行うこととした。

なお、スクリーニング期間はランダム化前 28 日以内とし、登録後 72 時間以内に治験薬を初回投与することとした。EOT 時／早期中止時の来院は治験薬の最終投与後 30 日（±2 日）とし、追跡調査期間は 24 ヵ月以上とした。

2.7.6.1.1.3 対象及び組入れ基準

組織学的に CD30 陽性の MF 又は pcALCL と確定診断され、画像で又は臨床的に測定可能な病変を有する 18 歳以上の男性又は女性患者を適格とした。MF 患者は 1 回以上の全身療法を、pcALCL 患者は 1 回以上の全身療法又は放射線療法を受けていることとした。また、ECOG performance status が 2 以下の患者を適格とした。

2.7.6.1.1.4 被験者数

予定被験者数：124 例

［設定根拠］

本試験では、約 124 例を各投与群に約 62 例ずつランダムに割り付けることとした。症例数は、治験責任医師が選択した化学療法群（メトトレキサート又はベキサロテン）の ORR4 を

40%と仮定したときに、本剤投与群で 30%の改善を期待した場合の検出力が 90%となるよう算出した。この算出は、nQuery Advisor 7.0 を用いて行い、有意水準 α=0.05 とした両側 χ^2 検定を想定し、脱落率は 10%と仮定した。また、pcALCL 患者 30 例以上（各投与群に 15 例ずつ）をランダムに割り付けることとした。

2.7.6.1.1.5 投与方法、投与量及び投与期間

各試験治療の投与方法及び投与量は以下のとおり。

試験治療	投与量	投与経路	ロット番号
ブレンツキシマブ ベドチン	1.8 mg/kg 21 日サイクルの Day 1 投与	静脈内	[redacted]
ベキサロテン	300 mg/m^2/day 1 日 1 回投与	経口	[redacted]
メトトレキサート	5～50 mg 週 1 回投与	経口	[redacted]

両投与群の被験者は最大 48 週間の試験治療を受けることとした。本剤群に割り付けられた被験者は本剤を最大 16 サイクル、治験責任医師が選択した化学療法群に割り付けられた被験者は対照治療（メトトレキサート又はベキサロテン）を最大 48 週間投与された。

2.7.6.1.1.6 評価項目及び評価基準

［有効性］

主要評価項目

・ORR4 を達成した被験者の割合（IRF 評価）

治験責任医師による mSWAT を用いた皮膚評価、IRF によるリンパ節及び内臓の画像評価、及び IRF における循環セザリー細胞の検出（MF 被験者のみ）で構成される GRS を用いて判定する。

重要な副次評価項目

・CR を達成した被験者の割合（CR 率）

・PFS

・Skindex-29 質問票（症状ドメイン）の変化

その他の副次的評価項目

・DOR

・皮膚奏効期間

・EFS

［薬物動態］

・本剤及び全抗体（TAb）の血清中濃度及び MMAE の血漿中濃度

・免疫原性評価

［安全性］

・NCI CTCAE 第 4.03 版に基づく有害事象、重篤な有害事象及び臨床検査値の評価

［患者報告アウトカムと医療経済］

・Skindex-29、EQ-5D-3L 及び FACT-G 質問票による QOL 評価

2.7.6.1.1.7 統計手法

有効性、薬物動態及び安全性評価項目の解析に用いた解析対象集団は以下のとおり。

・全登録被験者集団は、本試験でランダム化された全被験者と定義した。ランダム化された投与群と実際に受けた治療が異なる場合、ランダム化された投与群に従って解析された。

・Intent-to-treat（ITT）解析対象集団は、Ventana CD30（Ber-H2）アッセイにより CD30 陽性と特定され、各投与群にランダム化された全被験者と定義した。ランダム化された投与群と実際に受けた治療が異なる場合、ランダム化された投与群に従って解析された。

・Per protocol（PP）解析対象集団は、ITT 解析対象集団のうち試験治療の投与を受け、メディカルモニターにより重大な治験実施計画書違反がなかったと判断された被験者（除外すべき被験者はデータベースロック前に判断した）による部分集団と定義した。PP 解析対象集団の全被験者を、実際に受けた治療に従って解析した。

・奏効評価可能集団は、ITT 解析対象集団のうち、ベースライン時に測定可能病変を有し、ベースライン後の奏効評価を 1 回以上実施した被験者による部分集団と定義した。ベースライン後の最初の皮膚奏効評価より前に新たな抗腫瘍療法を開始した被験者は、奏効評価可能集団から除外した。

・安全性解析対象集団は、試験治療の投与を 1 回以上受けた全ての被験者と定義した。安全性解析対象集団の全被験者を、実際に受けた治療に従って解析した。

・薬物動態解析対象集団は、薬物動態パラメータを推定するための十分な試験治療の投与を受け、十分な薬物動態データを有する被験者と定義した。

・薬力学解析対象集団は、薬力学パラメータを測定するための十分な試験治療の投与を受け、十分な薬力学データ〔バイオマーカー、皮膚 T 細胞誘因ケモカイン（CTACK）、胸腺及び活性化調節ケモカイン（TARC）又は sCD30 のうち少なくとも 1 つ〕を有する被験者と定義した。

［有効性］

主要評価項目及び重要な副次評価項目の主解析は、ITT 解析対象集団を用いて実施した。さらに、全登録被験者集団、PP 解析対象集団及び奏効評価可能集団を用いて、有効性評価項目の感度分析を実施した。

ORR4 の投与群間差の検定には、ベースライン時の診断疾患（MF 又は pcALCL）を層別因子とした Cochran-Mantel-Haenszel 検定を用いた。ORR4 の投与群間差の 95%信頼区間（CI）も算出した。

ORR4（IRF 判定）の主解析は、ITT 解析対象集団を対象に実施した。感度分析は、皮膚 T 細胞リンパ腫（CTCL）患者を対象としたロミデプシンのピボタル多施設共同試験で使用された客観的な原疾患の治療効果判定基準（OPDREC）を用いて実施した。また、治験責任医師判定による GRS 評価に基づき ORR 及び ORR4 の感度分析を実施した。さらに、直近の CT

スキャンや血液を評価した GRS 評価に基づく主解析結果の頑健性を評価するための感度分析も実施した。ORR4 の部分集団解析は、ベースライン時の診断疾患、ECOG performance staus、性別、年齢、地域、人種、対照薬、ベースライン時の病変（追加解析）及び mSWAT に基づくベースライン時の皮膚腫瘤スコア（追加解析）の各部分集団について、各投与群に 10 例以上の被験者がいる場合、必要に応じて実施した。

主要評価項目と重要な副次評価項目の検定は固定逐次検定手順を用いて行った。主要評価項目が統計学的に有意であった場合のみ、重要な副次評価項目を重み付き Holm 法を用いて検定した。ベースライン時の診断疾患（MF 又は pcALCL）を層別因子とした Cochran-Mantel-Haenszel 検定を用いて投与群間の CR 率を比較し、CR 率の投与群間差の 95% CI を算出した。

PFS は、ランダム化から疾患進行又は死亡（原因を問わない）までの期間と定義した。EFS は、ランダム化から疾患進行、治験薬の投与中止又は死亡（原因を問わない）を含む治療不成功までの期間と定義した。奏効が確認された被験者の DOR は、最初の奏効が記録された時点から疾患進行までの期間と定義した。皮膚奏効期間は、最初の皮膚の奏効から皮膚の疾患進行までの期間と定義した。Time-to-event 関連の有効性評価項目（PFS、EFS、DOR 及び皮膚奏効期間）は、Kaplan-Meier 法を用いて推定した。投与群間の PFS 及び EFS を層別ログランク検定を用いて比較し、PFS 及び EFS のハザード比及びその 95% CI を層別 Cox 回帰モデルを用いて推定した。

［薬物動態］

抗体薬物複合体（ADC）、TAb 及び MMAE の薬物動態は、選択基準に合致し、試験治療を受け、評価可能な薬物動態データが得られた全被験者の血清及び血漿中濃度対時間から算出した。ADC、TAb 及び MMAE の最高血漿／血清中濃度、最高血漿／血清中濃度到達時間及びトラフ濃度は、測定された濃度データから算出した。なお、母集団薬物動態解析の結果は、母集団薬物動態解析報告書で別途報告した。

［安全性］

安全性は、TEAE の発現頻度、有害事象の重症度及び種類、並びにバイタルサイン、ECOG performance status 及び臨床検査値のベースラインからの変化によって評価した。治験薬への曝露及び中止理由を集計した。有害事象は、ICH 国際医薬用語集（MedDRA）第 19.0 版を用いて読み替え、TEAE（全ての TEAE 及び治験薬との因果関係が否定できない TEAE）、Grade 3 以上の TEAE（全ての TEAE 及び治験薬との因果関係が否定できない TEAE）、重篤な TEAE 及び治験薬の投与中止に至った TEAE 等を集計した。

全ての規定時の臨床検査（血液学的検査及び血液生化学的検査）とバイタルサインの実測値及びベースラインからの変化量の記述統計量を経時的に示した。ECOG performance status 及びそのベースラインからの変化量を要約し、投与群別に集計した。治験責任医師による心電図モニタリングの評価（正常、臨床的に意味のある異常又は臨床的に意味のない異常）は、規定外又は再検査された測定値を含めて一覧表に提示した。

2.7.6.1.2 試験成績（最終解析）

治験総括報告書のための最終解析結果を要約する（データカットオフ日：2016 年 5 月 31 日）。最終解析は、最終被験者登録の 10 ヵ月後に計画、実施した。

2.7.6.1.2.1 被験者の内訳

被験者 131 例が登録され、本剤群に 66 例、治験責任医師が選択した化学療法群に 65 例がランダムに割り付けられた。診断疾患の内訳は、MF が 100 例、pcALCL が 31 例であった。

本剤群の 23 例（35%）及び治験責任医師が選択した化学療法群の 5 例（8%）が、治験実施計画書で規定された最大投与（16 サイクル／48 週間）を完遂した。治験薬投与を中止した理由の内訳は、疾患進行が本剤群 13 例（20%）及び治験責任医師が選択した化学療法群 40 例（62%）、有害事象が本剤群 17 例（26%）及び治験責任医師が選択した化学療法群 5 例（8%）であった。最終解析時点で、本剤群で 3 例（5%）が治験薬の投与を継続していた。治験責任医師が選択した化学療法群は全例が投与を完了又は中止していた。

解析対象集団は、全登録被験者 131 例、ITT 解析対象集団 128 例、安全性解析対象集団 128 例、PP 解析対象集団 117 例、奏効評価可能集団 119 例、薬物動態解析対象集団 66 例、薬力学解析対象集団 125 例であった。

2.7.6.1.2.2 ベースラインの人口統計学的特性及びその他の関連特性

本試験の被験者の人口統計学的特性は投与群間で概ね均衡が取れていた。ITT 解析対象集団（128 例）のうち 70 例（55%）が男性、109 例（85%）が白人であった。被験者の年齢の中央値は 60.0 歳（範囲：22～83 歳）であった。

ベースライン時の疾患特性のうち、ECOG performance status 及び試験登録時の骨髄病変は、投与群間で類似していた。ITT 解析対象集団（128 例）のうち 123 例（96%）は ECOG performance status が 0（70%）又は 1（27%）であり、124 例（97%）で試験登録時の骨髄病変は確認されなかった。

本剤群の被験者は、治験責任医師が選択した化学療法群の被験者と比較して、疾患負荷（腫瘍量）が大きく、病期は進行しており、内臓病変が多く、初回診断から時間が経過していた。pcALCL 被験者のうちステージ T3 の被験者は、本剤群 12 例（75%）及び治験責任医師が選択した化学療法群 6 例（40%）（以降同順）、MF 被験者のうちステージ IV B の被験者は、それぞれ 7 例（15%）及び 0 例（0%）、pcALCL 被験者のうち内臓転移を有する M1 の被験者は、それぞれ 4 例（25%）及び 1 例（7%）であった。また、ITT 解析対象集団の初回診断からの時間の中央値は、それぞれ 42.17 ヵ月及び 36.99 ヵ月であった。

2.7.6.1.2.3 有効性の評価

ORR4（IRF 判定）を達成した被験者は、本剤群 36 例（56.3%）及び治験責任医師が選択した化学療法群 8 例（12.5%）、ORR4 の投与群間差は 43.8%であり、投与群間に統計学的に有意な差がみられた（p<0.001）。CR（IRF 判定）を達成した被験者は、本剤群 10 例（15.6%）及び治験責任医師が選択した化学療法群 1 例（1.6%）、リスク差は 14.1%（正規近似法による 95% CI：[4.7, 23.5]）であり、投与群間に統計学的に有意な差がみられた（p=0.0046、調整後 p=0.0046）。PFS（IRF 判定）の中央値は、本剤群 16.7 ヵ月及び治験責任医師が選択した

化学療法群 3.5 ヵ月であり、投与群間に統計学的に有意な差がみられ（p<0.001、調整後 p<0.001）、ハザード比は 0.270 であった（95% CI：[0.169, 0.430]）。Skindex-29（症状ドメイン）スコアのベースラインからの最大変化量の平均値は、本剤群−27.96 ポイント（標準偏差：26.877）及び治験責任医師が選択した化学療法群 8.62 ポイント（標準偏差：17.013）、投与群間差の推定値は-18.9 ポイント（95% CI：[-26.6, -11.2]）であり、投与群間に統計学的に有意な差がみられた（p<0.001、調整後 p<0.001）。

2.7.6.1.2.4 薬物動態の評価

薬物動態解析の結果は、本剤の既知の薬物動態特性と一致しており、MF 被験者と pcALCL 被験者の薬物動態に違いは示唆されなかった。

2.7.6.1.2.5 薬力学／バイオマーカーの評価

ベースラインの CD30 発現の中央値は各投与群で同様であった（本剤群 32.50、治験責任医師が選択した化学療法群 31.25）。サイクル 3 の Day 21 及び EOT 時に両投与群で CD30 発現の減少が認められた。CD30 発現のベースラインからの変化量の中央値は、サイクル 3 の Day 21 は本剤群-20.50、治験責任医師が選択した化学療法群-11.58 であり、EOT 時は本剤群-17.50、治験責任医師が選択した化学療法群-13.25 であった。

ベースライン時の sCD30 濃度は被験者間で大きなばらつきがみられたが、中央値は両投与群でほぼ同程度であった。sCD30 濃度は、いずれの投与群でも投与期間中又は EOT 時に顕著な変化は認められなかった。

ベースライン時の TARC 濃度及び CTACK 濃度は被験者間で大きなばらつきがみられたが、ベースライン時の TARC 濃度及び CTACK 濃度は両投与群で同程度であった。TARC 濃度は投与期間中に低下した。CTACK 濃度は本剤群では経時的に低下し、治験責任医師が選択した化学療法群では経時的に増加した。投与群間に経時的な顕著な差は認められなかった。

2.7.6.1.2.6 免疫原性の評価

安全性解析対象集団において、本剤群の 60 例（91%）で免疫原性の評価が可能であった〔MF 被験者 46 例（92%）及び pcALCL 被験者 14 例（88%）〕。MF 被験者のうち 42 例（84%）はベースライン時に抗薬物抗体（ADA）陰性であり、42 例中 19 例が本剤投与後に ADA を発現した。pcALCL 被験者 14 例全例はいずれもベースライン時に ADA 陰性であり、14 例中 6 例が本剤投与後に ADA を発現した。安全性解析対象集団における ADA 陽性率は 42%（60 例中 28 例）であり、そのうち 16 例（24%）は一時的 ADA 陽性であり、23 例（35%）は抗体価が低値（25 以下）であった。ADA 発現の有無は、有効性又は安全性に明らかな影響を及ぼさなかった。

2.7.6.1.2.7 安全性の評価

TEAE 全般の発現頻度及び重症度は、投与群間で同様であった。安全性解析対象集団 128 例のうち 119 例〔93%：本剤群 63 例（95%）、治験責任医師が選択した化学療法群 56 例（90%）〕が 1 件以上の TEAE を発現した。重篤な TEAE（因果関係を問わない）及び治験薬との因果

関係が否定できない Grade 3 以上の TEAE は、いずれも両投与群の被験者の 29%で報告された〔本剤群 19 例（29%）、治験責任医師が選択した化学療法群 18 例（29%）〕。

本剤群で報告された主な TEAE は、末梢性感覚ニューロパチー〔30 例（45%）〕、悪心〔24 例（36%）〕、疲労及び下痢〔各 19 例（29%）〕、発熱、そう痒症及び嘔吐〔各 11 例（17%）〕であった。治験責任医師が選択した化学療法群で報告された主な TEAE は、疲労〔17 例（27%）〕、発熱及び高トリグリセリド血症〔各 11 例（18%）〕、悪心及びそう痒症〔各 8 例（13%）〕であった。

各投与群で報告された死亡例数は同程度であった〔本剤群 16 例（24%）及び治験責任医師が選択した化学療法群 14 例（23%）〕。本剤群では、本剤の最終投与後 30 日以内に 4 例が死亡し、そのうち 1 例は、治験責任医師により内臓リンパ腫転移部位に対する本剤の治療効果に起因するものとされた。残りの 12 例（75%）は、本剤の最終投与後 120 日以降に死亡した。

本剤の因果関係が否定できない試験期間中（本剤の最終投与後 30 日以内）の死亡の叙述を 2.7.6.1.5 に示した。

重篤な TEAE は、本剤群 19 例（29%）及び治験責任医師が選択した化学療法群 18 例（29%）に計 60 件発現した。本剤群の 2 例以上に報告された重篤な TEAE は、蜂巣炎及び発熱〔各 2 例（3%）〕であった。治験責任医師が選択した化学療法群の 2 例以上に報告された重篤な TEAE は、発熱〔4 例（6%）〕及び敗血症〔3 例（5%）〕であった。因果関係の否定できない重篤な TEAE は、本剤群 9 例（14%）及び治験責任医師が選択した化学療法群 3 例（5%）に計 20 件発現した。各投与群で 2 例以上に報告された因果関係の否定できない重篤な TEAE はなかった。

重篤な有害事象の一覧を 2.7.6.1.6 に示した。

治験薬の投与中止に至った TEAE は、21 例〔本剤群 16 例（24%）及び治験責任医師が選択した化学療法群 5 例（8%）〕で発現した。本剤群では、9 例（14%）が MedDRA 標準検索式（SMQ）に基づく末梢性ニューロパチー関連事象〔以下、末梢性ニューロパチー（SMQ）〕により治験薬の投与を中止した〔末梢性感覚ニューロパチー5 例（8%）、末梢性ニューロパチー2 例（3%）、末梢性運動ニューロパチー及び感覚鈍麻各 1 例（2%）〕。その他の治験薬の投与中止に至った TEAE は、いずれの投与群でも 1 例のみに報告された。

末梢性ニューロパチー（SMQ）は、本剤群 44 例（67%）及び治験責任医師が選択した化学療法群 4 例（6%）で報告された。本剤群で報告された主な末梢性ニューロパチー（SMQ）は末梢性感覚ニューロパチー〔30 例（45%）〕であった。治験責任医師が選択した化学療法群で報告された末梢性ニューロパチー（SMQ）は筋力低下、神経痛、錯感覚及び末梢性感覚ニューロパチー〔各 1 例（2%）〕であった。末梢性ニューロパチー（SMQ）の発現頻度は、試験治療への曝露量の増加と関連していた。本剤群で末梢性ニューロパチー（SMQ）のために本剤の投与を中止した被験者 9 例の曝露量の中央値は 11 サイクルであった（範囲：4～15 サイクル）。本剤群で末梢性ニューロパチー（SMQ）を発現した被験者のうち、36 例（82%）

で発現した事象が最終来院時点で回復又は改善していた。最終来院時点で未回復であった末梢性ニューロパチー（SMQ）は全て Grade 1 又は Grade 2 であった。

本剤の投与を受けた 9 例（14%）に注入に伴う反応が認められた。そのうち 2 件は Grade 3 であり（蕁麻疹及び薬物過敏症）、Grade 3 の蕁麻疹は治験薬の投与中止に至った。いずれの注入に伴う反応も重篤な有害事象とは判断されなかった。

本試験では、本剤を投与した被験者でまれに報告される肺毒性を示唆する有害事象、スティーブンス・ジョンソン症候群、腫瘍崩壊症候群、進行性多巣性白質脳症などは報告されなかった。

2.7.6.1.3 試験成績（試験終了時の更新）

治験総括報告書補遺で報告した試験終了時の有効性及びその他の試験評価項目の更新結果を要約する（データカットオフ日：2018 年 9 月 28 日）。この解析結果の更新は、全ての被験者が約 24 ヵ月間の追跡調査を完了したのちに実施した。

2.7.6.1.3.1 有効性の評価

ORR4（IRF 判定）を達成した被験者は、本剤群 35 例（54.7%）及び治験責任医師が選択した化学療法群 8 例（12.5%）、ORR4 の投与群間差は 42.2%であり、投与群間に統計学的に有意な差がみられた（p<0.001）。CR（IRF 判定）を達成した被験者は、本剤群 11 例（17.2%）及び治験責任医師が選択した化学療法群 1 例（1.6%）、リスク差は 15.6%であり、投与群間に統計学的に有意な差がみられた（p=0.002、調整後 p=0.002）。PFS（IRF 判定）の中央値は、本剤群 16.7 ヵ月及び治験責任医師が選択した化学療法群 3.5 ヵ月であり、統計学的に有意な差がみられ（p<0.001、調整後 p<0.001）、ハザード比は 0.378 であった（95% CI：[0.247, 0.577]）。Skindex-29（症状ドメイン）スコアのベースラインからの最大変化量の平均値は、本剤群-28.08 ポイント（標準偏差：26.863）及び治験責任医師が選択した化学療法群-8.62 ポイント（標準偏差：17.013）、投与群間差の推定値は-19.0 ポイント（95% CI：[-26.7, -11.4]）であり、投与群間に統計学的に有意な差がみられた（p<0.001、調整後 p<0.001）。

2.7.6.1.3.2 末梢性ニューロパチーの追跡調査

治験実施計画書で未回復の末梢性ニューロパチー（SMQ）を有する被験者を回復又は試験が終了するまで追跡することを規定していたため、最終データを用いて末梢性ニューロパチー（SMQ）の最終評価を行った。

最終追跡調査の時点で、本剤群で末梢性ニューロパチー（SMQ）が発現した 44 例のうち 38 例（86%）で回復又は改善が認められ、その内訳は全事象の回復が 26 例（59%）及び改善が 12 例（27%）であった。

本剤群で発現した末梢性ニューロパチー（SMQ）が回復又は改善するまでの期間の中央値は 29.0 週間であった。このうち、Grade 2 の末梢性ニューロパチー（SMQ）が回復するまでの期間の中央値は 37.0 週間、改善までの期間の中央値は 23.0 週間であった。最終追跡調査の時点で、18 例では末梢性ニューロパチー（SMQ）が未回復であったが、いずれも Grade 1 又は Grade 2 であり、Grade 3 の末梢性ニューロパチー（SMQ）は報告されなかった。

2.7.6.1.4 結論

- CD30 陽性 CTCL 患者において、本剤は治験責任医師が選択した化学療法と比較して主要評価項目である ORR4（IRF 判定）で統計学的に有意な改善をもたらした（56.3%対 12.5%、p<0.001）。
- 重要な副次評価項目〔CR 率（IRF 判定）、PFS（IRF 判定）及び Skindex-29（症状ドメイン）スコアの〕はいずれも本剤のベネフィットを支持しており、統計学的に有意な改善を示した。
- 本剤による ORR4 の統計学的に有意な改善は、全ての解析対象集団で一貫していた。また、ORR4 の OPDREC を用いた感度分析及び部分集団解析の結果も、同様に一貫していた。
- 重要な副次評価項目である PFS の感度解析及び部分集団解析では、全ての感度分析及び部分集団で本剤のベネフィットが示された。
- 本試験で確認された本剤の安全性プロファイルは、概して既存の添付文書情報及び既知の安全性プロファイルと一致していた。最終投与後 30 日以内に 4 例の死亡が認められ、そのうち 1 例は、治験責任医師により、内臓リンパ腫転移部位に対する本剤の治療効果に起因するものであり本剤との因果関係が否定できないと判定された。
- 薬物動態の結果は、本剤の既知の薬物動態特性と一致しており、pcALCL 患者と MF 患者間の薬物動態の差及び反復投与時の経時的な ADC、TAb 又は MMAE の薬物動態の変化は示唆されなかった。
- 本試験では、ADA 発現の有無は有効性又は安全性に明らかな影響を及ぼさなかった。
- 試験終了時に更新した有効性評価項目の結果は、最終解析時の結果を支持していた。また、末梢性ニューロパチー関連事象の回復又は改善に関する更新結果も、既存の知見を支持していた。

2.7.6.1.5 付録 1：本剤との因果関係が否定できない試験期間中の死亡の叙述

本試験で報告された本剤との因果関係が否定できない試験期間中（本剤の最終投与後 30 日以内）の死亡の叙述を表 2.7.6.1-1 に、当該被験者で発現した有害事象を表 2.7.6.1-2 に示した。なお、全ての死亡及び重篤な有害事象の叙述は、C25001 試験　治験総括報告書（5.3.5.1-1）に記載している。

表 2.7.6.1-1　本剤との因果関係が否定できない試験期間中の死亡の叙述（1）

症例番号	[redacted]	人種	白人
年齢／性別	5[redacted] 歳／女性	試験治療	ブレンツキシマブ　ベドチン（SGN-35）
重篤な有害事象（MedDRA 基本語）／重症度／転帰	膵炎／Grade 4／回復（後遺症あり） 腸管穿孔／Grade 4／回復 多臓器機能不全症候群／Grade 5／死亡		
原疾患／病歴	原発性皮膚未分化大細胞リンパ腫／該当せず		
併用薬	スルファメトキサゾール・トリメトプリム、リネゾリド、メロペネム、エノキサパリンナトリウム、アミカシン硫酸塩、ダプトマイシン、フルコナゾール、anidulafungin、ピペラシリンナトリウム・タゾバクタムナトリウム、ペチジン塩酸塩、メタミゾール（スルピリン）、アセトアミノフェン、フロセミド、ヒドロコルチゾンリン酸エステルナトリウム、モルヒネ塩酸塩、ロラゼパム、ナイスタチン、フェンタニル、コリスチン硫酸塩		
経過・処置	20[redacted] 年 [redacted] 月 [redacted] 日（Day -188）：原発性皮膚未分化大細胞リンパ腫と診断された。前治療はメトトレキサート及びプレドニゾンであった（*診断3ヵ月後から *診断6ヵ月後）。 20[redacted] 年 [redacted] 月 [redacted] 日（Day -55）：コンピュータ断層撮影（CT）スキャンの結果、肝臓、膵臓、腸に結節は認められず、皮膚病変のみが認められた。同日の臨床検査では、アラニンアミノトランスフェラーゼ 91（正常値 49 未満）、アスパラギン酸アミノトランスフェラーゼ 88（正常値 37 未満）、アルカリホスファターゼ 63（正常値 136 未満）及びアミラーゼ 90（正常値 118 未満）（単位未報告）であった。 手術歴、病歴及び併用薬は報告されなかった。被験者は高脂血症を併発していた（注：臨床試験では合併症の報告なし）。被験者に既知のアレルギーはなかった。 20[redacted] 年 [redacted] 月 [redacted] 日（Day -4）：陽電子放出断層撮影（PET／CT）により、内臓転移（肺及び肝臓に多発性転移、膵頭部及び回腸に単発性転移）及び左腋窩リンパ節転移が認められた。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 1）：臨床検査（投与前）の結果、アミラーゼ 76 U/L（正常値範囲：28～100）及びリパーゼ 57.5 U/L（正常値範囲：16～63.0）であった。同日、ブレンツキシマブ　ベドチン（21 日ごとに 1.8 mg/m^2 の静脈内投与）の投与を開始した（実際の投与量は確認中）。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 8）：腹痛のため救急治療室を受診し、その後入院した。主に恥骨及び臍部で変動を伴う潜行性の腹痛を呈し、経口メタミゾールによる鎮痛に抵抗性を示した。疲労及び下痢（1 日 1～2 回の軟便）も報告されたが、下痢は正常色で病的兆候はなく、悪心及び胃内容物の嘔吐を伴っていた。 同日の臨床検査では、ビリルビン 3.76 mg/dL（0～1.1）、アミラーゼ 1182 IU（0～100）、クロール 103 mEq/L、クレアチニン 0.9 mg/dL、カリウム 3.88 mEq/L、ナトリウム 134 mEq/L、C 反応性蛋白 11.9 mg/dL、ヘマトクリット 28.9%、ヘモグロビン 9.6 g/dL、好中球数 1.9×1000/μL、血小板数 124×1000/μL、赤血球数 3.3×1000^2/μL、及び白血球数 2.2×1000/μL であった。被験者は酸素飽和度 88%で呼吸苦を呈していた。バイタルサインは、心拍数 91 bpm、体温 36.1°C、血圧 116/68 であった。 臨床検査の結果は肝機能検査値の変化と一致し、アミラーゼ増加は膵炎の発現と一致していた。 胸部 X 線写真により白色の陰影を認めた。クレアチニン値は入院時には正常であったが、20[redacted] 年 [redacted] 月 [redacted] 日（Day 9）には 1.16 mg/dL 及び 1.26 mg/dL に上昇した。 臨床的には、ブレンツキシマブ　ベドチン投与による薬剤誘発性と考えられる急性		

表 2.7.6.1-1　本剤との因果関係が否定できない試験期間中の死亡の叙述（1）（続き）

経過・処置（続き）	膵炎、細胞溶解性胆汁うっ滞性混合パターンの肝機能検査値の変化（薬剤誘発性又は一次的なリンパ増殖過程による肝変化）及び軽度の無症候性低ナトリウム血症と判断された。肝機能検査値の変化は薬物毒性による可能性が最も高かったが、非ホジキンリンパ腫（NHL）の肝浸潤の影響も否定できなかった。 膵頭部のリンパ腫の結節の他に小腸にもリンパ腫の結節が認められた。ブレンツキシマブ　ベドチンの投与により、皮膚病変は劇的に改善し、大部分の病変の壊死が認められた。小病変は消失し、残存斑が残るのみであった。 20[redacted]年[redacted]月[redacted]日（Day 9）：リパーゼは 2083 IU（正常値範囲 60 未満）であった。シプロフロキサシン 500 mg/12h 及びピペラシリン･タゾバクタム 4 g/6h 投与による抗生物質療法を開始した（骨髄毒性の可能性によりトリメトプリム・スルファメトキサゾールによる治療は中断した）。同日、便培養検査により、クロストリジウム・ディフィシル毒素陰性及び正常細菌叢が確認された。 20[redacted]年[redacted]月[redacted]日（Day 11）：アミラーゼは 439 IU、リパーゼは 384 IU（正常値範囲 60 未満）であった。アミラーゼ及びリパーゼは、典型的な膵炎ではまれな非常に急速な低下を示した。リパーゼの値は 220 前後を維持した（正常値範囲 100 未満）。CT スキャンでは、膵臓の典型的な浮腫は認められなかった。同日、治験責任医師により初めて下血が認められた。 同日、経直腸の鮮血を伴う黒色便が認められた。上部内視鏡検査を実施したが、活動性出血及び残血は認められなかった。 20[redacted]年[redacted]月[redacted]日（Day 12）：内視鏡検査及び CT スキャンにより腸管穿孔が認められ、被験者は外科的処置を受けた。 大腸内視鏡検査及び回腸内視鏡検査により回盲弁を介した凝血塊の排出が認められた。同日、CT スキャンにより、得られた所見は下腹部に局所異所性ガス及び鏡面像を伴う小腸穿孔と一致することが示唆された。膵臓が腫大し、二次性の膵炎や腫瘍浸潤である可能性があり、閉塞によると考えられる膵頸部、体部、尾部の主膵管（Wirsung 管）の拡張がみられた。 入院中、腹部超音波検査では結石症、胆嚢炎、胆管拡張の所見は認められなかった。超音波検査で胆嚢炎、胆管炎及び胆管閉塞の所見が認められなかったことから、この時点では抗生物質療法は適応とされなかった。高熱の場合に備え、血液培養用の検体を 2 つ採取し、抗生物質療法を開始することとした。灌流療法により血圧が 125/70 mmHg となり、排尿が認められた。 20[redacted]年[redacted]月[redacted]日（Day 16）：血液培養でオキサシリン耐性コアグラーゼ陰性ブドウ球菌が陽性となった（2 検体中 1 検体）。 20[redacted]年[redacted]月[redacted]日（Day 20）：腹部及び骨盤の CT スキャンにより、血管障害の初期徴候を伴う腸閉塞及び下腹部の内側に位置する回腸－回腸吻合の管腔径の変化が認められた。管腔内血栓も認められた。小さな脾梗塞も認められた。 20[redacted]年[redacted]月[redacted]日（Day 21）：血液凝固による小腸閉塞が発現した。同日、新たな小腸穿孔に対して 2 回目の外科的処置を行った。 20[redacted]年[redacted]月[redacted]日（Day 23）：2 回目の手術の病理組織学的報告では、大型で著しく不整なリンパ球の腫瘍増殖が認められ、一部はリード・シュテルンベルグ様の外観を呈していた。多くはアポトーシスを示し、有糸分裂像が多数認められた。悪性細胞は免疫染色で CD4、CD30、パーフォリン及びグランザイム陽性であった。増殖指数は 90%であった。 20[redacted]年[redacted]月[redacted]日（Day 26）：腹部と骨盤の CT スキャンを実施し、20[redacted]年[redacted]月[redacted]日（Day 20）に実施された CT スキャンの結果と比較した。左側腹部に位置する空腸の腹壁が長い範囲で不規則となっており、遊離液の貯留がみられたことから、左側腹部の微小穿孔の可能性が示唆された。結腸の肥厚は大腸炎に関連していると考えられた。膵尾部が肥大し、周囲の液体貯留もみられたことから、急性膵炎と診断した。

表 2.7.6.1-1　本剤との因果関係が否定できない試験期間中の死亡の叙述（1）（続き）

経過・処置（続き）	20[redacted] 年 [redacted] 月 [redacted] 日（Day 29）：臨床検査の結果、アミラーゼ 24 IU/L（0～100）、ビリルビン 5.25 mg/dL（0～1.1）、クロール 102 mEq/L、クレアチニン 0.92 mg/dL、カリウム 4.46 mEq/L、ナトリウム 137 mEq/L、C 反応性蛋白 22.78 mg/dL、ヘマトクリット 32.2%、ヘモグロビン 10.8 g/dL、絶対好中球数 2.6×1000/μL、血小板数 17×1000/μL、赤血球数 3.67×1000^2/μL 及び白血球数 5.8×1000/μL であった。 2 回目の手術後、血行動態が不安定な状態が持続し、昇圧薬による補助が必要となった。鎮静状態で人工呼吸器を引き続き使用し、持続的静静脈血液濾過による腎代替療法も継続していた。電気生理学的な不安定性により発作性心房細動が発現したため、アミオダロンを静脈内投与して管理した。乳酸アシドーシスを伴う難治性ショックを発現した。被験者の家族と相談のうえ、延命処置は最小限とし、適切な緩和処置を行うこととした。20[redacted] 年 [redacted] 月 [redacted] 日（Day 29）、被験者は死亡した。死因は多臓器不全、腸管穿孔及び膵炎であった。剖検は実施されなかった。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 44）：病理組織検査の報告によると、小腸の切除域の粘膜はほぼ保たれていたが、肉眼で分かる穿孔部では腸管壁全層に至る断裂があり、肉芽組織が正常組織と置換されていることが観察された。 治験責任医師により、膵炎の事象が致死性であったこと及び膵炎の炎症が血中酵素値により当初は改善したものの、腸管穿孔に伴って追加の合併症が発現したことが確認された。 また、治験責任医師により、膵炎及び腸管穿孔が、膵頭部に位置するリンパ腫結節に対するブレンツキシマブ　ベドチンの作用に続発するものであることが確認された。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 22）にブレンツキシマブ　ベドチンの投与中止が報告された。 治験責任医師により、膵炎、腸管穿孔及び多臓器不全はブレンツキシマブ　ベドチンと関連性ありと判断された。 以降の情報収集は予定していない。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 445）に受領した追加情報により症例経過（narrative）を修正した。追加情報：報告者の詳細、臨床経過、腸穿孔の入院確認、臨床検査。
治験責任医師及び治験依頼者の見解	治験依頼者の見解： 膵炎の事象は、一時的にブレンツキシマブ　ベドチン投与と関連しており、因果関係は否定できない。腸管穿孔と多臓器不全の事象との因果関係を評価するには情報が不足している。治験依頼者は、今後発現する同様の事象を引き続きモニタリングする。 治験責任医師の見解： 治験責任医師は、膵炎、腸管穿孔及び多臓器不全の事象はブレンツキシマブ　ベドチンと関連ありと判断した。

出典：C25001 試験　治験総括報告書　Table 14.4.2.2、Listing 16.2.4.1、Listing 16.2.4.3、Listing 16.2.4.4 及び Listing 16.2.8.9 並びに Section 15.3.3.1（CIOMS）

被験者の情報のうち、年齢／性別、人種、試験治療、重篤な有害事象／重症度／転帰、病歴及び併用薬は治験総括報告書の Listing を参照した。経過・処置並びに治験責任医師及び治験依頼者の見解は、治験総括報告書の Section 15.3.3.1（CIOMS）を参照した。

経過・処置の Study Day は、報告された日から Cycle 1 Day 1 の治験薬の初回投与日を引き、初回投与日以降の日付の場合は 1 を足して算出した（初回投与日を Day 1 とする）。

MedDRA/J 第 19.0 版を用いてコード化した。

表 2.7.6.1-2　本剤との因果関係が否定できない死亡の叙述（1）（当該被験者で報告された有害事象）

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Brentuximab Vedotin	[redacted] F/5[redacted]/White	Cycle 1 Day 1	1	8	Escherichia infection/大腸菌感染 [ESCHERICHIA COLI INFECTION (WOUND EXUDATE)]	Drug (or dose) discontinued permanently/ Concomitant medication administered	No	Grade 1	Resolved
		Cycle 1 Day 8	8	29	Pancreatitis/膵炎 [PANCREATITIS]*	Concomitant medication administered/ Concomitant procedure performed/ Discontinued from study	Yes	Grade 4	Resolved with sequelae
		Cycle 1 Day 11	11	29	Melaena/メレナ [MELENA]	Concomitant procedure performed	Yes	Grade 4	Resolved
		Cycle 1 Day 12	12	29	Intestinal perforation/腸管穿孔 [INTESTINAL PERFORATION]*	Concomitant procedure performed/ Discontinued from study	Yes	Grade 4	Resolved
		Cycle 1 Day 16	16	23	Oropharyngeal candidiasis/中咽頭カンジダ症 [OROPHARYNGEAL CANDIDIASIS]	Concomitant medication administered	No	Grade 1	Resolved
		Cycle 1 Day 22	22	-	Klebsiella infection/クレブシエラ感染 [INGUINAL KLEBIELLA PNEUMONIAE INFECTION]	Concomitant medication administered	No	Grade 1	Unresolved
		Cycle 1 Day 29	29	29	Multiple organ dysfunction syndrome/ 多臓器機能不全症候群 [MULTIORGANIC FAILURE]*	Discontinued from study	Yes	Grade 5	Death

出典：C25001 試験　治験総括報告書　Listing 16.2.4.1、Listing 16.2.5.2 及び Listing 16.2.7.1

AE：有害事象、F：女性、MedDRA：ICH 国際医薬用語集、PT：基本語、-：未消失、*：重篤な有害事象

有害事象は MedDRA/J 第 19.0 版を用いてコード化した。

(a) 有害事象の発現日（Study Day）は、有害事象の発現日から Cycle 1 Day 1 の治験薬の初回投与日を引き、1 を足して算出した。
(b) 有害事象の消失日（Study Day）は、有害事象の消失日から Cycle 1 Day 1 の治験薬の初回投与日を引き、1 を足して算出した。

2.7.6.1.6 付録 2：重篤な有害事象の一覧

本試験で報告された重篤な有害事象（試験期間中の死亡を含む）の一覧を表 2.7.6.1-3 に示した。

表 2.7.6.1-3　重篤な有害事象の一覧

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Brentuximab Vedotin	[redacted] M/6[redacted]/White	Cycle 1 Day 22	22	39	Rash maculo-papular/斑状丘疹状皮疹 [EXTENSIVE ERYTHEMATOUS MACULOPAPULAR RASH PREDOMINANTLY AFFECTING TRUNK AND LIMBS]	Dose delayed/ Concomitant medication administered/ Concomitant procedure performed	Yes	Grade 3	Resolved
		Cycle 4 Day 16	87	107	Drug eruption/薬疹 [DRUG INDUCED BULLOUS ERUPTION]	Drug (or dose) discontinued permanently/ Concomitant medication administered	Yes	Grade 4	Resolved
Brentuximab Vedotin	[redacted] F/3[redacted]/White	Cycle 3 Day 18	68	74	Lower respiratory tract infection/下気道感染 [CHEST INFECTION]	Dose delayed/ Concomitant medication administered	No	Grade 3	Resolved
		Cycle 3 Day 33	83	92	Stress/ストレス [EMOTIONAL STRESS]	Concomitant medication administered	No	Grade 2	Resolved
		Cycle 4 Day 1	86	89	Hypotension/低血圧 [HYPOTENSION]	Concomitant medication administered	No	Grade 3	Resolved
		Cycle 4 Day 1	86	89	Pyrexia/発熱 [FEVER]	Concomitant medication administered	No	Grade 1	Resolved
		Cycle 4 Day 17	102	112	Cellulitis/蜂巣炎 [CELLULITIS]	Dose delayed/ Concomitant medication administered	No	Grade 3	Resolved

表 2.7.6.1-3　重篤な有害事象の一覧（続き）

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Brentuximab Vedotin	[redacted] F/3[redacted]/White	Cycle 1 Day 20	20	-	Haemolytic uraemic syndrome/溶血性尿毒症症候群 [HAEMOLYTIC URAEMIC SYNDROME]	Dose reduced/ Dose delayed/ Concomitant medication administered/ Concomitant procedure performed	No	Grade 4	Unresolved
		Cycle 2 Day 9	44	44	Sepsis/敗血症 [SEPSIS SKIN]	No action taken	No	Grade 5	Death
Brentuximab Vedotin	[redacted] M/7[redacted]/White	Cycle 14 Day 6	279	282	Urinary retention/尿閉 [URINARY RETENTION]	No action taken	No	Grade 3	Resolved with sequelae
		Cycle 14 Day 17	290	295	Urinary tract infection/尿路感染 [URINARY TRACT INFECTION]	Dose delayed/ Concomitant medication administered	No	Grade 3	Resolved
Brentuximab Vedotin	[redacted] F/6[redacted]/White	Cycle 7 Day 8	140	147	Sinusitis/副鼻腔炎 [SINUSITIS]	Concomitant medication administered	No	Grade 3	Resolved
Brentuximab Vedotin	[redacted] F/5[redacted]/Not Reported	Cycle 1 Day 3	3	29	Diarrhoea/下痢 [DIARRHEA]	No action taken	Yes	Grade 3	Resolved
		Cycle 1 Day 22	22	29	Hepatocellular injury/肝細胞損傷 [CYTOLYSIS OF LIVER CELL]	Dose reduced/ Dose delayed/ Concomitant medication administered	Yes	Grade 3	Resolved

表 2.7.6.1-3　重篤な有害事象の一覧（続き）

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Brentuximab Vedotin	[redacted] F/7[redacted]/White	Cycle 5 Day 3	89	96	General physical health deterioration/全身健康状態低下 [GENERAL PHYSICAL HEALTH DETERIORATION]	Concomitant procedure performed	Yes	Grade 3	Resolved
		Cycle 7 Day 2	136	178	Extravasation/溢出 [EXTRAVASATION]	Concomitant medication administered/ Concomitant procedure performed	No	Grade 3	Resolved
Brentuximab Vedotin	[redacted] M/8[redacted]/Not Reported	Cycle 5 Day 1	91	114	Hyperglycaemia/高血糖 [HYPERGLYCEMIA]	Concomitant medication administered	No	Grade 3	Resolved
Brentuximab Vedotin	[redacted] M/4[redacted]/Other	Cycle 16 Day 18	340	456	Demyelinating polyneuropathy/脱髄性多発ニューロパチー [SENSORIMOTOR POLYNEUROPATHY OF MIXED AXONAL DEMYELIATING TYPE]	No action taken	Yes	Grade 2	Resolved
Brentuximab Vedotin	[redacted] F/5[redacted]/White	Cycle 11 Day 5	292	364	Fracture/骨折 [BONE FRUCTURE]	Concomitant procedure performed	No	Grade 2	Resolved
Brentuximab Vedotin	[redacted] M/6[redacted]/White	Cycle 4 Day 6	69	69	Lymphoma/リンパ腫 [LYMPHOMA PROGRESSION]	Discontinued from study	No	Grade 5	Death
Brentuximab Vedotin	[redacted] F/5[redacted]/White	Cycle 1 Day 8	8	29	Pancreatitis/膵炎 [PANCREATITIS]	Concomitant medication administered/ Concomitant procedure performed/ Discontinued from study	Yes	Grade 4	Resolved with sequelae

表 2.7.6.1-3　重篤な有害事象の一覧（続き）

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Brentuximab Vedotin（続き）	[redacted] F/5[redacted]/White（続き）	Cycle 1 Day 12	12	29	Intestinal perforation/腸管穿孔 [INTESTINAL PERFORATION]	Concomitant procedure performed/ Discontinued from study	Yes	Grade 4	Resolved
		Cycle 1 Day 29	29	29	Multiple organ dysfunction syndrome/多臓器機能不全症候群 [MULTIORGANIC FAILURE]	Discontinued from study	Yes	Grade 5	Death
Brentuximab Vedotin	[redacted] M/5[redacted]/White	Cycle 3 Day 3	45	-	Neuropathy peripheral/末梢性ニューロパチー [TINGLING FINGERS (PERIPHERAL NEUROPATHY)]	Drug (or dose) discontinued permanently	Yes	Grade 3	Unresolved
Brentuximab Vedotin	[redacted] F/5[redacted]/White	Cycle 10 Day 12	267	289	Cellulitis/蜂巣炎 [CELLULITIS]	Dose held/ Concomitant medication administered	Yes	Grade 3	Resolved
Brentuximab Vedotin	[redacted] F/3[redacted]/Black or African American	Cycle 5 Day 15	98	103	Pyrexia/発熱 [FEVER]	Concomitant medication administered	No	Grade 2	Resolved
		Cycle 14 Day 20	289	291	Pyrexia/発熱 [FEVER]	No action taken	No	Grade 2	Resolved

表 2.7.6.1-3　重篤な有害事象の一覧（続き）

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Brentuximab Vedotin	[redacted] F/5[redacted]/Asian	Cycle 3 Day 12	59	103	Impetigo/膿痂疹 [IMPETIGO]	Drug (or dose) discontinued permanently/ Concomitant medication administered/ Concomitant procedure performed/ Discontinued from study	Yes	Grade 3	Resolved
Brentuximab Vedotin	[redacted] M/7[redacted]/White	Cycle 1 Day 15	15	15	Pulmonary embolism/肺塞栓症 [PULMONARY EMBOLISM]	Drug (or dose) discontinued permanently/ Discontinued from study	No	Grade 5	Death
Brentuximab Vedotin	[redacted] M/6[redacted]/White	Cycle 1 Day 9	9	18	Diverticulitis/憩室炎 [ACUTE DIVERTICULITIS]	Concomitant medication administered/ Concomitant procedure performed	Yes	Grade 3	Resolved
		Cycle 1 Day 21	21	22	Musculoskeletal chest pain/筋骨格系胸痛 [INTRACTABLE RIB PAIN]	Concomitant medication administered	Yes	Grade 3	Resolved
		Cycle 1 Day 21	21	22	Neck pain/頚部痛 [INTRACTABLE RIGHT NECK PAIN]	Concomitant medication administered	Yes	Grade 3	Resolved

表 2.7.6.1-3　重篤な有害事象の一覧（続き）

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Brentuximab Vedotin	[redacted] M/8[redacted]/White	Cycle 1 Day 28	28	46	Dizziness/浮動性めまい [DIZZINESS]	No action taken	No	Grade 3	Resolved
		Cycle 1 Day 28	28	46	Fatigue/疲労 [WORSENING FATIGUE]	No action taken	No	Grade 3	Resolved
Methotrexate	[redacted] F/8[redacted]/White	Cycle 1 Day 2	2	29	Dermatitis bullous/水疱性皮膚炎 [BULLOUS DERMATITIS]	Concomitant medication administered	Yes	Grade 2	Resolved
Methotrexate	[redacted] M/4[redacted]/White	Cycle 12 Day 17	248	250	Parotitis/耳下腺炎 [PAROTID GLAND INFECTION]	Concomitant medication administered	No	Grade 3	Resolved
Methotrexate	[redacted] F/6[redacted]/White	Cycle 4 Day 9	73	84	Neuralgia/神経痛 [NEUROPATHIC PAIN WORSENING]	Concomitant procedure performed	No	Grade 2	Resolved with sequelae
Methotrexate	[redacted] M/5[redacted]/White	Cycle 3 Day 26	69	87	Erysipelas/丹毒 [ERYSIPELAS LEFT CHEEK]	Concomitant medication administered	No	Grade 3	Resolved
Methotrexate	[redacted] F/4[redacted]/White	Cycle 2 Day 17	38	-	Skin infection/皮膚感染 [INCREASING INFILITRATION OF SKIN LESION WITH SIGN OF SUPERINFECTION]	Concomitant medication administered	No	Grade 3	Resolved
Methotrexate	[redacted] M/4[redacted]/White	Cycle 2 Day 12	33	50	Pyrexia/発熱 [FEVER]	Dose reduced/ Dose delayed/ Concomitant medication administered	Yes	Grade 2	Resolved
		Cycle 3 Day 19	68	75	Pyrexia/発熱 [FEVER]	Concomitant medication administered	Yes	Grade 2	Resolved
		Cycle 3 Day 19	68	87	Sepsis/敗血症 [SEPTICEMIA]	Concomitant medication administered	Yes	Grade 4	Resolved

表 2.7.6.1-3　重篤な有害事象の一覧（続き）

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Methotrexate（続き）	[redacted] M/4[redacted]/White（続き）	Cycle 3 Day 22	71	-	Skin erosion/皮膚びらん [EROSION SKIN LESIONS]	Concomitant medication administered	Yes	Grade 1	Unresolved
Methotrexate	[redacted] M/7[redacted]/White	Cycle 1 Day 18	18	-	Crystal arthropathy/結晶性関節障害 [CRYSTAL ARTHROPATHY]	Dose reduced/ Concomitant medication administered	No	Grade 2	Unresolved
Methotrexate	[redacted] M/4[redacted]/White	Cycle 1 Day 17	17	22	Pyrexia/発熱 [FEVER]	Concomitant medication administered	No	Grade 1	Resolved
		Cycle 1 Day 28	28	31	Pyrexia/発熱 [FEVER]	No action taken	No	Grade 1	Resolved
Methotrexate	[redacted] M/4[redacted]/Asian	Cycle 4 Day 21	84	98	Pyrexia/発熱 [FEVER]	Concomitant medication administered	No	Grade 3	Resolved
Bexarotene	[redacted] F/4[redacted]/Other	Cycle 2 Day 16	37	61	Periorbital infection/眼窩周囲感染 [PERIORBITALLY SUPERIMPOSED INFECTION DUE TO DISEASE PROGRESSION]	Drug (or dose) discontinued permanently/ Concomitant medication administered	No	Grade 3	Resolved
		Cycle 2 Day 24	45	61	Sepsis/敗血症 [SEPTICEMIA]	Concomitant medication administered	No	Grade 4	Resolved
Bexarotene	[redacted] F/7[redacted]/White	Cycle 6 Day 8	106	-	Peripheral vascular disorder/末梢血管障害 [PERIPHERAL VASULAR DISEASE - BILATERAL LOWER LEGS]	Concomitant procedure performed	No	Grade 2	Unresolved
Bexarotene	[redacted] M/6[redacted]/White	Cycle 9 Day 3	178	207	Squamous cell carcinoma of skin/皮膚有棘細胞癌 [SQUAMOUS CELL CARCINOMA OF THE SKIN]	Concomitant procedure performed	No	Grade 2	Resolved

表 2.7.6.1-3　重篤な有害事象の一覧（続き）

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Bexarotene	[redacted] F/8[redacted]/White	Cycle 2 Day 9	30	33	Haematuria/血尿 [HEMATURIA, HOSPITALIZATION]	Drug (or dose) discontinued permanently	Yes	Grade 3	Resolved
Bexarotene	[redacted] M/6[redacted]/White	Cycle 1 Day 7	7	14	Hypernatraemia/高ナトリウム血症 [WORSENING HYPERNATREMIA]	Drug (or dose) discontinued permanently/ Discontinued from study	No	Grade 2	Resolved
		Cycle 1 Day 18	18	19	Hypernatraemia/高ナトリウム血症 [WORSENING HYPERNATREMIA]	No action taken	No	Grade 2	Resolved
		Cycle 1 Day 21	21	24	Hypernatraemia/高ナトリウム血症 [WORSENING HYPERNATREMIA]	No action taken	No	Grade 2	Resolved
Bexarotene	[redacted] M/6[redacted]/White	Cycle 6 Day 35	141	145	Superinfection bacterial/細菌重複感染 [CUTANEOUS SUPERINFECTION DD STREPTOCOCCUS AND PSEUDOMONAS]	Concomitant medication administered	No	Grade 3	Resolved
Bexarotene	[redacted] M/5[redacted]/White	Cycle 1 Day 22	22	38	Peripheral ischaemia/末梢性虚血 [PERIPHERAL ISCHEMIA - LEFT FOOT]	Dose held/ Concomitant medication administered/ Concomitant procedure performed	No	Grade 3	Resolved
Bexarotene	[redacted] F/6[redacted]/Black or African American	Cycle 13 Day 49	303	-	Urosepsis/尿路性敗血症 [UROSEPSIS]	Concomitant medication administered	No	Grade 3	Unresolved

表 2.7.6.1-3　重篤な有害事象の一覧（続き）

Treatment Group	Patient ID Sex/Age/Race	Cycle Day	AE Start Date (Study Day)(a)	AE Stop Date (Study Day)(b)	MedDRA PT [Verbatim Text]	Action Taken	Treatment Related?	Intensity	Outcome
Bexarotene	[redacted] M/2[redacted]/Asian	Cycle 3 Day 37	79	85	Pyrexia/発熱 [FEVER]	Concomitant medication administered	No	Grade 2	Resolved
		Cycle 3 Day 48	90	-	Pyrexia/発熱 [FEVER]	Concomitant medication administered	No	Grade 4	Unresolved

出典：C25001 試験　治験総括報告書　Table 14.4.2.2、Listing 16.2.4.1 及び Listing 16.2.5.3
F：女性、M：男性、MedDRA：ICH 国際医薬用語集、PT：基本語、-：未消失
有害事象は MedDRA/J 第 19.0 版を用いてコード化した。
(a) 有害事象の発現日（Study Day）は、有害事象の発現日から Cycle 1 Day 1 の治験薬の初回投与日を引き、1 を足して算出した。
(b) 有害事象の消失日（Study Day）は、有害事象の消失日から Cycle 1 Day 1 の治験薬の初回投与日を引き、1 を足して算出した。

2.7.6.2 国内第 2 相医師主導治験（SGN-35-OU 試験）

：添付資料番号 5.3.5.2-1（評価）

試験の標題

再発又は難治性の CD30 陽性皮膚原発悪性リンパ腫を対象としたブレンツキシマブ　ベドチンの有効性及び安全性を確認する多施設共同第 II 相医師主導治験

実施医療機関

岡山大学病院　皮膚科を含む国内計 6 医療機関

公表文献

該当なし

試験期間

2019 年 2 月 18 日（最初の被験者の組入れ日）～2021 年 12 月 28 日（最後の被験者の完了日）

試験の種類

第 2 相

2.7.6.2.1 試験方法

2.7.6.2.1.1 試験の目的

CD30 陽性の菌状息肉症（MF）又は原発性皮膚未分化大細胞リンパ腫（pcALCL）を有する被験者群（コホート 1）及びコホート 1 以外の CD30 陽性リンパ増殖異常症を有する被験者群（コホート 2）のそれぞれにおいてブレンツキシマブ　ベドチンの有効性及び安全性を評価する。

2.7.6.2.1.2 試験デザイン

治験薬投与前 28 日以内に文書による同意が得られ、選択基準に示す基準を満たし、かつ除外基準に示す基準に該当せず、適格と判断された被験者に対し、原則としてスクリーニング時の体重を基にブレンツキシマブ　ベドチンを体重 1 kg あたり 1.8 mg で静脈内投与した。

投与は 1 サイクル 3 週（21 日）ごとに行い、3 サイクル目まで投与した後、3 サイクル目の 16～21 日目に効果判定を行い、部分寛解（PR）又は完全寛解（CR）と判定された被験者には、引き続き次のサイクルを継続のうえ、最大 16 サイクルまで治験を継続した。また、安定状態（SD）と判定された被験者には、治験責任医師等の判断で最大 16 サイクルまで治験を継続可能とした。治験中の任意の時点で、進行（PD）と判定された被験者については、投与を中止することとした。

全ての被験者は、PD が認められた時点又は投与が終了した時点までフォローされた。治験終了時〔治療の終了（EOT）又は早期中止〕において PD 以外の被験者について、後観察期（PTFU）・生存調査として EOT／早期中止から最長 12 ヵ月間までは 12 週ごとに、更にそ

の後は 6 ヵ月ごとに、PD 判定、治験からの脱落、死亡又は EOT／早期中止まで追跡することとした。

本試験は非盲検試験であるが、治験実施中に行う独立評価委員会（IRF）による総合的な有効性の評価は、治験責任医師等及び被験者の盲検下で行うこととした。

2.7.6.2.1.3 対象及び組入れ基準

【選択基準】

（1）治験審査委員会（IRB）等が承認した説明文書・同意文書により、自由意思による同意を取得した患者

同意は、治験に関わる検査を実施する前に取得すること。

（2）同意取得時点で 20 歳以上の男性又は女性の日本人患者

（3）施設病理判定にて組織学的に確認された CD30 陽性リンパ増殖異常症（pcALCL、CD30 陽性 MF を含む）患者

・コホート 1：組織学的に、pcALCL、CD30 陽性 MF と診断された患者

・コホート 2：コホート 1 以外の CD30 陽性リンパ増殖異常症と診断された患者

（4）前治療で 1 サイクル以上の全身療法〔インターフェロン（IFN）・ベキサロテン・ボリノスタット・抗腫瘍化学療法など〕を受け、効果が不十分であった患者。pcALCL においては、前治療で放射線療法を受け、効果不十分であった患者も含む。なお、効果不十分と判断されるのは、通常、1 サイクル以上の全身療法を行い、病勢の増悪が認められる場合とし、医師が臨床症状、画像所見等を総合的に判断して決定する。

（5）Eastern Cooperative Oncology Group（ECOG）performance status が 2 以下の患者

（6）前治療の全身療法による臨床的に重要な副作用の重症度全てが、米国国立がん研究所（NCI）による有害事象共通用語規準（CTCAE）v5.0 の Grade 1 以下に回復している患者

（7）スクリーニング検査時に以下の基準を満たした患者

1）好中球絶対数 ＞1,500 /μL

2）血小板数 ＞75,000 /μL

3）総ビリルビン ＜1.5×正常範囲の上限（ULN）

4）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） ＜3×ULN

AST、ALT は、その上昇が肝臓浸潤のためであることが判明している場合、ULN の 5 倍以下まで適格である。

5）クレアチニンクリアランス又は算出されたクレアチニンクリアランス ＞40 mL/分

6）ヘモグロビン ＞8 g/dL

（8）適切な避妊方法をスクリーニング時から EOT／早期中止まで実施することに同意した患者

妊娠の可能性のある閉経前の女性患者は説明文書・同意文書に署名してから治験薬の最終投与後 6 ヵ月まで、又は妊娠能力を有する男性患者の場合には治験薬投与期間及び治験薬の最終投与後 6 ヵ月まで、医学的に承認された方法により避妊することに同意した患者

（9）抗がん治療を行っている場合、同意取得後、治験薬投与前までに 3 週間のウォッシュアウトが可能な患者
（10）抗体療法､免疫グロブリンに基づく免疫療法又は他のモノクローナル抗体療法を行っている場合、同意取得後、治験薬投与前までに 12 週間のウォッシュアウトが可能な患者。ただし、治験責任医師等が，病勢の急激な増悪等の理由により被験者に早急な治験薬投与開始が必要と判断した場合には、ウォッシュアウト期間を 3 週間とすることができるものとする。

【除外基準】
（1）全身性未分化大細胞リンパ腫（sALCL）の合併
（2）セザリー症候群又は B2 疾患の合併
末梢血セザリー細胞数の計測は施設判定にて行うものとする。なお、異常リンパ球数が 750/μL を越えて登録する場合には中央判定手順に従い計測を行い、治験調整医師が結果を総合的に判断して当該被験者の適格性を判断する。
（3）登録前 6 ヵ月以内の心血管状態又は検査値が下記のいずれかに該当する患者
1）心筋梗塞
2）ニューヨーク心臓協会（NYHA）クラス III 又は IV 心不全
3）心臓不整脈、うっ血性心不全、狭心症、又は急性虚血の心電図所見若しくは臨床的に有意な伝導系異常を含むコントロールされていない心血管所見
（4）少なくとも 3 年間寛解していない他の原発悪性腫瘍の既往
ただし、上皮内病変の非メラノーマ皮膚癌や、生検での上皮内子宮頸がん、細胞診での子宮頸部上皮内腫瘍のような上皮内癌を完全に切除できている場合は、3 年間の制限を設けない。
（5）進行性多巣性白質脳症（PML）の徴候又は症状を含む既知の活動性脳／髄膜疾患
（6）これまでにヒト免疫不全ウイルス（HIV）が確認されている患者
なお、HIV 検査を実施したことがない被験者については、本治験の適格性判断のための HIV 検査は必須とはしない。
（7）既知の B 型肝炎表面抗原陽性、既知の活性型 C 型肝炎感染又はその疑い
（8）治験薬投与前の 1 週間以内に、全身療法（抗菌剤・抗ウイルス剤・抗真菌剤等の静脈内投与等）を必要とする重度の活動性・全身性のウイルス性、細菌性又は真菌性感染（ただし予防のための経口抗生物質は許可される）。
合併症を伴わないブドウ球菌感染症（ブドウ球菌の菌種を問わない）患者では、スクリーニング前から一定用量の抗菌治療薬投与（ただし抗菌剤の静脈内投与を除く）でコントロールされている場合は適格である。
（9）治験薬投与前 12 週間以内に､抗体指向性又は免疫グロブリンベースの免疫療法（例えば、免疫グロブリン置換、他のモノクローナル抗体療法）を受けた患者
（10）治験薬投与前 3 週間以内に皮膚 T 細胞リンパ腫（CTCL）の治療のための全身又は局所のコルチコステロイド療法を受けた患者。ただし、登録前から継続中で、かつスクリーニング期間に SD であるストロングクラス以下の局所外用療法は併用可能である。

（11）治験薬投与前 3 週間以内に CTCL の治療のため 1 日あたり 15,000 IU 以上のビタミン A 又はビタミン A 誘導体（エトレチナート）の全身投与を受けた患者
（12）製剤に含まれる組換えタンパク質、マウスタンパク質、若しくは薬物成分に対する過敏症の既往がある、又は合併する患者
（13）妊娠中若しくは授乳中の女性患者、又はスクリーニング期間中の血清妊娠検査若しくは任意のサイクルの 1 日目の尿妊娠検査で陽性の女性患者
（14）治験薬投与前 3 週間以内に、放射線療法、他の皮膚指向療法（SDT）又は他の治験薬による治療を受けた患者
SDT には以下のものを含む；ステロイド外用療法・ニムスチン塩酸塩（ACNU）外用療法、紫外線治療〔狭帯域紫外線 B（NB-UVB）、エキシマライト、ソラレンと紫外線 A（PUVA）〕、局所放射線照射など
（15）膵炎又は重大な危険因子（例えば、膵炎の既往、コントロールされていない高脂血症、過度のアルコール摂取、コントロール不良な糖尿病、胆道疾患及びトリグリセリドレベルの上昇、又は膵臓毒性と関連する薬剤の併用）若しくは、スクリーニング時のアミラーゼ値 ＞ULN かつリパーゼ値 ＞3×ULN 以上の患者
（16）過去にブレンツキシマブ　ベドチンによる治療歴のある患者
（17）その他、治験責任医師等が被験者として不適当と判断した患者

2.7.6.2.1.4 被験者数

［計画時］
コホート 1 及び 2 の合計として 15 例以上（最大 17 例）
コホート 1：pcALCL 被験者 3 例以上を含め、MF 被験者と合わせて 12 例
コホート 2：コホート 1 以外の CD30 陽性リンパ増殖異常症被験者として 3 例以上（最大 5 例）

2.7.6.2.1.5 投与方法、投与量及び投与期間

［被験薬］
治験薬名：SGN-35
一般名：ブレンツキシマブ　ベドチン（遺伝子組換え）

［用量及び投与方法］
治験薬は、3 週間ごとに実施するサイクルの 1 日目に 30 分間以上かけて静脈内に点滴投与した。投与時反応（アナフィラキシーショック）予防のため、投与時間が 30 分以上となるよう、注入速度を調整して投与した。本治験薬は、静脈内への側管注入又は急速投与してはならないこととした。また、専用の静脈ラインにて投与し、他の薬剤との混合は避けることとした。
・本治験薬の投与量は 1.8 mg/kg とし、投与量はスクリーニング時の被験者の体重に基づいて算出した。ただし、スクリーニングから 10%以上の体重変化があった場合、投与量を再計算し、調整することとした（調整は同一被験者においては 1 回のみ）。

・投与量の算出には体重の実測値を使用し、体重が 100 kg を超える被験者については 100 kg として投与量を計算した。
・治験薬の用量はミリグラムで決定し、小数点以下を切り捨て整数値とした。

［治療期間］
1 サイクルを 3 週（21 日）として、3 サイクル投与後、最大 16 サイクルまで投与継続

［ロット番号］
[redacted]、[redacted]、[redacted]

2.7.6.2.1.6 評価項目及び評価基準

［有効性］

主要評価項目

ORR4：少なくとも 4 ヵ月持続する客観的奏効（CR＋PR）を達成した被験者の割合（IRF 判定）

副次評価項目

（1）奏効率（実施医療機関の医師による判定）
（2）皮膚奏効率〔実施医療機関の医師による判定、modified severity-weighted assessment tool（mSWAT）〕
（3）全生存期間（OS）
（4）無増悪生存期間（PFS）〔IRF 判定、mSWAT 及び global response score（GRS）〕
（5）皮膚病変の奏効期間（実施医療機関の医師による判定、mSWAT）
（6）皮膚病変の奏効に至るまでの期間（実施医療機関の医師による判定、mSWAT）
（7）皮膚病変の最良総合効果（実施医療機関の医師による判定、mSWAT）
（8）ORR1：少なくとも 4 週間持続する客観的奏効を達成した被験者の割合（実施医療機関の医師による判定及び IRF 判定）
（9）GRS 総合効果判定
（10）合計 mSWAT

［安全性］

（1）有害事象
（2）臨床検査（血液学的検査、生化学的検査、膵機能検査、尿検査）
（3）バイタルサイン（収縮期血圧／拡張期血圧、脈拍数、体温）、体重
（4）ECOG performance status

2.7.6.2.1.7 統計手法

［解析対象集団］

解析対象集団として「最大の解析対象集団（FAS）」、「調整された最大の解析対象集団（mFAS）」及び「安全性データの解析対象集団（SAF）」を設けた。

・有効性解析：FAS は「治験に症例登録され、治験薬を少なくとも 1 回以上投与された被験者」、mFAS は「治験に症例登録され、治験薬を少なくとも 1 回以上投与された被験者のうち、CD30 の中央病理判定において陰性と判定されたものを除外したもの」とした。
・安全性解析：SAF は「治験薬を少なくとも 1 回以上投与された被験者の集団」として定義した。

FAS、mFAS 及び SAF はコホート 1 及びコホート 1+2 について設け、それぞれ FAS1 及び FAS2、mFAS1 及び mFAS2、SAF1 及び SAF2 と記載した。

なお、解析対象集団の詳細規定は、別途「解析上のデータハンドリング・ルール」として定めた。

［主要評価項目の解析方法］

(1) 主解析

FAS1 及び FAS2 に対して、ORR4 の点推定値及びその両側信頼区間（CI）（Exact 法）を推定した。さらに、帰無仮説 12%に対する Exact 二項検定を FAS1、FAS2 の順に閉検定手順に従い実施した。

(2) 副解析

mFAS1 及び mFAS2 に対する主解析と同様の解析により、結果の安定性を評価した。

(3) 探索的解析

FAS1、FAS2、mFAS1 及び mFAS2 に対して、性別（男性、女性）、年齢（64 歳以下、65 歳以上）、原疾患（MF、pcALCL、その他）、ECOG performance status（0～1、2）、スクリーニング時の合計 mSWAT スコア（中央値未満、中央値以上）、病期分類（区分方法は事前背景集計に基づき決定）により層別化のうえ、例数と割合（%）、両側 CI の算出を行った。

［副次評価項目の解析方法］

FAS1、FAS2、mFAS1 及び mFAS2 を解析対象として、各評価項目に対応して以下の解析を行った。

(1) (2) 割合及びその両側 CI を推定した。

(3) ~ (6) 解釈上意味があり、かつ解析可能な場合には、以下の解析を行った。

Kaplan-Meier 法で累積生存率を推定し、Greenwood の公式に基づき両側 CI を推定した。

さらに、各副次評価項目の中央値及びその両側 CI を推定した。

なお、(6)は奏効例を対象に要約統計量を算出した。

(7) 評価カテゴリ水準ごとの頻度並びに割合を算出し、CR、CR・PR 及び SD の各割合の両側 CI を推定した。

(8) ORR1 の点推定値及びその両側 CI を推定した。

(9) 評価カテゴリ水準ごとの頻度並びに割合を算出した。

(10) 評価時点ごとに要約統計量及び平均の両側 CI を推定した。

［安全性の解析方法］

SAF1、SAF2 を解析対象として、主に以下の集計解析を行った。

- 有害事象は医薬品規制調和国際会議（ICH）国際医薬用語集日本語版（MedDRA/J）を用いて読み替え、器官別大分類（SOC）別、基本語（PT）別に要約のうえ、発現頻度並びに発現割合を集計した。
- 有害事象は因果関係別、Grade 別などの集計を行った。
- CTCAE v5.0 に Grade が定義されている検査項目について、投与前 Grade と投与開始後における最悪 Grade のシフトテーブルを作成した。
- 各検査値について、評価時点ごとに、データの尺度に応じて要約統計量の算出及び頻度集計を行った。

［その他の解析］

Dermatology Life Quality Index（DLQI）

FAS1、FAS2、mFAS1 及び mFAS2 を解析対象として、評価時点ごとに要約統計量及び平均の両側 CI を推定することとした。

評価時点ごとに要約統計量及び平均の両側 CI を推定し、治療期のサイクル 1 の投与前及び EOT／早期中止後には EOT／早期中止時点をそれぞれ起点として、それ以降の時点の変化量について要約統計量及び平均の両側 CI を推定した。

さらに、DLQI と臨床反応（ORR4、ORR1、%BSA、mSWAT）及び有害事象との関連性を探索的に評価した。

［信頼係数］

CI は両側 CI として構成し、その際の信頼係数として、95%及び 90%を用いた。

2.7.6.2.2 試験成績

2.7.6.2.2.1 被験者の内訳

被験者の内訳は、コホート 1 及びコホート 2 でそれぞれ 13 例及び 3 例であり、全例に治験薬が投与された。治験薬投与を最大 16 サイクルまで完了した症例は、コホート 1 及びコホート 2 でそれぞれ 9 例（治験薬投与中止 4 例）及び 1 例（治験薬投与中止 2 例）であり、このうち PTFU を含めて治験を終了したのは、同様にそれぞれ 7 例（PTFU 中止 2 例）及び 1 例（PTFU 中止 0 例）であった。

解析対象集団ごとの内訳は、SAF では SAF1 及び SAF2 がそれぞれ 13 例及び 16 例、FAS では FAS1 及び FAS2 がそれぞれ 13 例及び 16 例であり、登録された全例が SAF 及び FAS に採用された。一方、mFAS では mFAS1 及び mFAS2 でそれぞれ 9 例及び 11 例が採用され、それぞれ 4 例及び 5 例が除外された。

2.7.6.2.2.2 ベースラインの人口統計学的特性及びその他の関連特性

被験者の年齢の中央値は FAS1 で 54.0 歳（範囲：32～76 歳）及び FAS2 で 52.5 歳（範囲：32～78 歳）（以降同順）であり、男性が多かった（それぞれ 62%及び 63%）。FAS1 の診断疾患は MF が 8 例（62%）、pcALCL が 5 例（38%）であった。また、FAS2 には、これらに

加えてコホート 2 で登録されたリンパ腫様丘疹症が 2 例（13%）、原発性皮膚 γδT 細胞リンパ腫が 1 例(6%)含まれた。ほとんどの被験者の ECOG performance status は 0 又は 1 であり、ECOG performance status が 2 の被験者は 2 例（それぞれ 15%及び 13%）であった。

MF 被験者のほとんどは試験登録時の病期が II B（6 例）であり、III A が 1 例、IV A2 が 1 例であった。病期 IV B であった被験者はいなかった。pcALCL 被験者の試験登録時の皮膚病変は T3a（1 例）又は T3b（4 例）であった。その他の診断疾患の被験者の試験登録時の皮膚病変は、T3b（2 例）又は T2a（1 例）であった。pcALCL 被験者及びその他の診断疾患の被験者で内臓病変を有している被験者はいなかった。

FAS1 及び FAS2 で試験中の中央病理判定で病理組織学的に CD30 陽性と判定された被験者は、FAS1 で 9 例（69%）、FAS2 で 11 例（69%）であった。これらの被験者をそれぞれ mFAS1 及び mFAS2 に含め、有効性評価を行った。

mFAS のベースライン時の疾患特性も同様であった。

2.7.6.2.2.3 有効性の評価

FAS1 に関しては、主要評価項目の主解析での IRF 判定による ORR4 の点推定値は、69.2%〔9/13 例、95%信頼区間（CI）[38.6, 90.9]）であり、帰無仮説 12%に対する Exact 二項検定（片側）で統計的有意性が認められた（p<0.0001）。副次評価項目の GRS を用いた治験責任医師判定の奏効率の点推定値は、53.8%（7/13 例、95% CI [25.1, 80.8]）であった。mSWAT を用いた治験責任医師判定の皮膚奏効率の点推定値は、61.5%（8/13 例、95% CI [31.6, 86.1]）であった。OS の中央値は、未達（イベント例数：1/13 例、打切り例数：12/13 例）であり、Kaplan-Meier 法で推定された累積生存率は、11 ヵ月時点が 100.0%、33 ヵ月時点が 90.0%であった。PFS の中央値は、GRS の IRF 判定に基づいて評価した結果、未達（イベント例数：3/13 例、打切り例数：10/13 例）であり、Kaplan-Meier 法で推定された累積生存率は、4 ヵ月時点が 100.0%、11 ヵ月時点が 92.3%、15 ヵ月時点が 83.1%、33 ヵ月時点が 71.2%であった。mSWAT における奏効例での mSWAT を用いた治験責任医師判定の皮膚病変の奏効期間の中央値は、13.6 ヵ月（イベント例数：5/9 例、打切り例数：4/9 例）であり、Kaplan-Meier 法で推定された累積奏効率は、4 ヵ月時点が 100.0%、6 ヵ月時点が 88.9%、7 ヵ月時点が 76.2%、13 ヵ月時点が 63.5%、27 ヵ月時点が 47.6%、30 ヵ月時点が 31.7%であった。mSWAT を用いた治験責任医師判定の皮膚病変の奏効に至るまでの期間の中央値は、1.8 ヵ月（イベント例数：9/13 例、打切り例数：4/13 例）であり、Kaplan-Meier 法で推定された累積奏効率は、1 ヵ月時点が 0.0%、2 ヵ月時点が 53.8%、4 ヵ月時点が 61.5%、16 ヵ月時点が 69.2%であった。奏効例（9 例）での奏効に至るまでの期間の中央値は、1.74 ヵ月であった。mSWAT を用いた治験責任医師判定の皮膚病変の最良総合効果は、CR が 38%、PR 及び SD が共に 31%であり、PD 及び再発はなかった。CR+PR 及び CR+PR+SD ではそれぞれ 69%及び 100%であった。治験責任医師判定及び IRF 判定の ORR1 の点推定値は、GRS が共に 69.2%（9/13 例、95% CI [38.6, 90.9]）であり、mSWAT も同様であった。GRS 総合効果判定は、CR が 31%、PR が 38%、SD が 31%であり、PD 及び再発はなかった。CR+PR 及び CR+PR+SD ではそれぞれ 69%及び 100%であった。合計 mSWAT のベースラインからの変化率（平均値±標準偏差、以下同様）は、サイクル 1 では 8.837±17.5673%であったが、サイクル 2 の-21.206±29.0663%以降は低下傾向となり、ベースライン未満を維持した。PTFU も同様に低い水準を維持した。その他の評価項目

の DLQI スコアのベースラインからの変化量（平均値±標準偏差、以下同様）は、サイクル 2 の-1.3±3.47 以降は低下傾向となり、ベースライン未満を維持した。PTFU も同様に低い水準を維持した。また、EOT／早期中止時点を起点とした場合の DLQI スコアの変化量については、PTFU12 週の-0.8±2.22 以降は低下傾向となり、ベースライン未満を維持した。臨床反応（ORR4、ORR1）の判定時期別 DLQI スコアのベースラインからの変化量は、ORR4 到達例（9 例）では-5.6±6.56、SD 例（4 例）では-1.8±2.87 であり、ORR4 未到達の ORR1 到達例、ORR1 未到達の CR+PR 例及び PD 例はいなかった。

FAS2 に関しても、上記各評価項目とも概ね同様の結果が認められたが、リンパ節病変の効果判定については、FAS1 で CR が 80%であり、CR+PR 及び CR+PR+SD はそれぞれ 80%及び 100%、FAS2 では、CR が 67%であり、CR+PR 及び CR+PR+SD はそれぞれ 67%及び 83%であった。リンパ節病変の効果判定は、FAS1 と比較して FAS2 の方がわずかに低い傾向が認められた。

なお、探索的解析での IRF 判定による ORR4 の点推定値は、FAS1 及び FAS2 共に、性別、年齢及びスクリーニング時の合計 mSWAT スコアの層別解析では、特筆すべき相違はなかったが、原疾患の pcALCL 及び ECOG performance status の 2 が共に 100.0%、MF 症例での病期分類の III A 及び IV A2 はそれぞれ 0.0%及び 100.0%であり、FAS2 も同様の傾向が認められた。

2.7.6.2.2.4 安全性の評価

SAF1 において、有害事象は 13 例（100%）に 127 件発現し、そのうち治験薬との因果関係が否定できない有害事象は 13 例（100%）に 75 件であった。死亡例はなく、重篤な有害事象は 5 例（38%）に 7 件発現し、全て治験薬との因果関係が否定できなかった。また、重要な有害事象は 13 例（100%）に 46 件発現し、そのうち治験薬との因果関係が否定できない重要な有害事象は 13 例（100%）に 29 件であった。投与中止に至った有害事象は 2 例（15%）に 2 件発現し、全て治験薬との因果関係が否定できなかった。2 例以上の被験者で発現した有害事象の内訳は、末梢性ニューロパチーが 8 例（62%）に 8 件、発熱が 5 例（38%）に 13 件、下痢及び好酸球増加症が各 4 例（31%）に各 4 件、関節痛が 3 例（23%）に 4 件、上咽頭炎、倦怠感及び薬疹が各 3 例（23%）に各 3 件、感覚鈍麻、足部白癬、上気道感染、C-反応性蛋白増加、γ-GTP 増加及び肝機能異常が各 2 例（15%）に各 3 件、末梢性感覚ニューロパチー、悪心、末梢性浮腫、高尿酸血症及びアレルギー性鼻炎が各 2 例（15%）に各 2 件であった。2 例以上の被験者で発現した治験薬との因果関係が否定できない有害事象は同様に、末梢性ニューロパチーが 8 例（62%）に 8 件、発熱が 4 例（31%）に 9 件、好酸球増加症が 4 例（31%）に 4 件、倦怠感が 3 例（23%）に 3 件、感覚鈍麻が 2 例（15%）に 3 件、末梢性感覚ニューロパチー、末梢性浮腫、下痢、悪心、薬疹、C-反応性蛋白増加、γ-GTP 増加及び肝機能異常が各 2 例（15%）に各 2 件であった。2 例以上の被験者で発現した Grade 3 以上の有害事象は、末梢性ニューロパチーが 3 例（23%）に 3 件、発熱が 2 例（15%）に 3 件、好酸球増加症が 2 例（15%）に 2 件であった。治験薬との因果関係が否定できない Grade 3 以上の有害事象の発現状況も同様であった。有害事象の重症度別発現状況は、Grade 4 の有害事象は好中球数減少の 1 例（8%）のみであった。Grade 3 の有害事象は、末梢性ニューロパチーが 3 例（23%）、発熱及び好酸球増加症が各 2 例（15%）であり、その他の Grade 3 の有害事象は各 1 例（8%）

に発現した。その他の有害事象は Grade 2 又は Grade 1 であり、Grade 5 の有害事象は発現しなかった。治験薬との因果関係が否定できない有害事象の重症度別発現状況も同様であった。重篤な有害事象は、好酸球増加症、鼠径ヘルニア、発熱、好中球数減少、高尿酸血症、急性腎障害及び肺毒性が各 1 例（8%）に 1 件発現し、全て治験薬との因果関係が否定できなかった。2 例以上の被験者で発現した重要な有害事象は、末梢性ニューロパチーが 8 例（62%）に 8 件、上咽頭炎が 3 例（23%）に 3 件、感覚鈍麻、足部白癬、上気道感染、γ-GTP 増加及び肝機能異常が各 2 例（15%）に各 3 件、末梢性感覚ニューロパチーが 2 例（15%）に 2 件発現した。そのうち治験薬との因果関係が否定できない重要な有害事象は、末梢性ニューロパチーが 8 例（62%）に 8 件、感覚鈍麻が 2 例（15%）に 3 件、末梢性感覚ニューロパチー、γ-GTP 増加及び肝機能異常が各 2 例（15%）に各 2 件であった。

SAF2 において、有害事象は 16 例（100%）に 138 件発現し、そのうち治験薬との因果関係が否定できない有害事象は 16 例（100%）に 82 件であった。死亡例はなく、重篤な有害事象は 5 例（31%）に 7 件であり全て治験薬との因果関係が否定できなかった。また、重要な有害事象は 15 例（94%）に 49 件であり、そのうち治験薬との因果関係が否定できない重要な有害事象は 15 例（94%）に 31 件であった。投与中止に至った有害事象は 3 例（19%）に 5 件発現し、全て治験薬との因果関係が否定できなかった。2 例以上の被験者で発現した有害事象の内訳は、末梢性ニューロパチーが 9 例（56%）に 9 件、発熱が 5 例（31%）に 13 件、下痢が 5 例（31%）に 5 件、薬疹及び好酸球増加症が各 4 例（25%）に各 4 件、関節痛及び肝機能異常が各 3 例（19%）に各 4 件、上咽頭炎、倦怠感及び高尿酸血症が各 3 例（19%）に各 3 件であった。2 例以上の被験者で発現した治験薬との因果関係が否定できない有害事象は同様に、末梢性ニューロパチーが 9 例（56%）に 9 件、発熱が 4 例（25%）に 9 件、好酸球増加症が 4 例（25%）に 4 件、薬疹、下痢、倦怠感及び肝機能異常が各 3 例（19%）に各 3 件であった。2 例以上の被験者で発現した Grade 3 以上の有害事象は、末梢性ニューロパチーが 3 例（19%）に 3 件であった。治験薬との因果関係が否定できない Grade 3 以上の有害事象の発現状況も同様であった。有害事象の重症度別発現状況は、Grade 4 の有害事象は好中球数減少の 1 例（6%）のみであった。Grade 3 の有害事象は、末梢性ニューロパチーが 3 例（19%）であり、その他の Grade 3 の有害事象は 2 例（13%）又は 1 例（6%）に発現した。その他の有害事象は Grade 2 又は Grade 1 であり、Grade 5 の有害事象は発現しなかった。治験薬との因果関係が否定できない有害事象の重症度別発現状況も同様であった。重篤な有害事象は SAF1 と同様であり、全ての事象が各 1 例（6%）に各 1 件発現し、全て治験薬との因果関係が否定できなかった。2 例以上の被験者で発現した重要な有害事象は、末梢性ニューロパチーが 9 例（56%）に 9 件、肝機能異常が 3 例（19%）に 4 件、上咽頭炎が 3 例（19%）に 3 件発現した。そのうち治験薬との因果関係が否定できない重要な有害事象は、末梢性ニューロパチーが 9 例（56%）に 9 件、肝機能異常が 3 例（19%）に 3 件であった。

なお、治験中止日（最終観察日）以降、治験薬の最後の投与の 30 日後以降の死亡が 1 例認められたが、治験実施計画書に定める有害事象の収集期間外であることから、有害事象及び重篤な有害事象の集計には含めなかった。死因は病勢進行によるものであった。

臨床検査に関連する有害事象のうち、重篤な有害事象は好中球数減少の 1 例 1 件であった。また、非重篤ではあったものの、重症度が Grade 3 の有害事象は、白血球数減少及び好中球数減少で各 1 例 2 件であった。その他は全て重症度が Grade 2 以下であった。バイタルサイ

ンに関連する有害事象のうち、重篤な有害事象は発熱の 1 例 1 件であった。また、非重篤ではあったものの、重症度が Grade 3 の有害事象は、発熱の 1 例 2 件であった。その他は全て重症度が Grade 2 以下であった。ECOG performance status 及び 12 誘導心電図による評価では、特筆すべき変化は認められなかった。また、免疫再構築評価では、CD19+B cells でベースラインから増加傾向が認められたが、その他の検査項目に特筆すべき変化は認められなかった。発現した有害事象の最大 Grade と当該最大 Grade の有害事象発現期間中の最大 DLQI スコアを評価した結果、FAS1 では最大 DLQI スコアが 0～1 では最大 Grade が Grade 2 の症例が 1 例（100%）、2～5 では Grade 3 及び Grade 2 が各 1 例（33%）及び 2 例（67%）、6～10 では Grade 4、Grade 3、Grade 2 及び Grade 1 が各 1 例（25%）、11～20 及び 21～30 では Grade 3 が各 2 例（100%）及び 1 例（100%）であった。FAS2 でも概ね同様の結果であった。

2.7.6.2.3 結論

再発又は難治性の CD30 陽性皮膚原発悪性リンパ腫の日本人患者において、ブレンツキシマブ　ベドチンの有効性が示唆され、安全性においても過去の情報と概ねプロファイルが一致しており、問題がないことが確認された。

2.7.6.2.4 付録 1：死亡及び重篤な有害事象の叙述

本試験で報告された死亡及び重篤な有害事象の叙述を表 2.7.6.2-1～表 2.7.6.2-6 に、当該被験者で発現した有害事象を表 2.7.6.2-7 に示した。

表 2.7.6.2-1　死亡の叙述

症例番号	[redacted]	人種	アジア人
年齢／性別	5[redacted] 歳／男性	試験治療	ブレンツキシマブ　ベドチン
重篤な有害事象（MedDRA 基本語）／重症度／転帰	左鼠径ヘルニア（鼡径ヘルニア）／Grade 3／回復		
原疾患／病歴	菌状息肉症／胃潰瘍、甲状腺機能低下症、不眠症		
併用薬	プロペト、フェキソフェナジン塩酸塩 OD 錠、チラーヂン S 錠、ネキシウムカプセル、ゾルピデム酒石酸塩錠、オーグメンチン配合錠、アセトアミノフェン錠、ミヤ BM 細粒、レスタミンコーワクリーム、ヘパリン類似物質クリーム 0.3%「ニプロ」、センノシド錠 12mg「サワイ」、アセトアミノフェン 500mg「マルイシ」、プロポフォール静注 1%20ml「マルイシ」、ロクロニウム静注液 50mg/5.0ml「マルイシ」、アセリオ静注液バック 1000mg/100ml、フェンタニル注射液 0.1mg/2ml、エフェドリン注射液 40mg/1ml、レミフェンタミル、セファゾリン Na 注射用 1g、プリンペラン注射用 10mg/2ml		
経過・処置	20[redacted] 年 [redacted] 月 [redacted] 日（Day -7）：本治験参加の同意取得。5[redacted] 歳の男性で、TNMB 分類が T3 N3 M0 B0、病期分類が IV A2、mSWAT 合計スコアが 7.50 であった。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 1）：サイクル 1 治験薬投与開始。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 63）：サイクル 4 治験薬投与。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 68）：被験者が、左鼠径部に腫瘤を確認した。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 85）：サイクル 5 治験薬投与。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 99）：左鼠径部に痛みを伴った。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 106）：サイクル 6 治験薬投与。当院の外科にコンサルとした。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 107）：外科にて、左鼠径ヘルニアと診断された。手術予定となった。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 128）：サイクル 7 治験薬投与。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 135）：手術目的のため、入院した。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 136）：腹腔鏡下左鼠径ヘルニア手術を施行した。問題なく終了した。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 138）：軽快、退院となった。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 148）：サイクル 7 の 16～21 日目の観察時に皮膚病変の効果判定で PR となり、皮膚反応確定となった。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 149）：サイクル 8 治験薬投与。有害事象なく投与終了した。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 171）：治験薬（ブレンツキシマブ　ベドチン）サイクル 9 治験薬投与。有害事象なく投与終了した。		

表 2.7.6.2-1　死亡の叙述（続き）

経過・処置（続き）	20■ 年 ■ 月 ■ 日（Day 191）：外科受診し、創クリア、左鼠径部膨隆なしが確認された。外科の診察内容、CT の結果より回復と判断した。 20■ 年 ■ 月 ■ 日（Day 234）：サイクル 1 治験薬投与。PR が維持されていた。 20■ 年 ■ 月 ■ 日（Day 260）：サイクル 12 の 16～21 日目の観察。皮膚病変の効果判定及び GRS が共に CR となった。 20■ 年 ■ 月 ■ 日（Day 276）：ORR4 の評価を行い、皮膚病変の効果判定及び GRS が共に CR であったが、末梢性ニューロパチーの発現によりサイクル 13 の 1 日目から延期されていた治験薬投薬の再開ができず、当日を以て治験中止と判断した。 20■ 年 ■ 月 ■ 日（Day 347）：治験中止後、被験者の希望により次治療は開始せずに経過観察となっていたが、本人からの電話で両眼瞼浮腫ありとの連絡を受け、次治療を再開する方針に変更した。 20■ 年 ■ 月 ■ 日（Day 349）：本人からの電話で、前日（20■ 年 ■ 月 ■ 日）に前胸部痛を自覚したとの連絡を受けたことから、急遽外来受診となった。来院時に両眼瞼浮腫及び発熱が認められたが、心電図では心筋梗塞・狭心症を示す所見は認められず、発熱に対して抗生剤投与のうえ入院経過観察とした。 20■ 年 ■ 月 ■ 日（Day 353）：38°C 台の発熱が持続していたが、朝方は意識澄明であり、バイタルも問題なく経過観察されていた。しかし、着替え中に硬直、意識消失となり、救命処置がとられたが死亡に至った。CT による死亡後の画像診断（AiCT）が実施されたが、直接的な死因となる所見は認められなかった。最終的に、病勢進行（MF の悪化）による死亡で、治験薬との因果関係は「関連なし」と判断された。
治験責任医師の見解	死亡原因として、死亡当日朝の血液検査で電解質異常が見られたこともあり、MF による電解質異常や、度重なる治療に伴う心負荷によって心停止が起きたものと思われる。発熱があり、入院時から抗生剤投与を行っていたが、炎症反応上昇などに乏しく、腫瘍そのものによる発熱であった可能性も考えられる。 以上の経緯から、病勢進行（MF の悪化）による死亡と判断し、治験薬との因果関係は「関連なし」と判断された。

出典：SGN-35-OU 試験　治験総括報告書　14.3.3、付録 16.2.1-1、付録 16.2.4-1、付録 16.2.4-2 及び付録 16.2.4-3
AiCT：死亡時画像診断、CR：完全奏効、CT：コンピュータ断層撮影、GRS：global response score、MedDRA：国際医薬用語集、MF：菌状息肉症、mSWAT：modified severity-weighted assessment tool、ORR4：4 ヵ月以上持続する客観的奏効率、PR：部分奏効、TNMB：Tumor-Node-Metastasis-Blood
被験者の情報のうち、年齢／性別、人種、試験治療、重篤な有害事象／重症度／転帰、病歴及び併用薬は治験総括報告書の Listing を参照した。経過・処置並びに治験責任医師の見解は、治験総括報告書の Section 14.3.3 を参照した。
経過・処置の Study Day は、報告された日から Cycle 1 Day 1 の治験薬の初回投与日を引き、初回投与日以降の日付の場合は 1 を足して算出した（初回投与日を Day 1 とする）。
有害事象は MedDRA/J 第 24.1 版を用いてコード化した。

表 2.7.6.2-2　重篤な有害事象の叙述（1）

症例番号	[redacted]	人種	アジア人
年齢／性別	7[redacted] 歳／男性	試験治療	ブレンツキシマブ　ベドチン
重篤な有害事象（MedDRA 基本語）／重症度／転帰	薬剤性肺障害（肺毒性）／Grade 3／軽快		
原疾患／病歴	原発性皮膚未分化大細胞リンパ腫(a)／高血圧症、IgA 腎症、便秘、糖尿病		
併用薬	ヒルドイドローション、ゲーベンクリーム 1%、ダイフェン配合錠、プレドニン錠、カルフィーナ錠、アミティーザカプセル、マグミット錠、ランソプラゾール OD 錠「サワイ」、テネリア錠、アムロジピン OD 錠「サワイ」、トラマール OD 錠、コカール錠、アレグラ錠、リンデロン VG 軟膏、ヒルドイドソフト軟膏、ゲンタマイシン硫酸塩軟膏、オーグメンチン配合錠、アモキシシリンカプセル、フェキソフェナジン塩酸塩 60mg「SANIK」、セフタジジム、センノシド錠、メトクロプラミド錠、コカール、ゼチーア錠、炭酸水素ナトリウム、アセトアミノフェン酸 200mg「三和」、アルファカルシドール錠 0.25μg「アメル」、フェキソフェナジン塩酸塩 OD 錠 60mg「NP」、レスタミンコーワクリーム、レボフロキサシン点滴静注バック 500mg「DSEP」、タゾピペ配合静注用 4.5「明治」		
経過・処置	20[redacted] 年 [redacted] 月 [redacted] 日（Day -22）：本治験参加の同意取得。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 1）：サイクル 1 治験薬投与開始。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 253）：サイクル 13 治験薬投与。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 272）：全身状態は良好であり、体温 36.7°C と発熱なし、CRP が 12.41 mg/dL と上昇する。サイクル 14 の治験薬投与予定であったが延期する。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 274）：全身状態は良好であり、CRP は 10.59 mg/dL とやや低下、体温 36.1°C と発熱もなく、WBC 上昇も認めない。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 279）：全身状態は良好であり、CRP が 9.33 mg/dL と高値、体温 36.8°C と発熱はないが、WBC が 10950/μL と上昇する。CT 上薬剤性肺炎・ニューモシスチス肺炎・ウィルス性肺炎が疑われ、 *Day 280 より入院加療することとなる。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 280）：精査加療のため入院する。呼吸器内科にコンサルとする。レボフロキサシン点滴バック 500 mg/100 mL とタゾピペ配合静注 4.5 g を点滴静注開始する。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 285）：胸部レントゲンにて、右上肺野の斑状影は消退傾向。CRP 3.14 mg/dL と低下。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 287）：CT で一部増悪が認められる。薬剤性肺炎が疑われる。治験は、中止する方向で検討。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 289）：CRP 1.33 mg/dL、WBC 6400/μL と炎症反応改善傾向、抗生剤点滴終了する。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 290）：退院する。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 295）：治験薬の投与期限が本日までであるが、薬剤性肺炎が完全に回復していないこと、また再投与（減量でも）による肺症状の悪化が懸念されるため治験を中止とする。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 335）：CRP が 15.84 mg/dL、WBC が 13290/μL と上昇し、体温 35.8°C。おそらく原発性皮膚未分化大細胞リンパ腫(a)による皮疹＋感染によるものと思われ、入院加療開始した。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 338）：CT の検査結果、呼吸器内科の医師の見解より薬剤性肺障害は、軽快と判断する。		

*新薬承認情報提供時に置き換え

表 2.7.6.2-2　重篤な有害事象の叙述（1）（続き）

治験責任医師の見解	本事象に対し、入院加療となったため、重篤な有害事象として報告する。 CT にて、両肺の広範に多数のスリガラス状濃度上昇域の出現を認め、薬剤性肺炎・ニューモシスチス肺炎・ウィルス性肺炎の鑑別が必要であった。細菌検査において、COVID（-）、インフルエンザを含む呼吸器感染ウィルス 15 種及びマイコプラズマ・百日咳・クラミジア陰性である。薬剤性肺障害が疑わしいが、抗菌薬投与により CRP 低下も認められたため、感染症の合併も考えられる。 治験薬との因果関係が否定できないため、治験は中止とする。 CT、細菌検査の結果より事象名を肺炎から薬剤性肺障害へ変更する。

出典：SGN-35-OU 試験　治験総括報告書　12.3.2、付録 16.2.1-1、付録 16.2.4-1、付録 16.2.4-2 及び付録 16.2.4-3

COVID : 新型コロナウイルス感染症、CRP : C 反応性蛋白、CT : コンピュータ断層撮影、MedDRA : 国際医薬用語集、WBC : 白血球数

被験者の情報のうち、年齢／性別、人種、試験治療、重篤な有害事象／重症度／転帰、病歴及び併用薬は治験総括報告書の Listing を参照した。経過・処置並びに治験責任医師の見解は、治験総括報告書の Section 12.3.2 を参照した。

経過・処置の Study Day は、報告された日から Cycle 1 Day 1 の治験薬の初回投与日を引き、初回投与日以降の日付の場合は 1 を足して算出した（初回投与日を Day 1 とする）。

有害事象は MedDRA/J 第 24.1 版を用いてコード化した。

(a) 当該被験者の原疾患は、「菌状息肉症」から「原発性皮膚未分化大細胞リンパ腫」に修正された（治験総括報告書　11.2）。

表 2.7.6.2-3　重篤な有害事象の叙述（2）

症例番号	[redacted]	人種	アジア人
年齢／性別	5[redacted] 歳／男性	試験治療	ブレンツキシマブ　ベドチン
重篤な有害事象（MedDRA 基本語）／重症度／転帰	左鼠径ヘルニア（単径ヘルニア）／Grade 3／回復		
原疾患／病歴	菌状息肉症／胃潰瘍、甲状腺機能低下症、不眠症		
併用薬	プロペト、フェキソフェナジン塩酸塩 OD 錠、チラーヂン S 錠、ネキシウムカプセル、ゾルピデム酒石酸塩錠、オーグメンチン配合錠、アセトアミノフェン錠、ミヤ BM 細粒、レスタミンコーワクリーム、ヘパリン類似物質クリーム 0.3%「ニプロ」、センノシド錠 12mg「サワイ」、アセトアミノフェン 500mg「マルイシ」、プロポフォール静注 1%20ml「マルイシ」、ロクロニウム静注液 50mg/5.0ml「マルイシ」、アセリオ静注液バック 1000mg/100ml、フェンタニル注射液 0.1mg/2ml、エフェドリン注射液 40mg/1ml、レミフェンタミル、セファゾリン Na 注射用 1g、プリンペラン注射用 10mg/2ml		
経過・処置	20[redacted] 年[redacted] 月[redacted] 日（Day -7）：本治験参加の同意取得。 20[redacted] 年[redacted] 月[redacted] 日（Day 1）：サイクル 1 治験薬投与開始。 20[redacted] 年[redacted] 月[redacted] 日（Day 63）：サイクル 4 治験薬投与。 20[redacted] 年[redacted] 月[redacted] 日（Day 68）：被験者が、左鼠径部に腫瘤を確認。 20[redacted] 年[redacted] 月[redacted] 日（Day 85）：サイクル 5 治験薬投与。 20[redacted] 年[redacted] 月[redacted] 日（Day 99）：左鼠径部に痛みを伴う。 20[redacted] 年[redacted] 月[redacted] 日（Day 106）：サイクル 6 治験薬投与。当院の外科にコンサルとする。 20[redacted] 年[redacted] 月[redacted] 日（Day 107）：外科にて、左鼠径ヘルニアと診断。手術予定となる。 20[redacted] 年[redacted] 月[redacted] 日（Day 128）：サイクル 7 治験薬投与。 20[redacted] 年[redacted] 月[redacted] 日（Day 135）：手術目的のため、入院する。重篤な有害事象の報告第 1 報提出。 20[redacted] 年[redacted] 月[redacted] 日（Day 136）：腹腔鏡下左鼠径ヘルニア手術施行。問題なく終了。 20[redacted] 年[redacted] 月[redacted] 日（Day 138）：軽快退院する。 20[redacted] 年[redacted] 月[redacted] 日（Day 140）：重篤な有害事象の報告第 2 報提出。 20[redacted] 年[redacted] 月[redacted] 日（Day 149）：サイクル 8 治験薬投与。有害事象なく投与終了する。 20[redacted] 年[redacted] 月[redacted] 日（Day 171）：サイクル 9 治験薬投与。有害事象なく投与終了する。 20[redacted] 年[redacted] 月[redacted] 日（Day 191）：外科受診、創クリア、左鼠径部膨隆なし。外科の診察内容、CT の結果より回復と判断する。		
治験責任医師の見解	本事象に対し、入院手術となったため、重篤な有害事象として報告する。 治験薬との因果関係は、治験薬投与後より発症しており否定はできない。腹腔鏡下左鼠径ヘルニア手術施行し、軽快退院となった。手術後治験薬投与を実施したが、有害事象なく投与終了している。上記より、被験者の安全性に問題ないため、引き続き治験継続と判断する。 なお、本事象は回復と判断し、最終報告とする。		

出典：SGN-35-OU 試験　治験総括報告書　12.3.2、付録 16.2.1-1、付録 16.2.4-1、付録 16.2.4-2 及び付録 16.2.4-3
CT：コンピュータ断層撮影、MedDRA：国際医薬用語集
被験者の情報のうち、年齢／性別、人種、試験治療、重篤な有害事象／重症度／転帰、病歴及び併用薬は治験総括報告書の Listing を参照した。経過・処置並びに治験責任医師の見解は、治験総括報告書の Section 12.3.2 を参照した。

経過・処置の Study Day は、報告された日から Cycle 1 Day 1 の治験薬の初回投与日を引き、初回投与日以降の日付の場合は 1 を足して算出した（初回投与日を Day 1 とする）。
有害事象は MedDRA/J 第 24.1 版を用いてコード化した。

表 2.7.6.2-4　重篤な有害事象の叙述（3）

症例番号	[redacted]	人種	アジア人
年齢／性別	5[redacted] 歳／男性	試験治療	ブレンツキシマブ　ベドチン
重篤な有害事象（MedDRA 基本語）／重症度／転帰	急性腎障害（急性腎障害）／Grade 3／回復		
原疾患／病歴	菌状息肉症／関節痛		
併用薬	ボアラ軟膏 0.12%、カロナール錠、ロコイドクリーム 0.1%、アムロジピン錠、ゼビアックスローション 2%、クラリス錠、ニューアンメルツヨコヨコ A、パスキネル FR テープ V、フェルビナクパップ 70mgNP、セルタッチテープ、カロナール、ベンザブロック S、プレコール持続性カプセル、ソルデム 1、セフトリアキソン Na 注		
経過・処置	20[redacted] 年 [redacted] 月 [redacted] 日（Day -47）：本治験参加の同意取得。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 1）：C1D1 治験薬投与開始。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 170）：C9D1 治験薬投与。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 188）：発熱、悪寒、食欲低下による感冒症状出現のため、カロナールとベンザブロック S を内服開始。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 189）：症状改善なし。体温 37.0°C 台の微熱が続くため、市販薬のプレコールに変更し様子を見ていた。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 191）：治験薬投与のため来院したところ、採血結果にて腎機能値の悪化あり。体重増加、両下肢浮腫あり。腎臓内科受診した結果、急性腎障害の診断。入院による治療が必要と判断される。アムロジピン、クラリス、市販薬の内服中止。本人の希望にて一旦帰宅。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 192）：精査、加療目的で入院となる。尿中白血球、細菌、亜硝酸塩を認めないが、腎盂腎炎の可能性も否定できずセフトリアキソン Na 注 1g/日、補液 1000mL/日開始となった。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 195）：採血実施。クレアチニン 1.28 mg/dL。補液終了となる。体重減少傾向。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 198）：採血実施。クレアチニン 1.16 mg/dL。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 202）：セフトリアキソン Na 注投与中止。抗核抗体 7.1。MPO-ANCA <1.00。クレアチニンクリアランス（24 時間蓄尿）101 であり、腎機能障害が残存しているか評価困難。炎症反応はベースライン程度まで回復。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 203）：治験薬との因果関係は否定できないこと、再投与によるリスクについてご本人へ説明。ご本人より治療継続の希望あり。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 204）：腎機能障害の回復を認めたため自宅退院となる。		
治験責任医師の見解	過去の副作用報告などから治験薬との因果関係は否定的と考えている。 現時点で原因不明のため、入院の上、精査を進めていく。 腎障害の原因として薬剤性、何らかの感染症の可能性を考え精査を進めたが、検査データと臨床所見が一致せず原因は不明であった。補液、抗生剤の点滴にて腎機能障害は改善した。腎障害の原因精査として腎生検も考慮されたが、リスクもあるため実施しなかった。プレコール持続性カプセルは過去に服用歴あり。ベンザブロック S は初めての内服であった。もともと内服していたアムロジピンとクラリスは中止し必要時別の薬剤を検討することとした。 今後、外来で心機能評価を実施後に治験薬再開予定であり、慎重に進めていく。 第 1 報で治験薬との因果関係なしと報告していたが、既知の事象であり、現時点では関連性を完全に否定できないため因果関係ありへ変更した。		

出典：SGN-35-OU 試験　治験総括報告書　12.3.2、付録 16.2.1-1、付録 16.2.4-1、付録 16.2.4-2 及び付録 16.2.4-3
CT：コンピュータ断層撮影、C：Cycle、D：Day、MedDRA：国際医薬用語集、MPO-ANCA：抗好中球細胞質ミエロペルオキシダーゼ抗体、WBC：白血球数
被験者の情報のうち、年齢／性別、人種、試験治療、重篤な有害事象／重症度／転帰、病歴及び併用薬は治験総括報告書の Listing を参照した。経過・処置並びに治験責任医師の見解は、治験総括報告書の Section 12.3.2 を参照した。
経過・処置の Study Day は、報告された日から Cycle 1 Day 1 の治験薬の初回投与日を引き、初回投与日以降の日付の場合は 1 を足して算出した（初回投与日を Day 1 とする）。
有害事象は MedDRA/J 第 24.1 版を用いてコード化した。

表 2.7.6.2-5　重篤な有害事象の叙述（4）

症例番号	[redacted]	人種	アジア人
年齢／性別	4[redacted] 歳／女性	試験治療	ブレンツキシマブ　ベドチン
重篤な有害事象（MedDRA 基本語）／重症度／転帰	発熱（発熱）／Grade 3／回復 好中球減少（好中球数減少）／Grade 4／回復 高尿酸血症（高尿酸血症）／Grade 1／回復		
原疾患／病歴	菌状息肉症／不眠症、喘息、便秘、ドライアイ、造影剤アレルギー、食物アレルギー、脂肪肝、甲状腺機能低下症、アレルギー性結膜炎、接触皮膚炎		
併用薬	リンデロン V 軟膏 0.12%、ヒルドイドクリーム 0.3%、ヒルドイドローション 0.3%、白色ワセリン、ロコイド軟膏 0.1%、亜鉛華（10%）単軟膏、アレロック OD 錠 5mg、チラーヂン S 錠 50μg、マグミット錠 330mg、ヒアレイン点眼液 0.1%、眼耳用リンデロン A 軟膏、ザイザル錠 5mg、ロキソプロフェン錠 60mg、レバミピド錠 100mg、デルモゾール軟膏 0.12%、ビーソフテンクリーム 0.3%、ユナシン錠 375mg、オロパタジン塩酸塩 OD 錠 5mg、メイアクト MS 錠、メトクロプラミド錠 5mg、クラビット点眼液 1.5%、フィルグラスチム BS 注 75μg、クラビット点眼液 0.5%、パタノール点眼液 0.1%、ニゾラールクリーム 2%、フィルグラスチム BS 注 150μg、フシジンレオ軟膏 2%、タリビット眼軟膏、ガチフロ点眼液 0.3%、ナゾネックス点鼻液 50μg、ジーラスタ皮下注 3.6mg/0.36ml、フルメトロン点眼液 0.1%、メチコバール錠 500μg、ケフラールカプセル 250mg、カロナール錠 200mg、ソルアセト F 輸液 500ml、フェブリク錠 10mg、ブロチゾラム OD 錠 0.25mg、セファゾリン Na 点滴静注用 1g、塩酸テルビナフィンクリーム 1%、ランソプラゾール OD 錠 15mg、ビオフェルミン配合散、塩酸テルビナフィンクリーム 1%、10%サリチル酸ワセリン軟膏東豊		
経過・処置	20[redacted] 年 [redacted] 月 [redacted] 日（Day -25）：本治験参加の同意取得。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 1）：C1D1 治験薬投与開始。夕方より倦怠感出現。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 2）：発熱なく、採血結果でも異常所見をみとめていないが倦怠感は持続。本日退院予定であったが、倦怠感と治験薬の因果関係は否定できず、経過観察のため延期とする。本事象は入院期間の延長を要する事象であるため SAE 報告とした。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 3）：0:30　体温 37.9°C の発熱あり。ロキソプロフェン内服し、1:30 には体温 38.2°C まで上昇するが、その後解熱。倦怠感は持続。17:10　体温 38.3°C まで上昇、ロキソプロフェン内服。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 4）：朝には体温 36.7°C と解熱。倦怠感軽減しており本事象は軽快と判断。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 8）：外来受診して，発熱はないことを確認。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 21）：　*Day 8 の受診日にて発熱は消失し回復と判断される。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 63）：C3 治験薬投与のために入院。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 64）：C3D1 治験薬投与。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 69）：白血球減少：Grade 2、好中球減少：Grade 3。 *Day 69 、*Day 70の 2 日間 G-CSF 投与。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 71）：白血球、好中球ともに著明に上昇。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 74）：再度、白血球減少：Grade 2、好中球減少：Grade 3 となり G-CSF 投与。経過観察のため入院延長が必要となり重篤と判断。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 75）：採血行い、白血球数・好中球数改善。		

*新薬承認情報提供時に置き換え

表 2.7.6.2-5　重篤な有害事象の叙述（4）（続き）

経過・処置（続き）	20[redacted]年[redacted]月[redacted]日（Day 76）：再検し、白血球減少：Grade 2、好中球減少：Grade 1。 20[redacted]年[redacted]月[redacted]日（Day 77）：退院。一週間後に再検予定。 20[redacted]年[redacted]月[redacted]日（Day 78）：他院で採血行い、白血球 1700：Grade 3、好中球 470：Grade 4。G-CSF 投与。 20[redacted]年[redacted]月[redacted]日（Day 92）：採血にて白血球・好中球数改善認める。 20[redacted]年[redacted]月[redacted]日（Day 105）：採血にて白血球数・好中球数低下なし。回復と判断される。 20[redacted]年[redacted]月[redacted]日（Day 189）：C8 治験薬投与のために入院。 20[redacted]年[redacted]月[redacted]日（Day 190）：C8D1 治験薬投与。 20[redacted]年[redacted]月[redacted]日（Day 192）：C8D1 投与後 3 日目から 1 日 1 回程度 BT37 度後半の発熱あり。 20[redacted]年[redacted]月[redacted]日（Day 196）：尿酸値の急上昇：Grade 1（投与前 UA:5.0→10.1）。その他は著明な電解質異常や排尿障害等なし。細胞外液 1000 mL/日。 20[redacted]年[redacted]月[redacted]日（Day 197）：UA:9.1。その他の電解質異常や腎障害は認めず。フェブリク内服開始。経過観察及び補液 500 mL/日投与のため入院延長が必要となった。 20[redacted]年[redacted]月[redacted]日（Day 198）：症状確認し退院となった。 20[redacted]年[redacted]月[redacted]日（Day 385）：C15D21 UA: 3.8。 20[redacted]年[redacted]月[redacted]日（Day 386）：C16D1 治験薬投与。全 16 サイクルの治験薬投与が終了した。 20[redacted]年[redacted]月[redacted]日（Day 390）：UA: 5.8。 20[redacted]年[redacted]月[redacted]日（Day 414）：EOT。UA: 4.2 のためフェブリク中止。 20[redacted]年[redacted]月[redacted]日（Day 456）：UA: 3.2。 20[redacted]年[redacted]月[redacted]日（Day 505）：PTFU。UA: 3.4。16 サイクル終了後はフェブリク中止後も尿酸値再上昇なし。回復と判断した。

表 2.7.6.2-5　重篤な有害事象の叙述（4）（続き）

治験責任医師の見解	20[redacted] 年 [redacted] 月 [redacted] 日： 「疲労感」により入院期間の延長を要したため SAE 第 1 報報告。「疲労感」は、治験薬投与後に発現していること、また、治験薬で既知の事象であることから治験薬との因果関係ありと判断した。 20[redacted] 年 [redacted] 月 [redacted] 日： 「疲労感」に続いて「発熱」がみられており、臨床経過より「疲労感」は「発熱」に包含される一連の事象であると判断する。このことより、事象名を「疲労」から「発熱」へ再考し SAE 第 2 報として報告する。なお、「発熱」は治験薬で既知の事象であることから治験薬との因果関係ありと判断する当初の見解からの変更はない。 因果関係の判断理由：本治験薬投与後に好中球減少が生じており、#3 コース目に追加した薬剤もなく、本治験薬の関与が妥当と考えられる。 因果関係の判定理由：本治験薬投与後に尿酸値上昇が生じており、時系列的に因果関係が否定できない。

出典：SGN-35-OU 試験　治験総括報告書　12.3.2、付録 16.2.1-1、付録 16.2.4-1、付録 16.2.4-2 及び付録 16.2.4-3
BT : 体温、CT : コンピュータ断層撮影、C : Cycle、D : Day、EOT : 治療終了、G-CSF : 顆粒球コロニー形成刺激因子、MedDRA : 国際医薬用語集、PTFU：治験後観察期間、SAE：重篤な有害事象、UA：尿酸、WBC：白血球数
被験者の情報のうち、年齢／性別、人種、試験治療、重篤な有害事象／重症度／転帰、病歴及び併用薬は治験総括報告書の Listing を参照した。経過・処置並びに治験責任医師の見解は、治験総括報告書の Section 12.3.2 を参照した。
経過・処置の Study Day は、報告された日から Cycle 1 Day 1 の治験薬の初回投与日を引き、初回投与日以降の日付の場合は 1 を足して算出した（初回投与日を Day 1 とする）。
有害事象は MedDRA/J 第 24.1 版を用いてコード化した。

表 2.7.6.2-6　重篤な有害事象の叙述（5）

症例番号	[redacted]	人種	アジア人
年齢／性別	3[redacted] 歳／男性	試験治療	ブレンツキシマブ　ベドチン
重篤な有害事象（MedDRA 基本語）／重症度／転帰	好酸球増多症（好酸球増加症）／Grade 3／軽快		
原疾患／病歴	原発性皮膚未分化大細胞リンパ腫／アトピー性皮膚炎、便秘、季節性アレルギー		
併用薬	ロキソプロフェン錠、ムコスタ錠、白色ワセリン、ゲンタマイシン硫酸塩軟膏、ロコイド軟膏 0.1%、ヒルドイドソフト軟膏 0.3%、トアラセット配合錠、トラマール OD 錠、センノシド錠、タリージェ錠、フェキソフェナジン塩酸塩錠、カロナール錠、プレドニン錠、ネキシウム懸濁用顆粒分包、タケキャブ錠、オメプラゾール錠、ダイフェン配合錠、フルコナゾールカプセル、ボナロン錠、ツムラ葛根湯エキス顆粒、リリカ OD 錠、ヒルドイドクリーム 0.3%、オロパタジン塩酸塩 OD 錠、ビラノア錠、バラシクロビル錠		
経過・処置	20[redacted] 年 [redacted] 月 [redacted] 日（Day -23）：本治験参加の同意取得。 20[redacted] 年 [redacted] 月 [redacted] 日（Day -3）：スクリーニング時、好酸球: 7.4%。治験薬投与及び状態観察のために入院。C2 投与終了まで入院の予定。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 1）：C1D1 治験薬投与開始。C1D5（20[redacted] 年 [redacted] 月 [redacted] 日）に好酸球: 12.0%（835/μL）。その後も上昇傾向。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 22）：C2D1 治験薬投与。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 24）：好酸球: 43.6%（3479/μL）。その他は著明なデータ異常認めず。トアラセット、トラマールの影響が疑わしく、トアラセットは中止、トラマールの内服を控えるように指示。経過観察及び薬剤調整のため、入院期間を延長した。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 33）：好酸球: 70.7%（10435/μL）となり、プレドニン 20 mg 服用開始。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 40）：好酸球: 29.8%（2333/μL）となり翌日（20[redacted] 年 [redacted] 月 [redacted] 日）よりプレドニン 10 mg に減量。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 42）：好酸球: 30.0%（2277/μL）となりプレドニンの内服を本日を以て一旦終了とする。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 43）：好酸球: 28.3%（2193/μL）。C3D1 治験薬投与。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 45）：好酸球: 46.5%（4026/μL）となり、プレドニン 20 mg/日で服用再開。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 49）：C3D5（20[redacted] 年 [redacted] 月 [redacted] 日）好酸球: 24.2%（1512/μL）。本日よりプレドニン 10 mg に減量し退院となったため、本事象は軽快と判断した。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 358）：プレドニン 5 mg/日に減量。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 496）：プレドニン 2.5 mg/日に減量。 20[redacted] 年 [redacted] 月 [redacted] 日（Day 692）：プレドニン内服継続にて好酸球 10%以下を維持している。状態安定しており、本事象は軽快のまま追跡不要と判断した。		
治験責任医師の見解	因果関係の判断根拠：入院後より徐々に好酸球上昇が生じており、新規開始の薬剤で頻度と開始のタイミングからトアラセット、トラマールの影響が疑わしいが、治験薬との因果関係も否定できない。 （　　*Day 45　　追記）トアラセット、トラマールの影響が疑われたが現在は中止している。ステロイド投与により一旦好酸球低下を認めたが、治験薬投与のタイミングで再上昇しており、治験薬との因果関係はありと考えるのが妥当である。		

*新薬承認情報提供時に置き換え

出典：SGN-35-OU 試験　治験総括報告書　12.3.2、付録 16.2.1-1、付録 16.2.4-1、付録 16.2.4-2 及び付録 16.2.4-3
C：Cycle、D：Day、MedDRA：国際医薬用語集
被験者の情報のうち、年齢／性別、人種、試験治療、重篤な有害事象／重症度／転帰、病歴及び併用薬は治験総括報告書の Listing を参照した。経過・処置並びに治験責任医師の見解は、治験総括報告書の Section 12.3.2 を参照した。
経過・処置の Study Day は、報告された日から Cycle 1 Day 1 の治験薬の初回投与日を引き、初回投与日以降の日付の場合は 1 を足して算出した（初回投与日を Day 1 とする）。
有害事象は MedDRA/J 第 24.1 版を用いてコード化した。

表 2.7.6.2-7　死亡及び重篤な有害事象の叙述（当該被験者で報告された有害事象）

登録番号 性別／年齢	原疾患	治験薬投与開始日	有害事象名	MedDRA PT	発現時期	発現日（日数）	消失日（日数）	発現期間（日）	重症度	重篤性(a)	転帰	治験薬に関する処置	因果関係	判定理由
[redacted] M/7[redacted]	pcALCL	20[redacted]	末梢神経障害	末梢性ニューロパチー	Cycle 1	20[redacted]（2）			1	非重篤	軽快	継続	関連あり	治験薬投与後に生じているため。
			CRP 上昇	Ｃ－反応性蛋白増加	Cycle 1	20[redacted]（2）	20[redacted]（20）	19	2	非重篤	回復	継続	関連なし	多発する皮膚の潰瘍によるものと判断する。
			悪心	悪心	Cycle 1	20[redacted]（2）	20[redacted]（62）	61	2	非重篤	回復	継続	関連あり	治験薬投与後より生じたため。
			脂質異常症	脂質異常症	Cycle 3	20[redacted]（41）	20[redacted]（272）	232	1	非重篤	回復	継続	関連あり	治験薬投与後に発症したため。
			γGTP 上昇	γ－グルタミルトランスフェラーゼ増加	Cycle 10	20[redacted]（188）	20[redacted]（295）	108	2	非重篤	回復	継続	関連あり	投与中止後、軽快方向にあるため。
			CRP 上昇	Ｃ－反応性蛋白増加	Cycle 13	20[redacted]（272）	20[redacted]（289）	18	2	非重篤	回復	休薬	関連あり	投与中止後、軽快方向にあるため。
			薬剤性肺障害	肺毒性	Cycle 13	20[redacted]（279）			3	重篤	軽快	投与中止	関連あり	投与中止後に軽快し、また各種感染症が否定的であり、CT 画像、血清 KL-6 上昇から、間質性肺障害を呈したため。
[redacted] M/5[redacted]	MF	20[redacted]	末梢神経障害	末梢性ニューロパチー	Cycle 1	20[redacted]（3）			3	非重篤	軽快	投与中止	関連あり	治験薬投与後に生じたため。
			発熱	発熱	Cycle 2	20[redacted]（29）	20[redacted]（30）	2	2	非重篤	回復	継続	関連あり	治験薬投与後より生じたため。
			皮疹	発疹	Cycle 2	20[redacted]（38）	20[redacted]（148）	111	1	非重篤	回復	継続	関連あり	投与後より皮疹が出現したため。
			発熱	発熱	Cycle 4	20[redacted]（64）	20[redacted]（65）	2	1	非重篤	回復	継続	関連あり	治験薬投与後に生じているため。
			発熱	発熱	Cycle 4	20[redacted]（79）	20[redacted]（81）	3	1	非重篤	回復	継続	関連なし	2 時間炎天下を自転車で移動したため。
			左鼠径ヘルニア	鼠径ヘルニア	Cycle 6	20[redacted]（107）	20[redacted]（191）	85	3	重篤	回復	継続	関連あり	投与後より出現し、悪化したため、治験薬との因果関係が否定できなかったため。

表 2.7.6.2-7　死亡及び重篤な有害事象の叙述（当該被験者で報告された有害事象）（続き）

登録番号 性別／年齢	原疾患	治験薬 投与 開始日	有害 事象名	MedDRA PT	発現時期	発現日 （日数）	消失日 （日数）	発現 期間 （日）	重症度	重篤性(a)	転帰	治験薬に 関する 処置	因果 関係	判定理由
[redacted] M/5[redacted]	MF	20[redacted]	関節痛	関節痛	Cycle 1	20[redacted] （1）	20[redacted] （2）	2	1	非重篤	回復	継続	関連なし	投与前から同症状が時々あり。
			末梢性感覚ニューロパチー	末梢性感覚ニューロパチー	Cycle 1	20[redacted] （4）			2	非重篤	未回復	減量	関連あり	投与後に出現していて、治験薬で出現頻度が高い症状のため。
			アスパラギン酸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	Cycle 1	20[redacted] （7）	20[redacted] （195）	189	1	非重篤	回復	継続	関連あり	治験薬開始後から出現したため。
			アラニン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	Cycle 1	20[redacted] （7）	20[redacted] （198）	192	1	非重篤	回復	継続	関連あり	治験薬開始後から出現したため。
			高血圧	高血圧	Cycle 2	20[redacted] （23）			2	非重篤	未回復	継続	関連なし	投与前から上昇傾向もみられたため。
			右肩痛	関節痛	Cycle 4	20[redacted] （82）	20[redacted] （336）	255	2	非重篤	回復	継続	関連なし	以前からたびたびあった症状のため。
			感冒	上咽頭炎	Cycle 9	20[redacted] （188）	20[redacted] （196）	9	2	非重篤	回復	継続	関連なし	偶発的事象のため。
			急性腎障害	急性腎障害	Cycle 9	20[redacted] （191）	20[redacted] （204）	14	3	重篤	回復	休薬	関連あり	過去の副作用報告などから。
			リパーゼ増加	リパーゼ増加	Cycle 9	20[redacted] （191）	20[redacted] （254）	64	2	非重篤	回復	継続	関連あり	治験薬投与後から増加したため。
			左室流出路狭窄	左室流出路閉塞	Cycle 9	20[redacted] （205）			1	非重篤	未回復	継続	関連なし	過去に報告がないため。
			足白癬	足部白癬	Cycle 10	20[redacted] （212）			1	非重篤	未回復	継続	関連なし	一般的な疾患のため。
			好酸球増加症	好酸球増加症	Cycle 14	20[redacted] （338）	20[redacted] （345）	8	1	非重篤	回復	休薬	関連あり	報告されている事象のため。

表 2.7.6.2-7　死亡及び重篤な有害事象の叙述（当該被験者で報告された有害事象）（続き）

登録番号 性別／年齢	原疾患	治験薬 投与 開始日	有害 事象名	MedDRA PT	発現時期	発現日 （日数）	消失日 （日数）	発現 期間 （日）	重症度	重篤性(a)	転帰	治験薬に 関する 処置	因果 関係	判定理由
[redacted] F/4[redacted]	MF	20[redacted]	発熱	発熱	Cycle 1	20[redacted] （1）	20[redacted] （8）	8	3	重篤	回復	継続	関連あり	投与直後より症状が発現しているため。
			倦怠感	倦怠感	Cycle 1	20[redacted] （1）	20[redacted] （505）	505	1	非重篤	回復	継続	関連あり	治験薬の副作用として妥当と考える。
			薬疹	薬疹	Cycle 1	20[redacted] （3）	20[redacted] （22）	20	1	非重篤	回復	継続	関連あり	投与直後より症状が発現しているため。
			高トリグリセリド血症	高トリグリセリド血症	Cycle 1	20[redacted] （8）	20[redacted] （15）	8	3	非重篤	回復	継続	関連なし	食生活によるものと考えられるため。
			中耳炎	中耳炎	Cycle 1	20[redacted] （19）	20[redacted] （64）	46	2	非重篤	回復	継続	関連なし	偶発的事象と考えられるため。
			悪心	悪心	Cycle 2	20[redacted] （25）	20[redacted] （505）	481	1	非重篤	回復	継続	関連あり	治験薬の副作用として妥当であると考えられるため。
			結膜炎	結膜炎	Cycle 2	20[redacted] （27）	20[redacted] （126）	100	2	非重篤	回復	継続	関連なし	偶発的事象と考えられるため。
			白血球減少	白血球数減少	Cycle 2	20[redacted] （36）	20[redacted] （43）	8	3	非重篤	回復	休薬	関連あり	治験薬としての副作用として妥当であると考えられるため。
			好中球減少	好中球数減少	Cycle 2	20[redacted] （36）	20[redacted] （43）	8	3	非重篤	回復	休薬	関連あり	治験薬としての副作用として妥当であると考えられるため。
			肝機能障害	肝機能異常	Cycle 2	20[redacted] （36）	20[redacted] （63）	28	3	非重篤	回復	休薬	関連あり	治療の時間的経過から妥当であると考えられるため。
			四肢浮腫	末梢性浮腫	Cycle 2	20[redacted] （41）			2	非重篤	軽快	継続	関連あり	治験薬の副作用として妥当と考える。
			末梢神経障害	末梢性ニューロパチー	Cycle 3	20[redacted] （63）	20[redacted] （673）	611	3	非重篤	回復	休薬	関連あり	治験薬の副作用として妥当であると考えられるため。
			足白癬	足部白癬	Cycle 3	20[redacted] （68）	20[redacted] （257）	190	2	非重篤	回復	継続	関連なし	偶発的事象であると考えられるため。
			白血球減少	白血球数減少	Cycle 3	20[redacted] （69）	20[redacted] （105）	37	3	非重篤	回復	減量	関連あり	治験薬の副作用として妥当であると考えられるため。
			好中球減少	好中球数減少	Cycle 3	20[redacted] （69）	20[redacted] （105）	37	4	重篤	回復	減量	関連あり	治験薬の副作用として妥当であると考えられるため。

表 2.7.6.2-7　死亡及び重篤な有害事象の叙述（当該被験者で報告された有害事象）（続き）

登録番号 性別／年齢	原疾患	治験薬 投与 開始日	有害 事象名	MedDRA PT	発現時期	発現日 （日数）	消失日 （日数）	発現 期間 （日）	重症度	重篤性(a)	転帰	治験薬に 関する 処置	因果 関係	判定理由
			アレルギー性鼻炎	アレルギー性鼻炎	Cycle 3	20[redacted] （93）	20[redacted] （151）	59	2	非重篤	回復	継続	関連なし	季節的な偶発的事象と考えられるため。
			発熱	発熱	Cycle 4	20[redacted] （107）	20[redacted] （108）	2	1	非重篤	回復	継続	関連あり	治験薬の副作用として妥当と考える。
			関節痛	関節痛	Cycle 4	20[redacted] （110）	20[redacted] （505）	396	1	非重篤	回復	継続	関連なし	白血球減少に伴いジーラスタを使用したため。
			好中球減少	好中球数減少	Cycle 5	20[redacted] （130）	20[redacted] （147）	18	3	非重篤	回復	継続	関連あり	治験薬の副作用として妥当と考える。
			白血球減少	白血球数減少	Cycle 5	20[redacted] （130）	20[redacted] （147）	18	2	非重篤	回復	継続	関連あり	治験薬の副作用として妥当と考える。
			発熱	発熱	Cycle 5	20[redacted] （131）	20[redacted] （132）	2	1	非重篤	回復	継続	関連あり	治験薬の副作用として妥当と考える。
			右頸部圧痛	頚部痛	Cycle 6	20[redacted] （161）	20[redacted] （176）	16	2	非重篤	回復	継続	関連なし	偶発的事象と考えられるため。
			毛包炎	毛包炎	Cycle 7	20[redacted] （186）	20[redacted] （192）	7	2	非重篤	回復	継続	関連なし	偶発的事象と考えられるため。
			発熱	発熱	Cycle 8	20[redacted] （192）	20[redacted] （211）	20	1	非重篤	回復	継続	関連あり	治験薬の副作用として妥当と考える。
			CRP 増加	Ｃ－反応性蛋白増加	Cycle 8	20[redacted] （193）	20[redacted] （197）	5	1	非重篤	回復	継続	関連あり	治験薬の効果として考えられるため。
			高尿酸血症	高尿酸血症	Cycle 8	20[redacted] （196）	20[redacted] （505）	310	1	重篤	回復	継続	関連あり	治験薬の効果として腫瘍崩壊がおきた可能性があるため。
			異汗性湿疹	異汗性湿疹	Cycle 10	20[redacted] （257）	20[redacted] （505）	249	2	非重篤	回復	継続	関連なし	偶発的事象と考えられるため。
			胸やけ	消化不良	Cycle 11	20[redacted] （276）			2	非重篤	軽快	継続	関連あり	治験薬投与後から生じているため。
			下痢	下痢	Cycle 11	20[redacted] （277）	20[redacted] （414）	138	1	非重篤	回復	継続	関連なし	偶発的事象と考えられるため。
			足白癬	足部白癬	Cycle 14	20[redacted] （343）	20[redacted] （505）	163	2	非重篤	回復	継続	関連なし	偶発的事象と考えられるため。

表 2.7.6.2-7　死亡及び重篤な有害事象の叙述（当該被験者で報告された有害事象）（続き）

登録番号 性別／年齢	原疾患	治験薬投与開始日	有害事象名	MedDRA PT	発現時期	発現日（日数）	消失日（日数）	発現期間（日）	重症度	重篤性(a)	転帰	治験薬に関する処置	因果関係	判定理由
[redacted] M/3[redacted]	pcALCL	20[redacted]	好酸球増多症	好酸球増加症	Cycle 1	20[redacted] （5）			3	重篤	軽快	継続	関連あり	治験薬投与後の上昇を認め、因果関係を否定できない。
			末梢神経障害	末梢性ニューロパチー	Cycle 2	20[redacted] （28）			3	非重篤	軽快	休薬	関連あり	治験薬に特徴的な副作用で開始時期にも合致するため
			四肢浮腫	末梢性浮腫	Cycle 2	20[redacted] （32）	20[redacted] （62）	31	1	非重篤	回復	継続	関連あり	投与後に出現したため。
			不眠症	不眠症	Cycle 2	20[redacted] （34）			1	非重篤	軽快	継続	関連なし	ステロイド全身投与後に出現したため。
			上気道炎	上気道の炎症	Cycle 7	20[redacted] （141）	20[redacted] （146）	6	2	非重篤	回復	継続	関連なし	偶発的事象のため。
			擦過傷	皮膚擦過傷	Cycle 14	20[redacted] （302）	20[redacted] （327）	26	2	非重篤	回復	継続	関連なし	偶発的事象のため。
			播種性帯状疱疹	播種性帯状疱疹	Cycle 16	20[redacted] （349）	20[redacted] （358）	10	2	非重篤	回復	該当せず	関連あり	投与後に発症し、関連性を否定できないため長期ステロイド服用により、免疫機能低下の可能性がある。
			血小板減少	血小板数減少	Cycle 16	20[redacted] （358）	20[redacted] （366）	9	1	非重篤	回復	該当せず	関連なし	播種性帯状疱疹後に出現し、本薬剤（ブレンツキシマブベドチン）との関連性は低いと考える。

出典：SGN-35-OU 試験　治験総括報告書　付録 16.2.4-1 及び付録 16.2.7-2

CT：コンピュータ断層撮影、F：女性、M：男性、MedDRA：国際医薬用語集、MF：菌状息肉症、pcALCL：原発性皮膚未分化大細胞リンパ腫、PT：基本語

有害事象は MedDRA/J 第 24.1 版を用いてコード化した。

(a) 重篤と判断した理由は「治療のため入院又は入院期間の延長が必要となるもの」であった。

2.7.6.2.5 付録 2：重篤な有害事象の一覧

表 2.7.6.2-8　重篤な有害事象の一覧

登録番号 性別／年齢	原疾患	治験薬 投与 開始日	有害 事象名	MedDRA PT	発現時期	発現日 （日数）	消失日 （日数）	発現 期間 （日）	重症度	重篤性(a)	転帰	治験薬に 関する 処置	因果 関係	判定理由
[redacted] M/7[redacted]	pcALCL	20[redacted]	薬剤性肺障害	肺毒性	Cycle 13	20[redacted] （279）			3	重篤	軽快	投与中止	関連あり	投与中止後に軽快し、また各種感染症が否定的であり、CT 画像、血清 KL-6 上昇から、間質性肺障害を呈したため。
[redacted] M/5[redacted]	MF	20[redacted]	左鼠径ヘルニア	鼡径ヘルニア	Cycle 6	20[redacted] （107）	20[redacted] （191）	85	3	重篤	回復	継続	関連あり	投与後より出現し、悪化したため、治験薬との因果関係が否定できなかったため。
[redacted] M/5[redacted]	MF	20[redacted]	急性腎障害	急性腎障害	Cycle 9	20[redacted] （191）	20[redacted] （204）	14	3	重篤	回復	休薬	関連あり	過去の副作用報告などから。
[redacted] F/4[redacted]	MF	20[redacted]	発熱	発熱	Cycle 1	20[redacted] （1）	20[redacted] （8）	8	3	重篤	回復	継続	関連あり	投与直後より症状が発現しているため。
			好中球減少	好中球数減少	Cycle 3	20[redacted] （69）	20[redacted] （105）	37	4	重篤	回復	減量	関連あり	治験薬の副作用として妥当であると考えられるため。
			高尿酸血症	高尿酸血症	Cycle 8	20[redacted] （196）	20[redacted] （505）	310	1	重篤	回復	継続	関連あり	治験薬の効果として腫瘍崩壊がおきた可能性があるため。
[redacted] M/3[redacted]	pcALCL	20[redacted]	好酸球増多症	好酸球増加症	Cycle 1	20[redacted] （5）			3	重篤	軽快	継続	関連あり	治験薬投与後の上昇を認め、因果関係を否定できない。

出典：SGN-35-OU 試験　治験総括報告書　付録 16.2.4-1 及び付録 16.2.7-2

CT：コンピュータ断層撮影、F：女性、M：男性、MedDRA：国際医薬用語集、MF：菌状息肉症、pcALCL：原発性皮膚未分化大細胞リンパ腫、PT：基本語

有害事象は MedDRA/J 第 24.1 版を用いてコード化した。

(a) 重篤と判断した理由は「治療のため入院又は入院期間の延長が必要となるもの」であった。