9 November 2017
EMA/753623/2017

Assessment report

Adcetris

International non-proprietary name: brentuximab vedotin

Procedure No. EMEA/H/C/002455/II/0048

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
ATA	antitherapeutic antibody
autoHSCT	autologous hematopoietic stem cell transplantation
BSA	body surface area
CD30+	CD30-positive
CMA	conditional marketing authorisation
CR	complete response
CTACK	cutaneous T-cell-attracting chemokine
CTCL	cutaneous T-cell lymphoma
DOR	duration of response
EBT	electron beam therapy
ECP	extracorporeal photopheresis
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOS	end of study
EOT	end of treatment
EQ-5D-3L	European Quality of Life 5-Dimension Three Level Version
GGT	gamma-glutamyl transferase
GRS	global response score
HDACi	histone deacetylase inhibitor
HDL	high-density lipoprotein
HL	Hodgkin lymphoma
HRQOL	health-related quality of life
IDMC	independent data monitoring committee
inv	investigator
IRB	institutional review board
IRF	independent review facility
IRR	infusion-related reaction
ISCL	International Society for Cutaneous Lymphoma
IST	investigator-sponsored trial
ITT	intent to treat
LCT	large cell histology
LDL	low-density lipoprotein
LPD	primary cutaneous $CD30^+$ lymphoproliferative disorders
LyP	lymphomatoid papulosis
MF	mycosis fungoides
MID	minimal important difference
MMAE	monomethyl auristatin E
mSWAT	modified severity-weighted assessment tool
NAb	neutralising antibody
NK	natural killer
ORR	objective response rate
ORR4	objective response rate lasting at least 4 months
pc	primary cutaneous
PCL	primary cutaneous lymphoma
pcALCL	primary cutaneous anaplastic large cell lymphoma
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PP	per protocol
PR	partial response

PRO	patient-reported outcome
PUVA	psoralen with ultraviolet light A
QOL	quality of life
r/r	relapsed and refractory
(O)RR	(objective) response rate
SA	scientific advice
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
sCD30	soluble CD30
SD	stable disease
SDT	skin-directed therapy
SS	Sézary syndrome
TAb	total antibody
TARC	thymus and activation regulated chemokine
TBSA	total body surface area
TEAE	treatment-emergent adverse event
tMF	large cell transformation of mycosis fungoides
TNM	Tumour-Node-Metastasis
TNMB	Tumour-Node-Metastasis-Blood
TSAT	time to subsequent antineoplastic therapy
TSEBT	total skin electron beam therapy
TTO	time to onset
ULN	upper limit of the normal range
UVB	narrow-band ultraviolet B

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 4 April 2017 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the new indication "ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) who require systemic therapy", based on data from study C25001 (the 'ALCANZA' study): "A Phase 3 Trial of brentuximab vedotin(SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma". As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated RMP (version 10) has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Adcetris was designated as an orphan medicinal product EU/3/08/595 and EU/3/08/596 on 15th January 2009 in the following respective indications: 'Treatment of anaplastic large cell lymphoma' and 'Treatment of Hodgkin lymphoma'.

The new indication, which is the subject of this application, falls within a separate orphan designation EU/3/11/939 granted 11th January 2012.

Following the CHMP positive opinion on this type II variation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Adcetris as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0168/2015 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	4 April 2017
Start of procedure:	22 April 2017
CHMP Rapporteur Assessment Report	16 June 2017
PRAC Rapporteur Assessment Report	23 June 2017
PRAC Outcome	6 July 2017
CHMP members comments	10 July 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 July 2017
Request for supplementary information (RSI)	20 July 2017
CHMP Rapporteur Assessment Report	13 October 2017
PRAC Rapporteur Assessment Report	13 October 2017
PRAC members comments	18 October 2017
PRAC Outcome	26 October 2017
CHMP members comments	30 October 2017
Updated CHMP Rapporteur Assessment Report	2 November 2017
CHMP opinion:	9 November 2017

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

Primary cutaneous lymphoma's (PCL) are defined as non-Hodgkin lymphoma that present in the skin with no evidence of extra-cutaneous disease at diagnosis.

2.1.2. Epidemiology

In Western countries the estimated annual incidence of PCL is around 1/100.000 and CTCL represent approximately 75 to 80 percent of all PCLs. CTCL is a heterogeneous group of neoplasms of skin-homing T cells that show considerable variation in clinical presentation, histologic appearance and prognosis.

2.1.3. Biologic features

The most common type of CTCL (50-60%) is mycosis fungoides (MF) and its histological variants. Classic MF is an epidermotropic CTCL clinically characterised by the progression from patch stage to plaques stage and lastly to tumour stage. In the literature, the percentage of CD30 positive cells in MF greatly varies (0-80%), but is usually low. The peak age is between 55 and 60 years and the incidence is between 1/350.000 and 1/110.000 (Orphanet).

Other CTCL subtypes

Sezary syndrome (SS, 3% of CTCL) is a leukaemia closely related to MF and should be treated with systemic treatment, such as IFN, retinoids, TSEBT and ECP. Some of the other rarely occurring subtypes also have an aggressive course with poor prognosis and require extensive systemic therapy or multi-agent chemotherapy (e.g. primary CTCL NOS, pc γδ T-cell lymphoma (though rare case with indolent course have been reported), extranodal NK/Tcell lymphoma nasal type). While other subtypes (subcutaneous panniculitis-like T cell lymphoma, pc CD4+ small/medium sized pleomorphic T cell lymphoma proliferative disorder and pc acral CD8+ T cell lymphoma) have excellent prognoses. CD30 expression has been observed for o.a. SS with a median 10% of cells positive. CD30 expression has also been described in PTCL NOS and extranodal NK/Tcell lymphoma in various levels, though literature, as these subtypes, is scarce.

Background CD30

CD30 is a type I transmembrane glycosylated protein and a member of the tumour-necrosis factor receptor superfamily. It was originally identified on Reed-Sternberg cells of Hodgkin Lymphoma, but is also expressed on cell subsets of non-Hodgkin Lymphoma, including anaplastic large cell lymphoma and CTCL as well as on embryonal carcinomas. The CTCL subtype "primary cutaneous CD30+lymphoproliferative disorders" (LPD) have (per definition) a strong and homogenous

CD30expression. Other CTCL subtypes may also express CD30 expression, however, at much lower and variable levels. Other subtypes in which CD30 expression is observed are MF, PTCL NOS and extranodal NK/Tcell lymphoma.

In non-malignant cells, CD30 is expressed on activated (T, B and NK cells), in lower levels of expression on activated macrophages, neutrophils and eosinophils and in negligible expression on naïve or resting lymphocytes. The CD30 signalling pathway mainly activates MAP kinases and NF-κB, which can promote cell proliferation and survival as well as induction of anti-proliferative responses and cell death, depending on the cell type and the co-stimulatory signals involved.

2.1.4. Clinical presentation and prognosis

Primary cutaneous CD30+ lymphoproliferative disorders (LPD) (>75% expression of CD30) are the second most common group of CTCL, accounting for around 30 percent. This group mainly constitutes of primary cutaneous anaplastic large cell lymphoma (pcALCL) (13%) and lymphomatoid papulosis (LyP) (19%). PcALCL presents with (ulcerating) skin tumours up to several centimetres. The mean age at presentation is 60 years. The exact incidence of pcALCL is unknown. PcALCL has considerable overlap with LyP, which is a recurrent, chronic, but (mostly) self-limiting disease.

Prognosis

MF is a disease with a persistent and relapsing course and prognosis is stage dependent. MF stage IA or IB has excellent prognosis, however progression to advanced stages occurs in around 25% of the patients. MF Stage IIB and III has a median survival of 4-6 years and stage IV has a poor prognosis with a median survival of less than 4 years. The prognosis for LPD is excellent with a ten year survival of 90% for pcALCL and 100% for Lyp. Up to 40% of the pcALCL localised lesions show some spontaneous regression. Most patients with pcALCL will attain a CR following initial therapy, however, recurrences occur often (>40%) and patients can experience serial relapses. Extra-cutaneous spread occurs in up to 13% at time of relapse.

Management

Due to the heterogeneity and rarity of PCL controlled trials are rare, there is no standard initial therapy. The early stages of MF can be managed with skin direct therapies (e.g. topical steroids, psoralens +UVA [PUVA], UVB, topical cytostatic agents, local electron beam therapy [EBT]). Ledaga (chlormethine as gel) was recently approved by the EMA for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients. In advanced stages (IIB-IV) recommended options include, in combination or alone: total skin EBT (CR44-74%), PUVA (CR 30-70%), interferon (RR30-60%) and retinoids (RR45-55%) including (second line option) bexarotene (RR30-50%). Many clinicians administer oral methotrexate in refractory (RR ±35%) or in advanced stage disease (RR30-50%), however methotrexate is currently not recommended for MF by the ESMO. In advanced refractory disease gemcitabine or liposomal doxorubicin (RR 40-80%) could be considered. Multi-agent chemotherapy is only indicated in patients with extensive disease (stage IV).

Although a broad spectrum of therapy regimens has been reported, these have been limited to small cohort series or case reports. PcALCL patients with isolated lesions should receive surgical excision or radiation, which can be again used in case of recurrence. With multiple recurrences and/or multiple lesions systemic therapy is recommended due to the morbidity of repeated surgery/radiation. First choice is oral methotrexate (RR 87%). Patients often have recurrence after discontinuation. In case of progression bexarotene (RR ±50% in CTCL patients) and interferon (RR 60% in CTCL patients) are

options. In case of wide spread nodal or visceral involvement or refractory disease gemcitabine and etoposide are options. Multi-agent chemotherapy is only indicated in patients presenting with extra-cutaneous disease or rapidly progressive skin disease (rare).

About the product

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) composed of the monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE). Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell MMAE is released via proteolytic cleavage and degradation of the drug linker. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.

A conditional marketing authorisation (CMA) for Adcetris was granted in October 2012 for the treatment of patients with relapsed or refractory (r/r) CD30+ HL following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. It is also indicated for the treatment of r/r systemic anaplastic large cell lymphoma (sALCL). Specific obligations related to the CMA include OS follow up data for the sALCL population, post-authorisation safety data in HL and sALCL and performing single arm studies in similar sALCL patients and r/r HL patients not eligible for ASCT.

In May 2016 Adcetris was approved for patients with CD30+ HL at increased risk of relapse or progression following ASCT.

The current Type II variation was submitted for the following extension of the indication:

"Adcetris is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) who require systemic therapy"

Extension of indication to include the new indication "ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) who require systemic therapy", based on data from study C25001 (the 'ALCANZA' study): "A Phase 3 Trial of brentuximab vedotin(SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma"

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Brentuximab vedotin is a protein, which is expected to be metabolised in the body and biodegrade in the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), brentuximab vedotin is exempt from the submission of an Environmental Risk Assessment as the product and excipients do not expect to pose a significant risk to the environment. Concerning the antimitotic small molecule MMAE, the PECsurfacewater calculation was adapted to include the newly added indication. The PECsurfacewater value is 0.0029 ug/L, which is below the trigger value for a phase II assessment. Overall, it is

considered that no significant increase in environmental exposure is anticipated with brentuximab vedotin.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data has been submitted for this application which is considered acceptable. Brentuximab vedotin is not considered to pose a significant risk to the environment. Brentuximab vedotin should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

2.2.3. Conclusion on the non-clinical aspects

The CHMP considers that the non-clinical data already submitted in the previous variations and the updated ERA are sufficient to address the non-clinical aspects of this application.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies:

Study	N (ITT)	Patient Population	Design	Treatment Regimen	Objective
C25001 (ALCANZA)	128	Histologically confirmed $CD30^+$ MF or pcALCL(stratified) at least 1 prior systemic therapy or prior radiation (pcALCL only)	Open-label, randomized, multicentre phase III trial	Test arm: brentuximab vedotin 1.8mg/kg iv, D1 of 21day cycle, up to 16cycles Control arm: inv.choice: -bexarotene 300mg/m^2/kg/day oral -methotrexate 5-50mg/week oral max 48weeks	ORR4 (objective response lasting 4 months)

In addition, the MAH provided a summary of the results from investigator-sponsored trials and published case studies to support efficacy of brentuximab vedotin in CTCL subtypes not included in the Alcanza study (Lyp, SS, γδ T cell lymphoma).

2.3.2. Pharmacokinetics

An overview of the clinical pharmacology of brentuximab vedotin was already provided in the assessment reports for the original MAA. Reference PK results for brentuximab vedotin and MMAE at time of initial registration in patients with CD30 positive haematological malignancies is shown in Table 1.

Table 1: PK parameters of ADC and MMAE following first dose of SGN35 1.8 mg/kg studies SG035-0001 and SGN35-008A.

ADC	study	AUC0-inf µg.day/ml	Cmax µg/ml	Tmax day	$t_{1/2}$ day	CL L/h	Vss L

	SG035-0001	79.4 (30%)	32.0 (29%)	0.089	4.4 (38%)	0.073 (17%)	8.2 (24%)
	SGN35-008A	89.8 (25%)	36.7 (34%)	0.024	2.9 (66%)	0.068 (26%)	10.0 (34%)
MMAE	study	AUC0-inf ng.day/ml	Cmax ng/ml	Tmax day	$t_{1/2}$ day	CL L/h	Vss L
	SG035-0001	37.0 (47%)	4.97 (43)	2.1	3.6 (25%)		
	SGN35-008A	40.1 (53%)	4.98 (67%)	3.0	3.7 (19%)		

This section therefore only summarizes additional findings from the Phase 3 study C25001 (ALCANZA) in (CTCL subtype) MF and primary cutaneous anaplastic large-cell lymphoma (pcALCL) patients.

Relevant PK and pharmacodynamic secondary and exploratory objectives in Study C25001 were:

- To further describe the PK of brentuximab vedotin ADC and MMAE in blood.
- To further determine the immunogenicity of brentuximab vedotin.
- To investigate possible correlations between expression of serum protein markers and response.

Distribution

PK parameters of brentuximab vedotin ADC from Study C25001

PK results for C_{max} and Ctrough of brentuximab vedotin ADC from Study C25001 are presented in Table 2 by individual and combined disease subgroups (pcALCL and MF). A concentration versus time curve showing median serum concentration of brentuximab vedotin is displayed in Figure 1.

Table 2: PK parameters of brentuximab vedotin ADC over time (PK population Study C25001)

Parameter	pcALCL N=16	MF N=50	All N=66
C_{max} (µg/mL)			
Cycle 1 Day 1			
n	15	50	65
Geometric mean (%CV)	37.38 (24.575)	37.40 (23.208)	37.39 (23.334)
Cycle 3 Day 1			
n	12	41	53
Geometric mean (%CV)	38.55 (31.630)	32.07 (38.833)	34.43 (37.015)
C_{trough} (µg/mL)			
Cycle 2 Day 1			
n	11	31	42
Geometric mean (%CV)	0.60 (283.199)	0.29 (89.827)	0.35 (381.365)
Cycle 4 Day 1			
n	8	28	36
Geometric mean (%CV)	0.85 (53.388)	0.56 (57.201)	0.61 (56.383)

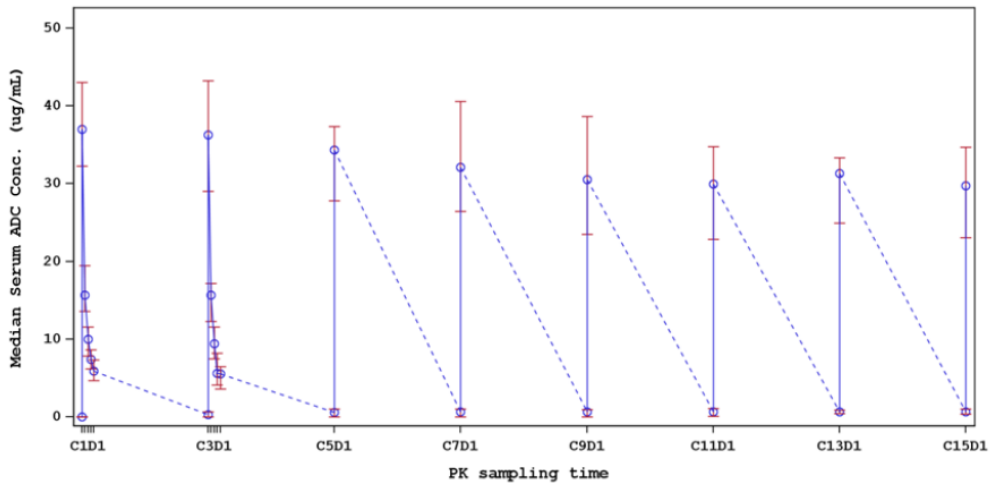


Figure 1: Median serum concentration of brentuximab vedotin ADC time curve (PK population Study C25001)

PK Parameters of Total Antibody from Study C25001

PK results for C_{max} and Ctrough of total antibody (Tab) are presented in Table 3 by individual and combined disease subgroups (pcALCL and MF). A concentration time curve showing median serum concentration of TAb is displayed in Figure 2.

Table 3: PK parameters of TAb over time (PK population Study C25001)

Parameter	pcALCL N=16	MF N=50	All N=66
C_{max} (µg/mL)			
Cycle 1 Day 1			
n	15	50	65
Geometric mean (%CV)	43.80 (21.545)	43.65 (21.600)	43.69 (21.421)
Cycle 3 Day 1			
n	12	41	53
Geometric mean (%CV)	41.51 (23.108)	36.96 (29.655)	37.94 (28.112)
C_{trough} (µg/mL)			
Cycle 2 Day 1			
n	11	32	43
Geometric mean (%CV)	1.63 (166.421)	0.68 (85.052)	0.85 (146.071)
Cycle 4 Day 1			
n	8	29	37
Geometric mean (%CV)	2.83 (50.056)	1.56 (61.762)	1.78 (59.333)

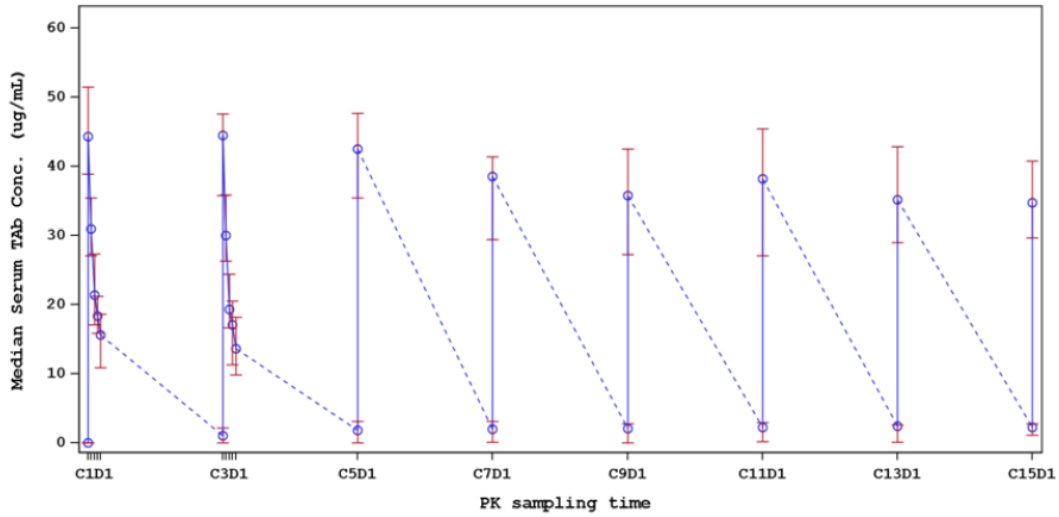


Figure 2: Median serum concentration of TAb-time curve (PK population Study C25001)

PK parameters of MMAE from Study C25001

PK results for C_{max} and Ctrough of MMAE data are presented in Table 4 by individual and combined disease subgroups (pcALCL and MF). A concentration time curve showing median plasma concentration of MMAE is displayed in Figure 3. Due to the sparse PK sampling scheme used in this study, PK samples were not obtained 24 hours post infusion after Cycle 3, which explains the apparent lower C_{max} for MMAE in these cycles.

Table 4: PK parameters of MMAE over time (PK population Study C25001)

Parameter	pcALCL N=16	MF N=50	All N=66
C_{max} (ng/mL)			
Cycle 1 Day 1			
N	13	46	59
Geometric mean (%CV)	2.27 (54.558)	2.90 (56.901)	2.75 (57.544)
Cycle 3 Day 1			
n	12	36	48
Geometric mean (%CV)	2.75 (39.724)	2.84 (41.409)	2.82 (40.658)
C_{trough} (ng/mL)			
Cycle 2 Day 1			
N	11	33	44
Geometric mean (%CV)	0.08 (84.976)	0.07 (66.567)	0.08 (73.058)
Cycle 4 Day 1			
n	10	34	44
Geometric mean (%CV)	0.11 (79.469)	0.08 (85.970)	0.09 (84.337)

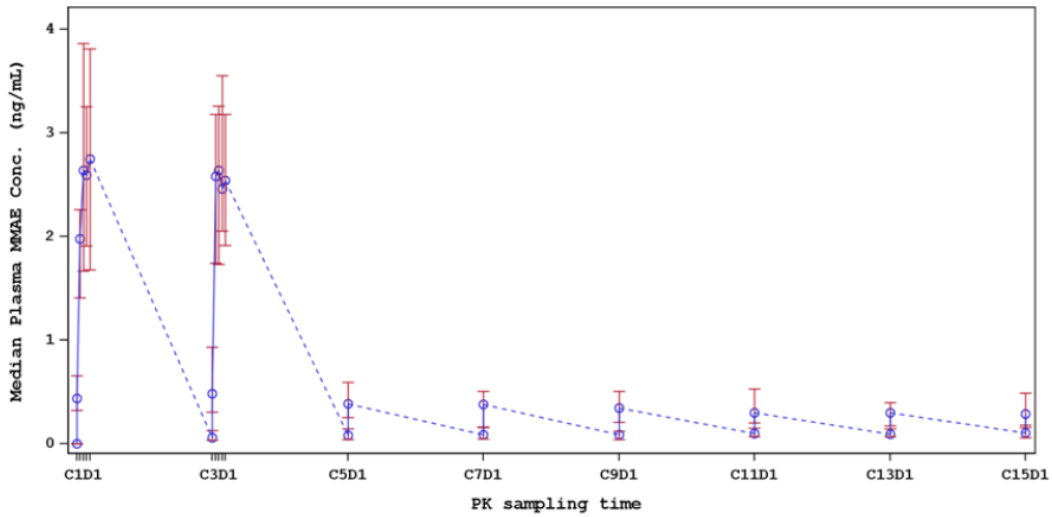


Figure 3: Median plasma concentration of MMAE-time curves (PK population Study C25001)

2.3.3. PK/PD modelling

Population pharmacokinetic modelling

Data obtained from Study C25001 were used in the population pharmacokinetic (PopPK) models for brentuximab vedotin ADCand MMAE. These models were built based on PK data collected in adult patients with CD30+ malignancies who received brentuximab vedotin. There were 380 patients in the dataset, which included data from patients with CTCL, i.e., MF, pcALCL, in Study C25001 combined with data from patients enrolled in 5 other studies with various tumour types (Hodgkin lymphoma (HL), anaplastic large-cell lymphoma (ALCL) and other hematologic malignancies) (SG035-0001, SG035-0002, SG035-0003, SG035-0004, C25007).

The objectives of the PopPK modelling were:

1. To understand the impact of various patient factors (covariates) on the PK of the brentuximab vedotin ADC and MMAE.

2. To use the PopPK models to summarize the systemic exposures of brentuximab vedotin and MMAE in patients with CTCL in Study C25001.

3. To provide a quantitative framework for derivation of individual patient-level exposure metrics for subsequent use in exposure-response analyses of efficacy and safety in Study C25001.

Methodology

Baseline demographic and characteristics data of the patients included in the PopPK model are summarised in Table 5 and Table 6. Age distribution for Study C25001 is depicted in Table 7.

Table 5: Summary of the categorical covariates for all patients in the PopPK dataset

Covariate	Category	N	%
Study	25001	66	17.4
	25007	60	15.8
	35001	48	12.6
	35002	46	12.1
	35003	102	26.8
	35004	58	15.3
Sex	Male	211	55.5
	Female	169	44.5
Race	White	317	83.4
	Black	24	6.3
	Asian	30	7.9
	Alaskan	2	0.5
	Other	7	1.8
Ethnicity	Not Hispanic	344	90.5
	Hispanic	28	7.4
	Not Reported	8	2.1

Table 6: Summary of baseline continuous covariates for all patients in the dataset for the PopPK model

Covariate	Mean	SD	25th Percentile	50th Percentile	75th Percentile	Range	N
Age (yr)	41.57	16.86	28	37	54	12-87	380
Height (cm)*	169.9	15.96	162.6	170.2	178.1	146-200	380
Weight (Kg)	76.46	20.31	61.4	73.1	88	39.1-168.1	380
Body Surface Area (m^2)*	1.865	0.2915	1.674	1.846	2.042	1.264-2.858	380
Albumin (g/L)	36.81	6.599	33	37	42	17-53	380
Alanine Aminotransferase (U/L)	24.64	21.81	13	19	29	4-232	380
Aspartate Aminotransferase (U/L)	24.01	16.97	16	21	27	8-226	380
Bilirubin (umol/L)	7.781	7.544	5.098	6.84	8.55	1.71-123.1	380
Creatinine (umol/L)	72.44	20.52	58.26	70.72	84.99	35.36-159.1	380
Creatinine Clearance (mL/min)	139.3	54.81	104	129.9	166.6	28.52-438.6	380

Table 7: Summary of age covariate for patients from Study C25001

Covariate	Mean	SD	25th Percentile	50th Percentile	75th Percentile	Range	N
Age (yr)	59.39	13.8	51	61	69	22-83	66

The population PK model was developed using a non-linear mixed-effect modelling approach. NONMEM 7.3 software with the first-order conditional estimation method (FOCE) was used.

The effect of intrinsic and extrinsic factors such as gender, body weight, race, age, ethnicity, disease, baseline albumin levels, baseline tumour size, indicators of renal and hepatic function, immunogenicity, and manufacturing process on the PK of ADC and MMAE were explored in the PopPK model.

The concentrations of brentuximab vedotin ADC and MMAE after treatment with brentuximab vedotin have been modelled previously with data available at the time of the original MAA. These previously developed models were used as the structural base models for the current analysis, which includes additional data from Study C25001 (ALCANZA) and Study C25007.

These previous PopPK models for ADC and MMAE were based on a base model which included structural components of the model, which was used to conduct a graphical evaluation of the covariates. Covariates that showed a graphical trend or required further evaluation based on physiological relevance or observation during previous clinical trials of BV were tested as single covariate models ($p<0.01$). A full model including all of the statistically relevant pre-specified covariate effects of interest was then developed. A final model was chosen by retaining only the statistically significant covariate effects ($p<0.001$). The magnitude of the impact of the covariates was also considered, if the magnitude of the impact was small (less than a 20% change over the range of covariate values in the database) or the covariate effect was poorly estimated [e.g., standard error (SE) > 45%] then the covariate was allowed to be reparameterised or discarded.

The final basic structural model was selected on the basis of goodness-of-fit as judged by change in objective function (OBJ), and various diagnostic plots [predicted(PRED)/individual predicted (IPRED) versus observed concentrations, WRES/individual weighted residuals (IWRES) versus time, WRES/IWRES versus PRED/IPRED]. CWRES was used in lieu of or in addition to WRES.

Data from the 6 studies used in the analysis included 22,660 records with 3,450 dosing records and 19,210 concentration records. Of the concentration records 9,541 were for ADC and 9,669 were for MMAE. Overall there were 1,287 concentration records that were BLQ, 649 MMAE (6.7%) and 638 ADC (6.7%) and about half (359 for ADC and 356 for MMAE) of these records were pre-dose concentrations. Therefore approximately 3% (279 for ADC and 393 for MMAE) of the post dose records for each analyte were BLQ. Due to the low proportion of BLQ records in the dataset, these were ignored.

The patients in C25001 were generally the oldest patients in the dataset. The median age for the patients in the entire dataset was 37 years old (mean 42 years) and the median age for patients in C25001 was 61 years old (mean 59 years).

ADC model

A schematic of the ADC PK model is shown in Figure 4 below and was based on the previous analysis. The model for brentuximab vedotin ADC PK was a linear 3-compartment model with zero-order input and first-order elimination.

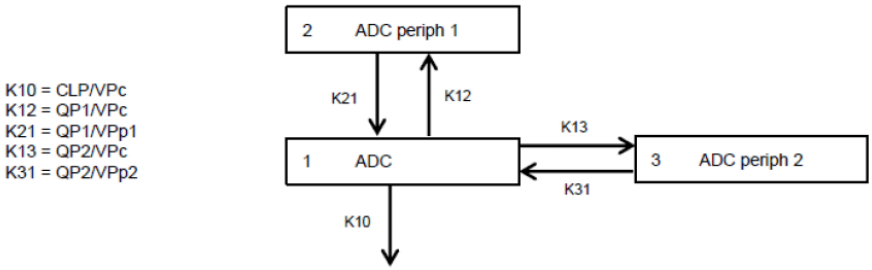


Figure 4: Schematic diagram of the ADC model.

The final model included the effect of pcALCL tumour type on CL, anti-therapeutic antibodies (ATA) on CL, albumin (ALB) on CL, and body surface area (BSA) on CL and central volume of distribution (Vc). There were 3 possible ATA status values in the database (positive, negative, or missing) with the base value (no additional parameters) for patients who had negative ATA status. Separate parameters were estimated for patients with missing values, patients from the older studies (SG035-0001, SG035-0002, SG035-0003, and SG035-0004) with positive values, and patients from the newer studies (C25001 and C25007) with positive values.

The results showed that ATA-positivity status, regardless of the assay used, consistently resulted in fractionally higher CLs. Further, patients with pcALCL (N=16) showed higher concentrations than patients with other tumour types. A pcALCL tumour-type effect was added to CL and resulted in a lower CL than the non-pcALCL patients. The other covariate effects in the model showed that brentuximab vedotin ADC CL and Vc increase with increasing body size, and brentuximab vedotin ADC CL decreases with increasing ALB concentration. The final brentuximab vedotin ADC model parameter estimates are shown in Table 8.

Table 8: Brentuximab vedotin ADC final PK parameters (PK data from Studies C25001, SG035-0001, SG035-0002, SG035-0003, SG035-0004, C25007)

Parameter	Population Mean (SE%)	%CV IIV (Shrinkage)
CL (L/hr)	0.0478 (2.7%)	40.0 (2.4%)
Central volume (V1) (L)	3.5 (1.2%)	14.9 (15.2%)
Intercompartmental CL 1 (Q2) (L/hr)	0.0673 (3.1%)	-
Peripheral volume 1 (V2) (L)	3.67 (2.3%)	-
Intercompartmental CL 2 (Q3) (L/hr)	0.0125 (3.3%)	-
Peripheral volume 2 (V3) (L)	5.79 (1.3%)	-
Antitherapeutic AB positive new studies on CL	0.125 (10.1%)	-
Antitherapeutic AB positive old studies on CL	0.177 (6.0%)	-
Antitherapeutic AB results missing	0.192 (9.4%)	-
BSA on V1	1.27 (4.9%)	-
ALB concentration on CL	-0.496 (3.6%)	-
BSA on CL	0.457 (16.8%)	-
pcALCL tumor type on CL	0.728 (8.9%)	-
Residual variability	29.1%CV (0.3%)	-

Source: Population PK Report Table 16.
AB=antibody; IIV=interindividual variability.

The final PopPK model was evaluated by the Visual Predictive Check (VPC) method. For the VPC evaluation, the 2.5th and 97.5th prediction intervals (PIs) were constructed by simulating replicates of the dataset from which the model was developed. The observed data were then overlaid and compared

with the PIs. For the model to be acceptable, approximately 2.5% of the observed data should lie above the 97.5th PI, and 2.5% should lie below the 2.5th PI. The combined data from all the studies as shown in Figure 5 were well predicted by the model. The observed and predicted 95% PI are similar and generally within the 95% confidence interval (CI) around the PI. Overall, the simulated concentrations appeared to be reasonably consistent with the observed concentrations, with no systematic bias.

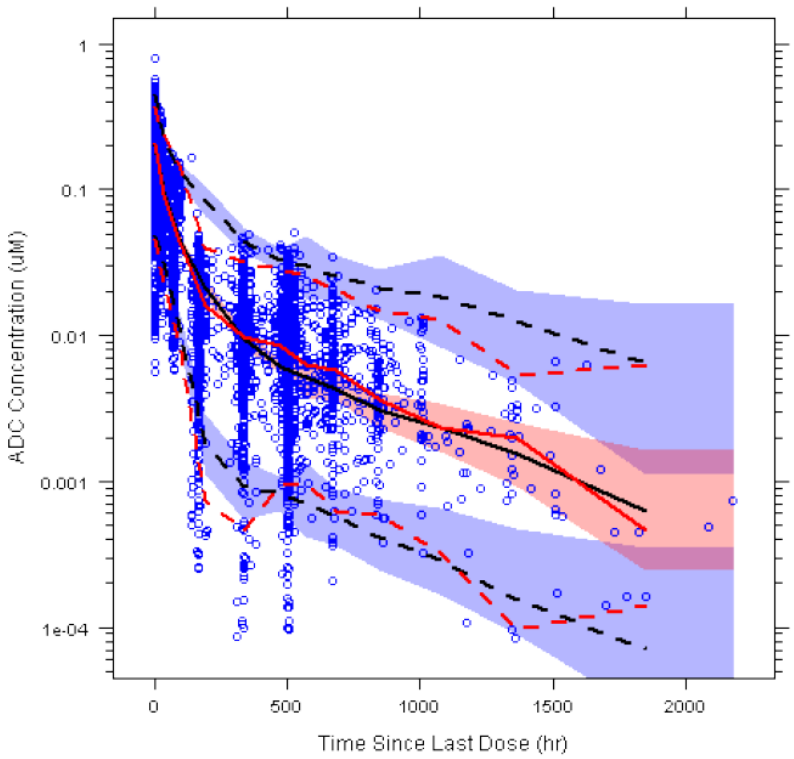


Figure 5: Brentuximab vedotin ADC final PK model VPC with all data combined
The **open blue symbols** are the observed data.
The **solid red line** is the median of the observed data. The **dashed red lines** are the lower 2.5th and upper 97.5th percentiles of the observed data.
The **solid black line** is the median of the simulated data. The **dashed black lines** are the lower 2.5th and upper 97.5th percentiles of the simulated data.
The **shaded red area** is the 95% CI of the simulated median, and the **shaded blue areas** are the 95% CI of the simulated 2.5th and 97.5th percentiles.

The final PK model for ADC was used to simulate the concentrations produced after a 1.8 mg/kg dose of BV every 21 days for 3 cycles. The dose was capped at 180 mg for patients weighing more than 100 kg. The results showed/confirmed that there is minor accumulation of ADC with this dosing regimen.

Simulation of the AUCs in the various tumour types indicated a 35% estimated higher geometric mean AUC in pcALCL vs non-pcALCL tumour types in the overall population, and 16% higher AUC in patients with MF in C25001 compared with patients with HL in Study C25007) (Figure 6).

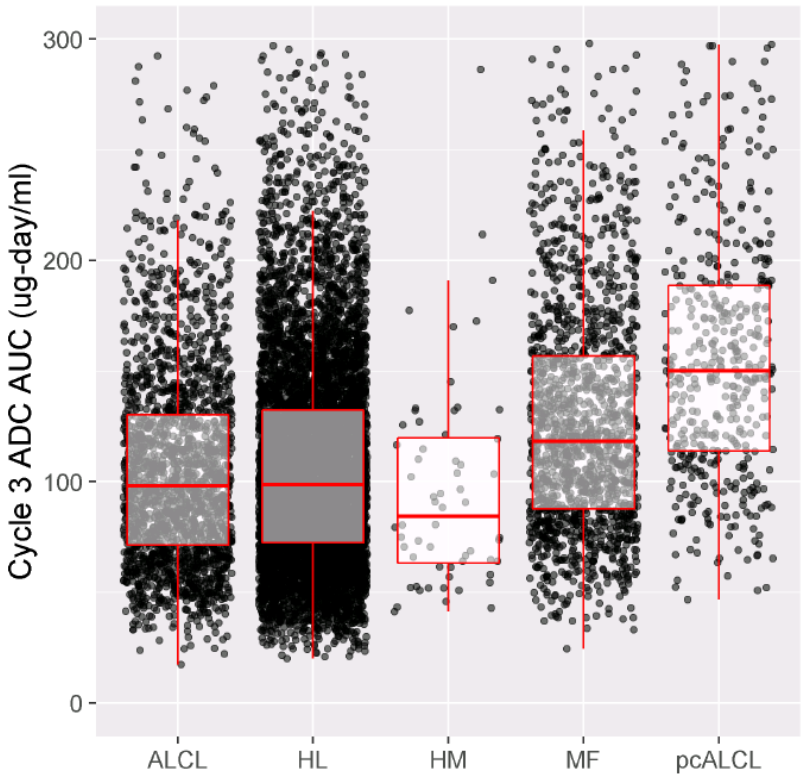


Figure 6: Simulated brentuximab vedotin ADC AUC for Cycle 3 Following a 1.8 mg/kg dose every 21 days

Age as a covariate

Plots of clearance (CL) for ADC at Cycle 1 and steady state (Cycle 3) based on the population pharmacokinetics (PK) model for Study C25001 (ALCANZA) are presented in Figure 7and Figure 8.

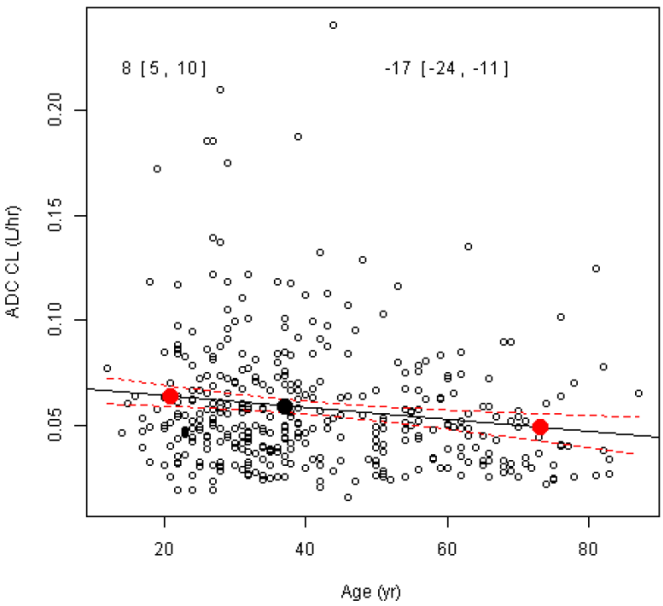


Figure 7: ADC CL versus age for Cycle 1 using the PK model for Study C25001

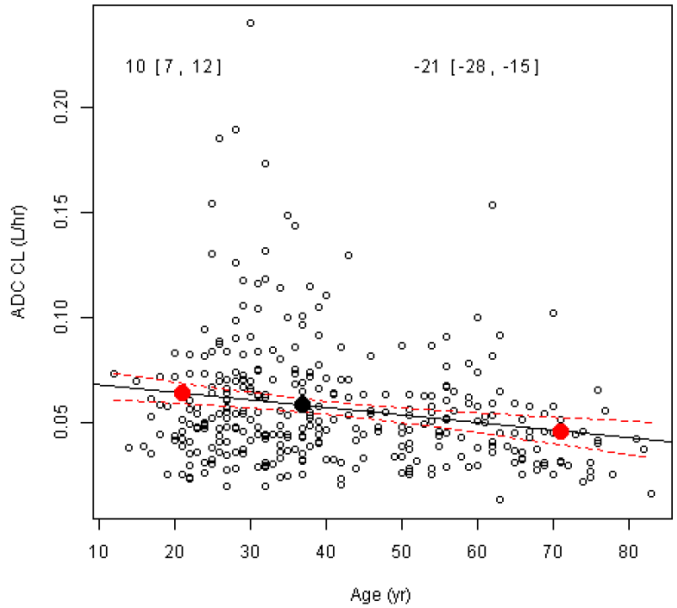


Figure 8: ADC CL versus age at steady state (Cycle 3) using the PK model for Study C25001

MMAE model

The model for MMAE included a link to brentuximab vedotin ADC elimination using the individual parameter estimates from the brentuximab vedotin ADC model to predict the brentuximab vedotin ADC concentrations in the MMAE model. The PK of MMAE was described by a 2-compartment model with first-order elimination and formation of MMAE both directly from brentuximab vedotin ADC and through binding of brentuximab vedotin ADC to a hypothetical target. The model had a lag compartment to describe the delay in formation of MMAE, both directly from brentuximab vedotin ADC and through binding of brentuximab vedotin ADC to the target. The fraction of MMAE formed directly from brentuximab vedotin ADC decreased following brentuximab vedotin ADC administration, relative to time after dose.

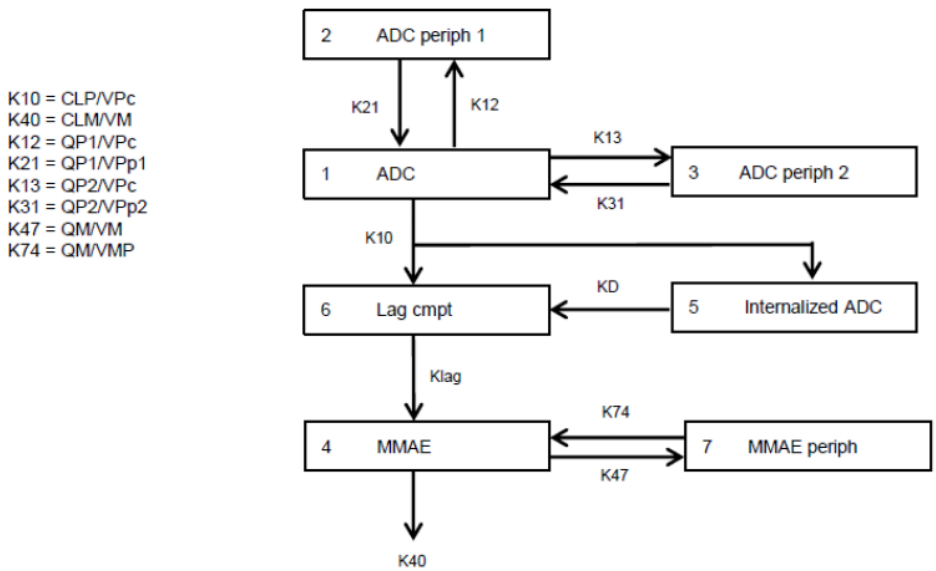


Figure 9: Schematic diagram of MMAE model

The final MMAE model included creatinine concentration, BSA, bilirubin concentration, and albumin (ALB) concentration on CL; and BSA on Vc. Specifically MMAE CL increases with increasing ALB concentration, and MMAE CL decreases with increasing creatinine and bilirubin concentration. This indicates that renal function shows a positive relationship with MMAE CL where higher values of creatinine CL resulted in higher MMAE CL. Hepatic function as assessed by bilirubin concentration showed that higher bilirubin concentrations, an indicator of lower hepatic function, showed a trend for lower MMAE CL. In addition, the model results showed that the Vc is consistently larger for larger patients based on BSA. The pcALCL tumour type was not found to be a statistically significant predictor of MMAE CL. Overall the MMAE model had acceptable precision of parameter estimates. The final MMAE model parameter estimates are shown in Table 9.

Table 9: MMAE final PK model parameters

Parameter	Population Mean (SE%)	%CV IIV (shrinkage)
CL (L/hr)	0.577 (1.2%)	42.5 (3.1%)
Central volume (V1) (L)	16.0 (1.4%)	66.7 (5.1%)
Binding rate constant (KD 1/hr)	0.00069 (1.6%)	-
Fraction metabolized	1 FIX	-
ADC to MMAE conversion rate (ALFM 1/hr)	2.64 (1.0%)	-
Rate constant for lag compartment (Klag 1/hr)	15.7 (1.0%)	-
Intercompartmental CL (Q2) (L/hr)	2.65 (1.2%)	-
Peripheral volume (V2) (L)	14.2 (1.1%)	-
ALB concentration on CL	0.982 (3.2%)	-
BSA on CL	2.81 (6.4%)	-
BSA on V1	0.89 (9.5)	-
Bilirubin concentration on CL	-0.1 (7.5%)	-
Creatinine concentration on CL	-0.143 (10.2%)	-
Residual variability	42.3% CV (0.3%)	-

A VPC plot for all the data in the dataset combined (Figure 10) shows that the data are well predicted by the model. The observed and predicted 95% PI are similar and generally within the 95% CI around the PI. Overall, the simulated concentrations appeared to be reasonably consistent with the observed concentrations, with no systematic bias.

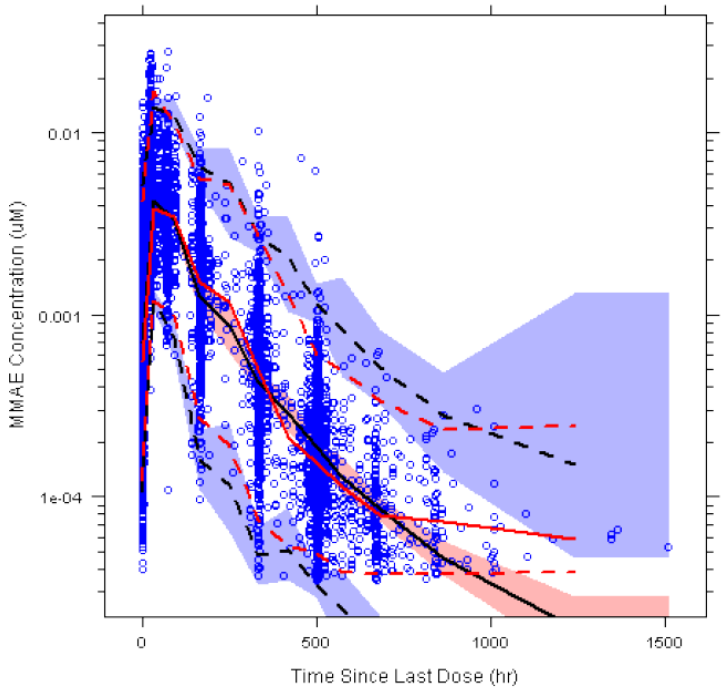


Figure 10: MMAE final PK model VPC with all data combined
The **open blue symbols** are the observed data.
The **solid red line** is the median of the observed data. The **dashed red lines** are the lower 2.5th and upper 97.5th percentiles of the observed data.
The **solid black line** is the median of the simulated data. The **dashed black lines** are the lower 2.5th and upper 97.5th percentiles of the simulated data.
The **shaded red area** is the 95% CI of the simulated median, and the **shaded blue areas** are the 95% CI of the simulated 2.5th and 97.5th percentiles.

Similar to the ADC model, the final PK model for MMAE was used to simulate the concentrations produced after a 1.8 mg/kg dose of BV every 21 days for 3 cycles with a capped dose of 180 mg for patients weighing more than 100 kg. The results showed that there is minor accumulation of MMAE with this dosing regimen.

These increases in brentuximab vedotin ADC exposure in pcALCL vs non-pcALCL tumour types (Figure 6) did not translate to higher MMAE exposure (Figure 11).

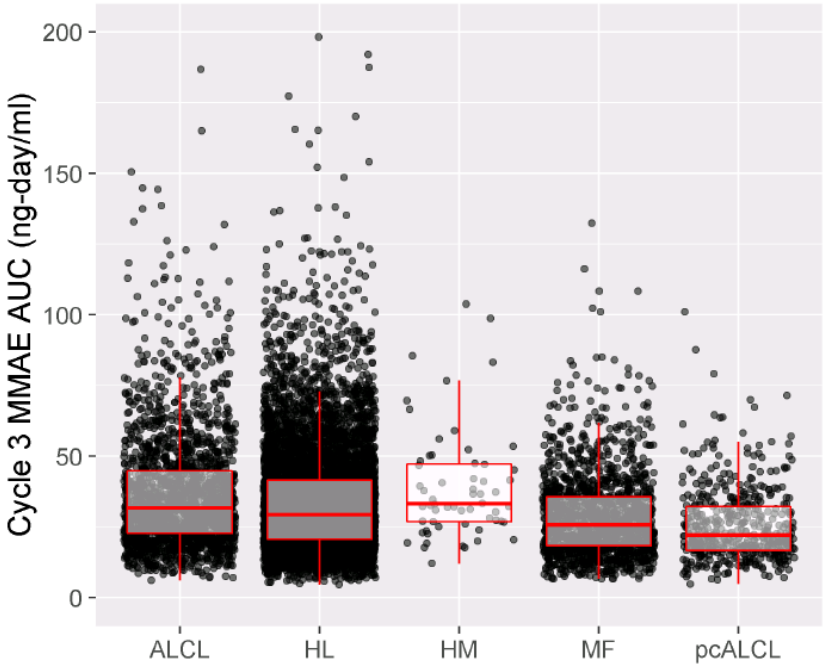


Figure 11: Simulated MMAE AUC for Cycle 3 Following a 1.8 mg/kg dose every 21 days

Immunogenicity assessments

Immunogenicity assessments (anti-therapeutic antibodies (ATA) and neutralising ATA) in Study C25001 were based on serum from blood samples collected before brentuximab vedotin dosing in the cycle of 1, 3, 5, 7, 9, 11, 13, and 15 and at EOT, and neutralising ATA was assessed for ATA-positive samples only. Sixty of 66 patients (91%) in the brentuximab vedotin arm were evaluable for immunogenicity assessments (14/16 patients [88%] with pcALCL and 46/50 patients [92%] with MF).

All 14 patients with pcALCL were ATA negative at Baseline, and 6 of the 14 patients developed ATA after the brentuximab vedotin administration. Forty-two of 50 patients (84%) with MF were ATA negative at Baseline, and 19 of the 42 patients developed ATA after brentuximab vedotin administration. Most of the patients who were ATA negative at Baseline continued to be ATA negative at all assessment time points during the study (8 of 14 evaluable patients with pcALCL and 23 of 46 evaluable patients with MF). Three of the 4 patients with MF who were ATA positive at Baseline remained transiently positive during the study; 1 patient with MF who was ATA positive at Baseline was ATA negative at all post-baseline time points. The total ATA-positive rate in Study C25001 was 42% (28/66 patients) among the safety population; however, 16 of the 28 patients who were ATA positive were transiently ATA positive, and 23 of the 28 ATA-positive patients had low titres. Also, 20 of the 28 ATA-positive patients were neutralising ATA positive.

Population PK results by ATA status

The impact of ATA status on the PK of the brentuximab vedotin ADC was evaluated in the PopPK analysis. A VPC plot comparing the observed and predicted brentuximab vedotin ADC concentration versus time since last dose for the studies that formed the basis of the original approval (SG035-0001, SG035-0002, SG035-0003, and SG035-0004) and the newer studies (C25001 and C25007) by ATA status is shown below. Notably the older studies had a large proportion of missing values, and the new studies had only 2 missing values. VPC plots show that the model generally predicts the 4 possible ATA status categories to a reasonable extent.

A VPC analysis was also performed using dose-normalised concentrations versus time since first dose, and these results are shown in Figure 12. The observed and predicted intervals generally overlap.

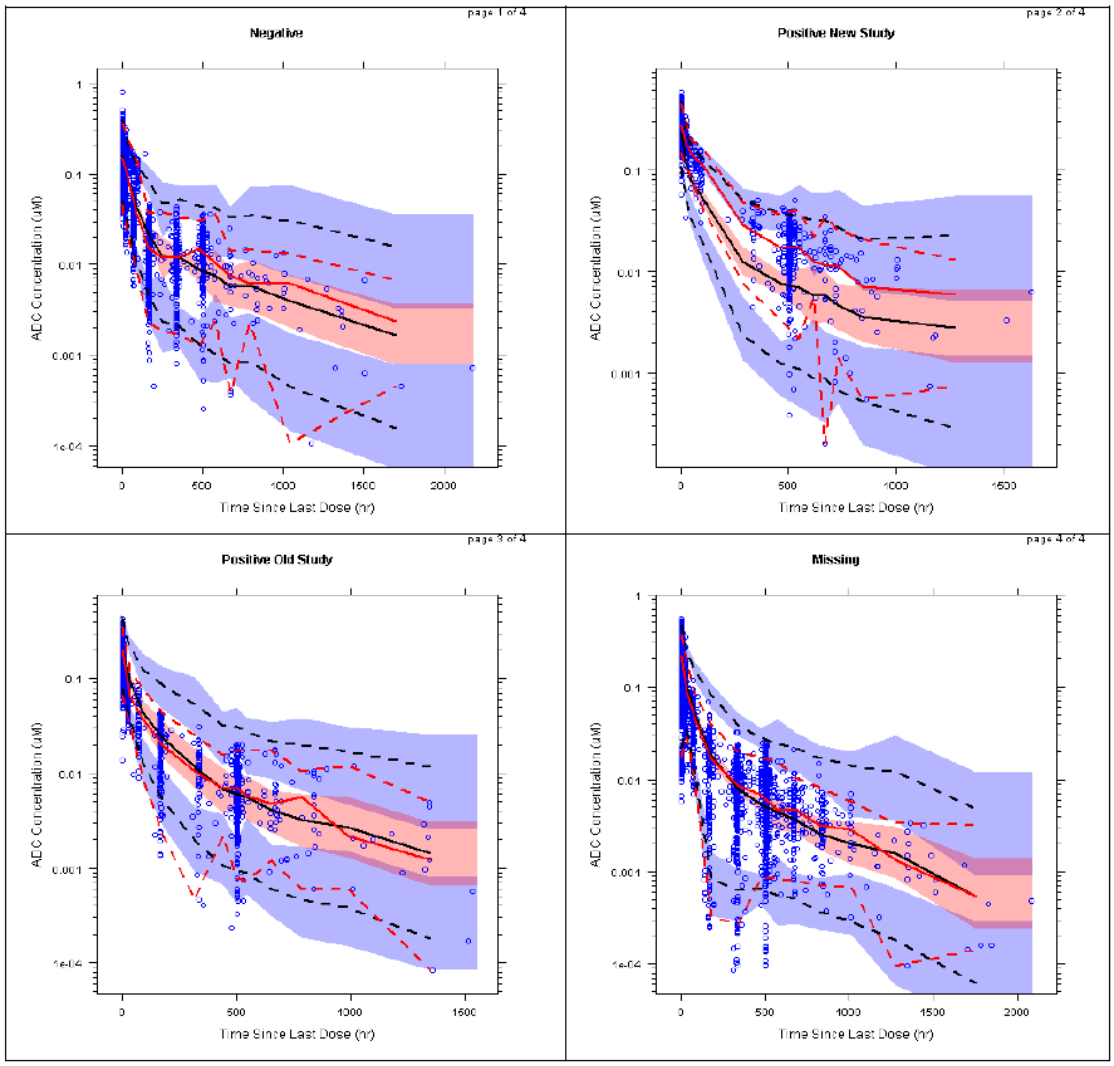


Figure 12: Brentuximab vedotin ADC final PK model VPC by ATA status and study type

The **open blue symbols** are the observed data.
The **solid red line** is the median of the observed data. The **dashed red lines** are the lower 2.5th and upper 97.5th percentiles of the observed data.
The **solid black line** is the median of the simulated data. The **dashed black lines** are the lower 2.5th and upper 97.5th percentiles of the simulated data.
The **shaded red area** is the 95% CI of the simulated median, and the **shaded blue areas** are the 95% CI of the simulated 2.5th and 97.5th percentiles.

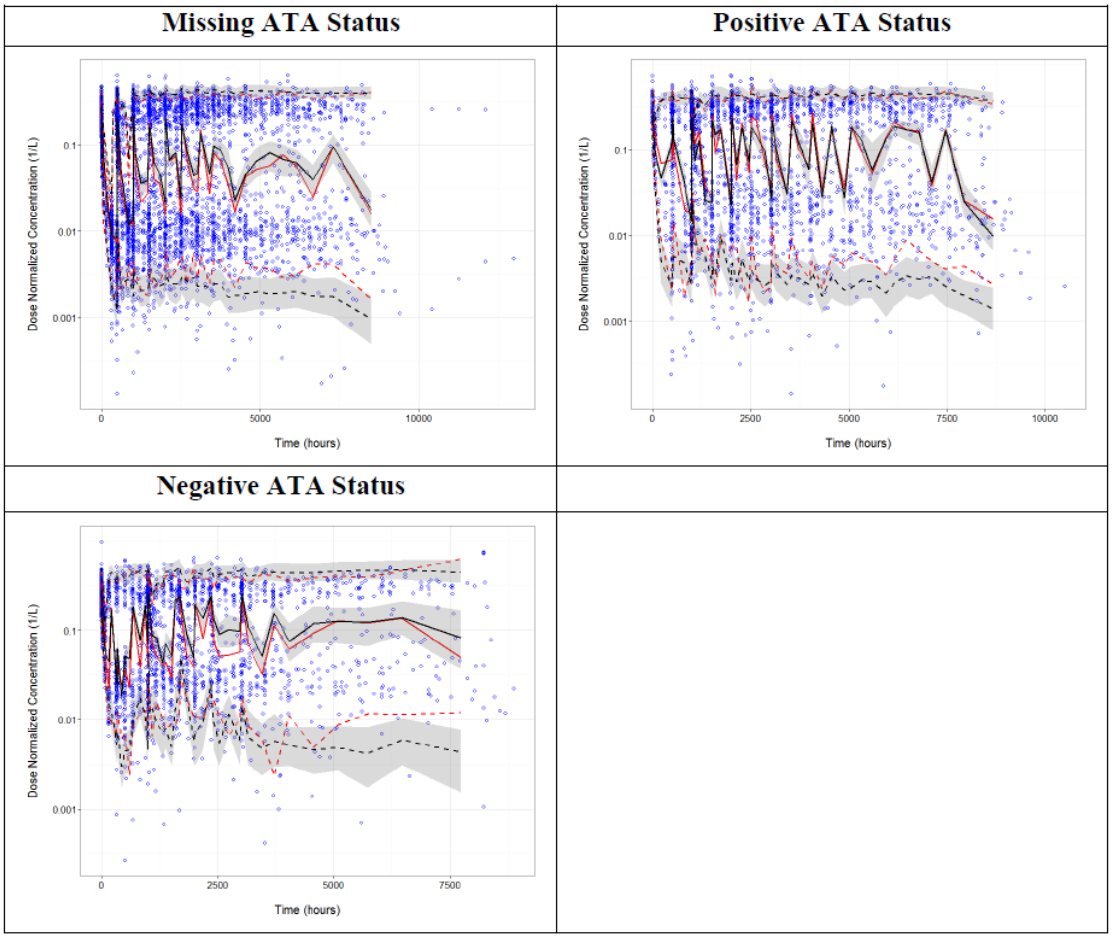


Figure 13: Brentuximab vedotin ADC final PK model using dose-normalised concentrations VPC by ATA status

The **open blue symbols** are the observed data.
The **solid red line** is the median of the observed data. The **dashed red lines** are the lower 5th and upper 95th percentiles of the observed data.
The **solid black line** is the median of the simulated data. The **dashed black lines** are the lower 5th and upper 95th percentiles of the simulated data.
The **shaded gray areas** are the 90% CIs of the simulated percentiles.

The brentuximab vedotin ADC CL values by antidrug antibody status are summarised in Figure 14 and

Table 10. There was significant overlap between the CL values among the antidrug antibody (ADA) statuses. Patients who were neutralising antidrug antibody positive (NADA+) had higher geometric mean CL (0.040 L/h) than patients who were antidrug antibody negative (ADA-, 0.036 L/h) or ADA+ and NADA- (0.031 L/h).

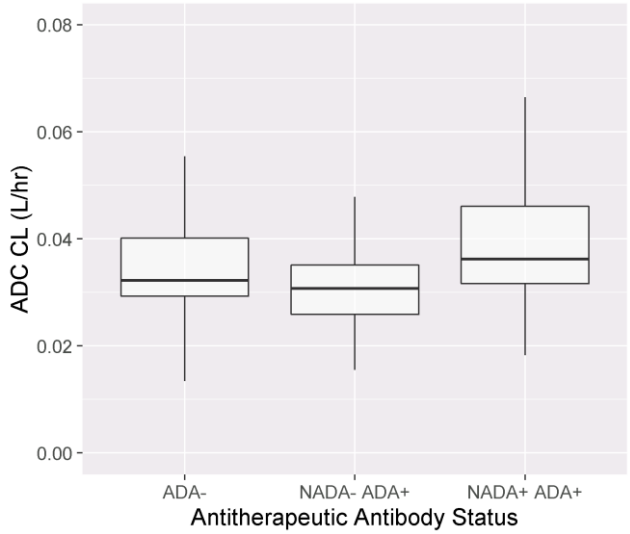


Figure 14: Box and Whisker plot of brentuximab vedotin ADC CL by ATA status for C25001 and C25007

Table 10: Summary table of brentuximab vedotin CL (L/hr) by ATA status for C25001 and C25007

ATA Status	N	Median	Mean	Geometric Mean	10th Percentile	90th Percentile	Standard Deviation	CV
NADA- ADA+	639	0.031	0.032	0.031	0.023	0.043	0.009	28%
NADA+ ADA+	351	0.040	0.043	0.040	0.030	0.058	0.018	42%
ADA-	801	0.033	0.038	0.036	0.025	0.054	0.017	45%

Although ATA positivity resulted in higher brentuximab vedotin ADC clearance (CL) per the covariate analysis in the PopPK model, the overall impact on steady-state area under the curve (AUC) in the analysis population was small (9%-12% lower steady-state AUC in ATA-positive vs ATA-negative patients) according to simulations from the final PopPK model.

Effect of NAbs on efficacy

The relationship between neutralising antibody (NAb) status and outcomes for primary efficacy endpoints (ORR4, ORR, and PFS) was explored in 58 patients who were immunogenicity evaluable (i.e., patients with a sample at baseline and at least 1 post-baseline visit) and received treatment with brentuximab vedotin in Study C25001. A summary of the data is shown in Table 11.

Table 11: Response by Neutralising ATA (ITT Population – Immunogenicity-Evaluable Patients Who Received Brentuximab Vedotin)

	Total N	ORR4 n (%)	ORR n (%)	PFS Event n (%)	Median PFS Month
ATA negative	31	17 (54.84)	22 (70.97)	17 (54.84)	15.77
ATA Positive	27	18 (66.67)	20 (74.07)	16 (59.26)	21.55
NAb negative	6	3 (50)	5 (83.33)	6 (100)	13.29
NAb positive	19	13 (68.42)	13 (68.42)	10 (52.63)	22.83
NAb missing/ unknown	2	2 (100)	2 (100)	0	NE

2.3.4. Discussion on clinical pharmacology

Brentuximab vedotin and MMAE PK in the (CTCL subgroups) MF and pcALCL patients in the pivotal Study C25001 do not appear to be markedly different from the PK that has been previously described.

Further analysis of the brentuximab vedotin and MMAE PK data was conducted using PopPK modelling. Overall the PopPK models for brentuximab vedotin ADC and MMAE appear to characterize the data sufficiently. The results indicated that body size, baseline ALB concentrations, tumour type, and ATA positivity affect brentuximab vedotin PK, but to an extent that is limited in relation to the overall variability in PK.

The final brentuximab vedotin PopPK model was used to simulate and derive summary statistics of brentuximab vedotin ADC and MMAE exposure by tumour type and ATA status. In the PopPK model, the patients with pcALCL from Study C25001 (N=16) showed a 35% higher brentuximab vedotin ADC concentrations than patients with other tumour types. This may be explained by the lower CD30-related disease burden in the pcALCL population compared with the HL and ALCL populations. Considering the previously demonstrated relationship between circulating sCD30 concentration and overall tumour burden, lower levels of tumour burden in CTCL may therefore result in relatively higher brentuximab vedotin ADC levels circulating in blood compared with other tumour types like HL and ALCL. However, when viewed in relation to the overall variability in brentuximab vedotin ADC PK (%CV in steady-state AUC of 39%-45% in ATA-negative patients), the magnitude of the differences in steady-state brentuximab vedotin ADC exposure across tumour types appear relatively modest (e.g., 35% estimated higher geometric mean AUC in pcALCL vs non-pcALCL tumour types in the overall population, and 16% higher AUC in patients with MF in C25001 compared with patients with HL in Study C25007). Further, these changes in brentuximab vedotin ADC in pcALCL patients did not translate to higher MMAE exposure.

Although ATA status was a statistically significant covariate on brentuximab vedotin ADC CL, the effect of this covariate on steady-state AUC was smaller than the overall extent of interpatient variability in brentuximab vedotin ADC PK (9-12% lower geometric mean steady-state AUC in ATA-positive vs ATA-negative patients with pcALCL). The other covariate effects in the model showed that brentuximab vedotin ADC CL and Vc increase with increasing body size, and brentuximab vedotin ADC CL decreases with increasing ALB concentration. The impact of these changes appears modest.

Based upon population PK analyses (see section 5.2 of the SmPC) and the safety profile in elderly patients, which are consistent with that of adult patients, the dosing recommendations for patients aged 65 and older are the same as for adults (section 4.2 of the SmPC).

Patients being positive for neutralising ATAs showed an increased clearance of brentuximab vedotin. However, the increased clearance of brentuximab vedotin in patients positive for neutralising ATAs is not associated with decreased efficacy compared to the general study population.

The final MMAE model included the effect of creatinine concentration, BSA, bilirubin concentration, and ALB concentration on CL; and BSA on Vc. However, pcALCL tumour type was not found to be a statistically significant predictor of MMAE CL. Overall, MMAE AUC and C_{max} in patients with CTCL in Study C25001 were similar to those in patients with relapsed/refractory HL in Study C25007.

The data from the pop-PK model show that brentuximab vedotin clearance appears to decrease with age to a limited extent (Cycle 1 Cl at 20 years approximately 0.07 l/h vs 0.05 l/h at 70 years). In line with these CL data, the simulated AUC for brentuximab vedotin increased by approximately 20% going from 20 to 70 years. Simulated MMAE AUC was almost unchanged in this age range (data not shown). Both for brentuximab vedotin and MMAE, Cmax was unchanged within this age range. These changes

are considered to be of no clinical relevance. Therefore, the dosing recommendations for patients aged 65 and older in the SmPC, have been updated and are the same as for adults.

Taken together, these analyses support the conclusion that there are no clinically meaningful differences in the systemic exposures of brentuximab vedotin and MMAE in patients with CTCL compared with patients with other tumour types.

2.3.5. Conclusions on clinical pharmacology

The PK data provided confirm the known clinical pharmacology of brentuximab vedotin and MMAE. No marked difference in exposure was apparent between the CTCL patients as compared with HL and sALCL patients. There is little accumulation of brentuximab vedotin and MMAE exposure, and steady-state AUC and C_{max} predicted in patients with CTCL in Study C25001 were very similar to those from patients with HL in Study C25007. This is supported by the PopPK modelling and simulation exercise. Further PK data from Study C25001 into the PopPK dataset increased the number of elderly patients in this dataset. The analysis showed that age was not a covariate in the PopPK models. Hence, the posology in section 4.2 of the SmPC has been updated for patients aged 65 and older, which is considered the same as for adults.

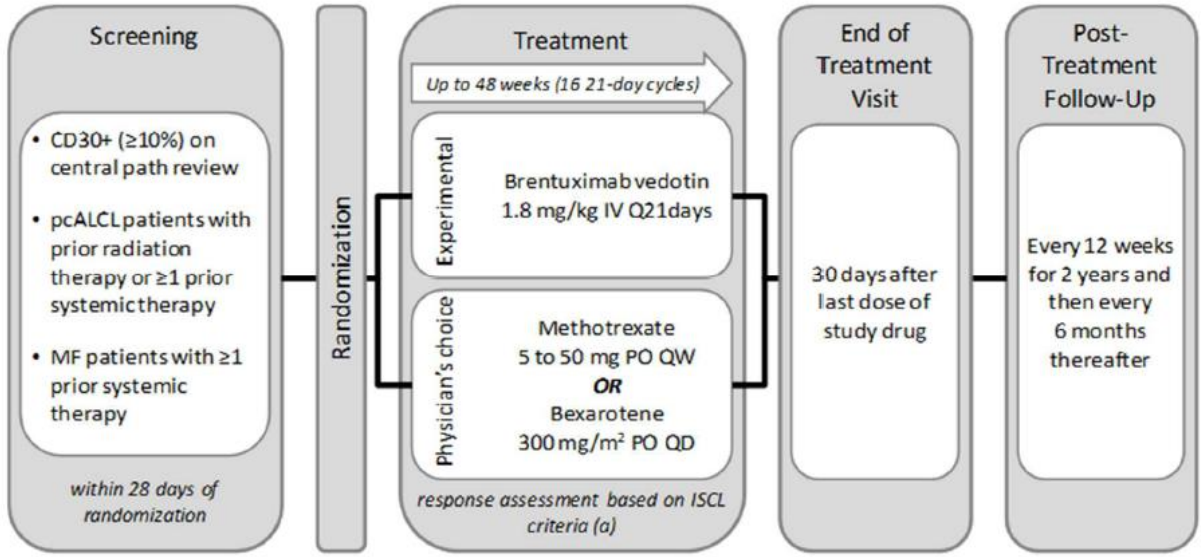
2.4. Clinical efficacy

2.4.1. Dose response study

No new dose response study was submitted. The recommended dose of brentuximab vedotin in the approved indications of HL and sALCL was used in the current study (1.8 mg/kg as IV infusion over 30 minutes Q3W).

2.4.2. Main study

C25001(Alcanza) - A randomised, open-label, phase III trial of brentuximab vedotin (SGN-35) versus physician's choice (Methotrexate or Bexarotene) in patients with CD30-positive cutaneous T-cell lymphoma



PO=oral administration, Q21days=dosing every 21 days, QD=daily dosing, QW=weekly dosing.
(a) Olsen et al, 2011 [9].

Figure 15: Overview of study design

Methods

Study participants

Patients with a diagnosis of MF or pcALCL and histologically confirmed CD30+ disease (≥10%) were eligible for study enrolment. Patients were to be stratified by MF or pcALCL.

The key main inclusion criteria were:

- Adults ≥18 years and ECOG≤2
- MF (received at least 1 prior systemic therapy) or pcALCL (received prior radiation therapy or at least 1 prior systemic therapy).
- Histological confirmation by central review of CD30 disease (CD30 positivity is defined as ≥10% target lymphoid cells demonstrating membrane, cytoplasmic and/ or Golgi staining pattern for CD30 at any intensity above background staining in at least 1 sample). Skin biopsy was required of at least 2 lesions for MF and 1 lesion for pcALCL
- Radiographically/clinically measurable disease
- Adequate liver and renal function
- 3 week washout period from previous treatment and 12 weeks washout for antibody-directed or immunoglobulin-based immune therapy (unless not in best interest of patient)

The key exclusion criteria were:

- Concurrent diagnosis of SS, B2 disease (high blood tumour burden) sALCL, or other non-Hodgkin lymphoma, excluding Lyp
- Progression on prior therapy with both bexarotene and methotrexate
- History of another primary malignancy not in remission for at least 3 years
- Known active cerebral/meningeal disease
- History of pancreatitis or significant risk factors for developing pancreatitis or elevated lipase value ≥3×ULN with an amylase level >ULN
- Known HIV infection, hepatitis B surface antigen positive or known/suspected hepatitis C infection
- Any severe active systemic viral, bacterial, or fungal infection within 1 week before first study drug dose requiring systemic antimicrobial therapy (Oral antibiotics for prophylaxis were allowed)

Treatments

Patients were randomised 1:1 to either receive brentuximab vedotin, or to receive the physician's choice of either bexarotene or methotrexate.

Brentuximab vedotin 1.8 mg/kg by IV infusion (outpatient) over approximately 30 minutes on Day 1 of each 21-day cycle. In patients above 100 kg the dose was based on 100 kg. Patients could receive a maximum of 16 cycles (approximately 48 weeks) of brentuximab vedotin.

Methotrexate once weekly as a single dose of 5 to 50 mg orally. Dosages adjustments (to max.50mg /week) to achieve optimal clinical response/lowest effective dose were allowed according to protocol. Patients could receive methotrexate for a maximum of 48 weeks.

Bexarotene once daily 300 mg/m2 orally, dose reduction was allowed to 200 mg/m2/day or 100 mg/m2/day. Bexarotene could be temporarily suspended for toxicity. Pre-treatment with fenofibrate 145 to 200 mg for 7 days (or reduced dose in case of creatinine≥1.5 mg/dL or nephrotic syndrome) was required. Concurrently a low dose of synthetic thyroxine (T4) was to be taken (adjusted along with dose of bexarotene). Continual monitoring of lipid and T4 concentrations was required during bexarotene treatment. Patients could receive bexarotene for a maximum of 48 weeks.

Objectives

Primary objective: to determine objective response lasting at least 4 months (ORR4), with brentuximab vedotin in patients with CD30+ MF or pcALCL compared to that achieved with therapy in the control arm.

Key secondary objectives: to determine CR rate, PFS and burden of symptoms with brentuximab vedotin compared to that achieved with therapy in the control arm.

Other secondary objectives: to determine duration of response (DOR) and duration of skin response in brentuximab vedotin. To determine event-free survival (EFS) with brentuximab vedotin compared to that achieved with therapy in the control arm. To describe PK of brentuximab vedotin and MMAE in blood. To determine the immunogenicity of brentuximab vedotin. To assess patient-reported QOL outcomes. To assess the safety of brentuximab vedotin.

Additional (exploratory) objectives: to investigate the relationship between baseline levels of CD30 expression and clinical response. To assess changes in CD30 expression before and after treatment. To investigate possible correlations between expression of serum protein markers and response. To examine correlation between biomarkers related to the disease pathway, drug mechanism, and drug clearance proteins, such as CD30, tubulin, Fcneo, and Fcγ receptors and clinical response. To assess healthcare utilisation. To collect patient-reported outcomes (PRO) data for utility-based economic evaluations.

Outcomes/endpoints

Primary endpoint: ORR4 is the proportion of patients who achieved an objective response (CR or PR) that lasted at least 4 months, as determined by an independent review facility (IRF).

Objective responses will be based on a Global Response Score (GRS), which consists of skin evaluation (mSWAT assessment) by investigator, nodal and visceral radiographic assessment by IRF, and detection of circulating Sézary cells (MF only) by IRF.

- Skin evaluation (mSWAT) performed at screening, before dosing on Day 1 of Cycles 1, -3 and at the end of every cycle beginning at Cycle 3, EOT, and at post treatment follow-up visits
- CT scans for patients without nodal or visceral involvement were performed at screening and during the cycle following the first skin response and 6 cycles (or ≥ 4 months) after that or in case of suspected new/progressive disease in the LN/viscera
- CT scans for patients with baseline nodal/visceral disease, were performed at screening and at the end of Cycles 3, 6, 9, 12, and 15, and per the follow-up schedule until PD or suspected new/progressive disease in the LN/viscera and at EOT
- Blood sample for Sézary cell enumeration in patients with MF performed at screening; at the end of Cycles 3, 6, 9, 12, and 15, at EOT, and per the follow-up schedule until PD or study closure

Key secondary endpoints:

- CR - proportion of patients who achieved a CR as their best response on study as determined by an IRF by GRS criteria
- PFS- time from randomisation until PD per IRF or death due to any cause, whichever occurs first
- Changes in symptom domain (7 items) according to Skindex-29 questionnaire (administered on Day 1 of Cycles 1 and subsequent even number cycles)

Other secondary endpoints:

- DOR- analysed for patients in the ITT population with a confirmed response per IRF
- DOR in skin- analysed for patients in the ITT population with skin response (CR or PR in skin) per investigator
- EFS- time from randomisation until any cause of treatment failure per IRF: PD, discontinuation of treatment for any reason, or death due to any cause, whichever occurs first.
- Concentrations of brentuximab vedotin (serum) and MMAE (plasma)
- Immunogenicity assessment
- QOL assessments according to Skindex-29 and FACT-G questionnaires
- AEs and SAEs, according to NCI CTCAE version 4.03 and assessments of clinical laboratory values

Exploratory endpoints

- Qualitative and quantitative measures of CD30 expression in biopsied tumour assessed before and after brentuximab vedotin treatment. The Quest clinical trial assay was initially used for screening to determine CD30 expression in tissue samples from skin biopsies. This assay was later replaced by the Ventana anti-CD30 (Ber-H2) assay (Amendment 3).
- Serum concentration of PD markers such as sCD30
- Presence or absence of gene or protein variation associated with CTCL or brentuximab vedotin mechanism of action
- Utilisation of health resources

Patient-reported QOL assessment per EQ-5D-3L for economic considerations

Sample size

Approximately 124 patients, approximately 62 patients per treatment arm, were to be randomised to 1 of the treatment arms in the study. The sample size was calculated to provide 90% power to detect a 30% improvement in ORR4 in the brentuximab vedotin treatment group, assuming ORR4 for the methotrexate or bexarotene treatment group was 40%. This calculation was based on a 2-sided chi-squared test with a significance level of alpha=0.05, and a 10% dropout rate using nQuery Advisor 7.0. A minimum of 30 patients with pcALCL, 15 patients per treatment arm were to be randomised in the study.

Randomisation

Patients will be randomised in an overall ratio of 1:1 to Arm 1 (brentuximab vedotin) or Arm 2 (physician's choice of MTX or bexarotene) using an interactive voice response system, stratified by baseline disease diagnosis (MF or pcALCL).

Blinding (masking)

This was an open label study.

Statistical methods

No interim analyses were planned for efficacy. In general, missing data was treated as missing, and no data imputation were applied unless otherwise specified.

The primary endpoint, ORR4 per IRF, will be analysed using a Cochran-Mantel-Haenszel test stratified by baseline disease diagnosis (pcALCL or MF) based on the ITT population. Difference in proportions were based on normal approximation. The objective response was considered maintained for patients with a previous CR who experienced recurrent disease (relapse) unless the criteria for disease progression were met. Patients who do not have any post baseline response assessment or no response before dropout, will be counted as non-responders. Patients whose first response occurs after the start of subsequent anti-cancer therapy, but otherwise meet the primary endpoint criteria will be excluded.

Pre-specified subgroups analyses were performed for the following subgroups: baseline disease diagnosis, ECOG PS, sex, age (<65, ≥65), region, race and physician's choice. Baseline disease involvement and baseline skin tumour involvement were not pre-specified.

The key secondary endpoints CR per IRF, PFS per IRF, symptom Skindex-29 were analysed using a fixed sequential testing procedure (weighted Holm procedure). The analyses for CR per IRF, PFS per IRF, and the changes in symptom domain of the Skindex-29 were assigned weights (0.7, 0.2, and 0.1, respectively). Comparison of the CR rates between the 2 treatment groups will be conducted using the stratified Cochran-Mantel-Haenszel test and normal approximation for difference in proportions. Patients who do not have any post baseline response assessment as specified in the protocol will be counted as non-responders.

Stratified log-rank test statistics will be used to compare PFS between the 2 treatment arms. The HRs and 95% CIs will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of the time-to event endpoints for each treatment. An alpha level of 0.01 (2-sided) was specified per the weighted Holm procedure.

Handling of missing data and censoring PFSs: The date of PD/response should be assigned based on the time of the first documentation regardless of violations or discontinuation of study drug. Patients who are lost to follow-up, withdraw consent, or those who discontinue treatment due to undocumented PD were censored at the last disease assessment. If death or PD occurs after a missed visit, then the patient is treated as progressed at the date of death or PD. Patients without baseline and/or no sufficient post baseline data for disease assessment and with no death recorded will be censored at the date of randomisation. If PD is documented between scheduled visits, then the date of the documented PD is the date of progression. If the patient starts new antineoplastic therapy before PD, then the patient is treated as progressed at the date of assessment at which PD was documented.

For skin symptoms (Skindex-29; symptom domain), the mean of symptom reduction between both arms is compared. 'Symptom reduction' is defined for each patient as the maximum reduction from baseline (sum of the 7 items related to skin symptoms normalised to a 1-100 scale) over the non-missing visits. The ANCOVA model controlling for baseline covariates (treatment group, baseline score, disease diagnosis, ECOG) will be employed for the analysis. No validated MID methods were available at time of data analyses. The Applicant calculated the MID using three methods based on the current dataset: half of standard deviation of the maximum score change; Cohen's moderate effect size (0.5x st.dev baseline score) and 'standard error of measurement' (std dev(baseline score)√(1-Cronbachs α).

Regarding the other secondary endpoints, EFS will be analysed similarly as the endpoint PFS. DOR and duration of skin response will be summarised descriptively using the Kaplan-Meier method. PRO endpoints include subscales of Skindex-29 and global and subscale scores of the EQ-5D and FACT-G questionnaires. All PRO scores (Skindex 29 total score, EQ-5D and FACT-G score) will first be scaled into numeric scores following published or pre-specified scoring guidelines for each PRO instrument employed in this trial. Scores will be summarised in descriptive statistics for the 2 treatment groups over time.

Handling of missing data and censoring secondary endpoints: The ITT principle will be used to determine the event time or censoring time for the EFS analysis. For EFS, patients who are lost to follow-up will be censored at last disease assessment. Patients who withdraw consent or start new antineoplastic therapy will be treated as if experiencing an EFS event. Patients without baseline and/or sufficient post baseline data for disease assessment and no treatment discontinuation or death recorded will be censored at the date of randomisation.

DOR will be analysed for patients with confirmed response (CR or PR) in the ITT population. Patients who are lost to follow-up, withdraw consent, or discontinue treatment due to undocumented PD after the last adequate disease assessment will be censored at the last disease assessment. If the patient starts new antineoplastic therapy before PD, the patient is treated as progressed at the date of assessment at which PD was documented. Duration of skin response will be analysed for patients with skin response (CR or PR in skin) in the ITT population). Data was handled similar to DOR. Patients without sufficient skin assessment data after the initial skin response and with no death recorded were censored at the date of the initial skin response.

Sensitivity analyses

- For ORR4 per IRF per response criteria which are published by Whittaker (2010) in the ITT and MF patients only
- ORR4 per IRF based on a subset of GRS time points, using the available CT scans and blood assessments for GRS at the time points they were taken. For patients with baseline nodal/visceral/blood disease, the sensitivity analysis used GRS assessed at time points with concurrent nodal/viscera/blood component assessments. For patients with skin-only disease, this analysis used the same GRS assessment frequency as the primary analysis.
- ORR4 per investigator GRS
- ORR per IRF and per investigator
- For the skin symptoms using the linear mixed model with repeated measures at each time point specified in the protocol SOE. The total score for skin symptoms (Skindex-29) will be imputed with the mean of the other items if there is no more than 1 missing item; otherwise, it will be considered invalid and excluded from the analysis.

- For CR sensitivity analysis will be performed for CR per the investigator's GRS assessment
- For PFS multiple sensitivity analyses with different handling of missing data/censoring rules (including according to FDA censoring guidelines and investigator-assessment)

Exploratory analysis

- ORR4 based on GRS consisting of skin evaluation (mSWAT assessment) by independent review of photos, nodal and visceral radiographic assessment, and detection of circulating Sézary cells (MF only) by IRF
- ORR4 in the All-Enrolled population, Response-Evaluable population, as well as the PP population.
- Time to next significant antineoplastic treatment
- Biomarker analyses
- Health utilisation
- QoL questionnaires

Results

Participant flow

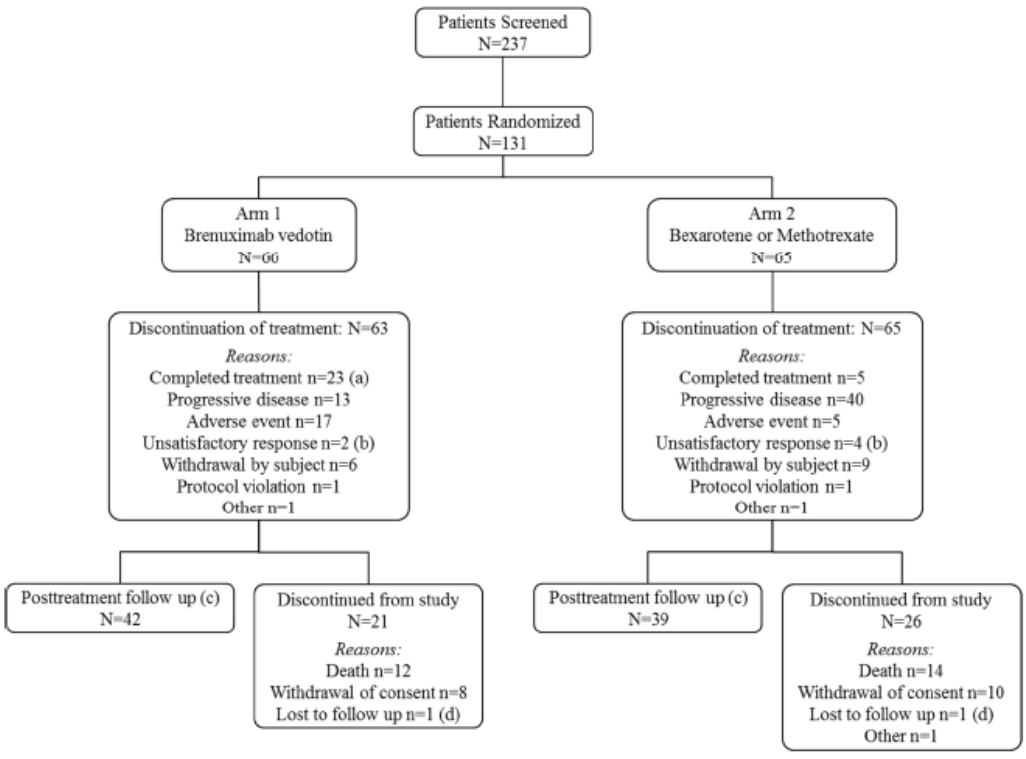


Figure 16: Participant flow schedule

Recruitment

The first patient was enrolled in the study on 13 August 2012. The last patient was enrolled in the study on 31 July 2015, and the last patient visit before the data cut-off was on 26 May 2016. Patients in this study were enrolled at 34 study centres. A total of 33 patients (25%) were enrolled in the United States, 68 patients (52%) in the European Union, 20 patients (15%) in Australia, 6 patients (5%) in Switzerland, and 4 patients (3%) in Brazil.

Conduct of the study

Study conduct was revised by 5 amendments to the original Protocol C25001. The major amendments are summarised below. Major protocol deviations were reported for 9 patients in the study. One protocol deviation related to the informed consent form, which was signed after randomisation and 2 days after rescreening visit. Other major protocol deviations are shown in

Table 12.

Amendment 1 (no patients enrolled)

Primary endpoint changed from ORR to ORR4. The study population was modified to include only patients with a primary diagnosis of MF or pcALCL(minimum 30 patients). Only patients who received at least 1 prior systemic therapy were allowed in to the trial. The confirmation of tumour CD30 positivity decreased from 75% to 10% based on phase II data.

Amendment 2 (46 patients enrolled)

Due to the occurrence of pulmonary toxicity use of bleomycin with brentuximab vedotin was contraindicated. For patients who completed either 48 weeks of study treatment discontinuation of therapy was to be attempted. After 48 weeks either subsequent standard of care (control arm) or re-initiation of brentuximab vedotin (interventional arm) was permitted.

Amendment 3 (no patients enrolled)

Patients with SD were allowed to continue to receive study treatment up to 16 cycles of brentuximab vedotin or 48 weeks with the control therapy. Patients with pcALCL were allowed to have received prior radiation therapy or at least 1 prior systemic therapy instead of the latter. The CD30 (screening) assay was changed from the Quest CTA to the Ventana anti-CD30 (Ber-H2) assay. Tumour samples from patients enrolled using the Quest assay were re-evaluated using the Ventana assay.

Protocol Amendment 5 (6 patients enrolled)

Amendment 5 included updated safety information and revised the existing eligibility criteria regarding patients at risk for pancreatitis, due to experiences in clinical studies and post marketing.

Table 12: Major protocol deviations

Treatment Arm	Deviation Type	Deviation Subtype	Deviation Comments
Brentuximab vedotin	Concomitant medication	Took prohibited medication during treatment	During hospitalization for SAE before Cycle 4, the patient was inadvertently given topical methylprednisolone 0.1% and betamethasone 0.05%.
Brentuximab vedotin	Inclusion/ exclusion	Inclusion criterion #3	Patient was diagnosed with pcALCL but had not received prior radiation therapy or at least 1 prior systemic therapy.
Brentuximab vedotin	Inclusion/ exclusion	Inclusion criterion #10	The protocol-required 3-week wash-out period was not met. The patient received the last dose of doxorubicin on 25 June 2013 and received the first dose of study drug on 08 July 2013. This was not discussed in advance with the project clinician.
Brentuximab vedotin	Inclusion/ exclusion	Inclusion criterion #8	The patient's AST value at screening was 6.1×ULN, which exceeded the protocol-defined limit of 5×ULN for patients with liver involvement.
Brentuximab vedotin	Inclusion/ exclusion	Exclusion criterion #8	Patient had Grade 4 lymphopenia at study entry after receiving alemtuzumab. PI confirmed that the patient had a history of Grade 2 lymphopenia. PI discussed with project clinician on 25 June 2015 and 21 July 2015.
Physician's choice	Concomitant medication	Took prohibited medication during treatment	The patient received another anticancer therapy (radiotherapy) while on study without informing the subinvestigator.
Physician's choice	Inclusion/ exclusion	Exclusion criterion #15	Patient received bexarotene within 3 weeks of the first dose of study drug.
Physician's choice	Inclusion/ exclusion	Exclusion criterion #8	Patient had bacterial infection at screening and received antibiotics, which she continued to take at the time of first cycle of study treatment.
Physician's choice	Inclusion/ exclusion	Inclusion criterion #9	Patient did not have clinically measurable disease at the time of randomization.

Baseline data

Baseline demographic data and baseline disease characteristics and staging are shown in **Table 13**

Table 13: Baseline demographic data and disease characteristics and staging

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64	Total N=128
Sex n (%)			
Male	33 (52)	37 (58)	70 (55)
Female	31 (48)	27 (42)	58 (45)
Ethnicity n (%)			
Hispanic or Latino	2 (3)	6 (9)	8 (6)
Not Hispanic or Latino	60 (94)	50 (78)	110 (86)
Not reported	2 (3)	8 (13)	10 (8)
Race n (%)			
White	56 (88)	53 (83)	109 (85)
Black or African American	3 (5)	3 (5)	6 (5)
Asian (a)	1 (2)	5 (8)	6 (5)
Not reported	3 (5)	1 (2)	4 (3)
Other	1 (2)	2 (3)	3 (2)
Age (years) (b)			
N	64	64	128
Mean (std dev)	59.5 (13.99)	56.6 (14.30)	58.1 (14.17)
Median	62.0	58.5	60.0
Min, max	22, 83	22, 83	22, 83

Source: Table 14.1.1.2.
Percentages are based on non-missing values.
Max=maximum, min=minimum, std dev=standard deviation.
(a) Includes subgroups of Asian Indian, Chinese, Not Reported, and Other.
(b) Age at date of informed consent.

	ITT Population	
	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64
ECOG performance status n (%)		
0	43 (67)	46 (72)
1	18 (28)	16 (25)
2	3 (5)	2 (3)
Time since initial diagnosis (months) (a)		
N	64	61
Mean (std dev)	75.30 (118.704)	62.23 (65.080)
Median	42.17	36.99
Min, max	2.6, 763.9	3.1, 273.2
TNM stages at study entry for patients with pcALCL n (%) (b)		
N	16	15
Skin		
T1	1 (6)	4 (27)
T2	3 (19)	5 (33)
T3	12 (75)	6 (40)
Node		
N0	10 (63)	11 (73)
N1	2 (13)	1 (7)
N2	2 (13)	1 (7)
N3	2 (13)	2 (13)
Visceral		
M0	12 (75)	14 (93)
M1	4 (25)	1 (7)

	ITT Population	
	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64
Overall staging at study entry for patients with MF, n (%)		
n	48	49
IA	4 (8)	1 (2)
IB	6 (13)	12 (24)
IIA	5 (10)	5 (10)
IIB	19 (40)	19 (39)
IIIA	4 (8)	2 (4)
IIIB	0 (0)	0 (0)
IVA_1	0 (0)	1 (2)
IVA_2	2 (4)	8 (16)
IVB	7 (15)	0 (0)
Unknown	1 (2)	1 (2)
Evidence of bone marrow involvement at study entry n (%)		
Yes	2 (3)	2 (3)
No	62 (97)	62 (97)

Source: Table 14.1.1.3.
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.
Max=maximum, min=minimum, std dev=standard deviation.
(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).

The majority of patients with pcALCL had skin only lesions with 9 (56%) patients treated with brentuximab vedotin and 11 (73%) with physician's choice of therapy, while 7 (44%) and 4 patients (27%) had extracutaneous disease, respectively.

Prior cancer-related therapies

In

Table 14 the prior cancer related therapies are summarised. One patient with pcALCL who was randomised to the brentuximab vedotin arm did not receive prior radiation therapy or at least 1 prior systemic therapy and is included in major protocol deviations. In MF patients a median of 2 prior systemic therapies was observed in both arms and in pcALCL subjects a median of 1 in the brentuximab vedotin and 2 in the control arm were observed. All but 1 pcALCL patient (see above) received prior systemic therapy in this study. The median time since progression from last line of prior therapy (radiotherapy excluded) was 2.4 months (range 0-112) in the brentuximab vedotin arm and 1.4 months (range 0-55) in the control arm.

In the physician's choice arm, 3 patients (8%) had previously received bexarotene for their CTCL and were assigned by their physician to bexarotene in this study. Similarly, 2 patients (8%) in the physician's choice arm had previously received methotrexate and received methotrexate as study drug. The listing of individual patient data indicate that for the 2 methotrexate retreated patients the best response on previous methotrexate was SD and PR. Both patients had also previously received bexarotene. For the bexarotene retreated patients the previous responses to bexarotene were documented as unknown. Only one of the bexarotene retreated patients was previously treated with methotrexate.

Four patients (3 (5%) in the brentuximab vedotin arm and 1 (2%) in the physician's choice arm) had prior bone marrow or stem cell transplant.

Table 14: Prior Therapy for Cancer Under Study (ITT Population)

	ITT Population	
	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64
Number of prior therapies		
Any therapy		
N	64	64
Median	4.0	3.5
Min, max	0, 13	1, 15
Skin-directed therapy		
N	64	64
Median	1.0	1.0
Min, max	0, 6	0, 9
Systemic therapy		
N	64	64
Median	2.0	2.0
Min, max	0, 11	1, 8
Type of prior therapy n (%)		
Skin-directed therapy	52 (83)	51 (80)
Topical steroids	7 (11)	14 (22)
Topical retinoids	1 (2)	0
Topical chemotherapy	3 (5)	2 (3)
Radiotherapy	40 (63)	41 (64)
Phototherapy	32 (51)	29 (45)
Other	2 (3)	0
Systemic therapy	63 (100)	64 (100)
Bexarotene	26 (41)	22 (34)
Chemotherapy	45 (71)	45 (70)
Methotrexate	26 (41)	25 (39)
Other	30 (48)	32 (50)
Nontopical retinoids	5 (8)	4 (6)
Photopheresis	3 (5)	4 (6)
Denileukin diftitox	0	1 (2)
Immunotherapy	26 (41)	29 (45)
HDACi	13 (21)	13 (20)
Other	18 (29)	13 (20)
Prior surgical procedures n (%)		
Yes	3 (5)	6 (9)
No	61 (95)	58 (91)
Prior bone marrow or stem cell transplant n (%)		
Yes	3 (5)	1 (2)
No	61 (95)	63 (98)
Type of transplant (a) n (%)		
Allogeneic	1 (33)	1 (100)
Autologous	2 (67)	1 (100)

Source: Table 14.1.1.4.
Percentages are based on the number of patients with nonmissing values in the ITT population with prior therapy/prior radiation/prior transplant procedure in each column.
For partial dates of progression, imputed dates were used in the calculation of number of months since progression from last line of therapy. When only the day was missing, the day was imputed to either 15 or min [15, day of first dose] when the year and month of progression were the same as the year and month of the first dose. When only year was available, day and month were imputed to either 30JUN or min [30JUN, day and month of first dose] when the year of progression was the same as the year of the first dose.
Max=maximum, min=minimum, std dev=standard deviation.
(a) Totals may exceed 100% because patients may have received >1 transplant.

The most common prior skin directed therapies in the ITT population were radiotherapy (64%), phototherapy (48%) and topical steroids (17%). The most common prior systemic therapies in the ITT population were chemotherapy (71%), immunotherapy (43%) and bexarotene (38%).

Concomitant medication and procedures

Nearly all patients received concomitant medication during the study, however concomitant medications which might have influenced outcomes were prohibited per protocol. The most common concomitant medication received by patients who received methotrexate (n=25) was folic acid in 13 patients (52%). In patients who received bexarotene (n=37), 27 patients (73%) received concomitant treatment with fenofibrate, and 33 patients (89%) received treatment with levothyroxine. In the brentuximab vedotin arm, 13 patients (20%) received levothyroxine, 12 patients (18%) received hydroxyzine, and 9 patients (14%) received fenofibrate other than the required premedication course. Statins were administered to 21 patients (32%) in the brentuximab vedotin arm.

Subsequent antineoplastic therapy

Table 15: Subsequent anticancer therapies in patients with at least 1 subsequent anticancer therapy

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64
Patients with at least 1 subsequent anticancer therapy	38 (59)	47 (73)
Type of therapy n (%) (a)		
Skin directed therapy	17 (45)	22 (47)
Radiotherapy	12 (32)	16 (34)
Phototherapy	6 (16)	6 (13)
Topical Steroids	1 (3)	5 (11)
Systemic therapy	34 (89)	44 (94)
Chemotherapy	23 (61)	22 (47)
Other	19 (50)	19 (40)
Methotrexate	8 (21)	6 (13)
Immunotherapy	9 (24)	5 (11)
Bexarotene	6 (16)	4 (9)
Brentuximab vedotin	5 (13)	29 (62)
Other	5 (13)	3 (6)
HDACi	4 (11)	3 (6)
Photopheresis	0	1 (2)
Other	1 (3)	4 (9)

Numbers analysed

The following populations were analysed, see Table 15 for their numbers.

- The All-Enrolled population included all patients randomised to treatment, analysed according to randomisation treatment.
- The ITT population included all patients who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomised to treatment; analysed according to randomisation treatment. The ITT population was used for the primary efficacy analysis and for all other efficacy analyses unless specified otherwise.
- The Per-Protocol (PP) population included a subset of ITT patients who received study drug and did not have major protocol violations as determined by the project clinician; analysed according to received treatment.
- The Response-Evaluable population is defined as a subset of the ITT population with measurable disease at Baseline and with at least 1 post baseline skin response assessment.

- The Safety population included patients who received at least 1 dose of study drug. All patients were analysed according to the actual treatment received.
- The PK/PD population included patients with sufficient dose and PK/PD data to reliably estimate PK/PD parameters. At least 1 of the biomarkers, CTACK, TARC, sCD30, or interleukin 6 was required to reliably measure PD parameters.

Table 16: Patient disposition

Patient Population	Brentuximab Vedotin Patients	Methotrexate or Bexarotene Patients	Total Patients	Analysis
All Enrolled	66	65	131	Supplemental analysis of the primary endpoint ORR4 and key secondary endpoints
ITT (a)	64	64	128	Primary efficacy analyses of all efficacy endpoints unless otherwise specified
PP	59	58	117	Supplemental analysis of the primary endpoint ORR4
Response Evaluable	61	58	119	Sensitivity analyses of ORR4, CR rate, ORR, and DOR
Safety (b)	66	62	128	All safety analyses
PK	66	NA	66	All PK analyses
PD	64	61	125	All PD analyses

Outcomes and estimation

The summary of primary endpoint analyses in the ITT is shown in Table 17, ORR4 per IRF based on baseline disease diagnosis (MF or pcALCL) is presented in Table 18 and results from the subgroup analyses for ORR4, are presented below, in Figure 17.

Table 17: ORR4 per IRF in the ITT population

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64	P-value (a)
Number (%) achieving ORR4 per IRF	36 (56.3)	8 (12.5)	<0.001
95% CI	(44.1, 68.4)	(4.4, 20.6)	
Difference (%) from physician's choice arm (b)	43.8		
95% CI for the difference from physician's choice arm	(29.1, 58.4)		

Table 18: ORR4 based on baseline disease diagnosis in the ITT

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64	P-value (a)
MF	48	49	
Number (%) achieving ORR4 per IRF	24 (50.0)	5 (10.2)	<0.001
95% CI	(35.9, 64.1)	(3.4, 22.2)	
Difference from physician's choice arm (b)	39.8		
95% CI for difference from physician's choice arm	(19.9, 56.2)		
pcALCL	16	15	
Number (%) achieving ORR4 per IRF	12 (75.0)	3 (20.0)	0.003
95% CI	(47.6, 92.7)	(4.3, 48.1)	
Difference from physician's choice arm (b)	55.0		
95% CI for difference from physician's choice arm	(19.7, 80.4)		

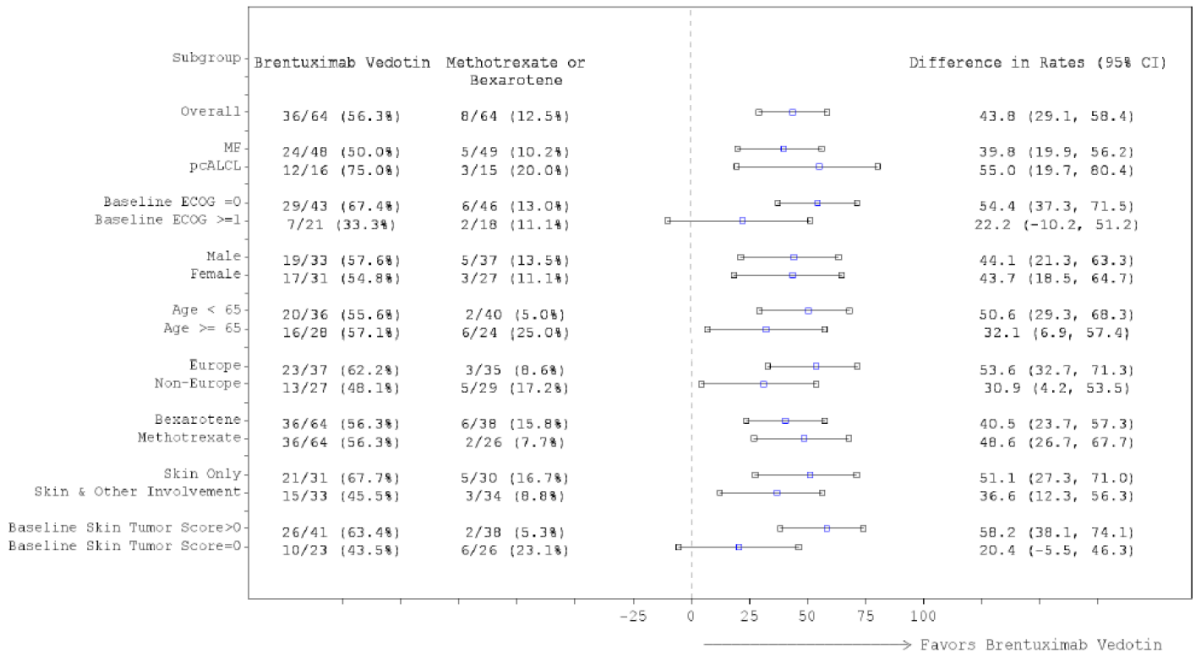


Figure 17: Forest plot of difference in ORR4 Per IRF (ITT Population)

Key secondary endpoints

CR

Per IRF assessment, study treatment led to CR in 10 patients (15.6%) (95%CI 6.7-24.5) in the brentuximab vedotin arm and 1 patient (1.6%) (95%CI 0-4.6) in the physician's choice arm (p-value=0.0046; adjusted p-value=0.0046; percentage difference of 14.1 (95% CI (-4.0, 31.5)).

PFS

The PFS analyses were performed with an median PFS follow-up of 17.5 months. At the time of data cut-off, 86 (67%) patients had experienced a PFS event: progressive disease per IRF in 74 patients (30 patients (47%) in the brentuximab vedotin arm and 44 patients (69%) in the physician's choice arm and death in 12 patients (6 patients (9%) in the brentuximab vedotin arm and 6 patients (9%) in the physician's choice arm.

PFS analysis per IRF is shown in Table 19, a Kaplan-Meier plot is shown in Figure 18 and subgroup analyses are shown in Figure 19.

Table 19: PFS analysis per IRF in the ITT population

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64	Total N=128	Hazard Ratio (a) (95% CI)	P-value (b) (Adjusted P-value) (c)
PFS (months)					
Number with events (%)	36 (56)	50 (78)	86 (67)	0.270 (0.169, 0.430)	<0.001 (<0.001)
Number censored (%)	28 (44)	14 (22)	42(33)		
25th percentile (95% CI)	9.1 (3.8, 14.9)	2.0 (1.4, 2.4)	2.8 (2.1, 3.8)		
Median (95% CI)	16.7 (14.9, 22.8)	3.5 (2.4, 4.6)	8.3 (4.9, 14.9)		
75th percentile (95% CI)	27.5 (21.6, 30.7)	6.3 (4.6, 21.0)	21.1 (16.7, 27.5)		
Min, max	0.0*, 32.6*	0.0*, 23.7	0.0*, 32.6*		
Kaplan-Meier estimates (d) (95% CI)					
6 months	82.0 (69.8, 89.6) [n=48]	26.1 (15.3, 38.2) [n=13]	55.2 (45.8, 63.7) [n=61]		
1 year	67.5 (53.7, 78.0) [n=29]	16.0 (7.6, 27.2) [n=7]	43.0 (33.8, 52.0) [n=36]		
1.5 years	40.3 (25.5, 54.7) [n=13]	16.0 (7.6, 27.2) [n=4]	28.5 (19.4, 38.3) [n=17]		
2 years	33.0 (18.5, 48.2) [n=7]	NE [n=0]	18.0 (9.6, 28.5) [n=7]		
Median PFS follow-up (e) (months) (95% CI)	19.0 (12.6, 26.1)	14.5 (10.3, NE)	17.5 (12.6, 22.9)		
Reason leading to PFS event					
Progressive disease	30 (47)	44 (69)	74 (58)		
Death	6 (9)	6 (9)	12 (9)		
Reason for censoring					
Lost to follow-up	0	1 (2)	1 (1)		
No baseline or postbaseline assessment	1 (2)	3 (5)	4 (3)		
Withdrawal by subject	3 (5)	2 (3)	5 (4)		
No death or progression	24 (38)	8 (13)	32 (25)		

Max=maximum, min=minimum, NE=not estimable.

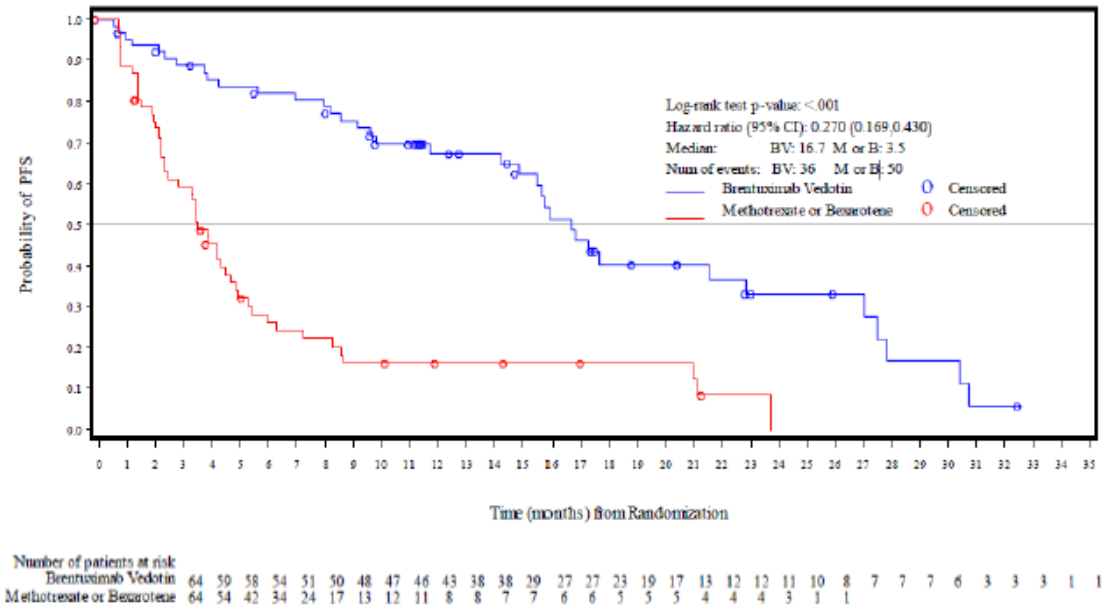


Figure 18: Kaplan-Meier Plot of PFS per IRF in the ITT Population

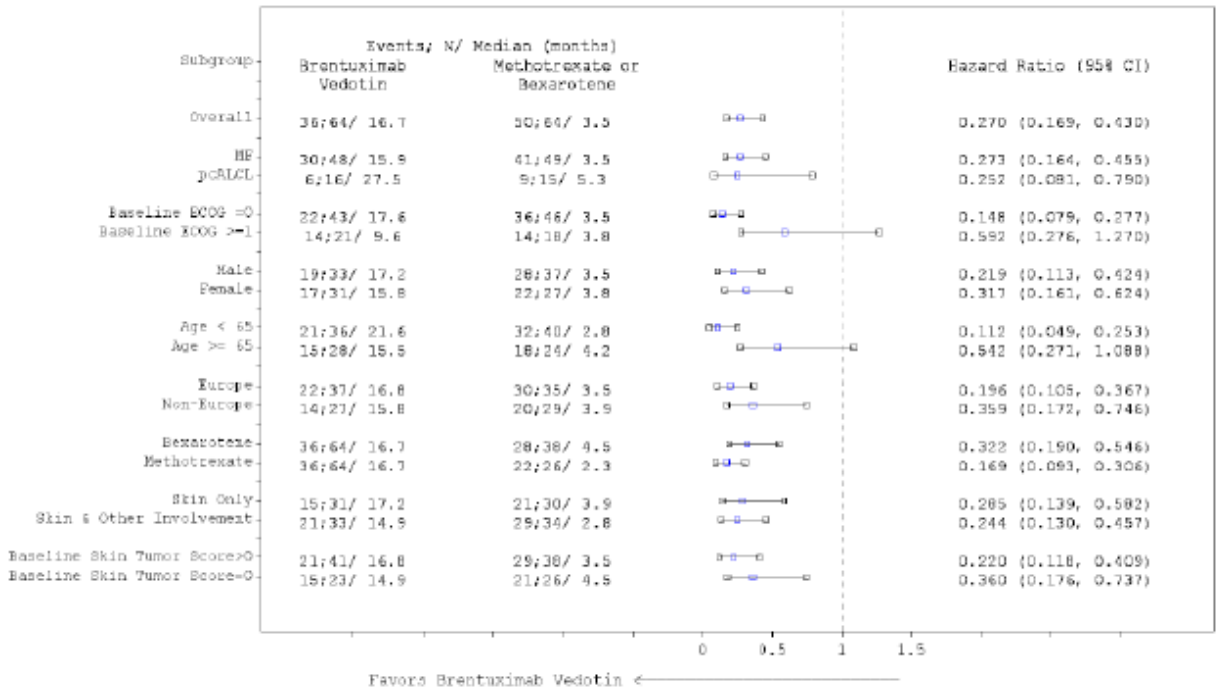


Figure 19: Forest Plot of PFS per IRF in the ITT Population.

Changes in symptom domain of Skindex-29 Score

The changes in symptoms are measured by the mean maximum change from baseline in disease symptoms, as measured by the Skindex-29 symptom domain score. The mean maximum change from baseline was -28 points (std dev- 26.9) in the brentuximab vedotin arm and -8.62 points (std dev 17.0) in the physician's choice arm (p-value<0.001; adjusted p-value<0.001). The median of the maximum reduction from baseline was -32.1 points (range, -78.6 to 42.9 points) in the brentuximab vedotin arm and -10.42 points (range, -50.0 to 28.6 points) in the physician's choice arm. The

calculated MID in the reduction in Skindex-29 symptom domain score was 12.3 using half of a standard deviation of change in score, 11.2 using Cohen's effect size, and 9.1 using standard error of measurement.

In Figure 20 the mean change from baseline Skindex-29 symptom score is shown troughout the time in the ITT Population.

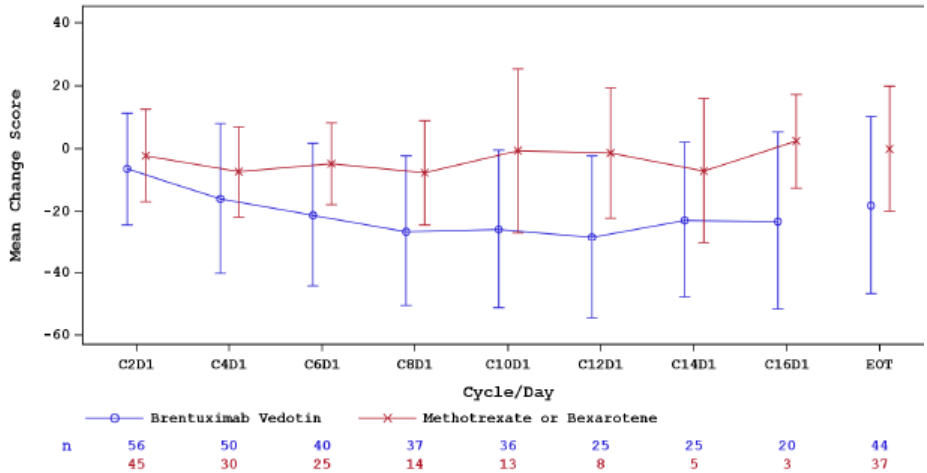


Figure 20: Mean change from baseline Skindex-29 symptom score time curves in the ITT Population

Other secondary endpoints

Duration of response

In patients who received brentuximab vedotin and experienced CR or PR (43 patients), the median DOR was 15.1 months (CI 9.7, 25.5). In patients who received either methotrexate or bexarotene and experienced CR or PR (13 patients), the median DOR was 18.3 months (CI 3.5, 18.4). Responses were ongoing at last assesment in 20 of the 43 responders (47%) in the brentuximab vedotin arm and 7 of the 13 patients (54%) in the physician's choice arm.

Duration of skin response

In patients who received brentuximab vedotin and experienced skin response (47 patients), the median duration of skin response was 20.6 months (14.1, 25.7). In patients who received either methotrexate or bexarotene and experienced skin response (19 patients), the median duration of skin response was 18.3 months (3.5, 18.9). Responses were ongoing at last assessment in 25 of the 47 responders (53%) in the in the brentuximab vedotin arm and 9 of the 19 patients (47%) in the physician's choice arm.

EFS

EFS per IRF is summarised in Table 20.

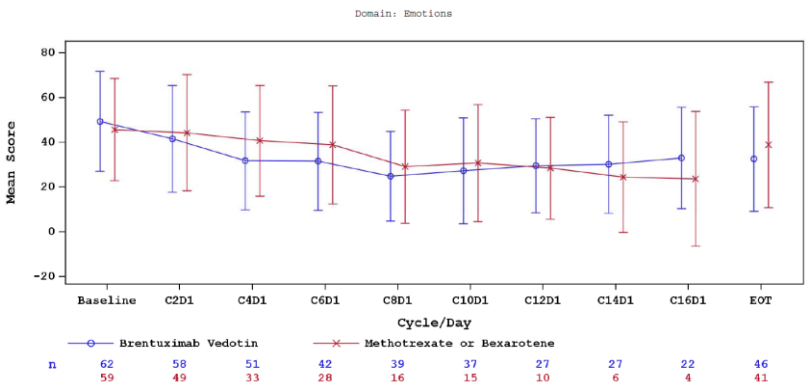
Table 20: EFS analyses per IRF in the ITT population

	Brentuximab vedotin N=64	Methotrexate or Bexarotene N=64	Total N=128	Hazard Ratio (a) (95% CI)	p-value (b)
EFS (months)					
Number with events (%)	54 (84)	63 (98)	117 (91)	0.285 (0.189, 0.429)	<0.001
Number censored (%)	10 (16)	1 (2)	11 (9)		
25th percentile (95% CI)	3.8 (2.3, 5.9)	1.4 (0.8, 1.7)	1.9 (1.4, 2.3)		
Median (95% CI)	9.4 (5.9, 11.7)	2.3 (1.7, 3.5)	4.2 (3.5, 5.4)		
75th percentile (95% CI)	14.7 (11.7, 15.9)	4.3 (3.5, 6.3)	10.6 (8.4, 12.5)		
Min, max	0.6, 27.5	0.0, 21.1	0.0, 27.5		
Kaplan-Meier estimates (c) (95% CI)					
6 months	62.5 (49.5, 73.1) [n=40]	15.6 (8.0, 25.5) [n=10]	39.1 (30.6, 47.4) [n=50]		
1 year	34.6 (23.0, 46.5) [n=17]	4.7 (1.2, 11.8) [n=3]	19.5 (13.1, 27.0) [n=20]		
1.5 years	9.8 (3.3, 20.5) [n=3]	2.3 (0.2, 9.6) [n=1]	6.1 (2.4, 12.2) [n=4]		
Median follow-up (d) (months) (95% CI)	17.5 (14.6, NE)	NE (12.1, NE)	26.1 (14.6, NE)		
Reason leading to EFS event					
Progressive disease per IRF	16 (25)	39 (61)	55 (43)		
Death	2 (3)	1 (2)	3 (2)		
Early treatment discontinuation	25 (39)	11 (17)	36 (28)		
AE	12 (19)	1 (2)	13 (10)		
Progressive Disease	4 (6)	1 (2)	5 (4)		
Protocol violation	1 (2)	1 (2)	2 (2)		
Unsatisfactory therapeutic response (e)	2 (3)	1 (2)	3 (2)		
Withdraw consent	6 (9)	6 (9)	12 (9)		
Other	0	1 (2)	1 (1)		
Start new antineoplastic therapy	11 (17)	12 (19)	23 (18)		
Reason for censoring					
Completed max number of cycles per protocol	7 (11)	1 (2)	8 (6)		
No event	3 (5)	0	3 (2)		

Patient reported outcomes

Skindex-29

The other domains (emotions, functioning) and the total score of the Skindex-29 scores were also measured. The Skindex-29 mean score time curves in the ITT population are shown for the domains: symptoms, emotions, functioning and total score.



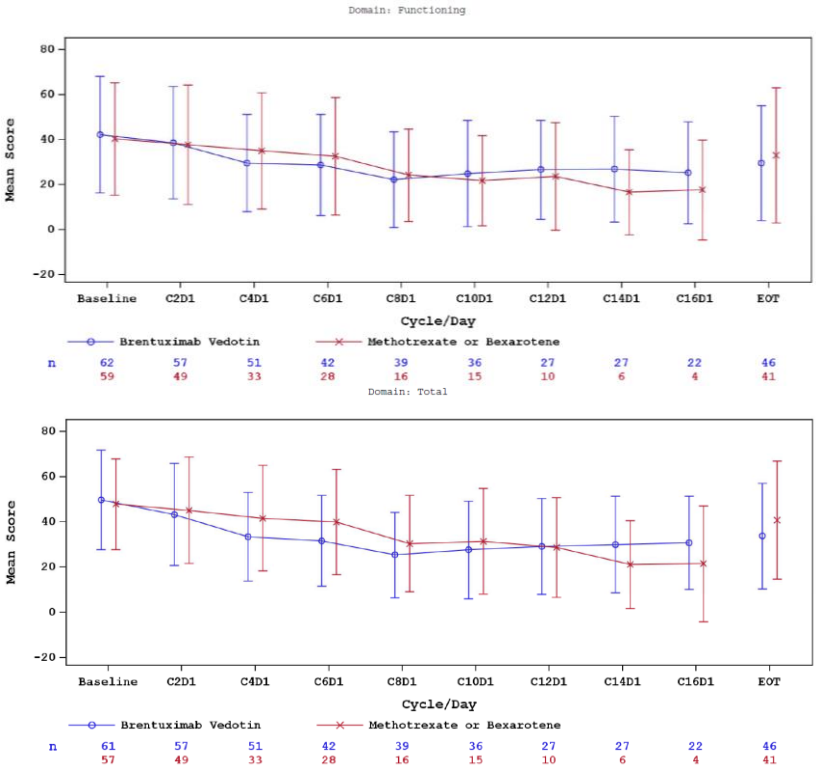


Figure 21: The Skindex-29 mean score time curves for the domains emotions, functioning and total score

Functional Assessment of Cancer Therapy-General (FACT-G)
No differences were observed between the two treatment arms; compliance was high and similar over the treatment course and both arms.

European Quality of Life 5-Dimension Three Level Version
Overall, no significant differences were seen between the 2 treatment arms. Patient compliance was high and similar between the 2 treatment arms during the course of the study.

Ancillary analyses

Sensitivity analyses

ORR4

- ORR4 per IRF using the OPDREC response criteria (guidelines in Whittaker 2010): a total of 35 patients (54.7% (CI 42.5-66.9)) in the brentuximab vedotin arm achieved ORR4, compared with 5 patients (7.8%(CI 2.6 -17.3)) in the physician's choice arm (p-value <0.001). Similar outcomes were observed in the MF only population.
- ORR4 per IRF based on a subset of GRS time points: a total of 32 patients (50% (CI 37.8-62.2)) in the brentuximab vedotin arm achieved ORR4, compared with 8 patients (12.5% (CI 4.4-20.6)) in the physician's choice arm (p-value <0.001).

- ORR4 per investigator GRS in the ITT: a total of 38 patients (59.4%) in the brentuximab vedotin arm achieved ORR4, compared with 5 patients (7.8%) in the physician's choice arm (p-value <0.001).
- ORR4 in which the patient's response after the start of next alternate therapy was censored at the start of next alternate therapy: a total of 35 patients (54.7%) in the brentuximab vedotin arm achieved ORR4, compared with 7 patients (10.9%) in the physician's choice arm (p-value <0.001).
- ORR4 in CR patients with recurrent disease considered as not maintained (i.e., relapse is treated as PD): a total of 36 patients (56.3%) in the brentuximab vedotin arm achieved ORR4, compared with 8 patients (12.9%) in the physician's choice arm (p-value <0.001).

CR

- CR per the investigator's assessment: 12 patients (18.8%) in the brentuximab vedotin arm versus 0 patients in the physician's choice arm achieved CR, with a risk difference of 18.8 (95% CI (0.7, 35.9)) in favour of brentuximab vedotin (p-value<0.001).

PFS

The PFS sensitivity analyses using different rules for handling of censoring/missing data are shown in Table 21 and a summary of PFS per investigator is shown in Table 22.

Table 21: Study C25001: sensitivity analyses of PFS per IRF in the ITT Population

	Brentuximab Vedotin N=64		Methotrexate or Bexarotene N=64			
Sensitivity Analyses	No. of Patients With Events (%)	Median (95% CI)	No. of Patients With Events (%)	Median (95% CI)	Hazard Ratio (a) (95% CI)	P-value (b)
Scenario 1	36 (56)	16.7 (14.9, 22.8)	50 (78)	3.5 (2.4, 4.6)	0.269 (0.169, 0.429)	<0.001
Scenario 3	23 (36)	17.2 (15.7, 27.9)	42 (66)	3.5 (2.3, 4.3)	0.181 (0.101, 0.324)	<0.001
Scenario 4	47 (73)	11.6 (8.6, 13.4)	58 (91)	2.8 (2.1, 3.7)	0.223 (0.142, 0.352)	<0.001
Scenario 5	32 (50)	16.7 (14.9, 27.0)	49 (77)	3.5 (2.4, 4.5)	0.262 (0.162, 0.423)	<0.001
Scenario 6	22 (34)	17.2 (15.7, 27.9)	42 (66)	3.5 (2.3, 4.3)	0.181 (0.101, 0.324)	<0.001

Source: Table 14.3.1.5B, Table 14.3.1.5D, Table 14.3.1.5E, Table 14.3.1.5F, Table 14.3.1.5G.
No.=number.
Discontinuation for undocumented progressive disease was determined by investigator assessment; Scenario 2 sensitivity analysis was therefore not performed for PFS per IRF.
Scenario 1: If disease progression was documented between scheduled visits, the date of the next scheduled visit was used as the date of progression.
Scenario 3: If the patient started new antineoplastic therapy with or without subsequent progression/death event, the patient was censored at the date of the last disease assessment before the start of antineoplastic therapy.
Scenario 4: If the patient started new antineoplastic therapy (with or without subsequent progression/death event), the patient was treated as progressed at the date of last disease assessment before the start of antineoplastic therapy.
Scenario 5: If death or progressive disease occurred after more than 1 missed visit, the patient was censored at the last disease assessment before the missed visits.
Scenario 6: If death or progressive disease occurred after more than 1 missed visit, the patient was censored at the last disease assessment before the missed visits. If the patient started new antineoplastic therapy with or without subsequent progression/death event, then the patient was censored at the date of the last disease assessment before the start of antineoplastic therapy.

Table 22: PFS per investigator in the ITT Population

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64	Total N=128	Hazard Ratio (a) (95% CI)	P-value (b)
PFS (months)					
Number with events (%)	40 (63)	51 (80)	91 (71)	0.318 (0.205, 0.495)	<0.001
Number censored (%)	24 (38)	13 (20)	37 (29)		
25th percentile (95% CI)	8.2 (3.7, 11.7)	1.9 (1.3, 2.5)	3.3 (2.1, 3.8)		
Median (95% CI)	15.7 (11.7, 17.2)	3.6 (2.5, 4.5)	8.0 (4.8, 11.7)		
75th percentile (95% CI)	27.0 (17.1, 30.7)	6.7 (4.5, 21.1)	17.6, 15.7, 27.0)		
Min, max	0.0*, 32.6*	0.0*, 23.7	0.0*, 32.6*		
Kaplan-Meier estimates (c) (95% CI)					
6 months	78.8 (66.4, 87.1) [n=48]	29.3 (18.1, 41.5) [n=15]	55.0 (45.6, 63.4) [n=63]		
1 year	63.2 (49.5, 74.1) [n=30]	15.4 (7.2, 26.4) [n=7]	40.5 (31.5, 49.3) [n=37]		
1.5 years	31.8 (18.8, 45.5) [n=12]	15.4 (7.2, 26.4) [n=4]	23.5 (15.3, 32.7) [n=16]		
2 years	28.2 (15.5, 42.4) [n=6]	NE [n=0]	15.6 (8.0, 25.3) [n=6]		
Median PFS follow-up (d) (months) (95% CI)	20.6 (14.9, 26.1)	17.1 (10.3, NE)	19.0 (14.5, 23.2)		
Reason leading to PFS event					
Progressive disease	35 (55)	46 (72)	81 (63)		
Death	5 (8)	5 (8)	10 (8)		
Reason for censoring					
Lost to follow-up	0	1 (2)	1 (1)		
No baseline or postbaseline assessment	1 (2)	3 (5)	4 (3)		
Withdrawal by subject	2 (3)	1 (2)	3 (2)		
No death or progression	21 (33)	8 (13)	29 (23)		

- Sensitivity analysis for PFS per IRF with mSWAT per IRF (based on IRF review of photos for skin assessment), the median PFS in the brentuximab vedotin arm was 19.9 months and the median PFS in the physician's choice arm was 5.3 months. The PFS HR was 0.372 (95% CI 0.217-0.639]; p-value <0.001 favouring the brentuximab vedotin arm over the physician's choice arm.

OS data

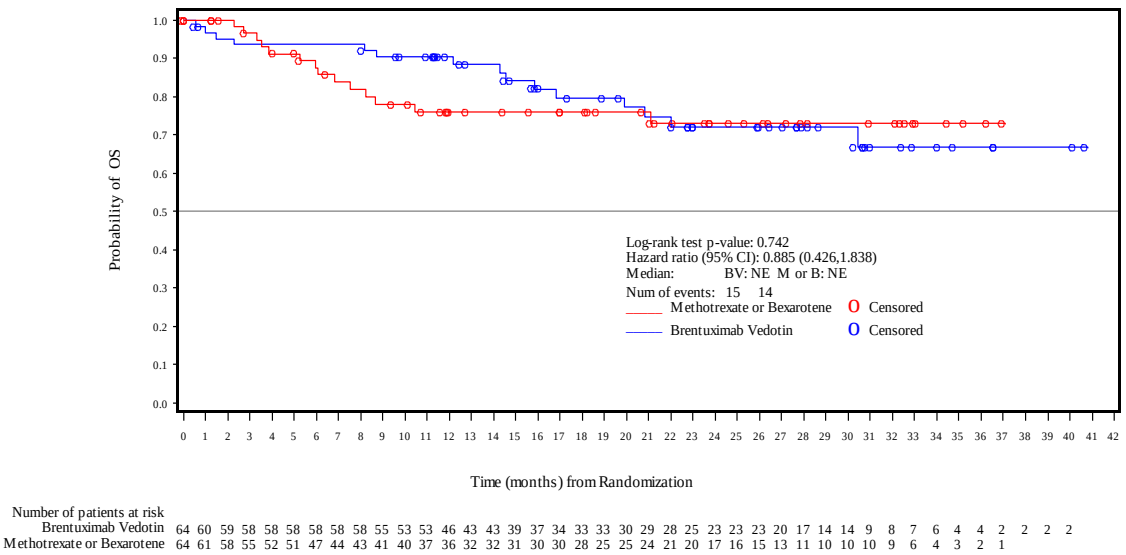
OS data is summarised by treatment group in Table 23. A Kaplan-Meier (KM) plot of OS is presented in

Figure 22. A summary of OS by disease subtype (MF or pcALCL) is presented in Table 24 and Table 25; these data are presented graphically in Figure 23 and Figure 24.

ITT population

Table 23: Summary of OS by Treatment Group (ITT Population)

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64	Total N=128	Hazard Ratio (a) (95% CI)	P-value (b)
OS (months)					
Number with events (%)	15 (23)	14 (22)	29 (23)	0.885 (0.426-1.838)	0.742
Number censored (%)	49 (77)	50 (78)	99 (77)		
Median (95% CI)	NE (30.4-NE)	NE (NE,NE)	NE (NE,NE)		
Min, max	0.6, 40.8*	0.1*, 37.1*	0.1*, 40.8*		
KM estimates (c) (95% CI)					
6 months	93.6 (83.8-97.5) [n=58]	87.6 (75.7-93.9) [n=47]	90.8 (84.0-94.8) [n=105]		
1 year	90.3 (76.1-95.5) [n=46]	76.1 (62.4-85.4) [n=36]	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]	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]	72.4 (62.2-80.3) [n=40]		
Median OS follow-up (d) (months) (95% CI)	23.2 (19.1-28.1)	20.8 (14.6-23.9)	22.9 (18.4-26.1)		
Reason for censoring					
End of study, due to	9 (14)	12 (19)	21 (16)		
Withdrawal by subject	8 (13)	10 (16)	18 (14)		
Lost to follow-up	1 (2)	1 (2)	2 (2)		
Other	0	1 (2)	1 (1)		
Alive at last contact	40 (63)	38 (59)	78 (61)		



Number of patients at risk

Brentuximab Vedotin	64	60	59	58	58	58	58	58	58	55	53	53	46	43	43	39	37	34	33	33	30	29	28	25	23	23	23	20	17	14	14	9	8	7	6	4	4	2	2	2	2
Methotrexate or Bexarotene	64	61	58	55	52	51	47	44	43	41	40	37	36	32	32	31	30	30	28	25	25	24	21	20	17	16	15	13	11	10	10	10	9	6	4	3	2	1			

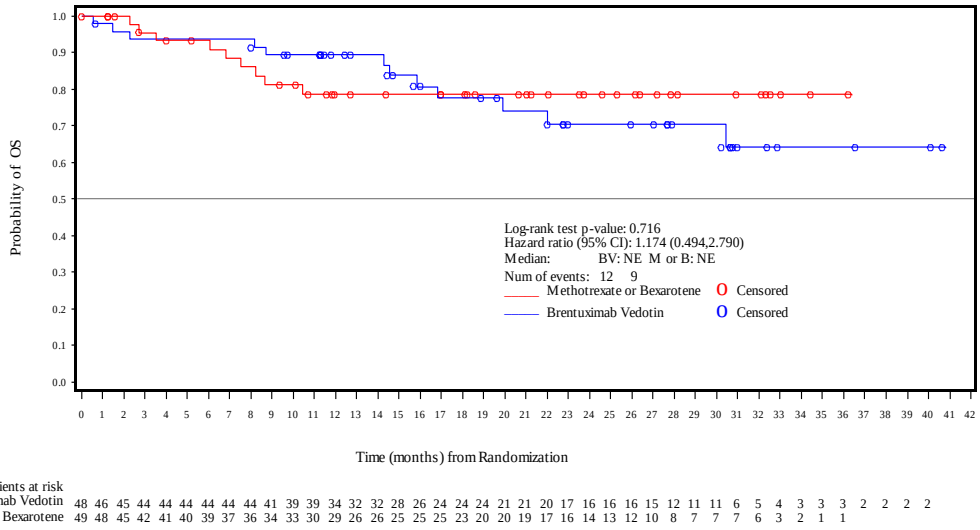
B=bexarotene, BV=brentuximab vedotin, M=methotrexate, Num=number.

Figure 22: KM Plot of OS (ITT Population)

MF population

Table 24: Summary of OS (MF Population)

	Brentuximab Vedotin N=48	Methotrexate or Bexarotene N=49	Hazard Ratio (a) (95% CI)	P-value (b)
OS (months)				
Number with events (%)	12 (25)	9 (18)	1.174	0.716
Number censored (%)	36 (75)	40 (82)	(0.494-2.790)	
Median (95% CI)	NE (30.4-NE)	NE (NE-NE)		
Min, max	0.6, 40.8*	0.2*, 36.4*		
KM estimates (c) (95% CI)				
6 Months	93.7 (81.6-97.9) [n=44]	93.3 (80.6-97.8) [n=39]		
1 Year	89.4 (76.3-95.4) [n=34]	78.8 (63.1-88.4) [n=29]		
1.5 Years	77.5 (60.8-87.8) [n=24]	78.8 (61.3-88.4) [n=23]		
2 Years	70.5 (52.3-82.8) [n=16]	78.8 (61.3-88.4) [n=14]		
Median OS follow-up (d) (months) (95% CI)	23.2 (16.2-28.1)	20.8 (14.6-24.8)		
Reason for censoring				
End of study, due to	8 (17)	8 (16)		
Withdrawal by subject	7 (15)	8 (16)		
Lost to follow-up	1 (2)	0		
Other	0	0		
Alive at last contact	28 (58)	32 (65)		



B=bexarotene, BV=brentuximab vedotin, M=methotrexate, Num=number.

Figure 23: OS by Treatment Group and Diagnosis Group (MF Population)

pcALCLpopulation

Table 25: Summary of OS (pcALCL Population)

	Brentuximab Vedotin N=16	Methotrexate Bexarotene N=15	Hazard Ratio (a) (95% CI)	P-value (b)
OS (months)				
Number with events (%)	3 (19)	5 (33)	0.415	0.217
Number censored (%)	13 (81)	10 (67)	(0.099-1.751)	
Median (95% CI)	NE (20.8-NE)	NE (5.3-NE)		
Min, max	0.6*, 36.7*	0.1*, 37.1*		
Kaplan-Meier Estimates[c] (95% CI)				
6 Months	93.3 (61.3-99.0) [n=14]	67.7 (34.9-86.5) [n=8]		
1 Year	93.3 (61.3-99.0) [n=12]	67.7 (34.9-86.5) [n=7]		
1.5 Years	85.6 (53.3-96.2) [n=9]	67.7 (34.9-86.5) [n=5]		

	Brentuximab Vedotin N=16	Methotrexate Bexarotene N=15	or Hazard Ratio (a) (95% CI)	P-value (b)
2 Years	76.0 (41.8-91.8) [n=7]	54.2 (20.4-78.9) [n=3]		
Median OS follow-up (d) (months) (95% CI)	26.1 (16.0-28.8)	15.8 (5.2-35.4)		
Reason for censoring				
End of study, due to	1 (6)	4 (27)		
Withdrawal by subject	1 (6)	2 (13)		
Lost to follow-up	0	1 (7)		
Other	0	1 (7)		
Alive at last contact	12 (75)	6 (40)		

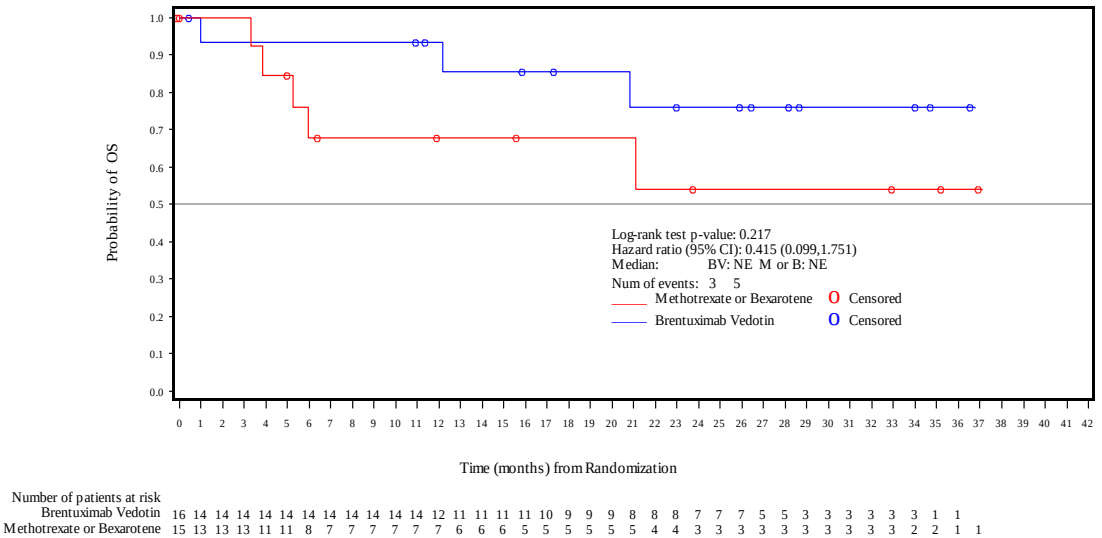


Figure 24: OS by Treatment Group and Diagnosis Group (pcALCL Population)
B=bexarotene, BV=brentuximab vedotin, M=methotrexate, Num=number.

Skin symptoms

- The linear mixed model with repeated measures and imputed scores were in line with the original analyses; though scores in the control arm were lower than in the original analysis.

Exploratory analyses

ORR4

- ORR4 per IRF based on GRS consisting of skin evaluation mSWAT assessment by independent review of photographs for skin response: a total of 22 patients (34% (CI 22.7-46.0)) in the brentuximab vedotin arm achieved ORR4 compared with 6 patients (9.4% (CI 2.2-16.5)) in the physician's choice arm (p-value <0.001).

Time to subsequent antineoplastic therapy

- The time to subsequent antineoplastic therapy was assessed in the ITT population with 38 patients (59%) in the brentuximab vedotin arm and 47 patients (73%) in the physician's choice arm who received at least 1 subsequent antineoplastic therapy. The median time to subsequent antineoplastic therapy was 14.3 (12.5, 20.4) months in the brentuximab vedotin arm and 5.5 (3.6, 7.2) months in the physician's choice arm with HR=0.236 (95% CI 0.145, 0.383) (p<0.001).

Best overall response (per GRS)

Table 26: Overall best response based on GRS per IRF in the ITT population

	ITT Population			
	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64	Bexarotene N=38	Methotrexate N=26
Overall best GRS response (a) per IRF				
CR	10 (16)	1 (2)	0	1 (4)
PR	33 (52)	12 (19)	10 (26)	2 (8)
CR+PR	43 (67)	13 (20)	10 (26)	3 (12)
SD	10 (16)	18 (28)	12 (32)	6 (23)
Progressive disease	5 (8)	22 (34)	9 (24)	13 (50)
Overall best skin response (a) per investigator				
CR	17 (27)	1 (2)	0	1 (4)
PR	30 (47)	18 (28)	13 (34)	5 (19)
CR+PR	47 (73)	19 (30)	13 (34)	6 (23)
SD	12 (19)	32 (50)	21 (55)	11 (42)
Progressive disease	2 (3)	7 (11)	1 (3)	6 (23)

Source: Tables 14.3.1.4A and 14.3.1.4D.
Patients who did not have any postbaseline response assessment as specified in the protocol were counted as nonresponders. GRS response per IRF consisted of a skin evaluation (mSWAT assessment) by investigator, nodal and visceral radiographic assessment by IRF, and detection of circulating Sézary cells (MF only) by IRF.
(a) Overall best response that occurred after the start of subsequent therapy was excluded.

Biomarker analyses

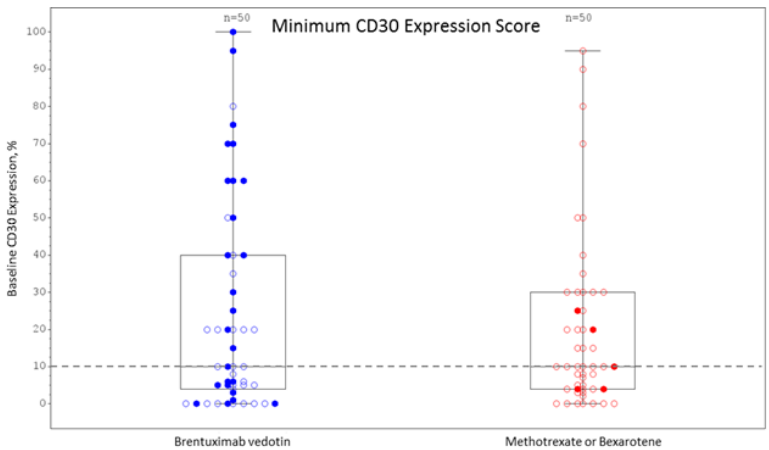
CD30 expression from skin biopsy

CD30 expression level (percentage of total cells) from skin biopsy was assessed at Baseline, Cycle 3 Day 21, and EOT.

Table 27: Summary of CD30 expression (%) from skin biopsy in the ITT Population

	Brentuximab Vedotin N=64	Methotrexate or Bexarotene N=64
Baseline		
n	64	64
Mean (std dev)	41.56 (32.775)	36.53 (29.785)
Median	32.50	31.25
Min (a), max	3.0, 100.00	5.0, 100.00
Number of biopsies		
Mean	2.1	2.1
Median	2.0	2.0
Min, max	1, 4	1, 4
Cycle 3 Day 21		
n	43	36
Mean	7.77 (16.424)	17.13 (23.819)
Median	0.50	5.00
Min, max	0.0, 80.0	0.0, 87.5
Change from Baseline at Cycle 3 Day 21 (%)		
n	43	36
Mean	-33.23 (34.301)	-15.41 (26.915)
Median	-20.50	-11.58
Min, max	-100.0, 52.0	-97.5, 42.5
EOT		
n	21	18
Mean (std dev)	20.79 (27.854)	21.11 (30.277)
Median	5.00	6.25
Min, max	0.0, 95.0	0.0, 90.0
Change from Baseline at EOT		
n	21	18
Mean	-27.41 (30.119)	-11.41 (24.765)
Median	-17.50	-13.25
Min, max	-94.5, 23.5	-40.0, 48.0

Figure 25 illustrates the distributions of baseline CD30 expression scores by treatment arm with the Filled circles indicating patients who achieved ORR4. Open circles indicate patients who did not achieve ORR4.



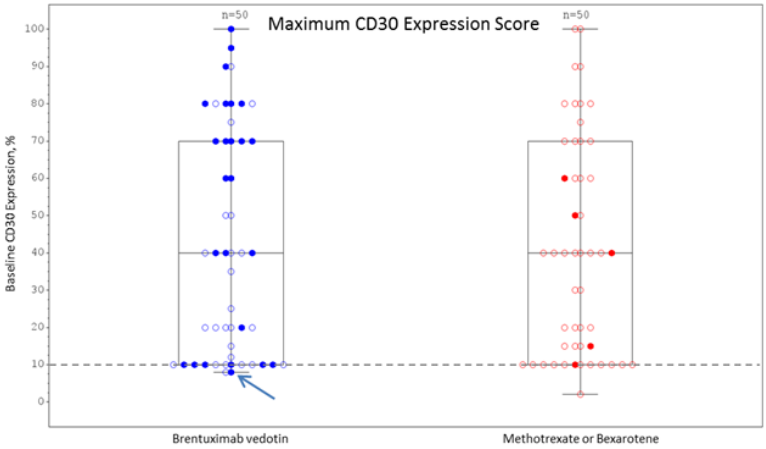


Figure 25: Boxplot of Baseline CD30 Expression With Subject Level ORR4 Status by Treatment Group (MF All-Enrolled Population)

Figure 26 shows the probability of achieving ORR4 according to minimum and maximum CD30 expression score in biopsies collected from each patient at the Baseline visit.

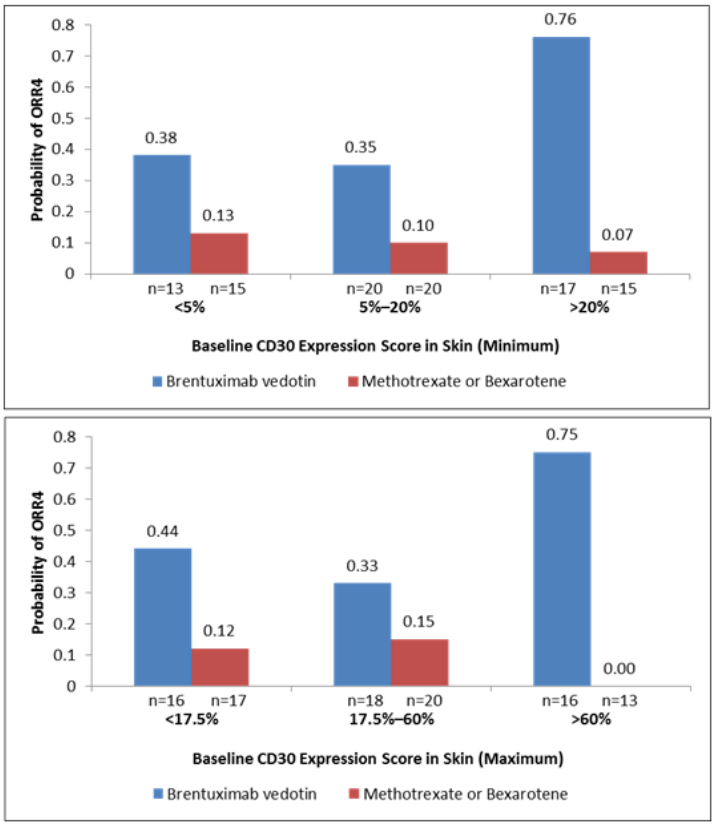


Figure 26: Probability of ORR4 by Baseline CD30 Expression Tercile (MF All-Enrolled Population)

Soluble CD30 expression, TARC, CTACK

Soluble CD30 (sCD30), Thymus and Activation-Regulated Chemokine (TARC), Cutaneous T-cell-Attracting Chemokine (CTACK) were measured in serum in both treatment arms at Baseline, before administration of study drug on Day 1 of Cycle 2 through Cycle 16, and at EOT. Levels of sCD30, TARC and CTACK were highly variable between patients. Mean baseline values of these three biomarkers

were similar at baseline. Mean sCD30 levels slightly increased throughout time in the interventional arm and did not change in the control arm. Mean levels of TARC declined over the course of treatment, moreso in the brentuximab vedotin arm compared to the control arm. CTACK mean levels declined in the brentuximab vedotin arm over time and increased in the physician's choice arm over time.

Immunogenicity/ATA Status

Sixty patients (91%) in the brentuximab vedotin arm were evaluable for immunogenicity assessments. From the total analysed population 56 (85%) were ATA negative at baseline. The total ATA positive rate in the study was 42% among the Safety population, of which 24% were ATA transiently positive and 18% persistently positive. There were no apparent differences in ORR4 per IRF by ATA response or titre status. In total 30% of the patients neutralising ATA was measured. No correlation between neutralising ATA status and efficacy were provided.

Health Economics Using Medical Resource Utilisation

The number of patients with at least one hospitalisation was 19 (30%) in the brentuximab vedotin arm and 28 (44%) in the control arm. The number of patients with at least one outpatient visits were 38 (59%) and 30 (47%) respectively. The median number of hospitalised days was 15 vs 20 days, respectively and the number of median number of outpatient visits was 5 days in the brentuximab vedotin arm and 13 in the control arm.

In both arms the number of patients with hospitalisation due to AEs was equal (45%). The median number of missed days from work was 9 days in the brentuximab vedotin arm and 5 days in the control arm.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28. Summary of Efficacy for trial CA25001 (ALCANZA)

Title: 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.			
Study identifier	CA25001		
Design	Randomized (1:1), open label, phase III trial		
	Duration of main phase:		11 June 2012 (first patients signed informed consent)- 26 May 2016 (last patients last visit)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Brentuximab vedotin/adcetris arm		brentuximab vedotin 1.8 mg/kg iv Q21 days max 16 cycles; n=64
	Control/physician's choice arm		methotrexate 5-50 mg po Q1W or bexarotene 300 mg/m^2 po Q1D, max 48 weeks
Endpoints and definitions	Primary endpoint	ORR4	The proportion of patients achieving an objective response that lasts at least 4 months as determined by an IRF based on GRS
	Key secondary endpoints	CR	Proportion of patients who achieved a CR as their best response on study as determined by an IRF

	Key secondary endpoints	PFS	Time from randomization until PD per IRF or death due to any cause, whichever occurs first.
	Key secondary endpoints	skin symptoms	Mean maximum reduction on the symptom domain of Skindex-29 from baseline
	Other secondary endpoint	DOR	Time between first documentation of response and PD per IRF
	Other secondary endpoint	DOR skin	Time between the first skin response and PD in skin per investigator
	Other secondary endpoint	EFS	Time from randomization until any cause of treatment failure: PD, discontinuation of treatment for any reason, or death due to any cause, whichever occurs first per IRF
Database lock	20 July 2016		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	**Treatment group**	**Brentuximab vedotin arm** (n=64)	**Control arm** (n=64)	**Effect estimate** HR (95%CI) p-value
	ORR4	36 (56.3%)	8 (12.5%)	-
	95%CI	*44.1, 68.4*	*4.4, 20.6*	p<0.001
	CR	10 (15.6%)	1 (1.6%)	-
	95%CI	6.7, 24.5	0, 4.6	p=0.0046*
	PFS - *median*	16.7	3.5	HR 0.27 (0.17-0.43)
	95%CI	*14.9, 22.8*	*2.4, 4.6*	p<0.001*
	Skin symptoms- mean maximum reduction	-28.0	-8.6	-
	std. dev	26.9	17	p<0.001*
	DoR-median	15.1	18.3	-
	95%CI	*9.7, 25.5*	*3.5, 18.4*	-
	DOR skin- median	20.6	18.3	-
	95%CI	*14.1, 25.7*	*3.5, 18.9*	-
	EFS- median	9.4	2.3	HR 0.29 (0.19, 0.43)
	95%CI	*5.9, 11.7*	*1.7, 3.5*	P<0.001

Notes	* Adjusted p-value DOR, DOR skin, and EFS are not adjusted for multiplicity.

Analysis performed across trials (pooled analyses and meta-analysis)

No analysis performed across trials for efficacy was submitted.

Clinical studies in special populations

Patients up to 83 years were included in the pivotal study. Subgroup analyses were performed for ORR4 and PFS between patients ≥65 years (28 (44%) in the brentuximab vedotin arm and 24 (38%) control arm) and patients <65 years. In patients ≥65 years decreased efficacy was observed compared to patients <65 years. The ORR4 subgroup analyses indicated a 32.1% difference in patients ≥65 compared to control arm vs 51% difference in younger patients. For PFS, HR: 0.54, in which the CI crosses 1 in older patients and HR: 0.11 in younger patients.

Supportive study(ies)

Published literature studies in CTCL subtypes were included in this submission. This included two phase 2 trials in which brentuximab vedotin was given at 1.8 mg/kg every 3 weeks and 1 retrospective study and several case studies.

The phase II trial by Kim et al (2015) included 30 patients of which 3 with Sézary Syndome (SS) and 27 with MF. Patients were allowed to receive up to 16 cycles. In the 3 SS patients different outcomes (1CR, 1PR, 1PD) were observed. The phase II trial by Duvic et al (2016) in MF and LPD (n=48) included 17 patients with Lyp (n=9) or mixed Lyp histology; these patients had a RR of 100% including 13CRs. Median duration of response was 26 weeks (range 6 to 44).

In a retrospective single centre study (Wieser 2016) in patients with Lyp and Lyp mixed histology, brentuximab vedotin was given in 21 patients (posology is not known). Patients' LyP lesions regressed with 1 to 2 infusions. A total of 10 patients (47.6%) achieved a CR and 7 (33%) patients had relapse after therapy was stopped.

Several case reports which apply different posology are included. For SS patients (2 PD, 1SD and 1 response) and for patients with pc γδ T-cell lymphoma (1CR, 2PR, 2SD) responses were observed.

In addition to the data collected in Study C25001, 2 investigator-sponsored trials (ISTs) were provided (Study 35-IST-001 and Study 35-IST-002). The main efficacy data is summarised below.

Table 30: Summary table for the main efficacy outcomes of the two brentuximab vedotin ISTs.

IST001	overall	MF	MF <10%	MF ≥10%	SS	pcALCL	Lyp	Lyp/MF	Mixed histology
n	72	41	20	20	2	3	13	11	13
ORR	67%	54%	55%	55%	50%	67%	92%	82%	85%
mPFS (mns)	10	10	7.2	10.8	5.5&4.2*	10	11.7	6.9	6.9

* For the SS patients the PFS is reported
Mixed histology: Lyp/MF, pcALCL/MF and pcALCL/Lyp

IST002	overall	MF	MF <10%	MF ≥10%	SS
n	36	32	17	15	4
ORR	64%	66%	53	80	50
ORR4	50%	53%	41	67	25
mPFS (mns)	25	25	-	25	7.8

Overall response rates for MF were 54-66%; pcALCL, 67%; SS, 50%; LyP, 92%; and mixed CTCL histology, 82-85%.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH submitted one pivotal trial (CA25001/ ALCANZA) which was an open label, randomised (1:1) phase III study to support the extension of the indication. The study included patients with CD30+ (≥10%) MF or pcALCL. During scientific advice (SA; Febr.2011), the MAH was recommended to include a sufficient number of CTCL types, as it was not regarded justified to pool efficacy results in a heterogeneous disorder. In principle, it could be possible to extrapolate to subtypes which might have similar prognosis as the studied subtypes as some of the subtypes are very rare and clinical trials are not feasible.

Patients were enrolled in the study after they had received at least 1 systemic therapy for MF and 1 prior systemic therapy or prior radiation for pcALCL. The choice of the control arm (bexarotene and methotrexate) is acceptable. Bexarotene is an approved second line therapy for CTCL and methotrexate is a frequently used therapy for MF and a recommended therapy for pcALCL. However, these two treatments have different efficacy (ORR4: 15.8% and 7.7%, median PFS, 4.5 and 2.3 months, respectively). Given that the majority of control patients were treated with bexarotene, which has better efficacy than methotrexate, the pooling of patients treated with bexarotene or methotrexate is not expected to change the outcome of the results.

A large part (45%) of the screened patients were not enrolled in the study. From the 106 patients (45%) who failed screening, 65 patients (61%) did not meet the criteria for CD30+ eligibility. The study included small patient numbers, especially for those with pcALCL. This is regarded acceptable, since both are very rare diseases. Demographic data and baseline clinical data are balanced between the two arms with the exception of more severe pcALCL and more time since initial diagnosis in the brentuximab vedotin arm compared to the treatment arm. However, most likely these differences will not have a large influence on the outcomes, or at most predispose for slight less favourable outcomes in the interventional arm.

Most MF patients did not have advanced staged disease (≥stage 2) and most pcALCL patients had stage 3 disease (generalised skin involvement) at study entry. In both arms MF patients received a median of two systemic therapies and all pcALCL patients (except 1 protocol violation) received at least one systemic therapy.

The primary endpoint was ORR4 per IRF, measured by the global response score (GRS) as recommended by EORTC/ISCL, is regarded as acceptable. ORR4 along with the secondary endpoint PFS, provides a more robust readout than only ORR in this disease. PFS is considered an acceptable endpoint, especially since this disease is characterised by frequent recurrences and an indolent course in early stages. The MAH followed the SA (Febr. 2011), where the mSWAT was performed by the investigator and sensitivity analyses were performed for ORR4 with mSWAT on photographs per IRF. This strategy is considered acceptable as a clinical assessment of the skin is preferred.

In terms of measuring response, patients who started new therapy for ORR4 and had an ongoing response at the time of the start of next alternate therapy were counted as responders. For ORR4 patients with a previous CR who experienced recurrent disease responses were considered maintained unless the criteria for disease progression were met. Results from sensitivity analyses in which the patient's response after the start of next alternate therapy was censored at the start of next alternate therapy were similar to the primary analyses. Key secondary endpoints (CR, PFS, skin symptoms) are analysed only after statistical significance of the primary endpoint ORR4 (fixed sequential testing procedure) and controlled for type I error (weighted Holm procedure). The analyses are considered acceptable. Most subgroups were pre-specified in the SAP and no interim analysis for efficacy was planned, which is regarded as appropriate. The protocol was amended 5 times. None of the amendments are considered critical for conduct of the study or the interpretation of data. Protocol deviations were equally balanced between treatment arms.

Patients with CTCL should receive up to 16 cycles (see section 5.1 of the SmPC).

Efficacy data and additional analyses

A clinically relevant and statistically significant difference in primary endpoint ORR4 favouring brentuximab vedotin over physicians' choice therapy was observed where ORR4 was 56.3% for the brentuximab vedotin arm compared with 12.5% for the control arm. This statistical significant difference was consistent over MF/pcALCL patients and over physician's choice treatment. ORR4 was generally consistent over the subgroups, though not significant in 2 subgroups (ECOG ≥1 and baseline skin tumour =0), which might relate to the small patient numbers. Sensitivity analyses show similar outcomes. In an exploratory analysis for ORR4 (per IRF including mSWAT by skin photographs per IRF) the difference still favoured the brentuximab vedotin arm over the control arm, however, a marked lower number of responses are assigned in the brentuximab vedotin arm, though still favouring brentuximab vedotin. This is considered acceptable as the difficulties in assessment of skin response per mSWAT by photographs are acknowledged, as are the associated difficulties to objectify the outcomes per IRF.

The CR rate was regarded as supportive of the primary endpoint with a higher CR in the brentuximab vedotin arm over the control arm. The PFS analyses showed a statistically significant PFS difference of 13 months for brentuximab vedotin over the physician's choice arm, which is regarded as compelling and clinically relevant. These data can be regarded as mature and were conducted after 67% of the patients experienced a PFS event, which resulted in a median follow up of 17.5 months. Sensitivity analyses with different handling of missing data and censoring rules were consistent with the original analyses. The PFS advantage of brentuximab vedotin over the control arms is generally consistent across the other subgroups.

MF and pcALCL have different prognoses, however subgroup analyses indicate statistically significant outcomes in both ORR4 and PFS and thus it can be concluded that efficacy of brentuximab vedotin in both types of CTCL compared to the physician's choice treatment can be demonstrated. In two subgroups, the PFS effect is not statistically significant (ECOG ≥1 and age ≥65), most likely related to the small sample sizes of the subgroups.

The disease symptoms, measured as the mean of the (per subject) maximum reduction from baseline in the Skindex-29 symptom domain was higher in the brentuximab vedotin arm compared to the control arm. However, no conclusion can be drawn on disease symptoms as the trial was open label and from cycle 6 onwards only a part of the total population was analysed. Regarding QoL, no meaningful differences were observed between both treatment arms in the Skindex domains emotions and functioning and skin symptoms. The FACT-G and EQ-5D-3L outcomes were similar between the two treatment arms. Due to the open label design and the small sample size, no firm conclusions can be drawn (SmPC section 5.1). Other secondary endpoints were supportive of the primary endpoints but since they were not adjusted for multiplicity, the results should be interpreted with caution.

OS curves were provided to exclude any detrimental effects from the treatment. In the pcALCL patients, there appears to be a trend towards a better survival for the brentuximab vedotin arm compared to the control arm and in MF patients, the curves mostly favour brentuximab vedotin but appear to cross around 17 months. A further updated data cut for OS did not allow to attribute the observation of better OS in the control arm to switching of control patients to brentuximab vedotin. As such, no definitive conclusions can be drawn on the longer-term survival of MF patients. Since the study was not powered to detect OS differences, the uncertainties relating to the OS data of MF patients are not considered to affect the totality of the favourable efficacy data in MF.

The proposed indication for "*adults with CD30+ cutaneous T-cell lymphoma (CTCL) who require systemic therapy*" is broader than the studied population. CD30 is expressed in high (per definition) and homogeneous levels by $CD30^+$ LPDs (pcALCL and Lyp) and CD30 may also be expressed by other CTCL types (Sézary Syndome (SS) and the more rare CTCL NOS and primary cutaneous γδ T cell lymphoma). The MAH provided more detailed data (full CSR) from the two investigator sponsored trails (ISTs) in which different CTCL subtypes (SS, Lyp and mixed histologies together with MF and pcALCL± 85% of CTCL,) were included. Disease activity was shown across all these subtypes. In the Lyp subtype had comparable efficacy to the MF and pcALCL patients. The ISTs SS and mixed CTCL efficacy outcomes were somewhat lower compared to the MF/pcALCL patients. Prognoses in CTCL mixed histology is not known, however the subtype SS is generally associated with worse prognoses, which could explain these numbers. The available data appears in support for the extrapolation of efficacy from MF and pcALCL to other subtypes (SmPC section 5.1).

Patients enrolled were only allowed in the study after they had received at least 1 systemic therapy for MF and 1 prior systemic therapy or prior radiation for pcALCL. There were no data submitted comparing brentuximab vedotin with current systemic treatments used in the first line setting (e.g. mono or combination therapy of ECP, total skin EBT, PUVA, interferon, retinoids). In addition, it is unknown whether there are possible differences between the first and second line+ populations, in relation to disease stage, CD30 expression, disease transformation, that could affect treatment efficacy in first line. Given these uncertainties, extrapolation of benefit/risk from the second to the first line setting was not considered acceptable.

2.4.4. Conclusions on the clinical efficacy

Study C25001 was a randomised trial with CD30+ MF and pcALCL patients, who had received at least 1 prior systemic therapy. A statistically significant and clinically relevant difference in ORR4, favouring the brentuximab vedotin arm over the physician's choice arm was observed. PFS and subgroup analyses also supported the efficacy data observed with brentuximab vedotin arm over the control arm. Furthermore, anti-tumour activity was also shown in several other CTCL subtypes in two phase 2 studies, providing enough evidence to extrapolate the indication to patients with CD30+ CTCL. Conversely, there was insufficient evidence to be able to extrapolate from second line to a first line indication.

2.5. Clinical safety

Introduction

The existing safety profile of brentuximab vedotin monotherapy was mainly based on two single arm phase II studies in 160 patients diagnosed with relapsed or refractory HL or sALCL, and one placebo controlled Phase III trial (AETHERA) in 165 HL patients at increased risk for relapse after ASCT. The median number of cycles with similar brentuximab vedotin dose was 9 in patients with relapsed or refractory HL, 15 in HL patients at increased risk of relapse, and 7 in patients with relapsed or refractory sALCL. Treatment-related adverse events were common, leading to treatment discontinuation in 19-32% of patients and dose modifications in 46-54% of patients. The most common brentuximab vedotin treatment-related AEs in the pivotal studies were peripheral neuropathy, myelosuppression, nausea, infections and infusion reactions. The majority of AEs were managed by dose delays or reduction.

The safety and tolerability of brentuximab vedotin in patients with CTCL was analysed in one pivotal randomised Phase 3 trial, the ALCANZA trial. The safety analysis set comprised 128 patients with the CTCL subtypes pcALCL or MF, who received ≥1 dose of any study drug. A total of 66 patients received brentuximab vedotin, and in the control arm 62 patients received physician's choice of either methotrexate or bexarotene.

With methotrexate treatment, there is a potential for serious toxic reactions, such as bone marrow, liver, lung, and kidney toxicities. Bexarotene is a retinoid that has been associated with birth defects in humans and can cause major lipid, liver function, and thyroid test abnormalities, leukopenia, and anaemia.

Patient exposure

Brentuximab vedotin 1.8 mg/kg was administered via IV infusion over approximately 30 minutes on Day 1 of each 21 day cycle.

Methotrexate was administered once weekly as a single oral dose of 5 to 50 mg once weekly. The initial recommended starting dose of bexarotene was 150 mg/m2 for 14 days, with close monitoring of thyroxine and lipid levels. The dose would then be titrated to a final total daily dose of 300 mg/m2 if TEAEs were manageable at the lower dose.

Because brentuximab vedotin was administered in 21-day cycles while bexarotene was dosed daily and methotrexate was dosed weekly, for purposes of comparison, 21 days of bexarotene or methotrexate

dosing was counted as 1 treatment cycle in the safety analyses. Patients were treated with 1.8 mg/kg of brentuximab vedotin intravenously over 30 minutes every 3 weeks for up to 16 cycles or physician's choice for up to 48 weeks. The median number of cycles was approximately 12 cycles in the brentuximab vedotin arm. In the physician's choice arm, the median duration of treatment (number of cycles) for patients receiving bexarotene was approximately 16 weeks (5.5 cycles) and 11 weeks (3 cycles) for patients receiving methotrexate.

The maximum number of cycles (16) was received by 36% of patients in the brentuximab vedotin arm and 8% in the physician's choice arm.

Table 29: Extent of Study Drug Exposure (ALCANZA Safety Population)

	Brentuximab Vedotin (N=66)	Physician's Choice	
		Bexarotene (a) (N=36)	Methotrexate (N=25)
Duration of treatment (days) (b)			
n	66	36	25
Mean (SD)	229.1 (123.39)	140.0 (111.64)	98.6 (90.24)
Median	268.5	114.0	77.0
Minimum, maximum	21, 420	7, 378	7, 336
Number of treated cycles (c)			
n	66	36	25
Mean (SD)	10.3 (5.58)	6.8 (4.77)	4.8 (4.26)
Median	12.0	5.5	3.0
Minimum, maximum	1, 16	1, 16	1, 16
Total amount of dose taken (mg) (d)			
n	66	36	25
Mean (SD)	1301.33 (738.410)	53895.83 (47646.430)	360.36 (361.443)
Median	1351.50	33787.50	275.00
Minimum, maximum	100.0, 2880.0	2100.0, 191100.0	25.0, 1536.0
Total number of doses taken			
n	66	36	25
Mean (SD)	10.4 (5.55)	130.9 (106.88)	14.0 (12.95)
Median	12.0	97.0	11.0
Minimum, maximum	1, 16	7, 378	1, 48
Dose intensity (mg/week) (e)			
n	66	36	25
Mean (SD)	43.60 (9.688)	2695.30 (908.550)	23.44 (10.385)
Median	43.04	2857.82	21.67
Minimum, maximum	20.9, 60.0	1050.0, 4200.0	5.8, 50.0
Relative dose intensity (%) (f)			
n	66	36	
Mean (SD)	95.01 (8.853)	90.31 (29.085)	
Median	99.63	94.26	
Minimum, maximum	68.1, 106.4	27.1, 152.1	

Patients in treated cycle, n (%) (c)			
Cycle 1	66 (100)	36 (100)	25 (100)
Cycle 2	61 (92)	34 (94)	20 (80)
Cycle 3	60 (91)	29 (81)	16 (64)
Cycle 4	56 (85)	23 (64)	12 (48)
Cycle 5	50 (76)	20 (56)	10 (40)
Cycle 6	46 (70)	18 (50)	8 (32)
Cycle 7	43 (65)	14 (39)	5 (20)
Cycle 8	42 (64)	13 (36)	3 (12)
Cycle 9	40 (61)	12 (33)	3 (12)
Cycle 10	39 (59)	11 (31)	3 (12)
Cycle 11	37 (56)	10 (28)	3 (12)
Cycle 12	34 (52)	7 (19)	3 (12)
Cycle 13	29 (44)	6 (17)	2 (8)
Cycle 14	28 (42)	4 (11)	2 (8)
Cycle 15	26 (39)	4 (11)	2 (8)
Cycle 16	24 (36)	3 (8)	2 (8)

Source: C25001 Table 14.1.1.5.

The difference in the median number of treated cycles and doses taken in the brentuximab vedotin arm is because of the method of recording dose interruptions. Patients with dose interruptions would appear to have received 2 doses in 1 treatment cycle.

(a) Patients randomized to bexarotene first received fenofibrate pre-therapy from Cycle 1 Day 1 to Day 7, followed by treatment with bexarotene starting on Cycle 1 Day 8. One patient assigned to bexarotene received only fenofibrate and is not included in this table.

(b) Duration of treatment was 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.

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

(d) Total amount of dose taken for the brentuximab vedotin arm was calculated as the sum of (prepared dose amount in mg*volume/prepared volume) over each dosing electronic case report form record.

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

(f) Relative dose intensity was defined as 100×(total amount of dose taken [mg])/total dose expected [mg]). See source table for details. Note that relative dose intensity was not calculated for methotrexate because dose modifications were permitted per protocol.

Dose modifications

Table 30: Dose Modifications (ALCANZA Safety Population)

Patients, n (%)	Brentuximab Vedotin (N=66)	Physician's Choice		
		Methotrexate/ Bexarotene Total (N=61)	Bexarotene (n=36)	Methotrexate (n=25)
Action on study drug (all cycles)	**48 (73)**	**44 (72)**	**31 (86)**	**13 (52)**
Dose reduced	17 (26)	21 (34)	16 (44)	5 (20)
Dose increased (a)	0	20 (33)	13 (36)	7 (28)
Dose held (b)	1 (2)	16 (26)	12 (33)	4 (16)
Dose missed (c)	0	8 (13)	8 (22)	0
Dose interrupted (d)	5 (8)	1 (2)	0	1 (4)
Dose delayed (e)	40 (61)	11 (18)	7 (19)	4 (16)

Source: C25001 Table 14.1.1.6.
A patient with multiple actions was counted only once.
(a) Dose increased: For methotrexate or bexarotene, it was possible for the dose to be first reduced and then increased. The action of dose increased does not necessarily mean that the increased dose was higher than the baseline dose.
(b) Dose held: As a result of an intentional physician intervention, the planned or scheduled dose was not given. No drug was administered.
(c) Dose missed: For reason(s) other than physician intervention, the dose was not administered.
(d) Not applicable for bexarotene or methotrexate, which are taken orally.
(e) Dose delayed: The scheduled dose was administered, but not within the protocol-specified timeframe for a particular scheduled dosing day/cycle. This was not applicable for bexarotene daily dosing.

Adverse events

Adverse events (AEs) were classified by system organ class (SOC) and preferred term using MedDRA. AEs were reported up through 30 days after the last dose of study treatment.

In the safety analysis set, at least 1 AE of any Grade was reported in 95% of patients in the brentuximab vedotin arm and 90% in the physician's choice arm. SAEs of any causality and drug-related treatment emergent adverse events (related TEAEs) ≥Grade 3 were each reported for 29% of patients in both treatment arms.

A higher percentage of patients in the brentuximab vedotin arm experienced a TEAE that resulted in study drug discontinuation compared with the physician's choice arm (24% vs 8%, respectively).

Table 31: Overview of TEAEs in ALCANZA and Pivotal Phase 2 and 3 Studies

	ALCANZA					
Patients, n (%)	Brentuximab Vedotin (N=66)	Methotrexate/ Bexarotene Total (N=62)	Bexarotene (n=37)	Methotrexate (n=25)	Pivotal Ph 2 Studies (N=160)	AETHERA Ph 3 Study (N=167) (a)
Any TEAE	63 (95)	56 (90)	33 (89)	23 (92)	158 (99)	163 (98)
Any ≥Grade 3 TEAE	27 (41)	29 (47)	20 (54)	9 (36)	92 (58)	93 (56)
Treatment-related TEAE	57 (86)	44 (71)	30 (81)	14 (56)	147 (92)	147 (88)
Treatment-related ≥Grade 3 TEAE	19 (29)	18 (29)	15 (41)	3 (12)	NR	76 (46)
Serious TEAE	19 (29)	18 (29)	9 (24)	9 (36)	50 (31)	41 (25)
Treatment-related SAE	9 (14)	3 (5)	1 (3)	2 (8)	25 (16)	19 (11)
TEAE resulting in treatment discontinuation	16 (24) (b)	5 (8)	4 (11)	1 (4)	36 (23)	54 (32)
Deaths ≤30 days after last dose	4 (6)	0	0	0	6 (4)	1 (1)

Source: C25001 Table 14.4.1.1; Module 2.7.4 Grouped Safety Variation (2015) Table 7.2.3.1; SGN35-005 Sections 12.2.1 and 12.3.1.1 and Table 14.3.1.7.9.
TEAE was 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.
NR=not reported, Ph=phase.
(a) Includes only the 167 patients who received at least 1 dose of brentuximab vedotin.
(b) Study drug was discontinued because of an AE in 1 additional patient in the brentuximab vedotin arm (C25001 Table 14.1.1.1), but the event was erroneously reported on the patient's EOT form. The AE (lymphoma progression) subsequently became fatal and is included in Section 3.5.1.

An additional safety analysis evaluated the incidence of TEAEs adjusted for study drug exposure, since patients in the brentuximab vedotin arm remained longer on study drug than patients in the physician's choice arm. When adjusted for total person-year exposure, the incidence density of TEAEs in the brentuximab vedotin arm was numerically lower compared with the physician's choice arm (13.15 vs 14.90 TEAEs per person-year, Table 32).

Table 32: Total TEAEs, Summarised by Incidence Density (ALCANZA Safety Population)

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

Source: C25001 Table 14.4.1.28.
Person years=(EOT date-first dose date+1)/365.25. For patients with a missing EOT date, the missing date was imputed as the earlier date of the last dose date +30 days or the date of death.
Incidence density=number of events/total person-years.
(a) Numbers of events are calculated as sum of event count from all TEAE PTs reported in the source table.

TEAEs

The treatment emergent adverse events (TEAEs) reported in ≥10% of patients in either treatment arm of ALCANZA are presented in Table 33. Among patients in the brentuximab vedotin arm of ALCANZA, the most frequently reported TEAEs included peripheral sensory neuropathy (45% vs. 2% physician's choice), nausea (36% vs. 13%), diarrhoea (29% vs. 6%), fatigue (29% vs. 27%), and pruritus,

pyrexia, and vomiting (17% each in brentuximab vedotin arm vs. 13%-18%-5% respectively, with physician's choice).

Among patients in the physician's choice arm of ALCANZA, the most frequently reported TEAEs were fatigue (27%), pyrexia and hypertriglyceridemia (18% each), and nausea and pruritus (13% each).

Table 33: TEAEs Reported in ≥10% of Patients in Either Arm of ALCANZA Versus the Pivotal Phase 2 and 3 Studies, by PT (Safety Populations)

	ALCANZA				Pivotal Ph 2 Studies	AETHERA Ph 3 Study
MedDRA PT	Brentuximab Vedotin (N=66)	BEX/MTX Total (N=62)	BEX (n=37)	MTX (n=25)	(N=160)	(N=167) (a)
Patients with ≥1 TEAE, n (%)	**63 (95)**	**56 (90)**	**33 (89)**	**23 (92)**	**158 (99)**	**163 (98)**
Peripheral sensory neuropathy	30 (45)	1 (2)	0	1 (4)	72 (45)	94 (56)
Nausea	24 (36)	8 (13)	4 (11)	4 (16)	66 (41)	36 (22)
Diarrhoea	19 (29)	4 (6)	3 (8)	1 (4)	54 (34)	33 (20)
Fatigue	19 (29)	17 (27)	12 (32)	5 (20)	69 (43)	40 (24)
Pruritus	11 (17)	8 (13)	6 (16)	2 (8)	27 (17)	20 (12)
Pyrexia	11 (17)	11 (18)	4 (11)	7 (28)	50 (31)	31 (19)
Vomiting	11 (17)	3 (5)	1 (3)	2 (8)	32 (20)	27 (16)
Alopecia	10 (15)	2 (3)	1 (3)	1 (4)	21 (13)	4 (2)
Decreased appetite	10 (15)	3 (5)	2 (5)	1 (4)	20 (13)	20 (12)
Arthralgia	8 (12)	4 (6)	2 (5)	2 (8)	24 (15)	30 (18)
Myalgia	8 (12)	2 (3)	2 (5)	0	26 (16)	18 (11)
Asthenia	7 (11)	5 (8)	2 (5)	3 (12)	9 (6)	13 (8)
Dyspnoea	7 (11)	0	0	0	24 (15)	21 (13)
Oedema peripheral	7 (11)	6 (10)	2 (5)	4 (16)	12 (8)	8 (5)
Pruritus generalised	7 (11)	1 (2)	1 (3)	0	0	4 (2)
Rash maculo-papular	7 (11)	3 (5)	2 (5)	1 (4)	5 (3)	3 (2)
Headache	5 (8)	6 (10)	5 (14)	1 (4)	30 (19)	19 (11)
Anaemia	3 (5)	6 (10)	6 (16)	0	15 (9)	14 (8)
Skin infection	2 (3)	7 (11)	4 (11)	3 (12)	0	2 (1)
Hypertriglyceridaemia	1 (2)	11 (18)	11 (30)	0	0	0

Source: C25001 Table 14.4.1.3E; Module 2.7.4 Grouped Safety Variation (2015) Table 7.2.4.3; SGN35-005 Table 14.3.1.4.4.
A patient was counted only once for the highest severity of each PT. Percentages were calculated using the number of treated patients as the denominator.
BEX=bexarotene, MTX=methotrexate.
(a) Includes only the 167 patients who received at least 1 dose of brentuximab vedotin.

Treatment related TEAEs

Overall, 79% of patients experienced ≥1 treatment-related TEAE, including 86% in the brentuximab vedotin arm and 71% in the physician's choice arm. The most common treatment-related TEAEs in the brentuximab vedotin arm included peripheral sensory neuropathy (44% vs.0% with physician's choice), nausea (32% vs.8%), and fatigue (27 vs. 23%).

The most common treatment-related TEAEs in the physician's choice arm included fatigue (23%), hypertriglyceridemia (18%), and headache (10%).

Adverse Drug Reactions

Frequencies of adverse reactions described Table 34 have been determined based on data generated from clinical studies. In the pooled dataset of Adcetris as monotherapy across HL, sALCL and CTCL studies (SG035-0003, SG035-0004, SGN35-005, SGN35-006, C25001 and C25007) the most frequent

adverse reactions (≥10%) were infections, peripheral sensory neuropathy, nausea, fatigue, diarrhoea, pyrexia, upper respiratory tract infection, neutropenia, rash, cough, vomiting, arthralgia, peripheral motor neuropathy, infusion-related reactions, pruritus, constipation, dyspnoea, weight decreased, myalgia and abdominal pain. The information in section 4.8 of the SmPC has been updated with the pooled dataset.

Table 34: Updated adverse drug reaction

System organ class	Adverse reactions	Overall Frequency * (%)	Severity by Grade* (%)				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infections and infestations							
Very common:	Infection[a] Upper respiratory tract infection	56 22	18 10	28 12	8 0	1 0	<1 0
Common:	Herpes zoster Pneumonia Herpes simplex Oral candidiasis	5 4 2 2	<1 <1 1 <1	4 1 1 2	<1 1 0 0	0 <1 0 0	0 0 0 0
Uncommon:	Pneumocystis jiroveci pneumonia Staphylococcal bacteraemia Sepsis Septic shock	<1 <1 <1 <1	0 0 <1 0	0 0 0 <1	<1 <1 0 <1	0 0 0 <1	0 0 <1 <1
Frequency not known:	Progressive multifocal leukoencephalopathy	0	0	0	0	0	0
Blood and lymphatic system disorders							
Very common:	Neutropenia	22	<1	3	13	5	0
Common:	Anaemia Thrombocytopenia	9 7	<1 <1	4 1	5 4	<1 2	0 0
Uncommon	Febrile neutropenia	<1	<1	0	0	0	0
Immune system disorders							
Uncommon:	Anaphylactic reaction	<1	0	0	0	<1	0
Metabolism and nutrition disorders							
Common:	Hyperglycaemia	5	1	<1	3	<1	0
Uncommon:	Tumour lysis syndrome	<1	0	0	<1	0	0
Nervous system disorders							
Very common:	Peripheral sensory neuropathy Peripheral motor neuropathy	46 13	16 1	22 9	8 4	0 0	0 0
Common:	Dizziness	7	6	1	<1	0	0
Uncommon:	Demyelinating polyneuropathy	<1	0	<1	<1	0	0
Respiratory, thoracic and mediastinal disorders							
Very Common:	Cough Dyspnoea	16 12	12 7	4 5	0 <1	0 <1	0 0
Gastro-intestinal disorders							
Very common:	Nausea Diarrhoea Vomiting Constipation Abdominal pain	30 26 16 12 11	22 17 9 9 7	6 7 5 2 3	2 2 2 1 1	0 0 0 0 <1	0 0 0 0 0
Uncommon:	Pancreatitis acute	<1	0	0	0	<1	0
Hepatobiliary disorders							
Common:	Alanine aminotransferase increased Aspartate aminotransferase increased	2 1	<1 <1	<1 <1	<1 <1	<1 0	0 0

Skin and subcutaneous tissue disorders							
Very common:	Rash[a] Pruritus	17 13	12 9	4 4	<1 <1	0	0
Common:	Alopecia	9	8	1	0	0	0
Uncommon:	Stevens-Johnson syndrome/toxic epidermal necrolysis	<1	0	0	<1	0	0
Musculoskeletal and connective tissue disorders							
Very common:	Arthralgia Myalgia	16 11	12 8	3 3	<1 <1	0 0	0 0
Common:	Back pain	9	5	3	<1	0	0
General disorders and administration site conditions							
Very common:	Fatigue Pyrexia Infusion-related reactions[a]	29 23 13	15 16 6	11 5 5	3 2 1	<1 0 <1	0 0 0
Common:	Chills	9	7	2	0	0	0
Investigations							
Very common:	Weight decreased	12	2	9	<1	0	0

Table 35: Treatment-Related TEAEs Reported in ≥10% of Patients in Either Arm of ALCANZA Versus the Pivotal Phase 2 and 3 Studies, by PT (Safety Populations)

	ALCANZA				Pivotal	
MedDRA PT	Brentuximab Vedotin (N=66)	BEX/MTX Total (N=62)	BEX (n=37)	MTX (n=25)	Ph 2 Studies (N=160)	AETHERA Ph 3 Study (N=167) (a)
Patients with ≥1 treatment-related TEAE, n (%)	**57 (86)**	**44 (71)**	**30 (81)**	**14 (56)**	**146 (91)**	**146 (87)**
Peripheral sensory neuropathy	29 (44)	0	0	0	67 (42)	90 (54)
Nausea	21 (32)	5 (8)	4 (11)	1 (4)	51 (32)	27 (16)
Fatigue	18 (27)	14 (23)	11 (30)	3 (12)	48 (30)	22 (13)
Diarrhoea	12 (18)	3 (5)	2 (5)	1 (4)	29 (18)	17 (10)
Alopecia	8 (12)	1 (2)	1 (3)	0	16 (10)	4 (2)
Vomiting	8 (12)	1 (2)	1 (3)	0	21 (13)	17 (10)
Decreased appetite	7 (11)	1 (2)	1 (3)	0	8 (5)	13 (8)
Pruritus	7 (11)	4 (6)	4 (11)	0	16 (10)	9 (5)
Headache	2 (3)	6 (10)	5 (14)	1 (4)	14 (9)	13 (8)
Hypertriglyceridaemia	0	11 (18)	11 (30)	0	0	0

Source: C25001 Table 14.4.1.6B; Module 2.7.4 Grouped Safety Variation (2015) Table 7.2.5.1; SGN35-005 Table 14.3.1.6.1.
A patient was counted only once for the highest severity of each PT. Percentages were calculated using the number of treated patients as the denominator.
BEX=bexarotene, MTX=methotrexate.
(a) Includes only the 167 patients who received at least 1 dose of brentuximab vedotin.

Grade 3-4 TEAEs

Grade 3 TEAEs were reported with similar frequency in both arms (32%). Grade 4 TEAEs were reported in 5% of brentuximab vedotin treated patients and 15% of patients in the physician's choice

arm. The most frequent Grade 3-4 TEAEs in the brentuximab vedotin arm were infections and infestations, and nervous system disorders.

Table 36: Grade 3 or 4 TEAEs Reported in ≥3% of Patients in Either Arm of ALCANZA Versus the Pivotal Phase 2 and 3 Studies, by SOC and PT (Safety Populations)

	ALCANZA										
	Brentuximab Vedotin (N=66)		Bexarotene/ Methotrexate Total (N=62)		Bexarotene (n=37)		Methotrexate (n=25)		Pivotal Ph 2 Studies (a) (N=160)	AETHERA Ph 3 (N=167) (b)	
MedDRA SOC											
PT	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 3	Gr 4
Patients with ≥1 Grade 3 or 4 TEAE, n (%)	21 (32)	3 (5)	20 (32)	9 (15)	14 (38)	6 (16)	6 (24)	3 (12)	92 (58)	73 (44)	25 (15)
Infections and infestations	9 (14)	0	9 (15)	3 (5)	4 (11)	2 (5)	5 (20)	1 (4)	14 (9)	10 (6)	1 (1)
Skin infection	2 (3)	0	1 (2)	0	0	0	1 (4)	0	0	0	0
Cellulitis	2 (3)	0	0	0	0	0	0	0	1 (1)	0	0
Parotitis	0	0	2 (3)	0	1 (3)	0	1 (4)	0	0	0	0
Sepsis	0	0	0	3 (5)	0	2 (5)	0	1 (4)	0	0	0
Nervous system disorders	7 (11)	0	0	0	0	0	0	0	30 (19)	25 (15)	0
Peripheral sensory neuropathy	3 (5)	0	0	0	0	0	0	0	16 (10)	17 (10)	0
Peripheral motor neuropathy	2 (3)	0	0	0	0	0	0	0	3 (2)	10 (6)	0
Dizziness	2 (3)	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders	4 (6)	1 (2)	0	1 (2)	0	0	0	1 (4)	13 (8)	16 (10)	1 (1)
Diarrhoea	2 (3)	0	0	0	0	0	0	0	3 (2)	3 (2)	0
General disorders and administration site conditions	4 (6)	0	3 (5)	1 (2)	0	1 (3)	3 (12)	0	12 (8)	8 (5)	0
Fatigue	3 (5)	0	1 (2)	0	0	0	1 (4)	0	5 (3)	3 (2)	0
Metabolism and nutrition disorders	4 (6)	0	6 (10)	4 (6)	5 (14)	3 (8)	1 (4)	1 (4)	13 (8)	10 (6)	1 (1)
Hyperglycaemia	3 (5)	0	0	0	0	0	0	0	5 (3)	4 (2)	0
Hypertriglyceridaemia	0	0	5 (8)	3 (5)	5 (14)	3 (8)	0	0	0	0	0
Skin and subcutaneous tissue disorders	3 (5)	1 (2)	2 (3)	0	2 (5)	0	0	0	3 (2)	2 (1)	0
Pruritus	1 (2)	0	2 (3)	0	2 (5)	0	0	0	0	1 (1)	0
Vascular disorders	3 (5)	0	1 (2)	0	1 (3)	0	0	0	4 (3)	2 (1)	1 (1)
Hypertension	2 (3)	0	0	0	0	0	0	0	2 (1)	1 (1)	1 (1)
Blood and lymphatic system disorders	2 (3)	3 (5)	6 (10)	0	6 (16)	0	0	0	44 (28)	41 (25)	16 (10)
Neutropenia (c)	2 (3)	1 (2)	3 (5)	0	3 (8)	0	0	0	32 (20)	37 (22)	12 (7)
Anaemia (d)	0	0	3 (5)	0	3 (8)	0	0	0	10 (6)	6 (4)	0
Immune system disorders	2 (3)	0	0	0	0	0	0	0	0	0	1 (1)
Drug hypersensitivity	2 (3)	0	0	0	0	0	0	0	0	0	0
Investigations	0	0	5 (8)	0	2 (5)	0	3 (12)	0	6 (4)	8 (5)	1 (1)
Alanine aminotransferase increased	0	0	2 (3)	0	0	0	2 (8)	0	2 (1)	2 (1)	1 (1)
Blood triglycerides increased	0	0	2 (3)	0	2 (5)	0	0	0	0	0	0

Source: C25001 Table 14.4.1.4B (m2.7.4 Appendix 11.1); Module 2.7.4 Grouped Safety Variation (2015) Table 7.2.12.3; SGN35-005 Table 14.3.1.7.1 and Table 14.3.1.8.1.
A patient was counted only once for the highest severity of each PT and SOC. Percentages were calculated using the number of treated patients as the denominator.
Gr=Grade, Ph=phase.
(a) For the pivotal phase 2 studies, ≥Grade 3 TEAEs are combined per available source data.
(b) Includes only the 167 patients who received at least 1 dose of brentuximab vedotin.
(c) Incidence was defined as TEAE of the PT, or the treatment-emergent laboratory abnormality (≥Grade 1 absolute neutrophil count).
(d) Incidence was defined as TEAE of the PT, or the treatment-emergent laboratory abnormality (≥Grade 1 hemoglobin).

Serious adverse event/deaths/other significant events

SAEs

Regardless of causality, 29% of patients in both treatment arms experienced ≥1 SAE (Table 37). SAEs reported for more than 1 patient in the brentuximab vedotin arm were cellulitis and pyrexia (2 patients each). SAEs reported for more than 1 patient in the physician's choice arm were pyrexia (4 patients) and sepsis (3 patients).

Table 37: Summary of Treatment-Emergent SAEs, by PT (ALCANZA Safety Population)

		Physician's Choice		
MedDRA PT	Brentuximab Vedotin (N=66)	Methotrexate/ Bexarotene Total (N=62)	Bexarotene (n=37)	Methotrexate (n=25)
Patients with ≥1 SAE, n (%)	**19 (29)**	**18 (29)**	**9 (24)**	**9 (36)**
Cellulitis	2 (3)	0	0	0
Pyrexia	2 (3)	4 (6)	1 (3)	3 (12)
Demyelinating polyneuropathy	1 (2)	0	0	0
Diarrhoea	1 (2)	0	0	0
Diverticulitis	1 (2)	0	0	0
Dizziness	1 (2)	0	0	0
Drug eruption	1 (2)	0	0	0
Extravasation	1 (2)	0	0	0
Fatigue	1 (2)	0	0	0
Fracture	1 (2)	0	0	0
General physical health deterioration	1 (2)	0	0	0
Haemolytic uraemic syndrome	1 (2)	0	0	0
Hepatocellular injury	1 (2)	0	0	0
Hyperglycaemia	1 (2)	0	0	0
Hypotension	1 (2)	0	0	0
Impetigo	1 (2)	0	0	0
Intestinal perforation	1 (2)	0	0	0
Lower respiratory tract infection	1 (2)	0	0	0
Lymphoma	1 (2)	0	0	0
Multiple organ dysfunction syndrome	1 (2)	0	0	0
Musculoskeletal chest pain	1 (2)	0	0	0
Neck pain	1 (2)	0	0	0
Neuropathy peripheral	1 (2)	0	0	0
Pancreatitis	1 (2)	0	0	0
Pulmonary embolism	1 (2)	0	0	0

MedDRA PT	Brentuximab Vedotin (N=66)	Physician's Choice		
		Methotrexate/ Bexarotene Total (N=62)	Bexarotene (n=37)	Methotrexate (n=25)
Rash maculo-papular	1 (2)	0	0	0
Sepsis	1 (2)	3 (5)	2 (5)	1 (4)
Sinusitis	1 (2)	0	0	0
Stress	1 (2)	0	0	0
Urinary retention	1 (2)	0	0	0
Urinary tract infection	1 (2)	0	0	0
Crystal arthropathy	0	1 (2)	0	1 (4)
Dermatitis bullous	0	1 (2)	0	1 (4)
Erysipelas	0	1 (2)	0	1 (4)
Haematuria	0	1 (2)	1 (3)	0
Hypernatraemia	0	1 (2)	1 (3)	0
Neuralgia	0	1 (2)	0	1 (4)
Parotitis	0	1 (2)	0	1 (4)
Periorbital infection	0	1 (2)	1 (3)	0
Peripheral ischaemia	0	1 (2)	1 (3)	0
Peripheral vascular disorder	0	1 (2)	1 (3)	0
Skin erosion	0	1 (2)	0	1 (4)
Skin infection	0	1 (2)	0	1 (4)
Squamous cell carcinoma of skin	0	1 (2)	1 (3)	0
Superinfection bacterial	0	1 (2)	1 (3)	0
Urosepsis	0	1 (2)	1 (3)	0

Source: C25001 Table 14.4.1.7B.
A patient was counted only once for the highest severity of each PT. Percentages were calculated using the number of treated patients as the denominator.

In the pooled dataset of Adcetris as monotherapy across HL, sALCL and CTCL studies (SG035-0003, SG035-0004, SGN35-005, SGN35-006, C25001 and C25007, see section 5.1) the most frequent adverse reactions (≥10%) were infections, peripheral sensory neuropathy, nausea, fatigue, diarrhoea, pyrexia, upper respiratory tract infection, neutropenia, rash, cough, vomiting, arthralgia, peripheral motor neuropathy, infusion-related reactions, pruritus, constipation, dyspnoea, weight decreased, myalgia and abdominal pain.

Serious adverse drug reactions occurred in 12% of patients. The frequency of unique serious adverse drug reactions was ≤1%.

Treatment related SAEs

Nine patients (14%) in the brentuximab vedotin arm and 3 patients (5%) in the physician's choice arm experienced a combined total of 20 SAEs that were assessed as related to study drug (Table 38). None of the events occurred in >1 patient in either treatment arm.

At the time of the data cut-off for the study, 16 events had resolved, and two remained ongoing (Grade 3 PN [brentuximab vedotin arm; resulted in treatment discontinuation] and Grade 1 skin

erosion [methotrexate]. One event of Grade 4 pancreatitis resolved with sequelae in a patient in the brentuximab vedotin arm who subsequently died of multiorgan failure.

Among the 9 patients in the brentuximab vedotin arm who had treatment-related SAEs, three experienced Grade 3 SAEs in the infection and infestations SOC: cellulitis, diverticulitis, and impetigo (1 patient each). All events resolved or resolved with sequelae. The impetigo SAE resulted in permanent discontinuation of study drug. One other drug-related SAE resulted in permanent discontinuation of brentuximab vedotin: Grade 4 drug eruption, reported in 1 patient.

In the physician's choice arm (methotrexate), 1 patient experienced a treatment-related SAE (Grade 4 sepsis) in the infections and infestations SOC; the event resolved and did not result in study discontinuation. One drug-related SAE resulted in permanent discontinuation of physician's choice (bexarotene): Grade 3 haematuria, reported in 1 patient.

Table 38: Treatment-Emergent Drug-Related SAEs by PT (Safety Population)

PT	Brentuximab Vedotin N=66 n (%)	Methotrexate or Bexarotene N=62 n (%)	Total N=128 n (%)
Patients with at least 1 drug-related SAE (a)	9 (14)	3 (5)	12 (9)
Cellulitis	1 (2)	0	1 (<1)
Demyelinating polyneuropathy	1 (2)	0	1 (<1)
Diarrhoea	1 (2)	0	1 (<1)
Diverticulitis	1 (2)	0	1 (<1)
Drug eruption	1 (2)	0	1 (<1)
General physical health deterioration	1 (2)	0	1 (<1)
Hepatocellular injury	1 (2)	0	1 (<1)
Impetigo	1 (2)	0	1 (<1)
Intestinal perforation	1 (2)	0	1 (<1)
Multiple organ dysfunction syndrome	1 (2)	0	1 (<1)
Musculoskeletal chest pain	1 (2)	0	1 (<1)
Neck pain	1 (2)	0	1 (<1)
Neuropathy peripheral	1 (2)	0	1 (<1)
Pancreatitis	1 (2)	0	1 (<1)
Rash maculo-papular	1 (2)	0	1 (<1)
Dermatitis bullous	0	1 (2)	1 (<1)
Haematuria	0	1 (2)	1 (<1)
Pyrexia	0	1 (2)	1 (<1)
Sepsis	0	1 (2)	1 (<1)
Skin erosion	0	1 (2)	1 (<1)

Source: Table 14.4.1.10B.
TEAE is defined as any AE 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 were coded using the MedDRA dictionary Version 19.0.
(a) A patient counted once for each PT. Percentages use the number of treated patients as the denominator.

Deaths

As of the cut-off date for the ALCANZA data analyses, which included the PFS follow-up period, the total number of deaths was 16 (24%) in the brentuximab vedotin arm and 14 (23%) in the physician's choice arm (Table 39).

Most of the deaths were attributed to the patients' underlying disease (75% of the deaths in the brentuximab vedotin arm and 71% of the deaths in the physician's choice arm) and were not considered related to study treatment.

Four deaths occurred within 30 days after the last study drug dose and all in the brentuximab vedotin arm. Events in 3 of the 4 patients were attributed by the investigator to the patients' underlying disease (sepsis, lymphoma and pulmonary embolism). In the fourth patient, a fatal event of multi-organ failure at cycle 1 day 29 was considered by the investigator as being related both to underlying disease and to a therapeutic effect of brentuximab vedotin on sites of visceral disease (including intestinal perforation and pancreatitis). This patient had not met study eligibility criteria at baseline (elevated liver function test results), and enrolment of this patient constituted a major protocol violation.

Seven deaths occurred 31 to 120 days after the last dose of the study drug, and all occurred in the physician's choice arm.

Table 39: Summary of Deaths (ALCANZA Safety Population)

Patients, n (%)	Brentuximab Vedotin (N=66)	Physician's Choice (N=62)
Deaths overall	**16 (24)**	**14 (23)**
Disease-related deaths (a)	12 (75)	10 (71)
Days since last dose of study drug	Number (%) of deaths occurring within time interval	
0-30 days	4 (6)	0
31-60 days	0	3 (5)
61-90 days	0	3 (5)
91-120 days	0	1 (2)
>120 days	12 (18) (b)	7 (11)

Source: C25001 Table 14.1.1.1, 14.4.2.1, and 14.4.2.4.
Data cutoff date: 31 May 2016.
(a) Disease-related death as assessed by the investigator. Percentages use the total number of deaths in the treatment arm as the denominator.
(b) Includes 1 patient in the Safety population in the brentuximab vedotin arm who was excluded from the ITT population, and thus, is not listed in Table 14.4.2.4, which presents only the ITT population.

Adverse events of special interest

Adverse events of interest were selected based on the known safety profile of brentuximab vedotin.

Peripheral neuropathy

At least 1 peripheral neuropathy (PN) TEAE was reported for 67% of patients (n=44) in the brentuximab vedotin arm and 6% (n=4) in the physician's choice arm (Table 40). PN SMQ TEAEs were considered treatment related for 41 of the 44 patients in the brentuximab vedotin arm of ALCANZA who reported PN events and for none of the patients in the physician's choice arm. The most commonly reported PN SMQ term for the brentuximab vedotin arm was peripheral sensory neuropathy in 30 patients (45%); in the physician's choice arm, 1 patient (2%) each reported muscular weakness, neuralgia, paraesthesia, and peripheral sensory neuropathy.

Of the patients with a PN TEAE in the brentuximab vedotin arm, most were Grade 1 or 2 (n=17 and 21 respectively), and for 6 patients (9%), a Grade 3 PN TEAE was reported. In the physician's choice arm all PN events were Grade 1 or 2. No Grade 4 events were reported for either arm.

The median time to first onset of any PN event was 12 weeks (range, 0-48 weeks) in the brentuximab vedotin arm and 2.5 weeks (range, 0-10 weeks) in the physician's choice arm.

Dose delays were reported for 16 of the 44 patients (36%) who experienced an event of PN in the brentuximab vedotin arm and none in the physician's choice arm.

With a median overall study follow-up of 22.9 months, PN SMQ events that had been ongoing had either improved or completely resolved in 36 of the 44 affected patients (82%) in the brentuximab vedotin arm and in 1 of the 4 affected patients (25%) in the physician's choice arm.

Complete resolution was reported for 22 of the 44 brentuximab vedotin patients (50%) and improvement was reported for 14 patients (32%). The maximum severity of those PN SMQ events that were ongoing at the last follow-up was reported as Grade 1 in 17 patients and Grade 2 in 5 patients; there were no ongoing Grade 3 events. The patients in the brentuximab vedotin arm who discontinued because of PN (n=9 patients) were able to complete a median of 11 treatment cycles (range, 4-15 cycles) of the possible 16 treatment cycles before discontinuation.

Four patients (6%) treated with brentuximab vedotin experienced treatment-emergent peripheral motor neuropathy; 2 patients had events with a maximum severity of Grade 2, and 2 patients had events with a maximum severity of Grade 3. Onset of peripheral motor neuropathy ranged from 8 to 24 weeks. One Grade 3 event was resolved by the EOT visit, and 2 events (1 Grade 3 and 1 Grade 2) were resolved at the last follow-up visit. One patient had an event of Grade 2 peripheral motor neuropathy that was reported as not resolved or improved at the time of the last follow-up, 10 weeks after EOT.

Table 40: Overview of PN SMQ TEAEs Reported in Brentuximab-Treated Patients in the ALCANZA, Pivotal Phase 2, and AETHERA Studies

	Safety Population (Indication Studied)		
	ALCANZA (CTCL) N=66	Pivotal Ph 2 (HL, sALCL) N=160	AETHERA Ph 3 (HL) N=167 (a)
Median age of patients, years (minimum, maximum)	62 (22, 83)	37 (14, 77)	33 (18, 71)
Patients with ≥1 PN SMQ TEAE, n (%)	**44 (67)**	**89 (56)**	**112 (67)**
Grade 1	17 (39)	39 (44)	28 (25)
Grade 2	21 (48)	29 (33)	62 (55)
Grade 3	6 (14)	21 (24)	22 (20)
Grade 4	0	0	0
Peripheral motor neuropathy (b)	4 (9)	15 (17)	44 (39)
Median time to onset of any PN SMQ TEAE, weeks	12	12	14
Median time to resolution or improvement of PN SMQ TEAEs, weeks	19	16	23
Discontinuations due to PN SMQ TEAEs	9 (20)	19 (21)	38 (34)
Treatment cycles received for patients who discontinued because of PN SMQs, median (range)	11 (4-15)	n/a	10.5 (2-15)
Patients with resolution or improvement of PN SMQ TEAEs at last follow-up	36 (82)	74 (83)	95 (85)
Severity of ongoing PN SMQ TEAEs as of last follow-up			
Grade 1	17 (39)	24 (27)	31 (28)
Grade 2	5 (11)	12 (13)	11 (10)
Grade 3	0	3 (3)	4 (4)

Source: C25001 Table 14.1.1.2, 14.4.1.15, 14.4.1.16, 14.4.1.18, 14.4.1.19, 14.4.1.20, and 14.4.1.21; SGN35-005 Section 11.2.1 and Section 12.3.1.5; Module 2.7.4 Grouped Safety Variation (2015) Table 7.2.2.4, 7.2.8.4, 7.2.8.18, 7.2.8.20, 7.2.8.25 and Section 2.1.4.2; European Union Risk Management Plan (version 6.0).
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 comparisons may not be exact. Percentages use the number of patients with ≥1 PN SMQ TEAE as the denominator.
n/a=not available, Ph=phase.
(a) Includes only the 167 patients who received at least 1 dose of brentuximab vedotin.
(b) "Peripheral motor neuropathy" includes patients for whom the verbatim term coded to any of the PTs peripheral motor neuropathy, peroneal nerve palsy, or peripheral sensorimotor neuropathy, or the verbatim term for the PN SMQ event contained "motor," "weakness," or "palsy."

Haematologic toxicities

Preferred terms in the MedDRA blood and lymphatic system disorders system organ class (SOC) were reported in 15% of patients in the brentuximab vedotin arm and 19% the physician's choice arm.

In the brentuximab vedotin arm, 3% of patients experienced a Grade 3 TEAE and 5% experienced a Grade 4 TEAE. The most common Grade 3 or 4 events in the brentuximab vedotin arm were neutropenia (Grade 3 in 2 patients [3%], Grade 4 in 1 patient [2%]). Grade 3 thrombocytopenia, Grade 4 thrombocytopenia, and Grade 4 haemolytic uremic syndrome were each reported in 1 patient (2%) in this arm.

A total of 10% of patients in the physician's choice arm experienced Grade 3 TEAEs in this SOC, with no patient experiencing a ≥Grade 4 TEAE. Grade 3 TEAEs in the physician's choice arm were anaemia

in 3 patients (5%) and neutropenia in 3 patients (5%). Nearly all of the events in the physician's choice arm (10 of 12 patients) were reported in patients with bexarotene.

Neutropenia

Neutropenia or decreased neutrophil count TEAEs were reported for 9% of patients in the brentuximab vedotin arm and 6% of patients in the physician's choice arm.

Grade 3 neutropenia events were reported in 3 patients in the brentuximab vedotin arm and in 2 patients in the physician's choice (bexarotene) arm. One patient (brentuximab vedotin arm) experienced ≥1 Grade 4 event. Among the patients with Grade 3-4 neutropenia TEAEs, 1 patient in the brentuximab vedotin arm and 1 patient in the physician's choice (bexarotene) arm also experienced ≥1 TEAE in the infections and infestations SOC. The brentuximab vedotin-treated patient experienced cellulitis, lower respiratory tract infection, and upper respiratory tract infection, and the bexarotene-treated patient experienced incision site infection, otitis externa, skin infection, and tinea cruris.

Neutropenia TEAEs required ≥1 dose delay for 4 patients in the brentuximab vedotin arm but did not require dose reductions, holds, or permanent discontinuations.

No events of febrile neutropenia were reported in either arm.

Table 41: Incidence of Neutropenia TEAEs Requiring Dose Modification (ALCANZA Safety Population)

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

Source: C25001 Table 14.4.1.25.
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: As a result of an intentional physician intervention, the planned or scheduled dose was not given. No study drug was administered.

IRR

IRRs were reported only for the brentuximab vedotin arm, since bexarotene and methotrexate are orally administered. IRRs occurred in 9 patients (14%) treated with brentuximab vedotin (Table 42).

Two patients experienced ≥1 Grade 3 IRR (urticaria and drug hypersensitivity). The urticaria IRR resulted in study drug discontinuation. All IRR preferred terms were reported in 1 patient each, except for Grade 1 pruritus, which was reported in 3 patients.

None of the IRRs were considered SAEs, and no Grade 4 IRRs or anaphylaxis TEAEs were reported.

IRRs occurred during Cycle 2 in 8 patients and in Cycle 3 in 2 patients.

Table 42: Overall Summary of IRRs Reported in Patients Treated With Brentuximab Vedotin in ALCANZA Versus the Pivotal Phase 2 and 3 Studies (Safety Populations)

Patients, n (%)	ALCANZA (N=66)	Pivotal Ph 2 Studies (N=160)	AETHERA Ph 3 Study (N=167)
Any IRR	9 (14)	17 (11)	25 (15)
Grade 3 IRR	2 (3)	0	3 (1)
Serious IRR	0	0	2 (1)
IRR resulting in dose modification (a)	4 (6)	7 (4)	6 (4)
IRR resulting in study drug discontinuation	1 (2)	1 (1)	2 (1)

Source: C25001 Table 14.4.1.12A and Listing 16.2.7.3; Module 2.7.4 Grouped Safety Variation (2015) Section 2.1.4.5; SGN35-005 Section 12.3.1.6 and Listings 16.2.5.1.2 through 16.2.5.1.4.
IRRs are defined as AEs related to the administration of brentuximab vedotin. A patient counts once for each type of event.
(a) Dose modification includes any dose interruption, delay, or reduction.

Patients in the brentuximab vedotin arm were tested for the presence of antitherapeutic antibodies (ATAs; Table 43). Of the 9 patients who experienced an IRR in ALCANZA:

- 1 patient was ATA positive at Baseline and was transiently ATA positive during the study, with consistently low titres of ATAs.
- 5 patients were ATA negative at Baseline and became ATA positive during the study (3 were persistently ATA positive and 2 were transiently ATA positive).
- 3 patients were ATA negative at study Baseline and remained ATA negative throughout the study.

No correlation could be made between ATA and neutralising antibody (Nab) status and occurrence of TEAEs.

Table 43: Overview of IRRs by ATA Response Status (ALCANZA Safety Population: Immunogenicity-Evaluable Population Subset)

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

Source: C25001 Table 14.4.1.12B.
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.
ATA Baseline positive was defined as patients with confirmed ATA-positive response at Baseline.
ATA Baseline negative was defined as ATA response negative (ie, not confirmed positive) at the Baseline visit.
Transiently positive was defined as 1 or 2 postbaseline-confirmed ATA-positive responses.
Persistently positive was defined as >2 postbaseline-confirmed ATA-positive responses.
Negative was defined as ATA response negative (ie, not confirmed positive) at all postbaseline time points.
(a) Number of patients with ATA negative status was used as denominator.
(b) Number of patients with transiently positive ATA status was used as denominator.
(c) Number of patients with persistently positive ATA status was used as denominator.
(d) Number of patients with transiently or persistently positive ATA status was used as denominator.

Laboratory findings

Serum chemistry abnormalities reported as Grade 3 TEAEs included Grade 3 hyperglycaemia, hypocalcaemia, ALT increased, and AST increased. Other serum chemistry abnormalities reported as TEAEs included Grade 2 hypocalcaemia and hypernatraemia; Grade 1 and Grade 2 GGT increased, AST increased, ALT increased, and hyperglycaemia; and Grade 1 transaminases increased, blood creatinine increased, hyponatraemia, hyposmagnesaemia, and hypokalaemia. A post baseline shift to Grade 3 increased ALT was reported for 1 patient in the brentuximab vedotin arm and 1 patient in the physician's choice arm.

Abnormal haematology laboratory values reported as TEAEs included Grade 1 and Grade 2 WBC count decreased (2 patients), Grade 2 neutrophil count decreased and Grade 1 WBC count increased (1 patient, each) in the brentuximab vedotin arm, and lymphocyte count decreased in 1 patient in the physician's choice arm. One patient in the brentuximab vedotin arm had a Grade 3 event of thrombocytopenia that resulted in dose delay and resolved.

Hematologic values were further discussed in the previous section hematologic toxicity.

ECG

Grade 1 tachycardia was reported in 2 patients in the brentuximab vedotin arm and 1 patient in the physician's choice arm. One patient in the brentuximab vedotin arm had an event of Grade 1 bradycardia. No clinically significant abnormal findings were reported for the Safety population.

ECOG performance status

The shift in ECOG score from baseline to worst post baseline score was no more than 1 point for the majority of patients in both treatment arms (88% in the brentuximab vedotin arm and 92% in the physician's choice arm. A shift of more than 1 point in worst post baseline score was reported for 8 patients in the brentuximab vedotin arm and 5 patients in the physician's choice arm. One patient in the brentuximab vedotin arm who had an ECOG score of 2 at Baseline improved to a worst post baseline score of 1 (this patient had an ECOG score of 0 at Cycle 4 through Cycle 16, and at EOT), and 1 patient in the physician's choice arm who had an ECOG score of 1 at Baseline improved to a worst post baseline score of 0.

Safety in special populations

Safety in additional CTCL subtypes (from published sources)

To provide additional support for the safety of brentuximab vedotin in CD30-expressing CTCL subtypes that were not included in the ALCANZA study (LyP and more aggressive forms of CTCL, such as SS, and primary cutaneous gamma-delta T-cell lymphoma), the applicant discussed results from two Phase 2 investigator-sponsored trials and published case studies/series.

Investigator sponsored trials

- Kim (2015)

  In this Phase 2 study, patients were included with MF or SS stages IB through IVB, who had experienced ≥1 systemic therapy failure. All patients could receive up to 8 cycles of brentuximab vedotin (1.8 mg/kg) administered every 3 weeks. Those showing continued clinical improvement were allowed a maximum of 8 additional cycles (total of 16 cycles); those with a CR were allowed to have 2 more cycles.

  Thirty-two patients were enrolled and included in the safety analysis with median age of 62 years (range, 20-87 years). Most patients had advanced disease (88% with stage ≥IIB). The median number of prior systemic therapies was 3; most had prior cytotoxic agents, one with prior allogeneic stem cell transplantation. Only 4 of the 32 patients had ≥50% CD30 expression levels.

  Three SS patients were included in the safety analysis, but safety data were not reported separated per CTCL subtype. PN was a commonly observed toxicity (66% of 32 patients). Other toxicities included fatigue (47%), nausea (28%), alopecia (22%), and neutropenia (19%). Three treatment-related SAEs were reported, including 1 event each of confusion, acute renal failure, and neuropathy. Ten patients had a dose delay and/or reduction (to 1.2 mg/kg), and 6 patients (19%) discontinued study treatment because of toxicities. PN was the most common cause of dose modification or toxicity-related early termination. Most PN was a combined sensory-motor neuropathy. Twelve of 21 patients with PN had Grade 2 PN. By Kaplan-Meier calculation, the median time to improvement of PN was 49.0 weeks, with 59% showing improvement or resolution by 12 months and 86% by 24 months.

- Duvic (2015)

  In this Phase 2 study, 48 patients (median age 60) with CD30+ LyP, CD30+ pcALCL or MF were included. Of these patients, 9 had only CD30+ LyP. Brentuximab vedotin was administered at 1.8 mg/kg every 21 days for up to 8 doses. Patients with a PR or stable disease could receive up to 8 additional doses. Patients with a CR could receive 2 additional doses. Patients with breakthrough lesions could receive 1.2 mg/kg every 2 weeks at the

discretion of the investigator. The median number of prior systemic therapies was 2 for patients with MF and 1 for patients with LyP/pcALCL. The median number of cycles of brentuximab vedotin was 7 for MF and 7.5 for LyP/pcALCL.

Again, safety data were reported in aggregate so safety within a particular CTCL subtype (e.g., LyP) cannot be well described. The most common dose-limiting toxicities were sensory PN in 67% of patients and fatigue in 35%. Grade 1 neuropathy occurred in 30 patients, with progression to Grade 2 neuropathy in 21 patients. Neuropathy resolved in 14 of 31 patients, with a median time to resolution of 41.5 weeks. Brentuximab vedotin was occasionally associated with a tumour flare, brisk inflammation in lesions and surrounding skin that resolved as treatment continued. Patients with high CD30 expression could experience itching and burning of their skin lesions. A pruritic hypersensitivity drug rash with epidermal spongiosis and eosinophilia occurred in 24% of patients during Cycles 2 and 3 that was managed with topical corticosteroids.

Case studies/series

- *SS*

  Three case reports were discussed reporting results of 3 SS patients treated with Brentuximab vedotin. The dose was not mentioned in one report, the other two reported an initial dose of 1.2 followed by 1.4 mg/kg every 3 weeks for 5 cycles; and 1.8 mg/kg for 2 cycles. No (new) adverse events were reported.

  Furthermore, one publication by Lamarque et al (2016) was discussed, reporting the findings of 56 peripheral T-cell Lymphoma treated with brentuximab vedotin (dose not presented), including 2 patients with SS. Safety was reported in aggregate. No new safety signal was reported, although two known AEs were reported with a substantially higher frequency than previously observed: neutropenia (37% vs. 9% in ALCANZA study) and thrombocytopenia (42% vs. <10% "common" in current SmPC).

- *Primary Cutaneous Gamma-delta T-cell Lymphoma*

  One case series (Talpur et al, 2016) was presented that included safety results. Four patients with primary cutaneous gamma-delta T-cell lymphoma were presented that received brentuximab vedotin after various previous therapies had failed. The following AEs were reported:
  - Patient 1 received 6 cycles with fatigue being the only reported side effect.
  - Patient 2 received 7 cycles, and discontinued due to Grade 1 PN.
  - Patient 3 received 6 cycles and discontinued for unknown reason. Reported AEs were Grade 1 PN and ulcerations on hands.
  - Patient 4 completed 2 cycles and was continuing at the time of the report. Reported AEs were fatigue, pruritus and mild neuropathy.

- *LyP*

  Wieser at al (2016) conducted a retrospective study of 180 patients with LyP of whom 21 patients received brentuximab vedotin. The most commonly reported side effect was PN (in 9 patients); information on other side effects was not provided in the publication.

Safety in patients with visceral CTCL involvement

In ALCANZA, 12 patients overall had visceral involvement at study entry, and 11 (92%) of these patients were randomised to the brentuximab vedotin arm.

Of the 12 patients with visceral involvement at study entry, 7 patients had MF and 5 patients had pcALCL.

- Four of the 5 patients with pcALCL were randomised to receive brentuximab vedotin, and one was randomised to the physician's choice arm and received bexarotene. Among the 4 patients with pcALCL who received with brentuximab vedotin, one died after receiving 1 dose. The cause of death was reported as intestinal perforation, multi-organ failure, and pancreatitis, which were attributed by the investigator to the therapeutic effect of brentuximab vedotin; the patient showed a clinical response after only 1 dose of brentuximab vedotin. Enrolment of this patient into the study constituted a violation of protocol eligibility criteria because of liver function test results at Screening. The remaining 3 patients with pcALCL who were assigned to receive brentuximab vedotin received >6 treatment cycles.
- Among the 7 patients with MF, all were randomised to the brentuximab vedotin arm. One of the 7 patients with MF who received brentuximab vedotin discontinued study drug after Cycle 1 because of a non-serious TEAE of Grade 2 maculopapular rash. The remaining 6 patients with MF went on to receive >6 cycles of brentuximab vedotin.

Hepatic and renal impairment

Only patients with adequate hepatic and renal function were included. No separate clinical study in patients with hepatic or renal impairment has been submitted.

Paediatric patients

No data is available in children and adolescents younger than 18 years.

Elderly

A total of 51 patients in the ALCANZA study were aged 65 years or older: 28 patients in the brentuximab vedotin arm and 23 patients in the physician choice arm. No meaningful differences in frequency and nature of AEs were observed for patients aged ≥60 years, aged ≥65 years, aged ≥70 years, or aged ≥75 years versus the patient population as a whole (Table 44).

Table 44: Overview of TEAEs in ALCANZA by Age Category (Safety Population)

	Brentuximab Vedotin					Methotrexate/Bexarotene				
Patients, n (%)	≥60 Years (N=35)	≥65 Years (N=28)	≥70 Years (N=16)	≥75 Years (N=9)	All Patients (N=66)	≥60 Years (N=30)	≥65 Years (N=23)	≥70 Years (N=12)	≥75 Years (N=4)	All Patients (N=62)
Any TEAE	33 (94)	26 (93)	15 (94)	8 (89)	63 (95)	27 (90)	21 (91)	11 (92)	4 (100)	56 (90)
Any ≥Grade 3 TEAE	15 (43)	12 (43)	6 (38)	4 (44)	27 (41)	13 (43)	11 (48)	5 (42)	2 (50)	29 (47)
Treatment-related TEAE	29 (83)	23 (82)	13 (81)	6 (67)	57 (86)	22 (73)	17 (74)	8 (67)	3 (75)	44 (71)
Treatment-related ≥Grade 3 TEAE	9 (26)	7 (25)	2 (13)	1 (11)	19 (29)	10 (33)	8 (35)	3 (25)	1 (25)	18 (29)
Serious TEAE	9 (26)	8 (29)	5 (31)	4 (44)	19 (29)	9 (30)	7 (30)	4 (33)	3 (75)	18 (29)
Treatment-related SAE	3 (9)	2 (7)	1 (6)	1 (11)	9 (14)	2 (7)	2 (9)	2 (17)	2 (50)	3 (5)
TEAE resulting in treatment discontinuation	11 (31)	10 (36)	5 (31)	2 (22)	16 (24) (a)	4 (13)	4 (17)	2 (17)	1 (25)	5 (8)
Deaths ≤30 days after last dose	2 (6)	2 (7)	1 (6)	1 (11)	4 (6)	0	0	0	0	0

Source: Module 2.7.4 Table ADT14.4.1.1 (m2.7.4 Appendix 11.1).
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 (C25001 Table 12.p), but the event was erroneously reported on the patient's EOT form. The AE (lymphoma) subsequently became fatal and is included in Section 3.5.1.

Pregnancy and lactation

No events of pregnancy in either a patient or a male patient's partner were reported during the study. No change to the existing warning in section 4.6 of the SmPC is proposed.

Discontinuation due to adverse events

Adverse events that led to treatment discontinuation

TEAEs resulted in discontinuation of study drug for 24% of patients (n=16) in the brentuximab vedotin arm and 8% (n=5) in the physician's choice arm. In the brentuximab vedotin arm, more than half of the patients (9 out of 16) discontinued study drug because of ≥1 TEAE included in the PN standardised MedDRA query (SMQ) search terms, including peripheral sensory neuropathy (8%), PN (3%), and peripheral motor neuropathy and hypoesthesia (2% each). All other TEAEs that led to study drug discontinuation were experienced by not more than 1 patient in either treatment group.

Table 45: TEAEs Resulting in Study Drug Discontinuation, by PT (ALCANZA Safety Population)

		Physician's Choice		
MedDRA PT	Brentuximab Vedotin) (N=66)	Methotrexate/ Bexarotene (N=62)	Bexarotene (n=37)	Methotrexate (n=25)
Patients with ≥1 TEAE resulting in study drug discontinuation, n (%)	**16 (24) (a)**	**5 (8)**	**4 (11)**	**1 (4)**
Peripheral sensory neuropathy	5 (8)	0	0	0
Neuropathy peripheral	2 (3)	0	0	0
Drug eruption	1 (2)	0	0	0
Drug hypersensitivity	1 (2)	0	0	0
Escherichia infection	1 (2)	0	0	0
Hypoaesthesia	1 (2)	0	0	0
Impetigo	1 (2)	0	0	0
Peripheral motor neuropathy	1 (2)	0	0	0
Pulmonary embolism	1 (2)	0	0	0
Rash maculo-papular	1 (2)	1 (2)	0	1 (4)
Urticaria	1 (2)	0	0	0
Vertigo	1 (2)	0	0	0
Asthenia	0	1 (2)	1 (3)	0
Haematuria	0	1 (2)	1 (3)	0
Hypernatraemia	0	1 (2)	1 (3)	0
Neutropenia	0	1 (2)	1 (3)	0
Periorbital infection	0	1 (2)	1 (3)	0
Somnolence	0	1 (2)	1 (3)	0

Source: C25001 Table 14.4.1.9B.
A patient counts only once for each PT. Percentages use the number of treated patients as the denominator.
(a) Study drug was discontinued because of an AE in 1 additional patient in the brentuximab vedotin arm (C25001 Table 14.1.1.1); the recorded action for this AE was "discontinued from the study" instead of "study drug discontinued". The AE (lymphoma) subsequently became fatal; a summary of the event is provided in Section 3.5.4.

Post marketing experience

Cumulatively as of August 2016, post marketing exposure to brentuximab vedotin was estimated at 25,458 patients worldwide since launch.

Table 46 presents the number of adverse drug reactions by SOC that had been received through spontaneous reporting sources as of August 2016, including reports from regulatory authorities and literature articles from both healthcare professionals and non–healthcare professionals.

Table 46: ADRs Reported From Postmarketing Sources, by SOC

	Spontaneous, Including Regulatory Authorities (Worldwide) and Literature Sources			Noninterventional Postmarketing Study and Reports From Other Solicited Sources (a)
MedDRA SOC	Serious	Nonserious	Total	Serious
Infections and infestations	199	78	277	75
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	152	41	193	43
Blood and lymphatic system disorders	117	103	220	128
Immune system disorders	87	24	111	8
Endocrine disorders	0	0	0	1
Metabolism and nutrition disorders	46	41	87	11
Psychiatric disorders	18	25	43	2
Nervous system disorders	186	341	527	63
Eye disorders	6	14	20	0
Ear and labyrinth disorders	4	6	10	0
Cardiac disorders	41	6	47	11
Vascular disorders	33	19	52	3
Respiratory, thoracic and mediastinal disorders	152	53	205	27
Gastrointestinal disorders	122	163	285	33
Hepatobiliary disorders	41	14	55	6
Skin and subcutaneous tissue disorders	65	299	364	15
Musculoskeletal and connective tissue disorders	26	94	120	3
Renal and urinary disorders	23	14	37	2
Pregnancy, puerperium and perinatal conditions	0	4	4	0
Reproductive system and breast disorders	1	8	9	0
Congenital, familial and genetic disorders	2	0	2	1
General disorders and administration site conditions	259	454	713	90
Investigations	95	122	217	48
Injury, poisoning and procedural complications	42	353	395	8
Surgical and medical procedures	4	4	8	0

Source: Periodic Safety Update Report dated 04 Oct 2016 (data cutoff date: 18 Aug 2016).
Table includes spontaneous individual case safety reports, including reports from healthcare professionals, consumers, scientific literature, competent authorities, and solicited noninterventional individual case safety reports, including those from noninterventional studies.
(a) Does not include interventional clinical trials or investigator-initiated studies.

2.5.1. Discussion on clinical safety

Patient population and exposure

The safety analysis set included 128 randomised patients with the CTCL subtypes pcALCL or MF, who received ≥1 dose of any study drug. The safety analysis set of the pivotal trial is considered sufficient,

although information concerning uncommon adverse events may be limited at this time. Safety data from the brentuximab vedotin arm of ALCANZA are largely consistent with those of the earlier monotherapy studies.

Adverse events, serious adverse events and deaths

No new safety signals were detected in the ALCANZA trial. Almost every patient experienced at least one TEAE (95% with brentuximab vedotin vs. 90% physician's choice). Although Grade ≥3 TEAEs, (41% vs. 47%), related Grade ≥3 TEAEs (29% in both arms) and SAEs (29% both arms) occurred with almost similar frequencies in both arms, treatment related TEAEs (86% vs. 71%) and treatment related SAEs (14% vs. 5%) were more frequently reported with brentuximab vedotin compared to physician's choice. Within the physician's choice arm, more (treatment related) TEAEs and (related) ≥ Grade 3 TEAEs were observed with bexarotene, while serious TEAEs and treatment related SAEs were observed more frequently with methotrexate. However, the safety profile of brentuximab vedotin appears generally similar when compared to one of the separate treatments or the combined physician's choice arm.

The most common treatment related TEAEs were peripheral sensory neuropathy (44% vs.0%), nausea (32% vs.8%), and fatigue (27 vs. 23%). None of the related SAEs occurred in >1 patient in either treatment arm, but three patients in the brentuximab vedotin arm (4.5%) experienced Grade 3 SAEs in the infection and infestations SOC: cellulitis, diverticulitis, and impetigo.

An additional safety analysis evaluated the incidence of TEAEs adjusted for study drug exposure, since patients in the brentuximab vedotin arm remained longer on study drug than patients in the physician's choice arm. When adjusted for total person-year exposure, the incidence density of TEAEs in the brentuximab vedotin arm was lower compared with the physician's choice arm (13.15 vs 14.90 TEAEs per person-year). This difference resolved after correction for study drug exposure.

The total number of deaths was 16 (24%) in the brentuximab vedotin arm and 14 (23%) in the physician's choice arm. A higher number of deaths occurred within 30 days after the last study drug dose in the brentuximab vedotin arm (n=4) vs. the physician's choice arm (n=0). Only one of these 4 deaths was considered treatment related (multi-organ failure including intestinal perforation and pancreatitis). Another 3 deaths in the brentuximab vedotin arm were not considered disease-related, as well as 4 deaths in the physician's choice arm. The cause of these deaths (other than disease related) was assessed and no new safety signals regarding deaths related to brentuximab vedotin treatment have been revealed.

TEAEs resulted in discontinuation of study drug for 24% of patients (n=16) in the brentuximab vedotin arm and 8% (n=5) in the physician's choice arm, which is in line with previous observed discontinuation rates for brentuximab vedotin. Almost half of the patients in the brentuximab vedotin arm discontinued due to peripheral neuropathy. All other AEs resulting in discontinuation were not reported for more than one patient. Dose modifications occurred in large proportions of both treatment arms (~73%), with peripheral neuropathy being the most common TEAE resulting in dose modifications. In the brentuximab vedotin, this mostly consisted of a dose delay (61% vs. 18%), in the physician's choice arm a dose modification mostly consisted of dose reduction (26% brentuximab vedotin vs. 34% physician's choice), - increase (0% vs. 33%) or dose held (2% vs. 26%). TEAEs resulting in dose modifications have been discussed by the applicant during the second and third round of assessment. No notable trend in PFS or response rates could be observed between patients that discontinued due to AEs vs. patients who remained on treatment, but no definitive comparisons could be performed due to the limited number of patients discontinuing study medication due to AEs.

Adverse events of special interest

Among the AEs of special interest, no new safety signals have been observed. The safety data in patients retreated with ADCETRIS (SGN35-006, see section 5.1) were consistent with those observed in the combined pivotal phase 2 studies, with the exception of peripheral motor neuropathy, which had a higher incidence (28% vs. 9% in the pivotal phase 2 studies) and was primarily Grade 2. Patients also had a higher incidence of arthralgia, Grade 3 anaemia, and back pain compared to patients observed in the combined pivotal phase 2 studies. The observed frequencies of the AEs peripheral neuropathy (67% brentuximab vedotin vs. 6% physician's choice), neutropenia (9% vs. 6%) and infusion related reactions (14% vs. 0%) were higher compared with the comparator arm, but in line with or with lower frequencies (neutropenia) than observed in the Phase 3 AETHERA trial in HL. Less-common TEAEs that have been previously observed with brentuximab vedotin treatment (e.g., Stevens-Johnson syndrome/toxic epidermal necrolysis, tumour lysis syndrome, and progressive multifocal leukoencephalopathy) were not reported in the ALCANZA study. AEs of special interest that were defined in previous studies with brentuximab vedotin, including thrombocytopenia and anaemia, pulmonary toxicity, hepatotoxicity, hyperglycaemia, secondary malignancies, and infections, were consistent with the known safety profile of brentuximab vedotin and within the range of that reported in the SmPC. In clinical trials, the majority of patients had improvement or resolution of their symptoms of peripheral neuropathy (see section 4.8 of the SmPC). The proposed changes regarding peripheral neuropathy in the SmPC section 4.4 (deletion of incidence) were acceptable as incidences of peripheral neuropathy in the different studies were moved to or already included in section 4.8 of the SmPC. The general warning regarding peripheral neuropathy has remained largely unchanged, and is therefore still acceptable.

Of the 28 patients (47%) that were anti-drug antibody (ATA) positive at any post-baseline visit, 12 (20% of total number of patients in the brentuximab arm) were persistently ATA positive. These frequencies seem higher compared to the AETHERA trial (>32% ATA positive, 8% persistently positive). It is however reassuring that the frequency of IRRs was in line with previous observed frequencies, and no relation between ADA status and occurrence of TEAEs has been observed.

Safety in other CTCL subtypes

The case series/reports presented seem to reveal no new safety signal in SS, primary cutaneous Gamma-delta T-cell Lymphoma or Lyp. Safety data has been presented separately for MF and pcALC and despite differences in some of the safety parameters (overall TEAE frequency 100% with MF vs. 81% with pcALCL, and discontinuations due to AEs 30% vs. 13%, primarily due to peripheral neuropathy), the overall safety profile seems largely similar. Related TEAEs, Grade ≥3 events and SAEs were reported with almost similar frequencies in MF patients compared to pcALCL patients. The safety database is small (n=50 MF vs n=16 pcALCL), however, no strong safety signal has been found that might indicate a different safety profile in MF or pcALCL and was similar to that observed in other indications (HL, sALCL). Extrapolation of safety data to other more rare CTCL subtypes can therefore be considered. However, since the safety database is limited in CTCL subtypes other than MF and pcALCL, the safety of these patients should be monitored through post-marketing pharmacovigilance via PSURs.

2.5.2. Conclusions on clinical safety

Overall, no new safety concerns have been identified with brentuximab vedotin treatment in MF and pcALCL patients. Moreover, the safety profile of brentuximab vedotin in patients with MF and pcALCL was similar to that observed in other indications (HL, sALCL). Safety data for other rare CD30+ CTCL subtypes included in the indication is very limited but nevertheless no findings in the data provided

could indicate a different safety profile between the different CD30+ CTCL subtypes. The frequency of ADRs has been updated in section 4.8 of the SmPC.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 10.1 with the following content:

Safety concerns

No amendments to the list of safety specifications, as a result of new indication, are proposed by the MAH.

List of Summary of safety concerns

Summary of safety concerns	
Important identified risks	1. Progressive multifocal leukoencephalopathy 2. Pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin 3. Peripheral neuropathy (sensory and motor) 4. Neutropenia 5. Febrile neutropenia 6. Thrombocytopenia 7. Anaemia 8. Infection including bacteraemia/sepsis/septic shock 9. Opportunistic infection 10. Infusion-related reactions 11. Hyperglycaemia 12. Stevens-Johnson syndrome / Toxic epidermal necrolysis 13. Tumour lysis syndrome 14. Antitherapeutic antibodies
Important potential risks	1. Pancreatitis acute 2. Hepatotoxicity 3. Pulmonary toxicity 4. Gastrointestinal complications 5. Reproductive toxicity 6. Thymus depletion (paediatric) 7. Interaction with drugs modifying CYP3A4 activity
Missing information	1. Safety in paediatrics 2. Safety in patients with cardiac impairment

Summary of safety concerns	
	3. Long term safety

As requested, safety in elderly is removed from the list of missing information.

Pharmacovigilance plan

No new pharmacovigilance activities have been proposed in this RMP update. The ongoing and planned studies in the PhV development plan are stated below.

Table 50. Ongoing and planned studies in the PhV development plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Submission Date of Interim / Final Report (Planned / Actual)
SGN35-014: Randomized, double-blind, placebo-controlled, ph 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in frontline treatment of patients with CD30-positive mature T-cell lymphomas (MTCLs) (Category 3; MEA 015)	Multi-agent efficacy (PFS, OS, CR); safety	Peripheral neuropathy (sensory & motor); IRRs; ATAs	Ongoing	CSR (primary endpoint): Sep 2019 (due)
C25002: Ph 1/2 PIP study of brentuximab vedotin in pediatric patients with r/r sALCL or HL (Category 3)	Safety; PK; pediatric maximum tolerated dose and/or RP2D Immunogenicity, antitumor activity	Safety in pediatrics; thymus depletion (pediatric); ATAs	Ongoing	CSR: Dec 2016 CSR addendum: March 2019
C25004: An Open-Label Study of Brentuximab Vedotin+Adriamycin, Vinblastine, and Dacarbazine in Pediatric Patients With Advanced Stage Newly Diagnosed Hodgkin Lymphoma [PIP Study 3] (Category 3)	Safety; determination of MTD or highest HPD in combination Evaluation of PK, immunogenicity, activity of combination therapy, and mobilization of peripheral blood stem cells for ASCT	Safety in pediatrics; thymus depletion (pediatric)	Planned	LPO: On/before Dec 2018

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Submission Date of Interim / Final Report (Planned / Actual)
C25006: Ph 4, open-label, single-arm study of brentuximab vedotin in patients with r/r sALCL (Category 2; SOB 010])	Single-agent efficacy (ORR, duration of tumor control, including duration of response, PFS, and CR; proportion of patients proceeding to SCT; OS), safety and tolerability, PK, immunogenicity	ATAs	Ongoing	Primary CSR: Q1 2021
MA25101 (PASS): Observational cohort study of the safety of brentuximab vedotin in the treatment of r/r $CD30^+$ HL and r/r sALCL (Category 2; SOB 008 & SOB 009)	Safety; identification of potential risk factors for peripheral neuropathy	Peripheral neuropathy (sensory & motor); neutropenia; infection including bacteremia/sepsis/ septic shock; opportunistic infection; IRRs; hyperglycemia; febrile neutropenia; acute pancreatits, hepatotoxicity, pulmonary toxicity (devoid of concomitant bleomycin); safety in elderly; longer-term safety	Ongoing	Interim CSR: Apr 2016 (completed) Second Interim Analysis: within the annual renewal 2017 Final CSR: Dec 2020

Risk minimisation measures

Table 51. Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Measures
IMPORTANT IDENTIFIED RISKS		
Progressive multifocal leukoencephalopathy (PML)	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin	SmPC Section 4.3, Contraindications, Section 4.4, Special warnings and precautions for use	Not applicable
Peripheral neuropathy (sensory and motor)	SmPC Section 4.2, Posology and method of administration; SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Neutropenia	SmPC Section 4.2, Posology and method of administration; SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Febrile neutropenia	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Thrombocytopenia	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects.	Not applicable
Anaemia	SmPC 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Infection including bacteraemia/sepsis/ septic shock	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Opportunistic infection	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Infusion-related reactions (IRRs)	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Hyperglycaemia	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Stevens-Johnson syndrome / Toxic epidermal necrolysis	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Tumour lysis syndrome (TLS)	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Antitherapeutic antibodies (ATAs)	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable Effects	Not applicable
IMPORTANT POTENTIAL RISKS		
Pancreatitis acute	SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable Effects	Not applicable
Hepatotoxicity	SmPC Section 4.2, Posology and method of administration; SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable Effects	Not applicable
Pulmonary toxicity	SmPC Section 4.3 Contraindications SmPC Section 4.4, Special warnings and precautions for use; SmPC Section 4.8, Undesirable effects	Not applicable
Gastrointestinal complications	SmPC Section 4.4, Special warning and precautions SmPC Section 4.8, Undesirable effects	Not applicable
Reproductive toxicity	SmPC Section 4.6, Fertility, pregnancy and lactation; SmPC Section 5.3, Preclinical safety data	Not applicable
Thymus depletion (paediatric)	SmPC Section 4.2, Posology and method of administration; SmPC Section 5.3, Preclinical safety data	Not applicable

Safety Concern	Routine Risk Minimization Measures	Additional Measures
Interaction with drugs modifying CYP3A4 activity	SmPC Section 4.2, Posology and method of administration; SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction; SmPC Section 5.2, Pharmacokinetic properties	Not applicable
MISSING INFORMATION		
Safety in paediatrics	SmPC Section 4.2, Posology and method of administration; SmPC Section 5.2, Pharmacokinetic properties	Not applicable
Safety in patients with cardiac impairment	SmPC Section 5.1, Pharmacodynamic properties	Not applicable
Long-term safety	SmPC Section 4.2, Posology and method of administration	Not applicable

The assessor, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures remains sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: a user consultation with target patient groups on the package leaflet was conducted in the context of the initial marketing authorisation application for Adcetris in 2012. This variation does not change the treatment regimen or the safety profile of Adcetris and only introduces minimal changes to the package.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH initially applied for the following indication:

- Adcetris is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) who require systemic therapy.

3.1.2. Available therapies and unmet medical need

CTCL is a very rare disease group of skin-homing T cell neoplasms with considerable variation in clinical presentation, histologic appearance and prognosis. CD30 is strongly and homogeneously expressed (per definition) by pcALCL and Lyp, and may also be expressed by other CTCL subtypes, however at much lower and variable levels. In MF, the most frequent CTCL type (50-60% of CTCL) varying CD30 levels have been described (0-80%), though most literature indicates lower expression rates (median 10-12% of cells express CD30). The studied population included patients with MF (incidence 0.3-0.9/100.000) and pcALCL (incidence unknown). There is no standard initial therapy for MF patients, however, systemic options bexarotene and methotrexate are frequently used in second line (both RR30-50%). Systemic therapies for pcALCL include methotrexate (RR 87%) and bexarotene (RR ±50%). Both diseases are characterised by frequent recurrences. pcALCL and the early stages of MF have an excellent prognosis, while the advanced stages of MF have a poor prognosis.

3.1.3. Main clinical studies

This application is based on one pivotal randomised, open-label, phase III trial (C25001; ALCANZA) conducted in 128 patients with CD30-positive (≥10%) MF or pcALCL (stratified per diagnosis), who received at least 1 prior systemic therapy (or prior radiation therapy in pcALCL). In this study, the effect of brentuximab vedotin versus physician's choice of methotrexate or bexarotene on the proportion of patients with objective response lasting at least 4 months (ORR4) was evaluated.

Supportive material is derived from two phase II investigator sponsored trials in CTCL patients after prior systemic therapy.

3.2. Favourable effects

The primary endpoint ORR4 (objective response that lasted 4 months) per IRF based on a Global Response Score (GRS) was 56.3% in the brentuximab vedotin arm and 12.5% in the control arm ($p<0.001$). The results are considered clinically relevant. ORR4 was generally consistent across subgroups and in different sensitivity analyses.

Key secondary endpoints (CR, PFS and skin symptoms) were analysed according to a fixed sequential testing procedure. The CR rate per IRF was 10 patients (15.6%) in the brentuximab vedotin arm and 1 patient (1.6%) in the physician's choice arm (adjusted p-value=0.0046). A median PFS differences of 13 months was observed favouring the brentuximab vedotin arm over the physician's choice arm with a median PFS 16.7 vs 3.5 months, respectively (HR 0.27; 95%CI 0.17-0.43). PFS analyses were performed with a median PFS follow-up of 17.5 months and 67% of the events reached. The treatment effect was mostly consistent across subgroups. All sensitivity analyses favoured the brentuximab vedotin arm over the control arm.

EFS analyses supports the primary endpoint. Durable response were observed both overall and in the skin in both treatment arms. Duration of response (15.1 [95%CI 9.7-25.5] vs 18.3 [95%CI 3.5-18.4]) and duration of skin response (20.6 [95%CI14.1-25.7] vs 18.3 [95%CI 3.5-18.9]) are comparable between the brentuximab vedotin and control arm. OS data in pcALCL patients do not indicate detrimental effects.

No differences in patient reported outcomes per FACT-G, EQ-5D and Skindex-29 total score were observed between the two treatment arms. Skin symptoms as measured by the Skindex-29 symptom domain appear to decrease with time in the brentuximab vedotin arm.

Two supportive phase II trials showed anti-tumour activity in the majority of other CTCL subtypes (SS, Lyp and mixed CTCL histology's ± 85% of CTCL, together with MF and pcALCL) with CD30 expression≤10%. Case series additionally indicate anti-tumour activity of brentuximab vedotin in patients with CTCL types primary cutaneous γδ T-cell lymphoma and folliculotropic MF (together 6% of the CTCL).

3.3. Uncertainties and limitations about favourable effects

CTCL subtypes other than MF and pcALCL were not included in the pivotal study. Subtypes SS, Lyp and mixed CTCL histology were studied in two non-comparative phase II trials. The case series in cutaneous γδ T-cell lymphoma and Lyp were submitted but the evidence is limited. From the remaining CTCL subtypes, most of which are very rare, (together<10% CTCL) no data is available.

Therefore, the size of the treatment effect in CD30 + CTCL subtypes other than MF and pcALCL is not clear due to lack of high level evidence. In two single arm phase II studies of brentuximab vedotin, disease activity has been shown in the subtypes SS, LyP and mixed CTCL histology. These data suggest that efficacy and safety can be extrapolated to other CTCL CD30+ subtypes. Nevertheless, Adcetris should be used with caution in other CD30+ CTCL patients after careful consideration of the potential benefit-risk on an individual basis (see section 5.1 of the SmPC).

3.4. Unfavourable effects

Risks

Unfavourable effects

In study C25001, at least 1 TEAE of any Grade was reported in almost all patients (95% brentuximab vedotin vs. 90% physician's choice). The most frequently reported TEAEs included peripheral sensory neuropathy (45% vs. 2%), nausea (36% vs. 13%), diarrhoea (29% vs. 6%), fatigue (29% vs. 27%), pruritus (17% vs. 13%), pyrexia (17% vs. 18%), and vomiting (17% vs. 5%).

When adjusted for total person-year exposure, the incidence density of TEAEs in the brentuximab vedotin arm was lower compared with the physician's choice arm (13.15 vs 14.90 TEAEs per person-year).

Treatment related TEAEs were reported more frequently in the brentuximab vedotin arm (86% vs. 71%). The most common treatment related TEAEs were peripheral sensory neuropathy (44% vs.0%), nausea (32% vs.8%), and fatigue (27 vs. 23%).

SAEs were reported in 29% of patients in both treatment arms. Treatment related SAEs occurred more frequently with brentuximab vedotin (14% vs. 5%). None of the related events occurred in >1 patient in either treatment arm, but three patients in the brentuximab vedotin arm (4.5%) experienced Grade 3 SAEs in the infection and infestations SOC: cellulitis, diverticulitis, and impetigo.

The total number of deaths was 16 (24%) in the brentuximab vedotin arm and 14 (23%) in the physician's choice arm. A higher number of deaths occurred within 30 days after the last study drug dose in the brentuximab vedotin arm (n=4) vs. the physician's choice arm (n=0). One of these 4 deaths was considered treatment related (multi-organ failure including intestinal perforation and pancreatitis).

A higher frequency of patients in the brentuximab vedotin arm discontinued study treatment due to AEs (24% vs. 8% with physician's choice). The most common AE leading to discontinuation was peripheral neuropathy. Dose modifications occurred in large proportions of both treatment arms (~73%). In the brentuximab vedotin, this mostly consisted of a dose delay (61% vs. 18%), in the physician's choice arm a dose modification mostly consisted of dose reduction (26% brentuximab vedotin vs. 34% physician's choice), - increase (0% vs. 33%) or dose held (2% vs. 26%).

As expected, higher frequencies of the AEs of special interest peripheral neuropathy (67% brentuximab vedotin vs. 6% physician's choice), neutropenia (9% vs. 6%) and infusion related reactions (14% vs. 0%) were observed compared with the comparator arm.

3.5. Uncertainties and limitations about unfavourable effects

Literature based safety data for patients with other, more rare CD30+ CTCL subtypes than MF or pcALCL included in the proposed indication is considered very limited. The case series/reports presented seem to reveal no new safety signal in SS, primary cutaneous γδ T-cell lymphoma or Lyp. However, no firm conclusion can be drawn due to the limited number of patients analysed and incomplete safety data for these patients. Therefore, safety information in other more rare CD30+ CTCL subtypes will be monitored by routine pharmacovigilance activities.

3.6. Effects Table

Table 52. Effects Table for Adcetris in CD30+ MF and pcALCL patients (data cut-off: 20 July 2016)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
ORR4	ORR at least 4 months per IRF based on GRS	n (%)	36 (56.3%) (95%CI 44.1, 68.4)	8(12.5%) (95%CI 4.4, 20.6)	• p<0.001 • does not reflect patient benefit beyond 4 mns • substantial level of subjectivity in skin assessments
CR	% of patients with CR by IRF per GRS	n (%)	10 (15.6%) (95%CI 6.7, 24.5)	1 (1.6%) (95% CI 0, 4.6)	• p=0.0046*
PFS	Time from randomization until PD per IRF or death	median-mns	16.7	3.5	• HR 0.27 (95%CI 0.17-0.43), p<0.001* • level of subjectivity in skin assessments
Skin symptoms	mean maximum reduction		-28.0 (sd 26.9)	-8.6 (sd 17)	• open-label design • small number of the total patients remaining throughout time • favours those with more measurements
DOR	Time between first response and PD per IRF	median-mns	15.1 (95%CI 9.7, 25.5)	18.3 (95%CI 3.5, 18.4)	• not supportive of PFS • Responses are ongoing in almost 50%
DOR skin	Time between first skin response and PD in skin per inv	median-mns	20.6 (95%CI 14.1, 25.7)	18.3 (95%CI 3.5, 18.9)	• Responses are ongoing in almost 50%
EFS	Time from randomization	median-	9.4 (95%CI 5.9, 11.7)	2.3 (95%CI	• HR 0.29 (95%CI 0.19, 0.43), p<0.001

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
	until any cause of treatment failure: PD, discontinuation of treatment for any reason, or death due to any cause	mns		1.7, 3.5)	• Not adjusted for multiplicity
Unfavourable Effects					
TEAE			95%	90%	Safety data presented is based on patients with MF and pcALCL. Safety data in other, more rare, CD30+ CTCL subtypes is very limited.
Related TEAE		%	86%	71%	
Related SAE		%	14%	5%	
Deaths overall <30 days after last study dose		% (n)	24% (n=16) n=4	23% (n=14) n=0	
Discontinuations due to AE		%	24%	8%	Primary reason peripheral neuropathy for brentuximab vedotin. Control arm: no single AE in more than 1 patient.

* adjusted p-value

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A higher number of responses lasting at least 4 months were observed in the brentuximab vedotin arm compared to the control arm. This primary efficacy endpoint (ORR4) is supported with a compelling and clinically relevant PFS difference and ORR, CR and EFS favouring brentuximab vedotin over bexarotene/methotrexate. Therefore, the efficacy of brentuximab vedotin is considered demonstrated in the studied population of MF and pcALCL patients who received at least 1 prior systemic therapy. The OS data does not show a detrimental effect thus far but the data are still immature for the pcALCL and the MF population. Considering the totality of the data and the effect of many subsequent therapies on OS, this uncertainty is regarded acceptable.

Although Grade ≥3 TEAEs (41% vs. 47%), related Grade ≥3 TEAEs (29% in both arms) and SAEs (29% both arms) occurred with almost similar frequencies in both arms, treatment related TEAEs (86% vs. 71%) and treatment related SAEs (14% vs. 5%) were more frequently reported with brentuximab vedotin compared to physician's choice. Likewise, treatment discontinuation occurred more frequently in the brentuximab vedotin arm (24% vs. 8%). Although the toxicity of brentuximab vedotin in the ALCANZA trial is considered substantial, safety data are largely consistent with the earlier monotherapy studies, and no new safety signals were reported.

No new safety signal has been found that might indicate a different safety profile in MF or pcALCL, despite the difference in CD30+ expression and tumour load between these different CTCL subtypes.

Because of the rarity of the disease, it is likely that there may be difficulties in acquiring additional comprehensive data in the CTCL subtypes other than MF and pcALCL. Currently, there is limited data on the safety in the rarest CTCL subtypes (<10% CTCL). The totality of the data provided indicate that the safety profile in CD30+ CTCL subtypes will likely be similar to the known safety profile of brentuximab vedotin. It is considered that the safety in the CTCL subtypes other than MF and pcALCL should be monitored post-marketing.

3.7.2. Balance of benefits and risks

The randomised phase III C25001 trial demonstrated a clinically relevant benefit of brentuximab vedotin compared to physician's choice chemotherapy in MF and pcALCL patients. Based on the efficacy data, the clinical benefit can be extrapolated to the other rarer subtypes of CD30+CTCL. No new safety signals have been reported for these patients and the presented frequencies and ADRs seem consistent with previous observed safety data for brentuximab vedotin monotherapy in HL. Therefore, the benefit risk balance for the proposed indication "ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy (see section 5.1)" is positive.

3.7.3. Additional considerations on the benefit-risk balance

The proposed indication in the studied population consisted of patients who had received a median of 2 systemic therapies. Extrapolation of benefit/risk from second line to first line setting was highly uncertain due to the lack of efficacy comparing brentuximab vedotin with possibly less toxic and effective treatment options in first line setting (e.g. mono or combination therapy of ECP, total skin EBT, PUVA, interferon and retinoids). There was concern that there could also be possible differences in the risk factors in patient populations being treated in first and second line plus setting (related to disease stage, CD30 expression, disease transformation etc.). Therefore, the extrapolation to the broader indication was not acceptable and a restriction to patients that had been previously treated with at least 1 prior systemic therapy, which reflects the patient population that had been included in the main pivotal study.

The CHMP considered that the benefit risk balance was positive for CD30+ CTCL. It is regarded that the benefit-risk in MF/pcALCL patients can be extrapolated to other CD30+ patients. The uncertainties regarding the effect size in other CTCL types than MF/pcALCL should be considered in the light of difficulties of performing trials in this very rare disease (SmPC section 4.4).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I and IIIB

	of a new therapeutic indication or modification of an approved one		

Extension of indication to include the new indication "ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy", based on data from study C25001 (the 'ALCANZA' study): "A Phase 3 Trial of brentuximab vedotin(SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma". As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Information on peripheral neuropathy was also updated in the SmPC. An updated RMP (version 10.1) has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Adcetris is not similar to Ledaga within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the new indication "ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy", based on data from study C25001 (the 'ALCANZA' study): "A Phase 3 Trial of brentuximab vedotin(SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma". As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated RMP (version 10.1) has also been submitted.

Summary

Please refer to the Scientific Discussion – Adcetris II-48.