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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

BRENTUXIMAB VEDOTIN (ADCETRIS)

(Seattle Genetics, Inc.)

Indication: Adult patients with primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have had prior systemic therapy.

Service Line:	CADTH pCODR Clinical Guidance Report
Version:	Final
Publication Date:	December 3, 2020
Report Length:	88 Pages

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
BV	brentuximab vedotin
CGP	Clinical Guidance Panel
CEOP	cyclophosphamide, etoposide, vincristine, prednisone
CGP	clinical guidance panel
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CI	confidence interval
CNS	central nervous system
CR	complete response
CTCL	cutaneous T-cell Lymphoma
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EFS	event free survival
EORTC	European Organization of Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
EQ-5D	European Quality of Life 5-Dimension
FACT-G	Functional Assessment of Cancer Therapy-General
GRS	global response score
HL	Hodgkin Lymphoma
HR	hazard ratio
HRQoL	health related quality of life
IRF	independent review facility
ISCL	International Society for Cutaneous Lymphomas
ITT	intent to treat
IQR	interquartile range
KM	Kaplan Meier
LCT	large cell transformation
MID	minimal important difference
MF	mycosis fungoides

MMAE	monomethyl auristan E
MRI	magnetic resonance imaging
mSWAT	modified severity weighted assessment tool
NCCN	National Comprehensive Cancer Network
NOC	notice of compliance
NR	not reported
PC	physician's choice
pcALCL	primary cutaneous anaplastic large cell lymphoma
PD	progressive disease
pERC	pCODR Expert Review Committee
PET	positron emission tomography
PFS	progression free survival
PML	progressive multifocal leukoencephalopathy
PR	partial response
ORR4	objective response rate lasting at least 4 months
OS	overall survival
RCT	randomized control trial
SAE	serious adverse event
SD	standard deviation
TNMB	tumour-note-metastasis-blood
TRAE	treatment related adverse event
ULN	upper limit of normal range
USCLC	United States Cutaneous Lymphoma Consortium
WDAE	withdrawal due to adverse event

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding brentuximab vedotin for patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expression mycosis fungoides (MF). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and input from Registered Clinicians.

The systematic review is fully reported in Section 6. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of brentuximab vedotin (Adcetris) for adult patients with CD30-pcALCL or CD30-expressing MF who have had prior systemic therapy.

Currently there is no standard therapy for patients with pcALCL or MF. Patients are provided with various treatment options, which include various skin-directed therapies, chemotherapies, and, in some cases, immunotherapies. Treatment is recommended based on disease stage with the ultimate goal of achieving a response with adequate organ function to eventually receive allogeneic stem cell transplant. For patients who are transplant ineligible, the goal of treatment is to increase survival, control disease, reduce symptoms and improve quality of life. The reimbursement request under review by CADTH is for brentuximab vedotin for the treatment of adult patients with pcALCL or CD30-expression MF who have had prior systemic therapy. A notice of compliance (NOC) was issued by Health Canada for brentuximab vedotin for this indication on December 21, 2018.[1,2] The reimbursement request is aligns with the approved Health Canada NOC.

Brentuximab vedotin is an antibody-drug conjugate, which consists of the antibody cAC10 chemically conjugated to monomethyl auristatin E (MMAE). MMAE is a synthetic analog of the naturally occurring cytotoxic agent, dolastatin10. cAC10 binds to cancer cell lines including Hodgkin lymphoma (HL), ALCL, and other lymphoproliferative disorders.[2,3] The recommended dosing of brentuximab vedotin is once every three weeks at 1.8 mg/kg administered through an IV infusion over 30 minutes, for up to 16 cycles.[2]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The CADTH systematic review included one randomized controlled trial (RCT), the ALCANZA (CA25001) trial (n=131).[4] A summary of the trial and its results are provided below.

ALCANZA

ALCANZA is an open-label, multicentre, phase III RCT comparing the efficacy and safety brentuximab vedotin (BV) compared to physician's choice (PC), either methotrexate or bexarotene, among patients with CD30-positive cutaneous T-cell lymphoma. Eligible patients included adults with CD30-positive (CD30+) MF who had received at least one prior systemic therapy or adults with pcALCL who had received at least one systemic therapy or radiotherapy, an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤2, with confirmed CD30 disease histology via central review. Confirmation of CD30 positivity, defined as having ≥10% CD30-positive malignant cells or lymphoid infiltrate, required two or more skin biopsies from separate lesions for patients with MF, and one or more skin biopsies for patients with pcALCL. Patients who had previously progressed on treatment with methotrexate and bexarotene were not eligible for enrolment.[4] Patients were randomized (1:1) to receive either BV or PC of methotrexate or

bexarotene. Patients were administered BV intravenously in a dose of 1.8mg/kg over a duration of 30 minutes on day 1 of each 21-day cycle. In patients above 100 kg the dose was based on 100 kg. Brentuximab vedotin could be given for a maximum duration of 48 weeks or 16 cycles.[5] Patients randomized to the comparator group received either:

- Methotrexate orally once per week at a single dose of 5-50 mg for a maximum duration of 48 weeks,[5] or
- Bexarotene orally once daily at a dose of 300mg/m^2 for a maximum duration of 48 weeks.[5]

Randomization occurred using an interactive voice and web response system. A Takeda statistician generated the randomization list, after which they were no longer involved in the trial.[4] The sponsor confirmed that before administration of the study treatment, a randomization number was assigned to each patient.[6] The randomization schedule also included the study-specific identifiers, such as, company name, protocol name, protocol number, and the date and time the randomization schedule was generated.[6] Stratification of patients was based on baseline disease diagnosis of pcALCL or MF.[5] Due to the open-label study design, both patients and investigators were aware of treatment received; however, aggregate efficacy results according to each treatment group were blinded to the study team, investigators, patients, and independent review facility (IRF) for the duration of the study.[7]

The primary endpoint in the trial was ORR4 assessed by an IRF and was defined as the proportion of patients that achieved an objective response (CR or PR) lasting at least four months (e.g. duration from the first response to last response is ≥4 months).[4] Objective response was determined based on a global response score (GRS) consisting of an mSWAT assessment by the investigator, nodal and visceral radiographic assessments by an IRF, and detection of Sézary cells for patients with MF only by IRF.[5] ORR4 is a composite endpoint and was chosen by the Sponsor as it was considered to be a more appropriate endpoint for patients in the ALCANZA trial who may be more symptomatic and frequently proceed to alternate therapies before meeting protocol-defined criteria for progression; based on patient characteristics of CTCL, ORR4 was considered to be a more appropriate measure of patient's response to treatment compared to other typical endpoints, such as PFS. Further, ORR4 was stated to represent a higher bar for patients' response to treatment compared to ORR because ORR4 allows for a meaningful representation of benefit among patients with chronic and incurable disease who experience relapse and require multiple lines of therapy. The endpoint of ORR4 was stated by the Sponsor to have been negotiated with the FDA and received scientific support from the EMA.[6]

Key secondary endpoints of the trial included the proportion of patients achieving CR, PFS, and symptom burden measured by the symptom domain of the Skindex-29, which is a health-related quality of life measure. Based on a fixed sequence testing procedure to control for the incidence of overall type 1 error, the key secondary endpoints were only tested if ORR4 was found to be statistically significant. A weighted Holm's procedure was then further used for testing of the key secondary endpoints using the following weights: 0.7 for CR, 0.2 for PFS, and 0.1 for the symptom domain of the Skindex-29.[4] Analyses of key secondary endpoints involved the use of adjusted p-values, which allowed for adjustment of multiplicity based on weighted Holm's procedure. Statistical significance was determined at the adjusted two-sided $p \leq 0.05$.[4]

Other secondary endpoints included DOR, duration of skin response, EFS, quality of life as per the Skindex-29 emotional and functional domains and the FACT-G, blood concentrations of BV (serum) and MMAE (plasma), immunogenicity assessment and safety.[5] The sponsor also conducted an analysis for OS which was not prespecified and should be considered exploratory.

A total of 131 patients were randomized in the ALCANZA trial, 66 of whom were randomized to receive BV and 65 patients randomized to receive PC of therapy (methotrexate or bexarotene). In the final ITT population, there were a total of 128 patients with 64 patients in each treatment group. Baseline characteristics were generally balanced between the two treatment groups. The median age was 62 years (range: 51-70) and 59 years (range: 48-67) in the BV and PC groups, respectively. There were 33 males (52%) and 37 males (58%) in the BV and PC groups, respectively. Most patients had an ECOG PS of 0 (67% in the BV group and 72% in the PC group) or 1 (28% and 25%) and were White (88% and 83%).[4] Patients diagnosed with MF comprised 76% of the ITT population (75% in the BV group and 77% in the PC group), and patients with pcALCL comprised 24% of the ITT population (25% in the BV group and 23% in the PC group); however, the proportion of patients with stage IVA2 MF in the PC group (16%) was greater than that of patients in the BV group (4%), and the proportion of patients with IVB MF was greater in the BV group (15%) than in the PC group (0%).[4] Further, the disease stage of patients with pcALCL also varied across treatment group, as there was greater presence of extracutaneous pcALCL in the BV group (44%) compared to the PC group (27%).[5] Time since progression on last therapy was also longer for patients in the BV group (2.4 months, range: 1.4-7.9) compared to the PC group (1.3 months, range: 0.9-3.7). Patients received a median number of four (range: 2.0-7.0) prior therapies in the BV group and 3.5 (range: 2.0-5.5) prior therapies in the PC group.[4] Patients with MF or pcALCL received a median of two systemic therapies in both the BV and PC treatment groups. Chemotherapy was the most commonly received prior systemic therapy in both treatment groups (71% in the BV group and 70% in the PC group) followed by immunotherapy (41% and 45%) and bexarotene (41% and 34%).[5]

Efficacy

The final results for the primary and key secondary outcomes from the ALCANZA trial, based on a database lock of September 28, 2018, are summarized in Table 1. The study was completed on July 6, 2018. After a median follow-up of 45.9 months (95% CI 41.0-49.4),[8] there were 35 patients (54.7%) in the BV group that achieved ORR4 per IRF compared to eight patients (12.5%) in the PC group p-value, p<0.001).[6,9] Results favoured treatment with BV compared to PC. Analysis of key secondary endpoints at the final analysis also favoured treatment with BV compared to treatment with PC:

- CR according to IRF for patients in the BV group was 11 patients (17.2%, 95% CI 7.9-26.4) compared to one patient (1.6%, 95% CI 0-8.4) in the PC group.[6]
- The median PFS according to IRF was 16.7 (95% CI not reported) months in the BV group compared to 3.5 months (95% CI not reported) in the PC group (HR=0.378; 95% CI, 0.247-0.577; p<0.001).[8,10]
- Regarding the symptom domain of the Skindex-29, the mean maximum reduction of patient reported burden of symptoms from baseline was -28.08 (standard deviation 26.863) in the BV group and -8.62 (standard deviation 17.013) in the PC group with a statistically significant difference of -19.0 (95% CI -26.7 to -11.4) in favour of the BV group.[6]

Patient Reported Outcomes – Skindex-29 Emotional and Functional Domains, FACT-G and EQ5D

For the emotional domain of the Skindex-29, the mean change from baseline to end of treatment was -14.43 (standard deviation: 20.901) for the BV group compared to -1.84 (standard deviation: 18.555) for the PC group. For the functional domain, the mean change from baseline to end of treatment was -11.10 (standard deviation: 25.312) for the BV group and -1.22 (standard deviation: 22.448) in the PC group. Neither the emotional nor functional domains of the Skindex-29 showed substantial differences over time. However, at the end of treatment, skin disease had less of an impact in both the emotional and functional domains for patients treated with BV compared to PC.[4] The mean change from baseline in Skindex-29 composite total score to the end of treatment visit for the total score was -14.84 (standard deviation: 22.681) for the BV group and -0.96 (standard deviation: 18.973) for the PC group. The difference in mean change from baseline at the end of treatment visit was -13.88 with 95% CI (-21.12 to -6.64), based on the normal approximation.[6] There were no substantial differences between the treatment groups.

There were no observed differences in the FACT-G and EQ-5D between the BV and PC groups.[5]

Exploratory Analysis of Overall Survival

The median OS was 48.4 months in the BV group (95% CI 41.0-51.7), and 42.9 months in the PC group (95% CI 38.6-49.4). Based on the exploratory analysis of OS, treatment with BV was favoured over treatment with PC (HR=0.745, 95% CI 0.421-1.318; p-value 0.310).[11] However, these results should be interpreted with caution as they were not prespecified, and were not powered to detect differences and not adjusted for multiplicity.

Harms

Safety data were not reported for the final analysis. Therefore, safety data presented in this report are from the primary analysis date (data cut-off: May 31, 2016) and based on a median follow up of 22.9 months. There were 66 patients in the BV group and 62 patients in the PC group that received treatment and were included in the safety population. AEs of any grade was similar between both treatment groups with 63 patients (95%) in the BV group and 56 patients (90%) in the PC group reporting at least one AE. Grade ≥3 adverse events were also similar between treatment groups, with 27 patients (41%) reporting grade 3 or higher AEs in the BV group compared to 29 patients (47%) in the PC group. The proportion of grade ≥3 AEs related to treatment was the same across both treatment groups with 19 patients (29%) and 18 patients (29%) in the PV and PC groups, respectively.[4]

Overall, the occurrence of grade ≥3 AEs (41% vs. 47%&, drug related grade ≥3 AEs (29% vs. 29%), and SAEs (29% vs. 29%) were similar in the BV and PC groups, respectively. A higher proportion of patients in the BV group discontinued treatment due to an AE as compared to patients in the PC group (16 patients (24%) and five patients (8%), respectively).[4]

In the BV group (n=66), the most frequently reported grade 3 treatment-emergent AEs (≥10% of patients) were peripheral sensory neuropathy in three patients (5%) and fatigue in three patients (5%). No frequently occurring (≥10% of patients) grade 4 treatment-emergent AEs occurred in the BV group. Of the patients that received methotrexate of the PC group (n=25), the most frequently reported grade 3 treatment-emergent AEs (≥10% of patients) were fatigue, pyrexia, and skin infection which occurred in one patient

(4%) each. There were no frequently occurring (≥10% of patients) grade 4 treatment-emergent AEs reported for patients that received methotrexate of the PC group. Of the patients that received bexarotene in the PC group (n=37), the most frequently reported grade 3 treatment-emergent AE (≥10% of patients) was hypertriglyceridemia, which occurred in five patients (14%). Similarly, the most frequently reported grade 4 treatment-emergent AE (≥10% of patients) was hypertriglyceridemia, which occurred in three patients (8%).[4]

Deaths were similar between both treatment groups, with 16 deaths (24%) and 14 deaths (23%) having occurred in the BV and PC groups, respectively.[4] There were four patients in the BV group that experienced on-treatment deaths; three were unrelated to study drug and caused by, one each of, sepsis, disease progression, and pulmonary embolism. The investigator stated that multiple organ dysfunction syndrome occurred in a patient with pcALCL with $T_{3b}N_0M_1$ who experienced tumor lysis (on sites of visceral lymphoma involvement) caused by BV.[4]

Limitations and Potential Sources of Bias

A complete list of limitations and sources of bias are available in section 6 of this report. A summary of major limitations and potential sources of bias are summarized below:

- The ALCANZA trial was an open-label study design; therefore, investigators and patients were aware of the treatments administered during the study. The lack of blinding may introduce bias affecting the measurement and reporting of outcomes potentially favouring results of treatment with BV compared to PC. Further, assessments of patient reported outcomes should be interpreted with caution as patients' knowledge of treatment assignment may bias their reporting of disease symptoms.
- The sponsor confirmed ORR4 is a composite endpoint used to capture durable response of patients to the study drug while being minimally affected by other therapies.[6] ORR4 was stated by the Sponsor to be a more meaningful and representative of clinical benefit than the rate of objective response alone, which could include responses of short duration that are not clinically relevant and which may not equate to meaningful benefit for patients.[11] Composite endpoints in clinical trials may result in an overestimation of effect and lead to misinterpretation. Therefore, it is recommended that a thorough assessment of the composite endpoint and its components are performed.[12] The effect of each component of ORR4 was not reported separately; therefore, the effect of each component of the composite endpoint is unclear and may be mostly driven by an effect on one of the components. Additionally, the use of ORR4 as a primary endpoint makes cross-trial comparisons to trials reporting on traditional outcome measures such as PFS and OS challenging.
- At the final analysis, the exploratory analysis of OS showed that OS was longer for patients treated with BV compared to patients treated with PC (HR=0.745, 95% CI 0.421-1.318; p-value 0.310).[9] It is important to note that the OS endpoint was not a formally prespecified endpoint per protocol and the ALCANZA trial was not powered to detect differences with this endpoint.[6] Therefore, results should be considered exploratory and no definitive conclusions can be drawn on the longer-term survival of patients with MF and pcALCL.

Table 1: Highlights of Key Outcomes

ALCANZA Trial		
	BV Group (N=64)	**PC Group (N=64)**
Primary Outcome (data cut-off: September 28, 2018)		
ORR4		
n (%) (95%CI)	35 (54.7) (42.5-66.9)	8 (12.5) (4.4-20.6)
Between Group Difference, % (95%CI)	43.8 (29.1–58.4)	
p-value	<0.001	
Key Secondary Outcomes (data cut-off: September 28, 2018)		
CR		
n (%) (95%CI)	11 (17.2) (7.9-26.4)	1 (1.6) (0-8.4)
Between Group Difference, % (95%CI)	NR	
p-value	NR	
PFS		
Events, n (%)	42 (66)	50 (78)
Median (95% CI)	16.7 (NR)	3.5 (NR)
HR (95%CI)	HR 0.378 (0.247-0.577)	
p-value	p<0.001	
Skindex-29 Symptom Domain		
Points change from baseline (SD)	-28.08 (26.863)	-8.62 (17.013)
Between Group Difference, % (95%CI)	-19.0 (95% CI -26.7 to -11.4)	
Harms Outcome (data cut-off: May 31, 2016), n (%)	**Group (N=66)**	**Group (N=62)**
AE (any grade)	63 (95)	56 (90)
Grade ≥3	27 (41)	29 (47)
Serious AE	19 (29)	18 (29)
TRAE	57 (86)	44 (71)
WDAE	16 (24)	5 (8)
On Treatment Deaths[a]	4 (6)	0

AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reported, SD = standard deviation, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event; BV = brentuximab vedotin, PC = physician's choice, ORR4 = objective global response rate lasting at least 4 months, CR=complete response; PFS=progression free survival

*HR < 1 favours brentuximab vedotin

[a] on-treatment deaths are defined as deaths that occur within 30 days after the last dose of study drug. Causes of death in the 4 patients in the brentuximab vedotin group were: lymphoma, sepsis, multiple organ dysfunction syndrome, and pulmonary embolism. Multiple organ dysfunction syndrome was considered by the investigator to be related to brentuximab vedotin treatment.

Data Sources: Prince et al., 2017,[4] EPAR 2017[5] Hortwitz et al., 2019,[9] Checkpoint Meeting Materials[6,8]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, PAG Input, and registered clinician input, respectively.

Patient Advocacy Group Input

One joint input was provided by Lymphoma Canada (LC) and the Canadian Skin Patient Alliance (CSPA) for the review for brentuximab vedotin (BV) (Adcetris) for pcALCL or MF. LC and CSPA conducted an online, anonymous survey sent to respondents registered in the LC database via email and made available between March 30, 2020 and April 20, 2020. In total, 86 patient respondents provided input through the survey; of note, there were no caregiver respondents. Most respondents were diagnosed with MF (96%). Many of the respondents indicated experiencing delays in obtaining a diagnosis for their condition. Over half of the respondents (54%) reported having waited more than one year to receive their diagnosis after first showing symptoms. Appearance of skin and itching skin were the most commonly reported symptoms to negatively impact quality of life. Many respondents also reported feelings of stress (77%), anxiety/worry (64%), and concerns about body image or physical appearance (52%) as significant concerns related to their disease symptoms. Respondents also indicated feelings of isolation from feeling the need to conceal their condition and its related symptoms. The number of clinic visits and treatment-related fatigue were aspects of daily living respondents felt were significantly impacted due to current treatment. Almost one-third of patients (31%) reported difficulty in accessing treatment, mainly due to treatments being unavailable in their local cancer centre or due to living in a community without a local cancer centre.

Five of the respondents indicated having experience with BV; of these five patients, four were diagnosed with MF and one was diagnosed with pcALCL. These five patients reported receiving a median of eight treatments prior to receiving BV. All five patients reported that treatment with BV was able to manage skin lesions related to cutaneous lymphoma. Peripheral neuropathy, fatigue, headache, and infusion reactions were the most commonly reported side effects due to BV. One of the patients had to discontinue treatment with BV due to a severe infusion reaction. The four patients who did not discontinue treatment reported that BV had improved their health and well-being and that they had an overall positive experience. Among all five patients with experience with BV, all reported that they would take this treatment again if they were recommended it as their best option by their doctor.

Overall, patients reported that having additional treatment options was highly valued. Especially among patients with advanced disease and prior experience with systemic therapies, additional treatment options are considered to be extremely important. In addition, longer survival, better quality of life, longer remission, and fewer side effects were important considerations for new treatment options for cutaneous lymphoma. LC and CSPA highlighted an unmet need for patients as cutaneous lymphoma is *"a long-term, chronic disease that can come and go over the course of time."*

Provincial Advisory Group (PAG) Input

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Use relative to other second line systemic options and stem cell transplant
- Use in various disease stages

Economic factors:

- Potential for drug wastage
- Additional nursing and clinic resources will be required

Registered Clinician Input

One registered clinician input was provided on behalf of one individual oncologist from Ontario. Various treatments were stated to be currently available to patients through public funding; alternatively, alemtuzumab is currently available to patients through compassionate access. While many treatment choices currently exist for patients, there is no treatment considered to be standard of care; therefore, no direct comparator was identified. Eligibility criteria from the pivotal trial were stated to be applicable to clinical practice. The clinician expected that BV would most likely be used very frequently in clinical practice due to the lack of gold standard treatments. After failure of an initial therapy, BV was suggested as a possible treatment in the second line. When asked how BV would be sequenced relative to allogeneic stem cell transplant, the clinician acknowledged that this indication would be rare; therefore, not many patients are expected to receive a sequence of treatments with BV and allogeneic stem cell transplant. Re-

treatment with BV was considered reasonable so long as a patient's response to BV was initially durable (i.e. 12 months). As patients are often first reviewed by expert hematopathologists or dermatopathologists, no companion diagnostic testing was stated to be needed. Morphological and clinical assessments were stated to be used as tools to monitor response to therapy.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of Generalizability of Evidence for Brentuximab Vedotin

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Outcomes	Appropriateness of Primary and Secondary Outcomes	Primary outcome: ORR4—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. ORR4 is based on global response, 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 Secondary outcomes: PFS, CR, and symptom burden	Were the primary and secondary outcomes appropriate for the trial design?	The CGP noted that the assessment of ORR4 was appropriate for the MF and pcALCL patient populations and the factors included in the global response were appropriate. The CGP also noted that assessing a response of at least 4 months is meaningful.

1.2.4 Interpretation

Burden of Illness and Need

Cutaneous T-cell lymphomas (CTCL) are classified as a heterogenous subgroup of Non-Hodgkin Lymphomas (NHL). Mycosis Fungoides (MF) and primary cutaneous CD30 positive anaplastic large cell lymphoma (ALCL) account for approximately 80-85% of all CTCLs.[13]

In Canada, there is no standard of care for patients with CD30 expressing MF as variation exists across clinical practice and jurisdictions. Patients may require several types of treatment and repeated courses of therapy to achieve disease control. Generally, patients with early stage MF tend to be prescribed skin-directed therapies such as topical steroids, nitrogen mustard, ultra-violet light (UVB or PUVA), local radiotherapy, total skin electron beam radiation (TSEB), and low-dose methotrexate. Patients with advanced MF (Stage III disease) are commonly treated with retinoids (bexarotene), interferon, TSEB, extracorporeal photopheresis (ECP), and low dose methotrexate. Patients with Stage IV MF are treated with systemic therapies including single-agent chemotherapy (e.g., gemcitabine and liposomal doxorubicin), multi-agent chemotherapy (e.g., CHOP or CEOP), alemtuzumab, and allogeneic stem cell transplant. At the time of relapse, patients are treated with therapies not previously exposed to. There are no curative treatment options for MF patients, with the exception of allogeneic stem cell transplant for patients who are healthy with adequate organ function.[14] For patients who are not candidates for allogeneic stem cell transplant, the intent of treatment is to prolong survival, provide disease control, lengthen remission, reduce symptoms, and improve quality of life.

For those with early stage pcALCL, initial treatment is generally with surgery and/or localized radiotherapy. There is no standard of care for those with advanced pcALCL for whom systemic therapy is preferred including methotrexate, bexarotene, interferon, romidepsin, pralatrexate, and single-agent chemotherapy (e.g., gemcitabine and liposomal doxorubicin). Multi-agent chemotherapy (such as CHOP or equivalent) is usually reserved for those with extensive disease who have failed single-agent therapy. As such, patients who receive current treatment for their MF and pcALCL may require several types of treatment and repeated courses of therapy to obtain disease control. This is supported by the patient input from Lymphoma Canada and the Canadian Skin Patient Alliance that noted the unmet need for treatments over the course of time as cutaneous lymphoma is a long-term, chronic disease that can come and go over the course of time. Current treatment options provide limited and poor durable response. The proportions of patients achieving an objective response for many monotherapies are 20-35% that last approximately four to six months. Multi-agent therapies are usually reserved for patients who do not respond to monotherapies or have substantial nodal or visceral disease and these regimens have similar responses. Therefore, there is a need for effective treatments for this chronic disease.

Effectiveness

ALCANZA is a phase III, international, RCT that compared BV to PC of methotrexate or bexarotene in adult patients with MF who have received at least one prior systemic therapy or pcALCL patients who received prior radiation or at least one prior systemic therapy. The ALCANZA trial randomized 66 patients to the BV group and 65 patients to the PC group (methotrexate or bexarotene). Patients diagnosed with MF comprised 76% of the ITT population and patients with pcALCL comprised 24% of the ITT population. The median age was 62 years (range: 51-70) and 59 years (range: 48-67) in the BV and PC group, respectively. In the BV group, 43 patients (67%) had an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 compared to 18 patients (28%) with an ECOG PS of 1 and 3 patients (5%) with an ECOG PS of 2. In the PC group, 46 patients (72%) had an ECOG score of 0 compared to 16 patients (25%) with an ECOG PS of 1 and 2 patients (3%) with an ECOG score of 2. There was a difference observed for time since progression on last therapy, which excluded radiotherapy, between the BV and PC groups as the time since progression for the BV group was approximately twice that of the PC group, 2.4 months versus 1.3 months.[4] Bexarotene and methotrexate were both received by some patients as prior therapies for their conditions; in the BV group, 41% of patients received prior treatment with bexarotene and 41% of patients received prior treatment with methotrexate. In the PC group 34% of patients received bexarotene and 39% of patients received methotrexate. Patients who had previously progressed on treatment with methotrexate and bexarotene were not eligible for enrolment in the study. Three patients (8%) in the PC group that received prior treatment with bexarotene without reported progressive disease, and 2 patients (8%) that received prior treatment with methotrexate without reported progressive disease were randomized to receive bexarotene and methotrexate, respectively.[3] Among the three patients retreated with bexarotene, previous responses to bexarotene were unknown and one of these patients had been previously treated with methotrexate. The two patients retreated with methotrexate had a previous best response to methotrexate of stable disease and partial response; both of these patients were also previously treated with bexarotene.[5] In the PC group, there were 11 patients (17.2%) that experienced disease progression on previous treatment with methotrexate and received bexarotene in the trial.

The primary endpoint in the ALCANZA trial was the proportion of patients achieving an objective response (complete response or partial response) lasting at least four months (ORR4) as assessed by the IRF. ORR4 was determined by independent review of global response scores (GRS) with objective response based on a modified severity weighted assessment tool (mSWAT) by the

investigator, nodal and visceral radiographic assessment by independent radiologists (IRF), and for the patients with MF only, detection of circulating Sézary cells by an IRF.[5] According to the sponsor, the inclusion of these components with a time frame of at least four months to assess response likely provides a more conservative estimate of treatment effect compared to using just the ORR alone, which could include short responses that are not clinically relevant. ORR4 was noted by the sponsor to be an endpoint that captures two clinically important aspects of treatment success including the proportion of patients achieving a response and the duration of response as a single measurement.[4,6] Though the use of composite endpoints may result in an overestimation of the effect and can be misinterpreted as each component of the composite endpoint should be assessed independently;[12] the CGP felt that ORR4 was a meaningful endpoint. At the primary analysis with a median follow-up of 22.9 months (95% CI 18.4-26.1), there were 36 patients (56.3%, 95% CI 44.1-68.4) in the BV group that achieved ORR4 per IRF compared to eight patients (12.5%, 95% CI 4.4-20.6) in the PC group in the ITT population.[5] The between group difference of 43.8% (95% CI 29.1-58.4, p-value <0.0001) was statistically significant in favour of the BV group compared to the PC group.[4] This represents a clinically meaningful difference in favour of BV compared to PC. At the final analysis with a median follow-up of 45.9 months, there were 35 patients (54.7%, 95% CI 42.5-66.9) the BV group that achieved ORR4 per IRF compared to eight patients (12.5%, 95% CI 4.4-20.6) in the PC group p-value, p<0.001).[8,9] The improvement of ORR4 in the BV group was consistent across all key subgroups compared with PC group. Although the effect of each component of ORR4 was not reported separately, the assessments included in ORR4 (skin assessment, nodal, visceral) were considered all important for assessing response and that the response observed was meaningful. An analysis of mSWAT showed that 20 (41%) of 49 patients with MF in the PC group compared to 37 (77%) of 48 patients in the BV group had a 50% or higher reduction in the mSWAT. Additionally, 10 (63%) of 16 patients with pcALCL in the BV group had 100% reduction in skin disease.[4] It is encouraging to observe that the independent assessment of mSWAT showed significant improvement with BV and underscores the acceptability of ORR4 as a meaningful endpoint in this patient population; the mSWAT analysis was conducted as one component of ORR4.

A key secondary endpoint in the trial was complete response (CR) which was observed in 10 out of 64 patients (15.6%, 95% CI 6.7-24.5) in the BV group compared to one out of 64 patients (1.6%, 95% CI 0-4.6) in the PC group, p-value=0.0046.[5,6] The higher percentage of patients achieving CR is clinically meaningful and significant. Additionally, the proportion of patients achieving an objective response (lasting any duration) was higher in patients that received BV (43 patients) with a median duration of response (DOR) of 15.1 months (CI 9.7, 25.5). In patients that received either methotrexate or bexarotene and experienced an objective response (lasting any duration) (13 patients), the median DOR was 18.3 months (CI 3.5, 18.4). Responses were ongoing at the last assessment in 20 of the 43 responders (47%) in the BV group and seven of the 13 patients (54%) in the PC group.[5]

At the primary data cut-off date, 86 patients (67%) experienced a PFS event; progressive disease per IRF was observed in 74 patients (58%) comprised of 30 patients (47%) in the BV group and 44 patients (69%) in the PC group, while death occurred in 12 patients with six deaths (9%) each in the BV and PC group. At the final analysis with a median PFS follow up 36.8 months (95% CI 31.7, 40.2), the median PFS according to IRF was 16.7 months in the BV group compared to 3.5 months in the PC group (HR 0.378; 95% CI, 0.247-0.577; p<0.001).[8,9]

Another key secondary endpoint measured burden of symptoms with the Skindex-29 as part of patient reported outcomes; the results showed significantly greater symptom reduction in the BV group, compared with the PC group, with a mean maximum reduction of -27.96 (SD 26.877) versus -8.62 (SD: 17.013; p<0.001; adjusted p<0.001), representing a difference in mean maximum reduction of -18.9 (95% CI -26.6 to -11.2).[4,5] Additionally, there were no substantial differences observed in Skindex-29 emotional or functional domains over time. Skin disease at end of treatment had less of an effect in patients in the BV group for both domains. Additionally, there were no observed differences in the FACT-G and EQ5D between the BV and PC groups.[5] However, the improvement in skin lesions as assessed by mSWAT may be indicative of improved quality of life in patients.

At the primary analysis with a median OS follow-up of 22.9 months (95% CI 18.4-26.1), the median OS follow-up in the BV and PC groups were 23.2 months (95% CI 19.1-28.1) and 20.8 months (95% CI 14.6-23.9), respectively (HR=0.885, 95% CI 0.426-1.838; p-value 0.742).[5] The median OS at the final analysis was 48.4 months (95% CI 41.0-51.7) in the BV group and 42.9 months (95% CI 38.6-49.4) in the PC group; treatment with BV was favoured over physician's choice (HR=0.745, 95% CI 0.421-1.318; p-value 0.310).[6] It is important to note that the study was not powered to detect OS differences and there is limited evidence as to whether improvement in ORR4 correlates to improved OS and no definitive conclusions can be drawn.

Safety

Serious adverse events were similar between both groups (19 patients (29%) and 18 patients (29%) in the BV and PC group, respectively). Overall, drug related grade ≥3 AEs (19 patients [29%] vs 18 patients [29%]) and serious adverse events (19 patients [29%] vs 18 patients [29%]) were similar in the BV and PC group, respectively.[4,5] In the BV group (n=66), the most frequently reported grade 3 treatment-emergent adverse events were peripheral sensory neuropathy in three patients (5%) and fatigue in three patients (5%). Of the patients that received methotrexate of the PC group (n=25), the most frequently reported grade 3 treatment-emergent adverse events were fatigue, pyrexia, and skin infection, which occurred in one patient (4%) each. Of the patients that received bexarotene of the PC group (n=37), the most frequently reported grade 3 treatment-emergent adverse events (≥10% of patients) was hypertriglyceridemia, which occurred in five patients (14%). There were no grade 4 treatment-emergent adverse events observed in the BV group or in patients that received methotrexate of the PC group. The occurrence of grade 4 treatment-emergent adverse events in patients that received bexarotene of the PC group was low; namely, hypertriglyceridemia occurred in three patients (8%).[4] A review of all grade 3 or grade 4 cardiac safety issues revealed only one patient in the PC group who received bexarotene experienced bilateral pedal edema with worsening of diastolic failure. There were no patients in the BV group that experienced grade 3 or grade 4 cardiac safety issues. Overall, the rates of grade 3 treatment-emergent adverse events were low in the BV group.[6] In terms of treatment discontinuation due to an adverse event, there was a higher proportion of patients in the BV group (16 patients, 24%) that discontinued treatment as compared to patients in the PC group (5 patients, 8%). Overall, no new safety signals were detected in the BV treatment group.[5]

1.3 Conclusions

The CGP concluded that there is a net clinical benefit of BV compared to PC for the treatment of adult patients with pcALCL or CD-30 expressing MF who have had prior systemic therapy. The CGP based this conclusion on a well conducted, randomized phase III open-label trial, which demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint, ORR4, and key secondary endpoints, CR and PFS. Furthermore, the trial results demonstrated the manageable toxicity profile of BV and no apparent detriment to quality of life compared to PC. Brentuximab vedotin is a treatment option that provides a more durable response compared to other agents available for patients with pCALCL and MF who have received at least one prior systemic therapy.

In making this conclusion, the CGP considered that this is the first phase III prospective trial of a novel therapy compared to standard therapy that demonstrated improved outcomes for patients with cutaneous T-cell lymphoma.

A number of questions were raised by the PAG if BV were to be recommended for reimbursement, specifically with respect to the eligible patient population, implementation factors, and sequencing of available treatments. The CGP's responses to these questions are summarized in Table 3.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
PAG noted that there is no current standard therapy and no curative treatment (with the exception of allogeneic stem cell transplant) for pcALCL or MF. Generally, patients with early stage disease tend to be prescribed skin-directed therapies such as surgery or local radiotherapy followed by maintenance with low-dose methotrexate. Patients with more advanced disease are commonly treated with systemic therapies such as CHOP or CEOP. Relapsed patients or patients with aggressive disease or extracutaneous involvement	The ALCANZA trial compared BV to PC of methotrexate and bexarotene. An indirect treatment comparison to other available agents for patients with MF or pcALCL was not included in the submission and therefore the comparative efficacy of BV to other available therapies is unknown. There is no current standard of care and no curative treatment for pcALCL or MF. Patients may require several types of treatment and repeated courses of treatments to obtain disease control. Patients may be treated with systemic therapies such as CHOP or CEOP, retinoids, interferon, gemcitabine, liposomal doxorubicin, and etoposide. Many treatment choices currently exist

PAG Implementation Questions	CGP Response
can be given isotretinoin or alitretinoin, interferon, bexarotene, alemtuzumab, or single-agent chemotherapy (gemcitabine, liposomal doxorubicin, etoposide); funding of these agents varies across provinces. Patients may require several types of treatment and repeated courses of therapy to obtain disease control. The ALCANZA trial compared BV to PC of methotrexate or bexarotene. PAG is seeking comparison between BV and retinoids, interferon, gemcitabine, liposomal doxorubicin, and etoposide.	without an overall direct comparator due to the lack of an available gold standard treatment.
Eligible Patient Population	
Patients with an ECOG performance score greater than 2	The CGP noted that patients with ECOG PS >2 were excluded from the ALCANZA trial. The CGP agreed that it would be appropriate to treat patients with ECOG PS greater than 2 with BV at the discretion of the treating physician. Poor performance status may be due to the underlying disease and treating physicians may decide to offer BV to these patients.
Patients with cardiac symptoms	The CGP noted that the risk of cardiac toxicity with BV is <5%. The CGP agreed that patients with stable cardiac disease should be eligible for BV.
Patients with Sézary syndrome showing CD30 positivity or other subtypes of CD30+ cutaneous T-cell lymphoma	The CGP noted that patients with Sézary syndrome showing CD30 positivity or other subtypes of CD30+ cutaneous T-cell lymphoma were excluded from the ALCANZA trial. Therefore, these patients would not be eligible for treatment with BV.
Patients who progressed on both previous methotrexate and bexarotene, but who would be eligible for other systemic therapies	Patients who have progressed on both methotrexate and bexarotene should be eligible for BV. These patients were excluded from the ALCANZA trial because they may have been randomized to the PC arm of methotrexate and bexarotene. Patients with prior treatment with methotrexate and bexarotene should be eligible for BV.
Patients with CNS involvement and PML symptoms	The CGP noted that the risk of CNS relapse is extremely low and patients with CNS involvement and PML symptoms were excluded from the ALCANZA study. Therefore, BV should not be offered to patients with CNS involvement and PML symptoms.
Patients with T-cell lymphoma transformed from MF who otherwise meet eligibility criteria	According to the sponsor, patients with transformed MF were eligible to enroll in the ALCANZA trial. Patients were deemed to have large cell transformation (LCT) if any single biopsy showed the presence of large cells with nuclei ≥4 times larger than those of normal lymphocytes present in >25% of total dermal infiltrate or forming microscopic nodules. The sponsor confirmed that of the 100 patients with MF, 96 were evaluated for LCT status (n=48 in each arm) and were included in the response-by-LCT analyses. Four patients had biopsies that could not be assessed due to crush artefacts and were therefore classified as having unknown LCT status.[6] Therefore, patients with transformed MF would be eligible for treatment with BV. An exploratory analysis of the efficacy of BV and PC by LCT status was presented at the ASH 2018 meeting; ORR4 was consistently higher with BV versus PC in patients with LCT (n=11 [64.7%] versus n=3 [17.6%]) and those without LCT (n=12 [38.7%] versus n=2 [6.5%]). In the BV group, a higher proportion of patients with LCT achieved an

PAG Implementation Questions	CGP Response
	ORR4 than those without LCT (64.7% [n=11] versus 38.7% [n=12]; P=0.155). Median PFS was improved with BV versus PC in patients with LCT (15.5 months [95% CI: 9.1, 22.8] versus 2.8 months [95% CI: 1.4, 7.3]; P=0.002) and without LCT (16.1 months [95% CI: 8.6, 21.6] versus 3.5 months [95% CI: 2.2, 4.3]; P<0.001).[15,16]
Previously untreated patients and patients who are not progressing but cannot tolerate a first line systemic therapy.	Patients previously untreated for pCALCL and MF would not be eligible for treatment with BV. The CGP noted that patients should initiate treatment with BV if they progress on a current therapy or are intolerant to a current therapy.
If recommended for reimbursement, PAG noted that patients who have already initiated second-line systemic therapy would need to be addressed on a time-limited basis. PAG seeks guidance on whether to switch these patients to BV or rather wait for disease progression. In addition, PAG noted a potential for indication creep with BV for patients with CD30+ Sézary Syndrome and for first-line treatment of pcALCL and MF. There is also potential for use in earlier stages of MF.	The CGP agreed that the preference is not to switch patients to BV who have already initiated second-line systemic therapy but have not progressed. It is appropriate to switch a patient to BV if a patient experiences disease progression on current treatment or has poor tolerance to a current treatment.
Implementation Factors	
The recommended dose of BV is 1.8 mg/kg every 3 weeks. BV is given until disease progression, unacceptable toxicity, or a maximum of 16 cycles (48 weeks). PAG is seeking a clear definition of disease progression for the development of discontinuation criteria.	The CGP noted that BV should be discontinued as per the ALCANZA trial. BV should be discontinued for patients who met the following criteria: • Completed 16 cycles of BV therapy or 48 weeks of reference therapy. • Experienced progressive disease
Additional resources (e.g., nursing and clinic visits) are required to monitor and treat infusion-related reactions and adverse events (e.g. diarrhea, neutropenia/febrile neutropenia, and peripheral neuropathy) as well as monitor complete blood count. The cost of supportive therapy (e.g. G-CSF) also needs to be considered in implementation as it will likely be required as primary prophylaxis.	The CGP noted that in the ALCANZA trial, the use of platelet and/or red blood cell (RBC) supportive growth factors or transfusions was allowed when applicable and the use of colony stimulating factors for the treatment of neutropenia was permitted during therapy according to institutional practice.[17]
Sequencing and Priority of Treatment	

PAG Implementation Questions	CGP Response
PAG is seeking to confirm the eligible patient population and line of therapy with BV, and the possible sequencing of treatments, including the scenarios below: • Eligibility to BV upon progression on maintenance with low dose methotrexate or other systemic therapies following skin-directed therapy. • Priority relative to all second-line and beyond systemic therapies including single- and multi-agent chemotherapy, retinoids, and interferon therapy. • Optimal sequencing with other systemic therapies and number of therapies that should be tried before a patient becomes eligible to BV. • Sequencing with allogeneic stem cell transplant. • Options after progression with BV. • Evidence of benefit from giving BV in combination with other systemic therapies. • Optimal stage of disease for treatment with BV. • Timing and appropriateness of re-treatment with BV if disease recurs after the 48-week treatment course. • Addition of CHP to BV in MF patients who have progressed to Sézary syndrome while on BV.	• The CGP noted that patients would be eligible to receive BV upon progression on maintenance with low dose methotrexate or other systemic therapies following skin-directed therapy. • The CGP noted eligibility criteria in the ALCANZA trial include patients with MF that received at least one prior systemic therapy or patients with pcALCL that received prior radiation therapy or at least one prior systemic therapy. • The CGP noted that there is currently limited evidence to guide sequencing of BV with other systemic therapies. • The number of patients who went on to receive allogeneic stem cell transplant in the ALCANZA trial were very low. In the BV group, one patient (1.6%) received allogeneic stem cell transplant following study treatment.[6] The CGP noted it may be reasonable to offer allogeneic stem cell transplant following treatment with brentuximab treatment if a patient achieved a complete response. • The CGP noted that disease stages included in the ALCANZA trial for pcALCL and MF would be eligible for treatment with BV. See Table 10: Patient Demographics of the ITT Population in Section 6 of this report. The trial population in terms of stage of disease at presentation is reflective of patients in Canadian clinical practice. Therefore, the stage of disease does not limit the interpretation of the trial results in the Canadian context. • In the ALCANZA trial, treatment beyond disease progression was not permitted.[6] In addition, patients were offered BV as subsequent therapy through a companion study (SGN35-10)[18] or by other means outside of the clinical trial which could impact OS.[6] The CGP also noted that the registered clinician input stated that similar to other lymphomas, patients who are chemo-sensitive to BV could be re-treated with BV if their response duration was reasonable (i.e. 12 months). The CGP noted that if a patient completed 16 cycles of BV therapy, responded well to BV, and had a durable response for at least 6 months, re-treatment with BV may be considered if disease occurs after the 48-week treatment course. • The CGP noted that there is no evidence from the ALCANZA trial to combine BV with other systemic therapies for patients with pcALCL or MF unless there is evidence of transformation to large cell lymphoma. Additionally, there is no evidence from the ALCANZA trial to guide the addition of CHP to BV in patients who have progressed to Sézary syndrome while on BV.

PAG = Provincial Advisory Group, CGP = Clinical Guidance Panel

2 Background Clinical Information

2.1 Description of the Condition

Cutaneous T-cell lymphomas (CTCL) are classified as a heterogenous subgroup of non-Hodgkin lymphomas (NHL). Mycosis Fungoides (MF) and primary cutaneous CD30 positive anaplastic large cell lymphoma (ALCL) account for approximately 80-85% of all CTCLs.[13] MF is the most prevalent subtype of CTCL and contributes to roughly 50% of all primary cutaneous lymphomas.[19]

Generally, the diagnosis of CTCL includes skin biopsy and requires a combination of clinical, histopathology, and immunohistochemistry data. In patients with MF, the skin is the primary site of disease involvement and characterized by patches, plaques, and tumours.[13,19] Sézary syndrome (SS) is characterized as a related variant of MF. Clinical staging of MF is based on a tumor-node-metastasis-blood (TNMB) classification system developed by the Mycosis Fungoides Cooperative Group in 1979, which was revised in 2007 by the ISCL/EORTC. Early stage (IA to IIA) disease has limited lymph node involvement and no visceral involvement.[20,21] Advanced stage (IIB tumour stage, to IV) disease can involve the lymph nodes, blood, and visceral organs. Based on the United States Surveillance, Epidemiology and End Results (SEER) dataset of patients with CTCL, the age-adjusted incidence rate per 100 000 person-years was 0.55 for MF with a male to female incidence ratio of 1.57.[22] According to the World Health Organization European Organization for Research and Treatment of Cancer (EORTC) classification, the disease-specific 5-year survival was 88% for MF.[19] While CD30 positivity among patients with ALCL was defined as tumour cell expression of ≥ 75%, a diagnostic cut-off of ≥10% was used for patients with MF.[17,23] pcALCL is characterised by solitary or grouped large, ulcerating tumours.[24] pcALCL diagnosis is based on clinical and histologic criteria that require a complete skin examination, biopsy of suspicious skin sites, and an immunohistochemistry panel. An analysis from the United States SEER database revealed an incidence rate for pcALCL of 0.12 per 1,000,000 age adjusted according to the United States standard population. The male to female incidence ratio was 1.42.[25] According to the EORTC classification, the disease-specific 5-year survival was 95% for pcALCL.[19]

2.2 Accepted Clinical Practice

In Canada, there is no standard of care treatment for patients with CD30 expressing MF as variation exists across clinical practice and jurisdictions. According to the European Society of Medical Oncology, a spectrum of treatment options is recommended for MF and corresponding variants according to disease stage.[26] Treatment guidelines developed by the National Comprehensive Cancer Network (NCCN) guidelines, the European Society of Medical Oncology (ESMO), and EORTC are reflective of the limited randomized controlled trials conducted and treatment management is multidisciplinary involving hematologists and dermatologists.[27]

The main goals of treatment are two-fold: patients who exhibit good or partial response from any treatment following previous lines of treatment and who are healthy with adequate organ function may be eligible to receive allogeneic stem cell transplant. For patients who are not candidates for transplant, treatment is intended to increase survival, control local disease, reduce symptoms, and improve quality of life.[14] The duration of current treatments that patients may receive is approximately nine to 12 months before a reduced response is observed (>50%). Overall, an unmet need exists for effective treatment for these patients and treatment is desired in order to keep the disease under control to allow patients to achieve an optimal quality of life.[14]

Generally, patients with early stage MF tend to be prescribed skin-directed therapies such as topical steroids, nitrogen mustard, ultra-violet light (UVB or PUVA), local radiotherapy, total skin electron beam radiation (TSEB), and low-dose methotrexate (MTX). Patients with advanced MF (Stage III disease) are commonly treated with retinoids (bexarotene), interferon, TSEB, extracorporeal photopheresis (ECP), and low dose methotrexate. Patients with Stage IV MF are treated with systemic therapies including single-agent chemotherapy (e.g., gemcitabine and liposomal doxorubicin), multi-agent chemotherapy (e.g., CHOP or CEOP), alemtuzumab, and allogeneic stem cell transplant. At the time of relapse, patients are treated with therapies not previously administered. Moreover, patients with aggressive disease or extracutaneous involvement can be given isotretinoin or alitretinoin, interferon, bexarotene, alemtuzumab, or single-agent chemotherapy (e.g., gemcitabine, liposomal doxorubicin, etoposide). There are no curative treatment options for MF patients, with the exception of allogeneic stem cell transplant for patients who are healthy with adequate organ function. For patients who are not candidates for allogeneic stem cell transplant, the intent of treatment is to prolong survival, provide disease control, lengthen remission, reduce symptoms, and improve quality of life.

For patients with early stage pcALCL, initial treatment is generally with surgery and/or localized radiotherapy. There is no standard of care for those with advanced cutaneous CD30 positive ALCL for whom systemic therapy is preferred including MTX, bexarotene, interferon, romidepsin, pralatrexate, and single-agent chemotherapy (e.g., gemcitabine and liposomal doxorubicin). Multi-agent chemotherapy (such as CHOP or equivalent) is usually reserved for those with extensive disease who have failed single-agent therapy. Ultimately, the choice of treatment selected by a clinician may vary according to patient characteristics (e.g., age, presence of comorbidities, etc.), relative efficacy, and tolerability of the agents. Current treatment options provide limited, less durable response and poor outcomes. Approximately 20-35% of patients achieve an objective response for many monotherapies that last approximately four to six months. With the evolving landscape of systemic therapy, BV was developed as an intravenous therapy consisting of a CD30-directed antibody, which targets cancer cells expressing CD30.[13,14,28] Studies investigating BV have demonstrated positive outcomes in patient populations including patients with relapse and refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma.[29] Small phase II studies evaluating BV have demonstrated activity in patients with MF and in patients with CD30 positive pcALCL.[30,31]

3 Summary of Patient Advocacy Group Input

One joint input was provided by Lymphoma Canada (LC) and the Canadian Skin Patient Alliance (CSPA) for the review for brentuximab vedotin (BV) (Adcetris) for pcALCL or MF. LC and CSPA conducted an online, anonymous survey sent to respondents registered in the LC database via email and made available between March 30, 2020 and April 20, 2020. The link for the survey was also shared with respondents via CSPA's social media channels on Twitter, Facebook and Instagram. Additionally, the survey links were circulated by the Cutaneous Lymphoma Foundation. Surveys consisted of multiple choice, rating and open-ended questions. Open-ended responses to questions were included verbatim. In total, 86 patient respondents provided input through the survey; there were no caregiver respondents. Respondent characteristics are provided in Table 3.1. Most respondents were diagnosed with MF (96%). Of the respondents that indicated their country of residence (n=76), a greater proportion were from the United States (58%). Of respondents who indicated their age (n=75), most were between 60 and 79 years of age (57%) or between 40 and 59 years of age (32%).

Table 3.1: Survey Respondent Characteristics

Respondents by type of cutaneous lymphoma, n	MF	pcALCL	Other	Total
Patients without BV experience	75	4	2*	81
Patients with BV experience	4	1	0	5
**Other includes: 1 patient with cutaneous follicle center lymphoma and 1 with Sezary syndrome*				

Respondents by Country, n	CAN	USA	UK	Other	Skipped	Total
Patients without BV experience	20	45	3	3*	10	81
Patients with BV experience	0	5	0	0	0	5
**Other includes: 1 each of Australia, Israel and Puerto Rico*						

Respondents by age (range in years), n	<40	40-59	60-79	≥ 80	Skipped	Total
Patients without BV experience	6	22	40	2	11	81
Patients with BV experience	0	2	3	0	0	5

Many of the respondents indicated experiencing delays in obtaining a diagnosis for their condition. Over half of the respondents (54%) reported having waited more than one year to receive their diagnosis after first showing symptoms. Appearance of skin and itching skin were the most commonly reported symptoms to negatively impact quality of life. Many respondents also reported feelings of stress (77%), anxiety/worry (64%) and concerns about body image or physical appearance (52%) as significant concerns related to their disease symptoms. Respondents also indicated feelings of isolation from feeling the need to conceal their condition and its related symptoms. Topical steroids were the most commonly reported previous treatment used by respondents (82%) to control their disease. Respondents also commonly reported receiving more than one type of therapy to control their disease, reporting a median of three therapies used concurrently to treat their condition. The most commonly reported side effects patients experienced from current therapies were skin itching, irritation or rash (61%). The number of clinic visits and treatment related fatigue were aspects of daily living respondents felt were significantly impacted due to current treatment. Almost one-third of patients (31%) reported difficulty in accessing treatment, mainly due to treatments being unavailable in their local cancer centre or due to living in a community without a local cancer centre.

Five of the respondents indicated having experience with BV; of these five patients, four were diagnosed with MF and one was diagnosed with pcALCL. These five patients reported receiving a median of 8 treatments prior to receiving BV. All five patients

reported that treatment with BV was able to manage skin lesions related to cutaneous lymphoma. Peripheral neuropathy, fatigue, headache, and infusion reactions were the most commonly reported side effects due to BV. One of the patients had to discontinue treatment with BV due to a severe infusion reaction. The four patients who did not discontinue treatment reported that BV had improved their health and well-being, and that they had an overall positive experience. Among all five patients with experience with BV, all reported that they would take this treatment again if they were recommended it as their best option by their doctor.

Overall, patients reported that having additional treatment options was highly valued. Especially among patients with advanced disease and prior experience with systemic therapies, having additional treatment options was considered to be extremely important. In addition, longer survival, better quality of life, longer remission and fewer side effects were important considerations for new treatment options for cutaneous lymphoma. LC and CSPA highlighted an unmet need for patients as cutaneous lymphoma is *"a long-term, chronic disease that can come and go over the course of time."*

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

Among those who responded to the online survey, most indicated being diagnosed more than two years ago (n=49/81, 60%). Table 3.2 summarizes the time since the respondent's diagnosis. Table 3.3 summarizes the time to receiving diagnosis after showing symptoms. Overall, many of the respondents indicated that receiving a diagnosis of cutaneous lymphoma after more than a year of first showing symptoms and visiting their clinician. LC and CSPA provided quotes from respondents that highlight the difficulty in receiving a diagnosis. One respondent commented that they had seen their *"family doctor several times for a skin rash over two years."* After two referrals for a dermatologist with no diagnosis, this respondent stated that they *had "begged for a biopsy at [their] last dermatologist appointment."* Another respondent stated, *"It took 19 years of biopsies before I was finally diagnosed."* Another respondent described *"being treated for eczema and fungal rash"* for five years before they *"finally asked to see a dermatologist. This was when my dermatologist right away believed it was MF and did two biopsies that confirmed her suspicions."*

Table 3.2: Time Since Respondent's Cutaneous Lymphoma Diagnosis

Time since diagnosis	Respondents (n = 81)
Less than 6 months	7 (9%)
Between 6 months to 1 year	14 (17%)
Between 1 to 2 years	11 (14%)
Between 2 to 5 years	19 (23%)
More than 5 years	30 (37%)

Table 3.3: Time to Receiving Diagnosis After Showing Symptoms

Time from first doctor visit to receiving a diagnosis	Respondents (n = 81)
Less than 3 months	26 (32%)
3 to 6 months	6 (7%)
6 to 12 months	5 (6%)

Time from first doctor visit to receiving a diagnosis	Respondents (n = 81)
More than 1 year	44 (54%)

Appearance of skin patches or lesions (n=64/81, 79%) and itching skin (n=50/81, 62%) were the most commonly reported symptoms to affect respondent's quality of life at diagnosis. Other symptoms are reported in Table 3.4, and almost all refer to the negative impact on respondents due to the visual nature of symptoms of cutaneous lymphoma, and difficulty in dealing with the symptoms. Two respondents provided the following comments regarding their symptoms:

- *"Had a large area on back of calf which was very red, scaly. Anything applied to it would feel like burning. Very itchy at other times."*
- *"I am not entirely covered but both arms, legs, hands and feet are covered with plaques, no longer sweat [and am] easily fatigued."*

Table 3.4: Symptoms Affecting Respondent's Quality of Life at Diagnosis

Symptoms that affected quality of life at diagnosis	# of Respondents (n = 81)
Visual appearance of skin patches or lesions (raised, scaly or discolored patches)	64 (79%)
Itching of skin	50 (62%)
Visual appearance of a rash-like skin redness over the entire body	15 (19%)
Thickening of skin on palms of hands and soles of feet	13 (16%)
Pain or burning of skin changes or lesions	11 (14%)
Hair loss	10 (12%)
Enlarged lymph nodes	5 (6%)
No symptoms that impacted quality of life	4 (5%)

Stress related to their diagnosis (n=62/81, 77%), anxiety/worry (n=52/81, 64%), and concerns about body image and their physical appearance (n=42/81, 52%) were the most commonly reported psychosocial symptoms related to respondents' condition at diagnosis (Table 3.5). Many of the concerns and symptoms respondents' felt at diagnosis continued to be ongoing issues they experienced with their condition. LC and CSPA highlighted concerns related to anxiety/worry and respondents' body image and physical appearance. The following respondent quotes indicate feelings of isolation and embarrassment due to symptoms related to their condition:

- *"It makes some things uncomfortable which makes it less likely I will participate in certain activities. It makes me self-conscious when being intimate. It also adds an extra layer of time when trying to get ready to go somewhere as I have to put on medication, let that dry and find something to wear that doesn't irritate my skin. I have definitely pulled back from social obligations because of this condition and there is intense stress whenever I have an upcoming appointment that I might find out the disease has progressed."*
- *"… it does affect my personal image as I deal with others who see the lesions and are afraid to get too close to me. I sometimes feel as if I have leprosy."*
- *"To avoid it being known at work I hide any and all references. I cannot actively participate in open forums on the subject and [am] constantly on my guard. Pretty isolating and feeling of being alone."*

Table 3.5: Psychosocial Impact of Cutaneous Lymphoma on Respondents At Diagnosis and Ongoing

Psychosocial impact	At diagnosis (n= 81)	Ongoing (n = 81)
Stress of diagnosis	62 (77%)	25 (31%)
Anxiety/worry	52 (64%)	36 (44%)
Concerns about body image/physical appearance	42 (52%)	33 (41%)
Depression	25 (31%)	12 (15%)
Difficulty sleeping	24 (30%)	24 (30%)
Problems concentrating	17 (21%)	15 (19%)
Loss of self-esteem	17 (21%)	14 (17%)
Isolation	10 (12%)	8 (10%)
Loss of sexual desire	8 (10%)	7 (9%)

3.1.2 Patients' Experiences with Current Therapy

Seventy-seven respondents reported information about their line of treatment for cutaneous lymphoma. Of these respondents, 34% (n=26) indicated they were currently receiving first-line treatment, 29% (n=22) reported they were in remission following one or more lines of treatment, and 27% (n=21) reported they were receiving treatment following one or more relapses. A few respondents also indicated they were receiving continuous "maintenance" therapy (n=3, 4%) or that the had not received any treatment for their cutaneous lymphoma (n=5, 7%). Table 3.6 reports the different treatments respondents reported having experience with for treatment of cutaneous lymphoma. Topical steroids were the most commonly reported treatment, followed by UVB light therapy, topical retinoids, topical mechlorethamine, local radiation therapy, and others.

Most patients (n=64/77, 83%) reported using more than one type of therapy to control their cutaneous lymphoma, such as topical therapy, phototherapy, radiotherapy, and systemic therapy. Over one-third of patients (n=36/77, 36%) reported using three or more types of therapy. Twenty-four respondents (31%) reported having experience with systemic therapy (including oral and intravenous therapies); of these, 79% (n=19) reported having used the other three types of therapies to treat their symptoms. Radiotherapy was reported by 29% (n=22) of patients. Overall, patients reported a median of three therapies used to manage their cutaneous lymphoma (range: 0-8). LC and CSPA highlighted the relapsing and remitting nature of the condition as well as the need for multiple treatments to keep patients' disease symptoms under control.

Table 3.6: Treatments for Cutaneous Lymphoma Received by Respondents

Treatment	# of Respondents (n = 77)	Treatment	# of Respondents (n = 77)
Topical steroids	63 (82%)	Interferon	8 (10%)
UVB light therapy	41 (53%)	Methotrexate	8 (10%)
Topical retinoids	21 (27%)	Imiquimod	6 (8%)
Topical mechlorethamine	18 (24%)	Total skin electron beam therapy	4 (5%)
Local radiation therapy	17 (22%)	Extracorporeal photopheresis	2 (3%)
Bexarotene (oral)	12 (16%)	Vorinostat	2 (3%)
UVA light therapy	10 (13%)	Carmustine (BiCNU)	1 (1%)
PUVA light therapy	9 (12%)	Resiquimod	1 (1%)

Table 3.7 summarizes side effects of current therapies reported by respondents. The most commonly reported side effects were skin itching, irritation or rash (61%) followed by fatigue (39%), skin discoloration (27%) and skin pain or burning (26%). Among patients treated with systemic therapies, hair loss (n=9/11, 82%), "chemo-brain" (n=6/7, 80%), infections (n=6/6, 100%), neutropenia (n=5/6, 83%), peripheral neuropathy (n=4/5, 80%), anemia (n=3/4, 75%), thrombocytopenia (n=2/2, 200%), and depression (n=2/2, 100%) were the most commonly reported side effects.

Table 3.7: Side Effects of Treatments for Cutaneous Lymphoma

Treatment side effect	# of Respondents (n = 77)	Treatment side effect	# of Respondents (n = 77)
Skin itching, irritation or rash	47 (61%)	Peripheral neuropathy	5 (6%)
Fatigue	29 (39%)	Anemia	4 (5%)
Skin discoloration	21 (27%)	Breathing difficulties	3 (4%)
Skin pain or burning	20 (26%)	Viral reactivation (e.g. shingles)	3 (4%)
Hair loss	11 (14%)	Diarrhea	2 (3%)
Nausea	9 (12%)	Thrombocytopenia	2 (3%)
"Chemo-brain" (memory problems or confusion)	7 (9%)	Mouth sores	2 (3%)
Neutropenia	6 (8%)	Irregular heartbeat	2 (3%)
Infections	6 (8%)	Decreased thyroid function	2 (3%)
Constipation	5 (6%)	Depression	2 (3%)
Cough	5 (6%)	Other	2 (3%)

Respondents were asked to rate on a scale from 1 (no impact) to 5 (very significant impact) the impact of different aspects of treatment on their daily life; Table 3.8 summarizes the average rating, and proportion of patient's who considered different aspects of treatment to significantly impact daily living. The number of clinic visits and treatment-related fatigue were reported as having a very significant impact on daily life for 28% and 25% of patients, respectively. Of note, impacts of treatment on patient's daily living were rated between 1.8-2.6 by a majority of the respondents.

Table 3.8: Impacts of Treatment on Patient's Daily Living

Aspect of treatment	Rating = 4 or 5 (Significant impact)	Average Rating	# of Respondents
Number of clinic visits	21 (28%)	2.6	76
Treatment-related fatigue	18 (25%)	2.5	72
Number or frequency of infections	9 (13%)	2.0	68
Other side effects of treatment	7 (10%)	1.8	73
*Number of patients responding to this question is unknown			

LC and CSPA asked respondents about difficulties they had with treatments for their disease. Thirty-one percent of patients (n=24/77) reported being unable to access one or more of their treatments in their own community; the most commonly reported reasons for this difficulty were that treatment was not available at their local cancer centre (n=10/22, 45%) or because they lived in a community without a cancer centre (n=10/22, 45%). The following quotes provided by patients describe the physical and emotional toll of treatments on patients:

- *"While on Methotrexate getting infections and not being able to take pain killers while on it was the most difficult to tolerate."*
- *"Going to UVB can only occur during normal business hours. Trying to keep this a secret at work requires making up the time and 'disappearing' when not noticed. Very had and really hampers going on treatment."*
- *"Most physical side effects were manageable over time but the constant requirement for needing to be in treatment of some kind or other over the course of time (30 years) takes a toll both physically, emotionally and financially."*
- *"Depression, which needed to be treated with medication and stopping interferon."*

3.1.3 Impact on Caregivers

No input from caregivers was provided.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Patients were asked to rate how important they thought it was to have a choice of treatment for cutaneous lymphoma on a scale from 1 (not important as long as there is at least one treatment choice) to 5 (extremely important to have choice of treatment). Among all patients, most (n=57/72, 79%) rated having a choice of treatment as extremely important; treatment choice was considered extremely important especially among patients who had advanced disease and had experience with systemic therapies (n=21/22, 95%).

Respondents were also asked whether they would be willing to take a treatment with known, and potentially serious, side effects if it was recommended by their physician as their best option. Forty percent of respondents (n=29/72) indicated "yes" to this question and 11% (n=8/72) indicated "no"; the remaining patients responded with "I'm not sure." Among patients with advanced disease and who had been treated with previous systemic therapies, 50% (n=11/22) responded to this question with "yes" versus 5% (n=1/22) who reported "no"; the remaining patients responded with "I'm not sure." LC and CSPA highlighted that patients with more advanced disease and who already received previous systemic therapies may feel a heightened sense of burden related to treatments and the lack of alternative treatment options.

When asked to rate the importance of different treatment outcomes on a scale of 1 (not important) to 5 (extremely important), all suggested treatment outcomes were indicated as being very important, including longer survival, better quality of life, longer remission and fewer side effects (Table 3.9). The following patient quotes were provided that reiterate the need for better treatments:

- *"it's a long-term, chronic disease that can come and go over the course of time. There are many impacts on my life depending upon how the disease is behaving I hope some day to live my life free of my disease."*
- *"This is a nasty disease and we hope for better treatments soon! I would not wish this on my worst enemy!"*
- *"I belong to our local CLF chapter and we've lost two of our members to MF over the past few years. While most of us are doing okay, people do die from this disease."*

Table 3.9: New Drug Expectations

Treatment Outcome	Rating Average (N = 72)
Longer survival	4.5
Better quality of life	4.4
Longer remission	4.2
Fewer side effects	3.9

3.2.2 Patient Experiences to Date

A total of five patients reported having experience with BV, all of whom were males living in the US between 50 and 79 years of age. Four of the five men were diagnosed with MF, and one patient was diagnosed with pcALCL (Table 3.10). At the time of being surveyed, three of these patients were still receiving BV, one patient had already completed their treatment and one patient had to stop treatment due to severe infusion reaction.

Table 3.10: Characteristics of Patients with Experience with Brentuximab vedotin

Gender	Age	Location	Diagnosis	BV start date	Access to drug
Male	50-59	USA	MF	> 2 years ago	Public drug program

Gender	Age	Location	Diagnosis	BV start date	Access to drug
Male	50-59	USA	MF	< 6 months ago	Private insurance
Male	70-79	USA	MF	1 -2 years ago	Public drug program
Male	60-69	USA	pcALCL	< 6 months ago	Private insurance
Male	60-69	USA	MF	6 months – 1 year ago	Public drug program

Patients reported receiving a median of 8 previous treatments (range: 5-11) before receiving BV, with four out of five men receiving three or more types of therapy (i.e., topical, phototherapy, radiotherapy or systemic). Receiving at least one prior systemic therapy was reported by four of five patients, with three of five patients reporting having received at least two prior to receiving BV.

LC and CSPA noted that not all five men with BV experience had experienced disease symptoms prior to receiving treatment. Table 3.11 summarizes the disease symptoms patients reported were managed by BV. All patients reported that skin lesions were managed with BV treatment.

Table 3.11: Symptoms of Cutaneous Lymphoma Managed with brentuximab vedotin

Disease symptom	# of respondents (N = 5)*
Skin lesions	5 (100%)
Skin pain	1 (20%)
Enlarged lymph nodes	1 (20%)
I was not experiencing symptoms	1 (20%)
*four of the patients were diagnosed with MF and one patient was diagnosed with pcALCL	

The most commonly reported side effects of BV are summarized in Table 3.12. Peripheral neuropathy, fatigue, headache, and infusion reactions were the most commonly reported side effects of BV. Due to a severe infusion reaction, one of the patients had to discontinue treatment with BV; this patient also reported that BV did not resolve their symptoms of fatigue and enlarged lymph nodes.

Table 3.12: Side Effects of Brentuximab vedotin

Treatment side effect	# of Respondents (n = 5)	Treatment side effect	# of Respondents (n = 5)
Peripheral neuropathy	3 (60%)	Neutropenia	1 (20%)
Fatigue	3 (60%)	Diarrhea	1 (20%)
Headache	3 (60%)	Lung problems	1 (20%)
Infusion reaction	3 (60%)	Itching	1 (20%)
Anemia	2 (40%)	Constipation	1 (20%)
Nausea/vomiting	2 (40%)	Shortness of breath	1 (20%)
Fever	2 (40%)	Muscle or joint pain	1 (20%)
Infections	2 (40%)	Other	1 (20%)

Patients were asked to rate how treatment with BV changed aspects of their daily living on a scale from 1 (much worse off) to 5 (greatly improved) (Table 3.13). According to LC and CSPA, most respondents indicated that their ability to participate in daily activities was unchanged or had improved.

Table 3.13: Aspects of Daily Living Changed due to Treatment with Brentuximab vedotin

Aspect of daily living	Worse off (score = 1-2)	Unchanged (score = 3)	Improved (score = 4-5)	N/A	Weighted Average
Ability to work	1 (20%)	2 (40%)	0	2	2.7
Ability to fulfill family obligations	1 (20%)	2 (40%)	1 (20%)	1 (20%)	3.3
Ability to perform household chores	1 (20%)	2 (40%)	1 (20%)	1 (20%)	3.0
Ability to exercise	1 (20%)	2 (40%)	1 (20%)	1 (20%)	3.0
Ability to volunteer	1 (20%)	2 (40%)	0	2 (40%)	2.3

Four of the five patients indicated that treatment with BV improved their health and well-being; these four patients reported having a positive experience with BV. The remaining patient indicated that their health remained unchanged; this was the patient who discontinued treatment due to a severe infusion reaction. Only the one patient reported having a poor experience with BV. Regardless of treatment experience, all five patients stated that they would take BV again if their doctor recommended it to them as their best option.

3.3 Companion Diagnostic Testing

LC and CSPA indicated that CD30 testing is routinely performed in CTCL diagnostic workup.

3.4 Additional Information

None provided.

4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary:

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Use relative to other second line systemic options and stem cell transplant
- Use in various disease stages

Economic factors:

- Potential for drug wastage
- Additional nursing and clinic resources will be required

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that there is no current standard therapy and no curative treatment (with the exception of allogeneic stem cell transplant) for pcALCL or MF. Generally, patients with early stage disease tend to be prescribed skin-directed therapies such as surgery or local radiotherapy followed by maintenance with low-dose methotrexate. Patients with more advanced disease are commonly treated with systemic therapies such as CHOP or CEOP. Relapsed patients or patients with aggressive disease or extracutaneous involvement can be given isotretinoin or alitretinoin, interferon, bexarotene, alemtuzumab, or single agent chemotherapy (gemcitabine, liposomal doxorubicin, etoposide); funding of these agents varies across provinces. Patients may require several types of treatment and repeated courses of therapy to obtain disease control.

The ALCANZA trial compared brentuximab vedotin (BV) to physician's choice of methotrexate or bexarotene. PAG is seeking comparison between brentuximab vedotin and retinoids, interferon, gemcitabine, liposomal doxorubicin, and etoposide.

4.2 Eligible Patient Population

The funding request if for the treatment of adult patients with primary cutaneous Anaplastic Large Cell Lymphoma (pcALCL) or CD30-Expressing Mycosis Fungoides (MF) who have received prior systemic therapy. In view of the characteristics of the patient population in the ALCANZA trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with BV:

- Patients with an ECOG performance score greater than 2
- Patients with Sézary Syndrome showing CD30 positivity or other subtypes of CD30+ cutaneous T-cell lymphoma
- Previously untreated patients
- Patients with CNS involvement and PML symptoms
- Patients with cardiac symptoms
- Patients with T-cell lymphoma transformed from MF who otherwise meet eligibility criteria
- Patients who are not progressing but cannot tolerate a first line systemic therapy
- Patients who progressed on both previous methotrexate and bexarotene, but who would be eligible for other systemic therapies.

If recommended for reimbursement, PAG noted that patients who have already initiated second line systemic therapy would need to be addressed on a time-limited basis. PAG seeks guidance on whether to switch these patients to BV or rather wait for disease progression. In addition, PAG noted a potential for indication creep with BV for patients with CD30+ Sézary Syndrome and for first-line treatment of pcALCL and MF. There is also potential for use in earlier stages of MF.

4.3 Implementation Factors

The recommended dose of BV is 1.8 mg/kg every 3 weeks. BV is given until disease progression, unacceptable toxicity, or a maximum of 16 cycles (48 weeks). PAG is seeking a clear definition of disease progression for the development of discontinuation criteria.

PAG noted that drug wastage is a significant barrier as only 50 mg vials are available and patients may require up to four vials (180 mg = 1.8 mg/kg IV for a 100 kg patient) per treatment cycle. Furthermore, the drug has 24 hours of stability after reconstitution and vial sharing may be difficult with a very small number of eligible patients. PAG identified that the 30-minute infusion is an enabler to implementation.

Additional resources (e.g., nursing and clinic visits) are required to monitor and treat infusion-related reactions and adverse events (e.g. diarrhea, neutropenia/febrile neutropenia, and peripheral neuropathy) as well as monitor complete blood count. The cost of supportive therapy (e.g. G-CSF) also needs to be considered in implementation as it will likely be required as primary prophylaxis.

BV is already used for other indications and health care professionals are familiar with its preparation, administration and monitoring for adverse events. Being an intravenous drug, BV would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of infusion related reactions. Intravenous chemotherapy drugs would be funded fully in all jurisdictions for eligible patients which is an enabler. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier to for these patients.

4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm the eligible patient population and line of therapy with BV, and the possible sequencing of treatments, including the scenarios below:

- Eligibility to BV upon progression on maintenance with low dose methotrexate or other systemic therapies following skin-directed therapy.
- Priority relative to all second line and beyond systemic therapies including single- and multi-agent chemotherapy, retinoids, and interferon therapy.
- Optimal sequencing with other systemic therapies and number of therapies that should be tried before a patient becomes eligible to BV.
- Sequencing with allogeneic stem cell transplant.
- Options after progression with BV.
- Evidence of benefit from giving BV in combination with other systemic therapies.
- Optimal stage of disease for treatment with BV
- Timing and appropriateness of re-treatment with BV if disease recurs after the 48-week treatment course.
- Addition of CHP to BV in MF patients who have progressed to Sézary syndrome while on BV.

4.5 Companion Diagnostic Testing

CD30 testing is routinely done in pathology labs across Canada and would not represent an additional burden.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

One registered clinician input was provided on behalf of one individual oncologist from Ontario. Various treatments were stated to be currently available to patients through public funding. Alemtuzumab was stated as currently available to patients through compassionate access. While many treatment choices currently exist for patients, there is no treatment considered to be standard of care; therefore, no direct comparator was identified. Eligibility criteria from the pivotal trial were stated to be applicable to clinical practice.

The clinician expected that brentuximab vedotin would most likely be used very frequently in clinical practice due to the lack of gold standard treatments. After failure of an initial therapy, brentuximab vedotin was suggested as a possible treatment in the second line. When asked how brentuximab vedotin would be sequenced relative to allogenic stem cell transplant, the clinician acknowledged that this indication would be rare, therefore, not many patients are expected to receive a sequence of treatments with brentuximab vedotin and allogenic stem cell transplant. Re-treatment with brentuximab vedotin was considered reasonable so long as patient's response to brentuximab vedotin initially was durable (i.e., 12 months).

As patients are often first reviewed by expert hematopathologists or dermatopathologists, no companion diagnostic testing was stated to be needed. Morphological and clinical assessments were stated to be used as tools to monitor response to therapy.

Please see below for details from the clinician input.

5.1 Current Treatment(s)

The clinician indicated that various treatments are currently funded or are available through compassionate access, such as alemtuzumab. Many treatment choices currently exist without an overall direct comparator due to the lack of an available gold standard treatment.

5.2 Eligible Patient Population

The trial eligibility criteria were stated to be applicable to clinical practice.

5.3 Relevance to Clinical Practice

The clinician providing input indicated that they did not have direct experience treating these subtypes of patients.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The clinician stated that brentuximab vedotin would most likely be frequently used as there is currently no gold standard of treatment.

5.4.1 Would brentuximab vedotin be used in patients who progress while on drug maintenance following skin-directed therapy?

The clinician suggested that patients who progress while on drug maintenance may be able to receive brentuximab vedotin following skin-directed therapy.

5.4.2 What circumstances would drive the choice and sequence of all therapies (including brentuximab vedotin) following failure of an initial systemic therapy?

Following failure of an initial systemic therapy, the clinician suggested that brentuximab vedotin would be used as therapy in the second line.

5.4.3 How should brentuximab vedotin be sequenced relative to allogenic stem cell transplant?

The clinician stated that sequencing of brentuximab vedotin relative to allogenic stem cell transplant would be rare.

5.4.4 Is there evidence of benefit from giving brentuximab vedotin in combination with other systemic therapies, including adding chemotherapy to brentuximab vedotin upon progression on the latter?

The clinician was unaware of other combination therapies with brentuximab vedotin.

5.4. Is there evidence to inform the decision and timing of re-treatment with brentuximab vedotin upon recurrence while off therapy?

Similar to other lymphomas, the clinician indicated that patients who are chemo-sensitive to brentuximab vedotin could be re-treated with brentuximab vedotin if their response duration was reasonable (i.e., 12 months).

5.5 Companion Diagnostic Testing

Companion diagnostic testing is not required. These patient cases are often reviewed by expert hematopathologists or dermatopathologists.

5.6 Implementation Questions

5.6.1 How is response to therapy monitored in practice?

The clinician highlighted that these patients are not commonly seen in hematology practices. However, response to therapy may be monitored mostly via morphological and clinical assessments

5.7 Additional Information

None.

6 Systematic Review

6.1 Objectives

To evaluate the safety and efficacy of brentuximab vedotin for the treatment of adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received at least one prior systemic therapy.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 4: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs, conference abstracts, posters	Adult patients with pcALCL multi-focal/extracutaneous or CD30-expressing MF who have received at least one prior systemic therapy Subgroups of Interest: • Age • ECOG PS • Sex • Patients with lymph node disease and patients without lymph node disease	Brentuximab vedotin	– Methotrexate – Bexarotene – CHOP – CEOP – Interferon-alpha – Retinoids – Gemcitabine – Liposomal doxorubicin – Etoposide – Total electron beam therapy – Allogeneic stem cell transplant	– **PFS** – **OS** – ORR – CR – **DOR** – **Safety** – Patient reported outcomes – **Quality of Life** – Change in symptoms – Proportion of patients receiving allogeneic stem cell transplant

Abbreviations: RCT=randomized controlled trial, pcALCL=Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL) , MF=Mycosis Fungoides, ECOG PS=Eastern Cooperative Oncology Group performance status, PFS=progression free survival, OS=overall survival, ORR=objective response rate, DOR=duration of response, CR=complete response, CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone, CEOP=cyclophosphamide, etoposide, vincristine, prednisone

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

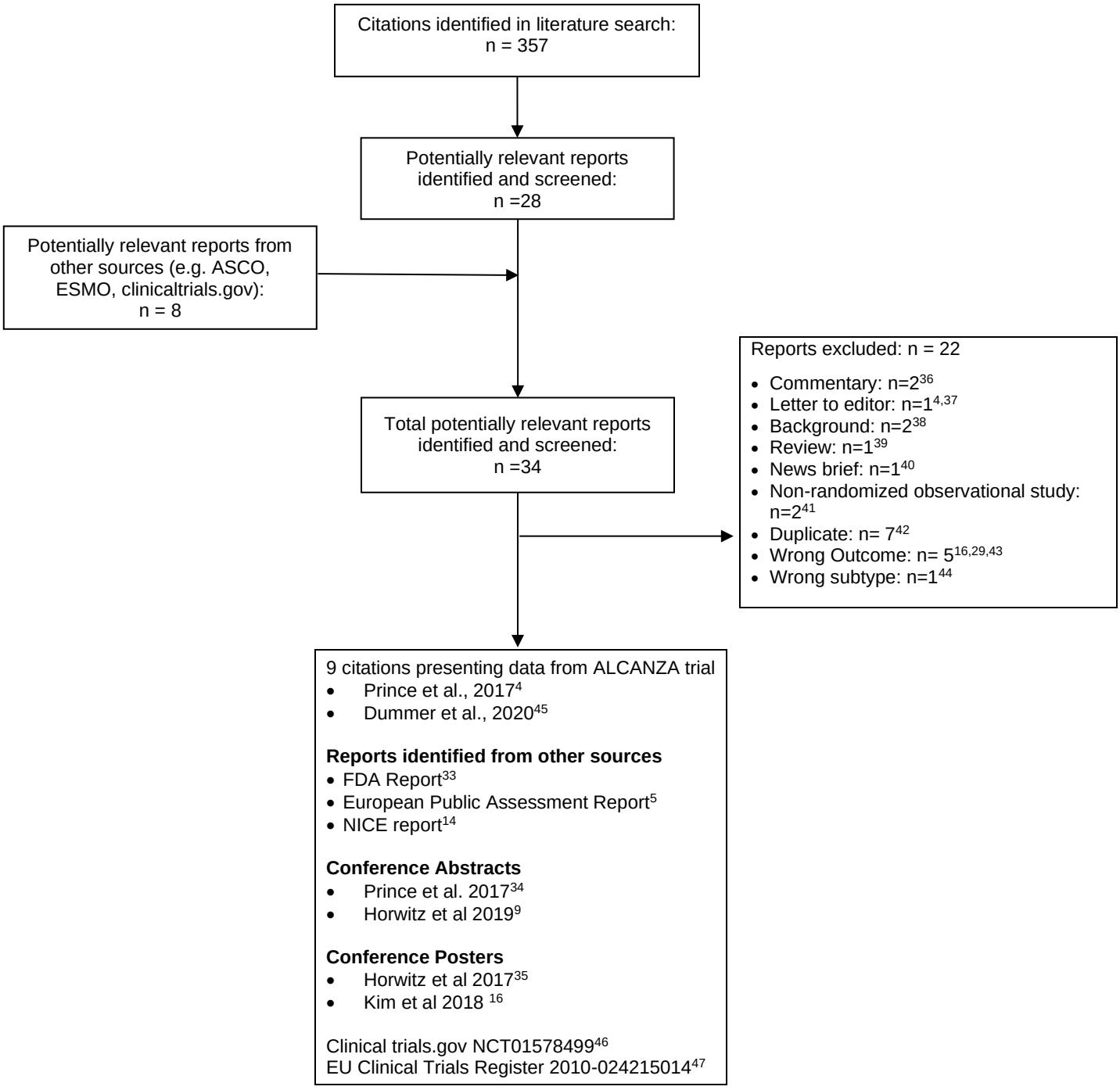
**There is currently no standard of care treatment. Treatment options vary across clinical practice and jurisdictions in Canada*

6.3 Results

6.3.1 Literature Search Results

Of the potentially relevant 26 reports identified, 11 citations[4,5,9,14,16,32-35] were included in the pCODR systematic review and 22 studies were excluded. Reasons for exclusion are outlined in Figure 1.

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to studies clinical summary,[48] Clinical Study Report,[3] and Checkpoint Meeting Materials[6,8,15,49] were also obtained through requests to the Sponsor by CADTH

6.3.2 Summary of Included Studies

One fully published clinical trial ALCANZA[4] was included in this systematic review, in addition to conference abstracts[9,34] and conference posters.[16,35] The key characteristics of this trial are summarized in Table 6.

6.3.2.1 Detailed Trial Characteristics

Table 5: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator[5]	Trial Outcomes[5]

NCT01578499
 	
Phase III, international, randomized, open-label, multicentre, active-controlled trial.
 	
Of the 237 patients screened,[5] 131 patients were randomized to receive treatment. Randomization was conducted in a 1:1 ratio in which 66 patients were randomized to received BV and 65 patients were randomized to PC (38 patients received bexarotene and 27 patients received methotrexate).[4]
 	
52 academic centres and 13 countries.[4] There were no patients from Canada.
 	
Patients were enrolled between August 13, 2012 and July 31, 2015.[4]
 	
Primary analysis data cut-off: May 31, 2016.[4,5,33]
 	
The sponsor confirmed the updated analysis data cut-off: August 16, 2017.[15,35]
 	
Pre-specified final analysis data cut-off: September 28, 2018.[9,35]
 	
Study Completion Date: July 6, 2018[46]
 	
The trial was funded by Millennium Pharmaceuticals, Inc. and Seattle Genetics, Inc.[4]
	Key Inclusion Criteria:[5]
	• Adults aged 18 years and older diagnosed with MF (received at least 1 prior systemic therapy) or pcALCL (received at least 1 systemic therapy or radiation therapy)
	• ECOG PS ≤2
	• Confirmation of CD30 disease histologically via central review
	  ○ For MF patients, two or more skin biopsies were required from separate lesions
	  ○ For pcALCL patients, one or more skin biopsies were required
	• Radiographically/clinically measurable disease[5] via mSWAT conducted by the investigator, CT scan by radiology, and blood assessment by central lab[6]
	• Sufficient liver and renal function
	• 3 week washout period from previous treatment and 12 week washout for antibody-directed or immunoglobulin-based immune therapy (unless not in best interest of patient— in the opinion of the investigator)[5]
		Intervention:
		BV was administered intravenously 1.8 mg/kg once every 3 weeks, for up to 16 3-week cycles.[4,5]
		
		Comparator:
		PC Conventional Therapy:
		Methotrexate was administered orally (5–50 mg) once per week, for a maximum duration of up to 48 weeks.[5]
		or
		Bexarotene was administered orally (300 mg/m²) once per day, for a maximum duration of up to 48 weeks.[5]
			Primary Endpoint:
			• Objective Response Rate that lasted at least 4 months (ORR4)
			Key Secondary Endpoints:
			• Complete Response
			• Progression Free Survival
			• Symptom burden
			Other Secondary Endpoints:
			• Duration of response
			• Duration of skin response
			• Event-free survival
			• Quality of life assessment according to Skindex-29 and Functional Assessment of Cancer Therapy (FACT-G)
			• Blood concentration of BV (serum) and MMAE (plasma)
			• Immunogenicity assessment

Trial Design	Inclusion Criteria	Intervention and Comparator[5]	Trial Outcomes[5]
	• Recovery from reversible effects of prior anti-cancer therapies (e.g. ≤ grade 1 toxicity) **Key Exclusion Criteria:**[4,5] • Coexisting diagnosis of the following diseases: Sézary syndrome, B_2 disease, systemic ALCL, or other non-Hodgkin lymphoma (note: concurrent lymphomatoid papulosis was permitted) • Cardiovascular conditions or values (e.g., myocardial infarction or New York Heart Association Class III or IV heart failure) within 6 months before first dose of study drug, or any evidence of currently uncontrolled cardiovascular conditions including cardiac arrythmias, congestive heart failure, angina, or electrocardiographic evidence of acute ischemia or clinically significant conduction system abnormalities • Patients that experienced progression while receiving prior treatment with both bexarotene and methotrexate • Presence of another primary malignancy not in remission for at least 3 years, except completely resected in situ carcinoma (e.g., non-melanoma skin cancer, cervical carcinoma in situ on biopsy, or a squamous intraepithelial lesion on Pap smear)		**Exploratory Endpoints:**[5] • CD30 expression in biopsied tumors • Serum concentrations of PD markers (e.g. sCD30) • Presence or absence of gene or protein variation associated with CTCL or BV mechanism of action • Utilization of health resources • Quality of life per EQ-5D • OS

Trial Design	Inclusion Criteria	Intervention and Comparator[5]	Trial Outcomes[5]
	• 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[5] • 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) • Previous receipt of BV • Receipt of systemic therapy with vitamin A in doses >15,000 IU (5,000 mcg)/day within 3 weeks before the first dose of study drug		

Abbreviations: MF=Mycosis Fungoides, pcALCL=primary cutaneious anaplastic lymphoma cutaneous lymphoma, ECOG PS=Eastern Cooperative Oncology Group performance score, mSWAT=Modified Severity Weighted Assessment Tool, IU=international unit, OS=overall survival, EQ-5D=European Quality of Life 5-Dimension, PD=progressive disease, MMAE=monomethyl auristatin E=, FACT-G=Functional Assessment of Cancer Therapy-General, BV=brentuximab vedotin, PC=physician's choice, ULN=upper limit of the normal range, sCD30=soluble CD30

a) Trials

ALCANZA (C25001) is an open-label, multicentre, phase III randomized controlled trial comparing the efficacy and safety brentuximab vedotin (BV) compared to physician's choice (PC), either methotrexate or bexarotene, among patients with CD30+ CTCL. The trial was sponsored by Millennium Pharmaceuticals, Inc. in collaboration with Seattle Genetics, Inc.[46] The protocol was approved by the ethics committee or review board. The trial enrolled patients from 52 academic centers across 13 countries.[4] There were 68 patients (52%) from the European Union, 33 patients (25%) in the United States, 20 patients (15%) from Australia, six patients (5%) from Switzerland, and four patients (3%) from Brazil. There were no patients enrolled from Canada.[5]

Trial Design

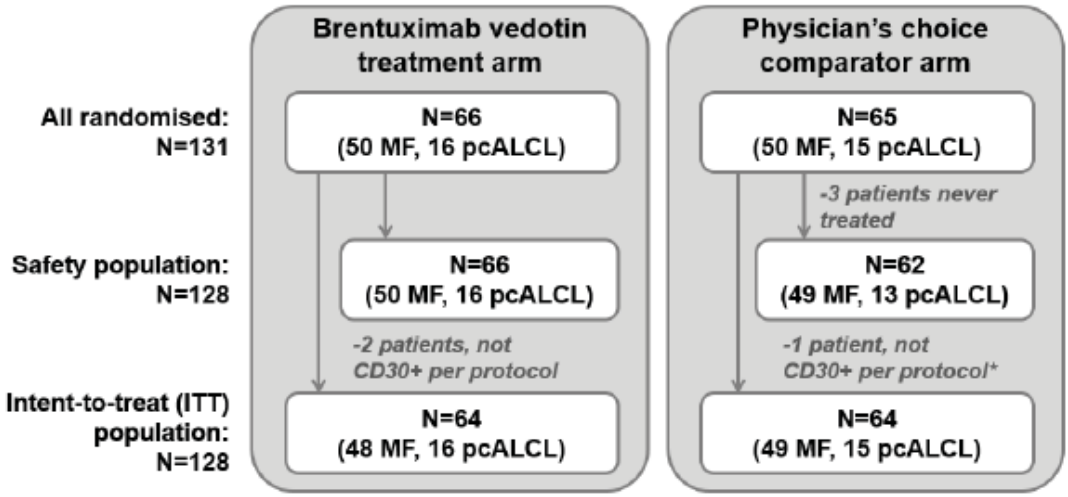
Screening, Eligibility Criteria, and Randomization

The study design is depicted in Figure 1 and key eligibility criteria are outlined in Table 6. In brief, eligible patients included the following: adults aged 18 years or older with an ECOG PS ≤ 2, and histologically confirmed CD30+ MF who received at least one prior systemic therapy or with CD30+ pcALCL who received at least one previous systemic therapy or radiation therapy. Patients

were considered to be CD30 positive if one or more biopsy samples were found to have 10% or more CD30+ malignant cells or lymphoid infiltrate, as assessed by central laboratory review. Two or more skin biopsy samples were taken from separate lesions for patients with MF, and one or more samples were taken from patients with pcALCL. Patients who had previously progressed on methotrexate and bexarotene were not eligible for enrolment.[4]

Patients were randomized (1:1) to receive either brentuximab vedotin or physician's choice of methotrexate or bexarotene using an interactive voice and web response system. A Takeda statistician generated the randomization list, after which they were no longer involved in the trial.[4] The sponsor confirmed that before administration of the study treatment, a randomization number was assigned to each patient.[6,7] The randomization schedule also included the study-specific identifiers, such as company name, protocol name, protocol number, and the date and time the randomization schedule was generated.[6] Stratification of patients was based on baseline disease diagnosis of pcALCL or MF.[5] Due to the open-label study design, both patients and investigators were aware of treatment received; however, aggregate efficacy results according to each treatment group were blinded to the study team, investigators, patients, and independent review facility (IRF) for the duration of the study.[7]

Figure 2: Study Design



Source: Reprinted from The Lancet, 390(10094), Prince HM et al., Brentuximab vedotin or physician's choice in CD30+ cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial, pgs. 555-566, Copyright (2017), with permission from Elsevier.[4]

The primary analysis was conducted based on a data cut-off May 31, 2016 (last patient last visit date of May 26, 2016).[5] The sponsor confirmed the updated analysis was based on a data cut-off of August 16, 2017. The final analysis was conducted on a data cut-off of September 28, 2018 (last patient last visit date of July 6, 2018).[6] There were no planned interim efficacy analyses.[5]

Disease Assessments

To determine the primary endpoint, ORR4, an IRF reviewed a global response score (GRS) to determine objective response, which consisted of several variables including: skin evaluation (mSWAT) assessment by the investigator, nodal and visceral radiographic assessment by IRF, and, for MF patients only, detection of circulating Sézary cells by IRF (Table 6).[5,17] The IRF consisted of independent dermatologists, independent radiologists, and an independent pathologist, who reviewed photos from skin and mSWAT assessments, review of CT, MRI and PET for nodal and visceral disease, and review of Sézary cells for blood components, respectively.[4]

Table 6: Global Response Score Assessment by Independent Review Facility

	Evaluation	Source	Evaluator(s)	GRS
T – Tumour (Skin)	mSWAT	Physical examination (data in eCRF)	Principal investigator	GRS determined by IRF for primary endpoint (ORR4)
N – Node	Node measurements	CT scan	Independent radiologist	
M – Metastases	Visceral evaluation	CT scan		
B – Blood	Sézary cell count	Central pathology lab	Independent pathologist	

CT=computed tomography. eCRF=electronic case report form. ORR4=overall response rate lasting ≥4 months.

TNM staging for pcALCL per Kim et al.[2]

Source: Reprinted from The Lancet, 390(10094), Prince HM et al., Brentuximab vedotin or physician's choice in CD30+ cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial, pgs. 555-566, Copyright (2017), with permission from Elsevier.[4]

Imaging results, laboratory values, and photographs of lesions were provided for IRF review. The lesions that were selected for biopsy were serially photographed at screening and before dosing on day 1 of cycles 1, 2, and 3. The photographs were also taken at the end of every cycle beginning at cycle 3 (days 16-21) or prior to dosing on day 1 of each subsequent cycle. Photographs were taken within 30 days after the last dose of study drug and at the post-treatment follow-up visits. The photographs included the head, trunk, legs, front, back, and side; photographs were uploaded for central review as per IRF.[17]

Skin evaluations were conducted at screening, before dosing on Day 1 of Cycles 1, 2 and 3, and at the end of every subsequent cycle starting at cycle 3, at the end of treatment, and at post treatment follow-up visits.[5] Due to ethical and logistical considerations, radiographic and blood assessments were conducted less frequently.[7] CT scans, for patients without nodal or visceral involvement, were conducted during screening as well as the following times:[5]

- during the cycle following a patient's first skin response, ideally corresponding to the confirmation of the skin response, and 6 cycles or a minimum of four months after that confirmed skin response,
- if there is suspected new or progressive disease in the LN/viscera.

For patients with nodal or visceral involvement, CT scans were conducted at screening as well as during the following times:[5]

- at the end of cycles 3, 6, 9, 12 and 15, and per the follow-up schedule until disease progression,
- if there is suspected new or progressive disease in the LN/viscera,
- at the end of the treatment period if the previous CT scan of the patient was performed >8 weeks before the end of treatment.[7]

For patients with MF, blood samples for Sézary cell enumeration were collected at screening as well as during the following times:[5]

- at the end of cycles 3, 6, 9, 12 and 15,
- at end of the treatment period,
- and per the follow-up schedule until progressive disease or study closure.

Efficacy Outcomes

The primary and key secondary endpoints were assessed using the ITT population which consisted of all patients who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay. In the ITT population, patients were analyzed according to treatment randomization. The ITT population was used for the primary efficacy analysis and for all other efficacy analyses unless specified otherwise.[5]

Primary Endpoint

The primary efficacy endpoint was ORR4 by IRF. ORR4 was defined as the proportion of patients that achieved an objective response (CR or PR) that lasted at least four months (e.g. duration from the first response to last response is ≥4 months) by IRF.[4] Objective response was determined by a global response score (GRS) consisting of an mSWAT assessment by the investigator, nodal and visceral radiographic assessments by an IRF, and detection of Sézary cells, for patients with MF only, by IRF.[5] Assessments for each component of ORR4 are described in the Disease Assessments section of this report. The key secondary endpoints included CR, PFS, and the Skindex-29 symptoms domain.

For patients with a previous CR who experience recurrent disease (e.g. relapse), the objective response was considered to be maintained unless criteria for progressive disease were met.[5]

ORR4 is a composite endpoint that characterizes the rate of a durable objective response lasting at least four months, and was chosen by the Sponsor as a more appropriate endpoint for patients compared to other endpoints, such as PFS which was stated to be confounded by patients who are symptomatic and who frequently proceed to alternate therapies before meeting the protocol-defined criteria for progression[4]. Further, the utility of OS was limited due to the chronic nature of CTCLs; CTCL has a long prognosis and can cause significant symptomatic burden and morbidity through persistent itching, secondary infection, disfigurement, and depending on lesion location, interference with activities of daily living. Therefore, ORR4 was used by the Sponsor to capture durable response of patients to the study drug, which is the aim of therapy for patients in this setting, while being minimally affected by other therapies.[6,15] The proportion of patients achieving a response and response duration as a single measurement were clinically important aspects of treatment success thought to be captured through ORR4. The sponsor concluded that ORR4 is more meaningful and representative of clinical benefit than the rate of objective response alone, which could include responses of short duration that are not clinically relevant and which may not equate to meaningful benefit for patients.[4,6,50] The sponsor stated that ORR4 represented a higher bar for assessment of clinical improvement among patients with MF or pcALCL than the primary endpoint ORR used for prior FDA approvals of recent agents (romidepsin, vorinostat, and bexarotene). The ORR4 endpoint was negotiated by the Sponsor with the FDA and also received scientific support from the EMA. The sponsor stated that this endpoint allows for meaningful representation of benefit among a population of patients with a chronic and incurable disease resulting in relapse and requiring patients to undergo multiple lines of therapy in their lifetime.[6]

Key Secondary Endpoints

Key secondary endpoints of the trial included the proportion of patients achieving CR, PFS, and symptom burden measured by the symptom domain of the Skindex-29 which is a health-related quality of life measure.

Complete response (CR) was defined as the proportion of patients that achieved a CR (as their best response on study, as assessed by an IRF based on GRS criteria).[5]

A sensitivity analysis was performed for CR per the investigators GRS assessment.[5,7]

Progression free survival (PFS) was defined as the time from randomization until disease progression, as assessed by IRF, or death due to any cause, whichever occurred first.[5]

The Skindex-29 is a 29-item health-related quality of life questionnaire used in dermatology comprised of the following three domains: symptoms, emotions, and functioning. The **symptom domain of the Skindex-29** consists of seven items scored on a 5-point scale from never (0) to all the time (4); a score was generated for each item, and the total score for all seven items was converted to an overall score on a 100-point scale whereby higher scores reflected a greater impact on quality of life.[5] Patients were expected to recall over a 28-day period.[17] Skindex-29 was administered on day 1 of cycle 1 and of subsequent even number cycles

(i.e., cycles 1, 2, 4, 6, 8, 10, 12, 14, and 16).[5] The questionnaire was administered to patients before any other study procedures were performed, at the end of the treatment period, and during post-treatment follow-up.

Since there was no validated MID method applicable to the Skindex-29 in the CTCL population, the Sponsor conducted an analysis to determine a MID to aid in the interpretation of the Skindex-29 symptoms results. The methods used by the Sponsor were stated to be consistent with the methods included in EMA guidance regarding the use of PRO measures in oncology studies.[3,45] The Sponsor obtained the MID using three methods based on the current dataset: 1) half of the standard deviation of the maximum score change; 2) Cohen's moderate effect size (*0.5 x standard deviation baseline score*); and 3) standard error of measurement (*standard deviation(baseline score)√(1-Cronbach's α*).[5] MIDs of 12.3, 11.2 and 9.0 using half a standard deviation approach, Cohen's moderate effect size and standard error of measurement methods, respectively, were prespecified by the sponsor to support the interpretation of the Skindex-29 symptoms.[45]

Other Secondary Endpoints

Other secondary endpoints included DOR, duration of skin response, EFS, quality of life as per the Skindex-29 emotional and functional domains and the FACT-G, blood concentrations of BV (serum) and MMAE (plasma), immunogenicity assessment and safety.[5] Results for EFS and duration of skin response are not summarized in this report.

Duration of Response (DOR) was determined in the ITT population with a confirmed response (CR or PR), as per IRF assessment.[5] Patients that were lost to follow-up, withdrew consent, discontinued treatment based on undocumented PD following the last disease assessment were censored at the last disease assessment.[7] DOR was summarized descriptively using the KM method.

Duration of skin response was determined in the ITT population with a confirmed response in skin (CR or PR in skin) as per investigator assessment.[5] Censoring of patients occurred when patients were lost to follow-up, withdrew consent, or discontinued treatment due to undocumented PD in skin after their last skin assessment.[7] Duration of skin response was summarized descriptively using the KM method.

Event Free Survival (EFS) was determined in the ITT population, and was defined as the time from randomization until any cause of treatment failure, including PD, discontinuation of treatment for any reason, or death due to any cause, whichever occurs first, as per IRF assessment. Patients were censored at their last disease assessment if they were lost to follow-up, withdrew consent, or discontinued treatment due to undocumented PD. Patients without baseline data, or sufficient post-baseline data were censored at the date of randomization.[5,7]

Quality of life was also measured using the emotional and functional domains of the **Skindex-29 and FACT-G** questionnaires. FACT-G questionnaire was comprised of 27 items that addressed four primary subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. FACT-G scores were calculated using previously established scoring guidelines (version 4); total scores were obtained by summing individual subscale scores.[3,45] Measurements were taken before the first dose of study treatment, on all even numbered cycles thereafter (i.e., cycles 1, 2, 4, 6, 8, 10, 12, 14, and 16, at the end of treatment and during post-treatment follow-ups. Higher scores on this questionnaire indicated better quality of life.[4,5]

The following were assessed in the **safety** analyses: incidence, severity, and type of AEs; clinically significant changes from baseline in the patient's physical examination; vital signs; ECOG PS; and clinical laboratory results using the safety population, exposure to study drug, and reasons for discontinuation.[3] In addition, treatment-emergent adverse events (TEAEs), grade ≥3 TEAEs, SAEs and events of peripheral neuropathy were summarized by treatment arm according to minimum baseline CD30 expression score ($CD30_{min}$ <10% versus ≥10%).[51] TEAEs were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[4]

Blood samples were obtained from patients one hour before and 30 minutes after receipt of study treatment for all odd-numbered cycles. Samples were taken more extensively for cycles 1 and 3, taking additional samples two or four days post-treatment or three and five days post-treatment. Immunogenicity was assessed before dosing on odd numbered cycles as well as at the end of treatment.[4]

Exploratory Endpoints

The following were considered exploratory endpoints: qualitative and quantitative measures of CD30 expression in tumour biopsies assessed both before and after treatment with BV, serum concentrations of PD markers (e.g. sCD30), the presence or absence of gene or protein variation associated with CTCL or BV mechanism of action, utilisation of health resources, and quality of life as measured by the EG-5D-3L questionnaire, which was administered for economic considerations.[5]

The sponsor also conducted an analysis for OS. Analyses pertaining to OS were not pre-specified in the protocol and the study was not powered to assess OS. While OS data were analyzed in the primary analysis using the treatment as randomized following ITT principle, the sponsor confirmed that the utility of OS as an endpoint in CTCL was limited due to the chronic nature of the disease. According to the sponsor, OS is predicted more by the stage and aggressiveness of the CTCL sub-type at time of initial diagnosis. Earlier stages of the disease tend to be limited to cutaneous involvement, and patients who undergo treatment may experience a relatively typical life expectancy. Patients diagnosed in later stages of disease, when lymph nodes, blood, and visceral organs may be affected, have reduced survival. For patients who did not experience OS events (i.e. death), the patients were censored at the time of the last contact.[6] A rank-preserving structural failure time (RPSFT) analysis was performed to adjust for crossover effects on OS for the ITT population and by disease type.[6]

Sample Size

A sample of size of 124 was calculated to provide 90% power in order to detect a 30% improvement in ORR4 in the BV group, assuming that 70% of patients in the BV group and 40% in the PC group were to achieve an objective global response lasting at least four months. Statistical analysis was based on a two-sided chi-square test with a significance level of 0.05 and 10% dropout rate using nQuery Advisor 7.0.[4,5] A minimum of 15 patients with pcALCL in each treatment group were to be randomized in the ALCANZA trial; although, this was not based on statistical consideration.[17]

Statistical Analyses

Primary Endpoint

ORR4 was assessed as by IRF in the ITT population using a Cochran-Mantel Haenszel chi-square test stratified by baseline disease status of patients (either pcALCL or MF). 95% CIs were calculated to determine the differences in ORR4 between the two treatment groups. Patients without post-baseline response assessments, as per protocol or without response before dropout were considered as non-responders. Objective response for patients was considered maintained unless criteria for disease progression were met. Patients were excluded from analyses if they experienced their response after start of a subsequent anti-cancer therapy but otherwise met the endpoint criteria for ORR4. No imputations were conducted for missing data.[5]

Subgroup analyses for ORR4 were pre-specified and performed for the following groups of patients: baseline disease diagnosis (pcALCL, MF), ECOG PS (0, 1, 2), sex (male, female), age (<65, ≥65), region (Europe, North America, Asia, rest of the world), race (white, non-white) and physicians choice of treatment (BV vs. bexarotene or methotrexate).[5,7] A minimum of 10 patients were required for each subgroup.[7] Baseline subgroup analyses were also conducted for baseline disease involvement and baseline skin tumour involvement, but these subgroups were not prespecified.[5] Based on a request by members of the CGP, an ad hoc subgroup analysis was conducted by the sponsor for patients with or without involved lymph nodes. These subgroup analyses are considered exploratory in nature.[6]

Key Secondary Endpoints

A fixed sequence testing procedure was used to control for the incidence of overall type 1 error for testing of the primary endpoint and key secondary endpoints; therefore, the key secondary endpoints were only tested if ORR4 was found to be statistically significant. A weighted Holm's procedure was then further used for testing of the key secondary endpoints using the following weights: 0.7 for CR, 0.2 for PFS, and 0.1 for the symptom domain of the Skindex-29.[4] According to the sponsor, weights for these three key secondary endpoints were chosen a priori, which took into consideration clinical significance and statistical operational characteristics (e.g., number of expected events, effect size).[15] The sponsor confirmed that a higher weight corresponded to more alpha allocation out of the overall level of $\alpha = 0.05$ and a better chance of meeting statistical significance. In an extreme case where a weight of 1 was assigned to one endpoint (0 to the other two), hypothesis testing was only formally performed on this one endpoint at alpha level of $\alpha = 0.05$.[15]

Analyses of key secondary endpoints involved the use of adjusted p-values, which allowed for adjustment of multiplicity based on weighted Holm's procedure. Statistical significance was determined at the adjusted two-sided p≤0.05.[4] CR, PFS and the symptom domain of the Skindex-29 were prespecified endpoints in the primary, updated, and final analysis.[15]

Analysis of CR and PFS were made as per IRF assessment. A stratified Cochran-Mantel-Haenszel test was conducted to detect differences in proportions of CR between treatment groups. Patients without baseline response assessment as specified in the protocol were considered non-responders. PFS was compared between treatment groups with p-values generated using stratified log-rank test statistics; cox regression models were used to estimate HRs and 95%CIs.[5] The sponsor confirmed that PFS was analyzed with the same statistical methods in the final analysis. The Skindex-29 symptom domain was a prespecified endpoint in the primary, updated, and final analysis.[15] Regarding the symptom domain of the Skindex-29, the mean maximum symptom reductions from baseline were compared between both treatment groups using analysis of covariance modelling, controlling for baseline covariates (treatment, baseline score, disease diagnosis, and ECOG PS).[4] According to the study protocol, a final analysis was conducted after 10 months from the last patient enrolled. Once all patients have completed 16 cycles of treatment with brentuximab vedotin or 48 weeks of treatment with the reference therapy and two years of post-treatment follow up, an updated analysis was to be performed.[17]

In order to estimate the time to event endpoints, the KM method was used. If the median times were estimable, these data were provided along with the 2-sided 95% CIs. Based on an assumed median PFS of nine and six months in the BV and PC treatment group, respectively, the number of PFS events was projected to be 101 at the time of the planned final analysis. This was based on a rough 2-year enrollment period, dropout rate of 10%, and an α level of 0.01 (2-sided).[7] Patients that dropped out, withdrew consent, or discontinued treatment based on undocumented progressive disease following the last disease assessment were censored at the last disease assessment. If mortality or progressive disease occurred following a missed visit, the patient was deemed progressed at the date of death or progressive disease. Patients with missing baseline and/or inadequate post-baseline data for disease assessment and with no death details were censored at the date of randomization. If progressive disease was documented between scheduled visits then the date of the documented progressive disease was the date of progression. If the patient commenced new anticancer therapy prior to progressive disease then the patient was treated as progressed at the date of assessment at which PD was documented.[7]

Safety Analysis

Safety was evaluated in the separate safety population, which included patients who received at least one dose of study drug. All patients were analyzed according to the actual treatment received.[5]

Sensitivity Analyses

Sensitivity analysis were performed for ORR4, CR, PFS, and skin symptoms (Skindex-29).[5] Sensitivity analyses were not adjusted for multiplicity, and mainly conducted to account for the censoring of study participants at different time points. Sensitivity analyses are not summarized in this report.

Protocol Amendments and Deviations

There were a total of five amendments to the original protocol. The protocol amendments are summarized in Table 7. Overall, none of the amendments impacted the study conduct nor interpretation of the data.[5]

Table 7: Summary of Protocol Amendments to the ALCANZA trial

Amendment	Description
Amendment 1	Zero patients were enrolled for this amendment.[5] A change was made to the primary endpoint from ORR to ORR4. The study population was altered to only include patients with a primary diagnosis of pcALCL or MF (minimum of 15 patients per treatment arm), and who received at least one prior systemic therapy.[5] Based on investigator-initiated phase II data, the confirmation of tumour CD30 positivity decreased from ≥75% to ≥10%.[3,5]

Amendment	Description
Amendment 2	46 patients enrolled for this amendment.[5] The use of bleomycin was outlined as a contraindication to BV due to the occurrence of pulmonary toxicity.[5] Information was added to the protocol regarding the occurrence of pulmonary toxicity.[3] Discontinuation of study treatment was attempted after the completion of 48 weeks to assist in the analysis of PFS as a key secondary endpoint. Patients could initiate subsequent standard of care treatment or re-treatment with BV (if in the interventional group) at the joint discretion of the Sponsor and investigator.[3,5]
Amendment 3	Zero patients were enrolled for this amendment.[5] Patients with SD were permitted to continue receiving study treatment for up to 16 cycles of BV or 48 weeks of control treatment.[5] This change was made in response to phase II trial data showing that patients may require longer treatment exposure to achieve clinical response, and discontinuation of treatment after only six cycles was considered suboptimal.[3,5] A change was made to allow for the eligibility of patients with pcALCL who had received prior radiation therapy or at least one prior systemic therapy, instead of only pcALCL patients with at least one prior systemic therapy; this change was made as radiotherapy is one of the most common therapies for solitary or localized pcALCL. A change was also made to the test used to determine CD30 expression from the Quest CTA to the Ventana anti-CD30 (Ber-H2) assay. As the Quest CTA was used to evaluate CD30 positivity during enrollment, samples patients enrolled on the basis of CD30 positivity were re-evaluated using the Ventana anti-CD30 (Ber-H2) assay;[5] if CD30+ status was not confirmed using the new test, these patients were permitted to remain in the study but were not included in the ITT population.[3]
Amendment 4	79 patients were enrolled for this amendment.[3] A revision to the calculation of BSA was made to determine dosing of bexarotene re-establishing the use of previously used standard formula to calculate BSA. All events of peripheral neuropathy were stipulated to be followed in patients for changes in severity until resolution to baseline or study closure, whichever occurred first, in order to strengthen reporting of safety data.[3]
Amendment 5	Six patients were enrolled for this amendment.[5] Safety information were updated. Eligibility criteria regarding patients at risk for pancreatitis were revised due to experiences in clinical studies and post-marketing.[5]

Major protocol deviations were associated with nine patients, five in the BV group and four in the PC group, which are outlined in Table 8.[5] There were two deviations related to concomitant medications and seven deviations associated with the inclusion/exclusion criteria.

Table 8: 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.

Source: EPAR 2017[5]

b) Populations

Baseline Disease and Demographic Characteristics

The ALCANZA trial randomized 131 patients, 66 patients to the BV group and 65 patients to the PC group (methotrexate or bexarotene). In the final ITT population, there were a total of 128 patients with 64 patients in each treatment group; due to insufficient CD30 expression, three patients were excluded. According to the study authors, baseline characteristics were generally balanced between the two treatment groups. Table 10 summarizes the baseline characteristics of patients. The median age was 62 years (range: 51-70) and 59 years (range: 48-67) in the BV and PC groups, respectively. There were 33 males (52%) and 37 males (58%) in the BV and PC groups, respectively. Most patients had an ECOG PS of 0 (67% in the BV group and 72% in the PC group) or 1

(28% and 25%) and were White (88% and 83%).[4] Patients diagnosed with MF comprised 76% of the ITT population (75% in the BV group and 77% in the PC group), with patients with pcALCL comprising 24% (25% in the BV group and 23% in the PC group); however, the proportion of patients with stage IVA2 MF in the PC group was greater than that of patients in the BV group (16% and 4%, respectively), and the proportion of patients with IVB MF was greater in the BV group than in the PC group (15% and 0%, respectively). Further, the disease stage of patients with pcALCL also varied across treatment group as there was greater presence of extracutaneous pcALCL in the BV group (44%) compared to the PC group (27%).[5] Time since progression on last therapy was also longer for patients in the BV group (2.4 months, range: 1.4-7.9) compared to the PC group (1.3 months, range: 0.9-3.7).[4]

Table 9: Patient Demographics of the ITT Population

	Brentuximab vedotin (n=64)	Physician's choice of methotrexate or bexarotene (n=64)	Overall (N=128)
Age (years)	62 (51–70)	59 (48–67)	60 (48–69)
Sex			
Male	33 (52%)	37 (58%)	70 (55%)
Female	31 (48%)	27 (42%)	58 (45%)
Race			
White	56 (88%)	53 (83%)	109 (85%)
Other	5 (8%)	10 (16%)	15 (12%)
Not reported	3 (5%)	1 (2%)	4 (3%)
ECOG PS			
0	43 (67%)	46 (72%)	89 (70%)
1	18 (28%)	16 (25%)	34 (27%)
2	3 (5%)	2 (3%)	5 (4%)
Median CD30 expression*	32·5% (12·5–67·5)	31·3% (12·0–47·5)	31·3% (12·5–60·0)
Time since initial diagnosis (months)	42·2 (12·8–87·4)	37·0 (12·3–102·7)	40·9 (12·7–96·8)
Time since progression on last therapy† (months)	2·4 (1·4–7·9)	1·3 (0·9–3·7)	1·9 (1·1–3·8)
Lines of previous therapy			
Total	4·0 (2·0–7·0)	3·5 (2·0–5·5)	4·0 (2·0–6·0)
Skin-directed	1·0 (1·0–2·0)	1·0 (1·0–2·0)	1·0 (1·0–2·0)
Systemic	2·0 (1·0–4·0)	2·0 (1·0–3·0)	2·0 (1·0–4·0)
Mycosis fungoides	48 (75%)	49 (77%)	97 (76%)
Disease stage‡§			
IA–IIA	15/48 (31%)	18/49 (37%)	33/97 (34%)
IIB	19/48 (40%)	19/49 (39%)	38/97 (39%)
IIIA–IIIB	4/48 (8%)	2/49 (4%)	6/97 (6%)
IVA1	0	1/49 (2%)	1/97 (1%)
IVA2	2/48 (4%)	8/49 (16%)	10/97 (10%)
IVB	7/48 (15%)	0	7/97 (7%)
pcALCL	16 (25%)	15 (23%)	31 (24%)
Disease stage‡			
Skin			
T_1	1/16 (6%)	4/15 (27%)	5/31 (16%)
T_2	3/16 (19%)	5/15(33%)	8/31 (26%)
T_3	12/16 (75%)	6/15 (40%)	18/31 (58%)
Node			
N_0	10/16 (63%)	11/15 (73%)	21/31 (68%)
N_1	2/16 (13%)	1/15 (7%)	3/31 (10%)
N_2	2/16 (13%)	1/15 (7%)	3/31 (10%)
N_3	2/16 (13%)	2/15 (13%)	4/31 (13%)
Visceral			
M_0	12/16 (75%)	14/15 (93%)	26/31 (84%)
M_1	4/16 (25%)	1/15 (7%)	5/31 (16%)

Data are median (IQR) or n (%), unless stated otherwise. Data shown are for the intention-to-treat population. ECOG PS=Eastern Cooperative Oncology Group performance status. pcALCL=primary cutaneous anaplastic large-cell lymphoma. T=tumour. N=node. M=metastasis. *Based on average CD30 expression among all biopsies for each patient's baseline visit. †Excluding radiotherapy. ‡Percentage in each subcategory in the total column is based on the number of patients in each disease subtype. §One patient in each group had incomplete staging data and are not included in the table.

Source: Reprinted from The Lancet, 390(10094), Prince HM et al., Brentuximab vedotin or physician's choice in CD30+ cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial, pgs. 555-566, Copyright (2017), with permission from Elsevier.[4]

In terms of prior therapies received, patients received a median number of four (range: 2.0-7.0) prior therapies in the BV group and 3.5 (range: 2.0-5.5) prior therapies in the PC group (Table 10).[4] Patients with MF or pcALCL received a median of two systemic therapies in both the BV and PC treatment groups. Chemotherapy was the most commonly received prior systemic therapy within both treatment groups (71% in the BV group and 70% in the PC group), followed by immunotherapy (41% and 45%) and bexarotene (41% and 34%). A median of one prior skin-directed therapy was reported among patients in both treatment arms. Among the skin-directed prior therapies in the ITT population, radiotherapy was the most common which was received by 63% of patients in the BV group and 64% of patients in the PC group, followed by phototherapy received by 51% and 45% of patients, respectively.[5] Due to a major protocol deviation, one patient with pcALCL randomized to the BV group did not receive prior systemic therapy in this study. Four patients (three in the BV group and one in the PC group) received prior bone marrow or stem cell transplant. There were 3 patients (8%) in the PC group that received prior treatment with bexarotene without reported progressive disease and 2 patients (8%) that received prior treatment with methotrexate without reported progressive disease that were randomized to receive bexarotene and methotrexate, respectively, in this study.[3] Among the three patients retreated with bexarotene, individual patient data indicated that the previous responses to bexarotene were recorded as unknown and one of these patients had been previously treated with methotrexate. The two patients retreated with methotrexate had a previous best response to methotrexate of stable disease and partial response; both these patients were also previously treated with bexarotene.[5] In the PC group, there were 11 patients (17.2%) that experienced disease progression on previous treatment with methotrexate and were assigned to receive bexarotene. There were 13 patients (20.3%) that experienced disease progression on previous treatment with bexarotene and were assigned to receive methotrexate.[6] In the BV and PC groups, there was one patient in each group (1.6%) that received allogeneic transplant prior to study treatment and one patient, in each group, (1.6%) that received allogeneic stem cell transplant following study treatment.[6]

Table 10: 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.

Source: EPAR 2017[5]

c) Interventions

Treatment

Brentuximab vedotin was administered intravenously with a dose of 1.8mg/kg over a duration of 30 minutes on day 1 of each 21-day cycle. Patients received treatment with BV for a maximum duration of 48 weeks or 16 cycles.[5] For patients that experienced peripheral neuropathy, dose modifications for BV were specified.[17]

Methotrexate was one of the options in the PC group. Patients received methotrexate orally once per week at a single dose of 5-50 mg. In order to reach optimal clinical response. Lowest effective dose, dose adjustments were tolerated up to 50 mg/week according to the protocol.[17] Patients received treatment with methotrexate for a maximum duration of 48 weeks.[5] In the event of methotrexate toxicity, dose modification is warranted. A 50% dose reduction is instructed for methotrexate when a patient experiences severe mouth ulcerations.[17]

Bexarotene was the other option in the physician's choice group. Patients received bexarotene orally once daily at a dose of 300mg/m^2. Dose reductions were tolerated to 200 mg/ m^2 /day or 100 mg/m^2 /day. If patients experienced any toxicity, bexarotene could be suspended. Fenofibrate at a dose of 145 to 200 mg for 7 days (or reduced dose recommended for patients with creatinine levels ≥1.5 mg/dL or nephrotic syndrome) as pre-treatment was required. A low dose of synthetic thyroxine (T4) was to be taken (dosage adjusted along with dosage of bexarotene) concurrently. While patients received bexarotene treatment, continual monitoring of lipid and T4 concentrations was required. Patients received treatment with bexarotene for a maximum duration of 48 weeks.[5]

For the BV and PC treatment groups, each cycle length lasted a duration of 21 days and patients were able to commence a new cycle provided the following criteria were met: absolute neutrophil count must be ≥1,000/mm^3 and resolved or improved drug related toxicity.[17]

In the ALCANZA trial, treatment beyond disease progression was not permitted. The Sponsor confirmed that patients with progressive disease at any time during the study were discontinued from study treatment.[6] The protocol stated the study drug should be discontinued for patients that met any of the following criteria*:* completed 16 cycles of BV therapy or 48 weeks of reference therapy or progressive disease.[5,17]

Duration of treatment

In the BV group, the median duration of treatment was 269 days, which is equivalent to 12 cycles (IQR 5-16 cycles). The median duration of bexarotene treatment was 114 days, which is equivalent to 5.5 cycles (IQR 3-11 cycles) and methotrexate over 77 days, which is equivalent to three cycles (IQR 2-6 cycles). The median relative dose intensity in the BV group was 99.6% (IQR 92.7-100.0) compared to 94.3% (IQR 73.6-100.0) for bexarotene. Among patients that received treatment with methotrexate, the physician determined the dose as 5-50 mg once per week and the median dose was 21.7 mg/week (IQR 16.7-30.6).[4]

Dose escalation rules

For patients in the BV group, dose escalation was not allowed whereas in the PC group, methotrexate or bexarotene could be escalated per the discretion of the treating physician according to the methotrexate or bexarotene product label.[17]

Dose reduction rules

Depending on the type and severity of toxicity, dose reduction to 1.2 mg/kg brentuximab vedotin was permitted. In the event of a dose reduction for BV, no re-escalation of dose was allowed.[17]

Concomitant Medications and procedures

According to the protocol, patients were authorized to receive concomitant hormonal therapy provided they were on a stable dosage for at least one month prior to enrollment. In addition, the following types of concomitant medications/procedures were allowed: platelet and/or red blood cell supportive growth factors or transfusions, colony stimulating factors for the treatment of neutropenia per institutional practice and the systemic, topical, or inhaled corticosteroids.[17]

While nearly all patients received concomitant medications during the ALCANZA trial (98% in the BV group compared to 100% in the PC group),[3] the use of concomitant medications, which could have influenced patient outcomes were not prohibited during the trial. Within the PC group, folic acid was the most common concomitant medication among patients receiving methotrexate (52%, n=13/25); fenofibrate (73%, n=27/37) and levothyroxine (89%, n=33/37) were the most common concomitant medications among patients receiving bexarotene.[5] Paracetamol was the most commonly received concomitant medication in the BV group (45%,

n=30);[3] patients in the BV group also received levothyroxine (20%, n=13), hydroxyzine (18%, n=12), fenofibrate (14%, n=9) and statins (32%, n=21).[5]

Subsequent anticancer therapy

A summary of subsequent therapies both at the primary and final analyses are reported in Table 11.The proportions of patients receiving subsequent therapies at the final analysis were similar to the primary analysis; chemotherapy continued to be the most common systemic therapy received by patients with 34 patients (68%) receiving chemotherapy in the BV group compared to 27 patients (56%) in the PC group. The most common skin directed therapy was radiotherapy, which was received by 15 patients (30%) in the BV group and 20 patients (42%) in the PC group.[9]

Additionally, the sponsor confirmed that crossover was not permitted in the ALCANZA trial and that treatment beyond progression was not permitted. According to the sponsor, patients were eligible to receive treatment with BV as a subsequent therapy both through enrollment in a companion study (SGN35-010)[18] after experiencing disease progression or outside the setting of a clinical trial. Enrollment in SGN35-010[18] required confirmation of progressive disease by IRF. At the final analysis, there were 12 patients (24%) in the BV group and 33 patients (69%) in the PC group that received subsequent treatment with BV.[6,9]

After study treatment allogeneic stem cell transplant was received by one patient in each of the treatment groups.

Table 11: Subsequent Anticancer Therapies in the ITT Population

	Primary analysis (data cut-off: May 31, 2016)		Final analysis (data cut-off: September 28, 2018)	
	Brentuximab vedotin n=64	Methotrexate or Bexarotene n=64	Brentuximab vedotin n=64	Methotrexate or Bexarotene n=64
Patients with ≥1 subsequent therapy, n (%)	38 (59)	47 (73)	50 (78)	48 (75)
Type of therapy, n (%):				
Skin-directed therapy	17 (45)	22 (47)	26 (52)	30 (63)
Radiotherapy	12 (32)	16 (34)	15 (30)	20 (42)
Phototherapy	6 (16)	6 (13)	13 (26)	13 (27)
Topical steroids	1 (3)	5 (11)	3 (6)	6 (13)
Systemic therapy	34 (89)	44 (94)	44 (88)	45 (94)
Chemotherapy	23 (61)	22 (47)	34 (68)	27 (56)
Other	19 (50)	19 (40)	28 (56)	23 (48)
Methotrexate	8 (21)	6 (13)	14 (28)	10 (21)
Brentuximab vedotin	5 (13)	29 (62)	12 (24)	33 (69)
Immunotherapy	9 (24)	5 (11)	12 (24)	9 (19)
Other	5 (13)	3 (6)	9 (18)	5 (10)
Bexarotene	6 (16)	4 (9)	6 (12)	6 (13)
Histone deacetylase inhibitor	4 (11)	3 (6)	6 (12)	4 (8)
Non-topical retinoids	NR	NR	3 (6)	0
Photopheresis	0	1 (2)	1 (2)	1 (2)
Other/unknown	1 (3)	4 (9)	1 (2)	4 (8)

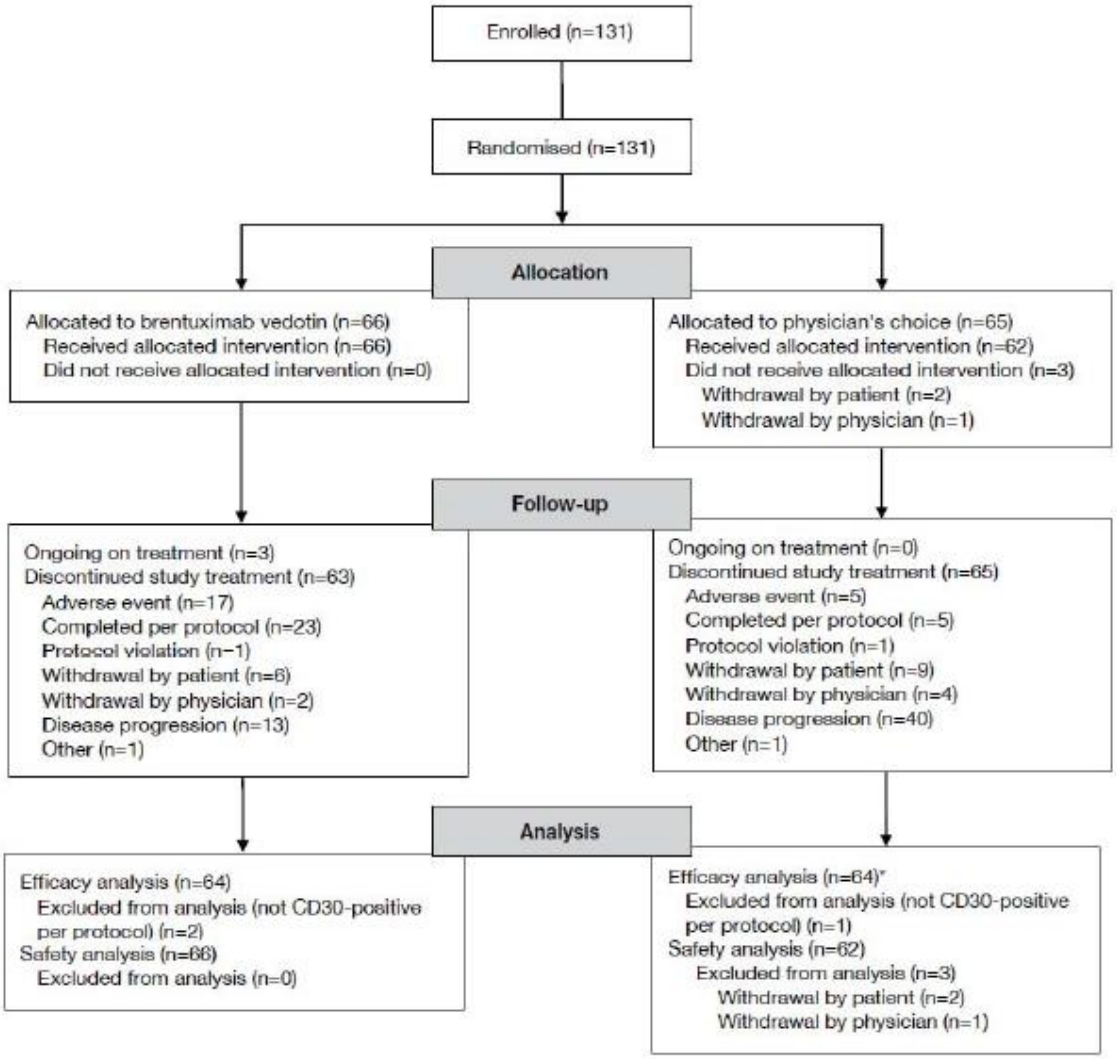
Data Sources: EPAR 2017,[5] Horwitz et al., 2019[9]

d) Patient Disposition

Of the 237 patients screened (first patient was screened on June 11, 2012),[5] the Sponsor confirmed that 131 patients met all inclusion and exclusion criteria, and the remaining failed screening due to failure to meet at least one of the eligibility criteria; 82% of patients did not meet inclusion criteria and 18% did not meet exclusion criteria. According to the Sponsor, the main reasons that patients failed screening included the following: CD30 expression <10% by central review (61%), lack of suitable venous access for the study (i.e. required blood sampling) including PK sampling (7%), lack of voluntary written consent given before performance of any study-related procedure not part of standard medial care (6%), and presence of another condition that, in the opinion of the investigator or project clinician, would interfere with a patient's ability to receive or complete the study (6%).[6] Patients were enrolled

from August 13, 2012 to July 31, 2015. The last patient enrolled in the study on July 31, 2015 prior to the data cut-off of May 31, 2016.[5] Following randomization in a 1:1 ratio, there were 66 patients in the BV group and 65 patients in the PC group. There were 66 patients (100%) that were treated with BV and 62 patients (95.4%) in the PC group that were treated, respectively.[4]

Figure 3: Patient Consort Diagram in the ALCANZA Trial



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At follow-up after the primary analysis, 63 patients (96%) discontinued treatment in the BV group, compared to all 65 patients (100%) in the physician's choice arm. The most common reason for discontinuing treatment in the BV group was having completed treatment per protocol among 23 patients (37%), followed by 17 patients (27%) that experienced AEs, and 13 patients (21%) who experienced disease progression. In the PC group, the most common reason for discontinuing treatment was due to disease progression among 40 patients (62%).[4] Reasons for loss to follow-up are presented in Figure 3.

e) Limitations/Sources of Bias

Overall, the ALCANZA trial was a well conducted phase III trial. It is the first phase III trial to demonstrate improved ORR4 for patients with CTCL. The CADTH Methods Team identified the following limitations and potential sources of bias that should be considered when interpreting the trial results.

Study Design

- The comparators in the ALCANZA trial were limited to methotrexate or bexarotene. While there is no standard of care in Canada for patients diagnosed with pcALCL or MF who have received at least one prior systemic therapy, treatment with methotrexate or bexarotene alone does not reflect the variety of treatment options that patients receive across clinical practices and jurisdictions in Canada. Patients may be treated with other systemic therapies such as CHOP or CEOP, retinoids, interferon, gemcitabine, liposomal doxorubicin, and etoposide. Many treatment choices currently exist without an overall direct comparator due to the lack of an available gold standard treatment. Therefore, the ALCANZA trial results that are limited to the comparators of methotrexate or bexarotene may not be generalizable in the Canadian context.
- Due to the open-label study design, the investigators and patients were aware of the treatment administered for the duration of the study. It is possible the trial results may be at risk for biases related to the lack of blinding that can affect the measurement and reporting of outcomes due to knowledge of the assigned treatment. Accordingly, the results may be biased in favour of the BV group compared to the PC group. In addition, due to the open-label nature of the study, assessment of disease symptoms by the Skindex-29, EQ-5D-3L, and FACT-G should be interpreted with caution as knowledge of treatment assignment within the trial could have influenced patient's reporting of symptoms.
- Due to small sample sizes, the Sponsor was limited in their ability to analyze subsets of patients within the heterogenous population of CTCLs. Subsets of patients with CTCL may vary based on demographic and disease characteristics, which may limit generalizability of trial results; however, as no specific subset of patients was excluded from the trial the results are applicable to other patients with similar prognoses. Further, as some subsets of CTCL are rare, conducting individualized clinical trials may not be feasible.[4,5] Therefore, it may be reasonable for BV to be efficacious among other CTCL subtypes; although, clinicians may consider patient characteristics when prescribing treatment, and remain vigilant in their monitoring of patients throughout treatment.
- Eligibility criteria of the ALCANZA trial originally required confirmation of CD30 positivity at ≥75%. To allow for greater eligibility of patients with MF the CD30 positivity confirmation was reduced to 10%, as higher CD30 expression in MF patients is infrequent. This cut-off was stated to be arbitrarily chosen and excluded some patients with MF or Sézary Syndrome with high blood Sézary cell count. As stated in the ALCANZA trial publication, patients with high Sézary cell counts and patients with lesions with low CD30 expression were shown to have responded to treatment with BV.[4] It is possible that patients with MF with lower levels of CD30 positivity who may have benefited from treatment with BV were not enrolled within the ALCANZA trial.
- The sponsor confirmed ORR4 is a composite endpoint.[6] ORR4 was used by the sponsor to capture durable response of patients to the study drug while being minimally affected by other therapies. Clinically important aspects of treatment success including the proportion of patients achieving a response and the response duration were thought to be captured through ORR4 as a single measurement. The sponsor noted that ORR4 is more meaningful and representative of clinical benefit than the rate of objective response alone, which could include responses of short duration that are not clinically relevant and which may not equate to meaningful benefit for patients.[6] According to the sponsor, this endpoint allows for meaningful representation of benefit among a population of patients with a chronic and incurable disease that results in relapse and requires patients to undergo multiple lines of therapy in their lifetime. In clinical trials that use composite endpoints, it is recommended that a thorough assessment of the composite endpoint and its components are performed. The use of composite endpoints may result in an overestimation of the effect and can be misinterpreted. When assessing the appropriateness of the results from a clinical trial using composite endpoints, in addition to the effect observed on the composite endpoint, effects on each component of the composite endpoint should be reported separately in a clear manner.[12] There is a potential risk of misinterpretations when there is heterogeneity of response among components of a composite endpoint. The effect of each component of ORR4 was not reported separately; therefore, the effect of each component of the composite endpoint is unknown. It is possible that the effect on a composite endpoint is mostly driven by an effect on one of the components. Additionally, the use of ORR4 as a primary endpoint makes cross-trial comparisons to trials reporting on traditional outcome measures such as PFS and OS challenging.
- In the updated analyses, the outcomes of ORR4, CR, PFS, and Skindex-29 symptoms domain were assessed via investigator and not by IRF. Outcomes assessed by investigator are subject to bias due to a potential conflict of interest and may not be a robust assessment of the outcomes compared to an IRF.

Protocol deviations

- There were seven out of nine major protocol deviations that involved modifications to inclusion/exclusion criteria, which suggests a possible selection bias and recruitment of patients that otherwise would have been ineligible.

Statistical Analyses

- There were many predefined subgroup analyses and multiple secondary efficacy outcomes assessed in the trial that were not adjusted to account for multiple comparison testing to control the risk of type 1 error. The trial was not powered to test specific hypotheses in these additional subgroups and outcomes; therefore, results of the subgroup analyses should be interpreted as exploratory in nature. Analyses of other secondary endpoints and exploratory endpoints were also not adjusted for multiplicity; these results may be considered as supplemental to the primary and key secondary endpoints, but should also be interpreted with caution.
- Since there was no validated MID method applicable to the Skindex-29 in the CTCL population, the Sponsor conducted an analysis to determine a MID to aid in the interpretation of the Skindex-29 symptoms results. The methods used by the Sponsor were stated to be consistent with the methods included in EMA guidance regarding the use of PRO measures in oncology studies.[3,45] Using a MID derived from the Sponsor may be biased towards finding a clinically meaningful improvement when one may not exist.
- For the Skindex-29 emotions and functioning domain to measure quality of life, the number of patients included in the calculation of mean change from baseline decreased as the number of cycles of treatment in the BV group increased, which resulted in small sample sizes and introduced uncertainty in the results.
- At the final analysis, exploratory analysis of OS tended to favour treatment with BV as the median OS was longer for patients treated with BV compared to patients treated with PC (HR=0.745, 95% CI 0.421-1.318; p-value 0.310).[9] It is important to note that the OS endpoint was not a formally prespecified endpoint per protocol, and the ALCANZA trial was not powered to detect differences this endpoint.[6] Therefore, results should be considered exploratory and no definitive conclusions can be drawn on the longer-term survival of patients with MF and pcALCL.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The results of the primary and key secondary endpoints at the primary (median follow-up: 22.9 months), updated (median follow-up: 33.9 months), and final (median follow-up: 45.9) analyses are reported in Table 12. The primary analysis was reported in the full trial publication and the updated and final analyses were reported in abstract form. A summary of these results is provided below.

Table 12: Summary of Primary and Key Secondary Results in the ITT Population

Domain	Primary Analysis (data cut-off: May 31, 2016)[3-6]		Updated Analysis[a] (data cut-off: August 16, 2017)[6,8,35]		Final Analysis (data cut-off: September 16, 2018)[6,8,9]	
	BV Group N (%) (95%CI)	**PC Group** N (%) (95%CI)	**BV Group** N (%) (95%CI)	**PC Group** N (%) (95%CI)	**BV Group** N (%) (95%CI)	**PC Group** N (%) (95%CI)
Median follow-up, months (95% CI)	22.9 (18.4-26.1)		33.9 (29.4-36.2)		45.9 (41.0-49.4)	
ORR4	36 (56.3) (44.1-68.4)	8 (12.5) (4.4-20.6)	39 (60.9) (49.0-72.9)	5 (7.8) (2.6-17.3)	35 (54.7) (42.5-66.9)	8 (12.5) (4.4-20.6)
Between group difference % (95% CI) p-value	43.8 (29.1-58.4) <0.001		NR		NR	
CR	10 (15.6) (6.7-24.5)	1 (1.6) (0-4.6)	12 (18.8) (9.2-28.3)	0 (0) (0-5.6)	11 (17.2) (7.9-26.4)	1 (1.6) (0-8.4)
Between group difference % (95% CI) p-value	14.1 (-4.0-31.5) p=0.0046		NR		NR	
PFS Median, months (95%CI)	16.7 (14.9-22.8)	3.5 (2.4- 4.6)	15.8 (14.1-17.2)	3.6 (2.5-4.5)	16.7 (NR)	3.5 (NR)
Median PFS follow-up, months (95%CI)	17.5 (12.6-22.9)		25.2 (21.4-29.4)		36.8 (31.7, 40.2)	
Events, n (%)	36 (56)	50 (78)	46 (72)	51 (80)	42 (66)	50 (78)
	HR=0.270; 95% CI, 0.169-0.430 p-value <0.001; adjusted p-value <0.001		HR=0.373; 95% CI, 0.245-0.569 p-value<0.001		HR=0.378; 95% CI, 0.247-0.577 p-value<0.001	
Skindex-29 Symptom Domain, points change from baseline (SD)	-27.96 (26.877)	-8.62 (17.013)	-28.08 (26.863)	-8.62 (17.013)	-28.08 (26.863)	-8.62 (17.013)
Between group difference % (95% CI) p-value	-18.9 (-26.6 to -11.2)		-19.0 (-26.7 to -11.4)		-19.0 (-26.7 to -11.4)	

BV = brentuximab vedotin, CI = confidence interval, PC = physician's choice, ORR4 = objective global response rate lasting at least 4 months, CR=complete response; PFS=progression free survival, NR=not reported, SD=standard deviation

[a] Investigator assessed

Data Sources: Prince et al., 2017,[4] EPAR 2017,[5] Horwitz et al., 2017,[35] Horwitz et al., 2019,[9] Checkpoint Meeting Materials,[6,8] Clinical Study Report[3]

Primary Endpoint – Objective Response Rate at least 4 months (ORR4)

At the primary analysis (data cut-off: May 31, 2016), there were 36 patients (56.3%, 95% CI 44.1-68.4) in the BV group that achieved ORR4 per IRF compared to eight patients (12.5%, 95% CI 4.4-20.6) in the PC group. The between group difference was 43.8% (95%

CI 29.1-58.4, p-value <0.001) statistically significantly in favour of the BV group compared to the PC group.[4,5] Results are presented below in Table 13.

Table 13: 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)		

Source: EPAR 2017[5]

Among patients with a diagnosis of MF, there were 24 patients (50%) in the BV group that achieved ORR4 compared to five patients (10.2%) in the PC group, as per IRF assessment. The between group difference of 39.8% was in favour of BV compared to PC (95% CI 19.9-56.2, p-value <0.001). Among patients with a diagnosis of pcALCL, there were 12 patients (75.0%) in the BV group that achieved ORR4 per IRF compared to three patients (20%) in the PC group. The between group difference of 55.0% was in favour of BV compared to PC (95% CI 19.7-80.4, p-value=0.003).[5] Results are presented in Table 14. The results for ORR4 stratified by baseline disease status (MF or pcALCL) were pre-specified in the statistical analysis plan of the ALCANZA trial[7]; however, there was no controlling for multiplicity.

Table 14: ORR4 based on Baseline Disease Diagnosis in the ITT Population

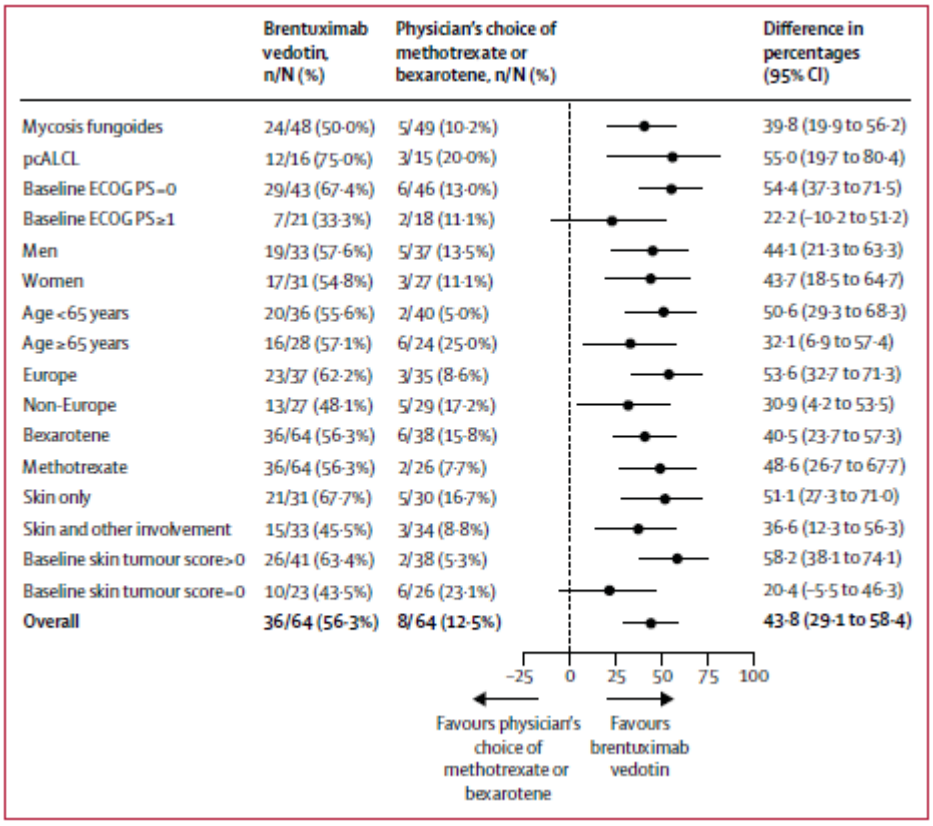
MF	48	49	
Number (%) achieving ORR4 per IRF	24 (50.0)	5 (10.2)	<0.001
95% CI	(35.9, 64.1)	(3.4, 22.2)	
Difference from physician's choice arm (b)	39.8		
95% CI for difference from physician's choice arm	(19.9, 56.2)		
pcALCL	16	15	
Number (%) achieving ORR4 per IRF	12 (75.0)	3 (20.0)	0.003
95% CI	(47.6, 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)		

Source: EPAR 2017[5]

Subgroup Analyses of ORR4

Members of CGP identified the following subgroups of interest: age, ECOG PS, sex, and patients with lymph node disease versus patients without lymph node disease. Brentuximab vedotin was favoured consistently across all subgroups compared to the PC, except for the following prespecified subgroups: baseline ECOG PS≥1 and baseline skin tumour score=0 (Figure 4).

Figure 4: Proportion of Patients Achieving ORR4



Abbreviations: pcALCL= primary cutaneous anaplastic large-cell lymphoma, ECOG PS=, ORR4=objective global response rate lasting at least 4 months

Source: Reprinted from The Lancet, 390(10094), Prince HM et al., Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial, pgs. 555-566, Copyright (2017), with permission from Elsevier.[4]

An ad hoc exploratory subgroup analyses was requested by the CGP in patients with MF or pcALCL that did not have lymph node disease (N_0) versus patients who had lymph node disease (N_{1-x}). The sponsor stated that given the wide difference in ORR4 between patients in the BV and PC treatment groups, ORR4 showed clinically meaningful benefit by excluding patients with short response duration (Table 15).[6] Given the exploratory nature of this analysis and small number of patients in each subgroup for MF and pcALCL patients, the interpretation of results is limited.

Table 15: Ad hoc Exploratory Subgroup Analysis of Patients with Lymph Nodes versus without Lymph Nodes

Cutaneous T-cell Lymphoma Subgroups	ORR4 BV n/N (%)	ORR4 PC n/N (%)
MF N_0	14/25 (56%)	2/23 (9%)
MF N_{1-X}	10/23 (43%)	3/26 (12%)
pcALCL N_0	8/10 (80%)	3/11 (27%)
pcALCL N_{1-X}	4/6 (67%)	0/4 (0%)

Source: Checkpoint Meeting Materials[6]

At the updated analysis (data cut-off: August 16, 2017), there were 39 patients (60.9%, 95% CI 49.0-72.9) that achieved ORR4 in the BV group compared to five patients (7.8%, 95% CI 2.6-17.3) in the PC group as assessed by investigator.[6] The analysis of ORR4 by investigator was consistent with the results for ORR4 as assessed by IRF in the primary analysis.

At the final analysis (data cut-off: September 28, 2018), there were 35 patients (54.7%) in the BV group that achieved ORR4 per IRF compared to eight patients (12.5%) in the PC group p-value, p<0.001).[9] Similarly, the ORR4 by IRF was consistent with the results in the primary analysis.

The sponsor conducted a number of sensitivity analyses for ORR4. The results from all sensitivity analyses were consistent to the primary analysis for ORR4, favouring outcomes for patients receiving BV compared to patients receiving PC.[5]

Key Secondary Endpoints

The key secondary endpoints are summarized in Table 12.

Complete Response (CR)

At the primary analysis (data cut-off: May 31, 2016) according to IRF assessment, CR was reported in 10 patients (15.6%) (95% CI 6.7-24.5) in the BV group compared to one patient (1.6%) (95% CI 0-4.6) in the PC group (p-value= 0.0046; adjusted p-value=0.0046). The risk difference was 14.1% (95%CI -4.0-31.5).[5]

At the updated analysis (data cut-off: August 16, 2017) the CR rate according to investigator assessment was observed in 12 patients (18.8%, 95% CI 9.2-28.3) in the BV group compared to zero patients (95% CI 0-5.6) in the PC group.[6,35] The investigator assessment of CR was consistent with the IRF assessment of CR in the primary analysis.

At the final analysis (data cut-off: September 28, 2018) CR according to IRF for patients in the BV group was 11 patients (17.2%, 95% CI 7.9-26.4) compared to one patient (1.6%, 95% CI 0-8.4) in the PC group.[6]

Progression Free Survival (PFS)

At the primary analysis (data cut-off: May 31, 2016), based on a median PFS follow-up of 17.5 months (95% CI 12.6-22.9) using EMA censoring guidelines, which counted all events despite missed visits or starting of new anticancer therapies before an event,[3] 86 patients (67%) experienced a PFS event in the ITT population per IRF; of these patients, 74 experienced progression of disease (30 patients [47%] in the BV group and 44 patients [69%] in the PC group), and 12 patients died (6 patients [9%] in both treatment groups). The median PFS was 16.7 months (95% CI 14.9-22.8) in patients that received treatment with BV compared to 3.5 months (95% CI 2.4-4.6) in the PC group. PFS was prolonged in the BV group compared to PC group (HR=0.27, 95% CI 0.169-0.430), p-value <0.001; adjusted p-value <0.001).[5] The estimated 12- and 24-month PFS rates were 67.5% (95%CI 53.7-78.0) and 33.0% (95%CI 18.5-48.2), respectively in the BV group. In the PC group, the estimated 12- and 24-month PFS rates were 16.0% (95%CI 7.6-27.2) and not estimable, respectively.[3,5] Results are presented in Table 16. The Kaplan-Meier plot of PFS per IRF in the ITT population is shown in Figure 5.

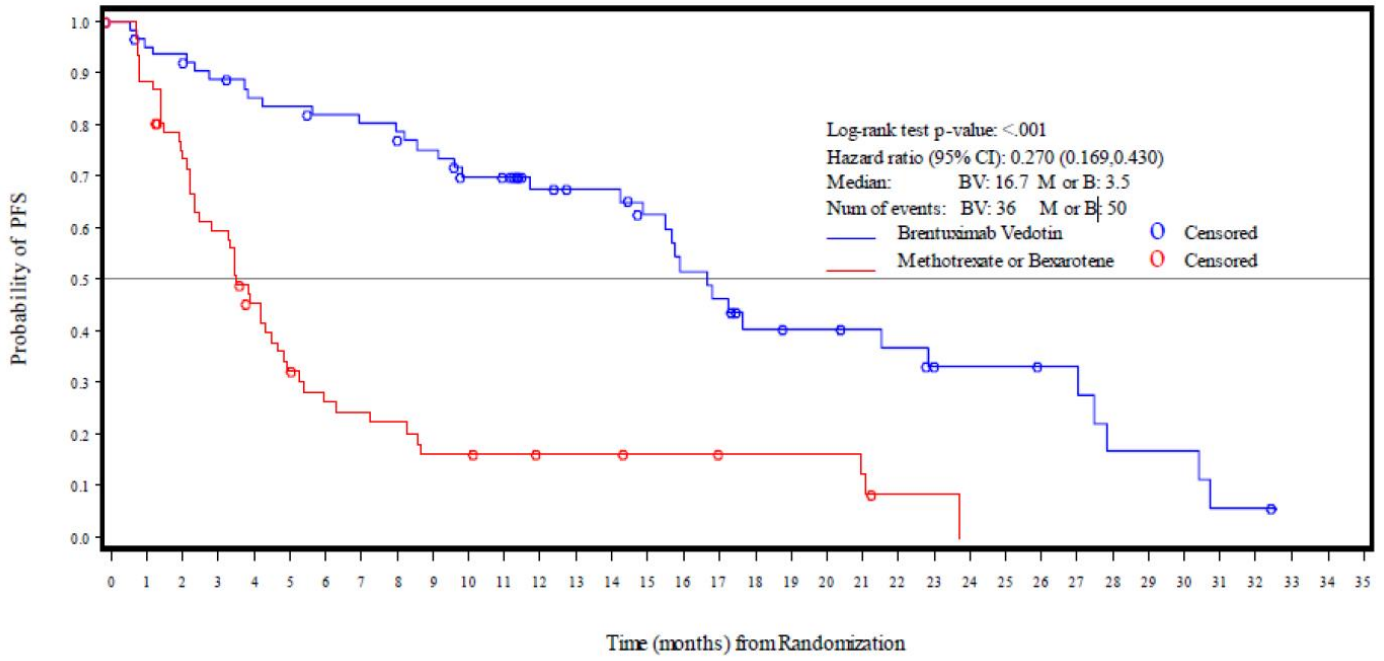
Subgroup analyses results in the ITT population for PFS were generally in favour of BV compared to PC for PFS per IRF. Of note, there were no differences in PFS for patients with baseline ECOG PS ≥1 or age ≥65 years (Figure 6).

Table 16: 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)		

Abbreviations: min=minimum, max=maximum, NE=not estimable
Source: EPAR 2017[5]

Figure 5: Kaplan-Meier Plot of PFS per IRF in the ITT Population

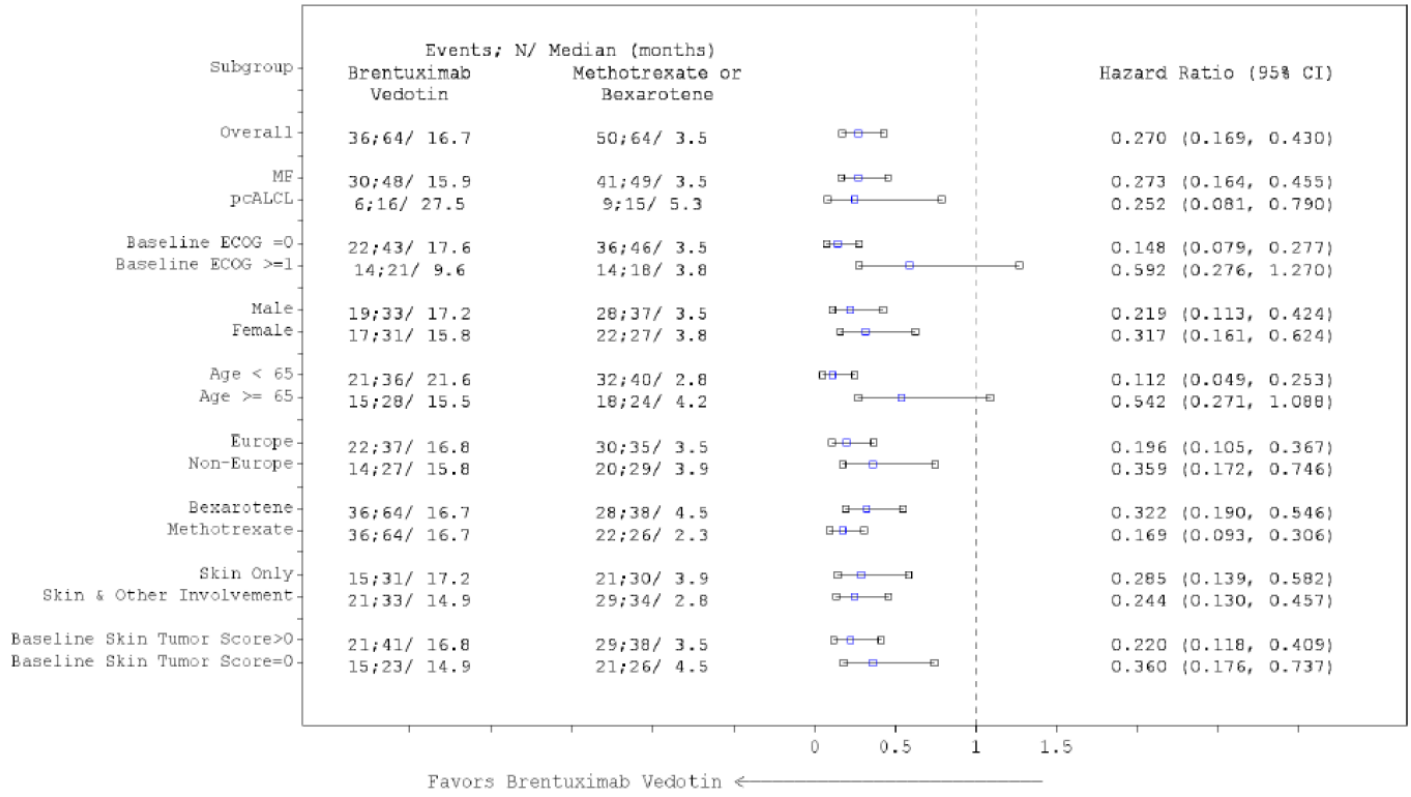


Number of patients at risk

Brentuximab Vedotin	64	59	58	54	51	50	48	47	46	43	38	38	29	27	27	23	19	17	13	12	12	11	10	8	7	7	7	6	3	3	3	1	1
Methotrexate or Bexarotene	64	54	42	34	24	17	13	12	11	8	8	7	7	6	6	5	5	5	4	4	4	3	1	1									

Source: EPAR 2017[5]

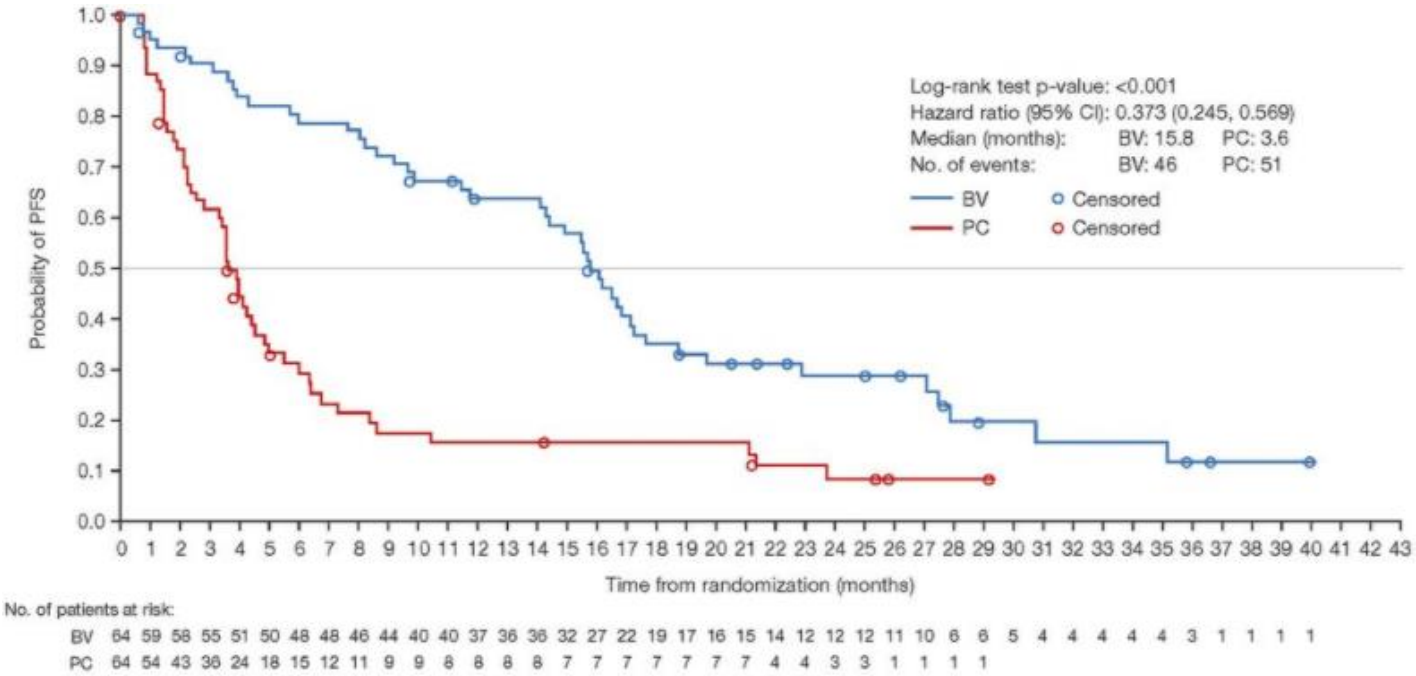
Figure 6: Forest Plot of PFS per IRF in the ITT Population



Source: EPAR 2017[5]

At the updated analysis (data cut-off: August 16, 2017), the median PFS follow-up was 25.2 months (95%CI 21.4-29.4),[8] as assessed by IRF. The median PFS was 16.5 months in the BV group compared to 3.5 months in the PC group (HR=0.322, 95%CI 0.207-0.501, p<0.001),[8] favouring treatment with BV. An additional analysis of PFS was conducted at the same data cut-off (August 16, 2017), assessed by investigator, showing similar results of PFS by IRF. The median PFS follow-up was 26.0 months (95%CI 21.6-29.4). The median PFS by investigator was 15.8 months (95% CI 14.1-17.2)[6] in the BV group compared to 3.6 months (95% CI 2.5-4.5) in the PC group (HR 0.373; 95% CI, 0.245-0.569; p<0.001).[8,35] The results for PFS by investigator assessment were consistent with the primary analysis of PFS by IRF. The Kaplan-Meier plot of PFS per IRF in the ITT population is shown in Figure 7.

Figure 7: Kaplan-Meier Plot of PFS per Investigator Assessment in the ITT Population (Data Cut-off: August 16, 2017)

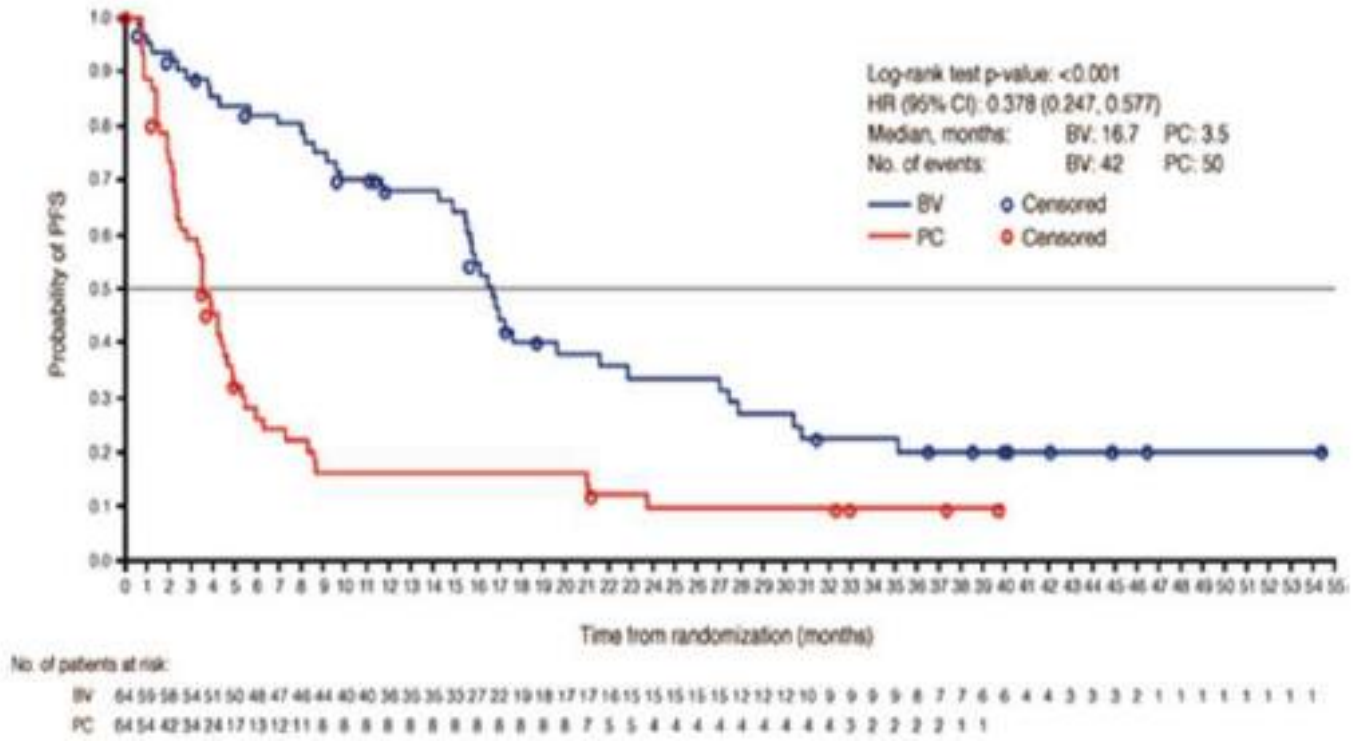


BV, brentuximab vedotin; CI, confidence interval; EMA, European Medicines Agency; PC, physician's choice; PFS, progression-free survival
*counted all events despite two or more missed visits or starting of subsequent anticancer therapy

Source: Used with permission of American Society of Hematology (ASH), from Updated analyses of the international, open-label, randomized, phase 3 alcanza study: longer-term evidence for superiority of brentuximab vedotin versus methotrexate or bexarotene for CD30-positive cutaneous T-cell lymphoma (CTCL), Horwitz SM et al, 130, Suppl 1, 2017; permission conveyed through Copyright Clearance Center, Inc.[35]

At the final analysis (data cut-off: September 28, 2018), the median PFS follow up was 36.8 months (95% CI 31.7, 40.2) as assessed by IRF. The median PFS according to IRF was 16.7 (95% CI not reported) months in the BV group compared to 3.5 months (95% CI not reported) in the PC group (HR=0.378; 95% CI, 0.247-0.577; p<0.001). The results of PFS per IRF assessment at the final analysis was consistent with the primary analysis.[8,9] The Kaplan-Meier plot of PFS per IRF in the ITT population is shown in Figure 8.

Figure 8: Kaplan-Meier Plot of PFS per IRF in the ITT population (Data Cut-off: September 28, 2018)



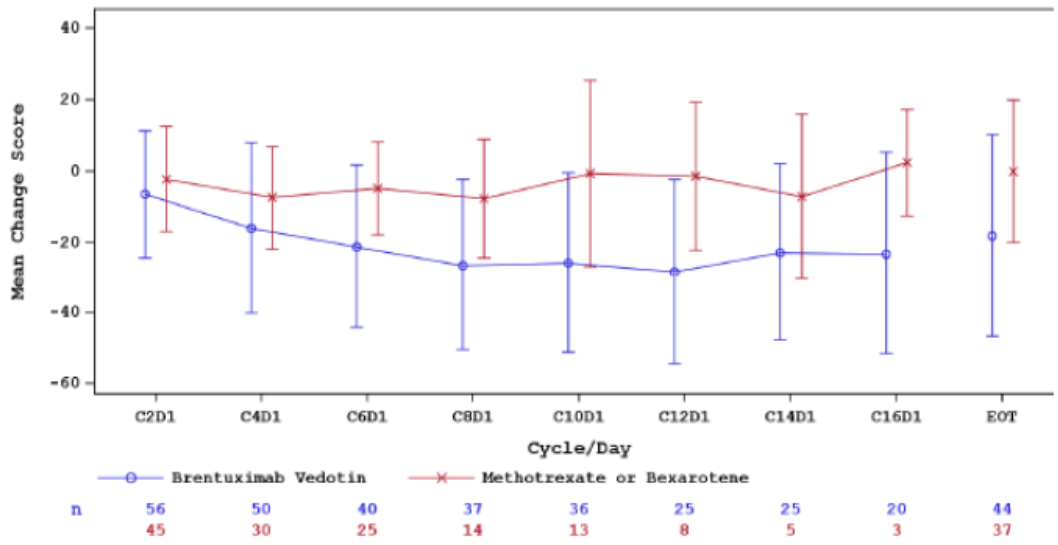
Source: Horwitz et al. Final data from the phase 3 ALCANZA study: brentuximab vedotin (BV) vs physician's choice (PC) in patients (PTS) with CD30-positive (CD30+) cutaneous tcell lymphoma (CTCL). Hematol Oncol. 2019;37(Suppl S2):286-288. Copyright © 2019 John Wiley and Sons. Reprinted with permission[9]

Skindex-29, Symptom Domain

At the primary analysis (data cut-off: May 31, 2016), the compliance rate (defined as the number of forms filled out as a proportion of forms anticipated to be filled out by patients)[49] at cycle 1 day 1 in the BV group and the PC group was 98.4%. At end of treatment, the compliance was 82.5% and 70.0% in the BV group and PC group, respectively.

The mean symptom domain scores for patients at baseline were 57.5 (standard deviation, 23.4) and 55.1 (standard deviation, 21.1) in the BV and PC groups, respectively.[45] The patient reported burden of symptoms assessed using the Skindex-29 demonstrated a greater symptom reduction in the BV group compared to the PC group; a mean maximum reduction of -27.96 points (standard deviation: 26.877) in the BV group was observed, compared to -8.62 (standard deviation: 17.013) in the PC group (p-value <0.001; adjusted p-value <0.001).[4,5] The difference in mean maximum reduction was -18.9 (95% CI -26.6 to -11.2) and was statistically significant in favour of the BV group compared to PC.[4] The MID for the Skindex-29 symptom domain computed by the Sponsor was 12.3 using half a standard deviation of change in score, 11.2 using Cohen's effect size, and 9.1 standard error of measurement. A clinically meaningful response was considered to have been obtained, as the maximum reduction difference from baseline (-18.9) exceeded all the MID thresholds.[5,45] The mean change from baseline Skindex-29 symptom score is shown below in Figure 9.

Figure 9: Mean Change from Baseline Skindex-29 Symptom Score in the ITT Population



Source: EPAR 2017[5]

At the updated analysis (data cut-off: August 16, 2017), the patient reported burden of symptoms assessed using the Skindex-29 tool demonstrated a greater reduction in the BV group of -28.08 (standard deviation: 26.863) versus -8.62 (standard deviation: 17.013) in the PC group with a statistically significant difference of -19.0 (-26.7 to -11.4) in favour of the BV group compared to the PC group.[6]

At the final analysis (data cut-off: September 28, 2018) the mean maximum reduction of patient reported burden of symptoms from baseline was -28.08 (standard deviation: 26.863) in the BV group and -8.62 (standard deviation: 17.013) in the PC group with a statistically significant difference of -19.0 (95% CI -26.7 to -11.4) in favour of the BV group.[6]

Other Secondary Endpoints

Other secondary endpoints are only reported for the primary analysis (data cut-off: May 31, 2016), with a median follow-up of 22.9 months.

Duration of Response (DOR)

DOR was evaluated by IRF for patients experiencing a CR or PR, including 43 patients in the BV group and 13 patients in the PC group. The median DOR was 15.1 months (95% CI 9.7-25.5) in the BV group and 18.3 months (95% CI 3.5-18.4) in the PC group. In the BV group, responses were ongoing at last assessment among 20 out of 43 responders (47%) compared to 7 out of 13 responders (54%) in the PC group; these patients had not experienced progressive disease and were censored for DOR assessments (Table 17).[3,5] DOR was highlighted by the CGP as being a clinically meaningful outcome. It should be noted that DOR as well as other secondary endpoints were not controlled for multiplicity.

Table 17: Duration of Response per IRF in the ITT Population

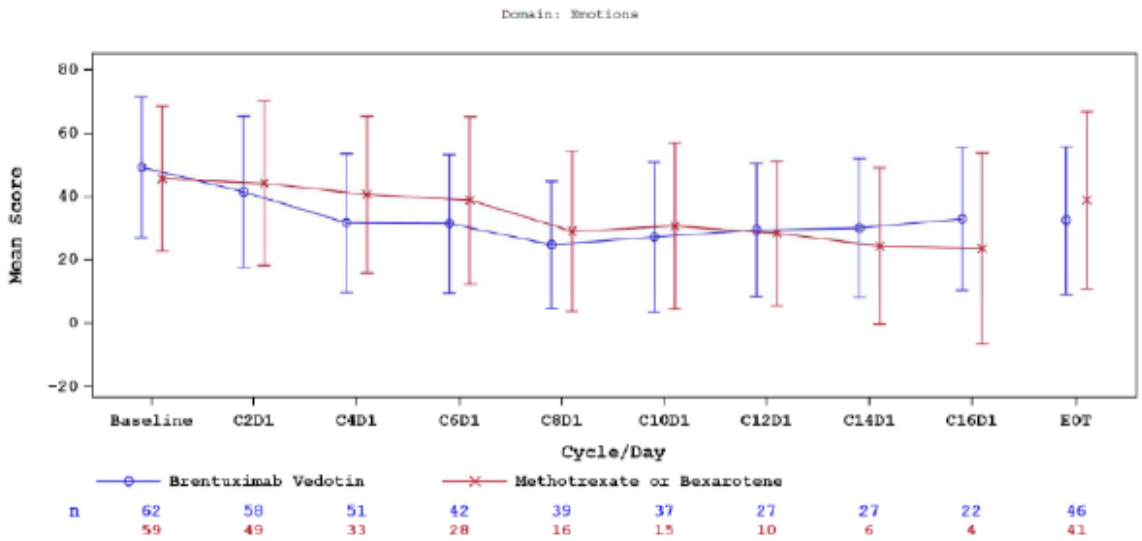
	Brentuximab Vedotin N=43	Methotrexate or Bexarotene N=13	Total N=56
DOR (months)			
Number with events (%)	22 (51)	5 (38)	27 (48)
Number censored (%)	21 (49)	8 (62)	29 (52)
25th percentile (95% CI)	8.5 (4.2, 13.4)	4.9 (2.1, 18.4)	8.5 (4.2, 14.4)
Median (95% CI)	15.1 (9.7, 25.5)	18.3 (3.5, 18.4)	15.6 (13.4, 20.6)
75th percentile (95% CI)	25.5 (18.8, 29.3)	18.4 (18.3, 18.4)	25.5 (18.4, 29.3)
Min, max	0.7, 29.3	1.6*, 18.4	0.7, 29.3
Kaplan-Meier estimates (a) (95% CI)			
6 months	83.0 (67.5, 91.5) [n=29]	72.2 (35.7, 90.2) [n=7]	80.9 (67.3, 89.3) [n=36]
1 year	64.0 (45.6, 77.6) [n=16]	72.2 (35.7, 90.2) [n=6]	66.3 (50.5, 78.1) [n=22]
1.5 years	44.0 (25.6, 61.0) [n=8]	72.2 (35.7, 90.2) [n=2]	49.8 (32.8, 64.7) [n=10]
2 years	32.1 (14.4, 51.4) [n=2]	NE [n=0]	29.1 (12.7, 47.7) [n=2]
Reason leading to DOR event			
Progressive disease	22 (51)	5 (38)	27 (48)
Reason for censoring			
Lost to follow-up	0	1 (8)	1 (2)
Withdrawal by subject	1 (2)	0	1 (2)
No progressive disease at last assessment	20 (47)	7 (54)	27 (48)

Source: EPAR 2017[5]

Patient Reported Outcomes – Skindex-29 Emotional and Functional Domains

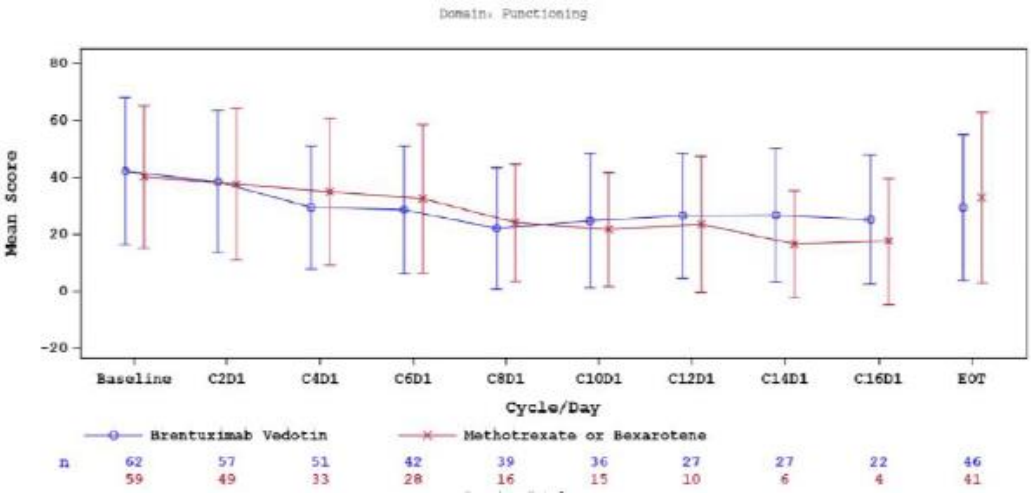
For the emotional domain of the Skindex-29, the mean change from baseline to end of treatment was -14.43 (standard deviation: 20.901) for the BV group compared to -1.84 (standard deviation: 18.555) for the PC group. For the functional domain, the mean change from baseline to end of treatment was -11.10 (standard deviation: 25.312) for the BV group and -1.22 (standard deviation: 22.448) in the PC group. Neither the emotional nor functional domains of the Skindex-29 showed substantial differences over time. However, at the end of treatment, skin disease had less of an impact in both the emotional and functional domains for patients treated with BV compared to PC.[4,45] The Skindex-29 mean score time curves for the emotional and functional domains in the ITT population are shown below in Figure 10 and Figure 11.

Figure 10: Skindex-29 Mean Score Time Curves in the ITT Population for the Emotions Domain



Source: EPAR 2017[5]

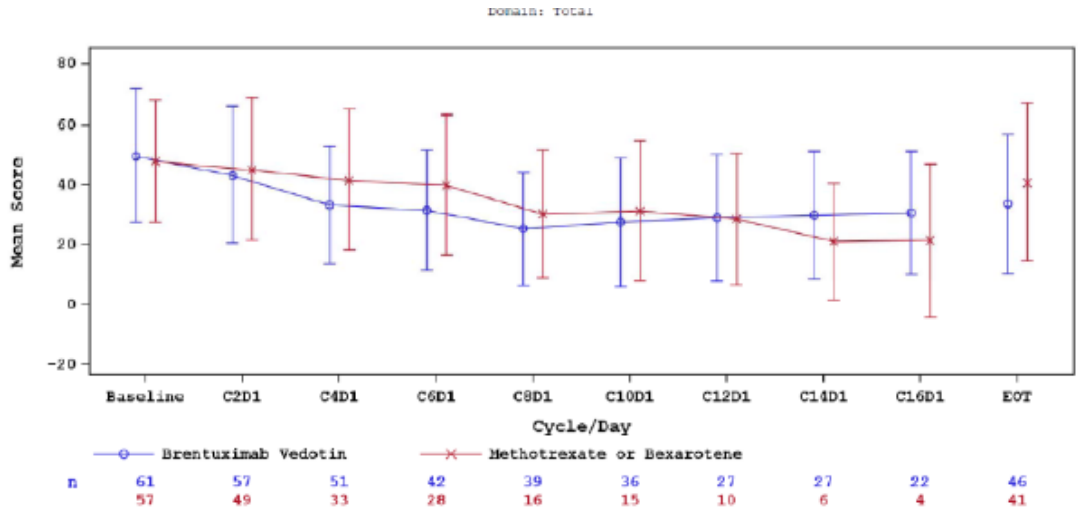
Figure 11: Skindex-29 Mean Score Time Curves in the ITT Population for the Functions Domain



Source: EPAR 2017[5]

According to the sponsor, the mean maximum reduction was not calculated for the Skindex-29 total score but the mean change from baseline in Skindex-29 composite total score was generated. The mean change from baseline to the end of treatment visit for the total score was -14.84 (standard deviation: 22.681) for the BV group and -0.96 (standard deviation: 18.973) for the PC group. The difference in mean change from baseline at the end of treatment visit was -13.88 with 95% CI (-21.12 to -6.64), based on the normal approximation.[6] Results for the Skindex-29 total score domain are presented in Figure 12. There were no substantial differences between the treatment groups.

Figure 12: Skindex-29 Mean Score Time Curves in the ITT Population for the Total Score Domain



Source: EPAR 2017[5]

Patient Reported Outcomes – FACT-G and EQ-5D

There were no meaningful differences observed in the FACT-G and EQ5D between the BV and PC groups. Both questionnaires were reported by the EMA to have had high compliance with similar compliance over the treatment course in both the BV and PC treatment groups.[5,45] Mean FACT-G total score changes from baseline to the end of treatment were 0.15 (SD=16.388) for patients in the BV group compared to -2.29 (SD=17.171) for patients in the PC group. A difference of greater than 5-7 points was required to indicate a MID for the FACT-G total score, although this was not met. However, overall scores for the FACT-G were stated to be greater for patients in the BV group from cycles 2 to 12, and at the end of treatment compared to patients in the PC group, suggesting better quality of life. There were no meaningful differences in FACT-G scores for emotional, social/family, physical and functional subscales.[45]

Mean EQ-5D changes from baseline to the end of treatment in EQ-5D USA time trade-offs were 0.02 and -0.02 in the BV and PC groups, respectively. The mean changes from baseline to the end of treatment in EQ-5D UK time trade-offs were 0.03 and -0.04, in the BV and PC groups, respectively. The MID was not reached for either the UK- and USA-indexed data requiring a score of greater than 0.074 (range -0.011 to 0.140). While no meaningful differences were observed between treatment groups, the BV group showed trends for higher overall scores.[45]

Exploratory Analyses – Overall Survival (OS)

Analyses for OS were not specified in the protocol of the ALCANZA trial and should be considered exploratory.

At the primary analysis (data cut-off: May 31, 2016), 29 patients (23%) experienced an OS event in the total ITT population for OS. Median OS was not estimable in either treatment group. The median OS follow-up in the BV and PC groups were 23.2 months (95%

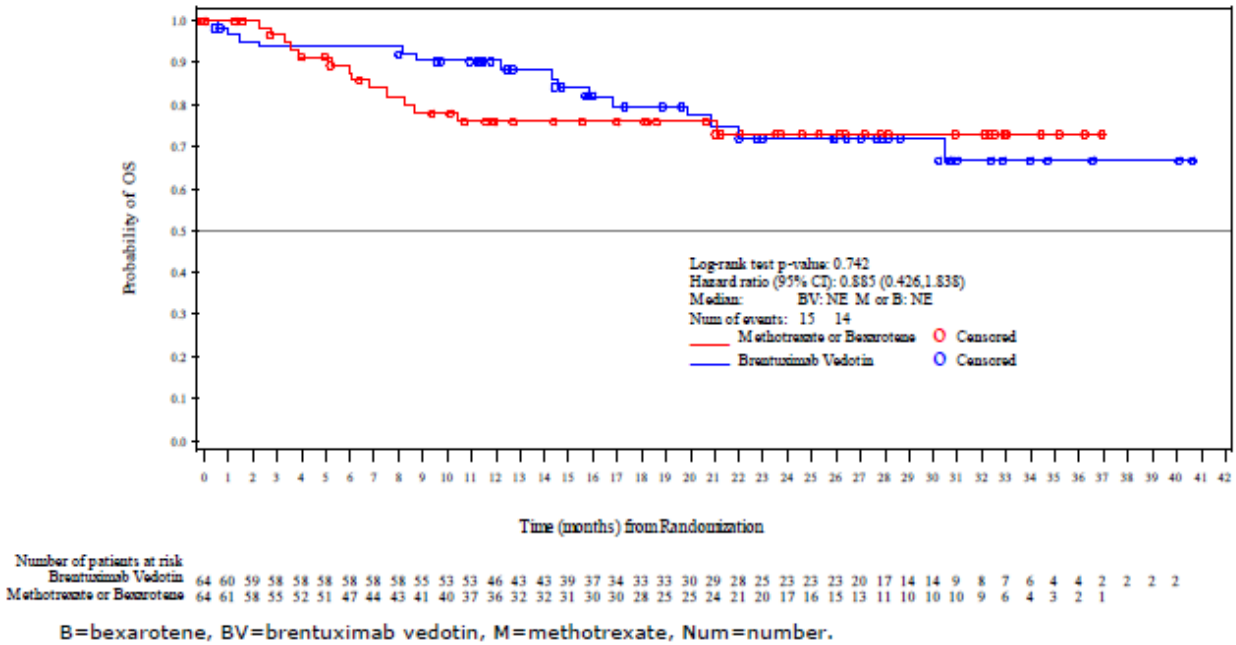
CI 19.1-28.1) and 20.8 months (95% CI 14.6- 23.9), respectively (HR=0.885, 95% CI 0.426-1.838; p-value 0.742).[5] The OS results are presented in Table 18 and the Kaplan-Meier plot for OS in Figure 13.

Table 18: 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)		

Source: EPAR 2017[5]

Figure 13: Kaplan-Meier Plot of OS in the ITT Population



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

Source: EPAR 2017[5]

At the final analysis (data cut-off: September 28, 2018), the median OS was 48.4 months in the BV group (95% CI 41.0-51.7) and 42.9 months in the PC group (95% CI 38.6-49.4). There was a trend in favour of the BV group compared to the PC group (HR=0.745, 95% CI 0.421-1.318; p-value 0.310).[6]

Deaths were similar among the two treatment groups, 23 patients and 25 patients in the BV and PC groups, respectively.[9]

mSWAT Assessment

The mSWAT assessment was included as a component of the skin response and was considered a main driver of GRS by the sponsor.[3] The mSWAT assessment was performed by the investigator. mSWAT assessment results at the primary analysis (data cut-off: May 31, 2016) are reported in Figure 14. Among patients with MF in the PC group, 20 patients (41%) compared with 37 patients (77%) in the BV group demonstrated a 50% or higher reduction in mSWAT. Among patients with pcALCL, 10 patients (63%) in the BV group demonstrated a greater than 100% reduction in skin disease.[4]

Figure 14: mSWAT Assessment of Global Response Score

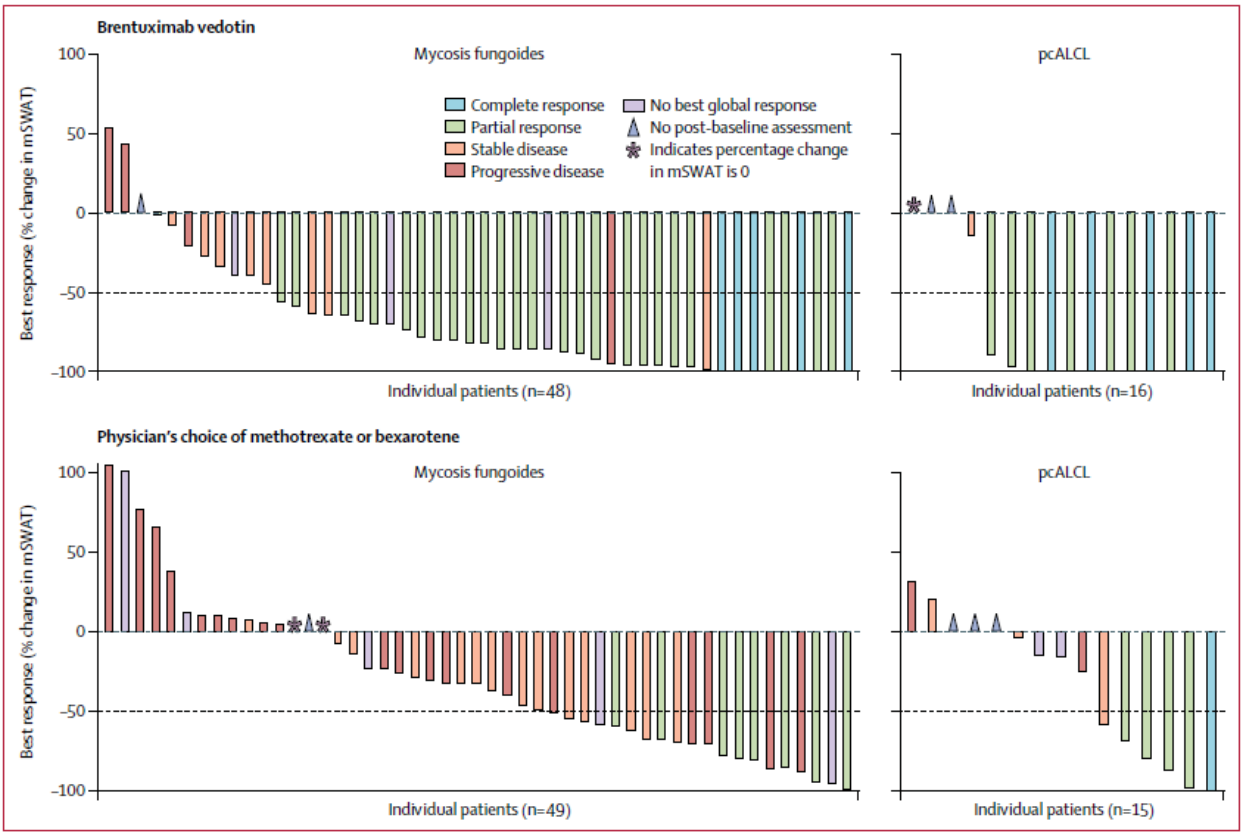


Figure 3: **Maximum percent change in skin mSWAT score**
mSWAT=modified severity weighted assessment tool. pcALCL=primary cutaneous anaplastic large-cell lymphoma.

Source: Reprinted from The Lancet, 390(10094), Prince HM et al., Brentuximab vedotin or physician's choice in CD30+ cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial, pgs. 555-566, Copyright (2017), with permission from Elsevier.[4]

Safety Outcomes

Results for safety are reported for the primary analysis (data cut-off: May 31, 2016). There were no safety results reported for the updated or final analysis. There were 66 patients in the BV group and 62 patients in the PC group that received treatment and were included in the safety population. Safety data are reported based on a median follow up of 22.9 months. The median duration of treatment was approximately 268.5 days (12 cycles) for patients in the BV group. For patients in the PC group, the median treatment duration was 114 days (5.5 cycles) for those receiving bexarotene, and 77.0 days (3.0 cycles) for those receiving methotrexate. A maximum number of 16 cycles was permitted within the trial, of which only 36% and 8% of patients received in the BV and PC groups, respectively.[5] The median relative dose intensity was 99.6% (IQR, 92.7-100.0) in the BV group and 94.3% (IQR, 73.6-100.0) for patients receiving bexarotene in the PC group; for patients receiving methotrexate, dose intensity was not calculated as a range of doses was permitted.[3]

Dose modifications are reported in Table 19. The proportion of dose modifications were similar between treatment groups, occurring at 73% in the BV group compared to 72% in the PC group; however, greater dose modifications were required for patients receiving bexarotene (86%) compared to methotrexate (52%).

Table 19: Dose Modifications in the ALZANZA Study Population

		Physician's Choice		
Patients, n (%)	Brentuximab Vedotin (N=66)	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.

Source: EPAR 2017[5]

Reporting of at least one AE of any grade was similar between both treatment groups with 63 patients (95%) in the BV group and 56 patients (90%) in the PC group. In the BV group, 27 patients (41%) experienced any grade ≥3 AEs in the BV group versus 29 patients (47%) in the PC group. Grade ≥3 AEs related to treatment occurred in similar proportions across both treatment groups with 19 patients (29%) and 18 patients (29%) in the BV and PC groups, respectively (Table 20).

Serious AEs were similar between groups occurring in 19 patients (29%) and 18 patients (29%) in the BV and PC groups, respectively. Overall, the occurrence of grade ≥3 AEs, drug related grade ≥3 AEs, and serious AEs were similar in the BV and PC groups. A higher proportion of patients in the BV group discontinued treatment due to an AE as compared to patients in the PC

group. Specifically, there were 16 patients (24%) in the BV group that discontinued treatment due to AE compared to five patients (8%) in the PC group.

Table 20: Overall Safety Profile (Safety Population)

	Brentuximab vedotin (n=66)	Methotrexate or bexarotene (n=62)	Total (N=128)
Any AE — n (%)	63 (95)	56 (90)	119 (93)
Any grade ≥3 AE — n (%)	27 (41)	29 (47)	56 (44)
Drug-related AE — n (%)	57 (86)	44 (71)	101 (79)
Drug-related grade ≥3 AE — n (%)	19 (29)	18 (29)	37 (29)
Serious AE — n (%)	19 (29)	18 (29)	37 (29)
Drug-related serious AE — n (%)	9 (14)	3 (5)	12 (9)
AE resulting in study drug discontinuation — n (%)	16 (24)	5 (8)	21 (16)
On-treatment deaths — n (%)*	4 (6)	0	4 (3)

AE=adverse event.

*On-treatment deaths are defined as deaths that occur within 30 days after the last dose of study drug. Causes of deaths in the four patients in the brentuximab vedotin arm were: lymphoma, sepsis, multiple organ dysfunction syndrome, and pulmonary embolism. Multiple organ dysfunction syndrome was considered by the investigator to be related to brentuximab vedotin treatment.

Source: Reprinted from The Lancet, 390(10094), Prince HM et al., Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial, pgs. 555-566, Copyright (2017), with permission from Elsevier.[4]

In the BV group (n=66), the most frequently reported grade 3 treatment-emergent AEs (≥10% of patients) were peripheral sensory neuropathy in three patients (5%) and fatigue in three patients (5%). No frequently occurring (≥10% of patients) grade 4 treatment-emergent AEs occurred in the BV group. Of the patients that received methotrexate of the PC group (n=25), the most frequently reported grade 3 treatment-emergent AEs (≥10% of patients) were fatigue, pyrexia, and skin infection, which occurred in one patient (4%) each. There were no frequently occurring (≥10% of patients) grade 4 treatment-emergent AEs reported for patients that received methotrexate of the PC group. Of the patients that received bexarotene of the PC group (n=37), the most frequently reported grade 3 treatment-emergent AE (≥10% of patients) was hypertriglyceridemia, which occurred in five patients (14%). Similarly, the most frequently reported grade 4 treatment-emergent AE (≥10% of patients) was hypertriglyceridemia, which occurred in three patients (8%).[4]

Table 21: Treatment-emergent Adverse Events Occurring in ≥ 10% of Patients

	Brentuximab vedotin (n=66)			Methotrexate (n=25)			Bexarotene (n=37)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Peripheral sensory neuropathy SMQ	30 (45%)*	3 (5%)	0	1 (4%)	0	0	0	0	0
Nausea	24 (36%)	1 (2%)	0	4 (16%)	0	0	4 (11%)	0	0
Diarrhoea	19 (29%)	2 (3%)	0	1 (4%)	0	0	3 (8%)	0	0
Fatigue	19 (29%)	3 (5%)	0	5 (20%)	1 (4%)	0	12 (32%)	0	0
Vomiting	11 (17%)	1 (2%)	0	2 (8%)	0	0	1 (3%)	0	0
Alopecia	10 (15%)	0	0	1 (4%)	0	0	1 (3%)	0	0
Pruritus	11 (17%)	1 (2%)	0	2 (8%)	0	0	6 (16%)	2 (5%)	0
Pyrexia	11 (17%)	0	0	7 (28%)	1 (4%)	0	4 (11%)	0	0
Decreased appetite	10 (15%)	0	0	1 (4%)	0	0	2 (5%)	0	0
Asthenia	7 (11%)	1 (2%)	0	3 (12%)	0	0	2 (5%)	0	1 (3%)
Dyspnoea	7 (11%)	0	0	0	0	0	0	0	0
Maculopapular rash	7 (11%)	1 (2%)	0	1 (4%)	0	0	2 (5%)	0	0
Peripheral oedema	7 (11%)	0	0	4 (16%)	0	0	2 (5%)	0	0
Pruritus (generalised)	7 (11%)	1 (2%)	0	0	0	0	1 (3%)	0	0
Arthralgia	8 (12%)	0	0	2 (8%)	0	0	2 (5%)	0	0
Myalgia	8 (12%)	0	0	0	0	0	2 (5%)	0	0
Headache	5 (8%)	0	0	1 (4%)	0	0	5 (14%)	0	0
Anaemia	3 (5%)	0	0	0	0	0	6 (16%)	3 (8%)	0
Skin infection	2 (3%)	2 (3%)	0	3 (12%)	1 (4%)	0	4 (11%)	0	0
Hypertriglyceridaemia	1 (2%)	0	0	0	0	0	11 (30%)	5 (14%)	3 (8%)

Shown are commonly reported (≥10% of patients) treatment-emergent adverse events in the safety population. SMQ=standardised Medical Dictionary for Regulatory Activities query. *Overall, events reported by investigators as peripheral neuropathy or peripheral sensory neuropathy (including events additional to those reported in ≥10% of patients) were reported as grade 1 in 17 patients, grade 2 in 21 patients, and grade 3 in six patients.

Source: Reprinted from The Lancet, 390(10094), Prince HM et al., Brentuximab vedotin or physician's choice in CD30+ cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial, pgs. 555-566, Copyright (2017), with permission from Elsevier.[4]

Adverse Events of Interest

Members of the CGP identified peripheral neuropathy and cardiac safety as an AE of interest. A total of 44 patients (67%) in the BV group experienced peripheral neuropathy compared to four patients (6%) in the PC group; of these 44 patients, 36 (82%) showed either improvement or resolution of peripheral neuropathy by the last follow-up. In the BV group, grade 3 peripheral neuropathy occurred in six patients (9%) compared to no events of grade 3 peripheral neuropathy in the PC group.[4] Peripheral neuropathy experienced by patients either improved or was resolved. Specifically, at end of treatment, three out of these six patients had improved, and at last follow-up four out of these six patients had complete resolution of their symptoms and two patients had improved. There were nine patients that discontinued treatment with BV due to peripheral neuropathy, compared to zero in the PC group.[4] According to the Sponsor, a review of all grade 3 or grade 4 cardiac safety issues revealed one patient in the PC group who received bexarotene experienced bilateral pedal edema with worsening of diastolic failure. There were no patients in the BV group who experienced grade 3 or grade 4 cardiac safety issues.[6]

According to the sponsor, at the updated analysis (data cut-off: August 16, 2017), 38 of the 44 patients (86%) showed either improvement or complete resolution of peripheral neuropathy in the BV group.[35] There were no ongoing patients with reported events of grade 3 or 4 peripheral neuropathy. Among the six patients who experienced grade 3 peripheral neuropathy in the BV group, two patients experienced improvement while four patients showed complete resolution.[6]

At the final analysis (data cut-off: September 28, 2018), there were no ongoing patients with events of grade 3 or 4 peripheral neuropathy.[6]

Deaths

Deaths were similar between both treatment groups, with 16 deaths (24%) and 14 deaths (23%) having occurred in the BV and PC groups, respectively.[4] Treatment related deaths were defined as deaths that occurred within 30 days after the last dose of study drug.[4] There were four patients in the BV group that experienced on-treatment deaths; three were unrelated to study drug and caused by lymphoma, sepsis, and pulmonary embolism (n=1 each).[4,5] One patient with pcALCL with $T_{3b}N_0M_1$ experienced multiple organ dysfunction syndrome which was attributed, by the investigator, to be due to tumor lysis (on sites of visceral lymphoma involvement) caused by BV.[4] Results are summarized in Table 21.

6.4 Ongoing Trials

There are no ongoing trials.

7 Supplemental Questions

None identified.

8 Comparison with Other Literature

None identified.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on brentuximab vedotin (Adcetris) for patients with pcALCL or CD30-expressig MF. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

#	Searches	Results
1	Brentuximab Vedotin/	3924
2	(Adcetris* or brentuximab* or adtsetrys* or cac10-vcmmae or cac10vcmmae or cac10-1006 or cac101006 or sgn-35 or sgn35 or 7XL5ISS668).ti,ab,ot,kf,kw,hw,nm,rn.	5097
3	or/1-2	5097
4	exp Lymphoma, T-Cell, Cutaneous/	23961
5	((cutaneous adj5 (T-cell lymphoma* or large cell lymphoma*)) or granulomatous slack skin).ti,ab,kf,kw.	14711
6	(primary cutaneous and (anaplastic large cell lymphoma* or T-cell lymphoma* or anaplastic cell lymphoma* or ((CD30+ T-cell or CD30 positive) adj3 T-cell))).ti,ab,kf,kw.	3358
7	(primary cutaneous adj5 lymphoma*).ti,ab,kf,kw.	4927
8	(primary adj5 CTCL).ti,ab,kf,kw.	468
9	(cutaneous and (CD30+ or CD30 positive) and (lymphoproliferative disease* or lymphoproliferative disorder* or LPD or LPDs)).ti,ab,kf,kw.	912
10	(pcALCL or pc-ALCL or (primary cutaneous adj5 ALCL)).ti,ab,kf,kw.	511
11	or/4-10	31484
12	(mycosis fungoides or granuloma fungoides or granuloma sarcomatodes or "Alibert-Bazin" or pagetoid reticulos* or Woringer-Kolopp Disease* or Ketron Goodman Disease*).ti,ab,kf,kw.	14322
13	(Sezary* adj2 (disease* or syndrome* or lymphoma* or erythroderma* or reticulos*)).ti,ab,kf,kw.	5406
14	or/12-13	16595
15	11 or 14	33442
16	3 and 15	570
17	16 use cctr	25
18	16 use medall	116
19	*brentuximab vedotin/	1141
20	(Adcetris* or brentuximab* or adtsetrys* or cac10-vcmmae or cac10vcmmae or cac10-1006 or cac101006 or sgn-35 or sgn35).ti,ab,kw,dq.	3590
21	or/19-20	3633
22	Anaplastic large cell lymphoma/	3717
23	((cutaneous adj5 (T-cell lymphoma* or large cell lymphoma*)) or granulomatous slack skin).ti,ab,kw.	14564
24	(primary cutaneous and (anaplastic large cell lymphoma* or T-cell lymphoma* or anaplastic cell lymphoma* or ((CD30+ T-cell or CD30 positive) adj3 T-cell))).ti,ab,kw.	3337
25	(primary cutaneous adj5 lymphoma*).ti,ab,kw.	4901
26	(primary adj5 CTCL).ti,ab,kw.	468
27	(cutaneous and (CD30+ or CD30 positive) and (lymphoproliferative or LPD or LPDs)).ti,ab,kw.	951

28	(pcALCL or pc-ALCL or (primary cutaneous adj5 ALCL)).ti,ab,kw.	508
29	or/22-28	20583
30	exp cutaneous T-cell lymphoma/	23961
31	(mycosis fungoides or granuloma fungoides or granuloma sarcomatodes or "Alibert-Bazin" or pagetoid reticulos* or Woringer-Kolopp Disease* or Ketron Goodman Disease*).ti,ab,kw.	14284
32	(Sezary* adj2 (disease* or syndrome* or lymphoma* or erythroderma* or reticulos*)).ti,ab,kw.	5370
33	or/30-32	26756
34	29 or 33	36386
35	21 and 34	592
36	35 use oemezd	374
37	(conference review or conference abstract).pt.	3775279
38	36 not 37	221
39	18 or 38	337
40	limit 39 to english language	319
41	17 or 40	344
42	remove duplicates from 41	247
43	36 and 37	153
44	limit 43 to english language	153
45	limit 44 to yr="2015 -Current"	130
46	42 or 45	377

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#16	Search #14 AND #15	5
#15	Search publisher[sb]	395270
#14	Search #1 AND #13	119
#13	Search #9 OR #12	14350
#12	Search #10 OR #11	7229
#11	Search Sezary disease*[tiab] OR Sezarys disease*[tiab] OR Sezary's disease*[tiab] OR Sezary syndrome*[tiab] OR Sezarys syndrome*[tiab] OR Sezary's syndrome* OR Sezary lymphoma*[tiab] OR Sezarys lymphoma*[tiab] OR Sezary's lymphoma*[tiab] OR Sezary erythroderma*[tiab] OR Sezarys erythroderma*[tiab] OR Sezary's erythroderma*[tiab] OR Sezary reticulos*[tiab] OR Sezarys reticulos*[tiab] OR Sezary's reticulos*[tiab]	2143
#10	Search mycosis fungoides[tiab] OR granuloma fungoides[tiab] OR granuloma sarcomatodes[tiab] OR "Alibert-Bazin"[tiab] OR pagetoid reticulos*[tiab] OR Woringer-Kolopp Disease*[tiab] OR Ketron Goodman Disease*[tiab]	6280
#9	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	13268
#8	Search pcALCL[tiab] OR pc-ALCL[tiab] OR (primary cutaneous[tiab] AND ALCL[tiab])	271

Search	Query	Items Found
#7	Search Cutaneous[tiab] AND (CD30+[tiab] OR CD30 positive[tiab]) AND (lymphoproliferative disease*[tiab] OR lymphoproliferative disorder*[tiab] OR LPD[tiab] OR LPDs[tiab])	358
#6	Search Primary[tiab] AND CTCL[tiab]	383
#5	Search primary cutaneous[tiab] AND lymphoma*[tiab]	2399
#4	Search primary cutaneous[tiab] AND (anaplastic large cell lymphoma*[tiab] OR T-cell lymphoma*[tiab] OR anaplastic cell lymphoma*[tiab] OR CD30+ T-cell[tiab] OR CD30 positive T-cell[tiab] OR CD30+ large T-cell[tiab] OR CD30 positive large T-cell[tiab])	1328
#3	Search (cutaneous [tiab] AND (T-cell lymphoma*[tiab] OR large cell lymphoma*[tiab])) OR granulomatous slack skin[tiab]	6522
#2	Search Lymphoma, T-Cell, Cutaneous[mh]	9692
#1	Search Brentuximab Vedotin[mh] OR 7XL5ISS668[rn] OR Adcetris*[tiab] OR brentuximab*[tiab] OR adtsetrys*[tiab] OR cac10-vcmmae[tiab] OR cac10vcmmae[tiab] OR cac10-1006[tiab] OR cac101006[tiab] OR sgn-35[tiab] OR sgn35[tiab]	1013

3. **Cochrane Central Register of Controlled Trials (CENTRAL)**
   (searched via Ovid)

4. **Grey literature search via:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Adcetris/brentuximab vedotin, primary cutaneous anaplastic large cell lymphoma

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Adcetris/brentuximab vedotin, primary cutaneous anaplastic large cell lymphoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)

https://www.esmo.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Adcetris/brentuximab vedotin, primary cutaneous anaplastic large cell lymphoma — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[52]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Adcetris (brentuximab vedotin) and primary cutaneous anaplastic large cell lymphoma.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of August 20, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[53] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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2. Adcetris® (brentuximab vedotin): lyophilized powder for reconstitution with 10.5 mL of sterile water for injection, USP 50 mg [product monograph]. Bothell (WA): Seattle Genetics; 2019 Nov 22.
3. Clinical Study Report: C25001. 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 [internal sponsor's report]. In: pan-Canadian Oncology Drug Review sponsor submission: Adcetris® (brentuximab vedotin), 50 mg lyophilized powder for injection in pcALCL or CD30-expressing MF. Bothell (WA): Seattle Genetics; 2020 Mar 30.
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