ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Brentuximab vedotin for treating relapsed or refractory CD30-positive cutaneous T-cell lymphoma [ID 1190]

Confidential until published

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UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Brentuximab vedotin for treating relapsed or refractory CD30-positive cutaneous T-cell lymphoma [ID 1190]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Nigel Fleeman, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Angela Stainthorpe, Health Economic Modeller, LR*i*G, University of Liverpool

Rachel Houten, Health Economic Modeller, LR*i*G, University of Liverpool

Marty Richardson, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Sophie Beale, Research Associate, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Eleanor Kotas, Information Specialist, LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Isabel Syndikus, Consultant in Clinical Oncology, Clatterbridge Centre NHS Foundation Trust

Correspondence to: Nigel Fleeman, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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Contributions of authors:

Nigel Fleeman	Project lead, critical appraisal of the clinical evidence and supervised the final report
Angela Stainthorpe	Critical appraisal of the economic evidence
Rachel Houten	Critical appraisal of the economic model
Marty Richardson	Critical appraisal of the statistical evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical evidence and economic advice, editorial input
Yenal Dundar	Critical appraisal of the adverse event data
Eleanor Kotas	Cross checking of the submission search strategies
Joanne McEntee	Critical appraisal of the company submission
Isabel Syndikus	Clinical advice and critical appraisal of the clinical sections of the company submission

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AE	Adverse event
alloSCT	Allogeneic stem-cell transplant
ASCT	Autologous stem-cell transplant
BAD	British Association of Dermatologists
BEX	Bexarotene
BSA	Body surface area
BV	Brentuximab vedotin
CD30	Cluster of differentiation
CD30+	CD30-positive
CD30+ LPDs	Primary cutaneous CD30-positive lymphoproliferative disorders
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CTCL	Cutaneous T-cell lymphoma
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECP	Extracorporeal photochemotherapy
EMA	European Medicines Agency
eMIT	Electronic market information tool
EOT	End of treatment
EPAR	European Public Assessment Report
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L	European Quality of Life 5-Dimension 3 Level Version
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy – General
HL	Hodgkin lymphoma
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
IFN-α	Interferon alpha
INV	Investigator
IV	Intravenous
IRF	Independent review facility
IRRs	Infusion-related reactions
ISCL	International Society for Cutaneous Lymphomas
ITT	Intent-to-treat
LPD	Lymphoproliferative disorders
LyP	Lymphomatoid papulosis
MF	Mycosis fungoides
mSWAT	Modified Severity Weighted Assessment Tool
MiMs	Monthly index of medical specialties
MTX	Methotrexate
nHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
ORR4	Objective global response lasting ≥4 months
OS	Overall survival
PC	Physician's choice
pcALCL	Primary cutaneous anaplastic large cell lymphoma

PFS	Progression-free survival
PHE	Public Health England
PR	Partial response
PROCLIPI	Prospective Cutaneous Lymphoma International Prognostic Index
PAS	Patient Access Scheme
PSA	Probability sensitivity analysis
PSS	Personal Social Services
PUVA	Psoralens + ultraviolet A light therapy (phototherapy)
QALY(s)	Quality adjusted life year(s)
sALCL	Systemic anaplastic large cell lymphoma
SCT	Stem-cell transplant
SD	Standard deviation
SDT	Skin directed therapy
SmPC	Summary of product characteristics
SS	Sézary syndrome
TNMB	Tumour-node-metastasis-blood
ToT	Time-on-treatment
TSAP	Trial statistical analysis plan
TSEB	Total skin electron beam therapy
UKCLG	United Kingdom Cutaneous Lymphoma Group
VAS	Visual Analogue Scale

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Takeda UK Ltd in support of the use of brentuximab vedotin (ADCETRIS), hereafter referred to as BV, for patients with relapsed or refractory cluster of differentiation 30-positive lymphoproliferative disorders (CD30+ LPDs) cutaneous T-cell lymphoma (CTCL) following skin directed therapies and/or at least one systemic therapy. The European Commission granted an extension of the marketing authorisation valid throughout the European Union for BV to include the treatment of adult patients with CD30+ CTCL after at least one prior systemic therapy on 15 December 2017.

1.2 Critique of the decision problem in the company submission

The focus of the company submission (CS) is a subgroup of the licensed population, namely patients with advanced stage CTCL. The company's rationale for this approach is that patients with advanced stage CTCL constitute the population most relevant to NHS clinical practice. Clinical advice to the ERG is that these patients are the most likely candidates for treatment with systemic therapies.

CTCL is a heterogeneous disease with many different subtypes. Only patients with mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL) were included in the ALCANZA trial, the company's main source of clinical evidence.

The company considers that the relevant comparators to BV are methotrexate (MTX) and bexarotene (BEX), which are described by the company, and in treatment guidelines, as *Category A* systemic therapies. It is anticipated by the company that *Category B* therapies would be used after BV in the treatment pathway (if required at all). *Category B* therapies include single or multi-agent chemotherapy regimens and total skin electron beam therapy. Clinical advice to the ERG is that (i) *Category A* therapies are the most relevant comparators to BV for patients with MF and (ii) *Category B* therapies would normally be preferred to *Category A* therapies for patients with advanced stages of pcALCL who have received at least one prior systemic therapy and are fit enough to tolerate the drugs. However, clinical advice is that MTX and BEX are likely to be appropriate comparators to BV for the patients included in the ALCANZA trial with pcALCL who were not fit for *Category B* drugs.

The company highlights that allogeneic stem cell transplant (alloSCT) may be a treatment option for some patients, namely those who have a good response to prior treatment. Therefore, for a proportion of patients, the company modelled alloSCT following treatment with BV or a comparator in its base case economic model.

1.3 Summary of the clinical evidence submitted by the company

The ALCANZA trial is an international, open-label, randomised, phase III, multicentre trial of BV versus treatment of physician's choice (PC) of MTX or BEX in patients with MF or pcALCL and was the only relevant randomised controlled trial (RCT) of BV identified by the company's literature searches. Evidence from three single-arm observational studies were also included in the CS, two of which were prospective phase II studies. The observational studies included patients with subtypes other than MF or pcALCL, including Sézary syndrome (SS) and lymphomatoid papulosis (LyP). Where reported (in the RCT and two observational studies), most patients had advanced stage MF.

A total of 131 patients were enrolled into the ALCANZA trial between 13 August 2012 and 31 July 2015 and randomly assigned (1:1) centrally by an interactive voice and web response system to receive BV (n=66) or PC (n=65). Randomisation was stratified by baseline disease diagnosis (MF or pcALCL). BV was administered intravenously at a dose of 1.8mg/kg once every 3 weeks, for a maximum of 48 weeks (i.e., 16 x 3-weekly cycles). In the PC arm, patients received oral MTX 5mg to 50mg once per week or oral BEX 300mg/m² once per day. Patients received MXT or BEX for up to 48 weeks. Patients were defined as having advanced stage CTCL if they had a diagnosis of MF ≥stage IIB or pcALCL. In total, 49 patients treated with BV and 46 patients treated with PC were classified as having advanced stage CTCL at baseline (n=95; 73% of all patients in the trial).

The ALCANZA trial primary outcome was objective global response lasting at least 4 months (ORR4), described by the company as a relatively new outcome measure used to assess the impact of therapy on the unique symptomatic burden of CTCL. This outcome captures objective response rate (ORR) and duration of response as a single measure. Other trial outcomes included ORR, progression-free survival (PFS), safety outcomes and health-related quality of life (HRQoL) outcomes. Overall survival (OS) was not a pre-specified outcome; however, OS data were collected and are reported in the CS. All analyses of efficacy, safety and HRQoL outcomes for patients with advanced stage CTCL (n=95) were conducted after a median follow-up of 33.9 months.

The ALCANZA trial has shown that, for patients with advanced stage CTCL, compared with treatment with PC, BV results in increased ORR4 (59% versus 9%), increased ORR (69.4%

versus 17.4%) and improved median PFS (16.5 months versus 3.5 months). The company notes that OS data were extremely immature and confounded by subsequent anticancer therapy received on disease progression. Subsequent treatment, which includes treatment switching, for patients with advanced stage CTCL was reported for 55% of patients in the BV arm and 63% of patients in the PC arm (46% of PC patients with advanced stage CTCL received subsequent anticancer treatment with BV). The company reports that, compared with treatment with PC, treatment with BV results in longer median OS (41.6 months and 43.6 months respectively) but highlights that these results are highly uncertain.

In the subgroup of patients with advanced stage CTCL in the ALCANZA trial, more patients treated with BV reported any-grade treatment-related adverse events (TRAEs), treatment-related serious adverse events (TRSAEs) and discontinuations due to adverse events (AEs) than patients with advanced stage CTCL treated with PC. On the other hand, there were more grade ≥3 treatment-emergent (TEAEs) reported by patients in the PC arm than were reported by patients in the BV arm. Peripheral neuropathy was the most common TEAE associated with BV for all patients treated with BV (reported by 67% of all patients at an earlier follow-up, median of 22.9 months) and was also the most common grade ≥3 TEAE for patients with advanced stage CTCL (14%). Grade ≥3 TEAEs were uncommon for patients treated with MTX but grade ≥3 hypertriglyceridemia was reported by a quarter of patients with advanced stage CTCL treated with BEX.

HRQoL findings presented in the CS from the ALCANZA trial for patients with advanced stage CTCL show that patients in the BV arm, but not in the PC arm, experienced clinically important reductions in skin symptoms as measured by the Skindex-29 questionnaire. Results from analyses of European Quality of Life 5-Dimension-3 Level Version (EQ-5D-3L) data were not statistically significant different between treatment arms.

The company assessed the feasibility of performing indirect comparisons to obtain (i) estimates of effectiveness of treatment with BV versus interferon alpha (IFN-α), another *Category A* therapy, and (ii) estimates of effectiveness of BV versus standard of care for patients with SS/LyP. It was not possible to conduct these indirect comparisons due to insufficient data being available.

Efficacy and safety results from two phase II studies, which included a small number of patients with SS and LyP, were reported narratively in the CS. Notably, ORR was 100% for 17 patients with LyP (8 of whom had LyP plus MF or LyP plus pcALCL) compared to 54% for 28 patients with MF only in one of the studies and 70% for 27 patients with MF and 67% for 3 patients with SS in the other. The findings for PFS and AEs were reported only for all patients

with CTCL and not by individual subtype in both studies and were consistent with results from the ALCANZA trial. These studies did not report OS.

1.4 Summary of the ERG's critique of submitted clinical effectiveness evidence

Clinical advice to the ERG is that, in the NHS, IFN-α is commonly prescribed to patients with MF before, or after, MTX or BEX. Furthermore, clinical advice is that all *Category A* therapies are considered to have equal efficacy. Therefore, the lack of a comparison of the effectiveness of BV versus IFN-α is not considered by the ERG to be a major limitation of the evidence base.

As the ALCANZA trial was stratified by baseline disease diagnosis, but not by disease stage, the subgroup of patients with advanced stage CTCL is not, technically, a randomised patient population. However, the proportions of patients with MF and pcALCL in the subgroup of patients with advanced stage CTCL are similar in both treatment arms; approximately two-thirds of patients with advanced stage CTCL had been diagnosed with MF (BV: n=33, PC: n=31) and approximately a third had been diagnosed with pcALCL (BV: n=16, PC: n=15). Clinical advice to the ERG is that the previous treatments received by the patients with advanced stage CTCL appear to be broadly in line with NHS clinical practice in England.

Treatment with BV is indicated for patients who had at least one prior systemic therapy. In the ALCANZA trial, most patients (62%) with advanced stage CTCL had received one (42%) or two (20%) prior systemic therapies and a quarter had received four or more prior systemic therapies. The median number of prior systemic therapies was two and the maximum number of prior systemic therapies that patients had received was 11.

On examination of data from the subgroup of patients in the ALCANZA trial with advanced stage CTCL, the ERG observed a sudden increase in PFS events in the BV arm between 64 weeks (14.7 months) and 77 weeks (17.7 months) of follow-up. The ERG considers this phenomenon is likely to be as a consequence of the timing of PFS assessments. Patients were required to cease treatment with BV after 16 cycles (approximately 48 weeks) and were then followed for survival every 12 weeks for a minimum of 24 months after the end of treatment (EOT) visit. A number of patients in the BV arm who finished treatment at 48 weeks without having progressed would not have been followed up until 12 weeks after their EOT visit. Therefore, patients who progressed between their EOT visit and the assessment 12 weeks later would all have been recorded as having progressed at the 12-week assessment point (approximately 60 weeks after starting treatment) Since the recording of progression events between the EOT visit and the follow-up assessment 12 weeks later may well have been delayed for some patients, the ERG considers that median PFS may have been

overestimated in the BV arm. The ERG also highlights that the median time to subsequent anticancer therapy in the BV arm was lower (14.2 months) than the median PFS in the BV arm (16.5 months).

The ERG notes that the Cox proportional hazards (PH) method was used to estimate the hazard ratios (HRs) for the outcomes of PFS and time to subsequent anticancer therapy. However, following examination of data collected from the subgroup of patients in the ALCANZA trial with advanced stage CTCL, the ERG considers that the PH assumption may be violated for both these outcomes. Since HRs are not an appropriate summary of treatment effect when the PH assumption does not hold, the ERG considers that the reported HRs for PFS and time to subsequent anticancer therapy for this subgroup should be interpreted with caution.

The ERG agrees with the company that OS results from the ALCANZA trial should be interpreted with caution due to confounding, the small number of patients included in the analysis and the small number of events that had occurred. The ERG also agrees with the company that none of the available methods of crossover adjustment are suitable for the ALCANZA trial and that it is not possible to obtain a robust estimate of the comparative efficacy, in terms of OS, of treatment with BV versus PC.

Safety data from the ALCANZA trial show that for patients with advanced stage CTCL, treatment with BV was not associated with new or unexpected toxicities and that the majority of reported AEs were grade 1 or grade 2 in severity. Clinical advice to the ERG is that peripheral neuropathy is the most common and clinically significant AE associated with treatment with BV. The ERG notes that the only TRAE that resulted in death occurred in the BV arm. However, this patient did not meet the trial eligibility criteria as the patient had elevated liver function test results at baseline and their enrolment, therefore, constituted a major protocol violation.

The ERG highlights that, in addition to Skindex-29 symptom and EQ-5D-3L data, Skindex-29 emotional and functioning domain data and Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire data from the ALCANZA trial have been presented in the published paper and in the European Public Assessment Report (EPAR) for BV. These results are presented for all patients in the trial, not just for patients with advanced stage CTCL. Nonetheless, the ERG highlights that no statistically significant or clinically meaningful differences between treatment arms were reported for these HRQoL measures. The ERG, therefore, concurs with the European Medicines Agency that no firm conclusions with regard to the impact of BV on HRQoL can be drawn.

The ERG considers that the company's indirect comparison feasibility assessments were appropriate and agrees with their conclusion that it was not possible to conduct an indirect comparison of treatment with BV versus IFN-α or of BV versus standard of care for patients with SS/LyP.

Limited evidence for efficacy of BV by different CTCL subtypes is available from observational study data presented in the EPAR for BV, alongside that of ORR from the two phase II studies. These data show that findings for ORR and median PFS observed in the non-randomised studies for different subtypes of CTCL are generally consistent across studies, and in line with the findings reported in the ALCANZA trial, albeit from small numbers of patients. Of the 218 patients in these non-randomised studies, 147 (67%) had MF, 19 (9%) had SS, 5 (2%) had pcALCL, 22 (10%) had LyP only, 22 (10%) had mixed subtypes (most commonly LyP and MF, n=18 [8%]) and 3 (1%) had other CTCL subtypes. It is therefore difficult to draw conclusions from these studies.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with BV versus PC for patients with advanced stage CTCL (i.e., MF stage ≥IIB and pcALCL) who have been previously treated with at least one systemic therapy. The model structure comprises five mutually exclusive health states: pre-progression, non-stem cell transplant (SCT) post-progression, Allogeneic SCT, Allogeneic SCT relapse and dead. The model time horizon is set to 45 years and has a 1-week cycle length. The model perspective is that of the UK NHS. As recommended by NICE, outcomes are measured in quality adjusted life years (QALYs), and both costs and QALYs are discounted at an annual rate of 3.5%.

In the model, data from the ALCANZA trial are used as the basis for estimating patient survival and patient utility. Resource use and costs are estimated based on information from the ALCANZA trial, skin systemic anticancer therapy treatment protocols, other published sources and advice from clinical experts. A Department of Health Patient Access Scheme (PAS) discount is applied to the cost of BV and full list prices are used to represent the cost of BEX and MTX.

The company uses fully parametric curves to estimate outcomes for PFS and OS for treatment with BV and PC. The company uses PFS Kaplan-Meier (K-M) data from the ALCANZA trial to generate two Weibull curves, one to estimate PFS for patients treated with BV and one to estimate PFS for patients treated with PC. The company fitted a single log-logistic curve to

OS K-M data from the PC arm of the ALCANZA trial to estimate long-term survival for both patients treated with BV and those treated with PC.

The company base case analysis includes the assumption that a proportion of patients who achieve a complete or partial response to treatment with BV or PC will receive an alloSCT after 18 weeks of treatment. Post-alloSCT outcomes are estimated by fitting parametric curves to digitised overall survival (OS) and disease-free survival (DFS) data.

Complete time on treatment (ToT) data are available from both arms of the ALCANZA trial. The company has adjusted these data to fit within the weekly-cycle structure of the model to directly estimate the length of time patients receive treatment in both arms of the model.

HRQoL data were collected during the ALCANZA trial. In the base case analysis, the company uses the results of a longitudinal mixed-effects regression model to adjust the EQ-5D-3L data collected during the trial to take into account progression status and Skindex-29 symptom domain score. The utility values used in the pre-progression health state differ by primary treatment, whilst in the progressed disease health state, the same utility value was used irrespective of primary treatment. The utility values in the alloSCT health states and in the post-progression health states were obtained from published sources.

Results from the company's base case comparison, using the PAS price for BV, show that treatment with BV dominates PC, being both cheaper ([redacted] and more effective (+1.2 life years, [redacted] QALYs). The company carried out a wide range of deterministic sensitivity analyses. The most influential parameters were the cost of CTCL end-stage care, the utility values of patients 3 months post-alloSCT, the cost of medium Allevyn dressings and the choice of utility value associated with the post-progression health state.

The company's mean probabilistic sensitivity analysis (PSA) results show that treatment with BV dominates treatment with PC. However, compared with the deterministic analysis results, the incremental costs from the PSA are [redacted]. The company presents the results of PSA iterations to show that, when the cost effectiveness of treatment with BV is compared with PC, there is a [redacted] probability of treatment with BV being cost effective at a threshold of £30,000 per QALY gained.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

1.6.1 ERG's preferred approach to estimating cost effectiveness

The ERG's preferred approach to estimating cost effectiveness within the confines of the existing model structure is to remove alloSCT from the treatment pathway and to adjust several parameter values used in the company model.

Removal of alloSCT from the treatment pathway

Results from the company base case analysis show that treatment with BV yields 1.2 years of incremental life gain when compared with PC. This survival gain is due entirely to the inclusion of alloSCT in the company model as, in the ALCANZA trial, there was no statistically significantly OS gain in favour of treatment with BV compared with PC. The ERG does not consider the inclusion of alloSCT in the base case analysis to be appropriate due to the lack of robust evidence relating to alloSCT effectiveness, outcomes following alloSCT in patients with advanced stage CTCL who have received prior treatment with BV, and the place of alloSCT in the treatment pathway. Due to these limitations, the ERG has removed alloSCT from the company's base case treatment pathway.

ERG revised parameter values

The ERG has implemented revised values in the company submitted model for the following parameters: utility values from the ALCANZA trial, AE disutility values and oral chemotherapy costs.

1.6.2 Areas of uncertainty

Parts of the model structure limit the ERG's ability to investigate the impact of varying assumptions about survival; however, restructuring the model is not within the ERG's remit. There are also parameter values relating to the post-progression health state that the ERG does not consider to be adequately supported by evidence, but for which it has not been able to identify robust alternatives. The ERG therefore considers there is substantial uncertainty in the reliability of the results of the cost effectiveness model.

Post-progression health state

The outcomes of the company model are very sensitive to any assumptions that affect the relative time that patients in the BV and PC model arms spend in the post-progression health state, specifically in the highly resource-intensive end-stage care phase. The ERG does not consider that there is robust evidence to support the assumptions that underpin the company's modelling of the post-progression health state, or that the company has provided reliable alternatives to the assumptions implemented therein.

Post-progression resource use

The ERG highlights that there is a lack of published evidence describing post-progression resource use (for example, which specific services and resources are needed, for how long, and the costs of these resources). Clinical advice to the ERG is that the post-progression resource use implemented in the company model may not adequately represent clinical practice in the NHS in England.

Assumption of equal OS resulting in zero OS gain

The company has assumed in the base case analysis (including alloSCT) that treatment with BV and treatment with PC are equally effective in terms of OS, since the results of the ALCANZA trial do not show a statistically significant OS difference for the comparison of treatment with BV compared with PC. The company argues that the limitations of the OS data from the ALCANZA trial (small numbers of patients and events, and high rates of crossover) prevent robust estimates of OS gain being generated. The ERG agrees that there is insufficient evidence from the ALCANZA trial to make robust claims about lifetime OS gain. Clinical advice to the ERG is that there is no robust evidence to either support or refute the assumption of zero OS gain as implemented in the company submitted model.

The ERG notes that the company's assumption of equal OS resulting in zero OS gain may appear to be a conservative approach. However, modelling zero OS gain alongside a PFS gain for treatment with BV means that, after progression, patients treated with BV die more quickly than patients treated with PC. Consequently, patients treated with BV spend less time in the highly resource-intensive end-stage care phase than patients treated with PC. This means that the costs accruing to the BV arm are lower than the costs accruing to the PC arm.

Populations and pathways in the company model

The company states that the populations that are represented in the model are patients with advanced stage MF and patients with pcALCL. However, as noted in the joint submission to the National Institute for Health and Care Excellence (NICE) from the Royal College of Pathologists and the British Society for Haematology as part of this appraisal, treatment decisions are made according to each patient's needs and the expertise of the centre. The relevance of the treatment pathways included in the model to the subgroup of patients with advanced stage MF and, in particular, patients with pcALCL is therefore unknown.

1.6.3 Model inflexibility and structural issues

The company has used a payoff approach to model patient outcomes after progression. The payoff approach imposes limitations on the flexibility of the company model and does not allow for specific parameters and/or assumptions to be investigated thoroughly. The ERG acknowledges that the company base case model – including alloSCT – benefits from the simplification introduced by the payoff approach. However, due to the limitations of the model, the ERG has only been able to produce a limited range of cost effectiveness results. For example, the ERG was unable to explore the sensitivity of the model results to the use of different parametric survival functions. There are also issues with the calculation of mean post-progression survival and the probability of transitioning into the post-progression health state.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

Clinical evidence

- The company provided a detailed submission that met the requirements of NICE's scope for the clinical effectiveness analysis. The ERG's requests for additional information were addressed to a good standard.
- The company's main source of clinical evidence is the ALCANZA trial. The ERG considers that the ALCANZA trial is a well-designed and good quality trial.
- The ALCANZA trial compares the efficacy of treatment with BV versus MTX or BEX (PC arm). MTX and BEX can be considered as standard of care for patients with MF in the NHS.
- The ALCANZA trial includes patients with two subtypes of CTCL (MF and pcALCL) and clinical advice to the ERG is that these patients are representative of patients who would be treated with MTX or BEX in clinical practice in England.
- Although the focus of the CS is only on patients with advanced stage CTCL (approximately 75% of the ALCANZA trial population), results for this subgroup are consistent with the results for the overall trial population.
- The inclusion of ORR4 as an endpoint in the ALCANZA trial captures ORR and duration of response as a single measure. This is a more appropriate and stringent measure of treatment success than ORR.

Cost effectiveness evidence

- The company provided a detailed submission that fulfilled the requirements of NICE's scope for the base case analysis. The ERG's requests for further clinical information were met to a good standard.
- The company model utilises the best available PFS, OS and ToT evidence for treatment with BV and PC in a population with advanced stage CTCL from the ALCANZA trial.

1.7.2 Weaknesses and areas of uncertainty

Clinical evidence

- RCT evidence is only available for two subtypes of CTCL: MF and pcALCL. There is limited supportive evidence from observational data presented in the EPAR for BV for patients with the other subtypes of CTCL. It is difficult to obtain clinical effectiveness evidence for these other patients given the rarity of CTCL, particularly subtypes other than MF.
- OS data from the ALCANZA trial are immature and confounded by subsequent anticancer therapy and treatment switching, meaning that the reliability of results from analysis of OS data are highly uncertain.
- The company's statistical approach to the analysis of data from the ALCANZA trial is mostly appropriate. However, the PH assumption required for use of the Cox PH model is subject to uncertainty for PFS and time to subsequent anticancer therapy. This means it is not possible to know whether the reported HRs overestimate or underestimate the effect of BV versus PC.
- Median PFS may be overestimated in the BV arm due to the timing of assessments following EOT.
- ORRs for patients in the PC arm of the ALCANZA trial are lower than have been previously reported in the literature, albeit they are typically from single-arm observational studies. The reasons for this discrepancy are unknown.
- Despite there being some evidence for improvement in skin symptoms from treatment with BV, results from analyses of HRQoL data are inconclusive.
- Treatment with BV is indicated for patients who had at least one prior systemic therapy. In the ALCANZA trial, most (62%) patients with advanced stage CTCL had received one (42%) or two (20%) prior systemic therapies, and a quarter had received four or more prior systemic therapies.
- While MTX and BEX are likely to be appropriate comparators to BV for the patients with MF included in the ALCANZA trial, clinical advice to the ERG is that *Category B* therapies would normally be preferred to *Category A* therapies for patients with advanced stages of pcALCL who have received at least one prior systemic therapy and are fit enough to tolerate the drugs.

Cost effectiveness evidence

- Many of the areas of uncertainty in the model are related to the underlying clinical data and are, therefore, difficult to resolve. For example, the condition is rare, there are several subtypes and the treatment pathway is complicated.
- The inclusion of alloSCT as an option in the treatment pathway is based on weak evidence and generates more uncertainty in a disease area that, due to its rarity and diversity in presentation, is already highly uncertain.
- There is no robust evidence for OS from the ALCANZA trial, so it is not possible to determine whether there is an OS gain from treatment with BV versus PC.
- The assumption of zero OS gain in the company model leads to patients treated with BV dying more quickly on progression than patients treated with PC, which may or may not be clinically plausible. The company has not robustly tested this assumption.
- The payoff approach used to structure the modelling of the post-progression health state prevents the production of reliable results when alternative OS assumptions are

implemented. There is considerable uncertainty surrounding the resource use, costs and time spent in the post-progression health state.

- The incremental costs generated by the PSA are substantially [redacted] than the incremental costs generated by the deterministic sensitivity analyses.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.8.1 ERG revisions to the company base case analysis

The ERG's preferred approach to estimating cost effectiveness is to remove alloSCT from the treatment pathway and to adjust several of the parameter values used in the company model. The ERG made these revisions to the company base case analysis and the results show that [redacted]. Implementing the ERG's revisions to the company base case comparison decreases incremental costs by [redacted] and incremental QALYs by [redacted]

These ERG revisions have a substantial impact on the [redacted] yielded by the company base case analysis; however, treatment with BV [redacted] over treatment with PC once the ERG's revisions are implemented. The ERG cannot be certain of the magnitude of the impact that these revisions would have if substantial changes were made to the structure of the company model.

1.8.2 ERG scenarios

The ERG notes that there are assumptions included in the model for which there is neither robust evidence nor extensive sensitivity analyses. The ERG has produced three scenarios to test the sensitivity of the model to alternative, plausible assumptions. These assumptions are: changes to the post-progression pathway (Scenario 1); changes to resource use frequencies (Scenario 2); and assuming an OS gain for treatment with BV (Scenario 3).

Using the ERG's revised base case (removal of alloSCT and use of alternative parameter values) combined with implementing each of the ERG's scenarios separately yields ICERs per QALY gained that are positive. The ICERs per QALY gained for the comparison of treatment with BV versus PC generated by the ERG's scenarios are [redacted]

The ERG cautions that i) the scenarios are intended to highlight the sensitivity of the model to plausible alternatives to the company assumptions that the ERG does not consider are supported by robust evidence, and ii) the structure of the model is inflexible which means that the scenario analyses may produce potentially meaningless results.

1.9 Cost effectiveness conclusions

The ERG's analyses highlight the high level of uncertainty around the company base case cost effectiveness results. The ERG cautions that the ICERs per QALY gained for the comparison of treatment with BV and PC presented in this ERG report may not be reliable.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem is succinctly summarised in Section A.1 of the company submission (CS) summary document. Additional information is provided in Section B1.1 and Section B1.2 of the CS. The Evidence Review Group (ERG) considers that the company's description accurately reflects the underlying health problem. Key points are summarised in Box 1 and further details are provided in Sections 2.1.1 to 2.1.4 of this ERG report.

Box 1 Key points from the company's description of underlying health problem

Description of disease

- CTCL is a rare disease which consists of a heterogeneous group of nHLs involving the skin and which rarely have evidence of extracutaneous disease at the time of diagnosis [1-3].
- While early stage/localised disease is considered indolent, approximately 25% of patients will progress to advanced stage disease during the course of their life [4].
- Advanced stage disease is associated with a poor prognosis, negative impact on daily functioning and HRQoL [5, 6] and significantly decreased survival versus early stage disease [7, 8].
- CTCL is nearly always incurable and for patients with advanced stage disease, death ultimately occurs due to disease recurrence, overwhelming sepsis and bone marrow depletion [9].

Epidemiology

- The age-standardised incidence of CTCL was 0.75 per 100,000 in England in 2013 [10].
- CTCL is more common in men than women, with a ratio of approximately 1.6:1 [10].

Burden of disease

- In addition to typical cancer-related burden, advanced CTCL is characterised by aggressive, devastating lesions (e.g., disfiguring tumours, ulceration, erythroderma), visceral spread, and possible blood involvement (circulating Sézary cells) [7, 11].
- Chronic skin manifestations and systemic symptoms cause severe pain, unrelenting itching, alopecia, chronic skin infections, and disfigurement [6, 11-14] depression, frustration, anger, anxiety and worry about dying from CTCL [15].
- Patients with CTCL may also become self-conscious due to the visibility of symptoms, especially when their disease affects exposed areas such as their face and hands [11].
- Carers of patients with CTCL also experience the demands of caring as well as negative impacts on intimacy, family dynamics and emotional wellbeing [16].
- As patients with CTCL tend to have longer survival than other malignancies [7, 8], patients spend substantial time in resource-intensive, end-stage care [12, 17].

CTCL=cutaneous T-cell lymphoma; HRQoL=health-related quality of life; nHL=non-Hodgkin lymphoma
Source: CS, adapted from summary document, Section A.1 and CS, Sections B.1.3.1 and B.1.3.2

The impact of cutaneous T-cell lymphoma (CTCL) on health-related quality of life (HRQoL) is explored at some length in the CS (Section B.1.3.2 Burden to patients, carers and society, pp31-39). Some of the issues relating to the burden of CTCL, including the impact on HRQoL are summarised by the ERG in Box 1. The ERG concurs that the burden of CTCL on patients and carers, including HRQoL, can be high but notes that the issues highlighted in Box 1 tend to be most pertinent for patients with advanced stage CTCL.

While CTCL is nearly always incurable, as stated in the CS (p28), overall survival (OS) varies by CTCL subtype and disease stage. The ERG also notes that disease burden is worse for

people with more advanced stage CTCL than for those with earlier stages of CTCL. Further information relating to subtype, age at diagnosis, disease stage and prognosis is presented in Sections 2.1.1 to 2.1.3 of this ERG report.

2.1.1 Subtypes of cutaneous T-cell lymphoma

As noted in Box 1, CTCL constitutes a rare, heterogeneous group of non-Hodgkin lymphomas (nHLs) [1, 7]. In 2005 a number of subtypes of CTCL were classified by the World Health Organization (WHO) - European Organization for Research and Treatment of Cancer (EORTC) [7]. The focus of the CS is on the following subtypes of CTCL:

- Mycosis fungoides (MF) and MF's leukaemic variant, Sézary syndrome (SS)
- Primary cutaneous cluster of differentiation 30-positive lymphoproliferative disorders (CD30+ LPDs):
    - Primary cutaneous anaplastic large cell lymphoma (pcALCL)
    - Lymphomatoid papulosis (LyP).

As highlighted in the CS (p23), MF is the most common subtype of CTCL, occurring in more than half of patients with CTCL (54% to 55%) [7, 10]. SS is much rarer (2% to 4%) [7, 10]. The reported incidence of CD30+ LPDs varies from 10% [10] to 26% [7]. The former estimate is from a Public Health England (PHE) study of 1659 people newly diagnosed with CTCL in England, between 2009 and 2013. The latter estimate by Willemze et al 2005 is based on data from 1476 patients with CTCL registered at the Dutch and Austrian Cutaneous Lymphoma Group between 1986 and 2002. These data were presented by the authors [7] in order to "…illustrate the clinical significance of the WHO-EORTC classification" (p3769). This study also separately presents estimates for pcALCL and LyP: 10% and 16% respectively.

In addition to the subtypes focussed on by the company, other subtypes of CTCL also exist (e.g. subcutaneous panniculitis-like T-cell lymphoma [SPTL]). The complete list of WHO-EORTC classifications of CTCL are summarised in Table 1 of the published paper by Willemze et al 2005 [7]. The ERG highlights that it is possible for patients to have more than one of some of the subtypes of CTCL at the same time [18, 19].

2.1.2 Age of patients with cutaneous T-cell lymphoma

Wilcox et al 2016 [2] highlight (p152) that "The incidence of CTCL increases significantly with age, with a median age at diagnosis in the mid-50s and a fourfold increase in incidence appreciated in patients over 70." The analysis conducted by PHE [10] found that, of the 1659 people newly diagnosed with CTCL in England between 2009 and 2013, approximately half were aged 50 to 74 years, approximately a quarter of patients were aged ≤50 years and approximately a quarter of patients were aged ≥75 years.

2.1.3 Prognosis of patients with cutaneous T-cell lymphoma

Clinical advice to the ERG is that it is often difficult to predict prognosis for patients who receive a CTCL diagnosis. Reasons for this include the fact that CTCL is a heterogeneous and rare condition and because many patients who present are older adults who often have comorbidities. Furthermore, many patients will have had symptoms attributed to eczema or parapsoriasis for many years before obtaining a definitive diagnosis. Wilcox et al 2016 [2] have noted that while, typically, the median time from symptom onset to diagnosis has been reported to be 3 to 4 years, for some patients, time from symptom onset to diagnosis may exceed four decades. However, it should also be noted that the 5-year OS rate has been reported as 88% for patients with MF, 24% for patients with SS [7], ≥83% for patients with pcALCL [20] and ≥90% for patients with LyP [3, 21, 22].

The disease stage of MF/SS can be categorised as early stage or advanced stage, based on tumour-node-metastasis-blood (TNMB) (see Appendix 1, Section 9.1.1, Figure 15). Early stage MF (stages IA to IIA) usually presents with cutaneous patches and plaques [23]. Advanced stage MF (stages IIB to IVB) is characterised by skin tumours, erythroderma, and nodal or visceral involvement. SS presents only in advanced stage disease with extreme pruritus, erythroderma, lymphadenopathy and circulating Sézary cells [21].

Following meetings of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the EORTC, it was concluded that the TNMB designations and descriptions helpful in MF/SS are not applicable for CTCL other than MF/SS [24]. Thus, the ISCL and the cutaneous lymphoma task force of the EORTC have established a consensus proposal for a TNM classification system (i.e. tumour, node, metastasis) applicable for other subtypes of CTCL (see Appendix 1, Section 9.1.2, Table 37) [24]. Due to the clinical and pathologic heterogeneity of CTCL, the authors highlight that this is meant to be primarily an anatomic documentation of disease extent and should not to be used as a prognostic guide [24]. Patients with pcALCL generally present with solitary or grouped, rapidly growing, and ulcerating large tumours or thick plaques (CS, p27); most patients with pcALCL, therefore, have localised disease [22, 25]. Extracutaneous spread (i.e., metastasis) is uncommon for patients with pcALCL; it is reported to occur in 13% of patients with pcALCL [22, 25]. Patients with LyP typically present with recurrent nodules and papules at distant sites which become necrotic before resolving to form an atrophic scar [21, 25]

The OS rates of patients with advanced stage MF, SS or pcALCL with regional or generalised involvement are much lower than those reported for patients with early stage disease (see Appendix 1, Section 9.1 of this ERG report). Generally, 5-year OS rates are approximately 50%, or lower, for patients with advanced stage MF and SS (being lower still for patients with

stage IV disease) [8, 26, 27]. Patients with pcALCL with regional lymph node involvement have been reported to demonstrate a 5-year OS rate of 76% [3]. Liu et al 2003 report disease-specific 5-year OS of 50% for generalised pcALCL (versus 91% for localised pcALCL) [22].

2.2 CD30-positive cutaneous T-cell lymphoma

The patient population under consideration in the current Single Technology Appraisal (STA) is patients with relapsed or refractory CD30-positive (CD30+) CTCL. CD30 is a surface protein expressed by activated (but not resting) T and B cells [28], previously known as Ki-1 antigen [29]. As stated by the company, classical Hodgkin lymphoma (HL), systemic anaplastic large cell lymphoma (sALCL), and subtypes of CTCL express CD30 as an antigen on the surface of their malignant cells, independent of disease stage (CS summary document, Table 1; CS, Table 2). While all patients with CD30+ LPDs have (per definition) a strong and homogenous CD30 expression, for other CTCL subtypes CD30 expression may be much lower and at variable levels [30]. Findings from a large, retrospective, multi-centre study of 1275 patients reported by Scarisbrick et al 2015 [27] suggest that 23% of patients with MF/SS have CD30+ CTCL.

Techniques for measuring CD30 expression vary in sensitivity, reliability and reproducibility [31] and there is no consensus on the definition of CD30 positivity [27, 31]. The definition of CD30+ used in the study by Scarisbrick et al 2015 [27] was ≥10% of tumoral cells stained positively and it is reported that it was only possible to test for CD30+ in 639 (50%) of cases [27]. Advice to the ERG is that this definition of CD30+ is universally accepted in UK clinical practice, that tests for CD30 are routinely carried out in NHS clinical practice and CD30 testing is conducted at a centralised laboratory for a number of regions in the UK.

2.3 Company's overview of current service provision

The company's overview of current service provision is summarised in Section A.2 of the CS summary document. In addition, more information is provided in Section B.1.3.3 of the CS. Key points are summarised in Box 2 and discussed further in Sections 2.3.1 to 2.3.4 of this ERG report. It should be noted that, as highlighted in the CS (p39), due to the rarity and complexity of CTCL, all patients with early stage MF refractory to skin-directed therapy (SDT) and late-stage MF/SS are treated at one of seven supra-regional centres in the UK (all based in England: Birmingham, Leeds, Liverpool, London, Manchester, Newcastle and Nottingham).

Box 2 Key points from the company's overview of current service provision

Current treatment options

- Patients with CTCL are managed primarily according to the subtype of CTCL and the stage of disease [32-34].
- Treatment either targets the skin (skin-directed) or the entire body (systemic); treatments may be used alone or in combination to provide the greatest benefit to the patient whilst minimising treatment-related toxicity [2, 25, 35].

Clinical pathway for advanced stage CTCL

- The current UK treatment pathway for advanced CTCL consists of initial systemic with *Category A* agents. As the disease progresses, *Category A* therapies become ineffective and the next stage of treatment is with *Category B* therapies [25, 34].
- *Category B* agents can only be taken for a short period of time (e.g., to a maximum of 6 months) due to drug-related toxicities. Patient co-morbidity may preclude the use of some *Category B* systemic therapies (e.g. CHOP due to neutropenia and the high sepsis susceptibility of CTCL patients).
- Overall, toxicity of treatment must always be balanced against the goals of disease control and improvement/maintenance of HRQoL.
- Current standard of care systemic therapies are characterised by low response rates, and short-lived durations of response [1, 36].
- While recent evidence demonstrates that alloSCT may achieve durable remissions and prolonged survival, this procedure can only be performed in patients who achieve at least a partial response to their induction/bridging therapy [37, 38].
- Because of the aforementioned ineffectiveness of current treatments, few patients become eligible for alloSCT with existing therapies.

alloSCT=allogeneic stem-cell transplant; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CTCL=cutaneous T-cell lymphoma; HRQoL=health-related quality of life
Source: CS, adapted from summary document, Section A.1 and CS, Section B.1.3.3

Clinical advice to the ERG supports the company's overview of service provision, i.e., that patients with CTCL are managed primarily according to the subtype of CTCL and the stage of disease, based on published guidelines [25, 32-34]. However, as the company notes (CS, p40) due to the limited efficacy of available systemic agents, the paucity of comparative data, and the lack of consensus on a preferred systemic therapy, the initial choice of treatment is generally made by the treating clinician on an individual patient basis [35, 36]. The ERG notes that evidence used to inform guidelines for subtypes of CTCL other than MF is often derived from anecdotal evidence. As noted in the joint submission to the National Institute for Health and Care Excellence (NICE) from the Royal College of Pathologists and the British Society for Haematology [39] as part of this appraisal, treatment decisions are made according to each patient's needs and the expertise of the centre (p4). Further consideration of available treatment options is presented in Sections 2.3.1 to 2.3.3 of this ERG report. Much of the information presented in the CS and, therefore, considered in these sections, is based on forthcoming British Association of Dermatologists (BAD)/United Kingdom Cutaneous Lymphoma Group (UKCLG) guidelines for CTCL [40].

2.3.1 Treatment for early stage disease

2.3.2 Clinical advice to the ERG is that, in line with published guidelines [25, 32-35] [redacted], and as stated in the CS (p26), early stage CTCL tends to be managed expectantly (i.e. "watch and wait") or with SDT. SDT can include application of topical treatments (e.g. corticosteroids), localised radiotherapy, psoralens + ultraviolet A light therapy (PUVA, also known as phototherapy), narrow-band ultraviolet B (UVB, another type of phototherapy) or a combination of these treatments. In the EORTC guidelines for treating CD30+ LPDs [25], the recommended treatment for patients with localised pcALCL is surgical excision and/or radiotherapy, while for patients with localised LyP, it is observation, phototherapy or topical steroids. [redacted] Total skin electron beam therapy (TSEB), which is considered to be the most intensive SDT, is typically reserved as a treatment option for patients with extensive generalised disease and severe skin symptoms, i.e., advanced stage CTCL [41]. However, in the BAD/UKCLG guidelines published in 2003 [33], PUVA in combination with interferon alpha (IFN-α, a type of immunotherapy) or TSEB were recommended as treatments for resistant early stage MF. The recent EORTC guidelines recommend systematic therapies (including *Category A* therapies – see Table 1) or TSEB for patients with resistant early stage MF. [redacted] Systemic therapies for advanced stage disease

The treatment pathway described in Box 2 of this ERG report represents a generalised version of the treatment pathway presented in published guidelines [32, 33] [redacted] i.e., typically *Category A* therapies are initially given to patients, and then *Category B* therapies. This is consistent with clinical opinion received by the ERG. The types of *Category A* and *Category B* therapies available are summarised in Table 1. Although methotrexate (MTX) is a chemotherapy drug, it is classified as a *Category A* therapy as opposed to a *Category B* therapy which includes chemotherapy regimens.

Table 1 *Category A* and *Category B* therapies

***Category A* therapies**	***Category B* therapies[a]**
Interferon alpha (IFN-α) Methotrexate (MTX) Bexarotene (BEX) Extracorporeal photopheresis (ECP)	Single agent chemotherapy regimens, most notably gemcitabine or pegylated liposomal doxorubicin (not available at all centres) Multi-agent chemotherapy regimens, most notably cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) Total skin electron beam therapy (TSEB)

[a] Willemze et al 2013 [32] note that other agents like the fusion toxin denileukin diftitox and histone deacetylase inhibitors, such as vorinostat and romidepsin, have been approved in the United States by the Food and Drug Administration (FDA) for treatment of patients with relapsed and refractory CTCL, but have not yet been registered for CTCL in Europe. Thus, these agents were not considered in the EORTC consensus guidelines published in 2017 [34]
CTCL=cutaneous T-cell lymphoma; EORTC=European Organization for Research and Treatment of Cancer; FDA=Food and Drug Administration
Source: CS summary document, Figure 1, CS, Figure 14 and published guidelines [25, 32-35] and review [41]

Extracorporeal photopheresis (ECP) is not listed as a *Category A* therapy in the CS but clinical advice to the ERG is that it may be used in NHS clinical practice for treating SS. Indeed, ECP is only recommended for treating SS [32, 33, 35, 41]. The specific systemic therapies recommended in published guidelines [25, 32-35] for each line of treatment differ by CTCL stage and subtype. [redacted]

However, generally, *Category A* therapies are preferred prior to *Category B* therapies.

Typically, where a *Category B* therapy instead of a *Category A* therapy may be considered upfront is for the treatment of patients with stage IVB MF/SS [34]. [redacted]

While the company states that bexarotene (BEX), a retinoid, is the only *Category A* therapy currently licensed for CTCL in Europe (CS summary document Table 2; CS, Table 1), clinical advice to the ERG is that, in general, choice of treatment often depends on the adverse events (AEs) associated with therapies. Hence, clinical advice to the ERG is that BEX is rarely used first-line in NHS clinical practice because it is considered to have a worse safety profile than either IFN-α or MTX. Furthermore, the ERG notes, BEX is only indicated for treating CTCL in adult patients refractory to at least one systemic treatment [42]. Clinical advice to the ERG is that IFN-α may increase the risk of fatigue and depression, but MTX can be carcinogenic for some patients. Thus, typically IFN-α or MTX is prescribed first and if a patient experiences disease progression, the other of these two *Category A* therapies is used. After further disease progression, patients will typically then receive BEX or a *Category B* therapy. Therefore, the

ERG considers that the company's approach to labelling *Category A* therapies as first-line treatments and *Category B* therapies as second-line treatments (Figure 1 of the CS summary document and Figure 14 of the CS) is slightly misleading.

Clinical advice to the ERG is that, in clinical practice, systemic therapies are rarely given in combination with other systemic therapies due to the increased toxicities associated with combination therapies. However, patients continue to use topical moisturisers, steroids and topical radiotherapy as required.

Regarding the efficacy of current treatment options, the company highlights (CS, p40) that efficacy is often supported by data from outdated studies and/or is supported by low levels of evidence, as recognised by the authors of treatment guidelines [33, 35]. Response to *Category A* therapies reported in the European Public Assessment Report (EPAR) for brentuximab vedotin (BV) (p8) vary from 30% to 60% for patients with advanced stage MF (or up to 87% for first-line treatment of pcALCL with MTX) [30]; in the CS, rates of between 33% to 86% are cited for patients with CTCL [43-53]. Response rates to the *Category B* therapies, gemcitabine or pegylated liposomal doxorubicin, are reported in the EPAR for BV [30] to vary from 40% to 80% for patients with advanced stage MF; the company cites rates of between 33% to 86% for patients with CTCL [54-58]. Clinical advice to the ERG is that response to treatment tends to be longer with *Category A* therapies than with *Category B* therapies, as is also suggested by data from the publications [36, 55, 57] cited in the CS (p41). As noted by the company, *Category B* agents can only be taken for a short period of time (maximum of 6 months) due to drug-related toxicities (CS, p41).

2.3.3 Allogeneic stem-cell transplant

The company highlights that allogeneic stem-cell transplant (alloSCT) may be a treatment option for some patients, namely those who have a good response to prior treatment. Transplants for CTCL which are performed in the UK use a reduced-intensity conditioning (non-myeloablative) regimen called the Stanford Protocol (CS, p44). The regimen consists of TSEB, total lymphoid irradiation and conditioning with anti-thymocyte globulin prior to transplant [59, 60], as shown in Figure 13 of the CS. The protocol does not include use of are used in both historical and other reduced-intensity conditioning regimens (company response to clarification question C3).

The company highlights (CS, p43) that, to date, the use of alloSCT in the NHS has been "modest" [redacted] [61]. This is attributed to the inability of currently available treatment agents to provide sufficient response rates to enable patients to qualify for transplant (i.e., achieving at least a partial response [PR] with systemic therapy prior to alloSCT) [62]. The company also

acknowledges (CS, p45) that alloSCT eligibility is restricted by age, co-morbidities and the ability to find a suitable donor. Clinical advice to the ERG is that another potential barrier is the patient's willingness to undergo a transplant; patients may be unwilling to have an alloSCT given that their disease is stable and that there are risks involved with the operation. In addition, many patients with CTCL are older adults who may not wish to have a transplant if they have already had many years of treatment with other therapies. As noted by the company (CS, p44), the leading centres for alloSCT in the UK are located in London and Birmingham.

Clinical advice to the ERG is that, currently, it is highly unlikely that a patient who has only had treatment with a *Category A* therapy would be a candidate for alloSCT. The company's depiction of the treatment pathway (CS summary document, Figure 1, CS, Figure 14) supports this view. Nonetheless, the company states (p45) that, with modern advances in matching patients with donors and in advancements in alloSCT procedures (i.e., adoption of the Stanford Protocol), UK clinical experts estimate that 40% of all patients in the UK with CTCL who achieve a PR or better could undergo an alloSCT. Clinical advice to the ERG is that this is likely to be a very high estimate, particularly given the barriers to alloSCT highlighted above. The company also states (CS, p43) that alloSCT is the only potentially curative treatment for CTCL, however, no evidence is presented to support this assertion.

2.4 Brentuximab vedotin

As described in the summary of product characteristics (SmPC) (pp12-13) [63], CS summary document (Table 1) and CS (Table 2), BV is an antibody drug conjugate (ADC) that delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. The CD30-targeted mechanism of action means that BV can overcome chemo-resistance (CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy).

The ERG notes that the company envisages BV as a treatment option for patients with advanced stage CTCL after *Category A* therapies and before *Category B* therapies (CS summary document, Figure 1; CS Figure 14), i.e., it could delay the need for *Category B* therapies in the treatment pathway. BV is also considered to have a role as a bridging or induction therapy to alloSCT, assuming a patient has had at least a PR whilst on treatment with BV, i.e., in some cases, it could also displace *Category B* therapies in the treatment pathway (CS summary document, p6 and Figure 1; CS pp13, 44, 46, 98 and Figure 14).

2.5 Number of patients eligible for treatment with BV

The company has not presented an estimate of the number of patients that it expects will be treated with BV each year. However, the company notes that CTCL affects <2.2 in 10,000

people in the EU (2012 estimate), and thus meets European Union criteria for designation as an orphan disease (i.e., <5 people per 10,000) [64]. The ERG attempted to estimate how many patients may be eligible for treatment with BV each year but concluded that there is considerable uncertainty as to how many patients would be eligible for treatment with BV in England each year (See Appendix 2, Section 9.2 for details).

Clinical advice received by the ERG is that, to date, in the Liverpool supra-regional centre, BV has been used to treat two patients with CTCL by the compassionate use programme (personal communication with Arvind Arumainathan, 12 October 2018). It is unclear how many more patients each year would be considered for treatment with BV should BV be recommended by NICE for treating CTCL.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's main comments on the decision problem outlined in the final scope issued by NICE [65] and addressed within the CS is presented in Table 2. Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.6).

Table 2 ERG comment on how the company's decision problem matches the NICE scope

Parameter	Specification in the final scope issued by NICE	ERG comment on decision problem addressed by the company
Intervention	BV	As per scope
Population	People with relapsed or refractory CD30+ CTCL following SDTs and/or at least one systemic therapy	Population differs from the licensed population. Within the CS, the company focusses on patients with advanced stage CTCL (i.e., narrower than the EMA licence) following SDTs and/or who have had at least one systemic therapy
Comparator (s)	Established clinical management without BV	It is anticipated that *Category B* therapies would be used after BV in the treatment pathway (if required at all) and, therefore, *Category A* therapies (including BEX and MTX) are the most appropriate comparators
Outcomes	The outcome measures to be considered include: OS, PFS, response rates, AEs and HRQoL	As per the NICE scope; the primary outcome considered in the ALCANZA trial of BV [66] was ORR4
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and PSS perspective The availability of any patient access schemes for the intervention or comparator technologies will be taken into account	As per the NICE scope
Other considerations	If the evidence allows, consideration will be given to subgroups based on cancer histology	No subgroup analyses by histology were presented in the CS for patients with advanced stage CTCL but were provided during clarification (for ORR4)
	If the evidence allows, the economic analysis should model stem-cell transplantation further down the treatment pathway	In the company's base case cost effectiveness analysis includes stem-cell transplantation following treatment with BV and PC for some patients with advanced stage CTCL
	Guidance will only be issued in accordance with the marketing authorisation	Clinical and cost effectiveness evidence is presented for patients with advanced stage CTCL, a subgroup of the licensed population

AEs=adverse effects of treatment; BEX=bexarotene; BV=Brentuximab vedotin; CD30+=CD30-positive; CS=company submission; CTCL=cutaneous T-cell lymphoma; EMA=European Medicines Agency; ERG=Evidence Review Group; HRQoL=health-related quality of life; MTX=methotrexate; NICE=National Institute for Health and Care Excellence; ORR4=objective global response lasting at least 4 months; OS=overall survival; PFS=progression-free survival; PSS=Personal Social Services; SDT=skin directed therapy; QALY=quality adjusted life year

Source: NICE scope [65] CS summary document, adapted from Table 2, CS, adapted from Table 1 and ERG comment (see also Sections 3.1 to 3.6)

3.1 Intervention

The intervention is BV (ADCETRIS, Takeda) as per the final scope issued by NICE [65]. Relevant to the current appraisal, BV is indicated for the treatment of adult patients with CD30+ CTCL after at least one prior systemic therapy [63]. BV currently has three other marketing indications in Europe (see Box 3). The European Commission granted an extension of the marketing authorisation valid throughout the European Union for BV to include the treatment of adult patients with CD30+ CTCL after at least one prior systemic therapy on 15 December 2017.

Box 3 Marketing indications for brentuximab vedotin (ADCETRIS) in Europe

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. following autologous stem-cell transplant (ASCT) or
2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

Source: Summary of Product Characteristics for brentuximab vedotin [63]

BV has been recommended by NICE as a treatment option for relapsed or refractory CD30+ HL [67] and sALCL [68]. NICE guidance is in development for BV as a treatment option for previously untreated advanced HL [69].

The recommended dose of BV is 1.8 mg/kg administered as an intravenous infusion (IV) over 30 minutes every 3 weeks [63]. Patients with CTCL may receive up to a maximum of 16 cycles (i.e., 48 weeks) of treatment. The list price for BV is £2,500 per 50mg vial (excluding VAT) (CS summary document, Table 1; CS, Table 2). However, a Patient Access Scheme (PAS) has been agreed with the Department of Health and the discounted price of BV is [redacted] per vial, a straight discount of [redacted](CS summary document, Table 1; CS, Table 2).

3.2 Population

As highlighted in Section 3.1, the licence for BV relevant to the current appraisal is for the treatment of adult patients with CD30+ CTCL who have received at least one prior systemic therapy. However, the focus of the CS is a subgroup of this population, namely patients with advanced stage CTCL. The company's rationale for limiting the population is that only patients with advanced stage CTCL will be candidates for treatment with BV in NHS clinical practice. The company states that this view is based on UK clinician feedback and also that it reflects

the positioning of the technology in the UK guidelines (CS summary document, Table 2; CS, Table 1). Clinical advice to the ERG concurs that patients with advanced stage CTCL are the most likely candidates for treatment with BV. However, the ERG highlights that the licence for BV does not preclude treatment with BV for patients with early stage disease, providing the patient has received at least one prior systemic therapy.

The ERG also highlights that while BV is licensed for patients with all subtypes of CTCL, the company has only presented evidence for patients with MF/SS or CD30+ LPDs (see Section 4.2 of this ERG report).

3.3 Comparators

Position of BV in the treatment pathway

The company considers that the relevant comparators to BV are MTX and BEX (two *Category A* therapies). These two therapies form the comparator arm (physician's choice [PC]) of the ALCANZA trial [66]. The company has not compared the clinical or cost effectiveness of BV with IFN-α (another *Category A* therapy). The company assessed the feasibility of indirectly comparing BV with IFN-α but concluded that this was not possible due to a lack of relevant data (see Section 4.10 of this ERG report). Clinical advice to the ERG is that, in NHS clinical practice, IFN-α may be used before or after MTX or BEX (see Section 2.3.2). Furthermore, clinical advice to the ERG is that all *Category A* therapies are generally considered to have equal clinical efficacy. Therefore, the lack of evidence for comparing the effectiveness of treatment with BV versus IFN-α is not considered by the ERG to be a major limitation of the evidence base.

It is anticipated by the company that *Category B* therapies would be used after BV in the treatment pathway (if required at all) and, therefore, *Category A* therapies (including BEX and MTX) are the most appropriate comparators. However, while the ERG considers *Category A* therapies to be the most appropriate comparators for treating MF, [redacted]

Clinical advice to the ERG is that (i) *Category A* therapies are the most relevant comparators to BV for patients with MF and (ii) *Category B* therapies would normally be preferred to *Category A* therapies for patients with advanced stages of pcALCL who have received at least one prior systemic therapy and are fit enough to tolerate the drugs. However, clinical advice is that MTX and BEX are likely to be appropriate comparators to BV for the patients included in the ALCANZA trial with pcALCL who might have had earlier stage disease or who were not fit for *Category B* drugs.

The company's base case cost effectiveness analysis accounts for the fact that some patients, depending on their response to systemic therapy, will receive an alloSCT. In this respect, choosing *Category A* therapies as comparators is problematic, since clinical advice to the ERG is that patients would rarely receive an alloSCT immediately after treatment with a *Category A* therapy (see Section 2.3.3).

Dosing schedules and duration of treatment

Clinical advice to the ERG is that MTX is used off-label for treating CTCL. MTX is administered orally in tablet form to patients with CTCL at a dose of 5mg to 50mg once a week and that, usually, patients receive MTX until disease progression or until they can no longer tolerate the drug.

BEX is indicated for the treatment of skin manifestations of advanced stage CTCL in adult patients refractory to at least one systemic treatment [42]. BEX is available in 75mg capsules and taken orally each day. The recommended starting dose of BEX is 300mg/m^2/day. The dose of BEX is based on the patient's body surface area (BSA). Normally, patients receive BEX until disease progression or until they can no longer tolerate the drug. The dose is adjusted depending on the patient's response to treatment or side effects.

Like MTX, IFN-α is used off-label for treating CTCL in NHS clinical practice. It is administered as a subcutaneous injection. Various treatment and dose escalation schedules are used. Typically, patients start their treatment by receiving 3 million units three times weekly and the dose is escalated if there is a lack of response or reduced if AEs occur (AEs tend to be dose dependent) [34].

3.4 Outcomes

The outcomes listed in the final scope issued by NICE [65] are outcomes commonly evaluated in studies of oncology treatments and are addressed by the company. Typically, OS and HRQoL are considered to be the most important outcomes from studies of oncology treatments. In relation to CTCL, however, the company states (CS summary document, p5; CS, p29) that the primary goals of treatment are disease control and amelioration of symptoms to maintain or improve HRQoL. Therefore, prolonging objective response rates (ORRs) and progression-free survival (PFS) are meaningful primary outcomes [70] (CS summary document, Table 2; CS, Table 1). The company argues that "OS is not generally considered when determining treatment success in CTCL" (CS summary document, p16; CS, p115). The company further argues that evaluation of OS is not feasible in most clinical trials of CTCL because the expected survival of patients exceeds the duration of the study [70]. Nonetheless, OS data have been collected as part of the ALCANZA trial [66] and are reported in the CS.

The primary outcome in the ALCANZA trial [66] is ORR4, a relatively new outcome measure used to assess the impact of therapy on the unique symptomatic burden of CTCL (CS, p30). ORR4 captures ORR and duration of response (DOR) as a single measure [66, 71]. The company argues that this is a more appropriate and stringent measure of treatment success than ORR (CS, p67). The ERG concurs with the company's view. The approach used in the ALCANZA trial [66] to determine ORR4 is provided in Box 4 (see also Box 5 and Box 6).

Box 4 Objective global response lasting ≥4 months (ORR4)

- ORR4 was determined by independent review (by IRF) of the GRS, determined using the consensus guidelines of the ISCL, the USCLC and the cutaneous lymphoma task force of the EORTC [25, 66, 70] – see Box 5
- Skin response was determined by clearance of lesions, with complete response being 100% clearance and partial response being 50% to 99% clearance and no new tumours [72]
- Overall response based on GRS was confirmed by sustained skin response per mSWAT assessment at the subsequent treatment cycle [66] – see Box 6
- ORR4 was also assessed by INV

EORTC=European Organisation for Research and Treatment of Cancer; GRS=global response score; INV=Investigator; IRF=Independent Review Facility; ISCL=International Society for Cutaneous Lymphomas; USCLC=US Cutaneous Lymphoma Consortium; mSWAT=Modified Severity Weighted Assessment Tool; ORR4=objective global response lasting ≥4 months
Source: CS, p67

Box 5 Global response score (GRS)

- GRS is a composite assessment of total tumour burden:
  - Skin based on the mSWAT per INV - see Box 6
  - Nodal and visceral radiographic assessment per IRF
  - Sézary cell count (patients with mycosis fungoides only) per IRF

INV=Investigator; IRF=Independent Review Facility; mSWAT=Modified Severity Weighted Assessment Tool
Source: CS, p67

Box 6 The modified severity weighted assessment tool (mSWAT)

- mSWAT is a method widely used to assess skin response to treatment in MF and SS:
  - The body is divided into 12 regions with pre-assigned percentages of total BSA
  - The extent of skin disease is assessed for each region and weighted for more severe lesions (patch=1; plaque=2; tumour=4)
  - The products (BSA x weighting) of each region total a sum 0–400 [66]
- St. John's Institute of Dermatology in London has developed the CL-App (Cutaneous Lymphoma Resource Tools) to assist healthcare professionals managing patients with cutaneous lymphoma. In addition to management guidelines and prognostic scoring, the tool provides a visual and user-friendly mSWAT calculator which allows clinicians to easily determine the mSWAT score used to assess response

BSA=body surface area; MF= mycosis fungoides; mSWAT= Modified Severity Weighted Assessment Tool; SS=Sézary syndrome
Source: CS, p30

3.5 Economic analysis

As specified in the final scope issued by NICE [65], the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 45 year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

3.6 Other considerations

As noted in Section 2.1.1, CTCL is a heterogeneous disease. Only patients with the MF or pcALCL CTCL subtypes were included in the ALCANZA trial [66]. Exploratory pre-specified and post-hoc subgroup analyses from the trial are presented in the CS (Figure 15) by histology (MF or pcALCL) and other factors (see Section 4.5 of this ERG report for further information). During the clarification process the ERG requested similar analyses for patients with advanced stage CTCL, which the company provided (company response to clarification question A7; see Section 4.6.1 for the presentation of these results).

Within the final scope issued by NICE [65], it is stated that 'If the evidence allows, the economic analysis should model stem-cell transplantation further down the treatment pathway'. As noted in Section 3.3, the company model includes alloSCT, following treatment with BV and comparator treatments, as a treatment for some patients (depending on their response to systemic therapy). However, the ERG considers that there is a lack of robust evidence relating to alloSCT effectiveness, outcomes following alloSCT in patients with advanced stage CTCL who have received prior treatment with BV, and the place of alloSCT in the treatment pathway. See Section 2.3.3 and Section 5.3.4 for further information relating to these two issues.

As noted in Section 2.4, a PAS has been agreed with the Department of Health and BV is available at a confidential, discounted price. There are no PAS agreements in place for any *Category A* or *Category B* therapies.

The company states (CS summary document, p6; CS, p47) that there are no equality considerations in relation to using BV to treat CTCL.

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

Details of the company's process and methods used to identify and select the clinical evidence relevant to the technology being appraised are presented in the CS, Section B.2.1 and Appendix D.

The ERG considered whether the review was conducted in accordance with key good practice processes (see Table 3). Further information about the review methods is provided in Sections 4.1.1 to 4.1.4 of this ERG report.

Table 3 ERG appraisal of systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	
Were appropriate sources searched?	Yes	The company also ran a rapid literature search "based on the strategy outlined in Appendix D" of the CS. Further information on the sources searched or search terms used is not provided
Was the timespan of the searches appropriate?	Yes	Initial searches were run in January 2017 and updated searches were run in January 2018. It appears from the CS (p91) that the rapid literature search was conducted subsequent to January 2018 although the date of the searches is not specified
Were appropriate search terms used?	Yes	
Were the eligibility criteria appropriate to the decision problem?	Partially	The company excluded studies of fewer than 20 patients (CS, p91, Appendix D.1.3 [Table 1]). Particularly for rare diseases such as CTCL, this may result in the exclusion of potentially useful studies
Was study selection applied by two or more reviewers independently?	Yes	
Was data extracted by two or more reviewers independently?	Not stated	
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	
Was the quality assessment conducted by two or more reviewers independently?	Not stated	
Were appropriate methods used for data synthesis?	Yes	

CS=company submission; CTCL=cutaneous T-cell lymphoma; ERG=Evidence Review Group
Source: LRiG Checklist 2018

Overall, the ERG considers the process and methods used to conduct the company's systematic review of clinical effectiveness evidence to be satisfactory. As a result, studies identified by the review are relevant to the decision problem and the results from the studies identified by the review should not be prone to bias.

4.1.1 Literature search

The company's searches were designed to identify efficacy and/or safety studies of BV and/or current therapies. Embase, MEDLINE and the Cochrane Library were all searched using predefined search strategies. Initial searches were run in January 2017 and updated searches were run in January 2018. While updating the search, proceedings from 12 appropriate dermatology and oncology conference websites were searched on 18 February 2018 to identify any recent studies for which there were currently no full-text publications. These searches were appropriately limited to the last 3 years (2014 to 2018, where available) as it was assumed that good quality studies published in abstract form prior to this date would have been published in full by the time of the searches.

The company's searches were designed to exclude studies published prior to 2007. The company states (CS, p90) that, "It was subsequently noted that earlier data on IFN may be of interest to the decision problem." Thus, a rapid literature search was conducted to identify studies of IFN-α published prior to 2007. It is unclear when the rapid search was conducted or whether all the same data sources were searched. However, it is stated (CS, p91) that this search was "…based on the strategy outlined in Appendix D" of the CS. The ERG, therefore, has assumed that Embase, MEDLINE and the Cochrane Library were searched using the same search terms as the January 2018 search.

4.1.2 Eligibility criteria

As the company's searches were designed to identify efficacy and/or safety studies of BV and/or current therapies, a wide range of therapies were considered to be eligible for inclusion, as specified in the appendices to the CS (Appendix D.1.1.3, Table 2). The ERG notes that the company states that they excluded studies with fewer than 20 patients (p91). For rare diseases such as CTCL, this could result in the exclusion of potentially useful studies, particularly where it is possible to include studies in a meta-analysis. However, in Appendix D.1.1.3 of the CS (Table 2), the company presents the criteria used to identify evidence relevant to the final scope issued by NICE [65]. Notably, the exclusion of studies of patients with fewer than 20 patients is not specified as an exclusion criterion. It is, therefore, unclear if this criterion only applied to the original 2017 search (CS, Appendix D.1.1.3 [Table 1]).

4.1.3 Data extraction

The ERG notes that the optimal approach to data extraction is dual data extraction. It is unclear if this approach was used in the systematic review of clinical effectiveness provided in the CS.

4.1.4 Quality assessment methods

The company's approach to risk of bias assessment followed the method recommended by NICE [73, 74]. It is, however, unclear to the ERG whether this assessment was completed by one reviewer, or independently by two reviewers. The latter method is considered to be the preferred method.

4.2 Identified trials

4.2.1 Studies of BV

The ALCANZA trial [66] was the only randomised controlled trial (RCT) of BV identified by the company. The ERG is not aware of any other RCTs of BV.

Except where stated, all information in the remainder of this ERG report that relates to the ALCANZA trial has been taken from the CS.

In addition, the company identified three non-randomised single-arm studies of BV [66, 75, 76]: two phase II single-arm observational studies (Duvic et al 2015 [18] and Kim et al 2015 [76]) and another study by Mathieu et al 2016 that was conducted retrospectively [75].

The ERG conducted its own electronic searches of the literature (Embase, MEDLINE and the Cochrane Library) on 31 July 2018. The purpose of the ERG's searches was to determine if any additional studies of BV or any RCTs of comparator treatments could be found. No additional RCTs were found by the ERG.

4.2.2 Studies of comparator treatments

The comparator specified in the final scope issued by NICE [65] and the company's decision problem is established clinical management without BV. As described in Section 2.3 and Section 3.3 of this ERG report, the company considered established clinical management for advanced stage CTCL to usually be a *Category A* therapy. Since the ALCANZA trial [66] included a comparator arm of PC, which constituted either MTX or BEX, the company also searched for studies of other potential comparators, in particular IFN-α.

In total, the company identified 32 publications [43-50, 53, 54, 56-58, 77-95] from its systematic review of studies of interventions, other than of BV, that they considered were potentially relevant to the final scope issued by NICE [65]. These included studies of MTX [78, 79], BEX [43-50, 86, 94] and IFN-α [53, 78, 79, 93]. However, MTX and IFN-α were only studied as combination therapies, as were most of the studies of BEX [46, 48-50, 86, 94]; only four BEX studies evaluated the effectiveness of BEX monotherapy [43, 44, 46, 47].

Other studies that the company considered to be potentially relevant also included studies of TSEB [83, 84, 87, 89, 92], acitretin (which, like BEX, is a retinoid) [80], *Category B* therapies [54, 56-58, 86, 94] (including in combination with BEX [86] or prior to treatment with BEX [94]) and alloSCT [77, 81, 82, 85, 88, 90, 91, 95]. The ERG notes that one of the included BEX studies [46] was published in 2001 and thus did not meet the company's stated eligibility criteria. However, this was one of only two RCTs [46, 79] identified by the company's systematic review searches, the other RCT compared IFN-α in combination with MTX versus IFN-α in combination with retinoids [79]. The company's rapid literature search identified an additional 19 studies of IFN-α [96-114], none of which were RCTs.

The company concluded it was not feasible to include any of the studies in an indirect comparison. The ERG concurs with the company (See Section 4.10 of this ERG report for details).

4.2.3 Studies not identified by the company's searches

The ERG did not identify any other relevant studies of BV or RCTs of comparator treatments from its own searches. However, the ERG did identify a retrospective analysis of 12 patients with LyP [115], of which nine patients had been included in the study by Duvic et al 2015 [18]. In addition, the ERG notes that three additional non-randomised studies of BV are referred to in the EPAR for BV [30]. These were not identified by the ERG's searches or included in the CS (Table 4). In the EPAR for BV [30], two of the studies are described as being investigator sponsored trials and the other is described as being authored by Wieser 2016. The ERG subsequently identified this as a published retrospective study [116] with the aim of evaluating characteristics, risk factors, associated malignancies, long-term outcome and treatment of LyP in a single-centre cohort of 180 patients. In this study, 21 (11.6%) patients had received treatment with BV.

Regarding treatments other than BV, a systematic review was published in 2012 that includes RCT evidence for the treatment of MF [117]. This Cochrane review includes RCTs of *Category A* therapies. However, all but one of the RCTs of *Category A* therapies included in this review are either only dose finding studies of BEX [46, 118] or RCTs of *Category A* therapies for early stage MF (IFN-α versus placebo [119, 120], IFN-α in combination with PUVA [121, 122], or ECP in combination with PUVA [123]). A further RCT which compared IFN-α in combination with acitretin versus IFN-α in combination with PUVA and which was published 20 years ago only included 8 (10%) patients with advanced stage CTCL [105]. The ERG is only aware of one RCT of a *Category A* therapy published since this review, an RCT comparing two types of IFN-α combination therapy regimens [79] which was identified by the company's rapid review searches.

Table 4 Additional publications of brentuximab vedotin not identified by the company's searches

Author	Description
Lewis et al 2017 [115]	This brief report is a subset analysis of nine patients with LyP enrolled in Duvic et al 2015 [18], a study identified by the company and included as part of the evidence base presented in the CS, plus three other patients with LyP not enrolled into the Duvec et al 2015 study
IST-001	This is described as investigator sponsored trial in the EPAR for BV [30]. The ERG did not identify this study from its searches and nor was the ERG able to identify this study from subsequent searches of the Internet. Efficacy data are reported for 72 patients from this study in the EPAR for BV [30]
IST-002	This is described as investigator sponsored trial in the EPAR for BV [30]. The ERG did not identify this study from its searches and nor was the ERG able to identify this study from subsequent searches of the Internet. Efficacy data are reported for 36 patients from this study in the EPAR for BV [30]
Wieser 2016 [116]	This is described as a retrospective single centre study in the EPAR for BV [30]. It is reported that 21 patients with LyP or LyP mixed histology received BV. The ERG has identified that this sample of patients is taken from a larger cohort of 180 patients with early and advanced stage CTCL and who received various types of treatment

BV=brentuximab vedotin; EPAR=European public assessment report; IFN=interferon; LyP=lymphomatoid papulosis; MF=mycosis fungoides; RCT=randomised controlled trial

4.3 Characteristics of the included studies of brentuximab vedotin

Aside from the different study designs, the most obvious differences in the clinical studies of BV were the patient populations, specifically in terms of the CTCL subtypes included. Most, if not all, patients in all studies had previously received at least one prior systemic therapy. Where available [18, 66, 75, 76], a brief summary of patient characteristics in terms of demographics, CTCL subtypes and stage of disease is presented by the ERG in Table 5.

Table 5 Characteristics of patient populations in studies of BV

Characteristic	ALCANZA trial		Duvic et al 2015	Kim et al 2015	Mathieu et al 2016
	All patients	BV only			
Number of patients at baseline	128	64	54	32	32
Age, median (range)	60 (48 to 69)	62 (51 to 70)	60 (31 to 77)	62 (20 to 87)	66
Sex: Male, n (%)	70 (55)	33 (52)	27 (50)	19 (59)	20 (62)
Race: White, n (%)	109 (85)	56 (88)	31 (57)	— [69][a]	—
CD30 expression ≥10%, n (%)[b]	97/97 (100)	48/48 (100)	18/28 (64)	18/32 (56)	—[c]
Type of CTCL, n (%)					
MF	97 (76)	48 (75)	31 (57)	29 (91)	19 (60)
SS	0	0	0	3 (9)	10 (31)
pcALCL	31 (24)	16 (25)	3 (6)	0	0[c]
LyP only	0	0	10 (19)	0	0[c]
Other	0	0	10 (19)[d]	0	3 (9)[c]
Stage of CTCL					
Early stage CTCL, n (%)	33 (34)	15 (31)	—	4 (13)	3 (9)
Advanced stage CTCL, n (%)	95 (74)	49 (75)	—	28 (88)	27 (90)
Not specified, n (%)	0	0	58 (100)	0	2 (6)
Type of advanced stage CTCL, n (% of advanced stage CTCL)					
IIB	38 (40)	19 (39)	—	18 (64)	9 (33)
IIIA-IIIB	6 (6)	4 (8)	—	0	5 (19)
IVA1	1 (1)	0	—	Stage IV: MF: 7 (25) SS: 3 (11)	5 (19)
IVA2	10 (11)	2 (4)	—		4 (14)
IVB	7 (7)	7 (14)	—		4 (14)
Other[e]	1 (1)	1 (1)	—	0	0
Advanced stage pcALCL	31 (33)	16 (33)	—	n/a	n/a[c]
Patients included in analyses	ITT: 128 Safety: 128	ITT: 64 Safety: 66	All: 48 MF: 28	30	32

'—'=not reported; BV=brentuximab vedotin; CTCL=cutaneous T-cell lymphoma; ITT=intention-to-treat; LyP=lymphomatoid papulosis; MF=mycosis fungoides; n/a=not applicable; pcALCL=primary cutaneous anaplastic large cell lymphoma; SS=Sézary syndrome

[a] Data on race are reported for 36 patients at a later data-cut on the ClinicalTrials.gov website for race: White=25 (69%) [124]. As the published paper [76] contains more detailed information and in order to ensure consistency with the CS, the ERG has reported data from the published paper [76] throughout this report, except for the data reported here for race

[b] In Duvic et al 2015 [18] and Kim et al 2015 [76], CD30 expression was graded as percentage of the entire lymphocytic infiltrate seen in the tissue (low: <10%; medium: ≥10% to ≤50%; high: ≥50%) whereas in the ALCANZA trial, all patients were described as being CD30+ if one or more biopsy samples had ≥10% CD30+ malignant cells or lymphoid infiltrate (by central review); in the CS, all patients with MF in Duvic et al 2015 [18] are described by the company as being CD30+ (CS, p81)

[c] It is unclear if pcALCL or LyP patients are included in this trial (and therefore classified under 'other'); it is stated in this study that "cutaneous lymphocytic infiltrate expressed CD30 in most cases"

[d] All 'other' patients had CD30+ lymphoproliferative disorders (CD30+ LPDs), i.e. LyP and MF (n=8) or LyP, MF and anaplastic large cell lymphoma (n=2)

[e] Two patients with unknown disease stage were classified as having advanced stage CTCL because, given the balance of the trial population favouring advanced stage disease, there was a higher probability that they had advanced stage CTCL rather than early stage (CS, p83)

Source: ALCANZA trial data taken from CS, (Table 10 and p79), clarification response to question A2 (Table1) and CSR, p84 and Table 11.d), observational study data taken from primary published papers [18, 76] and abstract [75]

Most patients included in the studies were white and had advanced stage MF, although there was variability in the proportions of patients with these characteristics across studies. Between 50% [18] and 62% [75] of patients in the studies were male. The study by Duvic et al 2015 **[18]** was the only study to include patients with LyP (LyP only, n=10; LyP plus a concurrent diagnosis, n=10). Kim et al 2015 [76] was the only study to include patients with SS (n=3).

4.3.1 The ERG notes that clinical advice to the ERG is that approximately 60% of patients with MF and 20% of patients with pcALCL seen in clinical practice have advanced stage CTCL, whereas much higher proportions of patients in all of the published studies had advanced stage MF or pcALCL. However, the population that the company has focussed on in this appraisal is patients with advanced stage CTCL, since these are the patients who are expected to be candidates for treatment with BV in UK clinical practice.

[redacted] Therefore, the greater proportion of patients with advanced stage CTCL included in these studies can be seen as a strength of the evidence base, rather than as a weakness. Except where stated, the focus of the evidence in the remainder of this ERG report is also on patients with advanced stage CTCL in order to be consistent with the CS.ALCANZA trial design

The ALCANZA trial was an international, open-label, randomised, phase III, multi-centre trial of BV versus PC (MTX or BEX) in patients with CD30+ CTCL. Patients were deemed to have CD30+ CTCL if one or more biopsy samples had 10% or more CD30+ malignant cells or lymphoid infiltrate by central review [66]. Advice to the ERG is that this is the same definition used in NHS clinical practice (personal communication with Geetha Menon, 13 August 2018). Only patients with the MF or pcALCL subtypes of CTCL were eligible for inclusion. Patients with a concurrent diagnosis of sALCL, SS and other nHL (except for LyP) were excluded. Patients must also have been assessed to have Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 to 2 and to have received at least one prior systemic therapy (MF and pcALCL) or radiotherapy (pcALCL only).

A total of 131 patients were enrolled between 13 August 2012 and 31 July 2015 and randomly assigned (1:1) centrally by an interactive voice and web response system to receive BV (n=66) or PC (n=65). Randomisation was stratified by baseline disease diagnosis (CS, Table 8) but not by disease stage (CS, p83). In total, patients were recruited from 34 centres across 11 countries, including the UK (24 patients from four centres) (CS, Table 8).

BV was administered intravenously at a dose of 1.8mg/kg once every 3 weeks, for a maximum of 48 weeks (i.e., 16 x 3-weekly cycles). In the PC arm, patients received oral MTX 5mg to

50mg once per week or oral BEX 300mg/m² once per day. It is also stated that patients received either PC treatment for up to 48 weeks (CS, Table 8). The ERG notes that, in clinical practice, patients are usually treated with either MTX or BEX until disease progression or x

It is reported in the EPAR for BV [30] that nearly all patients received concomitant medication during the study (e.g. hydroxyzine, statins, folic acid, fenofibrate, levothyroxine). As noted in Section 2.3.2 of this ERG report, in clinical practice, patients continue to use topical moisturisers, steroids and topical radiotherapy alongside systemic therapy, as required. In the ALCANZA trial, concomitant medications that might have influenced outcomes were prohibited as per protocol and patients were not permitted to receive these within 3 weeks of first dose of study treatments. Radiotherapy was not explicitly listed as an excluded concomitant therapy but the ERG notes that a major protocol deviation listed in the EPAR for BV [30] relates to a patient who received radiotherapy without informing the subinvestigator. Another major protocol deviation was related to concomitant use of topical methylprednisolone 0.1% and betamethasone 0.05% (see Section 4.4).

The first analysis of the data took place after a median follow-up of 22.9 months. A clinical study report (CSR) [125] was produced for this data-cut and made available to the ERG during the clarification process. A second data-cut occurred after a median of 33.9 months. There is no CSR available for this data-cut.

At both data-cuts, the following efficacy outcomes relevant to the final scope issued by NICE [65] and company's decision problem were analysed: ORR4 (primary outcome), ORR, PFS and OS. In addition, outcomes relating to safety (AEs) and HRQoL were also analysed.

While the trial enrolled 131 patients (BV=66; PC=65), all analyses included 128 patients:

- Efficacy and HRQoL outcomes were analysed for the intention-to-treat population (ITT). Three patients were excluded from the ITT analysis as they had been found not to have CD30+ CTCL (BV=2; PC=1). Thus, the ITT population included 64 patients in each arm.
- The three patients excluded from the ITT analysis were, however, included in the safety analysis but a different three patients were excluded from the safety analysis (all in the PC arm) because they had not received at least one dose of study drug. Two patients withdrew themselves prior to treatment and one other patient was withdrawn by the physician. Thus, in the safety analysis, there were 66 patients in the BV arm and 62 patients in the PC arm.

Results from analyses of data from the first data-cut have been published in a peer reviewed paper by Prince et al 2017 [66]. **As previously highlighted, the focus of the CS is on patients with advanced stage CTCL, a subgroup of the overall ALCANZA trial population (n=95).** Results from data analyses for this subgroup have been presented in the CS after a median follow-up of 33.9 months (CS summary document Section A.7.2; CS section B2). This subgroup includes a proportion of patients from the UK (n=19 [20%], clarification response to A3, Table 3).

4.3.2 Baseline characteristics of advanced stage patients enrolled in the ALCANZA trial

The baseline characteristics of ALCANZA trial patients with advanced stage CTCL were provided by the company during the clarification process (response to A2, Table 1). This included patients with MF stage IIB or above and all pcALCL patients. In the EPAR for BV [30], it is noted that the majority of patients with pcALCL had skin only lesions, 9 (56%) and 11 (73%) patients who were treated with BV and PC respectively. The remainder (7 [44%] treated with BV and 4 [17%] treated with PC) were described as having extracutaneous disease.

As the ALCANZA trial was stratified by baseline disease diagnosis (CS, Table 8) but not by disease stage (CS, p83), the subgroup of patients with advanced stage CTCL is not, techically, a randomised patient population. Stratified randomisation ensures that patient characteristics are balanced within each strata, i.e. within the subgroup of patients with MF and within the subgroup of patients with pcALCL for the ALCANZA trial. However, since randomisation was not stratified by disease stage, the randomisation procedure used in the ALCANZA trial did not ensure that patient characteristics were balanced within the subgroup of patients with advanced stage CTCL. However, the proportions of patients with MF and pcALCL in the subgroup of patients with advanced stage CTCL was similar in both treatment arms (clarification response to A2, Table 1); approximately two-thirds of patients had MF (BV=33; PC=31) and approximately a third had pcALCL (BV=16; PC=15).

The company considered that patient characteristics were generally well balanced between treatment arms for the subgroup of patients with advanced stage CTCL, although it noted that patients in the BV arm were generally older than patients in the PC arm (CS, p83). Additional differences were observed by the ERG from the data presented in the clarification response to A2, Table 1. Median time since initial diagnosis was greater in the BV arm than in the PC arm. The BV arm also included more patients with stage IVB MF and pcALCL patients with T3 and/or M1 involvement than the PC arm. Median lines of total prior therapy were also greater in the BV arm than in the PC arm, although for previous SDT and systemic therapies, the

proportions were similar. There were fewer UK patients in the BV arm (n=7 [14% of all patients treated with BV in the subgroup of patients with advanced stage CTCL]) than in the PC arm (n=12 [26% of all patients treated with PC in the subgroup of patients with advanced stage CTCL]). Given the small numbers of patients in the trial, such imbalances are not unexpected. The ERG considers that if any of these differences led to bias, this bias would most likely favour the PC arm rather than the BV arm.

For the subgroup of patients with advanced stage CTCL, patients in both trial arms had received a median of one prior SDT (clarification response to A3, Table 1). The range of prior SDTs was 0 to 6 in the BV arm and 0 to 7 in the PC arm (clarification response to A3, Table 1). Patients in both trial arms in the subgroup of patients with advanced stage CTCL had received a median of two prior systemic therapies (CS, Table 17). The range of prior systemic therapies was large in both arms, 0 to 11 in the BV arm and 2 to 8 in the PC arm (CS, Table 17). Most patients (62%) had received one (42%) or two (20%) prior systemic therapies and 25% had received four or more prior systemic therapies.

The mean number of prior SDTs was similar for UK patients to that of non-UK patients in both arms of the trial. For UK patients, the mean (standard deviation [SD]) was 1.4 (0.98) in the BV arm and 1.8 (1.14) in the PC arm whereas for non-UK patients, the mean (SD) was 1.7 (1.55) and 1.6 (1.84), respectively (clarification response to A3, Table 3). However, patients in the UK typically received fewer lines of systemic therapy than those outside of the UK (Table 6). The ERG urges caution in drawing conclusions from these results given the small numbers of UK patients, particularly in the BV arm.

Table 6 Number of prior systemic therapy received by patients with advanced stage CTCL in the ALCANZA trial, UK versus non-UK

Number of prior systemic therapies	UK			Non-UK		
	BV (n=7)	PC (n=12)	All (n=19)	BV (n=42)	PC (n=34)	All (n=76)
0	0	0	0	1 (2)	0	1 (1)
1	3 (43)	6 (50)	9 (47)	16 (38)	15 (44)	31 (41)
2	2 (29)	4 (33)	6 (32)	6 (14)	7 (21)	13 (17)
≥3	2 (29)	2 (17)	4 (21)	19 (45)	12 (35)	31 (41)
Mean (SD)	2.0 (1.15)	1.7 (0.78)	-	3.6 (3.17)	2.4 (1.78)	-

CTCL=cutaneous T-cell lymphoma; SD=standard deviation; UK=United Kingdom
Source: clarification response to A3, adapted from Table 3

There were also some differences in the type of therapy previously received between UK and non-UK patients (Table 7). Most notably, MTX was a prior treatment for a greater proportion of non-UK patients than UK patients. However, as noted in Section 2.3.2, MTX is commonly used for first- or second-line treatment of CTCL in NHS clinical practice. The lower proportion of patients treated with MTX in UK patients may therefore be reflective of the fewer lines of

prior systemic therapies that UK patients had generally received in comparison to non-UK patients. Overall, the ERG considers that the previous treatments received by patients with advanced stage CTCL appear to be broadly in line with NHS clinical practice in England.

Table 7 Types of prior systemic therapy received by patients with advanced stage CTCL in the ALCANZA trial, UK versus non-UK

Type of prior systemic therapies	UK			Non-UK		
	BV (n=7)	PC (n=12)	All (n=19)	BV (n=42)	PC (n=34)	All (n=76)
IFN-α	4 (57)	7 (58)	11 (58)	21 (51)	15 (44)	36 (47)
IFN-α-2a	0	0	0	3 (7)	2 (6)	5 (7)
MTX	1 (14)	1 (8)	2 (11)	19 (46)	16 (47)	35 (46)
BEX	3 (43)	5 (42)	8 (42)	16 (39)	10 (29)	26 (34)
Chemotherapy, not MTX	4 (57)	6 (50)	10 (53)	21 (51)	15 (44)	36 (47)
Alemtuzumab	0	0	0	2 (5)	2 (6)	4 (5)
Mogamulizumab	0	0	0	1 (2)	0	1 (1)
HDACi	0	0	0	9 (22)	7 (21)	16 (21)
Other	2 (29)	2 (17)	4 (21)	13 (32)	8 (24)	21 (28)
Unknown	0	0	0	8 (20)	2 (6)	10 (13)

BEX=bexarotene; CTCL=cutaneous T-cell lymphoma; HDACi=histone deacetylase inhibitor; IFN-α=interferon alpha; MTX=methotrexate; UK=United Kingdom
Source: clarification response to A3, adapted from Table 3

4.4 Quality assessment

The company assessed the risk of bias in the ALCANZA trial using the minimum criteria set out in the NICE STA: User guide for company evidence submission template [74], adapted from the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care [126]. The ERG considers that the ALCANZA trial was generally well designed and well conducted and the ERG agrees with the company's conclusion that the trial has a low risk of bias for most domains (see Appendix 3, Section 9.3, Table 41). While the open-label design provides the opportunity for subjective results and investigator-assessed outcomes to be biased, the primary outcome of ORR4 plus the secondary outcome of PFS were assessed by an Independent Review Facility (IRF), conducted in a blinded manner. The other key trial outcome is OS, and this an objective outcome that should not be prone to bias.

In addition to assessing the quality of the ALCANZA trial, the company also conducted quality assessments of the two prospective observational studies, Duvic et al 2015 [18] and Kim et al 2015 [76], using criteria developed by the Effective Public Health Practice Project National Collaborating Centre for Methods and Tools [127]. The findings from these quality assessments are reported in Appendix D.1.5 of the CS (Table 25). The company concluded that the overall global ratings for both studies were weak. The ERG concurs with the company's conclusion.

4.5 Statistical approach adopted for the ALCANZA trial

Information relevant to the statistical approach taken by the company has been extracted from the clinical study report (CSR) [125], the trial statistical analysis plan (TSAP) [128], the trial protocol [129], and from the CS.

A summary of checks made by the ERG to assess the statistical approach used to analyse data from the ALCANZA trial is provided in Table 8.

Table 8 ERG assessment of statistical approach used to analyse data from the ALCANZA trial

Review process	ERG comment
Was an appropriate sample size calculation specified in the trial protocol/TSAP?	Yes (TSAP, p12)
Were all primary and secondary outcomes presented in the CS pre-specified?	The primary outcome and some secondary outcomes were pre-specified in the TSAP (TSAP, pp16-17, p19). Time to subsequent anticancer therapy and maximum change in mSWAT score were presented in the CS (CS, pp73-77) but were not pre-specified in the TSAP. The company states that OS was not a pre-specified outcome of the ALCANZA trial since evaluation of OS is not feasible in most clinical trials of patients with CTCL because expected survival of patients exceeds the duration of the study (CS, p29). However, the ERG notes that OS data were collected and presented in the CS (CS, pp77-78); the ERG considers the company's approach to be appropriate
Were definitions for all relevant outcomes provided?	Definitions for all pre-specified outcomes were provided in the TSAP (pp16-17, p19). Time to subsequent anticancer therapy was defined in the CSR (p116). No clear definition was provided for maximum change in mSWAT score
Were all relevant outcomes defined and analysed appropriately?	PFS was assessed using two criteria: 1) pre-specified criterion that counted all events despite ≥2 missed visits or starting of subsequent anticancer therapy (EMA criteria) 2) sensitivity analysis criterion that censored patients at last assessment before the missed visit or starting of subsequent anticancer therapy (FDA criteria) The ERG notes that PFS and time to subsequent anticancer therapy were analysed using the Cox PH method. The company confirmed in their clarification response to question A9 that the PH assumption was assessed by visually assessing log cumulative hazard plots and concluded that the assumption of PH for both outcomes is subject to uncertainty (see text below table for more information). Key secondary endpoints (CR per IRF, PFS per IRF, and symptom Skindex-29) were analysed using a fixed sequential testing procedure (weighted Holm procedure). The analyses for CR per IRF, PFS per IRF, and the changes in symptom domain of the Skindex-29 were assigned weights (0.7, 0.2, and 0.1, respectively) (EPAR, p33)

Review process	ERG comment
Were all subgroup analyses and sensitivity analyses presented in the CS pre-specified?	For the ITT population of the ALCANZA trial, the company presented results of subgroup analyses for the primary outcome, ORR4 (CS, p69), for several patient characteristics that were pre-specified in the TSAP (TSAP, pp18-19). Additional subgroup analyses for the primary outcome were also presented that were not explicitly pre-specified in the TSAP (skin involvement and baseline skin tumour score), although it is stated in the TSAP that subgroup analyses would not be limited to the list of pre-specified characteristics. The ERG is not concerned about the reporting of these additional subgroup analyses. The company presents data for various efficacy, safety and HRQoL outcomes for the subgroup of patients with advanced stage. The ERG notes that this is a post-hoc analysis; all data presented for the population relevant to the company's decision problem are based on this post-hoc subgroup analysis. As part of the company's response to the ERG clarification letter, the company provided the results of subgroup analyses for a range of patient characteristics for the outcome of ORR4 in the advanced stage CTCL patient population. These subgroup analyses were performed for the same set of patient characteristics as for the subgroup analyses of ORR4 in the ITT population. No sensitivity analyses for the efficacy outcomes of the ALCANZA trial were presented in the CS.
Were all protocol amendments carried out prior to analysis?	The conduct of the study was modified by five amendments to the original protocol. Protocol amendments and rationale for these amendments are provided in the CSR (CSR, pp71-76). The ERG is satisfied with the rationale for the amendments and notes that all amendments were made before the data cut-off date for the primary analysis (31st May 2016), so amendments were not driven by the results of the trial.
Was a suitable approach employed for handling missing data?	The company's approach for handling missing data was pre-specified in the TSAP (TSAP, p18, pp20-23, p25). The ERG considers the company's approach to be suitable.

CR=complete response; CSR=clinical study report; CTCL=cutaneous T cell lymphoma; EMA=European Medicines Agency; EPAR=European public assessment report; FDA=Food and Drug Administration; HRQoL=health-related quality of life; IRF=independent review facility; ITT=intention-to-treat; mSWAT=modified severity weighted assessment tool; ORR4=objective global response lasting ≥4 months; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; TSAP=trial statistical analysis plan
Source: CS, CSR, company response to the ERG clarification letter, TSAP

Generally, the ERG is of the opinion that the company's statistical approach for the analysis of data from the ALCANZA trial was appropriate. The ERG notes that the Cox proportional hazards (PH) method was used to estimate the hazard ratios (HRs) for the outcomes of PFS and time to subsequent anticancer therapy. The validity of this method relies on the event hazards associated with the intervention and comparator data being proportional over time [130]. Since the company focuses on patients with advanced stage CTCL in their submission, the ERG assessed the validity of the PH assumption for PFS and time to subsequent anticancer therapy for this subgroup. The results reported for patients with advanced stage CTCL are from the updated analysis of the ALCANZA trial (33.9 month median follow-up), with disease progression determined by IRF assessment.

From examining the Kaplan Meier (K-M) data provided by the company in their response to the ERG clarification letter, the ERG considers that the PH assumption may be violated for IRF-assessed PFS data from patients with advanced stage CTCL. The ERG notes that the company also assessed the PH assumption for PFS data for patients with advanced stage CTCL by visual examination of the log-cumulative hazard plot and quantile-quantile plot. The

company also concludes that the PH assumption may not be appropriately justified. To investigate the PH assumption for the outcome of time to subsequent anticancer therapy, the ERG digitised the K-M graph provided in the CS (CS, Figure 35). The ERG also considers that the PH assumption may be violated for time to subsequent anticancer therapy data for patients with advanced stage CTCL.

Consequently, the ERG considers that the reported HRs for IRF-assessed PFS and time to subsequent anticancer therapy in the subgroup of patients with advanced stage CTCL should be interpreted with caution as HRs are not an appropriate summary of treatment effect when the PH assumption does not hold. It is not possible to know whether the reported HRs would overestimate or underestimate the effect of BV versus PC. See Appendix 4, Section 9.4 for further details on the ERG assessment of PH for IRF-assessed PFS and time to subsequent anticancer therapy for patients with advanced stage CTCL.

4.6 Efficacy results from the ALCANZA trial

As the company focuses on patients with advanced stage CTCL, except where stated, only efficacy results for these patients are presented in this section. All results for this patient subgroup are from the updated analysis of the ALCANZA trial (median 33.9 months follow-up). Although labelled as being investigator assessed in the CS, the company has clarified that all objective response and disease progression data were actually determined by IRF assessment.

A summary of efficacy results for patients with advanced stage CTCL is provided in Table 9. Further information is provided in Sections 4.6.1 to 4.6.5 of this ERG report. The company also provided K-M data for the outcomes of PFS, time to subsequent anticancer therapy, and OS (CS summary document, Figure 5; CS, Figure 33, Figure 35 and Figure 36).

Table 9 Efficacy results for the ALCANZA trial, subgroup of patients with advanced stage CTCL, (33.9 month follow-up)

Outcome		BV (n=49)	PC (n=46)
ORR4			
n % (95% CI)		29 59.2 (45.4 to 72.9)	4 8.7 (2.4 to 20.8)
% difference (95% CI) p-value[a]		50.5 (31.6 to 66.4) p<0.001	
PFS			
Median, months (95% CI)		16.5 (15.5 to 27.5)	3.5 (2.4 to 4.9)
HR (95% CI)		0.30 (0.18 to 0.50)	
Response rates			
ORR	n % (95% CI)	34 69.4 (56.5 to 82.3)	8 17.4 (6.4 to 28.3)
	% difference (95% CI) p-value[a]	52.0 (35.1 to 68.9) p<0.001	
Complete response	n % (95% CI)	10 20.4 (9.1 to 31.7)	1 2.2 (0.1 to 11.5)
	% difference (95% CI) p-value[a]	18.2 (-2.0 to 37.6) p=0.005	
Partial response	n (%)	24 (49.0)	7 (15.2)
Stable disease	n (%)	8 (16.3)	12 (26.1)
Progressive disease	n (%)	3 (6.1)	16 (34.8)
Not evaluable	n (%)	4 (8.2)	10 (21.7)
Time to subsequent anticancer therapy			
Median, months (95% CI)		14.2 (12.2 to 20.4)	5.5 (3.4 to 9.5)
HR (95% CI)		0.31 (0.19 to 0.51)	
OS			
Median, months (95% CI)		43.6 (41.0 to NA)	41.6 (21.1 to NA)

[a]P-value calculated using a CMH test stratified by baseline disease diagnosis (pcALCL and MF)
BV=brentuximab vedotin; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CTCL=cutaneous T cell lymphoma; HR=hazard ratio; MF=mycosis fungoides; NA=not available; ORR=objective response rate; ORR4=objective global response lasting ≥4 months; OS=overall survival; PC=physician's choice; pcALCL=primary cutaneous anaplastic large cell lymphoma; PFS=progression-free survival
Source: CS, pp85-86, 89-90; company response to the ERG clarification letter, question A6, question A8, question A10

4.6.1 Objective response lasting at least 4 months

In the subgroup of patients with advanced stage CTCL, a statistically significantly greater proportion of patients in the BV arm had an objective response lasting at least 4 months than patients in the PC arm (percentage difference=50.5, 95% CI: 31.6 to 66.4). As previously mentioned, for the analysis of ORR4 in the subgroup of patients with advanced stage CTCL, objective response was determined by IRF assessment. The company did not provide results for ORR4 by investigator assessment. However, the ERG notes that, in the ITT population, at the time of the primary analysis (22.9 months follow-up), the results for ORR4 by investigator assessment (BV versus PC: 59.4% versus 7.8%) were broadly comparable to those for ORR4 by IRF assessment (BV versus PC: 56.3% versus 12.5%).

As part of the ERG's clarification letter to the company, the ERG asked the company to perform subgroup analyses for the outcome of ORR4 in the subgroup of patients with advanced stage CTCL in the ALCANZA trial. The ERG asked for these subgroup analyses to be carried out using the same set of patient characteristics as were used for the subgroup analysis of ORR4 in the ITT population. The company provided the results of these subgroup analyses in Figure 2 of their response to the ERG clarification letter (replicated in Figure 15 of this ERG report). Point estimates of efficacy were in favour of BV across all patient subgroups, including whether patients had MF or pcALCL, or whether patients were treated with MTX or BEX in the PC arm. Apart from baseline ECOG PS ≥1 and a baseline skin tumour score of 0, which included a small number of patients (≤30 in both arms) and events (≤7 in both arms), the results were all statistically significantly different.

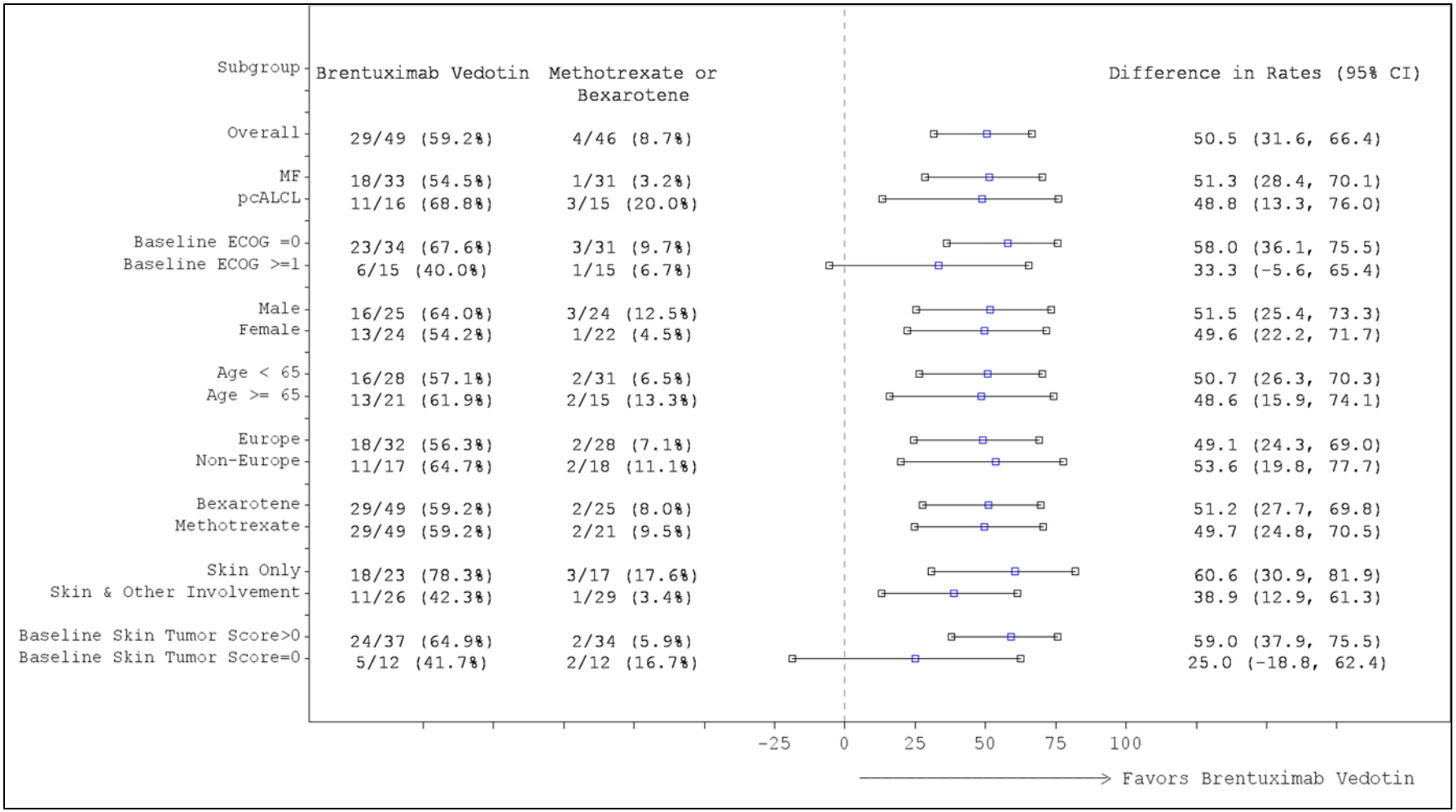


Figure 1 Subgroup analyses of ORR4 per IRF; advanced stage CTCL patient population (33.9 month follow-up)

CI=confidence interval; CTCL=cutaneous T cell lymphoma; MF=mycosis fungoides; IRF=Independent Review Facility; ORR4=objective global response lasting ≥4 months; pcALCL=primary cutaneous anaplastic large cell lymphoma
Source: Company response to the ERG clarification letter, question A7 (Figure 2)

4.6.2 Response rates

Response rates favoured treatment BV over PC in the subgroup of patients with advanced stage CTCL, with a greater proportion of patients experiencing an objective response (complete response [CR] or PR) in the BV arm in comparison to the PC arm (69.4% versus 17.4%, respectively). The proportion of patients experiencing a CR was also higher in the BV arm than in the PC arm (10% versus 1%, respectively). Although the company did not provide results for ORR or CR by investigator assessment, the ERG notes that, in the ITT population, results for CR by investigator assessment (BV versus PC: [redacted]) were broadly comparable to those for CR by IRF assessment at the time of the primary analysis (BV versus PC: 16% versus 2%).

The ERG notes that these ORRs for patients in the PC arm are lower than have been previously reported in the literature, albeit they are typically from single-arm observational studies (Section 2.3.2). Reasons for this are unknown.

4.6.3 Progression-free survival

The BV arm median PFS was considerably longer than PC arm median PFS (16.5 months versus 3.5 months, respectively). The company also reported a statistically significant HR for this comparison. However, due to concerns about the validity of the PH assumption (see Section 4.5 of this ERG report), the ERG considers that this HR should be interpreted with caution.

On examination of the K-M data for IRF-assessed PFS in the subgroup of patients with advanced stage CTCL (Figure 2), the ERG noted that there is a short period of time when a large number of PFS events occur in the BV arm; between approximately 64 weeks (14.7 months) and 77 weeks (17.7 months), 11 PFS events occur. The TSAP for the ALCANZA trial states that all patients randomised to the BV arm were allowed to receive a maximum of 16 cycles of treatment (a treatment duration of approximately 48 weeks), and also that patients were to be followed for survival every 12 weeks for a minimum of 24 months after the end of treatment (EOT) visit (TSAP, p6). The K-M data combined with these details from the TSAP suggest that a number of patients in the BV arm who finished treatment at 48 weeks without having progressed would not have been followed up until 12 weeks after their EOT visit. Therefore, patients who progressed between their EOT visit and the assessment 12 weeks later would all have been recorded as having progressed at the 12-week assessment point (approximately 60 weeks after starting treatment). The ERG considers that this is the most likely explanation for the sudden drop in PFS between 64 weeks (14.7 months) and 77 weeks (17.7 months) of follow-up. The ERG also notes that median PFS is reached within this period

(at approximately 71 weeks [16.5 months]). Since the recording of progression events between the EOT visit and the follow-up assessment 12 weeks later may well have been delayed for some patients, the ERG considers that median PFS may have been overestimated in the BV arm.

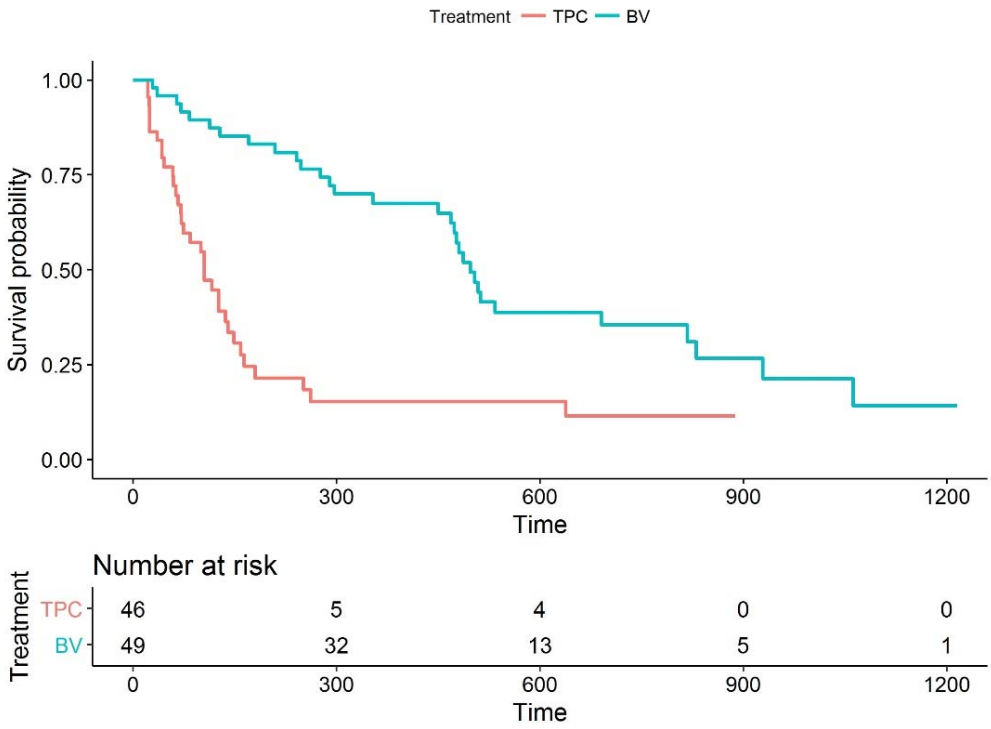


Figure 2 K-M graph for IRF-assessed PFS in the advanced stage CTCL patient subgroup of the ALCANZA trial (33.9 month follow-up)

BV=brentuximab vedotin; CTCL=cutaneous T cell lymphoma; KM=Kaplan-Meier; IRF=Independent Review Facility; PFS=progression-free survival; TPC=treatment by physician's choice
Note: Time measured in days
Source: CS, Figure 31

As part of the company's response to the ERG clarification letter, the company provided K-M data for PFS by investigator assessment for the subgroup of patients with advanced stage subgroup CTCL after a median of 33.9 months. The ERG considers that the results for PFS by investigator assessment are similar to those for PFS by IRF assessment, as shown by the K-M curves presented in Figure 3.

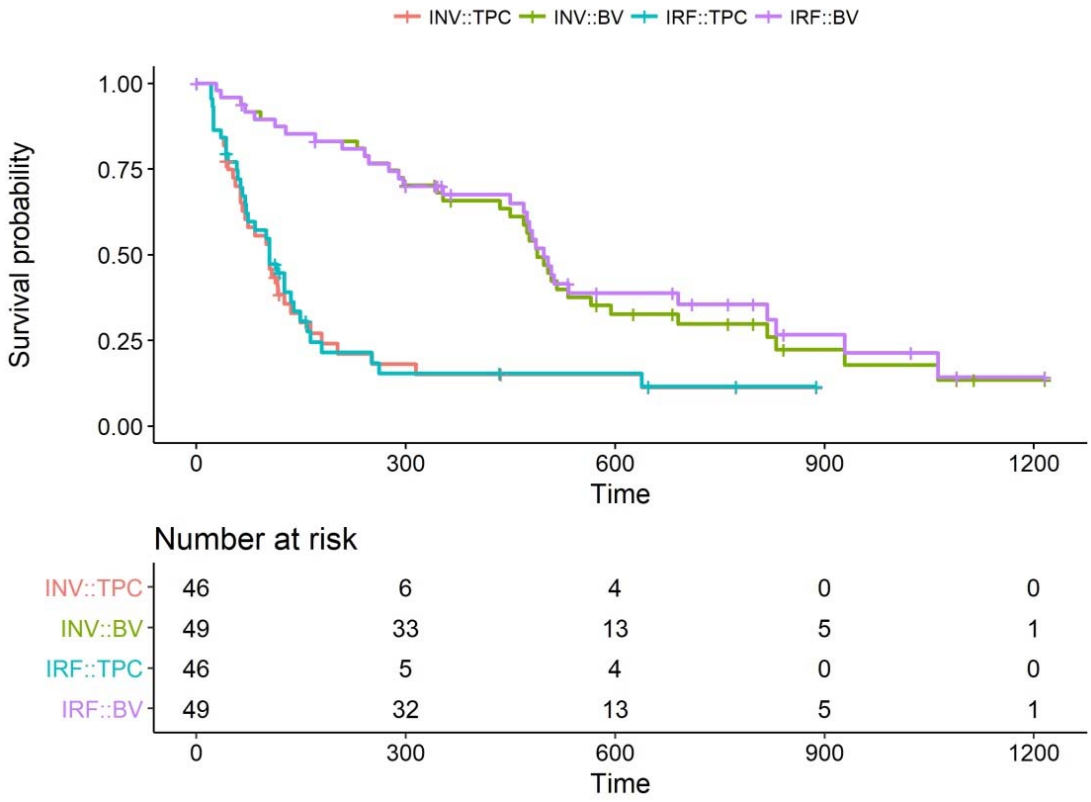


Figure 3 K-M curves for IRF-assessed PFS and investigator-assessed PFS for the subgroup of patients with advanced stage CTCL

BV=brentuximab vedotin; CTCL=cutaneous T cell lymphoma; INV=investigator; IRF=Independent Review facility; K-M=Kaplan-Meier; PFS=progression-free survival; TPC=treatment by physician's choice
Note: Time measured in days
Source: Additional response to clarification question B1

Subgroup analyses of PFS were not presented in the CS. They were, however, presented in the published paper [66] but only after 22.9 months and only for all patients enrolled into the trial, i.e., including those with early stage disease. Point estimates of efficacy were in favour of BV across all patient subgroups, including whether patients had MF or pcALCL, or whether patients were treated with MTX or BEX in the PC arm. Apart from baseline ECOG PS ≥1 and patients aged ≥65 years, which showed no statistically significant difference between arms, the results were all statistically significantly different in favour of BV.

4.6.4 Time to subsequent anticancer therapy

The BV arm median time to subsequent anticancer therapy was considerably longer than that for the PC arm (14.2 months versus 5.5 months, respectively). The company also reported a statistically significant HR for this comparison, although due to the concerns about the validity of the PH assumption (see Section 4.5 of this ERG report), the ERG considers that this HR should be interpreted with caution.

The ERG notes that the median time to subsequent anticancer therapy was lower than median PFS in the BV arm but higher than median PFS in the PC arm. As suggested by the ERG in Section 4.6.3, this may support the ERG consideration that median PFS appears to be overestimated in the BV arm due to the timing of assessments.

As part of the company's response to the ERG clarification letter, the company provided a breakdown of subsequent anticancer therapies for patients with advanced stage CTCL in the ALCANZA trial. The table provided by the company is replicated in this ERG report in Table 10.

Table 10 Subsequent anticancer therapies for patients with advanced stage CTCL

Subsequent systemic therapy	BV (n=49)	PC (n=46)
≥1 subsequent anticancer therapy, n (%)[a]	27 (55.1)	29 (63.0)
Skin-directed therapy, n (%)[b]		
Phototherapy	5 (18.5)	5 (17.2)
Radiotherapy	6 (22.2)	10 (34.5)
Topical chemotherapy	0	1 (3.5)
Topical steroids	0	1 (3.5)
Systemic therapy, n (%)		
BV	8 (29.6)	21 (71.4)
MTX	7 (25.9)	7 (24.1)
BEX	6 (22.2)	4 (13.8)
Chemotherapy other than MTX	18 (66.7)	16 (55.2)
Denileukin diftitox	1 (3.7)	0
HDACi	4 (14.8)	4 (13.8)
Immunotherapy	6 (22.2)	1 (3.5)
Other	7 (25.9)	4 (13.8)

BEX=bexarotene; BV=brentuximab vedotin; CTCL=cutaneous T-cell lymphoma; HDACi=histone deacetylase inhibitor; MTX=methotrexate; PC=physician's choice
[a]Percentages are reported based on the number of patients in each arm
[b]Percentages are reported based on the number of patients who received ≥1 subsequent anticancer therapy
Source: company response to the ERG clarification letter, question A4

Most patients in both arms received subsequent anticancer therapy. For patients in both arms of the trial, this was often chemotherapy, a *Category B* therapy. In both arms of the trial, a quarter of patients who received subsequent anticancer therapy also received MTX, a *Category A* therapy. Approximately a quarter of patients in the BV arm received immunotherapy, which is likely to have included IFN-α, another *Category A* therapy. However, the most common therapy received in the PC arm was BV. As noted in the CS (p89), 46% of patients crossed over from the PC arm to receive BV as a subsequent anticancer therapy (of

whom 30% received it as their first subsequent anticancer therapy). Nearly a third of patients receiving subsequent anticancer therapy in the BV arm also received additional BV. This was, however, only eight patients which highlights the difficulty in interpreting the data from such a small sample of patients.

As part of their response to the ERG clarification letter (question A5), the company also provided details about how many patients in each arm of the ALCANZA trial received an alloSCT. This information appears to be provided for all patients enrolled into the trial, not just for patients with advanced stage CTCL. In total, seven patients in the ALCANZA trial received an alloSCT; five patients received an alloSCT before the time of the primary data analysis (median follow-up 22.9 months) and an additional two received an alloSCT before the time of the updated data analysis (median follow-up 33.9 months). Of the seven patients that received an alloSCT, five were in the BV arm and two were in the PC arm (both received MTX). Both PC arm patients who received an alloSCT had crossed over to the BV arm and had received additional subsequent systemic therapies prior to the alloSCT. Of the five patients in the BV arm who received an alloSCT, two patients received the alloSCT directly after their study treatment; the remaining three patients received additional subsequent systemic therapies prior to their alloSCT. Of the seven patients who received an alloSCT, four were based in the UK; this equates to 17% of UK patients enrolled in the ALCANZA trial subsequently receiving an alloSCT.

4.6.5 Overall survival

While OS was not a pre-specified endpoint in the ALCANZA trial, OS data were collected and are presented in the CS (pp89-90). The company reported that there appears to be a trend towards longer OS observed in the BV arm versus PC (median OS [95% CI]: 43.6 months [41.0 months to not estimable] versus 41.6 months [21.1 months to not estimable], respectively). However, as noted by the company, OS data are “extremely immature at 33.9 months of follow-up” (p89) and confounded by subsequent anticancer therapy and crossover. Furthermore, the company states that interpreting results from this analysis involves high uncertainty, as illustrated by the single figure difference in the number of observed events. The ERG concurs this result should be interpreted with caution due to confounding, the small number of patients included in the analysis and the small number of events that had occurred by the 33.9 month follow-up date (16 events [33%] in the BV arm and 18 events [39%] in the PC arm [CS, Table 27]).

The company explored various methods of adjusting for treatment switching, as suggested by the NICE Decision Support Unit guidance [131]. However, none of these methods were particularly well suited to the data given the small number of patients and events and the lack

of a secondary common baseline at the time data were collected on time-dependent covariates (a prerequisite for the two-stage method of crossover adjustment). The ERG agrees with the company that none of the available methods of crossover adjustment are suitable for the ALCANZA trial and considers that it is not possible to obtain robust estimates of clinical effectiveness for BV in comparison to PC for the outcome of OS.

4.7 Efficacy results from non-randomised studies

The company presents results from Duvic et al 2015 [18] and Kim et al 2015 [76] as supporting evidence for the efficacy of BV, these studies include other subtypes of CTCL i.e., not MF and pcALCL. The ERG has summarised the findings, reported in the CS, for these two studies, for the retrospective study by Mathieu et al 2016 [75], and the findings from the studies (the unpublished IST-001 and IST-002 studies and Weiner 2016 [116]) reported in the EPAR for BV [30] in Table 11 and Table 12. The ERG urges caution in interpreting these findings, particularly in comparing results across studies, given likely differences in the patient populations. The findings are, however, illustrative of the effects of BV treatment across these different patient populations.

Baseline characteristics for the studies included in the CS [18, 75, 76] have been previously summarised in Section 4.3 (Table 5) of this ERG report. Two of these studies [75, 76] included mostly (≥88%) patients with advanced stage CTCL. The stage of disease of patients included in the study by Duvic et al 2015 [18] is not reported. However, the median (range) number of previous systemic therapies in the Duvic et al 2015 study [18] was 2 (1 to 10) for patients with MF and 1 (0 to 5) for patients with CD30+ LPDs, similar to the patterns in the ALCANZA trial. The types of previous therapies are not reported [18]. The median (range) number of previous systemic therapies in the Kim et al 2015 study [76] was 3 (1 to 13) for all patients. In this study [76] most patients had received prior treatment with cytotoxic agents and one patient had had an alloSCT. The number of previous lines of therapies in Mathieu et al 2016 was reported to be between 2 and 14 [75]. There are no data available regarding the patient characteristics of patients treated with BV for the three studies (IST-001, IST-002 and Weiner 2016 [116]) which were reported in the EPAR for BV [30]. It is, therefore, unknown how many patients in these studies had advanced stage CTCL or how many previous lines of therapy patients in these studies had received.

The numbers of patients with CTCL subtypes other than MF included in all of the studies are small. The CTCL subtype was known for patients in all but the Wieser 2016 study. Of the 218 patients in these studies, 147 (67%) had MF, 19 (9%) had SS, 5 (2%) had pcALCL, 22 (10%) had LyP only, 22 (10%) had mixed subtypes (most commonly LyP and MF, n=18 [8%]) and 3 (1%) had other CTCL subtypes.

Only in the IST-002 study were findings for ORR4 reported. The findings (reported in Table 11) for patients with MF (50%) and MF with CD30 expression ≥10% (67%) were broadly similar to ORR4 findings for patients treated with BV in the subgroup of patients with advanced stage CTCL (59.2%) and the ITT population (60.9%) of the ALCANZA trial after a median of 33.9 months follow-up. The ORR4 findings for patients with SS (25%) were notably lower (but, nonetheless, much higher than reported for patients in the PC arm of the ALCANZA trial [7.8% in the subgroup of patients with advanced stage CTCL, 8.7% in all patients, after a median follow-up of 33.9 months]).

Table 11 ORR4 results for patients treated with brentuximab vedotin in IST-002

CTCL subtype	Number of patients	ORR4
All patients	36	50%
MF	32	53%
MF, CD30 expression <10%	17	41%
MF, CD30 expression ≥10%	15	67%
SS	4	25%

CD30=cluster of differentiation; CD30-=cluster of differentiation-negative (CD30 expression <10%) CD30+=cluster of differentiation -positive (CD30 expression ≥10%); CTCL=cutaneous T-cell lymphoma; CD30=cluster of differentiation; MF=mycosis fungoides; ORR4=objective global response lasting ≥4 months; SS=Sézary syndrome
Source: EPAR, adapted from Table 30

All studies reported findings for ORR and most also report findings for PFS (Table 12). The data (albeit from small numbers of patients) show that findings for ORR and median PFS observed in the non-randomised studies for different subtypes of CTCL are generally consistent across studies and are also in line with the findings reported in the ALCANZA trial. However, median PFS reported in the IST-002 study (25.0 months) was longer for patients with MF than was reported for all patients in the Duvic et al 2015 study [18] (13.2 months), or in the subgroup of patients with advanced stage CTCL or for all patients in the ALCANZA trial (16.5 months and 15.8 months, respectively, after a median follow-up of 33.9 months).

Results from the IST-001 and IST-002 studies showed that median PFS for patients with SS (≤7.8 months) tended to be lower than those for patients with other CTCL subtypes (≥13.2 months). Study IST-001 presents the duration of PFS for each individual patient with SS and it is noticeable that the shortest duration (4.2 months) is nonetheless longer than the median PFS reported for patients in the PC arm of the ALCANZA trial (3.5 months in the subgroup of patients with advanced stage CTCL and 3.6 months in all patients, after a median of 33.9 months follow-up). Extreme caution must be taken when interpreting these findings for patients with SS as the studies only included a total of six patients with SS.

It is reported by Duvic et al 2015 [18] that patients with LyP and pc-ALCL lesions responded more rapidly than patients with MF lesions, but that responses were of shorter duration. Regarding the association between CD30 expression and response, the company describes

all patients in this study as having CD30+ CTCL (CS, p81), however, the authors of the study [18] state that CD30 expression was graded as percentage of the entire lymphocytic infiltrate seen in the tissue (low, <10%; medium, ≥10% to ≤50%; or high, >50%). The authors found that CD30 in baseline MF skin lesion biopsies did not seem to correlate with response to brentuximab vedotin [18].

The ERG found, from its searches, that an additional subset analysis of nine patients enrolled in Duvic et al 2015 [18] plus three patients not enrolled in that study had been conducted by Lewis et al 2017 [115]. All patients were 18 years or older, had a diagnosis of LyP and were required to have scarring, more than 10 lesions, or active lesions on the face, hands, or feet. As also reported by Duvic et al 2015 [18], ORR was 100% in this study [115].

Table 12 ORR and PFS results of non-randomised studies of brentuximab vedotin

CTCL subtype	Duvic et al 2015 [18]		Kim et al 2015 [76]		Mathieu et al 2016 [75]		IST-001 [30]		IST-002 [30]		Wieser 2016 [116]	
	n	ORR	n	ORR	n	ORR	n	ORR	n	ORR	n	ORR
All patients	48	73%	30	70%†	32	50%	72	67%	36	50%	21	67%*
MF	28	54%	27	--	19	--	41	54%	32	53%	--	--
CD30- MF	--*	--[a]	*n/a*	*n/a*	--	--	*20*	*55%*	*17*	*41%*	--	--
CD30+ MF	--[a]	--[a]	*n/a*	*n/a*	--	--	*20*	*55%*	*15*	*67%*	--	--
SS	n/a	n/a	3	--	10	--	2	50%	4	25%	--	--
pcALCL	n/a	n/a	n/a	n/a	--	--	3	67%	n/a	n/a	--	--
Lyp only	9	100%	n/a	n/a	--	--	13	92%	n/a	n/a	--	--
Lyp/MF	7	100%	n/a	n/a	--	--	11	82%	n/a	n/a	--	--
Mixed	9[b]	100%	n/a	n/a		--	13[c]	85%	n/a	n/a	--	--
Other	--	--	--	--	3	--	--	--	--	--	--	--
PFS	**n**	**Median**	**n**	**Median**	**n**	**Median**	**n**	**Median**	**n**	**Median**	**n**	**Median**
All patients	48	13.2 mos§	30	NR	32	NR	72	10.0 mos	36	25.0 mos	--	--
MF	28	--	27	--	19	--	41	10.0 mos	32	25.0 mos	--	--
CD30- MF[a]	--[a]	--[a]	*n/a*	*n/a*	--	--	*20*	*7.2 mos*	*17*	--	--	--
CD30+ MF	--[a]	--[a]	*n/a*	*n/a*	--	--	*20*	*10.8 mos*	*15*	*25.0 mos*	--	--
SS	n/a	n/a	3	--	10	--	2	5.5 mos¥ 4.8 mos¥	4	7.8 mos	--	--
pcALCL	2	n/a	n/a	n/a	--	--	3	10.0 mos	n/a	n/a	--	--
Lyp only	9	--	n/a	n/a	--	--	13	11.7 mos	n/a	n/a	--	--
Mixed	9[b]	--	n/a	n/a		--	13[b]	6.9 mos	n/a	n/a	--	--
Other	--	--	--	--	3	--	--	--	--	--	--	--

'—'=not reported; CD30=cluster of differentiation; CD30-negative (CD30 expression <10%) CD30+=CD30-positive (CD30 expression ≥10%); CI=confidence interval; CTCL=cutaneous T-cell lymphoma; LyP=lymphomatoid papulosis; MF=mycosis fungoides; n/a=not applicable; mos=months; NR=not reached; ORR=objective response rate; pcALCL=primary cutaneous anaplastic large cell lymphoma; PFS=progression-free survival; SS=Sézary syndrome

[a]The company describes all patients in Duvic et al 2015 [18] as being CD30+ (CS, p81), however Duvic et al 2015 [18] report some patients did have CD30 expression <10% (number not reported)

[b] Mixed histology subtypes: Lyp/MF (n=7), pcALCL/Lyp (n=1) and pcALCL/MF (n=1)

[c] Mixed histology subtypes reported to be Lyp/MF (n=11), pcALCL/Lyp (n=1) and pcALCL/MF (n=1)

† 95% confidence interval (CI): 53% to 83%

§ 95% CI: 10.8 mos to 16.8 mos

¥ Individual patient PFS duration, not medians

4.8 Safety

Safety data for the ALCANZA trial are presented for all patients after a median follow-up of 22.9 months or 33.9 months in the CS (Section B.2.10.1). Some data for patients with advanced stage CTCL are also presented in the CS (pp96-97), and additional data for this subgroup were provided by the company during the clarification process. All data for patients with advanced stage CTCL relate to analyses undertaken after a median follow-up of 33.9 months. Safety data from the two prospective non-randomised studies [18, 76] are also reported in the CS (Section B.2.10.2 and Section B.2.10.3). In addition, the ERG has extracted the limited safety data from the abstract of the retrospective study [75]. These three studies also include some patients with subtypes of CTCL other than MF and pcALCL (see Section 4.3 of this ERG report).

Following consideration of the safety data presented below (Section 4.8.1 to Section 4.8.5 and Appendix 5, Section 9.5) the ERG concurs with the company that the results from the ALCANZA trial and single-arm observational studies [18, 75, 76] indicate that treatment with BV has not been associated with new, or unexpected, toxicities. The majority of reported AEs were grade 1 or grade 2 in severity, and the ERG notes that, compared to studies of BV for other indications (HL and sALCL) reported in the EPAR for BV [30], grade ≥3 TEAEs were reported less frequently in the ALCANZA trial. As noted by the company, and supported by clinical advice to the ERG, peripheral neuropathy appears to be the most clinically important AE associated with BV.

The ERG also notes the conclusions reached by the EMA (pp99-100 of the EPAR for BV [30]). In particular, the EMA states that toxicity from BV was “substantial” in the ALCANZA trial, but largely consistent with earlier studies of BV. The EMA also considered the lack of safety data for patients with other subtypes of CTCL and, whilst they concluded that the safety data from the ALCANZA trial could be extrapolated to patients with other subtypes of CTCL, they considered that safety in the CTCL subtypes other than MF and pcALCL should be monitored post-marketing.

4.8.1 Exposure to study treatment

Median duration of treatment with BV reported in the studies of BV is summarised in Table 13. It is noticeable that in the overall ALCANZA trial population, patients in the BV arm were on treatment for longer than patients in the PC arm. Duration of BV treatment in the ALCANZA trial was also longer than that for patients with CTCL who were enrolled in the single-arm observational studies [18, 75, 76].

Table 13 Duration of treatment reported in the studies of BV

Study, treatment (number of patients)	3-weekly cycles, median (range)	Days, median
ALCANZA trial, median 22.9 months follow-up		
BV (n=66)	12 (5 to 16)	269
MTX (n=25)	3 (2 to 6)	77
BEX (n=37)	5.5 (3 to 11)	114
Duvic et al 2015 BV for MF (n=28) / BV for LyP/pcALCL (n=20)	7 (2 to 9) / 7.5 (2 to 16)	Not reported
Kim et al 2015 BV (n=30)	6 (1 to 16)	Not reported
Mathieu et al 2016 BV (n=32)	4.8	Not reported

BEX=bexarotene; BV=brentuximab vedotin; LyP=lymphomatoid papulosis; MF=mycosis fungoides; MTX=methotrexate; pcALCL=primary cutaneous anaplastic large cell lymphoma
Source: CS, data extracted from p93 and p97 and data extracted from Mathieu et al 2016 [75]

After median follow-up of 22.9 months, the median relative dose intensity for the ALCANZA trial overall population was 99.6% (inter-quartile range [IQR] 92.7% to 100.0%) for BV and 94.3% (IQR 73.6% to 100.0%) for BEX (CS, p93). The median dose of MTX was 21.7 mg/week (IQR 16.7mg to 30.6mg). Three patients remained on treatment (all in the BV arm) at this data-cut.

After a median of 33.9 months follow-up, mean duration of exposure to BV for patients with advanced stage CTCL was 237 days, and mean duration of exposure to PC was 130 days (CS, p96). As only mean duration for this subgroup is reported, these data cannot be compared with the data in Table 13.

4.8.2 Safety profile in the ALCANZA trial

A summary overview of all AEs and deaths, for all patients, after a median of 22.9 months follow-up in the the ALCANZA trial is presented in Table 19 of the CS. During the clarification process, the ERG requested the same data for the subgroup of patients with advanced stage CTCL after a median of 33.9 months follow-up and these data are presented in Table 14 of this ERG report. The ERG observes that the results for the overall trial population after a median of 22.9 months follow-up and in the subgroup of patients with advanced stage CTCL after a median of 33.9 months follow-up are very similar.

Table 14 Summary of ALCANZA trial AEs

Type of adverse event, n (%)	Overall trial population, median 22.9 months follow-up		Subgroup of patients with advanced stage CTCL, median 33.9 months follow-up	
	BV (n=66)	PC (n=62)	BV (n=49)	PC (n=44)
Any TEAE	63 (95)	56 (90)	46 (94)	40 (91)
Grade ≥3 TEAE	27 (41)	29 (47)	19 (39)	24 (55)
Any TRAE	57 (86)	44 (71)	41 (84)	31 (70)
Grade ≥3 TRAE	19 (29)	18 (29)	14 (29)	15 (34)
Any SAE	19 (29)	18 (29)	13 (27)	16 (36)
Any TRSAE	9 (14)	3 (5)	7 (14)	3 (7)
AE leading to discontinuation	16 (24)	5 (8)	12 (24)	4 (9)
On-treatment deaths	4 (6)	0	3 (6)	0

AE=adverse event; BV=brentuximab vedotin; PC=physician's choice SAE=serious adverse event; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event; TRSAE=treatment related serious adverse event
On-treatment deaths were defined as deaths occurred within 30 days after the last dose of study drug.
Source: CS, adapted from Table 19, subsequent clarification response to A12

As presented in Table 14, the vast majority of patients in both the BV and PC arms of the ALCANZA trial reported at least one any-grade treatment-emergent adverse event (TEAE). Nausea, fatigue and pyrexia were common AEs associated with all three therapies (Appendix 5, Section 9.5, of this ERG report). Peripheral neuropathy was reported to be the most common reason for premature discontinuation of treatment with BV (CS, p49); after a median follow-up of 22.9 months, 9 (56%) discontinuations in the BV arm were attributable to peripheral neuropathy (CSR, p176). As highlighted on p89 of the EPAR for BV [30], other AEs that led to study drug discontinuation were experienced by no more than one patient in either treatment group.

It is reported on p89 of the EPAR for BV [30] that within the PC arm of the ALCANZA trial, after a median follow-up of 22.9 months, more treatment-related adverse events (TRAEs) and grade ≥3 TRAEs were experienced by patients treated with BEX than by patients treated with MTX. Conversely, serious adverse events (SAEs), including treatment-related SAEs, were experienced more frequently by patients treated with MTX than by patients treated with BEX.

4.8.3 Common types of severe (grade ≥3) adverse events

The ERG highlights that the grade ≥3 TRAEs included in the company model are those that occurred in ≥5% of patients in the ALCANZA trial (either arm) with advanced stage CTCL (CS summary document, Section A.11.4). Therefore, within this section, the ERG has focused only on grade ≥3 AEs. Further information on any-grade AEs is presented in Appendix 5, Section 9.5 of this ERG report. However, the ERG notes that grade ≥3 AE data reported in the published paper [66] for the overall trial population and company clarification response for

patients with advanced stage CTCL (response to A12, Table 9) are presented for grade ≥3 TEAEs, not grade ≥3 TRAEs.

Few grade ≥3 TEAEs were experienced by two or more patients treated with either BV or BEX in either the overall ALCANZA trial population after a median of 22.9 months follow-up (published paper, Table 3 [66]) or in the subgroup of patients with advanced stage CTCL after a median of 33.9 months follow-up (company clarification response to A12, Table 9). No grade ≥3 TEAE occurred at all in two or more patients treated with MTX in either the overall trial population or in the subgroup of patients with advanced stage CTCL.

In the subgroup of patients with advanced stage CTCL, the grade ≥3 TEAEs occurring in two or more patients in the BV arm were peripheral sensory neuropathy (8%), neutropenia (6%) and peripheral motor neuropathy (4%); grade ≥3 fatigue (5%), diarrhoea (2%) and skin infection (2%) were also reported by at least two patients in the overall trial population. In the subgroup of patients with advanced stage CTCL treated with BEX, grade ≥3 hypertriglyceridemia (25%), neutropenia (8%) and anaemia (8%) occurred in two or more patients; grade ≥3 pruritus occurred in two patients treated with BEX in the overall trial population (5%).

In the CS, the grade ≥3 AEs experienced by patients with advanced stage CTCL are grouped into system classes (CS, Table 22 and Table 33). The most common AEs in the BV arm were peripheral neuropathy (14%), gastrointestinal disorders (14%) and blood and lymphatic system disorders (anaemia, neutropenia and thrombocytopenia) (12%). In the PC arm, the most common AEs were hypertriglyceridemia (20%) and investigations (alanine aminotransferase, aspartate aminotransferase or blood triglycerides increased, lymphocyte count decreased, raised triglycerides) (14%). The data for the PC arm were not presented for MTX and BEX separately. The ERG notes that there appear to be more AEs of blood and lymphatic system disorders in the BV arm and hypertriglyceridemia in the PC arm included in the system classes (n=6 and n=9, respectively) than were reported in the company's clarification response (n=4 and n=7, respectively). It is unclear if this is because the former relates to occurrences of the AE (in which case, an event experienced by a patient more than once is counted more than once) whereas the latter relates to the number of patients experiencing a specific AE (in which case an event experienced by a patient more than once is counted only once).

As per the ALCANZA trial, few grade ≥3 TRAEs were experienced by two or more patients with BV in the prospective observational studies; grade ≥3 data are not presented in the abstract of the retrospective study [75]. In Duvic et al 2015 [18], the most common grade ≥3

TRAE was neutropenia (6%) followed by nausea (4%), unstable angina or myocardial infarction (4%), arthralgia (4%) and infection (4%). Neutropenia (13%) and skin eruption (9%) were the only grade ≥3 TRAEs reported by two or more patients in the study by Kim et al 2015 [76]. The only other grade ≥3 TRAE reported in this study was peripheral neuropathy, which was reported to have been experienced at grade 4 severity by one patient (3%). It is reported that this patient died of pneumonia as a complication of the neuropathy [76].

4.8.4 Adverse events of special interest (patients with early stage and advanced stage CTCL)

Peripheral neuropathy, haematological toxicities including neutropenia, and infusion-related reactions (IRRs) are described as AEs of special interest (AESI) in the EPAR for BV [30]. The company has focussed on peripheral neuropathy in the CS (pp94-96), which the company has described as a "known toxicity" of treatment with BV.

Peripheral neuropathy

After a median follow-up of 22.9 months in the ALCANZA trial, 44 (67%) patients in the BV arm had peripheral neuropathy. This was the most common any-grade and grade ≥3 TEAE for all patients treated with BV observed in this trial. The company states (CS, p94) that 82% of patients with peripheral neuropathy had either improvement (≥1 grade) or resolution of peripheral neuropathy after discontinuation, dose reduction, dose delay, or completion of treatment and that most patients did not need to delay treatment. The ERG observes that after a median follow-up of 22.9 months, 16 (36%) patients required at least one delay (p79 of the EPAR for BV [30]) and 9 (20%) patients with peripheral neuropathy discontinued treatment with BV (CSR, Table 12.r). These data are not mutually exclusive (i.e., patients requiring a dose delay may also have subsequently discontinued treatment). Data reported in the EPAR for BV [30] also show that the median time to any peripheral neuropathy was 12 weeks (range 0 weeks to 48 weeks) in the BV arm and 2.5 weeks (range 0 weeks to 10 weeks) in the PC arm (p79).

Data, from the updated analysis (33.9 months) of all patients in the ALCANZA trial reported in the CS (Table 21), indicate that there were no new cases of peripheral neuropathy between 22.9 months and 33.9 months. Furthermore, peripheral neuropathy had now improved in 86% of patients: 59% had had a complete resolution (median time to resolution: 30 weeks) and 27% had ≥1 severity grade improvement (median time to improvement: 13 weeks). Nonetheless, the ERG notes that, at the time of this more recent data-cut, 41% of patients in the BV arm still had ongoing peripheral neuropathy: 34% of grade 1 severity and 7% of grade 2 severity (CS, Table 21). Median time to resolution was shorter for the four patients with

peripheral neuropathy in the PC arm (10.5 weeks) than the 44 patients in the BV arm (30.0 weeks) (CS, Table 21).

As per the ALCANZA trial, peripheral neuropathy was often reported to be reversible in the prospective observational studies [18, 76]: 45% of patients with peripheral neuropathy in the study by Duvic et al 2015 [18] had complete resolution and 59% of patients with peripheral neuropathy in the study by Kim et al 2015 [76] had improvement or resolution by 12 months. Median time to resolution or improvement was reported to be longer in these studies [18, 76] than in the ALCANZA trial (CS, pp97-98 and Table 21). Furthermore, data from the observational studies also show that peripheral neuropathy often deteriorates before it improves. It is reported by Duvic et al 2015 [18] that, of 31 patients with peripheral neuropathy, 30 patients had grade 1 events, of whom 21 (70%) progressed to grade 2 severity. Kim et al 2015 [76] report the median time to any peripheral neuropathy was 13 weeks (range 3 weeks to 89 weeks) and the median time to grade 2 peripheral neuropathies was 20.8 weeks (range 15 weeks to 46 weeks).

Neutropenia

As reported on p81 of the EPAR for BV [30], neutropenia or decreased neutrophil count TEAEs were reported for 9% of patients in the BV arm and 6% of patients in the PC arm. From data reported in Table 36 of the EPAR for BV [30], grade ≥3 neutropenia was reported at a much lower incidence for patients treated with BV in the ALCANZA trial after a median of 22.9 months (3%) than in previous studies for sACLC or HL (20% to 22%). However, grade ≥3 neutropenia was also reported in the ALCANZA trial at a lower frequency than in the prospective observational studies of CTCL (6% to 13%) (Section 4.8.3 of this ERG report). It is reported on p81 of the EPAR for BV [30] that neutropenia TEAEs required ≥1 dose delay for four patients in the BV arm but did not require dose reductions, holds, or permanent discontinuations. No events of febrile neutropenia were reported in either arm.

Infusion-related reactions

As reported on pp81-82 of the EPAR for BV [30], IRRs occurred in nine patients (14%) treated with BV; all events occurred during cycle 2 or cycle 3. Two patients experienced a grade 3 IRR (urticaria and drug hypersensitivity). None of the IRRs were considered SAEs, and no grade 4 IRRs or anaphylaxis TEAEs were reported. One patient discontinued treatment with BV as a result of a grade 3 urticaria.

4.8.5 Treatment-related deaths

As reported in in the CS (p94), after a median follow-up of 22.9 months, in the overall trial population of the ALCANZA trial, 24% of patients in the BV arm and 23% in the PC arm had

died. Four (6%) patients in the BV arm experienced on-treatment deaths (defined as deaths that occurred within 30 days of their last dose of study drug). In patients with advanced stage CTCL, after a median of 33.9 months follow-up, there were three (6%) on-treatment deaths in the BV arm (subsequent clarification response to A12). There were no on-treatment deaths in the PC arm.

There was only one treatment-related death. The treatment-related death occurred in a patient with pcALCL within 30 days of their last dose of BV. Their cause of death was attributed to multiple organ dysfunction syndrome. This was attributed by the investigator to tumour lysis caused by BV on sites of visceral lymphoma involvement. Although not reported in the CS, the ERG observes from the EPAR for BV [30] (p78) that this patient did not meet the trial eligibility criteria as they had elevated liver function test results at baseline and their enrolment, therefore, constituted a major protocol violation.

As highlighted above, one patient (3%) with treatment-related grade 4 peripheral neuropathy died in the study by Kim et al 2015 [76].

4.9 Health-related quality of life

HRQoL results are reported in the CS, a published paper [66] and the EPAR for BV [30] for all patients in the ALCANZA trial. The CS also includes an analysis for patients with advanced stage CTCL. HRQoL was measured using three different instruments:

- The Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire [132], a 27-item general cancer HRQoL instrument with four primary subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being.
- The Skindex-29 [133], a 30-item, dermatology-specific, self-reported questionnaire designed to assess 3 domains: symptoms (pre-specified as a key secondary endpoint in the ALCANZA trial), emotions, and function.
- The European Quality of Life 5-Dimension 3 Level (EQ-5D-3L) questionnaire and EQ-5D Visual Analogue Scale (VAS) [134], generic instruments for collecting patient-reported HRQoL; EQ-5D-3L is a 5-item questionnaire which assesses the dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, whilst the VAS was used to record self-rated health on a 20-cm vertical line ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

All HRQoL questionnaires were completed by patients still on treatment on day 1 of cycles 1, 2, 4, 6, 8, 10, 12, 14, and 16 (before any other study procedures were performed). Patients who were progression-free and no longer on study treatment completed HRQoL questionnaires within 30 days +/- 2 days of EOT. Progression-free patients then had their HRQoL measured every 12 weeks (± 2 weeks) after EOT for at least 24 months, and then every 6 months (± 1 month) until progression or the end of the study. Patients whose disease had progressed were followed-up every 12 weeks after EOT for up to 24 months and then every 6 months until withdrawal, death or the end of the study. For patients not required to return to clinic for post-treatment follow-up, questionnaires were completed by phone or by mail. Results are presented in the CS up to EOT.

The ERG notes that the FACT-G questionnaire is an instrument that has been validated for use for many different types of oncology, including nHL [135]. The company highlights that Skindex-29 has been extensively studied and validated in different patient populations with skin diseases, including CTCL [13, 14, 136]. However, the company questions the appropriateness of the EQ-5D-3L for patients with CTCL. Company results show a poor correlation between the symptom domain of Skindex-29 and the EQ-5D-3L results for patients with advanced stage CTCL. Results presented in the CS (p30 and Section B.2.7.4, Figure 33) from the Skinindex-29 questionnaire classified these patients as severely symptomatic but results from the EQ-5D-3L questionnaire suggested that patients were close to perfect health (i.e., an average score of close to 1.0). A large proportion of patients with relatively high EQ-5D-3L scores (≥0.7) also had a Skindex-29 symptom score of >52 (CS, p99). The company

notes (p87) that symptom scores >52 are classified as having a severe negative impact on HRQoL (scores of 42 to 51 are classified as moderate and scores of 39 to 41 are classified as mild) [137].

HRQoL data for patients with advanced stage CTCL are only included in the CS (pp86-88). The data reported are from an analysis of the symptom domain of Skindex-29 (which relates to skin problems) and EQ-5D-3L. The company reports (CS, p86) that patients with advanced stage CTCL treated with BV had a greater symptom reduction compared with those treated with PC (change from baseline to EOT, mean [SD]: –16.31 [28.98] versus –2.41 [21.04], respectively). The difference was described as being clinically meaningful. No statistically significant difference in EQ-5D-3L values was found between arms (CS, p88).

Similar findings to those reported for the subgroup of patients with advanced stage CTCL after a median follow-up of 33.9 months were reported for the Skindex-29 and EQ-5D-3L scores in the ITT population after a median follow-up of 22.9 months and after a median follow-up of 33.9 months. For other measures of HRQoL in the ITT population, no differences between arms in scores obtained by FACT-G or EQ-5D VAS were reported. It is also reported in the published paper (p560) that “No substantial difference in Skindex-29 emotional or functioning domains was seen over time” [66]. For more information about HRQoL findings in the ITT population, see Appendix 6, Section 9.6 of this ERG report.

When interpreting all of the HRQoL results, it is important to consider the number of patients who completed the questionnaires. Whilst compliance was reported to be high over time from baseline to EOT (i.e., most of those eligible to complete questionnaires did so), the number of eligible patients at each point in time the data were collected decreased, reflecting the higher number of patients who had disease progression over time. This decrease was more pronounced in the PC arm than in the BV arm and was particularly noticeable from cycle 4 onwards, when the number of patients in the PC arm had halved from baseline, and from cycle 8 onwards when the number of patients in the PC arm was <10 (Table 15). As patients who remain on treatment in either arm are those who are benefitting from treatment (i.e., progression-free and/or no serious or severe AEs), it is perhaps unsurprising that there are no statistically significant differences in many of the aspects of HRQoL captured by the FACT-G, EQ-5D-3L or EQ-5D VAS questionnaires. The ERG, therefore, concurs with the view expressed by the EMA in the EPAR for BV [30] that, in relation to the impact of BV on HRQoL, “no firm conclusions can be drawn” (p64).

Table 15 Number of patients with advanced stage CTCL in the ALCANZA trial completing Skindex-29 questionnaire at each cycle

Cycle	BV (n=49)		PC (n=46)	
	n	% of baseline	n	% of baseline
1	48	98	43	93
2	43	88	35	76
4	40	82	22	48
6	33	67	17	37
8	32	65	8	17
10	30	61	8	17
12	26	53	7	15
14	23	47	4	9
16	20	41	3	7
EOT	34	69	26	57

BV=brentuximab vedotin; CTCL=cutaneous T cell lymphoma; EOT=end of treatment; PC=physician's choice
Source: CS, adapted from Figure 32

4.10 ERG critique of the indirect evidence

As the ALCANZA trial did not include IFN-α as a treatment option in the PC arm, the company assessed the feasibility of performing indirect comparisons to obtain estimates of effectiveness for treatment with BV versus IFN-α (CS summary document Section A.8.2.1; CS, Section B.2.9.1). As the ALCANZA trial did not include patients with CTCL other than MF or pcALCL, the company also considered the feasibility of treatment with BV versus standard of care for patients with SS/LyP (CS summary document Section A.8.2.2; CS, Section B.2.9.2).

4.10.1 Feasibility of comparing brentuximab vedotin with interferon-alpha

The company's feasibility assessment of indirectly comparing treatment with BV and IFN-α focused on the relevant patient population, patients with advanced stage CTCL. The company states that only studies that reported PFS and/or OS data were considered for inclusion in the indirect comparison, as these outcomes are the key inputs for the economic model. The ERG notes that as well as studies of IFN-α, the company also considered studies of other IFN preparations such as IFN-gamma [112] for inclusion.

In total, the company identified 23 publications relevant to IFN in CTCL [53, 78, 79, 93, 96-114]. The company assessed the viability of each publication as a data source for the indirect comparison (Appendix D to the CS, Table 18). The company determined that none of the identified studies could be used as a data source for the indirect comparison for various reasons. The company therefore concluded that it was not feasible to conduct an indirect comparison of treatment with BV versus IFN-α. While reasons for excluding studies from a systematic review or indirect comparison are sometimes arrived at in a hierarchical manner,

the company has not employed such an approach. Therefore, in some instances, studies have been excluded for multiple reasons and the number of reasons for exclusion therefore exceeds the numbers of studies that were excluded. The reasons cited by the company for exclusion were as follows:

- IFN-α used as combination therapy rather than monotherapy (12 studies)
- lack of relevant outcomes reported (8 studies)
- patient population not consistent with that of the ALCANZA trial or relevant to the decision problem (2 studies)
- IFN preparation was not consistent with UK clinical practice (3 studies).

The ERG agrees with the company's assessment that there is insufficient evidence to perform an indirect comparison.

4.10.2 Feasibility of comparing brentuximab vedotin with standard of care for patients with SS/LyP

The company's search for evidence of the clinical effectiveness of treatment with BV in patients with SS/LyP identified only two phase II studies of BV [18, 76] (see Section 4.2.1 and Section 4.3) for an overview of these studies). Kim et al 2015 [76] only included three patients with SS whereas Duvic et al 2015 [18] only included 10 patients with LyP. Neither study reported OS or PFS results for patients with SS or LyP. Furthermore, both trials were single-arm studies and any indirect comparison would have required the use of population adjustment methods (such as matching-adjusted indirect comparison and simulated treatment comparison). Both these approaches involve fitting regression models including multiple covariates. This was not considered feasible given the small sample sizes available. Furthermore, even if the use of these methods was feasible, the company did not identify any data sources for of standard care for patients with SS or LyP to form a comparator dataset. The company determined that it was not possible to conduct an indirect comparison for treatment with BV versus standard of care for patients with SS/LyP for the reasons discussed. The ERG agrees with the company's conclusion.

4.11 Summary of findings for the overall ALCANZA trial population

In addition to subgroup evidence for patients with advanced stage CTCL, the company also presents evidence for the overall trial population of the ALCANZA trial after a median follow-up of 22.9 months and 33.9 months. In all trial patients, results were consistent at both data-cuts. The key efficacy findings from the subgroup of patients with advanced stage CTCL are consistent with those for the overall trial population (after a median follow-up of 33.9 months) (see Table 16). Safety and HRQoL findings for the subgroup of patients with advanced stage

CTCL are also similar to, and consistent with, those for the overall trial population (See Sections 4.8 and 4.9 of this ERG report).

Table 16 Summary of key efficacy findings from the ALCANZA trial after median follow-up of 33.9 months

Outcome, population	Summary of results
ORR4	
ITT population	Favours BV (n=64) versus PC (n=64): 60.9% versus 7.8%
Advanced stage subgroup	Favours BV (n=49) versus PC (n=46): 59.2% versus 8.7%
PFS	
ITT population	Favours BV (n=64) versus PC (n=64): 15.8 months versus 3.6 months
Advanced stage subgroup	Favours BV (n=49) versus PC (n=46): 16.5 months versus 3.5 months
OS	
ITT population	"no difference" between treatment arms
Advanced stage subgroup	"not possible to claim a difference" between treatment arms

BV=brentuximab vedotin; ITT=intention-to-treat; ORR4=objective global response lasting ≥4 months; OS=overall survival; PC=physician's choice; PFS=progression-free survival
Note: ORR4 and PFS outcomes are per Independent Review Facility (note: data at 33.9 months were wrongly labelled as per investigator in the CS)
Source: CS summary document, adapted from p13 and p16; CS, adapted from p68, p70, p78, p85 and pp89-90

4.12 Conclusions of the clinical effectiveness section

The majority of the evidence is derived from the ALCANZA trial, an international, open-label, randomised, phase III, multicentre trial of treatment with BV versus PC (MTX or BEX) in patients with CD30+ CTCL (n=131). The ALCANZA trial is a well-designed and good quality trial. The company's statistical approach to the analysis of data from the ALCANZA trial was appropriate, with the exception that the PH assumption required for the appropriate use of the Cox PH model is subject to uncertainty for PFS and time to subsequent anticancer therapy. Therefore, it is not possible to know whether the reported HRs overestimate or underestimate the effect of treatment with BV versus PC.

The focus of the company's decision problem is patients with advanced stage CTCL (n=95) as these are the patients considered by the company that would be candidates for treatment with BV in NHS clinical practice. The ERG concurs with this viewpoint. Moreover, the ERG notes that the results from the subgroup of patients with advanced stage CTCL in the ALCANZA trial are consistent with results from the overall ALCANZA trial population.

The ERG considers that the patient characteristics for patients with advanced stage CTCL in the ALCANZA trial are reasonably similar to the characteristics of patients who would be seen in NHS clinical practice in England. Thus, the results from the ALCANZA trial are likely to be generalisable to patients in NHS clinical practice.

The comparators (MTX and BEX) in the PC arm of the trial are two of the most commonly used therapies for NHS patients with MF who have had a median of two previous lines of systemic therapy, as was the case in the ALCANZA trial. Clinical advice to the ERG is that (i) *Category A* therapies are the most relevant comparators to BV for patients with MF and (ii) *Category B* therapies would normally be preferred to *Category A* therapies for patients with advanced stages of pcALCL who have received at least one prior systemic therapy and are fit enough to tolerate the drugs. However, clinical advice is that MTX and BEX are likely to be appropriate comparators to BV for the patients included in the ALCANZA trial with pcALCL who were not fit for *Category B* drugs. As the ALCANZA trial did not include IFN-α as a treatment option in the PC arm, the company assessed the feasibility of indirectly comparing BV with IFN-α but concluded that this was not possible due to a lack of relevant data. Since IFN-α is commonly used before or after MTX or BEX in NHS clinical practice and since MTX, BEX and IFN-α are generally considered to have equal clinical efficacy, the lack of evidence to compare treatment with BV to IFN-α is not considered be a major limitation.

The ALCANZA trial has shown that compared with PC, for patients with advanced stage CTCL, BV results in increased ORR4 and improved PFS; reflecting these improvements,

patients were treated with BV for longer than with MTX of BEX. However, median PFS may be overestimated in the BV arm due to the timing of assessments following EOT. The OS data from the ALCANZA trial are immature and confounded by subsequent anticancer therapy and crossover and so the relative effect of treatment on OS is unclear. ORRs for patients in the PC arm are also lower than have been previously reported in the literature, albeit they are typically from single-arm observational studies. The reasons for this discrepancy are unclear.

The safety data from the ALCANZA trial show that for patients with advanced stage CTCL, treatment with BV was not associated with new or unexpected toxicities, the majority of reported AEs being grade 1 or grade 2 in severity. However, compared with patients treated with PC, more patients treated with BV reported any-grade TRAEs, TRSAEs and discontinuation due to AEs. Peripheral neuropathy is the most common AE associated with treatment with BV and is the most clinically significant. There were four on-treatment deaths in patients with advanced stage CTCL, all in the BV arm. However only one death was considered to be treatment related. The patient who died did not meet the trial eligibility criteria as the patient had elevated liver function test results at baseline and their enrolment, therefore, constituted a major protocol violation.

Regarding HRQoL, patients with advanced stage CTCL treated with BV had a greater skin symptom reduction compared with those treated with PC, as measured by the Skindex-29 questionnaire. This improvement is reported by the company to be clinically meaningful. However, there were no statistically significant or clinically meaningful differences in HRQoL reported from scores obtained by EQ-5D-3L or EQ-5D VAS.

The relative efficacy of treatment with BV compared to PC for patients with subtypes of CTCL other than MF and pcALCL is uncertain as all patients in the subgroup of patients with advanced CTCL in the ALCANZA trial either had MF (n=64) or pcALCL (n=31). Evidence for other subtypes is limited to single-arm studies only. Given the rarity of CTCL, particularly for subtypes other than MF, obtaining evidence for the relative efficacy of patients with other CTCL subtypes is difficult. Consequently, cost effectiveness evidence is only available for patients with MF and pcALCL (see Section 5 of this ERG report).

A final uncertainty with the evidence from the ALCANZA trial relates to the possible impact that prior treatment may have on efficacy, safety and HRQoL. While most patients (62%) in the subgroup of patients with advanced stage CTCL had received one (42%) or two (20%) prior systemic therapies, a quarter had received four or more prior systemic therapies. The maximum number of prior systemic therapies that patients had received was 11.

5 COST EFFECTIVENESS

This section provides a summary and structured critique of the economic evidence submitted by the company in support of the use of BV. The two key components of the economic evidence presented in the CS are (i) a systematic review of relevant literature and (ii) a report of the company's de novo economic evaluation. The company has also provided an electronic copy of their economic model, which was developed in Microsoft (MS) Excel.

5.1.1 Objective of the company's systematic review

The company performed a systematic search of the literature to identify studies that evaluated the cost effectiveness of treatment, or provided costs and resource use estimates, for people with CD30+ CTCL who had received at least one previous treatment.

5.1.2 Company searches

The company initially searched the databases listed in The search strategies used are shown in Appendix G and are used to identify cost effectiveness studies and cost and resource use estimates.

Table 17 in December 2017. These searches were updated on 23rd February 2018. The search strategies used are shown in Appendix G and are used to identify cost effectiveness studies and cost and resource use estimates.

Table 17 Details of the databases searched for economic evidence

Database	Interface
Excerpta Medica Database (Embase®)	Embase.com
Medical Literature Analysis and Retrieval System Online (MEDLINE®)	Embase.com
Cochrane Library (including the databases: HTA, NHS EED, DARE, CENTRAL and the Cochrane Database of Systematic Reviews	Wiley.com
EconLit®	Ebsco.com

CENTRAL=Cochrane Central Register of Controlled Trials; DARE=Database of Abstracts of Reviews of Effects; HTA=Health Technology Assessment; NHS EED=NHS Economic Evaluation Database;
Source: CS, Appendix G

The company also carried out electronic searches to identify relevant proceedings from 13 conferences relating to haematology, oncology and dermatology which took place between 2016 and 2018.

Additionally, the company searched HTA websites (NICE, the Scottish Medicines Consortium [SMC], Haute Autorité de santé [HAS], Canadian Agency for Drugs and Technologies in Health [CADTH] and Pharmaceutical Benefits Advisory Committee [PBAC]) for relevant information contained within submissions to those organisations.

5.1.3 Eligibility criteria used in study selection

The main inclusion and exclusion criteria used by the company to select studies are shown in Table 18 and Table 19.

Table 18 Economic evaluation review inclusion and exclusion criteria

Characteristic	Inclusion	Exclusion
Population	Patients with relapsed and/or refractory CTCL (defined according to the 2008 WHO classification)	In vitro studies, animal studies Healthy volunteers Animal studies
Intervention/comparators	Not restricted by intervention	-
Outcomes	Main outcomes: ICER: cost per QALY ICER: cost per DALY ICER: cost per event avoided Additional outcomes: Range of ICERs as per sensitivity analyses Assumptions underpinning model structures Key costs drivers Sources of clinical, cost and quality of life inputs Discounting of costs and health outcomes Model summary and structure	Studies with no outcomes of interest
Study types	Economic models: Cost utility analyses Cost effectiveness analyses Cost benefit analyses Cost minimisation analyses	Interventional or observational study designs (registry, chart review, administrative claims) Systematic literature reviews

CTCL=cutaneous t-cell lymphoma; DALY=disability adjusted life years; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years; WHO=World Health Organisation.
Source: CS, Appendix G, Table 28

Table 19: Resource use and cost review inclusion and exclusion criteria

Characteristic	Inclusion	Exclusion
Population	Adult CD30+ CTCL in patients who have received at least one previous treatment (defined according to the 2008 WHO classification [138]; updated in 2016 [139])	Studies reporting children, in vitro Not CD30+ CTCL in patients who have received at least one previous treatment
Interventions/Comparators	Not restricted by intervention/comparator	NA
Outcomes	Direct costs Direct medical and pharmacy healthcare costs per patient per year (interventions, concomitant medications, treatment of AEs/co-morbidities) Method of valuation Indirect costs Productivity loss costs Presenteeism: at work productivity level (also from patients' viewpoint) Short- and long-term sick leave (absenteeism) Withdrawal from labour force Method of valuation (Human capital or friction cost approach or contingent valuation) Patient and family/caregiver costs Travel, co-payments Annual loss of income Formal and informal care Caregiver burden	No cost or recourse information
Study design	Objectives of the study must include an assessment of costs of illness or an assessment of interventions in management of CTCL Studies reporting predictors of costs were considered for inclusion	Studies that do not provide cost or resource use for the concerned population Not original studies

AE=adverse events; CTCL=cutaneous t-cell lymphoma; WHO=World Health Organisation.
Source: CS, Appendix I, Table 45

5.1.4 Included and excluded studies

The company search identified 4,312 unique citations, of which 37 remained after title and abstract screening. Details of the screening process and the reasons for study exclusions are presented in the CS (Section B.3.1 and Appendix G).

For the review of economic evaluations at full-text stage, the majority (20/37) of abstracts are excluded as they did not contain any of the outcomes listed in Table 18. All but one of these are excluded based on a review of the full texts. One abstract is identified from the search of conference proceedings and 3 further publications are obtained from hand searching of HTA websites. This resulted in 5 publications included at full-text review (1/37 plus 4 from additional searches). Only one of these 5 articles, a submission to the SMC [140]. reported results for a

UK population with CTCL, This study is an evaluation of ECP which, as mentioned in Section 2.3.2, is only recommended for use in patients with SS.

The 37 full-text articles obtained from the literature search were reviewed for cost and resource use information relevant to the company economic model. All but two of these studies are excluded. An additional two papers were found through hand searching of the grey literature. None of the four articles reported resource use and cost information for people with CD30+ CTCL who have received at least one previous treatment in the UK, however one paper reported medical costs for people with MF in Italy and three papers contained information about resource use and costs relevant to people with CD30+ CTCL in the US.

5.1.5 Findings from cost effectiveness review

Economic evaluations

The SMC guidance paper [140], includes a report of the evaluation that was undertaken to assess the cost effectiveness of ECP for people with CTCL compared with current standard treatment (ST). It is reported in the SMC paper that the results generated by an economic model with a 3-year time horizon suggest that ECP dominates ST, and the authors demonstrate that this finding is robust to sensitivity analyses (cost of treatment, survival and utility estimates). Total costs for ECP are £39,580 and £94,452 for ST and total quality adjusted life years (QALYs) are 3.40 for ECP and 1.63 for ST. The company presents results in the CS (Tables 23 and Table 24) but states there are not enough details of the methods or parameters used reported in the paper to be enable to use in their economic model

Resource use and costs

The company describe the information contained in four the papers providing resource use and costs information (CS, Appendix I, Table 46). However, as none of the studies include UK resource use or costs information, and therefore lack relevance to the NHS, the company do not use any of these estimates in their model.

5.1.6 ERG critique of the company's review of cost effectiveness evidence

Summary details of the ERG's appraisal of the company's cost effective systematic review methods are provided in Table 19.

The ERG considers the databases searched and the search terms used by the company are reasonable. The inclusion criteria, with respect to the population of interest, differ between the economic evaluation review and the review that was carried out to source resource use and cost information to inform the economic model. The ERG considers this approach is

appropriate as the economic evaluation review is designed to locate economic evaluations of relevance to the population defined in the final scope issued by NICE, whereas the resource use and cost information review is specific to the narrower, advanced stage CTCL population, that the company describes in the CS.

The ERG considers that although the SMC guidance paper [140] met the review inclusion criteria specified by the company it is not relevant to this appraisal. This is because ECP is not listed as a comparator to BV in the final scope issued by NICE, and because the focus of the company model is people with MF and, to a lesser extent, pcALCL, and ECP is used to treat people with SS.

Table 20 ERG appraisal of systematic review methods (cost effectiveness)

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Unclear. The search terms appear reasonable however the economic search filter is complicated and not cited so the ERG is unclear whether this filter has been tested.
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes – ran in December 2017 and then updated in February 2018
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied, independently, by two or more reviewers?	Yes
Were data extracted, independently, by two or more reviewers?	Yes
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted, independently, by two or more reviewers?	Unclear – whether data extraction was conducted by two or more reviewers
Were any relevant studies identified?	One study was identified, although the ERG consider it lacks relevance to the decision problem.

Source: LRiG Checklist 2017

5.2 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of treatment with BV versus treatment with PC (MTX or BEX) in adults with advanced stage CTCL who had had at least one previous treatment.

5.2.1 Model structure

The company developed a partition survival model in MS Excel. The model structure comprises five mutually exclusive health states (see Figure 4). It includes two different pathways which are only differentiated by the inclusion of alloSCT in one of the pathways.

At baseline, the whole model population is in the pre-progression health state and is in receipt of BV or PC. Patient eligibility for an alloSCT is based on response to treatment in the pre-progression health state. All eligible patients move to the Allogeneic stem-cell transplant (SCT) health state at 18 weeks. On disease progression patients transition to the Non-SCT post-progression or Allogenic SCT relapse states. The resource use and costs in these two post-progression states are assumed to be the same, with the exception of the use of TSEB as a subsequent anticancer therapy, which is excluded from the Allogenic SCT relapse state as the patients receiving an alloSCT are assumed to have had TSEB therapy as part of their pre-alloSCT conditioning regimen.

Patients in the post-progression health states (Non-SCT post-progression and Allogenic SCT relapse) receive subsequent therapies for a defined period of time and then progress to end stage symptom management, where they remain until death.

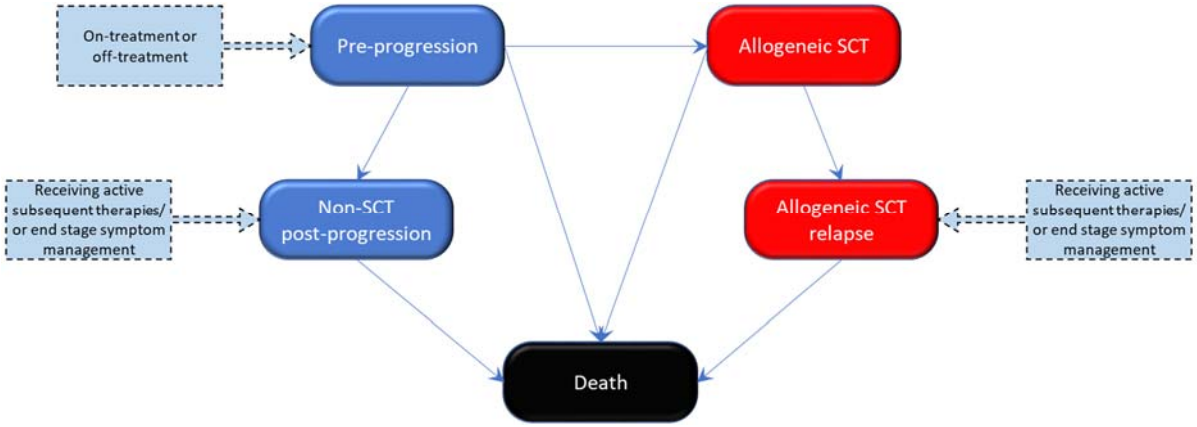


Figure 4 Health state structure of the company model

Source: CS summary document, Section A.10 (Figure 6); CS, Section B.3.2.3 (Figure 38)

5.2.2 Population

The company model population is patients with advanced stage CTCL (MF Stage IIB or greater, and patients with pcALCL) previously treated with at least one systemic therapy. The focus on patients with advanced stage CTCL disease is narrower than the population described in the final scope issued by NICE. At baseline, the mean age of the cohort (57.1 years), the percentage of females (47.83%) and other baseline characteristics reflect the

characteristics of the subgroup of patients in the ALCANZA trial with advanced stage CTCL (approximately 75% of the overall trial population).

5.2.3 Interventions and comparators

Intervention

The EMA [63] licensed dosing regimen for BV is 1.8mg/kg IV infusion administered every 3 weeks for up to a maximum of 16 cycles (48 weeks). The use of BV is estimated in the company model using data from the ALCANZA trial, a method of moments calculation to account for wastage and a relative dose intensity of 95%. In the ALCANZA trial, if patients' disease progressed before 48 weeks then treatment was stopped on disease progression. Time-on-treatment (ToT) data from the ALCANZA trial are used directly in the model.

Comparators

In the final scope issued by NICE, it is stated that the comparator should be established clinical management without BV. The company uses data from the PC arm (MTX or BEX) of the ALCANZA trial to populate their model. MTX is administered in tablet form once a week. The licensed prescribed dose ranges from 5-50mg and the company model uses the mean dose in the ALCANZA trial of 23.44mg once a week. BEX is also administered in tablet form with a recommended dose of 300mg/m^2 and tablets taken once a day. The dose in the company model is based on a method of moments calculation of the drug usage in the ALCANZA trial and a dose intensity of 90%. ToT data from the ALCANZA trial are used directly in the model.

The company states that IFN-α is commonly used in NHS practice and, therefore, is a relevant comparator. However, the company was unable to locate any (direct or indirect) evidence comparing treatment with IFN-α versus BV for the population of interest and, therefore, treatment with IFN-α is not included in the company's economic model.

Upon progression patients are treated in the economic model with active therapies which include chemotherapy and TSEB.

5.2.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the NHS perspective. The cycle length is 1-week and the model time horizon is set at 45 years. Both costs and outcomes are discounted at 3.5% per annum, in line with the NICE Reference Case [73], and, due to the short cycle length, a half-cycle correction is not used.

5.2.5 Treatment effectiveness and extrapolation in the base case

The company model is populated with clinical effectiveness data from the ALCANZA trial (33.9 months median follow-up). The ALCANZA trial did not contain any data that could be used to inform the clinical pathway of people undergoing an alloSCT, nor provide alloSCT outcomes. The company, therefore, used evidence from the supra-regional centre based in London [37] to generate estimates for these parameters.

Progression-free survival

In the company economic model reflects disease progression, as established by the ALCANZA trial IRF.

The company report that the log-cumulative hazard plot and the quantile-quantile plot suggest that the PH assumption is not valid for IRF assessed PFS. Six standard parametric models were fitted to each arm of the ALCANZA trial K-M data (see Figure 5). Goodness of fit was assessed visually and also using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), with the final specification based on clinical advice. In the base case, separate Weibull parametric curves are used to estimate PFS for both the BV and PC model arms.

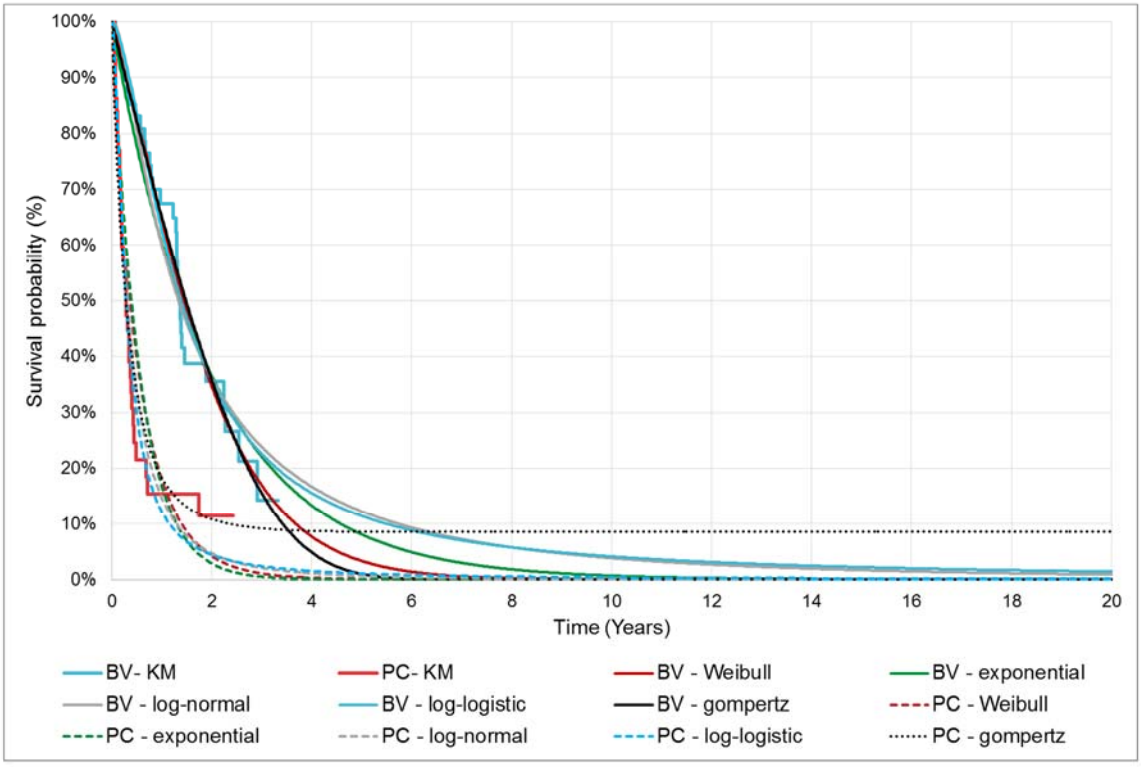


Figure 5: ALCANZA trial PFS K-M data and fitted parametric survival curves

BV=brentuximab vedotin; KM=Kaplan-Meier; PFS=progression-free survival; PC=physician's choice
Source: CS, figure 40

Overall survival

The OS data from the ALCANZA trial are immature and are considered unreliable due to both the small number of events and the high proportion of patient crossover. The company attempted to adjust OS estimates for crossover; however, none of the methods used produced clinically plausible results. The company then assume that, in the model, unadjusted OS data for patients in the PC arm of the trial could be used to represent OS for all patients. The clinical experts consulted by the company supported this assumption as trial results showed that, compared with PC, treatment with BV delivered no definitive OS benefit.

The company fitted six parametric models to OS data from each am of the ALCANZA trial. The AIC and BIC goodness-of-fit values were used initially to identify the survival model with the best statistical fit to the trial data. The company's preferred model is, however, chosen based on clinical plausibility and on how closely the parametric curves aligned with historical data collected from UK patients with advanced stage MF and SS [8, 26]. The log-logistic parametric model is considered to have the best fit and is used in the company's base case analysis. The OS extrapolations and one of the validation datasets [26] are shown in Figure 6.

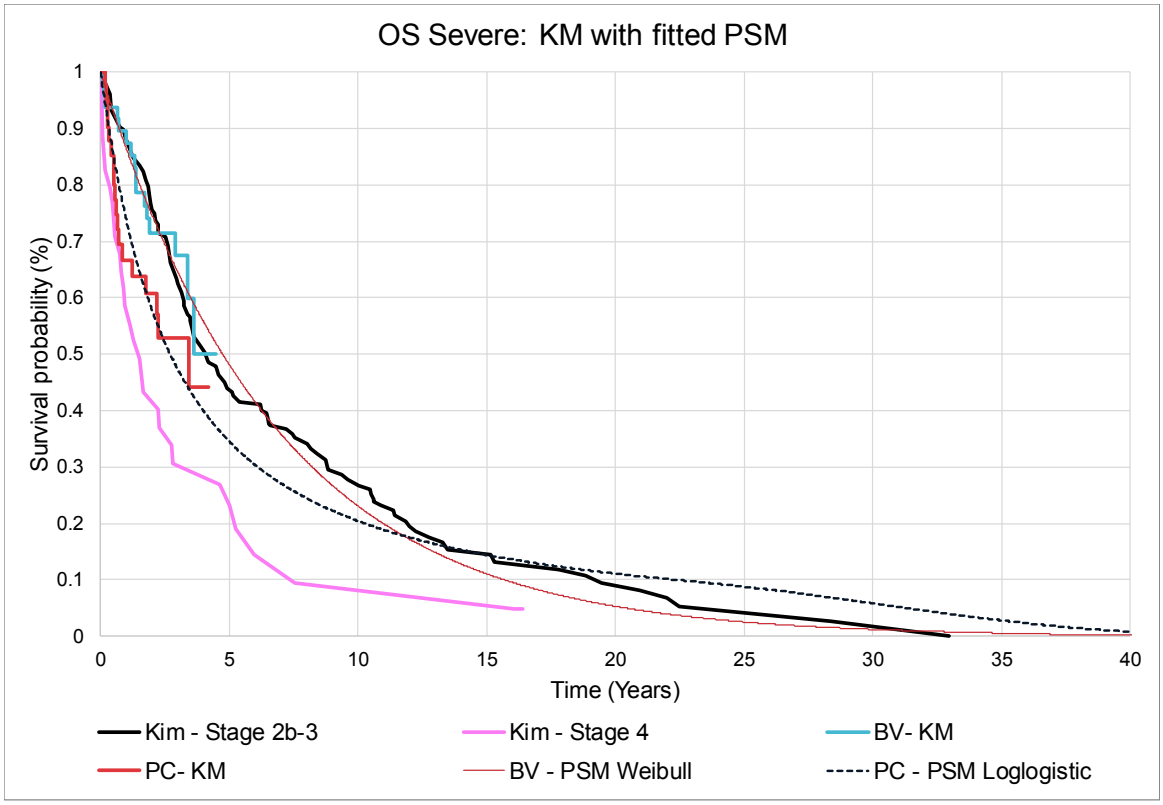


Figure 6 OS ALCANZA trial K-M data, extrapolations and published data [26]

BV=brentuximab vedotin; K-M=Kaplan-Meier; OS=overall survival; PC=physician's choice; PSM=parametric survival model
Source: company model

Time on treatment

Patients could only receive BV or PC for a maximum of 48 weeks. Extrapolation of ToT is not required as the ToT data are complete. However, adjustments are made to the data to enable it to fit within the model 1-week cycle framework, i.e., transitions were modelled to occur at the end of each weekly cycle rather than on the actual day on which they occurred. The company states that the impact of this adjustment is negligible.

AlloSCT outcomes

The company states that alloSCT is an option for people with refractory CTCL but eligibility for the procedure primarily depends on the fitness of the individual. Level of fitness encompasses age, health issues and how well the individual has responded to CTCL treatment. Data from people attending the London supra-regional centre for CTCL [37] to receive an alloSCTs are used to estimate alloSCT outcomes in the company model. The company assumes that all patients who receive a transplant do so at 18 weeks, this assumption is based on advice to the company from clinical experts.

Patients eligible for alloSCT

The ORR results from the ALCANZA trial show that 68.8% and 17.8% for patients treated with BV and PC respectively, achieved a partial or complete response to treatment. In the company base case it is assumed, based on clinical advice, that 40% of patients showing at least a partial response to treatment, as measured by the ORR, are eligible for an alloSCT. As a consequence, in the company base case, 27.5% of patients treated with BV and 7.11% of people treated with PC are modelled to have an alloSCT.

Post-alloSCT disease-free survival

The company digitised K-M disease-free survival (DFS) data, from the London supra-regional centre [37], for patients who had had minimal intensity alloSCT (following the Stanford Protocol for bridging therapy) and fitted six parametric models to these data. The goodness of fit of the curves is determined using the AIC and BIC statistics, visual examination and an assessment of clinical plausibility. The company states that the K-M data suggest that there is a decreasing probability of relapse for approximately the first 12 months and that beyond 12 months no relapses occur. Clinical advice to the company supported this view and the company, therefore, used the Gompertz model, which follows this specification, in their model (see Figure 7).

Figure 7 Post-alloSCT disease-free survival curves

DFS=disease-free survival; alloSCT=allogeneic stem-cell transplant; PSM=parametric survival model
Source: Company model

Post-alloSCT overall survival

The company estimated survival after an alloSCT using digitised post-alloSCT OS data from the London supra-regional centre [37]. Six parametric curves (exponential, Weibull, Gompertz, generalised gamma, log-normal and log-logistic) were fitted to the data, and goodness of fit was assessed using the AIC and BIC statistics, visually and clinical opinion. The company states that the OS data demonstrate a long-term remission plateau for disease-free patients, as shown in the DFS data, but also that worse outcomes are expected for those people who have relapsed. The company chose a log-normal model to represent post-alloSCT survival as it considered that it most approp DFS tured the available DFS K-M data.

In the company model, the DFS and OS curves converge at 12.8 years, which implies that all patients who had relapsed had died by this point. This is much shorter than survival in the progressed health state without an alloSCT, which can be up to 25 years; however, clinical advice provided to the company was that this was the most clinically plausible of the estimated parametric curves presented to them by the company. Figure 8 depicts the estimates used in the company economic model.

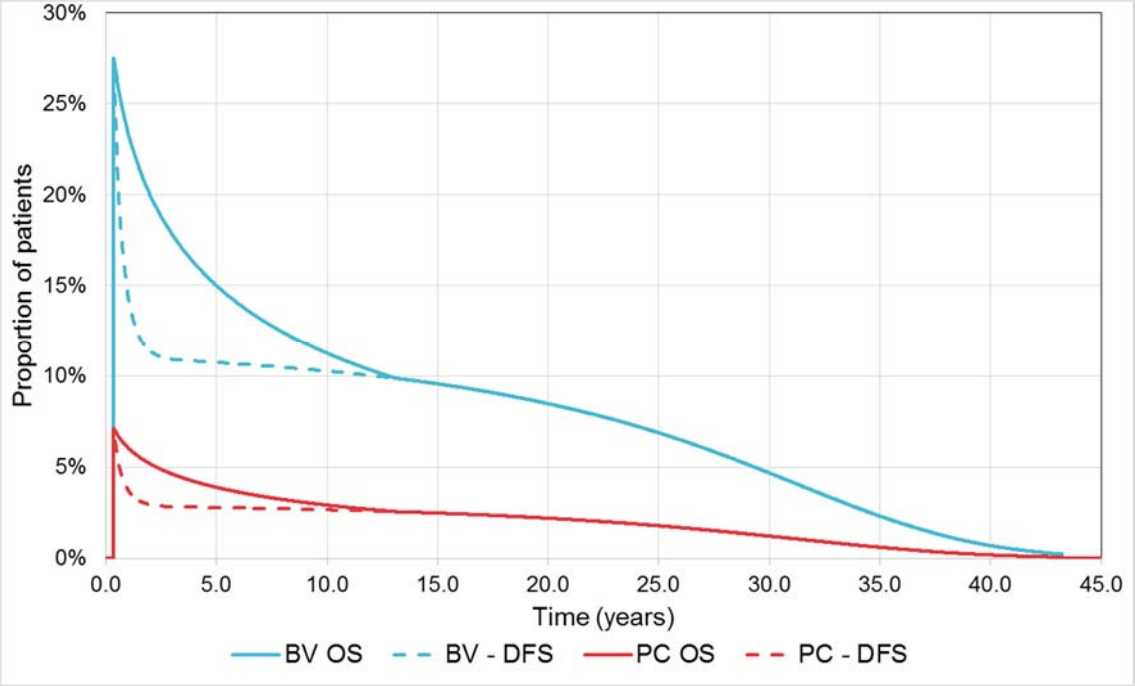


Figure 8 Modelled post-alloSCT DFS and OS

alloSCT=allogenic stem-cell transplant; BV=brentuximab vedotin; DFS=disease-free survival; OS=overall survival;
Source: CS, Section B.3.3.4.3 Figure 51

5.2.6 Health-related quality of life

The EQ-5D-3L, the Skindex-29 symptom domain and the FACT-G were used, in the ALCANZA trial, to collect data HRQoL data and the company conducted a literature searches to identify HRQoL studies. However, they were unable to find any studies that evaluated HRQoL using either the EQ-5D-3L or EQ-5D-5L tool in populations of people with CD-30+ CTCL.

Utility values, estimated from a longitudinal mixed-effects regression model are used in the company base case, with the EQ-5D-3L tariff values for the advanced stage CTCL population as the dependent variable. A stepwise selection process was used to derive the best model specification which included progression status and Skindex-29 symptom domain score as the explanatory variables. Goodness of fit was assessed using the AIC and BIC statistics, the clinical plausibility of the estimates and by comparing the predicted results to the utility values collected during the ALCANZA trial. In the company base case the PFS utility values differ by treatment.

The company use a published estimate [141] to reflect the HRQoL of people in the end-stage management state. Due to the absence of evidence, general post-alloSCT utility values are used in the company model. Post-progression HRQoL is assumed to be the same for all

patients regardless of transplant status. A summary of the utility values used in the company model is provided in Table 21.

Table 21 Summary of utility values used in the company model

State	Utility value: mean (standard error)	95% CI	Source	Justification
PFS – BV	0.68	0.62 to 0.76	ALCANZA trial	Utility regression based on phase III trial
PFS - PC	0.64	0.57 to 0.72	ALCANZA trial	Utility regression based on phase III trial
SCT (0-14 days)	0.42	0.38 to 0.46	Van Agthoven et al 2001 [142]	No CTCL source; selected source is well-recognised for alloSCT HRQoL
SCT (14 days – 3 months)	0.60	0.54 to 0.65	Van Agthoven et al 2001 [142]	No CTCL source; selected source is well-recognised for alloSCT HRQoL
SCT (>3 months)	0.77	0.69 to 0.84	Van Agthoven et al 2001 [142]	No CTCL source; selected source is well-recognised for alloSCT HRQoL
PD	0.61	0.52 to 0.70	ALCANZA trial	Utility regression based on phase III trial
End Stage Symptom Management care	0.38	0.33 to 0.44	Swinburn et al 2015 [141]	No CTCL source; Swinburn is based on closest related lymphoma

alloSCT=allogenic stem-cell transplant; CI=confidence interval; CTCL= cutaneous t-cell lymphoma; HRQoL= health-related quality of life; PD=progressive disease; PFS=progression-free survival;
Source: CS, Section B.3.4.6. Table 41

5.2.7 Adverse events

Treatment related grade 3 or 4 AEs experienced by at least 5% of the total ALCANZA trial population are included in the company model. In addition, following clinical advice to the company, all treatment related incidences of septicaemia and peripheral neuropathy are also included in the model.

Experiencing an AE is assumed to result in a decrement to HRQoL. The company has linked each AE with a utility decrement selected from a targeted review of NICE appraisals of treatments for lymphoma indications. In the absence of an estimate for a specific AE, the disutility estimate from a comparable AE is applied. The incidence of each AE is sourced from the ALCANZA trial and used to calculate a weekly rate of occurrence. Information on the duration of each AE is taken by pooling duration of each of the adverse events across treatment arms from the ALCANZA trial. A per cycle rate for each AE is calculated using the pooled durations and, separately for BV and PC, the total time on treatment. This AE rate is then used to calculated AE costs and AE associated utility decrements.

Table 22 shows the adverse event rates and the disutility values used in the company model.

Table 22 Summary of adverse event utility decrements used in the company economic model

Adverse event	Number of events		Duration (days)		Disutility	Assumptions	Source of disutility value
	BV	PC	Mean	SD			
Blood and lymphatic system disorders	6	4	15.5	16.6	-0.10	Reported for anaemia	Beusterien et al 2010 [143]
Gastrointestinal disorders	7	0	10.7	8.7	-0.103	Reported for diarrhoea	Lloyd et al 2006 [144]
General disorders and administration site conditions	4	0	81.8	135.8	-0.07	Assumed equivalent to fatigue	Nafees et al 2008 [145]
Multiorgan failure	1	0	1.0	1.0	-0.20	No decrement available assumed equivalent to grade III/IV pneumonia and associated with significant decrement	Beusterien et al 2010 [143]
Infections and infestations	3	0	26.0	17.7	-0.14	Reported as severe skin condition	Brown et al 2001 [146]
Septicaemia	0	1	20.0	20.0	-0.20	No decrement available assumed equivalent to grade III/IV pneumonia and associated with significant decrement	Beusterien et al 2010 [143]
Peripheral neuropathy	7	0	258.0	301.1	-0.11	Assumed to be grade 1/2 peripheral sensory neuropathy	Swinburn et al 2015 [141]
Skin and subcutaneous tissue disorders	0	0	0.0	0.0	-0.03	Equivalent to rash	Nafees et al 2008 [145]
Investigations	0	6	18.2	5.2	0	Assumed 0	NA
Hypertriglyceridemia	0	9	50.9	81.7	0	Assumed 0	NA

BV=brentuximab vedotin; PC=physician's choice; SD=standard deviation; NA=not applicable
Source: CS, adapted from, Tables 33 and 40

Clinical opinion was used by the company to estimate the proportion of each of the AEs requiring treatment, and the setting in which that treatment took place. The assumptions used in the company model are shown in Table 23.

Table 23 Adverse event resource use assumptions in the company model

Adverse event	Actively treated	Treatment setting			
		Inpatient	Day case	Outpatient	Primary/community care
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: company model

The unit costs as detailed in Table 24, are sourced from NHS Reference Costs (2016/2017) [147]. Unit costs are applied to cycle event probabilities from the ALCANZA trial to produce AE cycle costs of £4.97 and £5.99 for patients treated with BV and PC respectively.

Table 24 Adverse event unit costs assumptions in the company model

Adverse event	Inpatient		Day case		Outpatient		General practice	
	Unit cost	NHS Reference Costs 2016-17 code and description [147]	Unit cost	NHS Reference Costs 2016-17 code and description [147]	Unit cost	NHS Reference Costs 2016-17 code and description [147]	Unit cost	Source
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

Adverse event	Inpatient		Day case		Outpatient		General practice	
	Unit cost	NHS Reference Costs 2016-17 code and description [147]	Unit cost	NHS Reference Costs 2016-17 code and description [147]	Unit cost	NHS Reference Costs 2016-17 code and description [147]	Unit cost	Source
[redacted]								

Source: Company model

5.2.8 Resources and costs

Pre-progression health state

Drug costs

Estimates of the quantity of BV, MTX and BEX used per patient, per week, and the split between the proportions of patient receiving MTX and BEX are estimated using ALCANZA trial data. Resource use estimates for these drugs took account of adherence. The resource use estimates for BV took account of patient weight and the estimates for BEX took account of body surface area. Vial sharing is not assumed to occur.

When generating results, a confidential PAS discount (CS summary document, Table 1; CS, Table 2) is applied to the list price of BV. The cost of MTX is taken from the drugs and pharmaceutical electronic market information tool (eMIT) [149]. A cost for BEX is not available from eMIT and, therefore, it is taken from the monthly index of medical specialties (MIMs) [150, 151].

MTX and BEX are taken orally. The cost, used in the company model, to reflect the cost of administering these treatments is the NHS Reference Outpatient Cost 'Delivery of exclusively oral chemotherapy', (£163.82 per week) [147].

BV is administered via IV infusion and the cost, used in the company model, to reflect the treatment administration cost is the NHS Reference cost 'Delivery of simple chemotherapy, £173.99 per dose [147].

Company model drug cost details are presented in Table 42 of the CS and reproduced in Table 25

Table 25 Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week for intervention and active comparators

Drug	Dosing regimen	Cost per vial/pack	Vial size / tablets per pack	Vials / tablets per admin[a]	Proportion of dose received	Total cost per week[b]
BV	[redacted]	[redacted][c]	[redacted]	[redacted]	[redacted]	[redacted]
MTX	[redacted]	[redacted]	[redacted]	[redacted][d]	[redacted]	[redacted]
BEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BEX=bexarotene; BV=brentuximab vetodin; MTX= methotrexate; IV=intravenous; Q3W=once every 3 weeks; Q1W=once a week
[a] Based on data from the ALCANZA trial
[b] Although costs in the table are provided by week, the model costs BV per administration, i.e. a single cost is applied every 3 weeks
[c] PAS price
[d] Based on mean dose in ALCANZA trial of 23.44mg
Source: CS, adapted from, Table 42 and economic model

Resource use

The resource use estimates for people in the pre-progression health state are derived from treatment protocols from the London Cancer Alliance (LCA) skin systemic anticancer therapy (SACT) database [152] and expert opinion. In the company model, a cost of £388.63 per weekly cycle per patient is applied in the pre-progression health state. Details of the individual resource use elements that are used to calculate the total pre-progression health state cost per cycle are provided in Table 26.

Table 26 Resource use in the pre-progression health state

	% of all patients	Frequency per week	Dose	Unit	Average weekly cost	Cost source
Hospital outpatient						
Clinical nurse specialist	100.00%	0.19	N/A	N/A	£16.39	NHS Ref Costs 2016/17 [147] WF01A:370 Total outpatient attendances, Non-consultant led, Medical oncology
Oncologist outpatient visit	100.00%	0.19			£30.21	NHS Ref Costs 2016/17 [147] WF01A:370 Total Outpatient Attendances, Medical Oncology
Consultant oncologist visit	100.00%	0.19			£33.05	NHS Ref Costs 2016/17 [147] WF01A:370 - Total outpatient attendances, Consultant led, Medical oncology
Home visit						
District nurse	100.00%	2.60	N/A	N/A	£96.01	NHS Ref Costs 2016/17 [147] - N02AF Total Other Currencies, District Nurse, Adult, Face to face
Investigations and tests						
Complete blood count	100.00%	0.25	N/A	N/A	£0.77	NHS Ref Costs 2016/17 [147] - DAPS05 Haematology
Liver function test	100.00%	0.25			£3.15	NHS Ref Costs 2016/17 [147] - DAPS09 Other - 5 tests required
U&Es	100.00%	0.25			£0.28	NHS Ref Costs 2016/17 [147] - DAPS04 Clinical Biochemistry
CT scan	50.00%	0.08			£5.10	NHS Ref Costs 2016/17 [147] - RD26Z, Total HRGs, CT Scan of Three Areas, with Contrast
Imaging - PET	50.00%	0.08			£19.94	NHS Ref Costs 2016/17 [147] -RN07A -Positron Emission Tomography (PET), 19 years+
Dressings						
Full body coverage	0.00%	0	0	Dressings	£0.00	The use of various sizes of allevyn, mepitel and mepilex dressings are assumed along with elasticated vest and leggings garments. The costs are all sourced from the BNF.
Localised coverage	60.00%	7	7	Dressings	£183.75	

PET=positron emission tomography; U&Es= urea and electrolytes test; CT=computed tomography, NHS Ref Costs= NHS Reference Costs
Source: CS, adapted from Section B.3.5.2 Table 45 and company model

AlloSCT resource use and costs

The company states that an accurate estimate of the cost of an alloSCT is difficult to obtain. They use an estimate from a French study by Debals et al 2018 [153] which includes procedural costs and the cost of follow-up for 2 years. The estimate of £96,956 used in the company model is derived by converting the published cost into pound sterling and uplifting the cost to current prices using the PSSRU hospital and community health service (HCHS) inflation index [148].

Post-progression health state

In the company model, the post-progression health state is split into two phases. During the first phase, patients receive subsequent active therapy for CTCL; the second phase starts when all active therapeutic options have been exhausted.

Data from the ALCANZA trial are used to estimate the total time spent in the post-progression health state and then a payoff approach is used to split this time into two phases. Mean costs and QALYs for active subsequent therapy and end-stage care are multiplied by the time spent in those phases and then summed to give mean costs and QALYs for the whole post-progression state. The company state that the payoff approach prevents the need for tunnel states whilst enabling time-dependent transitions from the subsequent active therapy phase to the end-stage care phase of the post-progression health state.

For people ineligible for an alloSCT, time spent in the post-progression health state is estimated as the area between the PFS and OS curves. The first phase is fixed at 1.86 years for people who have not had an alloSCT and the resource use in this time period includes the costs of chemotherapy and TSEB treatments, as well as costs associated with hospital visits, district nurse home visits, investigations and tests, and other drug treatments (for example, for pain relief). The resource use that is in addition to the subsequent active drug therapy is assumed to be the same for everyone regardless of whether they had an alloSCT. The details of the resource use and cost assumptions are shown in Appendix 7, Section 9.7, Table 43

For people who had undergone an alloSCT, the area between OS post-alloSCT and alloSCT DFS curves are used to estimate the time spent in the post-progression health state. The first phase in post-progression for this group is treatment with chemotherapy and excludes TSEB treatment as it is assumed that these patients would have received TSEB as part of their alloSCT. This time period for the subsequent active therapy phase of the post-progression health state is set at 0.94 years for post-alloSCT patients. During this time resource use that

is in addition to chemotherapy and its delivery is also included, as shown in Appendix 7, Section 9.7, Table 43.

Although the first phase in post-progression differs in duration according to whether or not the patients received an alloSCT, the resource use and costs estimates following this first phase are the same for both groups. End-stage care forms the second phase of the post-progression health state and includes the resource use and costs of hospital visits, home visits, investigations and tests and drug treatments for pain relief or depression for example. The details of the company's End stage care phase resource use assumptions are shown in Appendix 7, Section 9.7, Table 44.

Post-progression active therapy phase: resource use and costs

The active therapies used as a third-line and subsequent treatments for people with CTCL are estimated from an international registry of data collected from people with CTCL, the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study [61]. Durations of treatment and response are sourced from the London Cancer Alliance (LCA) skin systemic anticancer therapy (SACT) protocols [152]. Table 27 shows the resource use and cost estimates for third line and subsequent active therapies. The dosing regimen and costs for 'other mono chemotherapy' are assumed, [redacted] to be for treatment with [redacted] Patients may receive treatments more than once and hence total proportions exceed 100%. The cost of the drugs used as third and subsequent lines of therapy are taken from eMit [149], where available and, if not available, are taken from MIMs [154-159].

Table 27 Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week for subsequent active therapies

Drug	Dosing regimen	Cost per vial/pack	Vial size / tablets per pack	Vials / tablets per admin	Total cost per model cycle	Proportion of patients treated	Mean time on treatment (weeks)	Total weighted cost
Gemcitabine	1000mg/m2 IV D1, D8, D15 in q28 days				£54.63	[redacted]	16.00	£655.55
		£2.97	200mg	2.00				
		£7.75	1000mg	0.53				
		£26.12	2000mg	2.40				
CHOP	IV; D1, D8, D15				£21.69	[redacted]	9.00	£54.66
Cyclophosphamide	750 mg/m2	£139.00	50mg/100	28.68	£13.29			
Hydroxydaunorubicin	50 mg/m2	£1.34	10mg/5	1.78	£2.76			
		£3.63	50mg/5	1.62				
Oncovin	1.4ml/ m2	£15.64	1ml/5	0.83	£2.89			
		£26.59	2ml/5	1.14				
Prednisolone	100mg	£23.15	25mg/56	4	£2.76			
Other mono chemotherapy					£151.17	[redacted]	24.00	£1,705.23
Pegylated liposomal doxorubicin	IV 20mg/m2	£360.23	20mg	2		[redacted][a]		
Chlorambucil	Oral, daily, 0.2mg/kg	£42.87	2mg/25	7		[redacted][a]		
		Cost per course		**Number of fractions per course**				
Total skin electronic beam therapy	Low dose 12Gy, 8 fractions over 2 weeks (cost split across DOR)	£3,475.95	N/A	8	£72.67	[redacted]	47.83[b]	£3,475.95

CHOP=Cyclophosphamide, Hydroxydaunorubicin, Oncovin & Prednisolone; D=day; DOR=duration of response; IV=intravenous; N/A=not applicable;; Q2W=once every 2 weeks;

[a] [redacted]

[b]=includes the assumption of 11 months duration of response

Source: CS, adapted from, Tables 46 and 47

The resource use estimates for people receiving active therapy in the post-progression health state are summarised in Table 43 (Appendix 7, Section 9.7). The company generated these estimates based on information from the LCA SACT [152] protocols and expert opinion. The

duration of post-progression active therapy is estimated as almost 97 weeks. The weekly cost in the model for resource use during the post-progression active therapy phase is [redacted].

Post-progression End-stage management phase:

In the absence of published or trial estimates of the resource use for people with CTCL in the End-stage management phase, the company conducted semi-structured interviews with clinicians who are responsible for the end-stage management of patients in the seven supra-regional centres for treating CTCL in England, and the Welsh centre in Cardiff. The purpose of the interviews was to obtain estimates of levels of resource use that arise as a consequence of pain, anxiety and depression, itch relief, skin care and wound management. Further details of this exercise can be found in the CS, Appendix L. Details of the resource use and cost estimates for end-stage CTCL management used in the model (£2,095 per weekly cycle per patient) are provided in Table 44 (in Appendix 7, Section 9.7). These costs include hospital outpatient appointments, tests and scans, care giver visits to the patients' home (for example, as Macmillan nurses and social care), as well as specialist dressings (for example, mepilex and allevyn) for wound care, and medications.

Cost of death

In addition to the end-stage resource use, the company model also includes the cost of generic oncology end-of-life care (£286 per week) applied to patients while in the end stage phase of the post-progression health state [160].

5.2.9 Cost effectiveness results

Base case results from the company's model, Table 28, show that treatment with BV generates an additional [redacted] QALYs at a cost saving of [redacted] compared with treatment with PC. This makes BV the dominant treatment.

Table 28 Base case fully incremental cost effectiveness results (PAS price for BV)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYG	QALYs	
PC	[redacted]	7.23	[redacted]				
BV	[redacted]	8.43	[redacted]	[redacted]	1.20	[redacted]	BV dominates

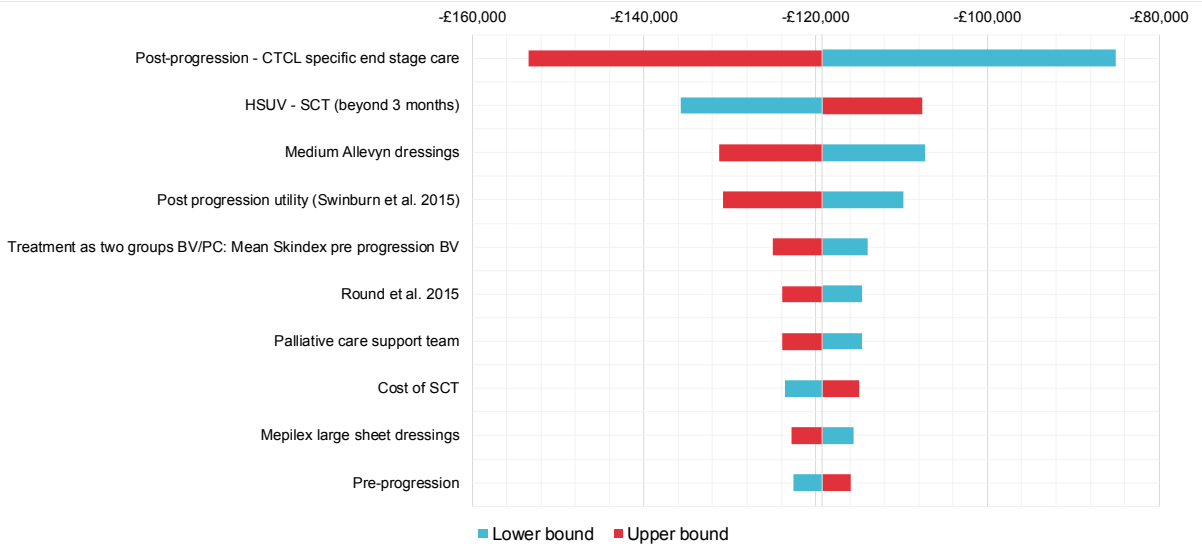
LYG=life year gained; PAS= Patient access scheme; PC=physician's choice; QALY=quality adjusted life year
Source: CS, adapted from summary document, Section A.13 Table 7; CS, Section B.3.7.1 Table 51

5.2.10 Sensitivity analyses

Deterministic sensitivity analysis

The company performed one-way sensitivity analysis (OWSA) on many of the variables included in the economic model. The parameter values are varied according to the 95% CIs of the distributions. Where Cis were not available ±10% of the mean value are used to set the bounds of the range. The company's OWSA results show that the cost of CTCL end-stage care, the utility value assigned to patients 3 months post alloSCT, the cost of medium allevyn dressings and the choice of utility associated with the end stage care phase of the post-progression health state have the greatest impact on the size of the ICER per QALY gained for the comparison of treatment with BV versus PC (see Figure 9).

Figure 9 Tornado diagram showing OWSA results for BV versus PC including PAS



CTCL=cutaneous T-cell lymphoma; HSUV=health state utility values; ICER=incremental cost-effectiveness ratio; SCT=stem-cell transplant;
Source: Company economic model

Probabilistic sensitivity analysis

Most of the input parameters are varied in the company probabilistic sensitivity analysis. The largest group of parameters not varied are the proportions of patients treated in each setting for AEs, e.g., general practice or as an inpatient. Figure 10 shows the uncertainty around the estimated mean cost per QALY difference between treatment with BV versus treatment with PC. The mean probabilistic ICER per QALY gained demonstrated that treatment with BV dominated treatment with PC. However, although the mean incremental QALYs generated by the PSA are similar to the deterministic results, there is a difference of almost [redacted]

between the mean incremental costs generated by the two analyses [redacted]).

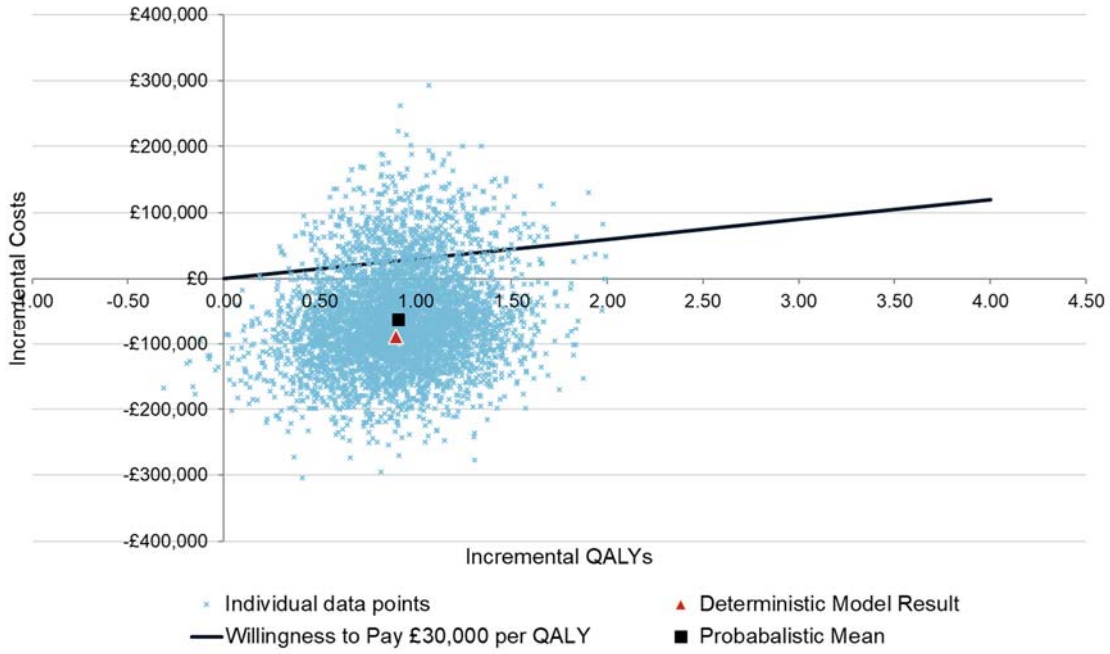


Figure 10 Scatter plot showing cost effectiveness of treatment with BV versus PC (5,000 iterations)

Source CS, Section B.3.8.1 Figure 56
QALY=quality adjusted life years

Figure 11 shows the probability of treatment with BV being the most cost effective treatment option at a willingness-to-pay threshold of £30,000 per QALY is 91.38%.

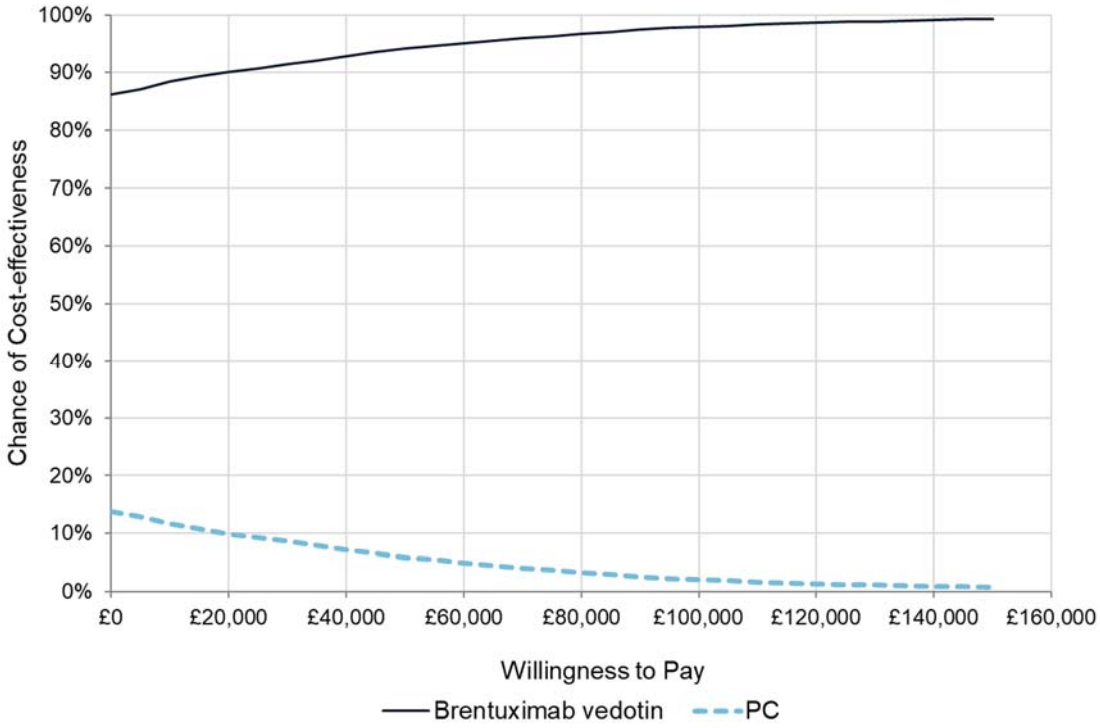


Figure 11 Cost effectiveness acceptability curve of treatment with BV vs PC

Source: CS Figure 57

5.2.11 Scenario analyses

The company presents the results of a number of scenario analyses, grouped by key areas (CS, Tables 54-58). In all of the scenarios treatment with BV dominates PC.

5.2.12 Model validation and face validity check

The company states that input from clinical experts was sought during model development to ensure that the model was built to reflect clinical reality. Additionally, a checklist designed to highlight modelling errors and assess assumptions was used and an economist not involved in building the model checked for coding errors and validated the model.

5.3 ERG detailed critique of company economic model

5.3.1 NICE Reference Case checklist

Table 29 NICE Reference Case checklist completed by the ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	Partial. The population considered in the economic model submitted by the company is a subgroup of the population (patients with advanced stage CTCL) described in the final scope issued by NICE.
Comparator(s)	As listed in the scope developed by NICE	Partial. The company presents comparator (MTX or BEX) evidence from the PC arm of the ALCANZA trial. IFN-α is also used in UK clinical practice to treat patients with advanced stage CTCL after one previous treatment. The company conducted a literature search to identify evidence for IFN-α, but did not find any relevant data.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	NHS perspective taken, unclear if all PSS costs are considered.
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on a systematic review	N/A
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Yes
Source of data for measurement of HRQoL	Standardised and validated instrument. The EQ-5D is the preferred measure of HRQoL in adults	Partial – EQ-5D-3L utility values obtained from the ALCANZA trial were adjusted to take into account the Skindex-29 symptoms domain score and progression status of patients.
Source of preference data for valuation of changes in HRQoL	Reported directly by patients and/or carers	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

BEX=bexarotene; BV=brentuximab vetodin; EQ-5D-3L=EuroQol-5 dimension-3 level; HRQoL=health-related quality of life; MTX=methotrexate; NMA=network meta-analysis; PC=physician's choice; PSS=Personal Social Services; QALY=quality adjusted life year

5.3.2 Drummond checklist

Table 30 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	The evidence is based on a post-hoc analysis of a subgroup of patients with advanced stage CTCL in the ALCANZA trial; OS data from this patient subgroup are based on small numbers of patients and events, are immature, are confounded by treatment crossover and do not show a statistically significant OS difference in favour of BV compared to PC. However, the company states that improvement in survival was not the treatment goal for this group of patients.
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partial	QALYs in the company base case were estimated using utilities calculated from a regression model incorporating two HRQoL measures (EQ-5D-3L and Skindex-29 symptom domain). Incorporating two different measures in this way means that the QALYs generated are not comparable with the QALYs estimated in other appraisals using the EQ-5D-3L method only.
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

BV=brentuximab vetodin; CD30+=CD30-positive; CTCL=cutaneous t-cell lymphoma; EQ-5D-3L=EuroQol-5 dimension-3 level; OS=overall survival; PC=physician's choice; QALYs=quality adjusted life years

5.3.3 Key issues in the company model

The key issues in the company model that the ERG has been able to address relate to the inclusion of alloSCT in the treatment pathway, the use of a regression model to estimate utility values (PFS and post-progression survival), the application of extra AE utility decrements and the cost of oral chemotherapy. However, there remains substantial uncertainty in the results of the cost effectiveness model once these issues have been addressed.

The model structure limits the ERG's ability to investigate the impact of varying assumptions about survival; however, restructuring the model is not within the ERG's remit. There are also parameter values relating to the post-progression health state that the ERG does not consider to be adequately supported by evidence or tested by extensive sensitivity analyses.

The ERG's preferred approach to estimating cost effectiveness is to remove alloSCT from the treatment pathway and to adjust several of the parameter values used in the company model. The ERG has then produced three scenarios to test the sensitivity of the model to alternative, plausible assumptions for which there is little evidence available. These assumptions are: changes to the post-progression pathway (Scenario 1); changes to resource use frequencies (Scenario 2); and the assumption of an OS gain for treatment with BV (Scenario 3).

5.3.4 ERG's preferred approach to estimating cost effectiveness

Allogenic SCT as a treatment option

The final scope issued by NICE suggests consideration of the use of alloSCT in the treatment pathway of patients with advanced stage CTCL if the evidence allows. The ERG does not consider there is sufficient evidence to allow alloSCT to be modelled robustly and so does not consider that alloSCT should be included in the model base case analysis. Uncertainties in the evidence are around i) outcomes after treatment with alloSCT, ii) outcomes following alloSCT in patients who have received prior treatment with BV, and iii) the position of alloSCT in the treatment pathway.

Outcomes after treatment with alloSCT in patients with advanced stage CTCL

The ERG considers that, although there is some published evidence [161] of outcomes following alloSCT in patients with advanced CTCL, data are lacking for the population included in the company model.

The company presents the results of a meta-analysis [38] in Section B.1.3.3 of the CS. This study included 19 patients who received an alloSCT in the US, one of these patients had early stage disease (stage IB). The patients analysed were younger than patients with advanced stage CTCL in the ALCANZA trial (median age=42 years versus 60 years) and had received

more systemic therapies (median=4.5 versus 2.0). The company does not use the data from this study [38] in the model, as a recent change in practice (use of a less-intensive conditioning regime prior to alloSCT in patients with advanced stage CTCL) has led to the results of the meta-analysis being out of date.

The data underpinning the post-alloSCT pathway in the company model are taken from a presentation made at a conference detailing the experiences of the UK's leading supra-regional centres for alloSCT [37]. The information included in the CS is not sufficient for the ERG to assess how representative the dataset used to inform the presentation are of the patients who receive alloSCT in the company model. Only 18/40 patients in the study [37] received the less-intensive conditioning regimen, which the company advocates as being best practice. The ERG considers that the small sample and the lack of clarity on the disease-stage of the population and/or number of prior treatments received generate too much uncertainty which leads to unreliable outcomes. Whilst the data presented by the company show that some outcomes may improve with alloSCT, the ERG considers that it is not possible to be certain which outcomes would improve, or how important they would be for patients with advanced stage CTCL who have received at least one previous treatment.

The ERG considered alternative sources of evidence for alloSCT outcomes and identified a Cochrane review that was published in 2013 [161] that had searched for evidence on alloSCT in patients with advanced stage CTCL. The authors of the review found case series and retrospective evidence that suggest that alloSCT can lead to sustained remission in patients with advanced stage CTCL but that comparative RCT evidence did not exist. The review findings generally support the use of alloSCT in patients with advanced stage CTCL. However, evidence of outcomes in older patients, particularly people aged 60 and older is lacking and, historically, studies have included patients who have been more heavily pre-treated with systemic therapies than the patients in the ALCANZA trial.

Outcomes following alloSCT in patients with advanced stage CTCL who have received prior treatment with BV

The ERG is not aware of any evidence of outcomes for alloSCT post-treatment with BV. The use of alloSCT outcomes from patients with pre-treatments that are reflective of current practice, as in the company model, assumes BV does not alter the course of the disease in any way that may influence the success of alloSCT. The ERG considers this assumption to be untested and, given the influence of the intensity of the conditioning regimen used on alloSCT outcomes, it would be premature to speculate what the effect of treatment with BV might have on these outcomes.

The position of alloSCT in the treatment pathway

Clinical advice to the ERG is that people with stage IIB and stage III disease often have periods during which the disease is well managed, and that the disease can remain stable for several years before progression occurs. In the company model, the proportion of patients (40%) achieving a PR or CR after treatment with BV or PC are eligible for alloSCT and receive their transplant at 18 weeks. The clinician advising the ERG noted that alloSCT carries a significant risk of complications such as infections and graft-versus-host disease, which can be fatal. It would therefore be unlikely for clinicians to offer the treatment to patients who are stable and feeling well and who have only thus far received a handful of treatments (and still have more treatment options available to them). It was also suggested that patients themselves would be unlikely to accept alloSCT at this point in the treatment pathway.

The number of patients both eligible for and willing to have an alloSCT is dependent on factors such as the patient's general health and comorbidities, the availability of matched donors and the capacity of the specialist centres performing the alloSCT treatments. Clinical advice to the ERG is that such factors would result in far fewer than 40% of complete or partial responders undergoing the procedure than has been assumed in the company model.

At clarification, the company provided additional information on the patients that had received alloSCT during the ALCANZA trial. As alloSCT was neither a pre-specified nor exploratory trial end-point, very few data were collected on alloSCT other than whether the procedure was undertaken. Seven patients from the ITT population of the ALCANZA trial received an alloSCT [BV=5, PC=2]. Only two patients received alloSCT directly after the study treatment, which is the point at which alloSCT occurs in the company model, all others had subsequent systemic therapies pre-alloSCT. Both of the patients in the PC arm who had an alloSCT received treatment with BV as a subsequent anticancer therapy prior to alloSCT.

The company states that, as four out of 24 UK based patients in the ITT population of the ALCANZA trial had an alloSCT, this demonstrates a 17% uptake. However, the ERG considers that as only two people who had an alloSCT in the trial did so directly after treatment, the proportion of patients that is more representative of patients having alloSCT, as modelled by the company, is 1.56% (2/128 ITT population); a similar estimate is not available for patients with advanced stage CTCL. The ERG considers that this approach demonstrates that the proportions of people eligible for alloSCT within the economic model are over-estimated and that this adds further weight to the argument that alloSCT is not part of standard care for patients with advanced stage CTCL in the NHS in England.

When alloSCT is removed from the treatment pathway, treatment with BV dominates treatment with PC. When compared to the company base case analysis results, incremental costs decrease by [redacted] and incremental QALYs decrease by [redacted]

Parameter values

Utility values: PFS and post-progression survival

The ERG acknowledges that utility values calculated using the direct results from the EQ-5D-3L questionnaires completed during the ALCANZA trial may not capture all aspects of HRQoL in patients with advanced stage CTCL (see Section 4.9 of this ERG report); however, the ERG prefers to use the EQ-5D utilities in the model to retain adherence to the NICE Reference case [73] and to ensure comparability with the ICERs per QALY gained that inform other STAs.

The ERG has investigated the impact on the ICER per QALY gained of using utility values for the progression-free health state and the post-progression (active therapy) health state calculated using the observed EQ-5D-3L values from the ALCANZA trial instead of those used by the company. Treatment with BV remains dominant when using observed EQ-5D-3L utility values. When compared to the company base case analysis results, incremental QALYs decrease by [redacted] for treatment with BV versus treatment with PC.

The observed ALCANZA trial EQ-5D-3L PFS utility values included in the company model are higher for treatment with BV than with PC due to differences at baseline. The ERG does not consider it appropriate to use different baseline PFS utility values in the model. The ERG has investigated the impact of assuming that the PFS utility values calculated using the observed EQ-5D-3L values are the same for patients treated with BV and PC by using an average (0.689) of the observed EQ-5D-3L values from the BV and PC arms of the ALCANZA trial.

Applying average observed EQ-5D-3L PFS utility values from the ALCANZA trial to the company's base case analysis results in a reduction in incremental QALYs for treatment with BV versus PC of [redacted] from [redacted] Treatment with BV remains dominant over treatment with PC.

Utility values: end-stage care

The company uses a published utility value [141] for progressed disease in a population with relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma to represent HRQoL in end-stage care in the company model. The ERG considers there is considerable uncertainty about whether this utility value (0.38) is appropriate for use in this way. It is not clear how closely HRQoL in patients with advanced stage CTCL is correlated with HRQoL in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell

lymphoma in general. Nor is it clear how closely HRQoL in patients with relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma who have experienced disease progression correlates with the HRQoL of patients with advanced stage CTCL who are in receipt of end-stage care. The ERG also notes that the mean age of patients in the published study [141] ranged between 32.5 and 43.4 years (depending on country), which is substantially younger than the mean age of the patients in the company model.

The ERG has not amended the utility value for the end-stage care phase in the company model, as it is not aware of any published estimates of utility that are more appropriate for this state. However, it cautions that the validity of the utility values used in the model for the end-stage care phase is subject to uncertainty.

Utility values: adverse event decrements

The company has included utility decrements for severe AEs in the base case analysis. The ERG considers that any changes in HRQoL that occur as a result of the AEs related to the study drugs would be captured in the mean EQ-5D-3L values from the ALCANZA trial; hence, the addition of a further utility decrement for severe AEs is likely to overestimate the impact of the study drugs on HRQoL. Removing the extra utility decrements for severe AEs from the company base case analysis increases incremental QALYs for treatment with BV versus PC by [redacted] from [redacted] Treatment with BV remains dominant over treatment with PC.

Oral chemotherapy administration costs

The company model includes an administration cost for exclusively oral chemotherapy using NHS Reference Costs 2016/17 [147] plus the cost of a pharmacist dispensing the medications. The company also includes the costs of additional blood tests, scans and outpatient visits in the resource use estimates for the progression-free state. The ERG considers that this approach represents double-counting of some of the aspects of the delivery of oral chemotherapy, particularly the pharmacy dispensing costs, but it is unclear if any of the other tests and hospital visits also form part of the NHS Reference Cost [147] for the delivery of exclusively oral chemotherapy. The ERG has removed the NHS Reference Cost [147] of £163.82 from the administration costs of oral chemotherapy.

Treatment with BV remains dominant over treatment with PC when the costs of oral chemotherapy are reduced. Incremental costs are reduced by [redacted] from [redacted] when compared to the company base case analysis results.

The combined result of the ERG's model amendments to the company base case is hereafter referred to as the ERG revised base case.

5.3.5 Areas of uncertainty

Post-progression health state

The ERG notes that mean time spent in the post-progression health state in the company model for patients who do not receive alloSCT is shorter for patients treated with BV than for patients treated with PC (Figure 12). This is due to the combined effect of three elements in the company model: mean PFS in the company model is longer for patients treated with BV than with PC; mean OS in the company model (for patients who do not receive alloSCT) is the same for both treatments; and mean post-progression survival is calculated as the difference between mean OS and mean PFS. This means that the risk of death after progression is modelled to be higher for treatment with BV than with PC.

The assumption that treatment with BV is associated with patients spending a shorter time in the post-progression health state than patients treated with PC is critical to the model cost effectiveness results. The differential end-stage care costs accrued by patients treated with BV versus PC in the ERG's revised base case are substantial [redacted]).

Clinical advice to the ERG is that it is unusual for patients to spend 3 to 4 years in a highly resource-intensive end-stage care phase. However, the ERG is unaware of any published evidence that robustly maps the post-progression phases experienced by patients with advanced stage CTCL. Given the impact of the costs accrued in the post-progression state in the company model, the lack of evidence for the assumptions made by the company about the post-progression pathway introduce substantial uncertainty into the model results.

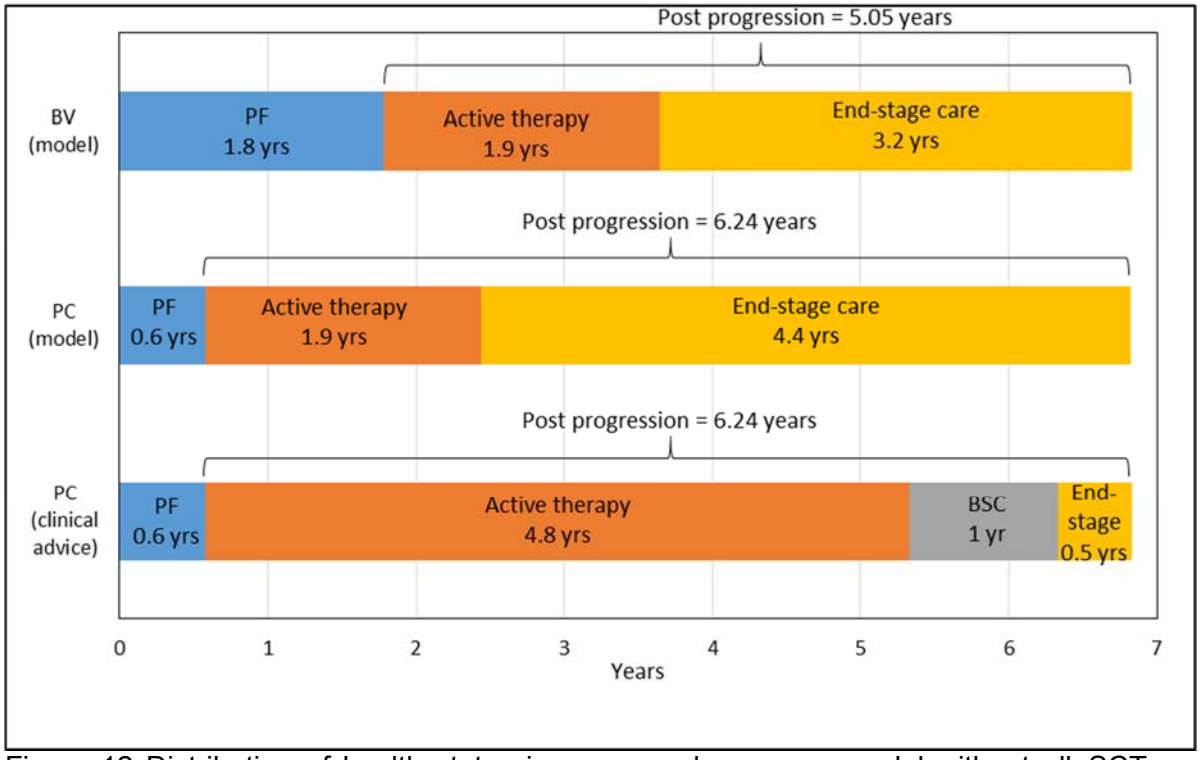


Figure 12 Distribution of health states in company base case model without alloSCT and according to clinical advice

BSC=best supportive care; BV=brentuximab vedotin; PC=physician's choice; PF=progression-free

Post-progression resource use

Clinical advice to the ERG is that resource use for patients receiving end-stage care is over-estimated by the company. Patients with advanced stage CTCL would not be sufficiently well to attend outpatient appointments at the frequency assumed by the company. It was also noted that the NHS and voluntary health care sector have neither the budget nor the capacity to enable several visits per week from district and Macmillan nurses.

Assumption of equal OS resulting in zero OS gain

The company has assumed in the base case analysis (for patients who do not receive alloSCT) that treatment with BV and treatment with PC are equally effective in terms of OS, since the results of the ALCANZA trial do not show a statistically significant OS difference for the comparison of treatment with BV compared with PC. The company argues that the limitations of the OS data from the ALCANZA trial (small numbers of patients and events, and high rates of crossover) prevent robust estimates of OS gain being generated. The ERG agrees that there is insufficient evidence from the ALCANZA trial to make robust claims about lifetime OS gain. Clinical advice to the ERG is that there is no robust evidence to either support or refute the assumption of zero OS gain as implemented in the company submitted model.

The ERG notes that the company's assumption of equal OS resulting in zero OS gain may appear to be a conservative approach. However, modelling zero OS gain alongside a PFS gain for treatment with BV means that, after progression, patients treated with BV die more quickly than patients treated with PC. Consequently, patients treated with BV spend less time in the highly resource-intensive end-stage care phase than patients treated with PC. This means that the costs accruing to the BV arm are lower than the costs accruing to the PC arm.

Populations and pathways in the company model

The company states that the populations that are represented in the model are patients with advanced stage MF and patients with pcALCL. However, as noted in the joint submission to the National Institute for Health and Care Excellence (NICE) from the Royal College of Pathologists and the British Society for Haematology [39] as part of this appraisal, treatment decisions are made according to each patient's needs and the expertise of the centre (p4). The relevance of the treatment pathways included in the model to the subgroup of patients with advanced stage MF and, in particular, patients with pcALCL is therefore unknown.

5.3.6 Model inflexibility and structural issues

Parts of the company model are inflexible or result in implausible outcomes due to structural issues in the model. These issues are not addressed by the ERG, since amending structural issues is outside the remit of the ERG.

Payoff approach

The company has used a payoff approach to model patient outcomes after progression. Mean costs and QALYs for active subsequent therapy and end-stage care are multiplied by the time spent in those phases and then summed to give mean costs and QALYs for the whole post-progression state. The payoff approach imposes limitations on the flexibility of the company model and does not allow for specific parameters and/or assumptions to be investigated thoroughly. In particular, the ERG was unable to explore the sensitivity of the model results to the use of different parametric survival functions. The ERG acknowledges that the company base case model – including alloSCT – benefits from the simplification introduced by the payoff approach. The payoff approach is described in more detail in in Appendix 8 (Section 9.8) and in NICE DSU TSD19 [162].

Mean post-progression survival

There is a zero risk of disease progression for patients treated with BV during the first 17 cycles of the company model. This is the combined result of i) the company's use of data from the PC arm of the ALCANZA trial to model OS for treatment with BV and PC, ii) the independent modelling of PFS for patients treated with BV and PC, and iii) a fix in the model

that stops PFS being greater than OS if the parametric curve estimates for PFS and OS overlap.

The combination of these three elements leads to no patients experiencing disease progression during the first 17 cycles of the model. A zero risk of disease progression in the early part of the model for patients treated with BV means that, for these patients, mean post-progression survival is underestimated by the company. However, comparison of the PFS and OS data from the ALCANZA trial, provided by the company at clarification, indicates that six patients treated with BV experienced disease progression during the first 17 cycles of treatment.

Proportion of patients with disease progression in each model cycle

The proportion of patients entering the post-progression health state in each cycle is estimated from the difference in PFS between cycles. For example, if PFS=90% in cycle 1 and PFS=80% in cycle 2, then 10% of patients would enter the post-progression health state in cycle 2. This method does not take into account the proportion of patients who die before experiencing disease progression. Not taking account of deaths in the progression-free state amounts to assuming a zero mortality risk before disease progression for treatment with BV and PC. A comparison of the PFS and OS K-M data from the ALCANZA trial indicates that five patients in the BV arm (16%) and six patients in the PC arm (18%) died before experiencing disease progression. The modelling of a zero risk of death before disease progression therefore does not reflect the trial evidence.

The proportion of patients who experience disease progression in each cycle is over-estimated in the company base case analysis and so costs and QALYs for the post-progression state are also over-estimated.

Probabilistic sensitivity analysis

In the CS, the company presents mean PSA results that are substantially different ([redacted]) compared with the deterministic results generated by the company model. The ERG is concerned that this difference may be the result of the non-standard methods used to implement some of the sensitivity analyses, but may also simply demonstrate the sensitivity of the model results to changes in parameter values.

5.3.7

5.4 Impact on the ICER per QALY gained of additional clinical and economic analyses undertaken by the ERG

The ERG has carried out the following revisions to the company base case ICERs per QALY gained for treatment with BV versus PC:

- Removal of alloSCT [R1]
- Utility estimates: observed EQ-5D-3L utility estimates from the ALCANZA trial [R2]
- Utility estimates: PFS utility equal for treatment with BV and PC [R3] (includes R2)
- Utility estimates: removal of AE decrements [R4]
- Removal of extra oral chemotherapy costs [R5]

Details of all Microsoft Excel revisions carried out by the ERG to the company's model are presented in Appendix 9 (Section 9.9).

A summary of the individual and combined effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with BV versus PC is shown in Table 31.

Table 31 Cost effectiveness results for ERG revisions to the company base case (PAS price for BV)

Revision	BV			PC			Incremental			ICER per QALY gained
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY	
Company original base case	[redacted]	[redacted]	***8.432***	[redacted]	[redacted]	***7.228***	[redacted]	[redacted]	***1.204***	***BV Dominates***
R1) Remove alloSCT	[redacted]	[redacted]	6.829	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.000	BV Dominates
R2) Utility estimates: observed EQ-5D-3L utility estimates from the ALCANZA trial	[redacted]	[redacted]	8.432	[redacted]	[redacted]	7.228	[redacted]	[redacted]	1.204	BV Dominates
R3) Utility estimates: PFS utility equal for treatment with BV and treatment with PC (includes R2)	[redacted]	[redacted]	8.432	[redacted]	[redacted]	7.228	[redacted]	[redacted]	1.204	BV Dominates
R4) Utility estimates: removal of AE decrements	[redacted]	[redacted]	8.432	[redacted]	[redacted]	7.228	[redacted]	[redacted]	1.204	BV Dominates
R5) Remove extra oral chemotherapy costs	[redacted]	[redacted]	8.432	[redacted]	[redacted]	7.228	[redacted]	[redacted]	1.204	BV Dominates
ERG revised base case	[redacted]	[redacted]	6.829	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.000	BV Dominates

AE=adverse events; alloSCT=allogeneic stem-cell transplantation; BV=brentuximab vedotin; PC=physician's choice; EQ-5D-3L=EuroQol 5 dimension-3 level; NHS=National Health Service; ICER=incremental cost effectiveness ratio; LY=life years; QALY=quality adjusted life year

5.5 ERG scenario analyses

The ERG notes that there are major assumptions included in the model for which there is neither robust evidence nor extensive sensitivity analyses. The ERG has produced three scenarios to test the sensitivity of the model to alternative, plausible assumptions. These assumptions are: changes to the post-progression pathway (Scenario 1); changes to resource use frequencies (Scenario 2); and assuming an OS gain for treatment with BV (Scenario 3).

The ERG cautions that the scenarios presented are intended to highlight the sensitivity of the model to plausible alternatives to the company assumptions that the ERG does not consider to be supported by robust evidence. The ERG also cautions that the results of the scenario analyses may not be meaningful, since the model is relatively inflexible and does not accommodate changes to certain parameters.

The ERG accepts that, given the evidence from the ALCANZA trial (see Section 4.6.5 of this ERG report) and based on clinical advice to the ERG, the company is justified in investigating a scenario in which a single OS curve is used to model survival for both treatment with BV and PC. However, it is critical to note the implications of this approach for assumptions about the natural history of advanced stage CTCL (Section 5.5.1).

Although there is insufficient evidence from the ALCANZA trial to model robustly any survival gain for treatment with BV, the ERG cautions that absence of evidence does not amount to evidence of absence and it remains plausible that there may be some survival gain attributable to treatment with BV without also modelling alloSCT as part of the treatment pathway. The ERG is concerned that modelling a small gain in OS without also modelling alloSCT may have a substantial impact on the size of the ICER per QALY gained as this approach reduces the difference in the time patients spend in the post-progression health state (Section 5.5.3).

5.5.1 Scenario 1: Changes to the post-progression pathway (zero OS gain for patients not receiving alloSCT)

Clinical advice to the ERG, regarding the patient pathway after progression in current NHS clinical practice, is that it is usual for patients to spend (i) almost 5 years receiving active subsequent treatments after disease progression, (ii) followed by 1 year receiving best supportive care (BSC) and (iii) then around 6 months receiving end-stage care (Figure 12).

The ERG notes that this revised post-progression pathway (Scenario 1) represents one of possibly many plausible alternatives to the company's original post-progression pathway.

ERG Scenario 1:

- Active subsequent therapy includes treatment with chemotherapy or TSEB, some medical resource use including nurse visits and dressings, and patients have a moderate HRQoL. The mean length of this phase is variable between treatments and depends on the difference between PFS and OS.

- BSC does not include active subsequent treatment but does include some medical resource use (assumed to the same as the medical resources used during active subsequent therapy), and patients have a HRQoL that is worse than the HRQoL of patients receiving active subsequent treatment but is better than the HRQoL of patients receiving end-stage care. The mean length of this phase is fixed at 1 year for both treatments.

- End-stage care does not include active subsequent treatment, but does include substantial resource use (including palliative care visits several times per week and expensive wound management, as per the company base case analysis) and patients have a very low HRQoL. The mean length of this phase is fixed at 6 months for both treatments.

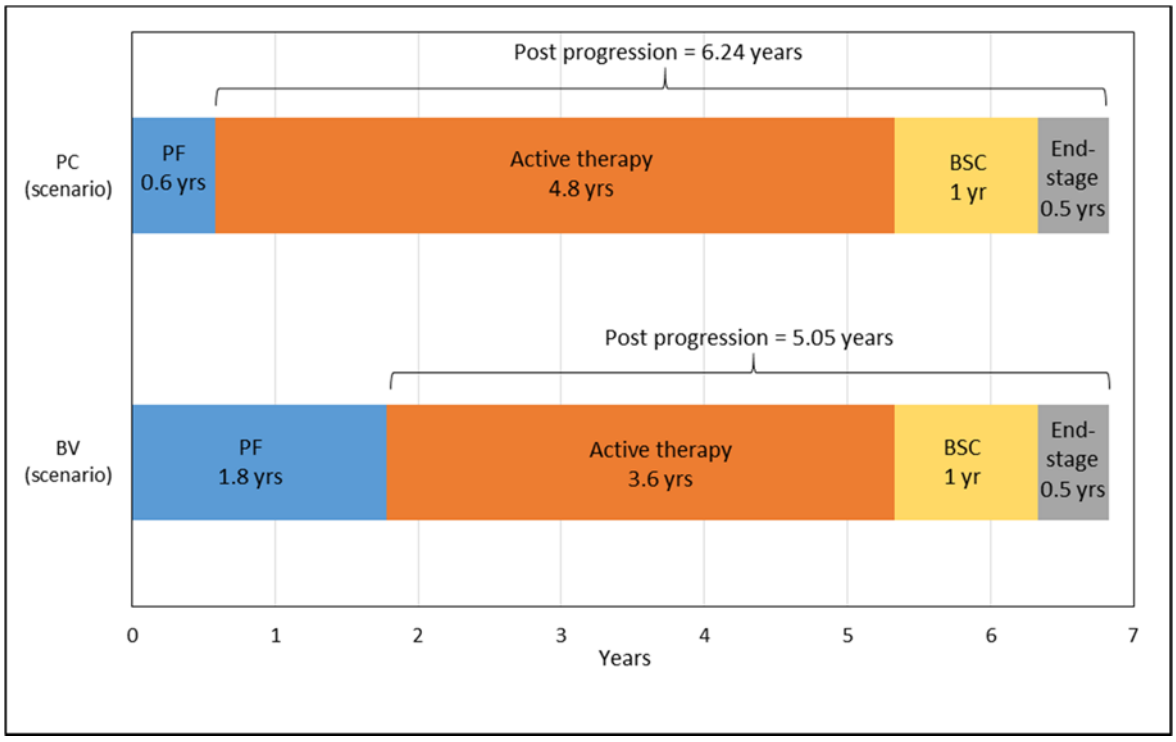


Figure 13 ERG Scenario 1: Changes to the post-progression pathway: distribution of health states

BSC=best supportive care; BV=brentuximab vedotin; PC=physician's choice; PF=progression free

The ERG used cost and utility estimates from the company base case model for the active subsequent therapy and end-stage care phases of the post-progression health state. The ERG assumed that the costs of being in the BSC phase would be the same as the cost of being in the active subsequent therapy phase minus treatment-related costs. The ERG also assumed that the utility value associated with being in the BSC phase would be the midpoint between the utility values used in the company model for active subsequent therapy and end-stage care.

Table 32 ERG Scenario 1: Changes to the post-progression pathway: cycle costs and utilities

Post-progression state	Weekly cycle cost	Utility
Active subsequent therapy	£965	0.64
BSC	£904[a]	Average of active therapy and end-stage=0.495
End-stage care	£2,381	0.38

BSC=best supportive care
[a] Equal to medical resource use and other costs (including hospital visits, home visits, tests and supportive drug therapies such as pain relief) in active therapy
Source: Company model

The ERG's exploratory analysis of the sensitivity of the results to changes in the assumptions used in the post-progression health state means that treatment with PC dominates treatment with BV.

5.5.2 Scenario 2: Changes to resource use frequencies (zero OS gain for patients not receiving alloSCT)

The ERG has re-estimated several of the resource use estimates used in the company model based on clinical advice (Table 33). If changes made to resource use brought the frequency of resource use in the end-stage care phase to below that of the same resources used in the pre-progression state or in the active subsequent treatment phase, the same estimates of resource use would also be applied to the other modelled health states for logical consistency (Table 34).

Table 33 ERG Scenario 2: Amendments to end-stage care phase resource use parameter estimates

	Company base case			ERG scenario 2*		
	% of all patients	Frequency per week	Duration per visit /dose (if applicable)	% of all patients	Frequency per week	Duration per visit/dose (if applicable)
Hospital outpatient						
Clinical nurse specialist	100	2.25		100	0.25	
Dermatologist visit	100	0.17		50	0.17	
Psychologist	50	0.25		5	0.25	
Home visit						
District nurse visit	100	2.63		100	0.25	
Macmillan nurse / Social services	100	1	7	100	0.25	1
Palliative care support team	100	2		100	0.25	
Dressings						
Mepitel dressings	25	7	3	12.5	7	3
Mepilex large sheet dressings	25	7	2	12.5	7	2
Mepilex small dressings	25	7	3	12.5	7	3
Mepilex heels	25	7	2	12.5	7	2
Elasticated garments	25	1	1	12.5	1	1
Medium Allevyn	75	7	7	37.5	7	7

[a] Changes to company base case in shaded cells; Source: company model; clinical advice to the ERG

Table 34 ERG Scenario 2: Amendments to resource use parameter estimates in pre-progression and post-progression (non end-stage care) states

	Company base case			ERG scenario 2[a]		
	% of all patients	Frequency per week	Duration per visit /dose (if applicable)	% of all patients	Frequency per week	Duration per visit/dose (if applicable)
Pre-progression						
Home visit						
District nurse	100	2.60		100	0.25	
Dressings						
Localised coverage	60	7	7	37.5	7	7
Post-progression (active subsequent therapy/BSC)						
Home visit						
District nurse	100	1.81		100	0.25	
Dressings						
Localised coverage	60	7	7	37.5	7	7

[a] Changes to company base case in shaded cells; Source: company model; clinical advice to the ERG

Using the ERG revised base case, implementing these resource use changes yields an ICER per QALY gained of £26,331.

Resource use unit costs

Clinical advice to the ERG is that less expensive alternatives to Allevyn, Mepilex and Mepitel dressings (included in the company model) may be used in NHS clinical practice. The ERG has not re-costed the dressings used in the model due to uncertainty around what constitutes standard practice in the NHS for treating wounds in patients with advanced stage CTCL. The ERG notes that, when comparing treatment with BV and PC, if the total costs of the end-stage care phase are reduced (due to the use of cheaper dressings), then the ICER per QALY gained would increase.

5.5.3 Scenario 3: Assuming an OS gain for treatment with BV versus PC

The ERG has investigated the impact of modelling an OS gain for treatment with BV versus treatment with PC. The ERG considers it reasonable to assume that mean OS gain is equal to mean OS in the company base case analysis (1.2 years) i.e., when alloSCT is included in the treatment pathway. The ERG used the company's base case log-logistic OS curve to represent survival for patients treated with PC. The ERG then adjusted the OS curve for treatment with PC using an acceleration factor (AF=0.779) to generate a 1.2 year mean OS gain for treatment with BV versus PC. The resulting OS curves are shown in Figure 14.

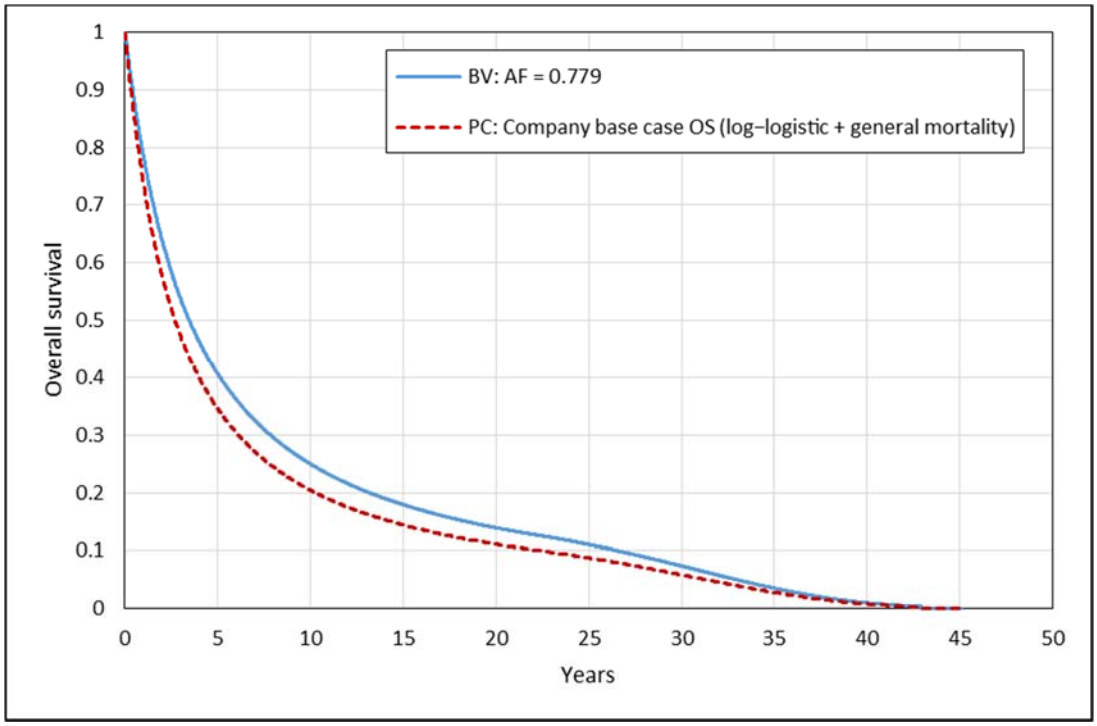


Figure 14 ERG scenario 3: OS gain (mean 1.2 years)

Source: company model; ERG calculations

The ERG cautions that this scenario has been included to highlight the sensitivity of the current model structure to the implementation of a potential survival gain for treatment with BV versus PC. The ERG is not suggesting that OS gain for treatment with BV is equal to 1.2 years or that the log-logistic curve is appropriate; only that this seems to be a reasonable assumption to test in a scenario. The ERG also cautions that the structure of the model is not flexible enough to allow a reliable result to be produced when changing the parametric curve used to estimate OS.

Using the ERG revised base case, the ICER per QALY gained generated when applying a mean OS gain of 1.2 years for the comparison of treatment with BV versus PC is £95,491.

5.6 Impact on the ICER per QALY gained of additional scenario analyses undertaken by the ERG

The ERG has carried implemented the following scenarios using the ERG revised base case:

- Changes to post-progression pathway [S1]
- Changes to resource use frequencies [S2]
- Assuming an OS gain for treatment with BV equal to company base case (1.2 years) (when alloSCT is included in the treatment pathway) [S3].

A summary of the individual effects of the scenarios modelled by the ERG on the company's base case cost effectiveness results for the comparison of treatment with BV versus PC is shown in Table 35.

Details of all Microsoft Excel revisions carried out by the ERG to the company's model are presented in Appendix 9 (Section 9.9).

Table 35 Cost effectiveness results for ERG scenarios (PAS price for BV)

Revision	BV			PC			Incremental			ICER per QALY gained
	Cost	QALYs	LY	Cost	QALYs	LY	Cost	QALYs	LY	
Company original base case	[redacted]	[redacted]	***8.432***	[redacted]	[redacted]	***7.228***	[redacted]	[redacted]	***1.204***	***BV Dominates***
ERG revised base case	[redacted]	[redacted]	***6.829***	[redacted]	[redacted]	***6.829***	[redacted]	[redacted]	***0.000***	***BV Dominates***
S1) Changes to post-progression pathway	[redacted]	[redacted]	6.829	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.000	BV Dominated
S2) Changes to resource use frequencies	[redacted]	[redacted]	6.829	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.000	£26,331
S3) Assuming an OS gain for treatment with BV equal to company base case (1.2 years)	[redacted]	[redacted]	8.029	[redacted]	[redacted]	6.829	[redacted]	[redacted]	1.201	£95,491

AE=adverse events; BV=brentuximab vedotin; PC=physician's choice; ICER=incremental cost effectiveness ratio; LY=life years; QALY=quality adjusted life y

5.7 Conclusions of the cost effectiveness section

The revisions and scenarios implemented by the ERG in the company model for the comparison of treatment with BV versus PC yield a mixture of effects. Incremental costs and incremental benefits both increase and decrease depending on the individual revision/ scenario or combination of revisions/scenarios.

Each of the ERG revisions to the company base case results in ICERs per QALY gained where BV dominates PC. The incremental costs vary from [redacted] (revised utility estimates) to [redacted] (when alloSCT is removed). The incremental QALYs range from [redacted] (removal of AE decrements) to [redacted] (when alloSCT is removed). When all the ERG revisions are combined BV still dominates PC with incremental costs of [redacted]

The resulting ICERs per QALY gained from the individual ERG scenarios vary from £26,331 (changes to resource use frequencies) to treatment with PC dominating treatment with BV (changes to post-progression pathway).

The ERG's analyses highlight the high level of uncertainty around the company base case cost effectiveness results. The ERG cautions that the ICERs per QALY gained for the comparison of treatment with BV and PC presented in this ERG report may not be reliable

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6 END-OF-LIFE CRITERIA

The NICE end-of-life criteria are as follows:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment

The company has not made a case for BV meeting the above criteria.

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness

The majority of the evidence is derived from the ALCANZA trial, an international, open-label, randomised, phase III, multicentre trial of BV versus PC in patients with CD30+ CTCL (n=131). The focus of the company's decision problem is only patients with advanced stage CTCL (n=95) as these are the patients considered by the company to be those who would be eligible for BV in clinical practice. The ERG concurs.

The PC arm of the ALCANZA trial consists of MTX or BEX. The ERG considers these are the most appropriate comparators for patients with MF. Clinical advice to the ERG is that (i) *Category A* therapies are the most relevant comparators to BV for patients with MF and (ii) *Category B* therapies would normally be preferred to *Category A* therapies for patients with advanced stages of pcALCL who have received at least one prior systemic therapy and are fit enough to tolerate the drugs. However, clinical advice is that MTX and BEX are likely to be appropriate comparators to BV for the patients included in the ALCANZA trial with pcALCL who might have had earlier stage disease or who were not fit for *Category B* drugs.

Results from the ALCANZA trial show that, compared with PC, treatment with BV results in improved ORR4 and PFS; reflecting these improvements, patients were treated with BV for longer than with MTX of BEX. However, improvements in OS or HRQoL have not been conclusively demonstrated. Furthermore, peripheral neuropathy is a very common AE for patients treated with BV which, although mostly of only grade 1 or 2 in severity, can lead to treatment discontinuation for approximately 16% of patients.

Overall, the ERG considers that the patients in the ALCANZA trial with advanced stage CTCL are similar to patients with advanced stage MF and pcALCL who would be seen in NHS clinical practice. The ERG highlights the lack of relative effectiveness evidence for other subtypes of CTCL. However, obtaining evidence for other subtypes is difficult given CTCL is an orphan disease and given other subtypes constitute less than half of all patients with CTCL.

7.2 Cost effectiveness

The ERG's analyses highlight the high level of uncertainty around the company base case cost effectiveness results. The ERG cautions that the ICERs per QALY gained for the comparison of treatment with BV and PC presented in this ERG report may not be reliable.

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9 APPENDICES

9.1 Appendix 1: CTCL staging and prognosis

9.1.1 MF/SS staging and prognosis

As described in the CS (p24), CTCLs are classified using the tumour-node-metastasis (TNM) system, where 'T' represents tumour involvement (which for CTCL is patches or plaques), 'N' represents lymph node involvement and 'M' represents the presence of metastasis [23, 24, 163]. The staging of MF/SS also includes an additional 'B' criterion (B0–B2), representing the degree of blood tumour burden (i.e., leukaemic blood involvement). 'B' staging is based on the presence/absence of Sézary cells in the blood, with B1 representing low- and B2 representing high-blood tumour burden. The TNMB designations for MF/SS are used to group CTCL into early stage (stages IA to IIA) or advanced stage (stages IIB to IVB) disease (Figure 15) [23, 164].

<table>
<tr><td></td><td></td><td></td><td colspan="4">Tumour (T)</td></tr>
<tr><td>Lymph nodes (N)</td><td>Metastasis (M)</td><td>Blood (B)</td><td>T1: Limited patches, plaques, or papules (<10% BSA affected)</td><td>T2: Generalised patches, plaques, or papules (≥10% BSA affected)</td><td>T3: ≥1 tumours</td><td>T4: Generalised erythema (≥80% BSA affected)</td></tr>
<tr><td>N0: No nodes are clinically involved</td><td rowspan="3">M0: No metastasis (no visceral organ involvement)</td><td>B0-1: absence of substantial blood involvement</td><td>IA (early stage)</td><td>IB (early stage)</td><td rowspan="2">IIB (advanced stage)</td><td>IIIA (advanced stage)</td></tr>
<tr><td>N1: Nodes enlarged, histologically uninvolved</td><td>B1: low tumour blood burden</td><td colspan="2">IIA (early stage)</td><td>IIIB (advanced stage)</td></tr>
<tr><td>N2-3: Nodes clinically normal (N2) or enlarged (N3), histologically involved</td><td rowspan="2">B0-2</td><td colspan="4">IVA†
(advanced stage)
IVA is separated into IVA1 (with blood involvement; B2) and IVA2 (lymph node involvement; N3)</td></tr>
<tr><td>N0-N3</td><td>M1: Metastasis present (visceral organ involvement)</td><td colspan="4">IVB
(advanced stage)</td></tr>
</table>

BSA=body surface area
Note: Sézary syndrome only presents in advanced stage

Figure 15 Classification and staging for mycosis fungoides and Sézary syndrome

Source: CS, adapted from Figure 4 and Pinter-Brown et al 2014, adapted from Table 2 [164]

Early stage MF (stages IA to IIA) usually presents with cutaneous patches and plaques [23]. Advanced MF (stages IIB to IVB) is characterised by skin tumours, erythroderma, and nodal

or visceral involvement. SS presents only in advanced stage disease with extreme pruritus, erythroderma, lymphadenopathy and circulating Sézary cells [21].

Median OS and 5-year survival rates by stage of disease from three studies of MF/SS [8, 26, 27] are presented in the CS (p28) and reproduced by the ERG (with the inclusion of additional information) in Table 36. The data clearly show that prognosis for patients with advanced stage disease differs markedly to prognosis for patients with early stage disease.

Table 36 Median OS and 5-year OS rates reported for patients with mycosis fungoides and Sézary syndrome

Study, outcomes	Early stage disease			Advanced stage disease					
	IA	IB	IIA	IIB	IIIA	IIIB	IVA1	IVA2	IVB
Median OS (years)									
Kim et al 2003 [26][a]	-	12.9		4.0			1.5		
Agar et al 2010 [8][b]	35.5	21.5	15.8	4.7	4.7	3.4	3.8	4.7	4.7
Scarisbrick et al 2015 [27][c]	Not applicable - study only included patients with advanced stage disease			5.7	-	5.2	4.4	2.4	2.8
					-		4.0		
				5.2					
Five-year OS rates									
Kim et al 2003 [26][a]	96%	75%		44%			27%		
Agar et al 2010 [8][b]	94%	84%	78%	47%	47%	40%	37%	18%	18%
Scarisbrick et al 2015 [27][c]	Not applicable - study only included patients with advanced stage disease			57.4%	60.2%	55.7%	48.3%	32.9%	39.0%
					58.2%		42.9%		
				51.9%					

OS=overall survival
'-' indicates median not reached
[a] Single-centre retrospective study, n=525 (all patients from the United States)
[b] Database analysis, n=1502 (all patients from the UK)
[c] Multi-centre retrospective study (29 centres spanning five continents), n=1275 (UK patients, n=261)

9.1.2 CD30+ LPDs staging and prognosis

The ISCL and the cutaneous lymphoma task force of the EORTC have established a consensus proposal for a TNM classification system (i.e. tumour, node, metastasis) applicable for other subtypes of CTCL (Table 37) [24]. Due to the clinical and pathologic heterogeneity of CTCL, the authors highlight that the currently proposed system is meant to be primarily an anatomic documentation of disease extent and should not to be used as a prognostic guide [24].

Table 37 Proposed TNM classification of cutaneous lymphoma other than mycosis fungoides and Sézary syndrome[a]

Classification	
Tumour (T)	
T1:	Solitary skin involvement
	T1a: a solitary lesion <5 cm diameter
	T1b: a solitary >5 cm diameter
T2:	Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions
	T2a: all-disease-encompassing in a <15-cm-diameter circular area
	T2b: all-disease-encompassing in a >15- and <30-cm-diameter circular area
	T2c: all-disease-encompassing in a >30-cm-diameter circular area
T3:	Generalised skin involvement
	T3a: multiple lesions involving 2 noncontiguous body regions
	T3b: multiple lesions involving ≥3 body regions
Lymph nodes (N)	
N0:	No clinical or pathologic lymph node involvement
N1:	Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
N2:	Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3:	Involvement of central lymph nodes
Metastasis (M)	
M0:	No evidence of extracutaneous non–lymph node disease
M1:	Extracutaneous non–lymph node disease present

[a] Proposed by the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization for Research and Treatment of Cancer (EORTC)
Source: Source: Kim et al 2007, adapted from Table 2 [24]

The company states (CS, p26) that it is implicit in the definition of CD30+ LPD that extracutaneous disease is absent and, therefore, all patients are classified as N0 and M0 at presentation and remain so during early stage disease. While pcALCL and LyP share the expression of CD30 antigen as a common immunophenotypic hallmark, they differ in regard to their clinical presentation [25]. The company highlights that patients with pcALCL generally present with solitary or grouped, rapidly growing, and ulcerating large tumours or thick plaques (CS, p27); most patients with pcALCL, therefore, have localised disease [22, 25]. Patients with N1–N3 and M1 classifications are considered to have advanced stage disease, where the lymphoma is active beyond the skin (i.e., in the nodes or blood) and beyond the nodes (metastasised). Extracutaneous spread (i.e., metastasis) is uncommon for patients with CD30+ LPDs; it is reported to occur in 13% of patients with pcALCL [22, 25]. The ERG notes that LyP tends to be self-resolving, typically occurring in early adulthood and presenting with recurrent nodules and papules at distant sites which become necrotic before resolving to form an atrophic scar [21, 25].

While staging for CTCL other than MF/SS is intended to be an anatomic documentation of disease extent and not a prognostic guide [24], the company highlights that significant survival

decrements are observed when comparing the prospects of patients with advanced versus early clinical stages (CS, p29). Broadly speaking, patients with regional or generalised involvement have more advanced stage disease than those with localised disease. The company highlights that patients with pcALCL with regional lymph node involvement demonstrate an overall 5-year OS rate of 76% [3]; the ERG notes that Liu et al 2003 report disease-specific 5-year survival of 50% for generalised pcALCL (versus 91% for localised pcALCL) [22].

9.2 Appendix 2: Estimated number of patients eligible for treatment with BV

Clinical advice to the ERG is that there may be 30 to 40 new cases of CTCL that are treated at the Liverpool centre each year. If replicated across all seven supra-regional centres in the UK, this equates to between 210 and 280 new cases in the UK each year. All these patients will have failed topical therapies and will be candidates for systemic therapies, but not all will have advanced stage CTCL.

The company highlights (CS, p23) that 1659 people were recorded as being newly diagnosed with CTCL in England between 2009 and 2013 (PHE data) [10]. Assuming incidence has remained unchanged during each year of this period, this equates to 332 patients per year. Not all of these patients would have had advanced stage CTCL. Prevalence figures cited in the CS (p24) from the PROCLIPI observational study suggest that [redacted] of patients in the UK have advanced stage CTCL. Thus, based on data from this study, approximately [redacted] patients may be diagnosed with advanced stage CTCL in England each year.

Clinical advice to the ERG is that a higher proportion of patients with MF have advanced stage disease than early stage disease, whereas the opposite is true for patients with pcALCL and LyP. The estimated proportions are summarised in Table 38.

Table 38 Estimated proportions of new patients with early stage and advanced stage CTCL

CTCL subtype	Early stage, %	Advanced stage, %
MF	40	60
SS	0	100
pcALCL	80	20
LyP	90	10

CD30+ LPDs=primary cutaneous CD30-positive lymphoproliferative disorders; CTCL=cutaneous T-cell lymphoma; LyP= Lymphomatoid papulosis; MF= mycosis fungoides; pcALCL=primary cutaneous anaplastic large cell lymphoma; SS=Sézary syndrome
Source: Clinical advice to the ERG

Crudely applying these estimates to PHE data [10], means that approximately 140 patients may be diagnosed with advanced stage CTCL in England each year (Table 39). However, this estimate is highly uncertain as it relies on four key assumptions, none of which may be true. First, it has been assumed that incidence remained unchanged during each year of the period between 2009 and 2013 and that incidence has not changed since. Second, it has been assumed that the estimated proportions of patients with early stage and advanced stage CTCL presented by the ERG are correct for England. Third, PHE data do not categorise patients with CD30+ LPDs further by their subtypes of pcALCL and LyP and so it has been assumed by the ERG that 15% of these patients have advanced stage CTCL. Fourth, it has also been assumed by the ERG that 15% of patients with all other subtypes of CTCL also have advanced

stage disease. In addition, the estimate fails to take into consideration that only 23% of patients with MF/SS may have CD30+ CTCL [27].

Table 39 Estimated number of patients with CTCL each year by stage of disease

CTCL subtype	Early stage, n	Advanced stage, n
MF	74	110
SS	0	8
CD30+ LPDs	27	5
Other[a]	91	16
Total	192	140

CD30+ LPDs= primary cutaneous CD30-positive lymphoproliferative disorders; CTCL=cutaneous T-cell lymphoma; MF=mycosis fungoides; SS=Sézary syndrome
[a] Other included patients categorised subcutaneous panniculitis-like T-cell lymphoma, cutaneous peripheral T-cell lymphoma-not otherwise specified, CD30+ LPDs, extranodal NK/T-cell lymphoma, nasal type and primary cutaneous gamma-delta T-cell lymphoma
Source: ERG estimates using data from Public Health England 2016 [10]

Not all new cases of advanced stage CTCL would receive treatment with BV. First, as highlighted above, not all patients would have CD30+ CTCL, the proportion of patients with CD30+ CTCL being unclear (see Section 2.2). However, if it is also assumed only 23% of patients with MF/SS have CD30+ CTCL, then the incidence of patients with advanced stage CTCL diagnosed with advanced stage disease in England each year may be as low as approximately 50 patients (Table 40). Second, based on the treatment pathway proposed in the CS (see also Section 2.3.2 of this ERG report), most newly diagnosed patients would probably initially receive a *Category A* therapy with only a proportion of these patients failing treatment and, therefore, being eligible to receive BV within the same year. Eventually, however, a reasonable proportion of patients would become candidates for treatment with BV.

Table 40 Estimated number of patients with CTCL each year by stage of disease, assuming only 23% of patients with MF/SS have CD30+ CTCL

CTCL subtype	Early stage, n	Advanced stage, n
MF	17	25
SS	0	2
CD30+ LPDs	27	5
Other[a]	91	16
Total	135	48

CD30+ LPDs= primary cutaneous CD30-positive lymphoproliferative disorders; CTCL=cutaneous T-cell lymphoma; MF=mycosis fungoides; SS=Sézary syndrome
[a] Other included patients categorised subcutaneous panniculitis-like T-cell lymphoma, cutaneous peripheral T-cell lymphoma-not otherwise specified, CD30+ LPDs, extranodal NK/T-cell lymphoma, nasal type and primary cutaneous gamma-delta T-cell lymphoma
Source: ERG estimates using data from Public Health England 2016 [10]

In summary, there is considerable uncertainty as to how many patients would be eligible for treatment with BV in England each year.

9.3 Appendix 3: Risk of bias assessment

Table 41 Assessment of risk of bias for the ALCANZA trial

Study question	Company assessment	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	Unclear	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Agree, the open-label nature of the trials provides an opportunity for subjective results and investigator-assessed outcomes to be biased
Were there any unexpected imbalances in drop-outs between groups?	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree, the company made available the clinical study report, protocol and statistical analysis plan alongside its submission
Did the analysis include an intention-to-treat analysis? If so, was this appropriate?	Yes	Agree
Were appropriate methods used to account for missing data?	Yes	Agree

Source: CS, Appendix D.1.5 (Table 24) and ERG comment

9.4 Appendix 4: ERG testing of proportional hazards for data from the ALCANZA trial

The validity of the PH assumption within the trial is best assessed by considering the H-H plot which shows the relationship between the cumulative hazard for each trial event at common time points in the two trial arms (IRF-assessed PFS, Figure 16; time to subsequent anticancer therapy, Figure 17). For the PH assumption to be valid, two criteria must be met:

- the data should follow a straight line trend, with individual data points randomly distributed close to and on either side of the trend line
- the linear trend line should pass through the graph origin (zero value on both axes).

9.4.1 Progression-free survival (assessment by independent review facility, subgroup of patients with advanced stage CTCL)

The H-H plot for the IRF-assessed PFS data from the advanced stage CTCL patient subgroup of the ALCANZA trial is provided in Figure 16. It is clear that the data do not follow a straight line trend; the linear model appears to underestimate PFS in the BV arm in the early and late stages of the trial, and overestimate PFS in the BV arm in the intervening period. However, the linear regression model does not estimate a statistically significant deviation from the origin of -0.085 (95% CI: -0.171 to 0.000). Nonetheless, based on visual inspection of the H-H plot, the ERG considers that the PH assumption may be violated for IRF-assessed PFS data from the subgroup of patients with advanced stage CTCL.

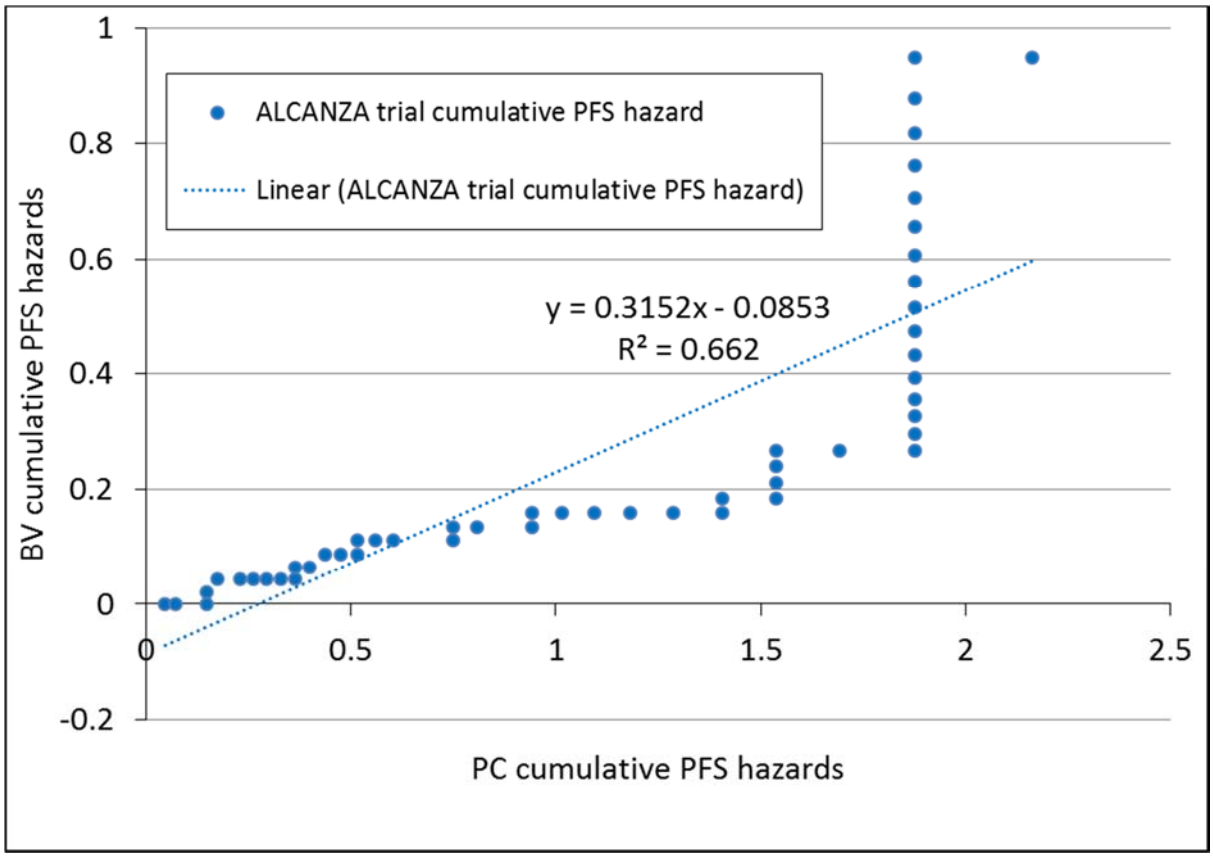

Figure 16 H-H plot for IRF-assessed PFS data from the advanced stage CTCL patient subgroup of the ALCANZA trial

BV=brentuximab vedotin; CTCL=cutaneous T cell lymphoma; IRF=independent review facility; PC=physician's choice; PFS=progression-free survival
Source: Company clarification response, question B1

9.4.2 Time to subsequent anticancer therapy (subgroup of patients with advanced stage CTCL)

Visual inspection of Figure 17 indicates that the PH assumption may not hold for time to subsequent anticancer therapy from the ALCANZA trial; the data do not follow a straight line trend. However, the linear regression model does not estimate a statistically significant deviation from the origin of -0.019 (95% CI: -0.092 to 0.054). Nonetheless, based on visual inspection of the H-H plot, the ERG considers that the PH assumption may be violated for time to subsequent anticancer therapy data from the subgroup of patients with advanced stage CTCL.

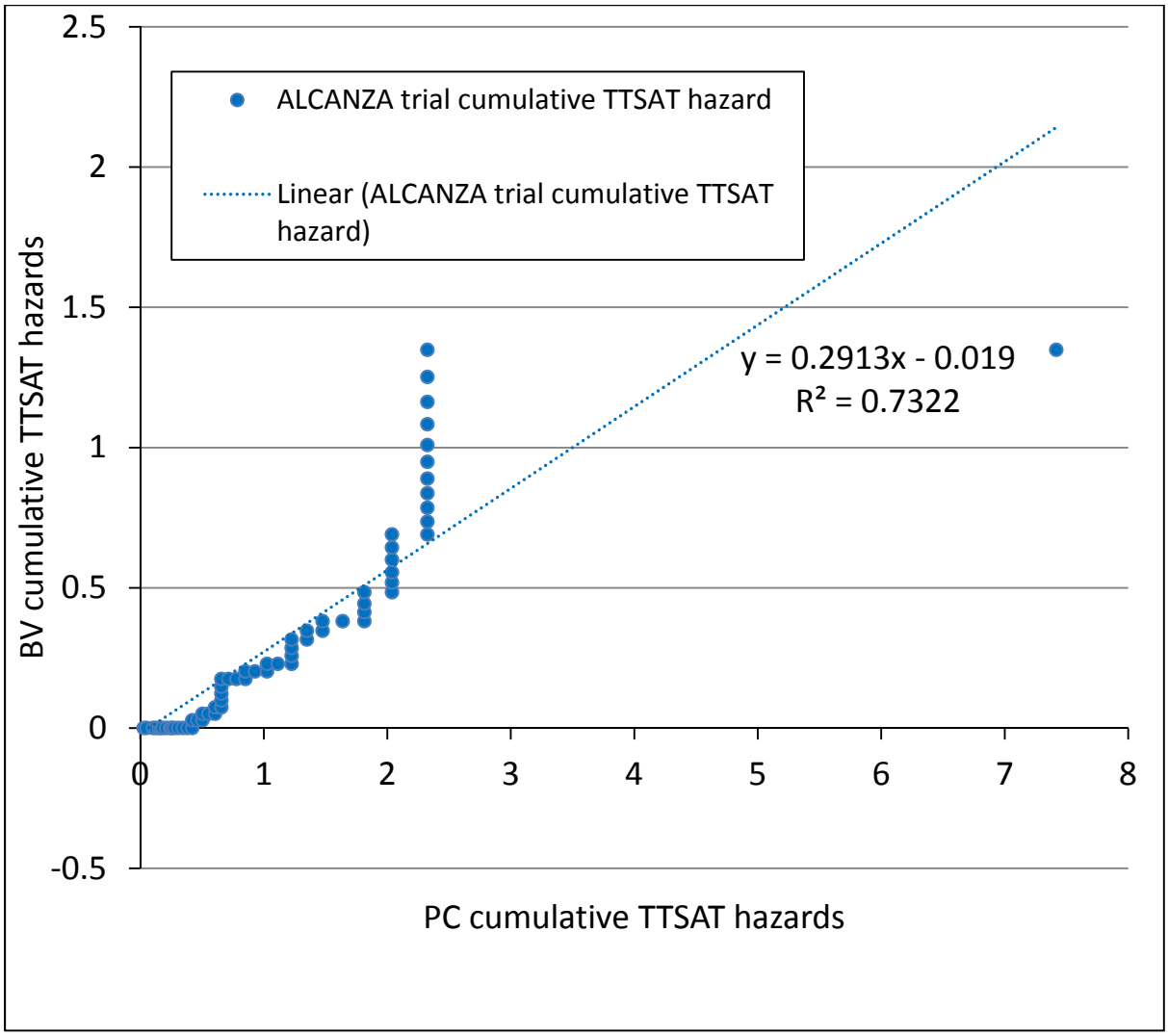

Figure 17 H-H plot for TTSAT data from the advanced stage CTCL patient subgroup of the ALCANZA trial

BV=brentuximab vedotin; CTCL=cutaneous T cell lymphoma; PC=physician's choice; TTSAT=time to subsequent anticancer therapy
Source: Digitisation of Figure 35 of the CS

9.5 Appendix 5: Common types of any-grade adverse events

The frequency of common any-grade TEAEs (occurring in ≥10% of patients after a median of 22.9 months follow-up) for all patients in the ALCANZA trial is presented in Table 20 of the CS. Data are presented for MTX and BEX separately in this table. The ERG notes that although labelled as TRAEs, the incidence of each AE in each arm is identical to the data presented in the published paper, labelled as TEAEs [66]. During the clarification process, the ERG requested the same data for the advanced stage subgroup after a median of 33.9 months follow-up. The company provided these data which were labelled as TEAEs and not TRAEs. The company also provided the CSR for the ALCANZA trial for the primary data-analysis (median 22.9 months follow-up). It is evident from consulting this document (Table 12.g) that the data presented in Table 20 of the CS are not in fact TRAEs but are TEAEs.

In total, in the overall trial population, 16 types of TEAEs occurred in ≥10% of patients in the BV arm, compared with six types of TEAEs for patients treated with MTX and six types of TEAEs for patients treated with BEX. In the advanced stage subgroup, 15 types of TEAEs occurred in ≥10% of patients in the BV arm, compared with eight types of TEAEs for patients treated with MTX and 11 types of TEAEs for patients treated with BEX. However, it should be noted that in the advanced stage subgroup of the ALCANZA trial, the 10% threshold was met if only two patients treated with MTX had a TEAE or three patients treated with BEX had a TEAE. Focusing instead on AEs that occurred in ≥15% of patients, the ERG highlights the most common TEAEs in Table 42.

Table 42 Most common (≥15%) any-grade treatment-emergent adverse events occurring in the ALCANZA trial

Type of adverse event, n (%)	Overall trial population, median 22.9 months follow-up			Advanced stage subgroup, median 33.9 months follow-up		
	BV (n=66)	MTX (n=25)	BEX (n=37)	BV (n=49)	MTX (n=20)	BEX (n=24)
Peripheral sensory neuropathy	30 (45)	1 (4)	0	25 (51)	0	0
Nausea	24 (36)	4 (16)	4 (11)	18 (37)	4 (20)	4 (17)
Fatigue	19 (29)	5 (20)	12 (32)	11 (22)	5 (25)	6 (25)
Pyrexia (Fever)	11 (17)	7 (28)	4 (11)	6 (12)	6 (30)	3 (13)
Hypertriglyceridaemia	1 (2)	0	11 (30)	0	0	7 (29)

BEX=bexarotene; BV=brentuximab vedotin; MTX=methotrexate
Source: CS, adapted from Table 20 and clarification response, A12 (adapted from Table 8)

In the advanced subgroup, peripheral sensory neuropathy (a type of peripheral neuropathy), occurred in half of all patients treated with BV, pyrexia (fever) occurred in nearly a third of all patients treated with MTX and hypertriglyceridemia occurred in nearly a third of all patients treated with BEX. Nausea and fatigue were common AEs associated with all three therapies.

In addition, diarrhoea was reported by 29% of patients in the BV arm of the overall ALCANZA trial population but only 12% in the subgroup with advanced stage CTCL. Vomiting and alopecia were also common AEs associated with treatment with BV (both occurring in 14% of patients with advanced stage CTCL treated with BV).

AEs reported in the prospective observational studies [18, 76] are described as TRAEs (CS, Appendix F). The most common TRAE reported in the observational studies was peripheral neuropathy (any-grade 67% in Duvic et al 2015 [18], 66% in Kim et al 2015 [76]). The frequencies of peripheral neuropathy were very similar to the frequency of peripheral neuropathy reported as a TEAE in the overall ALCANZA trial population after a median of 22.9 months follow-up (67%). However, with the exception of diarrhoea and nausea, which were reported less frequently in the observational studies than in the overall trial population of the ALCANZA trial, the frequencies of the most common AEs tended to be higher in the prospective observational studies [18, 76] than in the ALCANZA trial. Most notably, any-grade fatigue and any-grade neutropenia was experienced by 47% and 19% of patients respectively in the study by Kim et al 2015 [76] compared to 29% and 8% of patients respectively in the overall ALCANZA trial population [66] (or 22% and 10% respectively in the advanced stage subgroup, see company clarification response, A12 [Table 8] and A15 [Table 10]).

In the retrospective analysis by Mathieu et al 2016 [75], peripheral neuropathy was reported by only 7 (22%) patients. Referring to the two previous observational studies [18, 76], the authors state in their abstract that: “They [the authors of the observational studies] also report fatigue, skin rashes, diarrhoea and neutropenia more often than we do.”

As reported in the EPAR for BV (p85) [30], Wieser at al 2016 [116] conducted a retrospective study of 180 patients with LyP of whom 21 patients received BV. The most commonly reported AE was peripheral neuropathy (in 9 [43%] patients). Information on other AEs was not provided in the publication.

9.6 Appendix 6: HRQoL results from the overall ALCANZA trial population

9.6.1 FACT-G

FACT-G results are not reported in the CS. After a median follow-up of 22.9 months, it is, however, reported in the published paper [66] that there were no statistically significant differences between arms in all patients. It is reported in the EPAR for BV (p50) [30] that compliance was high in both arms over time. [redacted] Whilst compliance was reported to be high over time from baseline to EOT (i.e., most of those eligible to complete questionnaires did so), the number of eligible patients at each point in time decreased, reflecting the higher number of patients who had disease progression.

9.6.2 Skindex-29

Statistically significant improvements in symptoms measured by Skindex-29 were reported for patients treated with BV compared to those in the PC arm (CS, pp72 to 73). After a median follow-up of 22.9 months, the mean maximum reduction from baseline in the ITT population was -27.96 in the BV arm and -8.62 in the PC arm ($p<0.0001$). After a median follow-up of 33.9 months, patients treated with BV continued to experience significantly greater symptom reduction versus those treated with PC (mean maximum reduction, -28.08 versus -8.62, respectively; $p<0.001$). As described in the EPAR for BV (p34 and p48) [30], the company also calculated whether the change was of clinical significance by determining the minimal important difference (MID) by three methods. The calculated MID in the reduction in Skindex-29 symptom domain score was 12.3 using half of a standard deviation of change in score, 11.2 using Cohen's effect size, and 9.1 using standard error of measurement. The difference between the treatment arms for the maximum reduction from baseline after a median of 22.9 months and a median of 33.9 months exceeded all the MID thresholds, demonstrating a clinically meaningful response.

The ERG notes that, as reported in the EPAR for BV (p49) [30] and published paper [66] but not in the CS, other domains (emotions, functioning) of Skindex-29 were also measured in the ALCANZA trial. It is reported in the published paper (p560) that "No substantial difference in Skindex-29 emotional or functioning domains was seen over time" [66]; however, skin disease at end of treatment had less of an effect in patients in the BV arm than the PC arm for both domains. Results for the total score of the Skindex-29 are presented in the EPAR (Figure 21) [30]. The results mirror those of the emotional and functioning domains.

Compliance with Skindex-29 assessments was reported to be high. It is reported in the CSR (p142) that compliance [redacted].

Whilst compliance was reported to be high over time from baseline to EOT, as with the FACT-G questionnaires, the number of eligible patients at each point in time decreased, reflecting the higher number of patients who had disease progression.

9.6.3 EQ-5D-3L and EQ-5D-VAS

Similar to the results from the analysis of FACT-G, there were no statistically significant differences between arms for EQ-5D-3L US time trade-off, EQ-5D-3L UK time trade-off, or EQ-5D VAS scores. Again, it is reported in the EPAR for BV (p50) [30] that compliance was high in both arms over time. [redacted] Whilst compliance was reported to be high over time from baseline to EOT, as with the FACT-G and Skindex-29 questionnaires, the number of eligible patients at each point in time decreased, reflecting the higher number of patients who had disease progression.

9.7 Appendix 7: Resource use

Table 43 Resource use in the active therapy phase of the post-progression health state

	Proportion of all patients	Frequency per week	Duration (if applicable)	Dose	Unit	Average weekly cost	Source
Hospital outpatient							
Clinical nurse specialist	100%	0.38	N/A	N/A	N/A	£32.77	NHS Reference Costs 2016/17 [147] WF01A:370 Total outpatient attendances, Non-consultant led, Medical oncology
Dermatologist visit	100%	0.50				£50.27	NHS Reference Costs 2016/17 [147] WF01A:330 Consultant led- Non-Admitted Face-to-Face Attendance, Follow-up
Oncologist outpatient visit	100%	0.38				£60.43	NHS Reference Costs 2016/17 [147] WF01A:370 Total Outpatient Attendances, Medical Oncology
Consultant oncologist visit	100%	0.54				£95.46	NHS Reference Costs 2016/17 [147] WF01A:370 Total outpatient attendances, Consultant led, Medical oncology
Home visit							
District nurse	100%	2.60	N/A	N/A	N/A	£96.01	NHS Reference Costs 2016/17 [147] - N02AF Total Other Currencies, District Nurse, Adult, Face to face
Investigations and tests							
Complete blood count	100%	0.67	N/A	N/A	N/A	£2.04	NHS Reference Costs 2016/17 [147] - DAPS05 Haematology
Liver function test	100%	0.33				£4.20	NHS Reference Costs 2016/17 [147] - DAPS09 Other - 5 tests required
U&Es (urea and electrolytes test)	100%	0.33				£0.38	NHS Reference Costs 2016/17 [147] - DAPS04 Clinical Biochemistry
LDH (lactate dehydrogenase)	100%	0.33				£0.84	NHS Reference Costs 2016/17 [147] - DAPS09, DAPS, Other
Computed tomography scan	50%	0.17				£10.19	NHS Reference Costs 2016/17 [147] - RD26Z, Total HRGs, Computerised Tomography Scan of Three Areas, with Contrast

	Proportion of all patients	Frequency per week	Duration (if applicable)	Dose	Unit	Average weekly cost	Source
Imaging - PET	50%	0.17				£39.88	NHS Reference Costs 2016/17 [147] - RN07A - Positron Emission Tomography (PET), 19 years and over
Dressings							
Full body coverage	0%	0	N/A	0	Dressings	£0.00	The use of various sizes of allevyn, mepitel and mepilex dressings are assumed along with elasticated vest and leggings garments. The costs are all sourced from the BNF.
Localised coverage	60%	7		7	Dressings	£510.38	
Other drug treatments							
Pain relief							
Oramorph	0%	14.00	N/A	60	mg	£0.00	eMit [149] where available or MIMs [165]
Oromorph (breakthrough pain / iv)	80%	1.00		10	mg	£0.08	
Antihistamines							
Hydroxyzine	50%	4.67		25	mg	£0.05	eMit [149] where available or MIMs [165]
Gabapentin	33.33%	14.00		300	mg	£0.38	
Antidepressants							
Mirtazapine	50%	7.00		30	mg	£0.13	eMit [149] where available or MIMs [165]
Pregabalin	50%	7.00		300	mg	£0.34	
Antibiotics							
Flucloxacillin	100%	4.83	N/A	500	mg	£0.39	eMit [149] where available or MIMs [165]
Aciclovir	25%	28.00	N/A	200	mg	£0.23	

PET=positron emission tomography; IV= intravenous
Source: CS, adapted from Section B.3.5.2, Table 48 and company model

Table 44 Resource use in the end-stage management phase of the post-progression health state

	Proportion of all patients	Frequency per week	Duration (if applicable)	Dose	Unit	Average weekly cost	Source
Hospital outpatient							
Clinical nurse specialist	100%	2.25	N/A	N/A	N/A	£196.65	NHS Reference Costs 2016/17 [147] WF01A:370 Total outpatient attendances, Non-consultant led, Medical oncology
Dermatologist visit	100%	0.17				£16.76	NHS Reference Costs 2016/17 [147] WF01A:330 Consultant led- Non-Admitted Face-to-Face Attendance, Follow-up
Consultant oncologist visit	100%	0.17				£29.37	NHS Reference Costs 2016/17 [147] WF01A:370 Total outpatient attendances, Consultant led, Medical oncology
Psychologist	50%	0.25	1	N/A	Hours	£6.63	PSSRU 2017 [148], Band 7 Clinical psychologist, per working hour
Hospital inpatient							
Dermatology Day Centre or Oncology Ward	20%	0.11	N/A			£117.48	Cost per admittance to control skin outbreak. Assumes similar cost to generic lymphoma admittance and inpatient stay NHS Reference Costs 2016/17 [147] Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's (all CC scores). SA31A: SA31F.
Home visit							
District nurse	100%	2.63	N/A	N/A	N/A	£96.93	NHS Reference Costs 2016/17 [147] N02AF Total Other Currencies, District Nurse, Adult, Face to face
Macmillan nurse / Social services	100%	1.00	7		Hours	£199.50	Macmillan 2017; The cost of Macmillan services fact sheet [166]
Palliative care support team	100%	2.00	N/A		N/A	£284.00	NHS Reference Costs 2016/17 [147]: Outpatient - medical specialist palliative care attendance SD04A
Skin and wound care							
Radiotherapy	90%	0.11	N/A	2	Fractions	£96.01	NHS Reference Costs 2016/17 [147]: Preparation for Simple Radiotherapy with Imaging and Dosimetry, outpatient (SC45Z) + Deliver a Fraction of Treatment on a Superficial or Orthovoltage Machine, outpatient (SC21Z)

	Proportion of all patients	Frequency per week	Duration (if applicable)	Dose	Unit	Average weekly cost	Source
Topical steroids							
Betnovate	100%	0.34	N/A			£1.40	eMit [149] where available or MIMs [165]
Dressings							
Full body coverage including elasticated garments							
Mepitel dressings	25%	7	N/A	3	Dressings	£74.81	The use of various sizes of allevyn, mepitel and mepilex dressings are assumed along with elasticated vest and leggings garments. The costs are all sourced from the BNF.
Mepilex large sheet dressings	25%	7		2	Dressings	£222.74	
Mepilex small dressings	25%	7		3	Dressings	£53.39	
Mepliex heels	25%	7		2	Dressings	£45.05	
Elasticated garments	25%	1		1	Garments	£6.53	
Localised coverage							
Medium allevyn	75%	7	N/A	7	Dressings	£637.98	The use of various sizes of allevyn, mepitel and mepilex dressings are assumed along with elasticated vest and leggings garments. The costs are all sourced from the BNF.
Other drug treatments							
Pain relief							
Oramorph	100%	14.00	N/A	60	mg	£7.94	eMit [149] where available or MIMs [165]
Oromorph (Morphine sulphate [breakthrough pain / iv])	80%	0.25		10	mg	£0.02	
Antihistamines							
Hydroxyzine	100%	4.67	N/A	25	mg	£0.10	eMit [149] where available or MIMs [165]
Gabapentin	50%	14.00	N/A	300	mg	£0.57	

	Proportion of all patients	Frequency per week	Duration (if applicable)	Dose	Unit	Average weekly cost	Source
Antidepressants							
Mirtazapine	50%	7.00	N/A	30	mg	£0.13	eMit [149]where available or MIMs [165]
Pregabalin	50%	7.00	N/A	300	mg	£0.34	
Antibiotics							
Flucloxacillin	100%	3.22	N/A	500	mg	£0.26	eMit [149]where available or MIMs [165]
Aciclovir	25%	28.00	N/A	200	mg	£0.23	
Antifungal							
Fucitec	80%	0.02	N/A	30	g	£0.10	eMit [149]where available or MIMs [165]

IV= intravenous
Source: CS, adapted from, Section B.3.5.2 Table 49 and company model

9.8 Appendix 8: "Payoff" approach

In the company's payoff approach, transition probabilities for progression and death are calculated from parametric curves fitted to PFS and OS K-M data from the ALCANZA trial. The proportion of patients in the post-progression state in each model cycle is calculated by subtracting PFS from OS. Mean post-progression survival (PPS) is then calculated using an area under the curve (AUC) approach. Mean time spent in an intermediate subsequent active therapy phase is calculated using registry data (see Section 5.2.8) and subtracted from mean PPS to give mean time spent in end-stage care. Mean costs and QALYs for active subsequent therapy and end-stage care are multiplied by the time spent in those phases and then summed to give mean costs and QALYs for the whole post-progression state. These mean post-progression costs are then applied on a cycle basis to patients newly entering the post-progression state based on the transition probabilities calculated from the modelled PFS and OS curves. The basic structure of the post-progression state in the company model is shown in Figure 18 and Figure 19.

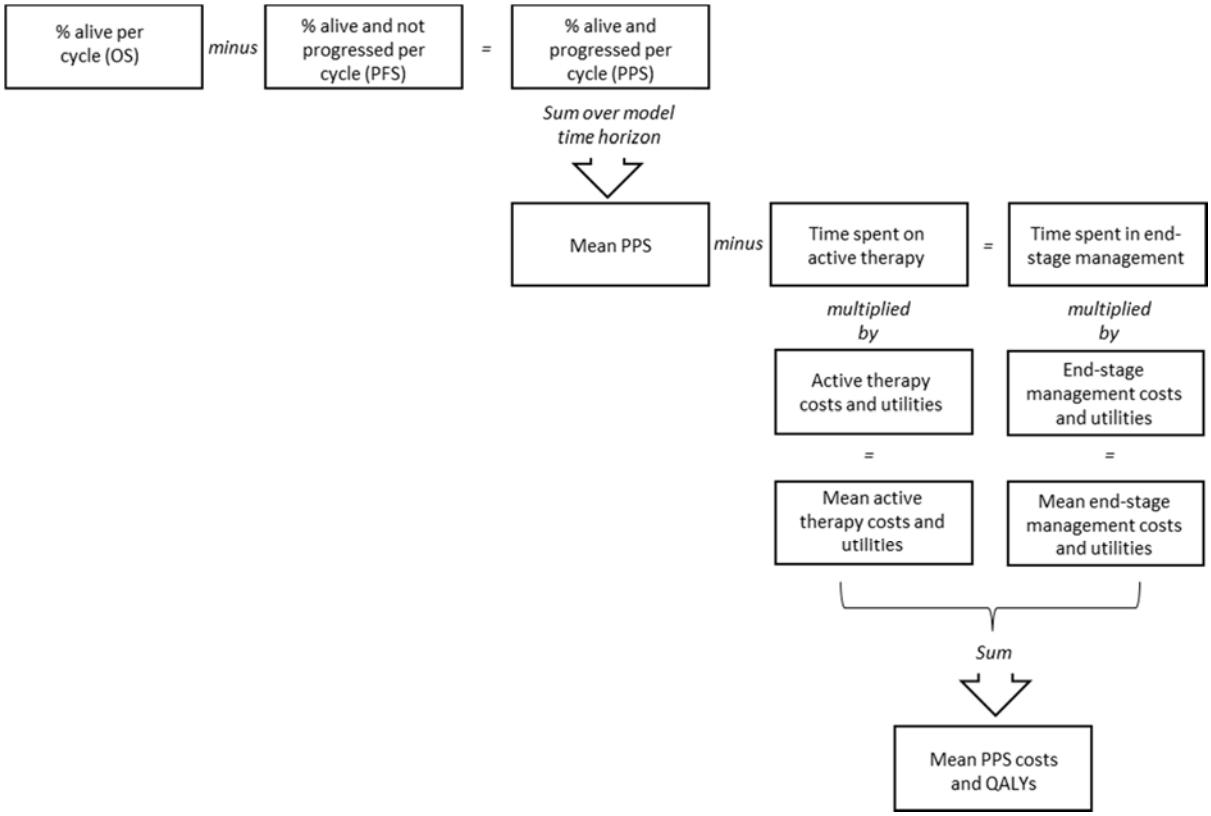

Figure 18 Simplified structure of calculation of mean PPS costs and QALYs in the company model

Note: the company base case includes further intermediate calculations to include costs and QALYs for alloSCT but the principles are as outlined in Figure 18

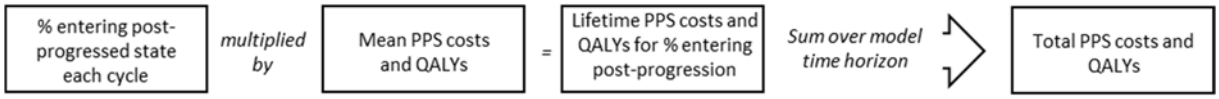

Figure 19 Simplified structure of calculation of total PPS costs and QALYs in the company base case

Note: the company base case includes further intermediate calculations to include costs and QALYs for alloSCT but the principles are as outlined in Figure 19

The company applies discounting in the post-progression state as a ratio of the difference in the exponentiated time entering a state and the time leaving versus time spent in the state (Equation 1). This method models a difference in discount rates applied to mean PPS costs and QALYs depending on the time an individual enters the post-progression state. However, the company method of discounting costs and benefits in the post-progression state also imposes a parametric structure on the transitions between the subsequent active therapy and end-stage care phases. The risks of moving from active subsequent therapy to end-stage care, and from end-stage care to death are assumed to be constant (albeit different) as a result of the exponential nature of the discount-rate calculation.

Equation 1 Company model post-progression state cycle discount rate calculation

$$Cycle\ discount\ rate = \frac{exp\left(\frac{cycle\ rate * time\ leaving\ state}{cycle\ rate}\right) - exp\left(\frac{cycle\ rate * time\ entering\ state}{cycle\ rate}\right)}{time\ spent\ in\ state} \quad (1)$$

$$\Rightarrow \frac{\exp(time\ leaving\ state) - \exp(time\ entering\ state)}{time\ spent\ in\ state}$$

This means that the shape of the OS curve has no relevance to model outcomes once patients have progressed and the impact of uncertainty in the survival trajectory – beyond estimating mean OS – cannot be explored in the company model. The ERG considers this to be a substantial limitation.

9.9 ERG Revisions to company's model

All revisions are activated by a logic switch. Logic switches are indicated by named range variables Mod_*number* where *number* = 1 to 8. A menu of revisions and Mod names appears below and on the 'Results' worksheet in the ERG amended model.

Instructions for modifying the updated company model

For individual revisions:

1. Populate the following named switch values in the 'Results' sheet

Name	Switch	Details
Mod_1	0	R1) Remove alloSCT
Mod_2	0	R2) Utility estimates: observed EQ-5D-3L utility estimates from the ALCANZA trial
Mod_3	0	R3) Utility estimates: PFS utility equal for treatment with BV and treatment with PC (includes R2)
Mod_4	0	R4) Utility estimates: removal of AE decrements
Mod_5	0	R5) Remove extra oral chemotherapy costs

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R1) Remove alloSCT	Mod_1	Controls	I133	=IF(Mod_1=0,"Yes","No") Amend named range **control_include_sct** to point to **Controls!$I$133**
R2) Utility estimates: observed EQ-5D-3L utility estimates from the ALCANZA trial R3) Utility estimates: PFS utility equal for treatment with BV and treatment with PC (includes R2)	Mod_2 Mod_3	Utilities	D18	=(IF(ctrl_population="Severe",IF(control_util_trt="2 (BV/PC)",IF(control_util_source="Regression equation",u_predict_pfree_BV_sev,p_u_observe_pfree_BV_sev),IF(control_util_source="Regression equation",u_trt3_predict_pfree_BV_sev,u_trt3_observe_pfree_BV_sev)), IF(control_util_trt="2 (BV/PC)",IF(control_util_source="Regression equation",u_predict_pfree_BV,p_u_observe_pfree_BV),IF(control_util_source="Regression equation",u_trt3_predict_pfree_BV,u_trt3_observe_pfree_BV))))*IF(AND(Mod_2=0,Mod_3=0),1,0)+p_u_observe_pfree_BV_sev*IF(AND(Mod_2=1,Mod_3=0),1,0)+(p_u_observe_pfree_BV_sev+p_u_observe_pfree_PC_sev)/2*IF(AND(Mod_2=0,Mod_3=1),1,0)
R2) Utility estimates: observed EQ-5D-3L utility estimates from the ALCANZA trial R3) Utility estimates: PFS utility equal for treatment with BV and treatment with PC (includes R2)	Mod_2 Mod_3	Utilities	D19	=(IF(ctrl_population="Severe",IF(control_util_trt="2 (BV/PC)",IF(control_util_source="Regression equation",u_predict_pfree_PC_sev,p_u_observe_pfree_PC_sev),IF(control_util_source="Regression equation",u_trt3_predict_pfree_MTX_sev,u_trt3_observe_pfree_MTX_sev)), IF(control_util_trt="2 (BV/PC)",IF(control_util_source="Regression equation",u_predict_pfree_PC,p_u_observe_pfree_PC),IF(control_util_source="Regression equation",u_trt3_predict_pfree_MTX,u_trt3_observe_pfree_MTX))))*IF(AND(Mod_2=0,Mod_3=0),1,0)+p_u_observe_pfree_PC_sev*IF(AND(Mod_2=1,Mod_3=0),1,0)+(p_u_observe_pfree_BV_sev+p_u_observe_pfree_PC_sev)/2*IF(AND(Mod_2=0,Mod_3=1),1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R2) Utility estimates: observed EQ-5D-3L utility estimates from the ALCANZA trial R3) Utility estimates: PFS utility equal for treatment with BV and treatment with PC (includes R2)	Mod_2 Mod_3	Utilities	D20	=(IF(ctrl_population="Severe",IF(control_util_trt="2 (BV/PC)",IF(control_util_source="Regression equation",u_predict_pfree_PC_sev,p_u_observe_pfree_PC_sev),IF(control_util_source="Regression equation",u_trt3_predict_pfree_BEX_sev,u_trt3_observe_pfree_BEX_sev)), IF(control_util_trt="2 (BV/PC)",IF(control_util_source="Regression equation",u_predict_pfree_PC,p_u_observe_pfree_PC),IF(control_util_source="Regression equation",u_trt3_predict_pfree_BEX,u_trt3_observe_pfree_BEX))))*IF(AND(Mod_2=0,Mod_3=0),1,0)+u_observe_pfree_PC_sev*IF(AND(Mod_2=1,Mod_3=0),1,0)+(p_u_observe_pfree_BV_sev+p_u_observe_pfree_PC_sev)/2*IF(AND(Mod_2=0,Mod_3=1),1,0)
R2) Utility estimates: observed EQ-5D-3L utility estimates from the ALCANZA trial R3) Utility estimates: PFS utility equal for treatment with BV and treatment with PC (includes R2)	Mod_2 Mod_3	Utilities	D26	=IF(ctrl_postprog_utility_source="ALCANZA",IF(ctrl_population="Severe",IF(control_util_trt="2 (BV/PC)",IF(control_util_source="Regression equation",u_predict_prog_sev,p_u_observe_prog_sev),IF(control_util_source="Regression equation",u_trt3_predict_prog_sev,u_trt3_observe_prog_sev)), IF(control_util_trt="2 (BV/PC)",IF(control_util_source="Regression equation",u_predict_prog,p_u_observe_prog),IF(control_util_source="Regression equation",u_trt3_predict_prog,u_trt3_observe_prog))),p_u_alt_postprog)*IF(AND(Mod_2=0,Mod_3=0),1,0)+u_observe_prog_sev*IF(OR(Mod_2=1,Mod_3=1),1,0)
R4) Utility estimates: removal of AE decrements	Mod_4	Controls	I93	=IF(Mod_4=0,"Yes","No") Amend named range **control_inc_AE_dec** to point to **Controls!$I$93**

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R5) Remove extra oral chemotherapy costs	Mod_5	Costs	C177	=(IF(ctrl_oraladmincost="Admin cost only",p_admincost_oral_NHSref,IF(ctrl_oraladmincost="Admin cost plus dispensing cost",p_admincost_oral_NHSref+p_admincost_oral_disp,"Error")))*IF(Mod_5=0,1,0)
R5) Remove extra oral chemotherapy costs	Mod_5	Costs	C178	=(IF(ctrl_oraladmincost="Admin cost only",p_admincost_oral_NHSref,IF(ctrl_oraladmincost="Admin cost plus dispensing cost",p_admincost_oral_NHSref+p_admincost_oral_disp,"Error")))*IF(Mod_5=0,1,0)

For scenarios:

1. Populate the following named switch values in the 'Results' sheet

Name	Switch	Details
Mod_6	0	S1) Changes to post-progression pathway
Mod_7	0	S2) Changes to resource use frequencies
Mod_8	0	S3) Assuming an OS gain for treatment with BV equal to company base case (1.2 years)

N.B. Revisions R1, R3, R4 and R5 (Mod_1, Mod_3, Mod_4 and Mod_5) should also be switched on when running each of the ERG's scenarios

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
S1) Changes to post-progression pathway	Mod_6	Results	N25	Hard code value for duration of end-stage care phase 0.5 Assign name to value **ERG_endstage_duration**
S1) Changes to post-progression pathway	Mod_6	Results	N26	Hard code value for duration of BSC phase 1 Assign name to value **ERG_BSC_duration**
S1) Changes to post-progression pathway	Mod_6	Results	N27	Calculate duration of active subsequent therapy phase for BV =p_mean_PPS_nonSCT_BV-ERG_endstage_duration-ERG_BSC_duration Assign name to cell **ERG_ActiveDuration_BV**
S1) Changes to post-progression pathway	Mod_6	Results	N28	Calculate duration of active subsequent therapy phase for PC =p_mean_PPS_nonSCT_PC-ERG_endstage_duration-ERG_BSC_duration Assign name to cell **ERG_ActiveDuration_PC**
S1) Changes to post-progression pathway	Mod_6	Results	N29	Assign utility value for BSC =AVERAGE(u_prog,u_endstage) Assign name to cell **ERG_utility_BSC**
S1) Changes to post-progression pathway	Mod_6	Results	N30	=p_active_nonSCT_PPS_drugcosts/SUM('Subsequent therapy'!F79:F82) Assign name to cell **ERG_ActiveDrugCost_weekly**
S1) Changes to post-progression pathway	Mod_6	Results	N31	=p_active_nonSCT_PPS_admincosts/SUM('Subsequent therapy'!F88:F91) Assign name to cell **ERG_ActiveAdminCost_weekly**
S1) Changes to post-progression pathway	Mod_6	Results	N32	=ERG_ActiveDrugCost_weekly*ERG_ActiveDuration_BV*52 Assign name to cell **ERG_ActiveDrugCost_total_BV**
S1) Changes to post-progression pathway	Mod_6	Results	N33	=ERG_ActiveAdminCost_weekly*ERG_ActiveDuration_BV*52 Assign name to cell **ERG_ActiveAdminCost_total_BV**

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
S1) Changes to post-progression pathway	Mod_6	Results	N32	=ERG_ActiveDrugCost_weekly*ERG_ActiveDuration_PC*52 Assign name to cell **ERG_ActiveDrugCost_total_PC**
S1) Changes to post-progression pathway	Mod_6	Results	N33	=ERG_ActiveAdminCost_weekly*ERG_ActiveDuration_BV*52 Assign name to cell **ERG_ActiveAdminCost_total_PC**
S1) Changes to post-progression pathway	Mod_6	Post-progression	AC24:AC2373	=($F24*p_active_nonSCT_PPS_drugcosts)*IF(Mod_6=0,1,0)+($F24*ERG_ActiveDrugCost_total_BV)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	AD24:AD2373	=($F24*p_active_nonSCT_PPS_admincosts)*IF(Mod_6=0,1,0)+($F24*ERG_ActiveAdminCost_total_BV)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	AE24:AE2373	=($F24*p_active_nonSCT_PPS_duration*p_active_PPS_MRU)*IF(Mod_6=0,1,0)+($F24*ERG_ActiveDuration_BV*p_active_PPS_MRU)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	AH24:AH2373	=($F24*p_mean_PPS_nonSCT_BV_endstage*p_endstage_PPS_MRU)*IF(Mod_6=0,1,0)+($F24*ERG_endstage_duration*p_endstage_PPS_MRU)*IF(Mod_6=1,1,0)+($F24*ERG_BSC_duration*p_active_PPS_MRU)*IF(Mod_6=1,1,0)+($F24*ERG_BSC_duration*p_active_PPS_indirect)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	AQ24:AQ2373	=($F24*(p_active_nonSCT_PPS_duration)*p_active_PPS_utility)*IF(Mod_6=0,1,0)+($F24*(ERG_ActiveDuration_BV)*p_active_PPS_utility)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	AR24:AR2373	=($F24*p_mean_PPS_nonSCT_BV_endstage*p_endstage_PPS_utility)*IF(Mod_6=0,1,0)+($F24*ERG_endstage_duration*p_endstage_PPS_utility)*IF(Mod_6=1,1,0)+($F24*ERG_BSC_duration*ERG_utility_BSC)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	AU24:AU2373	=($F24*p_active_nonSCT_PPS_duration)*IF(Mod_6=0,1,0)+($F24*ERG_ActiveDuration_BV)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	AV24:AV2373	=($F24*p_mean_PPS_nonSCT_BV_endstage)*IF(Mod_6=0,1,0)+($F24*ERG_endstage_duration)*IF(Mod_6=1,1,0)+($F24*ERG_BSC_duration)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	CP24:CP2373	=($BV24*p_active_nonSCT_PPS_drugcosts)*IF(Mod_6=0,1,0)+($BV24*ERG_ActiveDrugCost_total_PC)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	CQ24:CQ2373	=($BV24*p_active_nonSCT_PPS_admincosts)*IF(Mod_6=0,1,0)+($BV24*ERG_ActiveAdminCost_total_PC)*IF(Mod_6=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
S1) Changes to post-progression pathway	Mod_6	Post-progression	CR24:CR2373	=($BV24*p_active_nonSCT_PPS_duration*p_active_PPS_MRU)*IF(Mod_6=0,1,0)+($BV24*ERG_ActiveDuration_PC*p_active_PPS_MRU)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	CU24:CU2373	=($BV24*p_mean_PPS_nonSCT_PC_endstage*p_endstage_PPS_MRU)*IF(Mod_6=0,1,0)+($BV24*ERG_endstage_duration*p_endstage_PPS_MRU)*IF(Mod_6=1,1,0)+($BV24*ERG_BSC_duration*p_active_PPS_MRU)*IF(Mod_6=1,1,0)+($BV24*ERG_BSC_duration*p_active_PPS_indirect)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	DD24:DD2373	=($BV24*(p_active_nonSCT_PPS_duration)*p_active_PPS_utility)*IF(Mod_6=0,1,0)+($BV24*(ERG_ActiveDuration_PC)*p_active_PPS_utility)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	DE24:DE2373	=($BV24*p_mean_PPS_nonSCT_PC_endstage*p_endstage_PPS_utility)*IF(Mod_6=0,1,0)+($BV24*ERG_endstage_duration*p_endstage_PPS_utility)*IF(Mod_6=1,1,0)+($BV24*ERG_BSC_duration*ERG_utility_BSC)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	DH24:DH2373	=($BV24*p_active_nonSCT_PPS_duration)*IF(Mod_6=0,1,0)+($BV24*ERG_ActiveDuration_PC)*IF(Mod_6=1,1,0)
S1) Changes to post-progression pathway	Mod_6	Post-progression	DI24:DI2373	=($BV24*p_mean_PPS_nonSCT_PC_endstage)*IF(Mod_6=0,1,0)+($BV24*ERG_endstage_duration)*IF(Mod_6=1,1,0)+($BV24*ERG_BSC_duration)*IF(Mod_6=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	D115	=(0.5+(0.5*C136*D136))*IF(Mod_7=0,1,0)+0.25*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	C136	=60%*IF(Mod_7=0,1,0)+37.5%*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	D165	=(0.5+(0.5*C186*D186))*IF(Mod_7=0,1,0)+0.25*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	C186	=60%*IF(Mod_7=0,1,0)+37.5%*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	D210	=(1/2+N("Routine visit every 2 weeks") +(C239*D239)+N("All full body coverage dressings by CNS"))*IF(Mod_7=0,1,0)+0.25*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	C211	=100%*IF(Mod_7=0,1,0)+0.5*IF(Mod_7=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
S2) Changes to resource use frequencies	Mod_7	Resource use	C214	=50%*IF(Mod_7=0,1,0)+0.05*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	D218	=(0.5*C245*D245+N("50% localised dressing applied by district nurse"))*IF(Mod_7=0,1,0)+0.25*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	D219	=1*IF(Mod_7=0,1,0)+0.25*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	D220	=2*IF(Mod_7=0,1,0)+0.25*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	C239	=25%*IF(Mod_7=0,1,0)+0.125*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	C240	=25%*IF(Mod_7=0,1,0)+0.125*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	C241	=25%*IF(Mod_7=0,1,0)+0.125*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	C242	=25%*IF(Mod_7=0,1,0)+0.125*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	C243	=25%*IF(Mod_7=0,1,0)+0.125*IF(Mod_7=1,1,0)
S2) Changes to resource use frequencies	Mod_7	Resource use	C245	=75%*IF(Mod_7=0,1,0)+0.375*IF(Mod_7=1,1,0)
S3) Assuming an OS gain for treatment with BV	Mod_8	Results	N40	Hard code value for duration of BSC phase 0.779 Assign name to value **ERG_OS_AF**

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
S3) Assuming an OS gain for treatment with BV	Mod_8	OS	I47:I2396	=(IF(control_BV_OS_source="ALCANZA PC arm",J47,IF(ctrl_BV_OS_noninferiority="No",IF(ctrl_population="Severe",AQ47,BJ47),IF(K47<=J47,I46*(J47/J46),IF(ctrl_population="Severe",AQ47,BJ47)))))*IF(Mod_8=0,1,0)+1/(1+((((H47*ERG_OS_AF)*EXP(-1*$BE$33))^(1/(EXP(-1*$BE$32))))))* IF(Mod_8=1,1,0)