HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Appraisal Consultation Document

The final scope and final matrix are available on the NICE website

The following documents are made available to consultees and commentators:

1. **Pre meeting briefing**

2. **Company submission** from Takeda Ltd

3. **New evidence addendum** from Takeda Ltd

4. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification
   - Company additional response to clarification question A12
   - Company additional response to clarification question B1

5. **Patient group, professional group and NHS organisation submission** from:
   - Lymphoma Action
   - Royal College of Pathologists-British Society of Haematology (joint submission)

6. **Expert personal perspectives** from:
   - Dr Julia Scarisbrick, Consultant Dermatologist – clinical expert, nominated by Royal College of Pathologists-British Society of Haematology
   - Professor Sean Whittaker – clinical expert, nominated by Takeda Ltd

7. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group

8. **Evidence Review Group report – factual accuracy check**

9. **Evidence Review Group report – erratum**

10. **Evidence Review Group report – addendum**

11. **Key issues for patient and clinical experts prepared by NICE**
    - Response from Teresa Kelly, patient expert nominated by Lymphoma Action

NICE National Institute for Health and Care Excellence

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Abbreviations (1)

Abbreviation	In full
AE	Adverse effect
AlloSCT	Allogenic stem cell transplantation
BEX	Bexarotene
BSA	Body surface area
BV	Brentuximab vedotin
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence intervals
CR	Complete remission/response
CTCL	Cutaneous T-cell lymphoma
DFS	Disease free survival
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EQ-5D-3L	European Quality of Life 5-Dimension 3 Level Version
ERG	Evidence review group
FACT-G	Functional Assessment of Cancer Therapy – General
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
INF	Interferon

Abbreviations (2)

Abbreviation	In full
INV	Investigator
ITT	Intention-to-treat
KM	Kaplan-Meier
LyP	Lymphomatoid papulosis
MAIC	Matching-adjusted indirect comparison
MF	Mycosis fungoides
MXT	Methotrexate
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PC	Physician's choice
pcALCL	Primary cutaneous anaplastic large cell lymphoma
PD	Progressed disease
PFS	Progression-free survival
PPS	Post-progression survival
PR	Partial response
QALY	Quality-adjusted life year
SD	Stable disease
SS	Sézary syndrome
ToT	Time on treatment
TSEB	Total skin electron beam (radiation therapy)

Key issues – clinical effectiveness

- Is brentuximab vedotin (BV) expected to have an effect on overall survival?
- What proportion of patients would receive subsequent allogeneic stem cell transplants (alloSCT) in clinical practice?
- How will BV affect the current treatment pathway?
- Is EQ-5D a suitable health related quality of life measure for cutaneous T-cell lymphoma (CTCL)?
- Is the supportive evidence suitable for subgroups not included in the ALCANZA trial?

Key issues – cost effectiveness

- Overall survival:
  - Is it appropriate to use a single survival curve to model overall survival in the BV and Physician's choice (PC) treatment arms?
  - Should the risk of death after progression be higher for BV than with PC?
- Should alloSCT be included in the base case model?
- Post progression state:
  - How long should patients spend in end stage care?
  - How should resource use be calculated for end-stage care?
- What utility values should be used in the model?
- What is the most plausible ICER?

Clinical implications on cost effectiveness

Key issues in the clinical effectiveness	Key issues in the cost-effectiveness
Is BV expected to have an effect on overall survival (OS)?	Is it appropriate to assume no OS gain and use a single survival curve to model OS for BV and PC?
	Should the risk of death after progression be higher for BV than with PC?
What proportion of patients would receive alloSCTs in clinical practice?	Should alloSCT be included in the base case model?
How will BV affect the current treatment pathway?	How long do people with advanced CTCL spend in end stage care? Would time on subsequent active treatment change based on treatment with BV or PC?
Is EQ-5D a suitable health related quality of life measure for CTCL?	What utility values should be used in the model?

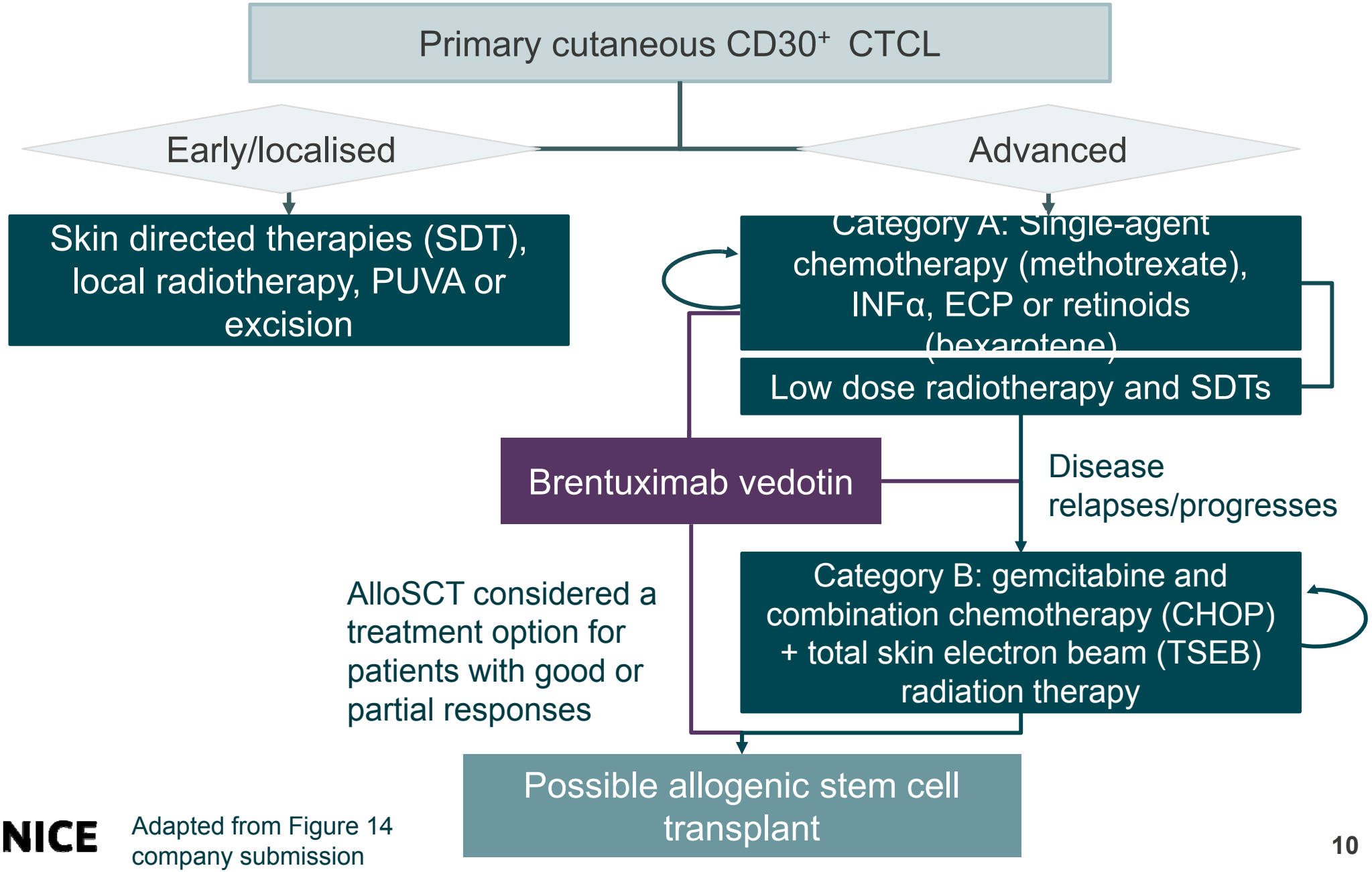
Disease background

- CTCL is a rare type of non-Hodgkin lymphoma that affects the skin
- CTCL patients have chronic disfiguring skin lesions and systemic symptoms, such as chronic pain and unrelenting itching, that can severely limit daily functioning
- CTCL has an annual incidence of 0.75 per 100,000 people
- Between 2009 and 2013, 1,659 people were newly diagnosed with CTCL
- The majority of people diagnosed with CTCL are men (ratio of 1.6:1) and are over the age of 50 but it can also affect young people
- Within the group of CTCL distinct subtypes can be distinguished:
  - primary cutaneous anaplastic large cell lymphoma [pcALCL]
  - mycosis fungoides [MF] (most common form)
  - Lyphomatoid papulosis [LyP]
  - Sézary syndrome [SS]
- Approximately 30% of patients present with advanced-stage CTCL

Treatment pathway

- CTCLs are usually incurable. Early stage/localised disease develops slowly, but approximately 25% of patients will progress to advanced stage disease
- Advanced stage disease is associated with a poor prognosis, negative impact on daily functioning and health related quality of life (HRQoL) and decreased survival compared with early disease
- Current strategies and goals of CTCL treatments include alleviation of symptoms, control of local disease, and improvement in quality of life
- Patients with CTCL receive treatment according to the type of CTCL and the stage of disease. Treatments either target the skin (skin-directed) or the entire body (systemic), there is no standard initial therapy and treatment options are diverse:
  - Early stage (IA-IIA) is managed with topical steroids, psoralens plus ultraviolet A (PUVA), total skin electron beam (TSEB) therapy and topical cytostatic agents
  - Advanced stage CTCL is treated by a multidisciplinary team of dermatologists, haematologists/ oncologists. First line systemic treatment options are oral methotrexate (MXT) and retinoids including bexarotene (BEX)
- AlloSCT have also been used for advanced disease if partial response is achieved with systemic therapy

Company's position in the treatment pathway



Adapted from Figure 14 company submission

Comments from patient and professional groups

- Symptoms of CTCL include inflammation, and painful, itchy, unsightly lesions;
  - Itching all the time can have a significant impact on quality of life, making it difficult to sleep, and reducing quality of life.
  - If inflammation is widespread, some people find it difficult to control their body temperature, and develop fevers, chills and shakes, even hypothermia
  - Skin may be painful, particularly if people have tumours or if areas of skin weep or become infected. There is a risk of infections when skin is broken and irritated
- People with CTCL are likely to be very self-conscious about the way their skin looks, which has a significant psychological impact
- Treatments for people with CTCL are decided by specialists on an individual patient basis according to specific patients needs and expertise of the specialist centre
- Current treatments are effective for 9-12 months before loss of response (>50%). Patients may survive several years and treatment options are very limited so patients suffer from painful, itchy, weepy skin lesions
- There is huge unmet need for effective treatments proven to keep CTCL under control for longer so that people with CTCL can have a better quality of life
- A number of patients have been treated with BV outside clinical trials using the compassionate use programme

Brentuximab vedotin

Mechanism of action	Antibody–drug conjugate comprising an anti-CD30 monoclonal antibody attached by an enzyme-cleavable linker to a potent chemotherapeutic agent, monomethyl auristatin E. The antibody–drug conjugate allows for the selective targeting of CD30-expressing cancer cells
Marketing authorisation	The European Commission granted an extension of the marketing authorisation for brentuximab vedotin on 15 December 2017 to include the treatment of adult patients with CD30-positive cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy
Administration and dosage	• The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks • Patients with CTCL should have up to up to 16 cycles
List price	• The NHS list price of brentuximab vedotin is £2,500 per 50mg vial (ex VAT) • Based on mean cycles of 12 for the average duration of therapy in ALCANZA, the mean cost per course for an average patient is estimated (including PAS) at approximately [redacted]

Decision problem (1)

Optimised

	NICE scope	Company
Population	People with relapsed or refractory CD30-positive CTCL following directed skin therapies and/or at least one systemic therapy	People with relapsed or refractory CD30-positive **advanced** cutaneous T-cell lymphoma (i.e mycosis fungoides [MF] stage IIB and above, primary cutaneous anaplastic large cell lymphoma [pcALCL] and Sézary syndrome [SS]) following directed skin therapies and/or at least one systemic therapy
Intervention	Brentuximab vedotin (BV)	
Comparators	Established clinical management without **BV**	Second-line systemic therapy in CTCL: • Bexarotene (BEX) • Methotrexate (MTX) • IFNα, while not licensed is considered relevant but **no clinical data available**
Outcomes	Overall survival (OS), progression-free survival (PFS) response rate, adverse effects of treatment (AEs), health-related quality of life (HRQoL)	As in the NICE scope with additional outcomes; ORR4 and Skindex-29 which were primary end points in the ALCANZA trial. Overall survival is not considered relevant for this condition

Company's rational for differences between NICE Scope and company submission

	Rationale for differences
Population	The population is narrower than the marketing authorisation because this population is most relevant to NHS clinical practice
Comparators	• Clinical feedback indicated that BV would be used after first-line systemic therapy; therefore the comparators exclude non-systemic therapies • Combination chemotherapy is used later in the treatment pathway so not considered a comparator • No clinical data available for INFα as identified studies did not report relevant outcomes or not generalizable to NHS clinical practice
Special considerations	None specified in the NICE scope • AlloSCT included as per scope and UK clinical pathway • UK clinical advisors stated patients in early stages of the disease will not require systemic therapy and therefore not included in subgroup considerations

Comments on decision problem

Population

ERG:

- The clinical advisor to the ERG supported the company's rationale that the advanced subgroup are the most likely candidates for treatment with BV in UK clinical practice
- The MA does not preclude treatment for patients with early stage disease
- Cost-effectiveness only includes evidence for subgroups MF and pcALCL

Comparator

ERG:

- Category A therapies (including BEX and MTX) are the most appropriate comparators for MF, SS and LyP. However, [redacted]
- [redacted]
- Category A therapies are all considered equally effective
- The lack of data on IFN-α as a comparator is not considered to be a major limitation as all therapies are considered equally effective
- AlloSCT is not considered a comparator as patients would rarely receive an alloSCT immediately after treatment with a Category A therapy

Clinical experts statements:

- Management will be similar in patients with pcALCL, MF and SS
- Low-dose methotrexate, bexarotene and IFN-α are used as 2nd line treatment options in clinical practice in England
- Multi-agent chemotherapy (CHOP) should not be considered a comparator

Company's evidence of clinical effectiveness

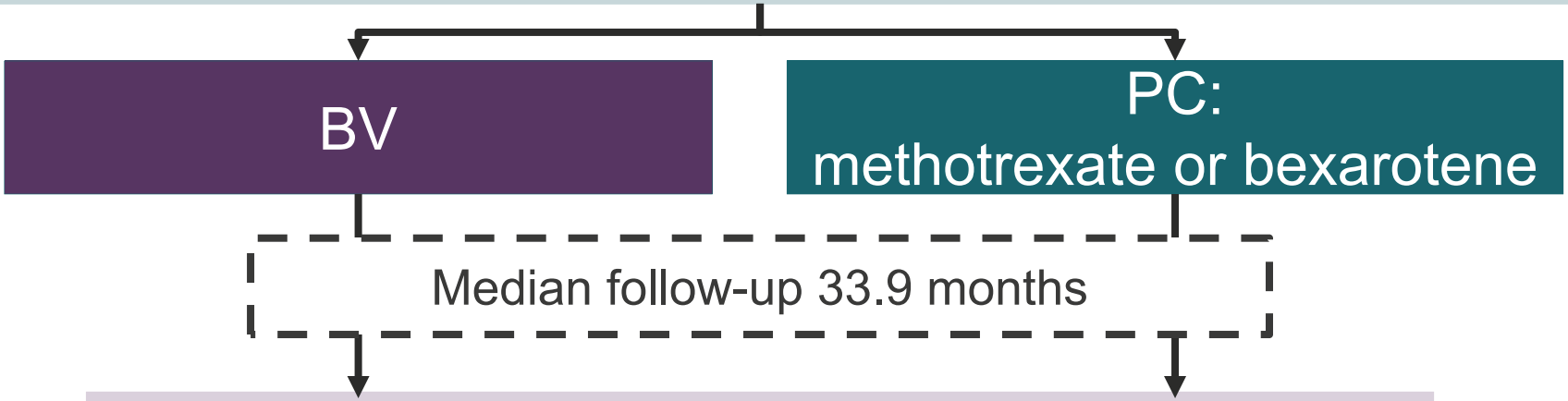
Evidence	Population	Used in clinical effectiveness	Used in cost effectiveness
ALCANZA – multicentre, randomised open-label study of BV vs. PC (MXT or BEX)	Adults with CD30+ CTCL (MF or pcALCL) who received prior radiation therapy or ≥1 prior systemic therapy (pcALCL) or ≥1 prior systemic therapy (MF) (n=128)	Yes	Yes
Kim et al 2015 - multicentre, open-label, single-arm study of BV	MF or SS, stages IB–IVB, with ≥1 systemic therapy failure (n=32)	Yes	No
Duvic et al 2015 – Single centre, open-label, single-arm study of BV	CD30+ LyP in need of systemic therapy, or previously treated pcALCL or MF (n=54)	Yes	No
Abbreviations: LyP, lymphomatoid papulosis; PC, Physician's choice			

ALCANZA trial - summary

128 adults (aged ≥18 years) who have ECOG performance status 0–2 with:

- CD30+ MF who received ≥1 previous systemic therapy, or
- CD30+ pcALCL who received ≥1 previous systemic therapy or radiotherapy
- No patients with SS or LyP included

34 centres across 11 countries. UK: 4 sites; 24 patients total



Outcomes:

- Objective response rate (ORR4) – primary
- Progression-free survival (PFS)
- Response rate
- Duration of response (DOR)
- Safety (adverse events)
- HRQoL
- Time to next antineoplastic therapy

ALCANZA baseline characteristics

Randomisation: disease diagnosis

Characteristic	Brentuximab vedotin (n=64)	Physician's choice: methotrexate or bexarotene (n=64)
Median age (IQR), years	62 (51-70)	59 (48-67)
Male, n (%)	33 (52)	37 (58)
White race, n (%)	56 (88)	53 (83)
ECOG performance group, n (%)		
PS = 0	43 (67)	46 (72)
PS = 1	18 (28)	16 (25)
PS = 2	3 (5)	2 (3)
CD30 expression, %, median (range)	32.5 (12.5–67.5)	31.3 (12.0–47.5)
Time since diagnosis, mo, median (range)	42.2 (12.8–87.4)	37.0 (12.3–102.7)
Time from progression, mo, median (range)	2.4 (1.4–7.9)	1.3 (0.9–3.7)
MF, n (%)	48 (75)	49 (77)
pcALCL, n (%)	16 (25)	15 (23)
Lines of prior therapy, n, median (range)		
Total	4.0 (2.0–7.0)	3.5 (2.0–5.5)
Skin directed	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Systemic	2.0 (1.0–4.0)	2.0 (1.0–3.0)

NICE

ALCANZA baseline characteristics (advanced disease) - not randomised by disease stage

Characteristic	Brentuximab vedotin (n=49)	Physician's choice: methotrexate or bexarotene (n=46)
Median age (range), years	62 (31-82)	54 (25-83)
Male, n (%)	25 (52)	24 (52)
White race, n (%)	44 (90)	31 (76)
ECOG performance group, n (%)		
PS = 0	34 (69)	31 (67)
PS = 1	12 (25)	13 (28)
PS = 2	3 (6)	2 (4)
CD30 expression, %, median (range)	40 (0–100)	33.8 (0–100)
Time since diagnosis, m, median (range)	40.9 (2.6–540.3)	28.0 (3.1–273.2)
Time from progression, m, median (range)	2.4 (0.6–112.2)	1.3 (0–45.7)
MF, n (%)	33 (67)	31 (67)
pcALCL, n (%)	16 (33)	15 (33)
Lines of prior therapy, n, median (range)		
Total	4.0 (0–13)	3.0 (1-13)
Skin directed	1.0 (0–6)	1.0 (0–7)
Systemic	2.0 (0-11)	2.0 (1–8)

ALCANZA results: advanced disease

Primary outcome: Objective response lasting at least 4 Months (ORR4) by IRF

	BV	PC	Difference (95% CI)	p-value
Number (%) achieving ORR4	29 (59.2)	4 (8.7)	50.5 (31.6 to 66.4)	<0.001

- Efficacy favoured BV across all subgroup analyses; including MF or pcALCL diagnosis, or if patients received MTX or BEX for PC
- All results were statistically significant apart from baseline ECOG PS ≥1 and a baseline skin tumour score of 0 which had small numbers of patients

Secondary outcome: Response rates by IRF assessment

Response	BV	PC	p-value
Overall response rate	34 (69.4)	8 (17.4)	<0.001
Complete response	10 (20.4)	1 (2.2)	0.005
Partial response	24 (49.0)	7 (15.2)	Not reported

ALCANZA results: Response rates ITT population

Primary outcome analysis: ORR4, objective response lasting at least 4 months

	BV (n=64)	PC (n=64)	Difference (%) (95% CI)	p-value
ITT per independent review (IRF) at 22.9 months follow-up				
Number (%) achieving ORR4	36 (56.3)	8 (12.5)	43.8 (29.1–58.4)	<0.0001
ITT per investigator (INV) at 22.9 months follow-up				
Number (%) achieving ORR4	38 (59.4)	5 (7.8)	51.6 (34.8–65.8)	<0.001

The results for INV assessment are broadly comparable to those by IRF assessment

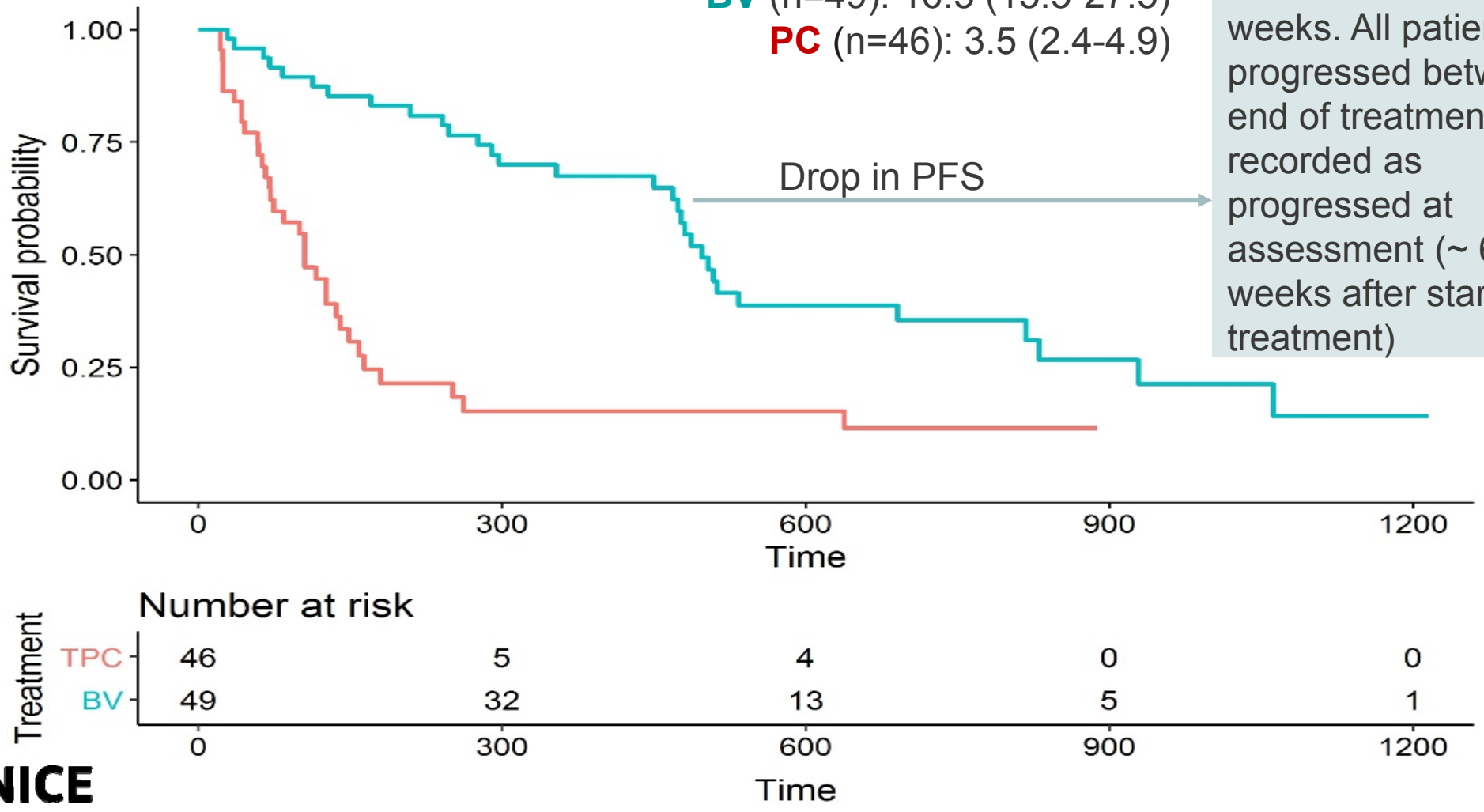
Secondary outcome analysis: ORR, overall response rate and CR, complete response

Stage at baseline, n/N (%)	BV (n=64)		PC (n=64)	
	ORR	CR	ORR	CR
ITT per independent review (IRF) at 22.9 months follow-up				
Number (%) achieving response	43 (67)	10 (16)	13 (20)	1 (2)
ITT per investigator (INV) at 22.9 months follow-up				
Number (%) achieving response	44 (69)	12 (19)	14 (22)	0 (0)

ALCANZA results: Progression-free survival

Secondary outcome: Kaplan-Meier (KM) curve for PFS assessed per IRF for the advanced population at 33.9 months follow-up

Median PFS (95% CI)
BV (n=49): 16.5 (15.5-27.5)
PC (n=46): 3.5 (2.4-4.9)



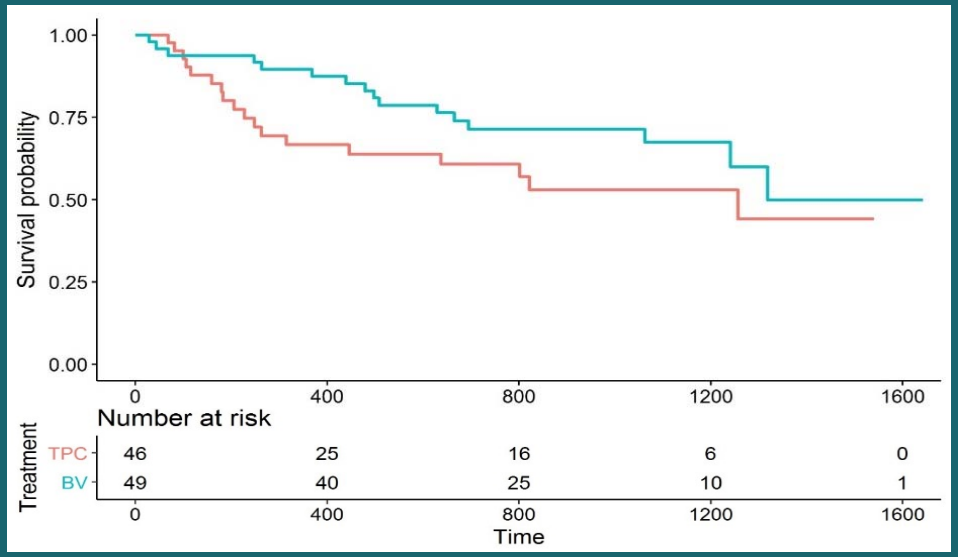
ERG: After 16 cycles of treatment patients not assessed for 12 weeks. All patients who progressed between end of treatment recorded as progressed at assessment (~ 60 weeks after starting treatment)

NICE

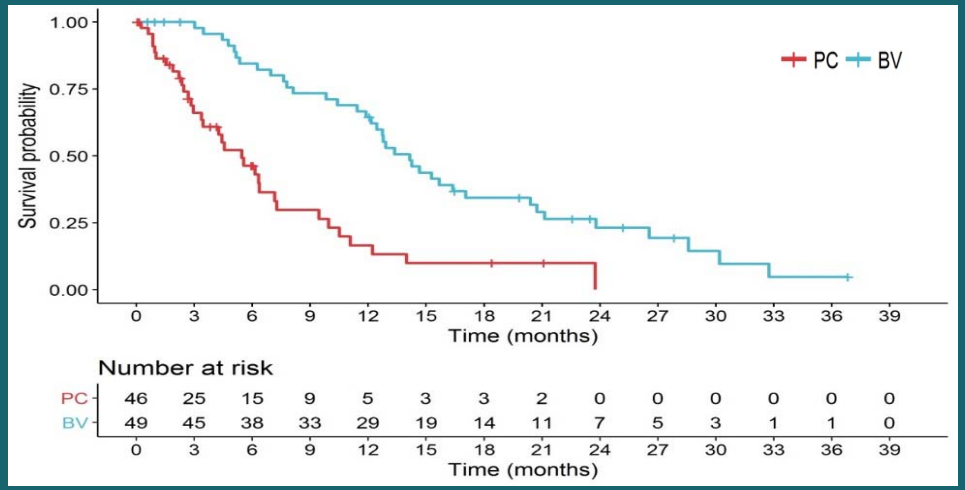
ALCANZA results: other

Outcome (months)	BV	PC	Result (95% CI)
Overall survival	43.6 (41.0–NA)	41.6 (21.1-NA)	Not possible to report
Overall survival was not a pre-specified end point • OS data are extremely immature • Very few events (16 events [33%] in the BV arm and 18 events [39%] in the PC arm) • 46% of patients with advanced-stage disease crossed-over from the PC treatment arm and received BV as a subsequent therapy			
Time to next treatment	14.2 (12.2–20.4)	5.5 (3.4–9.5)	HR 0.310 (0.19-0.51)
• More than 55% of patients in both treatment arms received ≥1 subsequent therapy			

Overall survival (advanced subgroup)

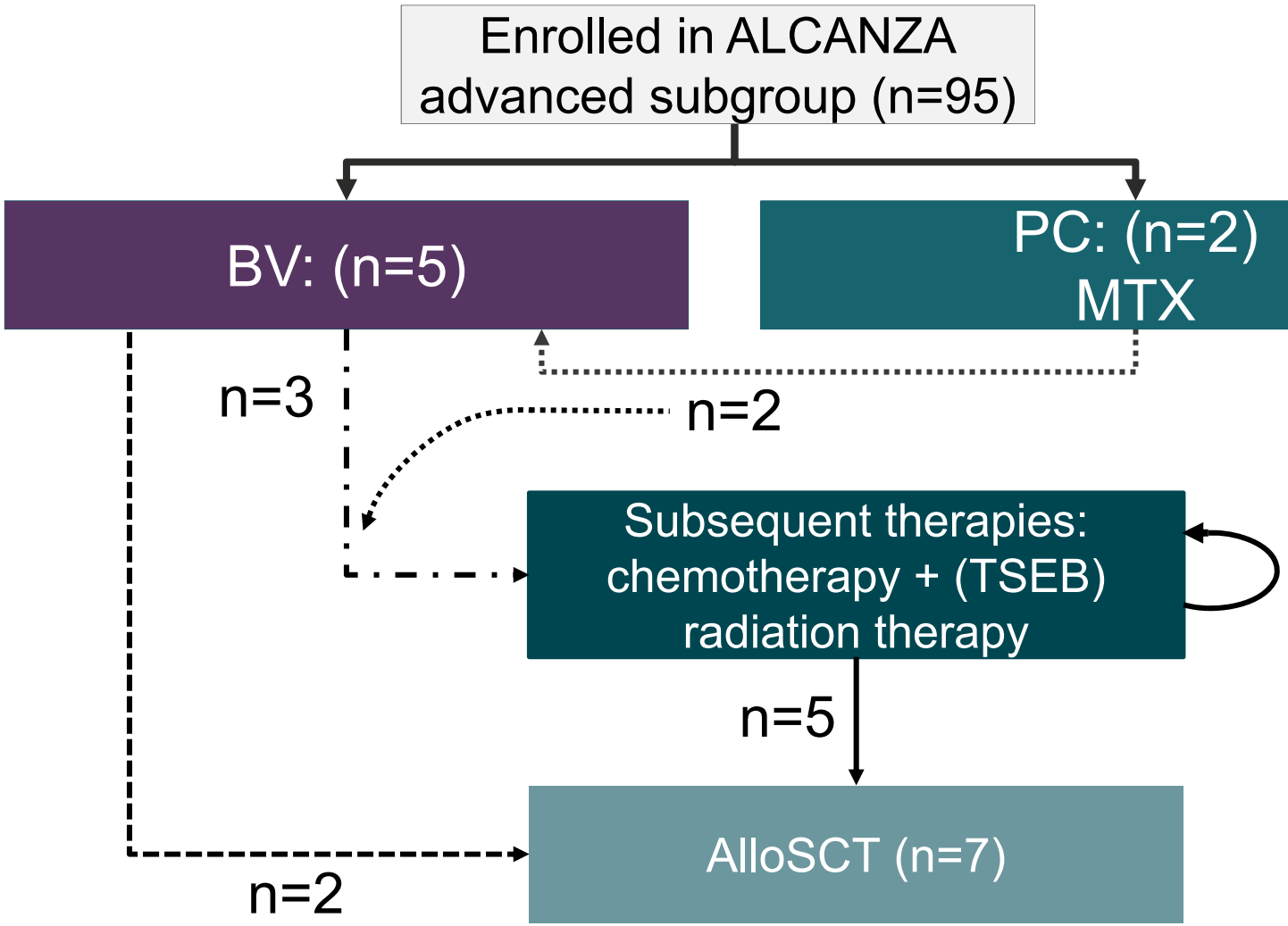


Time to next treatment (advanced subgroup)



NICE

ALCANZA results: Allogeneic stem cell transplants



Of the 7 patients who received alloSCTs 4 were based in the UK.
24 patients enrolled in the ALCANZA trial from the UK.
17% of UK patients received an alloSCT

ALCANZA: health-related quality of life

The European Quality of Life 5-Dimension (**EQ-5D**) is a generic instrument for patient-reported HRQoL. EQ-5D measures:

- mobility
- self-care
- usual activities
- pain/discomfort
- anxiety/depression

Skindex-29 is a 30-item, dermatology-specific, self-reported questionnaire which has been utilised and validated in CTCL. It assesses 3 domains:

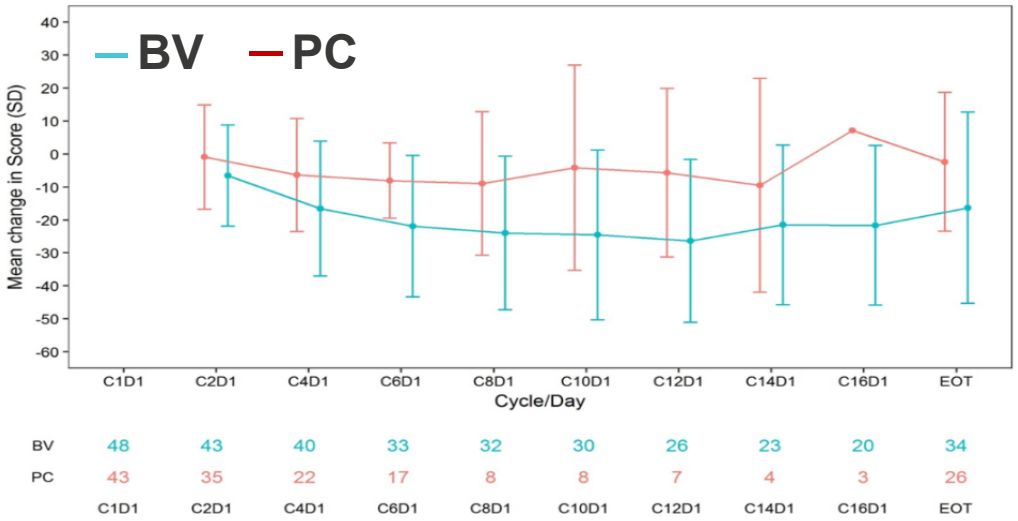
- symptoms
- emotions
- function

EQ-5D and Skindex-29 data was collected during ALCANZA.

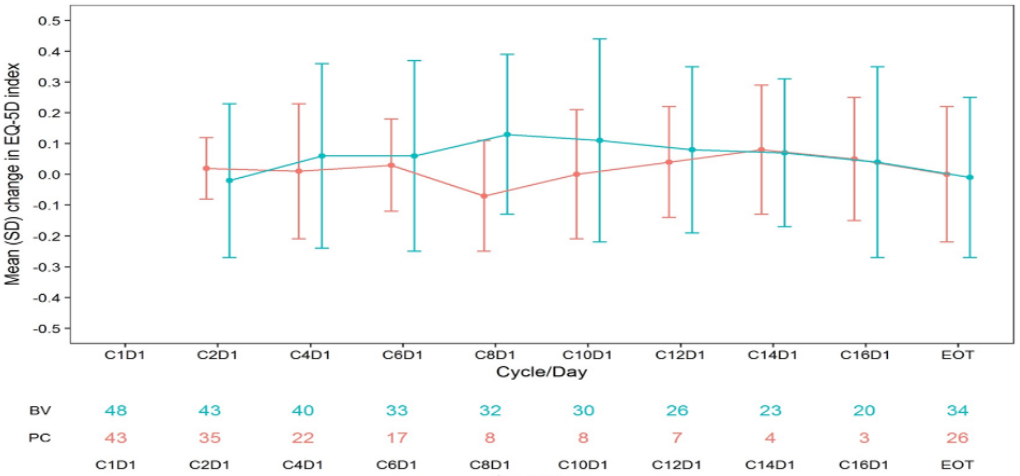
EQ-5D is the preferred measure of HRQoL for the NICE reference case but the company stated that this may not be sensitive enough to demonstrate impact of CTCL symptoms on HRQoL e.g. constant severe, intense itching causing insomnia.

ALCANZA results: health-related quality of life (advanced disease subgroup)

Symptom relief measured by Skindex-29
(change from baseline to end of treatment)
BV had greater symptom reduction



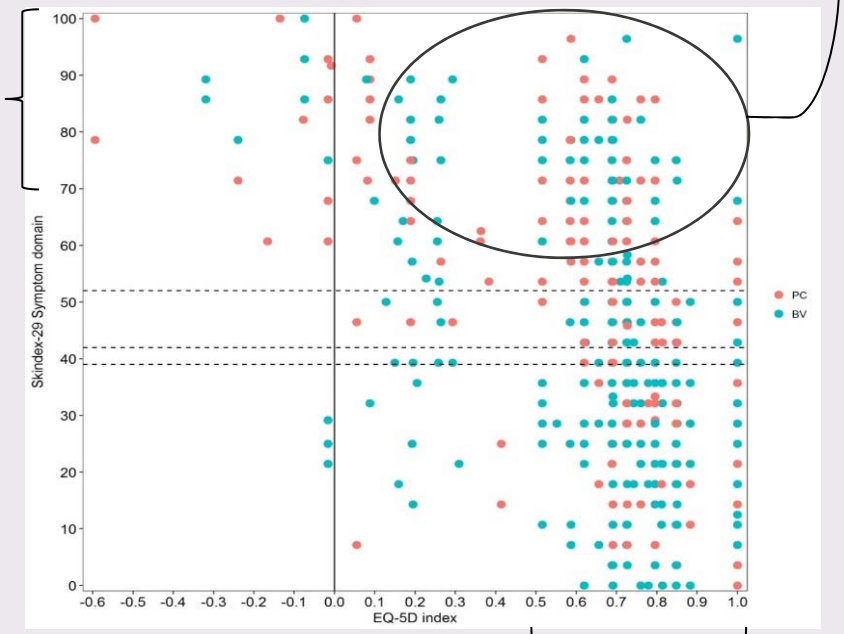
EQ-5D-3L no change in HRQL was found



Comparison of Skindex-29 and EQ-5D scores

High Skindex-29 symptom score (severe negative impact on QoL)

Poor correlation



High EQ-5D (moderate to good QoL)

Supporting evidence: baseline characteristics

Characteristic	ALCANZA trial All patients	ALCANZA trial BV only	Duvic et al 2015	Kim et al 2015	Mathieu et al 2016
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
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
LyP	0	0	10 (19)	0	0
Other	0	0	10 (19)	0	3 (9)
Stage of CTCL					
Early CTCL, n (%)	33 (34)	15 (31)	-	4 (13)	3 (9)
Advanced CTCL, n (%)	95 (74)	49 (75)	-	28 (88)	27 (90)
Not specified, n (%)	0	0	58 (100)	0	2 (6)
Advanced stage pcALCL	31 (33)	16 (33)	—	n/a	n/a

Subgroup not included in ALCANZA

Advanced disease population

NICE

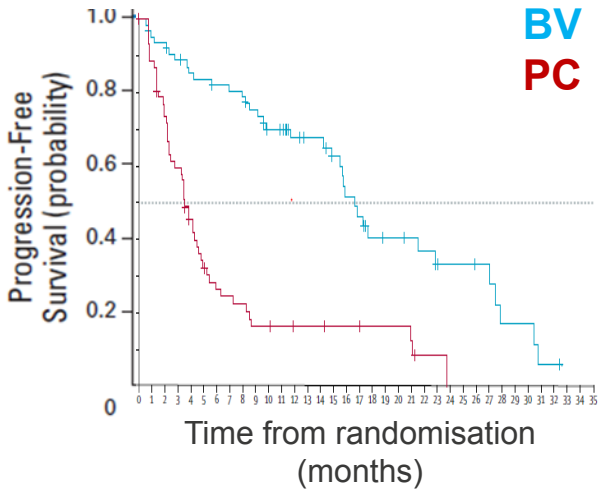
Supporting Results: Kim et al 2015 and Duvic et al 2015

Notable subtypes of CTCL, SS and LyP were not included in the ALACANZA trial but are included in the marketing authorisation. Phase II trials, Kim et al 2015 (SS: n=3) and Duvic et al 2015 (LyP: n=10) show consistent outcomes with ALCANZA trial

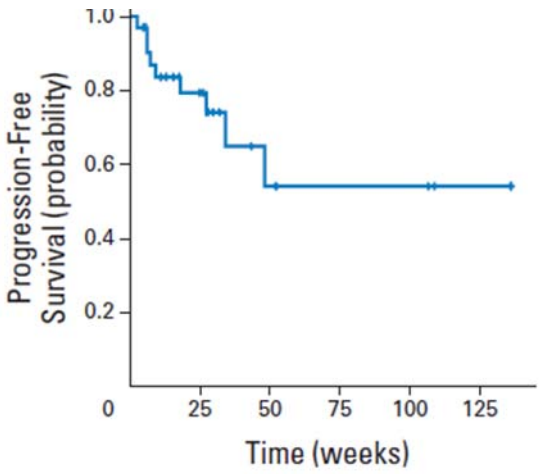
Outcome	*ALCANZA (n=49) IRF assessed*	*Kim et al 2015 (n=30)*		*Duvic et al 2015 (n=48)*		
		MF	SS	MF	LyP	Other
ORR	34 (69.4)*	19 (70.3)	2 (66.7)	15 (54.0)	9 (100)	9 (100)
CR	10 (20.4)	0 (0)	1 (33.3)	2 (7.1)	5 (55.6)	8 (88.9)
PR	24 (49.0)	19 (70.3)	1 (33.3)	13 (46.4)	4 (44.4)	1 (11.1)

Progression-free survival

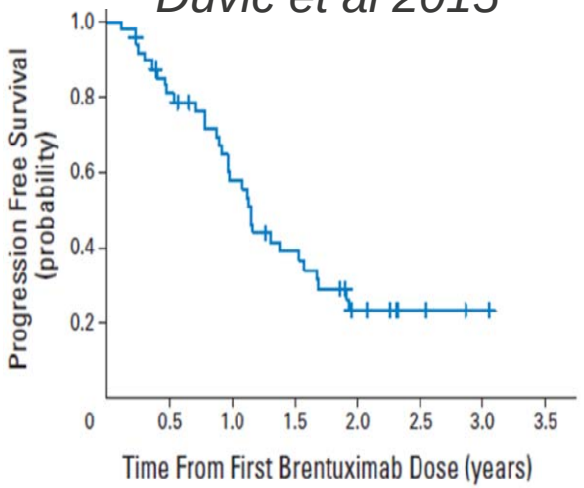
ALCANZA



Kim et al 2015



Duvic et al 2015



ALCANZA results: adverse events

n (%)	BV	PC
	Advanced (n=49)	Advanced (n=44)
Any AE	46 (94)	40 (91)
Any grade ≥3 AE	19 (39)	24 (55)
Drug-related AE	41 (84)	31 (70)
Drug-related ≥3 AE	14 (29)	15 (34)
Serious AE	13 (27)	16 (36)
Drug-related serious AE	7 (14)	3 (7)
AE resulting in study drug discontinuation*	12 (24)	4 (9)
On-treatment deaths†	3 (6)	0

ITT and advanced disease stage populations were very similar

BV was generally well tolerated

Only 1 grade ≥3 event was experienced by >10% of patients

- The most common grade ≥3 TRAE observed with BV treatment was **peripheral neuropathy**. 86% had improvement or resolution
- BEX treatment was associated with **hypertriglyceridaemia** (30%)
- Most common AE with MXT was **pyrexia** (28%)

Evidence from Duvic et al 2015 and Kim et al 2015 reported similar AE profiles to that observed in the main and updated ALCANZA analyses

NICE

ERG's comments: clinical results

Baseline imbalance

- Patients in ALCANZA appear to be representative of clinical practice
- Small imbalance in baseline characteristics, those in BV treatment arm older, more heavily pre-treated, bias likely to favour the PC treatment arm compared to BV treatment arm
- BV subgroup had higher baseline EQ-5D scores

ALCANZA outcomes

- Appropriate outcomes were assessed
- BV results in increased ORR4 and improved PFS
- The results for INV are broadly comparable to those by IRF assessment for all outcomes
- HRs for time to treatment and PFS should be interpreted with caution as proportional hazards assumption does not hold
- Agrees with the company that OS data are immature and confounded by subsequent treatment switching, results should be interpreted with caution. Not possible to obtain robust estimates of effectiveness for OS
- HRQoL data is limited as small number of eligible patients which decreased over time - no firm conclusions can be drawn

Supporting evidence

- Evidence limited to small single-arm studies for SS and LyP
- Supporting data show that findings for ORR and median PFS are generally consistent across studies
- Data limited for rare subtypes, cost effectiveness evidence is only available for patients with MF and pcALCL

NICE

ERG's comments: ALCANZA safety results

ALCANZA Exposure to study treatment

- Patients in the BV arm were on treatment for longer than patients in the PC arm (median time 237 BV and 130 days in PC)
- Duration of BV treatment in the ALCANZA trial longer than for patients in the single-arm observational studies

ALCANZA Safety

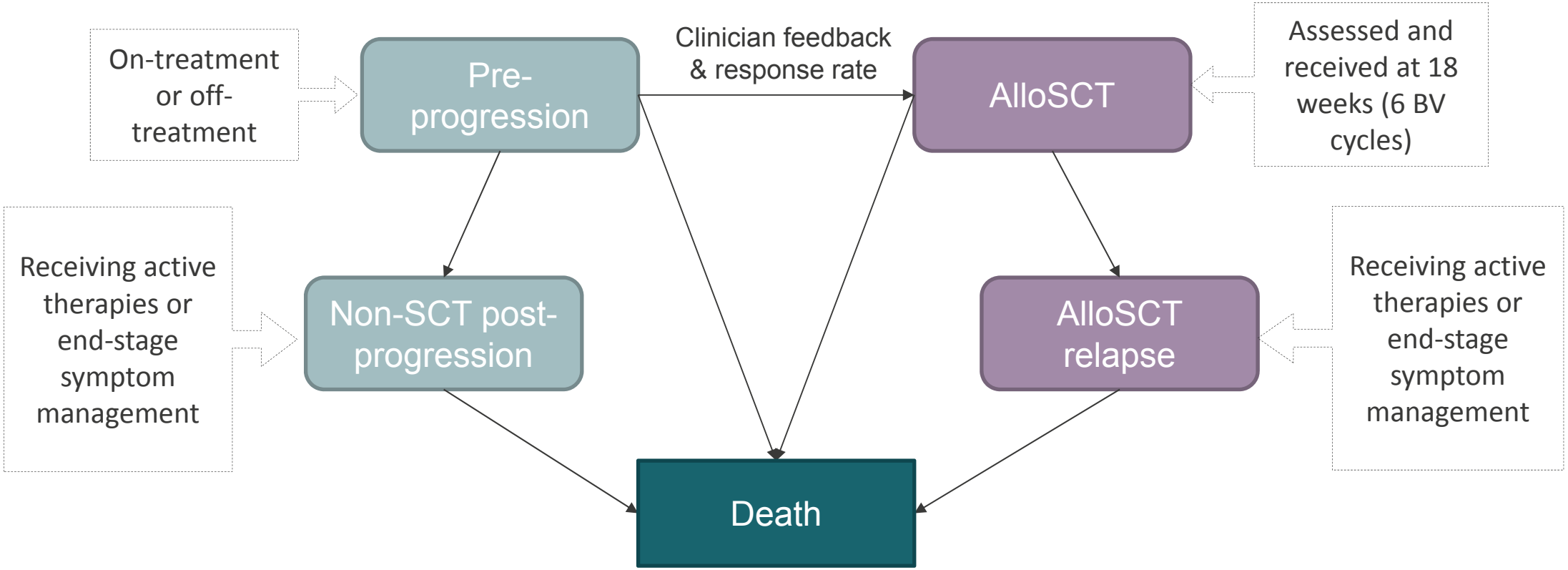
- Safety results for the overall trial population and the advanced stage subgroup are very similar
- ≥90% of patients in both the BV and PC arms of the ALCANZA trial reported at least one any-grade treatment-emergent adverse event (TEAE)

ALCANZA adverse events

- Few grade ≥3 TEAEs were experienced by two or more patients treated with either BV or BEX
- 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%)
- 86% of patients with peripheral neuropathy had either improvement or resolution, but 9 (20%) patients with peripheral neuropathy discontinued treatment with BV
- one treatment-related death - patient did not meet the trial eligibility criteria due to elevated liver function tests

Cost-effectiveness

Company model [1]



- Partitioned survival model - OS and PFS modelled independently
- The analysis uses data from the advanced subgroup from ALCANZA including patients with MF or pcALCL only
- PFS, OS and time-on-treatment (ToT) data for pre-progression/post-progression states from ALCANZA trial
- Disease free survival (DFS) and OS data for post-alloSCT taken from real world data CTCL patients at Hammersmith Hospital, London
- Time horizon: 45 years, Cycle length: 1 week, Discount rate: 3.5%

Company model [2]

Payoff approach

To calculate the costs of subsequent therapy in post-progression, the company used a 'payoff approach'

The payoff approach works by calculating the mean time spent in the post-progression state and dividing it into: (1) active therapy and (2) end-stage management

The mean time spent in post-progression retains the partitioned survival approach. It was calculated by the area between the OS and PFS curves for non-alloSCT outcomes, and area between the alloSCT OS and DFS curves for alloSCT outcomes

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

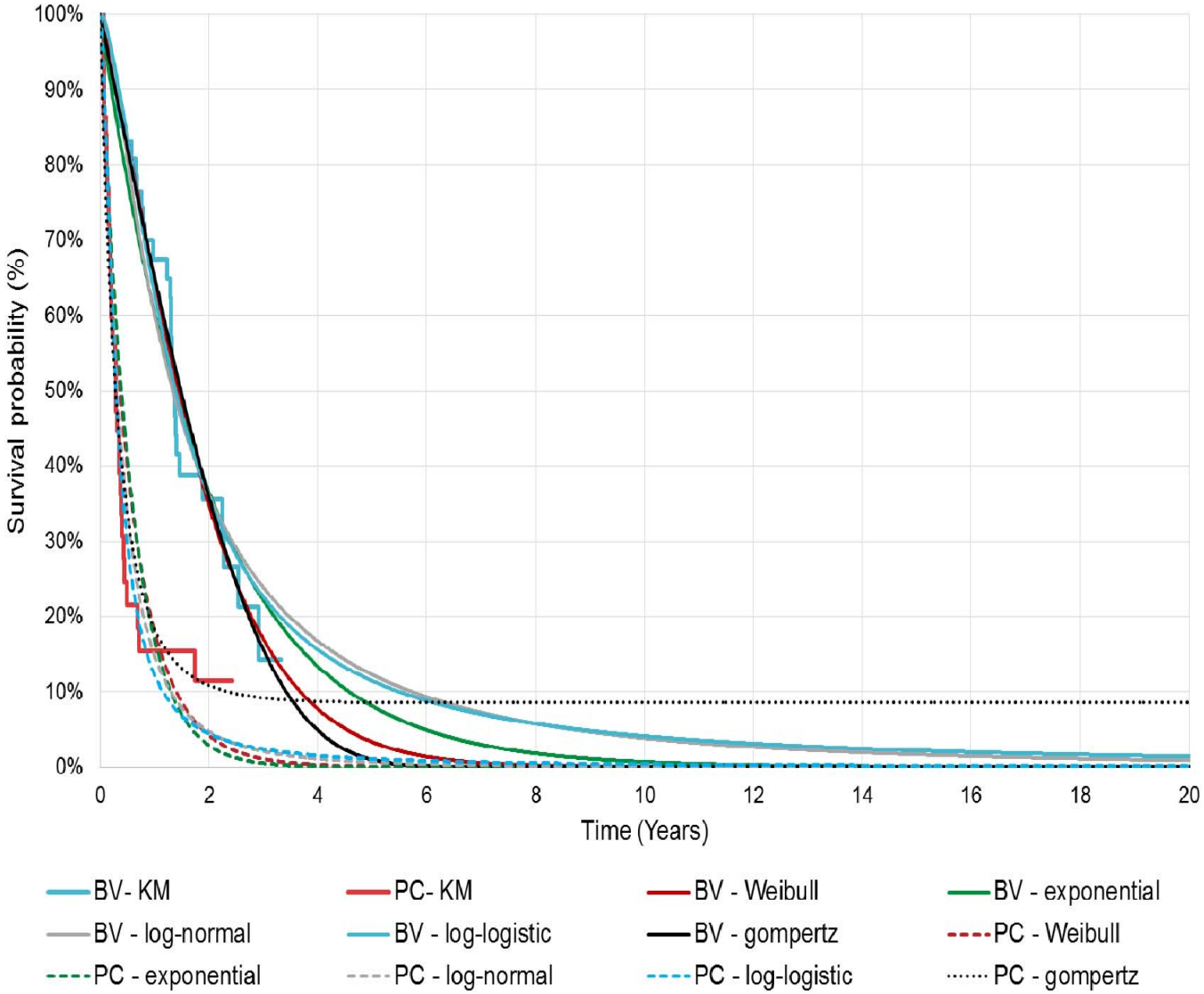
The ERG states that the company applies discounting in the post-progression state as a ratio of the difference in the exponentiated time entering a state and the time leaving versus time spent in the state.
The full impact of discounting is not captured by the payoff approach.
Different distributions with the same mean lifetime will produce different overall costs and QALYs due to discounting. This means the shape of the OS curve has no relevance to model outcomes once patients have progressed beyond estimating mean OS.

Company's extrapolation of survival in the model

Company's choice of parametric curves

Patient group	Survival curve	BV	PC
Outcomes without an alloSCT	PFS	Weibull	Weibull
	OS	Data from PC arm applied to BV patients	Loglogistic
	ToT	Direct ALCANZA data	Direct ALCANZA data
Outcomes for patients who receive alloSCT	Percentage of patients undergoing alloSCT	Clinician feedback – 40% of responders would be eligible for alloSCT	
	DFS	Gompertz	
	OS	Log-normal	

Company's model inputs: extrapolation of progression-free survival (without alloSCT)



Company chose the Weibull parametric curve to model both BV and PC based on clinical expert feedback

Brentuximab vedotin (BV)

	AIC	BIC
Exponential	284	286
Weibull	286	290
Gompertz	286	290
Log-logistic	287	291
Log-normal	287	291

Physician's choice (PC)

	AIC	BIC
Exponential	232	233
Weibull	233	237
Gompertz	229	233
Log-logistic	231	235
Log-normal	229	233

NICE

Company's model inputs: extrapolation of overall survival (without alloSCT) [1]

Clinical data

OS was not a primary or secondary endpoint in ALCANZA. Data are:

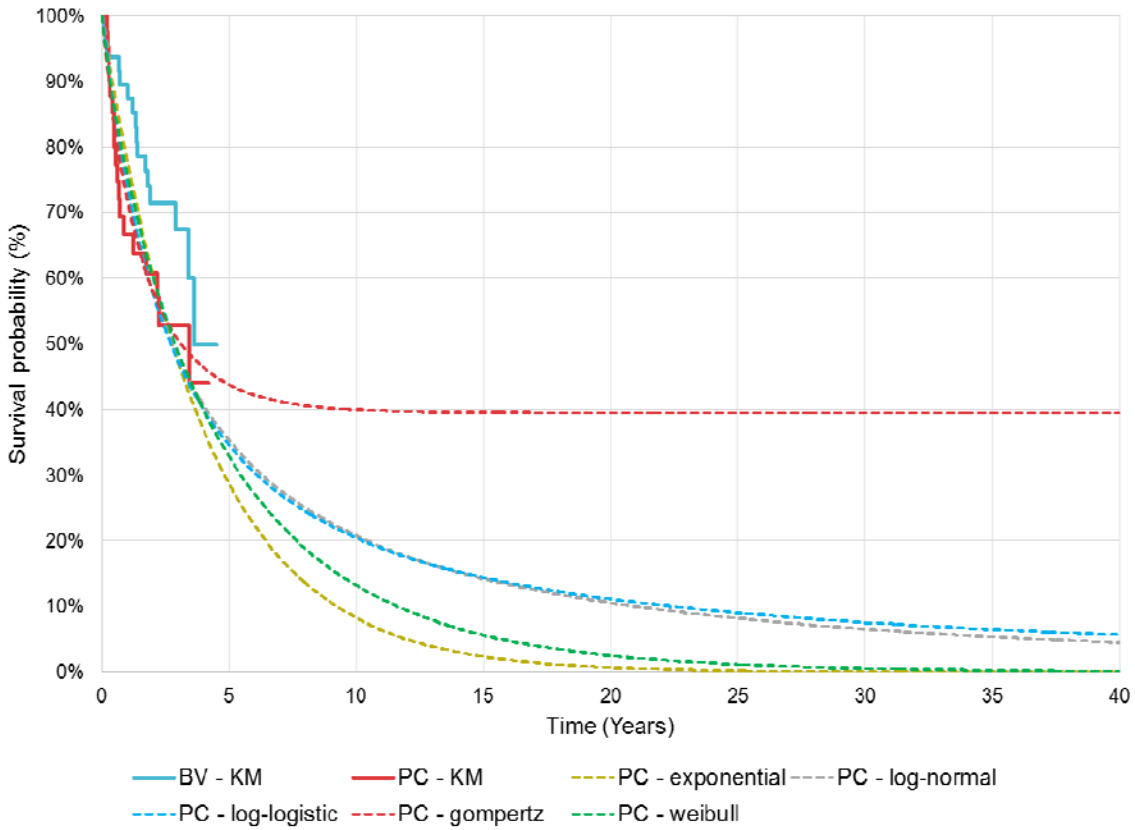
- Immature
- Based on a small sample size with few events
- Confounded because of crossover, 46% of PC patients had BV on progression

- A rank preserving structural failure time (RPSFT) model estimated an increase in OS for BV at earlier time-points and a higher rate of long-term OS for PC - Company stated this was not clinically plausible
  - BV was not expected to worsen survival
  - No increase in OS was expected with BV (except in patients who bridged to alloSCT)

Company assumptions for the cost-effectiveness modelling

- Company assumed OS was equivalent for both BV and PC
- Base-case OS for both arms based on parametric curves fit to the PC OS data
- Scenario analysis considers the use of independent curves
- Company validated model outcomes of OS against Kim et al 2003 and Agar et al 2010 adjusted for proportional severity observed in ALCANZA

Company's model inputs: extrapolation of overall survival (without alloSCT) [2]



Company chose the log-logistic parametric curve to model OS as it was the most likely to represent long-term outcomes

Physician's choice (PC)

	AIC	BIC
Exponential	300	302
Weibull	302	305
Gompertz	300	303
Log-logistic	300	304
Log-normal	298	302

Proportion of patients surviving at various time points by parametric curve

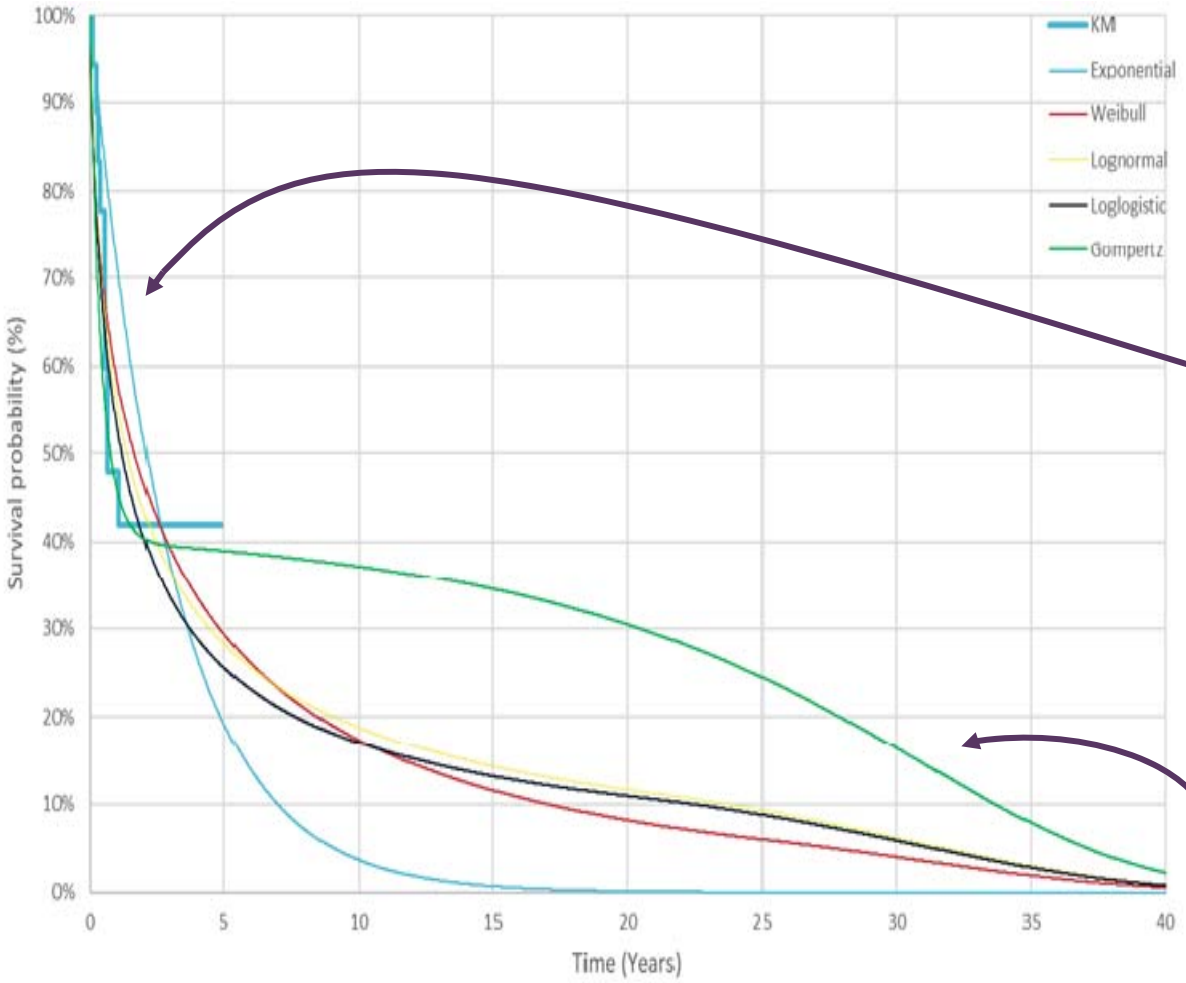
	1-year	3-years	5-years	10-years	20-years
Exponential	77.98%	47.41%	28.83%	8.27%	0.68%
Log-normal	73.95%	47.92%	35.39%	20.79%	10.52%
Log-logistic	73.88%	47.42%	34.64%	20.46%	11.10%

Company's model inputs: percentage of patients undergoing alloSCT

- In clinical practice, eligibility for an alloSCT is defined by underlying fitness (age, comorbidities) and depth of response
- The proportion of patients receiving alloSCT in the model was based on clinician feedback and response rates (ORR)
- It was assumed up to 40% of responders would be eligible to receive an alloSCT because of age, co-morbidities, likelihood of matching to a donor and patient choice
- 27.50% of patients who had BV and 7.11% who had PC would be eligible for alloSCT
- AlloSCT in the model occurred at week 18 (post 6 cycles of BV)

Treatment	Total N	Complete response	Partial response	Stable disease
BV	48	10	23	8
PC	45	1	7	12

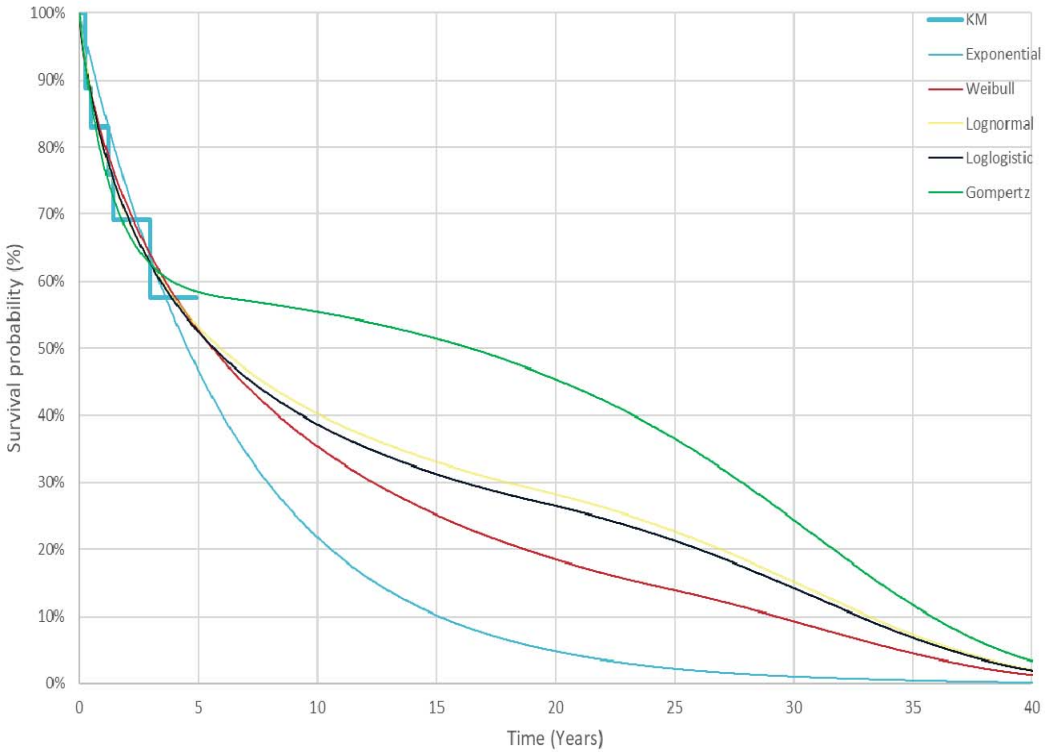
Company's model inputs: extrapolation of disease free survival (DFS) after alloSCT



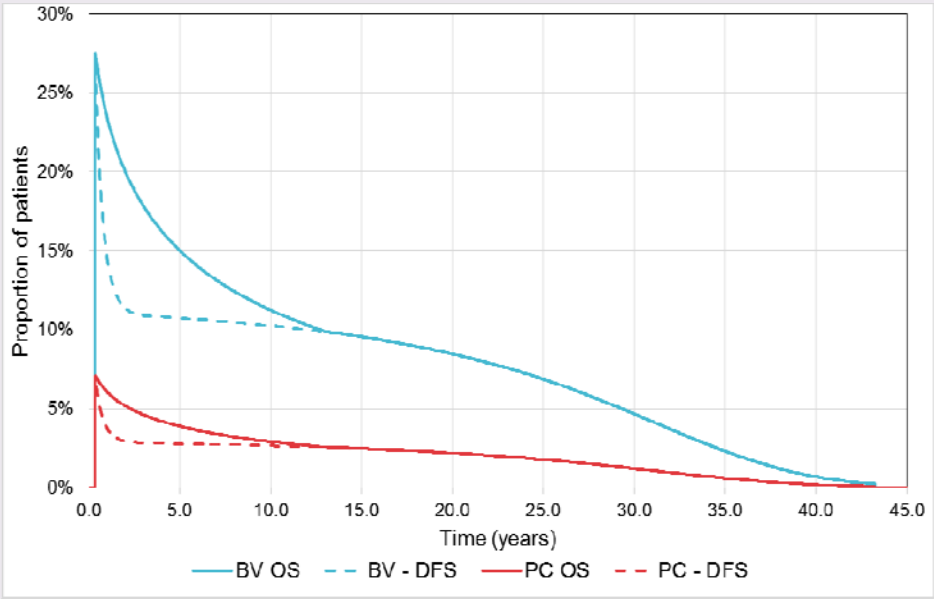
- Patients eligible for alloSCT transition to the 'alloSCT' health state
- In this state transitions are determined by disease free survival and OS parametric curves fitted to real-world outcomes from Hammersmith Hospital (London supra-regional centre)
- Visual inspection of the KM data shows relapsing after alloSCT is likely to occur in the first twelve months following the transplant
- The observed DFS real-world data was digitised and parametric survival models were fitted and assessed
- Company chose the Gompertz curve because it is the only curve that reflects the decreasing probability of relapse reducing over time

Company's model inputs: overall survival following an alloSCT

- Patients relapsing after an alloSCT transition to the 'alloSCT relapse' health state
- Overall survival was extrapolated using the log-normal parametric curve
- Patients who relapse are represented by the difference between the DFS and OS curve
- DFS curve converges with the OS curve at ~12.8 years
- After this time point survival is driven by the maximum of the probability of relapse and the probability of death based on background mortality



Modelling of DFS and OS incorporating background mortality



Company's model inputs: Utility values

- HRQoL data collected using EQ-5D and Skindex-29
- Utility values in model based on EQ-5D as the preferred measure of QoL by NICE. However, EQ-5D is not sensitive to CTCL symptoms and so may not be an accurate reflection of a patient's quality of life
- No mapping mechanism exists for the Skindex-29, but the score was included in a regression model fit to the EQ-5D data from the ALCANZA trial
- The differences in utility values by treatment (both observed and predicted) was driven by the difference in Skindex-29 score
- Adverse event disutility's applied to ALCANZA trial data for grade 3 or 4 AEs experienced by at least 5% of patients

Utility Values

Health state	Treatment	Utility value	Source
PFS	BV	0.68	ALCANZA using regression modelling
	PC	0.64	
Allogeneic SCT	(0-14 days)	0.42	Van Agthoven et al. No CTCL source, well recognised alloSCT HRQL
	(14 days – 3 months)	0.60	
	(>3 months)	0.77	
Progressed disease		0.61	ALCANZA
End Stage Symptom Management care		0.38	Swinburn et al. related lymphoma

NICE

Company's model inputs: Costs and resource use

Cost/Resource	Source
Drug costs	eMIT or MIMS, British National Formulary The dose schedule of BV aligned with ALCANZA and MA BV and PC drugs were costed according to actual use in the trial
Administration costs	NHS National Schedule of Reference Costs 2016-17
Pre-progression health state	Clinical expert opinion and London Cancer Alliance (LCA) skin systemic anti-cancer therapy (SACT) protocols
Post-progression health state (with and without alloSCT)	Resource use: Payoff approach – Active treatment data from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. End stage management informed by clinical expert opinion (interviews) Costs: informed by clinical expert opinion and LCA SACT protocols
Transplant costs and 2yr follow-up	Debals et al 2018 Scenario using National Schedule of Reference Costs 2016-17
Adverse events	Costs: NHS National Schedule of Reference Costs 2016-17
Miscellaneous	Cost of death, generic to oncology disease areas, Round et al 2015

Company's base case assumptions

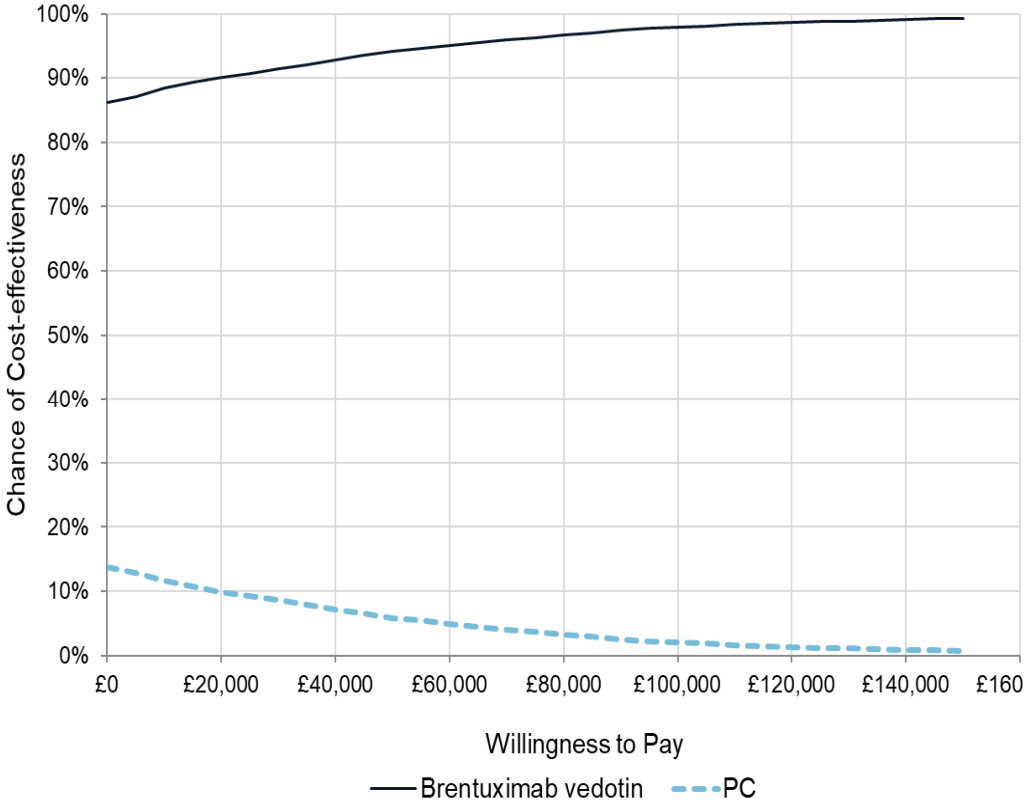
		Assumptions and adjustments
Clinical		• ALCANZA trial comparing BV with PC (including MF and pcALCL only)
Extrapolation	Without alloSCT	• Weibull distribution for BV and PC PFS data • Equivalent survival for BV and PC - loglogistic distribution
	With alloSCT	• Assumed 40% of responders (PR and above) would be eligible for alloSCT • Gompertz distribution for DFS following an alloSCT • log-normal distribution for OS following an alloSCT
HRQoL		• Utility values derived from ALCANZA trial and literature review • Skindex-29 used in regression model fit to the EQ-5D data • Patients receiving end-stage management experience lower utility values derived from Swinburn et al 2015 • Adverse event (AE) disutility from literature applied to ALCANZA trial data for grade 3 or 4 AEs experienced by at least 5% of patients
Costs		• ToT costs from ALCANZA trial and NHS reference costs • Assumed drug wastage • Assumed higher costs for alloSCT compared with NHS Reference costs

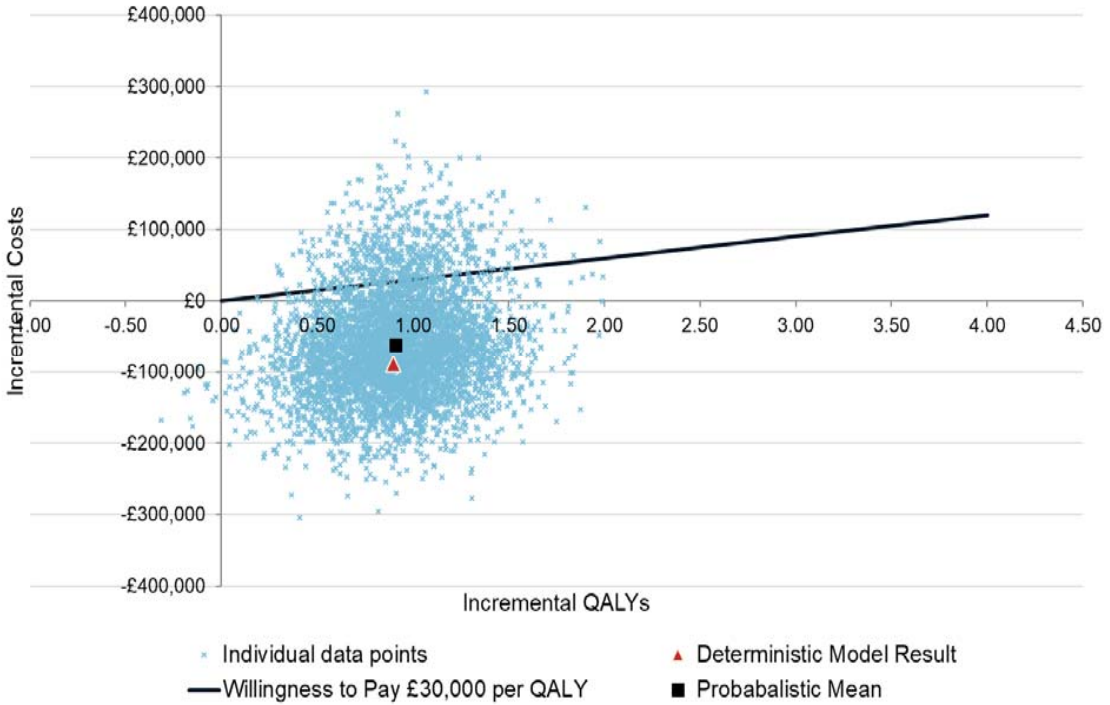
Company's deterministic base case cost-effectiveness results

Company's base-case analysis with commercial arrangement (confidential simple discount)

Treatment	Total costs (£)	Total		Incremental		ICER (£/QALY)	NMB
		LYs	QALYs	costs (£)	QALYs		
PC	[redacted]	7.23	[redacted]	-	-	-	-
BV	[redacted]	8.43	[redacted]	[redacted]	[redacted]	BV dominates	£134,218

Company's probabilistic analyses



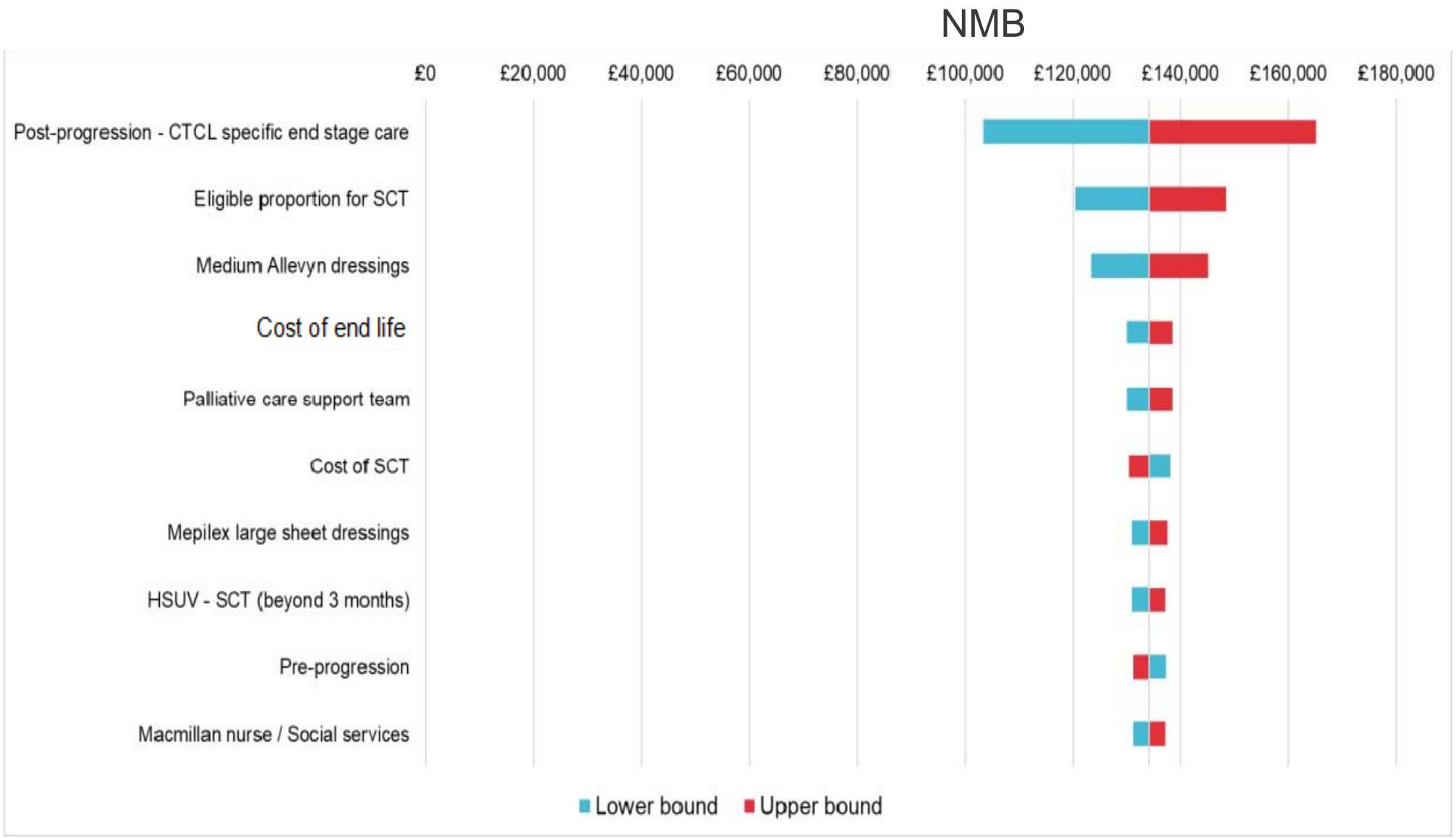


- The probabilistic ICER from 5,000 iterations remains dominant as in the deterministic result
- The Cost-Effectiveness Acceptability Curve (CEAC) – at a willingness to pay threshold of £30,000, BV was cost-effective in 91.38%

The ERG noted that the company's PSA results are substantially different ([redacted]) compared with the deterministic results

NICE

Company's deterministic analyses



Company's scenario analyses

Scenario	ICER (£/QALY)	NMB
Company base case	**BV Dominates**	**£134,218**
Use of KM data directly for PFS	BV Dominates	£127,530
Lognormal fit to PC OS curve (used for both BV and PC)	BV Dominates	£133,464
Percentage of patients eligible for alloSCT reduced to 20%	BV Dominates	£98,563
Cost of alloSCT reduced to £65,154 (NHS Reference costs)	BV Dominates	£140,906
Percentage of patients eligible for alloSCT reduced to 5%	BV Dominates	£58,723
Observed utility value data from ALCANZA	BV Dominates	£134,151
Reduce post progression active therapy cost by 20%	BV Dominates	£131,703
Reduce end-stage care cost by 20%	BV Dominates	£102,842

Summary of ERG's comments on the company's cost-effectiveness modelling

Clinical uncertainty

alloSCT

- The ERG does not consider including alloSCT in the base case to be appropriate as there is limited data to support the company's placement or rate of transplant

Overall survival and post progression state

- Modelling zero OS gain results in lower post-progression survival (PPS) for patients in the BV arm. Patients spend less time in costly end-stage care compared to patients in the PC arm
- Results are sensitive to changes made to the costs and benefits accrued in the PPS state

Model structure

- Probabilistic results are considerably different to the company's deterministic results
- The company's payoff approach simplifies the model but reduces flexibility for sensitivity analyses

Population

- ALCANZA data (advanced subgroup) used for patients who do not receive an alloSCT
- Post alloSCT data from supra-regional centres in London
- The company model does not present any evidence for BV in people with SS or LyP

Health-related quality of life

- Utility values for PFS calculated from ALCANZA EQ-5D data adjusted by the Skindex-29; does not reflect NICE methods guide
- Utilities for end-stage care may not reflect CTCL patients
- Not appropriate to use different PFS utility values for BV and PC

ERG's preferred approach to model cost effectiveness: alloSCT

The ERG considers that there is too much uncertainty in the expected outcomes and duration of those outcomes to include alloSCT in the pathway

- No available evidence of outcomes for alloSCT post treatment with BV
- 7 patients received alloSCTs in ALCANZA, (17%) UK patients in ALCANZA received alloSCTs
- The place in the treatment pathway does not seem to represent clinical practice –patients whose disease progresses on 2nd line therapy have other treatment options available. AlloSCT carries a significant risk of complications and is not likely to be accepted by all at this point in the pathway
- Limited data presented on the patients with CTCL from the supra-regional centres in London who received allosSCTs to know if they are representative of the patients in the company model who receive alloSCTs
- The rate of SCT (40% of all responders after 18weeks of treatment) appears an overestimate

ERG's alternative modelling scenarios	Incremental			ICER per QALY gained
	Costs	QALYs	LYs	
Company base case	[redacted]	[redacted]	1.204	BV Dominates
Revised company base case (no alloSCT)	[redacted]	[redacted]	0.000	BV Dominates

ERG's preferred approach to model cost effectiveness: Utility values and costs

Utility values – progression free health state

- The company used a regression model including Skindex-29 scores to calculate utility values for the progression-free state
- This is not reflective of the NICE methods guide: the ICERs per QALY gained are on a different scale to the ICERs per QALY gained produced by models calculated without the Skindex-29 score
- Observed ALCANZA utility values are higher for treatment with BV than with PC because of differences at baseline
- The ERG considered it more appropriate to assume that the PFS utility values are equal for BV and PC. The preferred utility values were calculated using an average of the observed EQ-5D-3L values from the BV and PC arms

Adverse event decrements

- Changes in HRQoL because of AEs would be captured in the observed EQ-5D-3L values from the ALCANZA trial, no need for further utility decrements

Costs – oral chemotherapy administration

- The ERG considered there was double counting in the administration costs of oral chemotherapy

ERG's amendments to the company base-case

Revision	Incremental			ICER per QALY gained
	Cost	QALYs	LY	
Company's base case	[redacted]	[redacted]	1.204	BV Dominates
Base case without alloSCT	[redacted]	[redacted]	0.000	BV Dominates
EQ-5D utility estimates	[redacted]	[redacted]	1.204	BV Dominates
Equal PFS EQ-5D utility estimates for BV and PC	[redacted]	[redacted]	1.204	BV Dominates
No AE decrements - already captured by HRQoL utility values	[redacted]	[redacted]	1.204	BV Dominates
Additional oral chemotherapy administration costs excluded	[redacted]	[redacted]	1.204	BV Dominates
ERG's revised company base case (all)	[redacted]	[redacted]	0.000	BV Dominates

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

3 scenarios analyses are presented to highlight the sensitivity of the model to alternatives assumptions

- **Scenario 1 - changes to the post-progression pathway**
- **Scenario 2 – overall survival gain**
- **Scenario 3 - resource use**

The ERG does not consider these scenarios to be supported by robust evidence.

The ERG stated that the results may not be meaningful, since the model is relatively inflexible and does not accommodate changes to certain parameters.

ERG's scenario analysis 1: changes to the post-progression pathway

Time spent in the post-progression state:

1. PFS in the model is longer for patients treated with BV than with PC
2. OS in the model (without alloSCT) is the same for both treatments
3. Post-progression survival (PPS) is calculated as the difference between mean OS and mean PFS

This means the risk of death after progression is higher for BV than with PC

Spending less time in the post-progression state is beneficial for the ICER because patients accrue fewer costs from resource intensive end-stage-management

The differential end-stage care costs accrued by patients treated with BV versus PC in the ERG's revised base case are substantial ([redacted])

The company's cost effectiveness results are sensitive to changes made to the costs and benefits accrued in the post-progression state

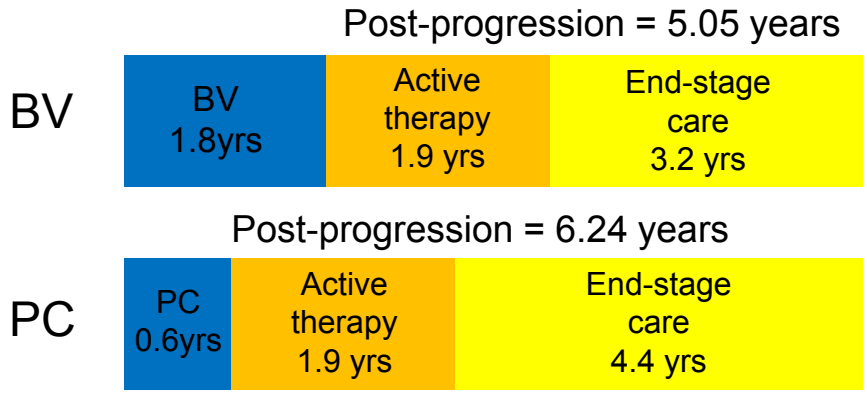
— To explore the uncertainty the ERG presented a sensitivity analysis on the post progression treatment pathway and time spent in end-stage care (Scenario 1)

ERG's scenario analysis 1: changes to the post-progression pathway

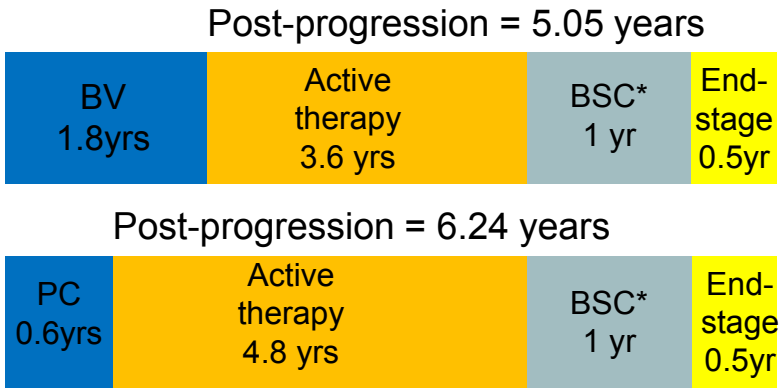
Plausibility of the clinical pathway after progression

- Clinical advice to the ERG - the company's treatment pathway after progression is implausible as it predicts that patients would spend 3 to 4 years in end-stage care
- Clinical advise to the ERG - patients would spend 5 years receiving subsequent therapies, 1 year receiving best supportive care (BSC) and 6 months receiving end-stage care

Company's proposed pathway



ERG's proposed pathway



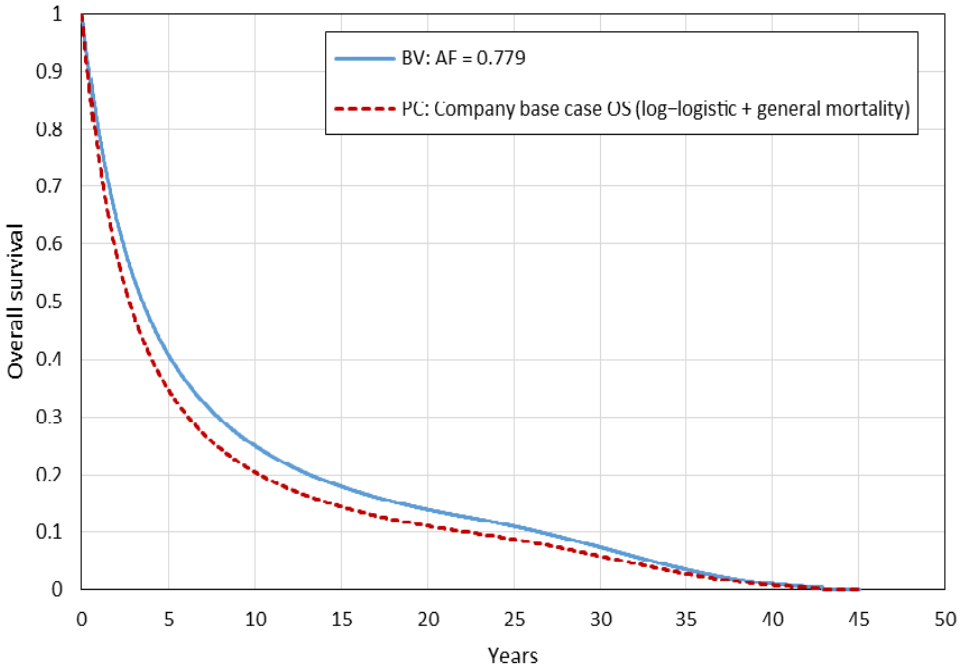
*Costs of BSC are same as the cost of being in the active therapies minus drug treatment costs

Utility value for BSC was the midpoint between active therapies and end-stage care (0.495)

Alternative modelling scenarios	Incremental Costs	Incremental QALYs	ICER
Company's base case	[redacted]	[redacted]	BV Dominates
ERG's revised company base case	[redacted]	[redacted]	BV Dominates
ERG's sensitivity scenario – PP pathway	[redacted]	[redacted]	£494,981

ERG's scenario analysis 2: overall survival gain

ERG: This scenario highlights the sensitivity of the model alternatives assumption around OS gain. Using the evidence presented it is not possible to say <u>whether or not</u> there is an OS gain associated with treatment with BV versus PC
The ERG is not suggesting that OS gain for treatment with BV is equal to 9.5 months



- Scenario 2 investigates an OS gain equal to mean PFS gain (9.5 month gain as in the company base case)
- It is assumed that treatment with BV does not affect the disease trajectory once a patient's disease has progressed
- The base case PC OS curve was used for PC
- For BV the OS curve was adjusted using an acceleration factor to generate a 9.5 month mean gain in OS

Revision	Incremental			ICER
	Cost	QALYs	LY	
Company's base case	[redacted]	[redacted]	1.204	BV Dominates
ERG's revised company base case	[redacted]	[redacted]	0.000	BV Dominates
ERG's sensitivity scenario – OS gain	[redacted]	[redacted]	0.794	£47,570

Alternative scenario analyses: overall survival

The company provided a scenario analyses where BV and PC are modelled independently using the ALCANZA trial data:

- Weibull parametric curve is selected for BV OS extrapolation
- Log-normal selected for PC OS extrapolation

Revision		Incremental			ICER
		Cost	QALYs	LY	
1	Company's base case	[redacted]	[redacted]	1.204	BV Dominates
2*	Company's scenario – OS from ALCANZA	[redacted]	[redacted]	1.240	BV Dominates
3	ERG's revised company base case	[redacted]	[redacted]	0.000	BV Dominates
4	ERG's scenario analysis – OS gain	[redacted]	[redacted]	0.794	£47,570

ERG's scenario analysis 3: resource use

Resource Use frequency

- Clinical advice to the ERG - patients in end-stage care would not be well enough to attend outpatient appointments as predicted in the company model (2.25 visits per week)
- The ERG also noted that the palliative care and Macmillan nurses are unlikely to have the capacity for several visits per week
- The ERG reduced the frequency of visits to 0.25 for district and Macmillan nurses, palliative support and outpatient nurse visits.

Resource use unit costs

- Less expensive dressings may also be used in clinical practice in the UK which could reduce the cost of end-stage care and increase the ICER

If resource use in the end-stage care phase was lower than the frequency in the pre-progression state or in the active subsequent treatment phase, the new resource use would also be applied to the other modelled health states

Revision	Incremental			ICER
	Cost	QALYs	LY	
Company's base case	[redacted]	[redacted]	[redacted]	BV Dominates
ERG's revised company base case	[redacted]	[redacted]	[redacted]	BV Dominates
ERG's sensitivity scenario – resource use	[redacted]	[redacted]	[redacted]	£26,331

ERG's scenario analysis 3: resource use

	Company base case		ERG scenario 3	
	% patients	Frequency per week	% patients*	Frequency per week*
End-stage care				
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	100	**0.25**
Palliative care support team	100	2	100	**0.25**
Dressings				
Mepitel dressings	25	7 (x3)	**12.5**	7 (x3)
Mepilex large sheet dressings	25	7 (x2)	**12.5**	7 (x2)
Mepilex heels	25	7 (x2)	**12.5**	7 (x2)
Elasticated garments	25	1 (x1)	**12.5**	1 (x1)
Medium Allevyn	75	7	**37.5**	7 (x3)
Pre-progression / Post-progression				
District nurse visit	100	2.60	100	**0.25**
Dressings – localised coverage	60	7 (x7)	**37.5**	7 (x7)

* Changes to company base case **bold**

ERG's scenario analyses

- The ERG cautions that the scenarios are intended to highlight the sensitivity of the model to plausible alternatives to certain key assumptions made by the company
- The ERG does not consider them to be supported by robust evidence. The ERG's scenarios are not necessarily more reflective of reality than those in the company's base case

Scenario	Incremental		ICER (£/QALY)
	Costs	QALYs	
Company's base case	[redacted]	[redacted]	**BV Dominates**
ERG's revised company base case	[redacted]	[redacted]	**BV Dominates**
S1: Changes to post-progression pathway	[redacted]	[redacted]	£494,981
S2: Assuming an OS gain for treatment with BV	[redacted]	[redacted]	£47,570
S3: Changes to resource use frequencies	[redacted]	[redacted]	£26,331
S1 and S3	[redacted]	[redacted]	£626,918
S1 and S2	[redacted]	[redacted]	£128,445
S2 and S3	[redacted]	[redacted]	£82,597
S1, S2 and S3	[redacted]	[redacted]	£125,854

Innovation

Company considers BV to be innovative

- BV could be a step-change in disease management for a population whom there is significant unmet need
- BV may allow more eligible patients to proceed to a potentially-curative alloSCT
- BV is administered every 3 weeks as an outpatient requiring patients to spend less time in hospital improving the QoL for patients and caregivers
- The QALY gain with BV is likely to be significantly underestimated due to the limitations of the EQ-5D as a quality of life instrument for CTCL
- Poor correlation of Sindex-29 (a more appropriate QoL instrument for CTCL) to EQ-5D data from the ALCANZA trial. No mapping algorithm available to covert Sindex-29 to EQ-5D

Clinical expert statements

- QoL is reduced in patients with advanced CTCL, they suffer pain, itching , insomnia, disfigurement, severe odour, depression, social isolation – not all captured in QALY
- Durable clinical responses are required which are rarely achieved for this group of CTCL
- The high response rates seen with BV will significantly reduce the major burden and morbidity of advanced skin disease in the advanced CTCL population

Equality

- There were no equality issues raised in the company submission, ERG report or in the patient and professional statements
- During scoping the following issue was raised:
  - "if CTCL with <5% CD30 expression was excluded this may deny a small number of patients a possibly efficacious drug as a study found 1 of 6 may respond with CD30<5%"

  The marketing authorisation does not specify a percentage of CD30 expression. Therefore this is not considered an equality issue.

End of life

- The company has not made a case for BV meeting the end-of-life criteria

Authors

Lorna Dunning
Technical Lead

Nicola Hay
Technical Adviser

with input from the Lead Team (Richard Nicholas, Matt Stevenson and Judith Wardle)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Document B

Company evidence submission

June 2018

File name	Version	Contains confidential information	Date
ADCETRIS_CTCL_NICE_STA_Document B_180619_STC	1.0	Yes	19 June 2018

Contents

List of Tables

List of Figures

Abbreviations

AE	Adverse event
alloSCT	Allogeneic stem cell transplant
ASCT	Autologous stem cell transplant
ATG	Anti-thymocyte globulin
BAD	British Association of Dermatologists
BM	Bone marrow
BSA	Body surface area
BV	Brentuximab vedotin
C	Cycle
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence interval
CNS	Clinical Nurse Specialist
COMP	Committee for Orphan Medicinal Products
CR	Complete response
CSA	Ciclosporin
CT	Computed tomography
CTCL	Cutaneous T-cell lymphoma
D	Day
DOR	Duration of response
EBRT	External beam radiation therapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECP	Extracorporeal photochemotherapy
EFS	Event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
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
FDA	United States Food and Drug Administration
FMF	Folliculotropic mycosis fungoides
GRS	Global Response Score
HCP	Healthcare provider

HL	Hodgkin lymphoma
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
INV	Investigator
IRF	Independent review facility
ISCL	International Society for Cutaneous Lymphomas
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
LCT	Large cell transformation
LPD	Lymphoproliferative disorders
LyP	Lymphomatoid papulosis
MAIC	Matching-adjusted indirect comparison
MDT	Multidisciplinary team
MF	Mycosis fungoides
MMF	Mycophenolate mofetil
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
mSWAT	Modified Severity Weighted Assessment Tool
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
ORR	Objective response rate
ORR4	Objective global response lasting ≥4 months
OS	Overall survival
PBSC	Peripheral blood stem cell
PC	Physician’s choice
pcALCL	Primary cutaneous anaplastic large cell lymphoma
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial response
PROCLIPI	Prospective Cutaneous Lymphoma International Prognostic Index
PUVA	Psoralens + ultraviolet A light therapy

QALY(s)	Quality adjusted life year(s)
QLQ-C30	Quality of Life Questionnaire – Core 30
QoL	Quality of life
RIC	Reduced-intensity conditioning
R/R	Relapsed/refractory
sALCL	Systemic anaplastic large cell lymphoma
SD	Stable disease
SD	Standard deviation
SDT	Skin-directed therapy
SF-36	36-Item Short-Form Survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SS	Sézary syndrome
STC	Simulated treatment comparison
TSEB	Total skin electron beam therapy
TTR	Time to response
UKCLG	United Kingdom Cutaneous Lymphoma Group
USCLC	United States Cutaneous Lymphoma Consortium
USD	US dollars
VAS	Visual Analog Scale
VGPR	Very good partial response

Executive Summary

Cutaneous T-cell lymphoma (CTCL) is a rare form of non-Hodgkin lymphoma (annual incidence of 0.75 per 100,000 people) whose primary presentation is in the skin. It impacts patients both physically and emotionally; CTCL patients have chronic disfiguring skin lesions and systemic symptoms, such as chronic pain and unrelenting itching, that can severely limit daily functioning. About 30% of patients present with advanced-stage CTCL and 25% of early-stage CTCL patients will progress to advanced disease. Quality of life (QoL) is severely reduced in advanced CTCL (i.e. mycosis fungoides [MF] stage IIB and above, primary cutaneous anaplastic large cell lymphoma [pcALCL] and Sézary Syndrome [SS]). While skin-directed treatment is used in early-stage disease, the standard of care for advanced CTCL is systemic therapy. Although a number of systemic therapies are available, the outcomes with these agents are characterised by poor response rates and short durations of response. A significant unmet need remains as advanced CTCL patients will exhaust systemic treatments relatively quickly and then live with a debilitating and highly symptomatic condition until eventual death due to overwhelming symptoms or sepsis.

Advanced CTCL is incurable for most patients; treatment is aimed at disease control and improving QoL. Allogeneic stem cell transplant (alloSCT) may achieve durable remissions and is the only potentially curative option in advanced CTCL. However due to the eligibility criteria (i.e. adequate fitness and partial or complete response to induction therapy), only a minority of patients currently benefit from this intervention. Resource demands for patients with advanced CTCL are high. Their care involves multiple specialised services within hospital, including haematology, oncology, dermatology, nursing, wound care, psychology, pharmacy, and outpatient services. This is particularly true in the end stage of the disease, after patients have exhausted systemic treatments and care is focused on symptom management. This end-stage care is characterised by a huge burden to the patients, their caregivers and the NHS, as patients require intensive support and frequent visits to healthcare professionals to deal with recurrent infections and symptoms such as severe pain, intractable pruritus and psychological distress. Patients have extensive skin lesions that necessitate frequent, lengthy nurse visits and the use of large quantities of expensive specialised dressings. In addition, patients with advanced CTCL tend to live much longer than other malignancies, meaning they are likely to spend a significant amount of time in this resource-intensive, end-stage care phase which is debilitating for the patients and the NHS.

Brentuximab vedotin is a targeted and highly innovative therapy which, in December 2017, was granted a marketing authorisation for the treatment of adults with CD30+ CTCL after at least 1 prior systemic therapy, an indication for which it has Orphan Drug status. It is seen by clinical experts as an exciting new therapy for advanced CTCL, with the potential to have a significant impact on CTCL patients in the UK. The best evidence for brentuximab vedotin comes from a Phase III randomised trial (ALCANZA) that directly compared it against physician's choice (PC) of either bexarotene or methotrexate, both used in the UK. Compared with these agents, brentuximab vedotin significantly increased: median PFS (16.5 months vs. 3.5 months, HR: 0.28 [95% CI: 0.1742–0.4647]); rate of objective response lasting at least 4 months (59.2% vs. 8.7%); and rate of complete response (20.4% vs. 2.2%) per investigator assessment at the longest

follow-up to date. Brentuximab vedotin also significantly reduced patient-reported symptom burden on the Skindex-29 scale vs PC, a recognised measurement of QoL for CTCL. Overall survival was not a pre-specified endpoint in ALCANZA and the data are both very immature (less than 30% events) and confounded due to a high rate of crossover in the comparator arm (46%). Due to the small patient numbers, statistical methods to adjust for these biases resulted in nonsensical output. To maintain the simplicity and transparency in the model and reduce uncertainty, equal survival was assumed for brentuximab vedotin and PC.

Although the ALCANZA trial enrolled CTCL patients of all stages, the focus of this submission is advanced CTCL patients (i.e. MF stage IIB+, pcALCL and SS), the population which is treated with systemic therapies in the UK. This matches brentuximab vedotin's positioning in the recently updated British Association of Dermatologists (BAD) and UK Cutaneous Lymphoma Group (UKCLG) guidelines for CTCL. For most patients with advanced CTCL, brentuximab vedotin will be used to provide disease control, delay progression, reduce symptom burden and improve QoL. For those advanced stage patients eligible for alloSCT, it could have a profound impact on the treatment pathway as it has the potential to be an effective bridge to transplant, supported by the unprecedented depth of response seen in ALCANZA. The high response rates, particularly CRs enabled with brentuximab vedotin, would allow more patients to proceed to alloSCT than is possible currently. It offers realistic hope of long-term remission of this traditionally incurable disease.

A health economic model was developed to assess the cost-effectiveness of brentuximab vedotin compared with physician's choice (bexarotene or methotrexate) for the treatment of advanced CTCL in the UK. In the base case analysis, brentuximab vedotin dominates PC and the reason for this finding is two-fold. Firstly, brentuximab vedotin controls patients' disease for longer than PC (i.e. extends PFS), meaning they spend less time in the end-stage care state where utility is poor and care costs are high. Secondly, due to its higher response rates compared to PC, brentuximab vedotin can bridge more potentially eligible patients to alloSCT. Patients who undergo alloSCT have increased OS, better utilities, and overall lower costs than patients who follow the non-alloSCT pathway.

Overall, the health economic analysis shows that brentuximab vedotin is a cost-effective (and indeed cost saving) option for the treatment of advanced CTCL; an option that is desperately needed by advanced CTCL patients who have few effective treatment choices and a devastating QOL. Arising from this, and building on the many benefits that it offers to patients, we would suggest that it should be recommended by NICE for routine use on the NHS for advanced CTCL.

B.1.1 *Decision problem*

This submission addresses the clinical and cost effectiveness of brentuximab vedotin within its marketing authorisation. Brentuximab vedotin is indicated for the treatment of adult patients with CD30-positive cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy. This submission focuses on patients with advanced CTCL defined as MF stage IIB and above, pcALCL and Sézary Syndrome.

The full statement of the decision problem is presented Table 1, and the rationale for any amendment or additional inclusion is also provided.

Brentuximab vedotin has previously been assessed by NICE for other indications within its marketing authorisation as follows:

- Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (TA524)
- Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma (TA478)

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with relapsed or refractory CD30-positive cutaneous T-cell lymphoma following directed skin therapies and/or at least one systemic therapy	People with relapsed or refractory CD30-positive advanced cutaneous T-cell lymphoma (i.e. MF stage IIB and above, pcALCL and Sézary syndrome) following directed skin therapies and/or at least one systemic therap	The proposed patient population is narrower than the marketing authorisation because this population is most relevant to NHS clinical practice (based on UK clinician feedback) and reflects the positioning of the technology in the UK guidelines.
Intervention	Brentuximab vedotin (Adcetris®)	As per scope	N/A
Comparator(s)	Established clinical management without brentuximab vedotin	For the purposes of this appraisal, relevant comparators for brentuximab vedotin as second-line systemic therapy in CTCL in the cost-effectiveness model comprise bexarotene and methotrexate. Based on the availability of clinical data, Takeda were not able to indirectly compare brentuximab vedotin with interferon-α. Patients may also receive an allogeneic stem-cell transplant depending on their response to systemic therapy	Feedback from an advisory board including 10 UK clinicians indicated that brentuximab vedotin would be used after first-line systemic therapy; therefore the comparators exclude non-systemic therapies. Advisors considered bexarotene the only licensed systemic therapy that would be an appropriate comparator in a second-line setting; methotrexate and IFN-α, while not licensed in the appraised indication, were also considered relevant comparators. Chemotherapy is used later in the treatment pathway and was therefore not considered a comparator

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	In addition to the outcomes defined in the scope, the brentuximab vedotin phase III trial, ALCANZA, also included ORR4 and Skindex-29 as outcomes. ORR4 was the primary endpoint in ALCANZA.	The ISCL, USCLC, and the EORTC have identified prolonged objective response rates (ORRs) and PFS as meaningful primary endpoints for trials in patients with MF and SS.[1] To assess the impact of therapy on the unique symptomatic burden of CTCL, newer endpoints, such as objective global response lasting at least 4 months (ORR4), have been evaluated. ORR4 combines ORR and DOR to capture response rate and duration as a single measure.[2] For CTCL, the Skindex-29 – a 30-item, dermatology-specific, self-reported questionnaire – may be a more appropriate measure of HRQL than EQ-5D-3L. Skindex-29 has been extensively studied and validated in different patient populations with skin diseases, including CTCL.[3-6] 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.[1]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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 Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	As per scope	N/A
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on cancer histology.	Brentuximab vedotin is expected to be used for patients who require systemic therapy, and have advanced-stage CTCL (defined as MF stage IIB and above, SS, and all pcALCL patients).	UK clinical advisors expressed that patients in early stages of the disease (i.e. MF stage IA–IIA) for the most part will have indolent disease and will therefore not require any systemic therapy. Therefore, the population anticipated to be treated with brentuximab vedotin are patients with worse prognosis who have advanced-stage after at least 1 prior systemic therapy and before standard chemotherapy.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	If the evidence allows, the economic analysis should model stem cell transplantation further down the treatment pathway. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Allogeneic stem cell transplantation included as per scope and UK clinical pathway.	N/A

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CTCL, cutaneous T-cell lymphoma; DOR, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; HRQL, health-related quality of life; ISCL, International Society for Cutaneous Lymphomas; MF, Mycosis Fungoides; ORR, objective response rate; OS, overall survival; pcALCL, periocular cutaneous anaplastic large cell lymphoma; PFS, progression-free survival; SS, Sezary Syndrome; USCLC, United States Cutaneous Lymphoma Consortium.

B.1.2 *Description of the technology being appraised*

The summary of product characteristics and European public assessment report can be found in Appendix C.

Brentuximab vedotin is an antibody drug conjugate which is composed of the monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE). It delivers an antineoplastic agent to CD30-expressing tumour cells resulting in selective apoptotic cell death. CD30 is a cell membrane protein which is highly expressed on certain tumours including Hodgkin lymphoma and some forms of CTCL.

Brentuximab vedotin has been designated an orphan medicine in the EU for Hodgkin lymphoma (HL), systemic anaplastic large cell lymphoma (sALCL), and primary cutaneous T-cell lymphoma (CTCL). Details of the licensed indication are presented in Table 2.

Table 2. Technology being appraised

UK approved name and brand name	Brentuximab vedotin (Adcetris®)
Mechanism of action	Brentuximab vedotin is an antibody drug conjugate (ADC) that delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. Nonclinical data suggest that the biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, monomethyl auristatin E (MMAE), is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.[7] Classical HL, sALCL and subtypes of CTCL (including MF and pcALCL) express CD30 as an antigen on the surface of their malignant cells. This expression is independent of disease stage, line of therapy or transplant status. These features make CD30 a target for therapeutic intervention. Because of the CD30-targeted mechanism of action brentuximab vedotin is able to overcome chemo-resistance as CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy, irrespective of prior transplant status. Contributions to the mechanism of action by other antibody associated functions have not been excluded.[7]
Marketing authorisation/CE mark status	The European Commission granted an extension of the marketing authorisation valid throughout the European Union for brentuximab vedotin on 15 December 2017 to include the treatment of adult patients with CD30-positive cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.[7]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Brentuximab vedotin is indicated for:[7] A. The treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (r/r HL): (i) following autologous stem cell transplant (ASCT) or; (ii) following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. B. The treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT C. The treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (r/r sALCL). D. Treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy

Method of administration and dosage	The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Brentuximab vedotin must not be administered as an intravenous push or bolus. Brentuximab vedotin should be administered through a dedicated intravenous line and it must not be mixed with other medicinal products. Patients with CTCL can receive up to 16 cycles.[7]
Additional tests or investigations	None
List price and average cost of a course of treatment	The NHS list price of brentuximab vedotin is £2,500 per 50mg vial (ex VAT). Based on mean cycles of 12 for the population covered in this submission, derived from the average duration of therapy in ALCANZA, the mean cost per course for an average patient is estimated at approximately [redacted] per patient without a PAS ([redacted] based on the PAS).
Patient access scheme (if applicable)	As per the agreement with the Department of Health, a patient access scheme (PAS) in the form of a simple discount applies for all licensed indications of brentuximab vedotin in the United Kingdom. Unless otherwise stated, the analyses in this resubmission reflect the 'with PAS' price of brentuximab vedotin. The current PAS for brentuximab vedotin is a straight discount of [redacted] bringing the NHS net acquisition price from £2,500 per vial to [redacted] per vial.

B.1.3 *Health condition and position of the technology in the treatment pathway*

B.1.3.1 Disease overview

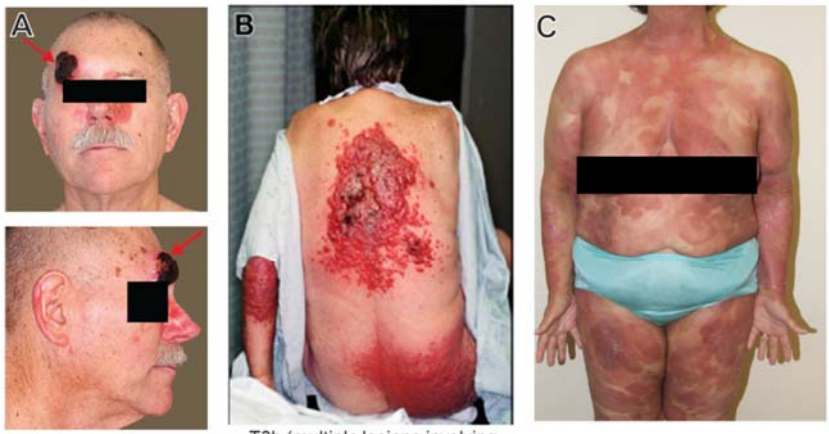
Cutaneous T-cell lymphomas (CTCLs) are a rare, heterogeneous group of non-Hodgkin lymphomas (NHLs) involving the skin, and rarely have evidence of extracutaneous disease at the time of diagnosis.[8-10] While early-stage/localised disease is considered indolent, approximately 25% of patients will progress to advanced-stage disease during the course of their life.[11] In addition, 30% of patients present with advanced-stage disease. Advanced-stage disease, associated with a poor prognosis and significantly decreased survival vs. early-stage disease ($p<0.001$), is characterised by the development of aggressive and devastating lesions (e.g., disfiguring tumours, ulceration, erythroderma, and eventual visceral spread).[12,13]

CTCL is nearly always incurable, and therefore the main goals of therapy are disease control and improvement of quality-of-life. Recent evidence demonstrates that allogeneic stem cell transplant (alloSCT) may achieve durable remissions or possibly cure in some patients with advanced-stage disease.[14-16] However, the procedure can only be performed in patients who achieve at least a partial response (PR) to induction/bridging therapy, and a minority of patients are able to meet this criterion with existing therapies.

Advanced-stage CTCL is characterised by the uncontrolled growth of T-cell lymphocytes, which manifest as patches, plaques, or tumours on the skin.[12] More aggressive forms or later stages of disease may also involve the blood (i.e., circulating Sézary cells), lymph nodes, and other organs.[17] Advanced-stage CTCLs have a devastating impact on both quality of life (QoL) and life expectancy.[3,13,18-21] Patients with advanced-stage CTCL endure intense,

unrelenting itching, pain, alopecia, and disfigurement (Figure 1),[18,20] and often die due to disease recurrence, overwhelming sepsis, and bone marrow depletion.[22]

Figure 1. Advanced-stage CTCL is characterised by chronic skin manifestations and systemic symptoms that cause severe pain and itching, alopecia, and disfigurement: (A) MF stage IIB; (B) pcALCL; (C) MF stage IVA with LCT[23-25]

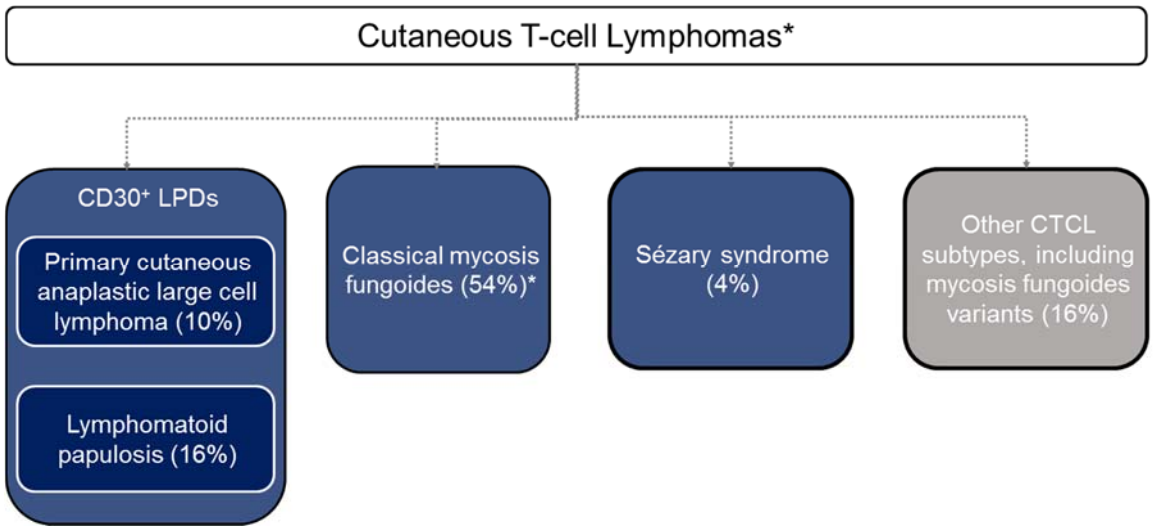


Abbreviations: CTCL, cutaneous T-cell lymphoma; LCT, large-cell transformation; MF, mycosis fungoides; pcALCL, primary cutaneous anaplastic large cell lymphoma. Images: Kim et al 2015, Fig1C[24]; Kim et al 2007, Fig6B[23]; Kim, slide27.[25]

The most common types of CTCL are summarised in Figure 2; they comprise[12,26]:

- Mycosis fungoides (MF; most predominant subtype, >50% of cases),
- MF's leukaemic variant, Sézary syndrome (SS; ~3–4% of cases), and
- Primary cutaneous CD30+ lymphoproliferative disorders (CD30+ LPDs; 30% of cases).The most commonly observed LPDs are primary cutaneous anaplastic large cell lymphoma [pcALCL, 8%–10%] and lymphomatoid papulosis [LyP, 16%]).

Figure 2. WHO-EORTC classification of CTCL[12]



*Percentages are based on 1476 patients with a primary cutaneous T-cell lymphoma registered at the Dutch and Austrian Cutaneous Lymphoma Group between 1986 and 2002.
Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; LPDs, primary cutaneous CD30+ lymphoproliferative disorders; WHO, World Health Organization.

While MF generally follows an indolent course,[12] approximately 25% of patients will progress to advanced-stage disease.[11] Advanced stages of MF/SS typically manifest as aggressive cutaneous tumours (with or without ulceration and secondary bacterial infection) or generalised erythroderma or lymphadenopathy.[12,17,27] Patients with advanced-stage disease may also experience intense, unrelenting pruritus, leukaemic involvement of the peripheral blood (resulting in abnormal immune function), and severe pain, all of which have a huge negative impact on daily functioning and QoL.[28,29]

The CD30+ LPDs comprise approximately 30% of CTCL cases and represent a spectrum of disorders including LyP and pcALCL.[12] Lesions associated with LyP and pcALCL may spontaneously regress, and although relapse is common, progression to extracutaneous involvement is rare.[12,30] However, with extensive cutaneous or extracutaneous spread of pcALCL, more intense systemic treatment is necessary.[31]

CTCLs are primarily managed according to the type of CTCL and the stage of disease.[32] Although skin-directed therapies are often effective for managing early-stage CTCL, systemic agents are used for patients with advanced-stage disease or other adverse prognostic features.[33] As there is no single systemic agent that provides clinical benefit across all CTCL subtypes, treatment is variable and primarily dictated by patient profile and physician choice. Furthermore, duration of response to therapies is variable but generally short lived, and patients will eventually experience progression in their disease.[34]

Epidemiology

The 2013 overall incidence of CTCL in England was approximately 0.75 per 100,000, and CTCL was more common in men than women (ratio approximately 1.6:1).[26]
In total, 1659 people were newly diagnosed with CTCL over the 5-year period spanning 2009 to 2013. More than half (55%) of these cases were MF, nearly 10% were primary cutaneous CD30+ LPDs, and 2.5% were SS.[26]

In Wales, 2013 estimates suggest a crude incidence rate of 0.48 per 100,000 person-years and an age-adjusted (to 2000 US standard population) incidence rate of 0.39 per 100,000 person-years. In 2010 and 2011, 17 and 13 patients, respectively, were diagnosed with primary CTCL in Wales.[35]

[redacted]

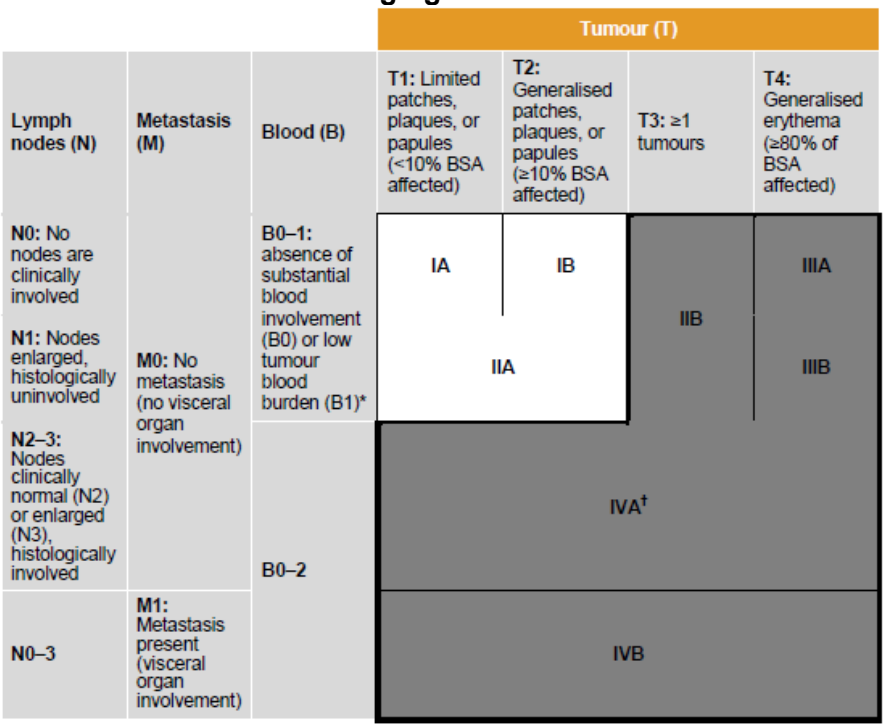
CTCL affects less than 2.2 in 10,000 people in the EU (2012 estimate), and thus, meets EU criteria for designation as an orphan disease (i.e., no more than 5 people per 10,000).[37] On 11 January 2012, brentuximab vedotin for treatment of CTCL was granted Orphan Designation by the European Medicines Agency (EMA; EU/3/11/939)[37]; this was reviewed by the Committee for Orphan Medicinal Products (COMP) at the time marketing authorisation was granted, and orphan designation was retained (7 December 2017).

Staging, and definition of advanced-stage disease

CTCLs are classified using the TNM system. The stage of disease worsens based on increasing size and body surface area affected (e.g., plaques, patches, or papules; classified as T1–T4), the degree of lymph node involvement (classified as N0–N3), and the presence of metastasis (i.e., visceral involvement; classified as M0 or M1).[23,38,39]

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 a low- and B2 representing a high blood tumour burden. TNMB designations for MF/SS are used to group CTCL into early-stage (stages IA–IIA) or advanced-stage (stages IIB–IVB) disease (Figure 4).[38,40]

Figure 4. TNMB classification and staging for MF and SS[38,40]



B=blood; BSA=body surface area; M=metastases; MF=mycosis fungoides; N=node; SS=Sézary syndrome; T=tumour.

White represents early-stage disease; Dark grey represents advanced-stage disease.

*IIIA is B0; IIIB is B1.

†IVA is separated into IVA1 (with blood involvement; B2) and IVA2 (lymph node involvement; N3).

The CD30+ LPDs (e.g., pcALCL) are divided into early-stage or advanced-stage disease based on the presence of nodal involvement or metastasis. Because it is implicit in the definition of primary cutaneous lymphoma that extracutaneous disease is absent, all patients are N0 and M0 at presentation, and remain so in early disease. N1–N3 and M1 classifications are considered advanced disease, where the lymphoma is active beyond the skin (i.e., in the nodes or blood) and beyond the nodes (metastasised; M1).[23,40]

Disease course

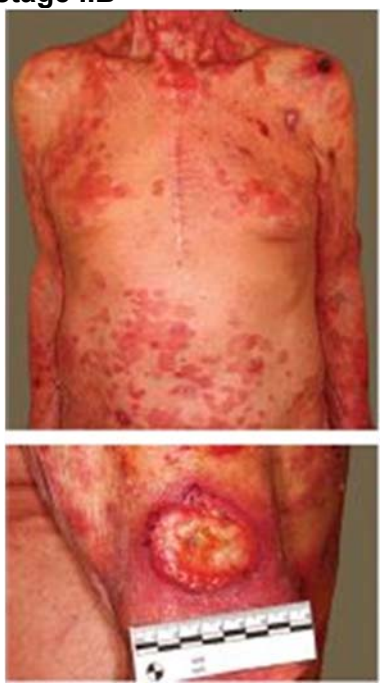
Early- and advanced-stage disease is different both in terms of the disease course and management. While patients with early-stage or indolent CTCLs are managed expectantly (i.e., “watch and wait”) or with skin-directed therapy, more advanced clinical stages are associated with greater patient[3,5,21,41] and caregiver[20] burden, reduced QoL[3] and increased risks of relapse, progression, and death.[13,42]

Advanced-stage CTCLs require treatment with systemic therapies.[16] Though a number of systemic agents are available, duration of response is generally short-lived and patients will eventually experience disease progression.[34]

Mycosis fungoides (MF)

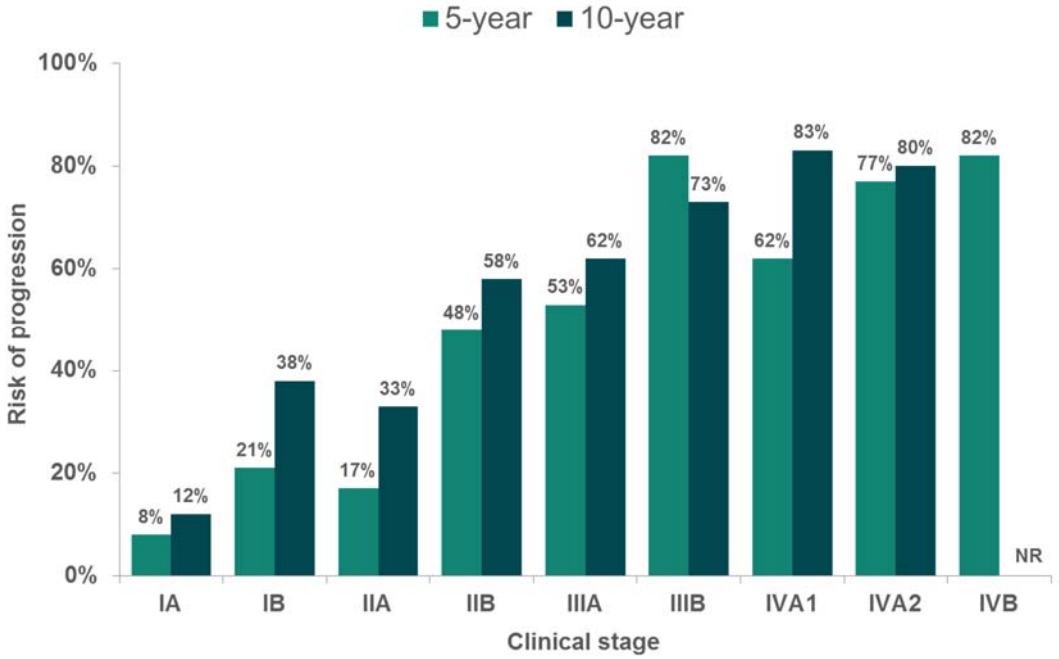
MF, the most common type of CTCL, is characterised by the presence of patches, plaques, and tumours. Lymph nodes and visceral organs become affected in later stages of the disease. While mycosis fungoides (MF; Figure 5) typically progresses slowly,[12] in a large UK cohort of predominantly MF patients, 34% had disease progression and 26% died due to their disease over a median follow-up of 5.9 years. Advanced-stage MF (i.e., stages IIB–IVB) is associated with a higher risk for progression than early-stage disease (Figure 6),[13] and neither treatment with skin-directed nor systemic therapies has been shown to reduce the risk of progression.[43]

Figure 5. Mycosis fungoides stage IIB[24]



Patient with MF stage IIB disease and ulceration on the left arm.

Figure 6. Risk of disease progression by stage in MF (n=1398)/SS (n=104)[13]



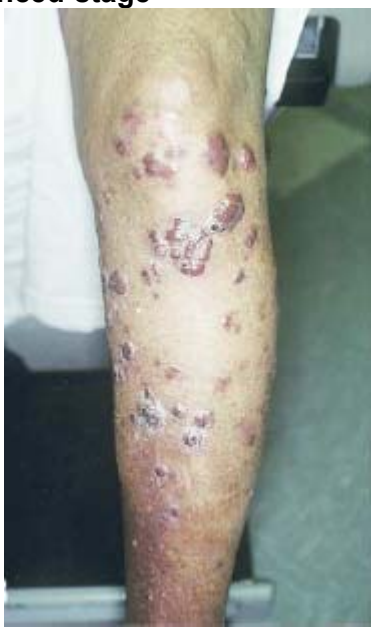
Abbreviations: MF, mycosis fungoides; NR, not reported; SS, Sézary syndrome.

Primary cutaneous anaplastic large cell lymphoma (pcALCL)

Primary cutaneous anaplastic large cell lymphoma generally presents with a solitary or grouped, rapidly growing, and ulcerating large tumours or thick plaques. Spontaneous partial or full regression of pcALCL lesions may occur (reported in up to 44% of patients), but relapse is frequently observed (41% with radiotherapy, 43% with surgical excision, and 62% with multiagent chemotherapy).[12,30,31]

While extracutaneous spread is uncommon (13%),[12,30,31] pcALCL can progress from solitary- to multifocal lesions and generalised involvement of the skin. Patients with extensive limb involvement and extracutaneous disease (Figure 7) have been shown to follow a more aggressive clinical course (at 2 years disease-specific survival of 50% with extensive limb involvement vs. 93% with typical pcALCL; p<0.001), and thus, require more aggressive treatment.[44]

Figure 7. Primary cutaneous anaplastic large cell lymphoma, advanced-stage*[30]

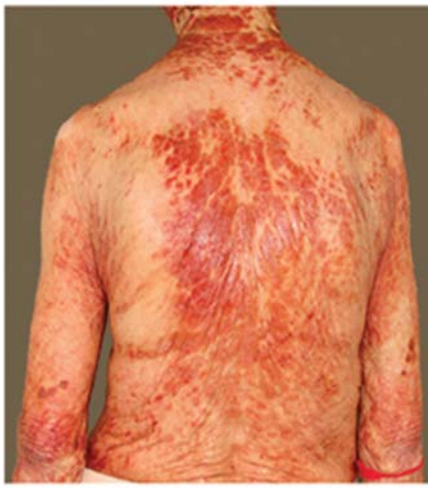


Defined as stage IV_{D+}: diffuse or disseminated involvement of ≥1 extralymphatic organs or tissues with or without associated lymph node enlargement.

Sézary Syndrome (SS)

Sézary syndrome is characterised by the triad of erythroderma, generalised lymphadenopathy, and presence of neoplastic T-cells (Sézary cells) in the skin, lymph nodes, and peripheral blood. It is typically a fast growing malignancy with an aggressive clinical behaviour (Figure 8), associated with marked skin exfoliation, oedema, and lichenification (hardening of the skin) which is intensely itchy. Additionally, patients may experience alopecia, onychodystrophy (abnormal change in nails), and palmoplantar hyperkeratosis. Many patients with SS eventually develop opportunistic, deadly infections due to immunosuppression (i.e., widespread impairment of cellular immunity as observed by defects in numerous cell lines in CTCL), with a median survival between 2 and 4 years.[12]

Figure 8. Sézary syndrome[24]



Patient with SS, stage IVA1 disease.

Life expectancy

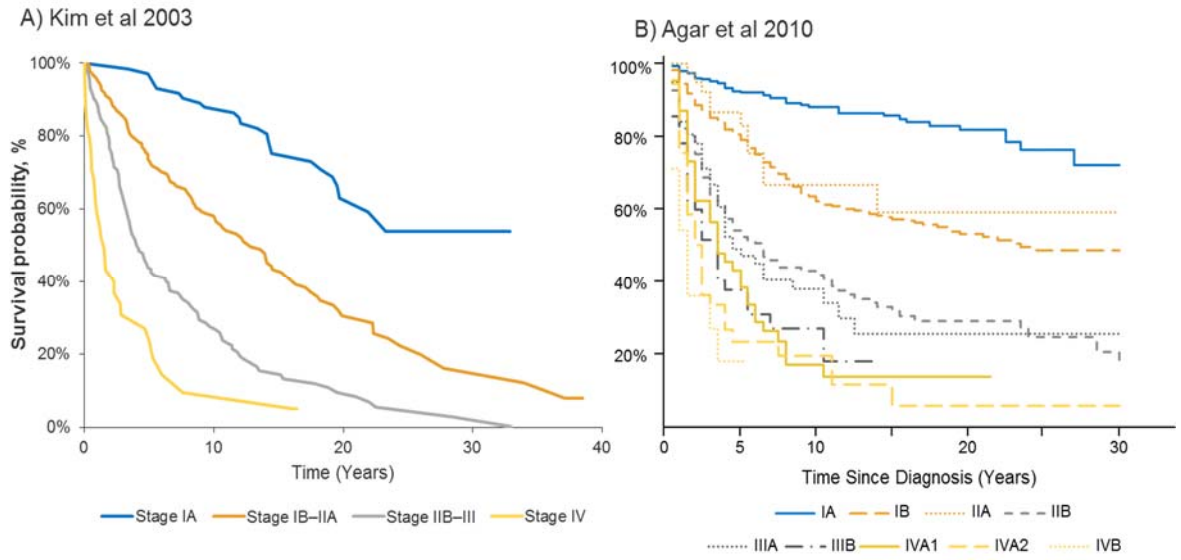
Survival varies by CTCL subtype and stage, and is worse with more advanced disease. In patients with early-stage MF (e.g., stage I–IIA), disease is confined to the skin, and those with a slower disease course have survival times measured in decades.[9,12] However, outcomes are substantially worse with advanced CTCL.

Kim et al 2003, a US-based study of 525 MF/SS patients, reported decrements in survival rates with advanced MF/SS vs early-stage disease. Five-year OS rates for patients with stages IA, IB/IIA, IIB/III, and IV disease were 96%, 75%, 44%, and 27%, respectively (Figure 9A). The median survival for the stage IIB/III group was 4.0 years and for the stage IV group was 1.5 years[45]; overall survival for patients with advanced-stage disease have not discernibly improved since.

In a 2010 study of 1502 UK patients with MF and SS by Agar et al, significant decrements in 5-year survival rates with advancing overall clinical stage were reported ($p<0.001$ for both OS and disease-specific survival with advancing overall clinical stage). The 5-year OS rate was 47% for stage IIB, and 18% for stage IV; median survival time was 4.7 years and 1.4 years, respectively (Figure 9B).[13]

Similarly, in a 2015 study of 1275 patients with advanced MF/SS from 29 centres (UK, n=3 centres and 261 patients), 5-year survival rates for stages IIB and IVB were 57% and 39%, respectively. In patients with advanced-stage MF/SS, reported median survival times ranged from 2.4 to 5.2 years, despite treatment.[46]

Figure 9. Survival by clinical stage in MF/SS (A) Kim et al 2003 US cohort, N=525 AND (B) Agar et al 2010 UK cohort, N=1502[13,45]



Survival according to stage at diagnosis in (A) Kim et al 2003, 525 patients with MF/SS; for stage IA vs IB/IIA disease, p<0.001; for stage IB/IIA vs IIB/III disease, p<0.001; and for stage IIB/III vs IV disease, p<0.001; and (B) Agar et al 2010 in 1502 patients with MF/SS
Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome.

Although patients with CD30+ LPDs typically have good prognoses, significant survival decrements are observed in advanced versus early clinical stages. In particular, patients with pcALCL with regional lymph node involvement demonstrate an overall 5-year survival rate of 76%.[10,30]

Treatment goals and evaluating treatment response

Because CTCLs are usually incurable, the primary goals of treatment are disease control and amelioration of symptoms to maintain or improve QoL.[16]

Several instruments are used to assess symptom burden and QoL in CTCL, although none were developed specifically for use in CTCL. The International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force (CLTF) of the EORTC have also identified relevant clinical trial outcomes measures.

Response rates and survival

The ISCL, USCLC, and the EORTC have identified prolonged objective response rates (ORRs) and PFS as meaningful primary endpoints for trials in patients with MF and SS.

- ORRs are based on a Global Response Score (GRS) and include patients with complete response (CR) or partial response (PR) to treatment. A CR is defined as complete disappearance of all clinical evidence of disease and a PR as regression of measurable disease.

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.[1] No therapy, beyond alloSCT, has been shown to improve OS and clinicians do not expect any treatment to show such a benefit. This is aligned with clinical practice, where the primary objectives are disease control, symptom decrease, and improvement of patients' QoL.

To assess the impact of therapy on the unique symptomatic burden of CTCL, newer endpoints, such as objective global response lasting at least 4 months (ORR4), have been evaluated. ORR4 combines ORR and DOR to capture response rate and duration of response as a single measure.[2]

Skin disease burden

The modified severity weighted assessment tool (mSWAT) is a method widely used to assess skin response to treatment in MF and SS. The body is divided into 12 regions with preassigned percentages of total body surface area (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.[47] 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.

Quality of life

For diseases affecting the skin, a specific and relevant measure of quality of life should be used to demonstrate clinically-meaningful improvement in symptoms and health-related quality-of-life (HRQL) as an outcome of treatment. The European Quality of Life 5-Dimension 3 Level Version (EQ-5D) is a generic instrument for patient-reported HRQL. While it has been utilised to assess HRQL across numerous cancers, its five domains –mobility, self-care, usual activities, pain/discomfort and anxiety/depression – may not always be sensitive enough to demonstrate impact of CTCL symptoms on HRQL (e.g., constant severe, intense itching causing insomnia).[6] In addition, the generic nature of the EQ-5D means that it may not capture the benefits of the treatment accurately, and is less sensitive to health status changes, such as vitality and cancer-related fatigue.[48]

For CTCL, the Skindex-29 – a 30-item, dermatology-specific, self-reported questionnaire designed to assess 3 domains: symptoms (key secondary endpoint in ALCANZA), emotions, and function – is a more appropriate measure of HRQL in CTCL than EQ-5D-3L. Skindex-29 has been extensively studied and validated in different patient populations with skin diseases, including CTCL.[3-5] The questionnaire comprehensively measures the effects of skin disease on HRQL, and can detect changes in patients over time, including effects specific for patients with CTCL such as itching and pain symptoms, worry, embarrassment, and frustrated emotions, and effects on relationships and sleeplessness.[3,5,49] The symptom domain of the Skindex-29 includes 7 items: my skin hurts; my skin condition burns or stings; my skin itches; water bothers my skin conditions (bathing, washing hands); my skin is irritated; my skin is sensitive; and my skin condition bleeds. Key attributes of the EQ-5D-3L and Skindex-29 instruments are summarised in Table 3. An analysis of the correlation between Skindex-29 and EQ-5D presented in Section B.2.7.4 shows a poor correlation with severely symptomatic patients scoring close to 1.0 on the EQ-5D, illustrating that EQ-5D may not accurately capture HRQL for patients with CTCL.

Table 3. Skindex-29 and EQ-5D-3L instruments

Questionnaire	Overview	Scoring	Attributes
Skindex-29[5,21,22]	• 30-item, dermatology-specific, self-reported questionnaire • 3 domains: emotions, functioning, and symptoms	• Scored using a 5-point Likert scale* • Scoring range: 0–116 • Higher scores indicate worse HRQL	• Useful for evaluating HRQL in patients with dermatological disease; has been utilised and validated in CTCL
EQ-5D-3L[50]	• 5-item questionnaire: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression • Also includes a linear VAS for self-assessment of overall health state	• 3 levels per dimension (no problems, some problems, and extreme problems) that corresponds with a 1-digit number; digits for the 5 dimensions combined into a 5-digit number representing patient's health state • VAS: A 20-cm vertical line ranging from 0 (worst imaginable health state) to 100 (best imaginable health state)	• Assesses utility values for pharmaco-economic analysis

*Likert scale: 0=not at all/strongly disagree, 1=rarely, 2=sometimes, 3=often, 4=all the time/very much/strongly agree. Abbreviations: CTCL, cutaneous T-cell lymphoma; EQ-5D-3L, European Quality of Life 5-Dimension 3 Level Version; HRQL, health-related quality of life; QoL, quality of life; VAS, Visual Analogue Scale.

B.1.3.2 Burden to patients, carers and society

Patients with advanced-stage CTCL may experience substantial symptomatic and HRQL burden of the disease for years (median survival time: 1.4 years to 4.7 years for stages IIB–IVB[13]). Coupled with the short duration of response provided by current treatment options, advanced-stage patients will live with a high symptom burden and require extensive symptom management for much longer than patients with most other cancers.

Physical CTCL symptoms, such as pruritus, alopecia, and other skin problems, lead to a substantial long-term burden of disease, exemplified by physical and functional impairments. The burden of physical symptoms, and a diagnosis of cancer, can also negatively impact patients' psychological and social well-being, personal relationships, and caregivers. Patients with advanced-stage disease place more burden on the healthcare system through greater resource use and associated costs compared to patients with early disease[51]; the burden of end-stage care is immense, with patients requiring intensive medical care and frequent bandage changes for non-healing wounds.[52] Carers of patients with CTCL also experience the demands of caring as well as negative impacts on intimacy, family dynamics, and emotional wellbeing.[20]

The focus of this submission is for advanced-stage patients, with high symptom burden, who have a substantial QoL decrement. Patients with advanced-stage CTCL endure much reduced QoL, shorter lifetimes, and increased financial strain compared with the general population.[12,13,18-21]

Burden of symptoms

Patients with CTCL report significant and embarrassing skin problems such as erythema, nail splitting, keratoderma (marked thickening of the skin), hypopigmentation, fissures, lumps, and signs associated with scratching (due to the intensity of itch).[3,18,20] These symptoms

negatively affect daily functioning, psychological wellbeing, employment, and relationships.[18,19,28] The impact of symptoms on patients' lives increases with advancing stage of disease.[3,5,21,41]

> *"I would say, eighty percent of your skin open, ulcerated, a lot of pain, huge amount of pain."*[52]

In semi-structured surveys, UK patients with MF/SS described their skin as oozing, infected, intensely dry, exfoliating, thin, and sensitive.[18]

> *"I can't sit down for very long. The skin's very thin and fragile so I can only sit down, well I can sit down ok on soft things but chairs, I have to have lots of cushions. I wear a sort of dressing, a hydrocolloid dressing which is sort of foam to try and protect the thin areas so that's been quite difficult"*[18]

They also described pain and practical limitations associated with skin cracking and bleeding, especially on hands and feet.[18]

> *"It affects the bottom of your feet. Your day-to-day sort of walking around in uncomfortable, because, because it hardens the skin and thickens it, areas, it doesn't matter what you do, whether you moisturize your feet all the time, use the steroid creams, it will crack and bleed, so it hurts"*[18]

Due to skin breakdown, patients become unable to regulate body temperature, becoming excessively hot (feeling burning) or cold (feeling chills), further exacerbating their discomfort. Those who feel excessively hot have reported that the heat increased the intensity of itching, especially at night. Overheating and discomfort were given as reasons for no longer sharing a bed with a partner. Individuals who feel excessively cold have reported that they need to have the heat on all the time.[18,36]

Skin symptoms, in particular, have a substantial negative impact on patients, caregivers, and resource use, with end-of-life care consisting of daily bandage changes, taking up to 2 hours at a time for district nurses and patients frequently in and out of the hospital for skin outbreaks (up to 10 days at a time).[3,5,21,41,52]

> *"It's just, you know, like blood everywhere and open sores every, all the time. They never seemed to really heal, like there was nothing that made it better really. You'd just cover them and eventually it might heal…"*[52]

Burden of itching or pruritus[5,28,53]

Pruritus is a common, unrelenting, permanent and potentially debilitating symptom.[19,28] It may become aggravated in the evening or by heat or water (e.g., bathing), and patients report that itching interferes with sleep or leads to insomnia.[18] In a survey of patients with CTCL, 88% of patients experienced pruritus, with 46% reporting that it affected them "often" or "all the time" per Skindex-29 assessment (mean [SD] Skindex-29 score: 2.2 [1.3]).[5]

> *"It really gets quite bad and…you want to scratch yourself to pieces. You'd like to just rip your skin off… even if you scratch it, it doesn't make any difference because it's the skin underneath"*[18]

In general, pruritus is more prevalent and severe in patients with advanced-stage CTCL than in those with early-stage disease (Table 4).[21,53]

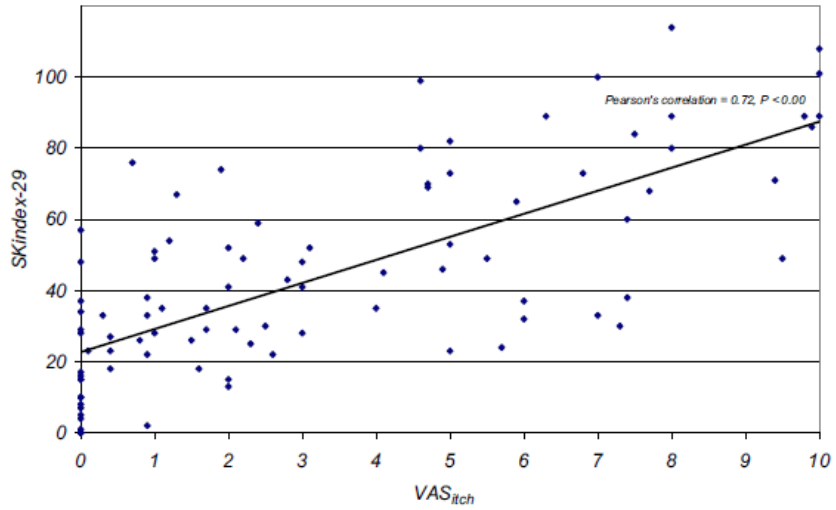
Table 4. Prevalence and severity of pruritus reported in patients with CTCL[53]

Patients	N	Prevalence, %	Severity, VAS_{itch}*	*P*-value (Severity, VAS_{itch})
CTCL, all	486	66.3	4.2 (0.18)	
Early-stage disease	373	61.9	3.4 (0.19)	<0.001
Late-stage disease (stages IIB–IVB)†	113	83.2	6.6 (0.36)	

*VAS_{itch} scale of 1–10 with higher scores indicating worse pruritus; data are reported as mean (standard error of the mean).
†Also referred to as advanced-stage disease.
Abbreviations: CTCL, cutaneous T-cell lymphoma; VAS, Visual Analogue Scale.

In advanced stages of disease, itching is described as ill-defined, severe, and diffuse resulting in a "burning pain" similar to neuropathic pain. Unlike pruritus in early-stage CTCL, which is often relieved by topical corticosteroids, this type of itching is not relieved by topical treatments (e.g., topical steroids or emollients) or oral antihistamines.[28] [redacted] In a study of 100 patients attending a UK referral centre for CTCL, greater pruritus intensity was associated with worse QoL (Figure 10).[5]

Figure 10. Correlation of intensity of pruritus (VAS_{itch}) and quality-of-life (Skindex-29 all domains)[5]



Skindex-29: higher scores indicate worse quality-of-life; VAS_{itch}: higher scores indicate increased intensity of itching.
Abbreviations: VAS, visual analog scale.

Burden of pain

Skin and musculoskeletal pain are common symptoms of CTCL, with 1 study (N=630) reporting 41% of respondents experienced "some pain" and 13% of respondents

experienced “quite a bit” or “very much pain”. Painful skin and joints associated with CTCL have also been reported to interfere with sleep, walking, and use of hands.[18,19]
EORTC Quality of Life Questionnaire – Core 30 (QLQ-C30) and SF-36 results showed that patients with SS experienced significantly greater pain compared with the general population.[21,54]

Patients have reported that skin pain prevents them driving, limits travel, and makes dressing changes uncomfortable.[18,22] Sore skin and musculoskeletal pain hampered sexual interactions and prevented participation in sports and hobbies.[18]

> *“Some of my joints are sore… that meant I couldn’t walk … so obviously I couldn’t play football… it was very, very painful”[18]*

Psychological, social and functional impact of CTCL

The psychological stressors of living with an often highly visible skin condition have a profound impact on patients’ emotional well-being, physical functioning, and relationships.[3] Patients experience depression, frustration, anger, anxiety, and worry about dying from CTCL.[19] They also become self-conscious due to the visibility of symptoms, especially when their disease affects exposed areas such as their face and hands.[18] In the 2005 National Cutaneous Lymphoma Foundation Survey, 62% of patients with predominantly early-stage MF reported that their disease made them feel unattractive, and nearly half reported that CTCL affected their social lives and desire to be with people.[19]

Hair loss, evidence of disease on hands or face, and red, scaling skin that sheds constantly cause embarrassment and body image concerns.[18]

> *“Losing hair is quite depressing and, especially for a woman, I think that that’s… the most difficult day to day thing... this takes your confidence completely away from you because of the way you look, and it’s on your face and arms, face, skin, hair, hands, you can’t hide that from people. And you have to keep putting a brave face on it, going out in to the street with a bright red face […] and pretending that you’re confident enough to do it”[18]*

Patients experience limited ability to fulfil the needs of their families, absences from work, restricted daily activities, negative impacts on social interactions, and disturbed sleep. More than half (66%) of respondents in the aforementioned National Cutaneous Lymphoma Foundation Survey reported that CTCL makes them feel tired. Fatigue and skin symptoms also interfered with sexual aspects of relationships.[18,19]

Caregiver burden in CTCL

CTCL places an extremely high burden on caregivers who, administer wound care and injections, and may be required to act as a dressing and wound specialist. Physicians report that many spouses of CTCL patients become fulltime caregivers, and that some patients require 3-4 hours of dressing changes per day.[55]

> *“But I did find it very difficult to do his dressings, when he couldn’t cope any more to do them […] The community nurses were coming in to do his dressings, because there, there was an awful one on his leg and I just, I couldn’t handle that one.”[52]*

Caregivers have the heavy burden of providing constant psychological support for patients whom – due to the nature of the disfiguring symptoms, isolation and social anxiety caused by

the disease – are sometimes suicidal.[20] Because of the rarity of the disease, few supportive resources (e.g., groups) are available.[20,52] The impact on caregivers, combating against depression and even suicidal thoughts by loved ones who have an incurable disease, should not be under-estimated.[20]

Caregivers reported sleep problems, panic attacks, and depression, even in cases where the patient was coping well. Although many caregivers cited the family unit as a source of support, some still experienced isolation and loneliness.[20] Overall, caregivers report witnessing a relative with CTCL progress from diagnosis to death was a prolonged and profoundly traumatic experience.[52]

"I saw a psychotherapist […] It's a traumatic illness […] traumatic to witness."[52]

Financial implications

Cutaneous T-cell lymphoma has a negative financial impact on patients, as well as their caregivers and families. Patients with MF or SS have reported greater financial problems than did the general population (as measured by the EORTC-QLQ-30),[21] and a US survey of CTCL patients (89% MF) revealed that 61% felt burdened financially by their disease.[19] Patients with CTCL may have to stop working, and financial strain is compounded when their caregivers need to reduce working hours to meet the demands of the disease.[20]

Health-related quality of life

CTCL causes significant morbidity and disfigurement, and adversely affects patients' quality of life.[3,18,19,21] Patients with advanced-stage CTCL reported significantly greater adverse effects on their general health, especially with regard to their physical, emotional, and functional well-being, compared to those with early-stage disease.[3] Similarly, a study of 100 UK patients with CTCL revealed that individuals with advanced-stage CTCL had significantly worse HRQL (as measured by the Skindex-29, where higher scores indicate lower HRQL; Table 5).[5] Similar trends in HRQL decrements for patients with advanced disease have been reported.[21,41]

Table 5. Skin-specific HRQL as measured by Skindex-29 in UK patients with MF/SS[5]

Skindex-29 and subscale scores	All Stages	Early-Stage	Advanced-Stage
Total Skindex-29	43.3 (27.7)	38.5 (26.7)	50.8 (27.9)*
Emotions	15.8 (10.3)	14.7 (9.7)	17.5 (11.2)
Symptom	11.3 (6.5)	10.3 (6.2)	12.9 (6.7)
Functioning	16.1 (13.4)	13.4 (13.2)	20.4 (12.9)*

Data are mean (SD); early stage defined as MF stages IA–IIA; advanced-stage defined as MF stages IIB–IVB.
*Significant difference vs. early-stage disease ($p<0.05$).
Skindex-29 scores range from 0–116 (total score), with higher scores indicating a worse HRQL.
Abbreviations: HRQL, health-related quality of life; MF, mycosis fungoides.

Healthcare resource use and societal burden

The CTCLs have, in effect, a 'double nature', meaning that in addition to the typical aspects related to cancer, they also present with major skin involvement which requires extensive

care to address both aspects of the disease.[21] Patients with advanced-stage CTCL suffer a higher symptom burden than early stage patients, and most eventually die from their disease, frequently due to complications associated with compromised skin and poor immune function (e.g. sepsis).[12,29] Furthermore, because patients with CTCL tend to live much longer than patients with many other malignancies, and quickly exhaust the available treatment options, they are likely to spend a significant amount of time in a resource-intensive, end-stage symptom management phase.

Resource demands for patients with advanced-stage CTCL are high, and their care involves multiple specialised services within a hospital, including haematology, oncology, dermatology, nursing, wound care, psychology, pharmacy, and outpatient services. There are additional challenges for patients who live far from the specialist centre.[36]

The vast skin involvement at late stages (e.g., up to 80% of total body coverage[52]), requires levels of health service utilisation that mirror those of severe skin conditions. In a US audit, skin disease was found to be one of the top 15 groups of medical conditions for which prevalence and health care spending increased the most between 1987 and 2000. This study found that the estimated annual cost of skin disease in 2004 was $39.3 billion, including $29.1 billion in direct medical costs (costs of health services and products) and $10.2 billion in lost productivity costs (defined as costs related to consumption of medical care, costs associated with impaired ability to work, and lost future earning potential because of premature death).[56] In a US administrative claims database from private and governmental insurance providers, cutaneous lymphoma was found to have the lowest prevalence (0.02%), but the highest cost relative to its prevalence compared to 23 other categories of skin disease (cost was 19.6 times greater than prevalence.[57]

Although these were US-based studies, the high health care resource utilisation and economic burden is likely to translate well to the burden placed on the NHS because the nature of skin conditions and their required care is consistent regardless of geography.

Limited literature exists on the resource utilisation and financial burden of CTCL. Our literature review identified three studies; one Italian (Ricci et al 2005[58]) and two US based (Gu et al 2016[59]; Tsang et al 2018[60]). The Italian study investigated direct medical costs of MF in specialised centres and found that the resource burden was high, particularly for day hospital care while patients were receiving systemic therapies (i.e., MF Stage ≥IIB). Meanwhile, full hospital admissions were common for patients in later stages, indicative of end-stage management. The study also reported significant in-hospital resource requirements for patients with CTCL;[58] however, due to the objective of the study, symptom management which takes place outside of the specialised centres, was not captured. This would have included infection control and wound care (i.e., dressings) which are fundatmental components of care in advanced-stage CTCL.

Two recent audits by a San Francisco group looked to quantify the financial and healthcare utility burden of patients with MF, both early and advanced stage. In both, a retrospective cohort study was conducted of commercially insured US populations based on the HealthCore Integrated Research Database on patients aged over 18 years with a diagnosis of MF CTCL.[59,60] Both studies found that, over a 12-month period, patients with severe MF CTCL had significantly higher healthcare utilisation and higher MF CTCL-related and all-cause costs than patients with mild-to-moderate MF CTCL. The larger 2018 cohort study further found that patients in the severe group had more than three times higher all-cause

total costs and more than five times higher MF CTCL-related total costs relative to mild-to-moderate patients (both p<0.0001), while controlling for other factors. The difference in resources used included emergency room visits, inpatient admissions, length of stay in hospitals (7.3 ± 16.9 days vs. 1.4 ± 8.3 days, p<0.0001), and pharmacy-related claims.[60] Of particular note was the very high frequency of physician visits and other outpatient services for severe disease.

Based on the natural history of CTCL (increasing symptom burden), the trend observed in both US studies of increased costs and resource utilisation with increased disease severity, end stages of the disease, once patients have exhausted all systemic treatment options and management, is focused on symptom control and are likely to have the largest resource burden. [redacted] No studies have looked at the quantitative resource impact of patients at this stage of CTCL. However, a qualitative study of bereaved families of CTCL patients offers some insights into the nature of treatments, as well as the frequency and length of visits characterised as lengthy, frequent, painful and with limited relief offered despite multiple treatments, especially related to pruritus and wound healing.[52]

[redacted]

End-stage care for patients with advanced CTCL

Most patients who progress to, or present with, advanced-stage CTCL die from their disease, frequently due to complications associated with compromised skin and poor immune function (e.g., sepsis).[12,29] Approximately 50% of patients with CTCL, particularly those with advanced-stage disease, ultimately succumb to infectious complications.[9]

The later stages of CTCL are characterised by a huge burden to patients, their carers and the healthcare system. In the end-stage, patients have to deal with recurring infections, severe pain, distressing and intractable itch; in addition, the psychological impact of the visual appearance of the skin is devastating to patients and caregivers.

The duration of response to currently available treatments in advanced CTCL is generally short and patients will likely exhaust these active treatment options quite quickly. Patients ultimately progress to an end stage where healthcare providers (HCPs) are only able to manage symptoms but no longer have active therapy options to control disease (see Response rates and survival, under section B.1.3.1). Unlike other cancers that require

supportive end-of-life care, in CTCL this state can be prolonged with some patients living for many months or even years, but requiring a high level of clinical input throughout that time period.

With limited options for alleviation of symptoms, there is substantial economic burden to the healthcare system; patients have multiple ulcerated lesions that are highly susceptible to infection requiring frequent and lengthy visits to the hospital for painful wound management with specialised dressings. Some patients with advanced CTCL need to be managed in burns units because these are the only places equipped to meet their wound care needs.[36]

Significant resources are required for the management of symptoms, including not just wound care, but pain management, other symptom control (including continuous pruritus, infections, bone marrow depletion), management of psychological distress and other comfort measures including localised radiation, topical steroids, occlusive dressings, wet wraps, wound dressings, and bandages.[61]

An account by a bereaved CTCL patient's husband profoundly describes this state:

> *"What you've got to realise is it's a very, very painful thing to have […] she had two morphine drivers, and it really is a slow lingering death, you wouldn't, you wouldn't really want to wish it on your worst, worst enemy*."[52]

Despite the progressive, incurable nature of end-stage CTCL, a recent systematic review found limited evidence related to the palliative care needs and outcomes in this population. The literature that does exist is predominantly qualitative and is based on semi-structured interviews; however, there is evidence of a profound negative impact on patients' quality of life (QoL).[22]

> *Husband: "I mean I'd got to a point where if I had the means I would, I would happily have, you know, put my wife to sleep, I can't see how they can allow a human being to suffer like that."*[52]

The objective of end-stage care for patients with advanced CTCL is to maintain QoL, which has been shown to improve symptom management, communication, and satisfaction of patients and caregivers in advanced CTCL. However, there is substantial unmet need with respect to psychosocial, spiritual, and caregiver support for these patients.[22]

Bereaved family caregivers reported having been overwhelmed by the demands of care-giving and the impact of CTCL on their lives. Unique to CTCL, traditional family means of care and comforting such as touching and hugging are sometimes not possible for end-stage CTCL patients due to the frailty of their skin, and this often has a profound negative impact on both the patients and carers.

Although visits to day clinics and homecare by peripheral support teams (i.e., district nurses and palliative support teams) is very frequent, the need to provide symptom relief is so constant that family members are also required to provide treatment. Some family members struggle to deal with the newfound demands of providing care to loved ones, particularly undertaking complex dressing changes and dealing with psychological distress, depression and suicidal tendencies. An example of the high impact on carers is illustrated by a bereaved wife's accounts:

> *'But I did find it very difficult to do his dressings, when he couldn't cope any more to do them. Um, I'm not a very brave person with things like that. […] I was ashamed to say really, 'cos it made me feel very weak.[…] The community nurses were coming in to do his dressings, because there, there was an awful one on his leg and I just, I*

couldn't handle that one. He thought I could, but I said "I can't, my love". So they came in and did that one'[52]

In summary, the CTCL end-of-life health state is poorly quantified in the literature and the published evidence as far as it exists is largely qualitative. Quantitative tools that have been used have been deemed inadequate to capture the depth and range of patient experiences.[18]

The current literature also fails to capture, and under-reports, the full details of the level of care required, which can range from hospital inpatient care to the use of burns units to outpatient support, requiring frequent visits from district nurses to assist with dressing changes and wound care.[36]

In order to fully capture the extent of care and resource use at the end-stage of CTCL, Takeda conducted questionnaire based semi-structured interviews with 6 of the 7 supra-regional centres in England and the leading Welsh centre. The findings from this research can be found in Appendix L and were used as inputs to the health economic model, as described in Section B.3 of this dossier.

B.1.3.3 Clinical pathway of care

Patients with CTCL are managed primarily according to the type of CTCL and the stage of disease.[16,32,62] 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.[9,17,31] Prolonged survival and the potential for a cure can only be achieved with alloSCT, however this is an option for the few patients who are able to achieve a good response with current standard of care (SOC).[19,34]

[redacted] This section will focus on these guidelines which are not anticipated to change prior to publication (Figure 11).

Supra-Regional Centres

Due to the rarity and completxity of CTCL, according to the 2006 NICE Guidance on Improving Outcomes for People With Skin Tumours Including Melanoma [CSG8][64] on CTCL management, all patients with early-stage MF refractory to skin-directed therapy (SDT) and late-stage MF/SS should be reviewed by supra-network multi-disciplinary teams (MDTs) to agree on a management plan and provide the opportunity for consideration in appropriate clinical trials. A supra-regional centre requires the following:

- a CTCL-specialised MDT,
- facilities to deliver total skin electron beam (TSEB) therapy, and
- facilities to deliver extracorporeal photochemotherapy (ECP)

Based on the aforementioned requirements, there are seven supra-regional centres in the UK, as listed in Appendix L. In addition to the seven supra-regional centres within England, Bristol and Southampton both have ECP facilities; however due to the absence of the other requirements, refer their patients to the London. In the devolved nations, Belfast, Cardiff and Glasgow offer network lymphoma services but this is based on guidance from their referral supra-regional network. The expertise on advanced CTCL and therefore the management of

patients in the UK is very concentrated with all advanced patients being treated by one of seven centres.This means this is a very high level of consistency in how patients are managed across the UK, and that for a new medicine like brentuximab vedotin, its use would be easy to monitor and standardise.

Treatment Pathway

EORTC[16] [redacted] list treatment options by disease severity and line of treatment. Due to the limited effi**c**acy of available 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.[16,34,62] No single agent prior to brentuximab vedotin has provided clinical benefit across CTCL subtypes, and current treatments are characterised by low response rates and short durations of response.[8,34,65,66]

Early-stage (IA–IIA) disease

[redacted]

Advanced-stage (IIB–IVB) disease

In advanced-stage CTCL, treatment is aimed at disease control and improving/ maintaining QoL.[19] Standard of care is systemic therapy, and a number of agents are available in the UK; however the outcomes with these agents are characterised by low response rates and limited duration of response (usually <1 year).[17,31,32] ORRs vary widely across subtypes and studies but can generally be characterised as suboptimal/low.[8,34,65,66] For patients with advanced disease, prognosis remains poor.[16]

Category A systemic therapies

Initial systemic treatment options for advanced CTCL (known as *Category A* systemic therapies) comprise low-dose methotrexate tablets [Maxtrex®], retinoid/rexinoids (e.g., bexarotene capsules [Targretin®]), and the biological response modifier interferon (IFN)-α (IntronA®).[16,31,67] Low-dose methotrexate and IFN-α are not currently licensed in Europe for the treatment of CTCL, however both are used as there are limited treatment options. In 2017 the EMA approved brentuximab vedotin (ADCETRIS®) for the treatment of adult patients with CD30+ CTCL after ≥1 prior systemic therapy.[7,68]

Category A systemic therapies are associated with minimal immunosuppression and a lack of cumulative toxicity, which allows them to be used to maintain remission.[33] However, EORTC and the previous version of the BAD/UKCLG guidelines from 2003 state that *Category A* therapies are supported by outdated studies and low levels of evidence.[17,62] Studies of bexarotene monotherapy, low-dose methotrexate monotherapy, and IFN-α combinations in patients with CTCL have yielded ORRs of 39%–86%,[65,66,69-74] 33%–58%,[75,76] and 68%,[77] respectively. Furthermore, responses to *Category A* therapies rarely last longer than 6–9 months in the first-line setting.[34] [redacted]

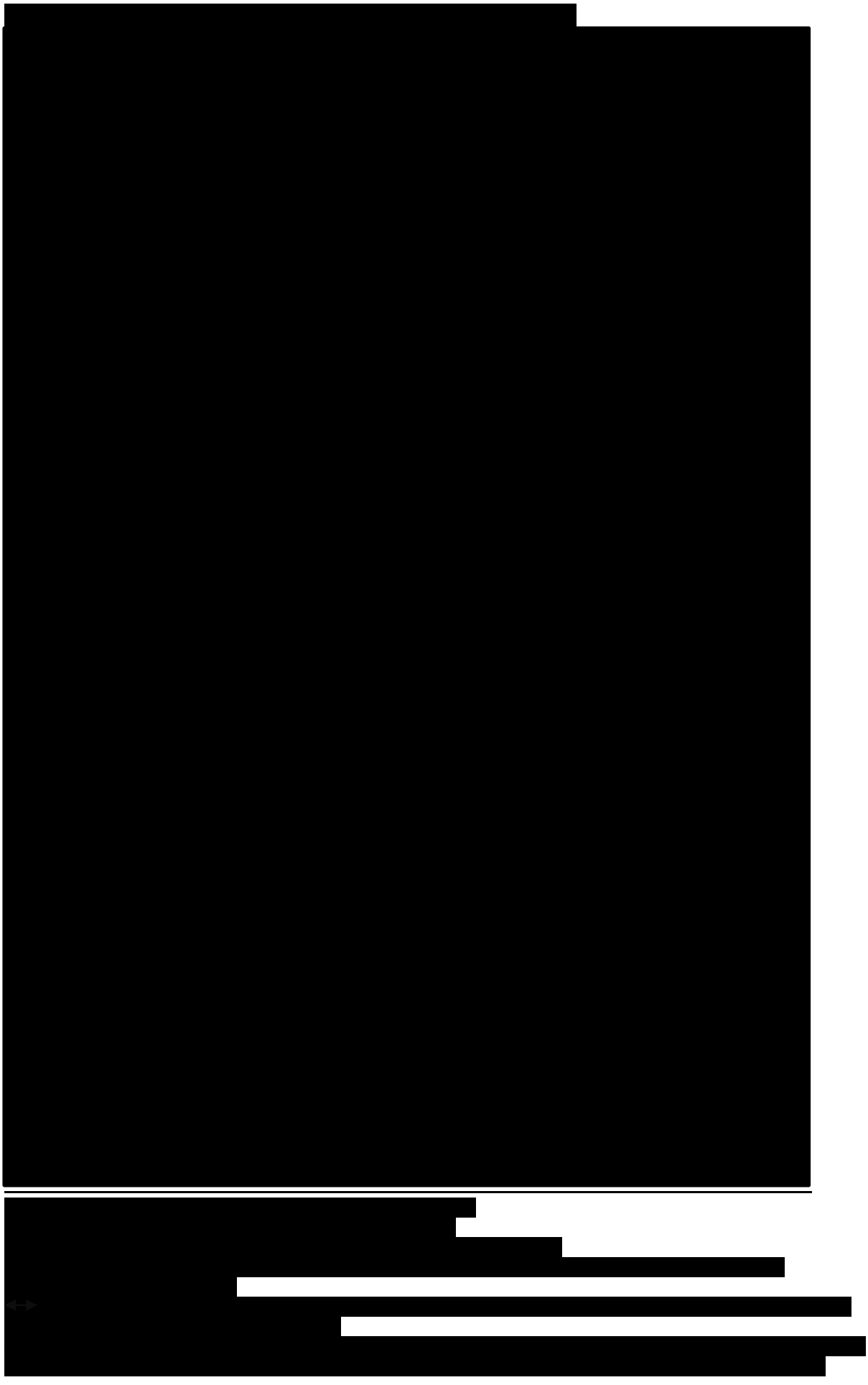
[redacted]

Category B systemic therapies

As patients progress and *Category A* therapies become ineffective, the next stage of treatment generally involves chemotherapies (known as *Category B* systemic therapies). *Category B* therapies include gemcitabine, pegylated liposomal doxorubicin (not available to all centres), and multi-agent chemotherapy regimens, most notably, CHOP.

After *Category A* systemic options have been exhausted, gemcitabine monotherapy is commonly used as many patients have difficulty completing multi-agent chemotherapy. Multi-agent chemotherapy is seen as a last resort due to toxicities such as increased immunosuppression, which is problematic for infection-suceptible CTCL patients.[8,16] In studies of gemcitabine monotherapy in patients with CTCL, ORRs were 48%–68%,[78-80] and durations of response were were 4.1 months.[79] Similarly, studies of pegylated liposomal doxorubicin returned ORRs of 41% (median duration, 6 months)[81] and 54%.[82] CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is used to treat advanced-stage MF, SS, and pcALCL,[16,30] but supportive studies are scant and dated. EORTC and UKCLG guidelines also include TSEB in their recommendations for treatment of advanced-stage MF and SS.[16,62] In a UKCLG study of TSEB in 103 patients with MF (advanced-stage, n=59), ORR was 87% (CR 18%; PR 69%; SD 8%; PD 5%). Median PFS was significantly longer in patients with stage IB disease compared with stage IIB (26.5 months vs 11.3 months; HR: 2.66; p=0.003), and compared with stage III (26.5 vs 10.2, respectively; HR:4.62; p=0.002).[83]

Category B agents can only be taken for a short period of time (e.g., to a max of 6 months) due to drug-related toxicities. Patient co-morbidity may preclude the use of some *Category B* systemics (i.e., CHOP due to neutropenia and the high sepsis susceptibility of CTCL patients). Overall, the toxicity of treatment must always be balanced against the goals of disease control and improvement/maintenance of QoL.



[redacted]

Allogeneic Stem Cell Transplantation (alloSCT)

[redacted].[63] A patient-level meta-analysis conducted by Wu et al 2009 reviewed all published literature on outcomes with autologous SCT (ASCT) and alloSCT in CTCL (N=39 advanced-stage MF/SS patients). While ASCT had limited effect on CTCL outcomes, alloSCT significantly improved survival outcomes. OS rates at 1 year and 5 years after SCT were 85% and 80%, respectively, in the alloSCT group vs. 68% and 23%, respectively, in the ASCT group (p=0.027; Figure 12A). Event-free survival (EFS) demonstrated a significantly more durable response with alloSCT over ASCT (p=0.002; Figure 12B). In the alloSCT group, 1-year and 5-year EFS rates were 65% and 60%, respectively.[14]

Figure 12. Overall survival and event-free survival with alloSCT vs. ASCT in Wu et al 2009[14]

A.

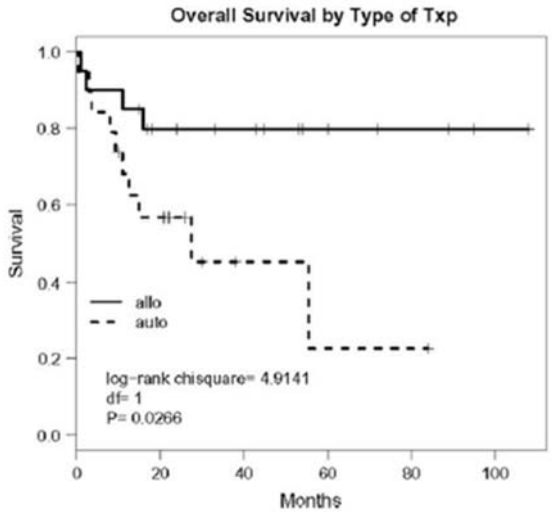


Figure 1. OS of patients with MF receiving an allogeneic transplant (allo) or an autologous transplant (auto), $P = .027$.

B.

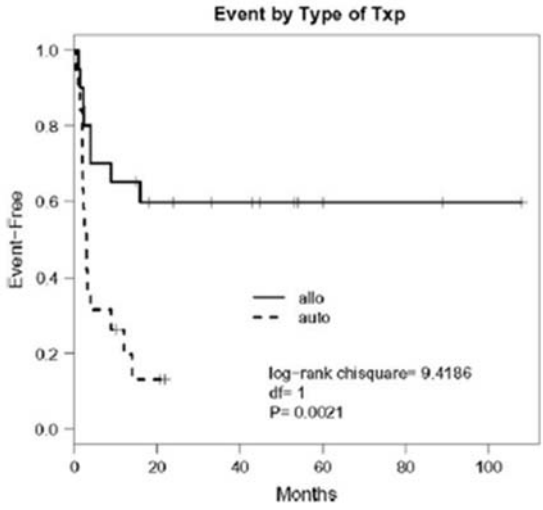


Figure 2. EFS of patients with MF receiving an allogeneic transplant (allo) or an autologous transplant (auto), $P = .0021$.

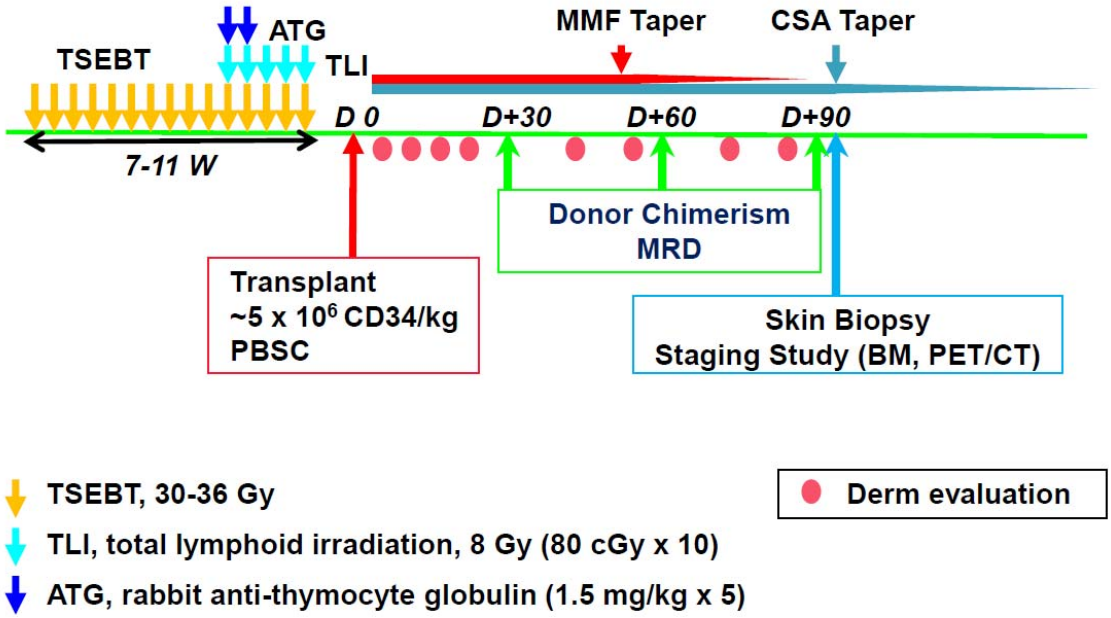
Abbreviations: alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant.

Despite the positive impact of alloSCT on survival, its use in the NHS has been modest to date due to the inability of currently available agents to provide sufficient response rates to enable patients to quality for transplant (i.e. achieving at least a PR with systemic therapy prior to alloSCT).[84] [redacted].[16,32,63]

Currently, the leading supra-regional centres for alloSCT in the UK are London (treatment decisions are made at Guy's and St. Thomas, while transplants are conducted at the Hammersmith hospital), and Birmingham. Due to the sepsis-prone nature of patients with CTCL and the associated symptom burden, alloSCT for CTCL is conducted using a different

conditioning regimen than for other diseases. Transplants performed in the UK and in other international centres for CTCL use a reduced-intensity conditioning (non-myeloablative) regimen called the Stanford Protocol, composed of TSEB in the weeks leading up to the procedure followed by conditioning with anti-thymocyte globulin (ATG) and total nodal lymphoid irradiation (Figure 13).[85] This combination is highly immunosuppressive, but has a lower risk of neutropenia than standard conditioning, which is a key consideration given that CTCL patients are highly prone to infections.[29,85]

Figure 13. Stanford protocol for reduced-intensity conditioning[25,85]



Abbreviations: ATG, anti-thymocyte globulin; BM, bone marrow; CSA, ciclosporin; CT, computed tomography; MMF, mycophenolate mofetil; MRD, minimal residual disease; PBSC, peripheral blood stem cell; PET, positron emission tomography; TSEBT, total skin electron beam therapy.

The introduction of the Stanford Protocol has improved outcomes from those observed in Wu et al (2009).[14] In this single-centre UK study of alloSCT with minimal-intensity conditioning in advanced CTCL, patients (n=18, median age, 47 years), 1- and 5-year OS rates of approximately 80% and 55%, respectively, were observed.[15] Outcomes from 32 patients transplanted over 5.5 years (MF + LCT, n=12; SS, n=20) demonstrated an ORR of 90% at median follow-up of 36 months (best clinical response at 3 months: CR, n=19; PR [near CR], n=7; SD, n=1; PD, n=2). The 2-year OS rate was 75% and 2-year PFS rate was 51%; median OS was not reached and median PFS was 42.9 months.[25]

Clinicians expect these outcomes to further improve with maturing data and with better patient selection of those eligible for an alloSCT. In addition, based on the experience in other lymphomas, the higher response rates (in particular CR rates) that can be achieved with brentuximab vedotin compared to previous bridging (induction) agents might reasonably be expected to lead to better outcomes post-alloSCT than have previously been possible.

Despite alloSCT being the only realistic hope for a cure for advanced-stage CTCL [redacted]

[redacted].[36] UK clinical experts attribute this low uptake of alloSCT to the poor PR and CR rates achieved with current treatment regimens. Although alloSCT eligibility is restricted by age,

co-morbidities and the ability to find a suitable donor, with modern advancements in matching and alloSCT procedures, UK clinical experts estimate that 40% of all patients with CTCL who achieve a PR or better could undergo an alloSCT in the UK.

End-stage care for patients with advanced CTCL

As patients have exhausted all active treatments, the focus of end-stage care is to provide symptom management and maintain QoL. End-stage care includes infection control, pain management, and other comfort measures including localised radiation, topical steroids, occlusive dressings, wet wraps, wound dressings, and bandages.[16,61,86] Some patients requiring intensive medical care are treated in burn units, because these are the only places equipped to meet their wound care needs.[36]

Takeda surveyed UK specialist lymphoma nurses and consultants at supracentres that treat patients with end-stage CTCL to assess what treatment patients receive [redacted]

Further information on the end-stage treatment pathway for patients with CTCL, and associated NHS resource use, is provided in Appendix L.

Place of brentuximab vedotin in the treatment pathway

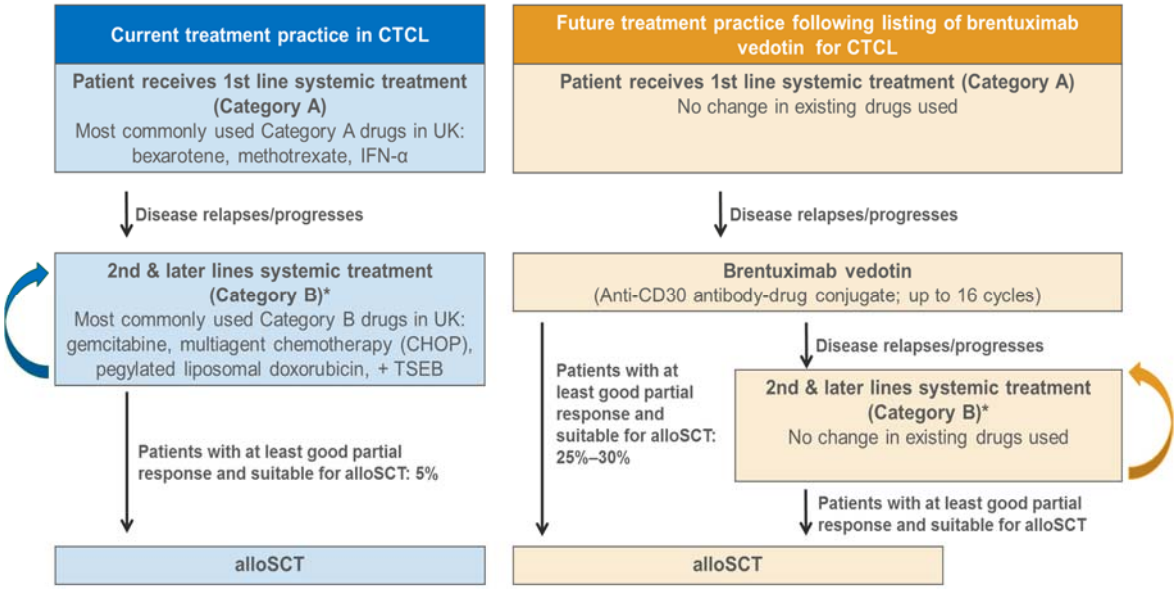
Per the licensed indication [redacted][63] it is anticipated that in the UK brentuximab vedotin will be used in the treatment of adult patients with CD30+ CTCL after at least 1 prior systemic therapy (second-line treatment option for stages IIB–IVB). [redacted][63] patients receiving brentuximab vedotin are anticipated to have advanced-stage disease and have received at least 1 *Category A* systemic treatment before receiving brentuximab vedotin (Figure 14). [redacted][36]

Brentuximab vedotin offers a new treatment option for patients with a high unmet need. It is anticipated to delay the use of second and later line, *Category B* systemic therapies by providing disease control and maintenance of quality of life. It also has the potential to displace *Category B* therapies in the treatment pathway should a patient achieve a sufficient response to be eligible for alloSCT.

Based on the much improved levels of disease response seen in the ALCANZA trial (an unprecedented 15.6% of patients achieved a CR with brentuximab vedotin, compared to only 1.6% for physician's choice of bexarotene or methotrexate), UK clinical experts believe that brentuximab vedotin offers excellent potential as a bridging agent in CTCL. The availability of brentuximab vedotin could therefore have a profound impact on the treatment pathway in the UK, allowing more patients with advanced disease the prospect of pursuing a potentially curative route. Using the response rates from ALCANZA for brentuximab vedotin and an age cut-off of 65 years for alloSCT, it is anticipated that 25%–30% of brentuximab vedotin-treated patients could be bridged to an alloSCT (as recommended in the BAD/UKCLG guidelines), compared with only ~5% currently.

Based on the agreed positioning of brentuximab vedotin in the BAD/UKCLG guidelines, should it become available on the NHS, the decision to prescribe brentuximab vedotin will be limited to the seven supra-regional centres. This will make it easy to standardise and monitor the prescribing of brentuximab vedotin for advanced CTCL.

Figure 14. CTCL treatment pathways – current and future including brentuximab vedotin



*Patient commonly receives several sequential Category B treatments.
Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CTCL, cutaneous T-cell lymphoma; IFN, interferon; TSEB, total skin electron beam therapy.

B.1.3.4 Equality considerations

There are no equality considerations for brentuximab vedotin treatment in CTCL.

B.2. Clinical effectiveness

The most robust evidence supporting the efficacy of brentuximab vedotin in treating CD30+ CTCL is the Prince et al 2017, ALCANZA trial. ALCANZA was an international, open-label, randomised, phase III multicentre trial of brentuximab vedotin versus physician's choice (PC) of methotrexate or bexarotene in patients with CD30+ CTCL who had received at least 1 prior systemic therapy (MF and pcALCL) or radiotherapy (pcALCL only).[47]

At the time of publication, ALCANZA was the first reported and largest phase III trial in CTCL of a systemic agent tested against active standard comparator. Unlike many previous studies, ALCANZA had a very robust measurement of efficacy, being the first trial to utilise current international consensus response criteria incorporating skin, nodal, visceral, and blood responses. Its primary endpoint, overall response rate lasting at least 4 months (ORR4), captured the aforementioned consensus response criteria as well as duration of response as a single measurement.[47] This is particularly relevant to the CTCL patient population, for whom short clinical responses do not always correlate with significant clinical benefit.[47] In addition, skin responses in ALCANZA were extremely stringent with CR being 100% clearance of lesions, and PR being 50%–99% clearance of lesions, with no new tumours.

The primary data analysis from ALCANZA was assessed per independent review facility (IRF) and investigator (INV) at a median (95% CI) follow-up of 22.9 months (18.4–26.1).[47] An updated analysis of treatment response and clinical benefit per INV was assessed after a median follow-up of 33.9 months (data cut-off 16 August 2017).[87]

- At 22.9 months follow-up, brentuximab vedotin significantly improved ORR4 vs. PC (56.3% vs. 12.5%, respectively; p<0.0001)[47]
- Patients treated with brentuximab vedotin had significantly longer progression free survival (PFS) of 16.7 months vs. 3.5 months with PC (p<0.0001)[47]
- Significantly more brentuximab vedotin patients achieved complete response (CR), defined as complete resolution of symptoms as assessed by global response score, vs. PC (15.6% [10 of 64] vs. 1.6% [1 of 64]; p=0.0046)[47]
- Brentuximab vedotin provided significant symptom relief for patients, as shown by a 27.96-point mean decrease in Skindex-29 scores vs. an 8.62-point decrease with PC (bexarotene or methotrexate; p<0.0001)[47]
- Brentuximab vedotin significantly delayed the time to subsequent anticancer therapy by up to 9 months compared with PC (14.3 months vs. 5.5 months; p<0.001)[88]

At a median follow-up of 33.9 months, ALCANZA data continued to support the superior clinical activity of brentuximab vedotin vs. PC in terms of improved ORR4, CR, ORR, progression-free survival (PFS), quality-of-life per Skindex-29, and time to subsequent anticancer therapy[87]

- At 33.9 months follow-up, patients treated with brentuximab vedotin had significantly longer PFS vs. PC (15.8 months vs 3.6 months; p<0.001); in addition, more advanced patients achieved CR with brentuximab vedotin vs. PC (20.4% vs 2.2%)[87]

The change in PFS and ORR between treatment arms was even more striking in the subgroup of patients with advanced-stage disease (MF stage IIB and above) at 33.9 months of follow-up.[89]

- Median PFS per INV: 16.5 months vs. 3.5 months, respectively
- ORR: 69.4% vs. 17.4%, respectively

Overall, 128 patients received study treatment and were included in the safety population (brentuximab vedotin, n=66; PC, n=62) at 22.9 months of follow-up. Treatment with brentuximab vedotin, compared with methotrexate or bexarotene, was not associated with any new or unexpected toxicities. Overall, brentuximab vedotin has a generally manageable toxicity profile, with the majority of adverse events reported as less than grade 3, in the CD30+ CTCL indication.[47]

Serious adverse events (AEs) were similar between groups, occurring in 19 (29%) of 66 patients in the brentuximab vedotin group vs. 18 (29%) of 62 patients in the PC group. Discontinuation due to AEs occurred in 16 (24%) patients in the brentuximab vedotin group, mainly due to peripheral neuropathy, vs. 5 (8%) in the PC group.[47]

At a median follow-up of 33.9 months, ALCANZA safety data were consistent with the primary analysis at 22.9 months of follow-up. The most common AEs were gastrointestinal disorders (n=9) and peripheral neuropathy (n=7) in the brentuximab vedotin arm; hypertriglyceridaemia was the most common AE in the PC arm (n=12).

In addition to ALCANZA, two single-arm trials (phase II, investigator-initiated trials: Kim et al 2015 and Duvic et al 2015) confirmed the efficacy and acceptable tolerability profile of brentuximab vedotin in the treatment of MF and pcALCL but also in SS and LyP.[24,90,91]

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to retrieve relevant RCT and non-RCT data from published literature regarding the efficacy and safety of brentuximab vedotin and current therapies for treating relapsed or refractory CTCL.

A comprehensive search strategy was designed to capture evidence for comparators beyond those defined in the appraisal scope. Searches were originally conducted on 9 January 2017 and were then searched again to update the SLR on 16 January 2018. In the original search the search term “transplant” was applied with an eligibility criterion to include autologous stem cell transplantation (ASCT) as an intervention. However during the January 2018 update of the current SLR, all citations were rescreened to include only allogeneic stem cell transplantation (alloSCT) to be consistent with clinical feedback and the current treatment paradigm. The citations from both the original and updated searches were rescreened to identify any studies that met this clarified eligibility criterion.

In May 2018, for the purposes of this submission, an additional exclusion criterion was added at the end of the SLR process. This was added to identify evidence relevant to NICE scope and local care pathways and exclude all other experimental or non-standard of care therapy approaches, or therapies not available in the UK.

The database search strings identified all relevant studies (full papers or abstracts from any conferences) indexed in MEDLINE and were modified for performing searches in Embase and the Cochrane Library, to account for differences in syntax and thesaurus headings. Searches included terms for free text and Medical Subject Heading (MeSH) terms. Full search strings and hits are provided in Appendix D.1.1.4.

Original review (January 2017)

The electronic database searches identified 7,916 citations, of which 6,624 citations were screened based on title and abstract after removal of 1,292 duplicates. Exclusion of 6,308 citations at this stage resulted in 316 remaining citations for which full publications were obtained and assessed. A further 282 citations were excluded based on the full text review. Hand-searching identified an additional 29 publications (n=9, congress presentation; n=20, bibliographic searching), resulting in 63 publications reporting on 54 unique studies that met the pre-defined inclusion criteria and were included in the SLR.

Update searches (January 2018)

The update search identified a total of 1,137 publications through the electronic searches. Upon removal of 235 duplicates, 902 titles and abstracts were screened. Full publication review was completed for a total of 80 references, at which stage a further 78 studies were excluded and the rationale documented. Two publications identified in the 2018 update search superseded conference abstracts identified in the original search were excluded.

Rescreen for studies with allogeneic stem cell therapy (alloSCT) as comparator

During the January 2018 update, alloSCT was identified as a comparator of interest. The citations from both the original and update searches were rescreened to identify any studies that met this eligibility criterion. Eleven studies were identified from the original search and no additional publications from the updated search.

Assessment of relevance to NICE scope (May 2018)

All included references from both 2017 and 2018 reviews were rescreened to identify only the evidence that met NICE inclusion criteria based on intervention. The SLR schematic is shown in Appendix D.

In total, four studies were identified that reported data on brentuximab vedotin (see Section B.2.2). In addition, 32 publications were identified that reported data on interventions relevant to the NICE scope. These studies did not directly compare efficacy and safety vs. brentuximab vedotin.

Appendix D details the full process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 *List of relevant clinical effectiveness evidence*

In total, four studies were identified that reported data on brentuximab vedotin (Table 6): one phase III trial, ALCANZA (Prince et al 2017), referred to by its trial name in this document; two single-arm trials (phase II, investigator-initiated trials: Kim et al 2015[24] and Duvic et al 2015[91]); and one retrospective study (Mathieu et al 2016[90]), and were considered relevant to the decision problem.

ALCANZA is the phase III international, randomised open-label label study of brentuximab vedotin vs. physician's choice of methotrexate or bexarotene and provides the most robust data for brentuximab vedotin for the treatment of CTCL with 131 patients enrolled and 128 analysed in the intent-to-treat population (ITT). To date, it is the largest phase III trial in CTCL of a systemic agent tested against active standard comparator.[47]

Table 6. Clinical effectiveness evidence

Study	Prince et al 2017; ALCANZA; NCT01578499[47]				
Study design	International, multicentre, randomised open-label study of brentuximab vedotin vs. PC (methotrexate or bexarotene)				
Population	Adults with CD30+ CTCL (MF or pcALCL) who received prior radiation therapy or ≥1 prior systemic therapy (pcALCL) or ≥1 prior systemic therapy (MF)				
Intervention(s)	Brentuximab vedotin, methotrexate, or bexarotene				
Comparator(s)	Methotrexate or bexarotene				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No	
Rationale if trial not used in model	*Not applicable*				
Reported outcomes specified in the decision problem	PFS, response rates, adverse effects of treatment, health-related quality of life				
All other reported outcomes	ORR4, DOR, duration of skin response, EFS[88]				

Abbreviations: CTCL, cutaneous T-cell lymphoma; DOR, duration of response; EFS, event-free survival; MF, mycosis fungoides; ORR4, rate of objective global response lasting ≥4 months; OS, overall survival; PC, physician's choice; pcALCL, primary cutaneous anaplastic large cell lymphoma; PFS, progression-free survival.

Study	Kim et al 2015; NCT01396070[24]				
Study design	Multicentre, open-label, single-arm study of brentuximab vedotin				
Population	MF or SS, stages IB–IVB, with ≥1 systemic therapy failure				
Intervention(s)	Brentuximab vedotin				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	
	No			No	X
Rationale if trial not used in model	The Kim study included a total of 32 patients of which 3 (9.4%) had SS. Median PFS was not reached and OS data were not reported, both key inputs into the cost effectiveness model. The trial is single-arm, and an indirect treatment comparison would require the use of population adjustment (e.g. MAIC), which was not considered realistic due to the low sample size. The ALCANZA trial was deemed the highest quality data available and was therefore used for MF.				
Reported outcomes specified in the decision problem	PFS, response rates, adverse effects of treatment				
All other reported outcomes	DOR, EFS, TTR				

Abbreviations: DOR, duration of response, EFS, event-free survival; MAIC, matching-adjusted indirect comparison; MF, mycosis fungoides; PFS, progression-free survival; SS, Sézary syndrome; SoC, standard of care; TTR, time to response.

Study	Duvic et al 2015; NCT01352520[91]				
Study design	Single-centre, open-label, single-arm study of brentuximab vedotin				
Population	CD30+ LyP in need of systemic therapy, or previously treated pcALCL or MF				
Intervention(s)	Brentuximab vedotin				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	
	No			No	X
Rationale if trial not used in model	A median PFS of 1.1 years (95% CI 0.9–1.4) for the overall study population was reported, but the OS data were immature. There were a total of 54 patients of whom 31 (57.4%) had MF and three patients (5.6%) had pcALCL. Ten patients (18.5%) had LyP and ten patients were diagnosed with multiple CTCL subtypes. The use of this trial for LyP economic analysis was explored however it was deemed inappropriate. As this was a single-arm trial, any indirect comparison would require the use of population adjustment (e.g. MAIC), which was not considered realistic due to the low sample size. ALCANZA data were used for the economic analysis of MF and pcALCL as it is the most robust trial.				
Reported outcomes specified in the decision problem	OS, PFS, response rates, adverse effects of treatment				
All other reported outcomes	DOR, TTR				

Abbreviations: DOR, duration of response; LyP, lymphomatoid papulosis; MF, mycosis fungoides; MAIC, matching-adjusted indirect comparison; pcALCL, primary cutaneous anaplastic large cell lymphoma; TTR, time to response; OS, overall survival; PFS, progression-free survival.

Study	Mathieu et al 2016[90]				
Study design	Retrospective, single-arm study of brentuximab vedotin				
Population	MF and SS				
Intervention(s)	Brentuximab vedotin				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	
	No	X		No	X
Rationale if trial not used in model	Study comprises a series of 32 cases of MF and SS treated with brentuximab vedotin. The lack of a comparison group for these data provides no statistical validity to include in the model.				

Reported outcomes specified in the decision problem	Response rates, adverse effects of treatment
All other reported outcomes	None

Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome.

B.2.2.1 Studies not included in the economic model

PFS and OS are the key clinical inputs in the cost-effectiveness model. Data reported for OS and PFS in Kim et al 2015 (NCT01396070)[24] and Duvic et al 2015 (NCT01352520)[91] were limited (Table 7). Duvic et al 2015 reported both OS and PFS from time of first dose of brentuximab vedotin and time from diagnosis. From the time of first dose, median PFS was 1.1 years (95% CI 0.9 to 1.4) in Duvic et al 2015.[91] Kim et al 2015 did not report OS and the PFS data reported were immature with median PFS not reached.[24]

There were no OS or PFS results reported for the individual subtypes in either Kim et al 2015 or Duvic et al 2015.[24,91]

Table 7. Survival endpoints in phase II studies

	Kim et al 2015 (N=32)[24]	Duvic et al 2015 (N=48)[91]	Mathieu et al 2016 (N=32)[90]
PFS, years, median (95% CI)*	Not reached	1.1 (0.9 to 1.4)	Not reported
OS, years, median (95% CI)*	Not reported	Not reached	Not reported

*Measured from first dose of brentuximab vedotin.
Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Kim et al 2015 and Duvic et al 2015 were both single-arm studies with no control arm and very small sample sizes (N=32 and N=48 [response-evaluable population], respectively).[24,91] Performing an ITC based on single-arm studies requires the use of methods for population-adjusted ITCs such as matching adjusted indirect comparison (MAIC) or simulated treatment comparison (STC).[92] Both approaches involve fitting regression models including multiple covariates. This was not considered realistic given the available sample sizes. Therefore, it was deemed most appropriate to utilise data from ALCANZA, the randomised, controlled, phase III multicentre trial, in the economic model for MF and pcALCL.[47]

There were no suitable data sources for SS or LyP patients receiving standard care to compare against. Therefore, an ITC for CTCL subtypes outside of those in the ALCANZA study was not considered feasible.

Outcomes from Kim et al 2015 and Duvic et al 2015 are included in sections B.2.2 to B.2.6 as they provide information on the efficacy and safety of brentuximab vedotin in patients with SS and in patients with CD30+ LyP in need of systemic therapy, consistent with the decision problem.[91,24]

Mathieu et al 2016 was a retrospective analysis of 32 case studies from 19 patients (60%) with MF, 10 patients (31%) with SS and three patients (9%) with '*another T cell lymphoma*' (undefined). The study was not used to populate the economic model because neither PFS, OS, nor statistical analyses are reported.[90]

B.2.3 *Summary of methodology of the relevant clinical evidence base*

B.2.3.1 ALCANZA

ALCANZA was an international, open-label, randomised, phase III, multicentre study designed to investigate the efficacy and safety of brentuximab vedotin versus physician's choice of methotrexate or bexarotene in previously-treated patients with CD30+ CTCL.[47]

Trial design, eligibility criteria, data collection setting/location, outcomes assessed and further trial methodology information for ALCANZA are summarised in Table 8.

Bexarotene and methotrexate were identified as appropriate comparators to brentuximab vedotin in ALCANZA because they are the most commonly used agents for CTCL worldwide. Both therapies are recommended for the treatment of MF or pcALCL as per European Society for Medical Oncology (ESMO) and EORTC guidelines.[16,32,47,93] Bexarotene is deemed to be the most commonly used first line systemic drug in all geographic areas that participated in the ALCANZA trial and is the only European Medicines Agency (EMA)- and US Food and Drug Administration (FDA)-approved medication for skin manifestations of advanced-stage CTCL in patients refractory to ≥1 systemic treatment.[47,93,94]

Both bexarotene and methotrexate are established Category A systemic therapies for the clinical management of CTCL in the UK, consistent with the decision problem for this appraisal, as described in Section B.1.1.

Table 8. Comparative summary of methodology of the RCTs

Trial no. (acronym)	ALCANZA[47]
Study objective	To investigate the efficacy and safety of brentuximab vedotin versus physician's choice of methotrexate or bexarotene in previously treated patients with CD30+ CTCL
Location	International
Trial design	Open-label, randomised
Method of randomisation	Randomly assigned (1:1) by an interactive voice and web response system to brentuximab vedotin or conventional therapy; randomisation list was generated by the Takeda statistician who was not involved in the remainder of the trial. Randomisation was stratified by baseline disease diagnosis
Method of blinding (care provider, patient and outcome assessor)	Treatments were administered open label
Eligibility criteria for participants	Adults (aged ≥18 years) with CD30+ MF who received ≥1 previous systemic therapy, or CD30+ pcALCL who received ≥1 previous systemic therapy or radiotherapy; ECOG performance status 0–2
Settings and locations where the data were collected	34 centres across 11 countries: Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, Poland, Spain, Switzerland, United Kingdom, United States UK: 4 sites; 24 patients total[88]
Duration of study	Median follow-up, primary analysis: 22.9 months Median follow-up, longer-term analysis: 33.9 months
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	Brentuximab vedotin: 1.8 mg/kg IV once every 3 weeks for up to a maximum of 16 three-week cycles (n=64), or 48 weeks Methotrexate: 5–50 mg orally once per week for up to 48 weeks (n=26) Bexarotene 300 mg/m^2 (target dose) orally once per day for up to 48 weeks (n=38)
Permitted and disallowed concomitant medications	Permitted: oral antibiotics for prophylaxis Disallowed: antibody-directed or immunoglobulin-based immune therapy within 12 weeks of first study drug, corticosteroid therapy for the treatment of CTCL within 3 weeks of first dose of study drug, any investigational products within 3 weeks before the first dose of study drug, oral retinoid therapy for any indication within 3 weeks of the first dose of study drug, systemic therapy with Vitamin A in doses >15,000 IU (5000 mcg) per day within 3 weeks before the first dose of study drug; treatment with radiotherapy or other skin-directed therapy or any investigational products within 3 weeks before the first dose of study drug

Primary outcomes (including scoring methods and timings of assessments)	Objective response rate 4 (ORR4), proportion of patients achieving an objective global response lasting (from first to last response) at least 4 months • IRF reviewed Global Response Scores (GRS) using consensus guidelines by ISCL and EORTC, and was comprised of independent dermatologists (for review of photos from skin and mSWAT assessments), independent radiologists (for review of CT, MRI, and PET for nodal and visceral involvement), and an independent pathologist (for review of Sézary cells for blood component in patients with MF) • GRS: composite of several variables, skin evaluation (mSWAT) per investigator, nodal and visceral radiographic assessment per IRF, and Sézary cell count per IRF (patients with MF) • The IRF assessed GRS at the end of each cycle until EOT • Investigators evaluated response (ORR4) at cycles 3, 6, 9, 12, 15, and EOT • All treated patients without disease progression at EOT were to be followed up for assessment of the GRS and survival every 12 weeks for a minimum of 24 months, then every 6 months until disease progression, death, withdrawal from the study, or study closure. Overall response based on GRS was confirmed by sustained skin response per mSWAT assessment at the subsequent cycle

Secondary/tertiary outcomes (including scoring methods and timings of assessments)	PFS: investigators assessed using 2 criteria; 1) prespecified criterion that counted all events despite ≥2 missed visits or starting of subsequent anticancer therapy (EMA criteria), and 2) sensitivity analysis criterion that censored patients at last assessment before the missed visit or starting of subsequent anticancer therapy (FDA criteria) Response rates (proportion of patients achieving CR and ORR): see above for scoring methods and timings Duration of skin response: time between the first skin response and disease progression in the skin; evaluated for all patients who achieved a skin response of CR (100% clearance of lesions) or PR (50%–99% clearance of lesions, with no new tumours), a stringent definition of response EFS: time from randomisation until any cause of treatment failure: disease progression, early discontinuation of treatment for any reason other than completed maximum number of cycles, start of subsequent anticancer therapy, or death due to any cause, whichever occurred first Safety: treatment-emergent AEs were assessed according to NCI CTCAE v4.03 • Response to treatment, progression, safety, and toxicity were assessed every 3 weeks before dosing on day 1 of each cycle and at EOT All quality-of-life questionnaires (Skindex-29 and EQ-5D-3L) were to be completed on day 1 of cycles 1, 2, 4, 6, 8, 10, 12, 14, and 16 (before any other study procedures were performed), at EOT and during post-treatment follow-up. Questionnaires were collected by phone or by mail for patients not required to return to clinic for post-treatment follow-up. Symptom burden (measured by symptom domain of Skindex-29): responses were scaled into 100-point scores using established scoring guidelines (higher scores indicated higher symptom burden and lower HRQL) EQ-5D-3L: assessed the dimensions of mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a “thermometer” VAS (recorded self-rated health on a 20-cm vertical line ranging from 0 [worst imaginable health state] to 100 [best imaginable health state]). The utility measurement was collected at study visits until progressive disease was confirmed, after which all questionnaires were completed by telephone or by mail DOR: time between first documentation of response and disease progression in patients with a confirmed response Time to next antineoplastic therapy: not prespecified but performed as exploratory analysis. Defined as time from randomisation to the date of first documentation of antineoplastic therapy or last contact date for patients who never took antineoplastic therapy
Pre-planned subgroups	Analyses were performed for the primary endpoint for the following subgroups with ≥10 patients in each subgroup per treatment arm: baseline disease diagnosis, ECOG performance status, sex, age (<65, ≥65 years), region (North America, Europe, Asia, and Rest of World), race (white, non-white), and physician’s choice (brentuximab vedotin compared with the reference therapy, either bexarotene or methotrexate)

Abbreviations: AEs, adverse events; CTCL, cutaneous T-cell lymphoma; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EMA, European Medicines Agency; EORTC, European Organisation for Research and Treatment of Cancer; EOT, end of treatment; FACT-G, Functional Assessment of Cancer Therapy – General; FDA, US Food & Drug Administration; GRS, global response score; HRQL, health-related quality of life; INV, investigator; IRF, independent review facility; ISCL, International Society for Cutaneous Lymphomas; IV, intravenous; MF, mycosis fungoides; mSWAT, modified severity weighted assessment tool; NCI CTCAE, National Cancer

Institute Common Terminology Criteria for Adverse Events; pcALCL, primary cutaneous anaplastic large cell lymphoma; PFS, progression-free survival; QoL, quality of life; VAS, visual analog scale.

B.2.3.2 Kim et al 2015; Duvic et al 2015

Kim et al 2015 was a phase II, investigator-initiated, multicentre, single-arm study designed to investigate the clinical activity and safety profile of brentuximab vedotin in patients with MF/SS, and assess for potential biomarkers of clinical response.[24] Duvic et al 2015 was a phase II, open-label, single-arm, single centre study designed to determine safety and preliminary activity of brentuximab vedotin in patients with LyP in need of systemic therapy, or in previously-treated patients with MF or pcALCL.[91]

Trial design, eligibility criteria, data collection setting/location, outcomes assessed and further trial methodology information for Kim et al 2015 and Duvic et al 2015 studies are summarised in Table 9.

Table 9. Comparative summary of methodology of phase II trials

Trial no. (acronym)	Kim et al 2015[24]	Duvic et al 2015[91]
Study objective	To explore the clinical activity of BV in patients with MF/SS with any CD30 expression level, establish the safety profile in an MF/SS population, and assess for potential biomarkers of clinical response	To determine safety and preliminary activity of brentuximab vedotin in patients with LyP in need of systemic therapy or in previously treated patients with MF or pcALCL
Location	Multiple institutions	Single location
Trial design	Open-label, single arm	Open-label, single arm
Eligibility criteria for participants	Patients with MF or SS (stages IB–IVB), who had ≥1 systemic therapy failure; all levels of CD30 expression (0%–100%) in the skin or other compartments; age ≥18 years; ECOG PS 0–2; absolute neutrophil count ≥1000/μL, platelet count ≥50,000/μL, serum creatinine level ≤2 times the upper limit of normal, ALT and AST levels ≤3 times the upper limit of normal	Patients age ≥18 years with a clinical and histologically confirmed diagnosis of CD30+ LyP, CD30+ pcALCL, or MF; ECOG PS ≤2; adequate bone marrow and organ function; skin lesions were required to have detectible CD30 present on malignant T cells. For LyP: >10 lesions, scarring, or active lesions on the face, hands, or feet requiring systemic treatment For MF or pcALCL: failed ≥1 prior systemic therapy ≥4 weeks before study entry No active infection, HIV, positive hepatitis B or C status, or known or suspected CNS involvement Patients who had received monoclonal antibodies required a washout of 12 weeks
Settings and locations where the data were collected	All patients were enrolled and treated the primary institution (Stanford University, Stanford CA, USA); Memorial Sloan Kettering Cancer Center, NY, NY USA, served as an independent review site for clinical and pathologic evaluations	University of Texas MD Anderson Cancer Center, Houston, TX, USA
Duration of study	48 weeks	48 weeks
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)	Brentuximab vedotin: 1.8 mg/kg IV once every 3 weeks for up to 8 three-week cycles; patients with continued clinical improvement could have up to 8 additional cycles; those with CR were allowed to have 2 more cycles (n=32)	Brentuximab vedotin: 1.8 mg/kg IV once every 21 days for up to 8 three-week cycles; patients with partial or stable response could have up to 8 additional cycles; those with CR were allowed to have 2 more cycles (n=48)
Permitted and disallowed concomitant medications	Topical or systemic corticosteroids were not allowed for treatment of MF or SS symptoms	None stated

Primary outcomes (including scoring methods and timings of assessments)	ORR with clinical response documentation requiring confirmation of response at the subsequent study visit	Safety: AEs recorded in accordance with NCI CTCAE, v 4.0 • Blood samples for chemistry and haematologic measurements and urine samples for urinalysis were taken at day 1 and every 21 days before each infusion • Patients were monitored for AE from initial infusion of study drug until 30 days after last dose • Neuropathy severity and duration, and overall survival were monitored until resolution
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	Skin disease burden measured by mSWAT (screening, before each dose of BV, at EOT, and every 2–3 months until progression) • Those with lymph node or visceral disease had whole body PET/CT at time of screening, end of cycles 2, 5, 8, 11, and 14, and EOT • Those with blood involvement had Sézary flow cytometry at same time points as skin assessments DOR: date of response to PD PFS: date of first BV dose to time of PD or death • For DOR/PFS, patients were censored at last follow-up visit if any new treatment was initiated before documentation of PD EFS: date of first BV dose to time of toxicity-related termination, PD, next significant therapy (e.g., use of a systemic agent or TSEB), or death by any cause (whichever occurred first) Safety: AEs recorded in accordance with NCI CTCAE, v 4.0 • For patients with grade 2 peripheral neuropathy, a formal neurologic evaluation was updated every 2 cycles or every 2 months (off study)	Disease-specific assessments were performed on day 1 of each treatment ORR: composite of responses from all compartments (skin, lymph nodes, blood >1000 cells/μL, and viscera) • SD: failure to attain a CR or PR and no evidence of disease progression in any compartment • PD: >25% increase from baseline in mSWAT (nonresponders) or loss of response in PR or CR (increase in mSWAT greater than the sum of the nadir plus 50% of baseline score) mSWAT: used to determine skin burden for MF pcALCL required 50% reduction from baseline for PR or 100% reduction and no disease elsewhere for CR • Sum of bidimensional measurement of index lesions and mSWAT were used Active LyP lesions were counted: CR=zero lesions; PR=reduction in lesions of 50% PET/CT at baseline and at response assessed responses in bulky tumours or lymph nodes Sézary cells in blood were monitored
Pre-planned subgroups	None stated	None stated

Abbreviations: BV, brentuximab vedotin; CR, complete response; CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; EFS, event-free survival; EOT, end of treatment; LyP, lymphomatoid papulosis; MF, mycosis fungoides; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; SD, stable disease; SS, Sézary syndrome.

B.2.3.3 Baseline characteristics and demographics

B.2.3.3.1 ALCANZA

In ALCANZA baseline characteristics were well balanced between treatment arms, with the exception of a greater number of patients with stage IVB MF and extracutaneous pcALCL in the brentuximab vedotin arm vs. the PC arm.[47] In ALCANZA, 95 of 128 patients had advanced-stage disease, defined as MF stage IIB or higher and all pcALCL patients (brentuximab vedotin arm, n=49; PC arm, n=46).[89] Patient characteristics for ALCANZA are summarised in Table 10.[47]

Table 10. Baseline patient characteristics and demographics in ALCANZA (ITT population)[47]

Characteristic			Brentuximab vedotin (n=64)	Physician's choice of methotrexate or bexarotene (n=64)	Overall (N=128)
Age, y, median (range)			62 (51–70)	59 (48–67)	60 (48–69)
Male, n (%)			33 (52)	37 (58)	70 (55)
White race, n (%)			56 (88)	53 (83)	109 (85)
ECOG PS, n (%)		**0**	43 (67)	46 (72)	89 (70)
		1	18 (28)	16 (25)	34 (27)
		2	3 (5)	2 (3)	5 (4)
CD30 expression, %, median (range)*			32.5 (12.5–67.5)	31.3 (12.0–47.5)	31.3 (12.5–60.0)
Time since initial diagnosis, mo, median (range)			42.2 (12.8–87.4)	37.0 (12.3–102.7)	40.9 (12.7–96.8)
Time since progression on last therapy (excl. radiotherapy), mo, median (range)			2.4 (1.4–7.9)	1.3 (0.9–3.7)	1.9 (1.1–3.8)
Lines of prior therapy, n, median (range)		**Total**	4.0 (2.0–7.0)	3.5 (2.0–5.5)	4.0 (2.0–6.0)
		Skin-directed	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
		Systemic	2.0 (1.0–4.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)
MF, n (%)			48 (75)	49 (77)	97 (76)
Disease stage, n/N (%)†		**IA–IIA**	15/48 (31)	18/49 (37)	33/97 (34)
		IIB	19/48 (40)	19/49 (39)	38/97 (39)
		IIIA–IIIB	4/48 (8)	2/49 (4)	6/97 (6)
		IVA1	0	1/49 (2)	1/97 (1)
		IVA2	2/48 (4)	8/49 (16)	10/97 (10)
		IVB	7/48 (15)	0	7/97 (7)
pcALCL, n (%)			16 (25)	15 (23)	31/97 (24)
Disease stage, n/N (%)	**Skin**	**T_1**	1/16 (6)	4/15 (27)	5/31 (16)
		T_2	3/16 (19)	5/15 (33)	8/31 (26)
		T_3	12/16 (75)	6/15 (40)	18/31 (58)
	Node	**N_0**	10/16 (63)	11/15 (73)	21/31 (68)

Characteristic			Brentuximab vedotin (n=64)	Physician's choice of methotrexate or bexarotene (n=64)	Overall (N=128)
		N_1	2/16 (13)	1/15 (7)	3/31 (10)
		N_2	2/16 (13)	1/15 (7)	3/31 (10)
		N_3	2/16 (13)	2/15 (13)	4/31 (13)
	Visceral	M_0	12/16 (75)	14/15 (93)	26/31 (84)
		M_1	4/16 (25)	1/15 (7)	5/31 (16)

*Based on average CD30 expression among all biopsies for each patient's baseline visit.
†One patient in each arm had incomplete staging data, which are not included in the table.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; ITT, intent-to-treat; M, metastases; MF, mycosis fungoides; N, node; pcALCL, primary cutaneous anaplastic large cell lymphoma; T, tumour.

B.2.3.3.2 Kim et al 2015

Patient characteristics for Kim et al 2015 are summarised in Table 11. Most patients had advanced disease (stage IIB or higher, 88%); the median (range) number of prior systemic therapies was 3 (1–13). Most patients had prior cytotoxic agents, and one had prior alloSCT.[24]

Table 11. Baseline patient characteristics and demographics in Kim et al 2015 (Safety population)[24]

Characteristic		Brentuximab vedotin (N=32)
Age, y, median (range)		62 (20–87)
Male, n (%)		19 (59)
Female, n (%)		13 (41)
Clinical stage, n (%)	**IB**	4 (13)
	IIB	18 (56)
	IV/SS	10 (31)
Adverse prognostic factors, n (%)	**LCT or FMF**	29 (90)
	LCT	16 (50)
	FMF	8 (25)
	LCT and FMF	5 (16)
No. of prior systemic therapies, n (%)	**<3**	15 (47)
	≥3	17 (53)
CD30 grouping at screening, n (%)	**A (<10%)**	14 (44)
	B (10% to 50%)	14 (44)
	C (>50%)	4 (13)

Abbreviations: FMF, folliculotropic mycosis fungoides; LCT, large cell transformation; SS, Sézary syndrome.

B.2.3.3.3 Duvic et al 2015

Patient characteristics for Duvic et al 2015 are summarised in Table 12. Overall, 28 patients had only MF, 2 had only pcALCL, 2 had pcALCL plus LyP or MF, 9 had only LyP, and 7 had both LyP and MF. Patients with MF were heavily pretreated, with a median (range) of 5 (1–13) prior therapies. The median (range) number of prior systemic therapies was 2 (1–10) for patients with MF and 1 (0–5) for patients with LyP/pcALCL.[91]

Table 12. Baseline patient characteristics and demographics in Duvic et al 2015 (all patients [safety population] and eligible patients who received ≥2 doses of brentuximab vedotin [efficacy population])[91]

Characteristic		All Patients* (N=54)	Eligible Patients† (n=48)
Age, y, median (range)		59.5 (31–77)	--
Male, n (%)		27 (50)	26 (54)
Race, n (%)	**White**	31 (57)	30 (63)
	African American	15 (28)	13 (27)
	Hispanic	8 (15)	5 (11)
Diagnosis, n	**MF**	31	28
	pcALCL	3	2
	LyP	10	9
	LyP and MF	8	7
	ALCL/LyP/MF	2	2

Dashed line represents data not reported.
*Defined as patients who received ≥1 dose of brentuximab vedotin and were included in the safety population.
†Defined as patients who received ≥2 doses of brentuximab vedotin and were analysed for efficacy.
Abbreviations: ALCL, anaplastic large cell lymphoma; LyP, lymphomatoid papulosis; MF, mycosis fungoides; pc, primary cutaneous.

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

The participant flow in the relevant randomised controlled trials is shown in Appendix D.1.3. A summary of statistical analysis and study groups for the three clinical trials is provided in Appendix D.1.4.

In ALCANZA, analyses were conducted at a median follow-up of 22.9 months, and at a median follow-up of 33.9 months. Data from both follow-up cut-offs are included in this submission. The cost-effectivness analysis uses only data from the 33.9 month follow-up.

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

A complete quality assessment of each trial is provided in Appendix D.

B.2.6 *Clinical effectiveness results of the relevant clinical trials*

Brentuximab vedotin was licensed for the treatment of adult patients with CD30+ CTCL after at least 1 prior therapy, including all subtypes of CTCL, based on results of 3 clinical trials (two phase II trials, and one phase III, ALCANZA).[7] ALCANZA was the pivotal, phase III open-label randomised multicentre study of brentuximab vedotin vs PC in patients with CTCL.[7] In the primary analysis of ALCANZA (median follow-up of 22.9 months), objective response and disease progression were determined by the IRF and by investigators. In the updated analysis (median follow-up of 33.9 months), objective response and disease progression were determined by investigator (INV) assessment.[87]

In the multicentre, phase II trial reported by Kim et al 2015, 70% of patients (90% CI, 53%–83%) with treatment-refractory or advanced MF/SS achieved an overall response when treated with brentuximab vedotin, meaning they had at least partial improvement in skin lesions.[24] The single-centre, phase II trial reported by Duvic et al 2015, found that 73% of patients with CD30+ pcALCL, LyP, or MF responded to brentuximab vedotin treatment, with ≥50% reduction in the number of lesions observed (ORR 73% [95% CI, 60%–86%]); 35% of patients achieved complete resolution of their skin lesions (CR 35% [95% CI, 22%–49%]).[91]

B.2.6.1 ALCANZA

B.2.6.1.1 Primary efficacy outcome

The primary endpoint in ALCANZA was ORR4, the rate of objective response rate that lasts at least 4 months. ORR4 was determined by independent review (by IRF) of the global response score (GRS) using the consensus guidelines of the International Society for Cutaneous Lymphomas (ISCL), the US Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the EORTC.[1,31,47] GRS, a stringent criterion, is a composite assessment of total tumour burden: skin (based on the mSWAT assessment per INV), nodal and visceral radiographic assessment per IRF, and Sézary cell count per IRF (patients with MF only). Skin response was determined by clearance of lesions, with CR being 100% clearance and PR being 50%–99% clearance and no new tumours.[88] Overall response based on GRS was confirmed by sustained skin response per mSWAT assessment at the subsequent treatment cycle.[47] ORR4 was also assessed by INV.[88]

ORR4 captures not only proportion of patients with a response but also the duration of a response as a single measurement, which reflects a more appropriate and stringent measure of treatment success than the proportion of patients with a response alone. This of particular relevance in a patient population for whom short clinical responses do not necessarily correspond with meaningful benefit[47]; lymphoma experts consider responses lasting 4 months or more to be clinically meaningful for patients with CTCL.[2,95] Previous studies in CTCL used less stringent and standardised assessment tools for response, focusing on assessment of the skin compartment only, without detailed nodal, visceral, or blood assessment. Therefore ORR4 is a clinically relevant endpoint for CTCL trials and was chosen to capture evidence of a durable response to the study drug that is minimally affected by other therapies.[47] Clinical experts agree that ORR4 meets the aim of treatment in CTCL, which is to reduce the patient's symptom burden for as long as possible.

In the primary analysis of ALCANZA (22.9 month follow-up), significantly more patients had a substantial, durable response to treatment (i.e., ≥50% clearance of skin lesions with no

new tumours, sustained for ≥4 months) with brentuximab vedotin than with bexarotene or methotrexate (ORR4 per IRF: 56.3% [n=36] vs. 12.5% [n=8], respectively; p<0.0001 for PC combined; Table 13). This improvement was observed in patients with[47]:

- MF (50.0% [24/48] vs. 10.0% [5/49], respectively), and
- pcALCL (75.0% [12/16] vs. 20.0% [3/11], respectively)

ORR4 per INV for the entire population was consistent with that for the IRF analysis (59.4% vs. 7.8%, respectively; p<0.001[88]; Table 13).

Table 13. ALCANZA: primary outcome analysis, ORR4 per IRF and per INV (ITT population)

	BV (n=64)	PC (n=64)	Difference (%) from PC (95% CI)	p-value	BEX (n=38)	MTX (n=26)
Per independent review (IRF)						
Number (%) achieving ORR4 (95% CI)	36 (56.3) (44.1, 68.4)	8 (12.5) (4.4, 20.6)	43.8 (29.1, 58.4)	<0.0001	6 (15.8) (4.2, 27.4)	2 (7.7) (0.9, 25.1)
Per investigator (INV)						
Number (%) achieving ORR4 (95% CI)	38 (59.4) (47.3, 71.4)	5 (7.8) (2.6, 17.3)	51.6 (34.8, 65.8)	<0.001	3 (7.9) (1.7, 21.4)	2 (7.7) (0.9, 25.1)

Abbreviations: BEX, bexarotene; BV, brentuximab vedotin; INV, investigator; IRF, independent review facility; MTX, methotrexate; ORR4, objective response lasting at least 4 months; PC, physician's choice.

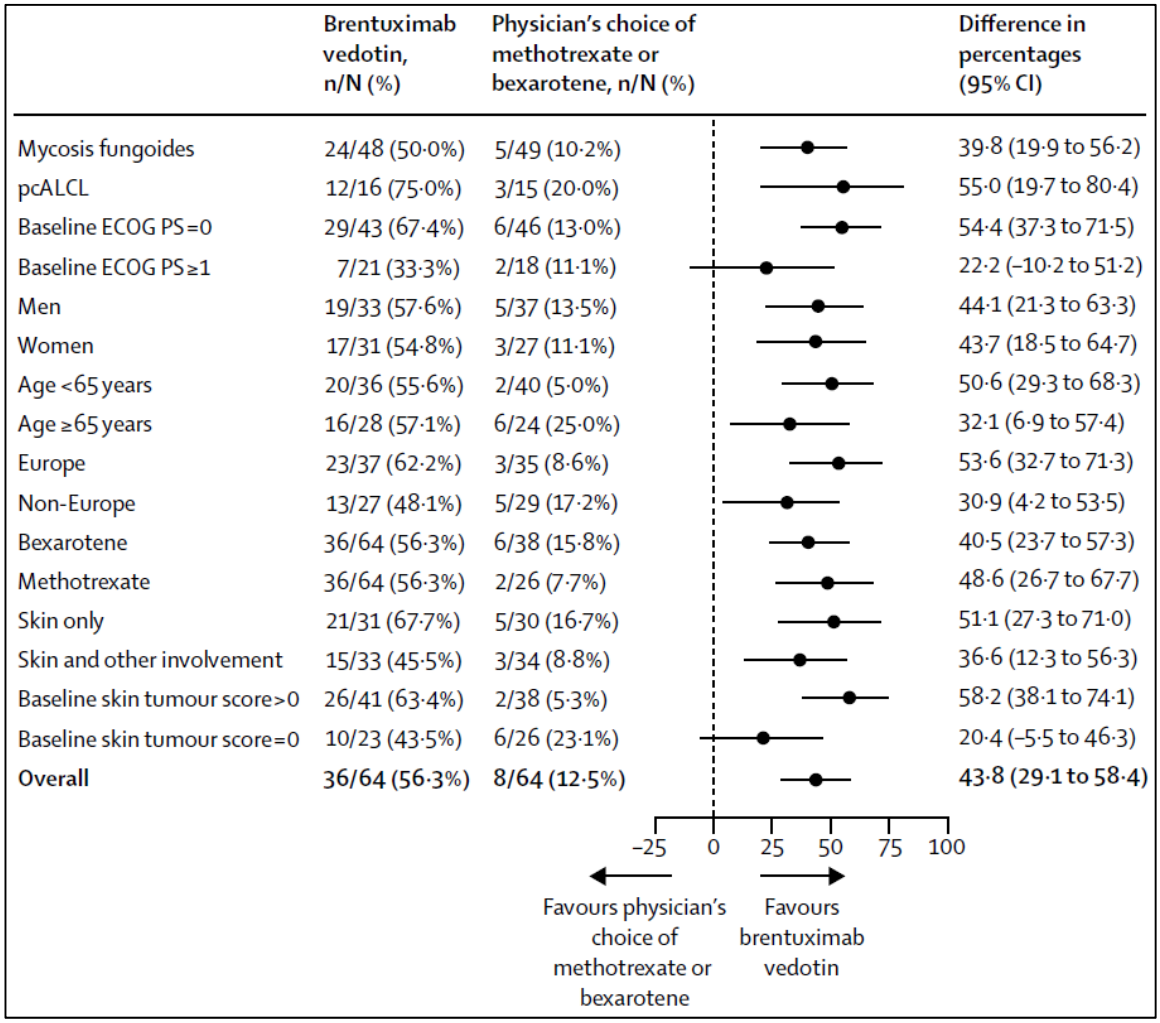
Updated analysis (33.9 month follow-up)

Data from the 33.9-month follow-up continued to support the superior clinical activity of brentuximab vedotin vs. PC as evidenced by a significantly improved ORR4 with brentuximab vedotin vs. PC (INV-assessed ORR4: 60.9% vs. 7.8%, respectively; HR [95% CI] 53.1 [36.5–67.2]; p<0.001).[87]

B.2.6.1.2 Secondary analysis of primary outcome

ORR4 was consistent across all subgroups of patients, including those with skin-only and extracutaneous disease, and favoured brentuximab vedotin treatment over PC as evidenced by all responses greater than 0 in Figure 15.[47]

Figure 15. ALCANZA: ORR4 by subgroups (ITT population)[47]



Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; ORR4, rate of objective global response lasting ≥4 months, assessed by independent review; pcALCL, primary cutaneous anaplastic large cell lymphoma.

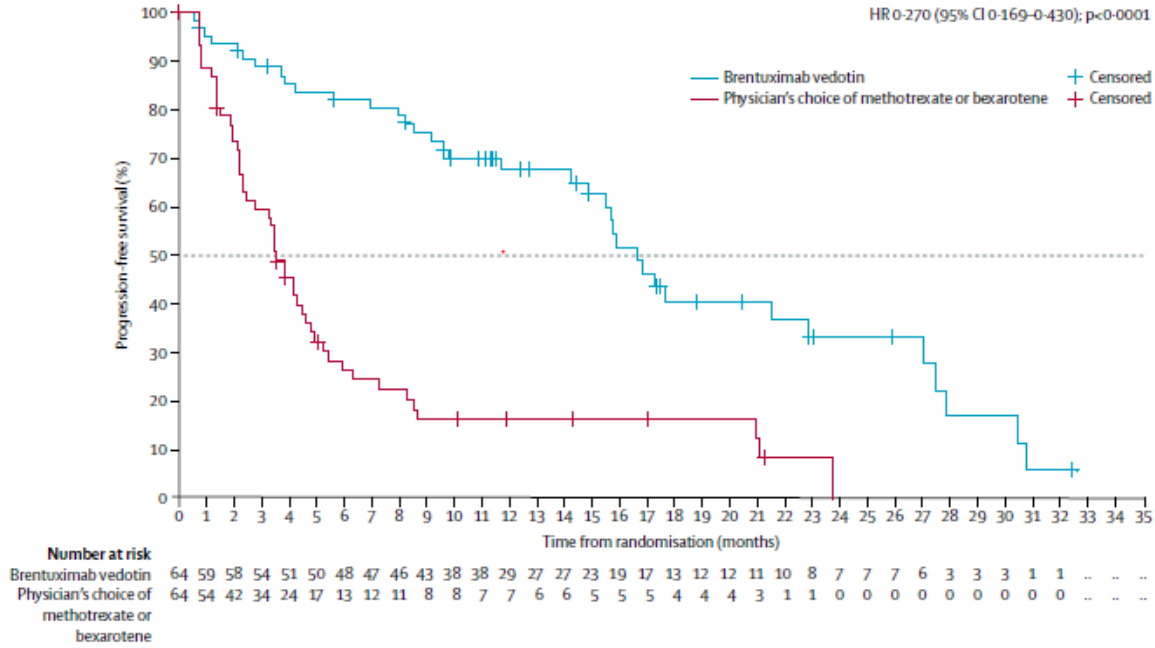
B.2.6.1.3 Key secondary efficacy outcomes

Progression-free survival

In the primary analysis of ALCANZA (22.9 months follow-up), brentuximab vedotin demonstrated a significant improvement in PFS, achieving a median PFS of 16.7 months vs. 3.5 months with PC as shown in Figure 16 (IRF using EMA censoring guidelines[96]; HR [95% CI] 0.270 [0.169–0.430]; p<0.0001).[47]

The estimated 1-year and 2-year PFS rates were 67.5% vs. 16.0% and 33.0% vs. not estimable, for brentuximab vedotin vs. PC, respectively.[88]

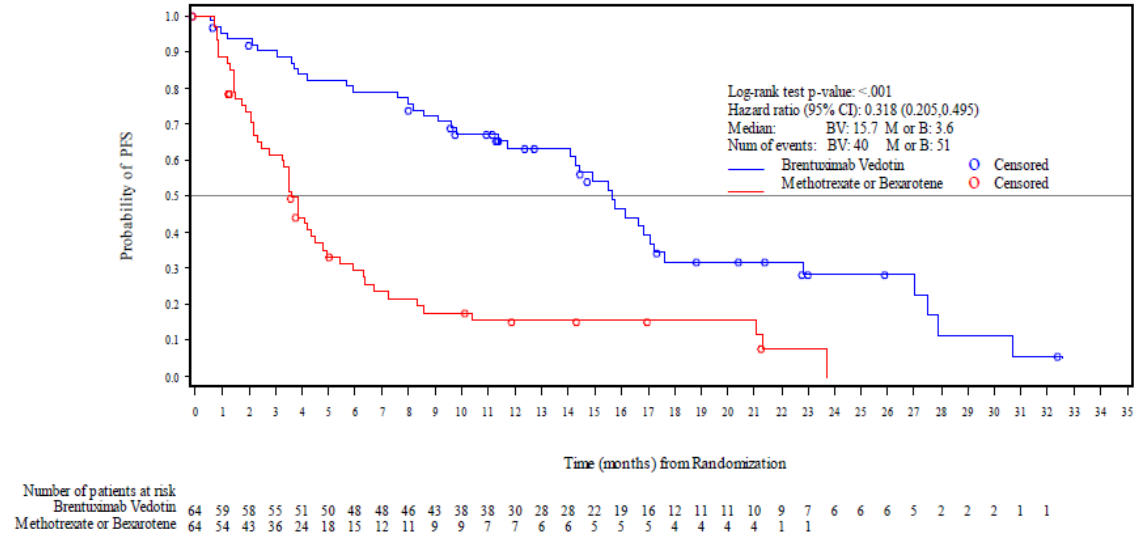
Figure 16. ALCANZA: PFS assessed per IRF (ITT population)[47]



Abbreviations: CI, confidence interval; HR, hazard ratio; IRF, independent review facility; ITT, intent to treat; PFS, progression-free survival.

Additionally, in the primary analysis of ALCANZA, PFS as assessed by INV yielded results comparable to the PFS per-IRF analysis. Median PFS per INV was significantly increased with brentuximab vedotin vs. PC (15.7 months vs. 3.6 months, respectively; HR [95% CI] 0.318 [0.205–0.495]; p<0.001) as shown in Figure 17.[88]

Figure 17. ALCANZA: PFS assessed per INV (ITT population)[88]

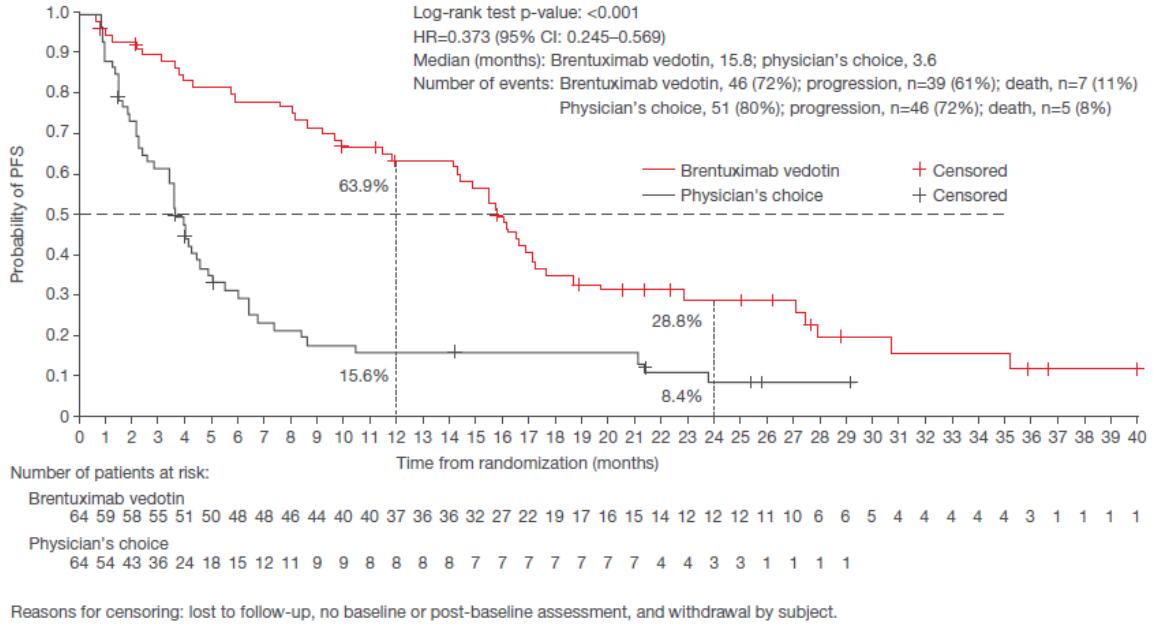


Abbreviations: B, bexarotene; BV, brentuximab vedotin; CI, confidence interval; INV, investigator; ITT, intent to treat; M, methotrexate; PFS, progression-free survival.

Updated analysis (33.9 month follow-up)

Data from longer follow-up of 33.9-months continued to show significant improvement in PFS for patients treated with brentuximab vedotin over PC (a median of 15.8 months vs. 3.6 months, respectively; HR [95% CI] 0.373 [0.245–0.569]; p<0.001). was maintained at 1 year (63.9% vs. 15.6%) and 2 years (28.8% vs. 8.4%) as shown in Figure 18.[87]

Figure 18. ALCANZA at 33.9 month follow-up: PFS per INV (ITT population)[87]



Abbreviations: CI, confidence interval; HR, hazard ratio; INV, investigator; ITT, intent to treat; PFS, progression-free survival.

Response rates

In the primary analysis of ALCANZA (22.9 month follow-up), significantly more patients treated with brentuximab vedotin achieved CR, defined as complete resolution of symptoms (100% skin clearance) as assessed by GRS, vs. PC (CR per IRF, 15.6% vs. bexarotene 0% or methotrexate 3.8% [1.6% for PC combined]; p=0.0046 for brentuximab vedotin vs. PC combined).[47,88]

The proportion of patients achieving an objective response (defined as either PR or CR) lasting any duration was higher with brentuximab vedotin treatment than with PC (ORR per IRF, 67% [43/64 patients] vs. 20% [13/64 patients]; p<0.0001). Overall, more patients treated with brentuximab vedotin achieved an objective response vs. PC at any stage of disease as shown in Table 14.[47]

Response rates per INV, both ORR and CR, were comparable those per IRF.[88]

Table 14. ALCANZA: Patient responses by clinical stage at baseline per IRF[47]

Stage at baseline, n/N (%)	Brentuximab vedotin (n=64)		Physician's choice of methotrexate or bexarotene (n=64)	
	ORR	CR	ORR	CR
ITT population	43/64 (67)	10/64 (16)	13/64 (20)	1/64 (2)
Mycosis fungoides*†	31/48 (65)	5/48 (10)	8/49 (16)	0
IA–IIA	8/15 (53)	1/15 (7)	5/18 (28)	0
IIB	13/19 (68)	3/19 (16)	3/19 (16)	0
IIIA–IIIB	3/4 (75)	0	0	0
IVA	2/2 (100)	1/2 (50)	0	0
IVB	4/7 (57)	0	NA	NA

pcALCL	12/16 (75)	5/16 (31)	5/15 (33)	1/15 (7)
Skin only†	8/9 (89)	4/9 (44)	5/11 (45)	1/11 (9)
Extracutaneous disease†	4/7 (57)	1/7 (14)	0	0

*Percentage in each subcategory in the total column is based on the number of patients in each disease subtype.
†One patient in each group had incomplete staging data and is not included in the table: one patient in the brentuximab vedotin group had partial response and one patient in the physician's choice group had no response.
Abbreviations: CR, achieved a complete response; ITT, intent to treat; NA, not applicable; ORR, achieved an objective response; pcALCL, primary cutaneous anaplastic large cell lymphoma.

Updated analysis (33.9 month follow-up)

The significantly better CR rate was maintained at the 33.9-month follow-up, with 18.8% (CR: 12/64) vs. 0% of patients achieving a CR (p<0.001) with brentuximab vedotin and PC, respectively. Likewise, ORR rates were significantly improved with brentuximab vedotin vs. PC (44/64 [68.8%] vs. 14/64 [21.9%], respectively; p<0.001).[87]

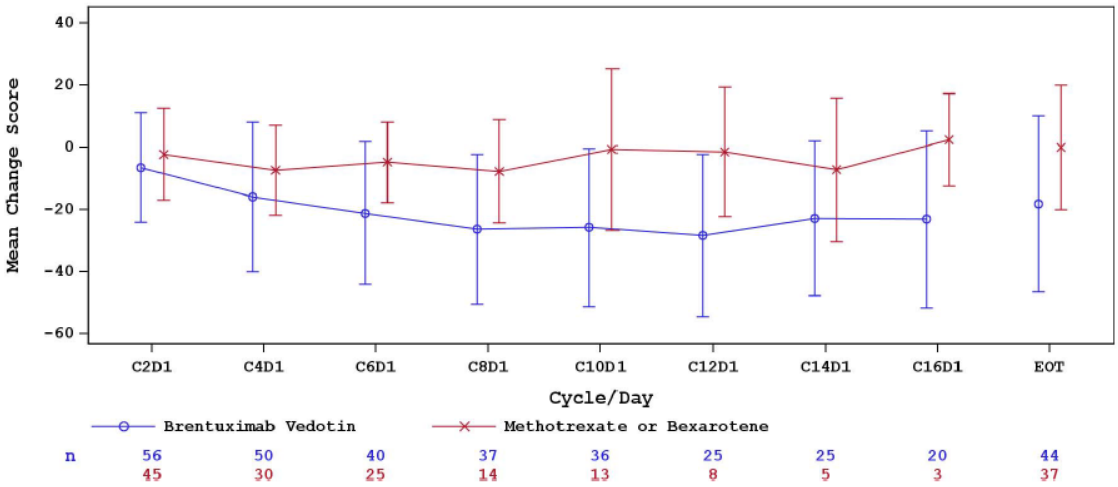
Health-related quality-of-life as measured by EQ-5D-3L

In the primary analysis of ALCANZA, EQ-5D-3L was assessed but showed no significant difference between the two treatment arms for EQ-5D US time trade-off, the UK time trade-off, or visual analog scores (mean [SD] baseline EQ-5D-3L visual analog scale score was 60.6 [20.3] in the brentuximab vedotin arm and 61.7 [23.6] in the PC arm). However, the mean changes from baseline to end of treatment were 0.02, 0.03, and 0.8, respectively, for patients treated with brentuximab vedotin and -0.02, -0.04, and -2.0, respectively, for patients treated with PC. Importantly, no differences in EQ-5D scores were observed between patients with and without peripheral neuropathy. It should be noted that the EQ-5D is a generic, non-disease–specific questionnaire used to measure health-related quality-of-life.[4] This was confirmed by an analysis of the correlation between EQ-5D scores and Skindex-29 symptom scores in advanced-stage patients from ALCANZA (see Section B.2.7.4 for results).

Symptom relief as measured by Skindex-29

In the primary analysis of ALCANZA (22.9 month follow-up), patients treated with brentuximab vedotin reported a clinically meaningful reduction of symptoms as measured by the symptom domain of the Skindex-29 (a 100-point response scoring tool where a higher score indicates a higher symptom burden, and lower health-related quality of life[49]). These same patients had significantly greater symptom reduction compared with those treated with PC (maximum reduction from baseline, mean [SD]: -27.96 [26.88] vs. -8.62 [17.01], respectively; p<0.0001) as shown by separation of curves in Figure 19.[47]

Figure 19. ALCANZA: Quality-of-life changes as assessed by mean change from baseline in symptom domain of the Skindex-29 questionnaire (ITT population)[88]

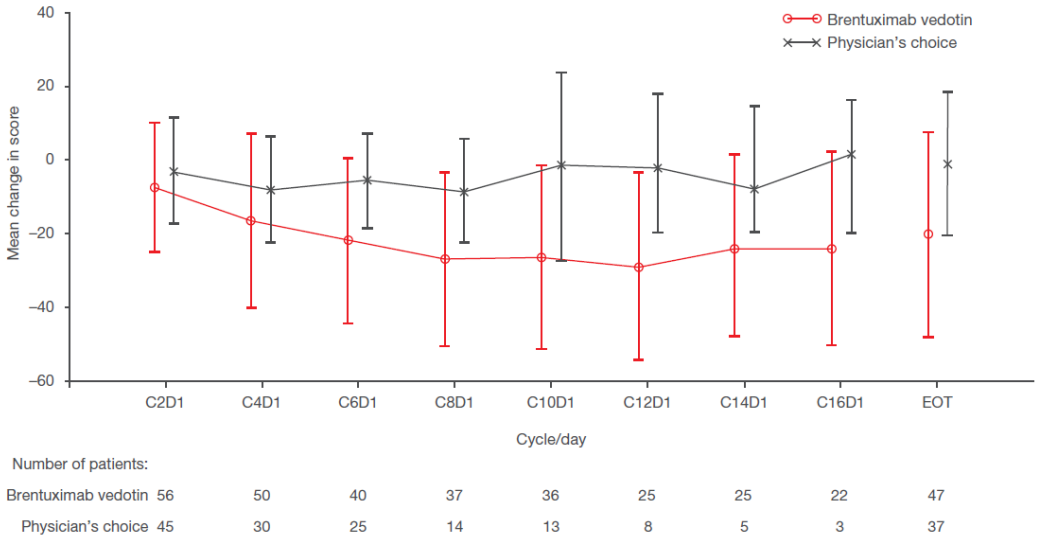


Higher score indicates greater impact of disease.
Bars represent mean ± SD.
Abbreviations: C, cycle; D, day; EOT, end of treatment; ITT, intent to treat.

Updated analysis (33.9 month follow-up)

In the 33.9 month follow-up analysis, patients treated with brentuximab vedotin continued to experience significantly greater symptom reduction vs. those treated with PC (mean maximum reduction, -28.08 vs. -8.62, respectively; p<0.001) as shown by separation of curves in Figure 20.[87]

Figure 20. ALCANZA at 33.9 month follow-up: Quality-of-life changes as assessed by mean change from baseline in symptom domain of the Skindex-29 questionnaire (ITT population)[87]



Higher score indicates greater impact of disease.
Abbreviations: C, cycle; EOT, end of treatment; ITT, intent to treat.

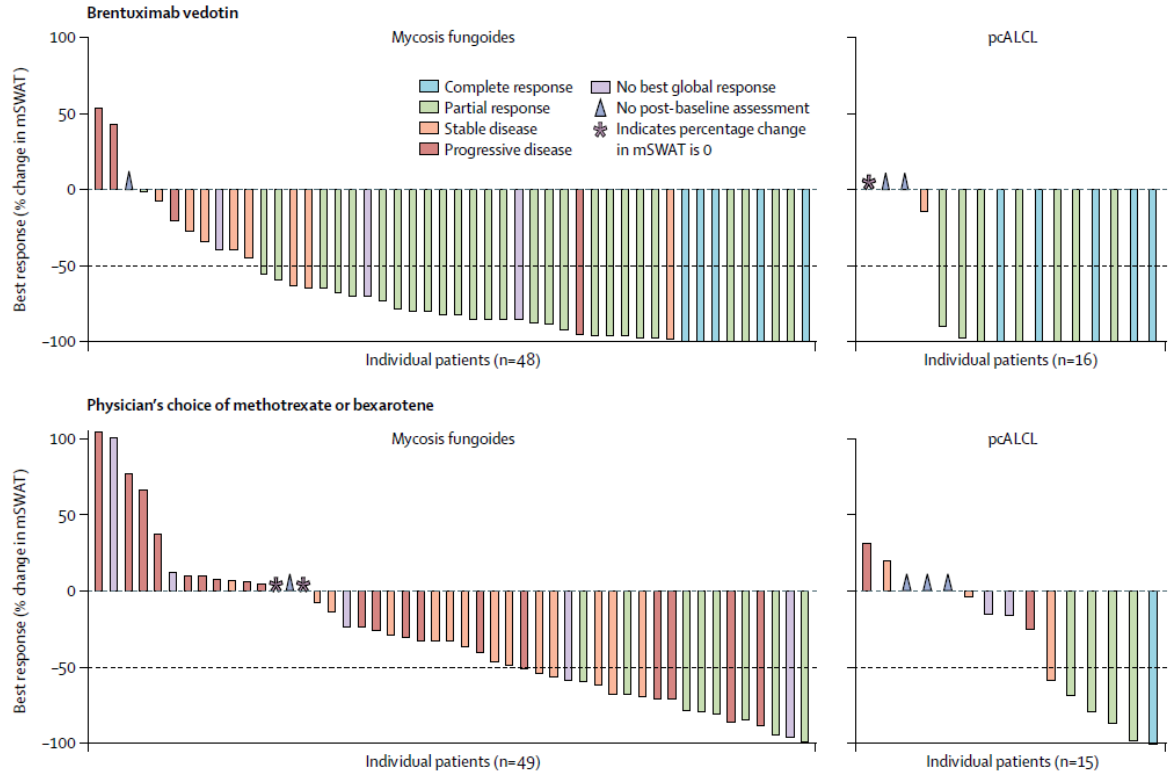
B.2.6.1.4 Other secondary efficacy endpoints

Maximum change in mSWAT score

The extent of skin resolution was reported as the maximum percentage change in mSWAT score in the primary ALCANZA analysis (22.9 month follow-up), which was performed by the investigator. As seen in Figure 21, more than half of patients with pcALCL who received brentuximab vedotin (62.5%) experienced complete resolution of skin disease. Furthermore, as demonstrated by the number of bars crossing the dotted line in the figure, more patients treated with brentuximab vedotin experienced ≥50% improvement in skin disease compared with PC (MF: brentuximab vedotin, 77% [37/48] vs. PC, 41% [20/49]; pcALCL: brentuximab vedotin, 75% [12/16] vs. PC, 40% [6/15], respectively).[47]

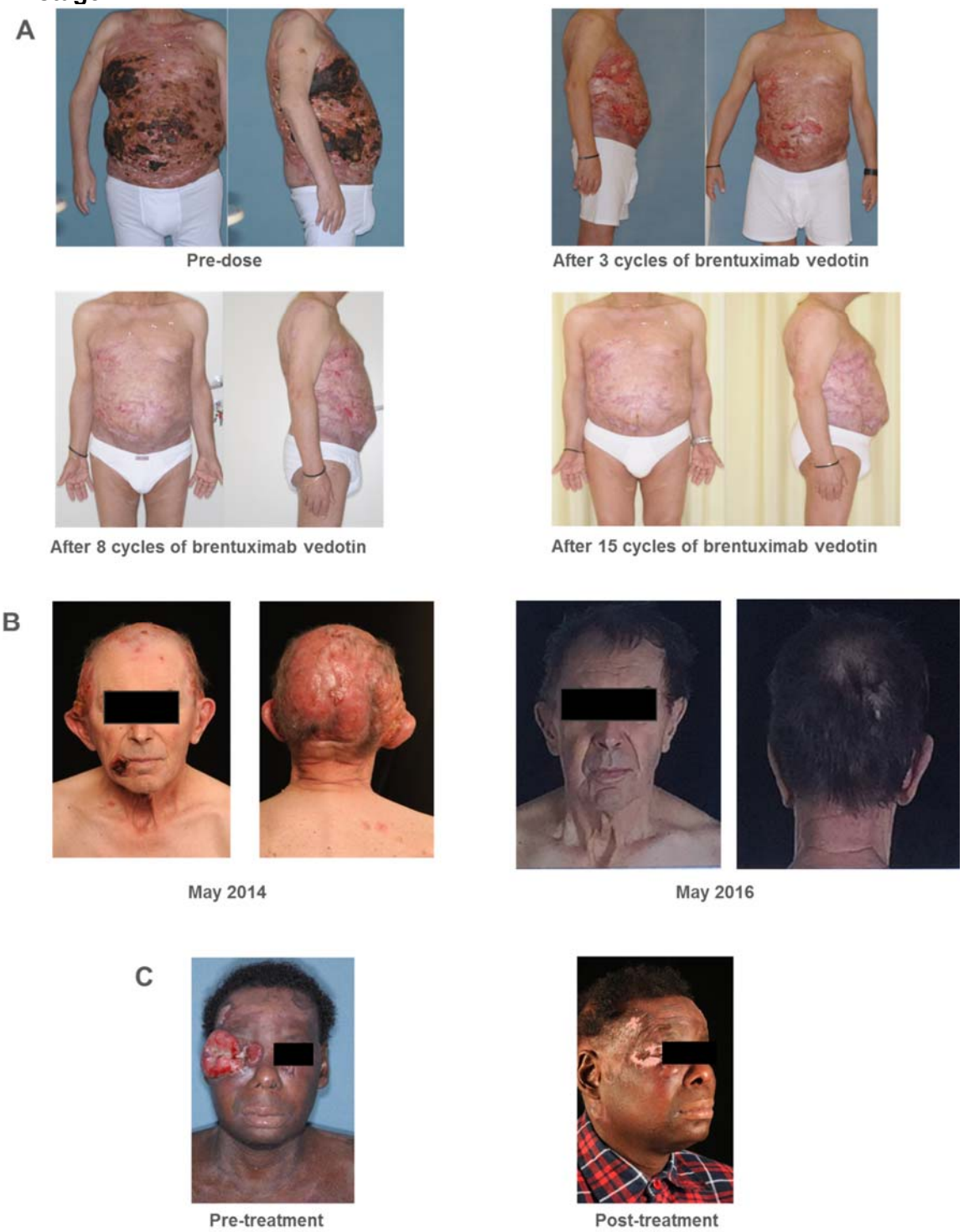
The unprecedented level of response and disease control with brentuximab vedotin treatment can be observed in pre- and post-treatment photos of ALCANZA patients shown in Figure 22.

Figure 21. ALCANZA: Maximum percentage change in skin mSWAT score[47]



Abbreviations: mSWAT, modified severity weighted assessment tool; pcALCL, primary cutaneous anaplastic large cell lymphoma.

Figure 22. Partial responses were observed with brentuximab vedotin treatment in A) a patient with MF (T3NXM0B0) after 15 cycles, B) an MF folliculotrophic patient after 2 years of treatment achieved durable CR, and C) an ALCANZA patient with MF stage IIB[36,97]



Abbreviations: B, blood; CR, complete response; M, metastases; MF, mycosis fungoides; N, node; T, tumour.

Duration of response

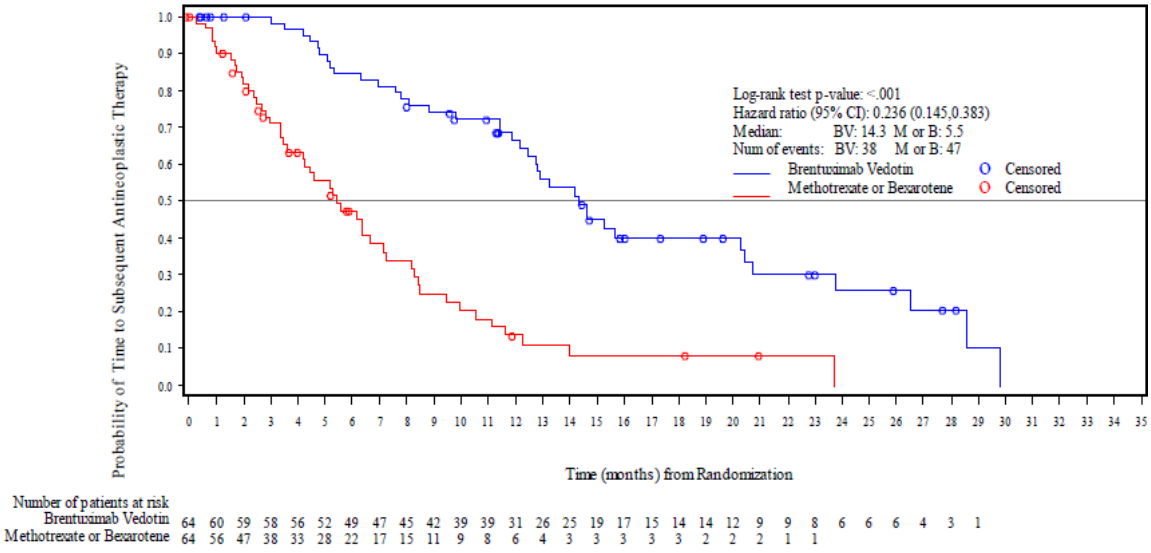
In the primary analysis of ALCANZA (22.9 month follow-up), the duration of response (DOR) in patients who achieved an objective response (43 patients treated with brentuximab vedotin and 13 patients treated with PC) was similar between the 2 treatments (median [95% CI]: overall DOR, 15.1 months [9.7–25.5] vs. 18.3 months [3.5–18.4], respectively). The median duration of skin response (95% CI) was 20.6 months (14.1–25.7) vs. 18.3 months (3.5–18.9) in the brentuximab vedotin arm (47 patients with a skin response) and PC arms (19 patients with a skin response), respectively.[47]

The relatively long DOR observed with PC in ALCANZA is consistent with previous studies of bexarotene and methotrexate which show that the relatively small number of patients who respond to treatment can experience a prolonged remission time.[34,47] However, despite a long overall DOR with PC, it is important to recognise that a much greater number of patients responded to treatment with brentuximab vedotin compared with PC (43 vs. 13, respectively; p<0.0001); therefore a much greater number of patients experienced the prolonged remission time with brentuximab vedotin than with PC.[47]

Time to subsequent anticancer therapy

In the primary analysis of ALCANZA (22.9 month follow-up), significantly fewer patients treated with brentuximab vedotin required ≥1 subsequent anticancer therapy compared with patients treated with PC (38 patients [59%] vs. 47 patients [73%], respectively; p<0.001). Treatment with brentuximab vedotin significantly delayed the time to subsequent anticancer therapy for patients with CTCL by up to 9 months compared with PC (median time to subsequent anticancer therapy: 14.3 months vs. 5.5 months, respectively; p<0.001) as shown in Figure 23.[47,88]

Figure 23. ALCANZA: Time to subsequent anticancer therapy (ITT population)[88]

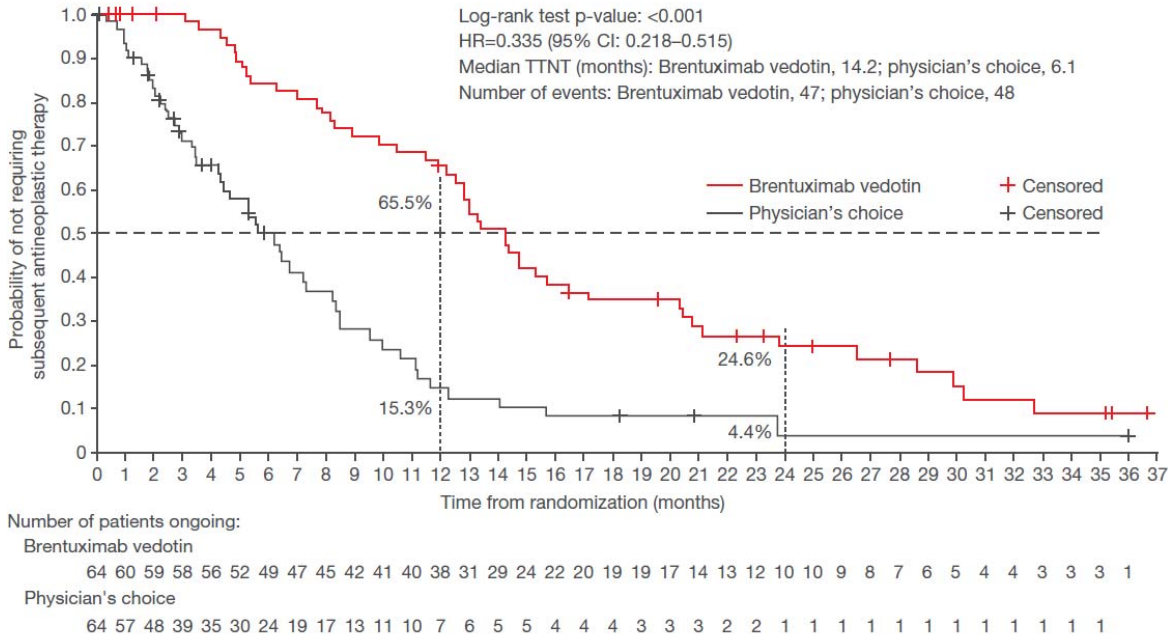


Abbreviations: B, bexarotene; BV, brentuximab vedotin; CI, confidence interval; ITT, intent to treat; M, methotrexate.

Updated analysis (33.9 month follow-up)

In the 33.9 month follow-up analysis, brentuximab vedotin treatment continued to significantly delay time to next treatment vs. PC as shown in Figure 24 (median time to next treatment: 14.2 months vs. 6.1 months, respectively; HR [95% CI] 0.335 [0.218–0.515]; p<0.001). The probability of patients not requiring subsequent anticancer therapy was greater at 1 year and 2 years for brentuximab vedotin vs. PC (65.5% vs. 15.3% and 24.6% vs. 4.4%, respectively).[87]

Figure 24. ALCANZA at 33.9 month follow-up: Time to subsequent anticancer therapy (ITT population)[87]



Reasons for censoring: death, withdrawal by patient, and lost to follow-up.
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent to treat; TTNT, time to next treatment.

B.2.6.1.5 Overall survival (OS)

Although survival is always an important outcome within oncology, in reality the primary goal of treatment for CTCL patients is disease control and symptom relief. The objective of systemic treatment in CTCL is tumour burden relief to improve the patients' QoL. Except for the potentially-curative alloSCT, no regimen has proven to improve survival and OS is not considered when determining treatment success in CTCL.Therefore OS is not prespecified as a primary nor secondary end point in clinical research.

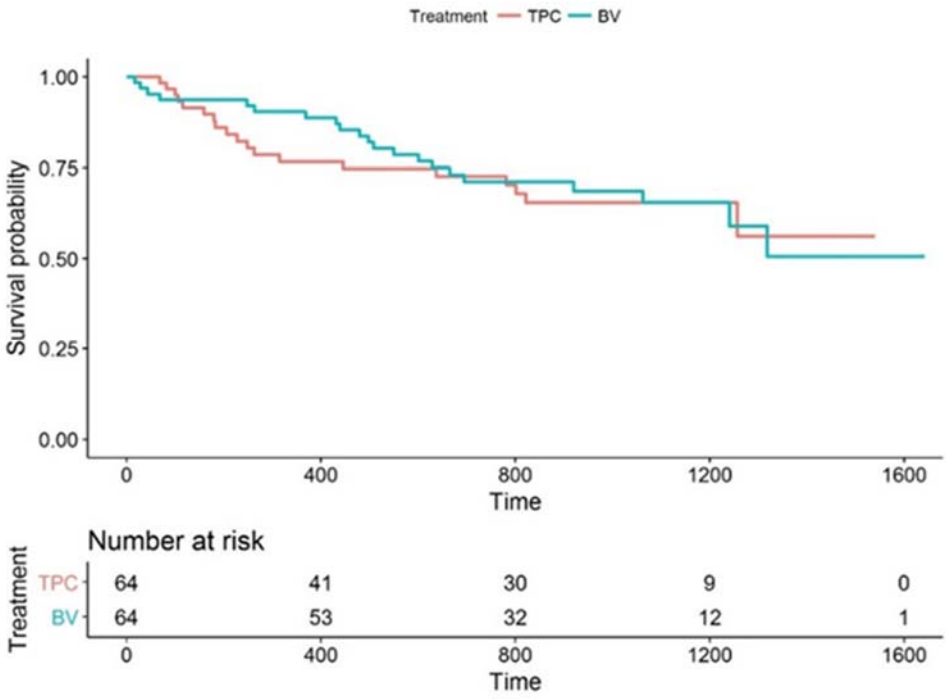
Consensus guidelines from the ISCL, USCLC, and EORTC regarding endpoints in clinical trials of MF/SS state that evaluation of OS is not optimal because the expected survival of most patients with MF/SS in clinical trials is much longer than the course of the trial.[1]

Although not a prespecified endpoint, OS data were collected for ALCANZA. In the primary analysis of ALCANZA (22.9 month follow-up), median OS had not been reached and these data were immature, with only ~30% of events having taken place to date. In total, 67% and 73% of patients were alive in the brentuximab vedotin and PC arms, respectively. Additionally, 50% of patients in the PC arm crossed-over and received brentuximab vedotin

after progression. The low number of survival events (n=21 and n=17 deaths observed for brentuximab vedotin and PC, respectively) confounded by the high cross-over rate makes it challenging to infer meaningful OS outcomes from the ALCAZNA trial. This validates the rationale for OS not having been either a primary or secondary endpoint in the ALCANZA trial, a position that is consistent with other trials in CTCL.

At the 33.9-month follow-up, there was no difference in survival between the brentuximab vedotin and PC arms (Figure 25).

Figure 25. ALCANZA at 33.9 month follow-up: Overall survival in the ITT population[89]



Abbreviations: BV, brentuximab vedotin; PC, physician's choice.

B.2.6.2 Brentuximab vedotin non-comparative phase II trials

The most notable subtypes of CTCL which are included within the EMA marketing authorisation of brentuximab vedotin but were not studied in ALCANZA are SS and LyP. The EMA granted brentuximab vedotin a marketing authorisation for these subtypes based on the efficacy and safety outcomes from the two phase II trials, Kim et al 2015 and Duvic et al 2015.[7] Efficacy observed for the phase II trials is consistent with that reported for the multicentre, randomised controlled, phase II trial ALCANZA[47]; the impressive activity and response rates also consistent for patients with SS and LyP.[24,91]

Of patients with evaluable disease included in the two phase II studies, three patients with SS were included in Kim et al 2015[24] and 10 patients with LyP were included in Duvic et al 2015.[91] Data for these patients are provided below. The remaining patients in both phase II studies either had multiple subtypes (i.e. patients presented with both LyP and MF) or had the subtypes studied in ALCANZA,[24,91] which was deemed a higher quality data set for economic evaluation.

B.2.6.2.1 Kim et al 2015

In the multicentre, phase II trial reported by Kim et al 2015, 70% of patients (90% CI, 53%–83%) with treatment-refractory or advanced MF (n=29 [stage IB, n=4; stage IIB, n=18; stage IV, n=7]) or SS (n=3) achieved an overall response with brentuximab vedotin (Table 15); 1 patient with SS achieved CR and 7 patients achieved >90% reduction in their mSWAT scores.[24]

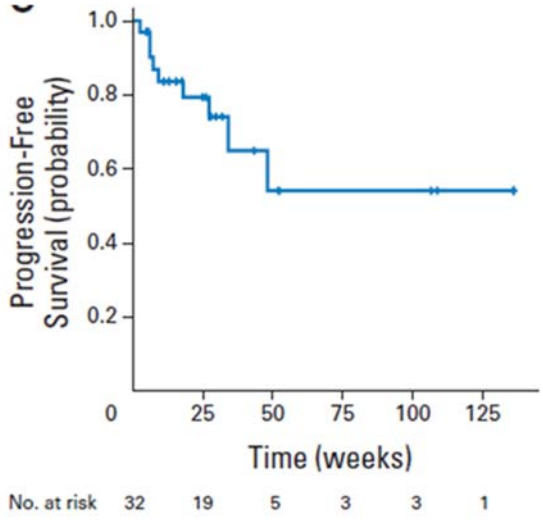
The 6- and 12-month PFS rates were 79% and 54%, respectively (median observation time: 71.7 weeks; Figure 26). Responses were durable; of the 21 responders, at 6 and 12 months, 90% and 79% of patients had continuing responses, respectively, and 79% and 54% of responders, respectively were progression free. These results were consistent with those seen in the larger and more robust brentuximab vedotin arm of the ALCANZA trial (1-year INV-assessed PFS: 63.9%; ORR: 68.8% at 33.9 month follow-up).[87]

Table 15. Kim et al 2015: Response outcomes (patients evaluable for response)[24]

n (%)	Brentuximab vedotin (N=30)*	
	MF (n=27)	SS (n=3)
ORR	19 (70.3)	2 (66.6)
CR	0 (0)	1 (33.3)
PR	19 (70.3)	1 (33.3)
SD	4 (14.8)	0 (0)
PD	4 (14.8)	1 (33.3)
NE	2 (7.4)	NA

*Only 30 out of 32 patients were evaluable for response.
Abbreviations: CR, complete response; MF, mycosis fungoides; NA, not available; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SS, Sézary syndrome.

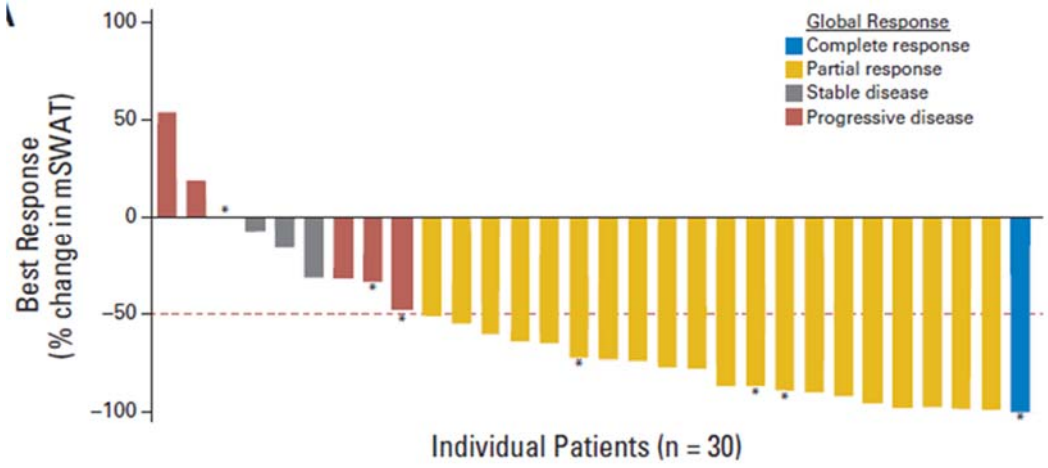
Figure 26. Kim et al 2015: PFS (all patients; n=32)[24]



Abbreviations: PFS, progression-free survival.

In total, the majority of patients had improvement in the skin, with a maximum mSWAT change from the time of screening (mSWATmax) median (range) score reduction of 73% (100% to –54%; Figure 27).[24]

Figure 27. Kim et al 2015: Maximum change in mSWAT score compared with baseline in all patients treated with brentuximab vedotin (patients evaluable for response; n=30)[24]



Horizontal line at −50% represents the threshold for defining PR in the skin.
*Patients with stage IV (extracutaneous) disease.
Abbreviations: mSWAT=modified Severity Weighted Assessment Tool.

B.2.6.2.2 Duvic et al 2015

In the single-centre, phase II trial reported by Duvic et al 2015, 73% of patients (95% CI, 60%–80%) with CD30+ MF (n=28), pcALCL (n=2), LyP (n=9), MF/LyP (n=7), or MF/pcALCL/LyP (n=2) achieved an overall response to brentuximab vedotin treatment, with 35% of patients (95% CI, 22%–49%) achieving complete resolution of skin lesions. In total, the ORR was 54% in patients with MF (15/28), and 100% for patients with all other subtypes (Table 16).[91]

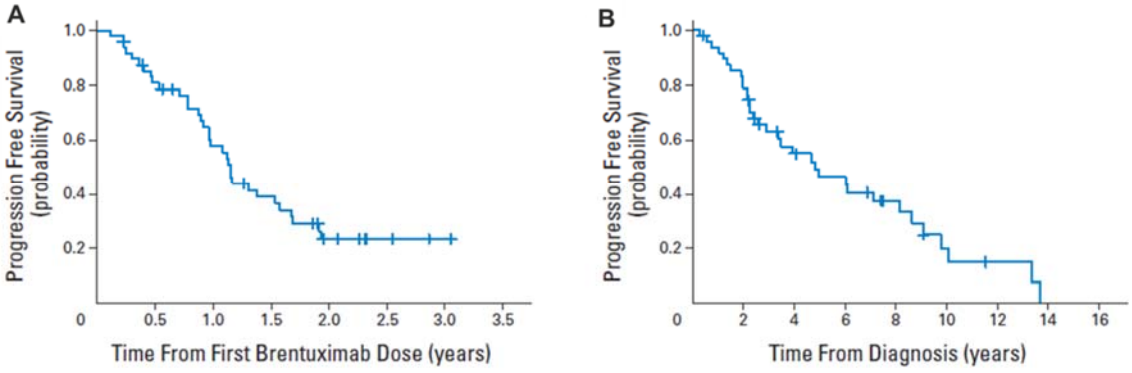
Table 16. Duvic et al 2015: Response outcomes (response-evaluable patients)[91]

	Duvic 2015 (N=48)[91]				
	MF (n=28)	LyP (n=9)	LyP/MF (n=7)	pcALCL/LyP (n=1)	pcALCL/MF (n=1)
ORR	15 (54)	9 (100)	7 (100)	1 (100)	1 (100)
CR	2 (7.1)	5 (55.6)	6 (85.7)	1 (100)	1 (100)
PR	13 (46.4)	4 (44.4)	1 (14.3)	NA	NA

Abbreviations: CR, complete response; LyP, lymphomatoid papulosis; MF, mycosis fungoides; NA, not available; NE, not evaluable; ORR, overall response rate; pcALCL, primary cutaneous anaplastic large cell lymphoma; PD, progressive disease; PR, partial response; SD, stable disease.

For the 48 patients (received ≥2 doses of brentuximab vedotin), median PFS was 13.2 months (95% CI, 10.8–16.8; reported as: 1.1 years [95% CI, 0.9–1.4]) from first treatment with brentuximab vedotin and 57.6 months (95% CI, 37.2–85.2; reported as: 4.8 years [95% CI, 3.1–7.1]) from date of diagnosis (median time to follow-up from first dose: 27 months for MF and 23 months for pcALCL/LyP; Figure 28).[91]

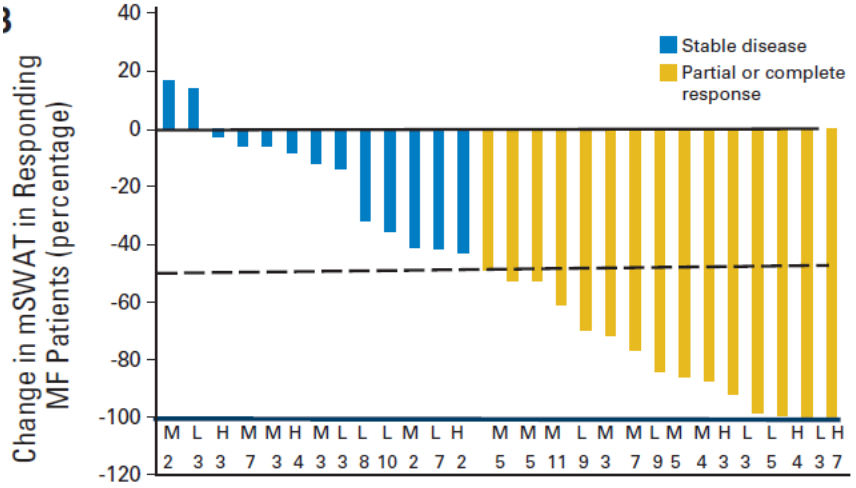
Figure 28. Duvic et al 2015: PFS from date of first treatment with brentuximab vedotin (A), and from date of diagnosis (B) in evaluable patients (N=48)[91]



Abbreviations: PFS, progression-free survival.

Of the 28 evaluable patients, 15 had a best response of CR or PR, as shown by a ≥50% decrease in mSWAT score at the time of best response (Figure 29).[91]

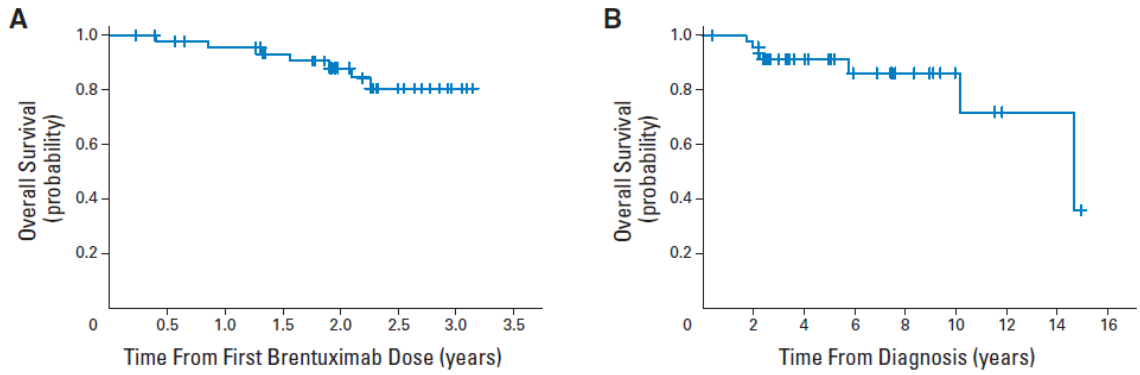
Figure 29. Duvic et al 2015: Percent change in mSWAT at time of best response for patients with MF[91]



Waterfall plot of percent change in mSWAT in responding patients with MF. The first line in the bottom of the graph indicates the level of CD30 expression in skin lesions at baseline—low (L), medium (M), or high (H). The second line shows the number of cycles at the time of best response.
Abbreviations: MF, mycosis fungoides; mSWAT, Modified Severity-Weighted Assessment Tool.

The median OS was 14.7 years (95% CI, 10.2 to not reached) from date of first diagnosis; median OS was not reached when calculated from first treatment with brentuximab vedotin (Figure 30).[91]

Figure 30. Duvic et al 2015: OS from date of first treatment with brentuximab vedotin (A), and date of diagnosis (B) in evaluable patients (N=48)[91]



Abbreviations: OS, overall survival.

B.2.7 *Subgroup analysis*

Based on UK clinical feedback and the newly-updated BAD/UKCLG guidelines, the population anticipated to be treated with brentuximab vedotin is advanced CTCL patients (i.e., MF IIB+, SS, and pcALCL) after at least 1 prior systemic therapy and before standard chemotherapy (e.g., gemcitabine or CHOP). Please refer to Section B.1.3.3 for the UK clinical pathway and positioning of brentuximab vedotin.

The clinical placement of brentuximab vedotin for the treatment of patients with advanced disease was consistently supported in one-to-one interactions with UK key opinion leaders, as well as in a Takeda-organised advisory board that was attended by 10 healthcare professionals (including dermatologists, oncologists, and haematologists) from across the UK.

KOL advisors expressed that patients in early stages of the disease (i.e. MF stage IA) for the most part will have indolent disease and will therefore not require any systemic therapy; this would include brentuximab vedotin.

[redacted]. Based on this, the focus of this NICE submission, is advanced-stage CTCL patients following one prior systemic therapy.

As the ALCANZA trial was an international, multicentre study, and treatment guidelines differ across countries, patients at all stages of CTCL were included in the trial. In order to provide efficacy and safety evidence for the population of interest for the UK and this NICE appraisal (i.e., advanced-stage CTCL), subgroup analyses were conducted on the main safety and efficacy outcomes observed in ALCANZA. Takeda based all subgroup analyses on the 33.9 month median follow-up per INV dataset as the longest follow-up was thought to be the most appropriate for decision making.

B.2.7.1 Methodology

The subgroup of patients from ALCANZA with advanced-stage disease (MF stages IIB–IV; pcALCL all enrolled patients) was evaluated at the 33.9 month median follow-up time point (the longer-term ALCANZA data update) using patient-level data.

B.2.7.2 Participant characteristics

In total, 49 patients treated with brentuximab vedotin and 46 patients treated with PC had advanced-stage disease at baseline (Table 17). Two patients with unknown disease stage were included in the advanced-stage population analyses because, given the balance of the trial population favouring advanced-stage disease, there was a higher probability that they were advanced stage rather than early stage. Patients in ALCANZA were not stratified by disease stage at randomisation. While patient characteristics were generally balanced between treatment arms for the advanced-stage subgroups, patients in the brentuximab vedotin arm were generally older than those in the PC arm. Although pcALCL is diferent than MF IIB+, the two groups were pooled due to the small sample size of pcALCL patients in ALCANZA (n=15 and n=17 for brentuximab vedotin and PC arms, respectively).[89]

Table 17. Baseline patient characteristics and demographics in ALCANZA – advanced-stage population[89]

Characteristic		Brentuximab vedotin (n=49)	Physician's choice of methotrexate or bexarotene (n=46)
Age, y, median (range)		62 (31–82)	54 (25–83)
Male, n (%)		25 (51.0)	24 (52.2)
ECOG PS, n (%)	**0**	34 (69.4)	31 (67.4)
	1	12 (24.5)	13 (28.3)
	2	3 (6.1)	2 (4.4)
Lines of prior therapy, n, median (range)	**Total**	4 (0–13)	3 (1–15)
	Systemic	2 (0–11)	2 (1–8)
MF, n (%)		33 (67.4)	31 (67.4)
Disease stage, n (%)	**IIB**	19 (57.6)	19 (61.3)
	IIIA	4 (12.1)	2 (6.5)
	IIIB	0	0
	IVA1	0	1 (3.2)
	IVA2	2 (6.1)	8 (25.8)
	IVB	7 (21.2)	0
	Unknown	1 (3.0)	1 (3.2)
pcALCL, n (%)		16 (32.7)	15 (32.6)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MF, mycosis fungoides; pcALCL, primary cutaneous anaplastic large cell lymphoma.

B.2.7.3 Statistical information

All end-points included in the subgroup analysis are based on the 33.9 month median follow-up and are assessed per INV using patient-level data. Following the primary end point assessment at a median of 22.9 months, all subsequent datasets were only available as per INV assessment. ORR4, PFS, response rates, symptoms (as assessed by Skindex-29 symptom domain), time to subsequent anticancer therapy, health-related quality-of-life (as assessed by EQ-5D), and OS were evaluated for patients with advanced-stage disease after a median of 33.9 months of follow-up. OS unadjusted for crossover was evaluated; PFS using Weibull models were chosen for both brentuximab vedotin and PC to give a conservative estimate of PFS benefit. ORR, CR, PR, and SD were reported for the entire subgroup and by disease stage. Adverse events (AEs) were summarised by number and duration of each AE was calculated.[89]

B.2.7.4 Results

Consistent with data for the ITT population and the unprecedented results observed across all data cuts of ALCANZA, brentuximab vedotin provided superior efficacy compared with PC for patients with advanced-stage disease at longer-term follow-up.

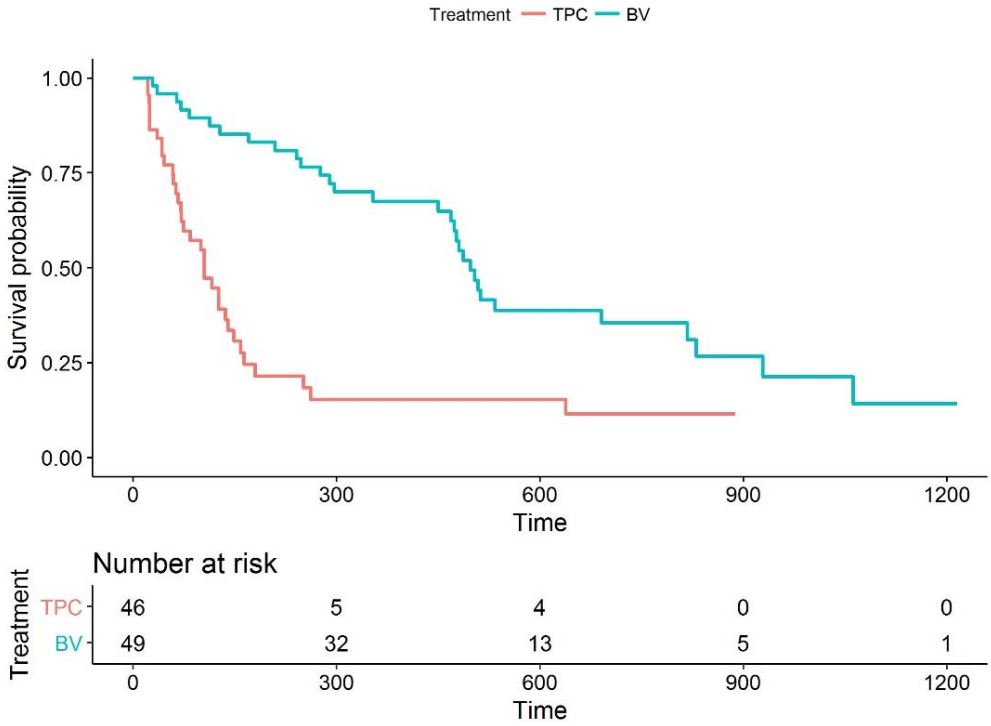
ORR4

At the 33.9-month follow-up of the subgroup of advanced-stage patients, more patients treated with brentuximab vedotin (29 patients [59.2%]) achieved an objective global response lasting ≥4 months (ORR4) over those treated with PC (4 patients [8.7%]).[89]

PFS

Median PFS was longer with brentuximab vedotin treatment over PC as shown in Figure 31 (16.5 months [95% CI: 15.5–27.5] vs. 3.5 months [95% CI: 2.4–4.9], respectively; HR based on a Cox proportional hazard model: 0.2973 [95% CI: 0.1769–0.4998]).

Figure 31. ALCANZA subgroup analysis: Advanced-stage patients at 33.9 months follow-up per INV – PFS[89]



Abbreviations: BV, brentuximab vedotin; PFS, progression-free survival; TPC, treatment with physician's choice.

Response rates

Response rates favoured brentuximab vedotin treatment over PC in advanced-stage patients at the 33.9 month follow-up (Table 18).

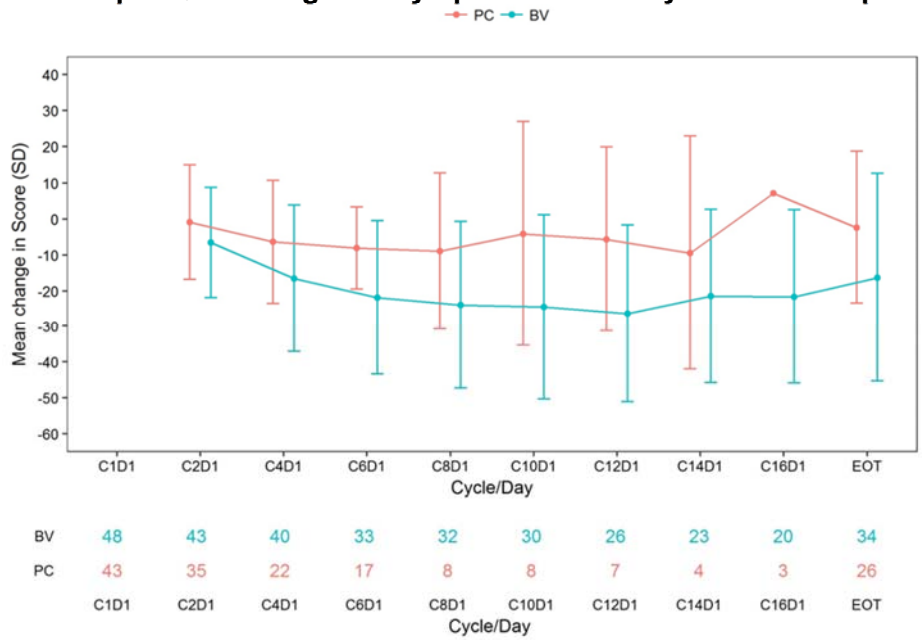
Table 18. ALCANZA subgroup analysis: Advanced-stage patients at 33.9 months follow-up per INV – Response outcomes[89]

n (%)	Brentuximab vedotin (n=49)	Physician's choice of methotrexate or bexarotene (n=46)
Objective response rate	34 (69.4)	8 (17.4)
Complete response	10 (20.4)	1 (2.2)
Partial response	24 (49.0)	7 (15.2)
Stable disease	8 (16.3)	12 (26.1)
Progressive disease	3 (6.1)	16 (34.8)
Not evaluable	4 (8.2)	10 (21.7)

Symptom relief as measured by Skindex-29

Advanced-stage patients treated with brentuximab vedotin had a greater symptom reduction compared with those treated with PC (change from baseline to end of treatment, mean [SD]: –16.31 [28.98] vs. –2.41 [21.04], respectively) as shown by separation of curves in Figure 32.[89]

Figure 32. ALCANZA subgroup analysis: Advanced-stage patients at 33.9 months follow-up – QoL changes in symptom domain by Skindex-29 questionnaire[89]



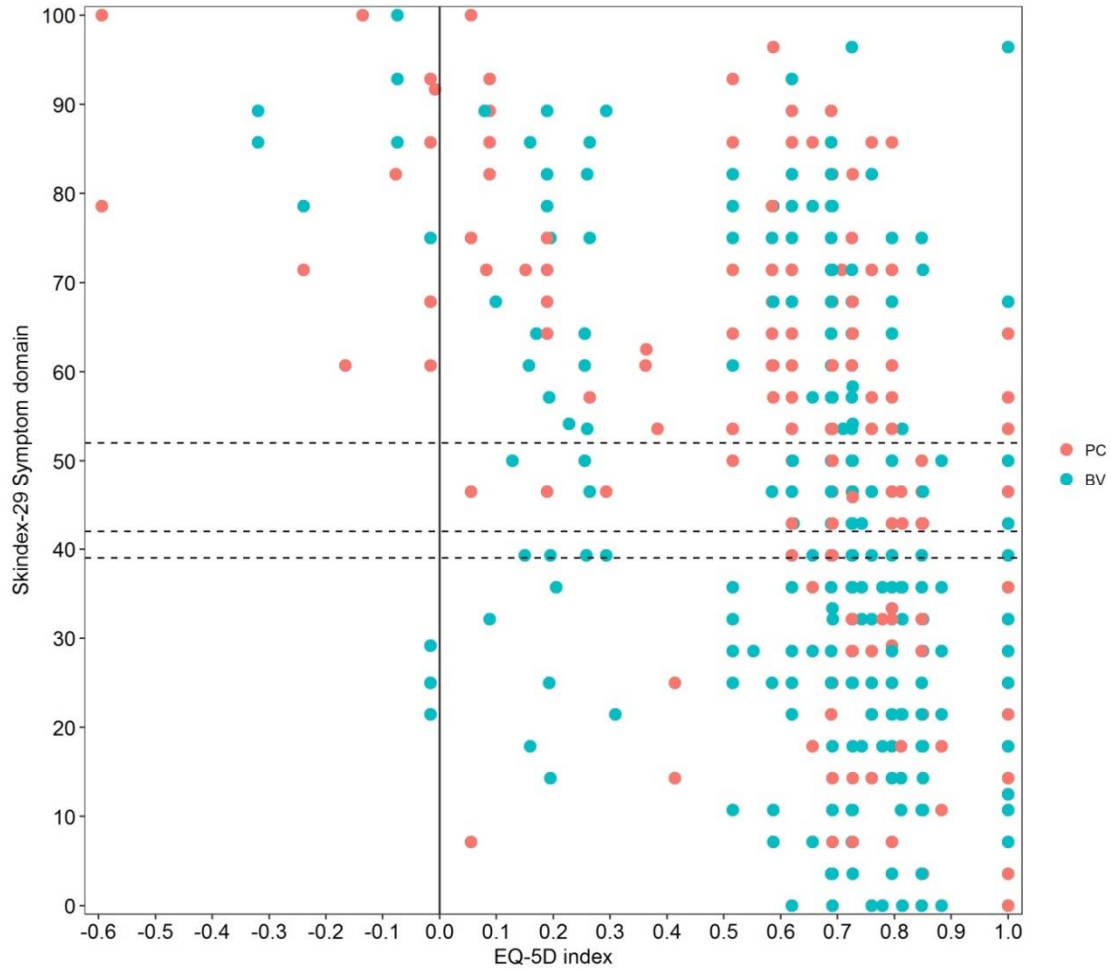
Higher score indicates greater impact of disease, or lower quality-of-life.
Bars represent mean ± SD; no error bar is presented at C16 because the SD is too small to be estimated.
Abbreviations: BV, brentuximab vedotin; C, cycle; D, day; EOT, end of treatment; PC, physician's choice; QoL, quality of life.

Correlation between Skindex-29 symptom scores and EQ-5D

In the Skindex-29 questionnaire (scored from 0–100, where higher scores indicate worse QoL), symptom scores >52 are classified as having a severe negative impact on QoL; scores of 42–51 are classified as moderate, and scores of 39–41 are classified as mild.[98]

The relationship between EQ-5D and Skindex-29 symptom domain scores was evaluated in advanced-stage patients. As shown in Figure 33, Skindex-29 symptom scores span the full range of possible EQ-5D values and vice versa. Most notable is the upper right corner of Figure 33, which shows that a large proportion of patients had high Skindex-29 symptom scores (i.e., severe negative impact on QoL), but still had high EQ-5D scores (i.e., moderate to good HRQL). If a good correlation between Skindex-29 symptom scores and EQ-5D existed, then the majority of observations would appear in the upper left corner (i.e., high Skindex-29 symptom score with a low EQ-5D score). This supports the case that EQ-5D does not fully capture the HRQL detriment associated with CTCL.

Figure 33. ALCANZA subgroup analysis: Comparison of Skindex-29 and EQ-5D scores in patients with advanced-stage disease[89]

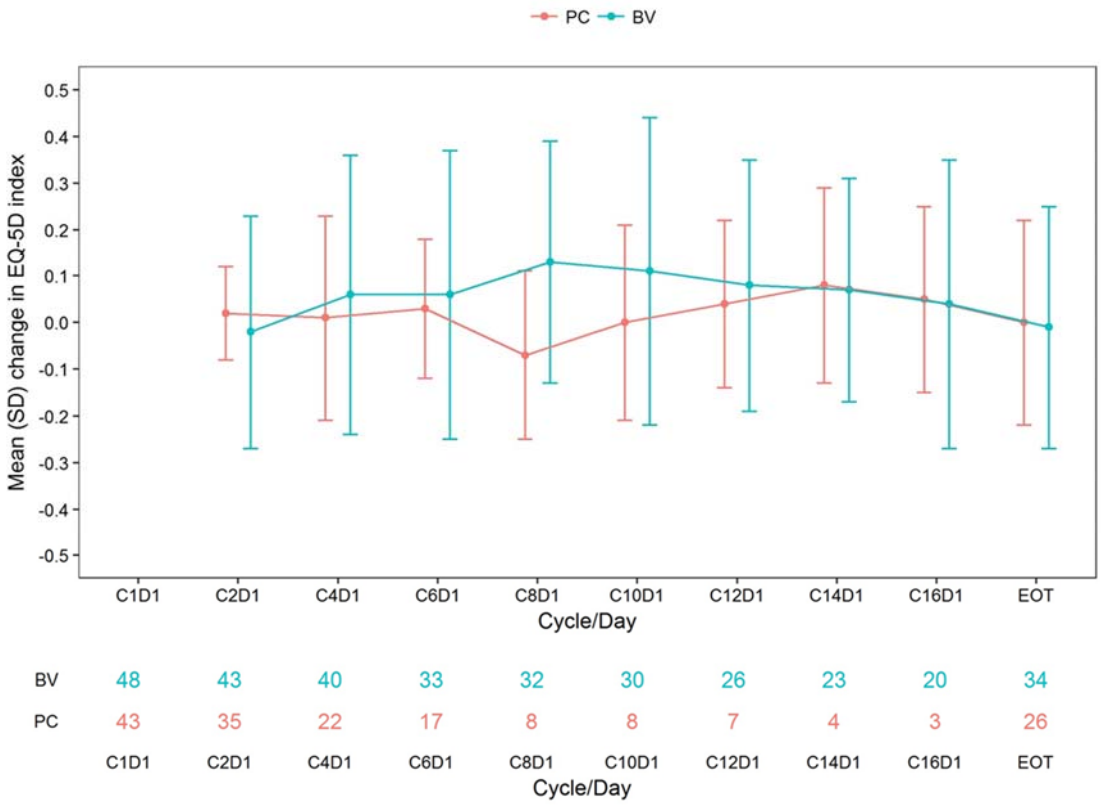


Abbreviations: BV, brentuximab vedotin; PC, physician's choice.

Health-related quality-of-life as measured by EQ-5D-3L

In advanced-stage patients, those in the brentuximab vedotin treatment arm had a higher baseline EQ-5D-3L score than those in the PC arm, indicating a better quality-of-life in the brentuximab vedotin arm (mean [SD] baseline EQ-5D-3L scores: 0.62 [0.3] vs. 0.57 [0.33], respectively). The mean (SD) change from baseline in EQ-5D-3L index scores was –0.01 (0.26) and 0 (0.22), respectively, indicating no change in HRQL as assessed by the EQ-5D (Figure 34).[89]

Figure 34. ALCANZA subgroup analysis: Advanced-stage patients at 33.9 months follow-up – QoL as assessed by EQ-5D-3L index score[89]

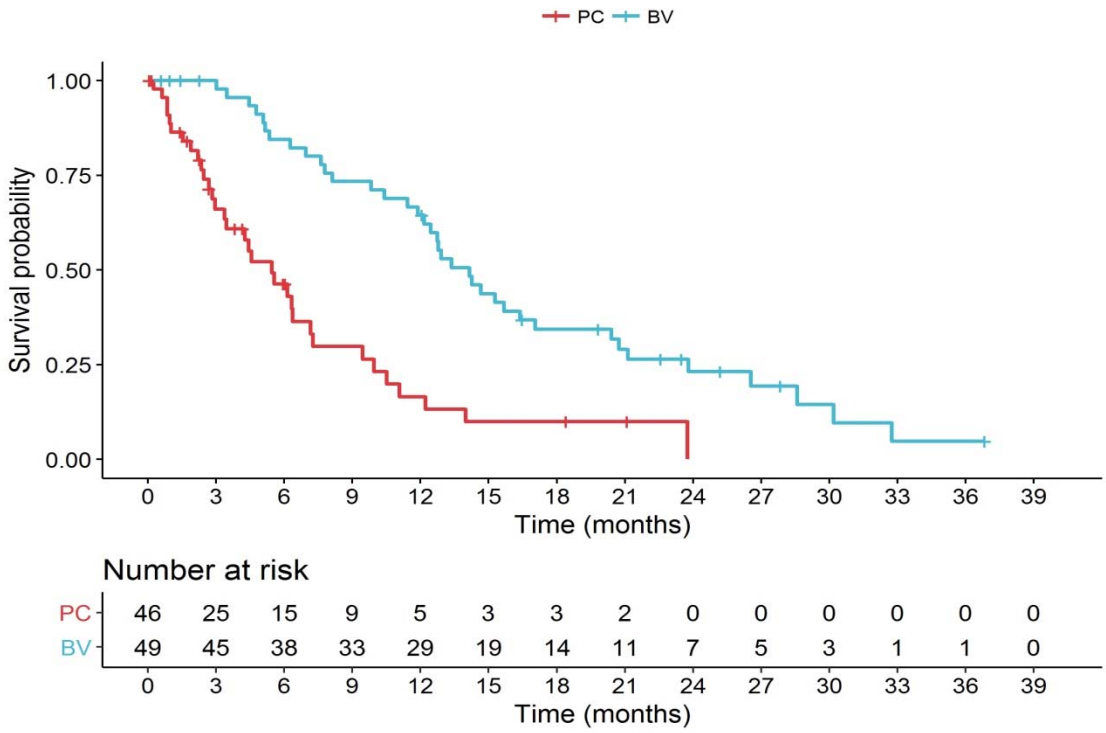


Higher score indicates better quality-of-life.
Bars represent mean ± SD.
Abbreviations: BV, brentuximab vedotin; C, cycle; D, day; EOT, end of treatment; PC, physician's choice.

Time to next treatment

Time to subsequent anticancer therapy was longer with brentuximab vedotin vs. PC for patients with advanced-stage disease (median time to next treatment: 14.2 months [95 %CI: 12.2–20.4] vs. 5.5 months [95% CI: 3.4–9.5], respectively) as shown in Figure 35.[89]

Figure 35. ALCANZA subgroup analysis: Advanced-stage patients at 33.9 months follow-up – Time to subsequent anticancer therapy[89]



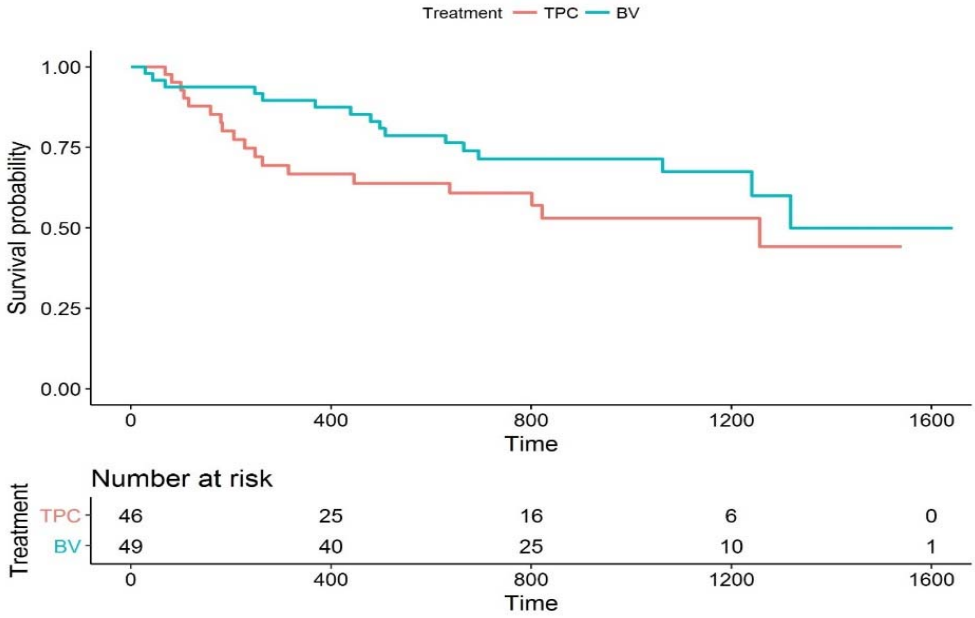
Abbreviations: BV, brentuximab vedotin; PC, physician's choice.

Overall survival

OS data were extremely immature at 33.9 months of follow-up, with very few events resulting in an even smaller sample size across both treatment arms compared to ITT. Although directionally there appears to be a trend towards longer OS observed in the brentuximab vedotin arm over PC (median OS [95% CI]: 43.6 months [41.0–NA] vs. 41.6 months [21.1–NA], respectively; Figure 36), this analysis is highly uncertain as illustrated by the single figure difference in the number of observed events. Furthermore, the data are highly confounded as 46% of patients crossed-over from the PC arm and received brentuximab vedotin as a subsequent therapy, of whom 30% received it as their first subsequent treatment.[89] SectionB.3.3.2.2 describes the efforts made to adjust for crossover; however none of the methods were particularly well suited to the data given the small number of patients and events. The impact of re-censoring was particularly pronounced in this small sample size with the loss of multiple events, and this effectively shortened follow-up for many patients, resulting in the advanced patient OS curves crossing multiple times. Furthermore, except for the potentially-curative alloSCT, no treatment to date has been shown to affect OS for patients with advanced CTCL. Likewise, based on the observed

events to date and the limitations described above, it is not possible to claim a difference in OS between the brentuximab vedotin and PC arms.

Figure 36. ALCANZA subgroup analysis: Advanced-stage patients at 33.9 months follow-up – Overall survival[89]



Abbreviations: BV, brentuximab vedotin; PC=physician's choice.

B.2.8 *Meta-analysis*

Systematic literature review identified only one comparative study for brentuximab vedotin vs. an active comparator (ALCANZA; physician's choice of bexarotene or methotrexate) for the treatment of CD30+ CTCL after one prior therapy. The cost effectiveness model was based on the outcomes of the ALCANZA trial as described in Section B.2.6.

Other than the two single-arm phase II trials which were deemed inappropriate for cost-effectiveness modelling (see section B.2.2.1), Takeda are not aware of any further studies for brentuximab vedotin that would enable a meta-analysis to be conducted.

B.2.9 *Indirect and mixed treatment comparisons*

B.2.9.1 Brentuximab vedotin vs. interferon

The use of IFN-α for the treatment of CTCL is recommended in the current ESMO,[32] EORTC,[16] [redacted][63]

Feasibility assessment of modelling IFN-α vs brentuximab vedotin will focus on its use in the population of interest, defined as advanced CTCL patients only.

Position in treatment pathway

Although IFN-α is only one of two systemic treatments recommended for frontline use in patients with advanced-stage CTCL, in the UK Advisory Board held by Takeda in January 2018, there was consensus among the 10 clinical experts present that IFN-α is most commonly used as a first-line systemic treatment option. [redacted].[36] IFN-α does not currently have a UK marketing authorisation for this patient population. Nonetheless, it is used by UK clinicians in the UK for the management of CTCL.[36]

As IFN-α is likely to have been exhausted as a treatment option by the time patients become eligible for treatment with brentuximab vedotin (i.e., after ≥1 prior systemic therapy), it is not in our opinion a primary comparator..

Nonetheless, as [redacted][63] and is used in clinical practice, Takeda made every effort to conduct an indirect comparison between brentuximab vedotin and IFN-α as described below.

Data requirements for modelling

For comparison with the ALCANZA data, studies of IFN-α in CTCL would require PFS and OS data as these are the key model inputs. Response rate data are unsuitable surrogates for modelling due to the different mechanisms of action of brentuximab vedotin and PC, and the uncertainty of the relationship between response rates and outcomes.

To have confidence in any analysis and perform more complex comparisons, a good overlap of patient characteristics and format of data outputs is required between ALCANZA and potential IFN-α studies.

Quality of published evidence

A systematic literature review (SLR) conducted to support the current submission identified four publications with IFN-α as an intervention for treatment of CTCL (see Appendix D.1.1.4 for the full SLR methodology). This review excluded studies published prior to 2007, and those including fewer than 20 patients. It was subsequently noted that earlier data on IFN may be of interest to the decision problem.

To ensure all relevant information relating to the management of CTCL with IFN was identified, a rapid literature review was performed to identify data published prior to 2007. The search was based on the strategy outlined in Appendix D and was focussed on interferon publications only. In addition, references excluded from theSLR due to publication date or sample size were rescreened in May 2018. The literature review rescreen and rapid review identified 11 and 8 unique refrences, respectively.

In total, 23 publications relevant to IFN in CTCL were identified. Appendix D.1.2.1 discusses each of the 23 identified publications and their viability as a source for the indirect comparison with brentuximab vedotin based on the aforementioned criteria.

Despite the availability of data on the use of IFN in CTCL, the studies are not appropriate for modelling, with no study allowing estimation of the outcomes that would be seen with IFN-α use in the NHS. Reasons for inability to use studies for modelling included (note that studies may have not met criteria for inclusion for multiple reasons):

- IFN-α used as combination therapy (IFN-α monotherapy is recommended therapy for CTCL): 12 studies
- Lack of relevant outcomes reported: 8 studies
- Patient population not consistent with that in ALCANZA/relevant to decision problem: 2 studies
- IFN preparation was not consistent with that used in the UK (IFN-α): 3 studies

While IFN-α is recommended and used as monotherapy in the UK, the literature mainly identified studies which assessed IFN-α as a combination treatment. For the reasons listed above (i.e., lack of comparable data), Takeda was not able to conduct an indirect comparison of brentuximab vedotin vs. IFN-α. Allied to the fact that IFN-α is not a primary comparator for many of the patients covered by this appraisal, this further supports the non-inclusion of IFN-α as a comparator in the economic model.

B.2.9.2 Brentuximab vedotin vs. standard of care for patients with SS/LyP

Evidence to support the clinical effectiveness of brentuximab vedotin in CTCL subtypes other than those in the ALCANZA study (MF and pcALCL) is very limited. There were two phase II studies which looked at the efficacy of brentuximab vedotin in other subtypes of CTCL, Kim et al 2015 and Duvic et al 2015. For a full description of the studies including their design and outcomes, please refer to section B.2.6.2 Brentuximab vedotin non-comparative phase II trials.

Of the subpopulations for CTCL subtypes not included in ALCANZA, Kim et al 2015 and Duvic et al 2015 included three patients with SS patients, and ten patients with LyP, respectively.[24,91] No OS or PFS results were reported for the individual subtypes in either trial. Since both trials were single-arm and did not include a control arm, it was unlikely that meaningful OS or PFS results could be obtained for patients with SS or LyP. Any ITC would require the use of population adjustment methods (e.g., MAIC or STC). Both approaches involve fitting regression models including multiple covariates, and were not considered realistic given the small sample sizes available. In addition, there were no suitable data sources for SS or LyP patients receiving standard care to compare against. Therefore, an ITC for CTCL subtypes outside of those in the ALCANZA study was not considered feasible.

Full details of the analysis of feasibility for comparative efficacy assessment for patients with SS or LyP are provided in Appendix D.1.2.2.

B.2.10 *Adverse reactions*

B.2.10.1 ALCANZA

Overall, 128 patients received study treatment and were included in the safety population (brentuximab vedotin, n=66; PC, n=62) for the primary analysis (at 22.9 months of follow-up). Treatment with brentuximab vedotin, compared with methotrexate or bexarotene, was not associated with any new or unexpected toxicities.[47] The safety profile of brentuximab vedotin was similar to what has been observed in the other well-known indications such as relapsed/refractory (R/R) Hodgkin lymphoma (HL).[99,100]

In the primary analysis of ALCANZA, the duration of exposure to brentuximab vedotin was substantially longer than in the PC group (median duration of treatment: 269 days [12 [IQR 5–16] 3-week cycles] of brentuximab vedotin vs. 114 days of bexarotene [equivalent to 5.5 [IQR 3–11] 3-week cycles] and 77 days of methotrexate [equivalent to 3 [IQR 2–6] 3-week cycles]). Median relative dose intensity was 99.6% (IQR 92.7–100.0) for brentuximab vedotin and 94.3% (IQR 73.6–100.0) for bexarotene. Treating physicians determined the methotrexate dose (5–50 mg once per week); the median dose was 21.7 mg/week (IQR 16.7–30.6). Three patients remained on treatment (all in the brentuximab vedotin group) at the time of data analysis. The most frequent reasons for treatment discontinuation were completion of 16 cycles in the brentuximab vedotin group (23 of 66 patients [35%]) and disease progression in the PC group (40 of 65 [62%]).[47]

Safety profiles for both groups are summarised in Table 19. Overall, serious adverse events (AEs) were similar between groups, occurring in 19 (29%) of 66 patients in the brentuximab vedotin group vs. 18 (29%) of 62 patients in the PC group. Discontinuation due to AEs occurred in 16 (24%) patients in the brentuximab vedotin group vs. 5 (8%) in the PC group. As expected, the most frequent cause of discontinuation due to AEs in the brentuximab vedotin group was peripheral neuropathy (9 patients).[47] AEs resulting in study drug discontinuation were: brentuximab vedotin, peripheral sensory neuropathy (n=5), neuropathy peripheral (n=2), drug eruption, drug hypersensitivity, Escherichia infection, hypoaesthesia, impetigo, peripheral motor neuropathy, pulmonary embolism, rash maculo-papular, urticarial, and vertigo (n=1 for each); PC, rash maculo-papular, asthenia, haematuria, hypernatraemia, neutropenia, periorbital infection, somnolence (n=1 for each).[88]

Table 19. Overall safety profile in ALCANZA (safety population)[47]

n (%)	Brentuximab vedotin (n=66)	Physician's choice of methotrexate or bexarotene (n=62)
Any AE	63 (95)	56 (90)
Any grade ≥3 AE	27 (41)	29 (47)
Drug-related AE	57 (86)	44 (71)
Drug-related ≥3 AE	19 (29)	18 (29)
Serious AE	19 (29)	18 (29)

Drug-related serious AE	9 (14)	3 (5)
AE resulting in study drug discontinuation*	16 (24)	5 (8)
On-treatment deaths†	4 (6)	0

*One additional patient in the brentuximab vedotin arm is reported as discontinuing study drug because of an AE in the overall disposition figure. This patient experienced a fatal treatment-emergent AE of lymphoma progression, and the recorded action was "discontinued from the study" instead of "study drug discontinued."
†On-treatment deaths were defined as deaths that occurred within 30 days after the last dose of study drug.
Abbreviations: AE, adverse event.

In total, 16 (24%) deaths occurred in the brentuximab vedotin group and 14 (23%) in the PC group at the 22.9-month follow-up. Four on-treatment deaths in the brentuximab vedotin group (3 unrelated to study drug and one multiple organ dysfunction syndrome in a patient with T3bN0M1 pcALCL, attributed by the investigator to tumour lysis caused by brentuximab vedotin on sites of visceral lymphoma involvement) occurred within 30 days of the last dose.[47]

The most common AE observed with brentuximab vedotin treatment was peripheral neuropathy. Bexarotene treatment is associated with hypertriglyceridaemia (ALCANZA primary analysis, 30% of patients [11 of 37] treated with bexarotene; 14% [5 of 37] had hypertriglyceridaemia of grade ≥3). The most frequently reported AE with methotrexate was pyrexia which affected 7 of 25 patients (28%) (Table 20).[47]

Peripheral neuropathy, a known toxicity with brentuximab vedotin, was reported in 44 (67%) patients in the brentuximab vedotin group (n=17 grade 1, n=21 grade 2, n=6 grade 3) and 4 (6%) of 62 patients in the PC group (n=1 grade 1, n=3 grade 2). In the majority of cases, peripheral neuropathy can be managed by dose reduction and/or dose delay. Following a median 22.9 months follow up, 36 of 44 patients (82%) in the brentuximab vedotin group had improvement (≥1 grade) or resolution of peripheral neuropathy,[47] after cessation (n=9 with a median of 11 cycles of treatment completed [range, 4–15 cycles]), dose reduction (to 1.2 mg/kg), dose delay, or completion of treatment. Most patients did not need to delay treatment (no delay, n=28; 1 dose delay, n=13; 2 dose delays, n=3).[88]

Table 20. ALCANZA: Common treatment-related AEs (≥10% of patients)[47]

Any Grade AE, n (%)	Brentuximab vedotin (n=66)	Methotrexate (n=25)	Bexarotene (n=37)
Peripheral sensory neuropathy SMQ	30 (45)*	1 (4)	0
Nausea	24 (36)	4 (16)	4 (11)
Diarrhoea	19 (29)	1 (4)	3 (8)
Fatigue	19 (29)	5 (20)	12 (32)
Vomiting	11 (17)	2 (8)	1 (3)
Alopecia	10 (15)	1 (4)	1 (3)
Pruritus	11 (17)	2 (8)	6 (16)
Pyrexia	11 (17)	7 (28)	4 (11)

Any Grade AE, n (%)	Brentuximab vedotin (n=66)	Methotrexate (n=25)	Bexarotene (n=37)
Decreased appetite	10 (15)	1 (4)	2 (5)
Asthenia	7 (11)	3 (12)	2 (5)
Dyspnoea	7 (11)	0	0
Maculopapular rash	7 (11)	1 (4)	2 (5)
Peripheral oedema	7 (11)	4 (16)	2 (5)
Pruritus (generalised)	7 (11)	0	1 (3)
Arthralgia	8 (12)	2 (8)	2 (5)
Myalgia	8 (12)	0	2 (5)
Headache	5 (8)	1 (4)	5 (14)
Anaemia	3 (5)	0	6 (16)
Skin infection	2 (3)	3 (12)	4 (11)
Hypertriglyceridaemia	1 (2)	0	11 (30)

*Overall, events reported by investigators as peripheral neuropathy or peripheral sensory neuropathy (including events additional to those reported in ≥10% of patients) were reported as grade 1 in 17 patients, grade 2 in 21 patients, and grade 3 in six patients.
Abbreviations: AE, adverse event; SMQ, standardised Medical Dictionary for Regulatory Activities query.

Updated analysis (33.9 month follow-up)

The safety profile of brentuximab vedotin remained consistent with the original analysis. After an additional 11 months of follow-up, the most common AEs were gastrointestinal disorders (n=9 events), peripheral neuropathy (n=7 events), blood and lymphatic system disorders (n=6 events), and skin and subcutaneous tissue disorders (n=5 events).[89] Data from the updated analysis show that peripheral neuropathy improved over time; at median 33.9 months follow-up in brentuximab vedotin-treated patients, ongoing peripheral neuropathy was grade 1/2 in 15/3 patients (no grade 3/4 peripheral neuropathy) compared with grade 1/2 in 17/5 patients in the original analysis. Encouragingly, with additional follow up, 86% (38/44) of patients in the brentuximab vedotin group who had peripheral neuropathy had complete resolution (26/44) or improvement (≥1 grade; 12/44) of all peripheral neuropathy symptoms. Overall, 9 patients discontinued treatment with brentuximab vedotin due to peripheral neuropathy, after a median of 11 treatment cycles (Table 21).[87]

Table 21. ALCANZA at 33.9 month follow-up: Incidence, duration, and severity of peripheral neuropathy (SMQ) (safety population)[87]

	Brentuximab vedotin (n=44)	Physician's choice of methotrexate or bexarotene (n=4)
Patients with resolution or improvement of peripheral neuropathy events, n (%)	38 (86)	2 (50)
Patients with resolution of all peripheral neuropathy events, n (%)	26 (59)	2 (50)
Median time to resolution	30.0 weeks	10.5 weeks
Patients with improvement in peripheral neuropathy events, n (%)	12 (27)	0
Median time to improvement	13.0 weeks	-
Patients with ongoing peripheral neuropathy events, n (%)	18 (41)	2 (50)
Maximum severity grade 1, n (%)	15 (34)	1 (25)
Maximum severity grade 2, n (%)	3 (7)	1 (25)

ALCANZA advanced-stage subgroup analysis

In advanced-stage patients at 33.9 months of follow-up, the mean duration of exposure to brentuximab vedotin was 237 days and to PC was 130 days. The safety profile of brentuximab vedotin was consistent with that observed in the primary (22.9 months) and updated (33.9 month) ALCANZA analyses of the ITT. In advanced-stage patients at 33.9 months of follow-up, the most common grade ≥3 AEs that occurred in brentuximab vedotin-treated patients (grouped by system class) were peripheral neuropathy and gastrointestinal disorders (7 events each; Table 22).[89]

Table 22. ALCANZA subgroup analysis: Grade ≥3 AEs that occurred in ≥5% of patients in either treatment arm[89]

Adverse Events	Number of events		Duration (days)	
	BV	PC	Mean	SD
Blood and lymphatic system disorders (anaemia, neutropenia, thrombocytopenia)	6	4	15.5	16.6
Gastrointestinal disorders (Constipation, diarrhea, intestinal perforation, melena, nausea, pancreatitis, vomiting)	7	0	10.7	8.7
General disorders and administration site conditions (asthenia, fatigue, general physical health deterioration)	4	0	81.8	135.8
Multiorgan failure	1	0	1.0	1.0
Infections and infestations (acute diverticulitis, cellulitis, impetigo, staphylococcus aureus skin infection)	3	0	26.0	17.7

Septicaemia	0	1	20.0	20.0
Peripheral neuropathy	7	0	258.0	301.1
Skin and subcutaneous tissue disorders (drug eruption, hives, maculopapular rash, pruritus)	0	0	0.0	0.0
Investigations (alanine aminotransferase increased, aspartate aminotransferase increase, blood triglycerides increased, lymphocyte count decreased, raised triglycerides)	0	6	18.2	5.2
Hypertriglyceridemia	0	9	50.9	81.7

Abbreviations: AEs, adverse events; BV, brentuximab vedotin; PC, physician's choice.

B.2.10.2 Kim et al 2015

The phase II, investigator-initiated trial Kim et al 2015 showed that overall brentuximab vedotin was generally well tolerated and reported a similar AE profile to that observed in the main and updated ALCANZA analyses. Consistent with ALCANZA, the most commonly observed AEs (all grades) were peripheral neuropathy (66%), fatigue (47%), nausea (28%), alopecia (22%), and neutropenia (19%) with brentuximab vedotin in the monotherapy setting (Appendix section F.1.1 Results of additional safety studies).[24]

The median (range) number of brentuximab vedotin doses was 6 (1–16). Grade 3/4 AEs occurred in 10 patients, with the most common being neutropenia (n=4) and skin eruption (n=3). Serious AEs occurred in 3 patients, with 1 event each of confusion, acute renal failure, and peripheral neuropathy.[24]

While peripheral neuropathy was the most common cause of dose modification or toxicity-related early termination, it was primarily grade 1 or 2 and resolved or improved in the majority of patients. Peripheral neuropathy was reversible in most patients; the median (range) time to improvement of peripheral neuropathy was 49.0 weeks (20.4–70.1), with 59% of patients with peripheral neuropathy showing improvement or resolution by 12 months, and 86% by 24 months. Peripheral neuropathy grade ≥2 occurred in 12/21 patients (grade 2, n=11; grade 3/4, n=1). The median (range) time to peripheral neuropathy was 13 weeks (3.0–38.6) and to grade 2 peripheral neuropathy was 20.8 weeks (15.0–46.0). The one patient with grade 4 peripheral neuropathy died of pneumonia as a complication of the neuropathy.[24]

B.2.10.3 Duvic et al 2015

The phase II, investigator-initiated trial Duvic et al 2015 showed that overall brentuximab vedotin was generally well tolerated and reported a similar AE profile to that observed in the main and updated ALCANZA analyses. Consistent with ALCANZA, the most commonly observed AEs (all grades) were peripheral neuropathy (67%), fatigue (35%), rash (24%), nausea (19%), myalgias (17%), localised skin infection (15%), neutropenia (15%), diarrhoea (15%), and alopecia (11%) with brentuximab vedotin in the monotherapy setting.[91]

The median (range) number of brentuximab vedotin cycles was 7 (2–19) for MF and 7.5 (2–16) for LyP/pcALCL. In total, 54 patients received ≥1 dose of brentuximab vedotin and were included in the safety analyses.[91]

Peripheral neuropathy was reported in 31 of 54 patients (67%). Grade 1 peripheral neuropathy was reported in 30 patients, with progression to grade 2 in 21 patients. In the event of neuropathy, brentuximab vedotin dose was held or reduced to 1.2 mg/kg. Overall, peripheral neuropathy resolved in 14 of 31 patients, with the median (range) time to resolution being 41.5 weeks (2–66).[91]

B.2.11 *Ongoing studies*

Figure 37 Ongoing clinical trials for brentuximab vedotin of relevance to the decision problem

NCT Number	Title	Recruitment	Comment
NCT02388490	Brentuximab Vedotin in Patients With Relapsed or Refractory EBV-and CD30-positive Lymphomas	Recruiting	Estimated Primary Completion Date-August 2018
NCT02588651	A Phase II Study of Single Agent Brentuximab Vedotin in Relapsed/Refractory CD30 Low (<10%) Mature T Cell Lymphoma (TCL)	Recruiting	Estimated Primary Completion Date - July 2018
NCT01196208	A Treatment-Option Protocol to Provide Brentuximab Vedotin to Eligible Patients Completing Studies SGN35-005 or C25001	Available	Expanded access trial

Abbreviations: EBV, Epstein-Barr virus.

B.2.12 *Innovation*

Brentuximab vedotin is a targeted and highly-innovative therapy that has shown unprecedented single-agent activity in the treatment of CTCL. It has a unique mechanism of action and published data outcomes for efficacy and safety, thus providing an opportunity to make a significant and substantial impact on health-related benefits and address an otherwise significant unmet medical need. With few new treatment options for CTCL introduced over the last few years, patient groups such as the Cutaneous Lymphoma Foundation have welcomed this new treatment option in Europe.[101] Based on its impressive single-agent response rates, brentuximab vedotin is seen by clinical experts as an exciting new therapy for advanced-stage CTCL, with the potential to substantially modify the trajectory of the disease by enabling significantly improved disease control to most patients for a sustained duration of time. Furthermore, for some patients, it could have a profound impact on the treatment pathway by allowing more eligible patients to proceed to a potentially-curative alloSCT. The latter use as a more effective bridging/induction agent prior to alloSCT represents a significant innovation that could fundamentally change the management of these patients by allowing increased use of alloSCT, a treatment that is regarded as the only potentially-curative intervention in advanced CTCL. Clinical experts believe that brentuximab vedotin may have a profound impact on the proportion of CTCL patients who are eligible for an alloSCT due to the unprecedented disease response observed in ALCANZA where 15.6% of patients achieved a CR at first analysis (which increased to 20.4% with 33.9 month follow-up) compared to only 2.2% with PC.[47] In this way, the introduction of brentuximab vedotin could open up the possibility of long-term remission for more patients with CTCL than is currently possible.

We believe the QALY gain with brentuximab vedotin is likely to be significantly underestimated due to the limitations of the EQ-5D as a quality of life instrument (see Section B.3.3.6 for limitations of the EQ-5D). Simply put, in a condition like CTCL that primarily affects the skin, we do not believe that the generic EQ-5D used in the ALCANZA trial has the sensitivity to pick up the full extent of the QoL decrement suffered by patients with CTCL (e.g., unrelenting itch) and the QoL benefits offered by brentuximab vedotin. Literature and clinical experts support that Skindex-29 is a more appropriate QoL instrument to use than EQ-5D, and we note the significant benefits on Skindex-29 scores that were seen with brentuximab vedotin compared to bexarotene or methotrexate in the ALCANZA trial. This is demonstrated by analysis presented in Section B.2.7.4, which shows poor correlation of Skindex-29 symptom scores and EQ-5D scores observed in ALCANZA. A large proportion of patients with relatively high EQ-5D scores of 0.7 or greater had a Skindex-29 symptom score of >52 which is classified as having a severe negative impact on QoL.[89,98] A search of the literature identified that there is no algorithm available that maps Skindex-29 scores onto the EQ-5D, therefore posing significant challenges to the measurement of quality-of-life gain. This supports our contention that the full HRQL benefit of brentuximab vedotin is not captured within the cost-effectiveness modelling.

In addition to its unprecedented efficacy in this patient population, brentuximab vedotin offers other benefits, at least some of which may not be adequately captured within the cost-effectiveness estimates. These include:

- A convenient administration schedule (one 30-minute infusion every 3 weeks) that means it can be administered on an out-patient basis. This allows patients to live a more normal life and spend less time in hospital during treatment
- Improved tolerability compared to traditional, non-targeted chemotherapy. As a result, brentuximab vedotin can help to maintain patients' QoL and for eligible patients it can deliver them to alloSCT in better condition than is the case after other bridging agents (i.e., less cumulative toxicity)
- A potentially positive impact on the QoL of caregivers and family members

The impact that brentuximab vedotin has offered to patients with CTCL through the clinical trial programme is illustrated by the following quote from a UK ALCANZA patient:

> *"So during the first infusion I had, it took about 40 minutes. And straight away the itching disappeared and I felt good. I didn't have any side effects. I didn't feel sick. I didn't feel ill. I was just able to carry on. And then during all the other infusions, I left work, had the drug, went back to work, and got on with my job. The lesions pretty much almost immediately started shrinking and shriveling. The itching had stopped. So I was very hopeful that this would be the end of the disease."*[36]

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

The ALCANZA trial represents the first demonstration of benefit in a randomised phase III trial with a novel systemic drug versus an active standard comparator in CTCL.[47]

While the primary aims of CTCL treatment are generally quite different from those of other lymphoma indications (i.e., disease control and improvement in QoL rather than prolongation of OS), ALCANZA showed a highly significant treatment effect for brentuximab vedotin in the disease-relevant metrics (e.g., disease control, ORR, and PFS). In this directly-comparative trial, treatment with brentuximab vedotin resulted in efficacy and QoL improvements over bexarotene and methotrexate, two of the most commonly used second-line systemic treatments for advanced-stage CTCL in the UK. Overall, compared with bexarotene or methotrexate, brentuximab vedotin significantly improved the proportion of patients achieving an ORR lasting at least 4 months (56.3% vs. 12.5%) and a CR (15.6% vs. 1.6%), significantly delayed progression (median PFS of 16.7 months vs. just 3.5 months), and significantly reduced patient-reported symptom burden (27.96-point vs. 8.62-point mean decrease in Skindex-29 scores). At longer-term follow-up of 33.9 months, the superior clinical activity of brentuximab vedotin vs. PC was continued across all endpoints, supporting the clear benefits of brentuximab vedotin in CTCL. These data provide compelling evidence favouring brentuximab vedotin over methotrexate or bexarotene for the treatment of adult patients with CD30+ CTCL after at least 1 prior systemic therapy.

For the majority of patients with CTCL, treatment is aimed at improving patients' QoL and reducing the disease burden.[16] Thus, for patients with advanced-stage CTCL, significantly improved ORR4, PFS, and Skindex-29 scores with brentuximab vedotin over PC are outcomes of direct relevance to patients with this debilitating, long-term disease.

Currently, the only realistic hope for a cure in patients with advanced CTCL is an alloSCT.[16] The intention of clinical experts in the UK is to take as many eligible patients as possible to an alloSCT, with the objective of achieving a long-term remission and potentially cure. The rate-limiting step historically for alloSCT has been the poor response rates with currently available bridging agents (minimum reponse of PR required), and this has significantly limited the number of patients who could be considered for this intervention.

However, based on the much higher response rates seen with brentuximab vedotin in the ALCANZA trial (especially the CR rate), clinical experts in the UK believe brentuximab vedotin could have a profound impact on the treatment pathway by allowing more eligible patients to receive alloSCT. For these patients, the use of brentuximab vedotin as a bridging agent could provide them with a realistic hope for long-term remission.

In terms of safety, brentuximab vedotin had a different, but non-inferior, safety profile to both bexarotene and methotrexate; it was tolerable and AEs were generally manageable. The majority of AEs reported were less than grade 3, and most AEs were managed through dose reduction or delay. While peripheral neuropathy, a known toxicity with brentuximab vedotin, was the most common AE reported, it improved or resolved in most patients after treatment completion or discontinuation. In the longer median follow up of ALCANZA at 33.9 months,

86% of patients in the brentuximab vedotin group had improvement (12 of 44) or resolution of symptoms (26 of 44).[47,87]

This safety profile observed with brentuximab vedotin treatment in ALCANZA is consistent with that observed with brentuximab vedotin monotherapy in other indications such as R/R HL and sALCL which have been available in the UK since 2014. The peripheral neuropathy reported in pivotal phase II trials in R/R HL and sALCL was cumulative and primarily sensory in nature (peripheral sensory neuropathy observed in 42% [43/102] and 41% [24/58] of patients, respectively). While peripheral neuropathy was cited as the primary cause of treatment-related discontinuations in HL and sALCL trials (n=6 for both), it was also shown to be generally reversible and manageable with modifications to dose and schedule.[99,100] In the R/R HL trial, 56 patients experienced peripheral neuropathy events of any grade, with the majority of events being grade 1 or 2 peripheral sensory neuropathy. In the sALCL trial, 53% of patients experienced some form of peripheral neuropathy of any grade (eg, peripheral sensory neuropathy, neuralgia, burning sensation). Overall, 80% and 81% of patients in the R/R HL and sALCL trials, respectively, had either resolution or some improvement (≥1 grade) of peripheral neuropathy with 50% of the R/R HL patients having complete resolution.[100]

In summary, the ALCANZA trial shows that brentuximab vedotin offers unprecedented benefits to patients with CTCL in terms of increased PFS, a reduction in the disease relevant Skindex-29 HRQL measure, and improved response rates, in particular CR rates which may enable patients to undergo a potentially curative alloSCT.

B.2.13.2 Strengths and limitations of the clinical evidence base for the technology

ALCANZA is the largest reported phase III trial in patients with CTCL to date. Additionally, ALCANZA was a randomised, controlled trial in which patients were randomly assigned 1:1 to brentuximab vedotin or physician's choice of bexarotene or methotrexate, comparators that are considered standard-of-care worldwide for the systemic treatment of CTCL.

ALCANZA used current international consensus response criteria (incorporating blood, skin, nodal, visceral, and blood responses) to obtain a global response score (GRS); overall response was confirmed by sustained skin response per mSWAT assessment. These measures resulted in a more stringent and more standardised method of evaluating response compared to those used in previous studies of methotrexate and bexarotene in CTCL which focused solely on assessment of the skin compartment (with CR being 100% clearance and partial response being 50%–99% clearance and no new tumours) without detailed nodal, visceral, or blood assessment.

An IRF was used to determine efficacy and disease progression, and included independent dermatologists (for review of photos from skin and mSWAT assessments), independent radiologists (for review of CT, MRI, and PET for nodal and visceral involvement), and an independent pathologist (for review of Sézary cells for blood component in patients with MF).[47] Other studies of bexarotene, methotrexate, and IFN-α have not utilised an IRF, and response was based on investigator assessment.[65,66,74,76,102]

The primary endpoint, ORR4 is a more appropriate and strict measurement of treatment success compared with the proportion of patients with a response alone. This is because in

CTCL, short clinical responses do not necessarily equate to with meaningful clinical benefit.[47] The EMA Committee for Medicinal Products for Human Use (CHMP) on 19 May 2011 stated that[36]:

- Objective response rate (ORR) as an endpoint should be supported by:
    - A time-dependent endpoint (e.g., progression-free survival [PFS])
    - PFS, duration of response, and event-free survival (EFS) as key secondary endpoints
- 30% improvement in ORR is acceptable in a superiority trial but only if no major safety concerns were observed

ALCANZA captured the aforementioned outcome measures specified by the EMA, including PFS, response rates (including ORR4), HRQL, EFS, and OS.[47]

In terms of limitations, the size of the study population in ALCANZA limited the ability to analyse specific patient subsets (e.g., ethnic and racial groups, certain disease characteristics [such large-cell transformation]). Some CTCL patients groups were not included in this trial (e.g., patients with SS or LyP). While ALCANZA did not include patients with SS, brentuximab vedotin has previously demonstrated significant clinical activity in patients with SS from the phase II trial, (Kim et al 2015).[24,47]

The low number of OS events and high crossover from the PC arm to brentuximab vedotin treatment made it difficult to ascertain the exact survival benefit brentuximab vedotin has over PC in patients with CTCL. The low number of deaths observed in ALCANZA is consistent with the known survival of patients with CTCL, despite the high burden these patients experience. Both of these factors have combined to limit the ability of ALCANZA to analyse the potential for an OS benefit with brentuximab vedotin.

Lastly, there were a restricted number of drugs available in the physician's choice group. In view of the absence of a single-drug standard of care therapeutic option for MF and pcALCL worldwide, bexarotene and methotrexate were identified as acceptable comparators to brentuximab vedotin because they are the most commonly used drugs for the management of CTCL.[47,93] Both of these agents are available and widely used in the UK, and we therefore regard them as very appropriate comparators for this appraisal.

B.3. Cost effectiveness

B.3.1 *Published cost-effectiveness studies*

B.3.1.1 Identification of studies

An extensive systematic literature review (SLR) to identify cost-effectiveness, cost and resource use evidence was conducted during December 2017 and updated 23 February 2018. The details of the search strategy, methodology and inclusion/ exclusion criteria are provided in Appendix G.

The SLR was performed to identify and summarise the relevant economic and cost and resource use evidence for adult patients with CD30-positive CTCL who have received at least one previous treatment. The search string provided in Appendix G combines disease, economic, cost and resource search terms. Separate inclusion and exclusion criteria were applied to the search results to collate economic and cost and resource use evidence separately. The results associated with economic evidence are presented in this Section (B.3.2). The results associated with cost and resource use evidence are presented in Section B.3.4 and Appendix I.

For the economic evidence, studies reporting cost-benefit, cost-minimisation, cost-utility, cost-effectiveness and cost-consequence analyses were included; all other study designs were excluded. Relevant conferences and health technology assessments (HTAs) were hand searched (see Appendix G). No restrictions were imposed on interventions, location or date of study.

Primary screening of abstracts and secondary screening of full-texts was conducted by two independent reviewers. Data extraction from identified full-text articles was also performed independently by two reviewers to ensure that all relevant information was captured.

B.3.1.2 Description of identified studies

In total, 5,412 studies (4,717 original and 695 from update) were identified from the electronic sources. Following removal of duplicates, 4,312 papers were eligible for abstract screening. Primary screening of the titles and abstracts against the pre-specified inclusion and exclusion criteria for economic evidence (presented in Appendix G) identified 37 studies from the electronic databases, one conference abstract and three health technology assessment (HTA) reports. The flow diagram of the economic SLR is presented in Appendix G.

Only one study reported cost-effectiveness results for the United Kingdom population (Scottish patients) summarised in Table 23. This economic model, developed for NHS Scotland, evaluated ECP vs. standard treatment for CTCL and chronic graft vs. host disease.[103]

The model demonstrated that for a patient with erythrodermic CTCL, the total treatment cost with ECP for 3 years was £39,580, compared with £94,450 with standard treatment in the same period. The total QALY gained was 3.40 under ECP and 1.63 under standard treatment, resulting in an incremental QALY gain of 1.78 with ECP. The results indicated that ECP dominated (more effective and less costly) standard care in this setting. Sensitivity

analyses demonstrated that the findings were robust to a wide range of changes in the values for the cost of treatment, survival estimates, and utilities. However, this publication contained very limited data, so was not utilised in the *de novo* cost-effectiveness model.

Other three studies (2 HTAs, one full text and related conference abstract) are summarised in Appendix G, Section 1.2.

Table 23. Summary list of published cost-effectiveness studies

Study name	Patient population	Interventions	Perspective	Clinical data	Cost data	Model details	Outcome	Cost	ICER	Appropriateness for the CEM
SMC UK[103] (Scotland)	Patients with CTCL†	ECP ST	Unclear	Survival data was derived from the BAD guidelines [62] Transition probabilities: NR	Currency: GBP Tx costs of ECP and ST were derived from an unpublished analysis developed for NSCAG	CUA Time horizon: 3 years Discounting: Costs: 3.5% Outcomes: NR Utilities: scores for ECP arm (0.68) were derived from a 9-year retrospective single-institution study[104] ST was an assumption based on a preference score for early stage Hodgkin's disease (0.5)	Total QALYs: ECP: 3.4 Standard treatment: 1.6	Total costs: ECP: £39,580 Standard treatment: £94,452	ICER/QALY, ECP vs ST: ECP dominates	Not appropriate: very limited data

†An analysis for patients with chronic GVHD was also conducted alongside the analysis for patients with CTCL; details of this analysis have not been extracted.

Abbreviations: BAD, British Association of Dermatology; CTCL, cutaneous T cell lymphoma; CUA, cost-utility analysis; ECP, extracorporeal photopheresis; GBP, Great British pound; NR, not reported; QALY, quality adjusted life year; SMC, Scottish Medicines Consortium; ST, standard treatment, Tx, treatment; UK, United Kingdom.

Table 24 presents a summary of the cost-effectiveness studies identified in the SLR; only one identified study reported cost-effectiveness results for the United Kingdom population (Scottish patients). Appendix G provides the details associated with the SLR and search strategy.

Table 24: Summary list of published cost-effectiveness studies taking a UK perspective

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
SMC UK (Scotland)	2010	CUA Time horizon: 3 years Discounting: Costs: 3.5% Outcomes: NR Utilities: scores for ECP arm (0.68) were derived from a 9-year retrospective single-institution study[104] ST was an assumption based on a preference score for early stage Hodgkin's disease (0.5)	Patients with CTCL†	Total QALYs: ECP: 3.4 Standard treatment: 1.6	Costs in British Pounds Total costs: ECP: £39,580 Standard treatment: £94,452	ICER/QALY, ECP vs ST: ECP dominates
Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.						

B.3.2 *Economic analysis*

The SLR did not identify any economic models considered relevant for evaluating brentuximab vedotin in the CTCL population. Therefore, a *de-novo* economic model was constructed to estimate the costs and benefits of treatment with brentuximab vedotin in this setting.

B.3.2.1 Patient population

Brentuximab vedotin is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma after at least 1 prior systemic therapy. As discussed in Section B.2.7, the patient population of interest for the purpose of this appraisal is 'advanced' CTCL patients (i.e., MF stage IIB and above, SS, and all pcALCL patients). This subset of patients is considered in the economic analysis, based on the position of brentuximab vedotin in the updated BAD/UKCLG guidelines, and UK clinical feedback on the proposed use of brentuximab vedotin as discussed in Section B.1.3.3. This advanced population is a narrower group than the NICE final scope.[105]

To populate the model with data relevant to this population, data from the 95 patients with MF stage IIB+ or pcALCL of the total 131 enrolled patients from the ALCANZA study were used (49 treated with brentuximab vedotin, 46 treated with PC). This subset represented approximately 75% of the total trial population and was well balanced between both arms, as discussed in Section B.2.7. As patients with SS were not included in ALCANZA and the sample size of the phase II data was not feasible to model as detailed in Section B.2.2.1, all parametric curves, statistics and results presented are derived from the ALCANZA data for MF stage IIB+ and pcALCL alone.

B.3.2.2 Patient flow in UK practice

Feedback from UK clinicians indicated that patients would be treated with brentuximab vedotin after progression from one prior systemic therapy and that patients are generally not treated with systemic therapies before reaching the advanced stage of disease. [redacted].[63]

Management of advanced-stage CTCL patients in the UK can follow two pathways; i) disease control with active systemic therapy or ii) achieve a good enough response to systemic therapy to undergo a potentially curative alloSCT. Most UK patients will fall into the first group due to reduced fitness and poor response. For the majority who are unable to undergo an alloSCT, their condition is incurable. As in other conditions where no cure is available for most patients, and where there is no evidence that standard treatment regimens can significantly prolong OS, maintaining disease control and QoL are the most important medical objectives.[21]

As described in Section, systemic therapies can be divided into *Category A* (i.e., bexarotene, methotrexate and IFN-α) and *Category B* treatments (i.e., chemotherapy), with the latter being reserved for later in the treatment once *Category A* options have

been exhausted. [redacted] insight from clinical experts anticipate the use of brentuximab vedotin will be after one prior *Category A* systemic treatment but before *Category B* chemotherapy.

At this stage of the disease, where systemic therapy is required, no single treatment is considered as the standard of care as durability of response is similar and limited across the available treatments. Therefore physicians will select the most appropriate agent from the recommended treatments within the line of therapy based on the patient presentation (i.e., bexarotene, IFN-α, or methotrexate as first-line systemic treatment). The design of the ALCANZA trial represented both the patient presentation-based decision making and the absence of a pre-defined set treatment for all patients by including PC of either bexarotene or methotrexate as the comparator arm, options which were defined based on international availability. [redacted][36,63] IFN-α was not an option within the PC options in ALCANZA. Whilst the exact agent used in clinical practice may vary among settings and patients, all existing therapies are expected to have similar efficacy and costs.

The potentially curative alloSCT may be considered for some patients. Eligibility for an alloSCT requires patients to be fit enough to undergo the procedure and achievement of either a CR or PR with bridging or induction therapy. Due to the infection-prone nature of CTCL patients, the intensity of the conditioning regimen that is given prior to an alloSCT in CTCL has been reduced over time; initially moving to an RIC to the recent development of the Stanford Protocol, which uses a combination of TSEB and a minimal intensity conditioning as described in Section B.1.3.3. This has led to better outcomes in recent years from alloSCT in CTCL, as the absence of highly myelosuppressive agents has decreased early treatment and disease-related morality. As a result, the UK has adopted the Stanford Protocol as the standard of care conditioning regimen for CTCL patients undergoing alloSCT, and [redacted][63]

The final NICE scope for this appraisal states that *"if the evidence allows, the economic analysis should model stem cell transplantation further down the pathway"*.[105] Therefore, in line with the scope and supported by UK clinicians and the guidelines, alloSCT is included within the modeled treatment pathway.

After progression on treatment with brentuximab vedotin or *Category A* systemic treatments, more toxic *Category B* therapies would be considered (i.e., single agent or combination chemotherapy) as well as retreatment with TSEB. Should patients progress from an alloSCT, the subsequent treatment options with chemotherapy would be similar although TSEB is not likely to be used as it is a part of the Stanford Protocol. Response to treatments at this stage of disease is limited and short lived, particularly as increasingly frail patients cannot complete the full course of treatment due to toxicities.[8,83] After progression with TSEB and a *Category B* systemic, most patients will cease to receive further active systemic treatment and will move to end-stage symptom management. It should be noted that few patients receive multiple subsequent lines of

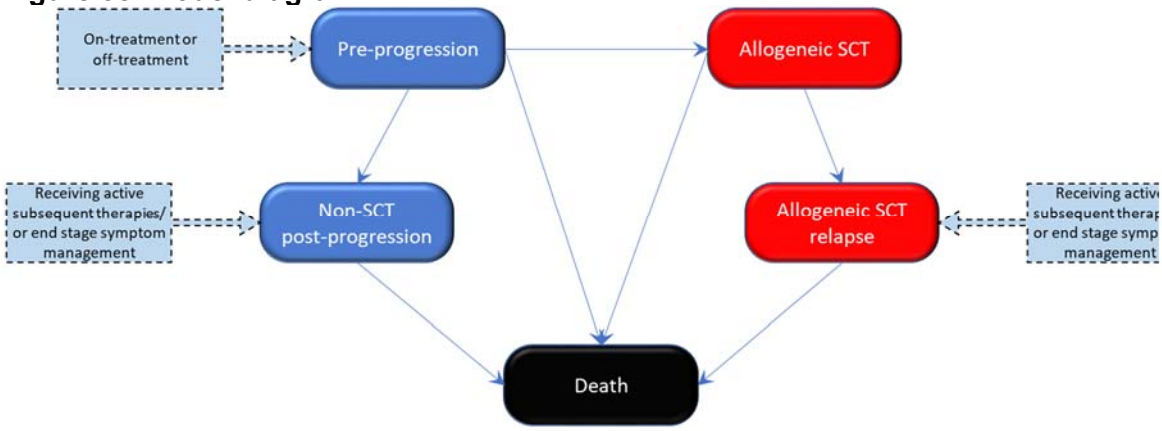
chemotherapy; this has been represented in the economic model based on the European PROCLIPI data.[36] For a full description of the current UK CTCL treatment pathway please refer to Section B.1.3.3. For patients with advanced disease, although many treatments provide effective relief for a short time, death ultimately occurs due to disease progression, overwhelming sepsis and bone marrow depletion.

Once patients have exhausted all treatment options they would move to end-stage care which consists of managing the large number of open wounds on their skin as well as internal symptoms from their underlying lymphoma. This end-stage care state is highly resource intensive (see Section B.1.3.2 and Appendix L).

B.3.2.3 Model structure

To demonstrate the value of brentuximab vedotin in CTCL, Takeda have developed a partitioned-survival economic model with five health states in Microsoft Excel®. The model conforms with the NICE Guide to the Methods of Technology Appraisal[6] and the NICE reference case criteria. A model diagram is presented in Figure 38; the blue health states reflect the pathway for a patient who has not met the eligibility criteria for an alloSCT and the red health states reflect the pathway for a patient meeting these criteria and receiving an alloSCT.

Figure 38. Model diagram



Abbreviations: alloSCT, allogeneic stem cell transplant

Patients enter the model in the pre-progression health state, where they receive treatment with either brentuximab vedotin or PC. In this state, transitions are determined by PFS and OS parametric curves fitted to the data observed in the ALCANZA study. Additionally, a proportion of transplant-eligible patients who achieved a PR or CR with brentuximab vedotin or PC can proceed to an alloSCT.

Whilst some alloSCT-ineligible patients will die in the pre-progression state, the majority will experience disease progression. These patients transition to the non-alloSCT post-progression health state where the costs and resource use associated with toxic single or multi-agent chemotherapy, TSEB and end-stage care are accrued. In this state, transitions are determined by OS parametric curves fitted to the ALCANZA data.

For patients fit enough to be considered for an alloSCT, patient eligibility for the procedure is assessed at 18 weeks (assumption based on UK clinical opinion, equivalent to 6 cycles of brentuximab vedotin) and is determined by response to induction treatment in the pre-progression state and clinician's feedback based on UK experience. All alloSCTs are assumed to be received at the same time point within the model (i.e., 18 weeks). This assumption negates the need for complex tunnel states and is a simplification supported by UK clinical experts.

Patients eligible for an alloSCT transition to the 'alloSCT' health state where the costs and resource use associated with the procedure and follow-up are accrued. In this state, transitions are determined by disease free survival (DFS) and OS parametric curves fitted to real-world outcomes data post-alloSCT from the Hammersmith Hospital representing the London supra-regional centre, and one of the biggest CTCL treaters in the UK. These data were presented at the 2017 EORTC Cutaneous Lymphoma Task Force annual meeting.[15] All patients in the utilised dataset underwent an alloSCT using the Stanford Protocol. Patients relapsing after an alloSCT transition to the 'alloSCT relapse' health state where the costs and resource use are aligned to the post-progression state of the non-transplant group (i.e., subsequent therapy followed by end-stage care) with the exception of TSEB as described above. This approach has been corroborated by UK clinical experts.

Model outcomes include: total costs, Quality Adjusted Life Years (QALYs), LYs and clinically-relevant outcomes (e.g., percentage of patients undergoing alloSCT, response rates, etc.). A weekly cycle is implemented (negating the need for a half-cycle correction) and results are presented over a lifetime time horizon of 45 years. Costs and QALYs are discounted at an annual rate of 3.5%. The base year for costs is 2016/2017 (i.e., financial year between April 2016 and March 2017). Where necessary, other costs were adjusted to 2016/2017 prices using inflation indices published by the Personal Social Services Research Unit (PSSRU).

B.3.2.4 Intervention technology and comparators

Intervention

The intervention assessed in the cost-effectiveness model is brentuximab vedotin for the treatment of advanced CD30-positive CTCL following at least one prior systemic therapy. The mechanism of action of brentuximab vedotin is described in Section B.1.2. The requested population matches the expected use of brentuximab vedotin in the UK, and is narrower than the marketing authorization described in Section B.1.3.3.

The observed data from the ALCANZA trial from the longer term 33.9 month follow-up per investigator were used to inform the clinical input parameters (OS, PFS, and ToT) within the model. The observed data for both ITT and advanced-stage patients (i.e., a MF stage IIB+ and all pcALCL), showed a statistically significant improvement in both response rate and PFS relative to PC. For a full description of the efficacy and safety results of ALCANZA, please refer to Section B.2.6.1.

Comparator

The NICE final scope states that the relevant comparator for brentuximab vedotin is established clinical management without brentuximab vedotin.[105] As described in Section B.1.3.3 and Patient Flow (Section B.3.2.2), the treatment choice for advanced-stage CTCL patients is selected by the physician, based on the patient presentation from available treatment options.

Treatment of advanced-stage CTCL is somewhat heterogeneous, as illustrated by the European PROCLIPI data.[36] Standard of care is guideline based, with a number of options by line or category based on response and toxicity. In the UK, advanced-stage patients receive systemic therapy *Category A* option first (i.e., most commonly IFN-α*,* bexarotene, or methotrexate) and subsequently *Category B* chemotherapy or alloSCT for eligible patients.

[redacted]This is in-line with the anticipated use of brentuximab vedotin from Takeda Advisory Board members and other clinical experts.

It is anticipated that brentuximab vedotin will be used after one prior *Category A* systemic treatment but before *Category B* chemotherapy. As described in Section B.1.3.3 clinical experts anticipate that patients will move directly to brentuximab vedotin following initial systemic treatment instead of receiving another *Category A* systemic due to the poor duration and depth of response of currently-available *Category A* systemic treatments.

Therefore, the most appropriate comparators for brentuximab vedotin in advanced CTCL after one prior therapy are bexarotene, methotrexate, and IFN-α. The multi-centre randomised phase III trial, ALCANZA, provides a direct comparison against physician's choice (PC) comprising bexarotene and methotrexate, which is used as the basis of this submission and the supporting cost-effectiveness model.

There are no data comparing brentuximab vedotin directly with IFN-α and no literature was identified from which an inidrect comparison with IFN-α could be conducted. Therefore, this comparator could not be included in the economic analysis. For more details please refer to Section B.2.9.1.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Methods of extrapolation

Six parametric distributions (exponential, Weibull, Gompertz, generalised gamma, log-normal and log-logistic) were fit to the data for PFS, OS without an alloSCT, DFS and OS following an alloSCT, in line with the NICE Decision Support Unit (DSU) guidance. The fit of each parametric model to the survival data was assessed via both internal and external validity using visual inspection of the fitted curves against the Kaplan-Meier curves, Akaike Information Criterion (AIC) and Bayesian information criterion (BIC)

goodness-of-fit statistics and experts' judgements on long-term clinical plausibility. All curves were fitted using the flexsurv package in the statistical software R.

B.3.3.2 Outcomes without an allogeneic stem cell transplant (alloSCT)

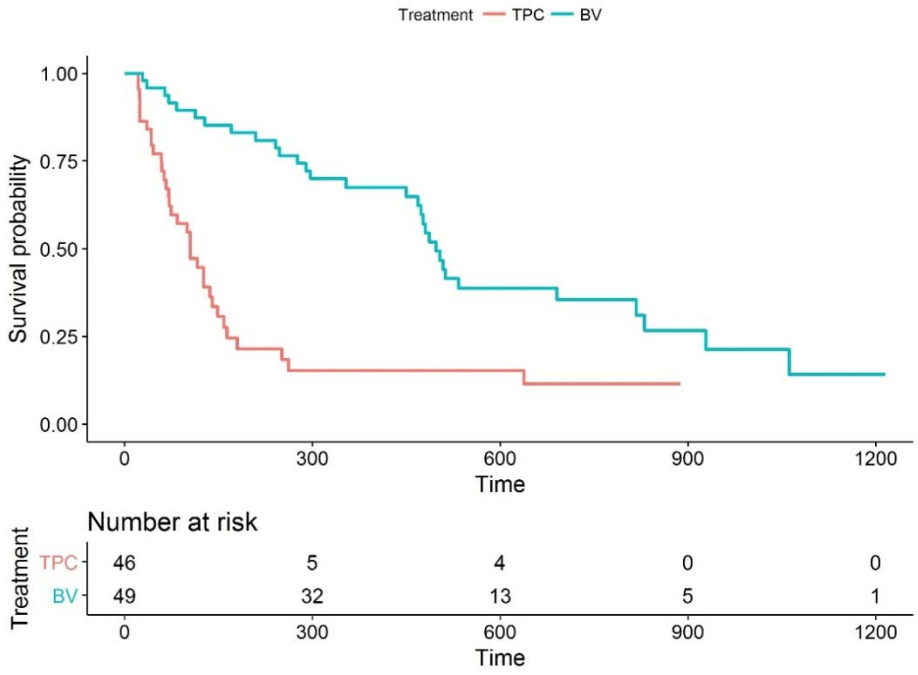
The key clinical inputs associated with the non-alloSCT pathway were informed by the latest data cut from the ALCANZA clinical trial. The analysis uses data from the advanced subgroup (i.e. MF stage IIB+ and pcALCL), aligning with expectations of clinical experts with regards to where brentuximab vedotin would be used in UK clinical practice.

Although the original ALCANZA data presented at the American Society of Haematology (ASH) 2016 conference and subsequently published in the *Lancet*,[47] was based on a median follow-up period of 22.9 months, the latest data cut of the ALCANZA trial, presented at ASH 2017,[87] was used to populate the cost-effectiveness model. The later data cut was considered more appropriate as it extends the median follow-up time to 33.9 months, thus providing more complete response rate, PFS based on investigator assessment and OS data. This analysis is referred to as 'ALCANZA 2017' data in the tables and figures to follow. Furthermore, due to the small sample size of the pcALCL population within ALCANZA (n=16 and n=15 for brentuximab vedotin and PC, respectively), all analyses are based on a pooled group of advanced MF and pcALCL patients.

B.3.3.2.1 Progression-free survival (PFS) without allogeneic stem cell transplant (alloSCT)

The PFS data from the ALCANZA study are extremely mature in the updated data cut of 33.9 months of median follow-up, as shown in Figure 39.

Figure 39. Advanced subgroup PFS – Kaplan-Meier curves, ALCANZA 2017 data



Abbreviations: BV, brentuximab vedotin; PFS, overall survival; TPC, treatment of physician's choice.

In the data, both medians and restricted means were significantly improved for brentuximab vedotin relative to PC (HR 0.335; 95% CI, 0.218–0.515; Table 25).

Table 25. Advanced subgroup PFS – Summary statistics, ALCANZA 2017 data

Treatment	Total, N	Events	Restricted mean (days)	Standard error of restricted mean	Median (days)
BV	49	31	568.00	53.11	497.91
PC	46	34	229.70	53.73	105.35

Abbreviations: BV, brentuximab vedotin; PFS, overall survival; PC, physician's choice.

In line with the NICE DSU 14 guidance, the applicability of the proportional hazards and the accelerated time failure assumptions informed the form of statistical model fit to the data. The log-cumulative hazard plot (LCHP) and quantile-quantile (QQ) plot are presented in Appendix O. The visual inspection of these plots indicates that the proportional hazards assumption may not be appropriately justified. Therefore, independent parametric models were fit to the PFS data for the brentuximab vedotin and PC treatment arms.

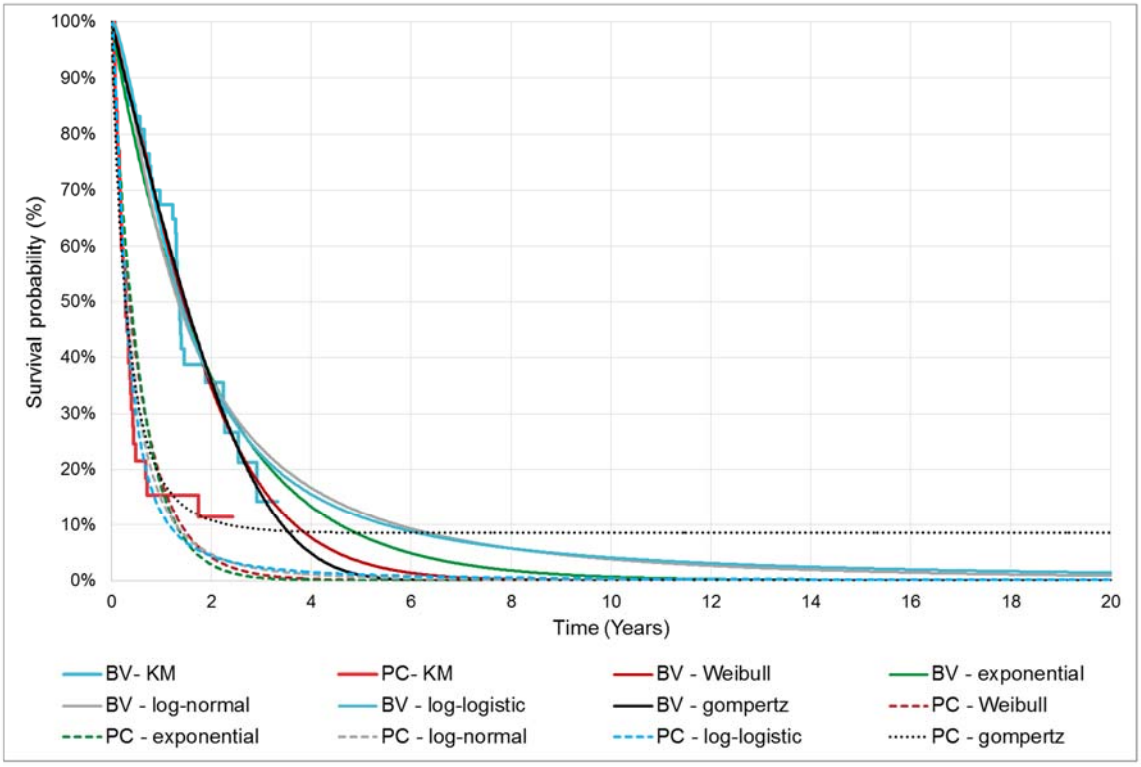
Due to the lack of convergence when fitting the generalised gamma distribution to the data, the outcomes associated with this curve are not presented for PFS. Table 26 summarises the AIC and BIC values for each parametric distribution. All stratified parametric survival models provide a good fit to the data; no more than eight points between the values for both brentuximab vedotin and PC treatment arms. The Kaplan-Meier curves and fitted distributions are presented in Figure 40.

Table 26. Advanced subgroup PFS – Statistical fit of stratified parametric survival models

	BV		PC	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	284	286	232	233
Weibull	286	290	233	237
Gompertz	286	290	229	233
Log-logistic	287	291	231	235
Log-normal	287	291	229	233

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BV, brentuximab vedotin; PFS, progression free survival; PC, physician's choice.

Figure 40. Advanced subgroup PFS – Parametric survival models



Abbreviations: BV, brentuximab vedotin; KM, Kaplan-Meier; PFS, progression-free survival; PC, physician's choice.

Based on clinical expert feedback from an Advisory Board conducted by Takeda, PFS outcomes were modelled using the Weibull parametric curve for both brentuximab vedotin and PC in the base case. Scenario analyses explore the impact of assuming the exponential distribution for brentuximab vedotin and PC data and the use of Kaplan-Meier data directly for PFS. To produce logical survival estimates, the model ensured the PFS curve could not cross the OS curve by applying the minimum of the PFS and OS

probabilities. However, this feature was not required when the base case curves were selected.

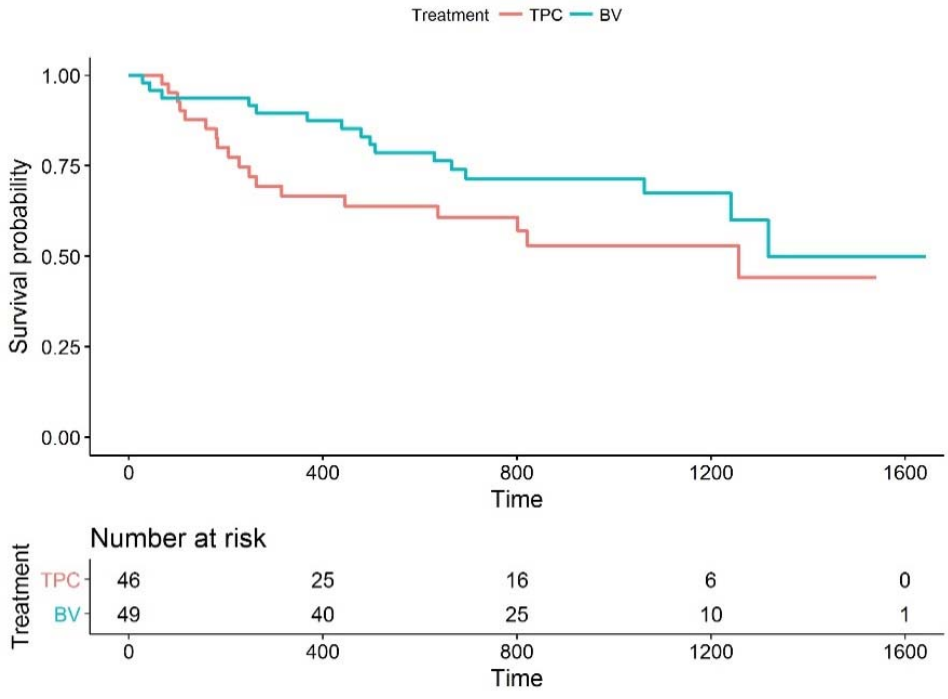
B.3.3.2.2 Overall survival (OS) without allogeneic stem cell transplant (alloSCT)

Survival is always an important outcome in oncology; however, the primary goal of treatment for patients with advanced CTCL is disease control and symptom relief. OS is not generally considered when determining treatment success in CTCL. Therefore, the ALCANZA trial was designed to assess the clinically relevant endpoints of ORR, ORR4, PFS and quality of life; OS was neither a primary nor secondary endpoint in ALCANZA (see Section B.2.6.1.5).

The OS data from ALCANZA are presented within this submission. However, these data must be interpreted carefully as they are: (1) highly immature, (2) based on a relatively small sample size with few events (particularly in the advanced subgroup which informs the economic analysis) and (3) confounded by biases such as crossover from the PC arm to the brentuximab vedotin arm. Figure 41 presents the Kaplan-Meier data for the advanced subgroup, where it can be seen the curves for brentuximab vedotin and PC initially cross, followed by some separation before tending together again.

Table 27 presents the summary statistics for this population.

Figure 41. Advanced subgroup OS – Kaplan-Meier curves, ALCANZA 2017 observed data



Abbreviations: BV, brentuximab vedotin; OS, overall survival; PC, physician's choice.

Table 27. Advanced subgroup OS – Summary statistics, ALCANZA 2017 observed data

Treatment	Total N	Events	Restricted mean (days)	Standard error of restricted mean	Median (days)
BV	49	16	1173.93	83.86	1318.83
PC	46	18	967.46	107.37	1257.21

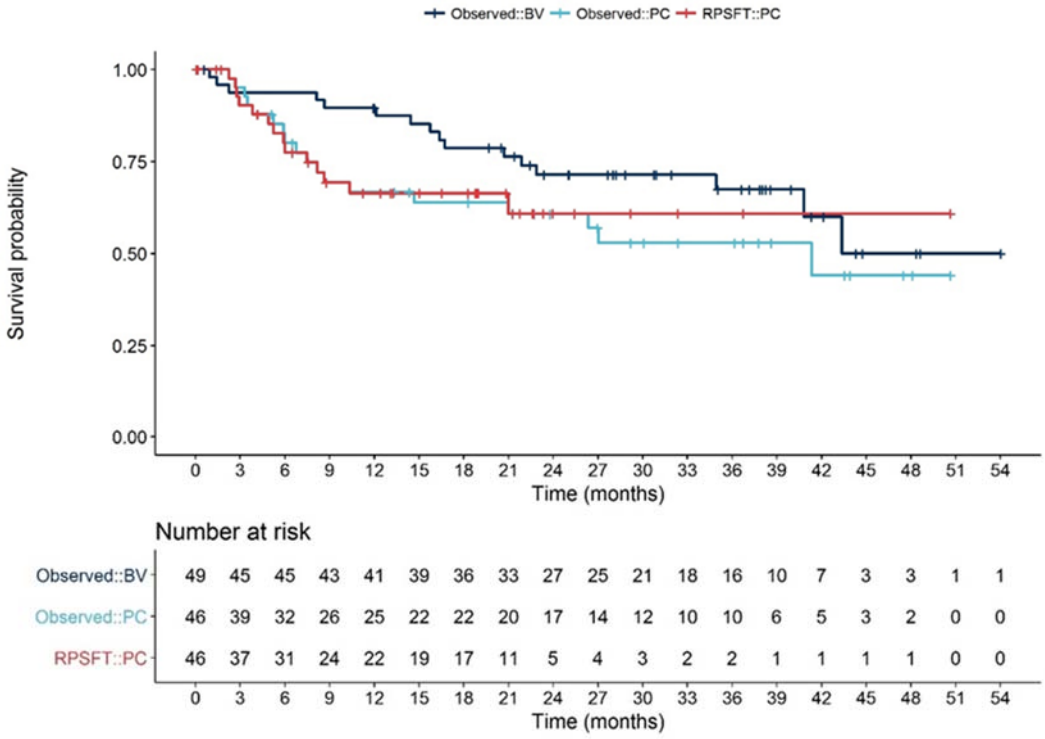
Abbreviations: BV, brentuximab vedotin; KM, Kaplan-Meier; OS, overall survival; PC, physician's choice.

Several approaches were considered for modelling OS for brentuximab vedotin and PC in the advanced subgroup. This task was complex because in ALCANZA patients were able to crossover on progression with PC to receive brentuximab vedotin, with 21/46 (46%) of PC patients having crossed over in the updated data cut. Fifteen patients received brentuximab vedotin as their first subsequent treatment, and 6 received it at later lines.

The NICE DSU guidance suggests that when treatment switching or crossover occurs, unadjusted OS data can underestimate the OS benefit of the intervention if some advantage of the intervention has been attributed to the comparator in the process of patients crossing over.[106] None of the available methods of adjusting for crossover suggested by the DSU guidance were particularly well suited to these data, given the small number of patients (n=15 or n=21 received brentuximab vedotin as a first subsequent therapyor later subsequent treatment, respectivelyit later), small number of events (precluding the use of the inverse probability of censoring weights method where n=500 was considered 'small' in DSU guidance), lack of common secondary baseline (for the two-stage method) and the loss of data due to re-censoring. The impact of re-censoring was particularly pronounced in this case with the loss of multiple events, and effectively shortened follow-up for many patients. A rank preserving structural failure time (RPSFT) model is presented, with corresponding Kaplan-Meier curves for the advanced population shown in Figure 42 and summary statistic in Table 28.

Fitted parametric curves estimated an increase in OS for brentuximab vedotin at earlier time-points and a higher rate of long-term OS for PC. Therefore, the RPSFT method had the perverse effect of improving OS for PC when removing the effect of brentuximab vedotin. Clinical experts advised this outcome was implausible, and that no increase in OS was expected with brentuximab vedotin (except in patients who bridged to alloSCT), despite its high rate of disease control. Brentuximab vedotin was also not expected to worsen survival as it provides disease control. This consistent with what is summarised in the clinical section of this dossier (see Section B.2.6.1.5).

Figure 42. Advanced subgroup OS – Kaplan-Meier curves, adjusted for crossover (RPSFT)



Abbreviations: BV, brentuximab vedotin; TPC, physician's choice of treatment; RPSFT: rank preserving structural failure time.

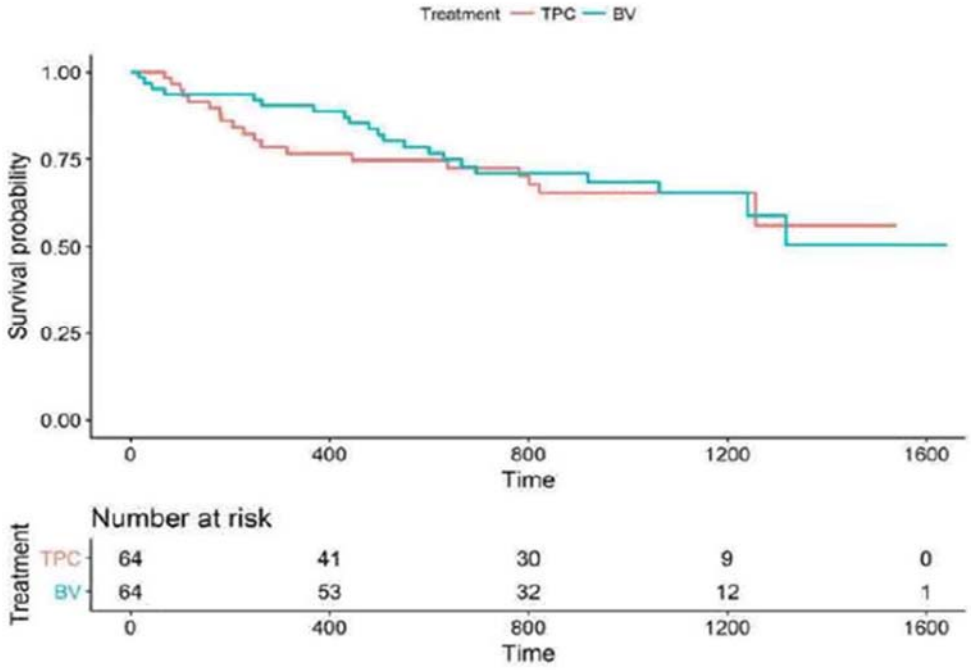
Table 28. Advanced subgroup OS – Summary statistics, adjusted for crossover (RPSFT)

Treatment	Data	Sample Size	Events	Median OS in months (95% CI)
BV	Observed	49	16	43.4 (40.8 to NE)
PC	Observed	46	18	41.3 (21.0 to NE)
PC	RPSFT adjusted	46	14	NE (21.0 to NE)

Abbreviations: BV, brentuximab vedotin; OS, overall survival; PC, physician's choice; RPSFT, rank preserving structural failure time.

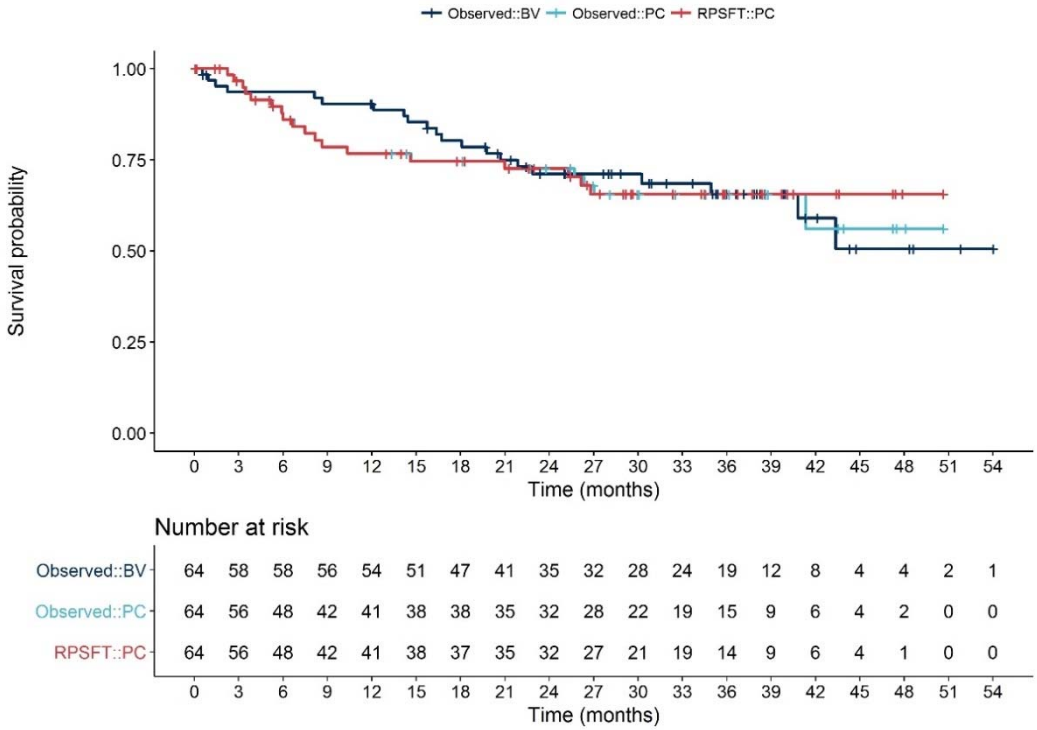
Due to the nonsensical and clinically implausible output from the crossover-adjustment, it is assumed that OS is equivalent for both brentuximab vedotin and PC. Therefore, survival in the model for both treatments is based on parametric curves fit to the PC arm. This simplification was supported by clinical experts who cannot definitely see an OS difference and is further supported by the larger ITT datasetdata (Figure 43); no trend towards improved OS was observed with brentuximab vedotin compared with PC – the OS curves are overlaid, and cross multiple times both with and without adjusting for crossover (Figure 43 and Figure 44, respectively). A scenario analysis considers the impact on results when independent curve fits are applied to the unadjusted OS data for brentuximab vedotin and PC.

Figure 43. ITT population OS – Kaplan-Meier curves, ALCANZA 2017 observed data



Time=days.
Abbreviations: BV, brentuximab vedotin; TPC, physician's choice of treatment.

Figure 44. ITT population OS – Kaplan-Meier curves, including adjusted for crossover (RPSFT)



Abbreviations: BV, brentuximab vedotin; PC, physician's choice of treatment; RPSFT: rank preserving structural failure time.

Independent parametric models were fit to the OS advanced subgroup data for the PC treatment arm. Due to the lack of convergence when fitting the generalised gamma distribution to the data, the outcomes associated with this curve are not presented for OS. Table 29 summarises the AIC and BIC values for each parametric distribution. The statistics indicate that all stratified parametric survival models provide a good fit to the data; no more than seven points between the values for the PC treatment arm. The Kaplan-Meier curves and fitted distributions are presented in Figure 45.

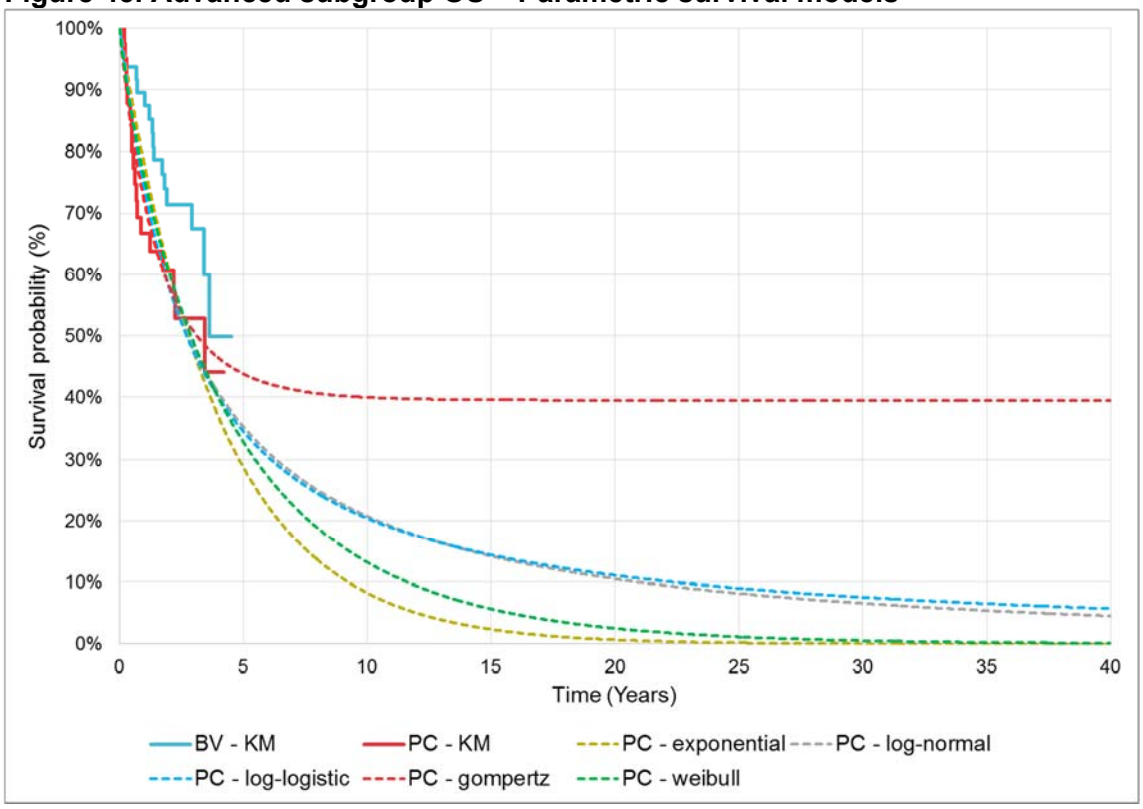
The log-logistic was selected in the base case as the most likely to represent long-term outcomes based on its level of congruence with UK historical data for advanced MF and SS patients (Agar et al 2010[13]), a similar shape to the survival data reported in Kim et al 2003[45] and feedback from UK clinical experts. Section B.3.3.6 provides the validation of the OS clinical parameters. Scenario analyses consider the impact of the log-normal distribution on results.

Table 29. Advanced subgroup OS – Statistical fit of stratified parametric survival models

	PC	
Model	**AIC**	**BIC**
Exponential	300	302
Weibull	302	305

Gompertz	300	303
Log-logistic	300	304
Log-normal	298	302

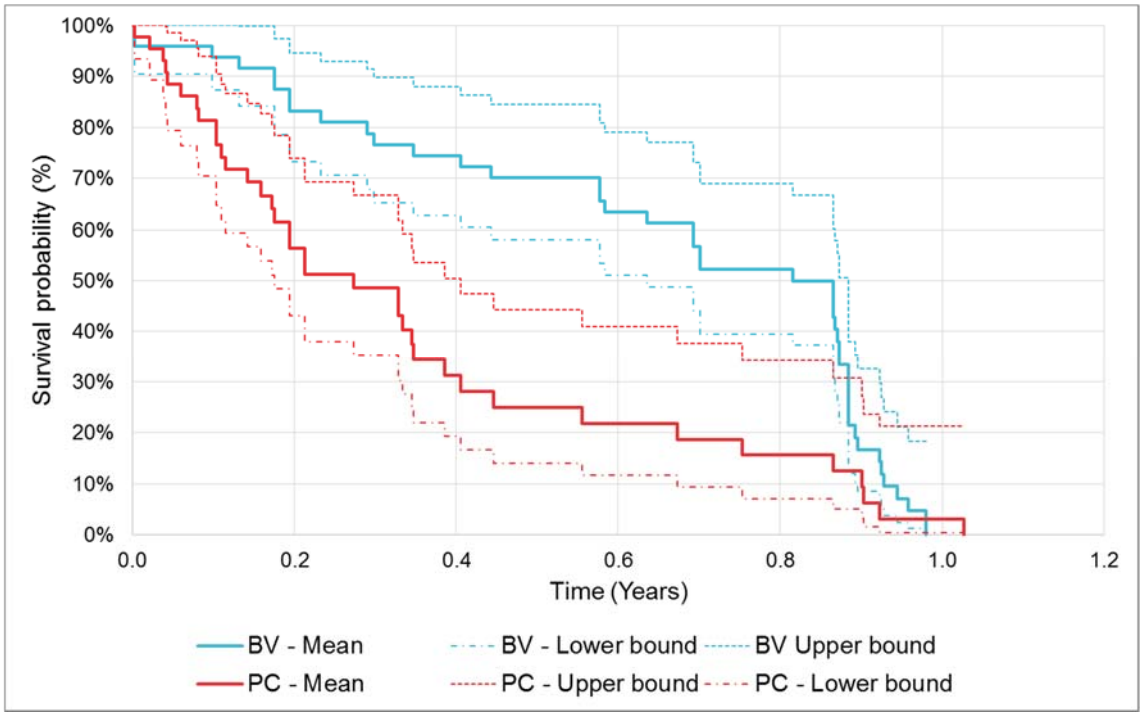
Figure 45. Advanced subgroup OS – Parametric survival models



B.3.3.3 Time on treatment (ToT)

The ToT data from ALCANZA at the 33.9 month median follow-up period were complete for both brentuximab vedotin and PC, as shown in Figure 46. Therefore, these data were applied directly to the economic model to accurately reflect the ToT observed in the clinical trial with no extrapolation required.

Figure 46. Advanced subgroup ToT – Kaplan-Meier curves with Greenwood's 95% CI



Abbreviations: BV, brentuximab vedotin; CI, confidence interval; ToT, time on treatment; PC, physician's choice.

Constraints posed by the structure of Markov models required a slight simplification of the available time-to-event data, specifically patients transitioning between health states at regular cycle lengths and not at a discrete time. This meant transitions occurred at the end of each weekly cycle instead of on the actual day the event occurred in the trial (e.g., if discontinuation occurred at day 10 in the trial, in the model this would be counted as an event at week 2, therefore day 14). A negligible difference resulted from this simplification; the short weekly cycle length aided this approach in minimising the error.

To capture the uncertainty associated with non-parametric statistics in the sensitivity analyses, Greenwood's 95% confidence intervals (CIs) were derived.[107,108]

B.3.3.4 Allogeneic stem cell transplant (alloSCT) outcomes

The key clinical inputs associated with the alloSCT pathway were informed by real-world evidence obtained from the London supra-regional centre using the minimal intensity Stanford Protocol regimen, as presented during the EORTC Annual Cutaneous Lymphoma Meeting in October 2017.[15] The London supra-regional centre for CTCL is St. John's Institute of Dermatology in Guy's and St. Thomas'; however all transplants from the centre are performed at the Hammersmith hospital, whose outcomes data are used in this submission. The data presented are associated with minimal intensity alloSCTs conducted according to the Stanford protocol for CTCL.

As discussed in section B.1.3.3 of the dossier, only alloSCT is used in CTCL, with autologous SCT not used.

B.3.3.4.1 Percentage of patients undergoing alloSCT

In clinical practice, eligibility for an alloSCT is defined by underlying fitness (i.e., age, comorbidities) and depth of response with an induction agent. Within the model, the proportion of patients receiving an alloSCT was based on feedback from transplant clinicians in the UK and the response rate defined by the ORR from the ALCANZA data (i.e., PR or CR).

The number of responders observed in the advanced subgroup from ALCANZA is shown in Table 30 by treatment arm; 68.8% were shown to achieve an ORR (PR or better) when treated with brentuximab vedotin compared with 17.8% when treated with PC. Based on clinical experience in the UK to date, of these responders, it was assumed that only 40% would be eligible to receive an alloSCT due to age, co-morbidities, likelihood of matching to a donor and patient choice. A scenario analysis considers the impact on results of reducing the eligibility to 20% of responders.

As a result, the base assumption is that 27.50% of patients treated with brentuximab vedotin and 7.11% treated with PC would be eligible for alloSCT. These patients received this procedure at 18-weeks within the model (i.e. post 6 cycles of brentuximab vedotin treatment); this assumption is based on expert opinion of the number of cycles likely to be received as bridging or induction therapy.

Table 30. Number of responders – ALCANZA 2017 data cut

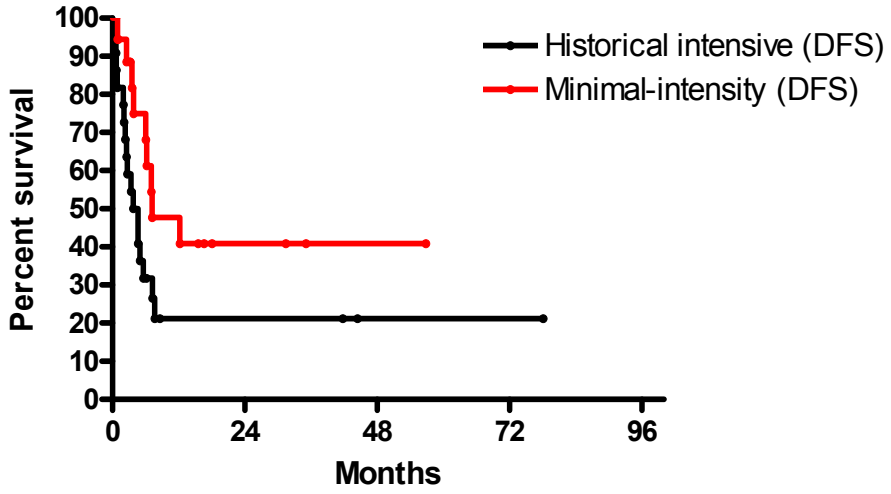
Treatment	Stage	Total N	Complete response	Partial response	Stable disease
BV	IIB	19	3	10	4
	IIIA–IIIB	4	0	3	1
	IVA	2	1	1	0
	IVB	7	0	4	2
	pcALCL	16	6	5	1
PC	IIB	19	0	3	5
	IIIA–IIIB	2	0	0	1
	IVA	9	0	0	3
	IVB	0	0	0	0
	pcALCL	15	1	4	3

Abbrevations: BV, brentuximab vedotin; N, number; pcALCL, primary cutaneous anaplastic large cell lymphoma; PC, physician's choice.

B.3.3.4.2 Disease free survival (DFS) following an allogeneic stem cell transplant (alloSCT)

Figure 47 presents the observed DFS Kaplan-Meier curve following a minimal intensity alloSCT (i.e Stanford Protocol) from the London supra-regional centre. Visual inspection of the observed data indicates that, if a patient were to relapse, this would likely be in the first twelve months following the alloSCT (represented by the gradient of the Kaplan-Meier curve between 0–12 months). This is in line with observed transplant outcomes for other lymphomas across different conditioning regimens (e.g., HL and ALCL). Following the initial year post-transplant, very few events are observed. Therefore, patients who have not relapsed are likely to remain in the disease-free state with a long term remission (represented by the leveling out of the Kaplan-Meier curve after 12 months).

Figure 47. Kaplan-Meier for DFS after alloSCT, London supra-regional centre data (EORTC 2017)[15]



Abbreviations: DFS, disease-free survival; SCT, stem cell transplant

The observed DFS real-world data above were digitised and six parametric survival models (exponential, Weibull, Gompertz, generalised gamma, log-normal and log-logistic) were fitted to the derived pseudo-patient-level data. The fit of each parametric model was assessed for both internal and external validity using visual inspection of the fitted curves against the Kaplan-Meier curves, AIC and BIC goodness-of-fit statistics and clinical experts' judgements on long-term clinical plausibility.

Due to the lack of convergence when fitting the generalised gamma distribution to the data, the outcomes associated with this curve are not presented. Table 31 summarises the AIC and BIC values for each parametric distribution. These statistics indicate that all parametric survival models provide a good fit to the data with no more than 19 points between the values. The Kaplan-Meier curves and fitted distributions are presented in Figure 48.

In terms of external validity, the Gompertz curve is the only curve that reflects the decreasing probability of relapse reducing over time to a zero probability (a plateau).

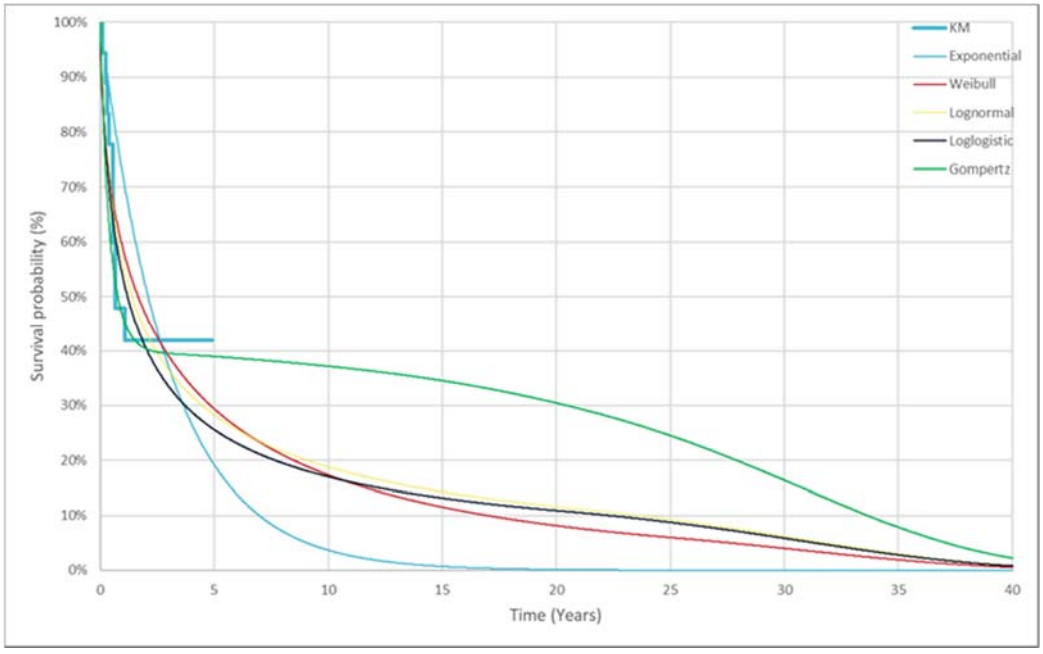
Feedback from clinical experts, including from the source of the modelled alloSCT data, supported the Gompertz curve as the most clinically plausible outcomes and aligning with expectations in clinical practice (i.e. patients who have not relapsed within 12 months of alloSCT would likely be in a long term remission with very few events expected beyond this point). This is in line with generally expected outcomes of an alloSCT and has been well documented across different cancers, particularly lymphomas. For this reason, the Gompertz curve is used to model outcomes associated with DFS after an alloSCT in the base case.

Table 31. Statistical fit of parametric survival models fitted to alloSCT DFS in CTCL

	DFS	
Model	**AIC**	**BIC**
Exponential	178	179
Weibull	171	173
Gompertz	160	162
Log-logistic	168	170
Log-normal	168	170

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; DFS, disease-free survival.

Figure 48. DFS after alloSCT – Digitized Kaplain-Meier data and parametric survival models

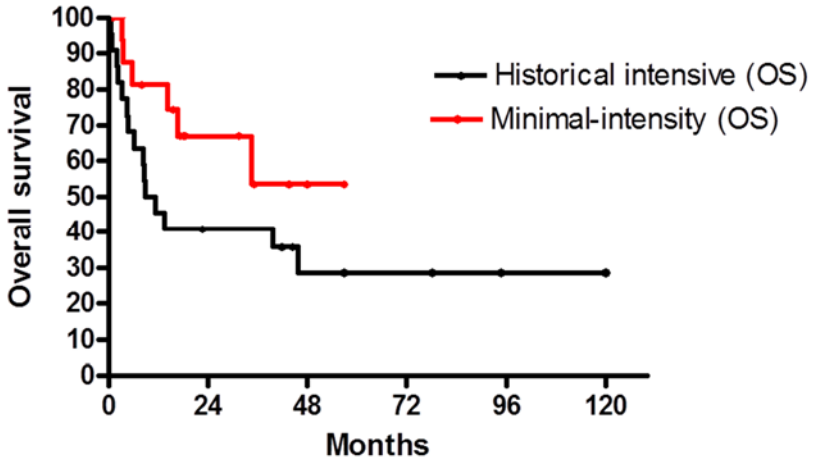


Abbreviations: DFS, disease-free survival; KM, Kaplan-Meier; alloSCT, allogeneic stem cell transplant.

B.3.3.4.3 Overall survival (OS) after alloSCT

Figure 49 presents the OS Kaplan-Meier curve following a minimal intensity alloSCT based on the Stanford protocol obtained from the real world evidence.

Figure 49. Kaplan-Meier for OS after alloSCT, London supra-regional center data (EORTC 2017)[15]



Abbreviations: OS, overall survival; alloSCT, allogeneic stem cell transplant.

The OS data relevant to the minimal intensity regimen were digitized and six parametric survival models (exponential, Weibull, Gompertz, generalised gamma, log-normal and log-logistic) were fitted to the derived pseudo patient level data. The fit of each parametric model was assessed for both internal and external validity using visual inspection of the fitted curves against the Kaplan-Meier curves, AIC and BIC goodness-of-fit statistics and clinical experts' judgements on long-term clinical plausibility.

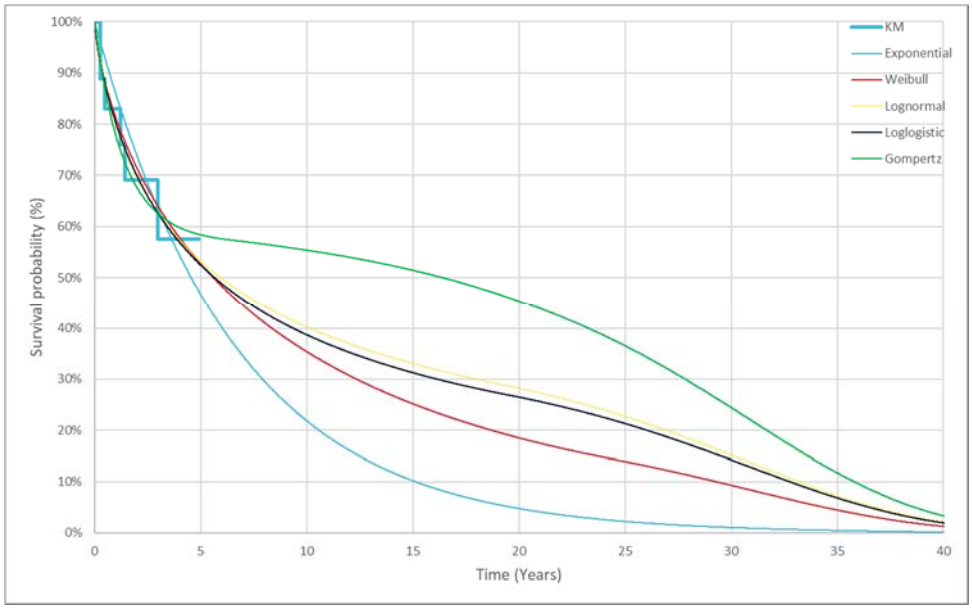
Due to the lack of convergence when fitting the generalised gamma distribution to the data, the outcomes associated with this curve are not presented. Table 32 summarises the AIC and BIC values for each parametric distribution. These statistics indicate that all parametric survival models provide a good fit to the data with no more than three points between the values. The Kaplan-Meier curves and fitted distributions are presented in Figure 50.

Table 32. Statistical fit of parametric survival models fitted to OS after alloSCT

	OS	
Model	**AIC**	**BIC**
Exponential	107	108
Weibull	108	110
Gompertz	107	109
Log-logistic	108	110
Log-normal	107	109

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; OS, overall survival.

Figure 50. OS after alloSCT – Digitized Kaplan-Meier data and parametric survival models



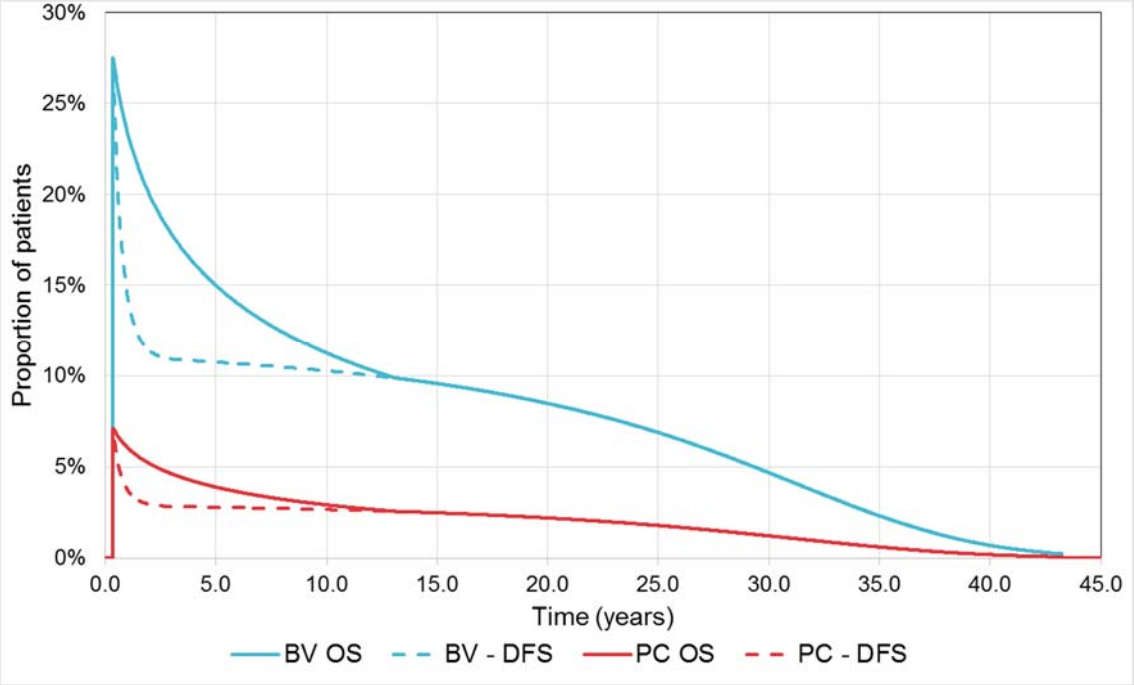
Abbreviations: KM, Kaplan-Meier; OS, overall survival; SCT, stem cell transplant.

The extrapolated data for OS is more complex to interpret – whilst the plateau evident in the DFS influences the OS, there are patients who are relapsed at the end of data collection, for whom whom worse outcomes are expectedrelapsedin long term remission. These patients are represented by the difference between the DFS curve and the OS curve after alloSCT.

To reflect the outcomes associated with these patients, the log-normal curve was selected in the base case. The combination of the log-normal curve for OS and the Gompertz curve for DFS results in the DFS curve converging with the OS curve at approximately 12.8-years. After this point survival is driven by the maximum of the probability of relapse and the probability of death based on background mortality (based on England and Wales' life tables 2014–2016).[109]

Patients who undergo an alloSCT and subsequently progress can stay in the relapsed state for up to a maximum of 12.8-years after which point all relapsed alloSCT patients are dead within the model. Section B.3.3.6 details the clinical validation for this selection. The resulting modelled DFS and OS incorporating background mortality are shown in Figure 51.

Figure 51. AlloSCT modelled DFS and OS



Abbreviations: BV, brentuximab vedotin, DFS, disease-free survival; OS, overall survival; PC, physician's choice.

B.3.3.5 Adverse events

Grade ≥3 treatment related AEs were included in the model if they occurred in ≥5% of all patients in either treatment arm of the ALCANZA trial in all patients (Table 33).

To simplify the list of included AEs, the majority of events were grouped by system classes as clinical opinion suggested cost and QoL impacts would be comparable between AEs of the same class. Clinical feedback suggested that septicaemia and peripheral neuropathy would have severe cost and QoL impacts and would differ from other AEs in the same system class. Therefore, these AEs were modeled separately and were included irrespective of whether or not they met the 5% inclusion criteria.

Feedback further indicated that the duration of AEs observed would not differ based on treatment received. Therefore, to utilise a greater sample size the mean duration of events were pooled across the treatment arms.

Table 33. Advanced subgroup - AEs included in the economic model; ALCANZA data

Adverse event: System class (adverse event)	Number of events		Duration (days)	
	BV	PC	Mean	SD
Blood and lymphatic system disorders (anaemia, neutropenia, thrombocytopenia)	6	4	15.5	16.6
Gastrointestinal disorders (Constipation, diarrhea, intestinal perforation, melena, nausea, pancreatitis, vomiting)	7	0	10.7	8.7
General disorders and administration site conditions (asthenia, fatigue, general physical health deterioration)	4	0	81.8	135.8
Multiorgan failure	1	0	1.0	1.0
Infections and infestations (acute diverticulitis, cellulitis, impetigo, staphylococcus aureus skin infection)	3	0	26.0	17.7
Septicaemia	0	1	20.0	20.0
Peripheral neuropathy	7	0	258.0	301.1
Skin and subcutaneous tissue disorders (drug eruption, hives, maculopapular rash, pruritus)	0	0	0.0	0.0
Investigations (alanine aminotransferase increased, aspartate aminotransferase increase, blood triglycerides increased, lymphocyte count decreased, raised triglycerides)	0	6	18.2	5.2
Hypertriglyceridaemia	0	9	50.9	81.7

Abbreviations: AEs, adverse events; BV, brentuximab vedotin; SD, standard deviation; PC, physician's choice.

The mean duration of exposure within the advanced subgroup safety population (brentuximab vedotin=237 days, PC=130 days) and the total number of patients on each arm from the ALCANZA trial (brentuximab vedotin n=49, PC n=44) were used to give the total exposure time in patient years. The rate of occurrence for different AEs was then calculated by dividing the total number of each event per treatment arm by the patient years on each treatment. This was then converted into a weekly rate for application in the model, see Table 34.

Table 34. Advanced subgroup - Weekly cycle AE incidence rates

Adverse event	Weekly Incidence Rate	
	BV	PC
Blood and lymphatic system disorders	0.36%	0.49%
Gastrointestinal disorders	0.42%	0.00%
General disorders and administration site conditions	0.24%	0.00%
Multiorgan failure	0.06%	0.00%
Infections and infestations	0.18%	0.00%
Septicaemia	0.00%	0.12%
Peripheral neuropathy	0.42%	0.00%
Skin and subcutaneous tissue disorders	0.00%	0.00%
Investigations	0.00%	0.73%
Hypertriglyceridemia	0.00%	1.10%

Abbreviations: AEs, adverse events; BV, brentuximab vedotin; PC, physician's choice.

B.3.3.6 Validation of clinical parameters

Section B.3.10 presents the validation undertaken for all the variables and outcomes in the economic model. This section summarises the validation undertaken for the clinical parameters only. Validation of clinical parameters considers two aspects: (1) the validation of outcomes associated with no alloSCT and (2) the validation of outcomes associated with an alloSCT.

The clinical parameters were validated by:

- Feedback from 12 UK clinicians
- An advisory board conducted with ten UK clinical experts
- Clinical outcomes were compared with those from relevant data: ALCANZA,[47] Kim et al 2003[45] and Agar et al 2010[13]

B.3.3.6.1 Validation of outcomes associated with no alloSCT

Predictions of OS outcomes were validated through initial feedback from ten clinical experts during the advisory and final validation was conducted with three clinicians. Clinicians were asked about the survival benefit of brentuximab vedotin relative to PC and it was considered that the main objective of treatment would not be to prolong survival. Therefore, due to the issues associated with the survival data from the ALCANZA trial, the assumption of equivalent survival was considered appropriate.

The proportion of patients surviving at 1-, 3-, 5-, 10- and 20- years was presented to clinical experts for each parametric curve fit (Table 35). It was explained that these data reflected patients without an alloSCT. It was considered that the log-logistic and the log-normal curve provided the clinically plausible predictions of what would be expected in UK clinical practice.

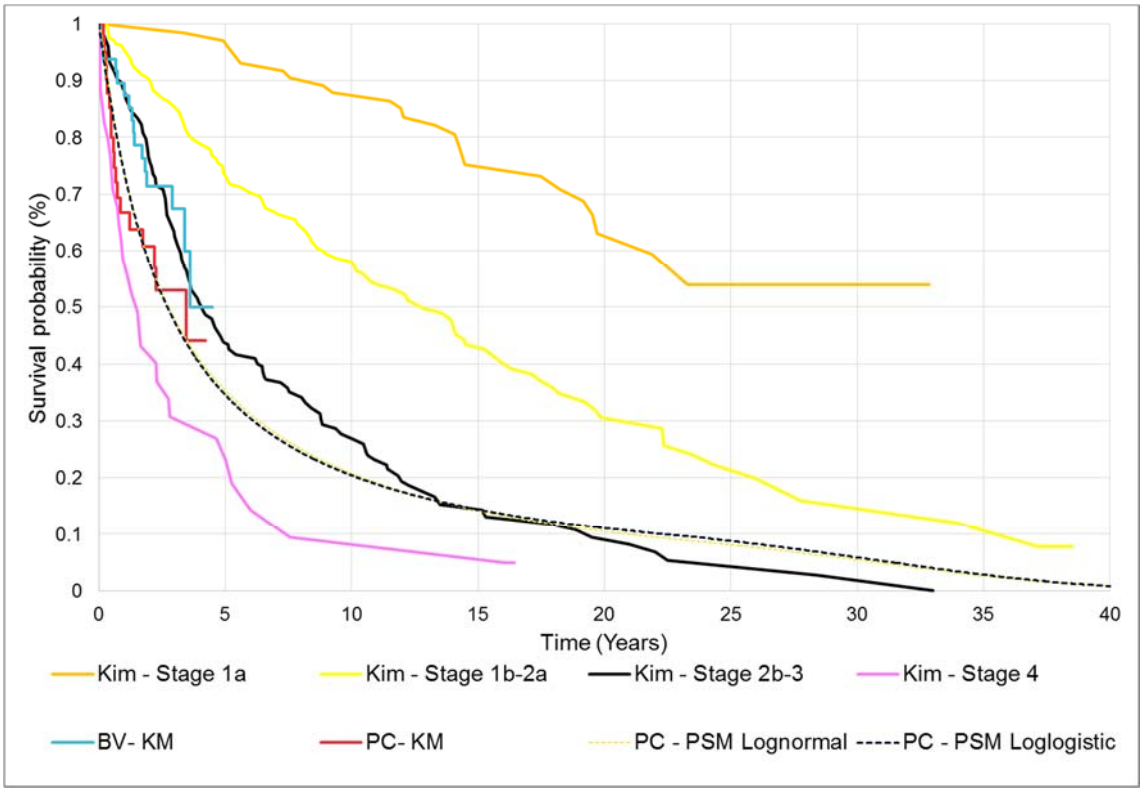
Table 35. Proportion of patients surviving at various time points by parametric curve

	1-year	3-years	5-years	10-years	20-years
Exponential	77.98%	47.41%	28.83%	8.27%	0.68%
Weibull	75.79%	48.93%	32.94%	13.24%	2.53%
Log-normal	73.95%	47.92%	35.39%	20.79%	10.52%
Log-logistic	73.88%	47.42%	34.64%	20.46%	11.10%
Gompertz	71.91%	50.70%	43.84%	39.78%	32.61%

Further validations of the modeled OS outcomes were undertaken at an advisory board with ten clinical experts present. It was concluded that the Weibull provided the best fit to the PFS curves (for both comprators) and that either the log-logistic or log-normal provided the most clinically plausible fit to the OS data.

Figure 52 presents the Kaplan-Meier OS data from the advanced subgroup of the ALCANZA trial, the log-logistic and log-normal parametric curves and the survival data presented in Kim et al 2003. The Kim et al 2003 study included 525 patients with MF and SS in the United States. The estimated curves are shown to lie in between the survival observed for Stage IIB-III patients and Stage IV patients in the Kim et al 2003 study, a frequently cited publication for OS outcomes in CTCL. These patients are relevant to the study population as of the MF subgroup, 45% of patients had stage IIB–III disease and 18% with stage IV disease of the MF subgroup within ALCANZA.

Figure 52. Comparison of fitted parametric curves with survival data presented in Kim et al 2003[45]

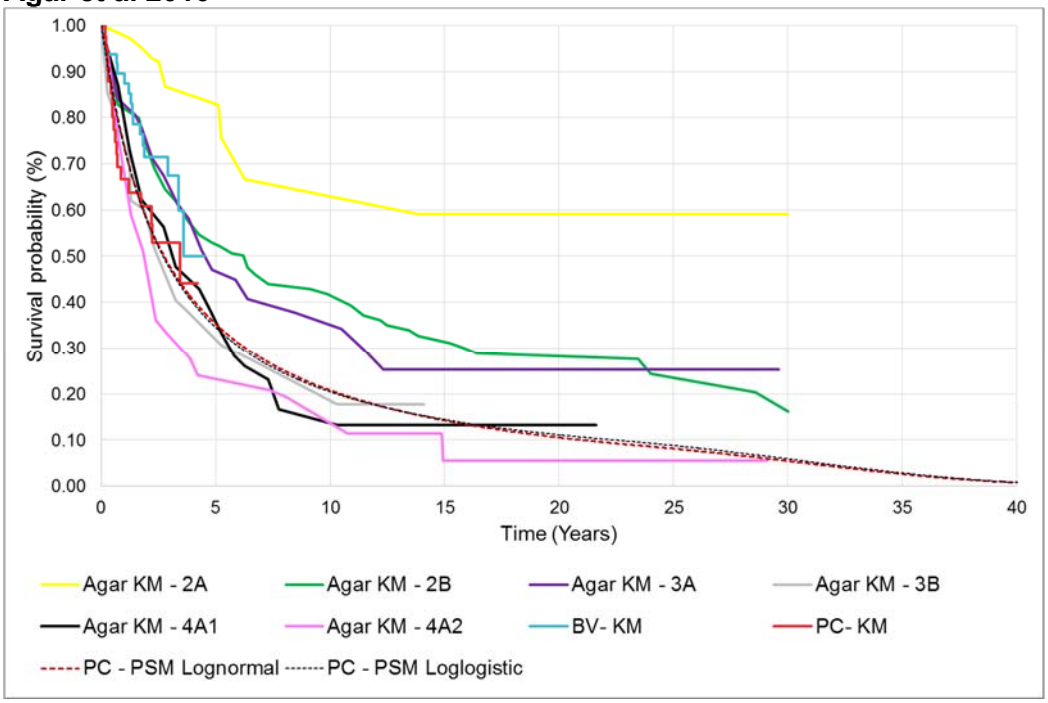


Abbreviations: BV, brentuximab vedotin; KM, Kaplan-Meier; PC, physician's choice; PSM, partitioned survival model

Figure 53 presents the Kaplan-Meier OS data from the advanced subgroup of the ALCANZA trial, the log-logistic and log-normal parametric curves and the survival data presented in Agar et al 2010. This study is a larger and more relevant historical cohort compared with Kim et al 2003 as it is based on data for 1,502 CTCL patients in the UK. As the Agar et al 2010 study is more recent, larger and from the UK, it is more representative of the likely OS outcomes in the UK. Although the Agar et al 2010 data are eight years old, the outcomes of patients today are not expected to be different and there have been no new medicines approved for the treatment for CTCL during in this time (other than brentuximab vedotin in 2017 which is not routinely available in the UK).

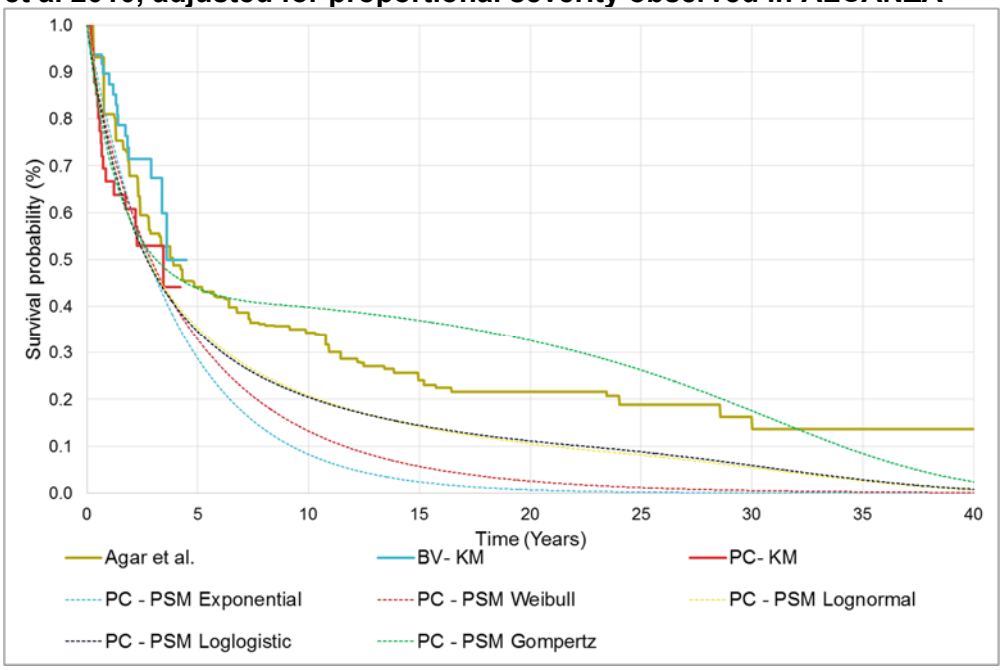
The estimated log-logistic and log-normal curves fall in-between the survival observed for stage IIIB, IVA1 and IVA2 patients in the Agar et al 2010 study. In order to simplify the Agar et al 2010 data and allow for easier comparison, a composite curve was created which applied the ALCANZA patient population distribution (see Section B.2.3.3.1) by disease stage to the observed outcomes of Agar et al 2010 (see Figure 53). The resulting curve depicted Agar et al 2010,[13] in Figure 54, supports the selection of either the log-normal or log-logistic curve for expected outcome with brentuxmab vedotin and PC.

Figure 53. Comparison of fitted parametric curves with survival data presented in Agar et al 2010[13]



Abbreviations: BV, brentuximab vedotin; KM, Kaplan-Meier; PC, physician's choice; PSM, partitioned survival model

Figure 54. Comparison of fitted OS parametric curves with surviva data from Agar et al 2010, adjusted for proportional severity observed in ALCANZA[13]



Abbreviations: BV, brentuximab vedotin; KM, Kaplan-Meier; PC, physician's choice; PSM, partitioned survival model

Based on clinical feedback and comparisons with the literature, the Weibull curve was selected in the base case for PFS outcomes (for both brentuximab vedotin and PC) and the log-logistic curve was selected for OS outcomes fit to the PC data (for both brentuximab and PC) Table 36 compares the median and mean clinical outcomes from the ALCANZA trial with the predicted model outcomes in the base case for OS and PFS including background mortality and assuming no alloSCT within the model.

The results of the extrapolations are shown to slightly underestimate OS and over-estimate PFS in terms of median outcomes; the relative differences between the estimates are similar across both treatment arms. Estimated PFS outcomes are shown to closely align with those observed in the clinical trial. OS outcomes across the trial period are below the restricted means calculated from the trial data. However, this disparity is observed across both treatment arms.

Table 36. Comparison of clinical outcomes with model outcomes

	Brentuximab vedotin		**PC**	
Outcome	**Clinical trial result**	**Model result**	**Clinical trial result**	**Model result**
Median outcomes				
OS	43.33	32.66	41.30	32.66
PFS	16.36	17.25	3.46	4.37
Mean outcomes				
OS	38.57*	23.51 (trial period) 81.94 (lifetime)	31.79*	23.51 (trial period) 81.94 (lifetime)
PFS	18.66*	18.52 (trial period) 21.38 (lifetime)	7.55*	6.95 (trial period) 7.07 (lifetime)

*Restricted mean outcomes
Abbreviations: OS, overall survival; PC, physician's choice; PFS, progression-free survival

B.3.3.6.2 Validation of outcomes associated with an alloSCT

Predictions of DFS and OS outcomes after receiving an alloSCT were validated through feedback from three clinical experts who specialize in the Stanford Protocol. It was agreed across all clinicians that the only curve to provide a clinically valid outcome for DFS was the Gompertz curve; it was considered that the risk of relapse would reduce substantially over time and if a patient had not relapsed in the first few years following transplant then they were unlikely to relapse – forming a "cured" population. When assuming a log-normal distribution for survival in the base case 46.13%, 39.48%, 38.94%, 37.15% and 30.45% of patients were predicted to be disease free at 1-, 3-, 5-, 10- and 20-years, respectively.

When the DFS curve converges with the OS curve, this implies that all patients that have relapsed have died (the difference between the DFS and OS curve) and that surviving

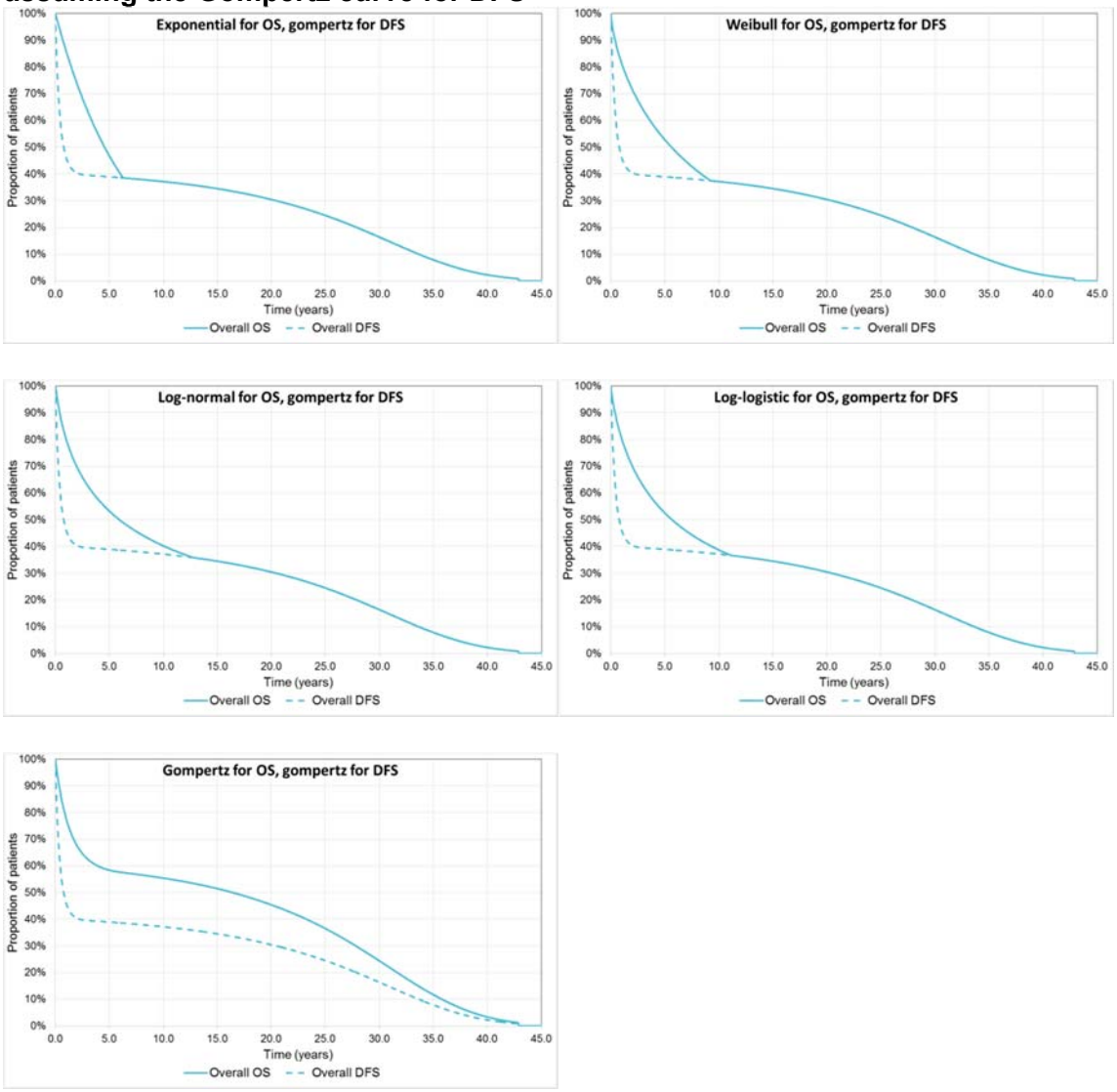
patients all form part of the “cured” population. Based on this information, the different parametric curves for OS were presented to clinical experts with the DFS Gompertz curve (Figure 55). Note time zero is not model baseline but time of alloSCT. The time point at which the DFS curve converged with the OS curve was highlighted and the implications of this explained. Based on this information it was considered that the log-normal had the most clinical credibility, as this assumed patients who had relapsed after an alloSCT would survive up to 12.8 years. Although this was considered shorter than the non-alloSCT population, where progressed patients could live up to 25-years, it was considered the most plausible out of the presented curves. Additionally, it was commented that outcomes after relapsing following an alloSCT may be worse than in the non-alloSCT population as these patients have been immunosuppressed. However, there are no data to corroborate this.

Survival associated with the “cured” patients was assumed to be determined by the maximum of the probability of relapse and the probability of death defined by background mortality estimates. Therefore, after the DFS curve hits the OS curve a slight change in the shape can be observed (Figure 55). This simplification was supported by clinical experts.

The proportion of patients surviving at 1-, 3-, 5-, 10- and 20- years after an alloSCT (note not from model baseline, alloSCT was assumed to occur after 18-weeks) was presented to clinical experts for each parametric curve fit (Table 37) assuming a Gompertz distribution for DFS outcomes. It was explained that these data reflected patients having had an alloSCT. It was considered that all parametric curves provided similar long-term estimates and there were no long term data available to advise choice of curve. Therefore, choice of curve should be guided by the clinical plausibility associated with the time the DFS curve hits the OS curve.

Based on clinical feedback, the Gompertz curve was selected in the base case for DFS and the log-normal curve was selected for OS.

Figure 55. Comparison of parametric curves fit to OS data after an alloSCT assuming the Gompertz curve for DFS



Abbreviations: alloSCT, allogeneic stem cell transplant; DFS, disease free survival; OS, overall survival

Table 37. Proportion of patients surviving at various time points by parametric curve

Curve choice for OS	1-year	3-years	5-years	10-years	20-years
Exponential	85.92%	63.43%	46.83%	37.13%	30.43%
Weibull	81.26%	63.94%	52.78%	37.14%	30.44%
Log-normal	80.09%	62.72%	53.29%	40.26%	30.45%
Log-logistic	80.27%	62.60%	52.55%	38.70%	30.44%
Gompertz	77.80%	62.53%	58.41%	55.40%	45.41%

Abbreviations: DFS, disease free survival; OS, overall survival.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Quality of life in CTCL

CTCL has devastating impacts on quality of life described in Section B.1.3.1. The EQ-5D is the preferred measure of quality of life by NICE; as such the economic analysis utilises the EQ-5D data collected in the ALCANZA trial. However, the EQ-5D is insensitive to particular burdens associated with CTCL and so may not be an accurate reflection of a patient's quality of life.

CTCL causes wounds to form on a patient's skin, which are both painful and distressing. Should these spread to the face, there is an additional burden which may not be captured in the EQ-5D. In addition to the pain, CTCL can cause patients to itch constantly and also lose the ability to sleep – both of which may not be captured in the EQ-5D. Furthermore, an analysis of ALCANZA QoL instruments found a lack of congruence between EQ-5D and the well recognized disease specific Skindex-29, suggesting EQ-5D may not be sensitive enough for CTCL. The limitations of EQ-5D's ability to fully capture HRQL of patients with advanced stage CTCL is described in Section B.1.3.1.

More sensitive instruments such as the Skindex-29 provide a more accurate reflection of a patient's quality of life with this disease. This measure was included in the ALCANZA trial. However, no mapping alogirthm exists to date to map these values into utilities for the purposes of economic evaluation. To attempt to fully capture the quality of life of these patients, the Skindex-29 score was included in a regression model fit to the EQ-5D data from the ALCANZA trial, described in Section B.3.4.3.

The deterioration of quality of life as the disease progresses to the pointpointpoisnt of end-stage care is well recognised with end-stage CTCL described as having a profound effect on HRQL. However, as all available trials include patients stll undergoing active systemic therapy, no data exists on the HRQL at this disease stageand studies.

B.3.4.2 Health-related quality-of-life studies

An extensive SLR to identify HRQL studies evidence was conducted on the 1st of May 2018. The aim of the SLR was to provide supporting HRQL evidence for brentuximab vedotin following PRISMA and Cochrane Collaboration guidelines.[110] The details of the search strategy, inclusion/exclusion criteria, PRISMA diagram and the outcome summary are provided in Appendix H.

The SLR was performed to identify and summarise the relevant HRQL evidence for CD30-positive CTCL in adult patients who have received at least one previous treatment. Due to the rarity of the disease and the anticipated scarcity of evidence, the population of interest was expanded to all adult CTCL patients. No restrictions were imposed on interventions, language, location or date.

The systematic literature review identified 18 records that reported HRQL measures. The majority of studies were based in the US (n=8) or were multicenter studies (n=5). The most common QoL measurement tool was Skindex-29 with 67% of identified CTCL

publications reporting on this measurement for HRQL (this value was calculated by pooling all ALCANZA data). In addition to Skindex-29, of the 18 studies:

- two reported EORTC QLQ-C30
- two reported Functional Assessment of Cancer Therapy – General (FACT-G)
- one reported EQ-5D-Visual analogue scale (EQ-VAS), and
- one reported the 36-item short form survey (SF-36).

No identified studies reported on EQ-5D as a measurement of HRQOL. The frequent use of Skindex-29 and lack EQ-5D observed in the literature supports the argument that Skindex-29 is a more suitable measurement of QoL in CTCL (see Section B.2.6.1).[48,111,112]

No studies reported health states utilities or adverse event disutilities suitable for incorporation into the de novo cost-effectiveness model. Appendix H provides a summary table of observed HRQL studies and their key results, with further commentary on the appropriateness of any Health State Utility Values (HSUV) identified for use in the cost-effectiveness model.

B.3.4.3 Health-related quality-of-life data from clinical trials

The ALCANZA trial collected the skin specific,well recognised Skindex-29 QoL questionnaire, (see Section B.2.6.1.4), as well as the more generic EQ-5D-3L. In line with the NICE Methods Guide, the data derived from the EQ-5D-3L for the advanced subgroup informed this economic analysis.

The EQ-5D-3L was collected on day 1 of cycles 1, 2, 4, 6, 8, 10, 12, 14 and 16. For patients without progression, assessments after the end of treatment were conducted every 12 weeks (± 2 weeks) for a minimum of 24 months, after which assessments were undertaken every 6 months (± 1 month) until progression or study closure.

To predict utility values for patients treated with brentuximab vedotin and PC, a longitudinal mixed-effects regression model was fitted to the EQ-5D-3L data, which accounted for the repeated measures structure of the data. EQ-5D-3L data were first converted into utilities using the EQ-5D UK Tariff values.[113] Stepwise selection was conducted to identify those variables that are significant predictors of health state utility and so should be accounted for in the regression equation.

Variables considered in the stepwise selection process were:

- Treatment
    - 2 groups: BV vs. PC as per the ALCANZA trial design.
    - 3 groups: BV vs. BEX; BV vs. MTX; and BV vs. PC.
- Response
    - Best Overall Response (BOR): progressive disease (PD), SD, PR, CR, Unknown
    - ORR: ORR = Yes vs. ORR = No; i.e. Responder vs. Non-responder
    - ORR4: ORR4 = Yes vs. ORR4 = No; i.e. Sustained response vs. No sustained response

- Age
    - Continuous: Change in EQ-5D for a 1-year difference in age
    - Dichotomous: Under 60 vs. Over 60
- Skindex-29
    - Continuous: Change in EQ-5D for a 1-point change in Skindex-29 total score
- Diagnosis
    - MF vs. pcALCL

Goodness of fit associated with the regression models was determined by the AIC and BIC values, clinical plausibility (i.e., did more severe states have a lower utility) and comparison of predicted with actual utility values. The resulting mixed-effects model which was found to perform best (once penalisation for additional variables was included) was the use of an intercept, progression status, and Skindex-29 score.

Table 38 presents the coefficients and variance-covariance matrices for the advanced subgroup. The observed and fitted utility values are presented in

Table 39 for both the advanced subgroup and the ITT population. In the base case, the mean utility values derived from the advanced subgroup data are applied in the economic model. The use of the regression equation leads to utilities slightly lower than observed in the ALCANZA study. The use of the observed values for advanced ALCANZA patients is tested in a scenario analysis.

The differences in utility by treatment (both observed and predicted) is driven by the difference in Skindex-29 score, with brentuximab vedotin providing a large benefit over PC (as discussed in Section B.2.6.1). The impact of Skindex-29 score was strong enough to remain a predictor of quality of life in the regression model, despite the penalisation incurred in both the AIC and BIC values. This demonstrates that whilst progression status remains important, the a patients skins symptoms (measured via the Skindex-29) are required to be incorporated to estimate quality of life – a 7 point change having a larger impact on estimated quality of life than disease progression.

Table 38. Results of utility regression – Advanced subgroup

Parameter	Coefficient	Variance-covariance matrix		
		Intercept	Progression	Skindex
Intercept	0.8470	0.000857	-0.000062	-0.000009
Progression	-0.0342	-0.000062	0.000357	0.000000
Skindex	-0.0049	-0.000009	0.000000	0.000000

Table 39. Predicted vs. observed utility values

Health state	Advanced utilities		ITT utilities	
	Predicted	Observed	Predicted	Observed
BV – progression free	0.68	0.70	0.72	0.72
PC – progression free	0.64	0.68	0.69	0.73
Progressed	0.61	0.64	0.66	0.68

Abbreviations: BV, brentuximab vedotin; PC, physician's choice.

B.3.4.4 Other HRQL data used in the economic model

No data were available for patients in the end-stage symptom management state (i.e., having exhausted all active systemic therapy) from neither the SLR nor the ALCANZA trial.which Therefore, it was assumed QoL would be similar to relapsed/refractory and end-of-life states of related lymphomas with larger literature base such as HL or sALCL. The value published for progressive disease associated with these conditions was applied to patients receiving palliative care in the model (0.38, Swinburn et al 2015[114]). The Swinburn study is well recognized and an often cited representation of highly-progressed lymphoma patients which has previously been utilised for multiple health technology appraisals, including by NICE.[115,116] The unanimous clinical feedback was that HRQL of patients with CTCL, particularly for highly symptomatic patients in the end stage, is among the worst of any condition due to its dual nature as a cancer and dermatologic condition. Therefore the Swinburn study is at a minimum appropriate if not conservative. It should be noted that many of the advisors consulted during the January 2018 Takeda Advisory Board are oncologists and haematologists who are familiar and treat other cancers and as well as other systemic lymphomas on which the Swinburn study was based.[36]

Limited data were available for patients receiving alloSCT in the ALCANZA trial (few patients underwent transplant in the study). Similarly, no published utilities for patients after an alloSCT were identified from a targeted review of the literature – even after expanding the scope to any lymphoma. Therefore, Agthoven et al. informs the utilities associated with patients undergoing alloSCT in the model (0.42 for the 14 days after SCT, 0.60 for 13 days to 3 months post alloSCT, and 0.77 for >3 months after SCT).[117] This source has been used to model quality of life associated with alloSCT in previous NICE assessments and NHS reports. Following relapse after an alloSCT, patients are assumed to have the same progressive disease utility applied in the non-SCT post-progression state (derived from the ALCANZA trial), followed by the same palliative care utility (Swinburn et al 2015[114]).

B.3.4.5 Impact of adverse events on health related quality of life

In addition to the health state specific utilities in the model, the impact of AEs on QoL is also included. Section B.3.4.5 presents the AEs included in the model. Utility decrements associated with each adverse event were sourced from a targeted review of previous NICE submissions focusing on lymphoma indications and are presented in Table 40.

Where no available estimate was identified, it was assumed that the decrement was equivalent to identified decrements relevant to a comparable adverse event.

Each utility decrement was multiplied by the relevant per-cycle rate of a grade 3/4 AE and weighted based on the pooled duration of AEs from ALCANZA (Table 33). The utility decrements associated with adverse events per cycle are 0.02160 and 0.00178 for brentuximab vedotin and PC, respectively.

Utility decrements associated with adverse events are applied in the base case. This approach may double count the quality of life impact reflected in the ALCANZA data as some patients will have been experiencing adverse events when completing the EQ-5D-3L. Therefore, a scenario analysis is explored excluding the impact of AEs on QoL.

Table 40. Adverse event decrements used in the model

Adverse event	Disutility	Assumptions	Source
Blood and lymphatic system disorders	-0.10	Reported for anaemia	Beusterien et al 2010[118]
Gastrointestinal disorders	-0.103	Reported for diarrhoea	Lloyd et al 2006[119]
General disorders and administration site conditions	-0.07	Assumed equivalent to fatigue	Nafees et al 2008[120]
Multiorgan failure	-0.20	No decrement available assumed equivalent to grade III/IV pneumonia and associated with significant decrement	Beusterien et al 2010[118]
Infections and infestations	-0.14	Reported as severe skin condition	Brown et al 2001[121]
Septicaemia	-0.20	No decrement available assumed equivalent to grade III/IV pneumonia and associated with significant decrement	Beusterien et al 2010[118]
Peripheral neuropathy	-0.11	Assumed to be grade I/II peripheral sensory neuropathy	Swinburn et al 2015[114]
Skin and subcutaneous tissue disorders	-0.03	Equivalent to rash	Nafees et al 2008[120]
Investigations	0	Assumed 0	NA
Hypertriglyceridemia	0	Assumed 0	NA

B.3.4.6 Values used in the economic model

Table 41 summarises the utility values used in the economic model for each health state (excluding the impact of AEs) and the end-stage symptom management state, with the full explanation and justification for each given above.

Table 41. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Source	Justification
PFS – brentuximab vedotin	0.68	0.62 – 0.76	ALCANZA[47]	Utility regression based on Phase 3 trial
PFS - PC	0.64	0.57 – 0.72	ALCANZA[47]	Utility regression based on Phase 3 trial
SCT (0-14 days)	0.42	0.38 – 0.46	Van Agthoven et al.[117]	No CTCL source; selected source is well-recognised for alloSCT HRQL
SCT (14 days – 3 months)	0.60	0.54 – 0.65	Van Agthoven et al.[117]	No CTCL source; selected source is well-recognised for alloSCT HRQL
SCT (>3 months)	0.77	0.69 – 0.84	Van Agthoven et al.[117]	No CTCL source; selected source is well-recognised for alloSCT HRQL
PD	0.61	0.52 – 0.70	ALCANZA[47]	Utility regression based on Phase 3 trial
End Stage Symptom Management care	0.38	0.33 – 0.44	Swinburn et al.[114]	No CTCL source; Swinburn is based on closest related lymphoma

Abbreviations: PC, physician's choice; PD, progressive disease; PFS, progression-free survival; SCT, stem cell transplant.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Treatment costs

The unit costs associated with treatment acquisition are shown in Table 42. Costs were taken from eMIT where appropriate, and otherwise taken from MIMS. A patient access scheme (PAS) is currently in place for bentuximab vedotin for the treatment of other approved indications via baseline commissioning, which reduces the unit cost from £2,500 per 50mg vial to £[redacted] a [redacted] discount from list price. Results are presented including and excluding the PAS for brentuximab vedotin.

The dose schedule of brentuximab vedotin is aligned with the ALCANZA clinical trial and the marketing authorisation for brentuximab vedotin; 1.8mg/kg administered on day 1 of each 21-day cycle. The base case accounts for wastage due to the assumption of no vial sharing using the method of moments approach,[122] informed by the relative dose intensity from the ALCANZA trial (95%). This led to a cost per model cycle for brentuximab vedotin of £[redacted] at list price or £[redacted] with the PAS applied. The cost per treatment cycle was £[redacted] and £[redacted] without and with PAS, respectively. Due to the rarity of advanced CTCL patients (BIM predicts on average 84 patients per year treated with brentuximab vedotin) it is highly unlikely that vial sharing would occur therefore this was not included as a sensitivity analysis

For PC the split of bexarotene and methotrexate from the ALCANZA study was used, with each drug costed according to actual use in the trial. Oral methotrexate was administered on day 1 of each 7-day cycle. Oral bexarotene was administered every day, continuously up to 48 weeks. For methotrexate a mean dose of 23.44mg once weekly (the recommended dose being in the 5-50mg range) was costed using eMIT (2.5mg x 100 tablets, £4.32), equating to £0.43 per model cycle. Bexarotene is more complex having been dosed at a recommended dose of 300mg/m^2/day. The required dose was calculated using the method of moments, costed via MIMS (75mg x 100 capsules, £937.50) with a dose intensity of 90% (taken from ALCANZA). The resulting cost per model cycle was £478.22.

Table 42. Drug unit costs

Treatment	Dose per unit (mg)	Pack size (eMIT)	Pack size (MIMS)	Unit cost (eMIT)	Unit cost (MIMS)
Initial treatment					
BV[123]	50 mg	NA	1	NA	£2,500.00
MTX[124]	2.5 mg	100	28	£4.32	£1.44
BEX[125]	75 mg	NA	100	NA	£937.50

Abbreviations: BEX, bexarotene; BV, brentuximab vedotin; MTX, methotrexate; NA, not available.

B.3.5.1.2 Administration costs

The cost of administration for all active treatments is also included in the economic model. These are taken from the NHS Reference Costs 2015/2016. Table 43 presents the administration unit costs applied in the model.

All IV therapies, including brentuximab vedotin, were assumed to be costed as simple therapies with the exceptions of doxorubicin (costed as complex chemotherapy), and CHOP, for which each of the three IV therapies is costed as simple chemotherapy, with no cost assumed for prednisolone. The resulting cost per administration of each treatment used in the model is given in

Table 44.

Table 43. Unit costs used in the economic model – administration unit costs

Definition and currency code	Unit cost	Description
Deliver simple parenteral chemotherapy (SB12Z)	£173.99	Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle.
Deliver more complex parenteral chemotherapy (SB13Z)	£264.56	Overall time of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle.
Deliver complex chemotherapy, including prolonged infusion treatment (SB14Z)	£269.86	Overall time of 60 minutes nurse time and over two hours chair time for the delivery of a complete cycle.
Deliver Exclusively Oral Chemotherapy (SB11Z)	£163.82	SB11Z will be assigned to regimens made up of only drugs administered orally and the costs should reflect current practice in light of recommendations within the NPSA report on oral chemotherapy. NHS reference costs 2016/17. NHS guidance document 2015/16.

Abbreviations: NHS, National Health Service; NPSA, National Patient Safety Agency; PSSRU, Personal Social Services Research Unit.

Table 44. Administration cycle costs by treatment

Treatment	Cost per cycle	Description
BV	£173.99	Infused over 30 minutes; cost for delivering simple parenteral chemotherapy (SB12Z) is used.
MTX	£163.82	Oral therapy; cost for delivering exclusively oral chemotherapy (SB11Z) is used.
BEX	£163.82	Oral therapy; cost for delivering exclusively oral chemotherapy (SB11Z) is used.
Gemcitabine	£173.99	Infused over 30 minutes on days 1, 8 and 15 of 28-day cycle; cost for delivering simple parenteral chemotherapy (SB12Z) is used.
CHOP	£521.98	LCA SACT protocol: Dox slow iv infusion, vin IV infusion over 5-10 minutes, cyc IV over 30 mins and pred oral admin but not costed to avoid overestimation. So, used the cost for delivering simple parenteral chemotherapy (SB12Z) multiplied by 3.
Doxorubicin	£264.56	LCA SACT protocol: IV infusion over 60-90 minutes on day 1, 8 of 28-day cycle so cost of delivering complex chemotherapy, including prolonged infusion treatment (SB14Z) is used.

Abbreviations: BEX, bexarotene; BV, brentuximab vedotin; IV, intravenous; LCA, London Cancer Alliance; MTX, methotrexate; SACT, systemic anti-cancer therapy.

B.3.5.2 Health-state unit costs and resource use

Due to the rarity of the condition and paucity of publicly available resource use data, resource use inputs were informed by expert opinion. Inputs were elicited from discussions with UK clinicians, and final assumptions were validated with a leading UK clinician.

B.3.5.2.1 Pre-progression health state

Resource use received in the pre-progression health state was informed by clinical expert opinion and London Cancer Alliance (LCA) skin systemic anti-cancer therapy (SACT) protocols. Unit costs associated with each item are presented in Appendix M, with the resulting cost per cycle presented in Table 45.

The weekly cost applied per cycle for resource use in the pre-progression health state was £388.63.

Table 45 Resource use in the pre-progression health state

	% of all patients	Frequency per week	Dose	Unit	Average weekly cost
Hospital outpatient					
Clinical nurse specialist	100.00%	0.19	NA	NA	£16.39
Oncologist outpatient visit	100.00%	0.19			£30.21
Consultant oncologist visit	100.00%	0.19			£33.05
Home visit					
District nurse	100.00%	2.60	NA	NA	£96.01
Investigations and tests					
Complete blood count	100.00%	0.25	NA	NA	£0.77
Liver function test	100.00%	0.25			£3.15
U&Es (urea and electrolytes test)	100.00%	0.25			£0.28
Computed tomography scan	50.00%	0.08			£5.10
Imaging - PET	50.00%	0.08			£19.94
Dressings					
Full body coverage	0.00%	0	0	dressings	£0.00
Localised coverage	60.00%	7	7	dressings	£183.75

B.3.5.2.2 Post-progression health state

Post-progression disease can be considered as having two phases: (1) when patients are receiving active therapy and (2) when patients have exhausted active therapy options and are receiving end-stage supportive care and symptom management only. The costs and resource use associated with non-alloSCT post-progression health state are also applied for the alloSCT relapse health state. Despite these health states representing different patient populations, it is considered that the pathway of care would be similar across the groups.

To calculate the costs of subsequent therapy in post-progression, the 'payoff approach' was used. This approach incorporates time-dependent transition rates from intermediate health states while retaining a simple model structure and removing the need to use complex and computationally intensive tunnel state calculations. The intermediate state in this case was a post-progression state where patients received active therapy. The payoff approach worked by calculating the mean time spent in the post-progression state and then dividing it into: (1) active therapy and (2) end-stage management. The mean time spent in post-progression retained the partitioned survival approach and was calculated by the area between the OS and PFS curves for non-alloSCT outcomes, and area between the alloSCT OS and DFS curves for alloSCT outcomes.

A mean payoff for both costs and QALYs was then applied to the proportion of patients entering the post-progression state (non-alloSCT post-progression or alloSCT relapse health states) incorporating the time spent receiving active subsequent therapy and end-stage management. This approach was discussed at length in NICE DSU TSD19.[126]

In the model base case, patients were estimated to spend 5.05 or 6.24 years in the non-alloSCT post-progression health state in the brentuximab vedotin and PC arm, respectively. Of which, 36.77% and 29.74% of time was spent receiving active therapy, respectively. Following an alloSCT, patients were estimated to spend 1.64 years in the alloSCT relapse health state, 57.10% of which was spent receiving active therapy.

Phase 1: Active therapy

To inform the active therapy phase, data were taken from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. PROCLIPI is a prospective international registry for patients with CTCL. Takeda was granted access to the confidential European data including patient stage and treatment by line for the purposes of this submission. As these data are confidential, all PROCLIPI inputs have been marked as Academic in Confidence (AiC).

Based on the marketing authorisation for brentuximab vedotin, to analyse relevant subsequent therapies, data from PROCLIPI on patients with stage IIB+ disease and third line onwards were considered. The duration of treatment and duration of response was obtained from the literature. Table 46 presents the proportion of patients receiving each identified subsequent therapy; these may sum to over 100% as patients may receive each treatment more than once.

Table 46: Active therapy received by stage IIB+ patients in the PROCLIPI study[36]

Treatment	Proportion of patients receiving therapy	Duration & Dosing	Source
[redacted]	[redacted]	DOT: 4 cycles Gemcitabine 1000mg/m2 IV D1, D8, D15 in q28 days	Proportion: EU PROCLIPI Data DOT: Duvic et al 2006[79]
[redacted]	[redacted]	DOT: 6m	Proportion: EU PROCLIPI Data DOT: Dummer et al 2012[81]
[redacted]	[redacted]	DOT: 3 cycles CHOP IV; D1, D8, D15	Proportion: EU PROCLIPI Data DOT: Clinical consultation
[redacted]	[redacted]	DOT: low dose 12Gy, 8 fractions over 2 weeks (cost split across DOR) DOR: 11m	Proportion: clinical input DOT: Morris et al 2017[83]
[redacted]			

Appendix M presents the unit costs associated with each of the subsequent therapies, sourced from eMIT where available and MIMS otherwise. Dosing regimens for subsequent therapies were obtained from clinical consultation with the LCA SACT protocols for non-melanoma indications.

Table 47 presents the resulting cost per week, mean time on treatment and total weighted costs for each of the subsequent therapies. The total weighted cost of active therapy per patient is £5,891 and £2,415 for post-progression without an alloSCT and with an alloSCT, respectively.

Table 47: Cost of subsequent therapies applied in the model

Subsequent therapy	Proportion of patients treated	Cost per week	Mean time on treatment (weeks)	Total weighted cost
[redacted]	[redacted]	£54.63	16.00	£655.55
[redacted]	[redacted]	£21.69	9.00	£54.66
[redacted]	[redacted]	£151.17	24.00	£1,705.23
[redacted]	[redacted]	£72.67	47.83	£3,475.95

Resource use received in the active therapy phase of the post-progression health state was informed by clinical expert opinion and LCA SACT protocols (Table 48). Unit costs associated with each item are presented in Appendix N, with the resulting cost per cycle presented in Table 48.

The weekly cost of resource use per patient applied each cycle of active therapy to the post-progression health state was £904.45.

Table 48: Resource use in the active therapy phase of the post-progression health state

	% of all patients	Frequency per week	Duration (if applicable)	Dose	Unit	Average weekly cost
Hospital outpatient						
Clinical nurse specialist	100%	0.38	NA	NA	NA	£32.77
Dermatologist visit	100%	0.50				£50.27
Oncologist outpatient visit	100%	0.38				£60.43
Consultant oncologist visit	100%	0.54				£95.46
Home visit						
District nurse	100%	2.60	NA	NA	NA	£96.01
Investigations and tests						
Complete blood count	100%	0.67	NA	NA	NA	£2.04
Liver function test	100%	0.33				£4.20
U&Es (urea and electrolytes test)	100%	0.33				£0.38
LDH (lactate dehydrogenase)	100%	0.33				£0.84
Computed tomography scan	50%	0.17				£10.19
Imaging - PET	50%	0.17				£39.88
Dressings						
Full body coverage	0%	0	NA	0	dressings	£0.00
Localised coverage	60%	7		7	dressings	£510.38
Other drug treatments						
Pain relief						

Oramorph	0%	14.00	NA	60	mg	£0.00
Oromorph (breakthrough pain / iv)	80%	1.00		10	mg	£0.08
Antihistamines						
Hydroxyzine	50%	4.67		25	mg	£0.05
Gabapentin	33.33%	14.00		300	mg	£0.38
Antidepressants						
Mirtazapine	50%	7.00		30	mg	£0.13
Pregabalin	50%	7.00		300	mg	£0.34
Antibiotics						
Flucloxacillin	100%	4.83	NA	500	mg	£0.39
Aciclovir	25%	28.00	NA	200	mg	£0.23

Phase 2: End-stage management care

There was a paucity of evidence in the literature associated with resource use relevant to patients with advanced-stage CTCL identified in the literature searches, particularly for end-stage management. Therefore, to elicit estimates of resource use for this stage, semi-structured interviews were conducted with clinical experts from all seven supra-regional centres for CTCL in England and a leading Welsh centre between March 2018 and June 2018. Each respondent was responsible for end-stage patient management within their catchment area. Interviews were guided by a questionnaire capturing resource use associated with pain, anxiety/depression, itch relief, and skin care and wound management. Please refer to Appendix L for more details regarding methods and results.

The data collected from the medical experts were collated and averaged to inform the economic model. The greatest burden was associated with dressings and wound care, which necessitated frequent and lengthy nurse visits (up to two hours) and constant therapies to control infection, pain and intractable pruritus. The questionnaire found that 100% of these patients needed expensive specialised dressings of which up to 20%–25% required full-body coverage of dressings, with the remaining 75%–80% requiring localised coverage. Due to the frailty of skin, specialised (non-adhesive borders) dressings are needed, costing up to £63.64 per dressing. Multiple interventions were reported to be given in an attempt to alleviate the symptoms of pruritus, including anti-histamines and anti-epileptics/anti-depressants. In addition, patients are treated with oral opioids for background pain with episodes of breakthrough pain requiring subcutaneous injections of morphine on average reported monthly. Table 49 presents the resource use and weekly costs applied in the economic model for end-stage care of post-progression. This resulted in a cost of £2,095 per patient per week.

Table 49: Resource use in the end-stage management phase of the post-progression health state

	% of all patients	Frequency per week	Duration (if applicable)	Dose	Unit	Average weekly cost
Hospital outpatient						
Clinical nurse specialist	100%	2.25	NA	NA	NA	£196.65
Dermatologist visit	100%	0.17				£16.76
Consultant oncologist visit	100%	0.17				£29.37
Psychologist	50%	0.25	1	NA	hours	£6.63
Hospital inpatient						
Dermatology Day Centre or Oncology Ward	20%	0.11	NA			£117.48
Home visit						
District nurse	100%	2.63	NA	NA	NA	£96.93
Macmillan nurse / Social services	100%	1.00	7		hours	£199.50
Palliative care support team	100%	2.00	NA		NA	£284.00
Skin and wound care						
Radiotherapy	90%	0.11	NA	2	fractions	£96.01
Topical steroids						
Betnovate	100%	0.34	NA			£1.40
Dressings						
Full body coverage including elasticated garments						
Mepitel dressings	25%	7	NA	3	dressings	£74.81

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	NA	7	dressings	£637.98
Other drug treatments						
Pain relief						
Oramorph	100%	14.00	NA	60	mg	£7.94
Oromorph (Morphine sulphate (breakthrough pain / iv))	80%	0.25		10	mg	£0.02
Antihistamines						
Hydroxyzine	100%	4.67	NA	25	mg	£0.10
Gabapentin	50%	14.00	NA	300	mg	£0.57
Antidepressants						
Mirtazapine	50%	7.00	NA	30	mg	£0.13
Pregabalin	50%	7.00	NA	300	mg	£0.34
Antibiotics						
Flucloxacillin	100%	3.22	NA	500	mg	£0.26
Aciclovir	25%	28.00	NA	200	mg	£0.23
Antifungal						
Fucitec	80%	0.02	NA	30	g	£0.10

B.3.5.3 alloSCT cost and resource use

The exact cost of alloSCT for advanced CTCL in the UK is uncertain as it follows the relatively new Stanford Protocol for conditioning.

In the base case, an estimate of £96,956 is applied per alloSCT. This estimate is based on a French study by Debals et al 2018.[127] The study compared cost and survival outcomes of haploidentical with unrelated alloSCT and estimated the mean costs as €98,304 and €151,373, respectively. These costs included the cost of procedure and follow-up over a 2-year time horizon. To inform the economic model, the average was taken which was then converted to pounds using the average of the 2014 exchange rates (0.81 pounds in the euro[128]) and uplifted to 2016/2017 values using the PSSRU (2017).[129]

This is in line with cited costs from UK clinicians; related and unrelated donor transplants cost £63,000 and £107,000, respectively. Due to the uncertainty included in the base case estimate, a scenario analysis is conducted using NHS Reference Costs for alloSCT weighted by proportion of unrelated to related donors – this total £64,152.

B.3.5.4 Adverse reaction unit costs and resource use

Costs for treating AEs were taken from the NHS Reference Costs 2015/2016 for each different potential setting: inpatient, outpatient, day case and general practice. Clinical opinion was elicited to inform what proportion of each AE would be actively treated and of those events treated, what proportion would be treated in each setting. Unit costs, relevant settings and proportion of patients treated are presented in Appendix M.

The cost per weekly cycle was then calculated by multiplying the weighted unit cost (weighted by setting) by the rate of AEs per cycle, resulting in weekly costs of: £4.97 for brentuximab vedotin and £5.99 for PC.

Costs associated with AEs were applied for the duration patients remained on-treatment in the pre-progression state, consistent with the events included being treatment emergent AEs. Adverse event costs relevant to treatments received as subsequent therapies were not included.

B.3.5.5 Miscellaneous unit costs and resource use

The costs associated with end-stage care reported above are specific to advanced CTCL. The model also includes a cost of death, generic to oncology disease areas. This is taken from Round et al 2015[130] using a weighted mean of all the cancers considered – equating to £9,914 (£286 per week). The weekly cost of generic end-of-life care is added to the weekly cost of end-stage care within the model.

B.3.6 *Summary of base-case analysis inputs and assumptions*

In line with the NICE reference case, the model considers a UK treatment provider's perspective and discounts costs and QALYs using a 3.5% discount rate. Results are presented over a lifetime (45-years) time horizon.

Data from the advanced subgroup in the ALCANZA trial inform the comparison of brentuximab vedotin and PC in the economic model. Appendix P summarises the variables applied in the economic model.

B.3.6.1 Summary of base-case analysis inputs

Table 50 presents the key model assumptions used in the base case of the economic model and provides a justification for each one.

Table 50: Key model assumptions and inputs

Source/assumption	Justification	Scenario analysis
Assumed Weibull distribution for brentuximab vedotin and PC PFS data	The Weibull, gompertz, exponential, log-normal and log-logistic were shown to provide a similar fit to the data. The Weibull curve was selected as clinically most representative at an advisory board conducted by Takeda.	Exponential distribution assumed for PFS outcomes for both brentuximab vedotin and PC.
Assumed equivalent survival for brentuximab vedotin and PC	No statistical difference observed in neither the advanced subgroup nor the ITT population data. Issues with the data in terms of: (1) immaturity, (2) small patient numbers and (3) confounding from crossover. Statistical methods to adjust for these biases gave nonsensical results. Feedback from clinicians indicated that survival was not a primary goal of treatment. Therefore, the simplification to assume equal survival was considered appropriate.	Independent curves fit to the brentuximab vedotin and PC unadjusted OS data (Weibull and log-logistic, respectively)
Assumed a log-logistic distribution for brentuximab vedotin and PC OS data	The Weibull, gompertz, exponential, log-normal and log-logistic were shown to provide a similar fit to the data. The log-logistic was selected as the most clinically plausible by clinical experts.	Log-normal distribution assumed for OS outcomes fit to the unadjusted PC OS data

Assumed 40% of responders (PR and above) would be eligible for transplant	Based on feedback from transplant clinicians in the UK.	Assumed 20% of responders would be eligible for transplant. Assumed that patients with stable disease would also be eligible for transplant.
Assumed patients would be eligible for an alloSCT at 18-weeks. All eligible patients receive an alloSCT at this time	Based on feedback from transplant clinicans in the UK. Required to maintain a simple model structure and avoid the use of tunnel states.	Assumed patients would be eligible for an alloSCT at 12- and 24-weeks.
Assumed a gompertz distribution for DFS following an alloSCT	The Weibull, gompertz, exponential, log-normal and log-logistic were shown to provide a similar fit to the data. The gompertz was considered the only plausible curve choice given that for patients who have not relapsed after an alloSCT by 12-months; these would be in long-term remission with very few events expected beyond this point.	None
Assumed a log-normal distribution for OS following an alloSCT	The Weibull, gompertz, exponential, log-normal and log-logistic were shown to provide a similar fit to the data. The log-normal was considered the only plausible curve choice given that it predicted a reasonable shape and survival time for relapsed patients (12.8-years). This was validated with clinicians.	Assume a Weibull distribution for OS following an alloSCT
Assumed that once the DFS curve and the OS curve after an alloSCT converged, survival was driven by the maximum of the probability of relapse and the probability of death based on background mortality	When the DFS curve converges with the OS curve the living population in the model represents those with long-term remission. As very few events are expected for these patients, survival is driven by what would be expected in the general population with a small adjustment made for continuing events.	None
Assumed that the utility of patients with progressed disease was reflected by the data from the ALCANZA clinical trial (0.61)	This utility value was derived directly from the patient responses in the ALCANZA trial.	A utility value of 0.50 was assumed for these patients.

Assumed that patients receiving end-stage management would experience a utility of 0.38	It was assumed quality of life would be similar to relapsed/refractory and end-of-life related lymphomas such as Hodgkin's' lymphoma or systemic anaplastic large cell lymphoma. Swinburn et al 2015[114] presents a utility values for these patients in the progressed disease health state which is applied to patients receiving end-stage care.	Assumed these patients would experience a utility of 0.50
Assumed drug wastage	Due to the small patient population, vial sharing is not considered a clinically plausible assumption	None
Assumed that the cost of an alloSCT in the UK is £96,956	No data are available on costs for minimal intensity regimen following the new Stanford protocol. This estimate is obtained from a French source. However, it aligns with cited sources from UK clinicians. A scenario analysis explores the impact of using costs from the NHS Reference Costs. However, these costs do not capture the follow up associated with an alloSCT and so are likely to be an underestimate.	Cost of alloSCT reduced to £65,154 (NHS Reference costs)

B.3.7 *Base-case results*

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case results for brentuximab vedotin compared with PC are presented in Table 51 including the PAS for brentuximab vedotin, and in Table 52 excluding this PAS.

Including the PAS discount, brentuximab vedotin provides an additional 1.20 LYs and [redacted] QALYs with a net cost saving of £[redacted]. This leads to brentuximab vedotin being dominant –the absence of an ICER can be hard to interpret, so the Net Monetary Benefit (NMB) has also been included in results (using a willingness to pay threshold of £30,000 per QALY).

The reason for this finding is two-fold. Firstly brentuximab vedotin controls a patients' disease, meaning they spend less time in end-stage care – where utility is poor and costs high. Secondly brentuximab vedotin acts as a bridge to alloSCT for a larger number of patients due to its high response rates (an estimated 27.5% vs. 7.1% of patients reaching transplant). Despite no survival gain being assumed for brentuximab vedotin directly, patients who undergo alloSCT show increased survival, better utilities, and overall, lower costs than patients who follow the non-alloSCT pathway.

Table 51: Base case results of the economic model including PAS

	Total			Incremental			Cost per QALY	NMB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Physician's choice	[redacted]	[redacted]	7.23					
Brentuximab vedotin	[redacted]	[redacted]	8.43	[redacted]	[redacted]	1.20	BV Dominates	£134,218

Abbreviations: LY, life year; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life year.

Table 52: Base case results of the economic model excluding PAS

	Total			Incremental			Cost per QALY	NMB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Physicians choice	[redacted]	[redacted]	7.23					
Brentuximab vedotin	[redacted]	[redacted]	8.43	[redacted]	[redacted]	1.20	[redacted]	[redacted]

Abbreviations: LY, life year; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life year.

Appendix J compares the model results to those from the clinical trial (both in the short and long term), and gives disaggregated results by health state.

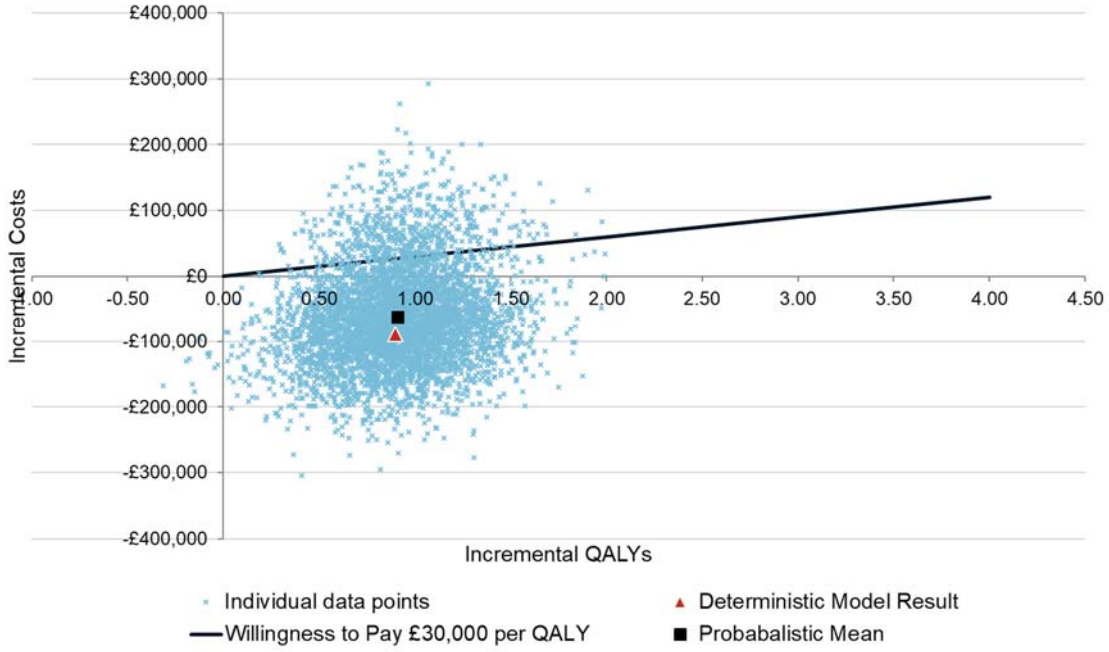
B.3.8 *Sensitivity analyses*

Extensive sensitivity and scenario analyses have been conducted, including probabilistic and one-way analyses as mandated by the NICE template. However, as the uncertainties in the economic model are mainly structural in nature a focus is given to scenario analyses where model settings (for example which parametric curves are selected) are changed. All sensitivity and scenario analyses are presented with the PAS for brentuximab vedotin included. For sensitivity analyses results without PAS, please refer to Appendix M.

B.3.8.1 Probabilistic sensitivity analysis

The PSA was conducted based on 5,000 simulations; Figure 56 presents these results in a cost-effectiveness scatter plot. This shows that the result does have a degree of uncertainty, spanning three quadrants (brentuximab vedotin is never dominated in the results).

Figure 56: Probabilistic sensitivity analysis – Scatterplot, including PAS



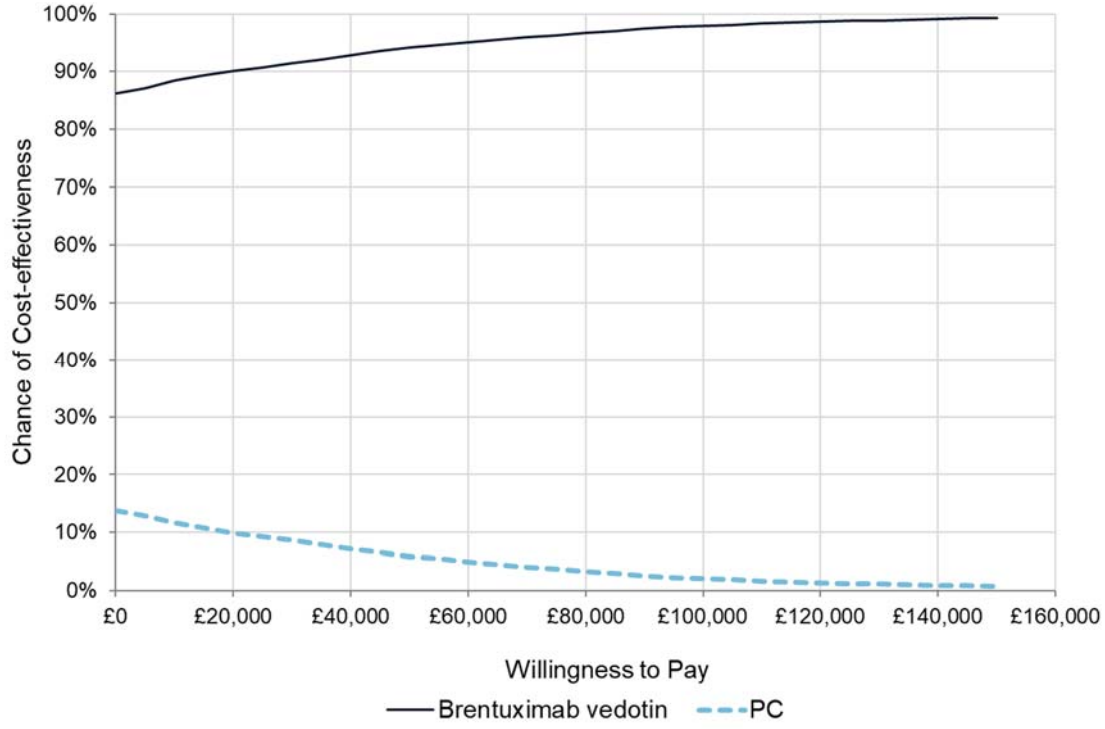
Abbreviations: PAS, patient access scheme; QALY, quality adjusted life year.

Mean probabilistic incremental QALYs gained from brentuximab vedotin were [redacted] and mean probabilistic incremental costs [redacted]. The resulting probabilistic ICER from 5,000 iterations was dominant, as in the deterministic result. The probabilistic net monetary benefit (NMB) was slightly lower than the deterministic result due to a similar probabilistic incremental QALY but a smaller probabilistic incremental cost (£[redacted] vs. £[redacted] respectively).

Figure 57 presents the resultant Cost-Effectiveness Acceptability Curve (CEAC) – unusually at a willingness to pay threshold of £0, this begins above zero since

brentuximab vedotin was dominant in many scenarios i.e. more effective and cheaper. Brentuximab vedotin was shown to be cost-effective at a threshold of £30,000 in 91.38% of scenarios.

Figure 57: Cost-effectiveness acceptability curve (CEAC) including PAS



Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS, patient access scheme.

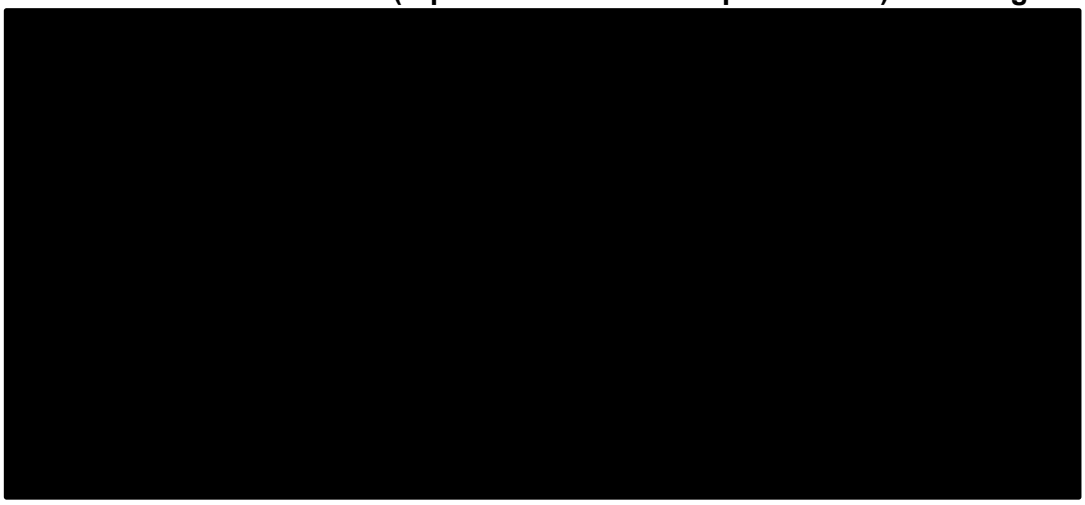
B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to deterministically investigate the impact of varying each parameter in isolation between its lower and upper bound. Upper and lower bound values for parameters were taken from 95% confidence intervals of the assigned distribution. If the required data were unavailable, a standard error of 10% of the mean value was assumed. Distributional information associated with each parameter is presented in Appendix P.

Figure 58 presents a tornado diagram with the ten most influential parameters shown in descending order of ICER sensitivity. Table 53 displays this information in a tabular format. For ease of interpretation, OWSA results were reported using the NMB.

Results showed that peripheral neuropathy duration and the cost associated with the end-stage care health state and the proportion of patients eligible for an alloSCT were the most influential. The model is relatively insensitive to remaining parameters. Of all the parameters varied in the OWSA, none result in a negative NBM i.e. brentuximab vedotin was cost-effective in all cases.

Figure 58: Tornado diagram: one way sensitivity analysis applied to the economic model base case (top 10 most influential parameters) including PAS



Abbreviations: AE, adverse event; BEX, bexarotene; BV, brentuximab vedotin; CTCL, cutaneous t-cell lymphoma; MTX, methotrexate; NMB, net monetary benefit; OWSA, one way sensitivity analysis; PAS, patient access scheme; SCT, stem cell transplant.

Table 53: Tabular format: one way sensitivity analysis applied to the economic model base case (top 10 most influential parameters) including PAS

Parameter	Lower bound	Upper bound	Difference
Post-progression - CTCL specific end stage care	£103,470	£164,965	£61,496
Eligible proportion of responders for alloSCT	£120,489	£148,399	£27,910
Peripheral neuropathy duration	£123,463	£144,972	£21,509
Cost of medium Allevyn dressings	£130,013	£138,422	£8,410
Rate of peripheral neuropathy (BV)	£130,049	£138,386	£8,337
End stage care generic oncology costs (Round et al 2015[130])	£138,092	£130,343	£7,749
Cost of palliative care support team	£130,948	£137,487	£6,538
Cost of alloSCT	£130,942	£137,138	£6,197
AE utility decrement: Peripheral neuropathy	£137,223	£131,212	£6,011
Cost of Mepilex large sheet dressings	£131,289	£137,146	£5,856

Abbreviations: AE, adverse event; BEX, bexarotene; BV, brentuximab vedotin; CTCL, cutaneous t-cell lymphoma; NMB, net monetary benefit; OWSA, one way sensitivity analysis; PAS, patient access scheme; SCT, stem cell transplant.

B.3.8.3 Scenario analysis

The scenario analyses conducted within the model are presented in Table 54 to Table 58. Due to the number of scenario analyses conducted, these have been grouped by the area they relate to. These scenarios aim to assess the impact of key assumptions on the cost-effectiveness results within the model. As there is the potential for the results of the model to change magnitude and quadrant, both an ICER and NMB at £30,000 per QALY are given for scenarios.

Table 54: Scenario analyses – Model settings, including PAS

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£134,218
Reduce starting age to 50	BV Dominates	£146,655
Reduce discount rate to 1.5%	BV Dominates	£153,265
Reduce time horizon to 5 years (not recommended – not all patients are dead)	BV Dominates	£121,139
Reduce time horizon to 10 years (not recommended – not all patients are dead)	BV Dominates	£121,052
Reduce time horizon to 25 years (not recommended – not all patients are dead)	BV Dominates	£132,652

Abbreviations: BV, brentuximab vedotin; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life year.

Table 55: Scenario analyses – Survival curves, including PAS

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£134,218
Use of Kaplan-Meier data directly for PFS	BV Dominates	£127,530
Exponential curve fits for PFS	BV Dominates	£151,734
Lognormal fit to PC OS curve (used for both brentuximab vedotin and PC)	BV Dominates	£133,464
Independent curve fits to observed data (Weibull for brentuximab vedotin)	BV Dominates	£135,386

Abbreviations: BV, brentuximab vedotin; ITT, intention to treat; NMB, net monetary benefit; OS, overall survival; PAS, patient access scheme; PC, physician's choice; PFS, progression-free survival; QALY, quality adjusted life year.

Table 56: Scenario analyses – Stem Cell Transplant, including PAS

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£134,218
Percentage of eligible patients reduced to 20%	BV Dominates	£98,563
Cost of alloSCT reduced to £65,154 (NHS Reference costs)	BV Dominates	£140,906
Use of Weibull curve for alloSCT OS	BV Dominates	£136,410
Allow SD patients to receive alloSCT	BV Dominates	£110,12
Duration of induction therapy prior to alloSCT reduced to 12 weeks (mean induction in HL)	BV Dominates	£136,688
Duration of induction therapy prior to alloSCT increased to 24 weeks (median TOT in ALCANZA	BV Dominates	£131,786
alloSCT rate of 5% in both arms	BV Dominates	£58,723

Abbreviations: alloSCT, allogeneic stem cell transplant; BV, brentuximab vedotin; DFS, disease free survival; NMB, net monetary benefit; OS, overall survival; PAS, patient access scheme; QALY, quality adjusted life year; SD, stable disease.

Table 57: Scenario analyses – Utility data, including PAS

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£134,218
Observed utility data	BV Dominates	£134,151
Exclude AE disutilities	BV Dominates	£134,557
PPS utility of 0.5 (on and off treatment)	BV Dominates	£129,917
PPS utility of 0.5 on treatment, 0.38 off treatment	BV Dominates	£135,084

Abbreviations: AE, adverse event; BV, brentuximab vedotin; NMB, net monetary benefit; PAS, patient access scheme; PPS, post-progression survival; QALY, quality adjusted life year

Table 58: Scenario analyses – Costs, including PAS

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£134,218
Exclude AE costs	BV Dominates	£134,252
Reduce PFS cost by 20%	BV Dominates	£138,285
Reduce post progression active therapy cost by 20%	BV Dominates	£131,703
Reduce end-stage care cost by 20%	BV Dominates	£102,842
Exclude CD30 testing	BV Dominates	£134,253

Abbreviations: AE, adverse event; BV, brentuximab vedotin; NMB, net monetary benefit; PAS, patient access scheme; PFS, progression-free survival; QALY, quality adjusted life year

B.3.8.4 Summary of sensitivity analyses results

The results of sensitivity analyses demonstrate that in all cases brentuximab vedotin is expected to provide a large increase in LYs and QALYs, whilst reducing overall NHS cost – every scenario has brentuximab vedotin as being dominant. The model is most sensitive to the proportion of patients achieving an alloSCT, end-stage care cost, and PPS utility. However, even when varying these parameters between their lower and upper bounds, brentuximab vedotin remains dominant.

Probabilistic analysis indicated that there is a 91.38% likelihood of brentuximab vedotin being cost-effective at a willingness to pay threshold of £30,000 per QALY.

B.3.9 *Subgroup analysis*

Not applicable. The group investigated in the model (advanced patients with CTCL), are a subgroup of the licensed population. This is discussed extensively in Section B.1.3.3 and Section 3.2.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

Internal validation

The model was quality-assured by the internal processes of the external economists who developed the economic model. In these processes, an economist not involved in model building reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modeling errors and questioning of the assumptions based upon the Phillips checklist.[131]

External validation

Section B.3.3.6 describes the validation undertaken for clinical parameters within the economic model.

No published papers were identified considering the cost-effectiveness of brentuximab vedotin in this population. Therefore, cost-effectiveness results could not be compared with other literature. However, to sense check the results the cost-effectiveness outcomes have been presented to UK experts.

On the conceptual level, the cost-effectiveness analysis was reviewed at a clinical Advisory Board, with curve fits and approaches to the modelling of both PFS and OS reviewed by clinicians for appropriateness. AlloSCT-related inputs were reviewed by experts in the transplant field based in the UK transplant centres with the largest volume of patients and who were therefore using Stanford Protocol based alloSCT for advanced CTCL. End-stage care resource use (once synthesised), was validated by an expert in the field. The model can therefore be said to reflect UK clinical practice.

B.3.11 *Interpretation and conclusions of economic evidence*

We have developed a health economic model to assess the cost-effectiveness of brentuximab vedotin compared with PC for the treatment of advanced CTCL in the UK setting. To date, no published data exist on the cost-effectiveness of any intervention in this population. Therefore, it is not possible to validate or compare these results with previous analyses. The modelled population from ALCANZA matches the anticipated use of brentuximab vedotin in the UK: the treatment of adults with advanced CTCL. In line with the NICE scope, established clinical management without brentuximab vedotin (reflected by PC) is the only comparator to brentuximab vedotin for this indication.

The main strengths of the evaluation are as follows:

- Clinical data for brentuximab vedotin and PC were derived directly from the ALCANZA phase III randomised trial which employed robust and stringent endpoints to evaluate response to treatment.
- Complete or almost complete data was available for ToT and PFS outcomes from the ALCANZA trial, limiting the uncertainty associated with long-term extrapolations
- Parametric survival curves that were used to extrapolate efficacy data were selected based on a comprehnsive assessment of goodness of fit, internal and external validations. Scenario analyses explore the impact of other data sources and parametric curve choices
- The modelled clinical trial results are in line with published literature, in particular a large UK based retrospective study of outcomes.[13] This provides reassurance that the benefits of brentuximab vedotin are being accurately modelled
- The utility data are derived from the ALCANZA trial directly using the EQ-5D-3L. No mapping involved which reduces the uncertainty associated with these estimates
- Extensive sensitivity and scenario analyses explore the assumptions and uncertainty associated with different data sources and methods. The analyses conducted demonstrate that in all scenarios, brentuximab vedotin is dominant – an important finding given the uncertainty around some inputs in what is a rare disease with fewer than 100 patients anticipated to be treated each year.

The main limitations associated with the cost-effectiveness analysis are:

- High uncertainty due to immature OS data with less than 30% events
- Cost-effectiveness analysis was done based on the advanced CTCL subgroup. Although highly clinically relevant, this was not a pre-specified group and therefore not significant and smaller sample size
- The efficacy results of pcALCL and MF are pooled together due to sample size
- Appropriateness of HRQOL data measured by EQ5D for CTCL patients. Furthermore, an inability to fully map Skindex-29 scores to EQ-5D
- Scarce if any literature on economic and QOL and resource data therefore to fill gaps best efforts were made to collect this data from local sources
- Overall, a lot of the assumptions and inputs are based on clinical opinion and local evidence generation (protocols, questionnaire) versus published literature

Conclusion

Brentuximab vedotin provides a valuable quality of life improving treatment option for many patients with a painful, disfiguring, and life limiting condition. For some patients it increases the prospect of being bridged to the only potentially curative intervention in advanced CTCL (i.e. alloSCT). Overall, this analysis has shown that brentuximab vedotin is a cost-effective (and indeed cost saving) option for the treatment of advanced CTCL. As such, we would suggest that it should be recommended by NICE for routine use on the NHS.

B.4. References

1. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol*. 2011;29(18):2598-2607.
2. Kim YH, Horwitz SM, Talpur R, et al. Exploring new meaningful endpoints for CTCL clinical trials in two phase II studies of brentuximab vedotin (BV) in patients with mycosis fungoides (MF) and Sézary syndrome (SS). Presented at: 3rd World Congress of Cutaneous Lymphomas, 2016; Columbia University, New York, NY, USA.
3. Demierre MF, Tien A, Miller D. Health-related quality-of-life assessment in patients with cutaneous T-cell lymphoma. *Arch Dermatol*. 2005;141(3):325-330.
4. Prince HM, Reinhard D, Whittaker S, et al. Patient-reported outcomes and quality of life in patients with cutaneous T cell lymphoma: results from the Phase 3 ALCANZA study. Presented at: International Conference on Malignant Lymphoma (ICML), 2017; Lugano, Switzerland.
5. Wright A, Wijeratne A, Hung T, et al. Prevalence and severity of pruritus and quality of life in patients with cutaneous T-cell lymphoma. *J Pain Symptom Manage*. 2013;45(1):114-119.
6. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/guidance/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed 6 December, 2017.
7. ADCETRIS (brentuximab vedotin). Summary of Product Characteristics, Takeda Austria GmbH, Linz, Austria, 2017.
8. Zinzani PL, Bonthapally V, Huebner D, et al. Panoptic clinical review of the current and future treatment of relapsed/refractory T-cell lymphomas: Cutaneous T-cell lymphomas. *Crit Rev Oncol Hematol*. 2016;99:228-240.
9. Wilcox RA. Cutaneous T-cell lymphoma: 2016 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2016;91(1):151-165.
10. Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood*. 2000;95(12):3653-3661.
11. Scarisbrick JJ. New drugs in cutaneous T-cell lymphomas. *Curr Opin Oncol*. 2016;28(5):384-389.
12. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785.
13. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol*. 2010;28(31):4730-4739.
14. Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. *Biol Blood Marrow Transplant*. 2009;15(8):982-990.
15. Palanicawandar R, Morris S, Lozano-Cerrada S, et al. Allogeneic stem cell transplantion for advanced cutaneous T-cell lymphoma with minimal-intensity conditioning. Presented at: EORTC, 2017.
16. Trautinger F, Eder J, Assaf C, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome - Update 2017. *Eur J Cancer*. 2017;77:57-74.
17. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. *Eur J Cancer*. 2006;42(8):1014-1030.
18. Beynon T, Selman L, Radcliffe E, et al. 'We had to change to single beds because I itch in the night': a qualitative study of the experiences, attitudes and approaches to coping of patients with cutaneous T-cell lymphoma. *Br J Dermatol*. 2015;173(1):83-92.
19. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. *Cancer*. 2006;107(10):2504-2511.
20. Selman LE, Beynon T, Radcliffe E, et al. 'We're all carrying a burden that we're not sharing': a qualitative study of the impact of cutaneous T-cell lymphoma on the family. *Br J Dermatol*. 2015;172(6):1581-1592.
21. Sampogna F, Frontani M, Baliva G, et al. Quality of life and psychological distress in patients with cutaneous lymphoma. *Br J Dermatol*. 2009;160(4):815-822.
22. Beynon T, Radcliffe E, Child F, et al. What are the supportive and palliative care needs of patients with cutaneous T-cell lymphoma and their caregivers? A systematic review of the evidence. *Br J Dermatol*. 2014;170(3):599-608.

23. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007;110(2):479-484.
24. Kim YH, Tavallaee M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. *J Clin Oncol*. 2015;33(32):3750-3758.
25. Kim YH. SY58: Cutaneous lymphoma - treatment strategies: Managing MF and SS with allogeneic HSCT. Available at: https://pdfs.semanticscholar.org/presentation/7968/26d2eeba8f156189cb33de8bcd3ca134a0fc.pdf. Accessed Jun 1, 2018.
26. Public Health England. Registration of Cutaneous T-Cell Lymphoma (CTCL) in England: National Cancer Registration and Analysis Services Short Report 2016397. Available at: http://www.ncin.org.uk/view?rid=3275. Accessed March 5, 2018.
27. Siegel RS, Pandolfino T, Guitart J, Rosen S, Kuzel TM. Primary cutaneous T-cell lymphoma: review and current concepts. *J Clin Oncol*. 2000;18(15):2908-2925.
28. Misery L. Chapter 8: Pruritus in cutaneous T-cell lymphomas. In: Carstens E, Akiyama T, eds. *Itch: Mechanisms and treatment*. Boca Raton, FL: CRC Press/Taylor & Francis; 2014.
29. Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. *N Engl J Med*. 2004;350(19):1978-1988.
30. Liu HL, Hoppe RT, Kohler S, et al. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. *J Am Acad Dermatol*. 2003;49(6):1049-1058.
31. Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Blood*. 2011;118(15):4024-4035.
32. Willemze R, Hodak E, Zinzani PL, et al. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 Suppl 6:vi149-154.
33. Horwitz SM, Olsen EA, Duvic M, Porcu P, Kim YH. Review of the treatment of mycosis fungoides and sezary syndrome: a stage-based approach. *J Natl Compr Canc Netw*. 2008;6(4):436-442.
34. Hughes CF, Khot A, McCormack C, et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sezary syndrome: a comparative study of systemic therapy. *Blood*. 2015;125(1):71-81.
35. Abbott RA, Aldridge C, Dojcinov S, Piguet V. Incidence of primary cutaneous T-cell lymphoma in Wales. *Br J Dermatol*. 2013;169(6):1366-1367.
36. Takeda UK data on file. Document number: Takeda/UK/DOF/003 Other claims. 2018.
37. European Medicines Agency. Public summary of opinion on orphan designation: Brentuximab vedotin for the treatment of cutaneous T-cell lymphoma (EMA/COMP/923105/2011 Rev.2). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2012/02/WC500121705.pdf.
38. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007;110(6):1713-1722.
39. Cutaneous Lymphoma Foundation. A patient's guide to understanding cutaneous lymphoma. Available at: https://www.clfoundation.org/sites/default/files/Guide%20Final_0.pdf. Accessed June 20, 2017.
40. Pinter-Brown L, Porcu P, Horwitz S, Lessin S. Understanding Treatment Options in Cutaneous Lymphoma: A Supplement to the Patient's Guide to Understanding Cutaneous Lymphoma. Cutaneous Lymphoma Foundation. Available at: http://flipbook.clfoundation.org/Understanding_Treatment_Options_in_Cutaneous_Lymphoma/files/assets/common/downloads/publication.pdf.
41. Demierre MF, Ferzli P, Miller D. Measuring HRQOL in patients with cutaneous T-cell lymphoma undergoing therapy with oral bexarotene and extracorporeal photopheresis. *Arch Dermatol*. 2007;143(5):659-661.
42. Latkowski JA, Heald P. Strategies for treating cutaneous T-cell lymphoma: part 1: remission. *J Clin Aesthet Dermatol*. 2009;2(6):22-27.
43. Alberti-Violetti S, Talpur R, Schlichte M, Sui D, Duvic M. Advanced-stage mycosis fungoides and Sezary syndrome: survival and response to treatment. *Clin Lymphoma Myeloma Leuk*. 2015;15(6):e105-112.

44. Woo DK, Jones CR, Vanoli-Storz MN, et al. Prognostic factors in primary cutaneous anaplastic large cell lymphoma: characterization of clinical subset with worse outcome. *Arch Dermatol*. 2009;145(6):667-674.
45. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol*. 2003;139(7):857-866.
46. Scarisbrick JJ, Prince HM, Vermeer MH, et al. Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sezary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. *J Clin Oncol*. 2015;33(32):3766-3773.
47. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet*. 2017;390(10094):555-566.
48. Garau M, Shah KK, Mason AR, et al. Using QALYs in cancer. *Pharmacoeconomics*. 2011;29(8):673-685.
49. Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. *Dermatol Clin*. 2012;30(2):231-236, xiii.
50. EuroQoL Research Foundation. EQ-5D-3L. Available at: https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/. Accessed June 20, 2017.
51. Gu T, Raspa S, Tsang Y, Drake W. The burden of illness of mycosis fungoides cutaneous T-cell lymphoma: A retrospective cohort study of a commercially insured population in the US. Presented at: ISPOR 19th Annual European Congress, October 29-31, 2016; Vienna, Austria.
52. Orlowska D, Selman LE, Beynon T, et al. "It's a traumatic illness, traumatic to witness." A qualitative study of the experiences of bereaved family caregivers of patients with cutaneous T-cell lymphoma. *Br J Dermatol*. 2018.
53. Vij A, Duvic M. Prevalence and severity of pruritus in cutaneous T cell lymphoma. *Int J Dermatol*. 2012;51(8):930-934.
54. Bouwhuis SA, Gonzalez-Arriaza HL, McEvoy MT, Davis MD. Physical and mental health survey of 20 patients with Sezary syndrome using the medical outcomes study 36-item short-form health survey. *J Eur Acad Dermatol Venereol*. 2003;17(6):724-725.
55. Expert opinion.
56. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55(3):490-500.
57. Lim HW, Collins SAB, Resneck JS, Jr., et al. The burden of skin disease in the United States. *J Am Acad Dermatol*. 2017;76(5):958-972 e952.
58. Ricci E, Cortelazzo S, Krulichova I, Garattini L. Direct medical costs of mycosis fungoides in specialized Italian hospital departments. *Haematologica*. 2005;90(2):270-272.
59. Gu T, Raspa S, Tsang Y, Drake W. The burden of illness of mycosis fungoides cutaneous T-cell lymphoma: A retrospective cohort study of a commercially insured population in the U.S. *Value Health*. 2016;19:A608.
60. Tsang Y, Gu T, Sharma G, et al. Healthcare resource utilization, costs of care, and treatment of mycosis fungoides cutaneous T-cell lymphoma patterns in a large managed care population: a retrospective US claims-based analysis. *J Dermatolog Treat*. 2018:1-7.
61. Poletick B. Wound management in cutaneous T-cell lymphoma (CTCL). *Loss, Grief, & Care*. 1996;7(3/4):181-184.
62. Whittaker SJ, Marsden JR, Spittle M, et al. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol*. 2003;149(6):1095-1107.
63. Whittaker S. Presentation: British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018.
64. National Institute for Health and Care Excellence (NICE). Improving outcomes for people with skin tumours including melanoma: Cancer service guideline [CSG8]. Available at: https://www.nice.org.uk/guidance/csg8. Accessed June 18, 2018.
65. Sokolowska-Wojdylo M, Florek A, Zaucha JM, et al. Polish Lymphoma Research Group Experience With Bexarotene in the Treatment of Cutaneous T-Cell Lymphoma. *Am J Ther*. 2016;23(3):e749-756.
66. Abbott RA, Whittaker SJ, Morris SL, et al. Bexarotene therapy for mycosis fungoides and Sezary syndrome. *Br J Dermatol*. 2009;160(6):1299-1307.
67. National Comprehensive Cancer Network. NCCN Guidelines Version 2.2017: T-cell lymphomas.
68. TARGRETIN® (bexarotene). Summary of product characteristics. Eisai Ltd., Hertfordshire, United Kingdom. Mar 2006.

69. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol*. 2001;19(9):2456-2471.
70. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. *Arch Dermatol*. 2001;137(5):581-593.
71. Izu R, Yanguas, I., Servitje, O., Ortiz, P., de Misa, R.F., Estrach, T., Monsalvez, V., . Experience with bexarotene in cutaneous T-cell lymphoma: A collaborative study of the Spanish Group of Cutaneous Lymphoma. *Journal of the American Academy of Dermatology.* 2014;70(5):Suppl.1; AB123.
72. Rupoli S, Canafoglia L, Goteri G, et al. Results of a prospective phase II trial with oral low-dose bexarotene plus photochemotherapy (PUVA) in refractory and/or relapsed patients with mycosis fungoides. *European Journal of Dermatology*. 2016;26(1):13-20.
73. Rupoli S, Goteri G, Micucci G, et al. Time to next treatment analysis for early and advanced stages of mycosis fungoides /sezary syndrome treated with bexarotene and puva in combination. *Haematologica*. 2017;102 (Supplement 2):466-467.
74. Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa-2b (Intron-A) for patients with cutaneous T-cell lymphoma. *Cancer*. 2007;109(9):1799-1803.
75. Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. *J Am Acad Dermatol*. 1996;34(4):626-631.
76. Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. *J Am Acad Dermatol*. 2003;49(5):873-878.
77. Nikolaou V, Siakantaris MP, Vassilakopoulos TP, et al. PUVA plus interferon alpha2b in the treatment of advanced or refractory to PUVA early stage mycosis fungoides: a case series. *J Eur Acad Dermatol Venereol*. 2011;25(3):354-357.
78. Jidar K, Ingen-Housz-Oro S, Beylot-Barry M, et al. Gemcitabine treatment in cutaneous T-cell lymphoma: a multicentre study of 23 cases. *Br J Dermatol*. 2009;161(3):660-663.
79. Duvic M, Talpur R, Wen S, et al. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. *Clin Lymphoma Myeloma*. 2006;7(1):51-58.
80. Pellegrini C, Stefoni V, Casadei B, et al. Long-term outcome of patients with advanced-stage cutaneous T cell lymphoma treated with gemcitabine. *Ann Hematol*. 2014;93(11):1853-1857.
81. Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. *J Clin Oncol*. 2012;30(33):4091-4097.
82. Quereux G, Marques S, Nguyen JM, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. *Arch Dermatol*. 2008;144(6):727-733.
83. Morris S, Scarisbrick J, Frew J, et al. The Results of Low-Dose Total Skin Electron Beam Radiation Therapy (TSEB) in Patients With Mycosis Fungoides From the UK Cutaneous Lymphoma Group. *Int J Radiat Oncol Biol Phys*. 2017;99(3):627-633.
84. Beitinjaneh A, Saliba RM, Medeiros LJ, et al. Comparison of survival in patients with T cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. *Biol Blood Marrow Transplant*. 2015;21(5):855-859.
85. Lowsky R, Takahashi T, Liu YP, et al. Protective conditioning for acute graft-versus-host disease. *N Engl J Med*. 2005;353(13):1321-1331.
86. The Pharmaceutical Benefits Advisory Committee (PBAC). Vorinostat, capsule, 100 mg. Public Summary Document - March 2011 [online]. Available at: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2011-03/pbac-psd-vorinostat-march11. Accessed March 6, 2018.
87. Horwitz SM, Scarisbrick J, Dummer R, Duvic M, Kim YH. Updated analyses of the international, open-label, randomized, phase 3 ALCANZA study: Longer-term evidence for superiority of brentuximab vedotin versus methotrexate or bexarotene for CD30-positive cutaneous T-cell lymphoma. Presented at: American Society of Hematology (ASH), December 9-12, 2017; Atlanta, GA, USA.
88. Takeda UK data on file. Document number: Takeda/UK/DOF/001 CSR and protocol claims. 2018.
89. Takeda UK data on file. Document number: Takeda/UK/DOF/002 severe baseline characteristic analysis. 2018.
90. Mathieu S, Ram-Wolff C, Quereux G, et al. The French experience of treatment of cutaneous T cell lymphoma with brentuximab vedotin: a series of 32 cases. Presented at: 3rd World Congress of Cutaneous Lymphomas, October 26-28, 2016; Columbia University, NY, USA.

91. Duvic M, Tetzlaff MT, Gangar P, et al. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. *J Clin Oncol*. 2015;33(32):3759-3765.
92. Phillippo DM, Ades AE, Dias S, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. Available at: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/Population-adjustment-TSD-FINAL.pdf.
93. Quaglino P, Maule M, Prince HM, et al. Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium. *Ann Oncol*. 2017;28(10):2517-2525.
94. Targretin® (bexarotene). Full Prescribing Information, Eisai Inc., Woodcliff Lake, NJ, 2011.
95. Prince HM, Gautam A, Kim YH. Brentuximab vedotin: targeting CD30 as standard in CTCL. *Oncotarget*. 2018;9(15):11887-11888.
96. European Medicines Agency. Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137126.pdf. Accessed Apr 25, 2017.
97. Scarisbrick J. Updated analyses of the international, open-label, randomised, phase 3 ALCANZA study: Longer-term evidence for superiority of brentuximab vedotin versus methotrexate or bexarotene for CD30-positive cutaneous T-cell lymphoma. Presented at: EORTC, 2017.
98. Prinsen CA, Lindeboom R, de Korte J. Interpretation of Skindex-29 scores: cutoffs for mild, moderate, and severe impairment of health-related quality of life. *J Invest Dermatol*. 2011;131(9):1945-1947.
99. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30(18):2190-2196.
100. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30(18):2183-2189.
101. Takeda. Press release: European Commission approves ADCETRIS® (brentuximab vedotin) for CD30-positive cutaneous T-cell lymphoma after one prior systemic therapy – providing an innovative treatment option to patients. Available at: https://www.takeda.com/newsroom/newsreleases/2018/european-commission-approves-adcetris-brentuximab-vedotin-for-cd30-positive-cutaneous-t-cell-lymphoma-after-one-prior-systemic-therapy-providing-an-innovative-treatment-option-to-patients/. Accessed June 15, 2018.
102. Roberge D, Muanza T, Blake G, et al. Does adjuvant alpha-interferon improve outcome when combined with total skin irradiation for mycosis fungoides? *Br J Dermatol*. 2007;156(1):57-61.
103. SMC submission.
Economic analysis of extracorporeal photopheresis compared with standard treatment for cutaneou s T-cell lymphoma and chronic graft versus host disease. Available at: http://www.nospg.nhsscotland.com/wp-content/uploads/2010/05/25-10_iii_c_ECP-for-CTCL-GVHD-economic-costings-for-NSCAG.pdf. Accessed June 15, 2018.
104. Bisaccia E, Gonzalez J, Palangio M, Schwartz J, Klainer AS. Extracorporeal photochemotherapy alone or with adjuvant therapy in the treatment of cutaneous T-cell lymphoma: a 9-year retrospective study at a single institution. *J Am Acad Dermatol*. 2000;43(2 Pt 1):263-271.
105. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma - Final scope. Available at: https://www.nice.org.uk/guidance/gid-ta10201/documents/final-scope. Accessed June 15, 2018.
106. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0089910/. Accessed 24 August 2016.
107. Collett D. Modelling Survival Data in Medical Research. *Texts in Statistical Science*. Second ed. Florida, USA: Chapman & Hall; 2003:24-25.
108. Greenwood M. *The natural duration of cancer. Reports on Public Health and Medical Subjects.* Vol 33. London: Her Majesty's Stationery Office; 1926.
109. Office for National Statistics. National life tables, UK: 2014-2016. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2014to2016. Accessed June 18, 2018.
110. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
111. Dobrez D, Cella D, Pickard AS, Lai JS, Nickolov A. Estimation of patient preference-based utility weights from the functional assessment of cancer therapy - general. *Value Health*. 2007;10(4):266-272.
112. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. *Oncologist*. 2007;12 Suppl 1:4-10.
113. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35(11):1095-1108.

114. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. *Leuk Lymphoma*. 2015;56(6):1839-1845.
115. National Institute for Health and Care Excellence (NICE). Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. TA524. June 2018.
116. National Institute for Health and Care Excellence (NICE). Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma. TA478. October 2017.
117. van Agthoven M, Vellenga E, Fibbe WE, Kingma T, Uyl-de Groot CA. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease. a prospective randomised trial. *Eur J Cancer*. 2001;37(14):1781-1789.
118. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes*. 2010;8:50.
119. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer*. 2006;95(6):683-690.
120. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. 2008;6:84.
121. Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. *Pharmacoeconomics*. 2001;19(11):1091-1102.
122. Hatswell AJ, Porter J, Lee D, Hertel N, Latimer NR. The cost of costing treatments incorrectly: errors in the application of drug prices in economic evaluation due to failing to account for the distribution of patient weight. *Value Health*. 2016;19(8):1055-1058.
123. Monthly Index of Medical Specialities (MIMS). Brentuximab vedotin - Adcetris. Available at: https://www.mims.co.uk/drugs/cancer/antineoplastics/adcetris. Accessed 01 May 2018.
124. Monthly Index of Medical Specialities (MIMS). Methotrexate. Available at: https://www.mims.co.uk/drugs/cancer/antineoplastics/methotrexate-oral-solution. Accessed 24 May 2018.
125. Monthly Index of Medical Specialities (MIMS). Bexarotene - Targretin. Available at: https://www.mims.co.uk/drugs/cancer/antineoplastics/targretin. Accessed 24 May 2018.
126. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU technical support document 19: Partitioned survival analysis for decision modelling in health care: A critical review. Available at: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/06/Partitioned-Survival-Analysis-final-report.pdf. Accessed June 15, 2018.
127. Debals-Gonthier M, Siani C, Faucher C, et al. Cost-effectiveness analysis of haploidentical vs matched unrelated allogeneic hematopoietic stem cells transplantation in patients older than 55 years. *Bone Marrow Transplant*. 2018.
128. Statista. Euro (EUR) to British pound sterling (GBP) average annual exchange rate from 1999 to 2017. Available at: https://www.statista.com/statistics/412806/euro-to-gbp-average-annual-exchange-rate/. Accessed June 15, 2018.
129. Curtis LA, Burns A. Unit Costs of Health and Social Care 2017. Personal Social Services Research Unit. Available at: https://kar.kent.ac.uk/65559/40/65559_rep_UCR-2017-v13finalKAR.pdf. Accessed June 18, 2018.
130. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliat Med*. 2015;29(10):899-907.
131. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment*. 2004;8(36).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Addendum of updated evidence for the consideration of the NICE Appraisal Committee

Submitted by Takeda UK Ltd.

Submitted 21st November 2018

File name	Version	Contains confidential information	Date
Addendum – Brentuximab vedotin for CD30+ CTCL ID1190	**1.0**	**Yes**	**21 November 2018**

List of Tables

List of Figures

Table of Contents

List of Abbreviations

Abbreviation	Definition
alloSCT	Allogeneic stem cell transplant
AIC	Akaike Information Criterion
BAD	British Association of Dermatologists
BIC	Bayesian Information Criterion
BV	Brentuximab vedotin
CR	Complete response
CTCL	Cutaneous T-cell lymphoma
DFS	Disease-free survival
EORTC	European Organisation for Research and Treatment of Cancer
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
MF	Mycosis fungoides
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PC	Physician’s choice
PFS	Progression-free survival
pcALCL	Primary cutaneous anaplastic large cell lymphoma
PR	Partial response
QALY	Quality-adjusted life year
RIC	Reduced-intensity conditioning
SS	Sézary syndrome
TSEB	Total skin electron beam therapy
UKCLG	United Kingdom Cutaneous Lymphoma Group

1. Executive summary

In June 2018, Takeda submitted to NICE a dossier that summarised the clinical and cost effectiveness of brentuximab vedotin (BV) for the treatment of CD30-positive cutaneous T-cell lymphoma (CTCL). The focus of this submission was advanced CTCL patients, which matches the positioning of BV within the recently updated British Association of Dermatologists (BAD) and UK Cutaneous Lymphoma Group (UKCLG) guidelines for the management of CTCL.[1] In line with these guidelines, after treatment with either BV or its comparator (methotrexate or bexarotene), patients can go on to receive an allogeneic stem cell transplant (alloSCT) if they are eligible and have achieved a sufficient response to therapy or, on progression, can go on to one of the so-called *Category B* systemic therapies.

To inform clinical outcomes following alloSCT, the original submission used real-world evidence from the London supra-regional centre for CTCL patients who had undergone an alloSCT. This data was first presented by Dr. Palanicawandar at the 2017 EORTC annual Cutaneous Lymphoma conference, and it showed the outcomes for CTCL patients who received either the historical intensive induction protocol prior to alloSCT (n=22) or the now preferred minimally intensive (Stanford) protocol prior to alloSCT (n=18).[2] In the latter group that followed the Stanford protocol, the observed 1-year and 5-year OS rates were about 80% and 55%, respectively. Current UK practice is to use the Stanford protocol.

During the 2018 EORTC Annual Cutaneous Lymphoma Meeting, Dr Stephen Morris of Guy's Cancer Centre, London presented an update that included not only a longer follow-up period for the original patient cohort described by Palanicawandar 2017[2] but also included outcomes for advanced CTCL patients who had undergone alloSCT at five other centres in the UK[3]. This update included outcome data for a total of 53 advanced CTCL patients, 22 of whom received the historical intensive induction protocol prior to alloSCT while the remaining 31 patients followed the Stanford protocol. Hence, the updated dataset includes both a longer follow-up and also more patients than the original dataset. [redacted], despite the addition of more patients and patients from centres other than London. This is encouraging and adds both validity and robustness to the original single-centre results. [redacted]

This Addendum includes the post-alloSCT clinical outcome data presented recently by Dr Morris and also shows the updated cost-effectiveness results derived by updating the existing health economic model with this new and expanded dataset. This Addendum is accompanied by an updated health economic model (file name: *"CTCL NICE model_alloSCT update.xlsm"*). The results show that the cost-effectiveness of BV is improved further by the inclusion of these updated post-alloSCT clinical outcomes data within the model. This updated evidence has been submitted for review by NICE, the Evidence Review Group and ultimately the Appraisal Committee. We believe this data is more robust than that provided earlier and hence should be used by the Committee for decision-making purposes.

2. Updated indirect and mixed treatment comparisons

2.1 Overview

Based on the UK Cutaneous Lymphoma Group (CLG) and British Association of Dermatology (BAD) guidelines for cutaneous T-cell lymphoma (CTCL) and clinical input on the management of CTCL across the UK, the model structure was developed to allow eligible patients to receive an allogeneic stem cell transplant (alloSCT). Eligibility for alloSCT was based on underlying patient characteristics including age, comorbidities and patient preference and, whether patients have received a sufficiently deep response with a bridging agent, defined as either a partial response (PR) or a complete response (CR).[1] Patients who did not achieve a good enough response or who were ineligible for an alloSCT transitioned to a post-progression state and were then assumed to receive *Category B* agents, namely chemotherapy.

To inform the outcomes following alloSCT, the original submission dossier used real-world evidence from the London supra-regional centre of CTCL patients undergoing alloSCT as presented by Dr. Ranuka Palanicawandar of the Hammersmith hospital, London at the 2017 EORTC annual cutaneous lymphoma (CL) conference.[2] The results of the original data are presented in section 2.1.1 of this addendum. For ease of reference, the original data presented by Dr Palanicawandar will be referred to as data cut 1 throughout the addendum.

An update to this data was recently presented by Dr Stephen Morris of Guy's Cancer Centre, London at the 2018 EORTC conference which includes longer follow-up and a larger number of patients across multiple centres, including the London supra-regional network on which the original data was based on. Background on the updated data is presented in section 2.1.2 of this addendum and the results of the updated analysis are presented in this addendum.[3] For ease of reference, the original data presented by Dr Morris will be referred to as data cut 2 throughout the addendum.

The outcomes following transplant, both overall survival (OS) and progression free survival (PFS) have been updated using the 2018 multi-centre data as presented by Dr Morris, with updated results reported below. Survival analyses have been repeated with data cut 2 and associated parametric curves implemented within the existing economic model. This addendum aims to describe the new data cut and the outcomes of the re-run analyses, as well as show the potential impact of this data on the cost-effectiveness of BV. Please note there were no changes in the proportion of patients bridging to a transplant nor the methods used for these statistical analyses compared with those reported in the original submission dossier (Section B.2.4), dated 19th June 2018, therefore, only the updated results are presented in this addendum.

2.1.1 Allogeneic Stem Cell Transplantation (alloSCT) in CTCL in the UK

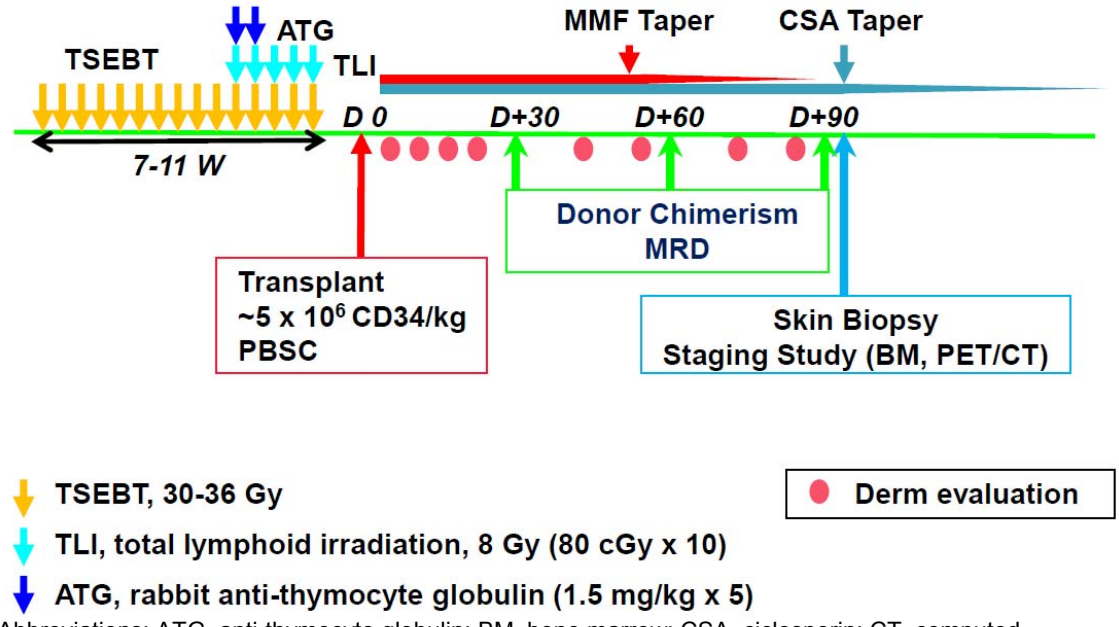
[redacted]

[redacted]

Despite the potentially positive impact of alloSCT on survival, its use in the NHS has been modest to date due to the inability of currently available agents to provide sufficient response rates to enable patients to quality for transplant (i.e. achieving at least a PR with systemic therapy prior to alloSCT).[4] [redacted]

Due to the sepsis-prone nature of patients with CTCL and the associated symptom burden, alloSCT for CTCL is conducted using a different conditioning regimen than for other diseases. Transplants performed in the UK and in other international centres for CTCL use a reduced-intensity conditioning (non-myeloablative) regimen called the Stanford Protocol, composed of TSEB in the weeks leading up to the procedure followed by conditioning with anti-thymocyte globulin (ATG) and total nodal lymphoid irradiation (Figure 1).[7] This combination is highly immunosuppressive, but has a lower risk of neutropenia than standard conditioning, which is a key consideration given that CTCL patients are highly prone to infections.[7, 8]

Figure 1. Stanford protocol for reduced-intensity conditioning[7, 9]



Abbreviations: ATG, anti-thymocyte globulin; BM, bone marrow; CSA, ciclosporin; CT, computed tomography; MMF, mycophenolate mofetil; MRD, minimal residual disease; PBSC, peripheral blood stem cell; PET, positron emission tomography; TSEBT, total skin electron beam therapy.

The most relevant data on alloSCT outcomes in the UK at the time of the original submission was a single-centre study by Palanicawandar 2017 of alloSCT in minimal-intensity conditioning in advanced CTCL patients (n=18, median age, 47 years). This data showed 1- and 5-year OS rates of approximately 80% and 55%, respectively.[2] Clinicians were expecting these outcomes to further improve with maturing data and with better patient selection of those eligible for an alloSCT. This has not been supported by the Morris 2018

update on the original data set and supplemented by data from additional centres across the UK, as presented below.

Despite alloSCT being the only realistic hope for a cure for advanced-stage CTCL [redacted] UK clinical experts attribute this low uptake of alloSCT to the poor PR and CR rates that can be achieved with current treatment regimens. Although alloSCT eligibility is restricted by age, co-morbidities and the ability to find a suitable donor, with modern advancements in matching and alloSCT procedures, as discussed in the company submission, UK clinical experts estimate that 40% of all patients with CTCL who achieve a PR or better could undergo an alloSCT in the UK.

2.1.2 Background on the alloSCT outcomes data sources

Original Data: Palanicawandar 2017 (referred to as datacut-1)

The key clinical Palanicawandar inputs associated with the alloSCT pathway were informed by real-world evidence obtained from the London supra-regional centre using the minimal intensity Stanford Protocol regimen, as presented during the EORTC Annual Cutaneous Lymphoma Meeting in October 2017 by Dr Palanicawandar, a transplant specialist based in the Hammersmith hospital, London.[2]

The London supra-regional centre for CTCL is St. John's Institute of Dermatology in Guy's and St. Thomas'; however all transplants from the centre are performed at the Hammersmith hospital, whose outcomes data are used in this submission. The data presented showed both the outcomes with the historically intensive induction protocol (n=22) and with the minimally intensive alloSCTs conducted according to the Stanford protocol for CTCL (n=18).[2]

The study looked at overall survival (OS) and disease-free survival (DFS) following an alloSCT as measures of outcomes. The analysis presented in the company submission focused on the minimally intensive conditioning regimen via the Stanford protocol only as this reflects current practice across the UK. In this study of alloSCT with minimal-intensity conditioning in advanced CTCL, patients (n=18, median age, 47 years), 1- and 5-year OS rates of approximately 80% and 55%, respectively, were observed.[2]

Updated Data: Morris 2018 (referred to as datacut-2)

An update of the original presentation from Palanicawandar was presented during the 2018 EORTC Annual Cutaneous Lymphoma Meeting. The updated data is a longer follow-up of the original patient group described by Palanicawandar 2017 and also now includes the outcomes of advanced CTCL patients with following alloSCT from other centres in the UK.[3] The following centres contributed to the updated data:

- Guys and St Thomas', London
- University Hospitals, Birmingham
- Oxford University Hospitals, Oxford
- Imperial College Healthcare, London

- Addenbrooke's NHS Trust, Cambridge
- Belfast Health and Social Care Trust, Belfast, Northern Ireland

This retrospective review included patients with advanced MF and SS (stage IIB to IVB), in line with the brentuximab vedotin requested population. The review looked at 53 patients who were treated with alloSCT from 2003 to 2018 in the UK. [redacted]

The main end-points in the Morris 2018 data presentation were OS, PFS, non-relapse mortality and relapse incidence. . The presentation of the updated result did not include DFS as presented by Palanicawandar in the previous year. Furthermore, although the OS data in the update was separated into the Historical intensive (i.e. Protocol 1) and Minimal-intensity (i.e. Protocol 2) conditioning regimens, only the pooled analysis was presented for PFS.

It is important to note that DFS and PFS are not interchangeable and have different defining criteria. The definitions of both are as follows:

- Progression-free survival (PFS): The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse.

- Disease-free survival (DFS): The length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. This measure requires patients to achieve a complete response (CR) to fulfil the criteria.[11]

2.1.3 Overall Survival following alloSCT (update of Section B.2.9.4.1)

Overall survival outcomes from the original data cut (Palanicawandar 2017) and the updated, expanded data cut (Morris 2018) are presented in Figure 2 and

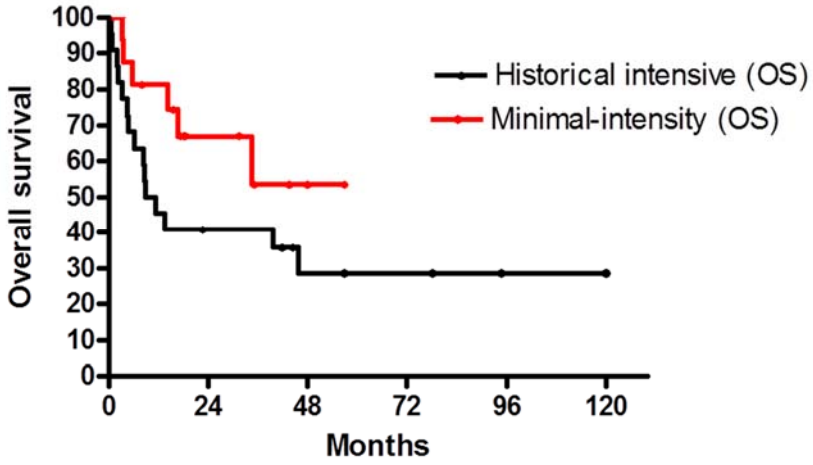
Figure 7, respectively. Both data sets separate the outcomes of the historically intensive conditioning regimen (referred to as Protocol 1 in Morris, 2018) and the minimal-intensity Stanford protocol (referred to as Protocol 2 in Morris, 2018).

The Morris 2018 data confirms the outcomes shown in 2017 as the OS curve is more or less consistent across both data cuts. The addition of more patients and other centres across the UK [redacted]

[redacted]

The analysis of parametric survival models for both the original and updated data are presented in Section 3.1.1.

Figure 2: Kaplan-Meier for OS after alloSCT, London supra-regional centre data (Palanicawandar, EORTC 2017)[9]



Abbreviations: OS, overall survival; alloSCT, allogeneic stem cell transplant.

Figure 3: Kaplan-Meier for OS after alloSCT, UK multi-centre data (Morris, EORTC 2018)

2.1.4 Disease-free and Progression-free survival following alloSCT (update of Section B.3.3.4.2)

Figure 4 below presents the observed DFS Kaplan-Meier curve following a minimal intensity alloSCT (i.e Stanford Protocol) from the London supra-regional centre.

Visual inspection of the observed data indicates that, if a patient were to relapse, this would likely be in the first twelve months following the alloSCT (represented by the gradient of the Kaplan-Meier curve between 0–12 months). This is in line with observed transplant outcomes for other lymphomas across different conditioning regimens (e.g., HL and ALCL). Following the initial year post-transplant, very few events are observed. Therefore, patients who have not relapsed are likely to remain in the disease-free state with a long-term remission (represented by the leveling out of the Kaplan-Meier curve after 12 months).

[redacted]

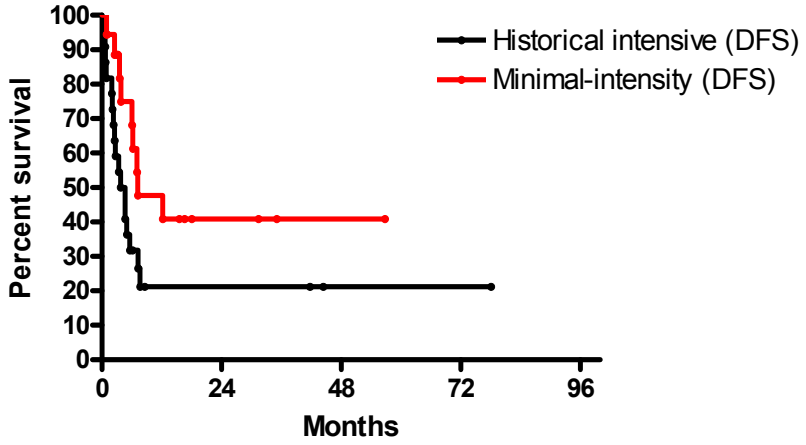
Please note that as the Morris 2018 data includes both the outcomes of Protocol 1 and Protocol 2 as well as data from other centers across the UK which may have longer follow-up, the overall length of the follow-up is significantly extended, [redacted] As data was not available on PFS for all advanced CTCL patients in Morris 201 (data cut 2), the combined Protocol 1 and Protocol 2 outcome data for PFS was used for the model input. This is a highly conservative estimate as demonstrated by Figure 6 which separated PFS by type of CTCL (MF or SS) and also by induction with either Protocol 1 or Protocol 2. [redacted] On balance, Takeda felt it was a more conservative approach to use the combined Protocol 1 and Protocol 2 data for all CTCL patients shown in Figure 5 as opposed to the data in Figure 6

As noted in Section 2.1.2 the Palanicawandar and Morris data present a different measurement outcome for disease control. Palanicawandar (data cut 1), reported DFS, meanwhile Morris 2018 (data cut 2), reported PFS. We were informed by the investigators that both endpoints were collected, but at this time, we only have data on the information that has been presented. As DFS is a more stringent endpoint (requiring a CR at or prior to transplant), the KM curve is expected to report a worse outcome for disease control than the PFS endpoint. This is due to the fact that patients who have achieved a very good partial response but who do not have 100% clearance of the skin would be considered as an event under the definition of DFS but would however be considered as responding under the definition of PFS. Clinical consultation has stated that PFS and not DFS is a more clinically relevant measurement of disease control in CTCL because CRs are very rare. The use of DFS would omit a large proportion of patients who have achieved clinically meaningful disease control and those who may require minimal radiotherapy following their alloSCT but are otherwise considered to be in remission.

The use of PFS instead of DFS is also consistent with the measurement of disease control reported in ALCANZA and used in other parts of the model; therefore Takeda believes it is a more relevant measurement to include in the economic model.

The analysis of parametric survival models for both the original and updated data are presented in Section 3.1.2.

Figure 4: Kaplan-Meier for DFS after alloSCT, London supra-regional centre data (Palanicawandar, EORTC 2017)9



Abbreviations: DFS, disease-free survival; SCT, stem cell transplant

Figure 5: Kaplan-Meier for PFS after alloSCT, UK multi-centre data, Protocol 1 and Protocol 2 combined (Morris 2018, EORTC)

Figure 6: Kaplan-Meier for PFS after alloSCT separated by MF and SS, UK multi-centre data (Morris 2018, EORTC)

3. Updated outcome analysis

3.1 Clinical parameters and variables (update of Section B.3.3)

In order to analyse the alloSCT outcome data, KM curves were digitised, and parametric survival models (PSMs) fitted to the derived pseudo patient level data of both the Palanicawandar 2017 and Morris 2018 data sets. As a reminder the Palanicawandar 2017 data is referred to as datacut1 and the Morris 2018 data is referred to as data cut 2 throughout the analysis presented below, The generated KMs with fitted PSMs for OS and PFS/DFS for each data-cut are presented below in

Figure 7 to Figure 10.

In accordance with recommendations from the NICE Decision Support Unit (DSU)[12], parametric survival models (PSMs) were fitted to allow extrapolation of immature survival outcomes. Six parametric distributions (exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma) were examined. All curves were fitted using the statistical software package R using the flexsurv package.[13, 14] Consistent with previous analyses, generalised gamma curves are not reported here due to poor fit and consistent failure of the models to converge.

The fit of each of the parametric distributions to the KM data was assessed by visual inspection and statistical fit (Akaike information criterion [AIC] and Bayesian information criterion [BIC]). Measures of statistical fit provided an estimate of relative fit of each distribution to the observed KM data. The statistical fit for each PSM for both data-cuts in terms of AIC and BIC are presented in Error! Reference source not found. **and Figure 12: Comparison of DFS and PFS from data cut 1 and data cut 2, respectively**

Table 2.

3.1.1 Overall survival (update of section B.3.3.2.2)

Figure 7 presents the parametric survival models fitted to the original data, data cut 1, Palanicawandar 2017.[2] Figure 8 presents the parametric survival models fitted to the updated data, data cut 2, Morris 2018.[3] A comparison of the OS outcomes from the two data sets can be found on

Figure 9.

Due to the similarity of survival analysis results between data cut 1 and 2 as shown by the analysis presented in

Figure 9, the prior base case survival curve selection of lognormal for OS was maintained.

Figure 7: First data-cut - alloSCT OS - KM curve with fitted PSMs (Palanicawandar, 2017)

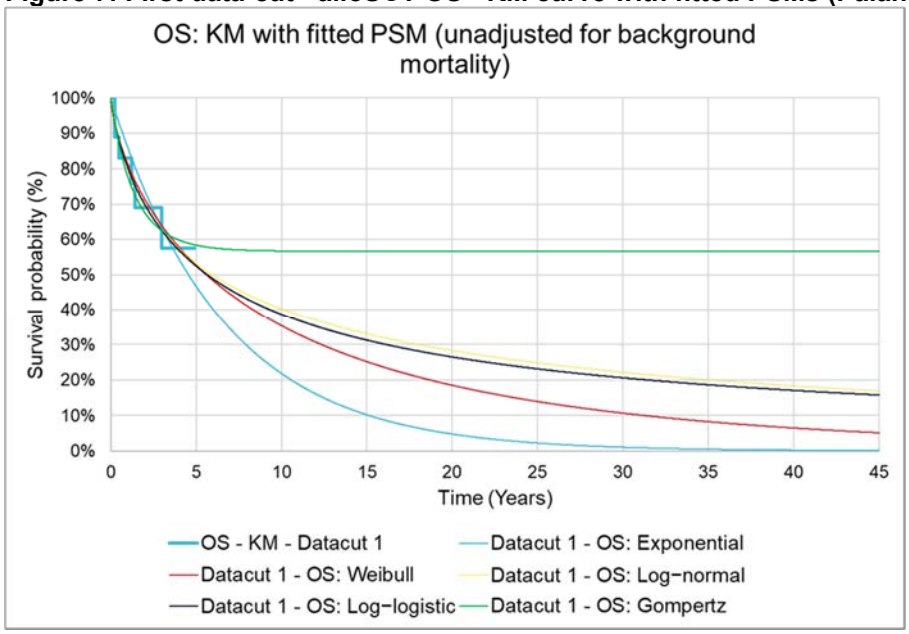


Figure 8: Second data-cut – alloSCT OS – KM curve with fitted PSMs (Morris, 2018)

[redacted]

Figure 9: Comparison of OS from Palanicawandar 2017 (data cut 1) and Morris 2018 (data cut 2)

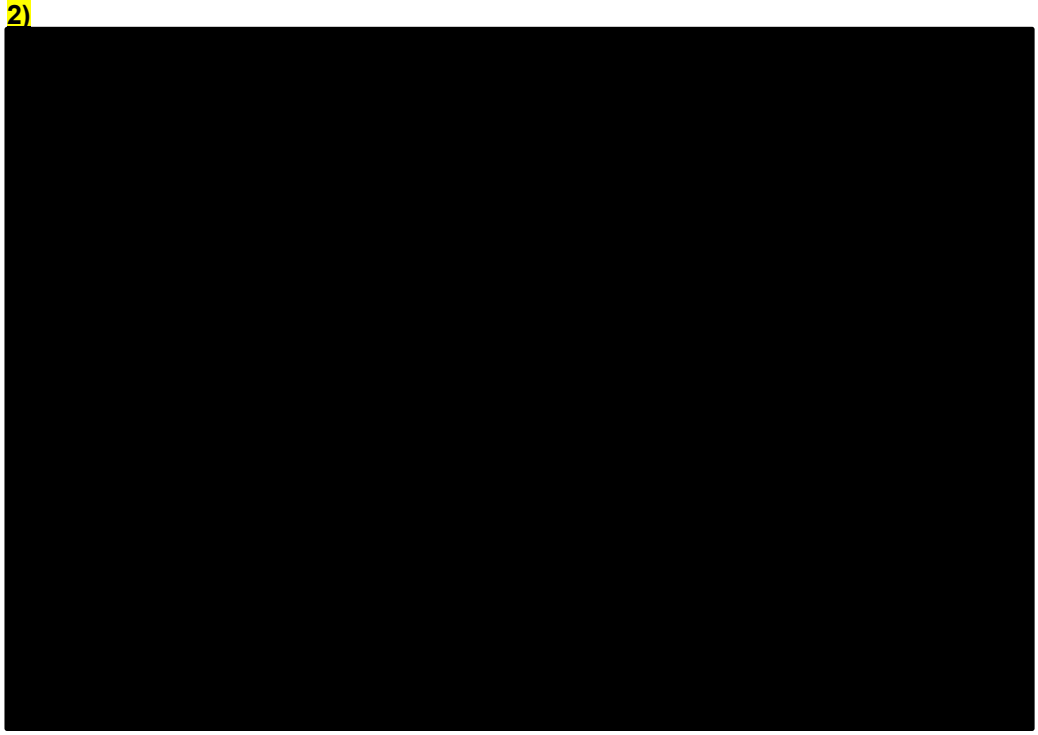


Table 1: Statistical fit of parametric survival models fitted to alloSCT OS

Model	Data-cut 1 (Palanicawandar. 2017)[2]		Data-cut 2 (Morris 2018)[3]	
	OS		OS	
	AIC	BIC	AIC	BIC
Exponential	107	108	196	197
Weibull	108	110	195	198
Gompertz	107	109	191	194
Log-logistic	108	110	194	197
Log-normal	107	109	193	196

Abbreviations: AIC, Akaike information criterion; alloSCT, allogenous stem cell transplant; BIC, Bayesian information criterion; OS, overall survival;

3.1.2 Disease-free and progression-free survival following alloSCT (update of Section B.3.3.2.1)

In the first data-cut, DFS data indicated a survival function synonymous with stem cell transplant outcomes, indicating that a proportion of patients had attained a long-term remission, remained disease-free at the last follow-up and may potentially be cured. Data cut 2 with a longer follow-up and more patients further supports the long-term remission shown in data cut1.

As in the original dossier based on data cut 1, the Gompertz curve is the only curve that reflects the decreasing probability of relapse with time reducing over time to a zero

probability (a plateau) for the updated Morris 2018 data (data cut 2). The longer follow-up and larger patient pool, supports the Gompertz curve as the most clinically plausible outcome and the most aligned with expectations in clinical practice (i.e. patients who have not relapsed within 12 months of alloSCT would likely be in long-term remission, with very few events expected beyond this point). This is in line with generally expected outcomes of an alloSCT and has been well documented across different cancers, particularly lymphomas. For this reason, the Gompertz curve was maintained to model PFS after an alloSCT in the base case.

The improvement in outcomes seen in the 2018 data is due to longer follow-up but also to the difference in end-points used to assess disease control. As discussed earlier, DFS as presented in datacut1 is a more stringent endpoint than PFS as presented in data cut2. The difference in disease control outcomes between the two datasets is presented in Figure 12 below. As discussed in Section 2.1.4 above, based on clinical feedback and the nature of CTCL, PFS is regarded as a more relevant measure of disease control for CTCL, this is also in-line with the outcomes data reported in ALCANZA and other sources used in the economic model.

Although the alloSCT data for PFS are immature (median OS not reached) and based on a relatively small sample size, it is reassuring that both datasets support the long-term remission and potential cure for CTCL patients induced by an alloSCT.

Figure 10: First data-cut - SCT DFS - KM curve with fitted PSMs

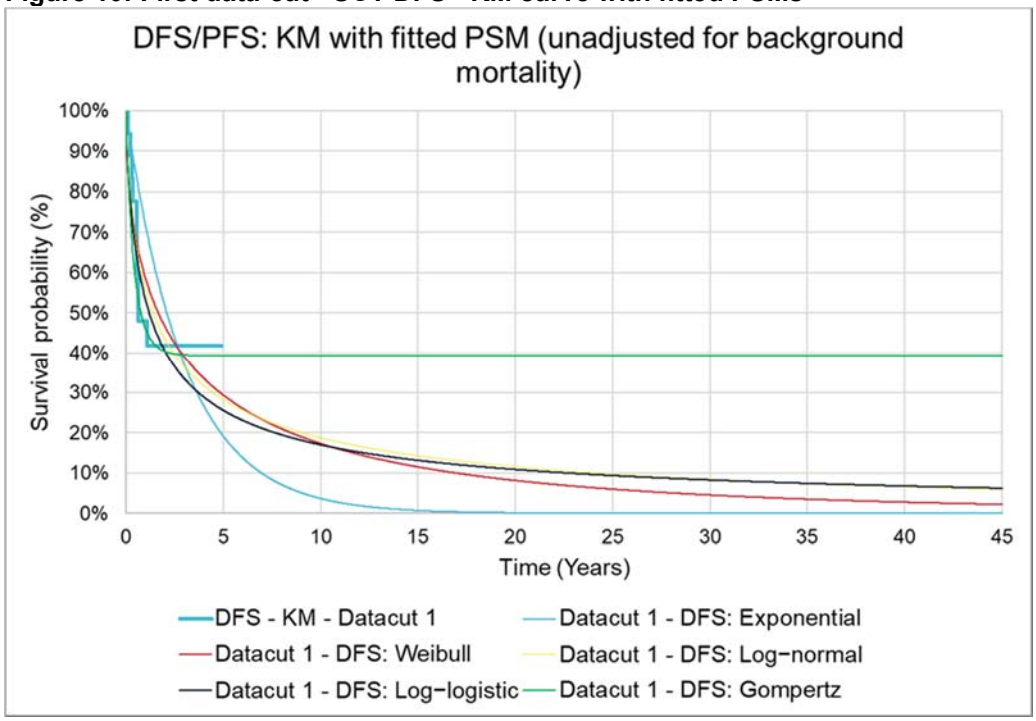


Figure 11: Second data-cut – SCT PFS – KM curve with fitted PSMs

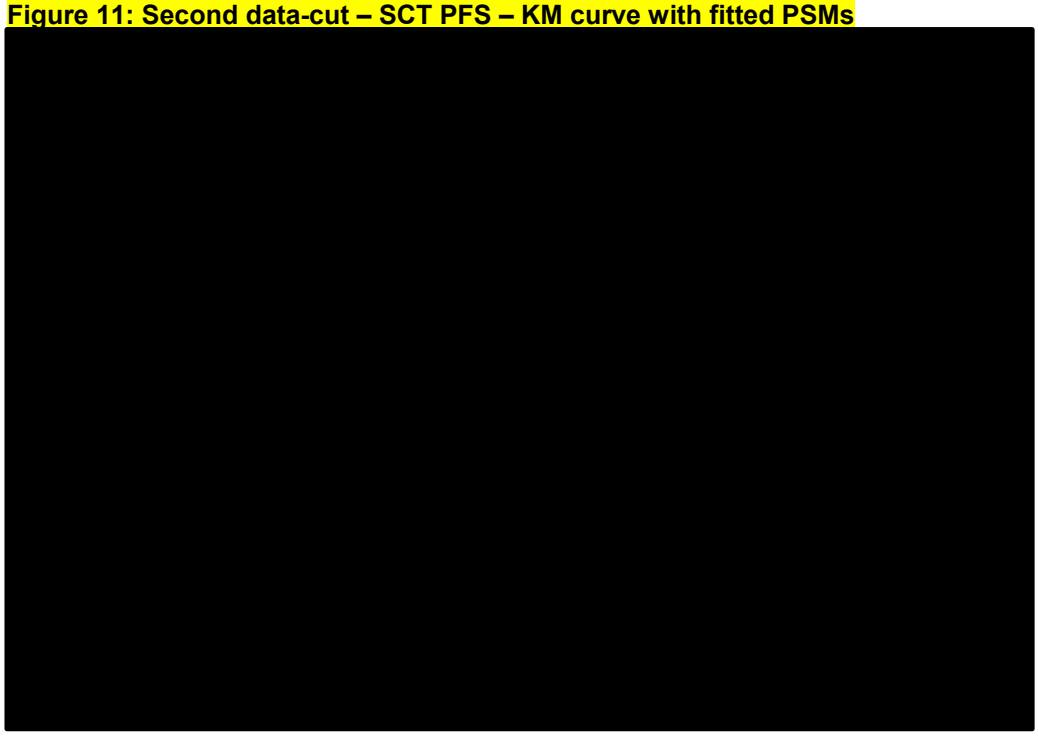


Figure 12: Comparison of DFS and PFS from data cut 1 and data cut 2, respectively

Table 2: Statistical fit of parametric survival models fitted to alloSCT DFS/PFS

Model	Data-cut 1 (Palanicawandar. 2017)[2]		Data-cut 2 (Morris 2018)[3]	
	DFS		PFS	
	AIC	BIC	AIC	BIC
Exponential	107	108	512	514
Weibull	108	110	446	449
Gompertz	107	109	399	403
Log-logistic	108	110	440	444
Log-normal	107	109	436	440

Abbreviations: AIC, Akaike information criterion; alloSCT, allogenous stem cell transplant; BIC, Bayesian information criterion; DFS, disease-free survival; PFS, progression-free survival;

4. Updated cost-effectiveness results

4.1.1 Base-case results (update of Section B.3.7)

4.1.1.1 Base-case incremental cost-effectiveness analysis results (update of Section B.3.7.1)

The base case results from the model for data cut 1 using the Palanicawandar 2017 original data and data cut 2 using the Morris 2018 longer and expanded data are presented in Table 3: Original submission: base case results using Palanicawandar et al. 2017 and

Table 4, respectively.
All results also apply the patient access scheme (PAS) discount for brentuximab vedotin. For application within the updated model all new data are held on the SCT sheet with the control "ctrl_SCTsurvivaldata" used to switch between the first (data cut 1) and second data cuts (data cut 2).

With the latest data cut (data cut 2) and including the PAS discount, brentuximab vedotin provides an additional 1.58 LYs and [redacted] QALYs with a net cost saving of [redacted]. This leads to brentuximab vedotin being dominant –the absence of an ICER can be hard to interpret, so the Net Monetary Benefit (NMB) has also been included in results (using a willingness to pay (WTP) threshold of £30,000 per QALY). The NMB with the updated data is £153,693.

The updated data cut leads to improved outcomes in the brentuximab vedotin pathway compared with the original submission and data cut 1. This is driven by improved outcomes shown in the alloSCT data which leads to an increase in LYs and QALYs for those patients who undergo an alloSCT within the model. Due to the impressive response rates observed with brentuximab vedotin, more patients are expected to be eligible to receive an alloSCT in this pathway compared with physician's choice. Therefore, the updated data has a bigger impact on the brentuximab vedotin arm.

Table 3: Original submission: base case results using Palanicawandar et al. 2017

Treatment	Total			Incremental			Cost per QALY	NMB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
PC	[redacted]	[redacted]	7.23					
BV	[redacted]	[redacted]	8.43	[redacted]	[redacted]	1.20	BV Dominates	£134,218

Key: BV, brentuximab vedotin; LY, life year; NMB, Net-monetary benefit; QALY, quality-adjusted life year.
Note: NMB assumed £30,000

Table 4: Updated results: base case results using Morris et al 2018

Treatment	Total			Incremental			Cost per QALY	NMB
	Costs	QALYs	LYs	Costs	QALYs	LYs		
PC	[redacted]	[redacted]	7.36					
BV	[redacted]	[redacted]	8.93	[redacted]	[redacted]	1.58	BV Dominates	£153,693

Key: BV, brentuximab vedotin; LY, life year; NMB, Net-monetary benefit; QALY, quality-adjusted life year.
Note: NMB assumed £30,000

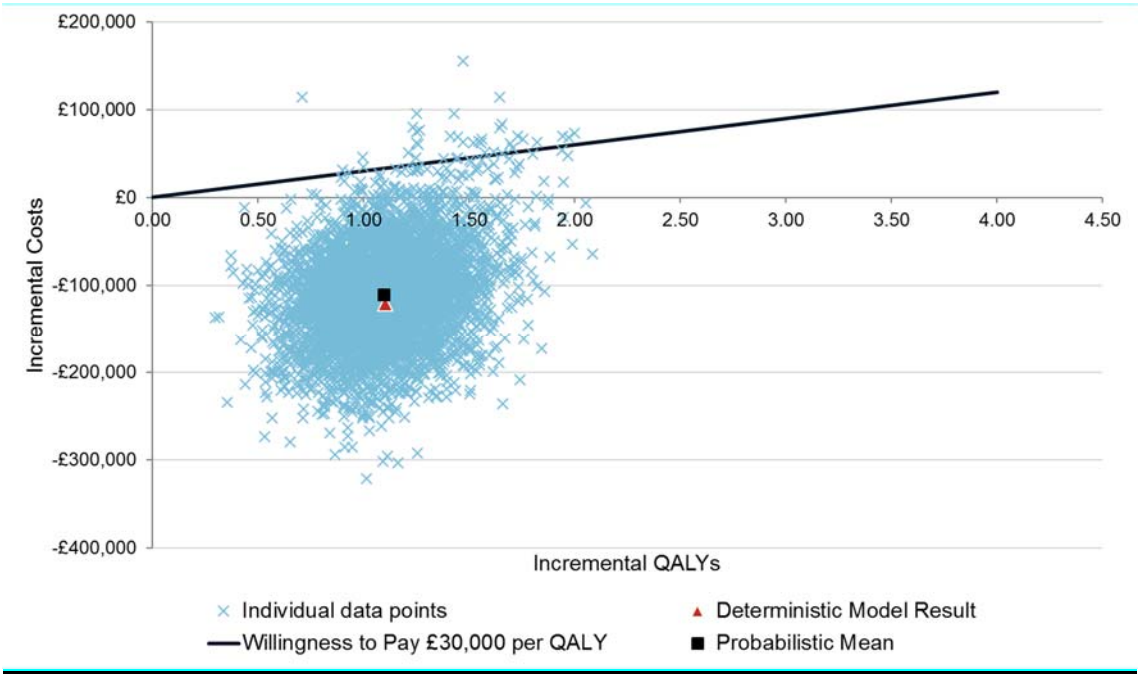
4.1.2 Sensitivity analyses (update of Section B.3.8)

4.1.2.1 Probabilistic sensitivity analysis (update of Section B.3.8.1)

Probabilistic sensitivity analysis (PSA) has been conducted including the updated data cut (data cut 2) and the PAS for brentuximab vedotin. The results of 5,000 PSA iterations are presented in Figure 12 (cost-effectiveness plane) and Figure 13 (cost-effectiveness acceptability curve (CEAC)).

Mean probabilistic incremental QALYs gained from brentuximab vedotin were [redacted] and mean probabilistic incremental costs [redacted]. The resulting probabilistic ICER from 5,000 iterations was dominant, as in the deterministic result. The probabilistic NMB was slightly lower than the deterministic result (£[redacted] vs. £ [redacted], respectively). This is driven by a similar probabilistic incremental QALY but a smaller probabilistic incremental cost (-£ [redacted] vs. -£ [redacted]).

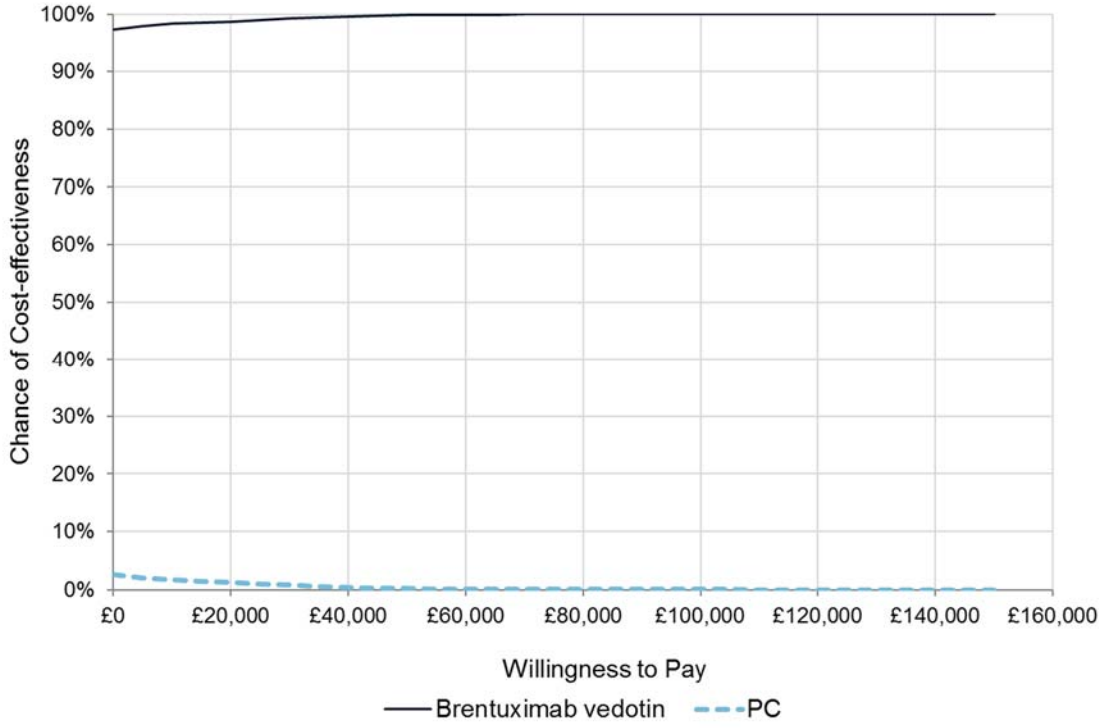
Figure 12: Cost-effectiveness plane from 5,000 iterations including PAS for brentuximab vedotin (update of Figure 56)



Abbreviations: QALY, quality adjusted life year

Based on the PSA iterations, the updated data (data cut 2) and the PAS price for brentuximab vedotin, the CEAC (Figure 13) suggests that there is a 99.22% likelihood of brigatinib being cost-effectiveness at a WTP threshold of £30,000 per QALY. The inclusion of the updated data cut is shown to increase the probability of cost-effectiveness for brentuximab vedotin (99.22% vs. 91.38% in the original submission). This is driven by the improved outcomes observed in data cut 2 for patients that undergo an alloSCT and – as discussed above – due to the impressive response rates of brentuximab vedotin more patients are eligible for transplant in this pathway compared with physician's choice.

Figure 13: CEAC including PAS for brentuximab vedotin (update of Figure 57)



Abbreviations: CEAC, cost-effectiveness acceptability curve; PAS, patient access scheme; PC, physician's choice

4.1.2.2 Deterministic sensitivity analysis (update of Section B.3.8.2)

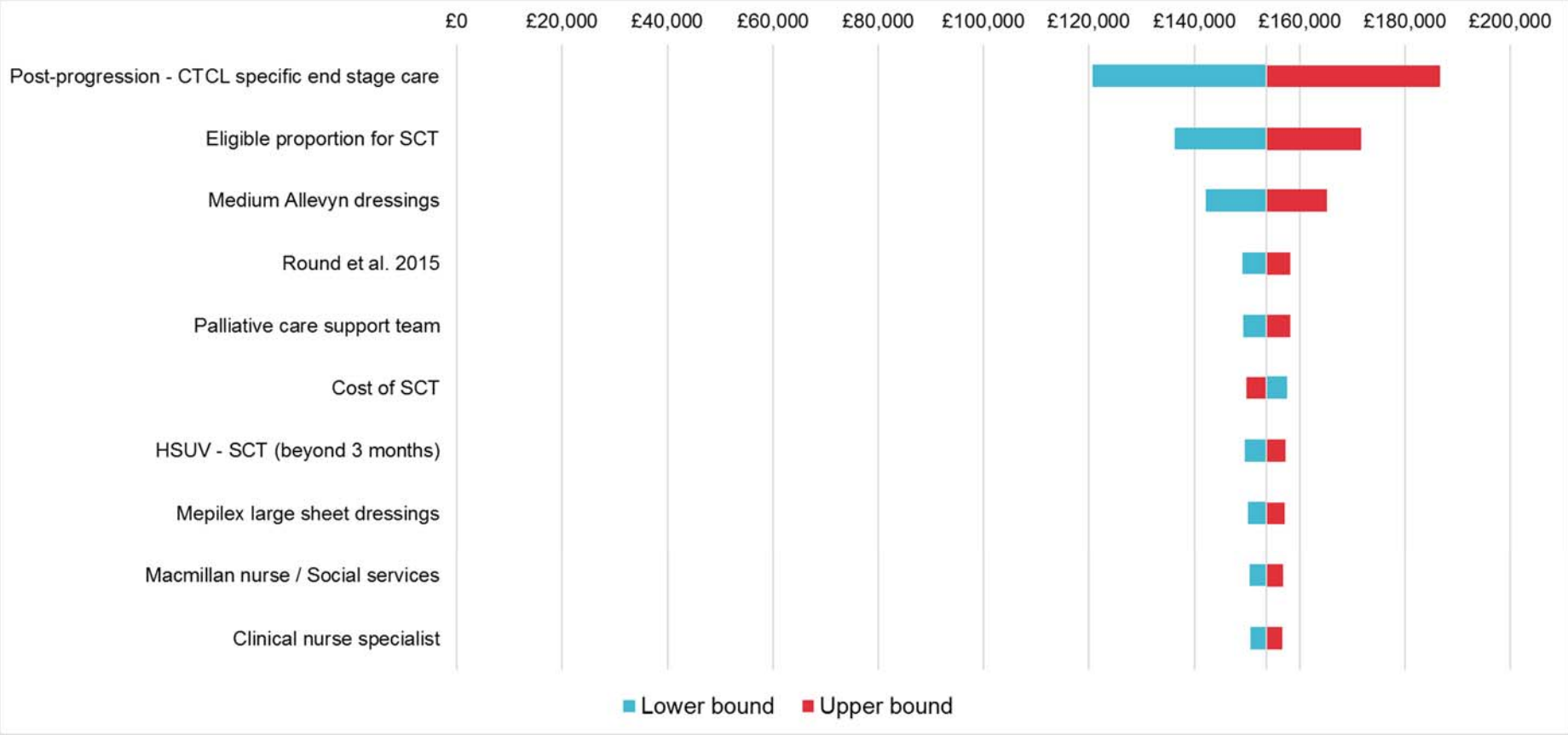
One-way sensitivity analysis (OWSA) has been conducted including the updated data cut (data cut 2) and the PAS for brentuximab vedotin. Upper and lower bound values for parameters were taken from 95% confidence intervals of the assigned distribution. If the required data were unavailable, a standard error of 10% of the mean value was assumed. Distributional information associated with each parameter is presented in the original submission appendices (Appendix P).

Figure 14 presents a tornado diagram with the ten most influential parameters shown in descending order of NMB sensitivity. BV, brentuximab vedotin; CTCL, cutaneous T-cell lymphoma; HSUV, health state utility value; NMB, net monetary benefit; PAS, patient access scheme; SCT, stem cell transplant

Table 5 displays this information in a tabular format. For ease of interpretation, OWSA results were reported using the NMB.

Results showed that the cost associated with the end-stage care health state, the proportion eligible for alloSCT and the cost of medium Allevyn dressings were the most influential on the NMB. However, of all the parameters varied in the OWSA, none result in a negative NBM i.e. brentuximab vedotin was cost-effective in all cases. The NMB is relatively insensitive to all other parameters.

Figure 14: Tornado diagram reported for NMB including PAS for brentuximab vedotin (update of Figure 58)



Abbreviations: BV, brentuximab vedotin; CTCL, cutaneous T-cell lymphoma; HSUV, health state utility value; NMB, net monetary benefit; PAS, patient access scheme; SCT, stem cell transplant

Table 5: Numerical results of OWSA using the NMB including PAS for brentuximab vedotin (update of Table 53)

Parameter	Lower Bound	Upper Bound	Difference
Post-progression - CTCL specific end stage care	£120,727	£186,659	£65,932
Eligible proportion for SCT	£136,216	£171,748	£35,532
Medium Allevyn dressings	£142,211	£165,176	£22,965
Round et al. 2015	£149,185	£158,201	£9,016
Palliative care support team	£149,224	£158,162	£8,938
Cost of SCT	£157,568	£149,819	£7,749
HSUV - SCT (beyond 3 months)	£149,652	£157,297	£7,645
Mepilex large sheet dressings	£150,188	£157,198	£7,010
Macmillan nurse / Social services	£150,554	£156,833	£6,279
Clinical nurse specialist	£150,633	£156,754	£6,121

Abbreviations: CTCL, cutaneous T-cell lymphoma; HSUV, health state utility value; NMB, net monetary benefit; OWSA, one-way sensitivity analysis; PAS, patient access scheme; SCT, stem cell transplant

4.1.2.3 Scenario analysis (update of Section B.3.8.3)

The scenario analyses have been conducted using the updated data (data cut 2) and including the PAS for brentuximab vedotin – results are presented in Table 6 to Table 10. Due to the number of scenarios conducted, the results have been grouped by the area they relate to. These scenarios aim to assess the impact of key assumptions on the cost-effectiveness results within the model. As there is the potential for the results of the model to change magnitude and quadrant, both an ICER and NMB at a WTP threshold of £30,000 per QALY are presented.

The results of the scenario analyses including the updated data (data cut 2) demonstrate that in all cases brentuximab vedotin is expected to provide a large increase in LYs and QALYs, whilst reducing overall NHS cost. The NMBs are consistently higher with the inclusion of the updated data (data cut 2) compared with those presented in the original submission.

Table 6: Scenario analyses – Model settings, including PAS (update of Table 54)

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£153,693
Reduce starting age to 50	BV Dominates	£165,718
Reduce discount rate to 1.5%	BV Dominates	£176,810
Reduce time horizon to 5 years (not recommended – not all patients are dead)	BV Dominates	£132,663
Reduce time horizon to 10 years (not recommended – not all patients are dead)	BV Dominates	£134,487
Reduce time horizon to 25 years (not recommended – not all patients are dead)	BV Dominates	£150,173

Abbreviations: BV, brentuximab vedotin; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life year.

Table 7: Scenario analyses – Survival curves, including PAS (update of Table 55)

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£153,693
Use of Kaplan-Meier data directly for PFS	BV Dominates	£147,006
Exponential curve fits for PFS	BV Dominates	£171,210
Lognormal fit to PC OS curve (used for both brentuximab vedotin and PC)	BV Dominates	£152,940
Independent curve fits to observed data (Weibull for brentuximab vedotin)	BV Dominates	£154,861

Abbreviations: BV, brentuximab vedotin; ITT, intention to treat; NMB, net monetary benefit; OS, overall survival; PAS, patient access scheme; PC, physician's choice; PFS, progression-free survival; QALY, quality adjusted life year.

Table 8: Scenario analyses – Stem Cell Transplant, including PAS (update of Table 56)

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£153,693
Percentage of eligible patients reduced to 20%	BV Dominates	£108,301
Cost of alloSCT reduced to £65,154 (NHS Reference costs)	BV Dominates	£160,382
Use of Weibull curve for alloSCT OS	BV Dominates	£153,688
Allow SD patients to receive alloSCT	BV Dominates	£125,784
Duration of induction therapy prior to alloSCT reduced to 12 weeks (mean induction in HL)	BV Dominates	£156,241
Duration of induction therapy prior to alloSCT increased to 24 weeks (median TOT in ALCANZA	BV Dominates	£151,185
alloSCT rate of 5% in both arms	BV Dominates	£58,723

Abbreviations: alloSCT, allogeneic stem cell transplant; BV, brentuximab vedotin; DFS, disease free survival; NMB, net monetary benefit; OS, overall survival; PAS, patient access scheme; QALY, quality adjusted life year; SD, stable disease.

Table 9: Scenario analyses – Utility data, including PAS (update of Table 57)

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£153,693
Observed utility data	BV Dominates	£153,617
Exclude AE disutilities	BV Dominates	£154,033
PPS utility of 0.5 (on and off treatment)	BV Dominates	£149,053
PPS utility of 0.5 on treatment, 0.38 off treatment	BV Dominates	£154,592

Abbreviations: AE, adverse event; BV, brentuximab vedotin; NMB, net monetary benefit; PAS, patient access scheme; PPS, post-progression survival; QALY, quality adjusted life year

Table 10: Scenario analyses – Costs, including PAS (update of Table 58)

Scenario	Cost per QALY	NMB
Base case results	BV Dominates	£153,693
Exclude AE costs	BV Dominates	£153,727
Reduce PFS cost by 20%	BV Dominates	£170,665
Reduce post progression active therapy cost by 20%	BV Dominates	£151,084
Reduce end-stage care cost by 20%	BV Dominates	£115,454
Exclude CD30 testing	BV Dominates	£153,729

Abbreviations: AE, adverse event; BV, brentuximab vedotin; NMB, net monetary benefit; PAS, patient access scheme; PFS, progression-free survival; QALY, quality adjusted life year

5. Conclusion

Additional data has recently become available to inform clinical outcomes following alloSCT for patients with advanced stage CTCL, treated in the UK [3] This update includes not only a longer follow-up period for the original single-centre patient cohort described in the initial company submission, but also includes outcomes for patients who have undergone alloSCT at five other centres in the UK. The updated dataset includes a total of 53 patients, 22 of whom received the historical intensive induction protocol prior to alloSCT while the remaining 31 patients followed the now UK preferred Stanford protocol. This compares with a total of 40 patients in the original single-centre patient cohort, only 18 of whom had received the Stanford protocol for induction prior to alloSCT.[2]

Hence, the updated dataset includes both a longer follow-up and also more patients than the original dataset. [redacted]

This is encouraging and adds both validity and robustness to the original single-centre results. [redacted]

The existing health economic model has been updated with this new and expanded dataset, and the results show that the cost-effectiveness of BV is improved further by the inclusion of these updated post-alloSCT clinical outcomes data. This updated evidence has been submitted for review by NICE, the Evidence Review Group and ultimately the Appraisal Committee. We believe this data is more robust than that provided earlier and hence should be used by the Committee for decision-making purposes.

6. References

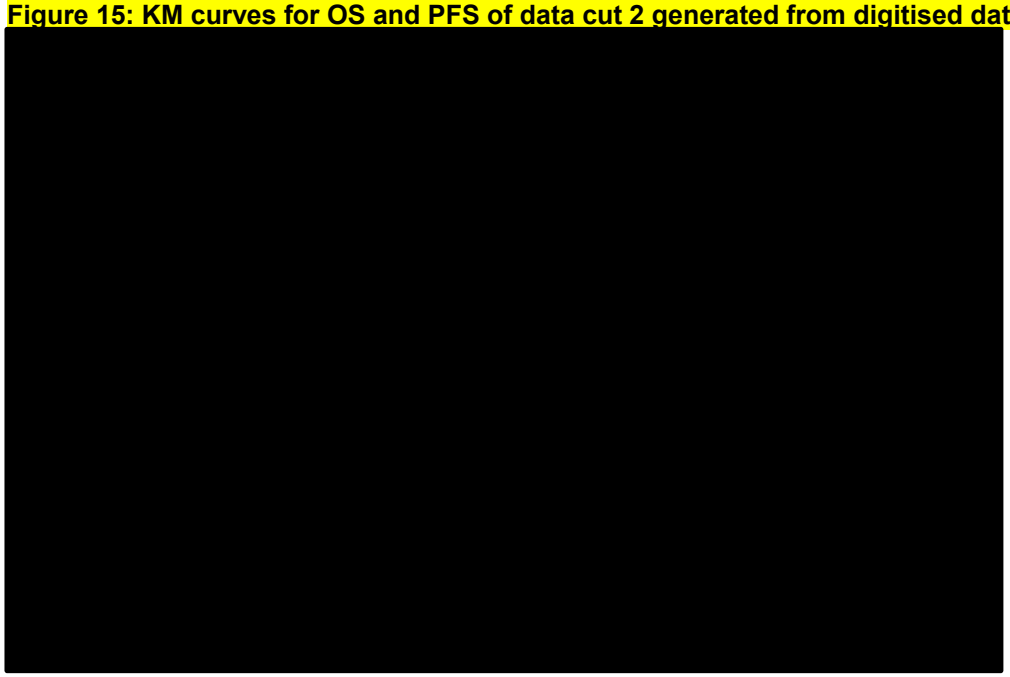
1. Whittaker S, editor Presentation: British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018.
2. Palanicawandar R, Morris S, Lozano-Cerrada S, et al., editors. Allogeneic stem cell transplantion for advanced cutaneous T-cell lymphoma with minimal-intensity conditioning. EORTC; 2017.
3. Morris S. Reduced intensity allogeneic stem cell transplantation for advanced stage mycosis fungoides and Sezary syndrome. A series of 53 patients from the UK. European Journal of Cancer 101 2018;101(Supplement 1):eS40.
4. Beitinjaneh A, Saliba RM, Medeiros LJ, et al. Comparison of survival in patients with T cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. Biol Blood Marrow Transplant. 2015;21(5):855-9.
5. Trautinger F, Eder J, Assaf C, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome - Update 2017. European journal of cancer (Oxford, England : 1990). 2017;77:57-74.
6. Willemze R, Hodak E, Zinzani PL, et al. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2013;24 Suppl 6:vi149-54.
7. Lowsky R, Takahashi T, Liu YP, et al. Protective conditioning for acute graft-versus-host disease. The New England journal of medicine. 2005;353(13):1321-31.
8. Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. The New England journal of medicine. 2004;350(19):1978-88.
9. Kim YH. SY58: Cutaneous lymphoma - treatment strategies: Managing MF and SS with allogeneic HSCT [Available from: https://pdfs.semanticscholar.org/presentation/7968/26d2eeba8f156189cb33de8bcd3ca134a0fc.pdf.
10. Takeda UK data on file. Document number: Takeda/UK/DOF/003 Other claims. 2018.
11. Institute NC. NCI Dictionary of Cancer Terms 2018 [Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/disease-free-survival.
12. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data 2013 [Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0089910/.
13. R Core Team. R: A language and environment for statistical computing 2016 [Available from: https://www.R-project.org/.
14. Jackson C. A platform for parametric survival modeling in R. Journal of Statistical Software. 2016;70(8):1-33.

7. Appendices

7.1 Methods

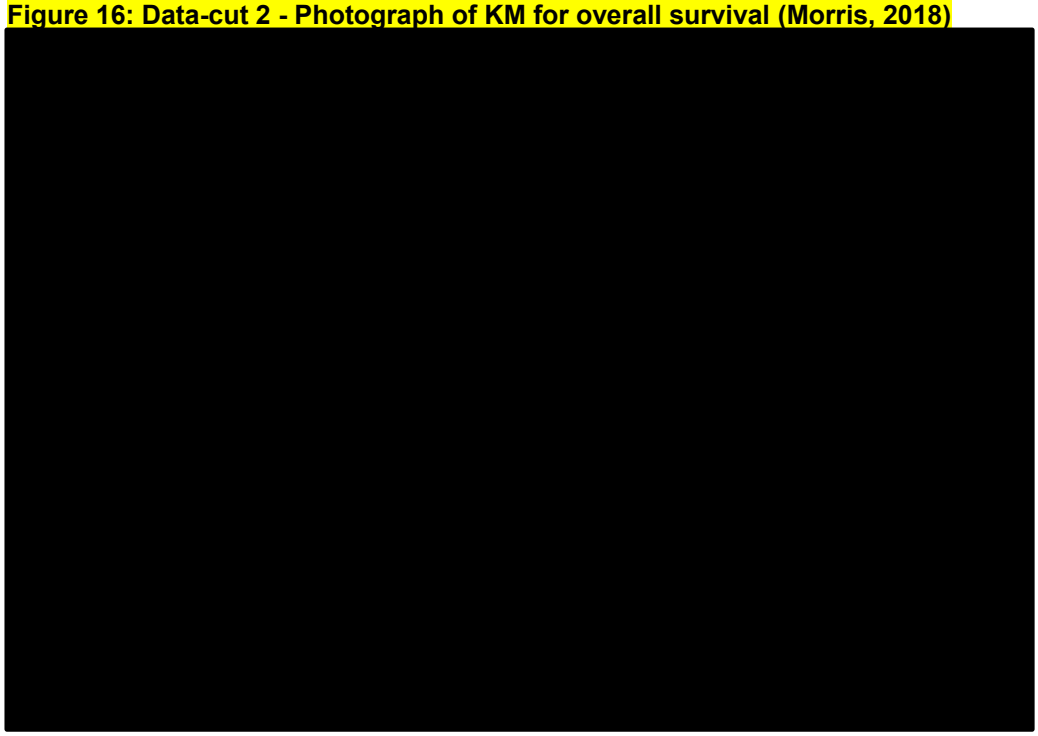
The Kaplan-Meier (KM) curves from data-cut 2 were supplied as photographs of slides that were presented at the EORTC Cutaneous Lymphoma group meeting, 2018. At the time of the model update, only photographs of the EORTC presentation by Dr Morris were available, Dr Morris provided a copy of his presentation shown in Section 2 at a later date, subsequent to the model update being complete. These curves were digitised to generate pseudo patient level data which was then used to estimate survival. PFS data was reported for 53 patients while for OS, data were reported separately for protocol 1 (n=22) and protocol 2 (n=31).

Figure 15: KM curves for OS and PFS of data cut 2 generated from digitised data



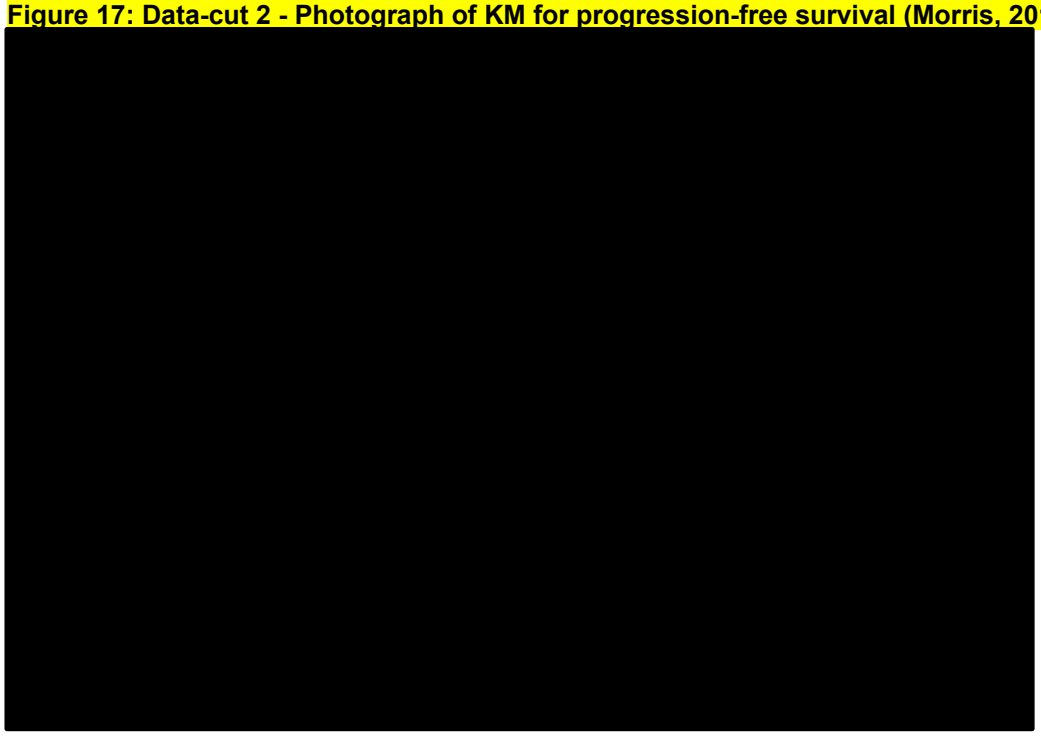
7.2 Source data for Morris, 2018

Figure 16: Data-cut 2 - Photograph of KM for overall survival (Morris, 2018)



Notes: Protocol 1 in black, Protocol 2 in blue

Figure 17: Data-cut 2 - Photograph of KM for progression-free survival (Morris, 2018)



7.3 British Association of Dermatologists and U.K. Cutaneous Lymphoma Group (CLG) guidelines for the management of primary cutaneous lymphomas 2018

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Dear Takeda UK,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRIG), and the technical team at NICE have looked at the submission received on 21st June 2018 from Takada UK. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by 5pm on Monday 6 August 2018. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Lorna Dunning, Technical Lead (lorna.dunning@nice.org.uk). Any procedural questions should be addressed to Stephanie Callaghan, Project Manager (Stephanie.callaghan@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser – Appraisals

On behalf of:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

ALCANZA trial

A1. **Priority question:** The company submission (page 18) notes that: "patients in early stages of the disease (i.e. MF [mycosis fungoides] stage IA–IIA) for the most part will have indolent disease and will therefore not require any systemic therapy". We note that all patients with early stages of MF in the ALCANZA trial have received at least one systemic therapy, as per the inclusion criteria. Please provide the rationale for not restricting eligibility for trial entry to only patients with advanced disease.

A2. **Priority question:** Please replicate Table 10 to include a breakdown of baseline characteristics for (i) patients with early disease and (ii) patients with advanced disease.

A3. **Priority question:** Please provide two additional tables detailing prior systemic therapy by region for (i) patients with early disease and (ii) patients with advanced disease in the ALCANZA trial similar to Supplementary Table S1 in the paper by Prince et al 2017. Please include information on the number of previous systemic therapies received, limit the regions to UK versus non-UK patients and provide data relating to previous immunotherapy (i.e. provide frequencies of patients who received previous interferon alpha [IFN-α], etc).

An example table is provided below.

Previous systemic therapy	**Brentuximab vedotin**		**Physician's choice**	
	UK n=?	**Non-UK n=?**	**UK n=?**	**Non-UK n=?**
Lines of prior systemic therapy				
0				
1	n (%)	n (%)	n (%)	n (%)
2	n (%)	n (%)	n (%)	n (%)
3	n (%)	n (%)	n (%)	n (%)

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

≥4	n (%)	n (%)	n (%)	n (%)
Type of prior systemic therapy				
Bexarotene	n (%)	n (%)	n (%)	n (%)
Chemotherapy	n (%)	n (%)	n (%)	n (%)
Methotrexate	n (%)	n (%)	n (%)	n (%)
Other chemotherapy	n (%)	n (%)	n (%)	n (%)
Oral retinoids	n (%)	n (%)	n (%)	n (%)
Photopheresis	n (%)	n (%)	n (%)	n (%)
Denileukin diftitox	n (%)	n (%)	n (%)	n (%)
Immunotherapy	n (%)	n (%)	n (%)	n (%)
interferon	n (%)	n (%)	n (%)	n (%)
interferon alpha	n (%)	n (%)	n (%)	n (%)
interferon alpha-2a	n (%)	n (%)	n (%)	n (%)
interferon gamma	n (%)	n (%)	n (%)	n (%)
alemtuzumab	n (%)	n (%)	n (%)	n (%)
monoclonal antibodies	n (%)	n (%)	n (%)	n (%)
mogamulizumab	n (%)	n (%)	n (%)	n (%)
HDACi	n (%)	n (%)	n (%)	n (%)
Steroids	n (%)	n (%)	n (%)	n (%)
Other/Unknown	n (%)	n (%)	n (%)	n (%)

A4. **Priority question:** Please provide a table with a breakdown of subsequent anticancer therapies for patients with advanced disease in the ALCANZA trial similar to Supplementary Table S2 to the published paper by Prince et al 2017.

A5. **Priority question:** Please clarify how many patients with advanced disease in each treatment arm of the ALCANZA trial subsequently received an allogeneic stem cell transplant (alloSCT) (i) without receiving any additional systemic therapy following their study treatment; and (ii) at any stage (i.e. having received at least one additional systemic therapy).

A6. Please provide (i) the confidence intervals for the percentage of patients in the advanced disease subgroup achieving objective global response lasting ≥4 months (ORR4) in each treatment arm, and (ii) the percentage difference between patients achieving ORR4 between treatment arms and corresponding 95% confidence interval and p-value.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A7. Figure 15 of the company submission presents subgroup analysis for the primary outcome (ORR4) for the ITT population after 22.9 months follow-up in the ALCANZA trial. Please clarify if all subgroups included in the analysis were pre-specified. If possible, please replicate Figure 15 for patients with advanced disease after 33.9 months follow-up in the ALCANZA trial.

A8. For (i) objective response rate (ORR), and (ii) complete response in the advanced disease patient subgroup, please perform the same statistical tests used to generate p-values for the differences in percentages of patients achieving ORR and complete response in the ITT patient population and provide the results of these statistical tests. Please note these analyses are not expected to be adjusted for multiplicity, as they are post-hoc analysis requests and are for exploratory purposes only.

A9. Please clarify if the validity of the proportional hazards assumption was tested for (i) progression-free survival (PFS) in the ITT population and (ii) time to next treatment in the ITT population? If so, please provide the results of these tests.

A10. The company submission notes that, for time-to-event outcomes, hazard ratios (HRs) and confidence intervals (CIs) were generated (Appendix D, Table 23). Please provide results for the HR for time to subsequent therapy in the advanced disease subgroup. If this is not possible please provide the rationale for its exclusion and clarify whether any testing of proportional hazards was performed.

A11. Please clarify which set of censoring rules was applied for the analysis of PFS in the advanced subgroup population, the US Food and Drug Administration (FDA) criteria, or the European medicines Agency (EMA) criteria.

A12. Adverse event (AE) data are reported by treatment arm for all patients after 22.9 months follow-up in Tables 19 and Table 20 of the company submission. Please provide the equivalent information for patients with advanced disease, preferably after 33.9 months follow-up. If possible, please provide a further breakdown for any Grade and Grade 3+ AEs as in the example table below.

Type of adverse event (AE)	**Brentuximab vedotin (n=66)**		**Methotrexate (n=25)**		**Bexarotene (n=37)**	
	Any Grade	Grade 3+	Any Grade	Grade 3+	Any Grade	Grade 3+
AE 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AE 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AE 3	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Etc	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

A13. Please clarify how pruritis differs to pruritis (generalised) in Table 20 of the company submission.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Data from other studies of brentuximab vedotin

A14. Please clarify whether patients in Kim et al 2015 and Mathieu et al 2016 had CD30-positive cutaneous T-cell lymphoma (CTCL).

A15. Page 97 of the company submission, reports AE in both prospective observational studies to be "Consistent with ALCANZA". However, neutropenia is listed for both observational studies but is not reported for the ALCANZA trial. Duvic et al 2015 also report rash as an AE. Please provide (i) any Grade and (ii) Grade 3+ data (treatment-related AEs) for neutropenia and rash from the ALCANZA trial. Please present the data the same format as the example Table for A12.

Section B: Clarification on cost-effectiveness data

Kaplan-Meier data

B1. **Priority request:** Please provide the Kaplan-Meier (K-M) analyses, listed in a-e below, to the following specifications:

Trial data set: ALCANZA
Format: Use the sample table shown below
Population: Advanced-stage population including all patients lost to follow-up or withdrawing from the trial

a. Time to death from any cause (overall survival [OS]) K-M analysis for the advanced subgroup of patients in the brentuximab vedotin arm of the trial

b. Unadjusted time to death from any cause (OS) K-M analysis for the advanced subgroup of patients in the physician's choice (PC) arm of the trial

c. Time to disease progression or death (PFS) K-M analysis for the advanced subgroup of patients in the brentuximab vedotin arm of the trial, based on investigator assessment

d. Time to disease progression or death (PFS) K-M analysis for the advanced subgroup of patients in the PC arm of the trial, based on investigator assessment

e. Time to study treatment discontinuation K-M analysis for the advanced subgroup of patients, stratified by study treatment.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses
- The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

B2. Please confirm whether utility values were collected for patients:

a. On treatment pre-progression

b. Off treatment pre-progression

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

c. Off treatment progressed

B3. Please provide the mean EQ-5D-3L utility values and the number of patients at each of the time-points collected during the trial, including at baseline, stratified by study treatment and progression status, to the following specifications:

Time point	**PFS**						**PPS**	
	Brentuximab vedotin		**Physician's choice**		**No longer on study treatment**		**All**	
	Mean	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	**N**
Baseline								
Cycle 1								
….								

Section C: Textual clarifications and additional points

C1. Please provide the protocol, trial statistical analysis plan (TSAP) and clinical study report (CSR) for the ALCANZA trial. Please provide the CSR for the median follow-up of 33.9 months if a CSR is available for this data-cut. If not, please provide the CSR for the median follow-up of 22.9 months.

C2. On page 91 of the company submission it is stated that "IFN-α is only one of two systemic treatments recommended for frontline use in patients with advanced-stage CTCL". Please list the other systemic treatment recommended for frontline use in the UK.

C3. On page 43 of the company submission it is stated that results reported in a meta-analysis by Wu et al 2009 showed OS rates at 1 year and 5 years after alloSCT to be 85% and 80%, respectively. However, on page 44, it is stated that

> "The introduction of the Stanford Protocol has improved outcomes from those observed in Wu et al (2009).[14] In this single-centre UK study of alloSCT with minimal-intensity conditioning in advanced CTCL, patients (n=18, median age, 47 years), 1- and 5-year OS rates of approximately 80% and 55%, respectively, were observed.[15]"

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Please clarify how the data reported from the latter study showed improved outcomes to those from the meta-analysis.

C4. Please clarify whether Grade 3/4 AEs reported in Kim et al 2015 are equivalent to “serious” AEs (as stated in the company submission, the last column of Table 26 of Appendix F) or “severe” AEs.

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Response to clarification questions

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute for Health and Care Excellence

6th August 2018

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AlloSCT	Allogenic stem cell transplant
AE	Adverse event
ASCT	Autologous stem cell transplant
BAD	British Association of Dermatology
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CSR	Clinical study report
CTCL	Cutaneous T-cell lymphoma
DFS	Disease free survival
EBRT	External Beam Radiotherapy with Photons or electrons
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporeal photopheresis
EFS	Event free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
ERG	Evidence review group
GvHD	Graft vs. host disease
HR	Hazard ratio
IFN-α	Interferon alpha
IRF	Independent review facility
ITT	Intend to treat
LRIG	Liverpool Reviews and Implementation Group
MF	Mycosis fungiodes
N	Number

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
PD	Progressive disease
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
PROCLIPI	Prospective Cutaneous Lymphoma International Prognostic Index
RIC	Reduced intensity conditioning
SD	Standard deviation
SD	Stable disease
SDT	Skin directed therapies
SS	Sézary syndrome
TTNT	Time to next treatment
TSEB	Total skin electron beam therapy
UK	United Kingdom
UK-CLG	UK Cutaneous Lymphoma Group

1. Overview

This document contains the response to the clarification questions from the Evidence Review Group (ERG), Liverpool Reviews and Implementation Group (LRIG), and the technical team at the National Institute for Health and Care Excellence (NICE) sent to Takeda on Monday 23rd July 2018. We have attempted to address all questions as fully as possible within the timeframe permitted (deadline of 6th August 2018).

2. Response to clarification questions

Please find below responses by Takeda to each of the questions raised by the ERG and the technical team at NICE.

Section A: Clarification on effectiveness data

ALCANZA trial

A1. **Priority question:** The company submission (page 18) notes that: "patients in early stages of the disease (i.e. MF [mycosis fungoides] stage IA–IIA) for the most part will have indolent disease and will therefore not require any systemic therapy". We note that all patients with early stages of MF in the ALCANZA trial have received at least one systemic therapy, as per the inclusion criteria. Please provide the rationale for not restricting eligibility for trial entry to only patients with advanced disease.

Response: The ALCANZA trial was an international, open-label, randomised, phase III, multicentre study which included 34 centres across 11 countries spanning four continents. While the statement on page 18 of the submission relating to the use of systemic therapies in early stage disease is representative of UK clinical practice and is in line with the newly updated UK Cutaneous Lymphoma Group (UK-CLG) and British Association of Dermatology (BAD) guidelines for the management of cutaneous t-cell lymphoma (CTCL)[1], it may not be applicable to all 11 countries which recruited patients to ALCANZA. As in many other conditions, local practices and clinical management of CTCL can vary by country.

The ALCANZA inclusion criteria were set up to be inclusive of all of the local guidelines and practices across the centres and countries involved in the ALCANZA trial, not only the UK. Therefore, no restrictions based on disease stage were listed in the inclusion and exclusion criteria. Note, only 33 of 128 (26%) patients enrolled in ALCANZA had early stage disease (MF IA-IIA) across both arms. The majority of ALCANZA patients (74%) had advanced disease and are representative of the patients who are currently treated with systemic therapies in the UK and would be considered for treatment with brentuximab vedotin.

A2. **Priority question:** Please replicate Table 10 to include a breakdown of baseline characteristics for (i) patients with early disease and (ii) patients with advanced disease.

Response: The baseline characteristics for ALCANZA patients with early stage disease and advanced disease can be found in Table 1. In the submission advanced CTCL was defined as those patients with mycosis fungoides (MF) stage IIB or above and all primary cutaneous anaplastic large cell lymphoma (pcALCL) patients. Consequently, the group of patients with early disease does not include any patients with pcALCL or with MF stage IIB or above. Similarly, the group of patients with advanced disease does not include any patients with MF stage IIA or below.

Table 1: Baseline characteristics for ALCANZA patients with early stage disease and advanced disease

Characteristic			Early		Advanced	
			Brentuximab vedotin (n=15)	Physician's choice of methotrexate or bexarotene (n=18)	Brentuximab vedotin (n=49)	Physician's choice of methotrexate or bexarotene (n=46)
Age, y, median (range)			60 (22-83)	64.5 (22-81)	62 (31-82)	54 (25-83)
Male, n (%)			8 (53.3)	13 (72.2)	25 (51.0)	24 (52.2)
White race, n (%)			12 (80)	18 (100)	44 (89.8)	35 (76.1)
ECOG PS, n (%)		**0**	9 (60)	15 (83.3)	34 (69.4)	31 (67.4)
		1	6 (40)	3 (16.7)	12 (24.5)	13 (28.3)
		2	0	0	3 (6.1)	2 (4.4)
CD30 expression, %, median (range)*			20.5 (0-70)	25 (0-100)	40 (0-100)	33.8 (0-100)
Time since initial diagnosis, mo, median (range)			56.1 (2.7-763.9)	55.4 (5.0-241.6)	40.9 (2.6-540.3)	28.0 (3.1-273.2)
Time since progression on last therapy (excl. radiotherapy), mo, median (range)			2.4 (0-10.1)	1.6 (0.4-55.1)	2.4 (0.6-112.2)	1.3 (0-45.7)
Lines of prior therapy, n, median (range)		**Total**	4 (2-9)	5 (2-12)	4 (0-13)	3 (1-15)
		Skin-directed	1 (0-5)	2 (0-9)	1 (0-6)	1 (0-7)
		Systemic	2 (1-6)	2.5 (1-6)	2 (1-8)	2 (0-11)
MF, n (%)			15 (100)	18 (100)	33 (67.4)	31 (67.4)
Disease stage, n/N (%)†		**IA–IIA**	15 (100)	18 (100)	0	0
		IIB	0	0	19 (57.6)	19 (61.3)
		IIIA–IIIB	0	0	4 (12.1)	2 (6.5)
		IVA1	0	0	0	1 (3.2)
		IVA2	0	0	2 (6.1)	8 (25.8)
		IVB	0	0	7 (21.2)	0
pcALCL, n (%)			0	0	16 (32.7)	15 (32.6)
Disease stage, n/N (%)	**Skin**	**T_1**	NA	NA	0	4 (26.7)
		T_2	NA	NA	3 (18.8)	5 (33.3)
		T_3	NA	NA	12 (75)	6 (40)
	Node	**N_0**	NA	NA	10 (62.5)	11 (73.3)
		N_1	NA	NA	2 (12.5)	1 (6.7)
		N_2	NA	NA	2 (12.5)	1 (6.7)
		N_3	NA	NA	2 (12.5)	2 (13.3)
	Visceral	**M_0**	NA	NA	12 (75)	14 (93.3)
		M_1	NA	NA	4 (25)	1 (6.7)

*Based on average CD30 expression among all biopsies for each patient's baseline visit

†One patient in each arm had incomplete staging data, which are not included in the table.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; ITT, intent-to-treat; M, metastases; MF, mycosis fungoides; N, node; pcALCL, primary cutaneous anaplastic large cell lymphoma; T, tumour.

A3. **Priority question:** Please provide two additional tables detailing prior systemic therapy by region for (i) patients with early disease and (ii) patients with advanced disease in the ALCANZA trial similar to Supplementary Table S1 in the paper by Prince et al 2017. Please include information on the number of previous systemic therapies received, limit the regions to UK versus non-UK patients and provide data relating to previous immunotherapy (i.e. provide frequencies of patients who received previous interferon alpha [IFN-α], etc).

Response: Prior systemic therapy is presented by region (UK vs. non-UK) for patients in ALCANZA with early disease and with advanced disease in Table 2 and Table 3, respectively.

Table 2: Prior systemic therapy by region (UK vs. Non-UK), early stage disease

	Brentuximab Vedotin		Methotrexate or Bexarotene	
	UK (n=1)	**Non-UK (n=14)**	**UK (n=4)**	**Non-UK (n=14)**
Number of prior therapies, n (%)				
Any therapy				
0	0	0	0	0
1	0	0	0	0
2	0	4 (29)	0	2 (14)
3	0	3 (21)	2 (50)	3 (21)
≥4	1 (100)	7 (50)	2 (50)	9 (64)
Mean [SD]	4.0	4.1 [2.23]	5.3 [3.30]	5.3 [2.87]
Skin directed therapy				
0	0	1 (7)	0	2 (14)
1	0	7 (50)	0	4 (29)
2	0	5 (36)	2 (50)	6 (43)
3	1 (100)	0	1 (25)	1 (7)
≥4	0	1 (7)	1 (25)	1 (7)
Mean [SD]	3.0	1.6 [1.16]	3.0 [1.41]	2.0 [2.18]
Systemic Therapy				
0	0	0	0	0
1	1 (100)	6 (43)	2 (50)	3 (21)
2	0	4 (29)	1 (25)	3 (21)
3	0	1 (7)	0	2 (14)
≥4	0	3 (21)	1 (25)	6 (43)
Mean [SD]	1.0	2.3 [1.64]	2.3 [1.89]	3.1 [1.70]
Type of Prior Therapy, n (%)				
Skin directed therapy	1 (100)	13 (93)	4 (100)	12 (86)
Topical Steroids	0	2 (14)	0	7 (50)
Topical Retinoids	0	0	0	0
Topical chemotherapy	0	1 (7)	0	0
Radiotherapy	1 (100)	8 (57)	4 (100)	8 (57)
Phototherapy	1 (100)	9 (64)	4 (100)	6 (43)
Other	0	1 (7)	0	0
Systemic therapy	1 (100)	14 (100)	4 (00)	14 (100)
Bexarotene	0	7 (50)	1 (25)	6 (43)
Chemotherapy	0	9 (64)	3 (75)	12 (86)
Methotrexate	0	6 (43)	2 (50)	6 (43)
Other	0	5 (36)	2 (50)	9 (64)
Non-topical retinoids	0	0	0	3 (21)
Photopheresis	0	0	1 (25)	1 (7)

Denileukin diftitox	0	0	0	1 (7)
Immunotherapy	1 (100)	2 (14)	3 (75)	5 (36)
interferon	0	0	0	1 (7)
interferon alpha	1 (100)	2 (14)	3 (75)	3 (21)
interferon alpha-2a	0	0	0	0
interferon gamma	0	1 (7)	0	0
alemtuzumab	0	1 (7)	1 (25)	0
monoclonal antibodies	0	0	0	1 (7)
Mogamulizumab	0	0	0	0
HDACi	0	4 (29)	0	6 (43)
Other	0	3 (21)	1 (25)	2 (14)
Other/Unknown	0	2 (14)	0	3 (21)

Abbreviations: HDACi, Histone deacetylase inhibitor; N, number; SD, standard deviation; UK, United Kingdom

Table 3: Prior systemic therapy by region (UK vs. Non-UK), advanced stage disease

	Brentuximab Vedotin		Methotrexate or Bexarotene	
	UK (n=7)	**Non-UK (n=42)**	**UK (n=12)**	**Non-UK (n=34)**
Number of prior therapies, n (%)				
Any therapy				
0	0	1 (2)	0	0
1	1 (14)	5 (12)	1 (8)	5 (15)
2	2 (29)	6 (14)	2 (17)	8 (24)
3	1 (14)	7 (17)	3 (25)	6 (18)
≥4	3 (43)	23 (55)	6 (50)	15 (44)
Mean [SD]	3.4 (1.90)	5.3 (3.75)	3.4 (1.31)	4.1 (3.04)
Skin directed therapy				
0	1 (14)	10 (24)	1 (8)	10 (29)
1	3 (43)	12 (29)	5 (42)	12 (35)
2	2 (29)	9 (21)	3 (25)	5 (15)
3	1 (14)	4 (10)	2 (17)	3 (9)
≥4	0	7 (17)	1 (8)	4 (12)
Mean [SD]	1.4 (0.98)	1.7 (1.55)	1.8 (1.14)	1.6 (1.84)
Systemic Therapy				
0	0	1 (2)	0	0
1	3 (43)	16 (38)	6 (50)	15 (44)
2	2 (29)	6 (14)	4 (33)	7 (21)
3	1 (14)	3 (7)	2 (17)	5 (15)
≥4	1 (14)	16 (38)	0	7 (21)
Mean [SD]	2.0 (1.15)	3.6 (3.17)	1.7 (0.78)	2.4 (1.78)
Type of Prior Therapy, n (%)				
Skin directed therapy	6 (86)	32 (78)	11 (92)	24 (71)
Topical Steroids	0	5 (12)	0	7 (21)
Topical Retinoids	0	1 (2)	0	0
Topical chemotherapy	1 (14)	1 (2)	0	2 (6)
Radiotherapy	5 (71)	26 (63)	10 (83)	19 (56)
Phototherapy	3 (43)	19 (46)	6 (50)	13 (38)
Other	0	1 (2)	0	0
Systemic therapy	7 (100)	41 (100)	12 (100)	34 (100)
Bexarotene	3 (43)	16 (39)	5 (42)	10 (29)
Chemotherapy	5 (71)	31 (76)	6 (50)	24 (71)
Methotrexate	1 (14)	19 (46)	1 (8)	16 (47)
Other	4 (57)	21 (51)	6 (50)	15 (44)
Non-topical retinoids	0	5 (12)	0	1 (3)
Photopheresis	1 (14)	2 (5)	0	2 (6)
Denileukin diftitox	0	0	0	0

Immunotherapy	4 (57)	19 (46)	7 (58)	14 (41)
interferon	0	0	0	0
interferon alpha	4 (57)	15 (37)	7 (58)	11 (32)
interferon alpha-2a	0	3 (7)	0	2 (6)
interferon gamma	0	0	0	0
alemtuzumab	0	2 (5)	0	2 (6)
monoclonal antibodies	0	0	0	0
Mogamulizumab	0	1 (2)	0	0
HDACi	0	9 (22)	0	7 (21)
Other	2 (29)	13 (32)	2 (17)	8 (24)
Other/Unknown	0	8 (20)	0	2 (6)

Abbreviations: HDACi, Histone deacetylase inhibitor; N, number; SD, standard deviation; UK, United Kingdom

A4. **Priority question:** Please provide a table with a breakdown of subsequent anticancer therapies for patients with advanced disease in the ALCANZA trial similar to Supplementary Table S2 to the published paper by Prince et al 2017.

Response: Subsequent anticancer therapies received by patients with advanced disease in the ALCANZA study are summarised in Table 4.

Table 4: Subsequent anticancer therapies for patients with advanced disease

Subsequent systemic therapy	Brentuximab vedotin (n = 49)	Physician's choice (n = 46)
≥1 subsequent anticancer therapy, n (%)[1]	27 (55.1)	29 (63.0)
Skin-directed therapy, n (%)[2]		
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 (%)		
Bexarotene	6 (22.2)	4 (13.8)
Brentuximab Vedotin	8 (29.6)	21 (71.4)
Chemotherapy, Methotrexate	7 (25.9)	7 (24.1)
Chemotherapy, Other	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)

1. Percentages are reported based on the number of patients in each arm
2. Percentages are reported based on the number of patients who received ≥1 subsequent anticancer therapy

Abbreviations: HDACi, Histone deacetylase inhibitor; n, number

A5. **Priority question:** Please clarify how many patients with advanced disease in each treatment arm of the ALCANZA trial subsequently received an allogeneic stem cell transplant (alloSCT) (i) without receiving any additional systemic therapy following their study treatment; and (ii) at any stage (i.e. having received at least one additional systemic therapy).

Response: The use of alloSCT was allowed within ALCANZA, but was neither a pre-specified nor an exploratory end-point. Therefore, very little data were collected on this procedure and any inferences should be treated with caution.

Seven patients in total received an alloSCT in the ALCANZA trial; five in the primary data analysis and an additional two in the longer follow-up. Of the seven patients that received a stem cell transplant, five were in the brentuximab vedotin arm and two were in the Physician's Choice (PC) arm (both received methotrexate). Both of the patients in the PC arm who went onto receive an alloSCT crossed over to brentuximab vedotin prior to their transplant. Two of the seven patients received an alloSCT directly after the study treatment and the remaining five received after additional subsequent systemic therapies prior to their alloSCT, including the two aforementioned patients who had crossed over to brentuximab vedotin from the PC arm.

Of the seven patients who received an alloSCT in the ALCANZA trial, four were based in the UK. This equates to approximately 17% of UK patients enrolled in ALCANZA subsequently receiving alloSCT (4 of 24 enrolled patients in the UK). Given that alloSCT was not a part of the protocol and the overall number of UK patients in ALCANZA is modest, the high proportion of UK patients who received a transplant supports the use of alloSCT in the UK for the treatment of CTCL and the potential role of brentuximab vedotin as a bridging agent to enable this curative procedure.

A6. Please provide (i) the confidence intervals for the percentage of patients in the advanced disease subgroup achieving objective global response lasting ≥4 months (ORR4) in each treatment arm, and (ii) the percentage difference between patients achieving ORR4 between treatment arms and corresponding 95% confidence interval and p-value.

Response: A summary of the requested data for the advanced subgroup achieving ORR4 as measured by the independent review facility (IRF) in each treatment arm is presented in

Table 5.

Table 5: Summary of Objective Response Lasting at least 4 Months (ORR4) per IRF, advanced disease subgroup, 33.9 month follow-up

	Brentuximab Vedotin N=49	Methotrexate or Bexarotene N=46	Bexarotene N=25	Methotrexate N=21	P-value[a]
Number (%) achieving ORR4 per IRF	29 (59.2)	4 (8.7)	2 (8.0)	2 (9.5)	<0.001
95% CI	(45.4, 72.9)	(2.4, 20.8)	(1.0, 26.0)	(1.2, 30.4)	-
Difference from comparator arm[b]	50.5	-	-	-	-
95% CI for the difference from comparator arm	(31.6, 66.4)	-	-	-	-

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IRF, independent review facility; N, number; ORR4, objective response rate lasting at least 4 months; pcALCL, primary cutaneous anaplastic large cell lymphoma
Confidence intervals for categorical data with numerators or the differences between numerators and denominators less than or equal to five are from the exact method, otherwise from the normal approximation.
[a]P-value is calculated using a CMH test stratified by baseline disease diagnosis (pcALCL and MF).
[b]95% C.I. for risk difference (Brentuximab Vedotin – Comparator: Methotrexate or Bexarotene).

A7. Figure 15 of the company submission presents subgroup analysis for the primary outcome (ORR4) for the ITT population after 22.9 months follow-up in the ALCANZA trial. Please clarify if all subgroups included in the analysis were pre-specified. If possible, please replicate Figure 15 for patients with advanced disease after 33.9 months follow-up in the ALCANZA trial.

Response: All subgroups shown in Figure 15 of the company submission were pre-specified in the Statistical Analysis Plan[2] of ALCANZA.

The Statistical Analysis Plan outlined that the primary endpoint, ORR4 per IRF, was to be analysed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline disease diagnosis (primary cutaneous anaplastic large cell lymphoma [pcALCL] or MF) based on the ITT population. The same analysis on ORR4 per IRF using a CMH test stratified by baseline disease diagnosis (pcALCL and MF) was performed for the primary endpoint on, but not limited to, the subgroups shown in

Figure 1. At least ten patients in each subgroup per treatment arm were required in order to perform the analysis; subgroups of less than ten were combined into their larger parent subgroup[2].

Figure 1: Subgroups as outlined in the ALCANZA Statistical Analysis Plan

Brentuximab vedotin (SGN-35)
Statistical Analysis Plan, Study C25001

Subgroup	Group Definition
Baseline disease diagnosis	MF, pcALCL
ECOG performance status	0, 1, 2
Gender	Female, male
Age	< 65 years, ≥ 65 years
Region	North America, Europe, Asia, and rest of world
Race	White, nonwhite
Physician's choice (bexarotene)	Brentuximab vedotin vs bexarotene
Physician's choice (MTX)	Brentuximab vedotin vs MTX

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MF, mycosis fungoides; MTX, methotrexate; pcALCL, primary cutaneous anaplastic large cell lymphoma

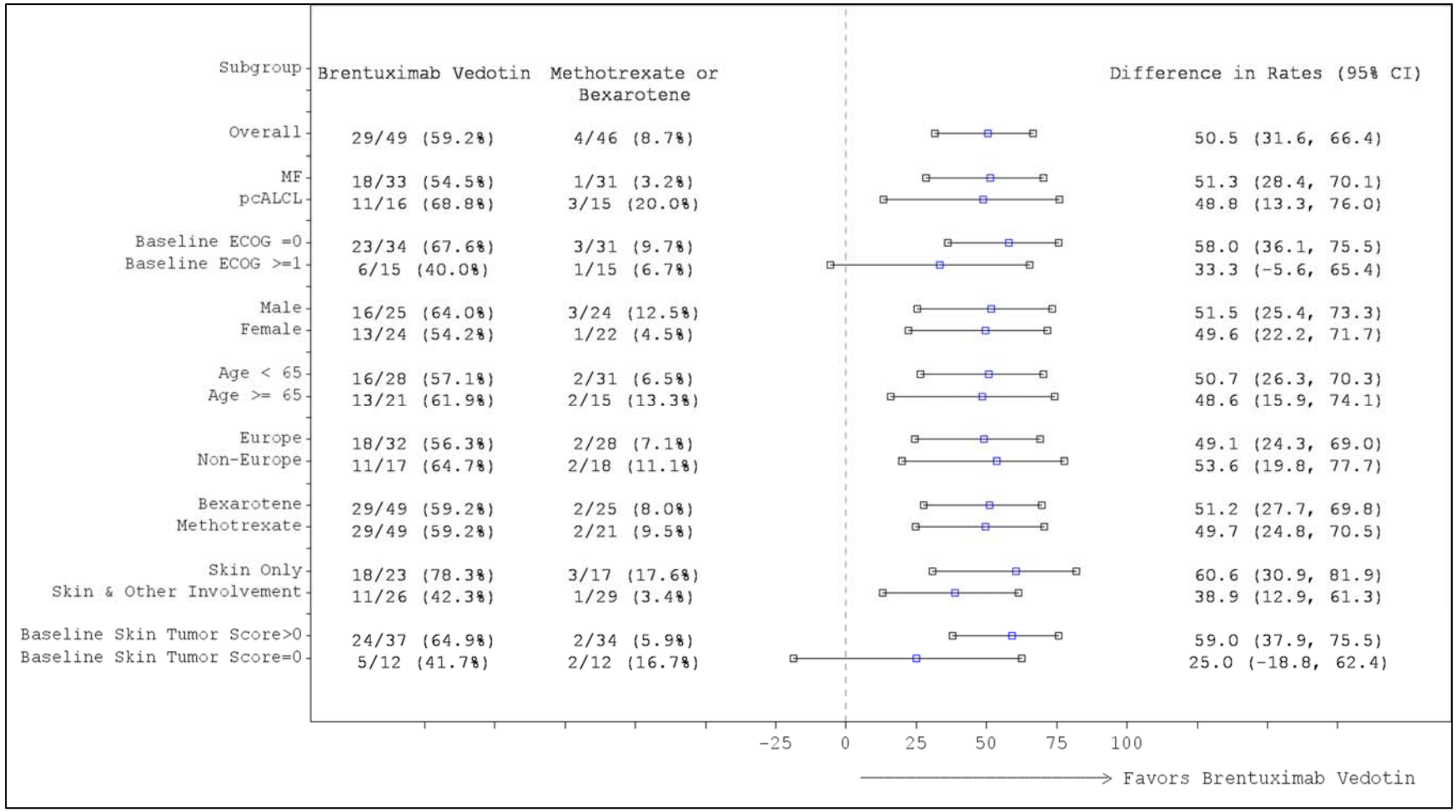
In addition to the subgroups outlined above, analysis of the primary endpoint for the extent of disease involvement (skin only, skin and other involvement) and baseline tumour score was performed as per the Statistical Analysis Plan.

The analyses of all of the aforementioned, pre-specified subgroups are presented in the Clinical Study Report (CSR) as part of the primary endpoint efficacy assessments and likewise the forest plot in Figure 15 of the company submission.

The subgroups of baseline ECOG=1 and baseline ECOG=2 were combined into 1 subgroup of baseline ECOG ≥1 because of the small sample size. Similarly, the subgroups North America, Asia, and rest of world were combined into non-Europe. The subgroup analyses of white and non-white were not performed because there were fewer than 10 non-white patients per treatment arm. All the subgroup analyses were also performed for the key secondary endpoint: progression free survival (PFS) per IRF.

Figure 2 below presents the ORR4 by subgroup in the advanced ALCANZA population based on the 33.9 month follow-up data. Point estimates for all were in favour of brentuximab vedotin, with ORR4 shown to be improved in patients with advanced disease treated with brentuximab vedotin in the majority of subgroups comprising more than ten patients.

Figure 2: Forest Plot of Difference in ORR4 per IRF, advanced disease subgroup



Abbreviations: ECOG, Eastern Cooperative Oncology Group; MF, mycosis fungoides; ORR4, rate of objective global response lasting ≥4 months, assessed by independent review; pcALCL, primary cutaneous anaplastic large cell lymphoma.

A8. For (i) objective response rate (ORR), and (ii) complete response in the advanced disease patient subgroup, please perform the same statistical tests used to generate p-values for the differences in percentages of patients achieving ORR and complete response in the ITT patient population and provide the results of these statistical tests. Please note these analyses are not expected to be adjusted for multiplicity, as they are post-hoc analysis requests and are for exploratory purposes only.

Response: Table 6 presents the p-values and risk difference for the overall (objective) response and complete response groups.

Table 6: Summary of Best Response to Treatment per IRF, advanced patient subgroup

	Brentuximab Vedotin N=49 n(%)(95% CI)	Methotrexate or Bexarotene N=46 n(%)(95% CI)	Bexarotene N=25 n(%)(95% CI)	Methotrexate N=21 n(%)(95% CI)	P-value[a]	Risk Difference (95% CI)[b]
Complete Response (CR)	10 (20.4) (9.1, 31.7)	1 (2.2) (0.1, 11.5)	0 (0.0, 13.7)	1 (4.8) (0.1, 23.8)	0.005	18.2 (-2.0, 37.6)
Overall Response (CR+PR)	34 (69.4) (56.5, 82.3)	8 (17.4) (6.4, 28.3)	6 (24.0) (7.3, 40.7)	2 (9.5) (1.2, 30.4)	<.001	52.0 (35.1, 68.9)

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; IRF, independent review facility; N, number;

[a]P-value is calculated using a CMH test stratified by baseline disease diagnosis (pcALCL and MF) between Brentuximab Vedotin and Comparator (Methotrexate or Bexarotene) arm.

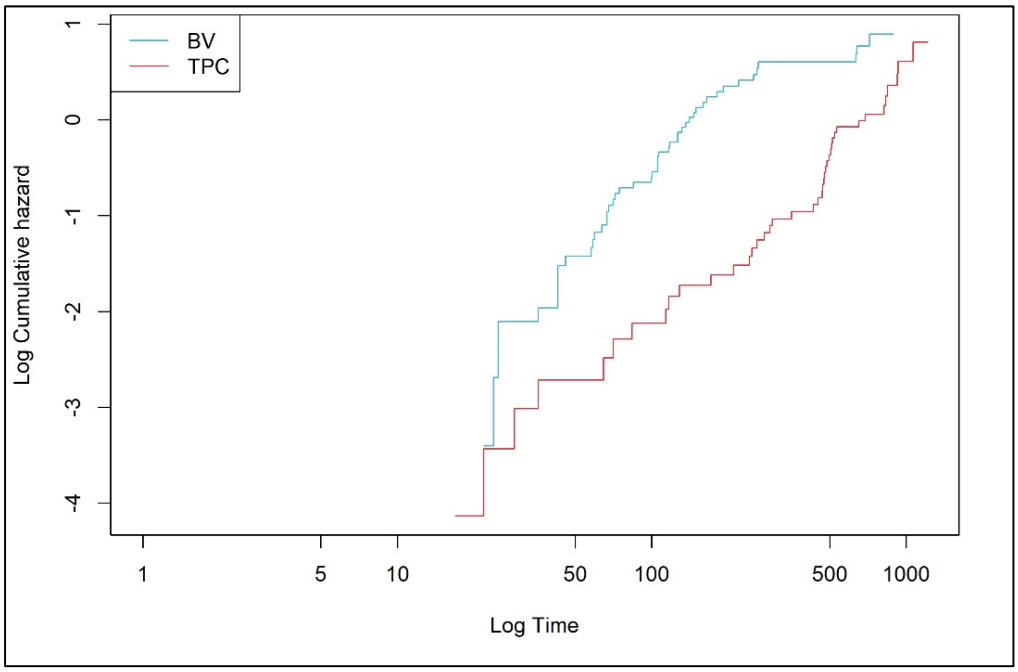
[b]95% C.I. for risk difference (Brentuximab Vedotin – Comparator arm: Methotrexate or Bexarotene).

A9. Please clarify if the validity of the proportional hazards assumption was tested for (i) progression-free survival (PFS) in the ITT population and (ii) time to next treatment in the ITT population? If so, please provide the results of these tests.

Response: The proportional hazards assumption was assessed in the ITT population for both PFS and time to next treatment (TTNT) using visual assessment of log cumulative hazard plots (see Figure 3 and Figure 4). Interpretation of these curves indicates that the assumption of proportional hazards is not obviously violated. However, a trend is observed for initial separation of the plots for the PFS outcome followed by a trend of curves coming together towards the end of the follow up time. Similarly, a trend is observed for the converging of the plots for the TTNT outcome. This indicates that the assumption of proportional hazards is subject to uncertainty.

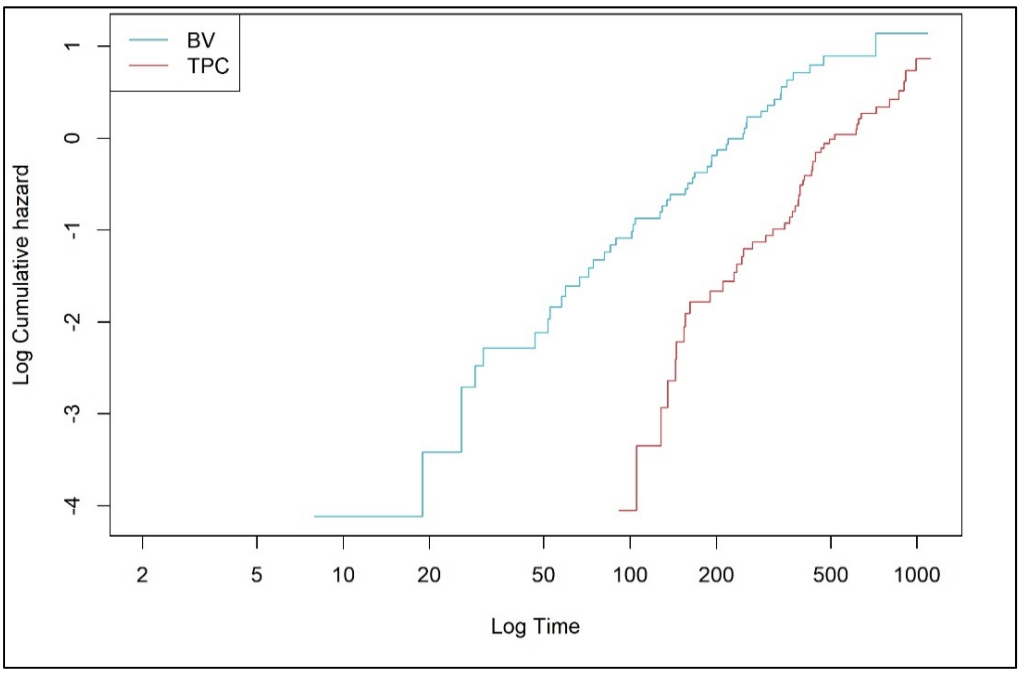
Figure 5 shows the log cumulative hazard plot for OS – which reflects the lack of a treatment effect on this outcome (curves crossing many times), rather than any major violation of proportional hazards assumption.

Figure 3: Log cumulative hazard plot for PFS in the ITT population



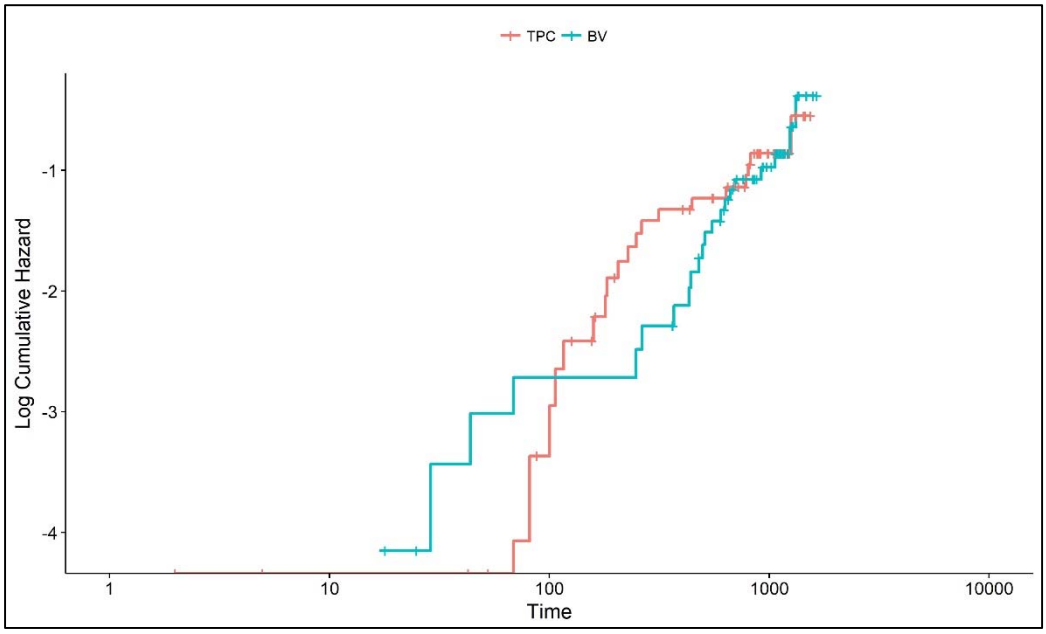
Abbreviations: BV, brentuximab vedotin; ITT, intend to treat; PFS, progression free survival; TPC, treatment of physician's choice

Figure 4: Log cumulative hazard plot for TTNT in the ITT population



Abbreviations: BV, brentuximab vedotin; ITT, intend to treat; TPC, treatment of physician's choice

Figure 5: Log cumulative hazard plot for OS in the ITT population



Abbreviations: BV, brentuximab vedotin; TPC, treatment of physician's choice

A10. The company submission notes that, for time-to-event outcomes, hazard ratios (HRs) and confidence intervals (CIs) were generated (Appendix D, Table 23). Please provide results for the HR for time to subsequent therapy in the advanced disease subgroup. If this is not possible please provide the rationale for its exclusion and clarify whether any testing of proportional hazards was performed.

Response: Table 7 presents the HR and confidence intervals estimated from a Cox proportional hazards model fitted to time to subsequent therapy in the advanced subgroup.

Table 7: HR for time to subsequent therapy, advanced disease subgroup

Variable	HR	lower95CI	upper95CI	Population	Reference
BV	0.309642	0.186193	0.514938	Advanced	PC

Abbreviations: BV, brentuximab vedotin; CI, confidence interval; HR, hazard ratio; PC, treatment of physician's choice

A11. Please clarify which set of censoring rules was applied for the analysis of PFS in the advanced subgroup population, the US Food and Drug Administration (FDA) criteria, or the European medicines Agency (EMA) criteria.

Response: The analysis of PFS for the advanced subgroup population of ALCANZA, presented in all clinical effectiveness and cost-effectiveness analyses of the company submission was evaluated applying the censoring rules as per the EMA guidelines.

A12. Adverse event (AE) data are reported by treatment arm for all patients after 22.9 months follow-up in Tables 19 and Table 20 of the company submission. Please provide the equivalent information for patients with advanced disease, preferably after 33.9 months follow-up. If possible, please provide a further breakdown for any Grade and Grade 3+ AEs as in the example table below.

Type of adverse event (AE)	**Brentuximab vedotin (n=66)**		**Methotrexate (n=25)**		**Bexarotene (n=37)**	
	Any Grade	Grade 3+	Any Grade	Grade 3+	Any Grade	Grade 3+
AE 1	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AE 2	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AE 3	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Etc	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Response: Treatment emergent adverse events (TEAEs) for the advanced population for the 33.9 month data cut are provided below. Table 8 presents the data for any grade adverse event, and

Table 9 presents adverse events of grade 3 and above. For any grade adverse event, results were filtered so that where any of the three treatment groups had >10% of patients with an observed TEAE, this event type was included. This method is consistent with previous reporting in ALCANZA and prevents excessive reporting of rare events.

For grade 3+ events, the filter of >10% of patients experiencing an event was not applied since only one grade 3+ event in the bexarotene treatment arm was experienced by >10% of patients. Please note that fields filled with 'NA' indicate the absence of observations of that adverse event for the specified treatment.

Table 8: Common TEAEs (>10%) for the advanced subgroup: any grade

Type of adverse event, any grade	Brentuximab vedotin (n=49)	Methotrexate (n=20)	Bexarotene (n=24)
Peripheral sensory neuropathy SMQ	25 (51)	NA (NA)	NA (NA)
Nausea	18 (36.7)	4 (20)	4 (16.7)
Fatigue	11 (22.4)	5 (25)	6 (25)
Diarrhea	8 (16.3)	NA (NA)	2 (8.3)
Alopecia	7 (14.3)	1 (5)	NA (NA)
Vomiting	7 (14.3)	1 (5)	1 (4.2)
Diarrhoea	6 (12.2)	NA (NA)	NA (NA)
Fever	6 (12.2)	6 (30)	3 (12.5)
Pruritus	6 (12.2)	NA (NA)	2 (8.3)
Asthenia	5 (10.2)	2 (10)	1 (4.2)
Hyperglycemia	5 (10.2)	NA (NA)	NA (NA)
Maculopapular rash	5 (10.2)	NA (NA)	2 (8.3)
Neutropenia	5 (10.2)	NA (NA)	4 (16.7)
Urinary tract infection	5 (10.2)	1 (5)	NA (NA)
Weight loss	5 (10.2)	NA (NA)	1 (4.2)
Headache	4 (8.2)	1 (5)	3 (12.5)
Anaemia	2 (4.1)	NA (NA)	4 (16.7)
Constipation	2 (4.1)	1 (5)	3 (12.5)
Insomnia	2 (4.1)	1 (5)	3 (12.5)
Skin infection	2 (4.1)	1 (5)	3 (12.5)
Cancer pain	1 (2)	2 (10)	3 (12.5)
Hypertriglyceridemia	1 (2)	NA (NA)	7 (29.2)
Epigastric pain	NA (NA)	2 (10)	NA (NA)
Staphylococcus aureus skin infection	NA (NA)	2 (10)	1 (4.2)
Urinary infection	NA (NA)	2 (10)	NA (NA)
Hypothyroidism	NA (NA)	NA (NA)	3 (12.5)
Notes: Peripheral sensory neuropathy SMQ; consistent with previous reporting events reported by investigators as peripheral neuropathy or peripheral sensory neuropathy were reported together.			

Abbreviations: NA, not available (no events reported); SMQ, Standardised MedDRA Queries

Table 9: Treatment-emergent adverse events for the advanced subgroup: grade 3 and above

Type of adverse event, grade 3 and above	Brentuximab vedotin (n=49)	Methotrexate (n=20)	Bexarotene (n=24)
Peripheral sensory neuropathy SMQ	4 (8.2)	NA (NA)	NA (NA)
Neutropenia	3 (6.1)	NA (NA)	2 (8.3)
Peripheral motor neuropathy	2 (4.1)	NA (NA)	NA (NA)
Acute diverticulitis	1 (2)	NA (NA)	NA (NA)
Asthenia	1 (2)	NA (NA)	NA (NA)
Cellulitis	1 (2)	NA (NA)	NA (NA)
Diarrhoea	1 (2)	NA (NA)	NA (NA)
Fatigue	1 (2)	NA (NA)	NA (NA)
Fatigue aggravated	1 (2)	NA (NA)	NA (NA)
General physical health deterioration	1 (2)	NA (NA)	NA (NA)
Impetigo	1 (2)	NA (NA)	NA (NA)
Intestinal perforation	1 (2)	NA (NA)	NA (NA)
Melena	1 (2)	NA (NA)	NA (NA)
Multiorgan failure	1 (2)	NA (NA)	NA (NA)
Nausea	1 (2)	NA (NA)	NA (NA)
Neck pain	1 (2)	NA (NA)	NA (NA)
Pancreatitis	1 (2)	NA (NA)	NA (NA)
Pruritus	1 (2)	NA (NA)	NA (NA)
Pruritus generalised	1 (2)	NA (NA)	NA (NA)
Rib pain	1 (2)	NA (NA)	NA (NA)
Specific allergy (drug)	1 (2)	NA (NA)	NA (NA)
Thrombocytopenia	1 (2)	NA (NA)	NA (NA)
Vomiting	1 (2)	NA (NA)	NA (NA)
Alanine aminotransferase increase	NA (NA)	1 (5)	NA (NA)
Lymphocyte count decreased	NA (NA)	1 (5)	NA (NA)
Septicemia	NA (NA)	1 (5)	NA (NA)
Anaemia	NA (NA)	NA (NA)	2 (8.3)
Blood triglycerides increased	NA (NA)	NA (NA)	1 (4.2)
Hematuria	NA (NA)	NA (NA)	1 (4.2)
Hypertriglyceridemia	NA (NA)	NA (NA)	6 (25)
Raised triglycerides	NA (NA)	NA (NA)	1 (4.2)

Abbreviations: NA, not available (no events reported); SMQ, Standardised MedDRA Queries

A13. Please clarify how pruritis differs to pruritis (generalised) in Table 20 of the company submission.

Response: In the ALCANZA trial, pruritus as an adverse event was categorised as either localised or generalised depending on whether the itch was localised/isolated or diffuse/widespread. Localised pruritus affecting a specific part or parts of the body was coded as 'pruritus' whereas 'pruritus (generalised)' referred to instances of overall pruritus or itch throughout the body. For example: if the trial site reported an adverse event as an 'all over itch', it would be coded to the Preferred Term of 'pruritus (generalised)'. Alternatively, an adverse event reported as 'itchy leg' would be coded to the Preferred Term of 'pruritus'.

Data from other studies of brentuximab vedotin

A14. Please clarify whether patients in Kim et al 2015 and Mathieu et al 2016 had CD30-positive cutaneous T-cell lymphoma (CTCL).

Response: Both the Kim *et al.* 2015[3] and the Mathieu *et al.* 2016[4] studies considered patients with CD30-positive CTCL.

A15. Page 97 of the company submission, reports AE in both prospective observational studies to be "Consistent with ALCANZA". However, neutropenia is listed for both observational studies but is not reported for the ALCANZA trial. Duvic et al 2015 also report rash as an AE. Please provide (i) any Grade and (ii) Grade 3+ data (treatment-related AEs) for neutropenia and rash from the ALCANZA trial. Please present the data the same format as the example Table for A12.

Response: The results for treatment emergent adverse events in the ITT population using the 33.9 follow-up from ALCANZA for neutropenia and maculopapular rash are presented in Table 10; events for the advanced population are presented in response to A12.

Table 10: TEAEs for neutropenia and maculopapular rash

Type of adverse event	Any grade TEAE			Grade 3 + TEAE		
	Brentuximab vedotin (n=64)	Methotrexate (n=24)	Bexarotene (n=37)	Brentuximab vedotin (n=64)	Methotrexate (n=24)	Bexarotene (n=37)
Neutropenia	5 (7.8)	NA (NA)	4 (10.8)	3 (4.7)	NA (NA)	2 (5.4)
Maculopapular rash	7 (10.9)	1 (4.2)	2 (5.4)	1 (1.6)	NA (NA)	NA (NA)

Abbreviations: n, number; NA, not available (no events reported); TEAE, treatment emergent adverse event

Section B: Clarification on cost-effectiveness data

Kaplan-Meier data:

B1. **Priority request:** Please provide the Kaplan-Meier (K-M) analyses, listed in a-e below, to the following specifications:

Trial data set: *ALCANZA*

Format: *Use the sample table shown below*

Population: Advanced-stage population including all patients lost to follow-up or withdrawing from the trial

a) Time to death from any cause (overall survival [OS]) K-M analysis for the advanced subgroup of patients in the brentuximab vedotin arm of the trial

b) Unadjusted time to death from any cause (OS) K-M analysis for the advanced subgroup of patients in the physician's choice (PC) arm of the trial

c) Time to disease progression or death (PFS) K-M analysis for the advanced subgroup of patients in the brentuximab vedotin arm of the trial, based on investigator assessment

d) Time to disease progression or death (PFS) K-M analysis for the advanced subgroup of patients in the PC arm of the trial, based on investigator assessment

e) Time to study treatment discontinuation K-M analysis for the advanced subgroup of patients, stratified by study treatment.

Response: The K-M analyses as requested are presented in

Table 11-

Table 16. Please note there were inconsistencies in the labelling of the PFS endpoint in the original submission document, and that all cost effectiveness data for the 33.9 months data cut is IRF assessed and not INV assessed. Therefore, the K-M analyses provided in

Table 13 and

Table 14 are for PFS per IRF.

Table 11: Time to death from any cause (OS) K-M analysis for the advanced subgroup of patients in the brentuximab vedotin arm of the trial

time	surv	std.err	n.risk	n.event	n.censor
0	1	0	49	0	0
28.82136	0.979167	0.020615	48	1	1
43.72895	0.958333	0.028842	47	1	0
68.57495	0.9375	0.034939	46	1	0
247.4661	0.916667	0.039893	45	1	0
263.3676	0.895833	0.044092	44	1	0
368.7146	0.873984	0.048127	41	1	2
439.2772	0.852134	0.051646	40	1	0
479.0308	0.830285	0.054749	39	1	0
497.9138	0.808435	0.057503	38	1	0
508.846	0.786585	0.059956	37	1	0
629.1006	0.763451	0.062497	34	1	2
664.8789	0.739593	0.064938	32	1	1
695.6879	0.714089	0.067522	29	1	2
1062.415	0.674418	0.074519	18	1	10
1241.306	0.599483	0.096845	9	1	8
1318.825	0.499569	0.121787	6	1	2

Abbreviations: K-M, Kaplan-Meier; n, number; OS, overall survival; surv, survival; std err, standard error

Table 12: Unadjusted time to death from any cause (OS) K-M analysis for the advanced subgroup of patients in the PC arm of the trial

time	surv	std.err	n.risk	n.event	n.censor
0	1	0	46	0	0
68.57495	0.97561	0.024091	41	1	5
81.49487	0.95122	0.033641	40	1	0
100.3778	0.926829	0.04067	39	1	0
106.3409	0.902439	0.04634	38	1	0
116.2793	0.878049	0.051105	37	1	0
159.0144	0.852224	0.055746	34	1	2
179.885	0.826399	0.05974	33	1	0
182.8665	0.800574	0.063209	32	1	0
205.7248	0.773888	0.066497	30	1	1
227.5893	0.747202	0.069352	29	1	0
248.46	0.720516	0.071826	28	1	0
262.3737	0.693831	0.073957	27	1	0
315.0472	0.667145	0.075775	26	1	0
446.2341	0.638139	0.077834	23	1	2
638.0452	0.607751	0.079839	21	1	1
802.0287	0.569767	0.083397	16	1	4
821.9055	0.529069	0.086804	14	1	1
1257.207	0.440891	0.108223	6	1	7

Abbreviations: K-M, Kaplan-Meier; n, number; OS, overall survival; PC, physicians choice; surv, survival; std err, standard error

Table 13: Time to disease progression or death (PFS) K-M analysis for the advanced subgroup of patients in the brentuximab vedotin arm of the trial, based on investigator assessment*

time	surv	std.err	n.risk	n.event	n.censor
0	1	0	49	0	0
28.82136	0.979167	0.020615	48	1	1
35.77823	0.958333	0.028842	47	1	0
64.59959	0.9375	0.034939	46	1	0
70.56263	0.916193	0.040119	44	1	1
83.48255	0.894886	0.044485	43	1	0
113.2977	0.87358	0.04826	42	1	0
128.2053	0.852273	0.051572	41	1	0
170.9405	0.830966	0.054507	40	1	1
209.7002	0.809098	0.057291	38	1	0
241.5031	0.787231	0.059771	37	1	0
247.4661	0.765363	0.061982	36	1	0
276.2875	0.743496	0.063952	35	1	0
290.2012	0.721628	0.065703	34	1	0
297.1581	0.699761	0.067253	33	1	0
353.807	0.674769	0.069339	28	1	4
450.2094	0.648817	0.071364	26	1	1
469.0924	0.622864	0.073076	25	1	0
474.0616	0.596911	0.074498	24	1	0
477.0431	0.570959	0.075644	23	1	0
481.0185	0.545006	0.076528	22	1	0
486.9815	0.519053	0.077159	21	1	0
497.9138	0.493101	0.077543	20	1	0
503.8768	0.467148	0.077684	19	1	0
508.846	0.441195	0.077582	18	1	0
512.8214	0.415243	0.077237	17	1	0
533.692	0.38756	0.076889	15	1	1
690.7187	0.355263	0.076967	12	1	2
817.9302	0.310855	0.079126	8	1	3
830.8501	0.266447	0.079311	7	1	0
929.2402	0.213158	0.079357	5	1	1
1062.415	0.142105	0.078515	3	1	1

Abbreviations: K-M, Kaplan-Meier; n, number; PFS, progression free survival; surv, survival; std err, standard error

* Note: as explained above, this data is per IRF rather than per investigator

Table 14: Time to disease progression or death (PFS) K-M analysis for the advanced subgroup of patients in the PC arm of the trial, based on investigator assessment *

time	surv	std.err	n.risk	n.event	n.censor
0	1	0	46	0	0
21.86448	0.954545	0.031402	44	2	2
23.85216	0.931818	0.037999	42	1	0
24.846	0.863636	0.051735	41	3	0
35.77823	0.840909	0.055141	38	1	0
42.73511	0.795455	0.06081	37	2	1
45.71663	0.770597	0.063789	32	1	2
58.63655	0.745739	0.066398	31	1	0
59.63039	0.720881	0.06868	30	1	0
63.60575	0.696023	0.070668	29	1	0
66.58727	0.671165	0.072384	28	1	0
70.56263	0.646307	0.073848	27	1	0
71.55647	0.621449	0.075075	26	1	0
74.53799	0.596591	0.076076	25	1	0
84.47639	0.571733	0.07686	24	1	0
100.3778	0.546875	0.077434	23	1	0
105.347	0.472301	0.077931	22	3	0
116.2793	0.446062	0.077893	18	1	1
126.2177	0.390304	0.077495	16	2	1
136.1561	0.362426	0.076811	14	1	0
140.1314	0.334547	0.075793	13	1	0
149.076	0.306668	0.074428	12	1	0
159.0144	0.276001	0.07303	10	1	1
163.9836	0.245334	0.071063	9	1	0
179.885	0.214667	0.068479	8	1	0
251.4415	0.184001	0.065202	7	1	0
262.3737	0.153334	0.061123	6	1	0
638.0452	0.115	0.0566	4	1	1

Abbreviations: : K-M, Kaplan-Meier; n, number; PC, physicians choice; PFS, progression free survival; surv, survival; std err, standard error

* Note:as explained above, this data is per IRF rather than per investigator

Table 15: Time to study treatment discontinuation K-M analysis for the advanced subgroup of patients, brentuximab vedotin arm

time	surv	std.err	n.risk	n.event	n.censor
0	1	0	49	0	0
1	0.959184	0.028266	49	2	1
36	0.938332	0.034496	46	1	0
48	0.917006	0.039761	44	1	1
64	0.874355	0.048006	43	2	0
71	0.831703	0.054318	41	2	1
85	0.809816	0.057128	38	1	0
106	0.787929	0.059629	37	1	0
109	0.766042	0.06186	36	1	0
127	0.744156	0.063847	35	1	0
148	0.722269	0.065613	34	1	0
162	0.700382	0.067176	33	1	0
211	0.656608	0.069745	32	2	0
213	0.634721	0.070771	30	1	0
232	0.612834	0.071635	29	1	0
253	0.567439	0.073168	27	2	1
256	0.522044	0.074022	25	2	0
298	0.499346	0.074202	23	1	0
316	0.428011	0.074156	21	3	1
317	0.404233	0.07375	18	1	0
318	0.380454	0.073144	17	1	0
319	0.332897	0.071314	16	2	0
323	0.214006	0.062603	14	5	0
326	0.190227	0.059993	9	1	0
327	0.166449	0.057012	8	1	0
337	0.14267	0.053597	7	1	0
338	0.118892	0.04966	6	1	0
339	0.095114	0.045062	5	1	0
345	0.071335	0.039576	4	1	0
350	0.047557	0.032758	3	1	0
358	0		2	2	0

Abbreviations: K-M, Kaplan-Meier; n, number; surv, survival; std err, standard error

Table 16: Time to study treatment discontinuation K-M analysis for the advanced subgroup of patients, PC arm

time	surv	std.err	n.risk	n.event	n.censor
0	1	0	44	0	0
1	0.977273	0.022468	44	1	0
8	0.954004	0.031774	42	1	1
14	0.930736	0.038589	41	1	0
15	0.907468	0.044085	40	1	0
16	0.884199	0.04871	39	1	0
22	0.860931	0.052693	38	1	1
29	0.837016	0.056396	36	1	0
30	0.813101	0.05964	35	1	0
38	0.765272	0.065018	34	2	0
40	0.741357	0.06724	32	1	0
42	0.717442	0.069194	31	1	1
52	0.692703	0.071093	29	1	1
58	0.667047	0.072942	27	1	0
63	0.641392	0.074512	26	1	0
64	0.615736	0.07582	25	1	0
71	0.564425	0.077699	24	2	0
78	0.513113	0.078652	22	2	0
100	0.486107	0.079013	19	1	1
120	0.432095	0.078926	18	2	1
122	0.403289	0.078746	15	1	0
126	0.374483	0.078213	14	1	1
127	0.343276	0.077672	12	1	0
141	0.312069	0.076624	11	1	0
148	0.280862	0.075048	10	1	0
163	0.249655	0.072909	9	1	0
203	0.218448	0.070157	8	1	0
246	0.187241	0.066715	7	1	0
275	0.156034	0.06247	6	1	0
316	0.124828	0.057242	5	1	0
329	0.093621	0.05073	4	1	0
330	0.062414	0.042344	3	1	0
337	0.031207	0.030581	2	1	0
375	0		1	1	0

Abbreviations: K-M, Kaplan-Meier; n, number; PC, physicians choice; surv, survival; std err, standard error

B2. Please confirm whether utility values were collected for patients:

On treatment pre-progression

Off treatment pre-progression

Off treatment progressed

Response: As per the ALCANZA protocol, patients enrolled in the trial were requested to complete quality of life questionnaires, including EQ-5D-3L and Skindex-29, at the beginning of every clinical visit [5]. The questionnaires were administered according to the Schedule of Events presented between pages seven and 12 of the study protocol. If patients were not required to return for a clinical visit (i.e. in progressive disease [PD]), questionnaires were completed over the telephone (except for visual analogue scales). The questionnaire collection schedules according to the specified states in question B2 are further explained below:

<u>On treatment pre-progression</u>

During the on treatment pre-progression state, according to the protocol, all questionnaires were to be completed on Day 1 of Cycles 1, 2, 4, 6, 8, 10, 12, 14, and 16 before any other study procedures are performed. Quality of life questionnaires were completed in person during the clinical visit[5].

<u>Off treatment pre-progression</u>

During the post-treatment follow-up period, quality of life questionnaires were initially completed within 30 days +/- 2 days of the End of Treatment (EOT). As specified in the protocol, all treated patients without disease progression after EOT were followed for objective response every 12 weeks (± 2 weeks) for a minimum of 24 months after the EOT visit, and then every 6 months (± 1 month); or until progressive disease, death or study closure[5]. According to the Schedule of Events, quality of life questionnaires were completed at the beginning of each clinical visit of the post treatment follow-up. During this state, questionnaires may be collected by phone or by mail for patients not required to return to clinic for posttreatment follow-up[5].

<u>Off treatment progressed</u>

According to the ALCANZA protocol, utility measurements after the development of confirmed PD were to be collected over the phone or by mail at every follow-up point as specified in the Schedule of Events of the ALCANZA study protocol[5]. Following the development of PD, all randomised patients were followed-up every 12 weeks for a minimum of 24 months after the EOT visit, and then every 6 months until patient withdrawal, death, or study closure.

B3. Please provide the mean EQ-5D-3L utility values and the number of patients at each of the time-points collected during the trial, including at baseline, stratified by study treatment and progression status, to the following specifications:

Time point	PFS						PPS	
	Brentuximab vedotin		Physician's choice		No longer on study treatment		All	
	Mean	N	Mean	N	Mean	N	Mean	N
Baseline								
Cycle 1								
….								

Response: Table 17 presents the mean EQ-5D-3L utility values and the number of patients at each of the time-points collected during the trial, in line with the collection schedules specified in the response to B2. These data are stratified by study treatment (brentuximab vedotin vs. Physician's Choice [PC] vs. no study treatment) and progression status (PFS vs. progressed). These utility data do not adjust for Skindex-29 scores which were shown to be a significant predictor of utility values (see Section B.3.4.3 of the company's submission Document B).

In line with the ALCANZA progression-free survival results (median PFS of 3.6 months for PC), after cycle four, there is a notable decrease in the number of completed EQ-5D-3L questionnaires in the PC arm. This is likely due to patients having progressed from the in-trial treatment of methotrexate or bexarotene and thereafter being reported in the post-progression survival group. As the maximum number of cycles of either treatment was sixteen, no PFS questionnaires beyond that point were captured. Due to the small patient numbers reporting quality of life at some collection points, particularly in the PPS category, no analysis in relation to change in utility over time was conducted, as it was considered that these results would be highly uncertain and lack robustness.

Table 17: Mean EQ-5D-3L utility values and number of patients at each timepoint, stratified by treatment and progression status

Time point	PFS						PPS	
	Brentuximab vedotin		Physician's choice		No longer on study treatment		All	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
CYCLE 1 DAY 1	0.64 (0.28)	45	0.60 (0.28)	40	-0.05 (0.66)	3	NA	NA
CYCLE 2 DAY 1	0.65 (0.24)	41	0.67 (0.27)	32	0.85 ()	1	0.1 (0.98)	2
CYCLE 4 DAY 1	0.73 (0.2)	37	0.63 (0.28)	19	0.74 (0.07)	2	0.43 (0.5)	3
CYCLE 5 DAY 1	0.19 ()	1	NA	NA	NA	NA	NA	NA
CYCLE 6 DAY 1	0.19 (NA)	1	0.72 (0.16)	12	0.39 (0.57)	2	0.49 (0.46)	5
CYCLE 8 DAY 1	0.74 (0.2)	31	0.72 (0.05)	5	0.66 (0.20)	2	0.62 (0.37)	3

CYCLE 10 DAY 1	0.79 (0.17)	30	0.72 (0.23)	5	0.69 (NA)	1	0.82 (0.21)	5
CYCLE 11 DAY 1	NA	NA	NA	NA	1()	1	NA	NA
CYCLE 12 DAY 1	0.73 (0.2)	27	0.76 (0.14)	5	0.77 (0.1)	3	0.78 (0.24)	3
CYCLE 13 DAY 1	NA	NA	NA	NA	0.81 ()	1	NA	NA
CYCLE 14 DAY 1	0.73 (0.23)	21	0.79 (0.15)	4	NA	NA	NA	NA
CYCLE 16 DAY 1	0.72 (0.25)	22	0.79 (0.18)	3	0.68 (0.28)	19	NA	NA
END OF TREATMENT	NA	NA	NA	NA	0.68 (0.22)	30	0.53 (0.39)	23
PFS FOLLOW-UP 998.25001	NA	NA	NA	NA	0.64 (0.32)	20	0.72 (0.18)	5
PFS FOLLOW-UP 998.25002	NA	NA	NA	NA	0.68 (0.34)	17	0.85 (0.22)	2
PFS FOLLOW-UP 998.25003	NA	NA	NA	NA	0.76 (0.12)	11	0.76 ()	1
PFS FOLLOW-UP 998.25004	NA	NA	NA	NA	0.78 (0.25)	12	NA	NA
PFS FOLLOW-UP 998.25005	NA	NA	NA	NA	0.8 (0.11)	6	0.73 ()	1
PFS FOLLOW-UP 998.25006	NA	NA	NA	NA	0.85 (0.18)	4	0.41 (0.29)	2
PFS FOLLOW-UP 998.25007	NA	NA	NA	NA	0.92 (0.11)	2	0.26 ()	1
PFS FOLLOW-UP 998.25008	NA	NA	NA	NA	0.85 (0.22)	2	NA	NA
OS FOLLOW-UP 998.75001	NA	NA	NA	NA	NA	NA	0.61 (0.32)	14
OS FOLLOW-UP 998.75002	NA	NA	NA	NA	NA	NA	0.68 (0.3)	14
OS FOLLOW-UP 998.75003	NA	NA	NA	NA	NA	NA	0.76 (0.26)	11
OS FOLLOW-UP 998.75004	NA	NA	NA	NA	NA	NA	0.59 (0.33)	10
OS FOLLOW-UP 998.75005	NA	NA	NA	NA	NA	NA	0.74 (0.16)	11
OS FOLLOW-UP 998.75006	NA	NA	NA	NA	NA	NA	0.66 (0.26)	7

OS FOLLOW-UP 998.75007	NA	NA	NA	NA	NA	NA	0.61 (0.42)	9
OS FOLLOW-UP 998.75008	NA	NA	NA	NA	NA	NA	0.63 (0.35)	10
OS FOLLOW-UP 998.75009	NA	NA	NA	NA	NA	NA	0.69 (0.29)	9
OS FOLLOW-UP 998.7501	NA	NA	NA	NA	NA	NA	0.63 (0.34)	6
OS FOLLOW-UP 998.75011	NA	NA	NA	NA	NA	NA	0.8 (0.01)	2
OS FOLLOW-UP 998.75012	NA	NA	NA	NA	NA	NA	0.75 (0.24)	3
OS FOLLOW-UP 998.75013	NA	NA	NA	NA	NA	NA	0.66 (0.1)	2
OS FOLLOW-UP 998.75014	NA	NA	NA	NA	NA	NA	0.85 ()	1
OS FOLLOW-UP 998.75015	NA	NA	NA	NA	NA	NA	0.85 ()	1
OS FOLLOW-UP 998.75016	NA	NA	NA	NA	NA	NA	0.78 (0.24)	3
OS FOLLOW-UP 998.75018	NA	NA	NA	NA	NA	NA	0.58 ()	1
OS FOLLOW-UP 998.7502	NA	NA	NA	NA	NA	NA	0.69 ()	1
OS FOLLOW-UP 998.75023	NA	NA	NA	NA	NA	NA	0.72 ()	1
OS FOLLOW-UP 998.75027	NA	NA	NA	NA	NA	NA	0.62 ()	1

Abbreviations: N, number; NA, not applicable; PFS, progression- free survival; PPS, post-progression survival; OS, overall survival; SD, standard deviation

Section C: Textual clarifications and additional points

C1. Please provide the protocol, trial statistical analysis plan (TSAP) and clinical study report (CSR) for the ALCANZA trial. Please provide the CSR for the median follow-up of 33.9 months if a CSR is available for this data-cut. If not, please provide the CSR for the median follow-up of 22.9 months.

Response: As requested the ALCANZA trial protocol and the trial Statistical Analysis Plan have been submitted. The CSR was not updated for the later data cut with the longer follow-up (i.e. 33.9 months); we have therefore provided the CSR for the original data cut with a median follow-up of 22.9 months.

C2. On page 91 of the company submission it is stated that "IFN-α is only one of two systemic treatments recommended for frontline use in patients with advanced-stage CTCL". Please list the other systemic treatment recommended for frontline use in the UK.

Response: The treatment and management of advanced CTCL is very complex and dependent on each individual patient and what is best for their disease.

According to the newly updated UK-CLG and BAD guideline for the management of CTCL, recommendations for frontline treatment are [redacted][1]. Please refer to *Section B.1.3.3 Clinical pathway of care* and Figure 11 of Document B from the company submission for a full description of the UK-CLG/BAD guideline for the management of CTCL. The following are the recommended frontline treatments and their category for advanced disease[1]:

[redacted]

Based on this, the frontline recommendations which are classified as systemic are [redacted], the statement made on page 91 of the company submission was referring [redacted] as these are the only recommended systemic therapies for frontline treatment in the updated UK-CLG/BAD guidelines for patients with MF stage IIB specifically.

Based on the UK Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) registry distribution by disease stage shown below, [redacted] of MF patients are stage IIB and represent the largest group within the advanced patients (see Figure 6). Takeda does recognise that the statement on page 91 was potentially misleading and that technically [redacted] recommended frontline treatments for advanced CTCL, albeit for a smaller group of patients.

Figure 6: UK CTCL prevalence by disease stage (PROCLIPI)[6]

C3. On page 43 of the company submission it is stated that results reported in a meta-analysis by Wu et al 2009 showed OS rates at 1 year and 5 years after alloSCT to be 85% and 80%, respectively. However, on page 44, it is stated that

> "The introduction of the Stanford Protocol has improved outcomes from those observed in Wu et al (2009).[14] In this single-centre UK study of alloSCT with minimal-intensity conditioning in advanced CTCL, patients (n=18, median age, 47 years), 1- and 5-year OS rates of approximately 80% and 55%, respectively, were observed.[15]

Please clarify how the data reported from the latter study showed improved outcomes to those from the meta-analysis.

Response: The meta-analysis by Wu *et al*.[7] includes 39 patients from 14 publications, dating back to 1986, with data from 20 patients that underwent alloSCT.

In response to the ERG's question we have sought the opinion of the UK's leading transplant specialist in CTCL and his view is that the Wu *et al.*[7] publication is a highly selected and biased study that does not reflect the real world. In particular, the 20 alloSCTs reported in Wu *et al.* are taken from 9 publications, and in 4 cases these are actually single-case reports. This makes it a highly selected and biased population because, in reality, there is a strong bias to only report positive outcomes in a single-case report. The specialist opinion is that although the Wu *et al.* data is informative on in its primary objective of describing outcomes between an alloSCT and an autologous SCT in CTCL, it is not reflective of outcomes that can be achieved with alloSCT in CTCL in the real world.

The London data presented during the 2017 annual EORTC conference[8] contained data on alloSCT outcomes in CTCL from a single centre comparing historical controls using chemotherapy conditioning prior to the alloSCT to a minimal-intensity (non-myeloablative)

conditioning regimen, called the Stanford Protocol, and demonstrated improved outcomes using this protocol.

The Stanford Protocol is different to a reduced intensity conditioning (RIC) regimen as it does not use chemotherapy agents such as melphalan, fludarabine nor cyclophosphamide which are used in both historical and RIC regimens.

When considering the outcomes after alloSCT, particularly in the long-term, the morbidity associated with chronic graft-versus-host-disease (GvHD) is an important clinical and patient relevant factor. Since the London data is based on a fully non-myeloablative conditioning regimen, it is expected that fewer GvHD events will occur and therefore outcomes in terms of both morbidity and survival will improve. This is a view that is shared by the relevant transplant centres in the UK, which have all adopted the Stanford Protocol as their standard of care conditioning regimen for CTCL patients undergoing alloSCT, [redacted].

C4. Please clarify whether Grade 3/4 AEs reported in Kim et al 2015 are equivalent to "serious" AEs (as stated in the company submission, the last column of Table 26 of Appendix F) or "severe" AEs.

Response: The Kim *et al.* 2015 study categorised adverse events as severe and not serious, as shown in Table 2 of the publication[3]. The use of the word 'serious AE' was a typographical mistake made by Takeda. Table 26 of Appendix F in the company submission should state *"severe AE"* and not *"serious AE"* to be in line with the adverse events as presented in Table 2 of the Kim *et al.* publication. We apologise for the confusion caused by this error.

References

1. Whittaker S, editor Presentation: British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018.
2. Takeda. Brentuximab vedotin (SGN-35) Statistical Analysis Plan, Study C25001. 2014.
3. Kim YH, Tavallaee M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(32):3750-8.
4. Mathieu S, Ram-Wolff C, Quereux G, et al., editors. The French experience of treatment of cutaneous T cell lymphoma with brentuximab vedotin: a series of 32 cases. 3rd World Congress of Cutaneous Lymphomas; 2016 October 26-28; Columbia University, NY, USA.
5. Takeda. Clinical Study Protocol C25001, Protocol Amendment 5. 2014.
6. Takeda UK data on file. Document number: Takeda/UK/DOF/003 Other claims. 2018.
7. Wu PA, Kim YH, Lavori PW, et al. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transplant. 2009;15(8):982-90.
8. Palanicawandar R, Morris S, Lozano-Cerrada S, et al., editors. Allogeneic stem cell transplantion for advanced cutaneous T-cell lymphoma with minimal-intensity conditioning. EORTC; 2017.

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Additional response to clarification question A12

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute for Health and Care Excellence

20th August 2018

Please find below the additional data requested by the Evidence Review Group (ERG) and NICE on 13th August 2018 in relation to Clarification Question A12 (i.e. a request to provide a simple breakdown of the occurrence of Adverse Events for the advanced subgroup from ALCANZA, as presented in Table 19 of Document B).

Response: A summary of the overall treatment-emergent Adverse Events (AEs) for the advanced subgroup (i.e. MF stage IIB+ and all pcALCL) from the 22.9 month follow-up of the ALCANZA trial is presented in Table 1. There is a high level of congruence between the AEs for both the ITT population (as shown on Table 19 in Document B of the Company submission) and the advanced subgroup observed within ALCANZA.

Table 1: Overall safety profile in ALCANZA (safety population), advanced subgroup*

n (%)	Brentuximab vedotin (n=49)	Physician's choice of methotrexate or bexarotene (n=44)
Any AE	46 (94)	40 (91)
Any grade ≥3 AE	19 (39)	24 (55)
Drug-related AE	41 (84)	31 (70)
Drug-related ≥3 AE	14 (29)	15 (34)
Serious AE	13 (27)	16 (36)
Drug-related serious AE	7 (14)	3 (7)
AE resulting in study drug discontinuation	12 (24)	4 (9)
On-treatment deaths†	3 (6)	0

*Based on the 2016 data cut with a median follow-up of 22.9 months
†On-treatment deaths were defined as deaths that occurred within 30 days after the last dose of study drug.
Abbreviations: AE, adverse event.

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Additional response to clarification question B1

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute for Health and Care Excellence

10th August 2018

Please find below the additional data requested by the Evidence Review Group (ERG) and NICE in relation to Clarification Question B1 (i.e. a request for the time to disease progression or death (PFS) K-M analysis for the advanced subgroup of patients in the brentuximab vedotin arm and the physician's choice (PC) arm of the trial, based on investigator (INV) assessment).

Response: The K-M analyses as requested are presented in Table 1 and Table 2 for brentuximab vedotin and physician's choice (PC), respectively.

Figure 1 shows both INV and independent review facility (IRF) assessed PFS for both brentuximab vedotin and PC. This highlights the concurrence of the INV and IRF reported outcomes. This is also indicated by the summary statistics in Table 3; for PC the outcomes are effectively the same (changing only at the 6th decimal place). Brentuximab vedotin looks to perform marginally worse when assessed by the INV (approximately nine days less in median PFS). Based on these minimal differences and the numbers at risk we do not expect INV assessed outcomes to drive results within the CE model.

Table 1: Time to disease progression or death (PFS) KM analysis for the advanced subgroup of patients in the brentuximab vedotin arm of the trial, based on investigator (INV) assessment

time	surv	std.err	n.risk	n.event	n.censor
	1		49		
28.82135524	0.979166667	0.020615177	48	1	1
35.77823409	0.958333333	0.028842444	47	1	0
64.59958932	0.9375	0.034938562	46	1	0
70.56262834	0.916193182	0.040118698	44	1	1
92.42710472	0.894886364	0.044485304	43	1	0
113.2977413	0.873579545	0.048259716	42	1	0
128.2053388	0.852272727	0.051572122	41	1	0
170.9404517	0.830965909	0.054506815	40	1	0
230.5708419	0.809659091	0.057122041	39	1	0
241.5030801	0.788352273	0.059459968	38	1	0
247.4661191	0.767045455	0.061552203	37	1	0
276.2874743	0.745738636	0.063423064	36	1	0
290.201232	0.724431818	0.065091644	35	1	0
297.1581109	0.703125	0.066573153	34	1	0
344.862423	0.680443548	0.06818002	31	1	2
353.8069815	0.657762097	0.069577864	30	1	0
435.301848	0.634270593	0.070947899	28	1	1
450.2094456	0.61077909	0.072104517	27	1	0
469.0924025	0.587287586	0.073057855	26	1	0
474.0616016	0.563796083	0.07381579	25	1	0
477.0431211	0.540304579	0.074384294	24	1	0
486.9815195	0.516813076	0.07476769	23	1	0
488.9691992	0.493321573	0.074968816	22	1	0
497.9137577	0.469830069	0.07498914	21	1	0
503.8767967	0.446338566	0.074828809	20	1	0
508.8459959	0.422847062	0.074486656	19	1	0
516.7967146	0.399355559	0.073960158	18	1	0
532.698152	0.375864055	0.07324534	17	1	0
565.4948665	0.352372552	0.072336619	16	1	0
594.3162218	0.327203084	0.071414445	14	1	1
690.7186858	0.297457349	0.070846783	11	1	2
817.9301848	0.26027518	0.071081471	8	1	2
830.8501027	0.223093012	0.06997934	7	1	0
929.2402464	0.178474409	0.068751762	5	1	1
1062.414784	0.133855807	0.064435568	4	1	0

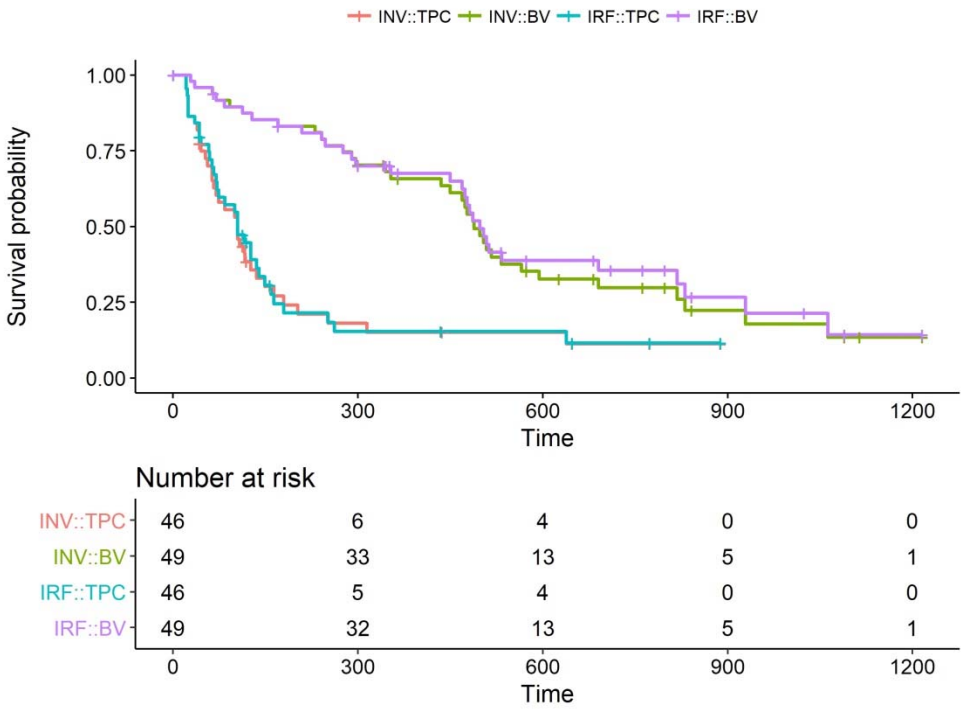
Abbreviations: INV, investigator; n, number; PFS, progression free survival; surv, survival; std err, standard error

Table 2: Time to disease progression or death (PFS) KM analysis for the advanced subgroup of patients in the physician's choice arm of the trial, based on investigator (INV) assessment

time	surv	std.err	n.risk	n.event	n.censor
	1		46		
21.86447639	0.954545455	0.03140224	44	2	2
23.85215606	0.931818182	0.03799912	42	1	0
24.84599589	0.863636364	0.051735471	41	3	0
35.77823409	0.840909091	0.055140521	38	1	0
39.75359343	0.818181818	0.05814565	37	1	0
42.73511294	0.772727273	0.06317721	36	2	1
45.71663244	0.748579545	0.065655831	32	1	1
52.67351129	0.724431818	0.067833381	31	1	0
56.64887064	0.700284091	0.069738067	30	1	0
63.60574949	0.651988636	0.072811483	29	2	0
66.58726899	0.627840909	0.074010781	27	1	0
70.56262834	0.603693182	0.075000203	26	1	0
74.53798768	0.579545455	0.07578797	25	1	0
84.47638604	0.555397727	0.07638032	24	1	0
100.3778234	0.53125	0.076781777	23	1	0
105.3470226	0.458806818	0.076863591	22	3	0
108.3285421	0.434659091	0.076517344	19	1	0
116.2792608	0.409090909	0.076168419	17	1	1
117.2731006	0.383522727	0.075577515	16	1	0
126.2176591	0.356128247	0.074979747	14	1	1
136.1560575	0.328733766	0.074047561	13	1	0
149.0759754	0.301339286	0.072768106	12	1	0
163.9835729	0.271205357	0.071458785	10	1	1
179.8850103	0.241071429	0.069583131	9	1	0
202.7433265	0.2109375	0.067093661	8	1	0
252.4353183	0.180803571	0.063918696	7	1	0
315.0472279	0.150669643	0.059949424	6	1	0
638.0451745	0.113002232	0.055549194	4	1	1

Abbreviations: INV, investigator; n, number; PFS, progression free survival; surv, survival; std err, standard error

Figure 1: Time to disease progression or death (PFS) K-M curves for the advanced subgroup of patients for investigator (INV) and independent review facility (IRF) outcomes



Abbreviations: BV, brentuximab vedotin; INV, investigator; IRF; independent review facility; TPC, the physician's choice; SE, standard error

Table 3: Time to disease progression or death (PFS) summary statistics for the advanced subgroup of patients for investigator (INV) and independent review facility (IRF) outcomes

Group	records	n.max	n.start	events	*rmean	*se(rmean)	median	0.95LCL	0.95UCL
INV assessed									
PC	46	46	46	35	227.2525	52.81450857	105.347023	66.58727	149.076
BV	49	49	49	35	541.0712	49.39528434	488.969199	450.2094	690.7187
IRF assessed									
PC	46	46	46	34	229.6979	53.73430486	105.347022	71.55647	149.076
BV	49	49	49	31	568.0035	53.10765568	497.9138	469.0924	830.8501

Abbreviations: BV, brentuximab vedotin; INV, investigator; IRF; independent review facility; PC, physician's choice; SE, standard error

NICE National Institute for Health and Care Excellence

Patient organisation submission

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Lymphoma Action
3. Job title or position	Senior Medical Writer
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are the UK's only charity dedicated to lymphoma. We've been providing in-depth, expert information for over 30 years, helping thousands of people affected by lymphoma, the fifth most common cancer. Our work drives improvements in the diagnosis, treatment and aftercare of lymphoma.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We asked patient contacts who we support to comment. We also had a call-out on our news section and on social media for patients to come forward who would like us to consider their views.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	People with CTCL can find it difficult to live with this condition, and it often has a significant impact on quality of life. It can take years to get a diagnosis, and many GPs and even haematologists, know little about it. This can feel very isolating. People with CTCL usually live with their condition for many years, and experience symptoms flaring up from time to time. Many people experience itching as a symptom, and often also as a side effect of treatment. Itching all the time can have a significant impact on quality of life, making people irritable and miserable. It can be difficult to sleep, so people with CTCL may frequently be very tired. If inflammation is widespread, some people find it difficult to control their body temperature, and develop fevers, chills and shakes, even hypothermia. Skin may be painful, particularly if people have tumours or if areas of skin weep or become infected. There is a risk of infections when skin is broken and irritated. People with CTCL are likely to be very self-conscious about the way their skin looks, which has a significant psychological impact.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are many possible treatments for CTCL, but the effects may be short-lived, and having to travel to hospital very regularly can be very onerous. Topical treatments and UV therapy can work for some people, but don't work for others. Many treatments are not tried and tested for skin lymphomas, but are used for other conditions. Coupled with most doctors' lack of knowledge about the disease, this increases patients' fears that the treatment won't work.

8. Is there an unmet need for patients with this condition?	There is unmet need for effective treatments proven to keep CTCL under control for longer so that people with this condition can have a better quality of life.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	None of the patients we surveyed have been treated with brentuximab, but they reported that existing treatments did not keep the disease under control for long. The duration of response would be a big advantage if proven to be greater than comparators.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There might be concerns over side effects. It would be important that clinicians explained the likely effects so patients could make an informed decision.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People live with this type of lymphoma for many years. Younger, working people might find it difficult to manage the condition alongside the demands of everyday life and are most likely to welcome a more intensive treatment that could give them longer disease control.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- People with CTCL can find it difficult to live with this condition, and it often has a significant impact on quality of life.
- Most existing treatments for CTCL have not been tested specifically for this population, but are used for other skin conditions or other cancers.
- Duration of response is very important when considering treatments for CTCL.
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Julia Scarisbrick**
2. Name of organisation	**Royal College of Pathologists/British Society for Haematology**

3. Job title or position	**Consultant dermatologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To reduce tumour burden with complete of partial response, delay time to next treatment and improve quality of life

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	At least a partial response reduction in tumour burden by 50% or more
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a desperate need for new and improved treatments patients suffer from painful, itchy, unsightly lesions with a huge impact on quality of life and represents a significant burden to the health system
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Immunotherapy (interferon , bexarotene and/or photopheresis) Chemotherapy
• Are any clinical guidelines used in the treatment of the	EORTC guidelines EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome– update 2017. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, Gniadecki R, Klemke C-D, Ortiz-

condition, and if so, which?	Romero P, Papadavid E, Pimpinelli N, Quaglino P, Ranki A, Scarisbrick J, Stadler R, Väkevä L, Vermeer M, Whittaker S, Willemze R, Knobler R. Eur J Cancer 2017;77:57-74 EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, Olsen E, Kim YH, Dummer R, Pimpinelli N, Whittaker S, Hodak E, Cerroni L, Berti E, Horwitz S, Prince HM, Guitart J, Estrach T, Sanches JA, Duvic M, Ranki A, Dreno B, Ostheeren-Michaelis S, Knobler R, Wood G, Willemze R. Blood. 2011 Oct 13;118(15):4024-35 BAD guidelines Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. Whittaker SJ, Marsden JR, Spittle M, Russell Jones R; British Association of Dermatologists; U.K. Cutaneous Lymphoma Group. Br J Dermatol. 2003 Dec;149(6):1095-1107
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are a number of treatments listed for first / second line therapy but not order of preference and treatments are decided by specialist centre on an individual patient basis according to specific patients needs and expertise of the centre
• What impact would the technology have on the current pathway of care?	Brentuximab would provide an additional effective therapy for CD30 expressing CTCL
10. Will the technology be used (or is it already used) in	Yes this would be an addition to our anti CTCL therapy

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	No difference
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None it is used for other lymphomas
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, brentuximab is effective and shown to be superior in response rates, response duration and quality of life compared to bexarotene or methotrexate with a similar rate of adverse effects
• Do you expect the technology to increase	Data not yet available but improved progression free survival would reduce the disease burden to patient and NHS

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	All CD30+ expressing CTCL >5%
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	There is no additional difficulties and drug is in regular use

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Improved quality of life
16. Do you consider the technology to be innovative in	Yes, brentuximab is superior to the comparators of bexarotene or methotrexate reducing tumour burden , improving progression free survival, time to next treatment and qualuty of life

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No it will be an additional option for CD30 expressing CTCL
• Does the use of the technology address any particular unmet need of the patient population?	Yes this is an important effective treatment option for CD30 expressing CTCL
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The number of adverse effects are similar to comparators of bexarotene or methotrexate There is a high rate of neuropathy but this is typically grade 1-2 and improves on stopping
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Response rate (complete + partial responses) Progression free survival Time to next treatment Quality of life (Skindex 29)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No the main adverse event is neuropathy which typically resolves / improves on stopping brentuximab

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	Not relevant
21. How do data on real-world experience compare with the trial data?	Limited experience has shown brentuximab to be highly effective in CD30 expressing CTCL out of clinical trials
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Brentuximab is currently available for non Hodgkin's lymphoma and systemic large cell anaplastic lymphoma but not cutaneous large cell anaplastic lymphoma

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Brentuximab is an effective therapy for CD30 expressing CTCL with response rates around 60%
- Brentuximab has improved response duration compared to comparator of bexarotene or methotrexate
- Brentuximab improves quality of life compared to comparator of bexarotene or methotrexate
- CD30 expressing CTCL are incurable lymphomas with considerable mortality and reduced quality of life from pain , itching and unsightly lesions
- Currently treatment options are limited and all options may be exhausted leaving the patients with palliation only

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**JULIA SCARISBRICK**
2. Name of organisation	**UNIVERSITY HOSPITAL BIRMINGHAM**

3. Job title or position	**CONSULTANT DERMATOLOGIST**
4. Are you (please tick all that apply):	**X**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with this condition? **X**☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** ☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Brentuximab will improve skin patch/plaque and tumour as well as lymph node and blood disease. Cure is generally not possible in MF but improving the tumour burden improves quality of life and may prolong survival. It may also give temporary remissions where a bone marrow transplant may be given with chance of cure.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	50% improvement is generally acceptable (partial response)
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	A massive unmet need , few systemic therapies available and nothing since bexarotene in 2000. Advanced patients should be treated with immunotherapies such as bexarotene , interferon alpha and brentuximab before chemotherapy which immunosuppresses a patient and reduces the innate protection against lymphoma. Treatments such as bexarotene and interferon are generally effective for 9-12 months before loss of response (>50%). Patients may survive several years and treatment options are very limited so patients suffer from painful, itchy , weepy skin lesions.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patient with CD30 positive lymphoma MF are typically treated with systemic treatments and may also have additional skin directed therapies (radiotherapy, TSE, steroids). The systemic therapies are bexarotene and interferon alpha, chemotherapy (gemcitabine, CHOP). Methotrexate and photopheresis are options in erythrodermic patients (red all over often with blood involvement) but these patients are not always CD30.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes the EORTC Guidelines Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, Gniadecki R, Klemke C-D, Ortiz-Romero P, Papadavid E, Pimpinelli N, Quaglino P, Ranki A, Scarisbrick J, Stadler R, Väkevä L, Vermeer M, Whittaker S, Willemze R, Knobler R. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome– update 2017. *Eur J Cancer* 2017;77:57-74 The UK Guidelines (2003) were recently updated and available soon Gilson D, Whittaker S, Child F, Scarisbrick J, Illidge T, Parry E, Rezvani K, Dearden C, Morris S. British Association of Dermatologists and UK Cutaneous Lymphoma Group Guidelines for the Management of Primary Cutaneous Lymphomas. *Br J Dermatol.* In Press 2018
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The management pathways are very similar in Europe, our guidelines list treatment options in no particular order of preference which is decided on an individual patient basis according to patient need. Due to the lack of available treatments most patients receive all treatment options with consecutive treatments given until loss of response. In US treatment pathways are similar (NCCN guidelines available at www.nccn.org) but they are a few more licenced treatment options available in the USA (romidepsin, vorinostat, denileukin diftitox, mogamuzilumab, brentuximab) I have experience with international treatment options in my role as Chair of the EORTC Cutaneous Lymphoma Gp and on the Board of Directors for the International Society of Cutaneous Lymphoma. As well

	as lead for the PROCLIPI study, an international study collecting data on MF and SS including treatment responses and quality of life (enrolled 1100 patients since 2015 from 47 Sites, 19 counties in 6 continents)
• What impact would the technology have on the current pathway of care?	Brentuximab has proven to be highly effective in CD30 positive MF and provides response rates around 60% with response duration >1years. This would add an effective therapy for our patients reducing morbidity from the skin lesions and improving quality of life.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, and we have been able to treat a number of patients outside clinical trials with this using the compassionate use program.
• How does healthcare resource use differ between the technology and current care?	n/a
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Prescribed in Specialist clinics but may be given locally by centres with experience of BV (which is already used for systemic LCAL) this will prevent some patients having to travel many miles to their specialist centre
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal training, most large hospitals familiar with the drug

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes , there is a unmet need for treatment of CD30 cutaneous lymphomas with patients suffering painful, itchy disfiguring lesions due to lack of effective therapies
• Do you expect the technology to increase length of life more than current care?	This may be a reality, not yet known
• Do you expect the technology to increase health-related quality of life more than current care?	Vastly improve
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	CD30 positive >5% skin lymphomas
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No , similar
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
16. Do you consider that the use of the technology will result in any substantial health-	We prefer using a skin related questionnaire as quality of life is reduced in our patients and they suffer pain, itching , insomnia, disfigurement, severe odour, depression, social isolation – not all captured in QALY

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It will provide another treatment option for patients which will likely alleviate symptoms and reduce tumour burden, increasing quality of life
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes , few current effective treatment options , usually exhausted

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The only adverse affect which may impact QOL is neuropathy but in my experience those with neuropathy which is typically grade 1 -2 and reverts to grade 1 on stopping doesn't affect QOL
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes Response rate, itch, QOL, progression free survival
• If surrogate outcome measures were used, do they adequately predict	n/a

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
21. Are you aware of any new evidence for the comparator treatments?	no
22. How do data on real-world experience compare with the trial data?	Same in my experience and others
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. All subgroups with advanced disease are included in the population eligible for brentuximab vedotin treatment. Would the approach to management be similar in patients with pcALCL, MF and SS?	Yes

25. Is it likely the effect of treatment would be equal in these subgroup populations?	yes
26. Low-dose methotrexate and IFN-α are not currently licensed in Europe for the treatment of CTCL but are included as comparators. Are these treatments used as 2nd line treatments in current clinical practice in England?	Yes and included in our guidelines
27. Gemcitabine monotherapy and multi-agent chemotherapy are not considered appropriate comparators as the company suggests brentuximab vedotin would be used before chemotherapy in the treatment pathway. Should multi-agent	No , this is not in line with our guidelines

chemotherapy (CHOP) be considered a comparator?	
28. EORTC and UKCLG guidelines include TSEB in their recommendations for treatment of advanced-stage MF and SS, is TSEB used in current clinical practice in England?	Yes
29. What proportion of patients treated with 2nd line systemic therapy whose disease responds sufficiently to treatment would become eligible for an alloSCT?	Difficult to predict , at present only ~5% with advanced disease receive an alloSCT
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Brentuximab is an effective treatment for CD30 CTCL, response ~60%
- Brentuximab is safe
- Brentuximab improves quality life
- There is an unmet need for effective therapies in CD30 CTCL and brentuximab will provide another treatment option
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Clinical expert statement

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Sean Whittaker**
2. Name of organisation	**Guys and St Thomas NHS Foundation Trust**

3. Job title or position	**Consultant Dermatologist** **Prof of Cutaneous Oncology Kings College London** **Co-Director of Kings Health Partners Comprehensive Cancer Centre**
	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? **X** a specialist in the clinical evidence base for this condition or technology? **X** other (please specify): Head of academic research group in CTCL
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	For refractory CTCL aim is to obtain high rates of good quality and durable clinical responses with a reduction in patient morbidity and disease progression rates and potential improved overall survival.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Significant and durable improvement in skin disease (mSWAT) and global disease response scores consisting of skin + node + blood responses as defined by Olsen et al (JCO)
9. In your view, is there an unmet need for patients and	Yes Current treatment options for refractory CTCL provide low response rates which are of short duration. There is also little evidence of an impact on PFS for CTCL and no data on OS. Patient morbidity is

healthcare professionals in this condition?	very high especially because of progressive skin disease as well as the consequences of extra-cutaneous involvement
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	See UK Cutaneous Lymphoma group (UKCLG) guidelines (2018)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Journal of Dermatology 2018 in press; Also US NCCN guidelines (website) and EU EORTC guidelines (EJC 2016)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes – well defined pathway through regional SSMDTs and Supra-network MDTs and clinics consisting of multidisciplinary clinical teams; Pathway defined according to “NICE IOG for skin cancers including melanoma”

• What impact would the technology have on the current pathway of care?	Improve clinical responses for refractory disease and improved durable responses compared to available options
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently used via access to compassionate use program for refractory CD30+ CTCL and will be used according to current care practices
• How does healthcare resource use differ between the technology and current care?	Other options have lower responses rates and shorter duration of response but no specific difference to resource (infrastructure) required to deliver technology compared to current care
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Should only be recommended through UK specialist supra-network centres but could be delivered in secondary care setting closer to patient's home if more convenient
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None as is currently used in secondary care setting for other indications
12. Do you expect the technology to provide clinically	Yes as improved response rates, better quality of response and longer duration of response will reduce the huge morbidity experienced by patients

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes especially if this technology allows a higher number of patients to be recruited for a reduced intensity allogeneic transplant (alloSCT)
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – the high quality responses reported will significantly reduce the major burden and morbidity of advanced skin disease which is currently an unmet medical need and a unique challenge to all healthcare sectors who have to support CTCL patients.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	No – intervention will be similar to other single agent chemotherapy regimes used for this clinical indication. No additional requirements above standard approaches for patients receiving chemotherapy.

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No – CD30 expression on tumour samples will be required to confirm utility of drug prior to starting but this is already part of the standard immune-profiling of these tumours. Discontinuation will be managed according to usual disease assessment guidelines and drug toxicity profiles
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	The intervention provides more durable clinical responses which are rarely achieved for this group of CTCL patients and this will reduce patient and carer dependency on complex skin care regimes delivered either in the community or hospital outpatient/inpatient settings. As such this would provide a significant benefit in terms of patient morbidity and costs.

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – quality/depth and durability of clinical response offer significant potential to reduce huge patient morbidity as outlined above. In addition toxicity is manageable and has not increased rates of sepsis which is currently seen with standard chemotherapy regimes.
• Is the technology a 'step-change' in the management of the condition?	Yes – substantial and durable clinical responses are very difficult to achieve for CTCL with current therapies and this technology has the potential to also allow some patients to be offered consolidation with an alloSCT which has a much higher success rate for those with minimal disease at the time of transplant.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – striking levels of chemo-resistance in CTCL has prevented patients achieving substantial and durable clinical responses in the past. High dose multi-agent chemotherapy regimens are also invariably associated with major sepsis complications in CTCL patients due to poor skin barrier function and disease associated restriction of the normal T-cell repertoire in CTCL. The technology will increase the numbers of

	patients eligible for alloSCT and therefore reduce the numbers of patients receiving only maintenance therapies with palliative intent.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Main side effect is peripheral neuropathy which can usually be managed easily and minimised through dose alterations. If symptoms of neuropathy are closely monitored and restricted to grade I-II, there is a high probability of improvement.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – see UKCLG 2018 guidelines
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Durable response rates – measured in trial as primary endpoint ORR4 Progression free survival – PFS measured as secondary endpoint

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any that have emerged since completion of the trial
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No but recent 2018 UKCLG guidelines have assessed the evidence in detail
21. Are you aware of any new evidence for the comparator treatments?	No
22. How do data on real-world experience compare with the trial data?	Our experience of subsequent use of Brentuximab on 25 patients since completion of the trial has shown similar efficacy and no new adverse effects. This has also enabled us to consider transplant options for a proportion of these patients with the potential to produce durable long term remissions and improve OS.

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. All subgroups with advanced disease are included in the population eligible for brentuximab vedotin treatment. Would the approach to management be similar in patients with pcALCL, MF and SS?	Yes for those patients with tumours showing CD30 expression

25. Is it likely the effect of treatment would be equal in these subgroup populations?	Yes
26. Low-dose methotrexate and IFN-α are not currently licensed in Europe for the treatment of CTCL but are included as comparators. Are these treatments used as 2nd line treatments in current clinical practice in England?	Whilst low dose methotrexate is not licensed for CTCL, it has been used for over 40 years in the UK management of CTCL patients as a second line option. There are actually only two licensed therapies for CTCL in Europe namely Alpha interferon and Bexarotene. Alpha interferon is used as second line for CTCL but was not the comparator in this trial. Bexarotene, which was the other comparator, is used for CTCL as second line.
27. Gemcitabine monotherapy and multi-agent chemotherapy are not considered appropriate comparators as the company suggests brentuximab vedotin would be used before chemotherapy in the treatment pathway. Should multi-agent	Multi-agent chemotherapy regimes, such as CHOP, are not routinely used for CTCL as a standard care because of lack of efficacy, except for rare patients, and significant toxicity especially sepsis reflecting the disease associated T-cell immune-suppression. Invariably CHOP is associated with partial responses after two cycles and progression after four cycles.

chemotherapy (CHOP) be considered a comparator?	
28. EORTC and UKCLG guidelines include TSEB in their recommendations for treatment of advanced-stage MF and SS, is TSEB used in current clinical practice in England?	Yes. TSEB is a critically important modality but only for treatment of patients with refractory skin disease. Low dose regimens (12Gy in 8 fractions) have enabled more patients to complete treatment with only a modest reduction in efficacy. Median duration of response is 12 months but patients with extra-cutaneous disease do not benefit.
29. What proportion of patients treated with 2nd line systemic therapy whose disease responds sufficiently to treatment would become eligible for an alloSCT?	All patients with stage III-IVA2 who achieve a response to 2nd line therapy are considered for an alloSCT if they are eligible in terms of age, performance status and identification of a matched donor. Therefore the proportion who are eligible would be at best 30%.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Technology associated with excellent durable response (ORR4) compared to two comparators including one (Bexarotene) of only two licensed EMA approved treatments for CTCL.
- Improved durability and depth of clinical benefit provide a significant benefit and address unmet treatment need for refractory CTCL.
- Safety profile is satisfactory and technology does not significantly increase sepsis risk in CTCL unlike chemotherapy regimens.
- Improved quality and durability of clinical response provide a bridge to alloSCT for eligible patients and potential for improved long term outcomes including overall survival after transplant.
- Technology addresses a key unmet need for CTCL patients and has the potential to reduce significant patient morbidity and associated costs.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

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

This report was commissioned by the NIHR HTA Programme as project number 17/56/12

Completed 25 October 2018

CONTAINS [redacted]
AND [redacted] DATA

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

Date completed: 25 October 2018

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 17/56/12

Acknowledgements: The authors would like to thank Arvind Arumainathan, Consultant Haematologist at The Clatterbridge Centre NHS Foundation Trust and James Mahon, Director of Coldingham Analytical Services who provided feedback on draft versions of the report. The authors would also like to thank Geetha Menon, Consultant Haematopathologist, Royal Liverpool University Hospital NHS Trust, who provided information on CD30-postive cutaneous T-cell lymphoma.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Declared competing interests of the authors: None.

This report should be referenced as follows: Fleeman N, Stainthorpe A, Houten R, Richardson M, Boland A, Beale S, Dundar Y, Kotas, E, McEntee J, Syndikus I. Brentuximab vedotin for treating relapsed or refractory CD30-positive cutaneous T-cell lymphoma [ID 1190]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2018

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

Table of contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

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.

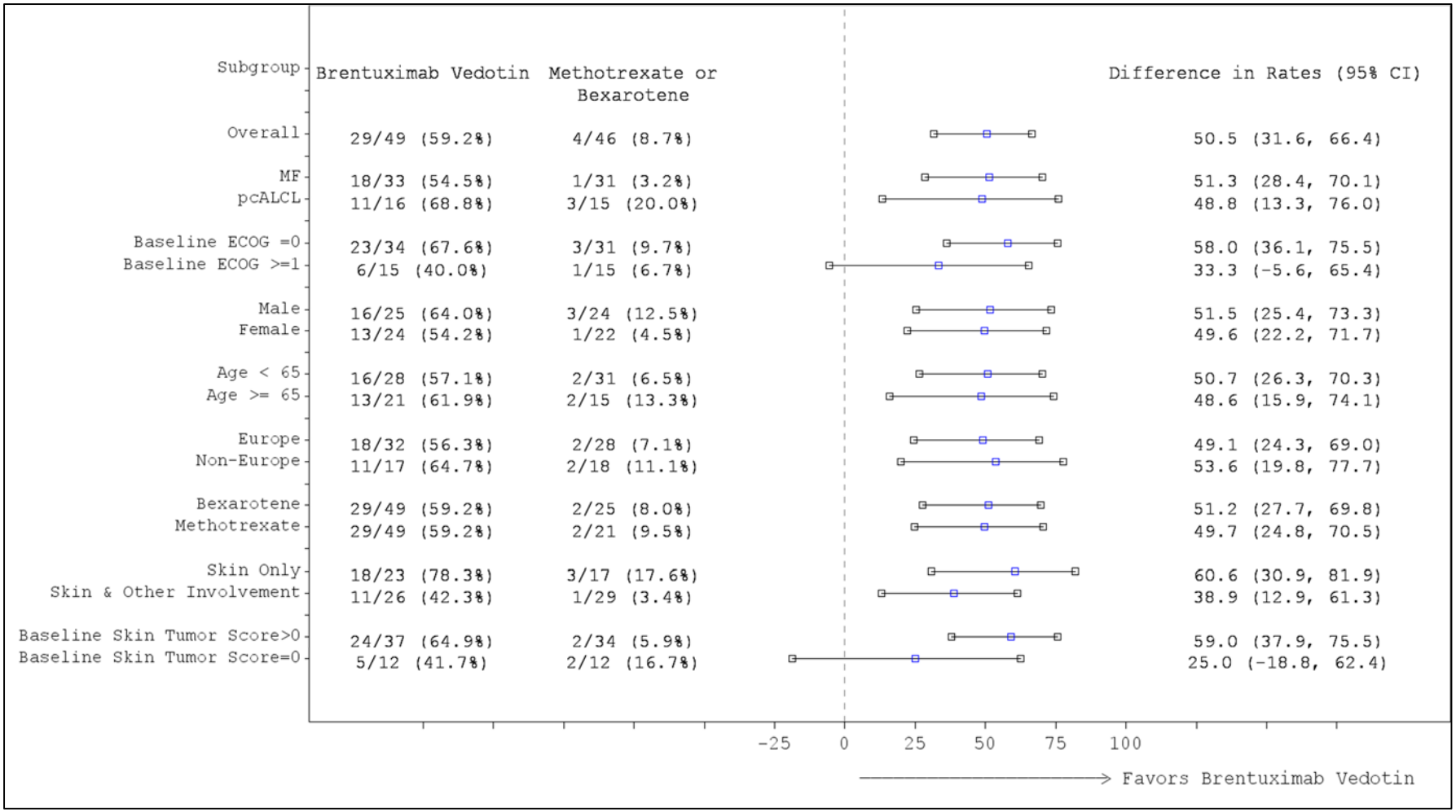


Figure 1 Subgroup analyses of ORR4 per IRF; advanced stage CTCL patient population (33.9 month follow-up)

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.

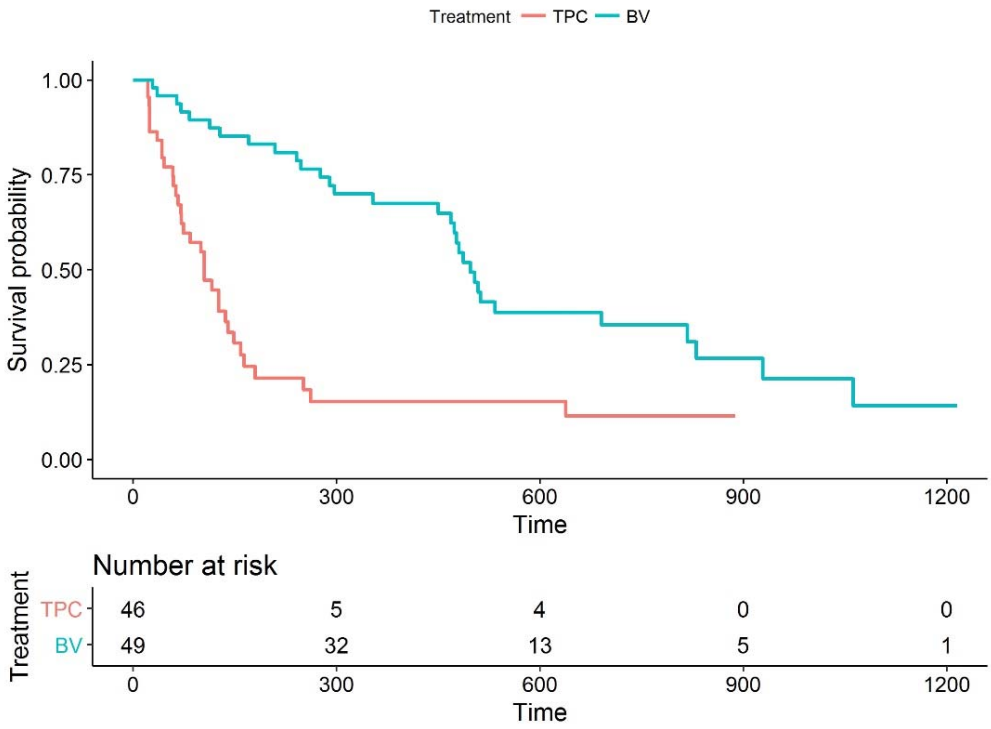


Figure 2 K-M graph for IRF-assessed PFS in the advanced stage CTCL patient subgroup of the ALCANZA trial (33.9 month follow-up)

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.

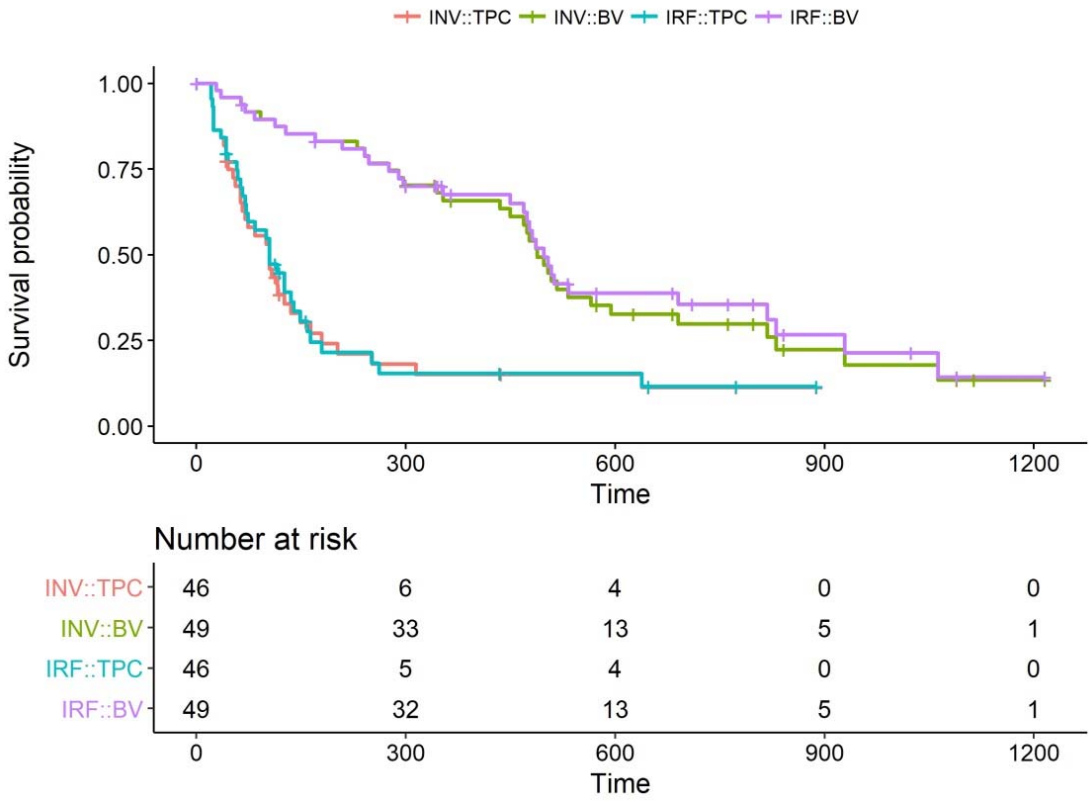


Figure 3 K-M curves for IRF-assessed PFS and investigator-assessed PFS for the subgroup of patients with advanced stage CTCL

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.

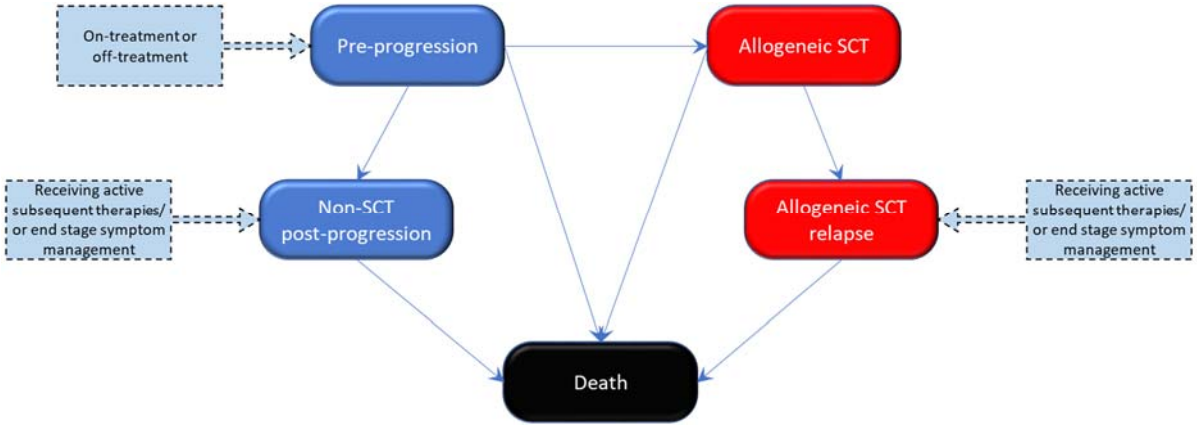


Figure 4 Health state structure of the company model

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.

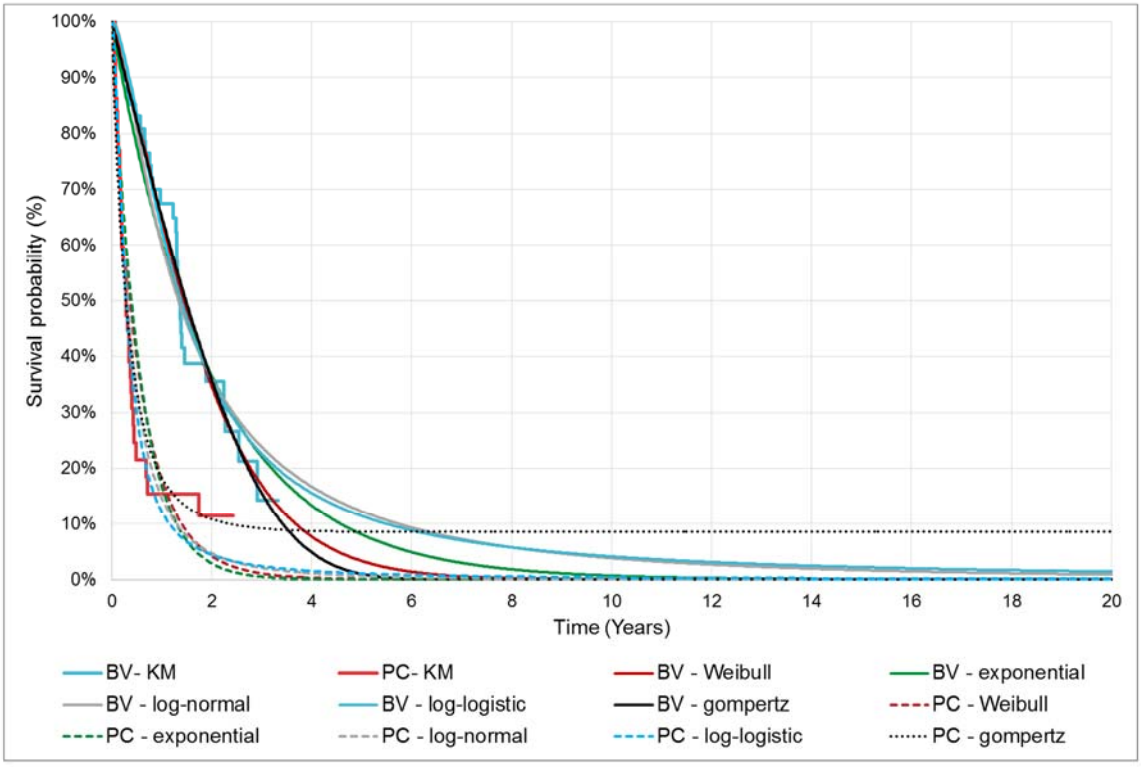


Figure 5: ALCANZA trial PFS K-M data and fitted parametric survival curves

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.

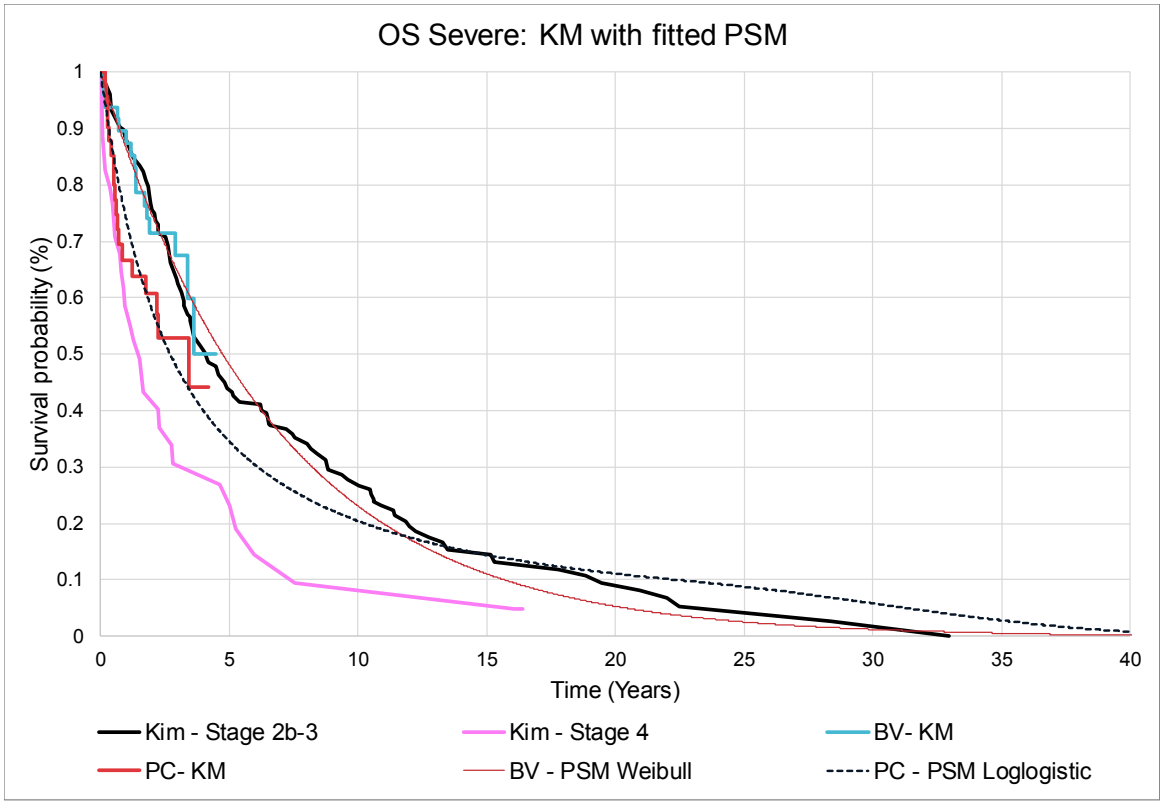


Figure 6 OS ALCANZA trial K-M data, extrapolations and published data [26]

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.

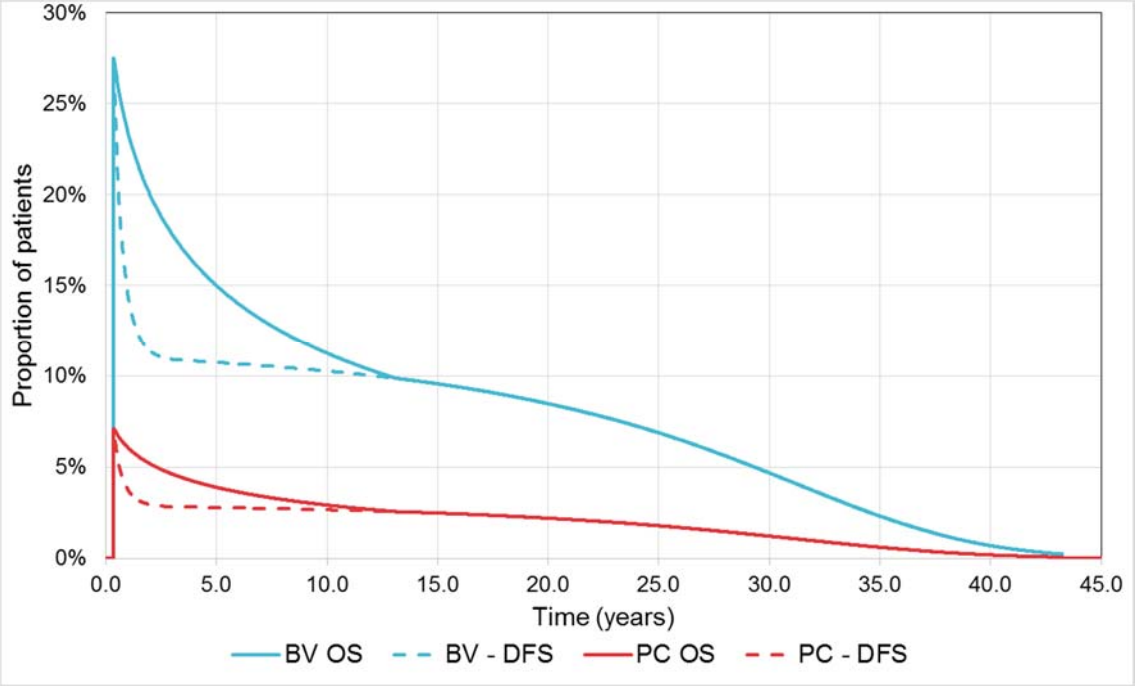


Figure 8 Modelled post-alloSCT DFS and OS

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

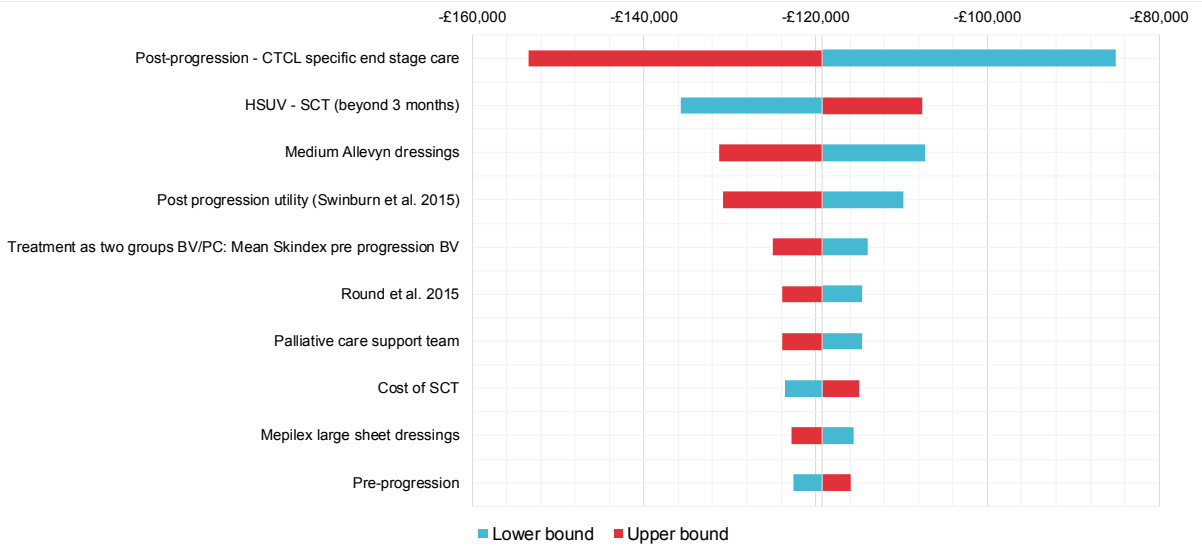
LYG=life year gained; PAS= Patient access scheme; PC=physician's choice; QALY=quality adjusted life year
Source: CS, adapted from summary document, Section A.13 Table 7; CS, Section B.3.7.1 Table 51

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]).

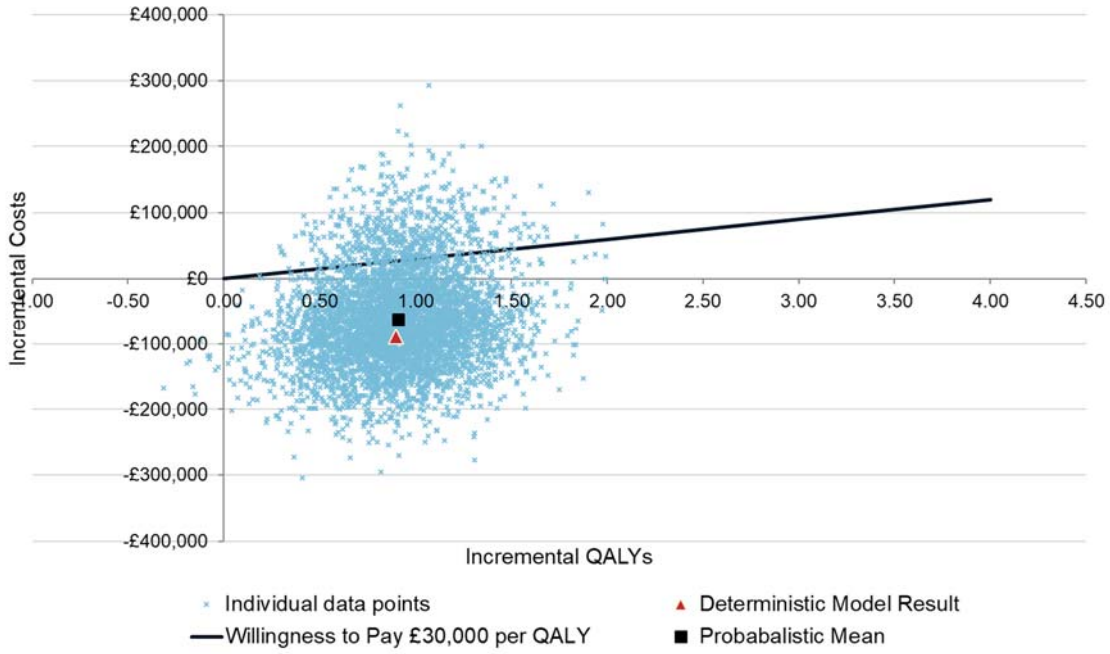


Figure 10 Scatter plot showing cost effectiveness of treatment with BV versus PC (5,000 iterations)

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%.

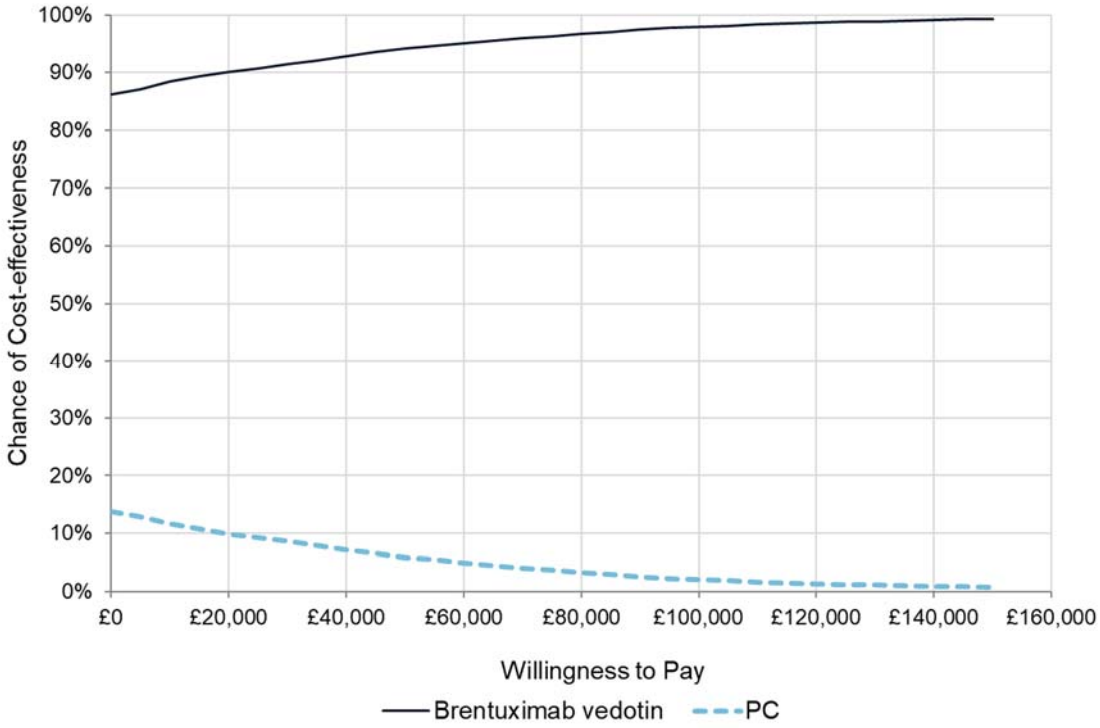


Figure 11 Cost effectiveness acceptability curve of treatment with BV vs PC

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.

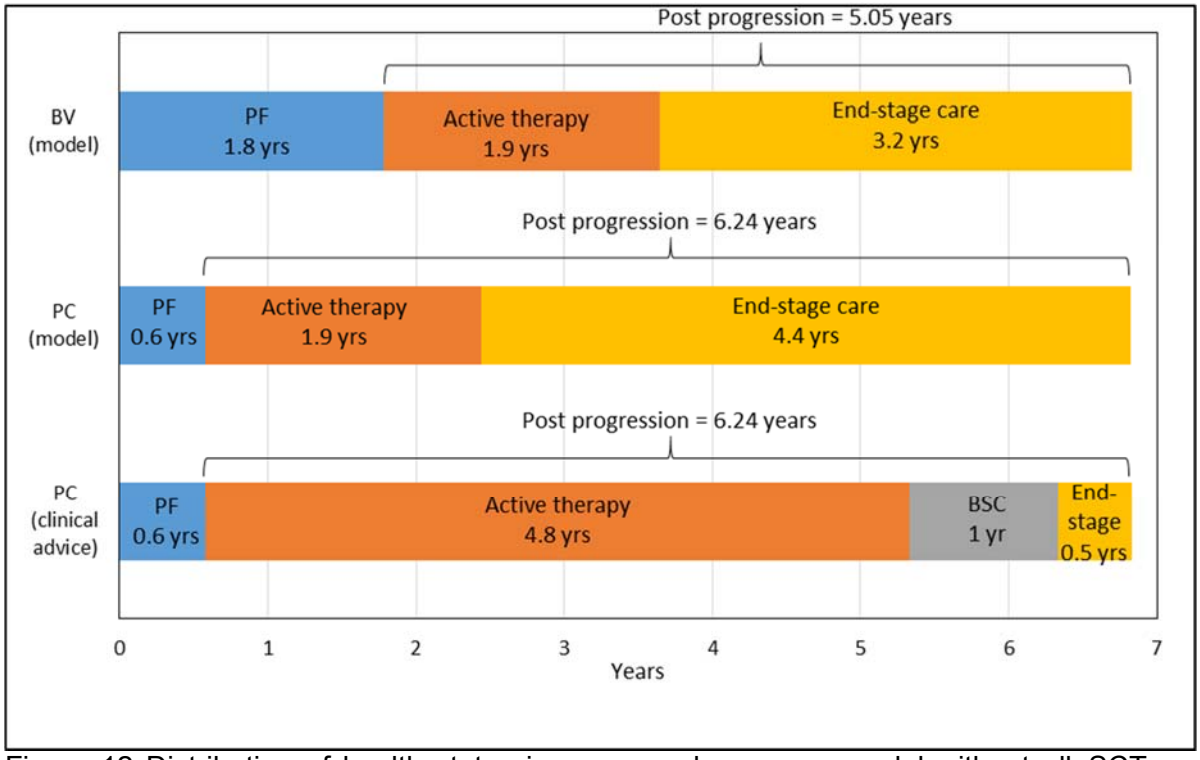


Figure 12 Distribution of health states in company base case model without alloSCT and according to clinical advice

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.

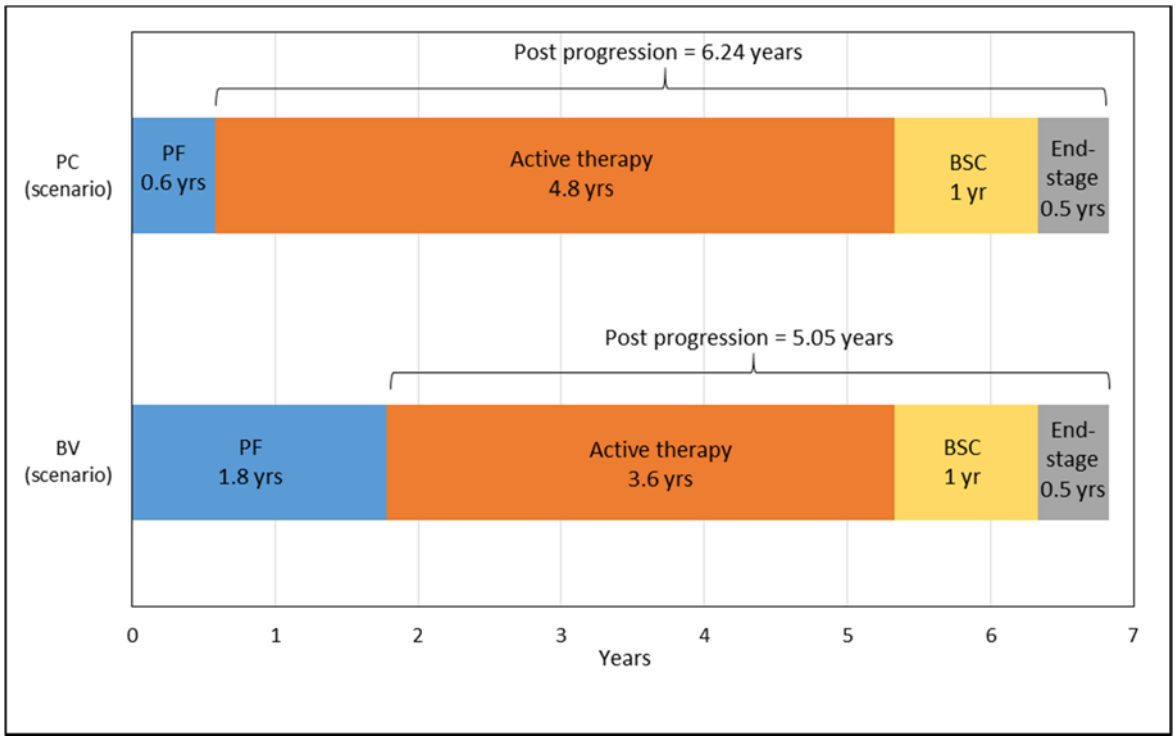


Figure 13 ERG Scenario 1: Changes to the post-progression pathway: distribution of health states

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.

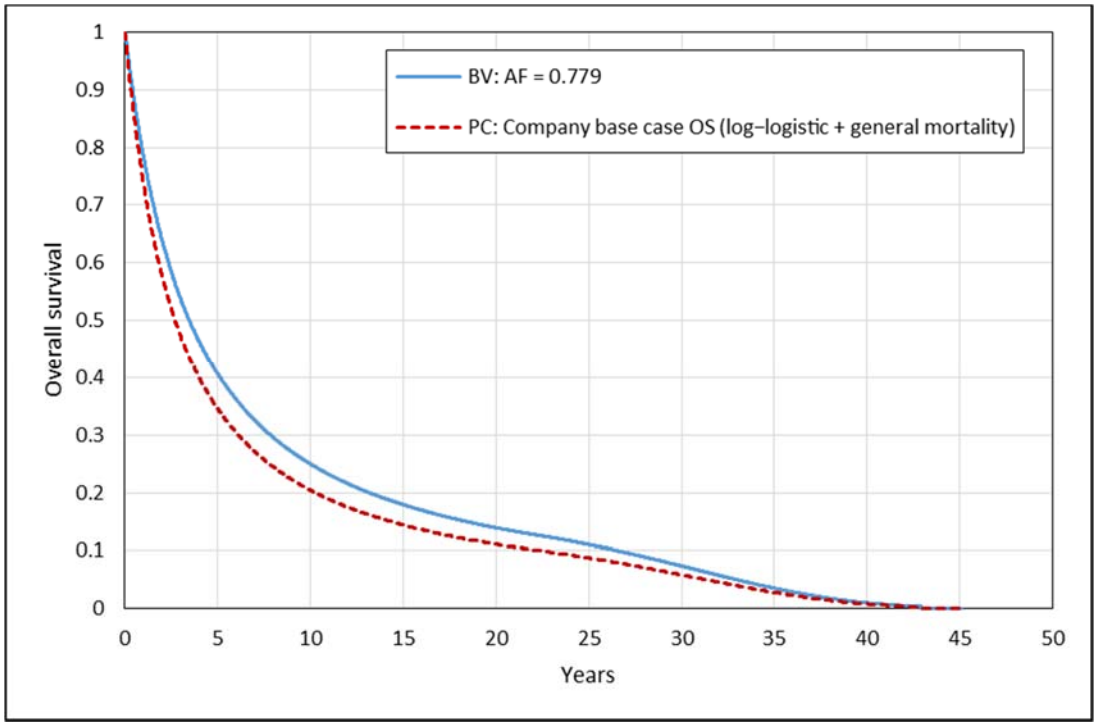


Figure 14 ERG scenario 3: OS gain (mean 1.2 years)

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

.

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.

8 REFERENCES

1. Zinzani PL, Bonthapally V, Huebner D, Lutes R, Chi A, Pileri S. Panoptic clinical review of the current and future treatment of relapsed/refractory T-cell lymphomas: Cutaneous T-cell lymphomas. Crit Rev Oncol Hematol. 2016 Mar;99:228-40.
2. Wilcox RA. Cutaneous T-cell lymphoma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016 Jan;91(1):151-65.
3. Bekkenk MW, Geelen FA, van Voorst Vader PC, Heule F, Geerts ML, van Vloten WA, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood. 2000 Jun 15;95(12):3653-61.
4. Kim YH, Whittaker S, Horwitz S, Duvic M, Dummer R, Scarisbrick JJ, et al. Brentuximab vedotin demonstrates significantly superior clinical outcomes in patients with CD30-expressing cutaneous T cell lymphoma versus physician's choice (methotrexate or bexarotene): The phase 3 ALCANZA study. Blood. 2016;128:182.
5. Misery L. Pruritus in cutaneous T-cell lymphomas. In: Carstens E, Akiyama T, editors. Itch: Mechanisms and treatment. Boca Raton, FL: CRC Press/Taylor & Francis; 2014. Chapter 8.
6. Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. N Engl J Med. 2004 May 06;350(19):1978-88.
7. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005 May 15;105(10):3768-85.
8. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010 Nov 01;28(31):4730-9.
9. Beynon T, Radcliffe E, Child F, Orlowska D, Whittaker S, Lawson S, et al. What are the supportive and palliative care needs of patients with cutaneous T-cell lymphoma and their caregivers? A systematic review of the evidence. Br J Dermatol. 2014 Mar;170(3):599-608.
10. Public Health England. Registration of Cutaneous T-Cell Lymphoma (CTCL) in England: National Cancer Registration and Analysis Services Short Report 2016397. 2016; Available from: http://www.ncin.org.uk/view?rid=3275 [Accessed 19 July 2018]
11. Beynon T, Selman L, Radcliffe E, Whittaker S, Child F, Orlowska D, et al. 'We had to change to single beds because I itch in the night': a qualitative study of the experiences, attitudes and approaches to coping of patients with cutaneous T-cell lymphoma. Br J Dermatol. 2015 Jul;173(1):83-92.
12. Orlowska D, Selman LE, Beynon T, Radcliffe E, Whittaker S, Child F, et al. "It's a traumatic illness, traumatic to witness." A qualitative study of the experiences of bereaved family caregivers of patients with cutaneous T-cell lymphoma. Br J Dermatol. 2018 Oct;179(4):882-8.
13. Demierre MF, Tien A, Miller D. Health-related quality-of-life assessment in patients with cutaneous T-cell lymphoma. Arch Dermatol. 2005 Mar;141(3):325-30.
14. Wright A, Wijeratne A, Hung T, Gao W, Whittaker S, Morris S, et al. Prevalence and severity of pruritus and quality of life in patients with cutaneous T-cell lymphoma. J Pain Symptom Manage. 2013 Jan;45(1):114-9.
15. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. Cancer. 2006 Nov 15;107(10):2504-11.
16. Selman LE, Beynon T, Radcliffe E, Whittaker S, Orlowska D, Child F, et al. 'We're all carrying a burden that we're not sharing': a qualitative study of the impact of cutaneous T-cell lymphoma on the family. Br J Dermatol. 2015 Jun;172(6):1581-92.
17. Tsang Y, Gu T, Sharma G, Raspa S, Drake B, 3rd, Tan H. Healthcare resource utilization, costs of care, and treatment of mycosis fungoides cutaneous T-cell lymphoma

patterns in a large managed care population: a retrospective US claims-based analysis. J Dermatolog Treat. 2018:1-7.
18. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. J Clin Oncol. 2015 Nov 10;33(32):3759-65.
19. Fauconneau A, Pham-Ledard A, Cappellen D, Frison E, Prochazkova-Carlotti M, Parrens M, et al. Assessment of diagnostic criteria between primary cutaneous anaplastic large-cell lymphoma and CD30-rich transformed mycosis fungoides; a study of 66 cases. Br J Dermatol. 2015 Jun;172(6):1547-54.
20. Woo DK, Jones CR, Vanoli-Storz MN, Kohler S, Reddy S, Advani R, et al. Prognostic factors in primary cutaneous anaplastic large cell lymphoma: characterization of clinical subset with worse outcome. Arch Dermatol. 2009 Jun;145(6):667-74.
21. Scarisbrick JJ. New drugs in cutaneous T-cell lymphomas. Curr Opin Oncol. 2016 Sep;28(5):384-9.
22. Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol. 2003 Dec;49(6):1049-58.
23. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007 Sep 15;110(6):1713-22.
24. Kim YH, Willemze R, Pimpinelli N, Whittaker S, Olsen EA, Ranki A, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007 Jul 15;110(2):479-84.
25. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood. 2011 Oct 13;118(15):4024-35.
26. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol. 2003 Jul;139(7):857-66.
27. Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Porcu P, et al. Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sezary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. J Clin Oncol. 2015 Nov 10;33(32):3766-73.
28. Mak TW, Saunders ME. 29 - Autoimmune Disease. In: Mak TW, Saunders ME, editors. The Immune Response. Burlington: Academic Press; 2006. pp963-1023.
29. Sauder MB, O'Malley JT, LeBoeuf NR. CD30+Lymphoproliferative Disorders of the Skin. Hematol Oncol Clin North Am. 2017;31(2):317-34.
30. European Medicines Agency. Assessment report: Adcetris. International non-proprietary name: brentuximab vedotin. Procedure No. EMEA/H/C/002455/II/0048. 9 November 2017. EMA/753623/2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002455/WC500242962.pdf [Accessed 17 August 2018]
31. Prince HM, Gautam A, Kim YH. Brentuximab vedotin: targeting CD30 as standard in CTCL. Oncotarget. 2018;9(15):11887-8.
32. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M, Group EGW. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct;24 Suppl 6:vi149-54.
33. Whittaker SJ, Marsden JR, Spittle M, Russell Jones R, British Association of D, Group UKCL. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma

Group guidelines for the management of primary cutaneous T-cell lymphomas. Br J Dermatol. 2003 Dec;149(6):1095-107.
34. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome - Update 2017. Eur J Cancer. 2017 May;77:57-74.
35. Trautinger F, Knobler R, Willemze R, Peris K, Stadler R, Laroche L, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. Eur J Cancer. 2006 May;42(8):1014-30.
36. Hughes CF, Khot A, McCormack C, Lade S, Westerman DA, Twigger R, et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sezary syndrome: a comparative study of systemic therapy. Blood. 2015 Jan 01;125(1):71-81.
37. Palanicawandar R, Morris S, Lozano-Cerrada S, Sevillano Zamarreno B, Wain M, Child F, et al. Allogeneic stem cell transplantion for advanced cutaneous T-cell lymphoma with minimal-intensity conditioning. EORTC; 2017.
38. Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transplant. 2009;15(8):982-90.
39. Royal College of Pathologists/British Society for Haematology. Professional organisation submission: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190].
40. Whittaker S. British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Unpublished PowerPoint presentation.
41. Horwitz SM, Olsen EA, Duvic M, Porcu P, Kim YH. Review of the treatment of mycosis fungoides and sezary syndrome: a stage-based approach. J Natl Compr Canc Netw. 2008 Apr;6(4):436-42.
42. European Medicines Agency. Targretin: bexarotene (EMEA/H/C/000326). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000326/human_med_001078.jsp&mid=WC0b01ac058001d124 [Accessed 17 August 2018]
43. Sokolowska-Wojdylo M, Florek A, Zaucha JM, Chmielowska E, Giza A, Knopinska-Posluszny W, et al. Polish Lymphoma Research Group Experience With Bexarotene in the Treatment of Cutaneous T-Cell Lymphoma. Am J Ther. 2016 May-Jun;23(3):e749-56.
44. Abbott RA, Whittaker SJ, Morris SL, Russell-Jones R, Hung T, Bashir SJ, et al. Bexarotene therapy for mycosis fungoides and Sezary syndrome. Br J Dermatol. 2009 Jun;160(6):1299-307.
45. Duvic M, Hymes K, Heald P, Breneman D, Martin AG, Myskowski P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol. 2001 May 01;19(9):2456-71.
46. Duvic M, Martin AG, Kim Y, Olsen E, Wood GS, Crowley CA, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol. 2001 May;137(5):581-93.
47. Izu R, Yanguas, I., Servitje, O., Ortiz, P., de Misa, R.F., Estrach, T., Monsalvez, V., . Experience with bexarotene in cutaneous T-cell lymphoma: A collaborative study of the Spanish Group of Cutaneous Lymphoma. J Am Acad Dermatol. 2014;70(5):Suppl.1; AB123.
48. Rupoli S, Canafoglia L, Goteri G, Leoni P, Brandozzi G, Federici I, et al. Results of a prospective phase II trial with oral low-dose bexarotene plus photochemotherapy (PUVA) in refractory and/or relapsed patients with mycosis fungoides. Eur J Dermatol. 2016 Jan-Feb;26(1):13-20.
49. Rupoli S, Goteri G, Micucci G, Federici I, Canafoglia L, Leoni P, et al. Time to next treatment analysis for early and advanced stages of mycosis fungoides /sezary syndrome treated with bexarotene and puva in combination. Haematologica. 2017 June;102 (Supplement 2):466-7.

50. Straus DJ, Duvic M, Kuzel T, Horwitz S, Demierre MF, Myskowski P, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa-2b (Intron-A) for patients with cutaneous T-cell lymphoma. Cancer. 2007 May 01;109(9):1799-803.
51. Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. J Am Acad Dermatol. 1996 Apr;34(4):626-31.
52. Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. J Am Acad Dermatol. 2003 Nov;49(5):873-8.
53. Nikolaou V, Siakantaris MP, Vassilakopoulos TP, Papadavid E, Stratigos A, Economidi A, et al. PUVA plus interferon alpha2b in the treatment of advanced or refractory to PUVA early stage mycosis fungoides: a case series. J Eur Acad Dermatol Venereol. 2011 Mar;25(3):354-7.
54. Jidar K, Ingen-Housz-Oro S, Beylot-Barry M, Paul C, Chaoui D, Sigal-Grinberg M, et al. Gemcitabine treatment in cutaneous T-cell lymphoma: a multicentre study of 23 cases. Br J Dermatol. 2009 Sep;161(3):660-3.
55. Duvic M, Talpur R, Wen S, Kurzrock R, David CL, Apisarnthanarax N. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma. 2006 Jul;7(1):51-8.
56. Pellegrini C, Stefoni V, Casadei B, Maglie R, Argnani L, Zinzani PL. Long-term outcome of patients with advanced-stage cutaneous T cell lymphoma treated with gemcitabine. Ann Hematol. 2014 Nov;93(11):1853-7.
57. Dummer R, Quaglino P, Becker JC, Hasan B, Karrasch M, Whittaker S, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J Clin Oncol. 2012 Nov 20;30(33):4091-7.
58. Quereux G, Marques S, Nguyen JM, Bedane C, D'Incan M, Dereure O, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. Arch Dermatol. 2008 Jun;144(6):727-33.
59. Kim YH. SY58: Cutaneous lymphoma - treatment strategies: Managing MF and SS with allogeneic HSCT. Available from: https://pdfs.semanticscholar.org/presentation/7968/26d2eeba8f156189cb33de8bcd3ca134a0fc.pdf [Accessed 1 June 2018]
60. Lowsky R, Takahashi T, Liu YP, Dejbakhsh-Jones S, Grumet FC, Shizuru JA, et al. Protective conditioning for acute graft-versus-host disease. N Engl J Med. 2005;353(13):1321-31.
61. Takeda UK data on file. Document number: Takeda/UK/DOF/003 Other claims. 2018.
62. Beitinjaneh A, Saliba RM, Medeiros LJ, Turturro F, Rondon G, Korbling M, et al. Comparison of survival in patients with T cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. Biol Blood Marrow Transplant. 2015 May;21(5):855-9.
63. European Medicines Agency. Adcetris: brentuximab vedotin (EMEA/H/C/002455). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002455/human_med_001588.jsp&mid=WC0b01ac058001d124 [Accessed 17 August 2018]
64. European Medicines Agency. Public summary of opinion on orphan designation: Brentuximab vedotin for the treatment of cutaneous T-cell lymphoma (EMA/COMP/923105/2011 Rev.2). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2012/02/WC500121705.pdf [Accessed 17 August 2018]
65. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal: Brentuximab vedotin for treating relapsed or refractory CD30-positive cutaneous T-cell lymphoma. Final scope. Issue date: October 2017. Available from:

https://www.nice.org.uk/guidance/gid-ta10201/documents/final-scope [Accessed 8 August 2018]
66. Prince HM, Kim YH, Horwitz SM, Drummer R, Scarisbrick J, Quaglino P, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017;390(10094):555-66.
67. National Institute for Health and Care Excellence (NICE). Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. Technology appraisal guidance [TA524]. Published date: 13 June 2018. Available from: https://www.nice.org.uk/guidance/ta524 [Accessed 16 October 2018]
68. National Institute for Health and Care Excellence (NICE). Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma. Technology appraisal guidance [TA478]. Published date: 04 October 2017. Available from: https://www.nice.org.uk/guidance/ta478 [Accessed 16 October 2018]
69. National Institute for Health and Care Excellence (NICE). Brentuximab vedotin for untreated advanced Hodgkin lymphoma [1258]. In development [GID-TA10224]. Expected publication date: TBC. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10224 [Accessed 16 October 2018]
70. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol. 2011 Jun 20;29(18):2598-607.
71. Kim YH, Horwitz SM, Talpur R, Rahbar Z, Li S, M. D. Exploring new meaningful endpoints for CTCL clinical trials in two phase II studies of brentuximab vedotin (BV) in patients with mycosis fungoides (MF) and Sézary syndrome (SS). 3rd World Congress of Cutaneous Lymphomas; 2016; Columbia University, New York, NY, USA. p. 96 (abs O-01).
72. Takeda UK data on file. Document number: Takeda/UK/DOF/001 CSR and protocol claims. 2018.
73. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Available from: https://www.nice.org.uk/guidance/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 [Accessed 6 December 2017]
74. National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template. Process and methods [PMG24]. Published date: January 2015. Last updated: April 2017. Available from: https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies [Accessed 18 September 2017]
75. Mathieu S, Ram-Wolff C, Quereux G, Oro S, Beylot-Barry M, Augbin F, et al. The French experience of treatment of cutaneous T cell lymphoma with brentuximab vedotin: a series of 32 cases. 3rd World Congress of Cutaneous Lymphomas; 2016 October 26-28; Columbia University, NY, USA.
76. Kim YH, Tavallaee M, Sundram U, Salva KA, Wood GS, Li S, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. J Clin Oncol. 2015 Nov 10;33(32):3750-8.
77. Almazan T, Armstrong R, Kim YH, Weng W. Determination of molecular remission in patients with mycosis fungoides (MF) and Sezary Syndrome (SS) following allogeneic transplant using high throughput sequencing (HTS). J Invest Dermatol. 2017;137(5 Supplement 1):S65.
78. Aviles A, Nambo MJ, Neri N, Castaneda C, Cleto S, Gonzalez M, et al. Interferon and low dose methotrexate improve outcome in refractory mycosis fungoides/Sezary syndrome. Cancer Biother Radiopharm. 2007;22(6):836-40.

79. Aviles A, Neri N, Fernandez-Diez J, Silva L, Nambo MJ. Interferon and low doses of methotrexate versus interferon and retinoids in the treatment of refractory/relapsed cutaneous T-cell lymphoma. Hematology. 2015;20(9):538-42.
80. Cheeley J, Sahn RE, DeLong LK, Parker SR. Acitretin for the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol. 2013 Feb;68(2):247-54.
81. de Masson A, Beylot-Barry M, Bouaziz JD, Peffault de Latour R, Aubin F, Garciaz S, et al. Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French Society of Bone Marrow Transplantation and French Study Group on Cutaneous Lymphomas. Haematologica. 2014 Mar;99(3):527-34.
82. Duarte RF, Canals C, Onida F, Gabriel IH, Arranz R, Arcese W, et al. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2010 Oct 10;28(29):4492-9.
83. Hinds GA, Alhariri J, Klein RQ, Wilson LD. Treatment of mycosis fungoides with total skin electron beam: response and relapse by ethnicity and sex. Am J Clin Oncol. 2013 Oct;36(5):481-5.
84. Hoppe RT, Harrison C, Tavallaee M, Bashey S, Sundram U, Li S, et al. Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials. J Am Acad Dermatol. 2015 Feb;72(2):286-92.
85. Hosing C, Bassett R, Dabaja B, Talpur R, Alousi A, Ciurea S, et al. Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. Ann Oncol. 2015 Dec;26(12):2490-5.
86. Illidge T, Chan C, Counsell N, Morris S, Scarisbrick J, Gilson D, et al. Phase II study of gemcitabine and bexarotene (GEMBEX) in the treatment of cutaneous T-cell lymphoma. Br J Cancer. 2013 Nov 12;109(10):2566-73.
87. Kroeger K, Elsayad K, Moustakis C, Haverkamp U, Eich HT. Low-dose total skin electron beam therapy for cutaneous lymphoma : Minimal risk of acute toxicities. Strahlenther Onkol. 2017 Dec;193(12):1024-30.
88. Lechowicz MJ, Lazarus HM, Carreras J, Laport GG, Cutler CS, Wiernik PH, et al. Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome. Bone Marrow Transplant. 2014 Nov;49(11):1360-5.
89. Lindahl LM, Kamstrup MR, Petersen PM, Wiren J, Fenger-Gron M, Gniadecki R, et al. Total skin electron beam therapy for cutaneous T-cell lymphoma: a nationwide cohort study from Denmark. Acta Oncol. 2011 Nov;50(8):1199-205.
90. Mehta-Shah N, Chou J, Maloy M, Zhang Z, Moskowitz AJ, Moskowitz CH, et al. Successful Treatment of Peripheral T-Cell Lymphoma with Allogeneic Stem Cell Transplantation: A Large Single-Center Experience. Blood. 2015;126(23):4392.
91. Menter T, Medani H, Olavarria E, Kanfer E, Naresh KN. Pathology findings in patients with cutaneous T-cell lymphomas treated with allogeneic haematopoietic stem cell transplantation. Br J Haematol. 2018 Mar;180(6):904-8.
92. Morris SL, McGovern M, Bayne S, Wain M, Child F, Whittaker S. Results of a 5-week schedule of modern total skin electron beam radiation therapy. Int J Radiat Oncol Biol Phys. 2013 Aug 1;86(5):936-41.
93. Roberge D, Muanza T, Blake G, Shustik C, Vuong T, Freeman CR. Does adjuvant alpha-interferon improve outcome when combined with total skin irradiation for mycosis fungoides? Br J Dermatol. 2007;156(1):57-61.
94. Straus DJ, Duvic M, Horwitz SM, Hymes K, Goy A, Hernandez-Ilizaliturri FJ, et al. Final results of phase II trial of doxorubicin HCl liposome injection followed by bexarotene in advanced cutaneous T-cell lymphoma. Ann Oncol. 2014 Jan;25(1):206-10.
95. Weng W-K, Armstrong R, Arai S, Johnston L, Laport GG, Lowsky R, et al. Non-Myeloablative Allogeneic Transplantation Resulting in Clinical and Molecular Remission with Low Non-Relapse Mortality (NRM) in Patients with Advanced Stage Mycosis Fungoides (MF) and Sézary Syndrome (SS). Blood. 2014;124(21):2544.

96. Bunn PA, Jr., Foon KA, Ihde DC, Longo DL, Eddy J, Winkler CF, et al. Recombinant leukocyte A interferon: an active agent in advanced cutaneous T-cell lymphomas. Ann Intern Med. 1984;101(4):484-7.
97. Knobler RM, Trautinger F, Radaszkiewicz T, Kokoschka EM, Micksche M. Treatment of cutaneous T cell lymphoma with a combination of low-dose interferon alfa-2b and retinoids. J Am Acad Dermatol. 1991;24(2 Pt 1):247-52.
98. Foss FM, Ihde DC, Breneman DL, Phelps RM, Fischmann AB, Schechter GP, et al. Phase II study of pentostatin and intermittent high-dose recombinant interferon alfa-2a in advanced mycosis fungoides/Sezary syndrome. J Clin Oncol. 1992;10(12):1907-13.
99. Altomare GF, Capella GL, Pigatto PD, Finzi AF. Intramuscular low dose alpha-2B interferon and etretinate for treatment of mycosis fungoides. Int J Dermatol. 1993;32(2):138-41.
100. Foss FM, Ihde DC, Linnoila IR, Fischmann AB, Schechter GP, Cotelingam JD, et al. Phase II trial of fludarabine phosphate and interferon alfa-2a in advanced mycosis fungoides/Sezary syndrome. J Clin Oncol. 1994;12(10):2051-9.
101. Kuzel TM, Roenigk HH, Jr., Samuelson E, Herrmann JJ, Hurria A, Rademaker AW, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sezary syndrome. J Clin Oncol. 1995;13(1):257-63.
102. Stadler R, Otte HG. Combination therapy of cutaneous T cell lymphoma with interferon alpha-2a and photochemotherapy. Recent Results Cancer Res. 1995;139:391-401.
103. Gottlieb SL, Wolfe JT, Fox FE, DeNardo BJ, Macey WH, Bromley PG, et al. Treatment of cutaneous T-cell lymphoma with extracorporeal photopheresis monotherapy and in combination with recombinant interferon alfa: a 10-year experience at a single institution. J Am Acad Dermatol. 1996 Dec;35(6):946-57.
104. Aviles A, Guzman R, Garcia EL, Diaz-Maqueo JC. Biological modifiers (etretinate (changed from etetrinate) and alfa 2a) in the treatment of refractory cutaneous T-cell lymphoma. Cancer Biother Radiopharm. 1996;11(1):21-4.
105. Stadler R, Otte HG, Luger T, Henz BM, Kuhl P, Zwingers T, et al. Prospective randomized multicenter clinical trial on the use of interferon -2a plus acitretin versus interferon -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood. 1998;92(10):3578-81.
106. Rupoli S, Barulli S, Guiducci B, Offidani M, Mozzicafreddo G, Simonacci M, et al. Low dose interferon-alpha2b combined with PUVA is an effective treatment of early stage mycosis fungoides: results of a multicenter study. Cutaneous-T Cell Lymphoma Multicenter Study Group. Haematologica. 1999;84(9):809-13.
107. Crovetti G, Carabelli A, Berti E, Guizzardi M, Fossati S, De Filippo C, et al. Photopheresis in cutaneous T-cell lymphoma: five-year experience. Int J Artif Organs. 2000;23(1):55-62.
108. Wollina U, Looks A, Meyer J, Knopf B, Koch HJ, Liebold K, et al. Treatment of stage II cutaneous T-cell lymphoma with interferon alfa-2a and extracorporeal photochemotherapy: a prospective controlled trial. J Am Acad Dermatol. 2001;44(2):253-60.
109. Suchin KR, Cucchiara AJ, Gottleib SL, Wolfe JT, DeNardo BJ, Macey WH, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Arch Dermatol. 2002;138(8):1054-60.
110. Tsimberidou AM, Giles F, Romaguera J, Duvic M, Kurzrock R. Activity of interferon-alpha and isotretinoin in patients with advanced, refractory lymphoid malignancies. Cancer. 2004;100(3):574-80.
111. Rupoli S, Goteri G, Pulini S, Filosa A, Tassetti A, Offidani M, et al. Long-term experience with low-dose interferon-alpha and PUVA in the management of early mycosis fungoides. Eur J Haematol. 2005;75(2):136-45.
112. Dummer R, Eichmuller S, Gellrich S, Assaf C, Dreno B, Schiller M, et al. Phase II clinical trial of intratumoral application of TG1042 (adenovirus-interferon-gamma) in patients with advanced cutaneous T-cell lymphomas and multilesional cutaneous B-cell lymphomas. Mol Ther. 2010;18(6):1244-7.

113. Schiller M, Tsianakas A, Sterry W, Dummer R, Hinke A, Nashan D, et al. Dose-escalation study evaluating pegylated interferon alpha-2a in patients with cutaneous T-cell lymphoma. J Eur Acad Dermatol Venereol. 2017;31(11):1841-7.
114. Talpur R, Weieser I, Wang C, Lyons G, Duvic M. Evaluation of health related questionnaire among mycosis fungoides and lymphomatoid papulosis. Blood. 2015;126:5603.
115. Lewis DJ, Talpur R, Huen AO, Tetzlaff MT, Duvic M. Brentuximab vedotin for patients with refractory lymphomatoid papulosis an analysis of phase 2 results. JAMA Dermatology. 2017 December;153(12):1302-6.
116. Wieser I, Oh CW, Talpur R, Duvic M. Lymphomatoid papulosis: Treatment response and associated lymphomas in a study of 180 patients. J Am Acad Dermatol. 2016 2016/01/01/;74(1):59-67.
117. Weberschock T, Strametz R, Lorenz M, Rollig C, Bunch C, Bauer A, et al. Interventions for mycosis fungoides. Cochrane Database Syst Rev. 2012 Sep 12(9):CD008946.
118. Guitart J, Tucker R, Stevens V. Low Dose Bexarotene (Targretin®) Capsules and Phototherapy for Early Stage Cutaneous T-Cell Lymphoma [Abstract 199]. The 63rd Annual Meeting of the Society for Investigative Dermatology, 15-18 May, Los Angeles, USA. Journal of Investigative Dermatology. 2002;119(1):241.
119. Vonderheid EC, Thompson R, Smiles KA, Lattanand A. Recombinant interferon alfa-2b in plaque-phase mycosis fungoides. Intralesional and low-dose intramuscular therapy. Arch Dermatol. 1987 Jun;123(6):757-63.
120. Wolff JM, Zitelli JA, Rabin BS, Smiles KA, Abell E. Intralesional interferon in the treatment of early mycosis fungoides. J Am Acad Dermatol. 1985;13(4):604-12.
121. Stadler R, Kremer A, Luger T, Sterry W. Prospective, randomized, multicentre clinical trial on the use of interferon a 2a plus PUVA versus PUVA monotherapy in patients with cutaneous T-cell lymphoma, stages I and II. J Clin Oncol. 2006;24(18_suppl):7541-.
122. Wozniak MB, Tracey L, Ortiz-Romero PL, Montes S, Alvarez M, Fraga J, et al. Psoralen plus ultraviolet A +/- interferon-alpha treatment resistance in mycosis fungoides: the role of tumour microenvironment, nuclear transcription factor-kappaB and T-cell receptor pathways. Br J Dermatol. 2009 Jan;160(1):92-102.
123. Child FJ, Mitchell TJ, Whittaker SJ, Scarisbrick JJ, Seed PT, Russell-Jones R. A randomized cross-over study to compare PUVA and extracorporeal photopheresis in the treatment of plaque stage (T2) mycosis fungoides. Clin Exp Dermatol. 2004 May;29(3):231-6.
124. Kim. NCT01396070. Brentuximab Vedotin (SGN-35) in Patients With Mycosis Fungoides With Variable CD30 Expression Level - Study Results - ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01396070 [Accessed 13 August 2018]
125. Millennium Pharmaceuticals Inc (Takeda Global Research and Development - US). Clinical Study Report. C25001. A Randomized, Open-Label, Phase 3 Trial of Brentuximab Vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma. 07 February 2017.
126. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare: Systematic Reviews (3rd Edition). 2009; Available from: https://www.york.ac.uk/crd/guidance/ [Accessed 25 October 2018]
127. National Collaborating Centre for Methods and Tools. Quality assessment tool for quantitative studies. 2008; Available from: http://www.nccmt.ca/resources/search/14 [Accessed 23 August 2018]
128. Millennium Pharmaceuticals Inc. Statistical Analysis Plan. A Randomized, Open-Label, Phase 3 Trial of brentuximab vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma. Protocol #: C25001. Draft 4.0. 26 Feb 2014.
129. Millennium Pharmaceuticals Inc. Clinical Study Protocol C25001 Amendment 5. Brentuximab vedotin (SGN-35). A Randomized, Open-Label, Phase 3 Trial of brentuximab

vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma. 02 December 2014.
130. Collett D. Modelling Survival Data in Medical Research. Texts in Statistical Science. Second ed. Florida, USA: Chapman & Hall; 2003.
131. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. School of Health and Related Research, University of Sheffield, Sheffield, UK. 2014:b12.
132. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9.
133. Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. Dermatol Clin. 2012;30(2):231-6, xiii.
134. EuroQoL Research Foundation. EQ-5D-3L. 2017; Available from: https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/ [Accessed 23 August 2018]
135. Yost KJ, Thompson CA, Eton DT, Allmer C, Ehlers SL, Habermann TM, et al. The Functional Assessment of Cancer Therapy - General (FACT-G) is valid for monitoring quality of life in patients with non-Hodgkin lymphoma. Leuk Lymphoma. 2013 Feb;54(2):290-7.
136. Prince HM, Reinhard D, Whittaker S, Horwitz SM, Duvic M, Scarisbrick J. Patient-reported outcomes and quality of life in patients with cutaneous T cell lymphoma: results from the Phase 3 ALCANZA study. International Conference on Malignant Lymphoma (ICML); 2017; Lugano, Switzerland. p. Poster 250.
137. Prinsen CA, Lindeboom R, de Korte J. Interpretation of Skindex-29 scores: cutoffs for mild, moderate, and severe impairment of health-related quality of life. J Invest Dermatol. 2011;131(9):1945-7.
138. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. In: Bosman FT, Jaffe ES, Lakhani SR, Ohgaki H, editors. World Health Organization Classification of Tumours. Lyon: International Agency for Research on Cancer 2008. pp269-320.
139. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.
140. SMC submission.
Economic analysis of extracorporeal photopheresis compared with standard treatment for cu taneous T-cell lymphoma and chronic graft versus host disease. May 20, 2010; Available from: http://www.nospg.nhsscotland.com/wp-content/uploads/2010/05/25-10_iii_c_ECP-for-CTCL-GVHD-economic-costings-for-NSCAG.pdf [Accessed 15 June 2018]
141. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Leuk Lymphoma. 2015;56(6):1839-45.
142. van Agthoven M, Vellenga E, Fibbe WE, Kingma T, Uyl-de Groot CA. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease. a prospective randomised trial. Eur J Cancer. 2001;37(14):1781-9.
143. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes. 2010;8:50.
144. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90.
145. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84.
146. Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. Pharmacoeconomics. 2001;19(11):1091-102.
147. NHS Improvement. Reference costs 2016/17. 2017; Available from: https://improvement.nhs.uk/resources/reference-costs/ [Accessed 18 June 2018]

148. Curtis LA, Burns A. Unit Costs of Health and Social Care 2017. 2017; Available from: https://kar.kent.ac.uk/65559/40/65559_rep_UCR-2017-v13finalKAR.pdf [Accessed 18 June 2018]
149. Department of Health. Drugs and pharmaceutical electronic market information (eMit). First published: 16 March 2011. Last update: 45 January 2018.; Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed 5 September 2018
[Accessed
150. Monthly Index of Medical Specialities (MIMS). Methotrexate. 2018; Available from: https://www.mims.co.uk/drugs/cancer/antineoplastics/methotrexate-oral-solution [Accessed 24 May 2018]
151. Monthly Index of Medical Specialities (MIMS). Bexarotene - Targretin. 2018; Available from: https://www.mims.co.uk/drugs/cancer/antineoplastics/targretin [Accessed 24 May 2018]
152. London Cancer Alliance West and South. LCA Skin Cancer Clinical Guidelines. 2014; Available from: www.londoncanceralliance.nhs.uk/media/74850/LCA_SkinClinicalGuidelines_FINAL.pdf [Accessed 5 September 2018]
153. Debals-Gonthier M, Siani C, Faucher C, Touzani R, Lemarie-Basset C, Chabannon C, et al. Cost-effectiveness analysis of haploidentical vs matched unrelated allogeneic hematopoietic stem cells transplantation in patients older than 55 years. Bone Marrow Transplant. 2018 Sep;53(9):1096-104.
154. Monthly Index of Medical Specialities (MIMS). Gemcitabine. 2018; Available from: https://www.mims.co.uk/drugs/cancer/antineoplastics/gemcitabine [Accessed 24 May 2018]
155. Monthly Index of Medical Specialities (MIMS). Cyclophosphamide. 2018; Available from: https://www.mims.co.uk/drugs/cancer/antineoplastics/cyclophosphamide [Accessed 24 May 2018]
156. Monthly Index of Medical Specialities (MIMS). Doxorubicin hydrochlor - Doxorubicin. 2018; Available from: https://www.mims.co.uk/drugs/cancer/antineoplastics/doxorubicin [Accessed 24 May 2018]
157. Monthly Index of Medical Specialities (MIMS). Oncovin - Vincristine (Vincristine sulf.) 2018; Available from: https://www.mims.co.uk/drugs/cancer/antineoplastics/vincristine [Accessed 24 May 2018]
158. Monthly Index of Medical Specialities (MIMS). Prednisolone. 2018; Available from: https://www.mims.co.uk/drugs/endocrine/inflammatory-disorders/prednisolone [Accessed 24 May 2018]
159. Monthly Index of Medical Specialities (MIMS). Caelyx - Doxorubicin hydrochlor in pegylated liposomes. 2018; Available from: https://www.mims.co.uk/drugs/cancer/antineoplastics/caelyx [Accessed 24 May 2018]
160. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med. 2015;29(10):899-907.
161. Schlaak M, Pickenhain J, Theurich S, Skoetz N, von Bergwelt-Baildon M, Kurschat P. Allogeneic stem cell transplantation versus conventional therapy for advanced primary cutaneous T-cell lymphoma. Cochrane Database Syst Rev. 2013(8).
162. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU technical support document 19: Partitioned survival analysis for decision modelling in health care: A critical review. June 2, 2017; Available from: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/06/Partitioned-Survival-Analysis-final-report.pdf [Accessed 15 June 2018]
163. Cutaneous Lymphoma Foundation. A patient's guide to understanding cutaneous lymphoma. 2014; Available from: https://www.clfoundation.org/sites/default/files/Guide%20Final_0.pdf [Accessed June 20, 2017]
164. Pinter-Brown L, Porcu P, Horwitz S, Lessin S. Understanding Treatment Options in Cutaneous Lymphoma: A Supplement to the Patient's Guide to Understanding Cutaneous

Lymphoma. 2014; Available from: http://flipbook.clfoundation.org/Understanding_Treatment_Options_in_Cutaneous_Lymphoma/files/assets/common/downloads/publication.pdf [Accessed 25 October 2018]
165. MIMS Online. Database of prescription and generic drugs, clinical guidelines. Available from: http://www.mims.co.uk/ [Accessed 5 September 2018]
166. Macmillan Cancer Support. The cost of Macmillan's services fact sheet,. 2018; Available from: http://be.macmillan.org.uk/Downloads/FactSheets/The-Cost-of-Macmillans-Services-fact-sheet-(2018)-v1.pdf [Accessed 5 September 2018]

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.

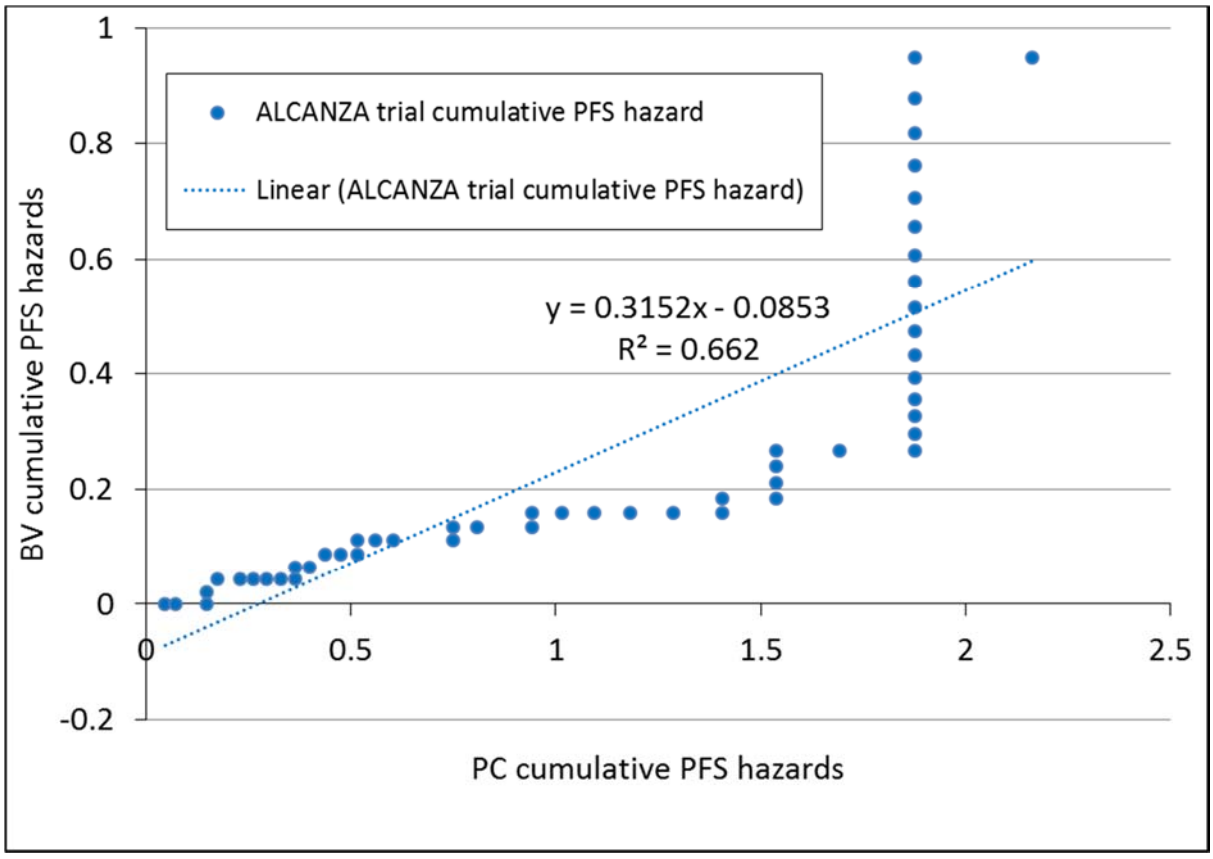


Figure 16 H-H plot for IRF-assessed PFS data from the advanced stage CTCL patient subgroup of the ALCANZA trial

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.

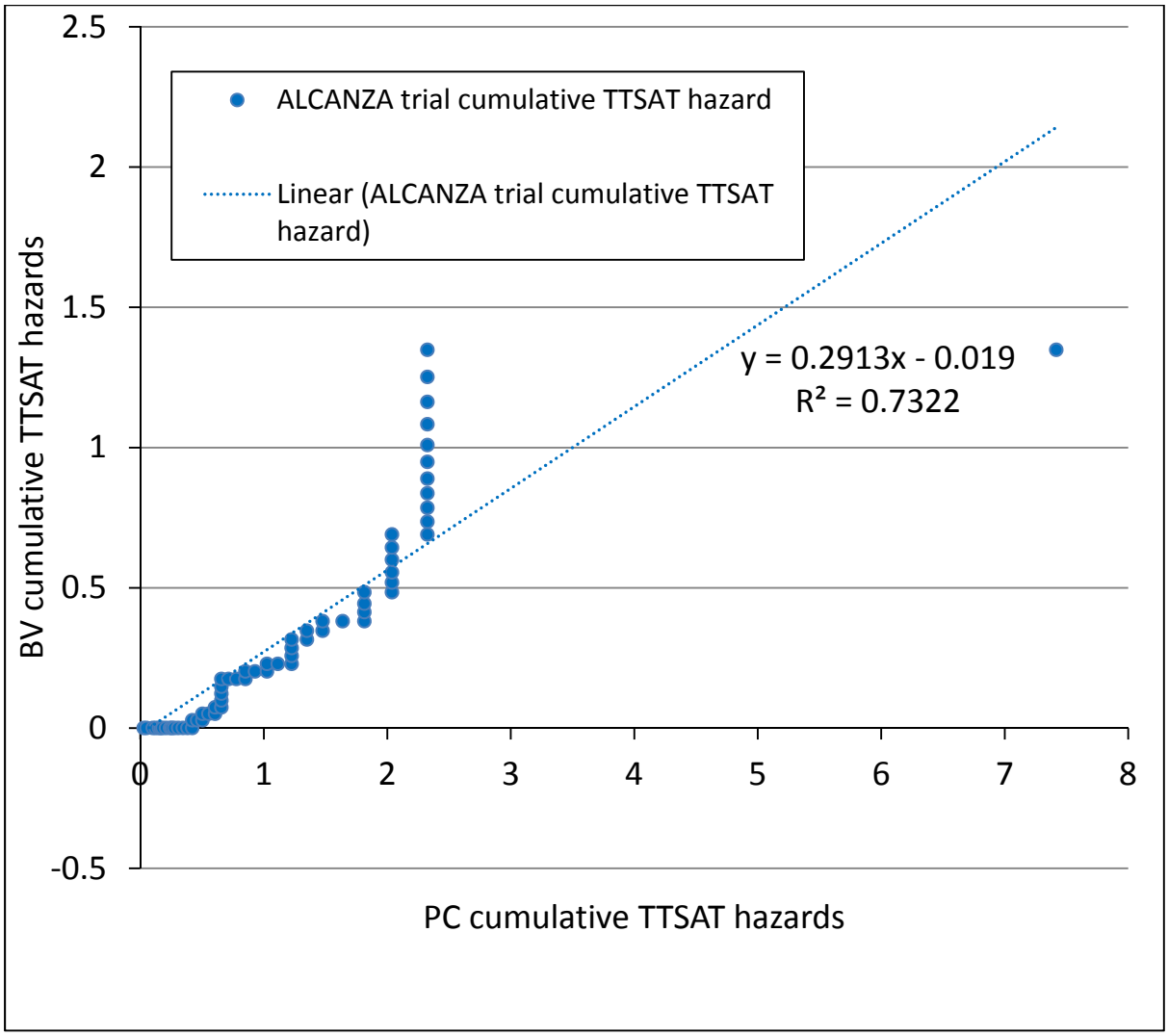


Figure 17 H-H plot for TTSAT data from the advanced stage CTCL patient subgroup of the ALCANZA trial

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.

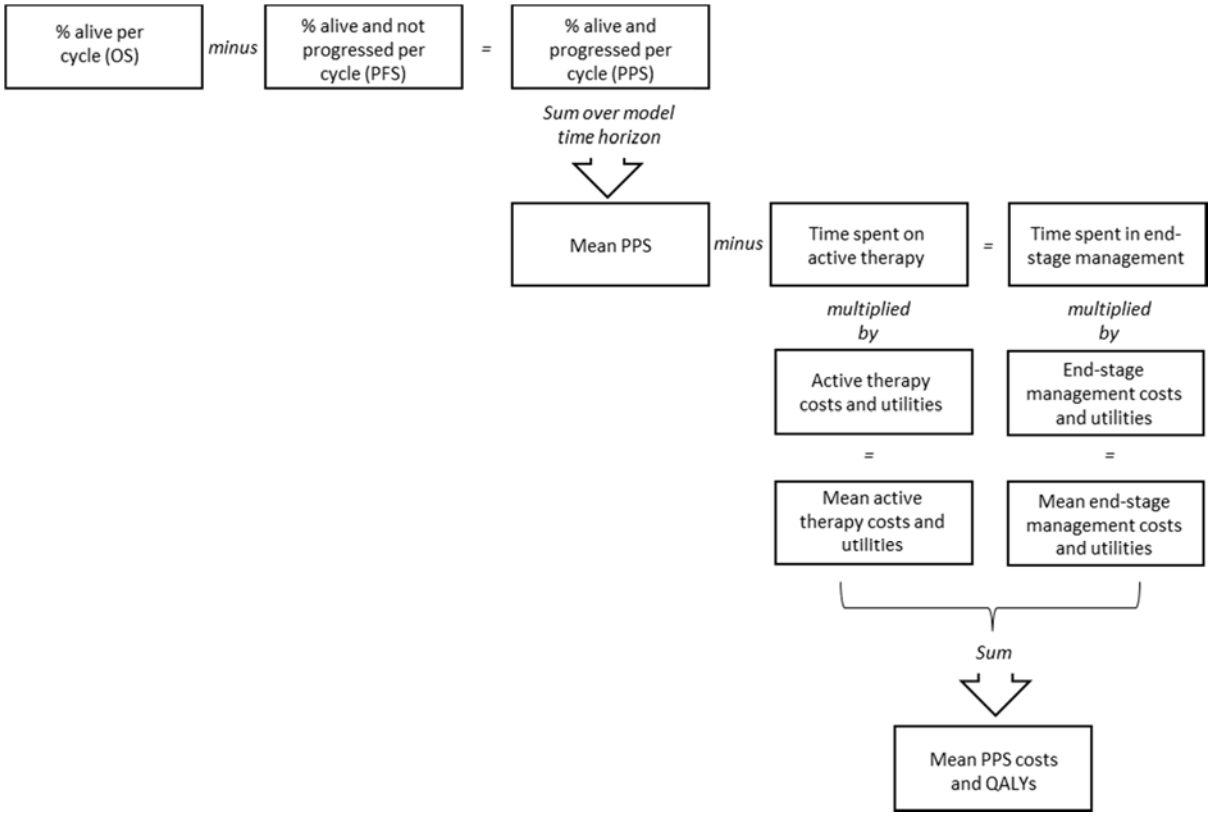


Figure 18 Simplified structure of calculation of mean PPS costs and QALYs in the company model

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

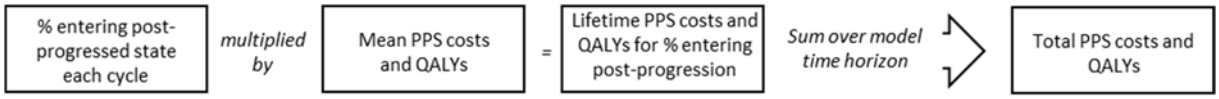


Figure 19 Simplified structure of calculation of total PPS costs and QALYs in the company base case

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)

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma [ID1190]

You are asked to check the ERG report from Liverpool Reviews and Implementation Group (LRIG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 6 November 2018** using the below proforma comments Table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Indication in scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, in the scope of the submission, the report states that: *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.* However, the Takeda UK submission is only on CD30 positive cutaneous t-cell lymphoma (CTCL) and not all lymphoproliferative disorders (LPDs).	Revise wording to: *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 (CD30+) cutaneous T-cell lymphoma (CTCL) following skin directed therapies and/or at least one systemic therapy.*	Incorrect characterisation of the population under consideration.	Text amended as suggested

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 in paragraph 2, line 1, text states that "The company's searches were designed to exclude studies published prior to 2007"	Revise wording to "The company's **eligibility criteria** were designed to exclude studies published prior to 2007"	None of the searches were restricted by date; studies published prior to 2007 were identified in the searches. Studies relating to the period before 2007 were screened out at the first pass screen.	Text amended as suggested

Issue 3 OS claim

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13, ERG report states that: *The company reports that, compared to treatment with PC, treatment with BV results in longer median OS (41.6 months and 43.6 months respectively), but highlight that these results are highly uncertain.* Clarification that Takeda UK does not claim a benefit or longer OS as it is stated above, but instead we believe the data is immature and highly confounded therefore we do not claim any OS advantage. Furthermore median OS has not been reached in either arm. For avoidance of doubt, Section B2.7.4 of the Takeda submission states: *Although directionally there appears to be a trend towards longer OS observed in the brentuximab vedotin arm over PC (median OS [95% CI]: 43.6 months [41.0–NA] vs. 41.6 months [21.1–NA], respectively; Figure 36), this analysis is highly*	*The company reports that, although there is a trend towards longer OS for treatment with BV compared to treatment with PC, these results are highly uncertain as illustrated by single figure differences in the number of observed events.*	Takeda UK does not claim nor state that there is a median OS advantage in the BV arm compared to the PC based on the immature and highly confounded data.	Text amended to: The company reports that median OS was 43.6 months with BV and 41.6 months with PC but highlights that these results are highly uncertain as illustrated by single figure differences in the number of observed events.

uncertain as illustrated by the single figure difference in the number of observed events.			

Issue 4 Non-randomised studied of brentuximab vedotin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the ERG report, the ERG mistakenly claims that there are additional non-randomised trials which were not included in the Takeda submission but were however in the EPAR. The following references were made to submitted non-randomised data: i) Page 16 states that there are 218 patients enrolled in non-randomised studies of brentuximab vedotin in CTCL. ii) Page 45, Table 4 lists the following non-randomised trials which appear in the EPAR but according to the ERG were not included in the Takeda submission: -Lewis 2017 -IST001	Page 16 should state a total of 138 patients have been enrolled in non-randomised studies of brentuximab in CTCL. This includes: -n=72 from IST002 (also reported as Duvic 2015 with n=48) -n=36 from IST001 (also reported as Kim 2015 with n=30 patients) -n=21 from Weiser 2016 -n=4 from Talpour 2016 -n=5 Lamaque 2016 Page 45, Table 4 and the associated text should be modified to remove IST001, IST002 and Lewis 2017 as these results were included in the Takeda UK submission and the relevant reference materials provided. Weiser 2016 was the only non-randomised study which was not included in the company submission but was in the EPAR.	Factual inaccuracy – confusion with study information leading to double counting of studies and patient numbers. Inaccurate description of information provided.	Thank you for clarifying, the relevant sections have been amended (including Section 4.7). Please note, Lewis was not referred to in the CS or CS appendices (although as stated in the ERG report, this mostly included patients also included in the Duvic 2015 study and so in that respect, it was included in the CS) and therefore only references relating to IST001 or IST002 have been amended

-IST002 -Weiser 2016 iii) Page 44, section 4.2.3 which states that the aforementioned studies have not been identified in the company searches which is inaccurate for all but the Weiser 2016 study. iv) Section 4.7 on pages 63-66. The statements of non-reported data are inaccurate for all but the Weiser 2016 publication as the other three listed publications are in fact the Duvic 2015 and Kim 2015 Phase II trials which were submitted. For clarification, the IST001 is the Kim 2015 trial and IST002 was the Duvic 2015 trial. There is a difference between patient numbers reported in the publications; this is because the Duvic 2015 and Kim 2015 trials were limited to patients exposed to the licensed dose of BV (1.8mg/kg) and therefore the patients who received a different does were excluded from the publications but do form a part of the trial reports included within the EPAR.			

Issue 5 Skindex-29 inclusion in EQ-5D

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 17 of the ERG Report: "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. " Pg. 91 of the ERG Report: "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." Table 29. Pg. 108 of the ERG Report: "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"	In several places the ERG state that the utility regression used progression status and Skindex-29 symptom score. This is not correct, utility regression analyses used Skindex-29 total score. Proposed amendment: In each case the words "symptom domain" should be replaced with 'total score'.	Factual inaccuracy.	Text amended

Issue 6 Prognosis of patients with cutaneous T-cell lymphoma

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26, in the last sentence of paragraph one of section 2.1.3, the report discusses the 5-year OS rates for patients with MF, SS, pcALCL and Lyp but for all stages of disease. Since the STA focuses on advanced CTCL patients, particularly advanced MF patients, but the reported rates in this sentence are for all stages of disease, the figures are misleading and should clarify that these survival rates are for all stages.	However, it should also be noted that the 5-year OS rate has been reported as 88% for patients with all stages of MF, 24% for patients with SS [7], ≥83% for patients with pcALCL [20] and ≥90% for patients with LyP [3, 21, 22].	Potential misinterpretation of expected survival for the population under consideration.	Text amended for clarity

Issue 7 Number of patients eligible for treatment with BV

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 inaccurately states that the company has not presented an estimate of the number of patients that it expects will be treated with BV. Following the new NICE submission template, the Budget Impact Analysis Document has the budget impact analysis which includes both the eligible patient	Please revise the section with the eligible and anticipated patient numbers as shown in the Budget Impact Analysis Document of the Takeda submission.	The comment is inaccurate; the budget impact analysis document was completed and submitted by Takeda UK which lays out the eligible patient numbers and the anticipate patients to be treated with brentuximab vedotin for CTCL. These figures can be found the Budget Impact Analysis Document of the company submission called *Brentuximab vedotin_CTCL_BIA-*	The ERG never received a copy of the Budget Impact Analysis Document from NICE although notes that the number of expected patients were included in the CS summary document. This was an oversight on the part of the ERG. The ERG has now received

population and the anticipated number of patients to be treated with brentuximab vedotin for CTCL. This document seems to have been missed by the ERG.		*submission_AIC_CIC.docx*, as per the new NICE submission template. The omission of the budget impact section is likely to have a major impact.	the Budget Impact Analysis Document and revised this section.

Issue 8 Clinical SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41, Table 3 (and cross-referenced on pages 42 and 43) states the following characterisations of the clinical SLR inaccurately: i) Information on the sources searched for search terms used is not provided ii) Search terms: the company also ran a rapid literature search, based on 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 iii) Time span: 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	Please revise the contents of Table 3 on page 41 to be in-line with the information in Appendix D of the company submission: i) Information on the sources searched for search terms used ~~is not provided~~ are provided in Appendix D Section 1.1.1 ii) Search terms: 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 in Appendix D Section 1.1.1 and 1.1.4. The rapid review reviewed original and updated searches. iii) Time span: 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~~ The rapid literature search was conducted on May 2018 as specified in Document B in section B.2.1.	Factual inaccuracy in the ERG report. Minimal impact.	These are not factual inaccuracies and no changes made. In summary: In relation to searches, the word "rapid" is not used at all in Appendix D and therefore no information relating to the "rapid review" is clearly available. No mention of data extraction or quality assessment is made at all in Appendix D Detailed response: i) and ii) The search terms are included for the original and updated searches but it is not clear these were the same searches as used for the rapid

to January 2018 although the date of the searches is not specified iv) Was data extracted by two or more reviewers independently? Not stated v) Was the quality assessment conducted by two or more reviewers independently? Not stated The above statements are not accurate with the information presented in Appendix D of the company submission.	iv) Was data extracted by two or more reviewers independently? ~~Not stated~~ Yes as stated in Appendix D section 1.1.3 v) Was the quality assessment conducted by two or more reviewers independently? ~~Not stated~~ Although not explicitly stated, the company submission did state that double-screening was utilized, following double screening best practices, thereby implying that quality assessment was also conducted by two or more reviewers. The above statements are not accurate with the information presented in Appendix D of the company submission.		review. Nor is it explicitly stated that the same databases were searched from the information provided. Thus, the statement that "Further information on the sources searched or search terms used is not provided" is factually correct. Please note, the ERG did however state (in the text on p42): "The ERG, therefore, has assumed that Embase, MEDLINE and the Cochrane Library were searched using the same search terms as the January 2018 search" iii) It is very unclear when the rapid review was conducted. It is stated that references were "rescreened" in May but confusingly, the rescreening is described in the CS (p92) as being "in addition" to the rapid review iv) No mention of data extraction is made in Appendix D. It is stated on p13 that "After dual, independent review of full-text papers, articles deemed eligible were included in the SLR and, where possible, analysed." This refers to the selection of papers for inclusion, not data extraction

			v) Screening, data extraction and quality assessment are three different stages of the review. The ERG disagrees that because double screening was employed, it can be assumed quality assessment was also conducted by two reviewers, independently.

Issue 9 Table 13 figure inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate figures in Table 13: i) Page 68 in Table 13, column 1 row 4, mentions number of patients n= 25 ii) Page 68 in Table 13, column 1 row 5, mentions number of BEX patients n= 37 iii) Page 68 in Table 13, column 2 row 7, states median (range) as "7 (2 to 9)"	i) Amend Table 13 MTX to "n= 26" ii) Amend Table 13 BEX to "n= 38" iii) Amend to "7 (2 to **19**)"	Factual inaccuracy in the ERG report. Minimal impact.	Text in Table amended as suggested

Issue 10 Kim et al 2015 PN timeline

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72, paragraph 2, line 11, states "Kim et al 2015 [76] report the median time to any peripheral	Revise wording to "weeks (range 3.0 to **38.6** weeks)"	Factual inaccuracy in the ERG report.	Text amended

neuropathy was 13 weeks (range 3 weeks to **89** weeks)"			

Issue 11 Economic SLR

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 81 Table 17 states that the interfaces searched for the economic SLR are:

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

The interfaced used were different as reported in Appendix G Section 1.1.1.</td>
<td>Please amend Table 17 to the following:

<table>
<tr><th>Database</th><th>Interface</th></tr>
<tr><td>Excerpta Medica Database (Embase®)</td><td><s>Embase.com</s>
Ovid</td></tr>
<tr><td>Medical Literature Analysis and Retrieval System Online (MEDLINE®)</td><td><s>Embase.com</s>
Ovid</td></tr>
<tr><td>Cochrane Library (including the databases: HTA, NHS EED, DARE, CENTRAL and the Cochrane Database of Systematic Reviews</td><td><s>Wiley.com</s>
Cochranelibrary.com</td></tr>
<tr><td>EconLit®</td><td><s>Ebsco.com</s>
Ovid</td></tr>
</table>
</td>
<td>Factual inaccuracy in the ERG report. Minimal impact.</td>
<td>Text amended</td>
</tr>
</table>

Issue 12 Adverse event inclusion in model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 94 of the ERG report: "all treatment related incidences of septicaemia and peripheral neuropathy are also included in the model."	Proposed amendment: "all treatment related incidences of grade 3 or 4 septicaemia and peripheral neuropathy are also included in the model, irrespective of whether they were experienced by greater than 5% of patients."	Further clarification to avoid misunderstanding.	Text amended

Issue 13 Subsequent thearpy response and duration source

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 102: "Durations of treatment and response are sourced from the London Cancer Alliance (LCA) skin systemic anticancer therapy (SACT) protocols" Durations of treatment and response for subsequent therapies were based on published literature as stated in Document B of the company submission.	Proposed amendment: "Durations of treatment and response are sourced from the published literature (Cite: Duvic, Chung, Dummer, Morris)"	Factual inaccuracy. Moderate to high impact.	The ERG could not locate the Chung reference in those submitted by the company nor in the CS document. Text amended as per company proposal including Duvic, Dummer and Morris references. References also added to Table 27.

Issue 14 Subsequent Therapy: Other monochemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 102 of the ERG report: "The dosing regimen and costs for 'other mono chemotherapy' are assumed, (based on data from the PROCLIPI study [61]), to be for treatment with doxorubicin (all formulations) and chlorambucil."	Proposed amendment: "The dosing regimen for Liposomal doxorubicin (Caelyx) was based on the published SACT protocol (CITE) while for chlorambucil the summary of product characteristics was used (CITE). These two treatments were grouped as 'other mono chemotherapy' with the proportion of patients receiving each therapy based on data from the PROCLIPI study."	Factual inaccuracy.	Text amended

Issue 15 Duration of post-progressive therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 103-104 of the ERG report: "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]"	Proposed amendment: The duration of post-progression active therapy for patients who are ineligible for SCT is estimated as almost 97 weeks. The duration of post-progression active therapy for patients who have already received SCT (SCT relapse) is 49 weeks given that they are assumed to have already received TSEB prior to alloSCT. The weekly cost in the model for resource use during the post-progression active therapy phase is [redacted]."	Factual inaccuracy.	Text amended

Issue 16 Pack size and price of Methotrexate and Bexarotene

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 99, Table 25, the vial size/tablet per pack for MTX should be 100 not 28. In addition the total cost for BEX should be £478.22 not £478.82	Please revise the entries in Table 25 to the following: -Vial size/ tablet per pack for MTX = 100 per pack -Cost of BEX £478.22	Factual inaccuracy in the ERG report. Minimal impact.	Text amended

Issue 17 Model structure characterisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Appendix 8 ERG report: "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." Pg. 117 of the ERG report:	The criticism of the model structure and specifically the use of the "payoff" approach are not accurate. In lieu of this, the proposed amendment for appendix 8 is: "The model does not impose a parametric structure on the transitions between the subsequent active therapy state and end-stage care state, because it does not model these transitions explicitly at all. Instead it applies mean outcomes which are then discounted appropriately. Use of an exponential distribution for discounting is widely used and commonly referred to as applying "continuous discounting". This method ensures outcomes are discounted as though they were accrued throughout a patient's time in the given health state, rather than simply upon entering the	Factual inaccuracy.	This is not an inaccuracy. However text has been amended for clarity on page 163: "However, the full impact of discounting is not captured by the payoff approach, which only uses mean time spent a state and does not allow for a different weighting of risk of transition over time (and so different levels of discounting). Different distributions with the same mean lifetime will produce different overall costs and QALYs due to discounting. For instance, a population in

“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.”	state. The methods described above are consistent with how the ‘payoff’ approach is described in NICE DSU TSD 19. The proposed amendment for pg.117 reads: “The payoff approach provides a suitable simplification of a complex patient pathway, by applying mean outcomes instead of explicitly modelling the transitions of patients between subsequent active therapies. Although clinical feedback received by the company indicated alloSCT has an important place in the treatment pathway for CTCL patients, it is important to highlight that the payoff approach can still be considered appropriate in the absence of alloSCT. The active subsequent therapy health state represents a combined pool of numerous therapies which are sometimes used repeatedly. Modelling the survival outcomes and transitions of patients between the intermediate active treatment state and the end-stage care state. Furthermore, the model allows suitable flexibility in exploring different ‘payoffs’ informed by alternative selections of survival curves.”		which everyone lives for 2 years has the same mean OS as a population for whom 90% live for 1 year and 10% live for 11 years. Without discounting, costs and QALYs would be the same for these two populations and the ICER per QALY gained would be 0. But discounting means that the population with a long tail of survival (where 10% live for 11 years) accrues lower costs and QALYs, which will result in incremental differences in costs and QALYs between the two populations.” This issue is implied in NICE DSU TSD 19: “Even where probabilities of transitioning from an intermediate state appear to be constant over time, if it is considered important to explore the sensitivity of the model to alternative parametric survival functions, then increased flexibility and complexity will need to be built in to models from the outset.”

Issue 18 Transition to post-progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement made by the ERG on page 118 is inaccurate as it incorrectly depicts the assumptions behind the proportion of patients entering the post-progression health state: "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%)	We propose the statement is removed completely or adapted to accurately represent the methods used, as outlined below. Proposed amendment: "The proportion of patients entering the post-progression health state in each cycle is estimated from the difference between the OS and the PFS curve (=1-OS-PFS). For example if PFS is 100% and the proportion who have died is 0% in cycle 1 and PFS falls to 98% in cycle 2 and those who have died are estimated to be 1% then the difference, 1%, move into the post-progression health state in cycle 2. This method <u>does</u> take into account the proportion of patients who die before experiencing disease progression."	Factual inaccuracy and misrepresentation of company modelling approach for a critical health-state. High impact.	Text deleted in Section 1.6.3 on page 20 Text deleted on page 118

died before experiencing disease progression. The modelling of a zero risk of death before disease progression therefore does not reflect the trial evidence."			

Issue 19 End-stage management resource use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 34, pg. 124 of the ERG report i) The frequency per week for the district nurse in the company base case was 2.60, not 1.81. ii) The duration of visit in ERG scenario 2 for Macmillan nurse / social services was not changed from 7 hours to 1 hour.	Proposed amendment: i) Value to be set at 2.60 as stated in company base case. ii) Removing shading from cell and state as 7 hours, as was used in company base case.	Factual inaccuracy.	i) Text amended in Table 34. ii) Text amended in Table 33

Issue 20 Dressings in end-stage management resource assumptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 125 of the ERG report: "The ERG notes that, when comparing treatment with BV and PC, if the total costs of the end-stage care phase are reduced	Proposed amendment for page 125: "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	Clarification of assumptions made by the ERG. Furthermore, a misrepresentation of the company assumptions on the cost and type of dressing included to	Text amended on page 126 to: "The ERG notes that, when comparing treatment with BV and PC, if the total costs of the end-stage care phase are

(due to the use of cheaper dressings), then the ICER per QALY gained would increase." This assumption does not consider the efficacy impact of less specialised dressings which should be clarified in the ERG assumptions. Furthermore, on page 126 the ERG states that *less expensive alternatives to Allevyn, Mepilex and Mepitel may be used in NHS local practice.* This is contrary to the input from across all UK centers interviewed which directly named the dressings included. The data will be published in ISPOR Europe 2018. For clarification, the company submission assumed a less expensive version of Allevyn based on clinical input. The 75% of patients treated with localised dressings are assumed to receive a cheaper medium Allevyn costing £6.25 per dressing and not the most expensive dressing.	per QALY gained would increase. However, this assumes that cheaper dressings would be equally effective. It should be noted that use of inferior dressings could both increase the frequency of dressing changes required and so increase district nurse costs or other staff. In addition, use of low-quality dressings could impact the QoL of patients through any failure of the dressings." Proposed amendment for page 126: Clinical advice to the ERG is that less expensive alternatives ~~to~~ as well as Allevyn, Mepilex and Mepitel dressings (included in the company model) may be used in NHS clinical practice.	artificially inflate the cost of dressings.	reduced (due to the use of cheaper dressings) without also affecting quality of life, then the ICER per QALY gained would increase." Text amended on page 126 to: "Clinical advice to the ERG is that less expensive alternatives as well as Allevyn, Mepilex and Mepitel dressings (included in the company model) may be used in NHS clinical practice."

Issue 21 Model Structure and Flexibility

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 126 of the ERG report: "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." The cause of limited OS extrapolation fits is due to the underlying clinical data and not the model structure as stated by the ERG.	Please amend statement on page 126 to: "The ERG also cautions that while it wished to explore results where a survival gain consistent with that estimated when alloSCT was included in the treatment pathway was generated; this was not possible with the available parametric survival curves. The fact that available parametric models fail to allow an arbitrary survival gain are ultimately a function of the underlying data."	Factual inaccuracy. The model is suitably flexible to allow a range of parametric survival models to be selected in order to inform patient survival. The fact that available parametric models fail to allow arbitrary survival gains which were not observed in the data but may be tested for exploratory purposes, are a function of the underlying data rather than the model structure.	Not a factual inaccuracy (see response to issue 17). No changes made.

Issue 22 ERG exploratory survival gain

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 127 or Scenario 3 of the ERG report which states that using the alloSCT modelled survival is a *reliable* estimate for modelling OS gain with brentuximab vedotin is highly flawed and baseless. Allogeneic SCT has been studied and reported to have a long-term impact on OS for CTCL both by UK centres and the EMBT. It is a	Remove or revise the OS extension with brentuximab vedotin to a more reasonable assumption based on clinical plausibility.	No evidence for one of the three main scenarios presented by the ERG. Evidence for the assumptions made for key drivers of the STA should be provided.	Not a factual error, however, the ERG has amended the OS scenario to reduce the potential OS gain for treatment with BV. Text amended on page 127 to: "The ERG reiterates that this

curative treatment for many lymphomas and shows similar promise for CTCL in published literature. Assuming that the same level of OS extension is a *reliable* assumption for a medicine, which although has highly significant PFS benefit has no current evidence of an OS benefit, is flawed and not supported by any clinical literature nor evidence.			scenario is intended to highlight the sensitivity of the model to plausible alternatives to the company assumption of zero OS gain attributable to treatment with BV, since the evidence is lacking on whether or not there is an OS gain associated with treatment with BV versus PC. The ERG considered it reasonable to investigate a scenario in which mean OS gain is equal to mean PFS gain. Assuming that mean OS gain is equal to mean PFS gain incorporates the assumption that survival after progression is the same for both treatments. That is, that treatment with BV does not affect the disease trajectory once a patient's disease has progressed. Mean PFS gain in the company base case is 9.5 months whereas mean PFS gain in the company model without including alloSCT is 1.2 years. The ERG chose to investigate the impact of a 9.5 month OS gain, which is the more conservative of the two options considered. Since mean PFS gain in the model without alloSCT is 1.2 years, the ERG's scenario of OS gain

			equals 9.5 months still implies that mortality risk after progression is higher for people treated with BV than with PC. 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=0.845) to generate a 9.5 month mean OS gain for treatment with BV versus PC." Figure 14 updated Text on page 127 amended to: "The ERG is not suggesting that OS gain for treatment with BV is equal to 9.5 months or that the log-logistic curve is appropriate; only that this seems to be a reasonable assumption to test in a scenario." "Using the ERG revised base case, the ICER per QALY gained generated when applying a mean OS gain of 9.5 months for the comparison of

			treatment with BV versus PC is £47.570." Text on page 128 amended to: "• Assuming an OS gain for treatment with BV equal to company base case (9.5 months)" Table 35 amended

Issue 23 General typographic Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Minor typographic errors	Page 9, List of Abbreviations, CD30 defined as Cluster of differentiation should be 'CD' instead of CD30 Page 12, misspelled that patients received MXT but should be MTX Page 13, second paragraph *">3 treatment-emergent (TEAEs)"* is missing *adverse events* prior to the brackets Page 14, paragraph four of section 1.4, *offtreament* misspelled -> off-treatment or off treatment Page 32, section 2.3.3 on allogeneic stem-cell transplant, the last sentence is missing a	Minor typographical errors.	The ERG could not find this error on p14. All other typographical errors have been corrected.

	word/section: *The protocol does not include use of are used in both historical and other reduced-intensity conditioning regimens (company response to clarification question C3).* Page 45, Table 4 “Duvec” -> “Duvic”” Page 49, paragraph 3 “techically” -> “technically” Page 72 “As reported in ~~in~~ the CS (p94),” Page 80, section 5.1.2 the following sentence is repeated twice in paragraph one: *The search strategies used are shown in Appendix G and are used to identify cost effectiveness studies and cost and resource use estimates.* Page 86, paragraph 2 AND page 83, Figure 8 footnote “Allogenic” -> “Allogeneic” Page 100, Table 5 footnote “vetodin” -> “vedotin” Page 106, paragraph 1 “Cis” -> “CIs”		

Extra error identified by ERG: Scenario 1

The ERG has identified an error in the calculation of the results for scenario 1 (Changes to post-progression pathway). Changes made in the report are:

Text amended on page 22 to:
The ICERs per QALY gained for the comparison of treatment with BV versus PC generated by the ERG's scenarios are £494,981 (Scenario 1), £26,331 (Scenario 2) and £95,491 (Scenario 3).

Text amended on page 123 to:
The ERG's exploratory analysis of the sensitivity of the results to changes in the assumptions used in the post-progression health state generates an ICER of £494,981 per QALY gained.

ERG revised base case row in Table 35 on page 128 (to align with results in Table 31 on page 120) amended to

ERG revised base case	[redacted]	[redacted]	***6.829***	[redacted]	[redacted]	***6.829***	[redacted]	[redacted]	***0.000***	***BV Dominates***

Row S1 in Table 35 on page 128 amended to:

S1) Changes to post-progression pathway	[redacted]	[redacted]	6.829	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.000	£494,981

Text amended on page 129 to:
The resulting ICERs per QALY gained from the individual ERG scenarios vary from £26,331 (changes to resource use frequencies) to £494,981 (changes to post-progression pathway).

ERG REPORT ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 17/56/12

Erratum completed 14 November 2018

CONTAINS IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 23 issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. The pages of the report where the ERG agreed that changes were necessary are presented here.

LIST OF ABBREVIATIONS

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
CD	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

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 (CD30+) 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 MTX 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 median OS was 43.6 months with BV and 41.6 months with PC but highlights that these results are highly uncertain as illustrated by single figure differences in the number of observed events.

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 adverse events (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

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. It is therefore difficult to draw conclusions from these studies.

1.4 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 total 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.

1.6.3 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.

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.

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 all stages of 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

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 chemotherapies such as melphalan, fludarabine nor cyclophosphamide which 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 presented an estimate of the number of patients that it expects will be treated with BV each year in the CS summary document (and related budget impact document). The

company estimates that 125 patients will be diagnosed with advanced stage CTCL in England each year. The company's estimate is derived as follows:

- PHE incidence rate of 0.75 per 100,000 in England for all CTCL [10]
- Half of CTCL patients have MF [10] (of whom [redacted] have advanced disease, based on PROCLIPI data [61]), 3% have SS [10] and 8% have pcALCL [7]

The company state that uptake of BV is expected to reach up to 75% after 5 years and on average, 84 patients per year will receive treatment with BV for advanced CTCL.

The ERG notes that the company's estimates do not take into account factors such as the proportion of patients with CD30+ MF and therefore 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).

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 eligibility criteria 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.

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 Duvic et al 2015 study
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.

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, technically, 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

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.

1.8 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. Additional data are reported in the EPAR for BV [30] for these two studies, referred (IST-002 and IST-001, respectively [30]). The ERG has summarised the findings, reported in the CS and in the EPAR for BV [30], for these two studies, findings for the retrospective study by Mathieu et al 2016 [75], and the findings from Weiner et al 2016 [116] 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 in Weiner et al 2016 [116]. It is, therefore, unknown how many patients in this study had advanced stage CTCL or how many previous lines of therapy patients in this study 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.

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

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

* Published trials were limited to only those patients exposed to the licensed dose of BV [18, 76], patients who received a different does were included in EPAR for BV [30].

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=26)	3 (2 to 6)	77
BEX (n=38)	5.5 (3 to 11)	114
Duvic et al 2015 BV for MF (n=28) / BV for LyP/pcALCL (n=20)	7 (2 to 19) / 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 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.

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 38.6 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 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

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 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®)	Ovid
Medical Literature Analysis and Retrieval System Online (MEDLINE®)	Ovid
Cochrane Library (including the databases: HTA, NHS EED, DARE, CENTRAL and the Cochrane Database of Systematic Reviews	Cochranelibrary.com
EconLit®	Ovid

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.

5.2.1 Model structure

The company developed a partition survival model in MS Excel. The model structure comprises five mutually exclusive health states (see Figure 1). 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 Allogeneic 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 Allogeneic 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 Allogeneic SCT relapse) receive subsequent therapies for a defined period of time and then progress to end stage symptom management, where they remain until death.

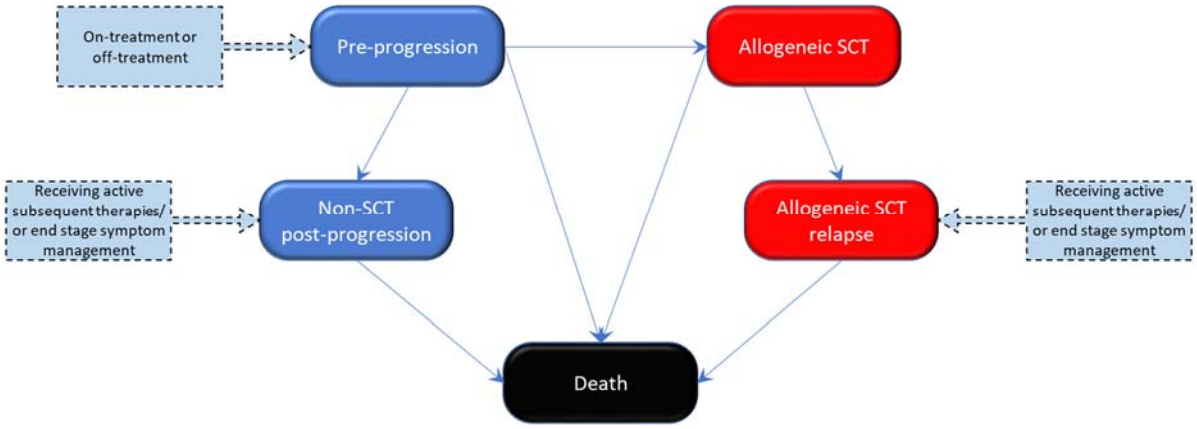


Figure 1 Health state structure of the company model

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

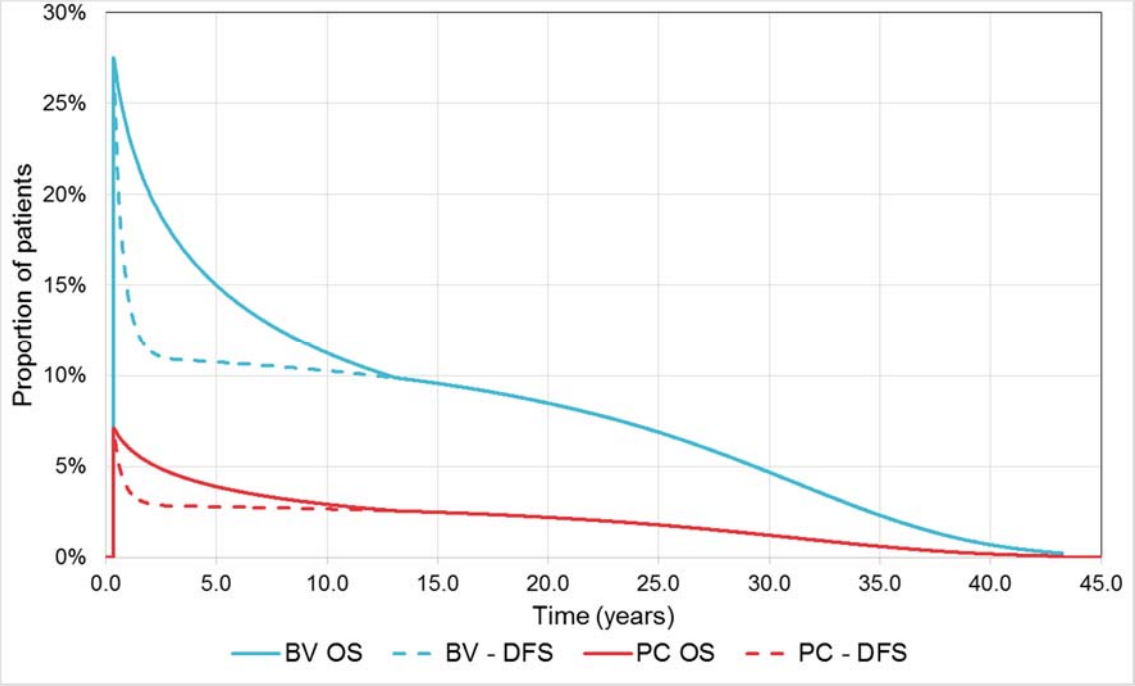


Figure 8 Modelled post-alloSCT DFS and OS

alloSCT=allogeneic 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 total 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

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 grade 3 or 4 septicaemia and peripheral neuropathy are also included in the model, irrespective of whether they were experienced by greater than 5% of patients.

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 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 vedotin; 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.

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 published literature [55, 57, 167]. Table 27 shows the resource use and cost estimates for third line and subsequent active therapies. The dosing regimen for Liposomal doxorubicin (Caelyx) was based on the published SACT protocol [152] while for chlorambucil the summary of product characteristics [169] was used. These two treatments were grouped as 'other mono chemotherapy' with the proportion of patients receiving each therapy based on data from the PROCLIPI study. 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 [55]	£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 [b]	£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 [57]	£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 [167] [c]	£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] Duration derived from consultation with clinicians

[c] 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 duration of post-progression active therapy for patients who have already received SCT (SCT relapse) is 49 weeks given that they are assumed to have already received TSEB prior to alloSCT. The weekly cost in the model for resource use during the post-progression active therapy phase is £904.45.

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

5.1.10 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).

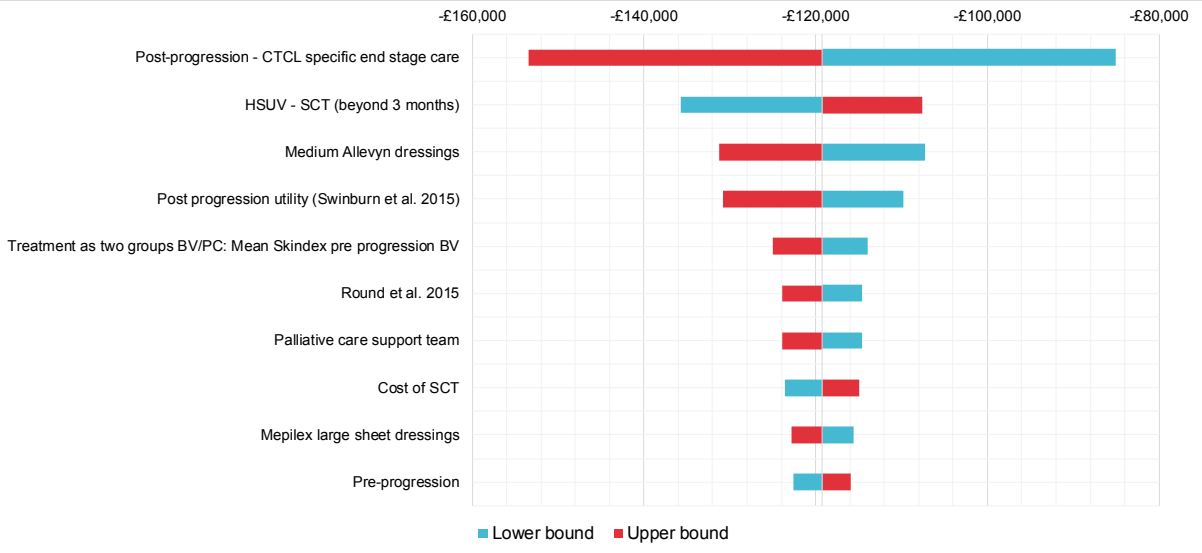


Figure 9 Tornado diagram showing OWSA results for BV versus PC including PAS

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]

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 total 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 vedotin; 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

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.

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.

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 generates an ICER of £494,981 per QALY gained.

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	7
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	2.60		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 as well as 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) without also affecting quality of life, 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 reiterates that this scenario is intended to highlight the sensitivity of the model to plausible alternatives to the company assumption of zero OS gain attributable to treatment with BV, since the evidence is lacking on whether or not there is an OS gain associated with treatment with BV versus PC.

The ERG considered it reasonable to investigate a scenario in which mean OS gain is equal to mean PFS gain. Assuming that mean OS gain is equal to mean PFS gain incorporates the assumption that survival after progression is the same for both treatments. That is, that treatment with BV does not affect the disease trajectory once a patient's disease has progressed. Mean PFS gain in the company base case is 9.5 months whereas mean PFS gain in the company model without including alloSCT is 1.2 years. The ERG chose to investigate the impact of a 9.5 month OS gain, which is the more conservative of the two options considered. Since mean PFS gain in the model without alloSCT is 1.2 years, the ERG's scenario of OS gain equals 9.5 months still implies that mortality risk after progression is higher for people treated with BV than with PC. 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=0.845) to generate a 9.5 month mean OS gain for treatment with BV versus PC. The resulting OS curves are shown in Figure 14.

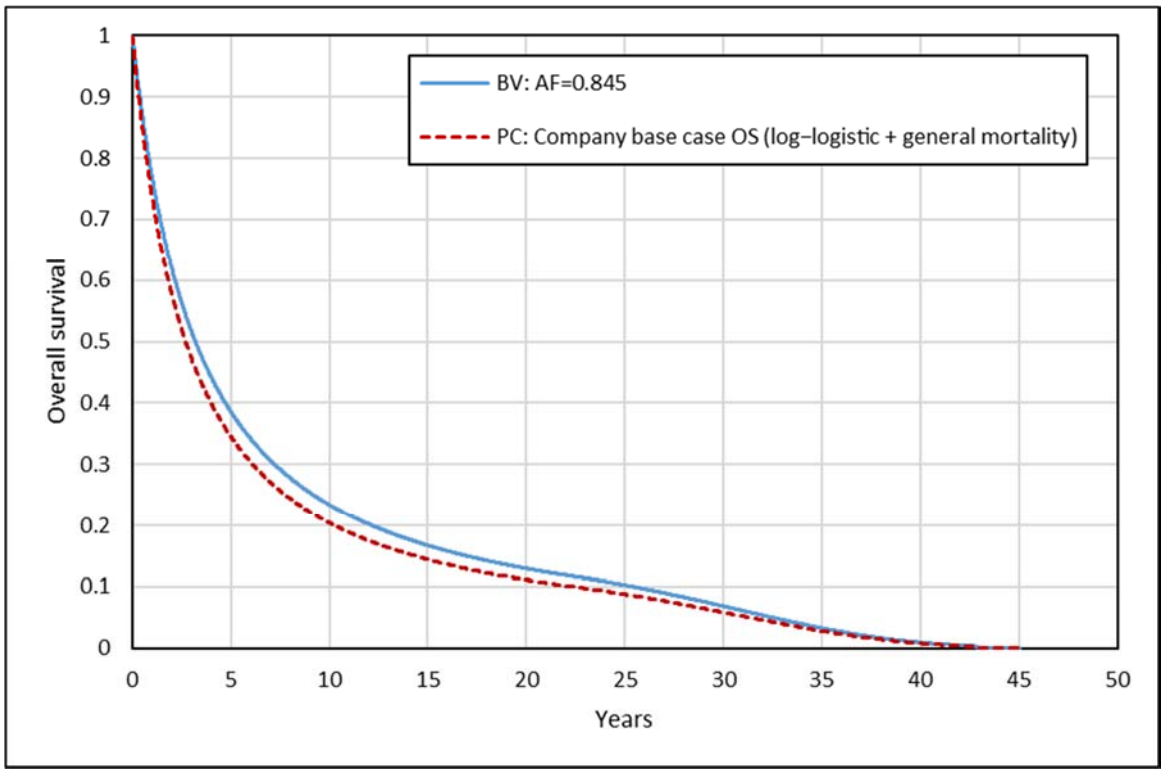


Figure 14 ERG scenario 3: OS gain (mean 9.5 months)

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 9.5 months 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 9.5 months for the comparison of treatment with BV versus PC is £47.570.

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 (9.5 months) (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	£494,981
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 (9.5 months)	[redacted]	[redacted]	7.623	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.794	£47,570

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

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 £494,981 (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.

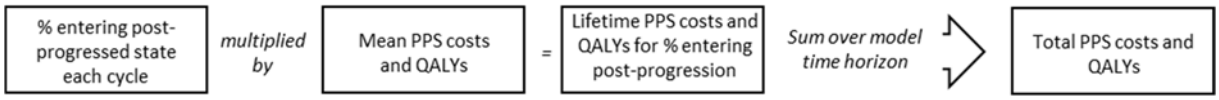


Figure 19 Simplified structure of calculation of total PPS costs and QALYs in the company base case

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.

However, the full impact of discounting is not captured by the payoff approach, which only uses mean time spent a state and does not allow for a different weighting of risk of transition over time (and so different levels of discounting).

Different distributions with the same mean lifetime will produce different overall costs and QALYs due to discounting. For instance, a population in which everyone lives for 2 years has the same mean OS as a population for whom 90% live for 1 year and 10% live for 11 years. Without discounting, costs and QALYs would be the same for these two populations and the ICER per QALY gained would be 0. But discounting means that the population with a long tail of survival (where 10% live for 11 years) accrues lower costs and QALYs, which will result in incremental differences in costs and QALYs between the two populations.

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.

ERG REPORT ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 17/56/12

Addendum completed 16 November 2018

CONTAINS IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

In response to a request from NICE, the ERG has produced a range of ICERs per QALY gained generated by combinations of the ERG scenarios included in the original ERG report. Each of the combined scenarios includes the ERG's revisions to the company base case.

The ERG's revisions to the company base case are:

- 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]

The individual scenarios are:

- 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 (9.5 months) [S3].

The combined results of the scenarios are shown in Table 1.

The ERG cautions that the scenarios presented in the original ERG report and in this addendum are intended to highlight the sensitivity of the model to plausible alternatives to certain key assumptions made by the company that the ERG does not consider to be supported by robust evidence. The ERG is not suggesting that the individual or combined ERG scenarios are necessarily more reflective of reality than those in the company base case, only that they represent plausible alternatives to the company base case assumptions that have a substantial impact on the model results.

Table 1 Cost effectiveness results for combined 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 company base case	[redacted]	[redacted]	***6.829***	[redacted]	[redacted]	***6.829***	[redacted]	[redacted]	***0.000***	***BV Dominates***
S1) Changes to post-progression pathway and S2) Changes to resource use frequencies	[redacted]	[redacted]	6.829	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.000	£626,918
S1) Changes to post-progression pathway and S3) Assuming an OS gain for treatment with BV equal to company base case (9.5 months)	[redacted]	[redacted]	7.623	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.794	£128,445
S2) Changes to resource use frequencies and S3) Assuming an OS gain for treatment with BV equal to company base case (9.5 months)	[redacted]	[redacted]	7.623	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.794	£82,597
S1) Changes to post-progression pathway and S2) Changes to resource use frequencies and S3) Assuming an OS gain for treatment with BV equal to company base case (9.5 months)	[redacted]	[redacted]	7.623	[redacted]	[redacted]	6.829	[redacted]	[redacted]	0.794	£125,854

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

Each of the combined scenarios generates an ICER per QALY gained above the level generally considered to be cost effective by NICE.

Incremental costs increase versus the ERG's revised base case in each combined scenario because either: the cost of resources is reduced in the model (Scenario 1 and Scenario 2), which affects treatment with PC more than treatment with BV as mean time spent in the most resource-intensive state is greater in the ERG's revised company base case for treatment with PC than with BV; or the time spent in the post progression state is increased for treatment with BV as a result of increasing OS (Scenario 3), which means that the intervention accrues costs for longer following progression than in the ERG's revised company base case.

Incremental costs in each of the combined scenarios are higher than in each scenario individually.

Incremental QALYs decrease in Scenario 1 as a result of increasing the time spent in active therapy following progression at the expense of time spent in the end-stage care state. The utility value applied for the active therapy state is relatively high (0.64) versus the utility value applied for end-stage care (0.38) and is similar to the PFS utility used in the ERG's revised company base case (0.69). This means that the QALY gain accrued in the pre-progression state for treatment with BV due to longer PFS is largely offset for treatment with PC by the QALYs accrued from spending longer in the active therapy state. Incremental QALYs in Scenario 3 increase versus the ERG's revised company base case due to the modelled OS gain. There is no impact on incremental QALYs in Scenario 2.

Adding Scenario 2 to any other scenario has no impact on incremental QALYs. Adding Scenario 1 to Scenario 3 reduces the incremental QALYs gained in Scenario 3 but incremental QALYs remain higher than in the ERG's revised company base case.

Questions for patient and clinical experts

Allogenic stem cell transplants (alloSCT)	
Questions for experts	• *What proportion of patients with advanced CTCL whose disease responds sufficiently to treatment would become eligible for an alloSCT?* • *Would patients with advanced disease accept alloSCT as a treatment option after only 2 or 3 previous systemic therapies when other treatment options exist? Would the acceptance vary by stage of disease?*
Background/ description of issue	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 company** assumed that 40% of patients showing at least a partial response to treatment, are eligible for an alloSCT (27.5% of all patients in the brentuximab vedotin treatment arm and 7.11% in the 'physician's choice' (PC) treatment arm). The company predicted survival separately for patients who had a stem cell transplant and those who did not. For patient who had an alloSCT data from people who attended the London supra-regional centre for CTCL and received alloSCTs was used for disease free and overall survival extrapolation to predict survival outcomes. All patients that did not receive an alloSCT followed progression-free and overall survival curves extrapolated from the ALCANZA trial data. **The ERG** does not consider the company's inclusion of alloSCT in the base case analysis to be appropriate. The ERG does not consider there is sufficient evidence to allow alloSCT to be modelled robustly. They consider there to be uncertainty around the company's placement of alloSCT in the treatment pathway (immediately after responding to a 2nd line systemic therapy with regards to patient acceptance of alloSCT when other treatment options are still available) and rate of alloSCT (ALCANZA data and clinical expert statements to NICE suggest the rate is lower than the 40% predicted by the company). The ERG noted that the survival gain seen in the cost effectiveness results was derived from more patients receiving alloSCT in the brentuximab vedotin treatment arm than in the PC treatment arm but that there is limited data on the outcomes of patients receiving alloSCTs after brentuximab vedotin treatment.

Overall survival (OS)	
Questions for experts	• *Is brentuximab vedotin expected to increase length of life more than current care without bridging patients to alloSCT?* • *Would the time spent on subsequent active therapies be expected to change after relapse with brentuximab vedotin compared with current treatment options?*
Background/ description of issue	**The company** state that the OS data from the ALCANZA trial are immature and potentially confounded by patient crossover. The company attempted to adjust overall survival estimates for crossover; however, none of the methods used produced clinically

	plausible results. In the company's base case it was therefore assumed that OS was equal for the 2 treatment arms and the unadjusted OS data for patients in the PC treatment arm of the trial could be used to represent OS for all patients. **The ERG** agreed that there was insufficient evidence from the ALCANZA trial to make robust claims about lifetime OS gain. However, The ERG noted that the company's assumption of equal OS alongside a progression-free survival (PFS) gain for treatment with brentuximab vedotin means that, after progression, patients who had brentuximab vedotin die more quickly than patients who had PC. Patients who had brentuximab vedotin therefore spend less time in the resource intense end-stage care than patients who received current treatment (PC).

Health-related quality of life (HRQoL)	
Questions for experts	• *Is* brentuximab vedotin *expected to increase HRQoL more than current care?* • *Will HRQoL for people with advanced CTCL be fully captured using standard HRQoL methodology (EQ-5D questionnaire)?*
Background/ description of issue	**The company's** results show a poor correlation between the symptom domain of Skindex-29 and the EQ-5D-3L results for patients with advanced stage CTCL. The company's base case utility values for the brentuximab vedotin and PC treatment arms were calculated from a regression model incorporating both HRQoL measures (EQ-5D-3L and Skindex-29 symptom domain). **The ERG** acknowledged 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. However, the ERG agreed with views expressed by the EMA that "no firm conclusions can be drawn" on the impact of brentuximab vedotin on HRQoL. The ERG prefers that EQ-5D utility values are used in the model to retain adherence to the NICE Reference case and to ensure comparability with the ICERs per QALY gained that inform other NICE technology appraisals. As baseline EQ-5D-3L PFS utility values were higher in the brentuximab vedotin treatment arm the ERG assumes that the PFS utility values calculated using the observed EQ-5D-3L values are the same for patients receiving brentuximab vedotin and PC by using an average (0.689) of the observed EQ-5D-3L values.

Responses from experts

Your name	**Teresa Kelly**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	

Allogenic stem cell transplants (alloSCT)
• *What proportion of patients with advanced CTCL whose disease responds sufficiently to treatment would become eligible for an alloSCT?* • *Would patients with advanced disease accept alloSCT as a treatment option after only 2 or 3 previous systemic therapies when other treatment options exist? Would the acceptance vary by stage of disease?*
When I reached stage 4A I understood that my best chance of survival was an alloSCT. At that stage the number of previous systemic therapies seemed irrelevant. I think I can say this on behalf of several other patients too. In my case I had only had one systemic therapy (Bexarotene) before I became stage 4A and the Brentuximab trial was offered as hopefully providing preparation for the transplant. With the dangers and risks of alloSCT , I would have wanted to try a safer treatment if I was at an earlier stage and such a treatment was available, unless someone could predict that the illness would progress to Stage 4 and I was advised that it was less dangerous to have a transplant at that earlier stage. At an earlier stage I wouldn't have wanted to take the risk considering the mortality rate of transplant and the fact that it is not a guaranteed cure.
Overall survival (OS)
• *Is brentuximab vedotin expected to increase length of life more than current care without bridging patients to alloSCT?* • *Would the time spent on subsequent active therapies be expected to change after relapse with brentuximab vedotin compared with current treatment options?*
Health-related quality of life (HRQoL)
• *Is* brentuximab vedotin *expected to increase HRQoL more than current care?* • *Will HRQoL for people with advanced CTCL be fully captured using standard HRQoL methodology (EQ-5D questionnaire)?*

Brentuximab cleared my skin very quickly. I seemed to be disease free in a way that I had not been since I was diagnosed. My quality of life therefore improved greatly during the trial. It was a relief to not have sore and itchy skin and there were few side effects during this time. A fellow patient had a similar experience and we were extremely pleased that we had been able to go on the trial. When I stopped the drug the disease went into my lymph nodes after 6 months and my fellow patient has had severe neuropathy as a result of the drug but it certainly increased our quality of life during the time we were on it.