NICE National Institute for Health and Care Excellence

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

Clinical effectiveness

Appraisal Committee Meeting 1 (27th November 2018)

Committee C

Lead team: Richard Nicholas, Judith Wardle and Matt Stevenson

ERG: LRIG

NICE technical team: Lorna Dunning and Nicola Hay

Company: Takeda

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?

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?

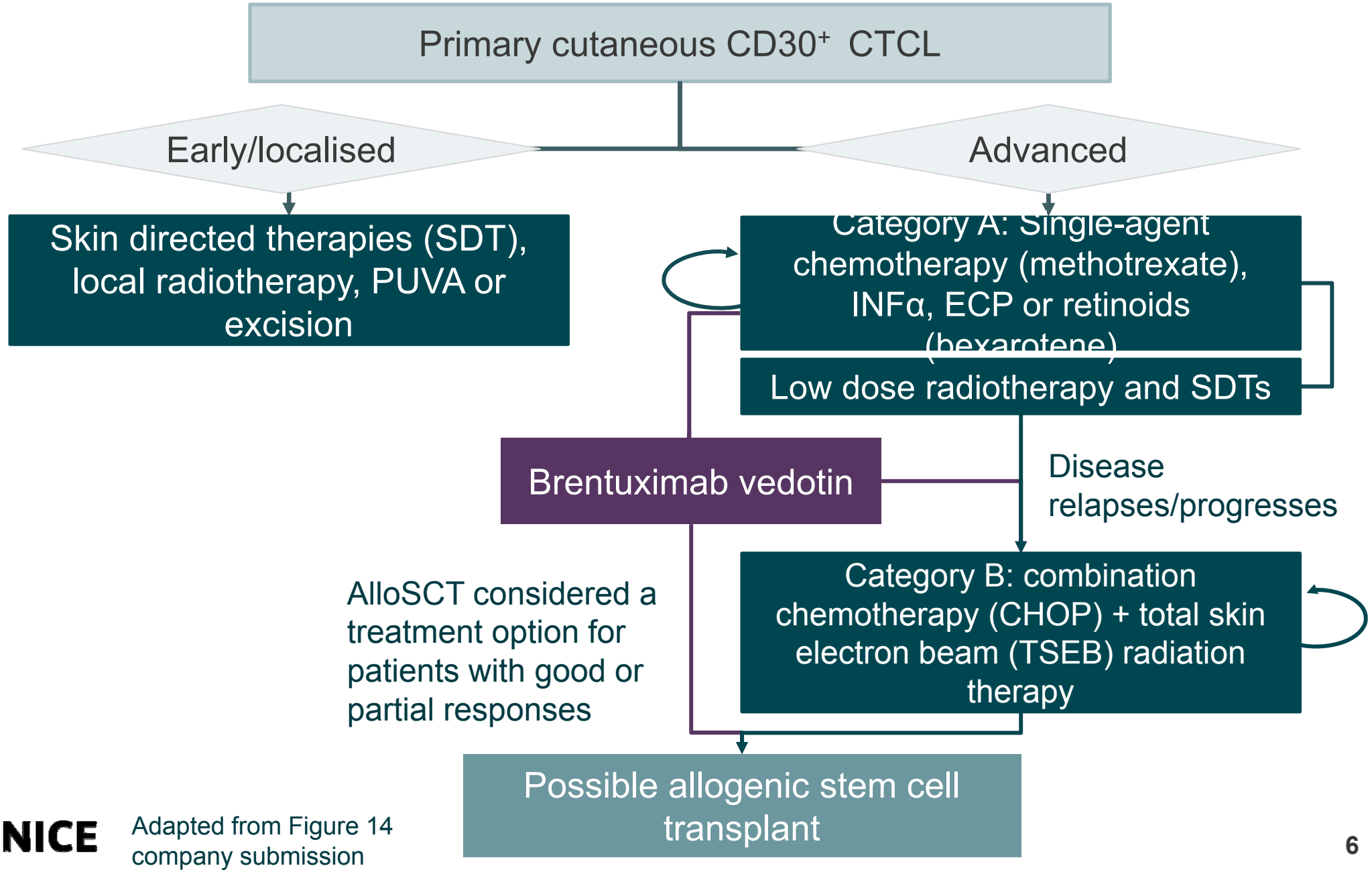
Disease background

- 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 and retinoids including bexarotene
- 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 a patient group: CTCL

- It can take years for people with CTCL to get a diagnosis
- Itching can be both a symptom and a side effect of current treatments. Since it can impair sleep, people may be very tired. This, combined with being self-conscious about their appearance can have a significant impact on 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.

Comments from a patient group: treatment

- Since current treatments may not be specific to this condition, patients fear that treatments may not work
- There is an unmet need for treatments that improve quality of life
- There might be concern about side effects
- Younger people trying to manage the condition alongside the demands of everyday life may welcome a more intensive treatment that gives them longer disease control
- The patient group has not spoken to people treated with brentuximab

Comments from professional groups

- 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
- Around 5% of patients receive alloSCTs with current treatment
- 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
- 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	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]
- 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

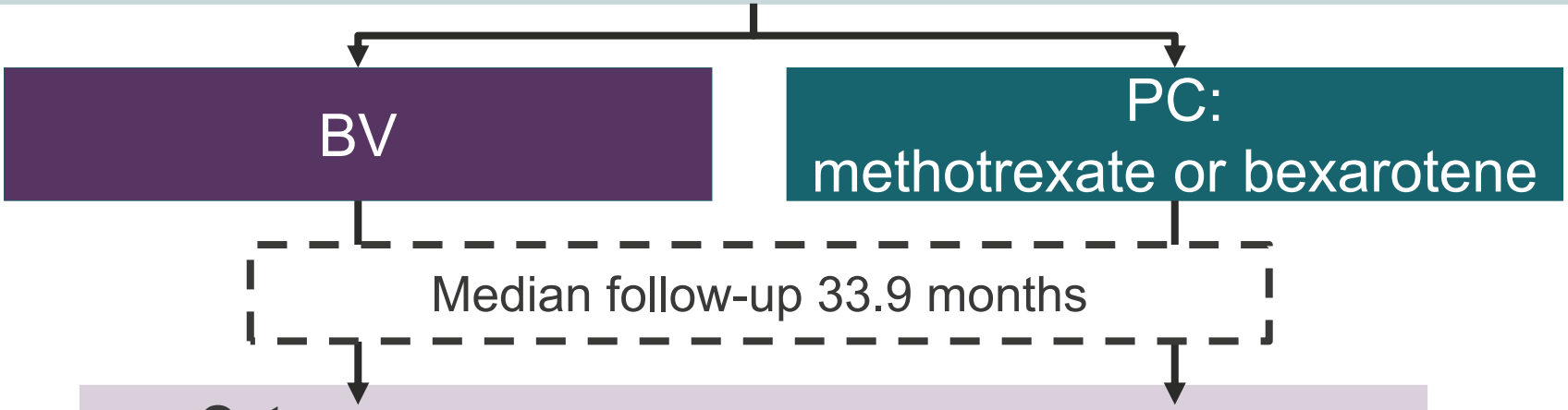
Evidence	Population	Used in clinical effectiveness	Used in cost effectiveness
ALCANZA – multicentre, randomised open-label study of BV vs. PC (MXT or BEX)	Adults with CD30+ CTCL (MF or pcALCL) who received prior radiation therapy or ≥1 prior systemic therapy (pcALCL) or ≥1 prior systemic therapy (MF) (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=48)	Yes	No
Abbreviations: LyP, lymphomatoid papulosis			

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)	4.0 (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)

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)
ECOG performance group, n (%)		
PS = 0	34 (69)	31 (67)
PS = 1	12 (25)	13 (28)
PS = 2	3 (6)	2 (4)
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 (1-15)
Skin directed	1.0 (0–6)	1.0 (0–7)
Systemic	2.0 (1-8)	2.0 (0–11)

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Question for committee: Are there any differences in baseline characteristics which are likely to impact relative treatment effect?

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 were treated with 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 at 33.9 months

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)

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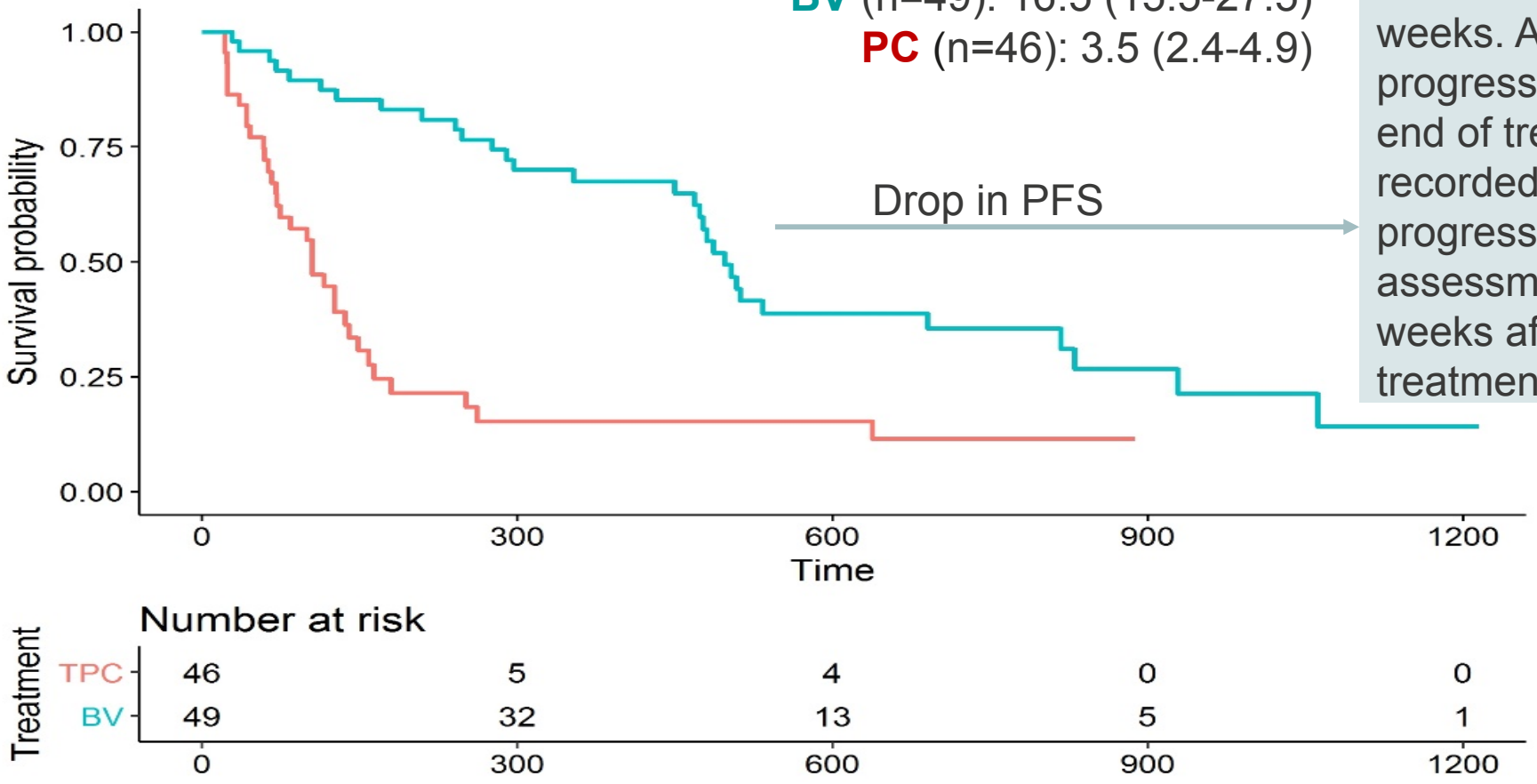
Question for committee: Is IRF a suitable outcome measure?

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)

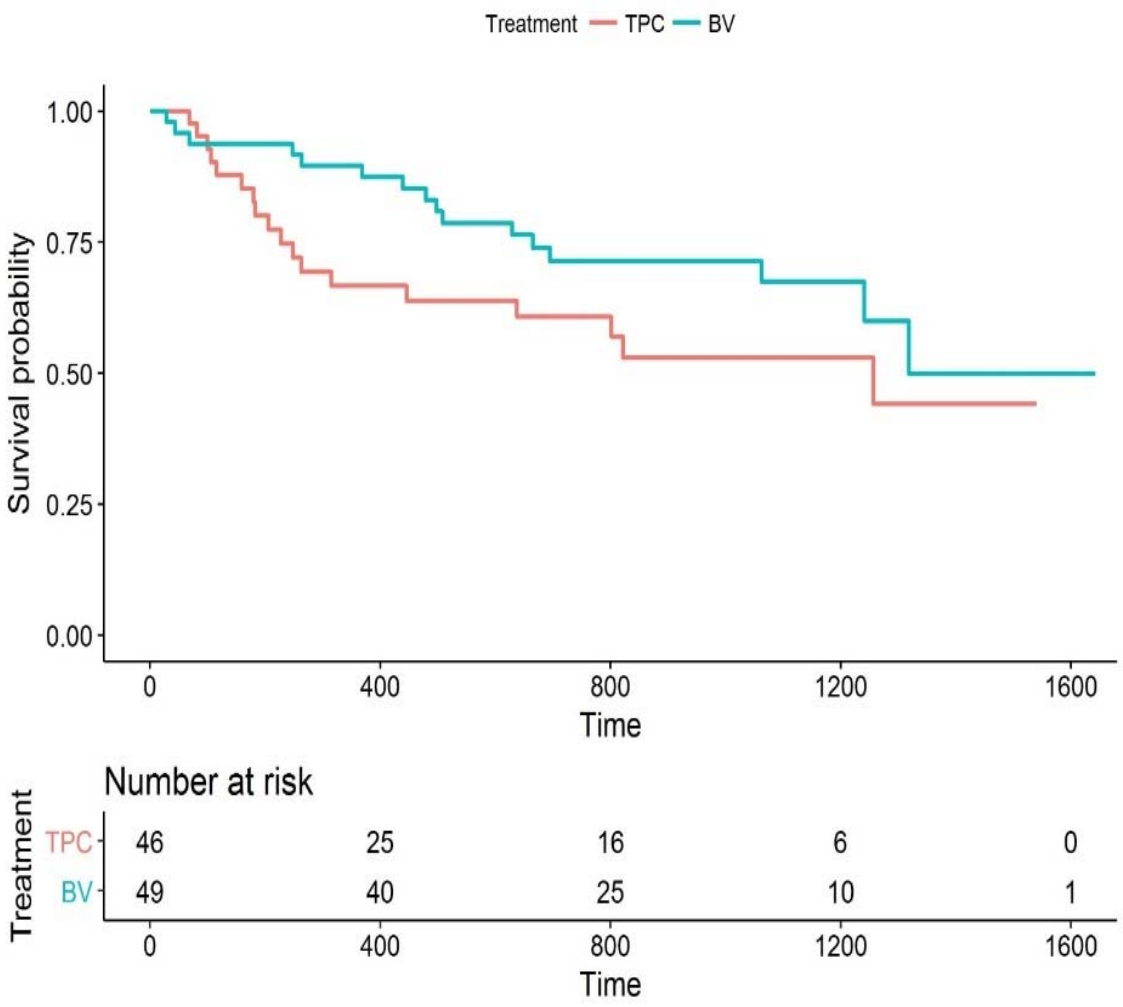
Question for committee: Does the evidence suggest brentuximab vedotin is clinically effective?

ALCANZA results: overall survival

Outcome (months)	BV	PC
Overall survival	43.6 (41.0–NA)	41.6 (21.1-NA)

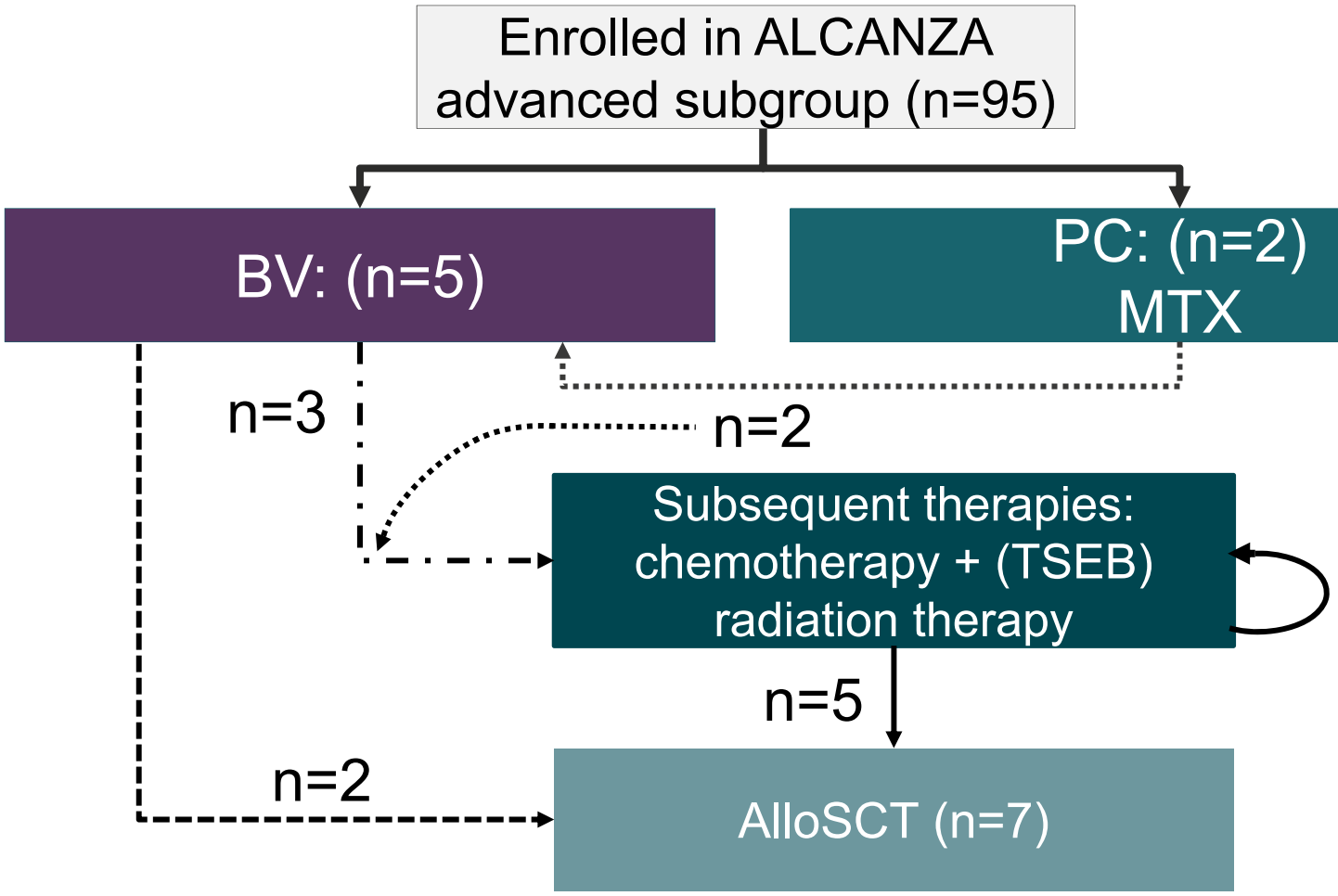
Overall survival was not a pre-specified end point

- 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



Question for committee: Is brentuximab vedotin (BV) expected to have an effect on overall survival?

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

Question for committee: What proportion of patients would become eligible for an alloSCT in clinical practice?

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 states this may not be sensitive enough to demonstrate impact of CTCL symptoms on HRQoL e.g. constant severe, intense itching causing insomnia.

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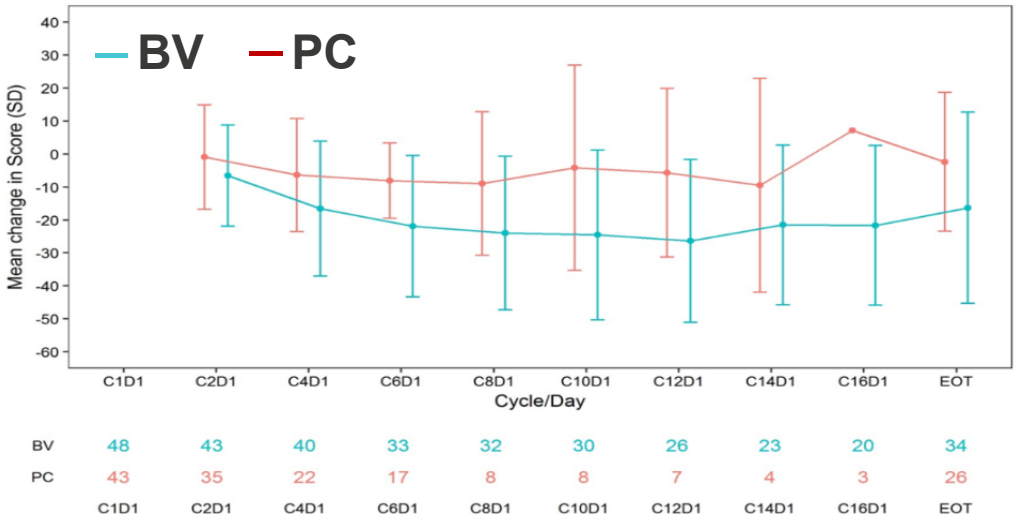
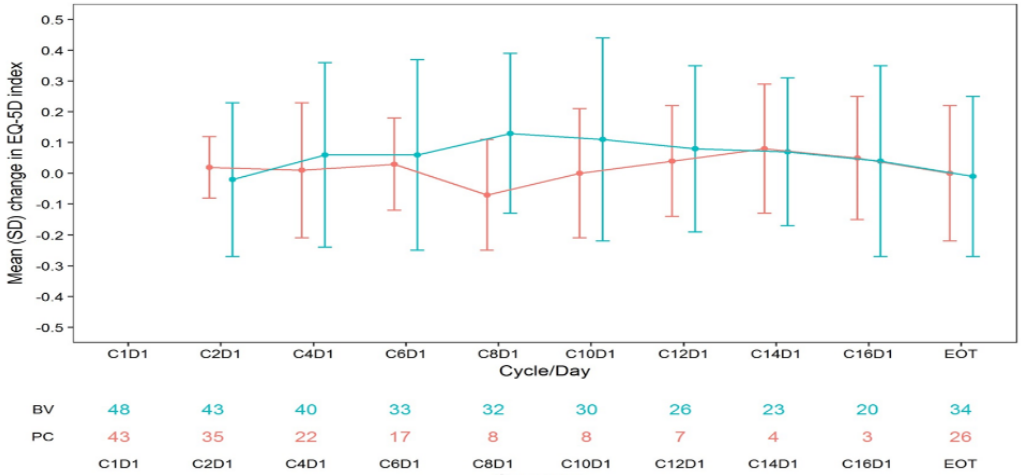
Question for committee: Is EQ-5D a suitable HRQoL measure for CTCL?

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



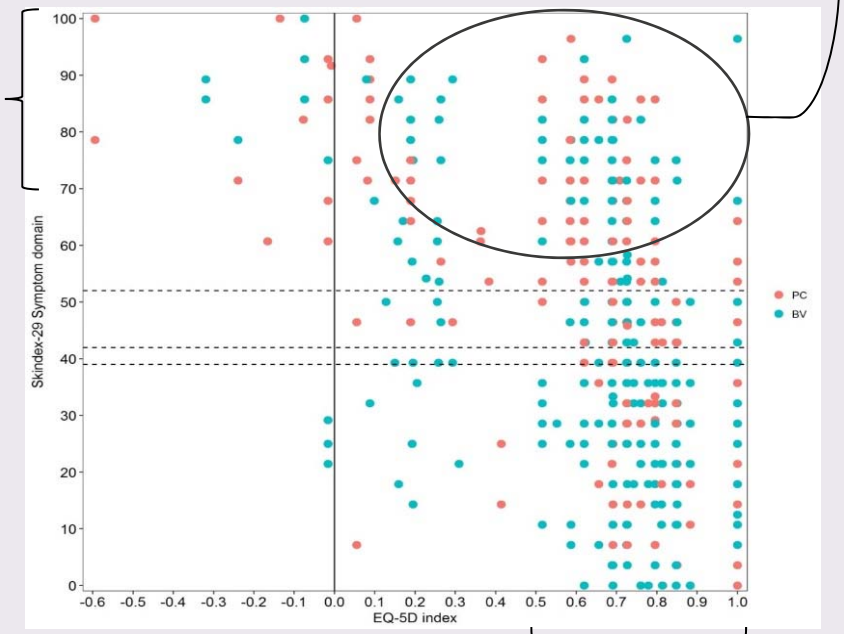
EQ-5D-3L no change in HRQL was found



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	58	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)	33 (34)	-	4 (13)	3 (9)
Advanced CTCL, n (%)	95 (74)	95 (74)	-	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

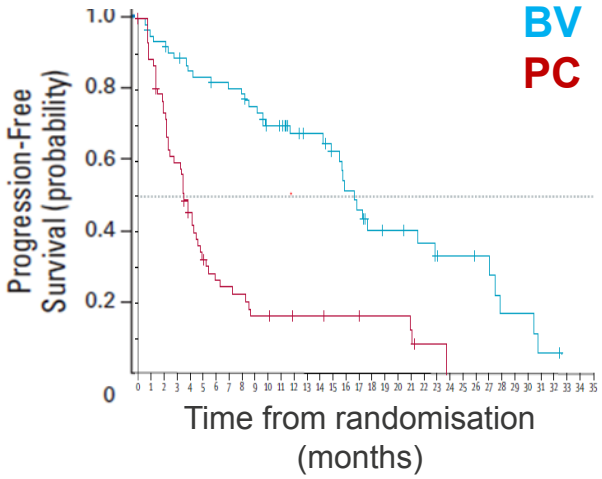
Supporting Results: Kim et al 2015 and Duvic et al 2015

SS and LyP were not included in the ALACANZA trial but are included in the MA
Kim et al 2015 and Duvic et al 2015 show consistent outcomes with ALCANZA trial

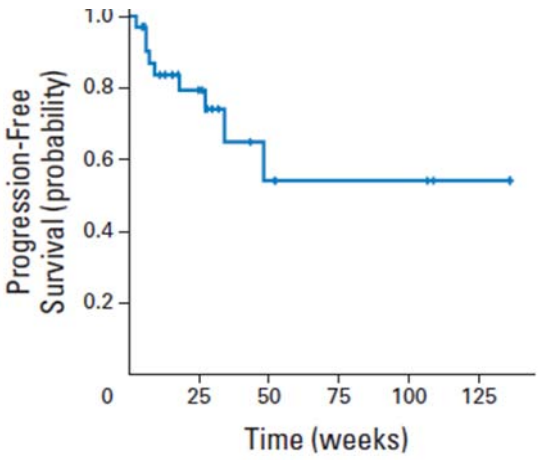
Outcome	*ALCANZA (n=64) - INV assessed*	*Kim et al 2015 (n=30)*		*Duvic et al 2015 (n=48)*		
		MF	SS	MF	LyP	Other
ORR	43 (67.2)	19 (70.3)	2 (66.7)	15 (54.0)	9 (100)	9 (100)
CR	10 (20.4)	0 (0)	1 (33.3)	2 (7.1)	5 (55.6)	8 (88.9)
PR	24 (49.0)	19 (70.3)	1 (33.3)	13 (46.4)	4 (44.)	1 (11.1)

Progression-free survival

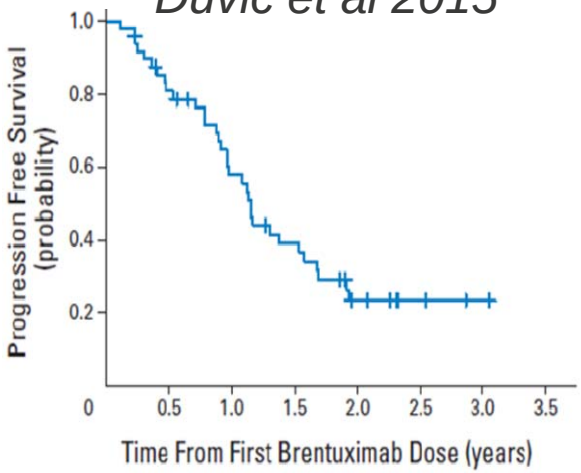
ALCANZA



Kim et al 2015



Duvic et al 2015



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ERG 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 rather than the 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 subsequent 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

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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

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ERG 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 (mean time 237 days BV and 130 days 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 advanced BV treatment 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

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?

NICE National Institute for Health and Care Excellence

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

Cost-effectiveness

Appraisal Committee Meeting 1 (27th November 2018)

Committee C

Lead team: Richard Nicholas, Judith Wardle and Matt Stevenson

ERG: LRIG

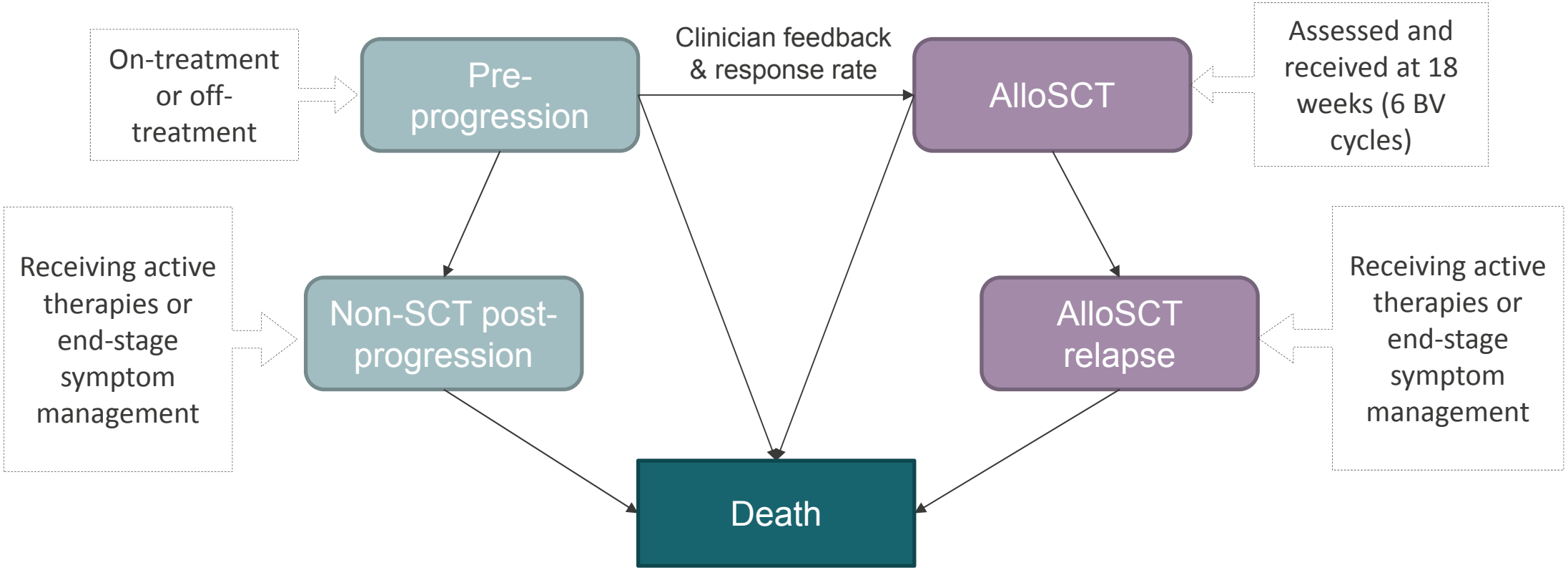
NICE technical team: Lorna Dunning and Nicola Hay

Company: Takeda

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?

Company model [1]



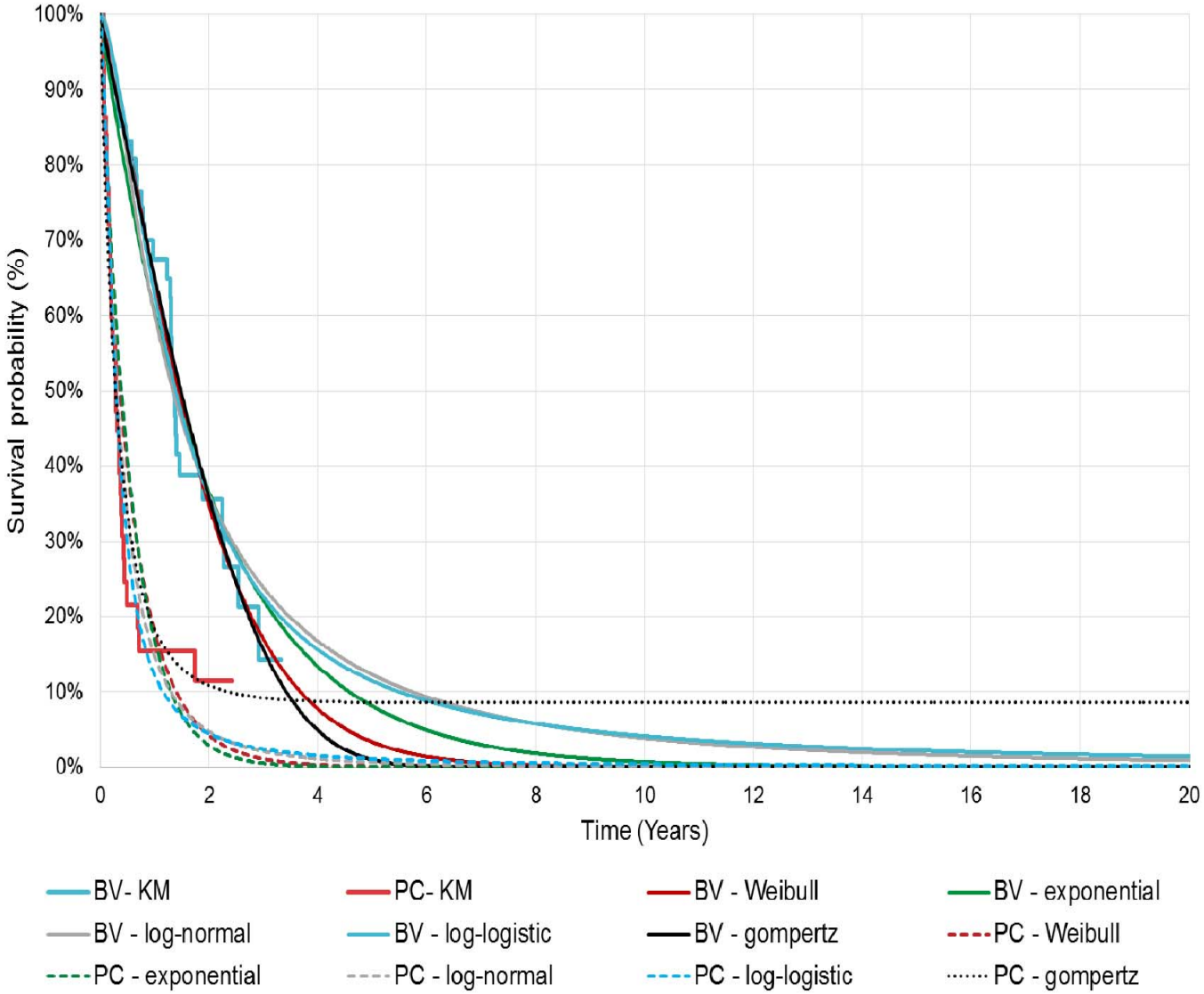
- Partitioned survival model - OS and PFS modelled independently
- The analysis uses data from the advanced subgroup from ALCANZA including patients with MF or pcALCL only
- PFS, OS and time-on-treatment (ToT) data for pre-progression/post-progression states from ALCANZA trial
- Disease free survival (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'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 treatment arm applied to BV treatment arm	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

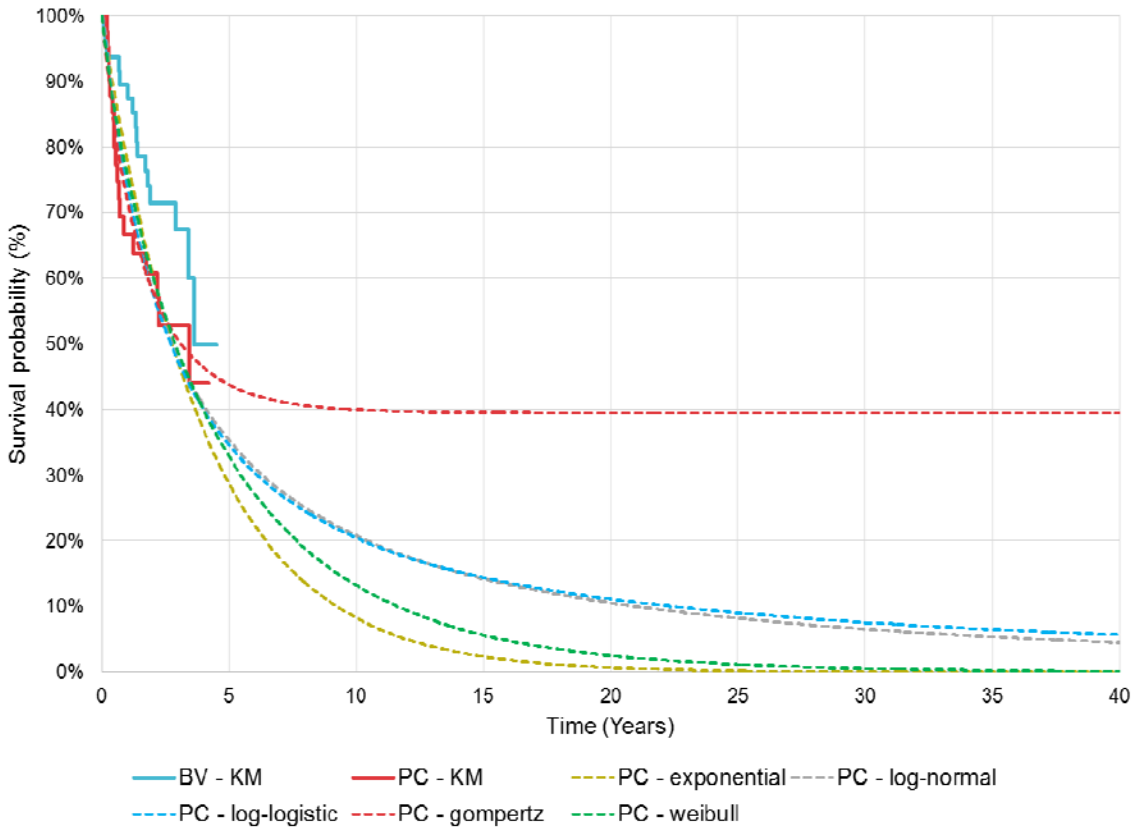
- A rank preserving structural failure time (RPSFT) model estimated an increase in OS for BV at earlier time-points and a higher rate of long-term OS for PC - Company stated this was not clinically plausible
  - BV was not expected to worsen survival
  - No increase in OS was expected with BV (except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

Question for committee: Is it appropriate to use a single survival curve to model OS in the BV and PC treatment arms given differences in PFS?

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

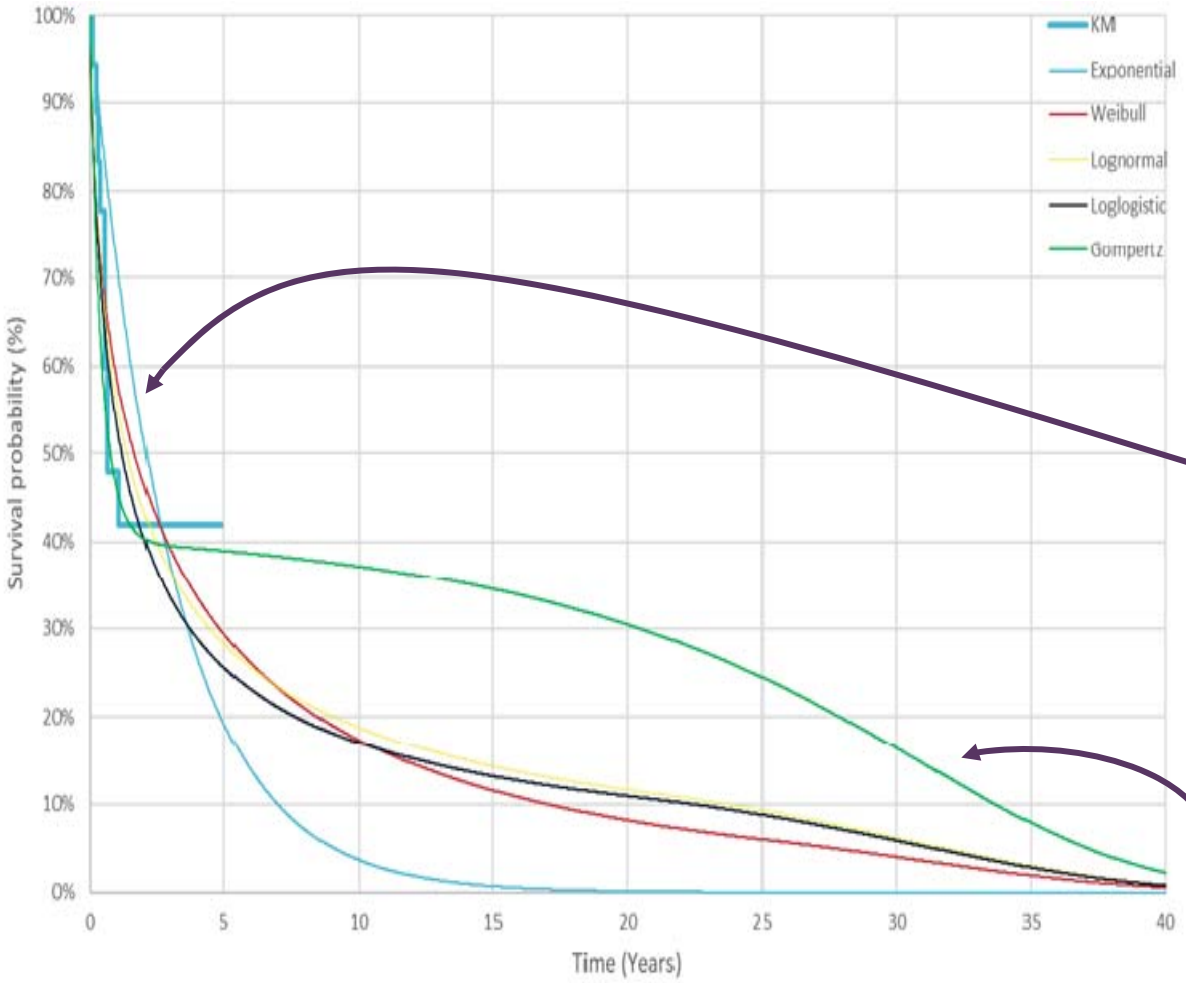
Proportion of patients surviving at various time points by parametric curve

	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)

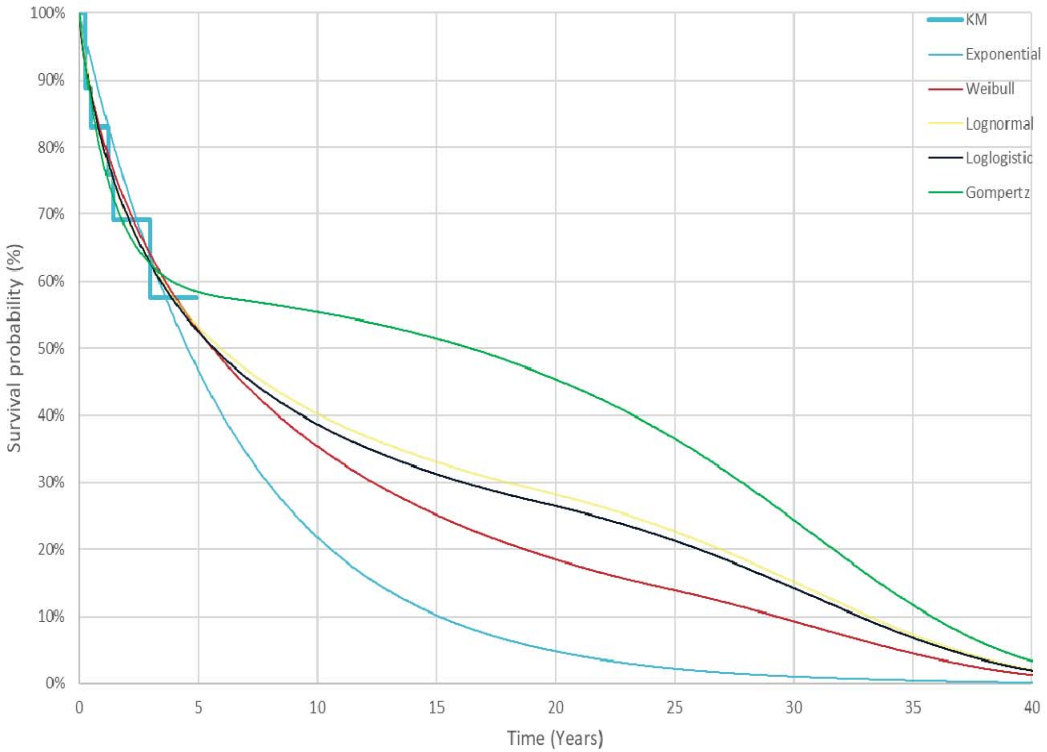
Company's model inputs: extrapolation of disease free survival (DFS) after alloSCT



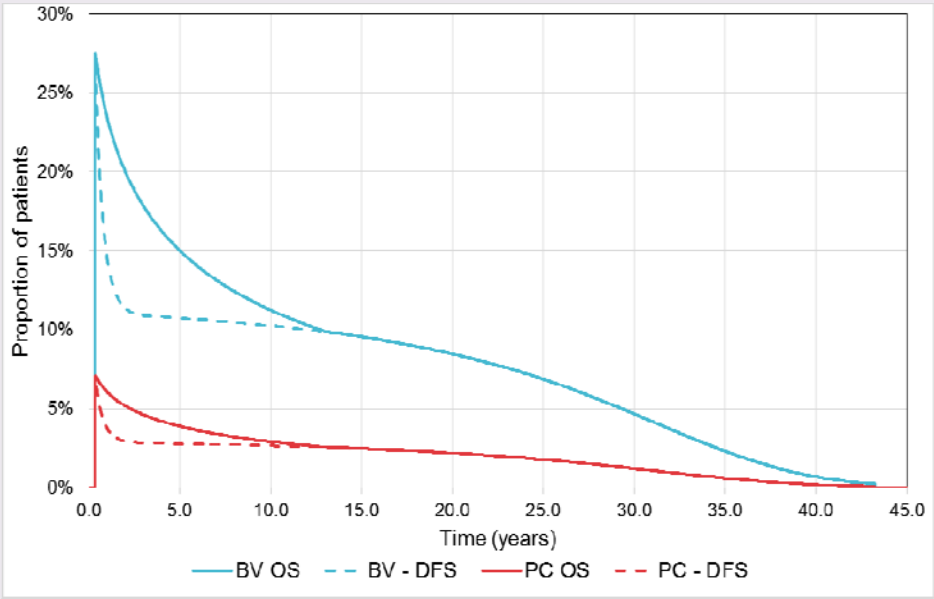
- Patients eligible for alloSCT transition to the 'alloSCT' health state
- Transitions are determined by DFS and OS parametric curves
- Data fitted to real-world outcomes from Hammersmith Hospital (London supra-regional centre)
- KM data shows relapsing after alloSCT likely to occur in the first twelve months
- Observed DFS data was digitised and parametric survival models were fitted and assessed
- Company chose Gompertz curve as it reflected 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



ERG's comments on the appropriateness of alloSCT

- Information included in the CS not sufficient to assess how representative the dataset is of the patients who receive alloSCT in the model
- The evidence of outcomes in older patients, particularly >60 is lacking. Historic studies have included patients more heavily pre-treated than in ALCANZA
- No evidence of outcomes for alloSCT post-treatment with BV
- Unlikely for clinicians to offer alloSCT to stable patients who have more treatment options available
- Clinical advice suggest < 40% would receive alloSCT
- 2/7 patients receiving alloSCT in ALCANZA had so after initial treatment – 2/128 ITT population is 1.6%

Questions for committee:

- Should alloSCT be included in the base case model?
- What proportion of patients would become eligible for alloSCT?
- Would people accept alloSCT at this point in the pathway?

Company's model inputs: Utility values

- HRQoL data collected using EQ-5D and Skindex-29
- 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

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 (£96,956) Scenario using National Schedule of Reference Costs
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 (includes 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

*BV dominates (more effective and less costly)

Abbreviations: NMB, net monetary benefit

Question for committee: The cost-effectiveness results come from ALCANZA trial data which includes patients with MF and pcALCL subgroups only. Can this data be extrapolated to SS and LyP subgroups?

Company's addendum: updated alloSCT outcomes

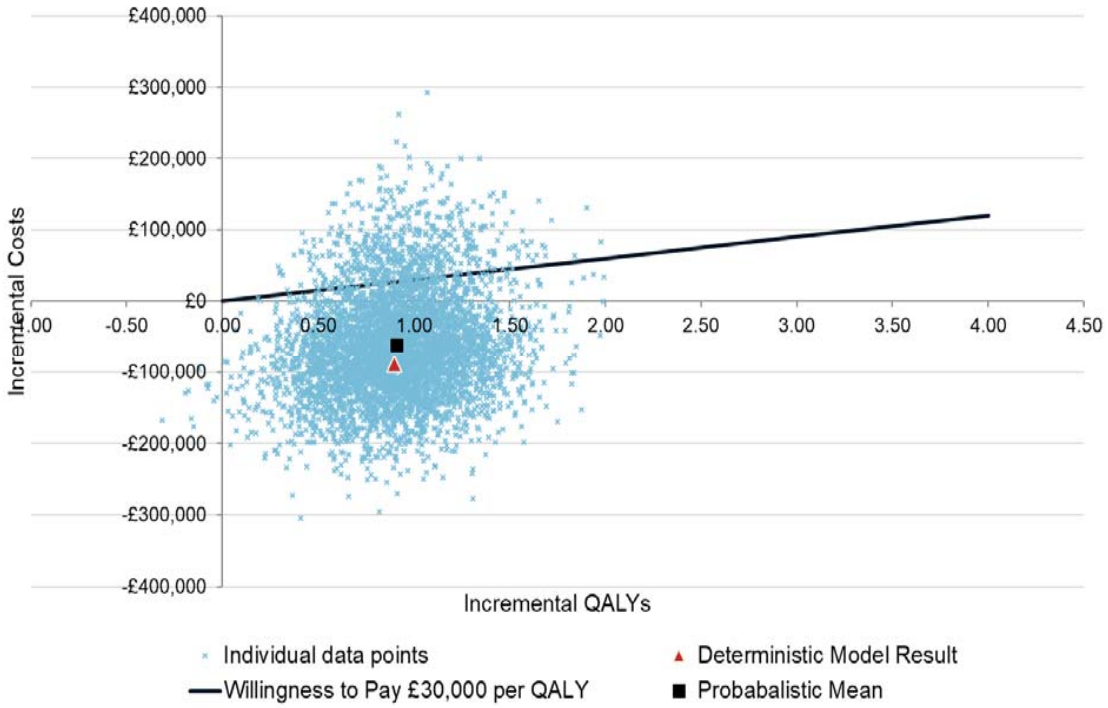
[redacted]

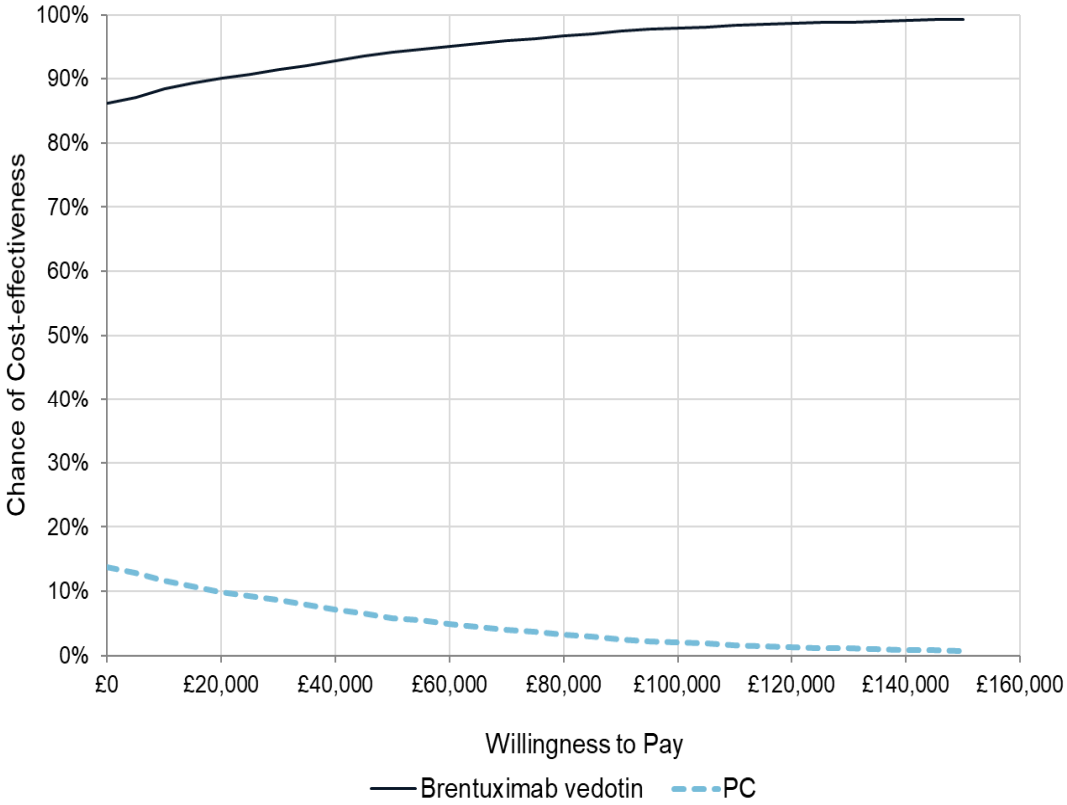
[redacted]

- Later data cut (datacut 2) presented at the 2018 EORTC included a longer follow-up period and additional patients with advanced CTCL who had undergone alloSCT at five other centres in the UK (n=53)
- [redacted]
- [redacted]
- DFS requires complete response in patients
- [redacted]
- Datacut-2 separated intensive and minimal intensity (UK preferred Stanford protocol) for OS but groups were combined for the analysis

Company scenarios	Incremental Costs	Incremental QALYs	LYs	ICER per QALY gained
Base case	[redacted]	[redacted]	1.20	BV Dominates
Updated base case	[redacted]	[redacted]	1.58	BV Dominates

Company's probabilistic analyses





- Probabilistic ICER (5,000 iterations) is dominant
- At a willingness to pay of £30,000 per QALY, BV was cost-effective in 91.38% of iterations

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

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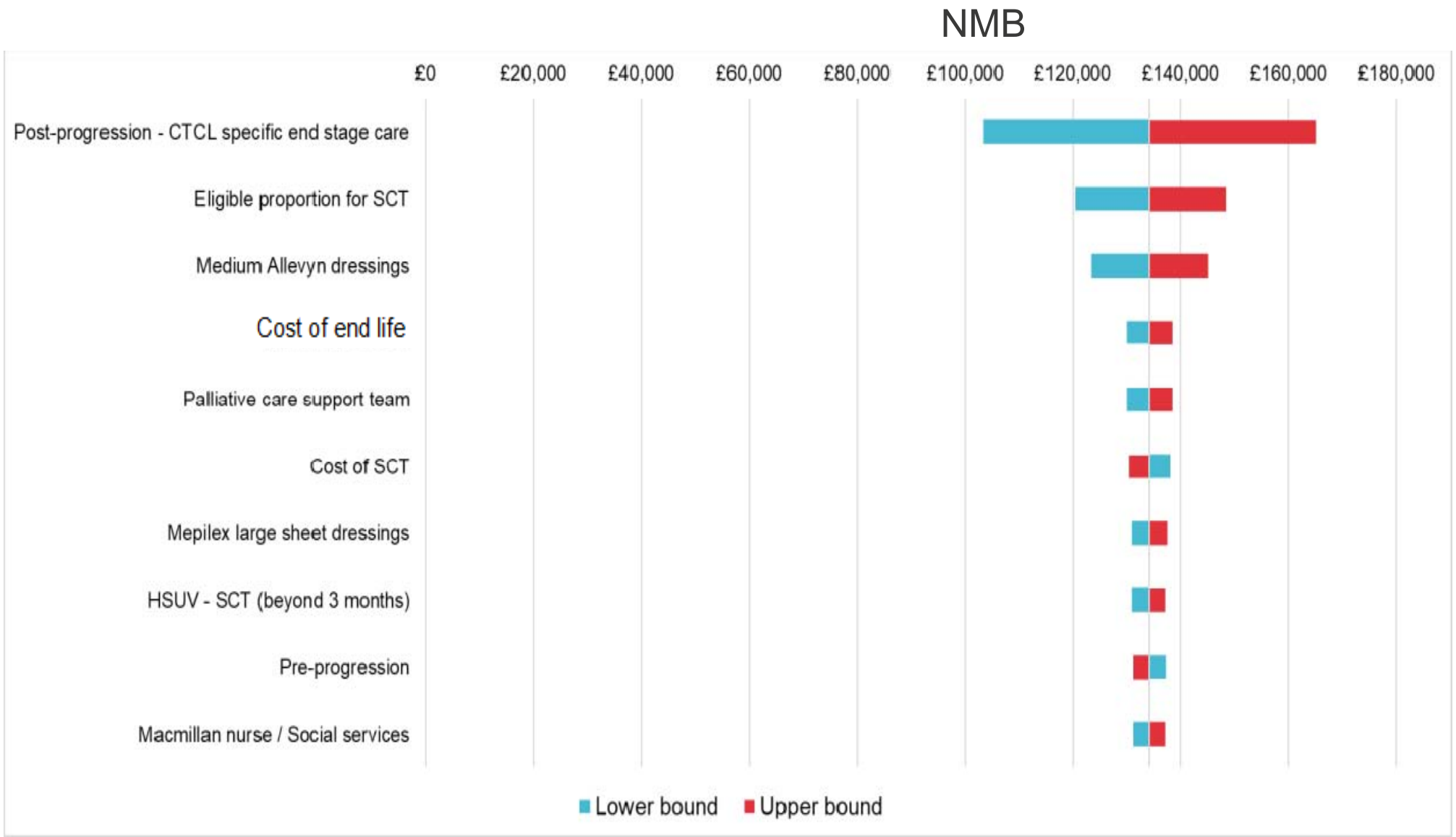
Company's deterministic analyses



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 who had BV. Patients spend less time in costly end-stage care compared with patients who had PC
- 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 (see Slide 11)

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

Question for committee: Should alloSCT be included in the base case?

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

Utility values – progression free health state

- The company use a regression model including Skindex-29 scores to calculate utility values for the progression-free state (see slide 12)
- This is not reflective of the NICE methods guide: the ICERs are on a different scale to the ICERs 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 considers 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 (0.689)

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

- ERG considers there is double counting in the administration costs of oral chemotherapy

Question for committee: What utility values should be used in the model?

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

NICE

Question for committee: What amendments should be made to the company's base case?

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 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 BV because patients accrue fewer costs from resource intensive end-stage-management

The differential end-stage care costs accrued by patients treated with PC versus BV in the ERG's revised company 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

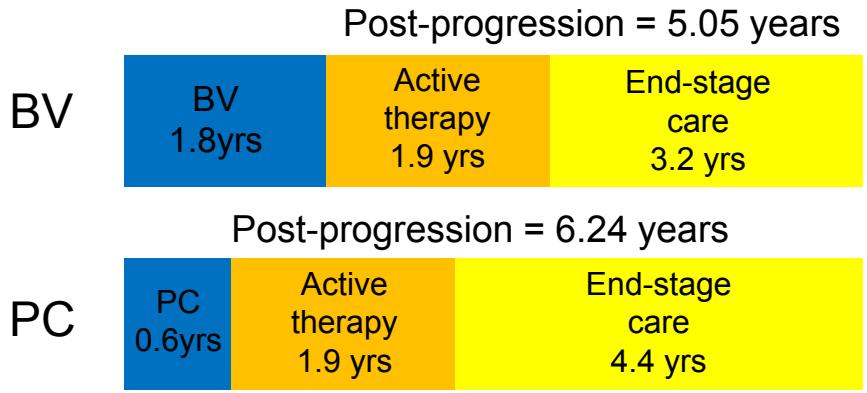
— To explore the uncertainty the ERG presented a sensitivity analysis on the post progression treatment pathway and time spent in end-stage care (Scenario 1)

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

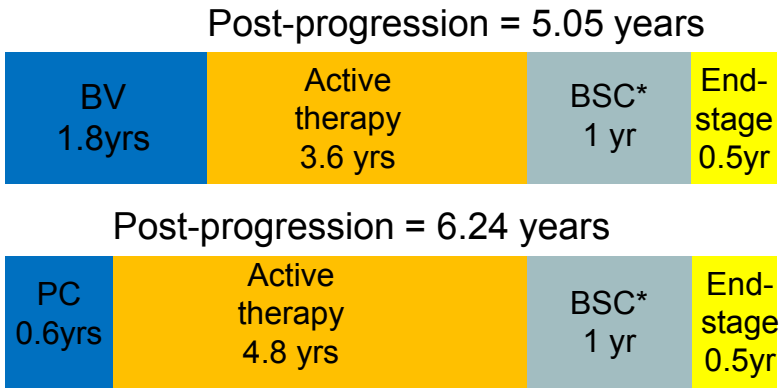
Plausibility of the clinical pathway after progression

- Clinical advice to the ERG - the time spent in end-stage care is implausible
- Clinical advice 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

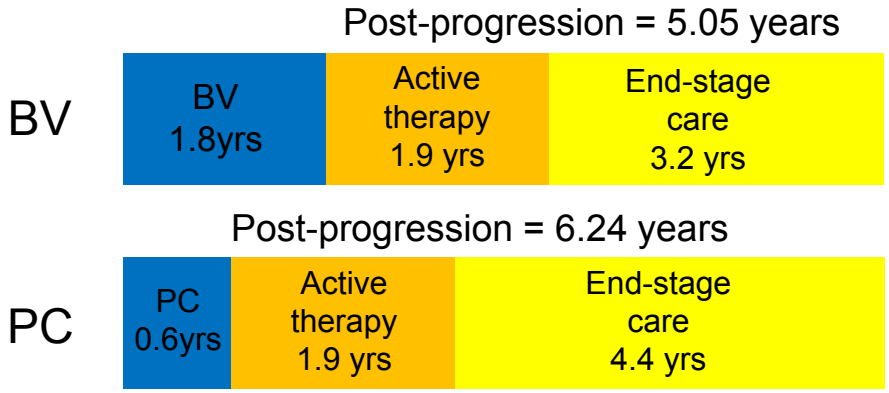


*BSC costs set to active therapy cost minus drug treatment costs
Utility value for BSC was the midpoint between active therapies and end-stage care (0.495)

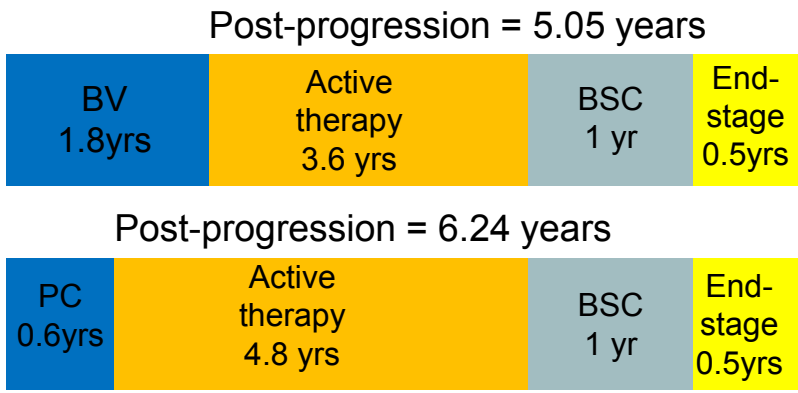
Alternative modelling scenarios	Incremental Costs	Incremental QALYs	ICER
Company's base case	[redacted]	[redacted]	BV Dominates
ERG's revised company base case	[redacted]	[redacted]	BV Dominates
ERG's sensitivity scenario – PP pathway	[redacted]	[redacted]	£494,981

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

Company's proposed pathway



ERG's proposed pathway

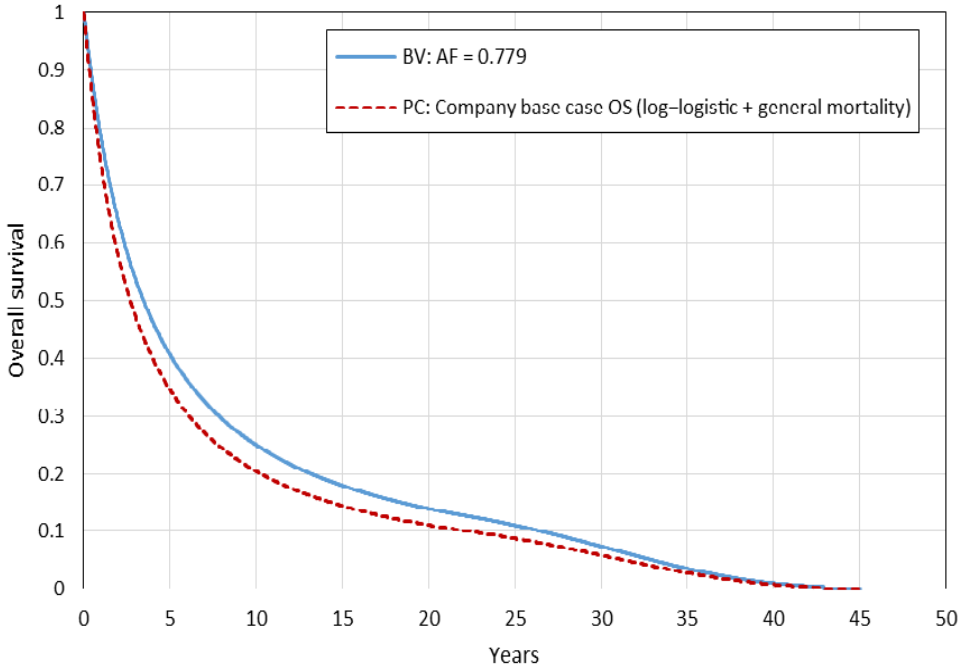


Question for committee:

- How long are patients likely to spend on active therapies?
- Would being on BV for longer than PC mean you would spend less time on subsequent active therapies?
- How long would patients spend in end-stage care?

ERG's scenario analysis 2: overall survival gain

ERG: This scenario highlights the sensitivity of the model to alternative assumptions 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 when alloSCT included)
- 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

Company's scenario analysis: 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

Question for committee:
What assumptions should be made around OS in the cost-effectiveness modelling?

*curves confounded – 46% of patients on PC crossed-over to BV

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 assumed 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

Where resource use in the end-stage care phase was lower than 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]	1.204	BV Dominates
ERG's revised company base case	[redacted]	[redacted]	0.000	BV Dominates
ERG's sensitivity scenario – resource use	[redacted]	[redacted]	0.000	£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	2.63 / 1.81	100	**0.25**
Dressings – localised coverage	60	7 (x7)	**37.5**	7 (x7)

* Changes to company base case **bold**

ERG 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 scenarios are not necessarily more reflective of reality than those in the company 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 Skindex-29 (a more appropriate QoL instrument for CTCL) to EQ-5D data from the ALCANZA trial. No mapping algorithm available to convert Skindex-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

Question for committee: Does the committee consider BV to be innovative?

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

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?