Slides for the projector and observers

Combined Lead team slides

Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma (CDF review of TA446) [ID1366]

1st Appraisal Committee meeting

Committee C.
Lead team: Peter Selby (Chair), Paul Tappenden, David Chandler

ERG: BMJ

NICE technical team: Victoria Kelly, Nicola Hay

Company: Takeda

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Description of the technology

Technology	Brentuximab vedotin (Adcetris, Takeda UK)
Marketing authorisation	For treating relapsed or refractory CD30-positive Hodgkin lymphoma in adults: • after autologous stem cell transplant *(recommended in TA446)* or • after at least 2 prior therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option *(recommended via CDF in TA446*) or • at increased risk of relapse or progression after autologous stem cell transplant *(**not** recommended in TA446)*
Mechanism of action	anti-CD30 monoclonal antibody attached by an enzyme-cleavable linker to a potent chemotherapeutic agent, monomethyl auristatin E (MMAE). The antibody–drug conjugate allows for the selective targeting of CD30-expressing cancer cells.
Administration & dosage	1.8 mg/kg administered by intravenous infusion over 30 minutes every 3 weeks.
Price	£2,500 for a 50-mg vial (There is a PAS simple discount applied to the list price)

Patient and professional organisations comments:

- When brentuximab vedotin was first introduced in 2012 it was considered a step-change in the management of HL (it had the highest demonstrated single agent activity in HL).
- Brentuximab vedotin offers greater effectiveness, ease of administration, fewer side effects, less toxicity and increased life expectancy. In patients having this as a ‘bridge’ to allogeneic transplant, some may eventually be cured.
- Brentuximab vedotin is only administered once every 3 weeks meaning patients only need to be in hospital for 2 days in each 3-week cycle. This is beneficial for those with mobility or other issues which make it difficult to travel to hospital on a more regular basis.
- Peripheral neuropathy is a common side effect. This can be severe. However brentuximab vedotin has been used now for some years and centres are used to monitoring for it.

TA446 Recommendations

1. Brentuximab vedotin is recommended as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:
   - they have relapsed or refractory disease after autologous stem cell transplant and
   - the company provides brentuximab vedotin at the price agreed with NHS England in the commercial access agreement.
2. Brentuximab vedotin is ***recommended for use within the Cancer Drugs Fund*** as an option for treating CD30-positive Hodgkin lymphoma in adults, only if:
   - they have relapsed or refractory disease after at least 2 previous therapies and
   - they cannot have autologous stem cell transplant or multi-agent chemotherapy and
   - the conditions of the managed access agreement are followed.

- In adults with CD30-positive Hodgkin lymphoma at an increased risk of disease relapse or progression after autologous stem cell transplant brentuximab vedotin was not recommended

Rationale for CDF recommendation in TA446

- In TA446 the rate of transplant post brentuximab vedotin treatment for population 3 (adults with relapsed or refractory disease after at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy is not an option) was 58%. Committee was concerned that this rate might not be generalisable beyond the 10 centres that contributed to this dataset.
- the ICER for brentuximab vedotin compared with single-agent chemotherapy was approximately £40,000 per QALY gained (between £28,332 and £53,998 per QALY gained). The key cost-effectiveness drivers were:
  - Model structure
  - Relative rate of post-chemotherapy and brentuximab vedotin SCT
  - Modelled estimates of progression free survival
- End-of-life not met for this population.
- Committee concluded not to recommend for routine commissioning but had plausible potential for cost-effectiveness
- Therefore committee required further data collection to address the clinical uncertainty which was: the proportion of patients treated with brentuximab vedotin or single agent chemotherapy that subsequently become eligible to receive a stem cell transplant (autologous or allogeneic)

Decision problem

	Scope issued by NICE*	Company's updated submission (if different)
Population	Adults with relapsed or refractory CD30-positive Hodgkin's lymphoma following: • at least 2 previous therapies and stem cell transplant or multi-agent chemotherapy not a treatment option.	NA
Intervention	Brentuximab vedotin	NA
Comparator	BSC	Single agent chemotherapy
Outcomes	• Overall survival • Progression-free survival • Objective response rate • Complete remission • Adverse effects of treatment • Health-related quality of life	Also includes: • Partial remission • Stem cell transplant rate

*as this was a CDF review, the original scope was issued without change, in line with NICE CDF processes and methods

Company's updated clinical effectiveness evidence

- The company have submitted the following updated clinical evidence for people with relapsed of refractory CD30-positive Hodgkin's lymphoma following at least 2 previous therapies and when SCT or multi-agent chemotherapy in not a treatment option:

1) Results from the Public Health England Report - Commissioned by NHS England on rate of SCT in adults with relapsed or refractory CD30-positive Hodgkin lymphoma following treatment with brentuximab vedotin on the CDF
2) Proposed a lower rate of SCT following standard single agent chemotherapy based on clinical expert opinion
3) Proposed using new sources of data from Reyal 2016 and Thomson 2013 to inform overall survival and progression free survival estimates following a SCT

CDF data collection on SCT rate after brentuximab vedotin treatment

Method	• Questionnaire sent to 223 consultants across 106 trusts in England. 496 HL patients received CDF funding for BV treatment (6 week data collection period)

Questions	• To determine whether the:
	  • patient was SCT-naïve and whether or not they received BV
	  • patients had been given BV with the intention of bridging to an SCT, if the patient had an SCT or not, and whether the patients required salvage chemotherapy after BV to bridge to an SCT

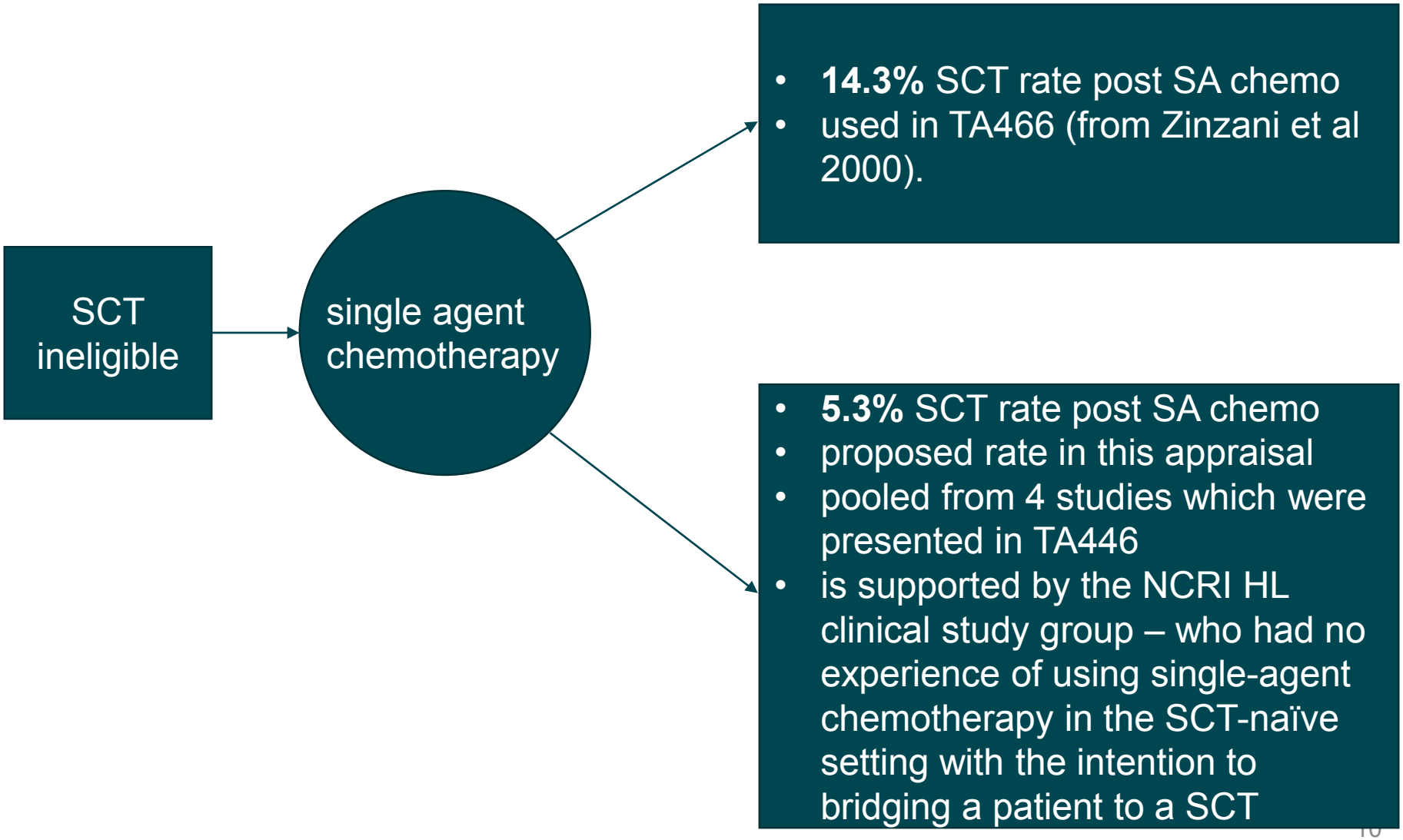
Results	• Response rate = 88% (436/496) no data for 60 patients
Main cohort	• 219 patients treated with BV with intention of a SCT
Sensitivity analysis (i)	• Main cohort + n=60 with no data
Sensitivity analysis (ii)	• Main cohort + n=93 who had BV with no intention of a SCT
Sensitivity analysis (iii)	• Main cohort + (i) & (ii)

Results from CDF data collection

Number and percentage of patients having a SCT for the different scenarios				
	Main cohort: BV with intention of getting a SCT	Main cohort + patients with no data (i)	Main cohort + those given BV with no intention of a SCT (ii)	Main cohort + combination of (i) and (ii)
Denominator for each cohort	219	279	312	372
Underwent an allogeneic SCT	45 (21%)	45 (16%)	45 (14%)	45 (12%)
Underwent an autologous SCT	33 (15%)	33 (12%)	33 (11%)	33 (9%)
Had salvage CT after BV before SCT	50 (23%)	50 (18%)	50 (15%)	50 (13%)
Underwent SCT after BV[a]	78 (36%)	78 (28%)	**78 (25%)**	78 (21%)
Underwent SCT after BV +/- salvage[b]	128 (58%)	128 (46%)	128 (41%)	128 (34%)

[a] Patients who had BV and then a SCT straight afterwards; [b] Patients who had BV then a SCT or BV then salvage chemotherapy and then a SCT

Company's proposed SCT rate following single-agent chemotherapy



Company's updated sources for PFS and OS following Allo-SCT

	TA446	ID1366
Dataset	• Sureda et al. (2012)	• Reyal et al. (2016)
Patients	• 78 patients with r/r HL who received an allo-SCT at 10 European centres between the years 2000 and 2007 • 4-year overall survival 24%	• 116 patients with r/r HL undergoing allo-SCT at 4 UK transplant centres between 2005 and 2014 • 4-year overall survival 77.5% for PET negative
Company comments	• 86% of the patients included in the trial had failed a previous ASCT prior to receiving allo-SCT	• Used a subgroup (Peggs analysis) of 86 patients (74% of the total cohort) who were receiving allo-SCT as their first SCT (matching population in this re-appraisal) • dataset uses the PET-response-adjusted transplantation strategy that is now routinely used across the UK

Company's updated sources for PFS and OS following ASCT

	TA446	ID1366
Dataset	• Sureda et al. (2001).	• Thompson et al (2013).
Patients	• 494 patients with r/r HL who received an ASCT between 1984-1998 at one of 46 Spanish centres. • 5-year overall survival 54.5%	• 28 patients with r/r HL treated at University College London with an ASCT and followed up over 5 years. • 3-year overall survival 92.9%
Company comments	• Not representative of UK clinical practice • PET-response-adjusted transplantation strategy was not followed in the dataset, meaning only 41% of patients in that dataset were in complete response prior to their ASCT while 15% had resistant disease prior to ASCT.	• UK study following UK clinical practice • dataset uses the PET-response-adjusted transplantation strategy that is now routinely used across the UK

ERG's comments on the company's updated clinical effectiveness data

Company's new data	ERG comment
CDF data collection	• the most appropriate population for consideration is sensitivity analysis (iii) because it includes the missing data from 60 patients (this includes patients who had BV with no intention of a SCT and all those who received salvage therapy after BV to bridge to SCT)
Post treatment SCT rates	• ERG prefers post BV treatment SCT rate of 34% (as above from sensitivity analysis iii) compared with company preferred of 25% • Post chemotherapy SCT rate of 5.3%.
Allo-SCT – Reyal (2016)	• agrees that study is highly relevant to current UK transplant practice
ASCT – Thompson (2013)	• sample size is small (28 patients), and data immature with substantial censoring • ERG prefers outcomes data from Reyal 2016 which is more mature and has larger samples size. • Outcomes for patients after ASCT are better than those for patients after allo-SCT therefore using Reyal data for ASCT will provide a conservative estimate

NHS England comments on the CDF data collection

- NHS England regards the response rate as being outstandingly high considering that this was a retrospective audit involving a very great number of clinicians.
- NHS England rejects the ERG's criticism that the proportion of missing data is large (n=60, 12%) given the size and type of this data collection in a real world NHS setting.
- SCT rate following chemotherapy i.e the comparator rate of SCT. 1st and 2nd line chemotherapy regimens for HL typically contain 4 and 3 drug combinations, respectively. This means that patients relevant to this appraisal have been exposed to 7 drugs yet have relapsed/refractory disease. Therefore responses to single-agent treatment are modest and generally of short duration. NHS England therefore agrees with a 5% figure for the SCT rate consequent to single agent chemotherapy.

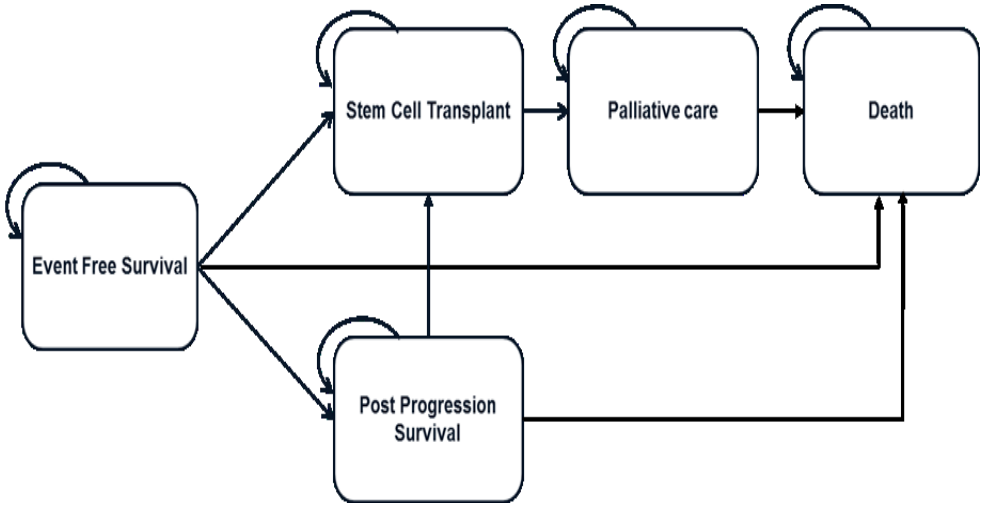
Company's updated cost-effectiveness evidence

- In TA446 the committee concluded that due to uncertainty in the model structure, overall survival and progression-free survival rates following SCT, and post-treatment SCT rates, it was difficult to determine a robust cost-effectiveness estimate and concluded that its preferred ICER for this population would likely be approximately £40,000 per QALY gained at the mid-point of the range £28,332 and £53,998 per QALY gained. In response to this the company have submitted the following new evidence:

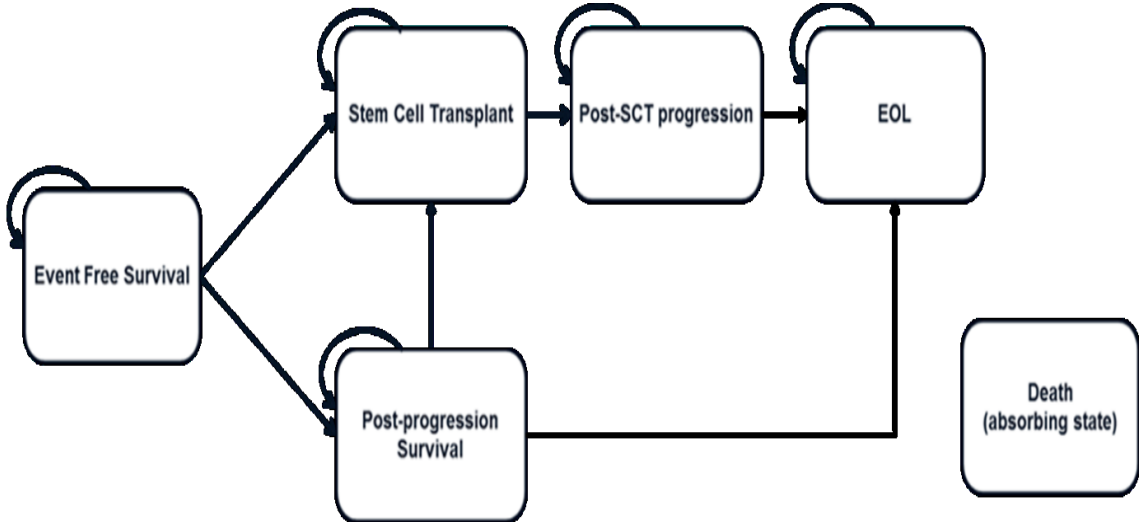
1) Cost of brentuximab includes PAS proposed in TA446
2) Updated model structure to account for the issue raised in TA446 that patients couldn't move back to an event-free or post progression survival state after a SCT
3) Updated evidence on rates of SCT post BV (from CDF data collection)
4) New costs and HRQoL data for the post-SCT progression state
5) New data sources for PFS and OS following SCT

Company's updated economic model

- Original model diagram (TA446). Time horizon of 70 years; 1-week model cycle



- Updated model diagram



- Company have updated the model structure to include:
  1. P*ost-SCT progression state* to account for the structural flaw that patients couldn't move back to event free or post progression survival state after transplant identified in TA446. Also includes EoL state.
  2. Tunnel states to correct errors in TP calculations.
  3. 28-day cycle length

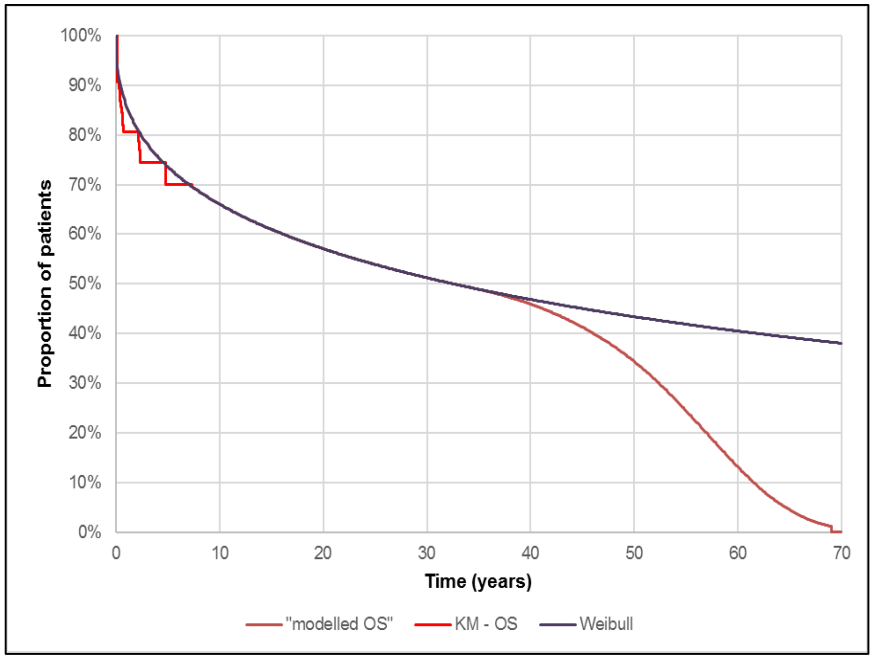
HRQoL & costs in the company's updated model for post-SCT progression state

Utility value *(value used in TA466 in the PPS state)*	0.38	
Costs of disease progression after ASCT	**% Pts.**	**£ per cycle**
GEM-P (Gemcitabine, cisplatin, methylprednisolone)	33%	£119
IVE (Ifosfamide, epirubicin, etoposide)	33%	£1,659
Bendamustine + steroids (assumed dexamethasone)	33%	£6,240
Treatment administration	100%	£322
Total	**-**	**£8,340**
Weighted total	**-**	**£2,995**
Costs of disease progression after Allo-SCT		
Gemcitabine & methylprednisolone	25%	£101
Bendamustine + steroids (assumed dexamethasone)	25%	£6,240
Donor lymphocyte infusion	50%	£7,100
Treatment administration	50%	£322
Total	**-**	**£5,457**
Weighted total	**-**	**£5,296**

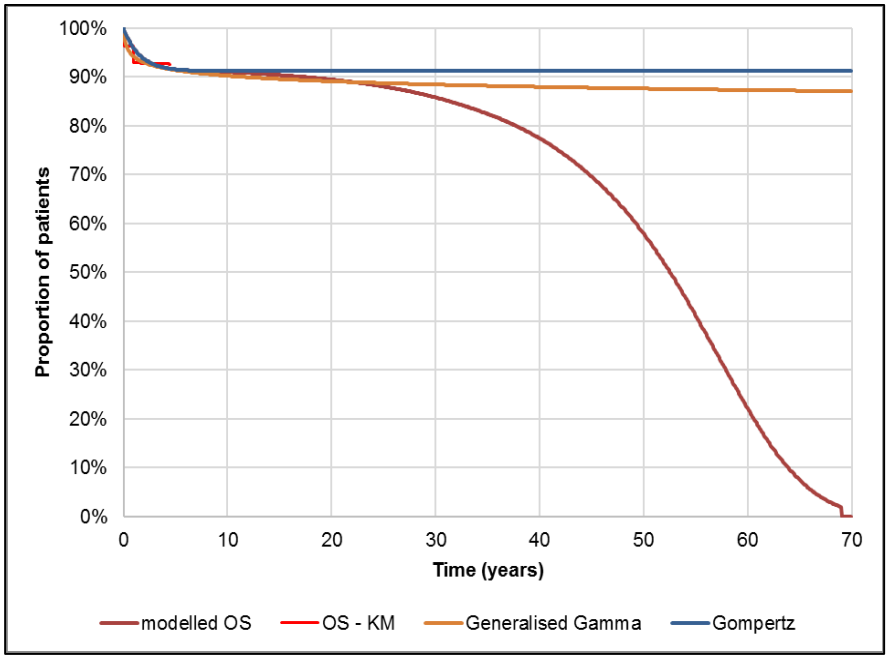
Company's costs informed by clinical expert opinion. Assumed treatment duration 2 months

Overall survival after allo-SCT and ASCT in the company's updated model

<u>Allo-SCT</u> - OS KM from Reyal *et al*. 2016 subset (first SCT, n=86) & modelled curves (Weibull)



<u>ASCT</u> - OS KM from Thomson *et al*. 2013 (n=28) & modelled curves (Gompertz)



- Both OS functions capped by general population mortality, with divergence from fitted curves at ~40 years for allo-SCT and ~5 years for ASCT
- PFS for both AlloSCT and ASCT were modelled using Gompertz

Company's base case results using updated model with PAS

- Company's cost-effectiveness results including corrections to errors identified by ERG at clarification:
  1. Applying age-related utility decrements (setting not applied)
  2. Using relative risks for time to SCT (not hazard ratios)
- Assumes SCT probabilities of 25% for brentuximab vedotin and 5.3% for single-agent chemotherapy

	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Standard care	[redacted]	[redacted]			
Brentuximab vedotin	[redacted]	[redacted]	[redacted]	[redacted]	£16,535

Company's scenario analyses

Scenario	Company rationale
SCT rate with BV 41%	In the CDF study an additional 50 patients proceeded to SCT following treatment with BV **and** salvage chemotherapy. This lead to an overall SCT rate of 128/312 (41%) among patients who received treatment with BV
Post-progression utilities from the Checkmate 205 study	0.715 from Checkmate 205 (nivolumab for r/r classical Hodgkin lymphoma after ASCT). 74% patients had received prior treatment with BV
Lower discount rate of 1.5% applied for costs and QALYs	Long-term health benefits (approx. 20% patients alive at 30 years).
TA466 model (25% SCT rate with BV)	Model used in TA466 updated with CDF data only.
TA466 model (41% SCT rate with BV)	Model used in TA466 updated with CDF data only.

Company's scenario analyses results with PAS

Scenario	Inc. Costs	Inc. QALYs	Pairwise ICER
SCT rate with BV 41% (includes people who received salvage chemo after BV but before SCT)	[redacted]	[redacted]	£13,503
post-progression utilities from the Checkmate 205 study	[redacted]	[redacted]	£16,584
lower discount rate of 1.5% applied for costs and QALYs	[redacted]	[redacted]	£11,269
TA466 model (25% SCT rate with BV)	[redacted]	[redacted]	£35,449
TA466 model (41% SCT rate with BV)	[redacted]	[redacted]	£29,825

ERG's comments on company's updated model (1)

Issue	ERG comment
Model functionality	ERG "extremely concerned" with structural and implementation changes. ERG could not properly validate the updated model because of the volume of code, size of model and running time
Changes in risk of death (tunnel states)	No justification for the company's rationale behind the changes in the model to account for changes in risk of death overtime. The change in the risk of death over time after SCT is accounted for in the underlying hazard of the best fitting survival curve.
Post-progression state	Time spent in health state determined from the extrapolated OS and PFS outcomes following ASCT and allo-SCT: • Proportion of time spent alive and progressed was calculated by comparing total time spent alive (OS AUC) with total time spent progression-free (PFS AUC), with the difference being the total time spent in this new post-SCT progression state. • The company justify this approach because it avoids further multiplication of tunnel states – this reinforces ERG's view that the use of tunnel states in the model is not suitable.

ERG's comments on company's updated model (2)

Issue	ERG comments
Cost of salvage chemotherapy	Company included costs of salvage chemotherapy in the comparator arm of the economic model. Patients receiving chemotherapy cannot receive subsequent salvage chemotherapy to bridge to SCT, therefore ERG does not see a clinical rationale for including these costs.
Conclusion	ERG's exploratory analyses uses original model from TA466 and includes: • Use of Reyal et al 2016 to inform OS and PFS after allo-SCT and ASCT and to update the estimated costs and QALYs expected after SCT. • 34% post BV SCT probability • 5.3% post chemotherapy SCT probability

Summary of company's updated model and ERG exploratory analyses (1)

Issue	Original model assumptions presented in TA446	Company's updated model	ERG changes to TA446 model
Post-SCT progression health state	Structural flaw - patients could not experience disease progression following SCT.	New post-SCT progression with higher resource use and lower quality of life compared with the pre-progression health state.	Not suitable. ERG used post-SCT OS/PFS from Reyal 2016 to update the company's previous model (replacing Sureda 2012 previously used).
Costs in the new SCT progression health state	NA	Proportion of patients receiving each treatment and associated costs informed by clinical expert opinion	Used costs provided by company and updated previous model by multiplying these by mean time on treatment (2 months). Used the Reyal data to inform proportion of newly progressed patients in each cycle

Summary of company's updated model and ERG exploratory analyses (2)

Issue	Original model assumptions presented in TA446	Company's updated model	ERG changes to TA446 model
Utility values post SCT disease progression	Committee noted company utility of 0.77 optimistic and ERG preferred of 0.50 pessimistic	0.38 (Swinburn 2015) expected that these patients would have a similar HRQoL to those in the post-progression survival from TA446	0.73 (weighted post-SCT in progressed disease state using the PFS and OS curves from Reyal).
SCT rate following BV	58% (UK observational dataset)	25% (CDF data – sensitivity analyses 2)	34% (includes people who received salvage chemo before SCT and missing data).
SCT rate following chemotherapy	14.3% (Zinzani 2000)	5.3% (pooled from 3 papers;UK NCRI Hodgkin study group)	5.3% and scenario analysis using 14.3%

ERG's exploratory analyses with PAS using original model from TA446

Scenarios	Inc. Costs	Inc. QALYs	Pairwise ICER
1) Using post-SCT OS curves from Reyal 2016 instead of Sureda	[redacted]	[redacted]	£15,756
2) Using updated costs associated with the post-SCT progressed disease state	[redacted]	[redacted]	£30,176
3) Using the ERG updated utility value associated with the post-SCT state	[redacted]	[redacted]	£31,685
4) Applying the **34%** estimate for the proportion of patients bridging to SCT	[redacted]	[redacted]	£30,751
5) As an alternative to 4), assuming that 21% of brentuximab patients bridge directly to SCT	[redacted]	[redacted]	£32,027
ERG's preferred ICER (scenarios 1-4)	[redacted]	[redacted]	**£17,885**
ERG's preferred ICER (scenarios 1-4) with 14.3% SCT probability post single agent chemotherapy	[redacted]	[redacted]	£21,339

End-of-life considerations

- In TA446 the committee noted that population 3 did not meet the end-of-life criteria because mean life expectancy was more than 24 months (this was based on the modelled mean OS for the comparator arm).
- The ERG's updated TA446 model for this appraisal using their preferred scenarios shows that modelled OS with the comparator is still more than 24 months.

Key issues

- What is the most appropriate SCT rate to use in the base case following treatment with brentuximab vedotin?
- Do the committee accept the rate of SCT post chemotherapy proposed by the company and accepted by the ERG and NHS England?
- Do the committee accept the use of new data sources for outcomes post SCT to replace the Sureda et al data in TA446?
- Does the CDF data collection and new evidence address the clinical uncertainties in TA446 for this population?
- Do the committee accept the structural changes made to the updated model by the company?
- What is the most plausible ICER for brentuximab vedotin vs single-agent chemotherapy?
- TA446 had plausible potential to be cost-effective. Can brentuximab be recommended for routine use in this population?
- End-of-life criteria
- Innovation
- Equalities