Lead team presentation

Brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma (STA)

1st Appraisal Committee meeting

Cost effectiveness

Committee C

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Company: Takeda UK

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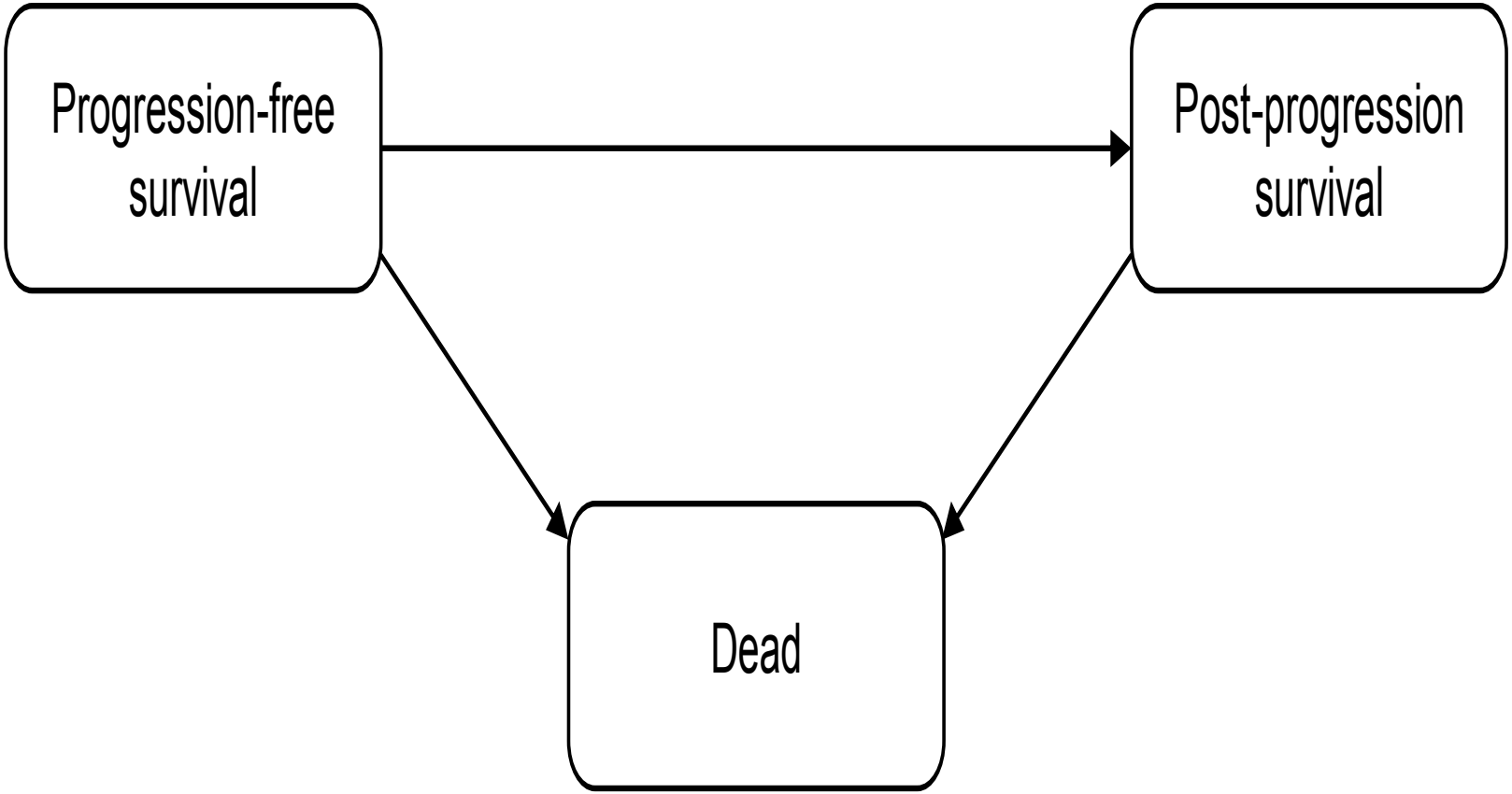
Model structure



Intervention: brentuximab vedotin; **Comparator**: multi-agent chemotherapy

Population cohorts

Technology	Model cohort	Name	Base case proportion
Brentuximab vedotin	1	Brentuximab vedotin, no SCT	71%
	2	Brentuximab vedotin + ASCT	14%
	3	Brentuximab vedotin + allo-SCT	16%
Chemotherapy	4	Chemotherapy, no SCT	86%
	5	Chemotherapy + ASCT	7%
	6	Chemotherapy + allo-SCT	7%

Treatment effectiveness and extrapolation

- Based on a combination of:
  - Clinical response rates (CR, PR, SD and PD)
  - Stem cell transplant rates by response categories
  - PFS and OS by transplant status (no SCT, ASCT and allo-SCT)

- Those who received a transplant: PFS and OS modelled to be equivalent irrespective of treatment arm

- Those who did not receive a transplant: substantial differences in PFS and OS between brentuximab vedotin and chemotherapy. Based on the unadjusted indirect comparison

Proportion who receive SCT

- Assumed that brentuximab vedotin acts as a bridge to SCT for a proportion of patients
- % of CRs and PRs receiving SCT based on 3 approaches:

Approach	CR	PR	Economic Analysis
Response-based (SG035-0004, ITT population)	42%	8%	Base-case
Response-based (clinical expert opinion)	69%	35%	Sensitivity
Equal rate in both treatment arms (Mak et al., 2013)	20%	20%	Sensitivity

- Response rates:
  - Brentuximab vedotin (SG035-0004)
  - Chemotherapy: Base-case (Self-control cohort,SG035-0004), Sensitivity analyses (Dong and Crump)

Response	Brentuximab vedotin	Chemotherapy		
		Self-control cohort	Dong (2013)	Crump (2004)
CR	66%	31%	46%	16%
PR	21%	13%	42%	33%
SD	7%	10%	4%	17%
PD	3%	36%	8%	17%

Proportion receiving type of SCT

- NCCN clinical practice guidelines do not indicate how to identify which patients should undergo ASCT or allo-SCT
- Base case analysis used the % of patients who went on to receive ASCT and allo-SCT from SGO35-0004, sensitivity analysis used clinical expert opinion

Approach	Proportion	
	ASCT	Allo-SCT
SG035-0004 (base case approach)	47% (8/17)	53% (9/17)
Clinical expert opinion (sensitivity analysis)	25%	75%

ERG's critique: Proportions receiving SCT

- Issues with using self-control cohort in SG035-0004 to estimate comparator response rates:
  - Could not determine if previous treatments used to estimate response rates were representative of the chemotherapy comparators applied in the model
  - Possible underestimation of complete response because of exclusion of patients who achieved long-term remission on chemotherapy or die prior to progression
  - Sources used in the sensitivity analyses of limited value as they report on patients with predominantly newly diagnosed PTLC (Dong et al.) or patients with recurrent/refractory B-Cell non-Hodgkin lymphoma (Crump et al.)
- ERG considered the higher rates of bridging to ASCT (14%) and allo-SCT (16%) with brentuximab vedotin compared with chemotherapy (7% for both ASCT and allo-SCT) to be plausible

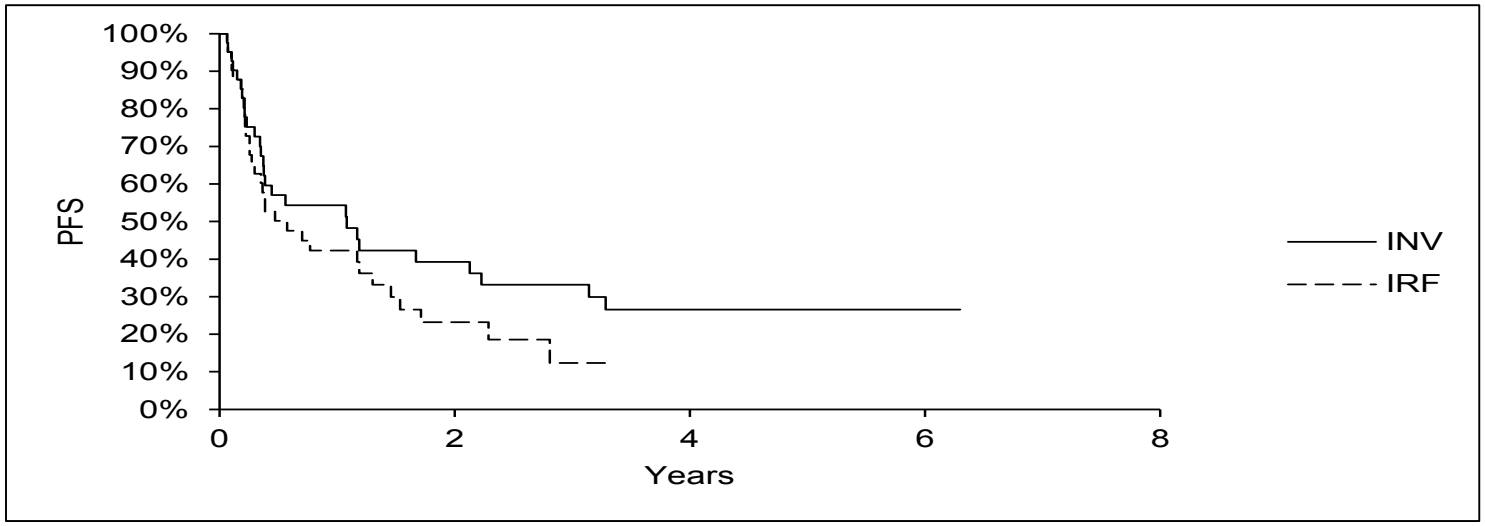
Trial based data sources for PFS and OS
Base case analysis

Treatment	Endpoint data source		Model cohort(s)
	PFS	OS	
Brentuximab vedotin, no SCT	SG035-0004; patients who did not receive subsequent SCT (*n*=41); INV assessment	SG035-0004; patients who did not receive subsequent SCT (*n*=41); INV assessment	1
Chemotherapy, no SCT	SG035-0004; self-control patients (*n*=39); INV assessment	Mak et al., 2013; PTCL patients with PS<2 (*n*=47)	4
ASCT	Smith et al., 2013; ASCT patients (*n*=115)	Smith et al., 2013; ASCT patients (*n*=115)	2,3,5,6
Allo-SCT	Smith et al., 2013; allo-SCT patients (*n*=126)	Smith et al., 2013; allo-SCT patients (*n*=126)	2,3,5,6

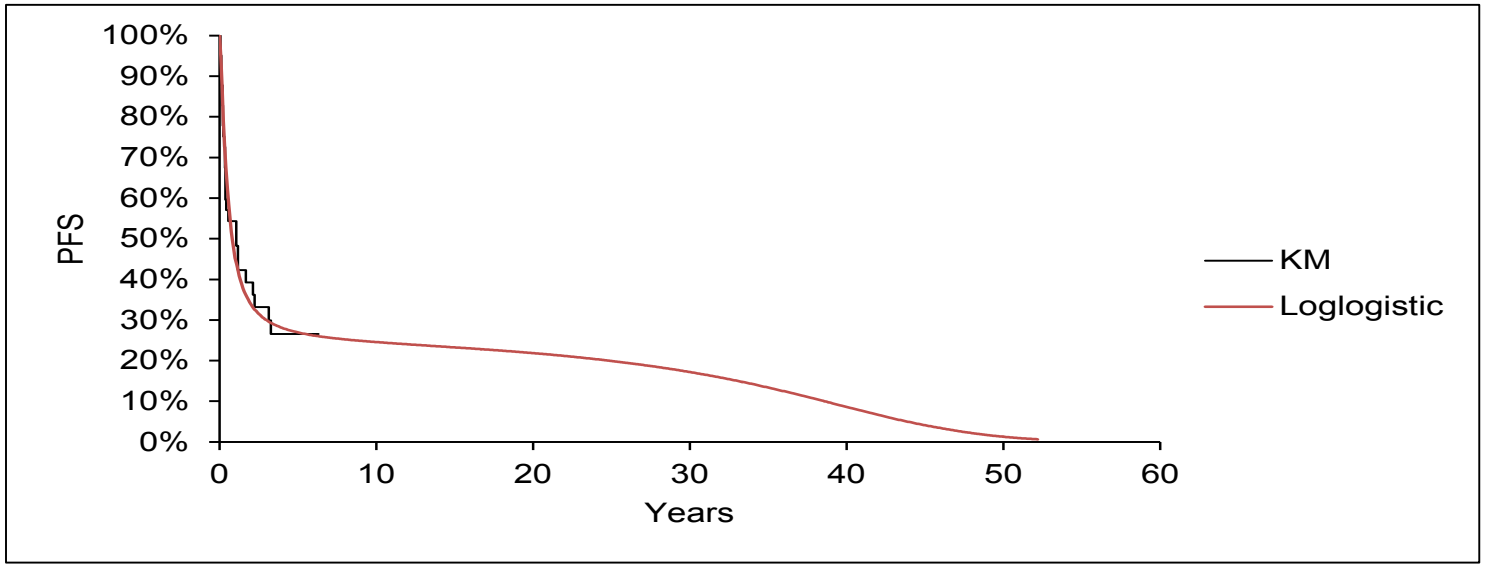
Extrapolation approaches for PFS and OS
Base case analysis

Treatment	PFS	OS	Model cohort(s)
Brentuximab vedotin, no SCT	• Mixture cure model • Log-logistic curve	• Mixture cure model • Log-logistic curve	1
Chemotherapy, no SCT	• Standard parametric model • Log-normal curve	• Standard parametric model • Log-normal curve	4
ASCT	• Mixture cure model • Gamma curve	• Mixture cure model • Log-normal curve	2,3,5,6
Allo-SCT	• Mixture cure model • Log-normal curve	• Mixture cure model • Log-normal curve	2,3,5,6

PFS: brentuximab vedotin (no SCT)
Company submission



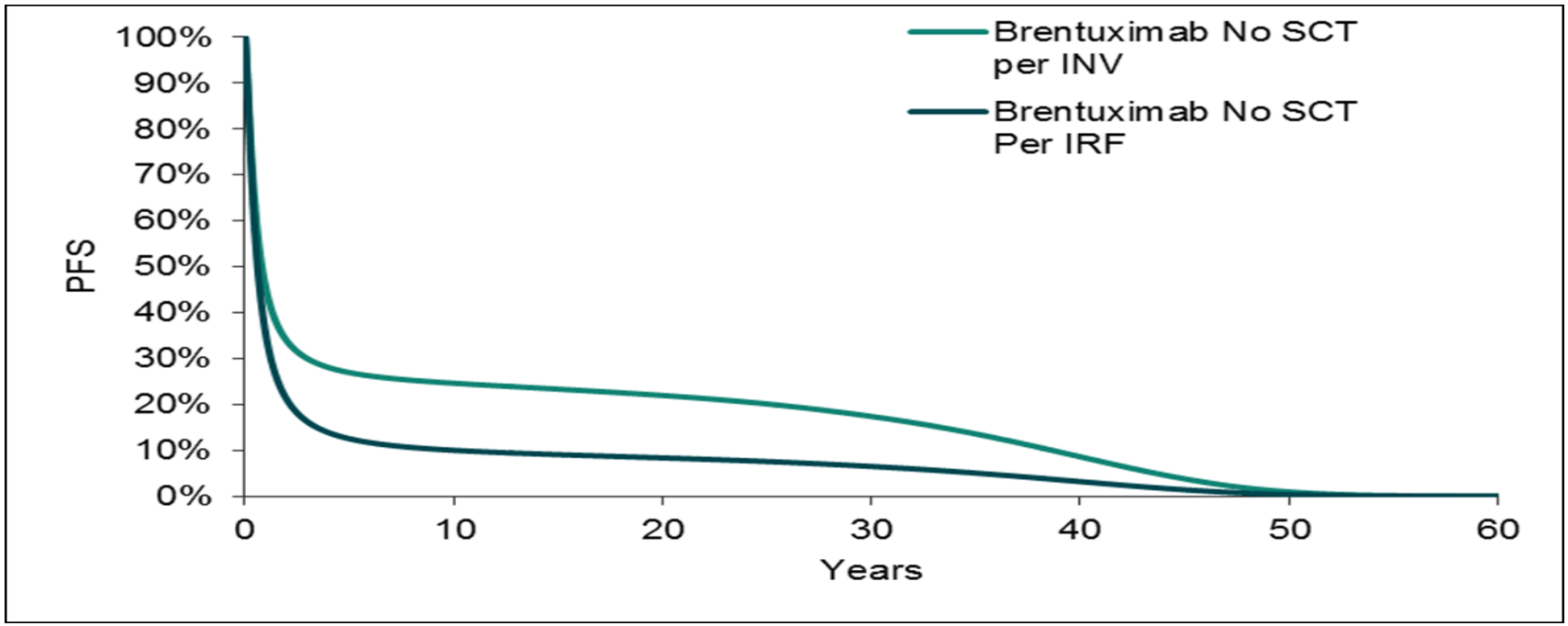
SG035-0004 Kaplan-Meier curves (follow up 71.4 months)



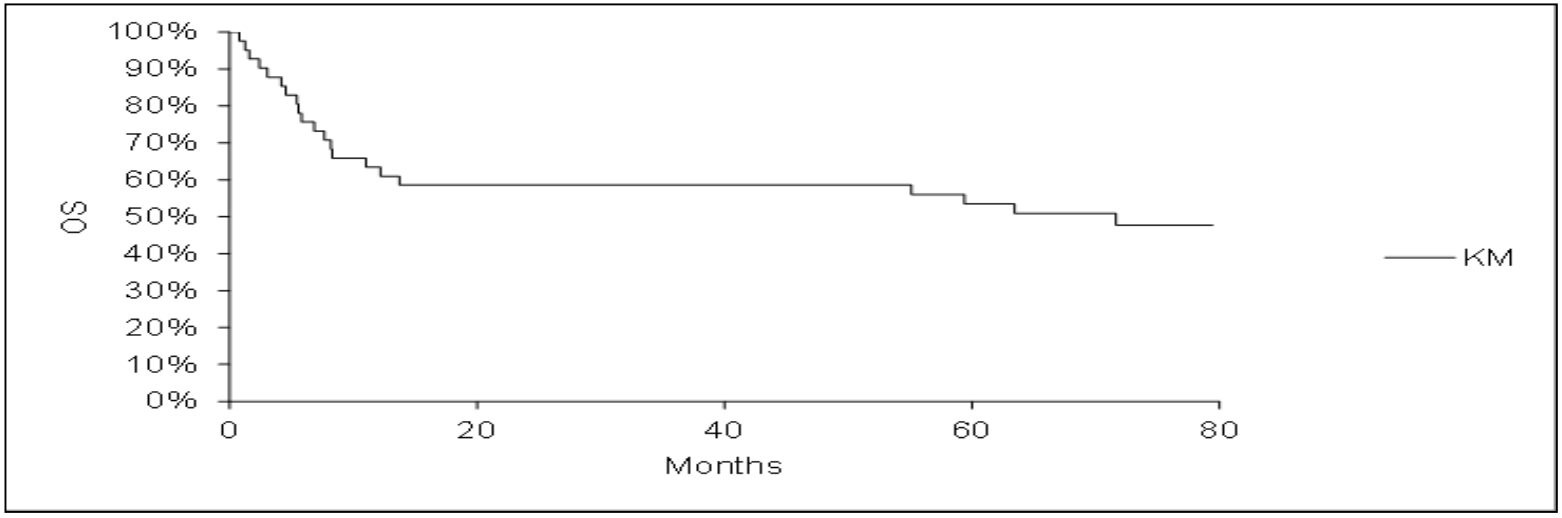
Lifetime extrapolation

ERG's critique: PFS Brentuximab vedotin (no SCT) *Extrapolation*

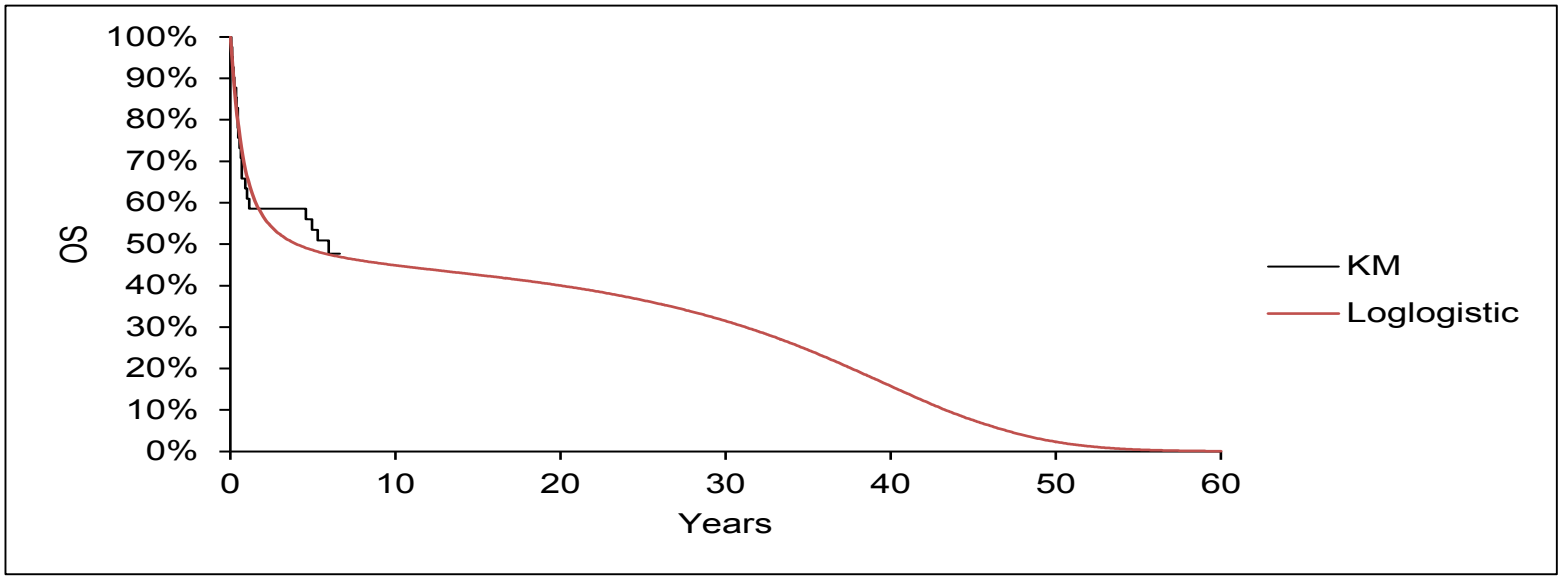
- Queried the appropriateness of a mixture cure model:
  - IRF data did not show evidence of cure
  - Cure fraction may be over estimated in the INV data. IRF KM curve showed lower PFS at end of follow-up
- Substantial additional PFS gain using INV data compared with IRF data



OS: Brentuximab vedotin (No SCT) Company submission

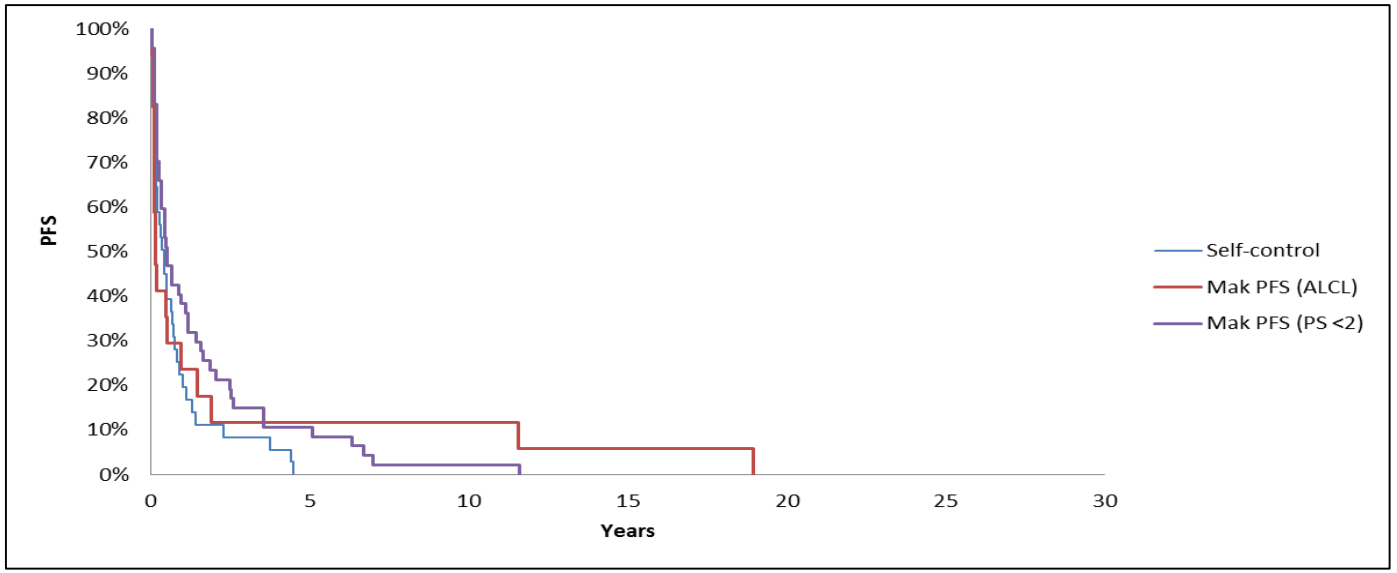


SG035-0004 KM curve (follow-up 71.4 months)

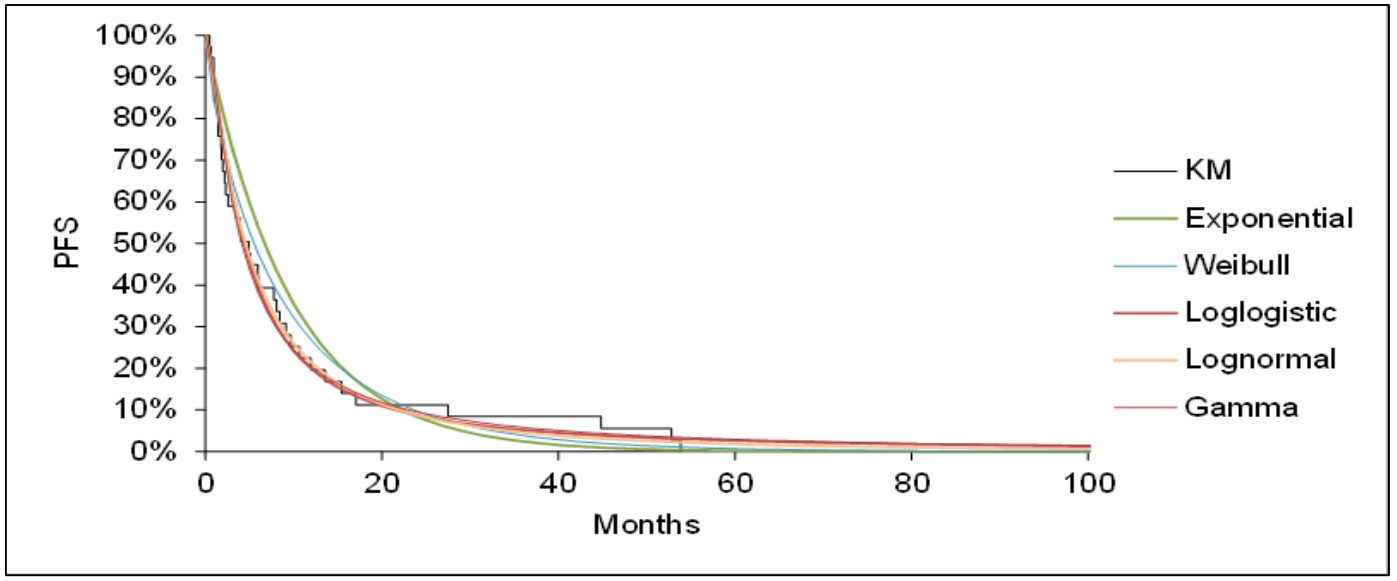


Lifetime extra-polation

PFS: Chemotherapy (no SCT)
ERG review



Comparison KM curves for self control cohort (SG035-0004) with Mak et al.



Parametric models based on self control cohort SG035-0004

ERG's critique
PFS Chemotherapy (no SCT)

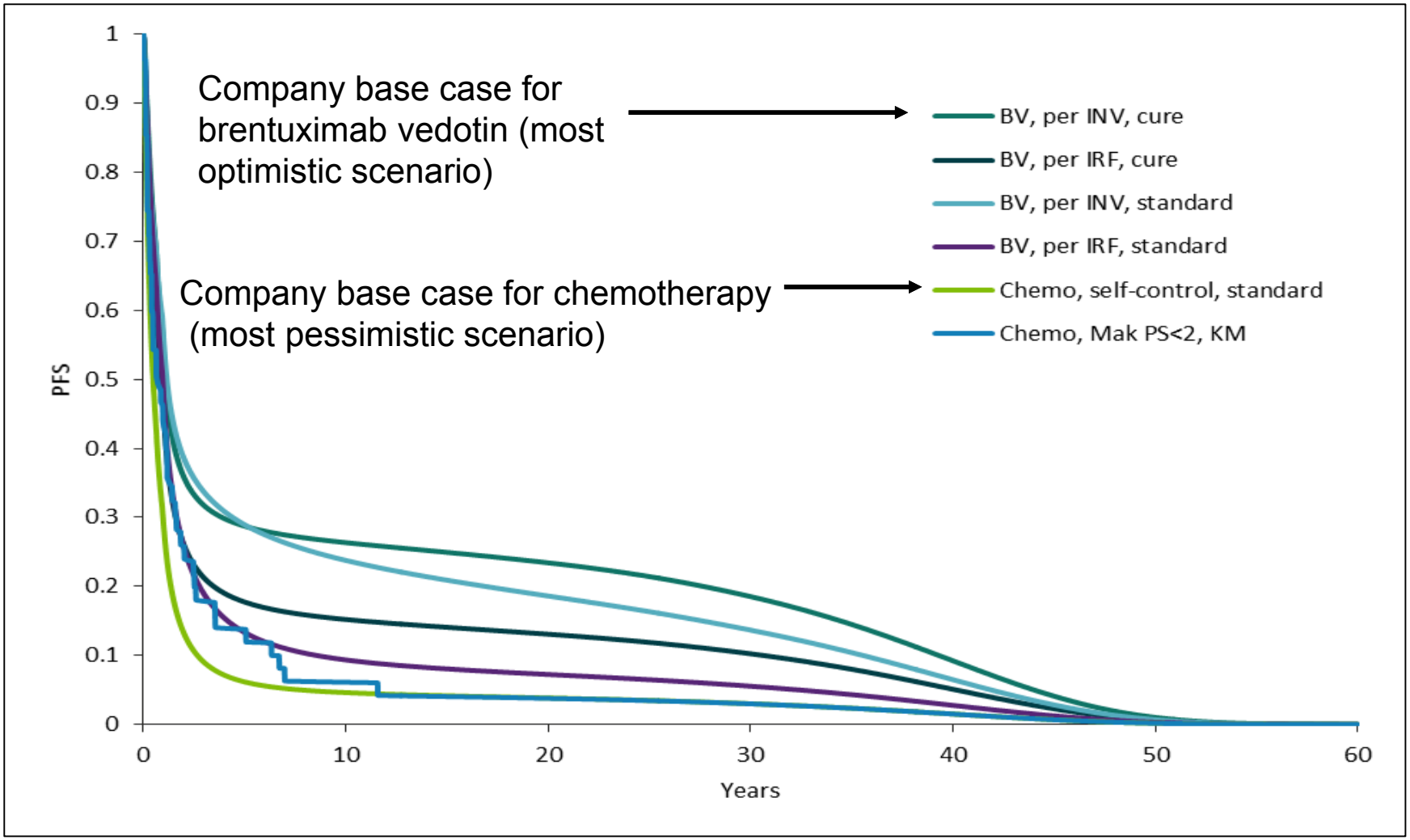
Trial based

- Preferred data from Mak et al. as source for PFS to counter potential biases favouring brentuximab vedotin associated with using the self-control cohort from SG035-0004

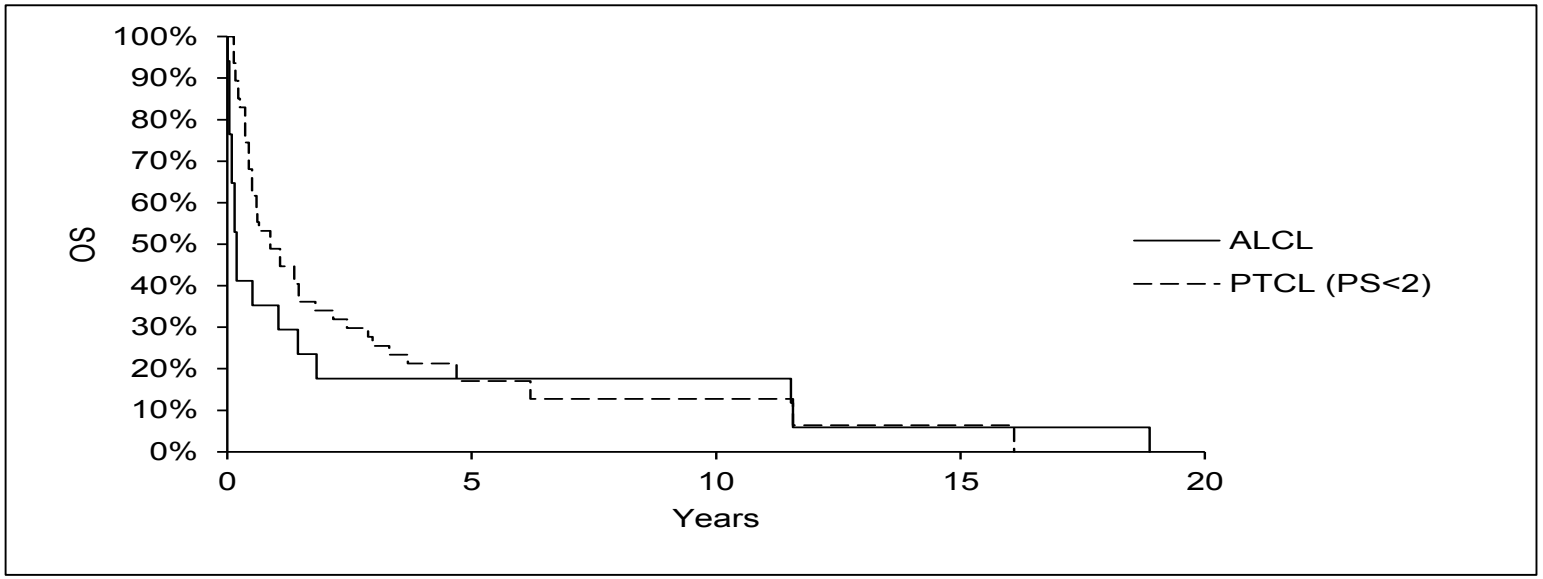
Extrapolation

- Clinical advice suggested that a small % of patients could be expected to achieve long term remission (therefore considered cured) using salvage chemotherapies
- Considered a conservative analysis in which both brentuximab vedotin and chemotherapy were modelled using standard parametric survival models to be more appropriate
- Noted substantial difference in the excess PFS benefit of brentuximab vedotin, depending on source of data and extrapolation approach used (6 survival curves for PFS explored to illustrate this uncertainty)

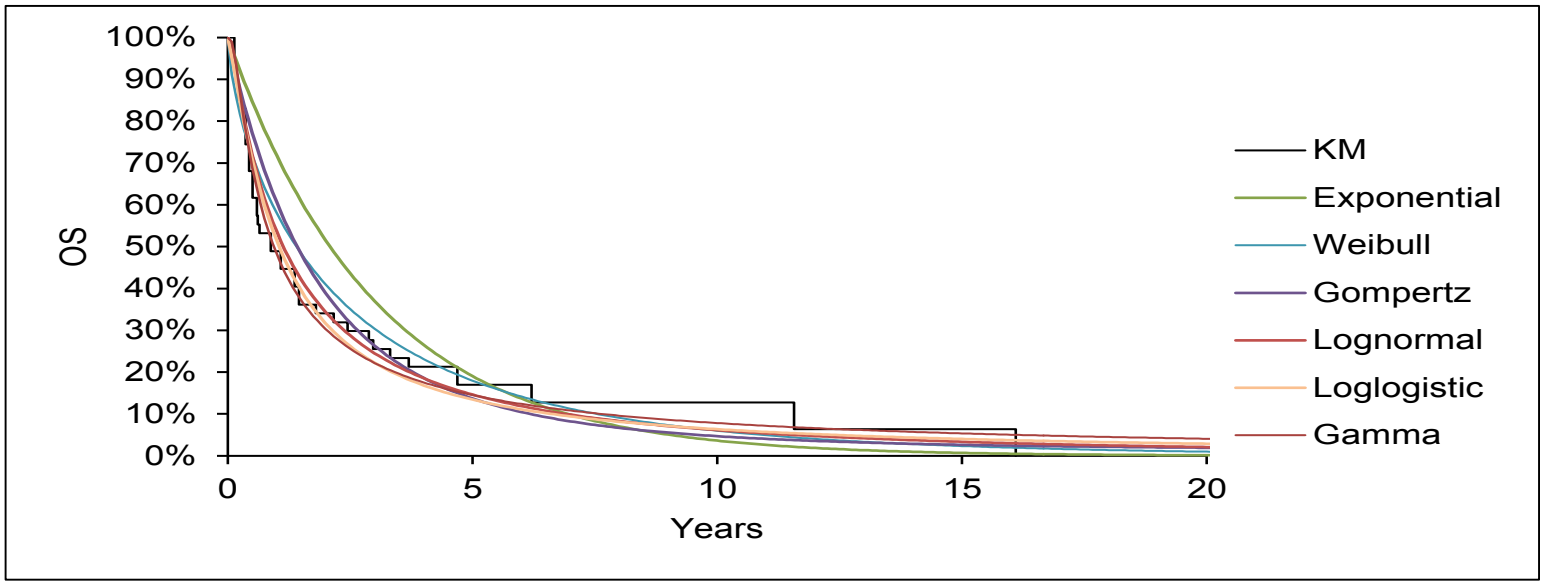
ERG's critique
PFS: chemotherapy (no SCT)
Exploration of impact of alternative data choices



OS: Chemotherapy (no SCT)
Company submission



Kaplan-Meir curves: Mak et al.



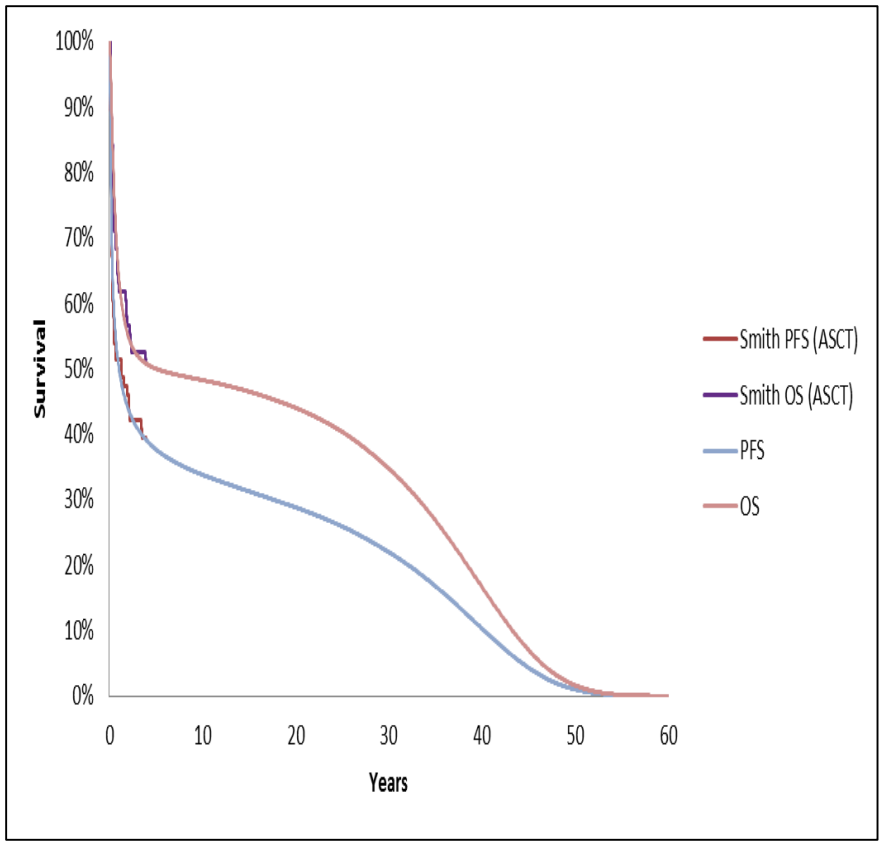
Parametric models PTCL PS<2 Mak et al.

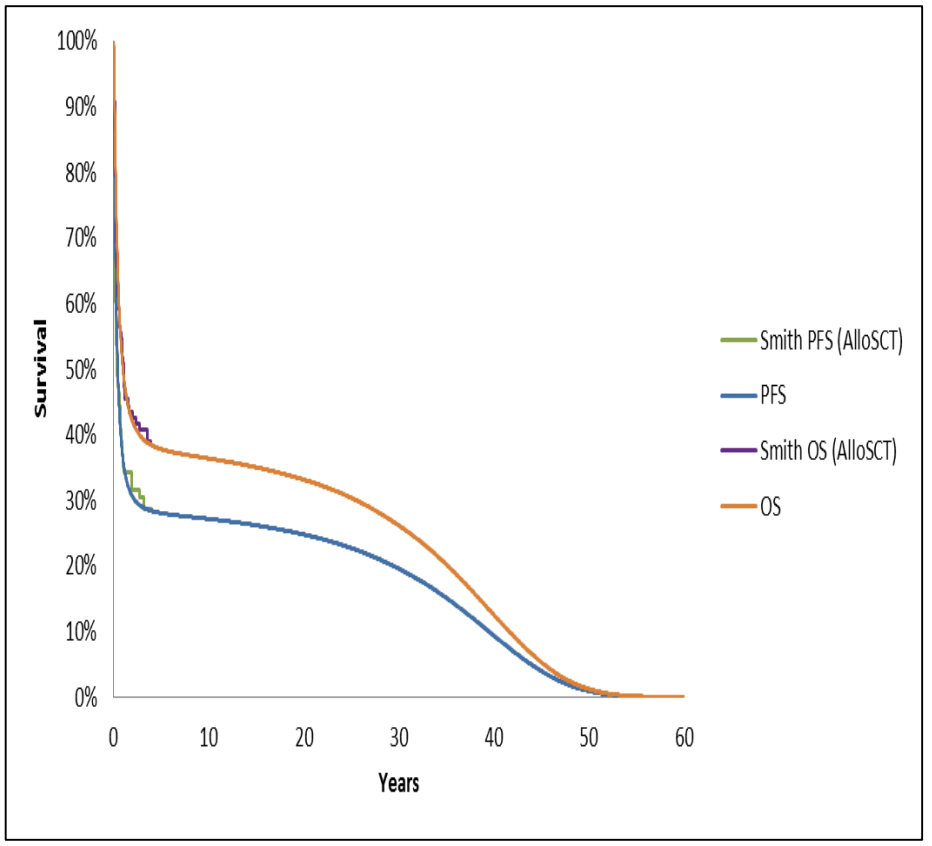
ERG's critique
PFS and OS: Chemotherapy (No SCT)

- Considered the use of data from Mak et al. to be appropriate
- Using different data sources for PFS and OS inappropriate.
  - ERG preferred to se Mak et al. data for both PFS and OS to avoid mis-match
- Questioned why Hux et al., which used individual data on 40 patients with sALCL from the Canadian BC Cancer registry was not considered for modelling PFS and OS
  - Cohort used by Hux et al. came from same source as Mak et al. and the KM curves for both were similar
- Considered company's preference of log normal and gamma distributions to model parametric distribution for OS to be appropriate. However, noted the substantial uncertainties driven by the long tail on KM curve for OS.

PFS and OS: ASCT and Allo-SCT

KM curves and extrapolation





Excess mortality risk

- To address uncertainty in mortality rate for patients who were long term survivors compared with the general population, excess mortality risk applied irrespective of estimated cure fraction or type of model
- Excess mortality risk based on advice of 1 clinical expert and applied to all data except those sourced directly from KM curves

Cohort	Excess mortality risk
Brentuximab vedotin (no SCT)	5%
Brentuximab vedotin (SCT)	10%
Chemotherapy (no SCT)	7%
Chemotherapy (SCT)	10%

ERG's critique

- Appropriate to apply an excess mortality risk
- Excess mortality risk applied to both PFS and OS in brentuximab vedotin arm but PFS in chemotherapy arm
- Little evidence to support assumption that long term excess mortality for brentuximab vedotin should be less than for chemotherapy

Utility values

‘No SCT’ cohorts

- Company used utility values obtained from Swinburn et al. Study reported utility values for both R/R Hodgkin Lymphoma and sALCL
- ERG noted that health state vignettes not directly reflective of EQ-5D dimensions. Furthermore, unclear how accurately the vignettes reflect the health state of the average patient by clinical response status

SCT cohorts

- For initiation of salvage therapy to SCT, utility values modelled as per the approach for ‘no SCT’ cohort
- Clinical expert onion suggested patients would experience a quality of life decrement following ASCT or allo-SCT. For time from SCT to progression or cure, decrements applied as the average of the 4 clinical experts’ opinion
- For time from cure to death, utility values in the PFS state after the cured time point revert to the general population norms with 5% excess utility decrement applied as in ‘no SCT’ cohorts
- QALY decrements for adverse events based on estimated durations of events and the associated utility decrement for each event from Swinburn et al., other published literature and previous NICE STAs

Resource use and costs

Brentuximab vedotin

- Cost calculated as per SmPC: 1.8mg/kg every 3 weeks until disease progression or unacceptable toxicity
- Per cycle drug costs based on average patient from SG035-0004
- 'No SCT' cohort received average of 8 cycles, SCT cohort received average of 8.8 cycles

Chemotherapy

- Used a weighted average cost based on % of patients assumed to receive each treatment
- Required dosing and time on treatment based on sources identified in NCCN guidelines on non-Hodgkin lymphomas

SCT

- Cost of SCT included cost of donation, BEAM conditioning, transplant and follow-up care for both ASCT and allo-SCT
- Costs sourced from the BMT Unit at the Beatson West of Scotland Cancer Centre. Base case analysis assumed total cost of £53,790 and £108,241 for ASCT and allo-SCT respectively
- In both cases, company provided an alternative sensitivity analysis, based on the national unit costs for key components of the transplant process

Post progression therapies

- In company's original model, 100% of patients assumed to receive a further line of treatment following progression. 80% of patients with PD following chemotherapy were modelled to receive brentuximab vedotin
  - ERG noted this not in line with NICE final scope
- In response to clarification, company provided a revised model incorporating 2 alternative distributions of post-progression therapy
  - Trial based: included the distribution of treatments according to the studies used to obtain OS data
  - Clinical expert based: developed after further contact with clinical experts
- Company suggested 'clinical expert distribution' should form base case analysis given that non-licenced treatments used in SG035-0004 following progression
- ERG preferred the 'trial based distribution' (to be in keeping with modelled effects) and used this as its preferred version of the company's base case

Company's deterministic base case (with CAA): Revised base case after clarification

Technologies	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER (per QALY)
Trial based post-progression therapy distribution (ERG preferred analysis)							
Chemotherapy	[redacted]	3.35	[redacted]	-	-	-	-
Brentuximab	[redacted]	9.53	[redacted]	[redacted]	6.18	[redacted]	£19,470
Post-progression therapy based on clinical expert							
Chemotherapy	[redacted]	3.35	[redacted]	-	-	-	-
Brentuximab	[redacted]	9.53	[redacted]	[redacted]	6.18	[redacted]	£12,873
ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years							

The ERG re-ran the probabilistic analyses using the revised company model. Probabilistic ICER for 'trial based' post-progression therapy distribution was £19,034 per QALY gained

ERG's base case (with CAA)

- ERG corrected 2 errors in the company's model (error in discounting of post-progression therapy costs and an error in the probabilistic sensitivity analysis)
- ERG's preferred base case incorporated the following:
  - trial based distribution of post-progression therapy costs
  - Costs of brentuximab vedotin removed from the chemotherapy arm
  - data from Mak et al. for both PFS and OS
- ERG's deterministic ICER: £21,267 per QALY gained. Probabilistic results shown below:

Comparator	Costs	QALYs	ICER	P (C/E) @ £20k	P (C/E) @ £30k	P (C/E) @ £50k
Brentuximab vedotin	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]				
Incremental	[redacted]	[redacted]	£20,667	53%	77%	99%

ERG's deterministic scenario analyses: key results

		BV		Chemo				
Analysis	**Description**	**Cost**	**QALY**	**Cost**	**QALY**	**Inc. Cost**	**Inc. QALY**	**ICER**
6	No. treatment cycles on brentuximab vedotin (No SCT) =4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,090
7	No. treatment cycles on brentuximab vedotin (No SCT) =16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,321
24	PFS & OS hazard (-25%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,127
25	PFS & OS hazard (-50%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,530
27	BV PFS based on IRF data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,296
30	Chemo PFS (KM data from Mak et al. PS<2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,267
31	Chemo OS (KM data from Mak et al.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,728
32	Combined scenarios 27 to 31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,783
33	Equal rates of SCT progression in both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,448
34	Combined scenarios 32 & 33 (worst case for BV)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,994

End of life

- Based on the company's cost effectiveness results, the company view was that it did not need to make a case for brentuximab vedotin to be considered for NICE's End of Life criteria

NICE End of life Criterion	Data available from cost-effectiveness analysis
The treatment is indicated for patients with a short life-expectancy, *normally* less than 24 months	Company's original submission: Mean OS 4.6 years* Company's 'Trial based post progression therapy distribution': Discounted Life Years 3.35 years
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	Company's original submission: Mean OS 16.31 years*. Represents an extension in mean OS of 11.7 years Company's 'Trial based post progression therapy distribution': Discounted Life Years 9.53 years

* Company's original submission: Table 5.71 page 188

Innovation

- First new medicine to be approved for the treatment of sALCL in more than 30 years,
  - Meets high unmet need as currently only treatment approved by the European Medicines Agency for patients with R/R sALCL
- Conditional marketing authorisation granted on only Phase II data
- Offers targeted therapy and has shown unprecedented single-agent activity in the treatment of R/R sALCL; viewed as a ‘step-change’ in management
- Improved tolerability and a more convenient schedule than chemotherapy.
- Additional treatment option where otherwise only best supportive care.
- Potential to act as bridge to allo-SCT

Equality considerations

- No equality issues raised by patient or professional groups
- Company stated:
  - Brentuximab vedotin has become established “standard of care” for patients with R/R sALCL because of its availability through the CDF. There would be a significant adverse impact on patients if brentuximab vedotin is not recommended by NICE and becomes unavailable to patients after the old CDF closes.
  - Potential equity issues could arise because patients with R/R sALCL in England who would previously have been able to access brentuximab vedotin through the CDF would be unable to, based purely on the timing of their relapse in relation to the NICE decision and the closure of the old CDF.
  - Within a UK context there could also potentially be an inequity of access if patients in Scotland and Wales are able to receive brentuximab vedotin through individual patient funding mechanisms while patients in England are not in the event of a negative NICE decision.

Key issues: cost effectiveness

- Brentuximab vedotin (no SCT):
  - For PFS, should the per INV or per IRF assessment from SG035-0004 be used in the base case analysis?
  - Is it appropriate to use a mixture cure model for PFS and OS?
- Chemotherapy (no SCT):
  - Which is the most appropriate source of data for chemotherapy?
  - Is it appropriate to use 2 alternative data sources for PFS and OS to model chemotherapy?
  - Is it appropriate to use a different extrapolation approach for chemotherapy (no SCT) to that used for brentuximab vedotin (no SCT)

Key issues: cost effectiveness

- Excess mortality risk
  - Is it appropriate to apply an additional excess mortality risk?
  - Which value is the most appropriate
- What is the most appropriate distribution of post progression therapies to use in the model?
  - Trial based post-progression therapy distribution (ERG's preferred analysis)
  - Post-progression therapy based on clinical expert (Company's preferred analysis)
- What is the most plausible ICER?
- Does brentuximab vedotin meet the end of life criteria?
- Does brentuximab vedotin represent an innovative treatment?
- Are there any potential equality issues?