# Chair's presentation

## Brentuximab vedotin for relapsed or refractory systemic anaplastic large cell lymphoma

2nd Appraisal Committee meeting

Committee C, 12 July 2017

Lead team: Iain Miller, Robert Walton, Judith Wardle

ERG: Health Economics Research Unit, University of Aberdeen

NICE technical team: Sana Khan, Nicola Hay, Thomas Strong

Company: Takeda UK

# Systemic anaplastic large cell lymphoma

- Anaplastic large cell lymphoma (ALCL) is a rare disease occurring commonly in children and young people
- 2 main types: systemic ALCL (sALCL) and primary cutaneous ALCL
- CD30+ is expressed on the surface of sALCL cells
- sALCL is most common and aggressive form of ALCL with 40% to 65% of patients developing recurrent disease after front-line therapy and requiring further treatment
- 2 subtypes of sALCL: defined by presence or absence of anaplastic lymphoma kinase (ALK) protein expression
- People with ALK-positive sALCL tend to be male, younger and have a better prognosis than those diagnosed with ALK-negative sALCL

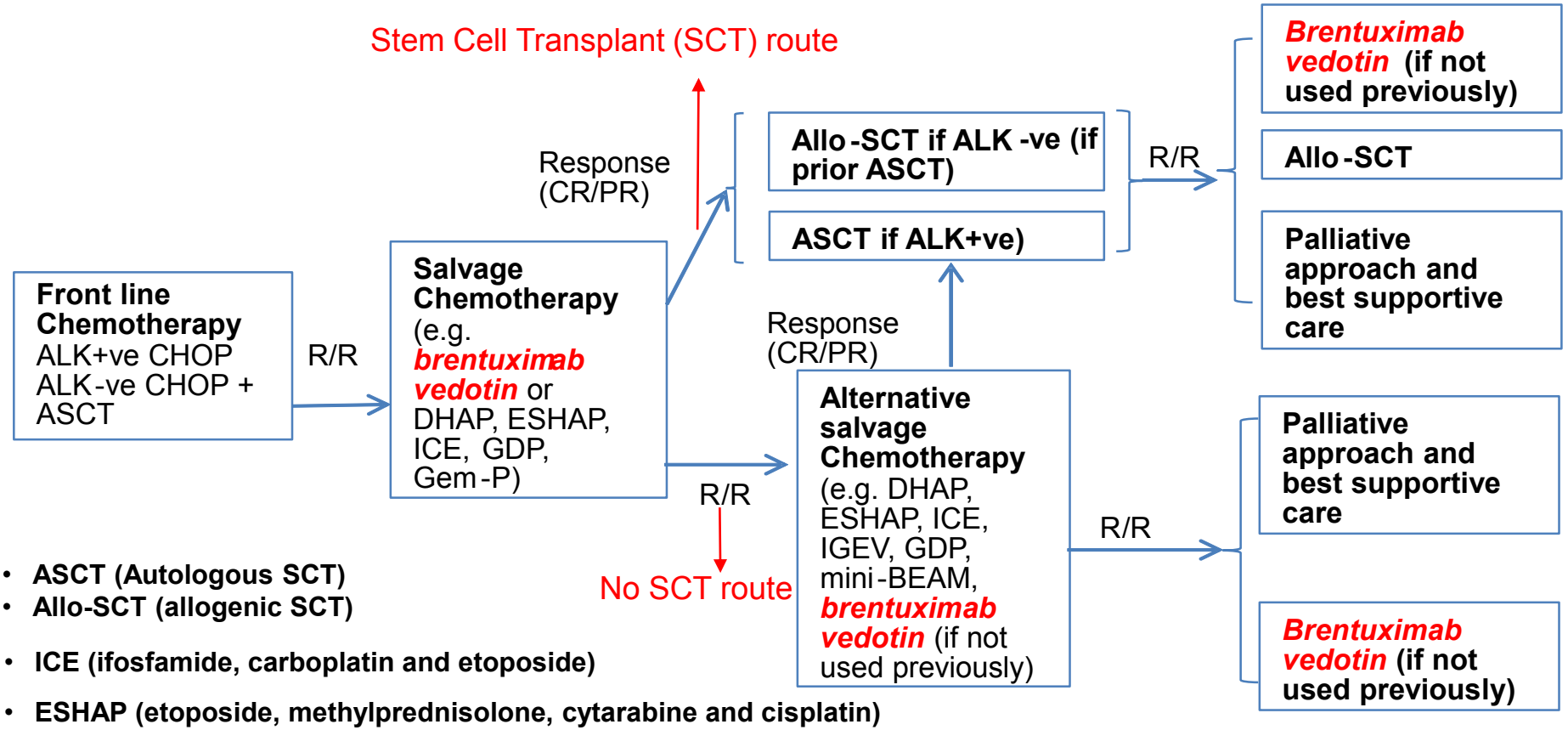
# Brentuximab vedotin (Adcetris)

*Takeda UK*

| | |
|---|---|
| **Marketing authorisation** | Adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)* |
| **Administration & dose** | 1.8 mg/kg administered intravenously over 30 minutes every 3 weeks |
| **Mechanism of action** | Antibody–drug conjugate: anti-CD30 monoclonal antibody with a potent chemotherapeutic agent.<br>Antibody–drug conjugate allows for the selective targeting of CD30-expressing cancer cells |
| **Cost** | List price: 50mg vial = £2,500<br>Average cost per cycle (at list price): £7,500<br>Average length of treatment: 5-6 cycles (median CDF), 8.2 cycles (mean of trial)<br>Presented analyses incorporate a commercial access agreement |

*Brentuximab vedotin has been available through the Cancer Drugs Fund in England since April 2013 for "relapsed or refractory systemic anaplastic large cell lymphoma". Number of patients forecast to receive it is expected to remain constant over the next five years at approximately 45 patients per year.

# Company treatment pathway




- **ASCT (Autologous SCT)**
- **Allo-SCT (allogenic SCT)**
- **ICE (ifosfamide, carboplatin and etoposide)**
- **ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin)**
- **DHAP (dexamethasone, high-dose cytarabine and cisplatin)**
- **GDP (gemcitabine, dexamethasone and cisplatin)**
- **Gem-P (gemcitabine, methylprednisolone and cisplatin)**
- **IGEV (ifosfamide,gemcitabine, vinorelbine and prednisone)**
- **Mini-BEAM (carmustine, etoposide, cytarabine & melphalan)**
- **CHOP (cyclophosphamide, hydroxydaunomycin,vincristine, prednisolone)**

# ACD preliminary recommendation

**Committee minded not to recommend**

No scenarios include all of committee's preferred assumptions

Request revised cost-effectiveness analysis to include:

- Extrapolation of PFS and OS using data from Mak et al. (2013)
- Explore number of parametric models for extrapolation including those already considered (accelerated failure time models) and others (e.g. proportional hazards models) if appropriate.
- Include a range of excess mortality rates higher than those used in the company's base-case analyses, identified through a systematic literature review rather than clinical expert opinion.

# ACD key assumptions

| Assumption | Company's preference – ACM1 | Committee's preference | Company – ACM2 |
|---|---|---|---|
| **Population** | Overall – 1 ICER for all 3 cohorts | Overall – 1 ICER for all 3 cohorts | Overall – 1 ICER for all 3 cohorts |
| **Excess Mortality** | Clinical expert informed | Higher values; informed by literature | Higher values; informed by literature |
| **Post-progression therapies** | Clinical expert informed distribution* | Clinical expert informed distribution | Clinical expert informed distribution |
| **Chemo survival data** | OS: Mak et al<br>PFS: self-control cohort | Mak et al data for both PFS and OS | Mak et al data for both PFS and OS |
| **Model type** | Mixture cure model (Accelerated failure time model explored) | Unable to make a judgement# | Further parametric models and curves explored |

*The ERG preferred a trial-based distribution, and this had a large impact on the ICER
#The company model did not allow for full investigation of different model types or parametric curves

# ACD consultation responses

- Consultee comments from:
  - Takeda (Brentuximab vedotin)
  - Leukaemia CARE
  - NCRI-ACP-RCP-RCR
- Clinical and patient experts:
  - 1x Clinical expert
- Commentator comments from:
  - None
- Web comments from:
  - 10x NHS professional; 1x patient organisation

# ACD consultation comments

**Comments from consultees, clinical expert, NHS professionals, and patient organisations**

- Disagree with the negative recommendation
- People with relapsed or remitting sALCL have a high unmet need. 2nd line chemotherapy is toxic, not tolerated by some, and results in a survival of a small number of months
- Brentuximab vedotin is a life-changing technology. It is very clinically effective compared with chemotherapy, with very high remission rates.
- Brentuximab vedotin appears to be a cost-effective use of NHS funds, with ICERs below the threshold where other technologies are recommended
- Lack of RCT evidence expected due to the high unmet need of this population
- There is evidence that this technology meets NICE's end-of-life criteria
- Withdrawing the drug after it has been offered through CDF, and proven to be clinically effective, would be unfair to patients

# Recap – ACM1
## *Survival curves*

**Trial based**

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

**Extrapolation**

- ERG Clinical advice suggested small percentage of patients could be expected to achieve long term remission using salvage chemotherapies
- ERG considered a conservative analysis in which both brentuximab vedotin and chemotherapy were modelled using standard parametric survival models to be more appropriate – but only accelerated failure time parametric model with gamma extrapolation available using the company's model
- ERG noted substantial difference in the excess PFS benefit of brentuximab vedotin, depending on source of data and extrapolation approach used
- Committee unable to make a judgement on the most appropriate extrapolation

# Company's new evidence
## *Survival curves*

Company have submitted new evidence which explore different standard parametric models.

- Different chemotherapy extrapolations have marginal impact on the ICER. Range of ICER*: £14,104 (PFS – Weibull, OS – lognormal) to £14,642 (PFS and OS – exponential)
- ICER* range for different brentuximab vedotin extrapolations of £13,391 (PFS - Log-logistic cure model and OS - gamma) to £25,355 (PFS and OS – exponential)
- The company chose parametric extrapolations in their revised base case, but highlight that the Log-logistic cure model for brentuximab vedotin PFS and OS (ACM1 base case) is still their preferred model - as the gamma curve does not capture the plateau as accurately as the cure model

The ERG reviewed the new evidence and conclude they have been adequately described and the selection of the preferred distributions has been justified

*ICER does not include a higher excess mortality assumptions

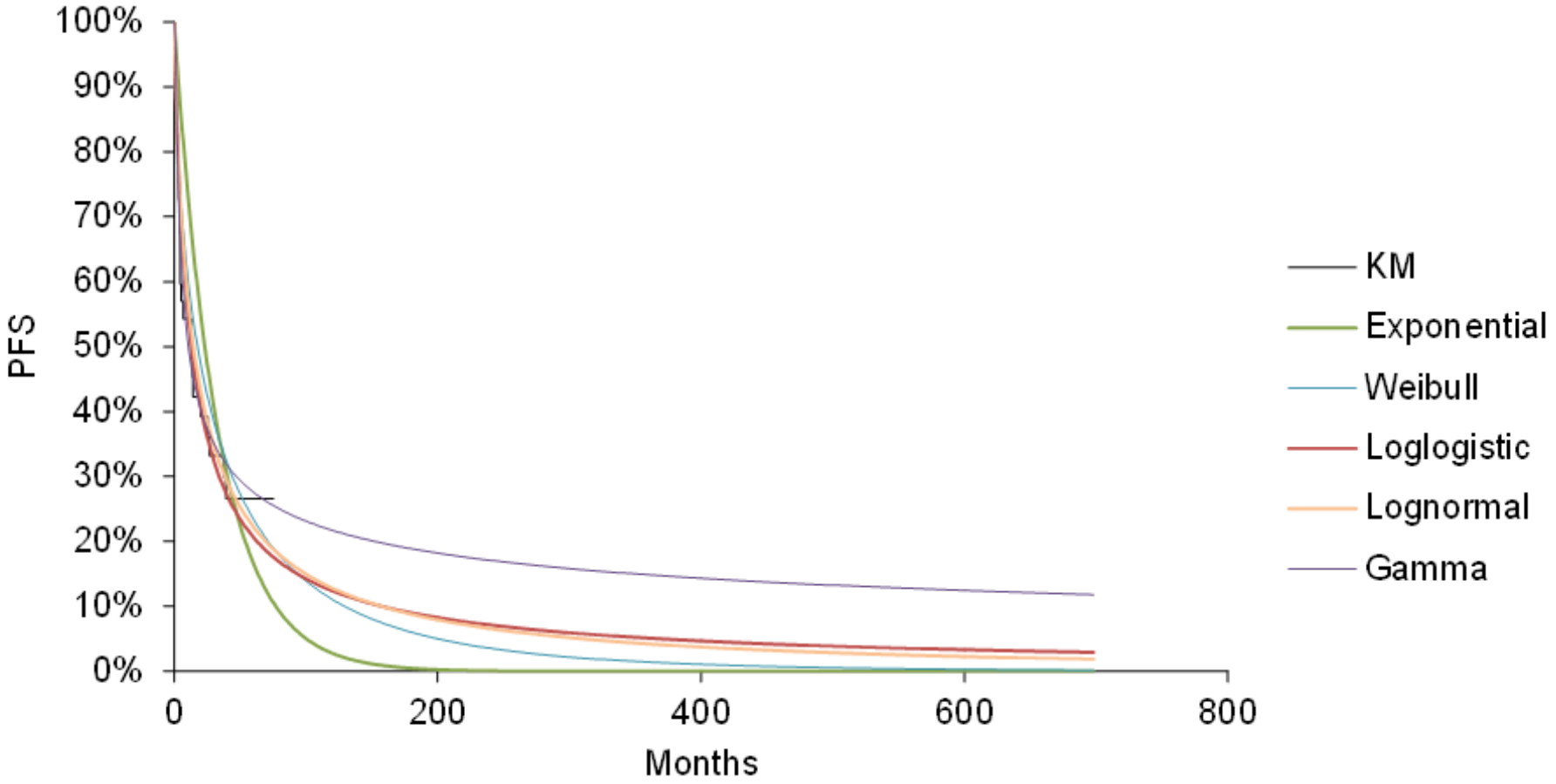
# Company's new evidence
## *Progression-free survival (I)*

| | Exp. | Weibull | Gompertz | Log-normal | Log-logistic | Gamma |
|---|---|---|---|---|---|---|
| **Progression-free survival for brentuximab vedotin (no SCT)** | | | | | | |
| **99% OS** | 12.8 | 34.0 | - | NR | NR | **NR** |
| **AIC** | 246 | 234 | - | 226 | 228 | **220** |
| **BIC** | 247 | 238 | - | 230 | 231 | **225** |
| **AIC rank** | 5 | 4 | - | 2 | 3 | **1** |
| **BIC rank** | 5 | 4 | - | 2 | 3 | **1** |
| **Progression-free survival for chemotherapy (no SCT)** | | | | | | |
| **99% OS** | 7.1 | 9.9 | 21.5 | **16.5** | 27.9 | 19.4 |
| **AIC** | 187 | 176 | 178 | **170** | 173 | 172 |
| **BIC** | 186 | 180 | 181 | **174** | 177 | 178 |
| **AIC rank** | 6 | 4 | 5 | **1** | 3 | 2 |
| **BIC rank** | 6 | 4 | 5 | **1** | 2 | 3 |

AIC, Akaike information criterion; BIC, Bayesian information criterion
Source: table 1.4 (page 9) and table 1.5 (page 13), Company ACD response appendix 1

# Company's new evidence
## *Progression-free survival (II)*

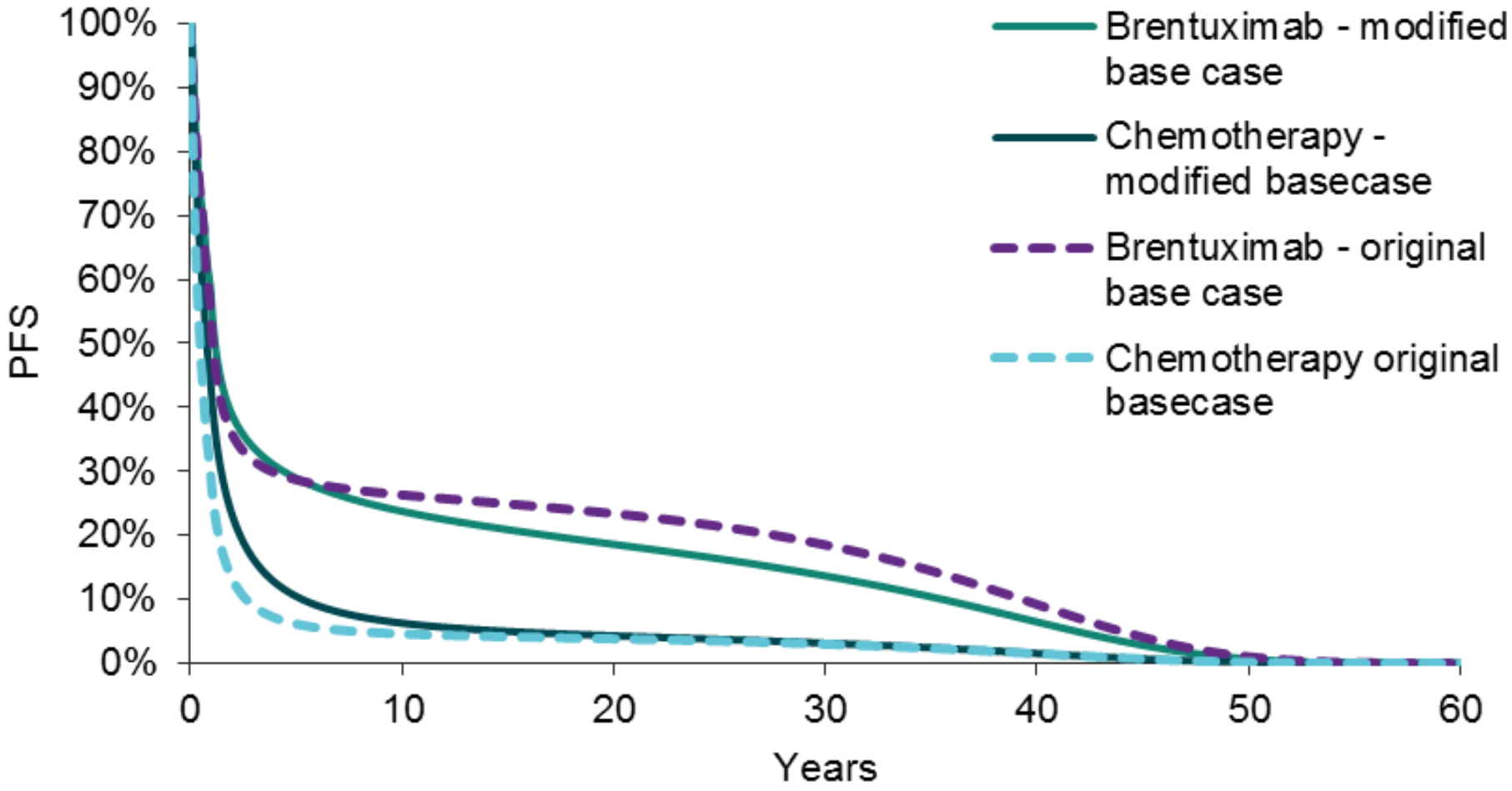
There is greater variation in the brentuximab vedotin PFS parametric extrapolations




Source: Figure 1.7 (page 14), Company ACD response appendix 1

# Company's new evidence

## *Progression-free survival (III)*




Source: Adapted from company model; does not include higher excess mortality

⊙ *Is the company's choice of extrapolation curve for PFS appropriate?*

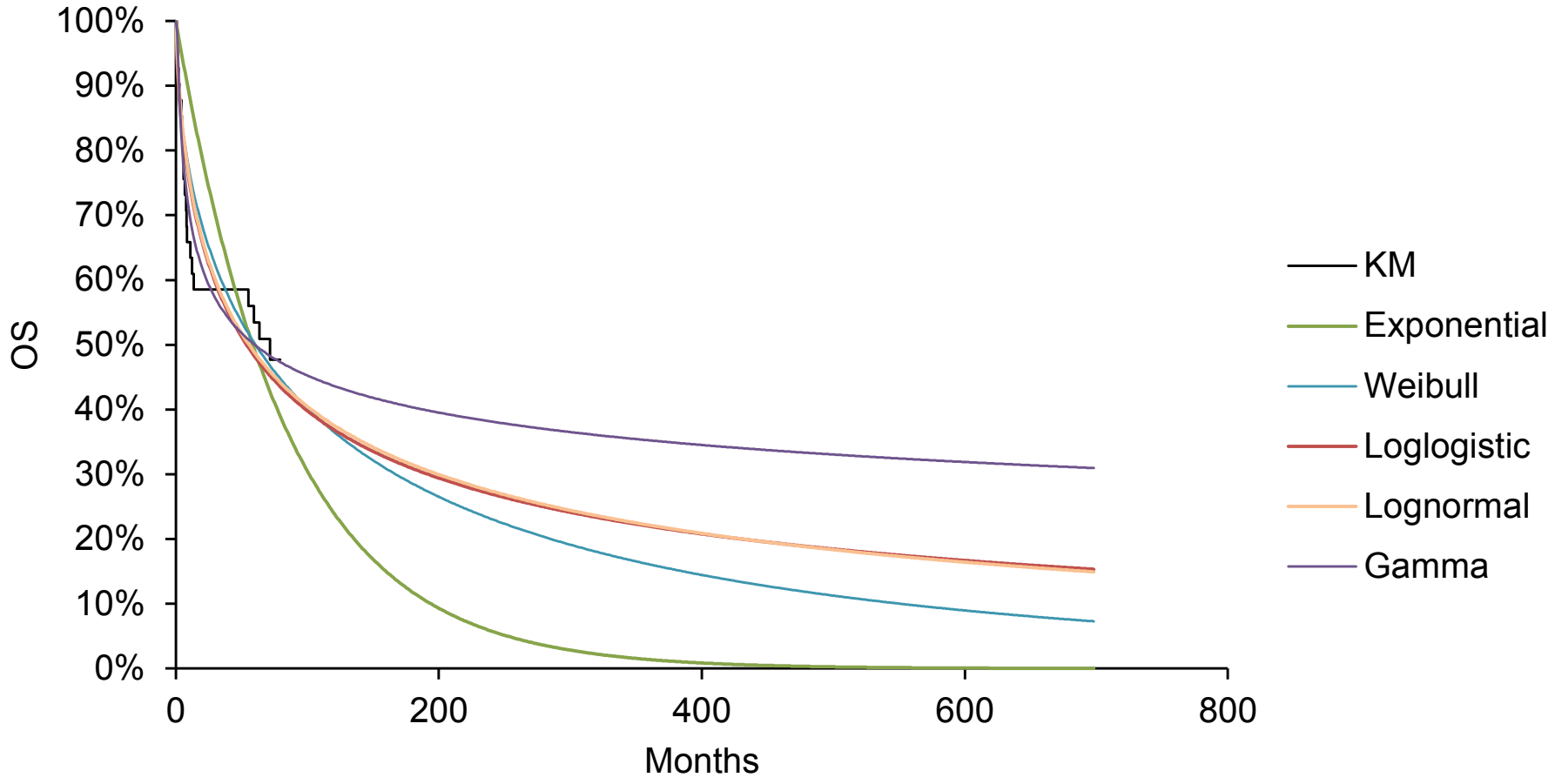
# Company's new evidence
## *Overall survival (I)*

| | Exp. | Weibull | Gompertz | Log-normal | Log-logistic | Gamma |
|---|---|---|---|---|---|---|
| **Overall survival for brentuximab vedotin (no SCT)** | | | | | | |
| **99% OS** | 32.3 yrs | NR | - | NR | NR | **NR** |
| **AIC** | 230 | 220 | - | 216 | 218 | **212** |
| **BIC** | 232 | 223 | - | 219 | 221 | **217** |
| **AIC rank** | 5 | 4 | - | 2 | 3 | **1** |
| **BIC rank** | 5 | 4 | - | 2 | 3 | **1** |
| **Overall survival for chemotherapy (no SCT)** | | | | | | |
| **99% OS** | 13.8 yrs | 19.9 yrs | NR | **30.1 yrs** | 49.3 yrs | NR |
| **AIC** | 188 | 178 | 180 | **170** | 173 | 170 |
| **BIC** | 190 | 182 | 184 | **173** | 176 | 175 |
| **AIC rank** | 6 | 4 | 5 | **2** | 3 | 1 |
| **BIC rank** | 6 | 4 | 5 | **1** | 3 | 2 |

AIC, Akaike information criterion; BIC, Bayesian information criterion; Company ACM2 base case in red
Source: table 1.6 (page 16) and table 1.7 (page 19), Company ACD response appendix 1

# Company's new evidence
## *Overall survival (II)*

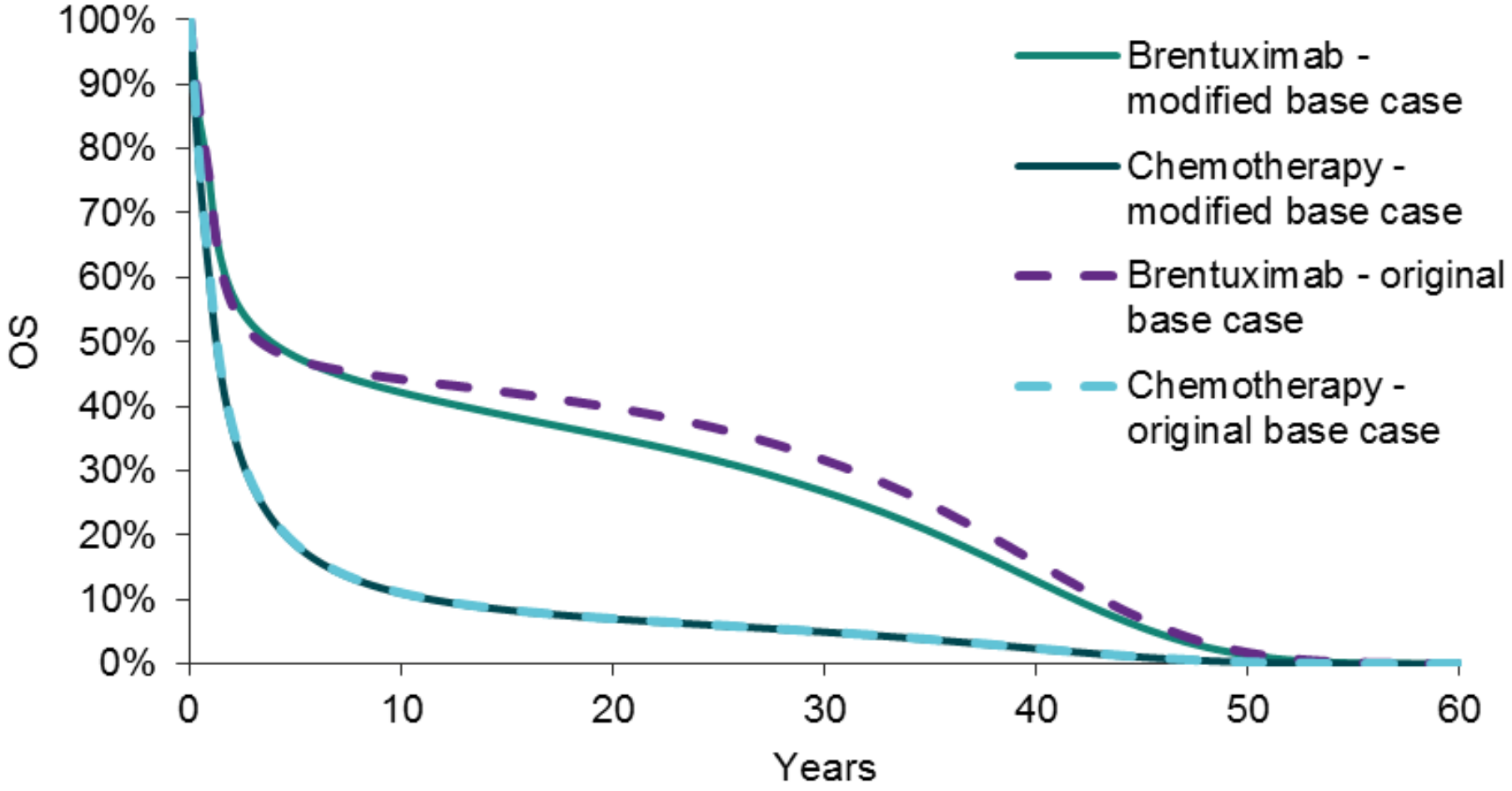
There is greater variation in the brentuximab vedotin OS parametric extrapolations




Source: Figure 1.11 (page 17), Company ACD response appendix 1

# Company's new evidence

## *Overall survival (III)*




Source: Adapted from company model; does not include higher excess mortality

⊙ *Is the company's choice of extrapolation curve for OS appropriate?*

# Recap – ACM 1
## *Excess mortality*

- Company model assumed that there will be a proportion of people who will have the same long-term mortality risk as the general population
- To address uncertainty in this assumption, residual excess mortality above the general population mortality risk is applied to all data not sourced from Kaplan Meier data
- Company ACM1 excess based on clinical expert opinion
- The ERG agreed that an excess mortality is appropriate but highlight that there is little evidence that excess mortality for brentuximab vedotin should be less than for chemotherapy, and prefer the excess to be equal

# Company's new evidence
## *Excess mortality (I)*

- Company have conducted a targeted search and solicited further clinical expert input to inform long-term survival
- 10 clinical experts state that relapsed/refractory sALCL and acute lymphoblastic leukaemia excess mortality are not comparable
- Sensitivity analysis range from ICER of £16,910 (0% excess) to £22,193 (500% excess for brentuximab vedotin and chemotherapy [no SCT])

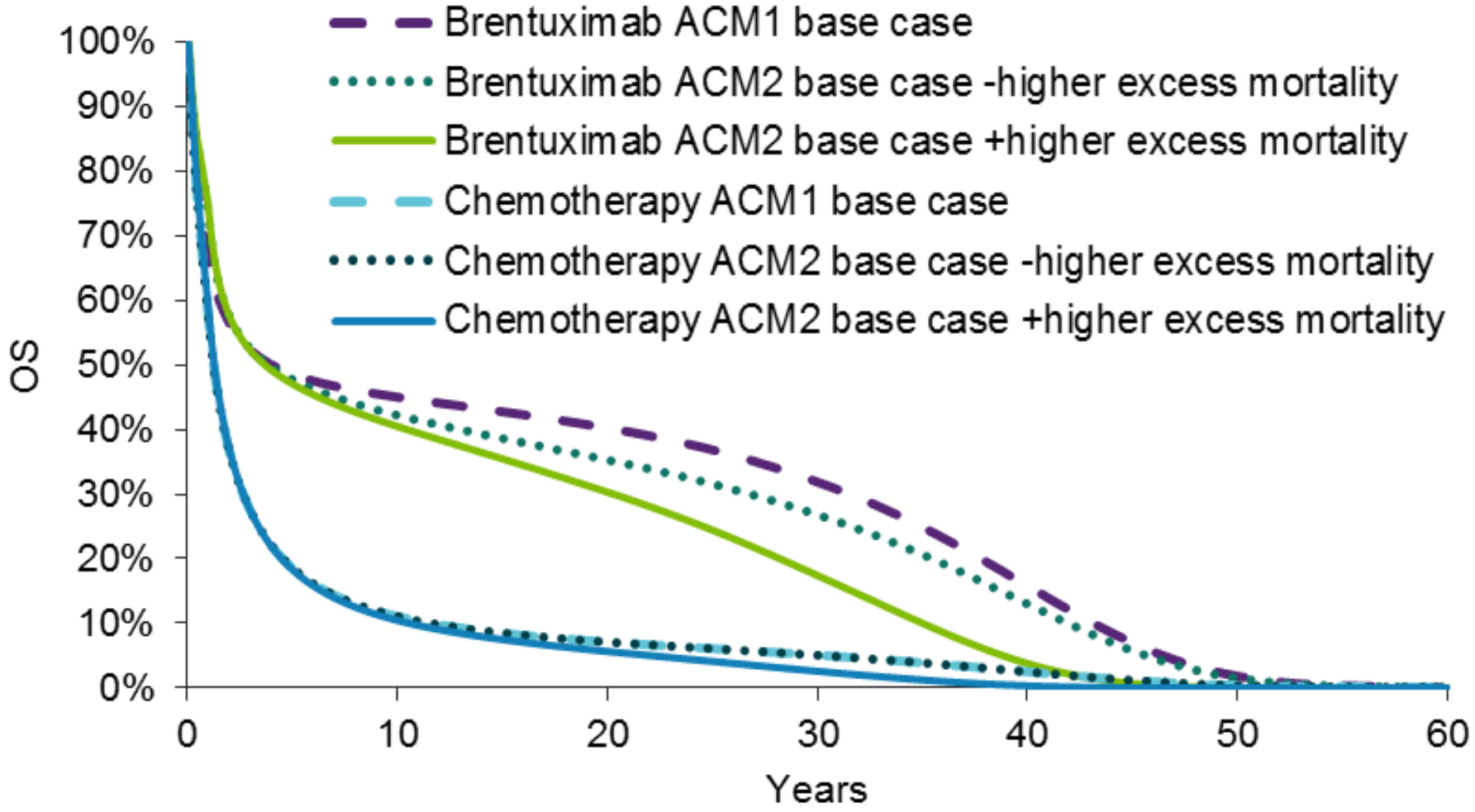
| Cohort | Excess mortality risk | |
|---|---|---|
| | Company – ACM1 | Company – ACM2 |
| Brentuximab vedotin (no SCT) | **5%** | **100%** |
| Brentuximab vedotin (ASCT) | **10%** | **200%** |
| Brentuximab vedotin (AlloSCT) | **10%** | **300%** |
| Chemotherapy (no SCT) | **7%** | **100%** |
| Chemotherapy (ASCT) | **10%** | **200%** |
| Chemotherapy (AlloSCT) | **10%** | **300%** |
| Source: Table 1.9 (page 25), Company ACD response appendix 1; | | |

The ERG are satisfied that these excess rates are justified by available literature

⊙ *Is the company's choice of excess mortality appropriate?*

# Company's new evidence
## *Excess mortality (II)*

- Higher excess mortality reduces the survival gain of brentuximab vedotin




Source: Adapted from Company model

# Company's new evidence

## *Base case*

| | Total costs (£) | Total QALYs | Incr. costs (£) | Incr. QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| **Company – Deterministic** | | | | | |
| **Chemo** | [redacted] | [redacted] | [redacted] | [redacted] | **£18,324** |
| **Brentuximab vedotin** | [redacted] | [redacted] | | | |
| **Company – Probabilistic** | | | | | |
| **Chemo** | - | - | [redacted] | [redacted] | **£20,399** |
| **Brentuximab vedotin** | - | - | | | |

Incr., incremental; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: table 1.14 (page 37), Company ACD response appendix 1;

- The ERG are content that the company have addressed and correctly implemented all of the requested analyses from the ACD

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# Company's new evidence

## *Impact of individual changes*

| | Incr. costs (£) | Incr. QALYs | ICER (£/QALY) | Δ ICER |
|---|---|---|---|---|
| **ACM1 base case** | [redacted] | [redacted] | **£12,873** | |
| Errors corrected* | [redacted] | [redacted] | £13,002 | +£129 |
| Mak et al parametric extrapolation | [redacted] | [redacted] | £14,222 | +£1,349 |
| Brentuximab vedotin parametric extrapolation | [redacted] | [redacted] | £14,703 | +£1,830 |
| Excess mortality (SCT) | [redacted] | [redacted] | £13,467 | +£594 |
| Excess mortality (no SCT) | [redacted] | [redacted] | £14,170 | +£1,297 |
| **ACM2 base case** | [redacted] | [redacted] | **£18,324** | **+£5,451** |
| Log-logistic mixture cure model scenario | - | - | £16,253 | -£2,071 |

*The company corrected the errors identified by the ERG report and minor errors identified during ACM consultation (for further details see page 5-6 of the company's response to consultation appendix 1)
Source: Table 1.14 and 1.16 (page 37 and 42), Company ACD response appendix 1

# ERG sensitivity analyses
## *survival curves*

- ERG investigated different parametric extrapolations with the inclusion of the higher excess mortality assumption

| | Incr. costs (£) | Incr. QALYs | ICER (£/QALY) | Δ ICER |
|---|---|---|---|---|
| **ACM2 base case** | [redacted] | [redacted] | **£18,324** | **-** |
| **Parametric models for brentuximab vedotin (both PFS and OS)** | | | | |
| **Weibull** | [redacted] | [redacted] | £25,353 | +£7,029 |
| **Exponential** | [redacted] | [redacted] | £32,801 | +£14,477 |
| **Log-Normal** | [redacted] | [redacted] | £24,064 | +£5,740 |
| **Log-Logistic mixture cure model** | [redacted] | [redacted] | £16,253 | -£2,071 |
| **Parametric models for chemotherapy (both PFS and OS)** | | | | |
| **Weibull** | [redacted] | [redacted] | £18,475 | +£151 |
| **Exponential** | [redacted] | [redacted] | £19,108 | +£784 |
| **Gamma** | [redacted] | [redacted] | £18,537 | +£213 |

Source: table 1 (page 7-8), ERG review of ACD response

# ERG sensitivity analyses

## *Cycles of brentuximab vedotin*

- Uncertainty in the expected number of cycles of brentuximab vedotin
  - SPC specifies minimum of 8 cycles, maximum of 16
  - Mean cycles from trial (used in model) is 8.2
  - Evidence from CDF indicates a median of 5 to 6 cycles
- In ACM 1 committee accepted that most people in clinical practice would have fewer cycles than specified in the SPC and the SG035-0004 trial.
- ERG conducted a sensitivity analysis to investigate the sensitivity of the ICER to different time on treatment assumptions

| | Incr. costs (£) | Incr. QALYs | ICER (£/QALY) | Δ ICER |
|---|---|---|---|---|
| **ACM2 base case (mean of 8.2 cycles)** | [redacted] | [redacted] | **£18,324** | - |
| **5 cycles of brentuximab vedotin** | [redacted] | [redacted] | £11,048 | -£7,276 |
| **16 cycles of brentuximab vedotin** | [redacted] | [redacted] | £35,848 | +£17,524 |

Source: table 1 (page 7-8), ERG review of ACD response

# End-of-life criteria

| Criterion | Data available |
|---|---|
| **Indicated for patients with a short life expectancy, normally less than 24 months** | Economic model (ACM2 base case) overall survival median is 15.18 months and mean of 3.98 years if SCT rate of 14% (7% ASCT and 7% AlloSCT) assumed.<br>Mak et al (2013). reported median overall survival of:<br>• 13.7 months for people with peripheral T-cell lymphoma and PS<2 (used in economic model)<br>• 3.0 months for people with systemic anaplastic large cell lymphoma (marketing authorisation population)<br>Haematological Malignancy Research Network provided new data: Overall survival mean of [redacted] years and median of [redacted]<br>EoL granted in other indications where there is a positive skew in survival, including relapsed or refractory Hodgkin lymphoma – a less aggressive lymphoma |
| **Normally ≤3 months extension** | • Economic model (ACM2 base case) increase of median overall survival of 2.61 years and mean overall survival of 8.3 years<br>• The committee agreed at ACM1 that brentuximab meets this criteria |

Source: Company ACD response appendix 2

# Key issues for consideration

- Is the new evidence submitted by the company appropriate for decision-making?
- Are there any changes in committee's preferred assumptions from ACM1?
  - What are the most appropriate excess mortality values?
  - Which parametric model and extrapolation curve is most appropriate for overall survival and progression-free survival?
- What is the most plausible ICER for brentuximab vedotin?
- Innovation: any health-related benefits not captured in the QALY?
- Is the new evidence submitted by the company sufficient to conclude that brentuximab vedotin meets the end-of-life criteria?
- Are there any equality issues?