Lead team presentation

Contains [redacted] and [redacted]

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma [ID1115]

1st Appraisal Committee meeting

Cost-effectiveness

Committee C

Lead team: Mike Chambers, Nigel Langford and Judith Wardle

Evidence Review Group: CRD and CHE Technology Assessment Group, University of York

NICE technical team: Lorna Dunning, Nicola Hay

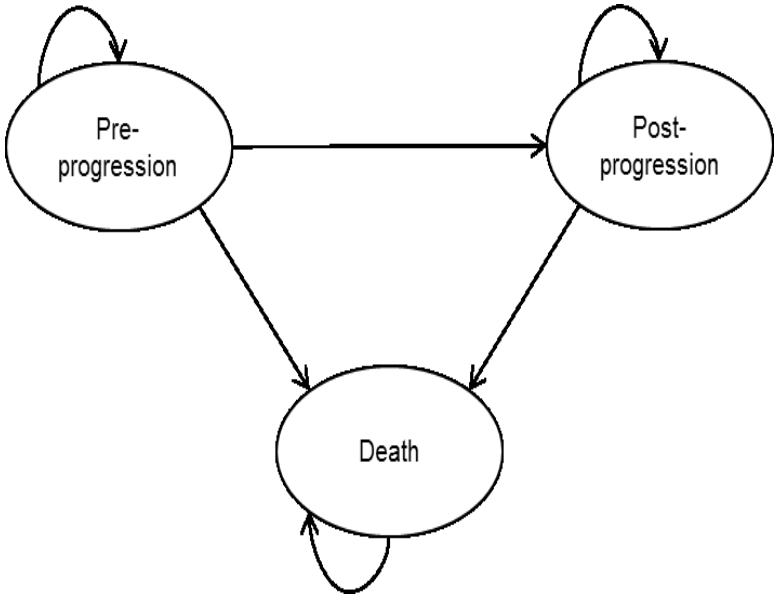
Company: Kite/Gilead

31st July 2018

Key issues – cost effectiveness

- ZUMA-1 has median 15.4m follow up resulting in high levels of censoring around 12 months and uncertainty in OS and PFS results beyond this time point. What extrapolation is appropriate for axi-cel OS, taking into consideration the potential for long-term survivors and cure?
- What extrapolation should be applied to mature BSC OS data?
- What assumptions should be made to account for the lack of PFS data in SCHOLAR-1?
- Do the assumptions around long term survivors HRQoL reflect clinical practice?
- What is the most appropriate way to include post-treatment SCT in the model?
- How should broader infrastructure and training requirements be incorporated into the model?
- Are QALYs from the group who did not receive axi-cel considered appropriately in the base case, is the ITT or mITT the most appropriate population to model?
- End-of-life considerations and the appropriate discount rate

Company's model

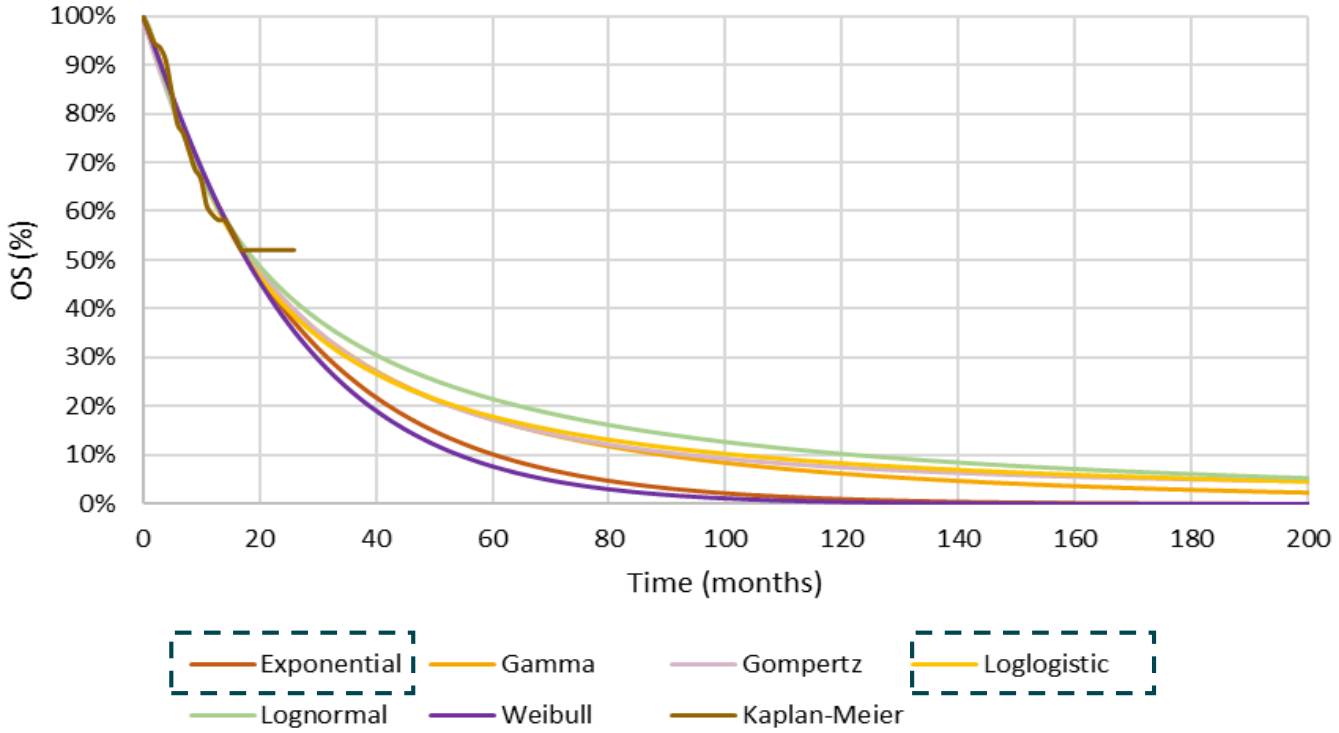


- Partitioned survival model - OS and PFS modelled independently
- Cycle length: 1 month
  Time horizon: 44 years
  Discount rate: 3.5%
- Axi-cel OS and PFS KM data from ZUMA-1 mITT population median 15.4 months follow-up
- After 24 months in the pre-progression state utilities/costs matched to general population
- OS for BSC from adjusted SCHOLAR-1. PFS (not recorded) uses OS:PFS ratio from ZUMA-1

ERG's comments on model structure

Model structure appropriate. ERG considers the concept of 'cure' and the assumptions around mortality risks for long term survivors to be subject to considerable uncertainty

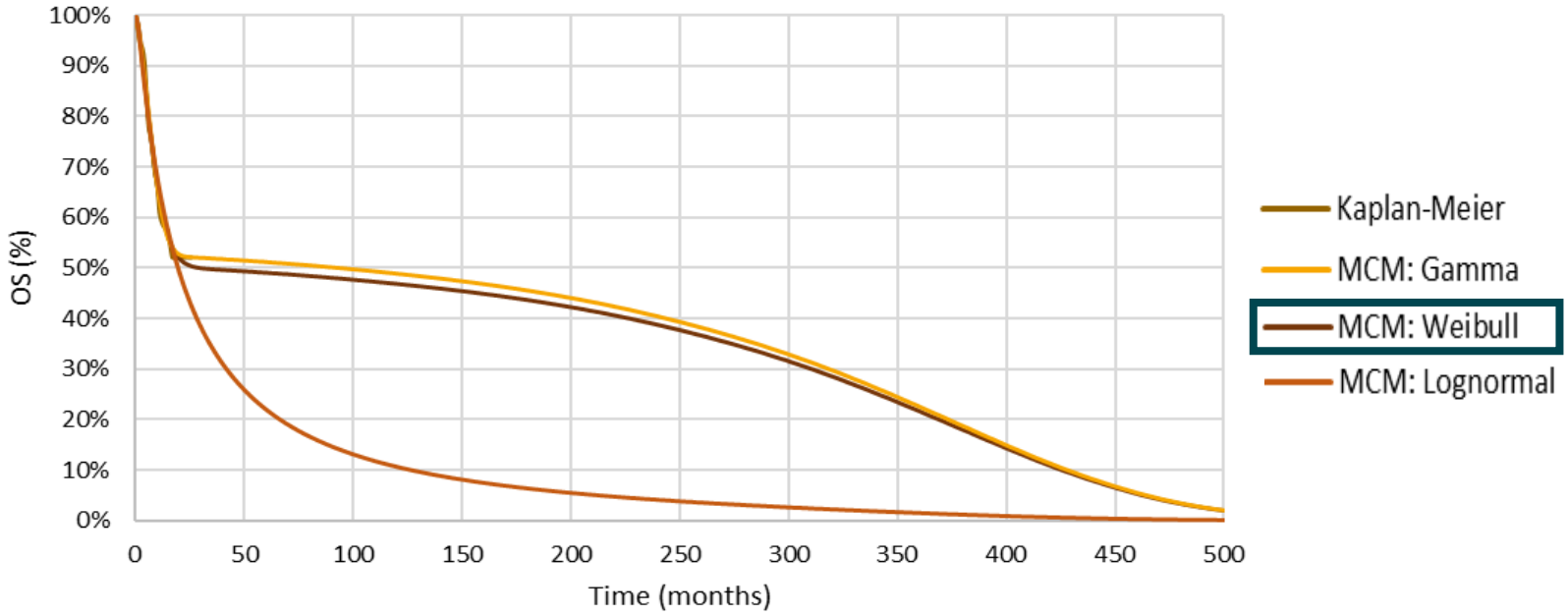
Axi-cel overall survival – company's extrapolation: parametric curves



Axi-cel

- Uses clinical data from ZUMA-1 (n=108)
- Median follow up 15.4m: 12m ~60 patients in ZUMA-1 at 18m ~10 patients
- Based on AIC and BIC statistics, loglogistic/exponential curves preferred
- Neither parametric curves fit the KM curve or provide plausible extrapolation of long-term survival

Axi-cel overall survival – company's extrapolation: mixture cure model

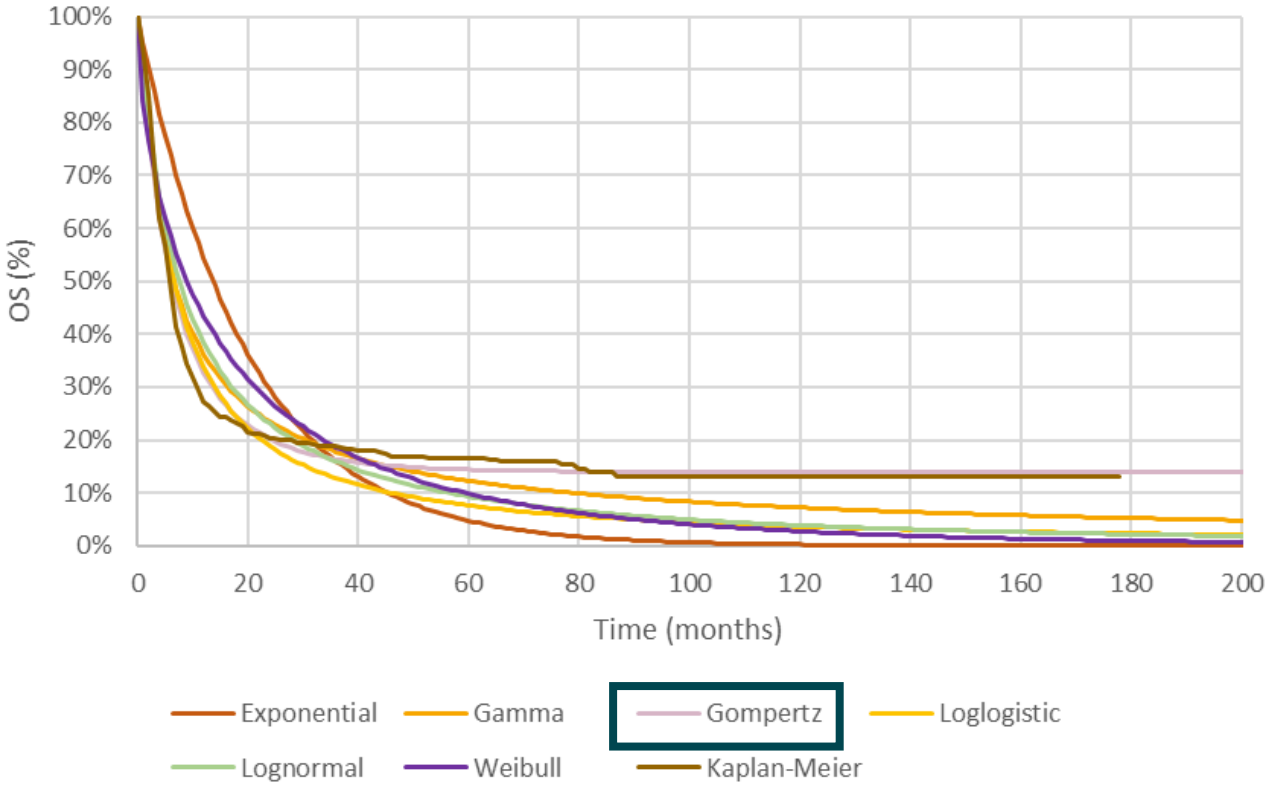


Distribution	Lognormal	Weibull	Gamma
Cure Fraction	1%	50%	53%

Axi-cel

- Mixture cure model use patient level data in a logistic regression model to estimate the "cure fractions". Cured patients follow general population health from time of infusion.
- Standard parametric curve estimates survival for those without long-term remission
- General population health assumed for long term survivors after 24m

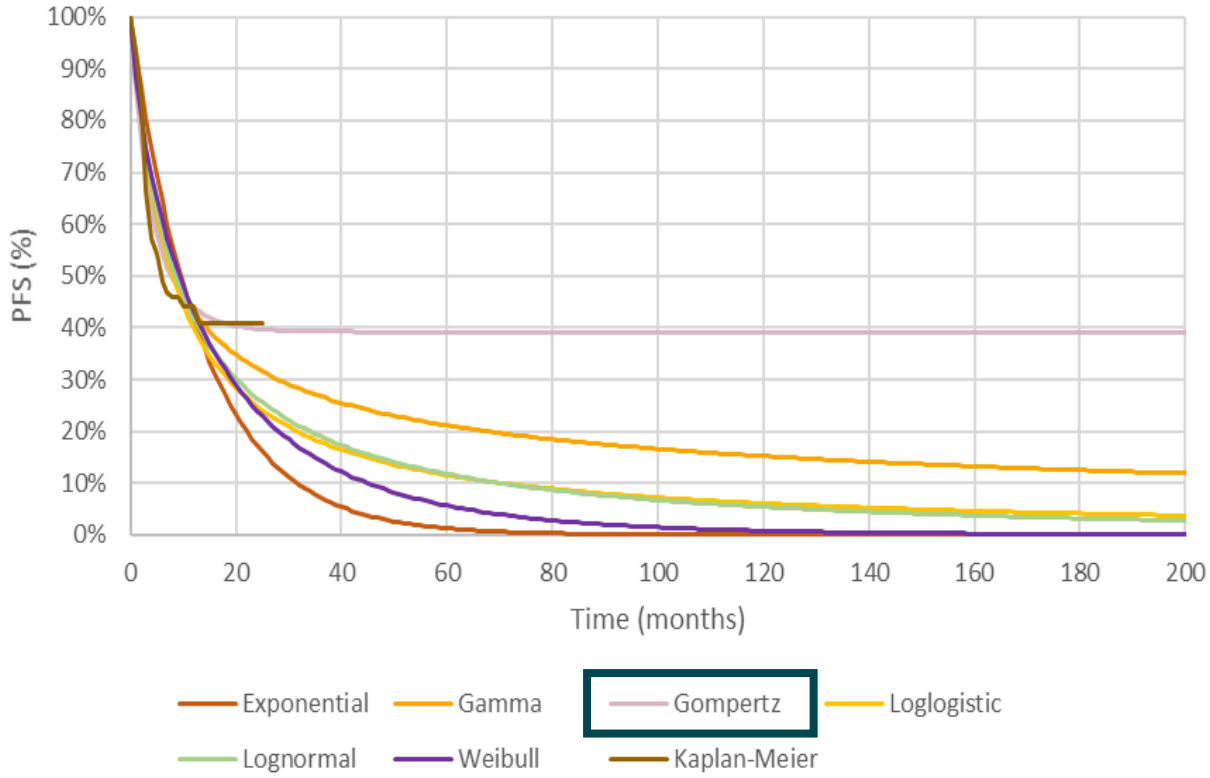
BSC overall survival – company's extrapolation: parametric curves



BSC

- SCHOLAR-1 adjusted to remove patients with ECOG score of 2-4
- Based on AIC and BIC statistics, visual inspection and clinical opinion Gompertz curve demonstrates the best fit
- Mixture-cure models are not used for BSC arm as simpler parametric curves are preferred by the company

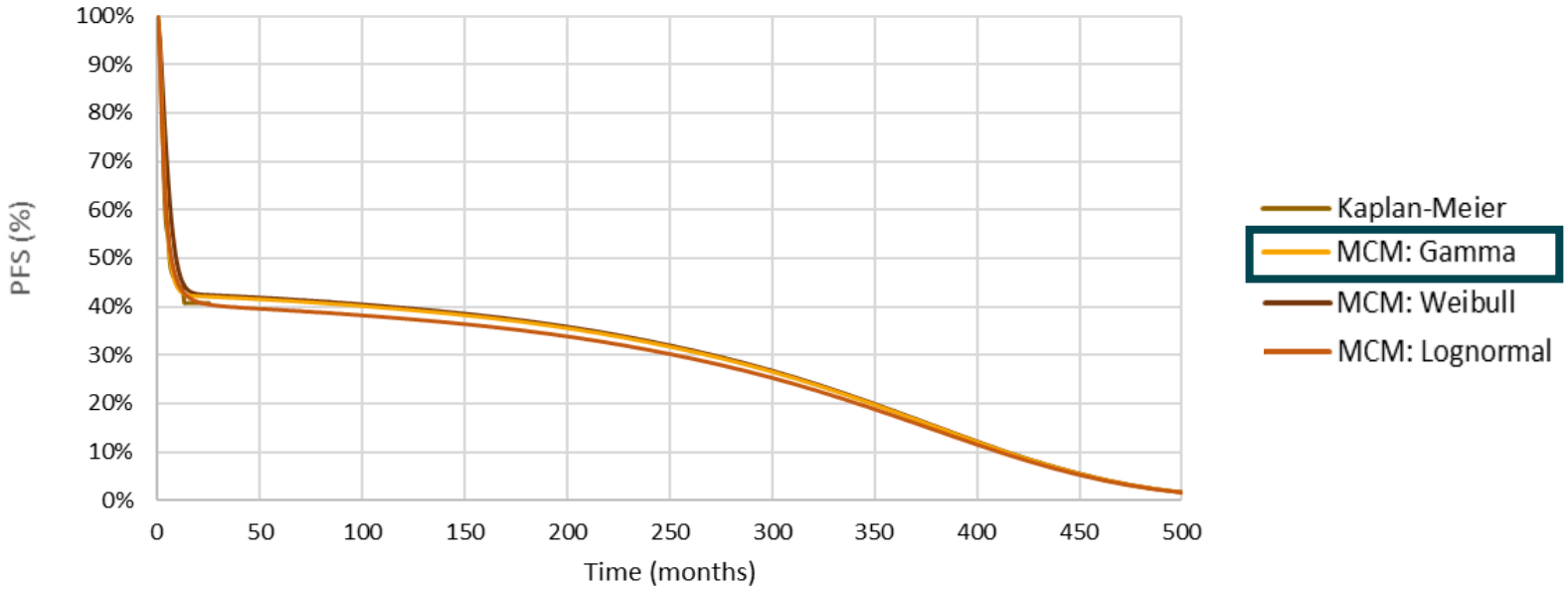
Axi-cel progression-free survival – company's extrapolation: parametric curves



Axi-cel

- Based on AIC and BIC statistics, visual inspection and clinical opinion Gompertz curve demonstrates the best fit
- Alternative curves were explored as part of the scenario analysis
- MCM model is not used as the company argue there is no consensus on the validity of using MCM for PFS

Axi-cel progression-free survival – company's extrapolation: mixture cure model

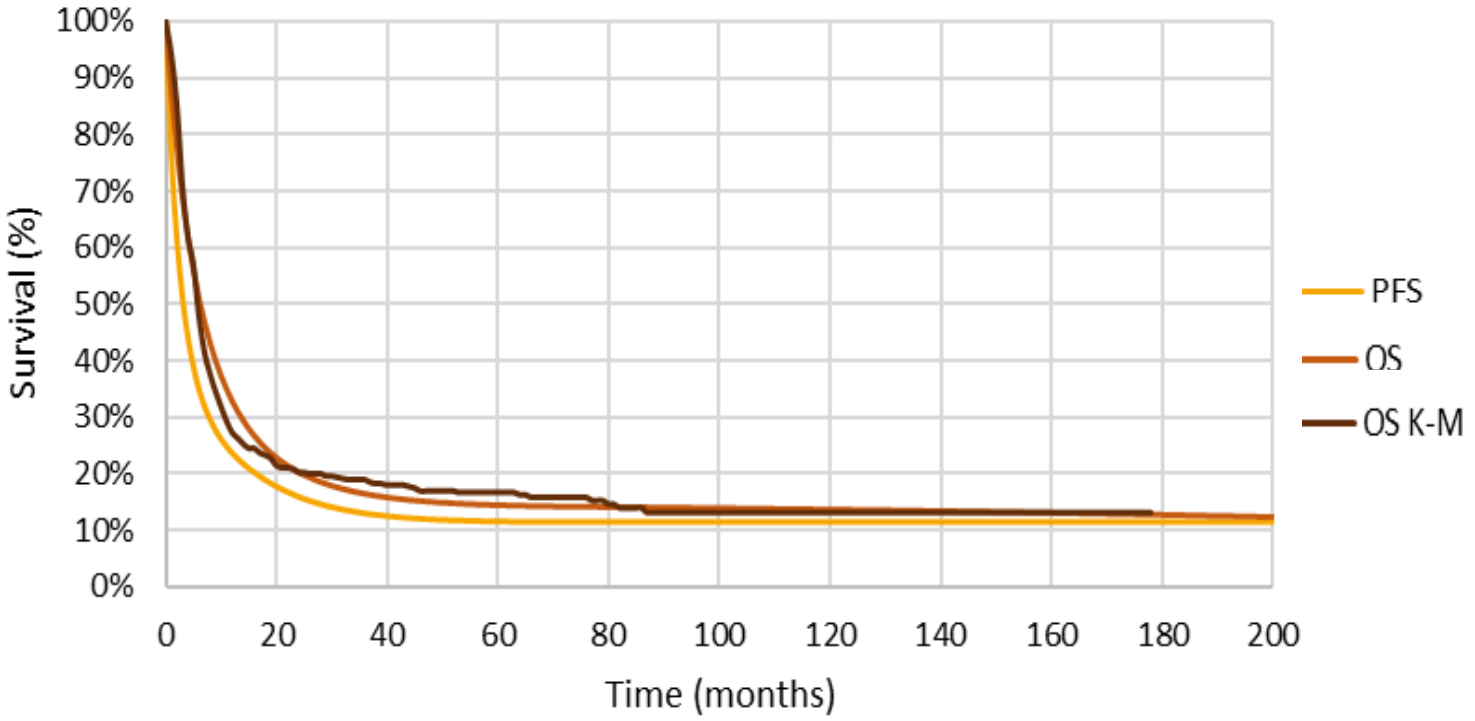


Distribution	Lognormal	Weibull	Gamma
Cure Fraction	41%	43%	42%

Axi-cel

- Provided after clarification
  - Company – "PFS end points do not have clear meaning"
- Background mortality used to estimate 'cure fraction' in OS and PFS
- More events in PFS allows the lognormal model to adjust to a more reasonable position than in the OS MCM modelling
- Single parametric curve preferred

BSC progression-free survival – company's extrapolation



BSC

- PFS not recorded in SCHOLAR-1 study
- PFS for BSC estimated by assuming the same ratio between PFS and OS at each time point in the axi-cel arm can be applied to BSC
- 2 scenario analyses explored:
  People receiving BSC spend 100% of time progression-free
  People receiving BSC spend 100% of time in progressed state

Company's survival functions

Outcome		Extrapolation	Base case	Scenarios
Overall survival	Axi-cel	• Extrapolation needed • Parametric for long-term survival curves implausible • MCM preferred	MCM Weibull	MCM gamma
	BSC	• Data almost complete • Simple single parametric curves preferred to MCM	Gompertz	Baseline adjustments & all functions
Progression-free survival	Axi-cel	• Extrapolation needed • Parametric curves preferred • MCM end points have no clear meaning	Gompertz	Gamma MCM Gamma
	BSC	• Not recorded for SCHOLAR-1	Ratio of axi-cel OS to PFS applied to BSC	All progress None progress
TTD		• Axi-cel assumes a one time infusion • BSC average no. cycles, average no. of days per cycle		

Key: BSC, best supportive care; MCM, mixture cure model; OS, overall survival; PFS progression-free survival; TTD, time to treatment discontinuation

ERG's comments – extrapolation of OS

Axi-cel extrapolation

- Agrees the use of single parametric curve would produce implausible results
- Difference in the cure fractions across alternative models of OS for axi-cel is likely to be caused by immature data
- Base-case mixture-cure model (MCM) overly optimistic:
  - Timing of cure is uncertain as survival data in ZUMA-1 is too immature with less than 2 years follow-up
  - Excess mortality risks appear likely to persist for at least 5 years
- Inclusion of patients re-treated with axi-cel may lead to a potentially positive bias in the OS data.

BSC extrapolation

- Only patients of known ECOG 0-1 should be included the SCHOLAR-1 cohort for comparison
- OS modelling approach for the BSC is inconsistent with that of axi-cel:
- MCM for BSC OS fit the observed data with robust estimates of cure fraction across distributions

ERG's comments – extrapolation of PFS

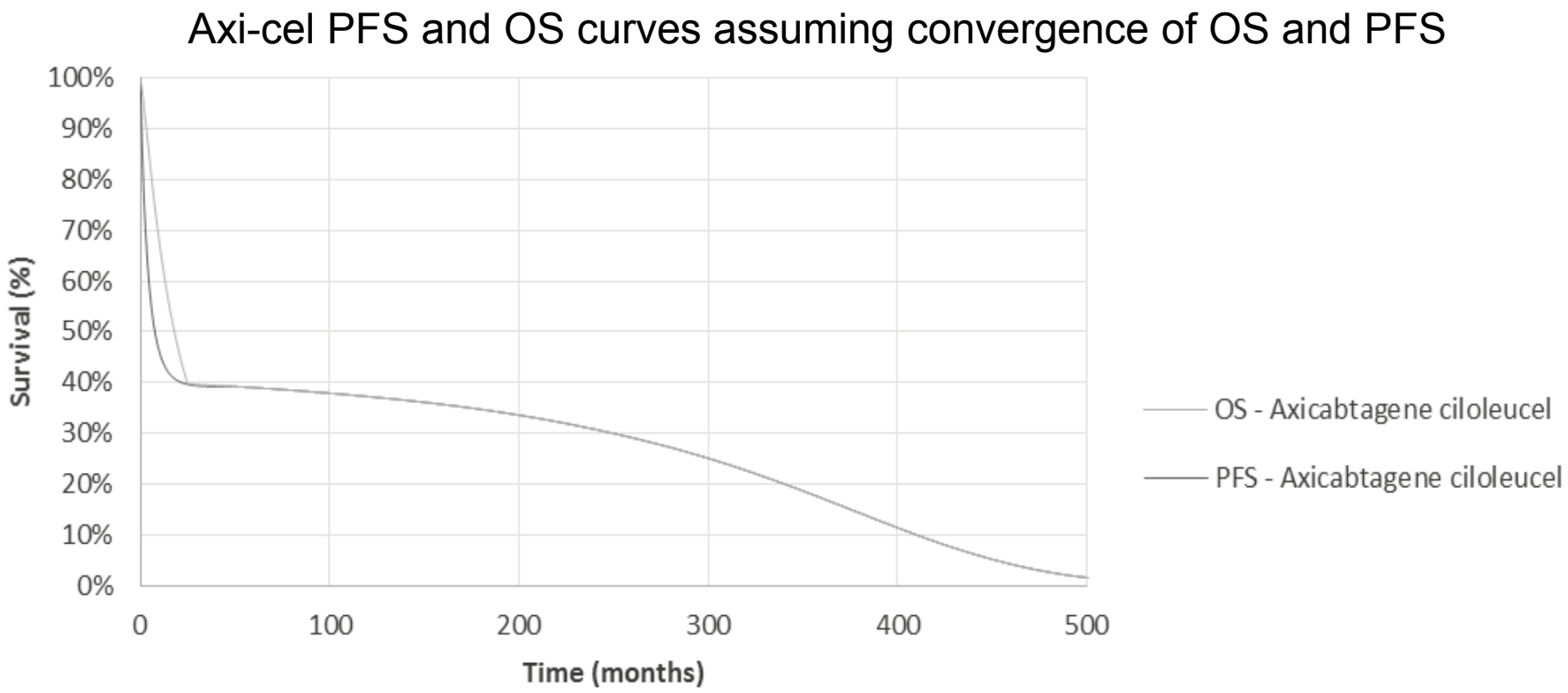
Axi-cel extrapolation

- Use of different survival models for PFS and OS suggests patients can be cured in terms of survival but not from disease progression
- MCM for PFS showed less variation in cure fraction than those of OS
  - Due to patients being cured following progression or
  - Immature OS data

BSC extrapolation

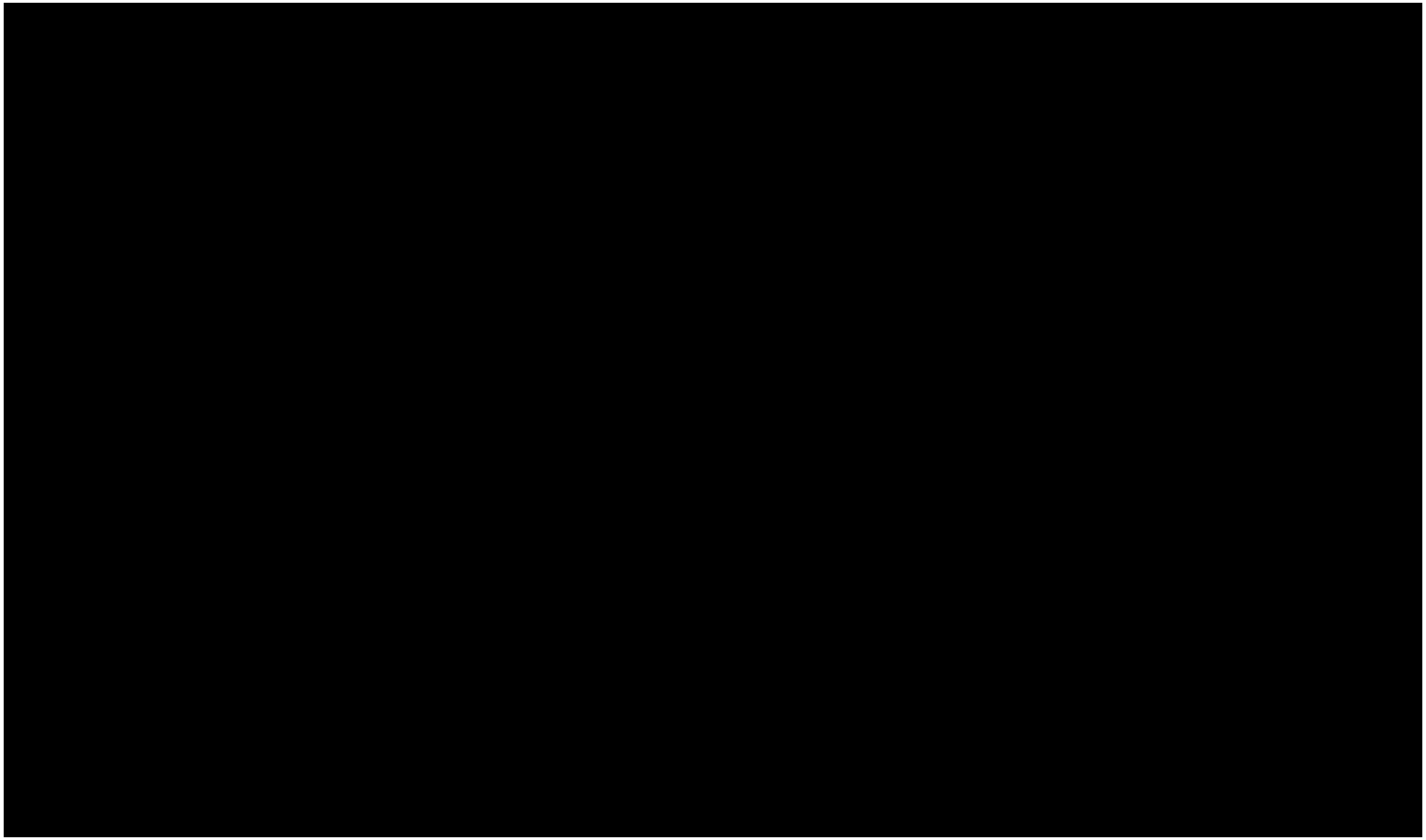
- Limited rationale for the company's approach to modelling PFS for BSC.
- Scenarios tested by the company correspond to the two extremes
- Given the different mechanisms of action it is possible the relationship between PFS and OS for BSC is different than for axi-cel
- An alternative modelling approach, assuming the proportional relationship between PFS and OS from a different published study in the US may have been more appropriate
- BSC PFS is subject to uncertainty but not a major driver of the ICER so no alterative scenarios were explored

ERG preferred approach to modelling OS and PFS for axi-cel



- ERG selected the best fitting single parametric OS curve for axi-cel (loglogistic) and constrained it so patients transitioned to general population mortality once the OS curve converged with the PFS curve
- This allowed for long-term survival in the model, but for a smaller cure fraction (approximately 40%) occurring around 52 months

ERG's preferred approach to modelling BSC overall survival



The ERG digitised the KM data from SCHOLAR-1 for patients with known ECOG 0-1 status (n=226) to provide a more appropriate basis for comparison with the ZUMA-1 population

Company and expert technical engagement responses

Extrapolation of ZUMA-1 survival data

- Clinical, patient and commissioning experts: Patients with progressed disease are not expected to survive for an extended period of time. The use of the PFS cure fraction was a reasonable approach
- Company: It is plausible there may be some clinical benefit from the persistence of CAR-T cells meaning patients with progressed disease have prolonged survival

Mortality risks for long term survivors

- Clinical experts: excess mortality for patients eligible for axi-cel would be expected to persist for several years
- Company: Using the MCM, the cured proportion follow age-matched general population mortality (from time zero) and the majority of uncured patients (>99%) have died by 2-3 years. Applying a cure assumption after 2 years is not appropriate

Questions for committee:

- What is the appropriate extrapolation of axi-cel OS?
- Would long term survivors experience excess mortality risks? For how long?

Health related quality of life (HRQoL)

- HRQoL data were collected from the safety management cohort of ZUMA-1 (n=34)

State	Utility value: mean (standard error)	Scenario analyses: mean (95% CI)	Source
Progression-free (base case)	0.72 (0.03)	0.76 (0.70-0.82)	Health-related quality-of-life EQ-5D data from ZUMA-1 Scenario from TA306
Progressed disease (base case)	0.65 (0.06)	0.68 (0.6-0.7)	
Progression-free after 2 years in PFS health state	General population	10% percentage decrement	Maurer et al (2014)
Adverse events: • CRS • Other AEs occurring in 10% of ZUMA-1 patients	 -0.72 (4 days) -0.09 to -0.15 (2-63 days)		Hettle et al., 2017 Nafees et al., 2008 Tolley et al., 2013 Swinburn et al., 2010

Company costs – one time costs for axi-cel (1)

Axi-cel	Cost	Assumption
Leukopheresis	£1,416	Cost per patient from weighted average + uplifting factor (1.102) for patients who didn't receive axi-cel
Conditioning chemotherapy	Hospital £5,063 Chemo £208	Cost per patient based on optimal drug combination and BSA data from ZUMA-1 (assumes wastage). Multiplier of 1.019 for the 2 patients who received conditioning therapy, but not axi-cel infusion
Drug acquisition	[redacted]	Cost per patient, includes shipping, engineering and generation of CAR T-cells. Assumes that cost of the drug will only be paid if axi-cel is administered to the patient
Drug administration	£6,760	Cost per patient for 17.6 elective inpatient days (from ZUMA-1 trial ~ 7.2 additional bed days from BCS) weighted HRGs from NHS reference costs
Re-treatment	£12,031	Additional cost per patient to account for retreatment of 9.26% of patients. Multiplier of chemotherapy and infusion costs

Key: BSA, body surface area; CRS, cytokine release syndrome; HRGs, healthcare resource group; ICU, intensive care unit; ITT, intention to treat

Company costs – one time costs for axi-cel (2)

Axi-cel		Cost	Assumption
Training		£83	Cost per patient. Cost calculated as time required to train 1 consultant (x2 days) per centre (treating 10 patients) with 2 years before retraining
Subsequent stem cell transplant		£75,385	Weighted average of allogeneic SCT HRGs applied for [redacted] of patients Costs taken from NHS National Schedule of Reference Costs. Includes follow up costs
Adverse events	CRS	£1,392 £1,363	Model updated after clarification response: Drug cost applied for the [redacted] of patients who receive tocilizumab ICU costs applied for 13% of patients who required hospitalisation (ICU stay) as a result of CRS
	All	£204	Cost of IVIG therapy applied for [redacted] patients who experienced Grade 1 or 2 hypogammaglobulinemia

Key: CRS, cytokine release syndrome; HRGs, healthcare resource group; ICU, intensive care unit; IVIG, intravenous immunoglobulin treatment

Costs – One time costs for BSC

BSC	Cost	Assumption
Drug acquisition	Month1: £1,415 Month 2: £1,415 Month 3: £1,264 Month 4: £781	Blended comparator is applied for BSC, comprised of four different regimes Equal efficacy is assumed for all comparator regimens Equal distribution is assumed for each regimen Drug costs calculated based on optimal vile usage, BSA and wastage is assumed.
Drug administration	£5,063	Cost per patient for the administration of BSC assumed a non-elective stay in hospital for 10.4 days
Subsequent stem cell transplant	£75,385	Weighted average of allogeneic SCT HRGs taken from NHS National Schedule of Reference Costs and follow up costs (applied for [redacted] of patients)
Adverse events	-	No adverse events are assumed in BSC

Key: BSC; best supportive care; BSA, body surface area; HRGs, healthcare resource groups; SCT, stem cell transplant

Costs - progression-free (PFS) and post-progression (PPS) health states

Resource	PFS	PPS	Source
Professional and social services	£407	£607.89	Includes: residential care, day care, home care and hospice
Healthcare professionals	£571	£1,256	Includes: oncologist, haematologist, radiologist, nurse, palliative care team, specialist nurse, GP, district nurse and CT scans
Treatment follow up	£30	£9	Includes: Full blood count, liver function, renal function, immunoglobulin and calcium phosphate tests No monitoring costs are assumed in the PFS state from month 24 for axi-cel
Hospitalisation	£160	£134	Includes: Inpatient days, haematologist visits, radiologists visits, specialist nurse visits, nurse visits, oncologist visits and GP visits
Total per cycle cost	**£1,168**	**£2,006**	

ERG's comments – costs and HRQoL

Long term survivors	• Uncertainty around the timing at which patients revert to aged-matched costs and utilities of the general population
Axi-cel administration costs	• Uncertainty in the assumptions around the costs of training, storage and ambulatory care • In response to the technical engagement, company provided additional scenario analyses on infrastructure and training costs
Costs of AEs for axi-cel	• Including grade 3-4 AEs costs within the costs of hospitalisation and administration of axi-cel was reasonable • **Error:** the unit costs for critical care represented a cost per diem instead of the average ICU hospitalisation period (4 days) • Costs for managing B-cell aplasia (incl. IVIG) and CRS (incl. tocilizimab) were added after clarification
BSC administration costs	• The blended comparator does not account the proportion of patients receiving regimens with rituximab in clinical practice • Company assumed BSC would be administered in an inpatient setting but possible to provided most in outpatient settings
Modelling of SCT	• Cost of SCT required recalculation to discount follow-up costs • Company assumed all patients received allogenic transplants • Potential negative impact of Allo SCT on HRQoL not captured

Summary of company's base case model

	Assumptions and adjustments
Clinical comparison	• Adjusted SCHOLAR-1 cohort removes patients with a baseline ECOG score of 2–4
Extrapolation	• Mixture cure model for OS axi-cel – 50% cure fraction follow general population health from time of infusion • PFS axi-cel and OS BSC: single parametric curve • PFS BSC estimated using ratio of axi-cel OS-PFS
HRQoL	• Utility values derived from ZUMA-1 trial and literature review • Disutilities associated with AEs applied to axi-cel only • General population utilities applied at 24m to patients in pre-progression state
Costs	• Blended comparator used for BSC in a 1:1:1:1 ratio • No costs applied after 2 years in progression-free health state • Treatment costs for AEs include only IVIG and CRS treatment • Undiscounted stem cell transplant long-term costs • All stem cell transplants assumed allogeneic • Training costs for one healthcare professional

Key: AEs, adverse events; BSC, best supportive care; CRS, cytokine release syndrome; HRQoL, health related quality of life; OS; overall survival; PFS, progression-free survival

Company's revised base case results (amended after clarification)

	Total			Incremental				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	ICER range
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**>£50,000**

Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

- Company's base case amended at clarification:
  - Costs for cytokine inhibitors (tocilizumab) applied for [redacted] of patients (ZUMA-1)
  - Costs of IVIG acquisition and administration applied for [redacted] patients who experienced hypogammaglobulinemia (ZUMA-1)

* Data on the on the proportion of patients requiring IVIG treatment was provided after clarification. The company provided scenario analyses on the duration of treatment in response to clarification after the technical engagement

Company's additional analyses

- In **one way sensitivity analyses** the most influential parameters were:
  - The cure fraction used in the mixture cure model of axi-cel OS
  - The constant coefficient for axi-cel PFS (lowering the constant of axi-cel PFS increases the time spent in pre-progression state)
  - BSC OS (lowering the value of the constant for BSC increases survival in the comparator arm)
- In **probabilistic analyses**:
  - The mean ICER was [redacted] per QALY, a difference from the deterministic ICER of 2%
  - The probability of axi-cel being the most cost effective treatment is 0.43% for a willingness-to-pay (WTP) threshold of £50,000.
- The company explored a number of **scenario analyses**:
  - ICERs ranged between [redacted] (all patients progressed in BSC arm) to [redacted] (gamma distribution for axi-cel PFS)
  - Key drivers were: time horizon, discount rate, PFS for BSC, PFS for axi-cel and OS for BSC

Company's scenario analyses – excluding patients who received SCT

	Total			Incremental				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	ICER range
Scenario 1: excludes patients with subsequent ASCT from SCHOLAR-1 cohort								
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**>£50,000**
Scenario 2: excludes patients with known ECOG status 2-4 and subsequent ASCT								
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**>£50,000**

Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

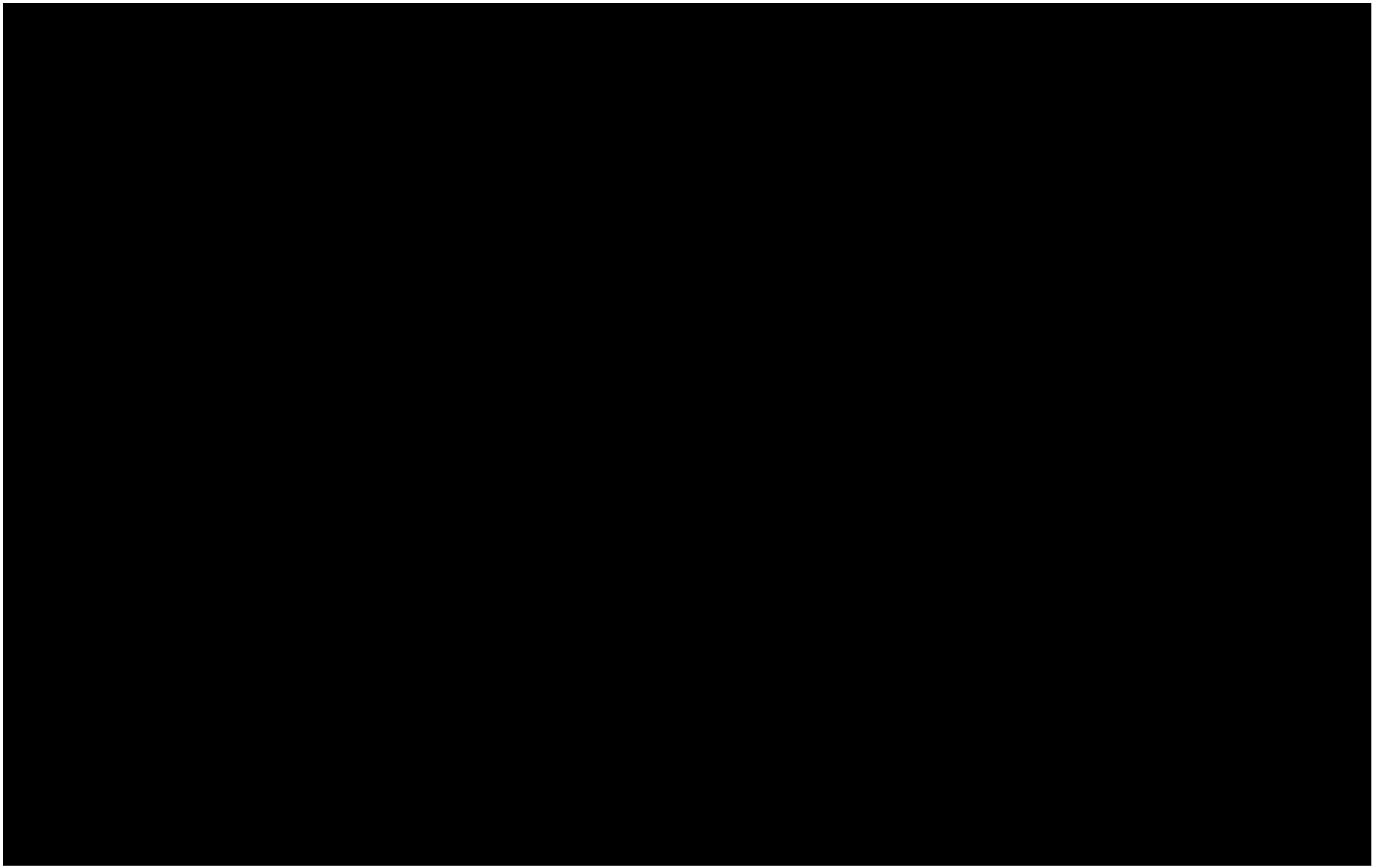
- Excluding SCT patients increases the incremental cost and increases the QALY gain which results in a lower ICER compared to the base case

Summary of ERG's preferred assumptions

	Assumptions and adjustments
Clinical comparison	• Adjusted SCHOLAR-1 data includes only patients with a known ECOG score of 0-1
Extrapolation	• Hybrid model for OS axi-cel, loglogistic single parametric curve constrained by the PFS curve – 40% cure fraction • BSC OS uses a single parametric curve • PFS BSC estimated using ratio of axi-cel OS-PFS
HRQoL	• Those in the pre-progression state assume general population utility & costs at 52m (convergence of axi-cel OS and PFS curves) • mITT population does not account for QALYs in those w/o axi-cel, consider use of ITT population
Costs	• CRS management occurs for 4 days • Discounted SCT long-term costs • BSC patients who received SCT all receive autologous SCT • Scenarios for training costs of 5-10 healthcare professionals

Key: AEs, adverse events; BC, base case; BSC, best supportive care; CRS, cytokine release syndrome; HRQoL, health related quality of life; ITT, intention to treat, OS; overall survival; PFS, progression-free survival; SCT, stem cell transplant

Use of ITT vs mITT population (1)



Use of ITT vs mITT population (2)

ERG's comments:

- The company's rationale for using the mITT population (patients who received axi-cel are compared to patients who received BSC) is reasonable
- Costs of conditioning chemotherapies and leukopheresis for patients unable to receive axi-cel are included but QALYs are not considered

Technical engagement responses:

- Time to treatment initiation is likely to be markedly lengthened for CAR T compared to conventional chemotherapy

ITT scenario was provided by the company in response to clarification
• [redacted] patients who did not receive axi-cel due to death and [redacted] due to AE a one off QALY (0.19) and a one off cost for post-progression monitoring was applied
• [redacted] patients who did not receive axi-cel due to disease progression the discounted QALY and costs from BSC were applied
• For the mITT group progression-free utility was applied from time from leukapheresis to axi-cel treatment (17 days)
• Total costs and QALYs calculated using a weighted average of the 3 populations

Questions for committee:

- Does the base case (mITT) population consider clinical and economic outcomes for patients who did not receive axi-cel appropriately?

ERG's preferred base case

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	ICER range
Company base case						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**> £50,000**
ERG's base case (mITT population)						
BSC	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**> £100,000**

ERG's assumptions:

- BSC OS based on ECOG 0-1 in SCHOLAR-1
- Alternative axi-cel OS extrapolation assumptions
- Alternative structural cure assumptions
- CRS management occurring for 4 days
- Discounted SCT long-term costs
- BSC patients who received SCT are assumed to have all undergone ASCT

Updated after factual accuracy check to include costs for [redacted] of BSC patients who received subsequent SCT

Breakdown of ERG's preferred base case

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	ICER range
BSC OS based on ECOG 0-1 SCHOLAR-1 subgroup						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**> £50,000**
ERG's alternative axi-cel OS extrapolation assumptions						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**> £50,000**
Combining ERG's alternative axi-cel and BSC OS extrapolation assumptions						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**> £100,000**
Combining ERG's alternative OS extrapolation assumptions and 52m cure assumption						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**> £100,000**
ERG's alternative survival and cure assumptions with ZUMA-1 ITT population						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**> £100,000**

Breakdown of the ERG's preferred base case

	ICER range
BSC OS based on ECOG 0-1 SCHOLAR-1 subgroup	
Excluding patients with unknown ECOG score increases the QALY gains in the BSC arm resulting in a higher ICER	**> £50,000**
ERG's alternative axi-cel OS extrapolation assumptions	
ERG's hybrid model reduces the QALY gains in the axi-cel arm increasing the ICER compared to the company's base case	**> £50,000**
Combining ERG's alternative axi-cel and BSC OS extrapolation assumptions	
Combining the ERG's preferred OS extrapolations reduces the incremental QALY gains and incremental costs increasing the ICER	**> £100,000**
Combining ERG's alternative OS extrapolation assumptions and 52m cure assumption	
Increasing the time patients are required to remain in the pre-progression state before being considered cured reduces the incremental QALY gains and increases the ICER	**> £100,000**
ERG's alternative survival and cure assumptions with ZUMA-1 ITT population	
Combining all of the ERG's preferred survival assumptions and incorporating QALYs from patients who did not receive axi-cel reduces QALY gains in the axi-cel arm and increases the ICER	**> £100,000**

ERG's additional scenario analyses:

	Company's base-case	Incremental costs	ICER (£/QALY)	ICER range
Company's revised base-case		[redacted]	[redacted]	**> £50,000**
CRS management: [redacted] days ICU	CRS management: 1 day ICU stay	[redacted]	[redacted]	**> £50,000**
CRS management: [redacted] days ICU		[redacted]	[redacted]	**> £50,000**
Discounted SCT long-term costs	Undiscounted SCT costs assumed allogeneic	[redacted]	[redacted]	**> £50,000**
Discounted SCT costs BSC SCT assumed autologous		[redacted]	[redacted]	**> £50,000**
BSC administered in outpatient setting	Inpatient setting	[redacted]	[redacted]	**> £50,000**
Blended comparator 50:50 of 2 rituximab	Blended comparator equal ratio 4 regimes	[redacted]	[redacted]	**> £50,000**
Blended comparator 50:50 of non-rituximab		[redacted]	[redacted]	**> £50,000**
Training for 5 healthcare professionals	Training costs for one healthcare professional	[redacted]	[redacted]	**> £50,000**
Training for 10 healthcare professionals		[redacted]	[redacted]	**> £50,000**

End of life

Criterion	Company	ERG
Short life expectancy: The treatment is indicated for people with a short life expectancy, normally less than 24 months	Yes • Canadian database study in R/R DLBCL patients ineligible for ASCT median OS 3.9m • SCHOLAR-1 study of SoC median OS: 6.3 months	Maybe • Median OS from SCHOLAR-1 lies between 5m-6.6m, but dependent on adjustment to SCHOLAR-1 data. ERG noted the mean survival from the model for BSC ([redacted] Company, [redacted] ERG)
Extension to life: There is sufficient evidence to indicate that the treatment offers an extension to life, (normally >3 months) compared with current treatment	Yes • Median OS for axi-cel in the ZUMA-1 study was not reached; lower 95% CI was 12.0m with an 18m OS rate of 52%. If current survival trends continue, improvement would be >5.7m	Yes • Submitted evidence shows OS will be greatly extended • However, the evidence submitted does not have appropriately long term follow-up to support the company's cure claim

Innovation and equality

Innovation

- Company considers axi-cel to be innovative because as the first CAR T-cell therapy it provides a complete personalised immunotherapy to a population for whom there is a poor prognosis, significant unmet need and limited treatment options.
- Axi-cel is given as a single infusion and single treatment rather than the recurrent cycles of traditional chemotherapy
- Clinical experts note that CAR T-cell therapy is a potential game changer. Axi-cel would be a step-change in management of patients with R/R disease if the preliminary results are substantiated

Equality

- Company note a potential age effect where axi-cel is a more suitable alternative for older men due to the epidemiology of the disease and likely treatment outcomes higher up the pathway
- ERG note that results are consistent by age and gender but the company fail to address high priority issues such as equality of delivery and access to treatment
- NHS England note that due to the novelty of the treatment, the expertise required and the logistics involved, there is a need for a phased implementation period. Access at the start will be worse than current access to chemotherapy/HSCT

Discount rate

Discount	Incremental costs	Incremental QALYs	Company's ICER	ICER threshold	% change from base-case ICER
1.5%	[redacted]	[redacted]	[redacted]	**> £50,000**	-22%

NICE methods guide	Company	ERG
• The reference case should use a discount rate of 3.5% for both costs and benefits. • Differential discounting should be applied where treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years)	• Axi-cel can provide long-term survival (model estimates a mean undiscounted OS of >10 years) • Total acquisition cost is incurred within the first model cycle	Criteria for applying a 1.5% discount rate were not met • Evidence submitted is not sufficiently mature to robustly demonstrate cure • The ERG notes the duration of health benefits is driven by a highly uncertain extrapolation of survival estimates

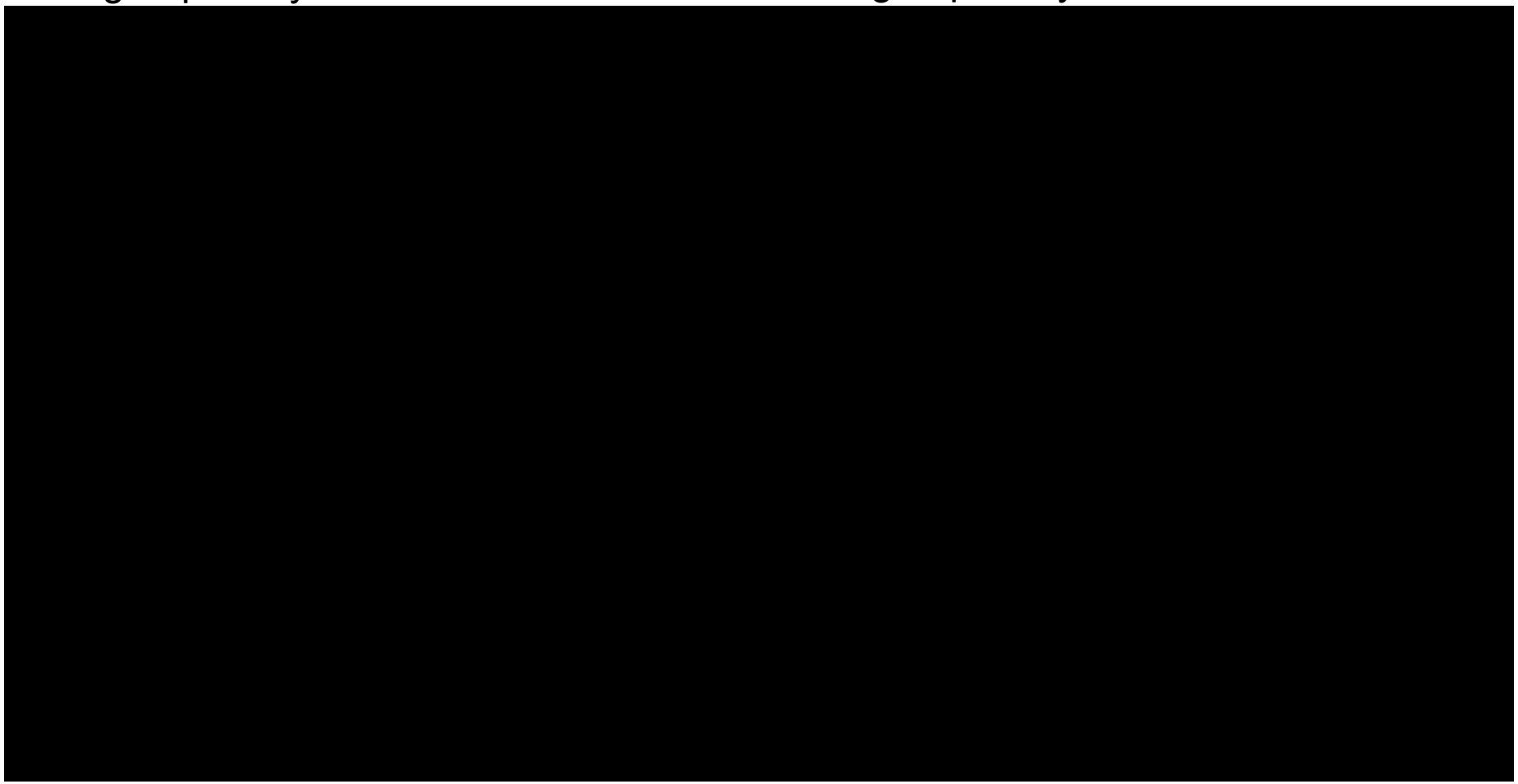
Key issues – cost effectiveness

- ZUMA-1 has median follow up of 15.4 months resulting in high levels of censoring around 12 months and uncertainty in OS and PFS results beyond this time point. What extrapolation is appropriate for axi-cel OS, taking into consideration the potential for long-term survivors and cure?
- What extrapolation should be applied to mature BSC OS data?
- What assumptions should be made to account for the lack of PFS data in SCHOLAR-1?
- Do the assumptions around long term survivors HRQoL reflect clinical practice?
- What is the most appropriate way to include post-treatment SCT in the model?
- How should broader infrastructure and training requirements be incorporated into the model?
- Are QALYs from the group who did not receive axi-cel considered appropriately in the base case, is the ITT or mITT the most appropriate population to model?
- End-of-life considerations and the appropriate discount rate

ZUMA-1 subgroup results

Sub-group analysis of ORR in ZUMA-1

Sub-group analysis of PFS at 6-months



Results were consistent across subsets defined by age, sex, disease type (DLBCL, PMBCL, or TFL), disease stage, ECOG and IPI risk score, refractory subgroup, number of prior chemotherapies, tumour burden, and use of steroids or tocilizumab.