NICE National Institute for Health and Care Excellence

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

Chair's presentation

2nd appraisal committee meeting

Committee C

Lead team: Nigel Langford, Judith Wardle and Mike Chambers

ERG: CRD and CHE Technology Assessment Group, University of York

NICE technical team: Lorna Dunning, Nicola Hay

Company: Kite/Gilead

27th September 2018

Key issues

- Alternative comparator data
- Appropriate incorporation of stem cell transplants:
  - in the comparator dataset (10% or 12.5% SCT)
  - in the cost-effectiveness modelling (auto vs allo)
- **Extrapolation of overall survival**
  - **axicabtagene ciloleucel**
  - **salvage chemotherapy**
- Mortality risks for long term survivors
- Effect of retreatment with axi-cel on overall survival
- **End of Life**
- **The most plausible ICER**
- CDF / data collection

[redacted]

Axicabtagene ciloleucel (Kite/Gilead)

Marketing authorisation	Marketing authorisation granted by EMA September 2018: for 'the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more lines of systemic therapy.'
Administration & dose	• Patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) • Each patient specific single infusion bag contains a dispersion of anti-CD19 CAR-T cells in approximately 68 mL for a target dose of 2 x 106 anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 x 106 – 2 x 106 cells/kg), with a maximum of 2 x 108 anti-CD19 CAR T cells
Mechanism of action	A chimeric antigen receptor (CAR) T-cell therapy that uses autologous T-cells engineered to express a novel surface receptor directed against the tumour antigen CD19
List price & Simple discount agreement	[redacted] per 68 ml single infusion bag Approved commercial arrangement (commercial in confidence)

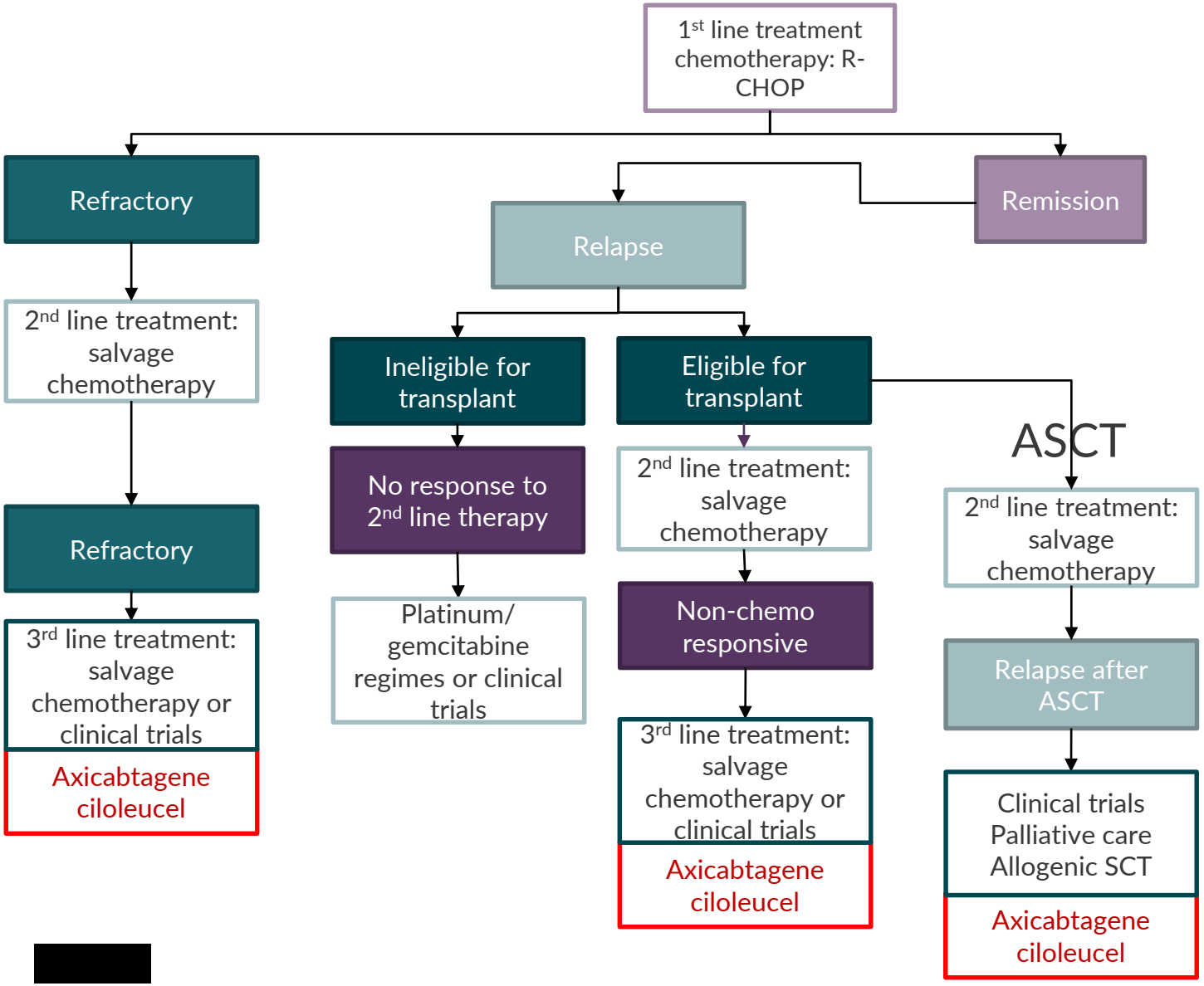
[redacted]

ACD Preliminary Recommendation

Axicabtagene ciloleucel is not recommended, within its anticipated marketing authorisation, for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies.

[redacted]

ACD: Treatment pathway and comparator treatments



ACD conclusions:
Axicabtagene ciloleucel could be used in 3 possible positions in the treatment pathway [3.3-3.6]

Axicabtagene ciloleucel would be used as an alternative to salvage chemotherapy (excluding pixantrone) [3.7]

ACD: Comparative effectiveness results

- **ZUMA-1** (axi-cel) single-arm study of 119 adults who had ECOG performance status of 0 or 1
- **SCHOLAR-1** (salvage chemotherapy) patient level historical control study from 4 sources

	ZUMA-1	SCHOLAR-1	Outcome
Unadjusted comparison			
ORR (%)	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]
Base case: Standardised by ECOG status (excluded patients with ECOG 2-4)			
ORR (%)	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]
Scenario 1: Standardised by ECOG status and subsequent ASCT			
ORR (%)	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]
Scenario 2: Standardised by ECOG status (only patients with known ECOG 0-1)			
ORR (%)	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]

*Stratified Cox model. Abbreviations: NE, not evaluable; OR, odds ratio; ORR, overall response rate; OS, overall survival

ACD conclusions:
Axicabtagene ciloleucel is clinically effective [3.8]

The adjustments to the SCHOLAR-1 dataset do not adequately account for the differences between the study populations of ZUMA-1 and SCHOLAR-1 [3.12]

[redacted]

ACD: Comparative effectiveness results

[redacted]

ACD conclusion:
The lack of appropriate comparator data means the size of the benefit compared with salvage chemotherapy is unknown [3.11]

Alternative comparator data is needed to better assess the clinical effectiveness of axicabtagene ciloleucel [3.13]

[redacted]

ACD: Base case assumptions and adjustments

	Company	ERG
Clinical	• Adjusted SCHOLAR-1, removes patients with baseline ECOG score of 2–4	• Adjusted SCHOLAR-1 data includes only patients with known ECOG score of 0-1
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	• 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 as in company's base case
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	• Utilities and disutilities as in company's base case • Those in the pre-progression state assume general population utility & costs at 52m (convergence of axi-cel OS and PFS curves)
Costs	• No costs applied after 2 years in progression-free health state • Treatment costs for AEs include only IVIG and CRS treatment • Undiscounted SCT long-term costs • All SCT assumed allogeneic • Training costs for one healthcare professional	• 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; BSC, best supportive care; CRS, cytokine release syndrome; HRQoL, health related quality of life; OS; overall survival; PFS, progression-free survival; SCT, stem cell transplant

ACD: Cost-effectiveness modelling assumptions

Issue	Committee consideration
Overall survival extrapolation for axicabtagene ciloleucel	• The company's extrapolation using a mixture cure model was likely to overestimate the size of the cure fraction, which was a major driver of the cost-effectiveness estimates • ERG's hybrid approach could be a conservative extrapolation of OS • The overall survival gain for axicabtagene ciloleucel was between the company's and ERG's estimates [3.17]
Retreatment with axicabtagene ciloleucel	• Retreatment with axicabtagene ciloleucel adds uncertainty to the long-term survival estimates [3.18]
Mortality risk for long-term survivors	• The assumption of no excess mortality risk for long term survivors was not appropriate [3.19]
Overall survival extrapolation for salvage chemotherapy	• The data for salvage chemotherapy came from SCHOLAR-1 which was not representative of the population eligible for axicabtagene ciloleucel. The progression-free and overall survival benefits for best supportive care were therefore unknown [3.20]
Costs of AEs and resource use	• The ERGs approach to calculating costs of administration for salvage chemotherapy, AEs and SCTs was preferred but SCTs should be allogeneic [3.21]

[redacted]

ACD: Cost effectiveness results

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	ICER range
Company's 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**

ACD conclusion:
There was a wide range between the company's and ERG's base-case ICERs and both had high degree of uncertainty because of:

- limitations in the data for the comparator
- immature survival data for axicabtagene ciloleucel

Concluded no 'most plausible' ICER for axicabtagene ciloleucel
Estimate likely to be higher than £50,000/QALY gained [3.23]

[redacted]

ACD: Other considerations

Issue	Committee consideration
Adverse events	• Axicabtagene ciloleucel is associated with a high rate of events • The need for intravenous immunoglobulins treatment after axicabtagene ciloleucel is unknown [3.14]
End of life	• Axicabtagene ciloleucel meets criterion for extension to life: – axicabtagene ciloleucel meets criterion for extension to life - in both the company's and ERG's modelling axicabtagene ciloleucel was associated with a gain in overall survival of over 3 months – The committee acknowledged that axicabtagene ciloleucel did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply - median survival in the comparator data was 6.6 months, but the company's modelling predicted a mean overall survival of more than 24 months. The committee also considered clinical expert opinion [3.26]
Innovation	• Axicabtagene ciloleucel is innovative but there are no benefits not captured in the analysis [3.24]
Equalities	• There were no equality issues relevant to the recommendations [3.27]
Discount rate	• A discount rate of 3.5% should be used for both costs and benefits [3.25]

[redacted]

ACD: Consultation responses

- Consultee comments from:
  - Kite/Gilead (company)
  - Bloodwise
  - Lymphoma Action
- Other:
  - NHS England
- No comment response from:
  - Department of Health and Social Care
- No web comments submitted

[redacted]

Unmet need for new treatments

Consultee comments

- There is urgent need for new treatment options. Patients who would be eligible for axicabtagene ciloleucel currently have no curative treatment options (all)
- The lack of treatment options puts strain on patients and carers (Bloodwise)
- Axicabtagene ciloleucel is innovative and represents a step-change in the management of people with relapsed or refractory disease (NHSE)
  - "*the transformative impact of CAR-T… should therefore be given further consideration by the committee*" (Bloodwise)

[redacted]

Comparator data

Consultee comments

- Policy query on chemotherapy as a comparator (Lymphoma Action)
- The lack of direct comparative data with salvage chemotherapy poses challenges for the committee to establish the true cost-effectiveness of axicabtagene ciloleucel
  - "*However, it is clear* [axicabtagene ciloleucel] *is significantly more clinically effective than chemotherapy and we hope that the manufacturer will be able to provide further evidence to demonstrate this*" (Bloodwise)

Company's comments:

- We do not agree that the lack of comparator data means the size of the benefit compared with salvage chemotherapy is unknown
- The SCHOLAR-1 dataset provides a robust and relevant historic comparison
- To address committee's comments adjustments to the SCHOLAR-1 dataset and two additional data sources are presented (Kite/Gilead)

[redacted]

Cancer Drugs Fund

Consultee comments

- Given the challenge of establishing the degree of clinical effectiveness, a recommendation in the Cancer Drugs Fund (CDF) would be a more appropriate decision for axicabtagene ciloleucel (Bloodwise)
- "*While promising patients great clinical benefits, axicabtagene ciloleucel is an ideal candidate for the Cancer Drugs Funds (CDF) due to the uncertainty around longer term clinical outcomes*" (NHSE)
- A recommendation for the Cancer Drugs Fund would offer more time for clinical trial data to mature during a CDF managed access period and real world data could be collected as an additional source of data (NHS England)

Company's comments:

- Kite/Gilead have made a formal application to the Cancer Drugs Fund

[redacted]

Company's comments: other

- Does not agree with the committee's view that the need for **intravenous immunoglobulins treatment** after axi-cel is unknown
  – intravenous immunoglobulins (IVIG) were rarely used in ZUMA-1 (8.3%)
  – are not expected to be required over a prolonged period of time
- Believes its approach to the **extrapolating overall survival for patients receiving axi-cel** is the most plausible and will be supported by the extended follow-up data from ZUMA-1. Believes the approach used by the ERG was not appropriate
- Agrees axi-cel meets NICE's criteria to be considered a life-extending treatment at the **end of life**, and provides further supporting data from additional sources

[redacted]

Company's new evidence

- In response to the ACD, company have:
  - Revised the SCHOLAR-1 dataset for comparative effectiveness results
  - Provided alterative data sources to validate the best supportive care (salvage chemotherapy) overall survival
    - Oxford audit dataset
    - Subset of CORAL (preferred in the on-going appraisal of Tisagenlecleucel-T for DLBCL [ID1166])
  - Updated the base case to include the committees preferred assumptions around costs of administration for salvage chemotherapy, ICU costs and stem cell transplants costs
  - Provided [redacted]
  - Cancer Drugs Fund proposal

[redacted]

Committee preferences and company's revised analyses

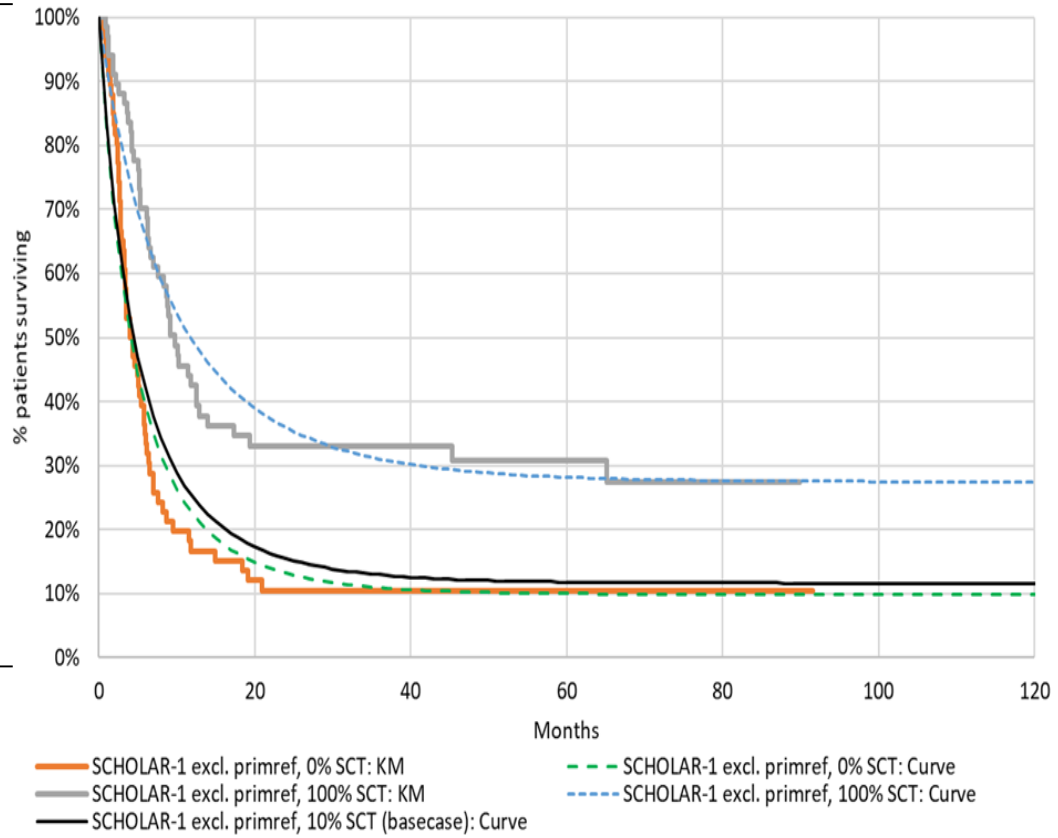
Committee preference:		Did company include?
1	Adjusted original comparator data (SCHOLAR-1) for proportion of patients receiving stem cell transplants to more closely match the eligible population in the UK	✓
2	Provided alternative comparator data source I.e. • ORCHARRD subgroups • Haematological Malignancy Research Network	✓ (x) (x)
3	Survival curves adjusted for re-treatment with axi-cel	x
4	Assumed long term survivors have greater than general population mortality	✓
5	Include costs of outpatient administration of salvage chemotherapy, discounted stem cell transplant costs and additional time spent in ICU by patients in ZUMA-1	✓

[redacted]

Company's revised approach to SCHOLAR-1

- Primary refractory and patients with ECOG 2-4 or unknown ECOG status were excluded
- N=133 patients, 67 (50.4%) underwent Stem cell transplants (SCT)
- Plotted KM curves for patients who did and did not receive SCT
- Weighted average of overall survival (OS) obtained to represent OS for a specified proportion of patients receiving SCT

Overall survival of BSC: SCHOLAR-1 (ECOG 0-1 only and excluding primary refractory) with 10% SCT



	100% SCT	10% SCT	0% SCT
6 months	70.1%	41.9%	34.8%
12 months	42.5%	25.2%	16.7%
18 months	34.6%	18.6%	15.2%
24 months	33.0%	15.5%	10.4%
60 months	30.8%	11.8%	10.4%
80 months	27.3%	11.6%	10.4%

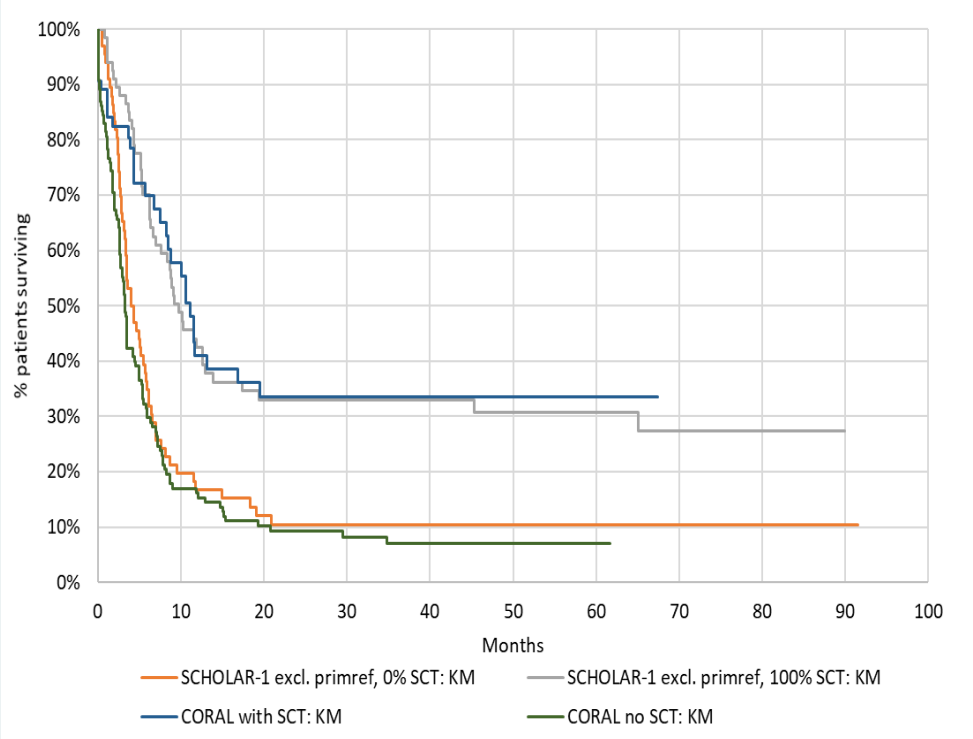
Overall survival at different time points for different SCHOLAR-1 scenarios

☐ suggested base case

Additional comparator data: CORAL extension study and Oxford audit

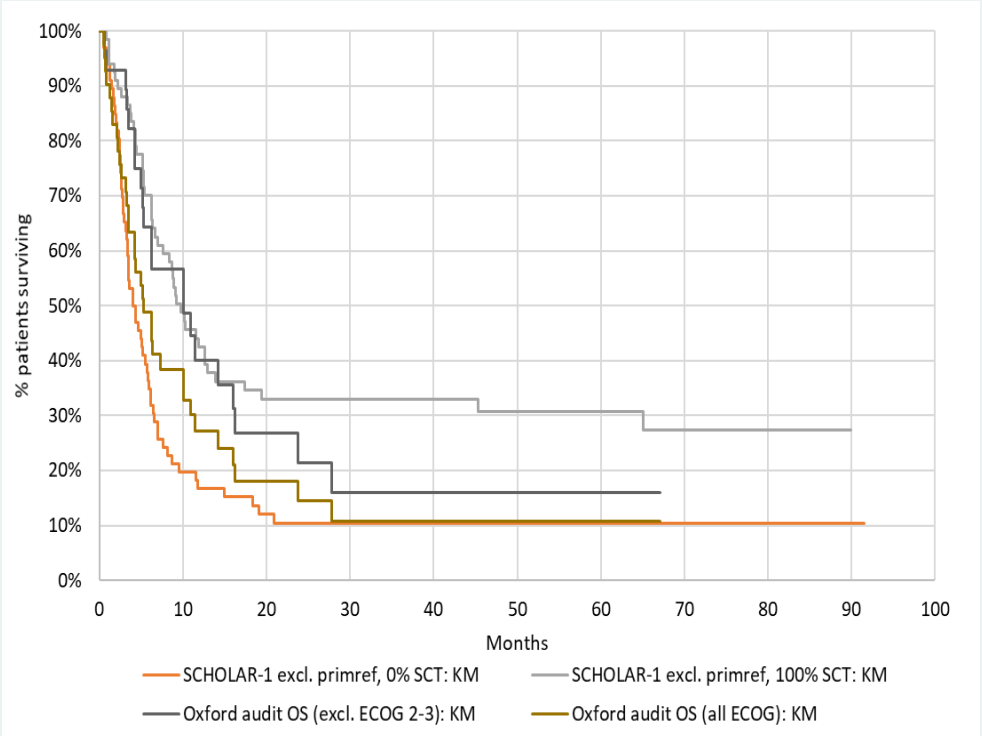
CORAL subpopulation – includes 203 patients who have received 2 or 3 prior therapies. Preferred in the ongoing appraisal [ID1166] Data based on published literature

Overall survival of SCHOLAR-1 vs CORAL



Oxford audit includes 41 UK patients with relapsed or refractory DLBCL, PMBCL and TFL who were ineligible for autologous SCT

Overall survival of SCHOLAR-1 vs Oxford audit dataset



[redacted]

Is the adjusted SCHOLAR-1 data a suitable comparator dataset?

Additional comparator data: Baseline characteristics

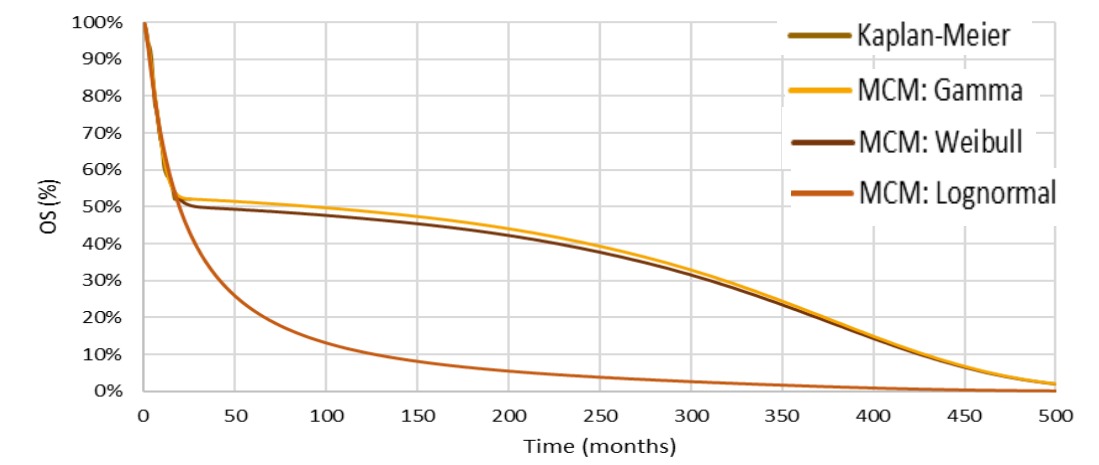
Characteristic	ZUMA-1 mITT (n=108)	SCHOLAR-1		Oxford audit		CORAL (n=203)
		All patients (n=593)	ECOG 0-1 (n=188)	All (n=41)	ECOG 0-1 (n=28)	
Age, n (%)						
<65 years	81 (75)	509 (86)	181 (96)	[redacted]	[redacted]	203 (100)
≥65 years	27 (25)	84 (14)	7 (4)	[redacted]	[redacted]	0 (0)
IPI score, n (%)						
0-1	27 (25)	69 (12)	69 (37)	[redacted]	[redacted]	35 (30)
2	33 (31)	61 (10)	54 (29)	[redacted]	[redacted]	60 (52)*
≥3	48 (44)	80 (13)	54 (29)	[redacted]	[redacted]	
Not assessed	N/A	383 (65)	11 (6)	[redacted]	[redacted]	[≥4] 20 (17)
Disease stage, n (%)						
I-II	18 (17)	69 (12)	62 (33)	[redacted]	[redacted]	NR
III-IV	90 (83)	149 (25)	119 (63)	[redacted]	[redacted]	NR
Not assessed/other	N/A	375 (63)	7 (4)	[redacted]	[redacted]	NR
Previous chemotherapy and ASCT received, n (%)						
1	2 (2)	89 (15)	44 (23)	[redacted]	[redacted]	0 (0)
2-3	65 (60)	464 (78)	143 (76)	[redacted]	[redacted]	203 (100)
≥4	35 (33)	37 (7)	1 (1)	[redacted]	[redacted]	0 (0)

OS extrapolations: axicabtagene ciloleucel

Company: used a mixture cure model (MCM) with 50% cure fraction (Weibull) and a separate cure assumption at 24m which reverts long term survivors to general population mortality

In response to the ACD, stated: [redacted]

Company's extrapolation of OS using MCM model



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

[redacted]

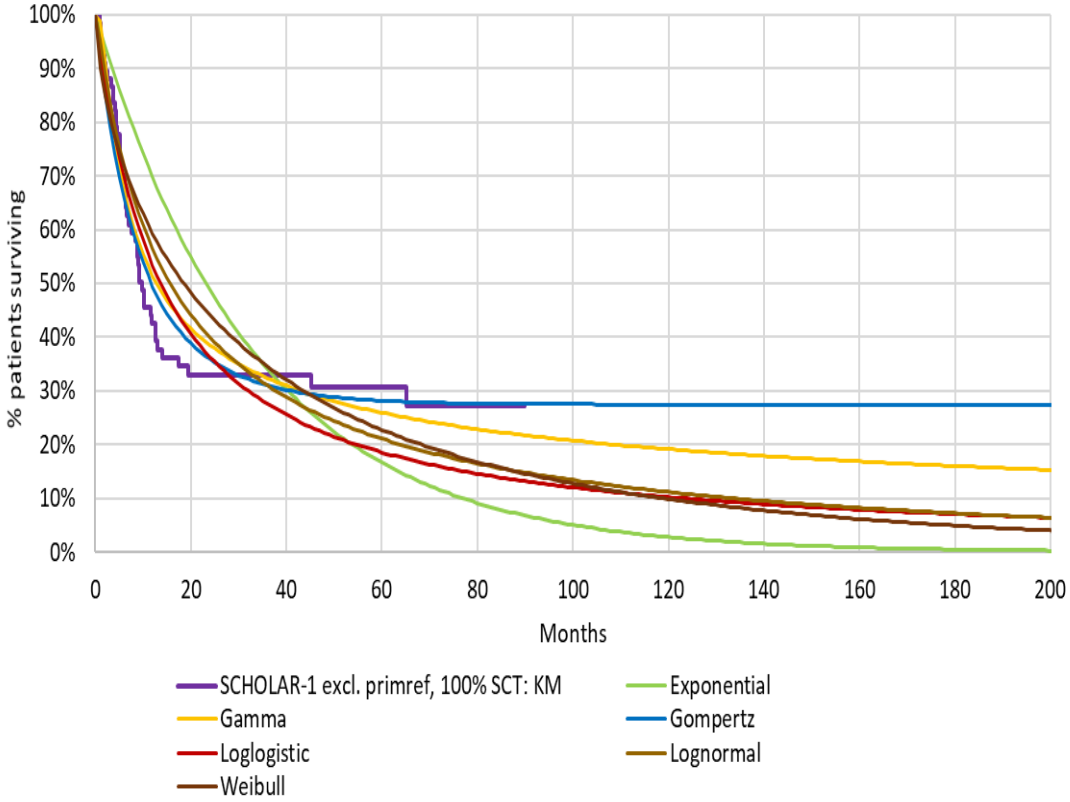
The company have proposed that axicabtagene ciloleucel would be suitable for inclusion in the CDF

The company also provide a scenario analysis to address the uncertainty of **excess mortality for long-term survivors**.

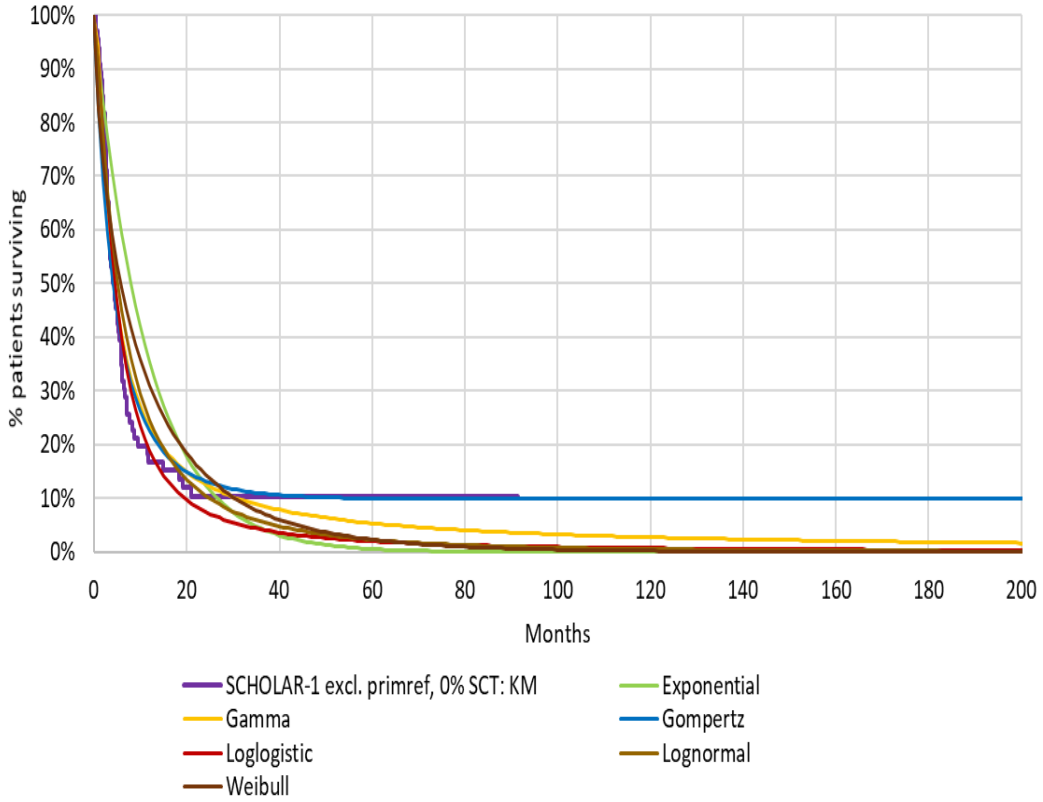
A **standard mortality ratio** (SMR) of 1.09 was used for alive patients after 60 months (see cost- effectiveness results)

OS extrapolations: best supportive care

Overall survival of BSC: adjusted SCHOLAR-1 with **100% SCT**, KM and fitted curves



Overall survival of BSC: adjusted SCHOLAR-1 with **0% SCT**, KM and fitted curves

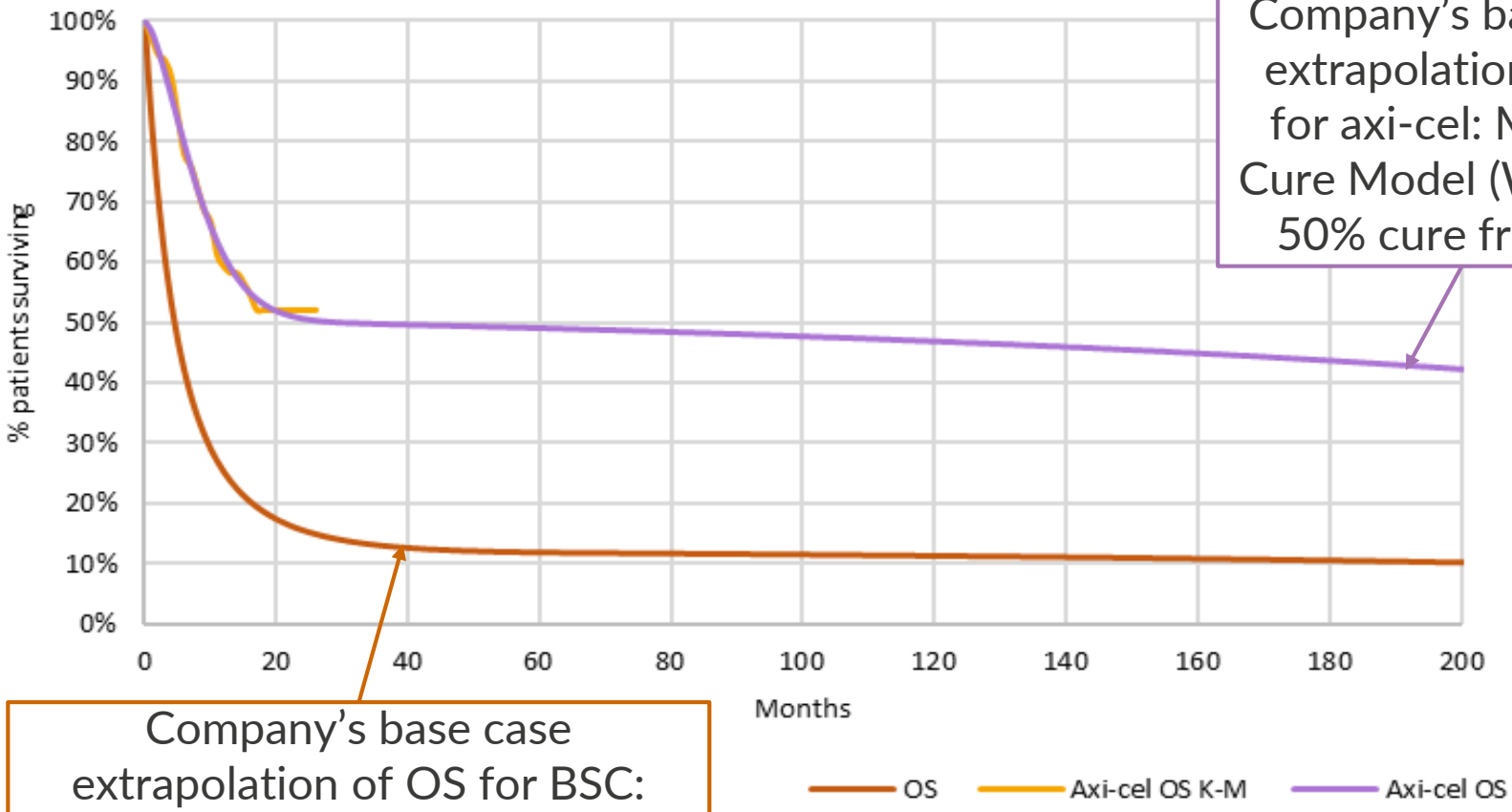


- Company stated that the **Gompertz** curves were used because visually they appear to best fit the observed data and represent the plateau of OS data
- Gompertz is also the most conservative choice of curve selection for BSC OS as it provides the best OS extrapolation

[redacted]

Clinical effectiveness of axicabtagene ciloleucel using new comparator data

Comparative OS of axi-cel and BSC (SCHOLAR-1, ECOG 0-1 only and excluding primary refractory with 10% SCT)



Company's base case extrapolation of OS for axi-cel: Mixture Cure Model (Weibull - 50% cure fraction)

Company's base case extrapolation of OS for BSC: (SCHOLAR-1, ECOG 0-1 only and excluding 1° refractory with 10% SCT) using Gompertz distribution

[redacted]

Company results & scenario analyses *including proposed Commercial Access Agreement (CDF proposal)*

Company's updated base case:

- SCHOLAR-1 comparative data: ECOG 0-1 only patients and primary refractory patients removed, adjusted OS representing 10% SCT
- BSC OS uses a single parametric curve (Gompertz)
- Axi-cel OS extrapolation using mixture cure model for OS (Weibull)
- Resource used and costs as in the ERG's base case, with the exception of SCT costs - all allogenic

Base case	Δ Costs	Δ QALYs	ICER	ICER range
Company's updated base case	[redacted]	[redacted]	[redacted]	< £50,000
Scenario analyses				
Company's updated base case + standard mortality ratio of 1.09 for patients alive after 60 months	[redacted]	[redacted]	[redacted]	< £50,000
Base case + resource use and costs from ERG base case, but with 50% alloSCT costs	[redacted]	[redacted]	[redacted]	< £50,000

[redacted]

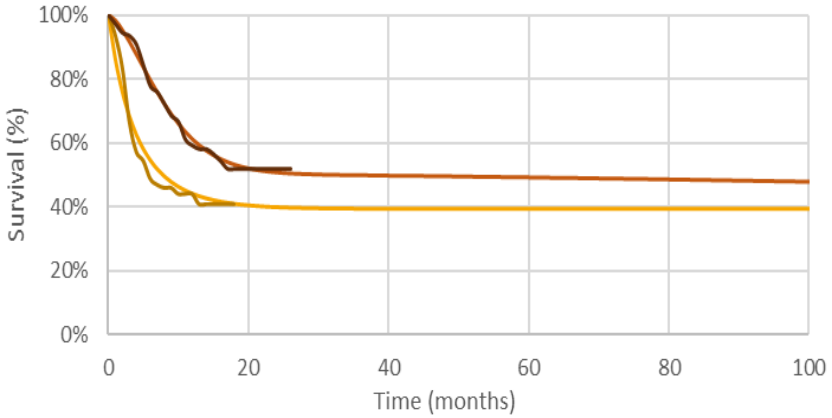
Does the company's updated base case include all committee's preferred assumptions?

ERG critique

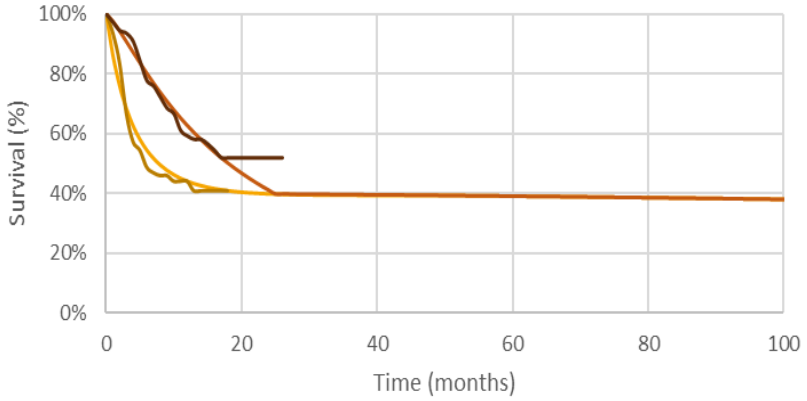
Adjustments to SCHOLAR-1	• The company's approach is consistent with the ERG's approach in the ID1166 appraisal which was found *"appropriate to model salvage chemotherapy"* • The company used a SCT rate of 10% - a rate of 12.5% appears more consistent with the committee's preferences reported in the ACD for ID1166
Validation of OS for BSC	• The ERG agrees with the company - survival predictions are very similar using the separate CORAL and SCHOLAR-1 cohorts • Limited data is provided from the small Oxford RWE dataset which shows different baseline characteristics to SCHOLAR-1 and CORAL
Extrapolation of OS for axi-cel	• The ERG is unable to either confirm or refute the company's findings as the data is confidential • The ERG disagree that their approach should not be considered as there is no evidence to supportive a curative potential of salvage chemotherapy or data to address the potential confounding of retreatment • ERG explores 3 alternative approaches to modelling OS for axi-cel
Resource use cost and IVIG use [redacted]	• Model changes are implemented correctly • The clinical views around SCTs expressed in this appraisal are not consistent with data from the CORAL extension study and so uncertainty remains about the relative use of autologous versus allogeneic transplant • In ID1166, the committee accepted the ERG's assumption that B-cell aplasia may persist for up to 3 years (compared to the company's assumption of 1 year)

Axicabtagene ciloleucel OS extrapolation: ERG's alternative modelling approaches

Company – partitioned survival approach (12.5% SCT)



ERG – alternative base case 'hybrid' approach



[redacted]

PFS OS PFS K-M OS K-M

Alternative analysis

[redacted]

ERG:

- Overall survival data for axi-cel is immature
- No evidence to supportive a curative potential of salvage chemotherapy provided
- No evidence on re-treatment with axi-cel provided
- [redacted]
- No single approach to modelling is 'optimal'
- All should be considered in CE modelling

*[redacted]

ERG base case analyses

- The ERG applied a SCT rate of 12% to the company's base case and compared 3 exploratory approaches for modelling axi-cel:
  - The company's revised base-case approach using partitioned survival modelling
  - Alternative analysis
  - The ERG's alternative 'hybrid' modelling approach

	Δ Costs	Δ QALYs	ICER	ICER range
Company's updated base case	[redacted]	[redacted]	[redacted]	< £50,000
ERG's exploratory analyses with 12.5% SCT for BSC				
Company's updated base case (partitioned survival model) axi-cel	[redacted]	[redacted]	[redacted]	< £50,000
Alternative analysis for axi-cel	[redacted]	[redacted]	[redacted]	> £50,000
ERG's hybrid modelling approach for axi-cel	[redacted]	[redacted]	[redacted]	> £50,000

What is the most plausible/appropriate extrapolation of axi-cel overall survival?

[redacted]

Cost-effectiveness results: ERG's exploratory analyses

		Modelling approach		
Scenario analyses	Effect on incremental costs/QALYs	Company's base case	Alternative analysis	ERG's hybrid model
Company base case	-	**<£50,000**	[redacted]	>£50,000
Auto (87%) vs Allo (13%) SCT	Increasing ASCT reduces the costs in the BSC arm, increasing incremental costs and ICER	**<£50,000**	[redacted]	>£50,000
IVIG use for 3 years instead of 1 year	Increasing time on IVIG increases the costs in the axi-cel arm, increasing incremental costs	**<£50,000**	[redacted]	>£50,000
Company's cure assumption applied at 5 years not 2 years	Increasing the time spent in the pre-progression state before being considered cured reduces the incremental QALY gains and increases the ICER	**<£50,000**	[redacted]	>£50,000
ITT analysis	Incorporating QALYs from patients who did not receive axi-cel reduces QALY gains in the axi-cel arm and increases the ICER	**<£50,000**	[redacted]	>£50,000
Above combined	Combining all of the ERG's preferred assumptions reduces incremental costs but also reduces the incremental QALY gains increasing the ICER	>£50,000	[redacted]	>£50,000

[redacted]

End of life considerations

Committee

- In ACM1 committee considered that axicabtagene ciloleucel meets criterion for extension to life but there is uncertainty about short life expectancy
- The committee acknowledged that axicabtagene ciloleucel did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply
- The committee concluded that axicabtagene ciloleucel met NICE's criteria to be considered a life-extending treatment at the end of life

Company

- Present data from the Oxford and CORAL datasets as further supporting evidence for End Of Life criteria for axi-cel
- Consistent with input by the clinical experts at the appraisal committee all the data sources show that for the vast majority the outcome is dismal
- the median is short and less than 6 months
- 80% or more have died within two years

ERG

- Marked difference between the median and mean OS estimates for BSC
- Driven by the model predictions that a small proportion of patients will experience long term survival with current treatment options
- Undiscounted life year estimates for BSC appear extremely sensitive to the choice of survival function
- The ICER is also sensitive to the survival function for BSC

[redacted]

End of Life: company's supporting evidence

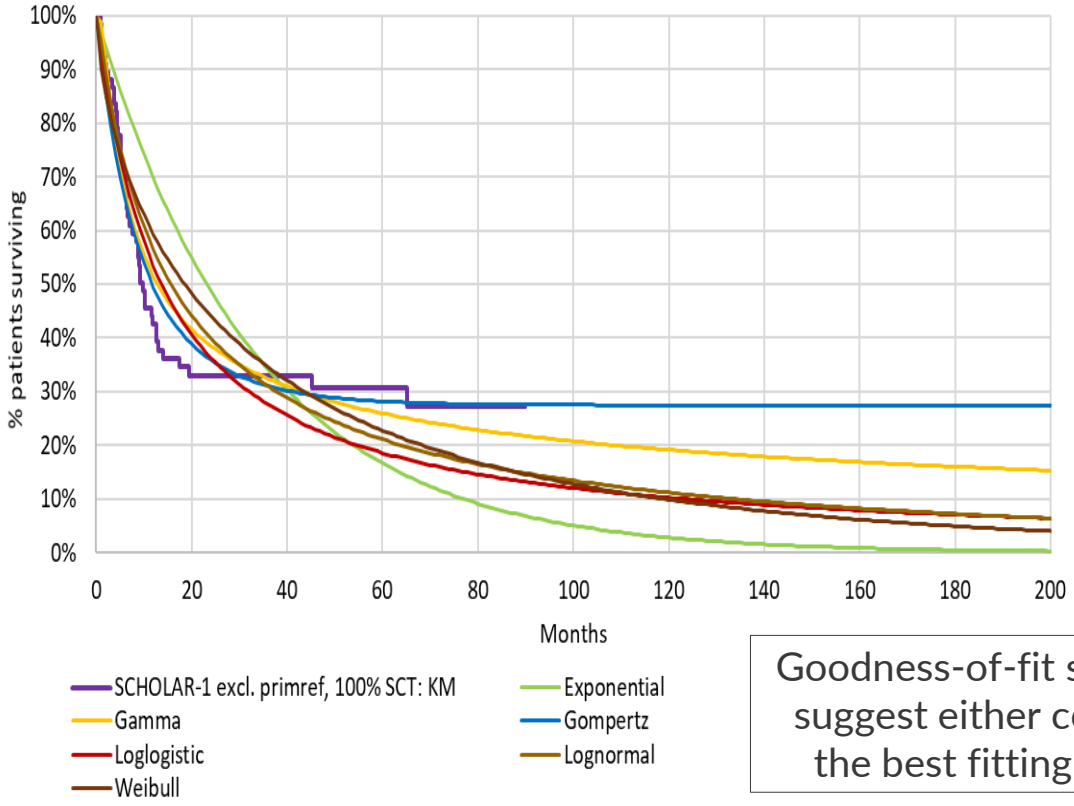
	SCHOLAR-1: 0% SCT	SCHOLAR-1: 100% SCT	CORAL: 0% SCT	CORAL: 100% SCT	Oxford audit (excl. ECOG 2-3)	Oxford audit (all ECOG)
Median OS (m)	4.0	9.7	3.3	11.1	[redacted]	[redacted]
Survival at:						
6 months	34.8%	70.1%	29.8%	69.80%	[redacted]	[redacted]
12 months	16.7%	42.5%	16.2%	40.90%	[redacted]	[redacted]
18 months	15.2%	34.6%	11.1%	36.10%	[redacted]	[redacted]
24 months	**10.4%**	**33.0%**	**9.3%**	**33.50%**	[redacted]	[redacted]
40 months	10.4%	33.0%	7.1%	33.50%	[redacted]	[redacted]
60 months	10.4%	30.8%	7.1%	33.50%	[redacted]	[redacted]

- In each analyses a small proportion of patients have longer term survival increasing the mean vs the median
- In the CORAL cohort over 80% of patients had died before the 2 year stage, consistent with the Oxford audit dataset

[redacted]

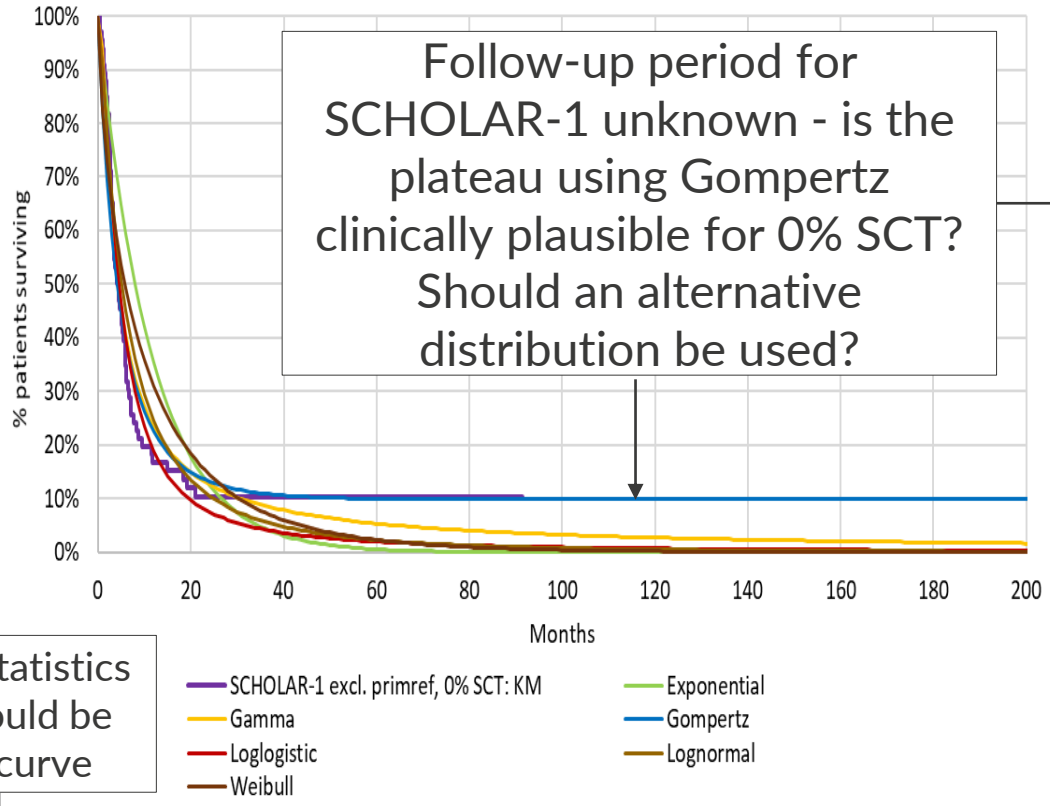
ERG's exploratory analyses: OS extrapolations best supportive care

Overall survival of BSC: adjusted SCHOLAR-1 with **100% SCT**, KM and fitted curves



	AIC	BIC
Exponential	416.95	419.16
Weibull	402.61	407.02
Gompertz	**378.04**	**382.44**
Loglogistic	389.03	393.44
Lognormal	387.40	391.81
Generalised gamma	**376.59**	**383.21**

Overall survival of BSC: adjusted SCHOLAR-1 with **0% SCT**, KM and fitted curves



Follow-up period for SCHOLAR-1 unknown - is the plateau using Gompertz clinically plausible for 0% SCT? Should an alternative distribution be used?

Goodness-of-fit statistics suggest either could be the best fitting curve

	AIC	BIC
Exponential	408.75	410.94
Weibull	396.66	401.04
Gompertz	**364.03**	**368.41**
Loglogistic	364.47	368.85
Lognormal	370.14	374.52
Generalised gamma	**360.82**	**367.39**

ERG's exploratory analyses: OS extrapolations for best supportive care

Given the uncertainty around the choice of distribution the ERG formally account for the uncertainty surrounding choice of survival distribution is to use a model averaging approach - choosing an alternative distribution has a large effect on the mean LE

Summary of goodness of fit statistics and AIC weights (ERG calculations)

	100% SCT		0% SCT		12.5% SCT rate
Distribution for OS (BSC)	AIC	AIC based weight	AIC	AIC based weight	Undiscounted Life Years (mean)
Exponential	416.95	0%	408.75	0%	[redacted]
Weibull	402.61	0%	396.66	0%	[redacted]
Gompertz	378.04	32.49%	364.03	14.65%	[redacted]
Loglogistic	389.03	0.13%	364.47	11.75%	[redacted]
Lognormal	387.40	0.3%	370.14	0.69%	[redacted]
Generalised gamma	376.59	67.08%	360.82	72.91%	[redacted]

[redacted] What is the most appropriate distribution for extrapolation of BSC?

Cost-effectiveness results: ERG's exploratory analyses

Distribution	Effect on incremental costs/QALYs	Modelling approach: Company's base case	Modelling approach: Alternative analysis	Modelling approach: ERG's hybrid model
Base case (12.5% SCT)				
Gompertz	-	**<£50,000**	[redacted]	>£50,000
Gamma	Reduced survival in BSC arm increases incremental costs and incremental QALY gains	**<£50,000**	[redacted]	**<£50,000**
Loglogistic	Lowest survival in BSC arm, increased incremental costs and incremental QALY gains	**<£50,000**	[redacted]	**<£50,000**
ERG's combined scenario (87% Autologous SCT, Cure at 5yrs, IVIG for 3yrs and ITT population)				
Gompertz	-	>£50,000	[redacted]	>£50,000
Gamma	Reduced survival in BSC arm increases incremental costs and incremental QALY gains	**<£50,000**	[redacted]	>£50,000
Loglogistic	Lowest survival in BSC arm, increased incremental costs and incremental QALY gains	**<£50,000**	[redacted]	**<£50,000**

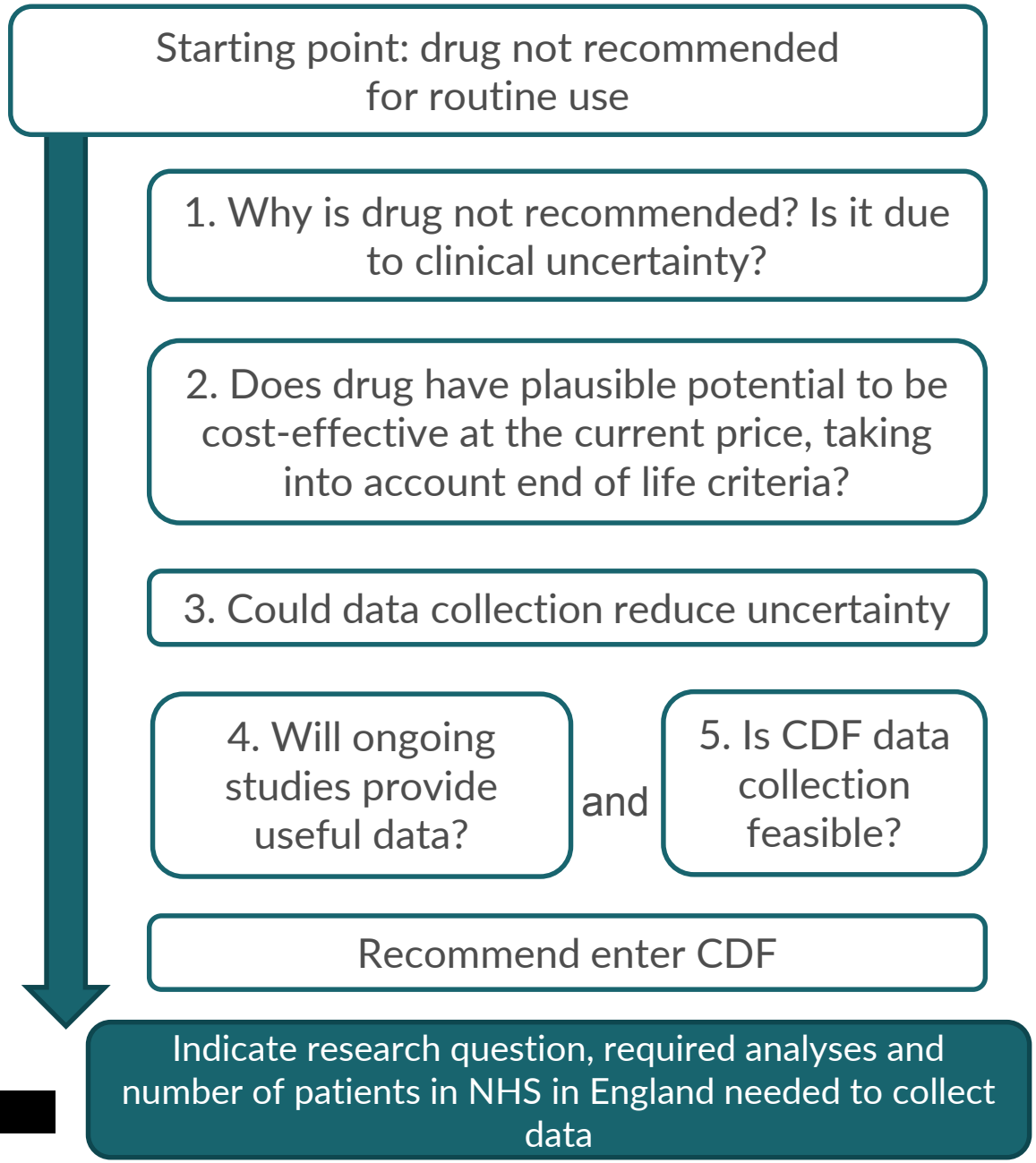
[redacted]

Key issues

- Alternative comparator data
- Appropriate incorporation of stem cell transplants:
  - in the comparator dataset (10% or 12.5% SCT)
  - in the cost-effectiveness modelling (auto vs allo)
- **Extrapolation of overall survival**
  - **axicabtagene ciloleucel**
  - **salvage chemotherapy**
- Mortality risks for long term survivors
- Effect of retreatment with axi-cel on overall survival
- **End of Life**
- **The most plausible ICER**
- CDF / data collection

[redacted]

Cancer Drugs Fund



The company have proposed that axicabtagene ciloleucel would be suitable for inclusion in the CDF as:

- Overall survival data from ZUMA-1 is immature (median 15 months follow-up)
- Clinical uncertainty could be reduced with results from the ongoing ZUMA-1 trial (2 year data cut)

[redacted]