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

Background and Clinical Effectiveness

Committee C

Lead team: Nigel Langford, Judith Wardle and Mike Chambers

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 – clinical effectiveness

- What is the correct placement of axi-cel in the treatment pathway?
- What is the appropriate comparator to axi-cel?
- High heterogeneity between studies included in SCHOLAR-1 raises concerns about pooled data. Is SCHOLAR-1 pooled data, the most appropriate source of data for the comparator?
- Are alternative data available for the comparator treatment arm?
- What adjustment to the SCHOLAR-1 data should be made to account for the inclusion of primary refractory patients, patients with ECOG score 0-4 and the high proportion of patients receiving SCT compared to clinical practice?
- What proportion of patients receiving 3rd line treatment are likely to become eligible for SCT in clinical practice?

B-cell non-Hodgkin lymphoma (NHL)

- There are many different types of non-Hodgkin lymphoma. They can be classified by the type of cell affected and whether they are slow growing ('indolent' or 'low-grade') or fast growing ('aggressive', or 'high-grade'). Most non-Hodgkin lymphomas derive from the B-lymphocytes (B-cell lymphomas).
- Three forms of NHL are relevant to this appraisal
  - Diffuse large B-cell lymphomas (DLBCL) – a fast growing ('aggressive'), high grade form of NHL accounting for 30%-40% of all NHL cases.
  - Primary mediastinal large B-cell lymphoma (PMBCL) – a rare subtype of DLBCL accounting for 2-4% of all NHL cases. Develops in the mediastinum
  - Transformed follicular lymphoma (TFL) – follicular lymphoma is a low-grade lymphoma, but in some people it transforms into a faster growing type. TFL is usually treated like a high-grade lymphoma, such as DLBCL
- There were around 11,690 new cases of NHL in England in 2015 with 6,322 of these DLBCL
- B-cell lymphomas can occur at any age, but are most common in people aged over 50 years with average age at diagnosis of 65 years
- 5-year survival rates for people with high grade lymphomas are around 65-70% for stage I and II and around 50% at stages III and IV

Treatment pathway for B-cell non-Hodgkin lymphoma

- The most widely used first-line treatment is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) for which 50% of people will be cured
- NICE guideline CG52 recommends salvage therapy with multi-agent immunochemotherapy for people with relapsed or refractory disease* followed by stem cell transplantation. If stem cell transplantation is not suitable, chemotherapy or immunotherapy may be used alone
- NICE TA306 recommends pixantrone monotherapy for people who have multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma, have been previously treated with rituximab and are on the third or fourth line of treatment, if provided under the agreed patient access scheme
- Outcomes for people with relapsed/refractory (R/R)* disease treated with standard of care (SoC) are poor, with low levels of response and limited survival
- Many people with refractory disease have no curative treatment options

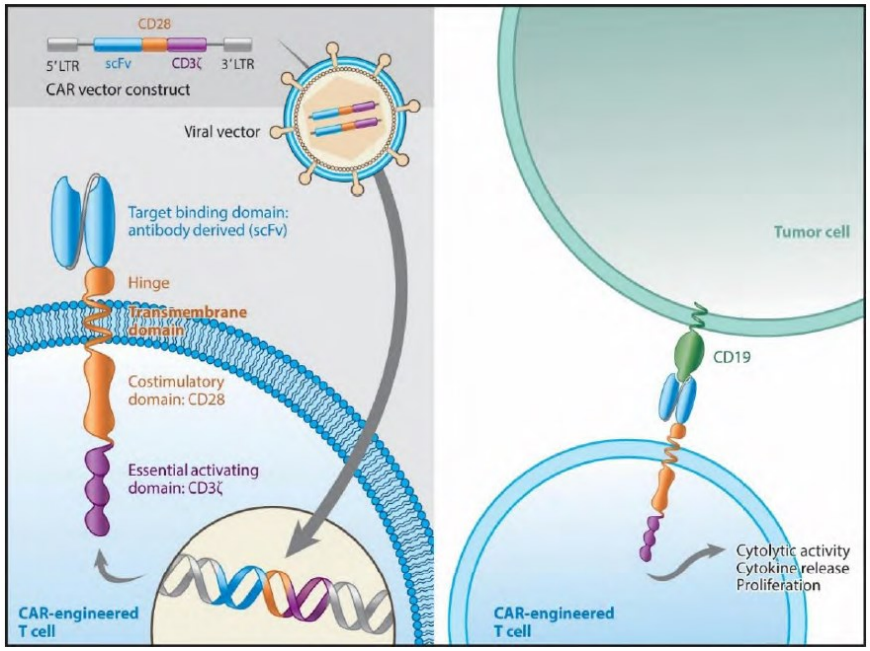
* People with refractory NHL have not responded to initial treatment.
People with relapsed NHL have previously responded to treatment but malignancy then return

Axicabtagene ciloleucel (Kite-Gilead)

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
Administration and dosage		• Patients undergo conditioning chemotherapy of cyclophosphamide 500mg/m^2 IV and fludarabine 30mg/m^2 IV • Genetically altered T-cells are administered as an intravenous infusion as 68 ml bag containing a maximum 2 x 10^8 anti-CD19 CAR T-cells
Marketing authorisation	Current	• Approval from the Committee for Human Medicinal Products (CHMP) received 28th June 2018 "Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after two or more lines of systemic therapy"
	Regulatory status	• Orphan Medicine Designation: Granted by EMA in Feb 2015 • Priority Medicines (PRIME) Status: Granted by EMA in May 2016
List price		[redacted] per 68 ml single infusion bag

Chimeric antigen receptor (CAR) T-cell therapies (1)

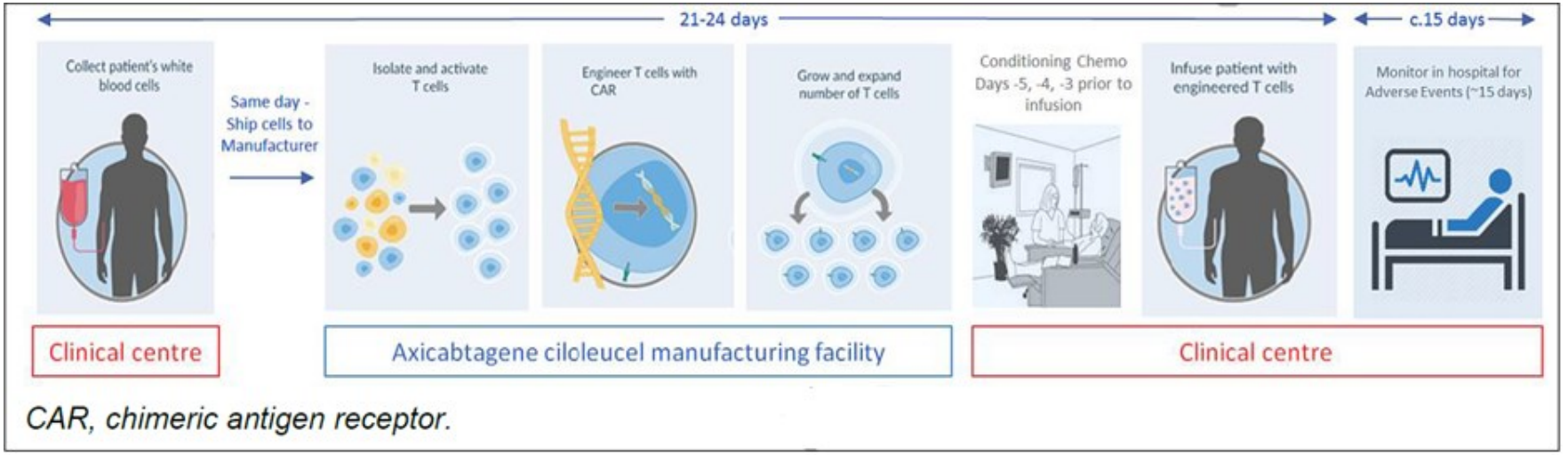
- Axicabtagene ciloleucel (axi-cel) is the first chimeric antigen receptor (CAR) T-cell therapy to be appraised by NICE for use in the NHS
- CAR T-cell therapies employ an inactive virus to insert genes into autologous human T-cells.
- The engineered T-cells express a novel cell surface receptor fragment antibody.
- The new receptors identify and lock onto CD19 bearing cells.
- Once locked onto CD19 the T-cell is activated to destroy the cells.



Source: Figure 1 in company submission

CAR T-cell therapies (2)

Multistep process:



1. Leukapheresis - collection of T-cells from patient (SCT accredited setting)
2. T-cells reengineered and multiplied (laboratory setting outside UK)
3. Patients receive conditioning chemotherapy (hospital setting)
4. CAR T-cells are thawed and infused into the patient (SCT accredited setting)
5. Patients are monitored for AEs (hospital ~17 days, within 2hrs of hospital ~1 month) - requirement for availability of ITU beds for axi-cel patients

Patient/carer experience of B-cell lymphomas and current treatments

- Most common symptoms swollen lymph nodes in neck, armpit and groin. Where nodes deeper, may be chest/abdominal pain, coughing or breathlessness. Also fevers and weight loss
- Multiple courses of chemotherapy have harsh side-effects including sickness, diarrhoea and mouth ulcers making eating difficult.
- A cycle of remission and relapse when undergoing successive treatments has major psychological as well as physical impact.
- Currently unmet need for patients who have failed available treatments

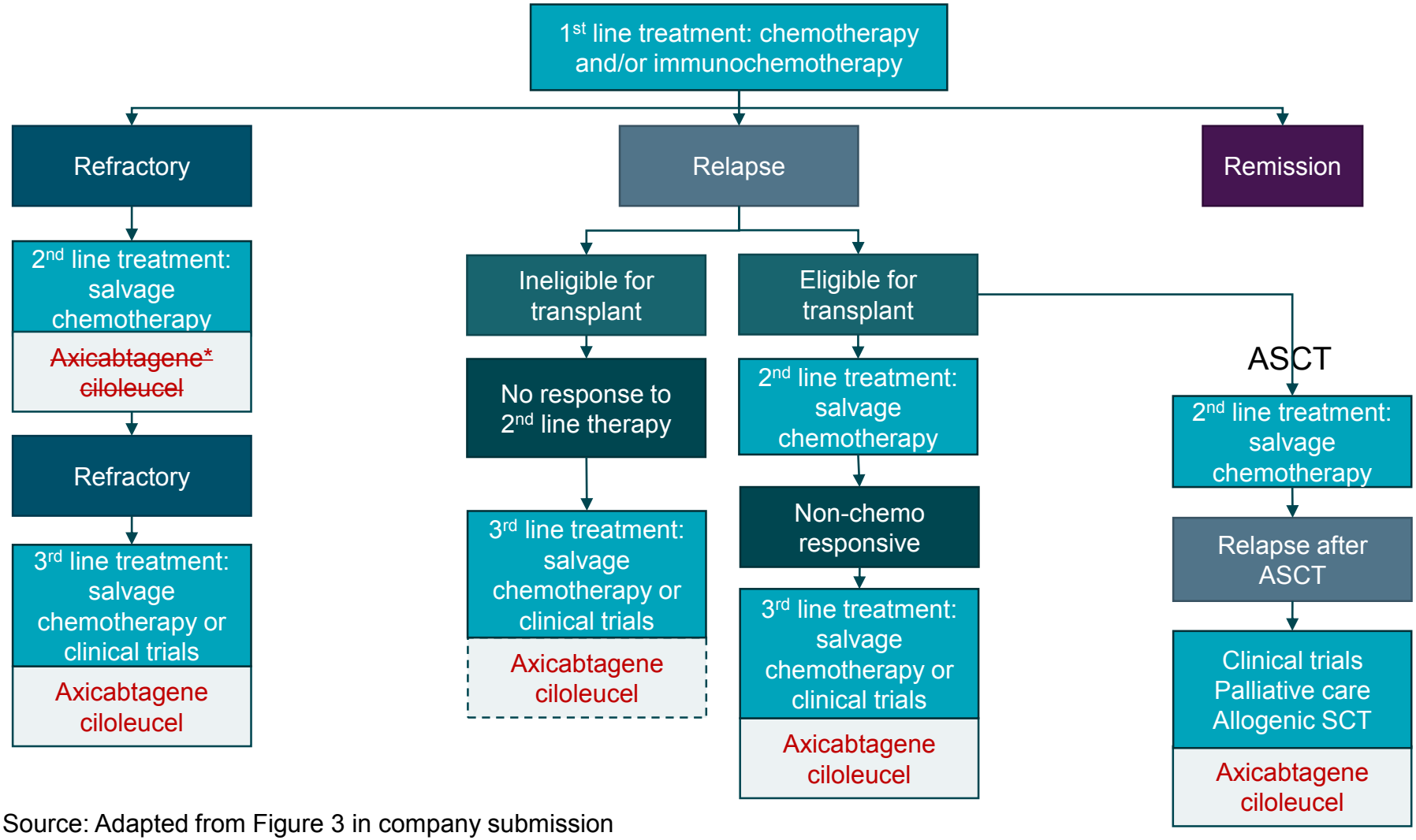
Patients' views on CAR T treatment

- Offers hope when other treatments failed
- Side effect of neutropenic sepsis very unpleasant but bearable if patient forewarned – helps that patients have easy access to hospital because required to stay close
- However, residence requirement puts strain on patients and family members
- Treatment is innovative and represents a real step-change for this condition.
- Concern that local teams have little knowledge of effects of current treatments and will need further training about CAR T-cell therapy

Statement from NHS England

- “Given the novelty, promise and toxicity of the treatment, it is expected axicabtagene ciloleucel will make fundamental differences to the treatment pathway compared to current care
- Requires new service specifications and substantial workforce and infrastructure changes
  - New training accreditation requirements
  - Changes to access arrangements to ITU support planning, booking and access
  - Support from other departments to treat patients who experience adverse events
- Commissioners need to ensure capacity for the CAR T-cell service without any adverse effect on current services
- Given the need for training and accreditation of many healthcare professionals NHS England plans a phased implementation and ongoing evaluation of the capacity needs in the NHS in order to successfully and safely deliver the treatment required”

Company's position of axi-cel in the treatment pathway for R/R DLBCL



Source: Adapted from Figure 3 in company submission
* amended following CHMP approval
- - - unlikely to be eligible due to overlap of fitness criteria for SCT and axi-cel

Who is eligible for axi-cel treatment

NHS England's interpretation:

- People eligible for axi-cel will have relapsed or refractory disease after 2nd line treatment
- If a SCT was planned as part of 2nd line treatment and patients respond sufficiently to chemotherapy, those patients should proceed to SCT and not to CAR T- cell therapy
- Patients who relapsed within 12 months of receiving the SCT would be eligible for axi-cel
- Fitness requirements for receiving axi-cel treatment would be very similar to those for patients requiring SCTs meaning patients would be required to have ECOG status 0-1

Questions for committee:

- Where is axi-cel's placement in the treatment pathway?

Decision problem – axi cel

	NICE scope	Company
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma or transformed follicular lymphoma	[redacted]
Comparators	• DHAP (w/wo rituximab) • GDP (w/wo rituximab) • ICE (w/wo rituximab) • IVE (w/wo rituximab) • Pixantrone monotherapy • Best supportive care	• DHAP (w/wo rituximab) • GDP (w/wo rituximab) • ICE (w/wo rituximab) • IVE (w/wo rituximab) • Best supportive care (including radiotherapy)
Outcomes	Overall survival (OS), progression-free survival (PFS), response rate (ORR), adverse effects of treatment, health-related quality of life	

* Since the ZUMA-1 trial the WHO definition of DLBCL has evolved to include the transformed follicular lymphoma population. This group is therefore not listed in the CHMP's positive opinion

Company's rationale for differences between NICE Scope and company submission

	Rationale for differences
Population	The population presented in the company submission reflects the marketing authorisation for axicabtagene ciloleucel (axi-cel)
Comparators	• Exclusion of pixantrone as a comparator: clinical experts confirmed that despite NICE approval in TA306 very few people are treated with pixantrone monotherapy in England. • A blended comparator including DHAP, GDP and ICE was used as a comparison to the ZUMA-1 trial
Special considerations	None specified in the NICE scope • Company suggests the potential for an age-related treatment bias in the patient population, as many older people will be ineligible for autologous stem cell transplant but would be unlikely to receive more aggressive chemotherapy options

Technical engagement responses: What is the appropriate comparator?

- **What is the appropriate comparator for patients needing 3rd line treatment?**
  Marketing authorisation is for people with relapsed/refractory disease after 2 lines of therapy. Current 3rd line treatment for those not eligible for SCT is salvage chemotherapy. Other options would be clinical trials of novel therapies and symptomatic therapy. A minority of people who respond to 3rd line chemotherapy and were fit would proceed to allogenic SCT
- **Should pixantrone be considered as a comparator?**
  All consultees in the technical engagement agreed despite NICE approval in TA306 pixantrone was not a relevant comparator as it is rarely used in clinical practice on account of poor efficacy.
- **Is a blended comparator appropriate?**
  There is no 3rd line standard therapy; one is clearly not superior to the others. 3rd line therapies would be one of DHAP/ESHAP/GDP/ICE/IVE ± rituximab with their use determined by local practice.

Questions for committee:
- What is the appropriate comparator?
- Is pixantrone a relevant comparator?

ZUMA-1 trial

	ZUMA- 1
Study design	International, multicentre, single-arm, open-label Phase 1/2 study
Population (ITT)	119 adults with aggressive B-cell NHL (DLBCL, PMBCL, and TFL) that was either refractory to treatment or had relapsed ≤12 months after ASCT with ECOG performance status of 0 or 1
Exclusion criteria	• History of allogeneic cell transplant • Autologous stem cell transplant within 6 weeks of trial • Prior CD19 targeted therapy • Presence of uncontrolled fungal, bacterial, viral infection • History or presence of CNS disorder
Intervention (mITT)	Axicabtagene ciloleucel (n=108) DLBCL n=77, PMBCL n=8, TFL n=16
Comparator	n/a (single-arm study)
Location	24 centres: (23) US and (1) Israel
Outcomes	Overall response rate (ORR) overall survival (OS) progression-free survival (PFS) duration or response (DoR) and safety

SCHOLAR-1 cohort

	SCHOLAR-1
Study design	Patient level historical control study from 4 sources: • MD Anderson Cancer Centre (MDACC) n=191 • Mayo Clinic and University of Iowa (MC/IA) Specialised Program of Research Excellence (SPORE) n=107 • The National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG) randomised Phase 3 study LY.12 n=353 • French Lymphoma Academic Research Organisation (LYSARC) randomised Phase 3 Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study n=210
Population	636 adults (DLBCL n=552, PMBCL n=14, TFL n=27 and other n=43) with refractory disease or who had relapsed ≤12m after ASCT
Treatment options	Salvage chemotherapy Rituximab maintenance Observation post-ASCT (autologous stem cell transplant)
Comparator	n/a (retrospective cohort study)
Outcomes	Response rate (RR), complete response rate (CRR), and overall survival (OS)

Baseline characteristics ZUMA-1 and SCHOLAR-1 (1)

Characteristic	ZUMA-1 (n=101)	SCHOLAR-1 (n=497)
Age, years, median (range)	58 (23–76)	55 (19–81)
Male, n (%)	68 (67.3)	321 (64.6)
ECOG, n (%)		
0-1	101 (100.0)	226 (45.5)
≥ 2	0 (0.0)	55 (11.1)
Not available	0 (0.0)	216 (43.5)
IPI score, n (%)		
0-1	27 (26.7)	73 (14.7)
2	26 (25.7)	66 (13.3)
≥ 3	48 (47.5)	76 (15.3)
Not available	0 (0.0)	282 (56.7)
Disease stage		
I-II	15 (14.9)	75 (14.6)
III-IV	86 (85.1)	149 (30.0)
Not available	0 (0.0)	273 (47.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index

☐ key difference in study populations

Baseline characteristics ZUMA-1 and SCHOLAR-1 (2)

Characteristic	ZUMA-1 (n=101)	SCHOLAR-1 (n=497)
Refractory subgroup		
Primary refractory	2 (2.0)	100 (20.1)
Refractory to 2nd line or later	78 (77.2)	310 (62.4)
Relapse within 12m of ASCT	26 (20.8)	87 (17.5)
Number of previous lines of therapy		
1	2 (2.0)	100 (20.1)
2	29 (28.7)	204 (41.0)
3	30 (29.7)	91 (18.3)
≥ 4	40 (39.6)	15 (3.0)
Not available	0 (0.0)	87 (17.5)
ASCT post treatment	[redacted]	[redacted]

Abbreviations: ASCT, autologous stem cell transplant; key difference in study populations

ERG's comments

Missing data was an issue for all the covariates in the SCHOLAR-1 data set and could lead to biased results unless appropriate adjustments are made

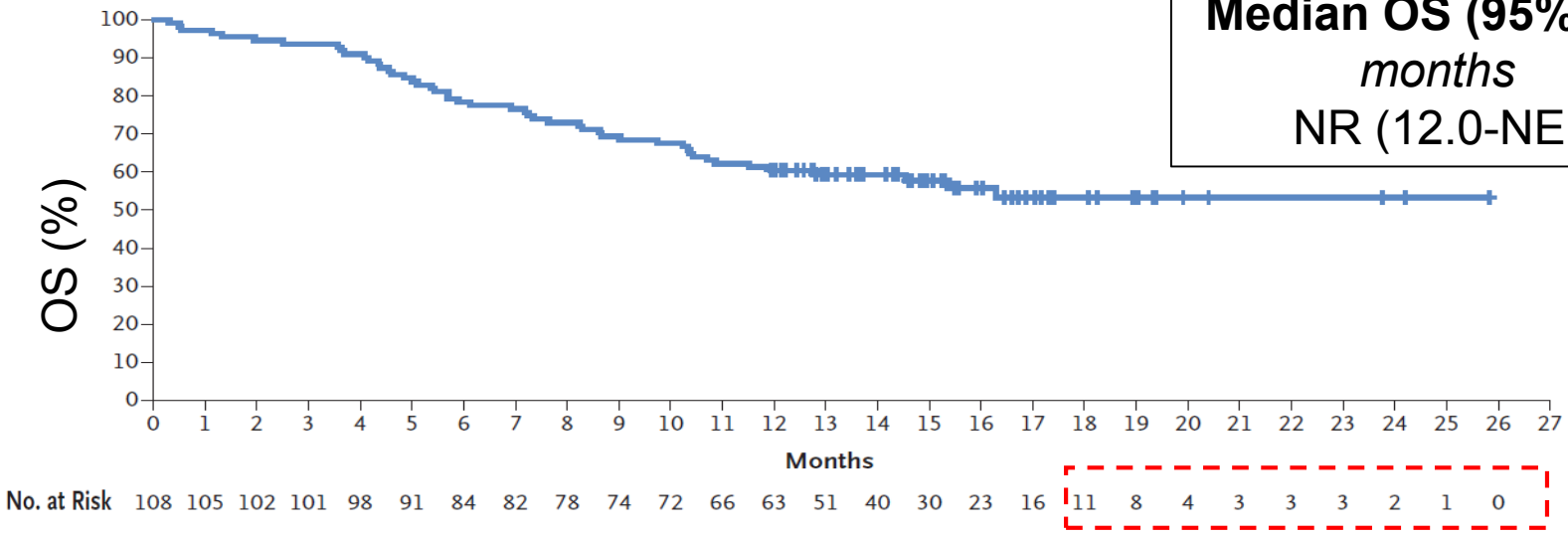
Differences in baseline characteristics - SCHOLAR-1 and ZUMA-1

Differences in baseline characteristic between the two studies:

- [redacted] of patients in SCHOLAR-1 subsequently received ASCT compared with ~~to~~ only [redacted] patients in ZUMA-1
- SCHOLAR-1 cohort included primary refractory patients. Only patients relapsed/refractory to 2 lines of therapy would be eligible for axi-cel. ZUMA-1 included 2 primary refractory patients
- SCHOLAR-1 included patients with ECOG scores 0-4 compared to ZUMA-1 only including those with ECOG score 0-1
- ZUMA-1 had a higher proportion of patients with Stage III-IV disease than SCHOLAR-1
- ZUMA-1 patients were more heavily pre-treated that those in SCHOLAR-1

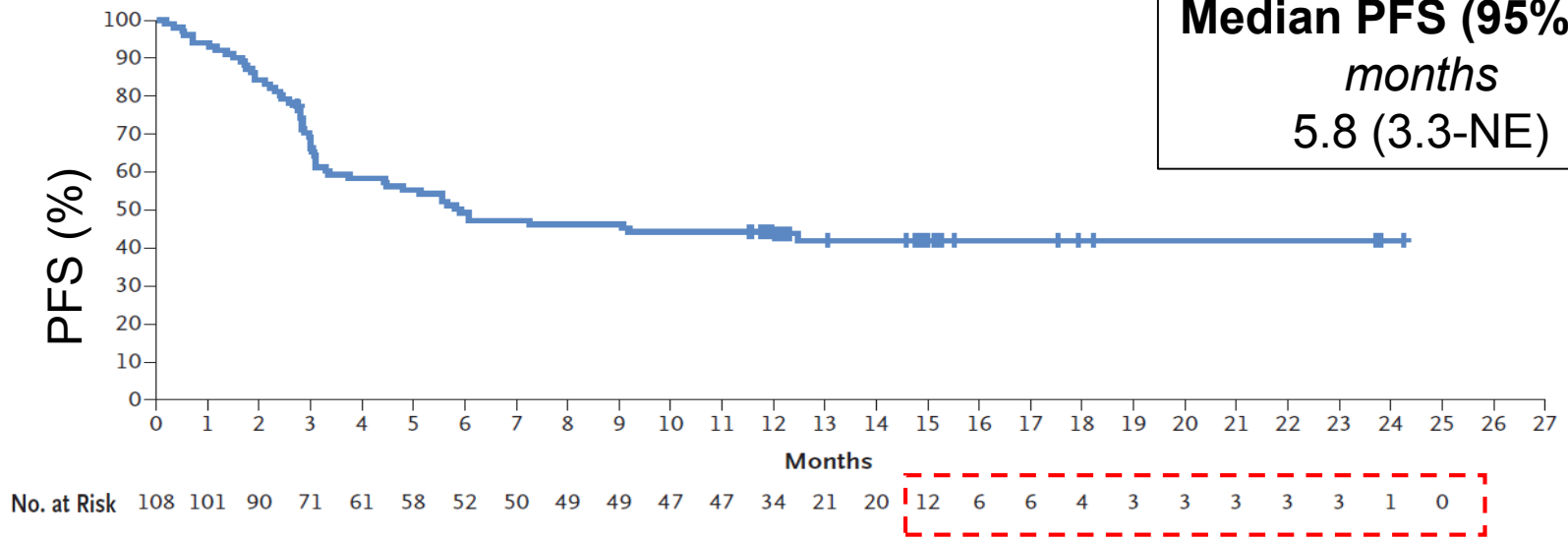
ZUMA-1 (mITT) results

Overall survival



Median OS (95% CL)
months
NR (12.0-NE)

Progression-free survival



Median PFS (95% CL)
months
5.8 (3.3-NE)

Company's unadjusted ZUMA-1 (mITT) and SCHOLAR-1 results

	ZUMA-1 (n=108)	SCHOLAR-1 (n=508)	Standardised difference* (95% CI)	Odds ratio (95% CI)
ZUMA-1 (mITT) and SCHOLAR-1 (last refractory categorization)				
ORR (%)	[redacted]	[redacted]	[redacted]	[redacted]
CR (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; mITT, modified intention to treat; NE, not evaluable; ORR, objective response rate; OS, overall survival. ORR calculated at data cut-off
*95% confidence interval calculated with Wilson's Score method

- Last refractory categorisation excludes patients without a current line of therapy present in SCHOLAR-1 after reaching their latest designation of refractory status. Total sample size was 593, only 508 patients were evaluable for response and 497 for survival.

Company's adjustments for baseline characteristics

Company's base case adjusts for imbalance using patient level data to exclude people in SCHOLAR-1 who would not have been eligible for ZUMA-1

- Base case: adjusted for ECOG status
  Justification: inclusion criteria of ZUMA-1 only allows ECOG 0–1 patients
- Scenario 1: adjusted for ECOG status and subsequent ASCT treatment
  Justification: subjects with ECOG 2–4 at baseline (as above) are likely to have worse outcomes. Patients who received post-refractory SCT would not be eligible for axi-cel in clinical practice and likely to have improved outcomes
- Scenario 2: Propensity score adjusted, weights for each individual SCHOLAR-1 to adjust for the differences in baseline characteristics*
  Justification: Used in TSD17 to reduce the bias of estimating relative treatment efficacy based on single arm trials or observational studies

*Not presented as part of company's clinical effectiveness results

Company's standardised comparisons

- ZUMA-1 mITT phase 2 population and SCHOLAR-1 last refractory categorisation (patients treated with chemotherapy after refractory status) n=508 for response n=497 for survival

	ZUMA-1 (n=101)	SCHOLAR-1 (n=508)	Odds ratio (p-value)
Base case: Standardised by ECOG status (excluded patients with ECOG 2-4)			
ORR (%)	[redacted]	[redacted]	[redacted]
CR (%)	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]
Scenario 1: Standardised by ECOG status and subsequent ASCT			
ORR (%)	[redacted]	[redacted]	[redacted]
CR (%)	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]

*Stratified Cox model. Abbreviations: CR, complete response; mITT, modified intention-to-treat; NA, not applicable; NE, not evaluable; OS, overall survival ORR, overall response rate

ZUMA-1 vs SCHOLAR-1

Base case: overall survival

Source: Figure 12 in company submission

SCHOLAR-1 results – Overall survival by ECOG category

*Company note [redacted] of patients included in the EGOC score 0-1 group received subsequent ASCT

Company's standardised analyses for patients with ECOG score 0-1 only

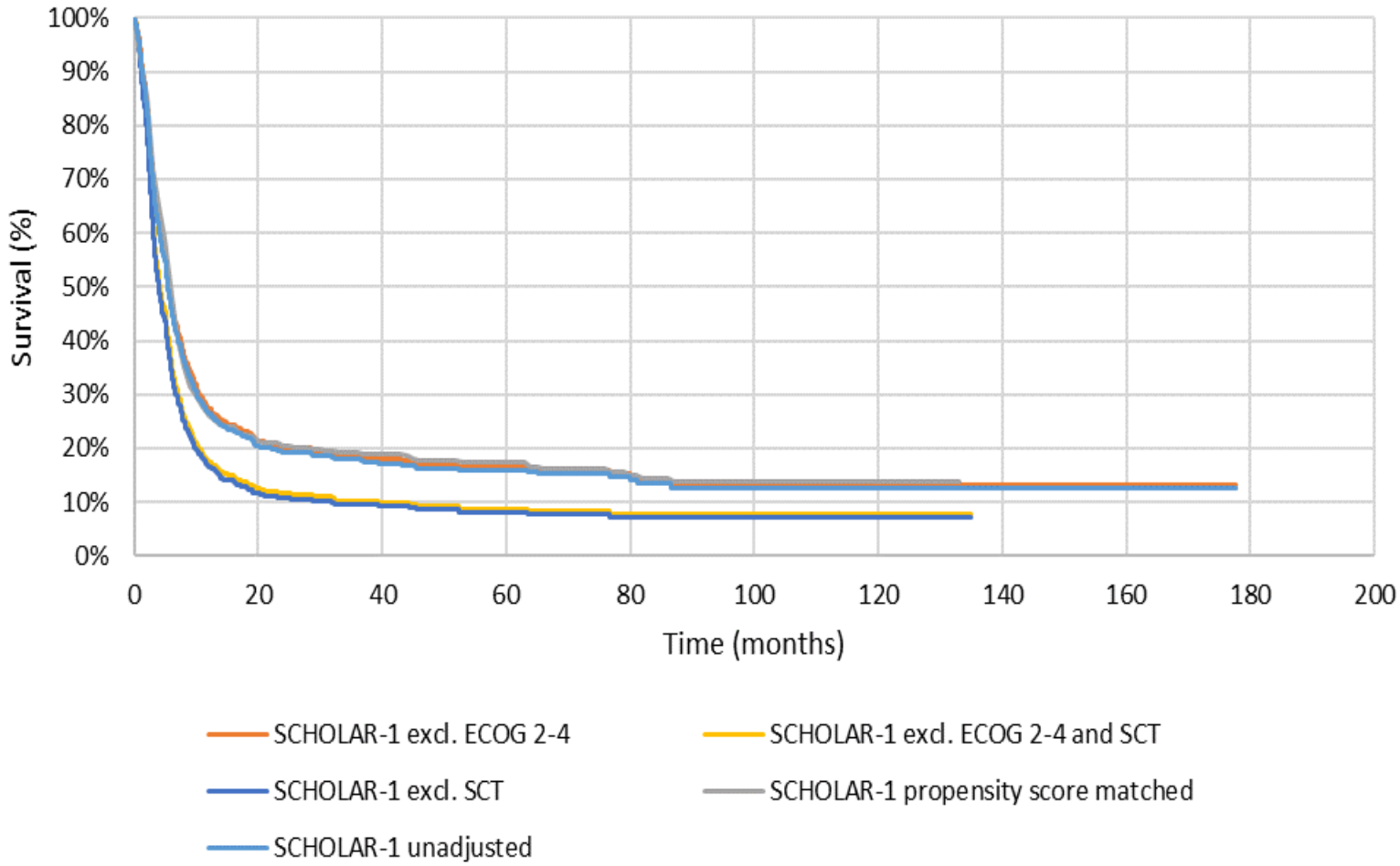
- Provided in response to clarification request- participants with missing ECOG status and ECOG 2-4 in the SCHOLAR-1 study excluded from the analysis

	ZUMA-1 (n=108)	SCHOLAR-1 (n=230)	Odds ratio (p-value)
ZUMA-1 phase I and II and SCHOLAR-1 ECOG 0-1 only (Last Refractory Categorization)			
ORR	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]
*Stratified Cox model. Abbreviations: CR, complete response; HR, hazard ratio; NE, not evaluable; OS, overall survival ORR, overall response rate			

*Company note [redacted] of patients included in the EGOC score 0-1 group received subsequent ASCT

SCHOLAR-1 results – Overall survival scenario analyses

SCHOLAR-1 excluding SCT versus existing SCHOLAR-1 scenarios



ERG's comments – clinical effectiveness data

Appropriate comparator

- Blended comparator appropriate given data limitations
- Agree pixantrone is not a relevant comparator

ZUMA-1 data

- Submitted evidence includes the ASCT eligible population
- Limited follow up from ZUMA-1 (15.4 months) means there is uncertainty in the OS and PFS results beyond 12 months

Use of SCHOLAR-1

- High heterogeneity between pooled studies in SCHOLAR-1 and between SCHOLAR-1 and ZUMA-1
- SCHOLAR-1 includes patients with ECOG 0-4 and high proportion of patients who received subsequent SCT
- SCHOLAR-1 reported ORR and OS only as outcomes

Comparative effectiveness results

- The company's standardised analyses do not adequately adjust for baseline imbalances:
  - Adjustment for ECOG status included patients with unknown ECOG data (43.5%). Appropriate analyses would include only patients with known ECOG score 0-1
  - Adjustments for ASCT did not exclude patients (n=10) re-treated with axi-cel
  - Propensity score (not presented) did not adjust for ECOG, IPI score and number of lines of previous therapy

Company and expert technical engagement responses

- All consultees in the technical engagement agreed it would not be appropriate to include patients with ECOG score 2-4 in the comparison. Only patients with ECOG score 0-1 would be eligible for axi-cel and outcomes of patients with higher ECOG score and worse performance status are likely to be worse.
- Clinical and commissioning experts were concerned the proportion of patients receiving SCT in the SCHOLAR-1 cohort does not reflect clinical practice in the UK. Consultees note this inclusion could inflate both survival and costs in the comparator arm.
- The company note no alternative data is available for the comparator arm. The ORCHARRD study would not be a suitable due to the inclusion of a high proportion of primary refractory patients and high levels of subsequent SCT

Questions for committee:

- Is SCHOLAR-1 the most appropriate data source?
- Is alternative data available for the comparator arm?
- What proportion of patients receiving 3rd line treatment are likely to become eligible for SCT in clinical practice?
- What adjustment to the SCHOLAR-1 cohort is most appropriate for the comparative effectiveness populations?

ZUMA-1 adverse events

- **No AE data were collected in the SCHOLAR-1 study**

Outcome	ZUMA-1 (n=101)
Patients with an AE, n (%)	101 (100)
Average duration of follow-up (months)	8.7
Patients with Grade ≥3 AE, n (%)	96 (95.0)
Grade ≥3 CRS	13 (12.9)
Grade ≥3 neurological event	28 (27.8)
Patients with an SAE, n (%)	[redacted]
Patients with Grade ≥3 SAE, n (%)	[redacted]
Deaths, n (%)	[redacted]
Death from PD	[redacted]
Death due to AE	[redacted]
Other	[redacted]
Abbreviations: AE, adverse event; CRS, cytokine release syndrome; PD, progressed disease; SAE, severe adverse event	

Source: Table 19 in company submission

ERG's comments – adverse events

Axi-cel

- Only adverse events that had an incidence equal or greater than 10% in ZUMA-1 were included in the economic model
- Adverse events are likely to occur in all patients
- Serious adverse events occurred in around half of patients who received axi-cel
- The requirements and usage of ICU beds for CRS has not been fully addressed by the company
- There is uncertainty surrounding the potential duration of IVIG treatment for patients with AEs
- Long-term term follow up data is required to fully understand the effects of adverse events occurring after treatment with axi-cel

BSC

- The exclusion of adverse events for BSC appears conservative

Key issues – clinical effectiveness

- What is the correct placement of axi-cel in the treatment pathway?
- What is the appropriate comparator to axi-cel?
- High heterogeneity between studies included in SCHOLAR-1 raises concerns about pooled data. Is SCHOLAR-1 pooled data, the most appropriate source of data for the comparator?
- Are alternative data available for the comparator arm?
- What adjustment to the SCHOLAR-1 data should be made to account for the inclusion of primary refractory patients, patients with ECOG score 0-4 and the high proportion of patients receiving SCT compared to clinical practice?
- What proportion of patients receiving 3rd line treatment are likely to become eligible for SCT in clinical practice?