Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable

For screen – CON information redacted

Technology appraisal committee C [02 October 2024]

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Company: Bristol-Myers Squibb

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- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on large B-cell lymphoma

Epidemiology

- Around 5,440 people are newly diagnosed with LBCLs each year in UK (annual incidence of 8.3 cases per 100,000 people)

Diagnosis and classification

- Numerous subtypes of LBCL exist (% of NHL cases): DLBCL (40%), HGBCL (1-2%), PMBCL (2-3%) and FL3B (1%) are considered within the company's submission

Symptoms and prognosis

- Swollen lymph nodes, night sweats, fever, weight loss and itching
- Approximately 60–70% of people are cured after 1L therapy
- 50% of people with early relapsed/primary refractory LBCL will be eligible for SCT and 10% patients will eventually be cured with current 2L SOC

Abbreviations: 1L, first line; 2L, second line; DLBCL; diffuse large B-cell lymphoma; FL3B, follicular lymphoma Grade 3B; HGBCL, high-grade B-cell lymphoma; LBCL, Large B-cell Lymphoma; NHL: Non-Hodgkin lymphoma; PMBCL, primary mediastinal B-cell lymphoma; SCT, stem cell transplant; SOC, standard of care

Patient perspectives

Submissions from Lymphoma Action and Blood Cancer UK (including 1 patient expert)

- Significant side effects from current treatments, frequent blood tests, extreme fatigue, compromised immunity, constant uncertainty, bone marrow biopsies and constantly worrying about the effects of the illness on family are described as being part of living with lymphoma
- Worry of relapsing or not responding to treatment, and that there will not be any further treatment options available
- Current treatments often need multiple or prolonged trips to hospital. One-time treatment with liso-cel is more convenient, but there are issues with accessibility and requirement to stay close to the hospital

People say that having another treatment option after first relapse or treatment failure would be an advantage:

"Difficult to know you have to wait to have 2 failed treatments before CAR-T"

People with liso-cel-induced remission:

"I am no longer a burden on the NHS. No longer going through repetitive procedures."

"Since my successful CAR-T treatment I feel almost reborn."

Abbreviations: CAR-T, chimeric antigen receptor T-cell; liso-cel, lisocabtagene maraleucel

Clinical perspectives

Submissions from 2 clinical experts

Treatment landscape:

- Still an unmet need for relapsed or refractory DLBCL, PMBCL, HGBCL or FL3B
- Aim of treatment is durable complete remission and potentially cure

Liso-cel:

- Considered innovative and a step-change
- Potential advantages over existing therapies:
    - Lower toxicity profile (compared with axi-cel and high dose chemotherapy with an auto transplant), and so easier to deliver and better patient HRQoL
    - Higher efficacy than SOC in baseline commissioning
    - Likely to offer shorter time in hospital
    - Likely to extend life more than some treatments

Abbreviations: axi-cel, axicabtagene ciloleucel; DLBCL; diffuse large B-cell lymphoma; FL3B, follicular lymphoma Grade 3B; HGBCL, high-grade B-cell lymphoma; HRQoL, health related quality of life; PMBCL, primary mediastinal B-cell lymphoma; SOC, standard of care

Equality considerations

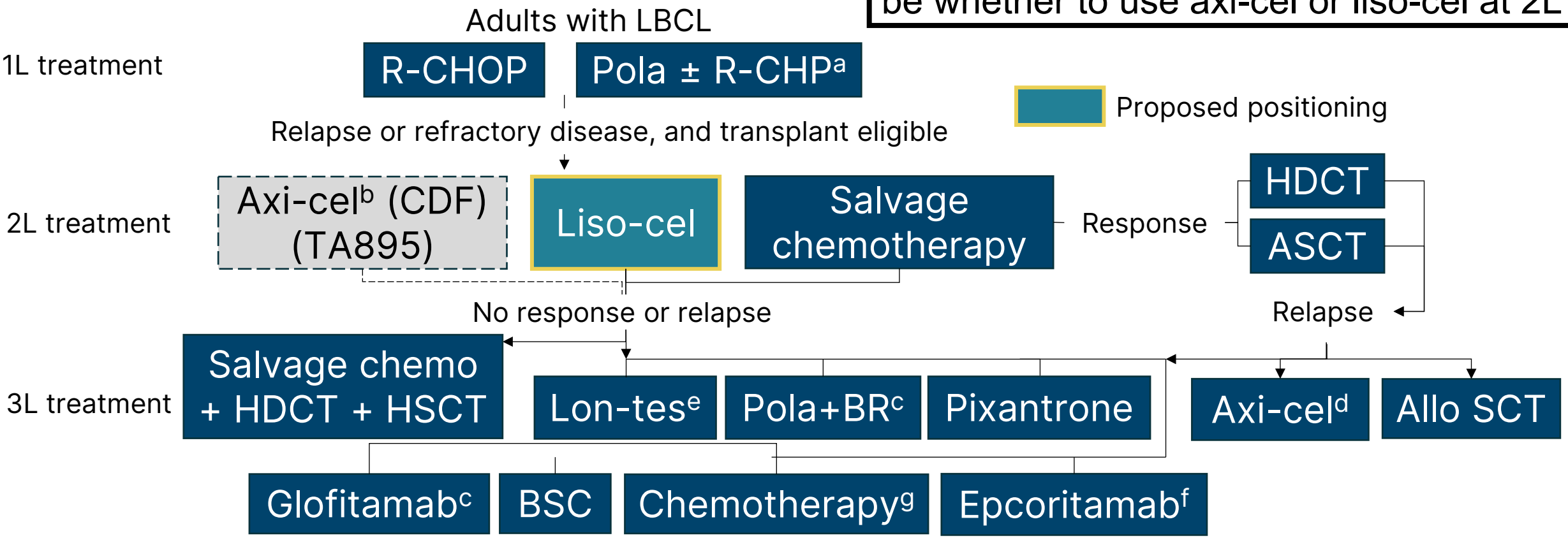
- Two stakeholders highlighted that, as with other CAR-T treatments, there is a potential for short-lived geographical inequalities in access to liso-cel. This is because CAR-Ts are only administered in specialist CAR-T centres, and the requirement to stay in close proximity to the centre post-infusion.

- At scoping, a stakeholder noted that clinicians have to consider the fitness of patients to have more intensive cancer treatments. The age of patients may be used as a proxy for levels of fitness, which then impacts whether they are treated for “curative intent”. Relapsed or refractory patients across all ages who are fit enough should have access to CAR-T, and specifically liso-cel.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; liso-cel, lisocabtagene maraleucel

Treatment pathway

Clinical expert: Treatment decision would be whether to use axi-cel or liso-cel at 2L



[a] only in people with DLBCL (TA874); [b] only in people with DLBCL (TA895); [c] only in people with DLBCL (TA927 and TA649); [d] only in people with DLBCL or PMBCL (TA872); [e] only in people with DLBCL or HGBCL who have received polatuzumab and are ineligible for treatment with CAR-T (NICE TA947); [f] only in people with DLBCL (TA954); [g]assumed to be 100% R-bendamustine in company's model

Abbreviations: 1L, first line; 2L, second line; 3L, third line; allo SCT, allogeneic stem cell transplant; ASCT, autologous stem cell therapy; axi-cel, axicabtagene ciloleucel; B, bendamustine; BSC, best supportive care; C, cyclophosphamide; CDF, Cancer Drugs Fund; diffuse large B-Cell lymphoma; H, doxorubicin; HDCT, high-dose chemotherapy; HSCT, hematopoietic stem cell transplantation; LBCL: large B-cell lymphoma; liso-cell, lisocabtagene maraleucel; lon-tes, loncastuximab tesirine; O, vincristine; PMBCL, primary mediastinal B-cell lymphoma; pola, polatuzumab vedotin; R, rituximab; P, prednisolone

Lisocabtagene maraleucel (Breyanzi, BMS)

Marketing authorisation	• MHRA approved marketing authorisation extension for liso-cel in the indication: 'for the treatment of adult patients with DLBCL, HGBCL, PMBCL and FL3B who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy'
Mechanism of action	• Autologous anti-CD19 CAR-T therapy
Administration	• Single dose IV infusion • Must be administered in a qualified treatment centre
Price	• The list price of one dose of liso-cel is £297,000 • A confidential patient access scheme is applicable

Population in appraisal is narrower: adults with early relapsed/primary refractory DLBCL, HGBCL, PMBCL or FL3B **who are eligible for SCT**

Abbreviations: DLBCL; diffuse large B-cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IV, intravenous; liso-cel, lisocabtagene maraleucel; PMBCL, primary mediastinal B-cell lymphoma; SCT, stem cell transplantation

Key issues

Link to other issues slide

Key issue	Questions for consideration	ICER impact
Generalisability of TRANSFORM trial for NHS care	Is TRANSFORM generalisable to clinical practice, and appropriate for decision making?	Unknown
Subsequent therapy distribution	• Should subsequent therapy use be based on TRANSFORM or UK clinical practice? • Should adjustments to the efficacy estimates (OS/PFS2) be considered, as well as costs?	Large
Extrapolation of OS	Is the company's (mixture cure) or EAG's (SurvInt) approach to modelling OS more appropriate?	Moderate
Extrapolation of TTNT	Should TTNT be modelled using the TTNT or EFS dataset?	Moderate
Adverse event costs at 3L	Should the cost of adverse events be excluded from the CAR-T tariff when applied at 3L?	Moderate
EFS or PFS2 for economic modelling structure	• Is the EFS or PFS2 endpoint preferred for the economic modelling structure? • Are the company's or EAG's preferred curves more appropriate?	Small

Abbreviations: 3L, third line; CAR, chimeric antigen receptor; EFS, event-free survival; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS2, progression free survival on subsequent therapy; TTNT, time to next treatment

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Key clinical trial: TRANSFORM

	TRANSFORM
Design	Open-label Phase 3 multinational RCT
Population	People with R/R LBCL who are eligible for ASCT • 184 patients with LBCL, including 118 with DLBCL, 43 with HGBCL, 17 with PMBCL, 5 with THRBCL and 1 with FL3B
Intervention	Liso-cel
Comparator(s)	Standard of care
Duration	Median follow-up of 33.9 months (final DCO; October 2023) • Trial began in October 2018, with the last patient randomised in [redacted]
Primary outcome	Event free survival
Key secondary outcomes	Response, PFS, PFS2, OS
Locations	Belgium, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, Switzerland, the United Kingdom, the United States
Used in model?	Yes

Abbreviations: ASCT, autologous stem cell transplantation; DCO, data cut off; DLBCL, diffuse large B-cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high grade B-cell lymphoma; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; OS, overall survival; PFS, progression free survival; PMBCL, primary mediastinal B-cell lymphoma; RCT, randomised controlled trial; THRBCL, T-cell histiocyte rich large B-cell lymphoma

Key clinical trial results – TRANSFORM – EFS and PFS

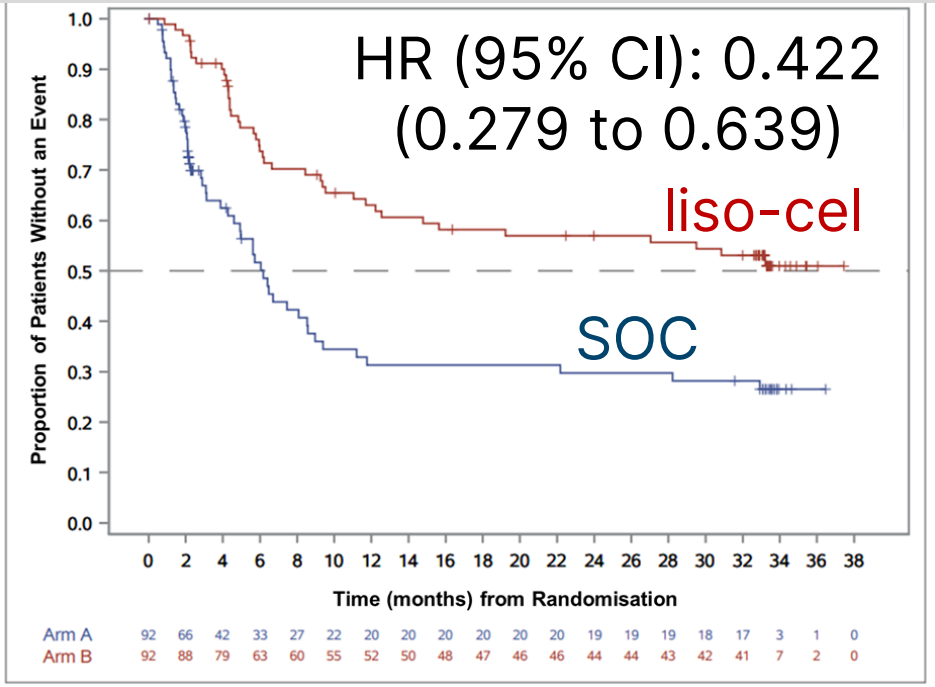
Primary outcome: EFS (October 2023 DCO)

[redacted]

HR (95% CI): 0.375
(0.259 to 0.542)

EFS: time from randomisation to PD; CR or PR not met by 9 weeks post-randomisation; start of a new antineoplastic therapy due to efficacy concerns; or death from any cause

PFS on IRC assessment (October 2023 DCO)



PFS: time from randomisation to death from any cause or PD

People in SOC arm eligible to crossover to liso-cel if CR or PR not met after 3 cycles of SOC, if they progressed at any time, or needed to start a new antineoplastic therapy due to lack of CR at 18 weeks

Abbreviations: CI, confidence interval; CR, complete response DCO, data cut off; EFS, event free survival; HR, hazard ratio; IRC, Independent Review Committee; liso-cel, lisocabtagene maraleucel; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SOC, standard of care

Key clinical trial results – TRANSFORM – PFS2 and OS

PFS2 (exploratory analysis)

[redacted]

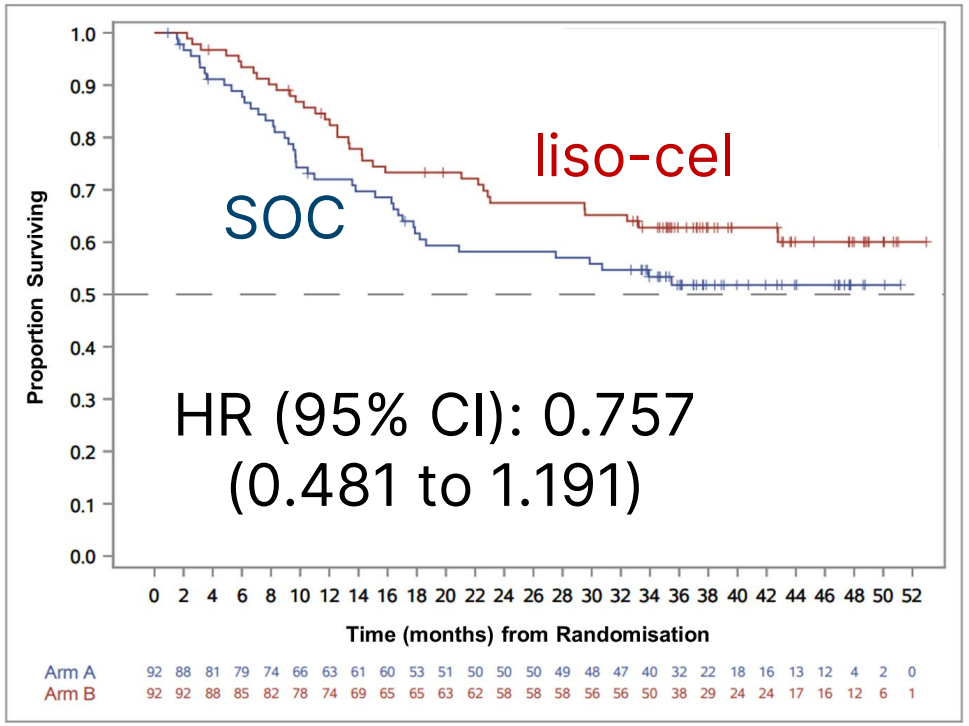
EAG estimated HR (95% CI): [redacted]

PFS2: time from randomisation to PD on the next line of subsequent treatment, or death

Patients were followed-up for disease progression for 36 months, then followed up for OS only. Liso-cel PFS2 KM dropping to 0% is based on a single death event that occurred after 36 months

Company's PFS2 plot did not contain censoring information

OS (October 2023 DCO)



66.3% of SOC patients crossed over to liso-cel

Abbreviations: AFT, accelerated failure time; CI, confidence interval; DCO, data cut off; HR, hazard ratio; KM, Kaplan-Meier; liso-cel, lisocabtagene maraleucel; PFS, progression free survival; OS, overall survival; PD, progressive disease; RPSFT, rank preserving structural failure time; SOC, standard of care

Key Issue: Generalisability of TRANSFORM

Company

- Ability to crossover to CAR-T, and use of chemotherapy-based bridging therapies in TRANSFORM reflects clinical practice unlike other CAR-T trials e.g. ZUMA-7
- SOC efficacy in TRANSFORM may be better than clinical practice (faster crossover to CAR-T, apheresis before ASCT may have improved T-cell fitness, more 3L CAR-T usage)
- Liso-cel efficacy in TRANSFORM may be underestimated versus clinical practice (more effective 3L+ treatments now available in clinical practice, e.g. bispecifics)

EAG comments

- Proportion of participants receiving bridging therapy is lower than in UK practice
- [redacted] prior use of pola+R-CHP in TRANSFORM (NICE recommended for 1L in 2023)
- All patients apheresed before randomisation, so crossover was quicker than expected in clinical practice (median time from discontinuation of SOC to liso-cel infusion = [redacted])
- Low drop out between leukapheresis and infusion in liso-cel arm is not reflective of clinical practice (89/92 patients [96.7%] in liso-cel arm received liso-cel infusion)
- Subsequent therapies are not reflective of recently approved therapies or UK practice

Clinical experts: Population and SOC reflective of UK clinical practice; optimal apheresis trial design

Is TRANSFORM generalisable to clinical practice, and appropriate for decision making?

Abbreviations: 1L, first line; 3L+, third and subsequent lines; ASCT, autologous stem cell therapy; CAR-T, chimeric antigen receptor T-cell; CHP, cyclophosphamide, doxorubicin and prednisone; liso-cel, lisocabtagene maraleucel; pola, polatuzumab; R, rituximab; SOC, standard of care

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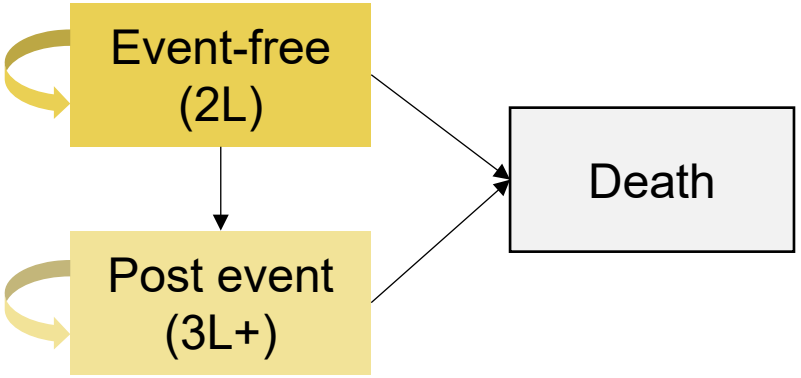
Company's model overview

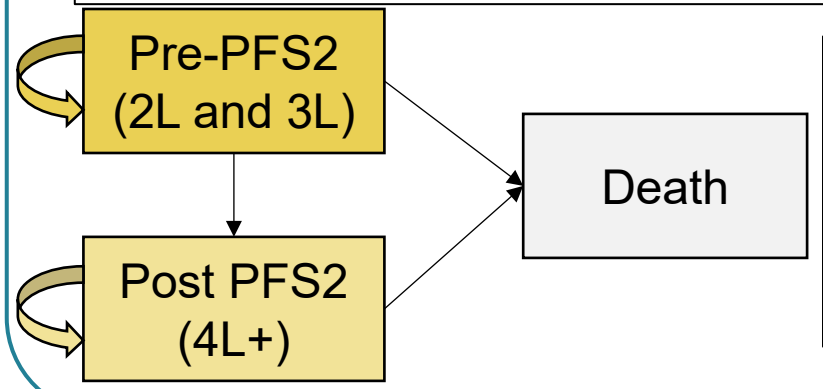
Cycle length: weekly for 5 years then annual

Partitioned survival model structure

Company's model (EFS endpoint)



EAG requested a model partitioned by PFS2 endpoint at clarification – see EFS or PFS2 slide



PFS2 only used to determine health state occupancy and utility. Resource use costs are still based on EFS curve

To align with TA895, long-term survivors (event-free after 5 years) are assumed to have:

- quality of life returned to general population values
- reduced resource use costs (2 GP visits per year and no end-of-life costs)

EAG comments

- Cost-effectiveness of liso-cel addressed in the company submission has been evaluated in line with the NICE reference case and is appropriate for this appraisal

Abbreviations: EFS, event free survival; GP, general practitioner; liso-cel, lisocabtagene maraleucel; PFS, progression free survival

Key Issue: EFS or PFS2 for economic modelling structure

Company

- EFS is primary endpoint of TRANSFORM and more clinically relevant than PFS, given curative intent of treatment
- Precedent for use of EFS for economic model structure in TA895
- Censoring of patients from PFS2 after 36 months is a key limitation of use of PFS2 data
- PFS2 approach assumes no HRQoL detriment for moving from 2L to 3L treatment

EAG comments

- EAG prefers to use PFS2 to inform model health states
- Progression from EFS to post-event health state does not reflect an objective change in health status
- In EFS structure, patients in SOC arm who experience cure at 3L+ do not receive the corresponding health benefits. Difference between EFS and OS cure fractions for SOC ([redacted] and 51%) suggests a significant proportion of patients will be cured at 3L+
- PFS2 has distinct division of cure in both 2L and 3L settings = better defined health-states
- EFS-based model was accepted in TA895, but suitable alternatives may not have been available for consideration

Is the EFS or PFS2 endpoint preferred for the economic modelling structure?

Abbreviations: EFS, event-free survival; OS, overall survival; PFS, progression free survival; PFS2, progression free survival on subsequent therapy; SOC, standard of care

Key Issue: EFS or PFS2 for economic modelling structure

N at risk							
Liso-cel EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company's PFS2 plot did not contain censoring information

Abbreviations: BC, base case; EFS, event-free survival; KM, Kaplan-Meier; liso-cel, lisocabtagene maraleucel; PFS2, progression free survival on subsequent therapy; SOC, standard of care

Key Issue: EFS or PFS2 for economic modelling structure

EFS extrapolation options

[redacted]

Arm	EFS curve	Cure fraction	AIC	BIC
Liso-cel	Log-normal	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]
SOC	Log-normal	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]

PFS2 extrapolation options

[redacted]

Arm	PFS2 curve	Cure fraction	AIC	BIC
Liso-cel	Log-logistic	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]
SOC	Log-normal	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]

Are the company's or EAG's preferred curves more appropriate, for the committee's preferred model structure?

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BC, base case; EFS, event-free survival KM, Kaplan-Meier; liso-cel, lisocabtagene maraleucel; PFS2, progression free survival on subsequent therapy; SOC, standard of care

Key Issue: Subsequent therapy distribution (1/3)

Background

- Company base case applies a one-off cost for subsequent therapy per arm, based on TTNT data from TRANSFORM
- % of TTNT events that were receipt of subsequent therapy (as opposed to death) was applied to TTNT extrapolations, before applying one-off cost

EAG comments

- EAG's clinical experts: % of TTNT events that were receipt of new therapy (94.2%) not reflective of clinical practice in SOC arm (1/3 get palliative care after unsuccessful 2L ASCT)
- Subsequent treatment distribution of novel therapies does not reflect UK practice
- EAG used distribution of subsequent therapies estimated by company's experts', as they were consistent with the EAG's clinical experts' values

Company

- EAG base case substantially underestimates subsequent treatment costs in SOC arm
- EAG's approach is misleading, changing costs with no attempt to adjust the efficacy does not accurately represent real-world and is inconsistent with UK clinical practice
- Did scenario which attempted to capture changes in efficacy associated with changing subsequent treatment distribution in both arms → EAG say this is not robust

Abbreviations: SOC, standard of care; TTNT, time to next treatment

Key Issue: Subsequent therapy distribution (2/3)

Company: clinical experts gave subsequent treatment market share %'s based on **all** patients who have 2L. So, input should be set to 100% when company's clinical experts' estimates are used

	Company preferred (Source: TRANSFORM)		EAG preferred	
	Liso-cel	SOC	Liso-cel	SOC
% of TTNT events that are receipt of subsequent therapy	69.6%	94.2%	69.6% (assumed same as TRANSFORM)	66% (EAG's clinical experts)
Subsequent treatment	Company preferred (Source: TRANSFORM)		EAG preferred (source: company's clinical experts)	
ASCT	9.38%	0%	1.25%	1.25%
Allo-SCT	25%	3.08%	3.75%	3%
3L+ chemotherapy	100%	35.38%	15%	11.75%
Other novel therapy	0%	0%	81.25%	54.75%
3L+ CAR-T	0%	93.85%	0%	66.25%
3L+ radiotherapy	12.5%	0%	0%	11.75%

Other novel therapy	Company's clinical expert estimates (used in model)		NHS England (treatment after 2L CAR-T)	
	Liso-cel	SOC	Liso-cel	SOC
Polatuzumab vedotin-BR	12.3%	16.9%	0% (0/44)	0% (0/225)
Glofitamab	40%	36.5%	80% (35/44)	70% (157/225)
Loncastuximab tesirine	7.7%	10%	4% (2/44)	15% (33/225)
Epcoritamab	40%	36.5%	16% (7/44)	15% (35/225)

Should subsequent therapy use be based on TRANSFORM or clinical expert opinion?

Abbreviations: 3L, third line; allo-SCT, allogenic stem cell transplant; ASCT, autologous stem cell transplant; liso-cel, lisocabtagene maraleucel; BR, bendamustine, rituximab; SOC, standard of care; TTNT, time to next treatment

Key Issue: Subsequent therapy distribution (3/3)

Technical team comments:

Subsequent CAR-T use in TA895

- In ZUMA-7, 56% of people in the standard care group had 3L CAR T-cell therapy
- At the time of the TA895 (2L axi-cel) appraisal, 3L CAR-T was not considered to be established practice and so not considered a relevant subsequent treatment
- The TA895 committee agreed with the company's crossover adjustment of standard care OS to remove the benefit of subsequent CAR T-cell therapy

Subsequent treatment distributions in TA895

- Clinical experts advised that some subsequent therapies included in ZUMA-7 were not reimbursed in NHS England, including pembrolizumab and nivolumab
- The company modelled subsequent therapies based on clinical expert opinion, the EAG preferred to use the ZUMA-7 trial data
- The TA895 committee preferred subsequent treatment distributions from ZUMA-7

Abbreviations: 2L, second-line; 3L, third-line; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; OS, overall survival

Key Issue: Extrapolation of OS (1/3)

Link to comparison of outcomes for liso-cel and axi-cel slide

Background

- Company uses log-normal mixture cure models for liso-cel and SOC
  - Liso-cel cure fraction (60.3%) close to range anticipated by experts ([redacted])
  - All SOC models (base case cure fraction: 51.0%) likely overestimate long-term survival (cure proportion range anticipated by experts [redacted]) – see TRANSFORM generalisability slide

EAG comments:

- Company's preferred liso-cel OS model is too optimistic
- OS data less mature than EFS and PFS2 so less likely to estimate the true cure proportion
- Company's liso-cel OS cure rate is higher than:
  - Predicted by PFS2 models (EAG expects PFS2 to be predictive of OS)
  - Models considered plausible by committee in TA895 (EAG estimates at 40-50%)
    - Published real-world study (Portuguese et al.) did not show clear OS benefit for liso-cel versus axi-cel, and 2 ITCs at 3L showed significant OS benefit for axi-cel (ZUMA-1)
- Company's EFS and OS curves cross in both arms; EAG finds this implausible due to potential for curative ASCT at 3L for some people (company say adjustment in model prevents crossing)
- Prefers to use SurvInt log-logistic models for both arms, with long-term ZUMA-7 data for liso-cel
  - ZUMA-7 more reliable than TRANSFORM (more mature OS follow-up and larger sample size)

Abbreviations: 3L, third line; ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; EFS, event-free survival; ITC, indirect treatment comparison; liso-cel, lisocabtagene maraleucel; OS, overall survival; PFS2, progression free survival on subsequent therapy; SOC, standard of care

Key Issue: Extrapolation of OS (2/3)

Company

- In the liso-cel arm, data from TRANSFORM and ZUMA-7 expected to underestimate clinical outcomes compared to UK clinical practice (more effective 3L+ treatments)
- Use of ZUMA-7 data in SurvInt to inform long-term efficacy for liso-cel is not appropriate
  - TRANSFORM trial design more closely reflects UK clinical practice
  - Liso-cel and axi-cel are different treatments with different manufacturing processes
  - Differences between ZUMA-7 and TRANSFORM (patient population, bridging therapy, crossover and lymphodepletion regimens) could account for the differences in the intervention arm efficacy results
- Large difference in PFS2 and OS cure rates is likely due to differences in censoring
- Critique on the EAG's use of SurvInt:
  - No recommendation in TSD14 for using a 3rd party tool for survival extrapolations
  - Analysis not aligned to NICE reference case (synthesis of evidence on health effects should be based on systematic review)
  - Approach ignores most of the TRANSFORM Kaplan-Meier data
  - Informed by only 3 arbitrarily chosen inputs: 2 survival points and a cure fraction

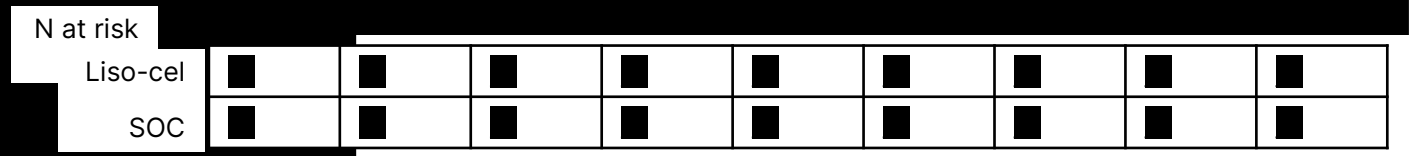
Abbreviations: 3L, third line; axi-cel, axicabtagene ciloleucel; liso-cel, lisocabtagene maraleucel; OS, overall survival; PFS2, progression free survival on subsequent therapy; TSD, Technical Support Document

Link to Modelled survival outcomes slide

Key Issue: Extrapolation of OS (3/3)

Arm	Approach	OS% for cured and non-cured patients		
		2 years	5 years	10 years
Liso-cel	Company BC	70.0%	59.4%	54.0%
	EAG BC	64.5%	50.4%	44.0%

[redacted]



Arm	Approach	OS% for cured and non-cured patients		
		2 years	5 years	10 years
SOC	Company BC	59.1%	50.2%	45.7%
	EAG BC	54.5%	39.2%	32.3%

Is the company's or EAG's approach to modelling overall survival more appropriate?

Abbreviations: BC, base case; KM, Kaplan-Meier; liso-cel, lisocabtagene maraleucel; OS, overall survival; SOC, standard of care

Key Issue: Extrapolation of time to next treatment (TTNT)

Company

- Modelling of subsequent treatments is informed by log-normal mixture cure models fitted to TTNT data for liso-cel and SOC
- Applied a multiplier to estimate new-treatment events out of all TTNT events
- Assumed no new TTNT events would occur related to the primary disease after 5 years

EAG comments

- Prefers mixture cure models fitted to EFS data to model TTNT
- Unclear why TTNT extrapolations are more optimistic than EFS, given similar descriptions
- TTNT extrapolations are more optimistic than those published in TA895
- EFS will be more mature, and likely to give a more reliable long-term extrapolation

	Company		EAG		TA895	
	Liso-cel	SOC	Liso-cel	SOC	CAR-T	SOC
Outcome modelled	TTNT	TTNT	EFS	EFS	TTNT	TTNT
Preferred mixture cure model	Log-normal	Log-normal	Generalised gamma	Log-normal	-	-
5-year estimate	[redacted]	[redacted]	[redacted]	[redacted]	40.6% - 43.0%	19.7% - 20.7%

Abbreviations: EFS, event-free survival; liso-cel, lisocabtagene maraleucel; OS, overall survival; SOC, standard of care; TTNT, time-to-next treatment

Key Issue: Extrapolation of TTNT

TTNT was defined as the time from randomisation to death due to any cause, or start of new antineoplastic therapy, whichever occurred first

N at risk							
Liso-cel EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Should TTNT be modelled using the TTNT or EFS dataset?

Abbreviations: BC, base case; EFS, event-free survival KM, Kaplan-Meier; liso-cel, lisocabtagene maraleucel; SOC, standard of care; TTNT, time-to-next treatment

Key Issue: Adverse event costs at 3L

Background

- A CAR-T tariff cost of £41,101 was accepted by the committee in TA895
- Assumed to include all costs of care from decision to have CAR-T to 100 days after infusion, excluding CAR-T acquisition costs, bridging therapy costs and costs associated with treatment of hypogammaglobulinemia

Company

- Assumed patients receiving 3L+ CAR-T accrued the CAR-T tariff cost, bridging therapy costs and the drug acquisition cost of axi-cel
- No costs associated with AEs were considered for other subsequent therapies

EAG comments

- AEs may be double counted for SOC but underestimated for liso-cel
  - Liso-cel – CAR-T tariff doesn't include AEs after 100 days after infusion
  - SOC – company applied cost of 3L CAR-T tariff (including AE costs to 100 days after infusion) **and** AEs in TRANSFORM
- EAG **excluded** estimated AE cost of £10,611 from the tariff for patients having 3L+ CAR-T to align with assumption of not including AE costs at 3L for liso-cel

Should the cost of AEs be excluded from the CAR-T tariff when applied at 3L?

Abbreviations: 3L, third line; AE, adverse event; CAR, chimeric antigen receptor; liso-cel, lisocabtagene maraleucel; SOC, standard of care

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case	Slide
Model structure	EFS	PFS2	17
a. For EFS structure	• Log-normal EFS curves for liso-cel and SOC	• Generalised gamma EFS curves for liso-cel and SOC	19
b. For PFS2 structure	• Log-logistic for liso-cel PFS2 curve • Log-normal for SOC PFS2 curve	• Weibull for liso-cel PFS2 curve • Log-logistic for SOC PFS2 curve	19
Subsequent therapy	TRANSFORM	Clinical expert opinion	20
OS curves	Mixture cure models	SurvInt	23
TTNT	TTNT dataset	EFS dataset	26
AE costs (CAR-T tariff at 3L)	Included	Excluded	28
Other issues			
Bridging therapy	TRANSFORM	Clinical practice (Boyle et al.)	42
Event-free/pre-PFS2 utility	0.852	0.785	43
Discounting	Annual discount rate during the weekly cycle period	Per cycle (weekly) discount rate during the weekly cycle period	-
Patient starting age	[redacted] years, based on TRANSFORM	59 years, based on current data for 2L axi-cel use in CDF	-

Abbreviations: 2L, second line; 3L, third line; AE, adverse event; CAR, chimeric antigen receptor; CDF, Cancer Drugs Fund; EFS, event-free survival; OS, overall survival; PFS2, progression free survival on subsequent therapy; TTNT, time to next treatment

Cost-effectiveness results

All cost-effectiveness estimates are reported in Part 2 slides because they include confidential discounts

Cost-effectiveness results to be presented include:

Scenarios

- Company base case
- EAG base case
- Scenarios for all differences between company and EAG base cases
- Scenarios exploring subsequent treatment, OS modelling, and patient starting age assumptions

Analyses

- Deterministic
- Probabilistic

MPSC prices

- Lowest, midpoint and highest available MPSC prices for rituximab and tocilizumab

	ICER (£/QALY) versus SOC
Company base case	<£30,000
EAG base case	>£30,000

Note: company concluded that liso-cel is **not eligible** for a severity modifier when compared to SOC, and the EAG agreed

Abbreviations: ICER, incremental cost effectiveness ratio; MPSC, Medicines Procurement and Supply Chain; OS, overall survival; QALY, quality adjusted life year; SOC, standard of care

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Company

- Submission is based on the final DCO from TRANSFORM and no further data are expected to become available in this patient population to inform decision making

Abbreviations: DCO, data cut-off

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

Link to other issues slide

Key issue	Questions for consideration	ICER impact
Generalisability of TRANSFORM trial for NHS care	Is TRANSFORM generalisable to clinical practice, and appropriate for decision making?	Unknown
Subsequent therapy distribution	• Should subsequent therapy use be based on TRANSFORM or UK clinical practice? • Should adjustments to the efficacy estimates (OS/TTNT) be considered, as well as costs?	Large
Extrapolation of OS	Is the company's (mixture cure) or EAG's (SurvInt) approach to modelling OS more appropriate?	Moderate
Extrapolation of TTNT	Should TTNT be modelled using the TTNT or EFS dataset?	Moderate
Adverse event costs at 3L	Should the cost of adverse events be excluded from the CAR-T tariff when applied at 3L?	Moderate
EFS or PFS2 for economic modelling structure	• Is the EFS or PFS2 endpoint preferred for the economic modelling structure? • Are the company's or EAG's preferred curves more appropriate?	Small

Abbreviations: 3L, third line; CAR, chimeric antigen receptor; EFS, event-free survival; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS2, progression free survival on subsequent therapy; TTNT, time to next treatment

Thank you.

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphomas after first-line chemotherapy when a stem cell transplant is suitable

Supplementary appendix

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Back to key issues slide

Other issues

Other issues	Questions for consideration	ICER impact
Utility value for “healthy” health state for first 5 years of model	Is an event-free / progression-free utility of 0.852 or 0.785 more appropriate?	Small 
Bridging therapy distribution	Is modelling bridging therapy use on TRANSFORM or Boyle et al. more appropriate?	Small 
Other areas of uncertainty		
Discounting	Should an annual or per cycle (weekly) discount rate be applied during the model’s weekly cycle period?	Small 
Patient starting age	Should the starting age of the modelled population be based on TRANSFORM or NHS data?	Small 

Abbreviations: ICER, incremental cost effectiveness ratio

Link to overall survival slide

Modelled survival outcomes per economic modelling structure

Preferred model structure/analysis

	EFS		PFS2		OS	
	Liso-cel	SOC	Liso-cel	SOC	Liso-cel	SOC
Company preferred curve	Log-normal	Log-normal (generalised gamma also plausible)	Log-logistic	Log-normal	Log-normal	Log-normal
Cure fraction	[redacted]	[redacted]	[redacted]	[redacted]	60.3%	51.0%
EAG preferred curve	Generalised gamma	Generalised gamma (log-normal also plausible)	Weibull (log-logistic also plausible)	Log-logistic (log-normal also plausible)	SurvInt log-logistic model	SurvInt log-logistic model
Cure fraction	[redacted]	[redacted]	[redacted]	[redacted]	50.0%	35.0%
External data landmark survival	ZUMA-7 (2L axi-cel): 39% at 4 years	-	-	ZUMA-1 5-year OS scaled down to 80-90% of population expected to receive 3L CAR-T: 34.08-38.34%	ZUMA-7: EAG estimated 52% at 5 years	ZUMA-1 (3L axi-cel): 42.6% at 5 years

Abbreviations: 2L, second line; 3L, third line; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; EFS, event-free survival; liso-cel; lisocabtagene maraleucel; OS, overall survival; PFS2, progression free survival on subsequent therapy; SOC, standard of care

Link to overall survival slide

Comparison of outcomes for liso-cel and axi-cel

		Axi-cel (ZUMA 7)	Liso-cel (TRANSFORM)	Difference
EFS:	1 year	49%	[redacted]	[redacted]
	2 year	44%		
	3 year	41%	45.8%	4.8%
	4 year	39%	N/A	-
OS:	1 year	76%	83.5%	7.5%
	2 year	60%	67.5%	7.5%
	3 year	56%	62.8%	6.8%
	4 year	55%	N/A	-
PFS:	1 year	52%	63.0%	11.0%
	2 year	46%	57.0%	11.0%
	3 year	44%	50.9%	6.9%
	4 year	41%	N/A	-
Predicted OS:		Generalised Gamma / Log-logistic	Log-normal / Exponential	
	5 year	50.5% / 46.2%*	59.4% / 57.5%	-
	10 year	47.7% / 41.1%*	54.0% / 50.2%	-
	15 year	43.8% / 37.0%*	48.5% / 44.8%	-

*Estimated from EAG digitisation from TA895 committee papers

Abbreviations: axi-cel, axicabtagene ciloleucel; EFS, event-free survival; liso-cel; lisocabtagene maraleucel; OS, overall survival; PFS, progression free survival

Link to overall survival slide

SurvInt

Gallacher D. SurvInt: a simple tool to obtain precise parametric survival extrapolations.
BMC Medical Informatics and Decision Making 2024;24(1):76.

- Freely available R Shiny tool that uses user specified population survival at key time points to produce parametric extrapolations that are consistent with the parameters specified by the user
- EAG's inputs for SurvInt:

SurvInt parameter	Liso-cel		SOC	
	Input	Source	Input	Source
[t1, S(t1)]	[11.05,0.85]	TRANSFORM	[6.59,0.86]	TRANSFORM
[t2, S(t2)]	[48.00, 0.55]	4-year follow-up from ZUMA-7	[17.76, 0.63]	TRANSFORM
Cure proportion	0.50	Estimated for consistency with cure proportions of PFS2 and extrapolations from ZUMA-7	0.35	Estimated for consistency with cure proportions of PFS2

Abbreviations: liso-cel, lisocabtagene maraleucel; PFS2, progression free survival on subsequent therapy; SOC, standard of care

Link to subsequent treatment slide

Company's subsequent treatment scenario analysis

Company

- TRANSFORM may underestimate OS for liso-cel and overestimate OS for SOC, compared to efficacy expected in UK clinical practice
- Company's scenario analysis for adjusting the differences in subsequent treatments between TRANSFORM and UK clinical practice, with respect to costs and efficacy:
  - Distribution of subsequent therapies based on UK clinical expert input
  - More optimistic Weibull curve for liso-cel OS (cure fraction [redacted])
  - Weighted average SOC OS curve: 66.25% of liso-cel OS curve from TRANSFORM, and 33.75% CORAL OS extrapolation
- Weightings based on assumption that TRANSFORM is representative of patients receiving 3L+ CAR-T and CORAL is representative of patients not receiving 3L+ CAR-T (to account for potential overestimate of TRANSFORM OS SOC)

EAG comments:

- Company's scenario analysis is not robust: unclear how weightings were obtained

Abbreviations: 3L, third line; CAR, chimeric antigen receptor; liso-cel, lisocabtagene maraleucel; OS, overall survival; SOC, standard of care

Key Issue: Bridging therapy distribution

		Company base case	EAG preferred
Receiving bridging therapy		63.04%	89.00%
Distribution of bridging therapy	R-GDP	[redacted]	6.74%
	R-DHAP	[redacted]	6.74%
	R-ICE	[redacted]	6.74%
	PolaBR	[redacted]	64.04%
	Radiotherapy	[redacted]	35.96%
Source		TRANSFORM	UK study of CAR-T use (Boyle et al.)

EAG comments

- Company applied 2L bridging therapy data from TRANSFORM to SOC group who receive 3L CAR-T, but this does not consider the potential for line-specific bridging therapy
- Clinical advice to EAG suggests the proportion of patients receiving bridging therapies and the distribution of bridging therapies will differ from the company base case
- EAG prefers to use UK specific data

Company

- EAG's approach is unlikely to be reflective of UK clinical practice as it does not consider the changing landscape (recommendation in 2023 for pola+R-CHP in 1L will reduce use of pola-BR in 2L), or the differences between 2L and 3L bridging therapy
- EAG's approach does not align costs with the modelled efficacy

Is modelling bridging therapy use on TRANSFORM or Boyle et al. more appropriate?

Abbreviations: 2L, second line; 3L, third line; BR, bendamustine and rituximab; CAR, chimeric antigen receptor; CHP, cyclophosphamide, doxorubicin and prednisone; DHAP, dexamethasone, cytarabine, cisplatin; GDP, gemcitabine, dexamethasone and cisplatin; ICE, ifosfamide, carboplatin and etoposide; liso-cel, lisocabtagene maraleucel; pola, polatuzumab vedotin; R, rituximab; SOC, standard of care

Key Issue: Utility for event-free/pre-PFS2 health state

Analysis	Heath state	Utility	Source
Company base case	Event-free	0.852	TRANSFORM EQ-5D analysis (final DCO; October 2023)
	Post-event	0.808	
Company's PFS2 scenario	Pre PFS2	0.852	TRANSFORM (EFS utility)
	Post PFS2	0.72	TA895 (post progression, ZUMA-1 3L axi-cel)
Long-term remission (5-year switch timepoint)		0.853	General population utility (based on company's [redacted] year starting age)

EAG comments

- Company's utility for the event-free and pre-PFS2 health state is too optimistic
  - Differs significantly from estimates used in TA895 (0.785 [event-free health state, based on ZUMA-7])
  - Similar to general population utility estimate of 0.853
- EAG prefers the TA895 value of 0.785 (patients may be unwell and face uncertainty over their prognosis)

Is an event-free / progression-free utility of 0.852 or 0.785 more appropriate?

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Abbreviations: 3L, third line; axi-cel, axicabtagene ciloleucel; DCO, data cut off; EFS, event-free survival; PFS2, progression free survival on subsequent therapy