Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

Slides for Zoom: confidential information redacted

Technology appraisal committee HST [21st August 2025]

2nd committee meeting

Chair: Paul Arundel

External assessment group: Birmingham Centre for Evidence and Implementation Science

Technical team: Janet Boadu, Victoria Kelly, Lorna Dunning

Company: Autolus Limited

Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

- ✓ **Background and ACM1 summary**
- ❑ Consultation responses
- ❑ Key issues
- ❑ Cost effectiveness results

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Obecabtagene autoleucel (Aucatzyl, Autolus Limited)

Marketing authorisation (MHRA, April 2025)	• Obecabtagene autoleucel is indicated for the treatment of adult patients (≥18 years) with relapsed or refractory B cell precursor acute lymphoblastic leukaemia
Mechanism of action	• Obecabtagene autoleucel is an autologous cancer therapy which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells
Administration	• Intravenous infusion
Price	• The list price for obecabtagene autoleucel £372,000.00 as a one-off cost • There is a confidential patient access scheme • NHSE has a tariff for delivering CAR T-cell therapies

Abbreviations: MHRA, medicines and healthcare products regulatory agency; CAR-T, chimeric antigen receptor T-cell; ALL, acute lymphoblastic leukaemia

Committee conclusions at ACM1 (1/2)

see appendix for all conclusions

Obe-cel not recommended, not cost-effective

- Committee noted important uncertainties in the clinical effectiveness and modelling.
- It decided that more evidence was needed to generate robust cost-effectiveness estimates.
- The committee could not conclude that obe-cel would represent a cost-effective use of NHS resources. So, obe-cel is not recommended

Committee preferred assumptions at ACM1	Adopted by company in base case for ACM2?
Choice of population: enrolled ITT population from cohorts 1A and 2A	Yes
Use of NHSE CAR T-cell tariff cost £60,462	Yes
EAG approach to calculating follow up costs after ASCT	Yes
EAG per-year discount rate of 3.5%	Yes
Utility values adjusted in the post-event health state using time-dependent utilities from TA541	Yes
Severity weight = 1.2	Yes

Abbreviations: ITT, intention-to-treat; NHSE, NHS England; ASCT, allogeneic stem cell transplant; TA, technology appraisal; ACM, appraisal committee meeting

Committee conclusions at ACM1 (2/2)

see appendix for all conclusions

Committee requested further clarification on:	Provided by company ?	Results in changes to company base case?
How the model accounts for ponatinib and inotuzumab being used as bridging therapies to improve outcomes before CAR T-cell therapy, and their relevant costs	Yes	No
Comparison using real-world data from NHS England for tisagenlecleucel	Partially	No
Further evidence and justification for applying the inverse hazard ratio to blinatumomab	Yes	No
Further clarification on the assumption that people who have had events can be considered cured at 3 years	Yes	No
Further evidence to support the assumption that a standardised mortality ratio of 3 is appropriate, especially for those who have had an event	Yes	No*
Range of scenarios exploring a proportion of less than 10% of people having ASCT after obe-cel in the ITT population	Yes	No*
Further clarification on how mortality was addressed in the SCT tunnel states	Yes	No
Further evidence and justification on the proportion people having intravenous immunoglobulin in the model, and the duration of treatment	Yes	Yes*

*Provided scenarios. Abbreviations: ITT, intention-to-treat; ASCT, allogeneic stem cell transplant; ACM, appraisal committee meeting; CAR-T, chimeric antigen receptor T-cell

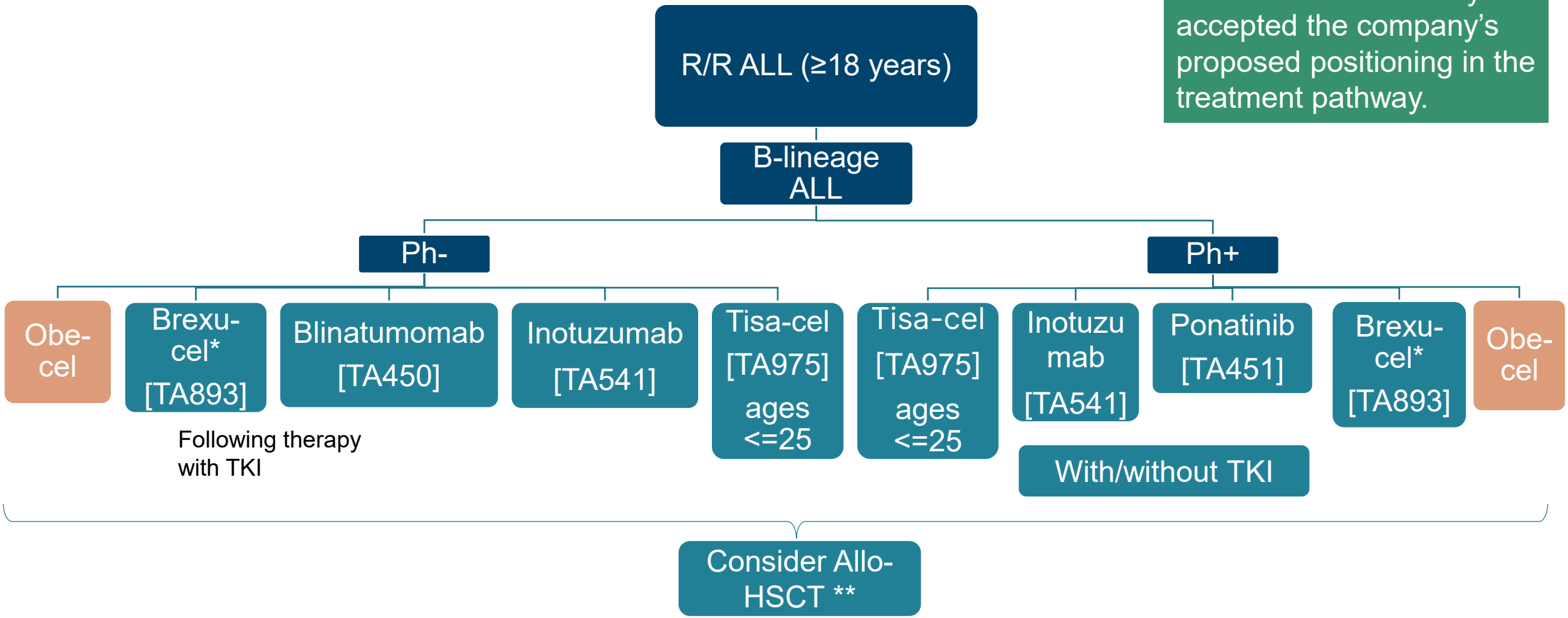
Key issues to resolve

Key issue	ICER impact
Comparison against tisa-cel	Unknown
How model accounts for bridging therapies	Small
Updated MAIC analyses and EFS/OS curve selections	Small
Inverse hazard ratio approach	Unknown
Cure assumption and SMR	Moderate
Appropriate costs associated with ASCT in the obe-cel arm	Moderate
Intravenous immunoglobulin use	Small
Benefits not captured in the QALY	Unknown
Key issues accepted by company in base case after ACM1*	
Use of enrolled population ITT population (cohorts 1A and 2A) (response to DG 3.11)	
CAR- T Tariff (response to DG 3.13)	
Mortality captured in the SCT tunnel states (response to DG 3.17)	
Severity modifier (response to DG 3.21)	

* The company accepted committee preferences but provided alternate scenarios. Abbreviations: ICER, incremental cost effectiveness ratio; EFS, event-free survival; OS, overall survival; SMR, standardised mortality ratio; CAR T; chimeric antigen receptor T-cell; ASCT, allogeneic stem cell transplant; MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison; QALY, quality-adjusted life year

Proposed positioning of obe-cel in the relapsed/refractory B-cell ALL treatment pathway

The committee broadly accepted the company's proposed positioning in the treatment pathway.



*Brexu-cel available through Cancer Drugs Fund (not considered comparator), **Allo-HSCT part of treatment pathway, but not considered comparator, rather an outcome: ALL, acute lymphoblastic leukaemia; allo-HSCT, allogeneic haematopoietic stem cell transplantation; Ph+, Philadelphia chromosome-positive; Ph-,Philadelphia chromosome negative; R/R, relapsed/refractory; TKI, tyrosine kinase inhibitor; Brexu-cel, Brexucabtagene autoleucel; Inotuzumab, Inotuzumab ozogamicin

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Stakeholder responses to Draft Guidance

Submissions from Anthony Nolan, Leukaemia UK, 1 patient expert and 2 clinical experts, 2 web comments

- A major advantage of obe-cel for B-ALL is the prolonged CAR persistence observed in a substantial number of people treated, which is significantly associated with durable remission without the requirement for ASCT
- There is clear need from people for an additional CAR-T treatment that has shown to have a more favourable side-effect profile and increased persistence over time
- Obe-cel is not just “another treatment option”, it has clear use for those aged 26 years and older who may not be fit enough to tolerate other CAR-T or transplant options and those who do not have access to an ASCT donor
- Treatment options for people with co-morbidities have limited treatment options and obe-cel represents a good treatment option for these groups

“Obe-cel has a record of less severe side effects, patients and carers feel that fewer severe side effects would greatly improve their quality of life.”

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Abbreviations: B- ALL; B cell acute lymphoblastic leukaemia; CAR T; chimeric antigen receptor T-cell; ASCT, allogeneic stem cell transplant

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Consultation comments – Company overview

The company submitted additional data that was not specifically requested by the committee including:

- Clinical efficacy evidence from the 2025 FELIX data cut
- Rerun pairwise MAIC versus all comparators (inotuzumab, blinatumomab and ponatinib)
- Conducted STC to address methodological uncertainties with the MAIC
- Accepted all committee preferences in revised base case, but highlight following key benefits are not considered by adopting these methods:
    - Considerably smaller proportion of people will be pre-treated but not infused with obe-cel in clinical practice, therefore using an enrolled population is a conservative approach
    - Benefits of obe-cel remain uncaptured, due to use of the NHS CAR-T tariff; including an improved safety profile, outpatient or ambulatory care use, UK manufacturing and a better patient management
    - Proportion of people who undergo subsequent ASCT following treatment with inotuzumab, blinatumomab and ponatinib likely higher than economic analysis; (clinical expert feedback indicated these treatments are not considered to be consolidation therapies and the goal would be to try and get a patient to a curative treatment (ASCT)).

Abbreviations: CAR T; chimeric antigen receptor T-cell; ASCT, allogeneic stem cell transplant; MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison

see appendix FELIX trial design and for ORR and DOR

Obe-cel study results: January 2025 date cut-off

Committee conclusion at ACM1: FELIX Cohort 1A and 2A enrolled population appropriate for decision making – Outcomes similar to previous data cut

	Cohorts 1A and 2A – enrolled (n=133) [committee preferred population]		Cohorts 1A and 2A – infused (n=107)
Date	February 2024	January 2025	January 2025
EFS	Without censoring for SCT	Without | with censoring	Without | with censoring
Median (months)	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]
OS	Without censoring	Without | with censoring	Without | with censoring
Median (months)	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
24 months	NR	[redacted]	[redacted]
36 months	NR	[redacted]	[redacted]

Abbreviations: ACM, appraisal committee meeting; SCT, stem cell transplant; EFS, event-free survival; OS, overall survival; NR, not reported

Unknown impact ?

Key issue: Comparison against Tisagenlecleucel (1/2)

Committee at ACM1:

- MA includes all people 18 years and older - company anticipated narrower age range for MA, so didn't provide a comparison with Tisagenlecleucel (tisa-cel) for 18-25 group
- Committee: tisa-cel is a suitable comparator in the 18 to 25 years age group and requested a comparison using FELIX data for obe cel alongside real-world data from the SACT dataset for tisa-cel

Company response to DG:

- FELIX obe-cel population aged 18 to 25 very small: [redacted]
- Several prognostic factors and TEMs not available from tisa-cel studies; analysis extremely uncertain; ESS very small
- Conducted unanchored MAIC analysis, weighting data for the 18-25 subgroup from cohort IIA only to population reported by Stackelberg et al. (this study combined the populations of several tisa-cel studies, including a combination of trial and real-world populations)
- Also compared against SACT data for tisa-cel
- Did not provide cost comparison

EAG comments

- Cohort 1A data could have been used – small change to population could have been influential on results
- Analysis at risk of bias – covariates imperfectly balanced
- Results lack face validity – HR for OS is larger than effect size for obe-cel vs inotuzumab
- Unclear why no separate MAIC was performed using characteristics specific to SACT population
- Naïve comparison to SACT follow-up suggests obe-cel may offer [redacted] OS, however highly uncertain
- Reliable comparison between obe-cel and tisa-cel unlikely possible based on currently reported data
- Provide cost-comparison in part 2 (equal efficacy)

Abbreviations: Abbreviations: MA, marketing authorization; OS, overall survival; SACT, Systemic Anti-Cancer Therapy; TEMs, treatment effect modifiers; MAIC; matching-adjusted indirect comparison; HR, hazard ratio

see appendix for covariates table

Unknown impact ?

Key issue: Comparison against Tisagenlecleucel (2/2)

Company: Non-significant OS benefit for obe-cel (age 18-25) vs tisa-cel (age <=25)

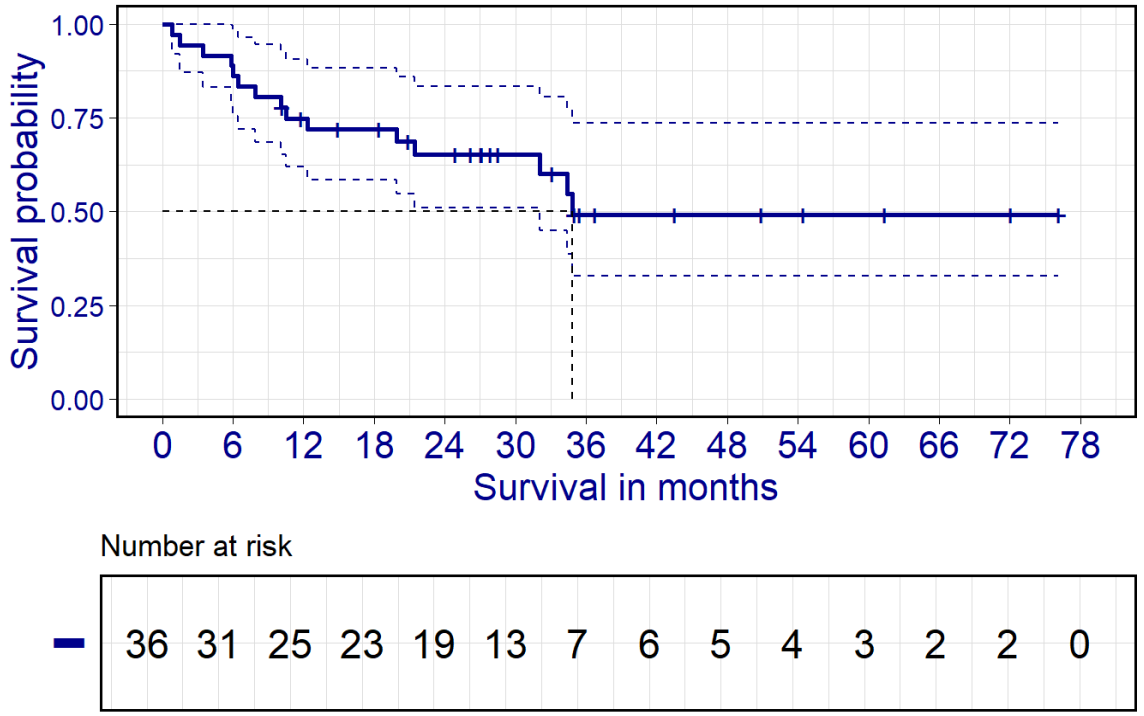
Treatment	Median OS	ESS	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Obe-cel	[redacted]	-	-	-
Tisa-cel	43.2	[redacted]	[redacted]	[redacted]

Company: KM plot of OS, FELIX Cohort 2A mITT – ages 18-25 vs tisa-cel pooled analysis (ages <=25)

[redacted]

Abbreviations: KM, Kaplan-Meier; OS, overall survival; HR, hazard ratio; EFS, event-free survival; mITT, modified intention-to-treat; SACT, Systemic Anti-Cancer Therapy

EAG Kaplan Meier plot for OS of tisa-cel SACT population (source: NHS England Report)



- Do the analyses provide a robust comparison with tisa-cel?

Small impact

Key issue: How model accounts for bridging therapies

Committee at ACM1:

- Most of the comparators are used as bridging therapies to ASCT or CAR T cell therapy
- Appropriate comparators are tisa-cel (18-25 years) and inotuzumab, blinatumomab (Ph-) and ponatinib (Ph+) if ASCT included as a subsequent treatment
- Requested further clarification on how the model accounts for ponatinib and inotuzumab being used as bridging therapies to improve outcomes before CAR T-cell therapy, and their relevant costs

Company response to DG:

- Costs associated for bridging with inotuzumab and ponatinib in model calculated as weighted average based on the proportion of people who received each bridging chemotherapy from FELIX and the associated acquisition and administration costs
- In pooled Cohorts 1A and 2A, (n=[redacted]) received inotuzumab; (n=[redacted] received ponatinib
- Impact on clinical efficacy from bridging therapy captured as efficacy data for obe-cel was informed by FELIX

EAG comments: Agrees model captures influence of therapies on obe-cel outcomes

- Bridging treatment costs: company estimated using a frequency derived from percentage of people enrolled who received bridging treatment
- Company use correction factor of <1 applied to bridging treatment costs to account for patients who undergo leukapheresis but fail to receive CAR T-cell infusion. Results in double-counting when ITT population used.
- EAG considers correction factor 1 most appropriate to avoid duplication

- Has sufficient evidence been provided to show how the model accounts for comparators as bridging therapies?
- Is a correction factor of 1 appropriate?

Abbreviations: CAR T; chimeric antigen receptor T-cell; ASCT, allogeneic stem cell transplant; Ph, Philadelphia chromosome; ITT, intention-to-treat

Small impact

Key issue: Updated MAIC and EFS/OS curve selections

Committee at ACM1:

- Company conducted MAIC to estimate the relative effectiveness of obe cel vs inotuzumab and blinatumomab for OS and EFS, and presented a naive unadjusted comparison with ponatinib
- Committee concluded because of the small sample size, results of the MAIC were highly uncertain

Company (response to DG)

- Updated MAIC using most recent (January 2025) FELIX data cut to inform the obe-cel arm
- To address potential methodological uncertainties, company conducted pairwise STCs using FELIX January 2025 data cut to inform the obe-cel arm, and data from the same published comparator trials to inform inotuzumab, blinatumomab and ponatinib arms that were used for MAIC analyses
- For each comparison, the company updated the ITCs and survival extrapolations, assessing both the infused and enrolled populations of cohorts 1A and 2A from FELIX, without censoring for subsequent ASCT

EAG comments

- Overall updated data cut has minimal impact on HRs applied in model; the EAG has no issue using revised HRs
- Notes occasional minor differences between MAIC and STC estimates, but differences not of concern
- EAG preferred more flexible approach for obe-cel EFS curve in the overall population and obe-cel EFS and OS curves in PH+ population [see appendix for details]

- Is the company's updated MAIC appropriate?
- Are the company's choice of curves appropriate?

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Abbreviations: OS, overall survival; EFS, event-free survival; MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison; HR, hazard ratio

see appendix for updated HRs, and curve selections

Key issue: Inverse hazard ratio approach (1/2)

Unknown impact ?

Committee at ACM1:

- Committee requested the company provide a more robust rationale for using inverse HR approach for comparison with inotuzumab and blinatumomab (Ph- population); committee noted approach would be appropriate if FELIX best reflected the NHS population, but it did not believe it had seen evidence that it was more representative than INO-VATE or TOWER

Company response to DG:

- Maintains use of inverse HR approach; EAG's suggestion of using standard MAIC approach doesn't allow for accurate incremental analysis in Ph- subgroup, given multiple comparators
- No Ph- subgroup specific data available from INOVATE; HRs based on the overall populations of inotuzumab and obe-cel; applying this HR to inotuzumab curve to estimate obe-cel efficacy introduces bias as neither obe-cel or inotuzumab curves would be representative of the Ph- subgroup
- Inverse HR approach anchors inotuzumab curve to subgroup-specific obe-cel data, reducing bias by using overall population data from INOVATE (in line with TA893 [brexu-cel]); approach ensures same baseline characteristics assumed for all arms compared to inotuzumab and blinatumomab, allowing for fair comparison
- Small ESS when matched to inotuzumab and blinatumomab highlights between trial differences and supports using MAIC results over a naïve comparison, as MAIC better aligns patient populations
- Acknowledges concerns on underlying proportional hazards assumption – EAG in TA893 noted use of a cure assumption means long term survival extrapolations not required so strong assumption of PH not necessary

Abbreviations: CAR T; chimeric antigen receptor T-cell; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Ph, Philadelphia chromosome; PH, proportional hazards; ESS, effective sample size; TA, technology appraisal

Unknown impact ?

Key issue: Inverse hazard ratio approach (2/2)

EAG comments

- Company have not implemented analyses which fit parametric models to MAIC weighted data, or follow-up from inotuzumab and blinatumomab studies, which would relax the proportional hazards assumption (acknowledged is violated in the original submission); but would not allow a fully incremental analysis
- The company has not presented any comparison of the relevant studies to support the use of basing analyses on the FELIX population, as requested by the committee
- Unable to explore alternative approaches; maintains assumption of hazard proportionality in comparisons to inotuzumab and blinatumomab

- Has the company sufficiently justified the use of the inverse hazard ratio approach?

Abbreviations: MAIC, matching-adjusted indirect comparison

Unknown impact ?

Key issue: Cure assumption (1/2)

see appendix for January 2025 data-cut results for pooled Cohort 1A and 2A, enrolled set for EFS and OS

Committee at ACM1:

- Company + EAG model included cure assumption for people in any treatment arm alive 3 years after treatment regardless of if they had experienced an event and a SMR of 3 was applied to people alive beyond 3 years
- Committee noted in original source (Martin et al. 2010), mortality risk ranged from 4–9 for people who survived without recurrence for at least 5 years; requested further clarification on SMR applied after cure assumption
- Requested further evidence that it would be reasonable for people who have had events to be considered cured and have the same SMR as people who had no events

Company response to 3- year cure assumption:

- Plateaus observed in the EFS and OS curves are well aligned, indicating that the cure assumption holds for all patients alive at the 3-year timepoint; cure timepoint validated with experts and in line with previous TAs

Company response to SMR of 3.0:

- Lack of divergence in the difference between EFS and OS in the plateau supports assumption that long-term mortality risk converges between the health states; using the same SMR in the EF and PD health states is appropriate and consistent with TA893 [brexu-cel]
- Data collected in Martin et al. were collected between 1970-2002; clinician experience with curative treatments likely improved, so SMR value closer to lower range may be more representative of the risk of mortality in people undergoing treatments with a curative potential
- Company provided scenario analyses using SMR of 4

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Abbreviations: CAR T; chimeric antigen receptor T-cell; SMR, standardised mortality ratio; EFS, event-free survival; OS, overall survival; PD, progressed disease; KM, Kaplan-Meier; EF, event-free; PD, progressed disease; TA, technology appraisal

Key issue: Cure assumption- SMR (2/2)

Unknown impact ?

EAG comments

- Considers that this issue remains uncertain, as the company acknowledge that late events do occur in the FELIX follow-up, but state that the latest deaths are unrelated to the disease; no further information provided to the EAG beyond this point to add supporting detail
- Maintains use of the 3-year cure assumption, but explores the impact of delaying this to 3.5 and 4 years, and also using a SMR of 4.0 in scenario analyses – the exact impact on the ICER varies depending on population but varying cure assumption to 4 years has a moderate increase to the ICER and changing the SMR to 4 has a small increase to the ICER

- Has sufficient evidence been provided to justify:
  - Cure assumption of 3 years and
  - Apply the same SMR of 3 to cured patients regardless of whether they experienced prior events in the model?

Abbreviations: SMR, standardised mortality ratio; ICER, incremental cost-effectiveness ratio

Key issue: Appropriate costs associated with ASCT (obe-cel arm)

Committee at ACM1:

- Company at ACM1 included benefits of ASCT in OS for obe-cel but not the costs
- At ACM1 experts estimate proportion receiving ASCT after CAR-T likely less than 10%
- Committee concluded wanted range of scenarios exploring proportion <10% of people having ASCT after obe cel in the ITT population

Company response to DG

- Updated base case: [redacted]% ASCT for obe-cel; and explored lower proportions (5% and 2.5%) → minimal ICER impact. Explored alternate costs using report by Ernst & Young (2021) showing hospital resource use remained significant beyond 100 days and showed costs to be higher than what is used in company base case → [redacted]

EAG

- [redacted] in ICER from alternate costs due to increase in costs in comparator arms (as these costs applied in both arms)
- Updated base case to [redacted]% to reflect expert and committee preference and explored lower proportions (5% and 2.5%)
- Agrees with company base case costs but acknowledges further investigation in alternate costs warranted

ASCT cost category	company base case (inflated to 2023 cost year)	Ernst & Young report (2021 cost year)
SCT costs	£115,591	£82,197
0-6 months follow-up	£34,347	£88,808*
6-12 months follow-up	£23,594	£35,963

- What is the most appropriate proportion to use when estimating number of patients receiving allo-SCT post CAR-T treatment?
- Are the base case costs appropriate?

*Calculated as the reported total per patient cost at ([initial transplant spell+ 0-100 days post transplant costs]-[transplant spell costs]+[100-200 days post transplant spell discharge costs]). Abbreviations: CAR T; chimeric antigen receptor T-cell; ASCT, allogeneic stem cell transplant

Small impact

Key issue: Intravenous immunoglobulin use (1/2)

Committee at ACM1:

- The CDF lead noted previous CAR T cell therapies, required prolonged IVIG use
- Company's base case modelled immunoglobulin costs by linking them to the adverse event of hypogammaglobulinemia, assumed to be 0% in the comparator arms and slightly higher for obe-cel
- Committee considered the company's model likely underestimated the proportion of people who have IVIG and the duration of treatment
- Committee requested updated scenarios exploring higher usage and longer duration of IVIG use

Company response to DG:

- Monthly IVIG dose calculated using ideal body weight, in line with NHSE Clinical Commissioning Policy for the use of therapeutic immunoglobulin
- Based on clinical expert input + new real-world data from FELIX following 6-month post-obe-cel → infused pooled population (Cohort 1A and 2A; n=104, mean IVIG use = [redacted] days); in UK-specific cohort (n=40; mean IVIG use = [redacted] days); shows model aligns with UK clinical practice and not underestimated
- Updated base case incorporates low IVIG duration from FELIX, with use reevaluated every 6 months across entire time horizon; a reduction in IVIG use applied, decreasing by 5% at months 6, 12, 18, followed by 2% reduction every 6 months thereafter
- Notes model does not capture IVIG use for people in comparator arms undergoing ASCT, where similar doses and rates of IVIG usage may be expected

Abbreviations: ASCT, allogeneic stem cell transplant; IVIG; intravenous immunoglobulin; ASCT, allogeneic stem cell transplant; IgG; immunoglobulin G

Small impact

Key issue: Intravenous immunoglobulin use (2/2)

EAG comments

Structural issues

- Undiscounted IVIG cost output from the model should align with the total IVIG cost calculated using the company's input parameters; model output ([redacted]) lower than calculated total one-off IVIG cost ([redacted]), [redacted]% underestimation - see appendix for EAG comparison

Proportion of patients receiving IVIG

- Company applies [redacted]%, which may reflect % with hypogammaglobulinaemia [FELIX], but likely underestimates the % requiring IVIG therapy in clinical practice
- In TA677 [brexu-cel], company reported 32% received IVIG. As of the February 2024 data cut-off, [redacted]% of people had received IVIG - without greater clarity, the EAG uses [redacted]% in its base case

IVIG dose and treatment duration

- Clinical commissioning policy recommends initiating treatment at 0.4–0.6 g/kg per month for 6-12 months; EAG considers 0.4 g/kg reasonable based on expert advice, but company's frequency ([redacted] days) appears underestimated – based on company model assumed IVIG duration is [redacted] months
- Considers company's approach to reduction in IVIG use confusing; likely underestimates real-world IVIG use
- The EAG's clinical expert confirmed most people remain on IVIG for over 12 months; to better reflect clinical practice, the EAG prefers to model IVIG administration over a 12-month duration applied in first model cycle
- Agrees with use of mean weight from mITT population, as IVIG use before infusion is uncommon

- What is the most appropriate proportion to use in the model for patients receiving IVIG?
- How should IVIG administration be captured over the model time horizon?

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Abbreviations: ASCT, allogeneic stem cell transplant; IVIG; intravenous immunoglobulin; ASCT, allogeneic stem cell transplant; TA, technical appraisal; mITT, modified intention-to-treat

Key issue: Benefits not captured in the QALY

Unknown impact ?

Equality considerations recap

Committee at ACM1:

- Committee concluded it would take potential uncaptured benefits of obe cel into account in its decision making

Company response to DG:

- Potential benefits of obe-cel, such as UK manufacturing, reduced ICU stays, fewer complications, and the potential for outpatient administration, are not fully captured in the current model
- Current curative treatment is limited to allo-SCT, which is restricted to a healthier and younger population – use of obe-cel means more people eligible for a potentially curative treatment; (older populations and ethnic minorities - less opportunities for a stem cell match)
- These advantages considered in detail in TA1048 (liso-cel); committee acknowledged relevance even though not fully included in the economic analysis
- CAR-T tariff is reflective of treatments with substantially worse safety profiles and CAR persistence, rendering a higher cost than what is likely to be observed in clinical practice for obe-cel - certain treatment delivery efficiencies associated with obe-cel may not be fully captured in the current modelling framework (reduced toxicity and improved patient selection, for example, through more effective bridging therapy, could allow an increasing proportion of patients to receive treatment in outpatient or ambulatory settings).

- Are there any further benefits to consider not captured in the QALY?

Abbreviations: ICU, allo-SCT, allogeneic stem cell transplant TA, technology appraisal; QoL; CAR T, CAR T; chimeric antigen receptor T-cell

Company comments on committee preferred assumptions included in its updated base case

Issue	Company comments	EAG comments
Enrolled ITT population from cohorts 1A and 2A (includes pre-infusion period /leukapheresis)	• Likely underestimates true obe-cel efficacy - 3 experts consulted by company noted FELIX population is "similar" or "fairly representative" of UK population, one clinician - infused population more aligned with UK patients	• Enrolled (leukapheresed) ITT population of 133 patients from cohorts IA and IIA to offer a more realistic reflection of clinical practice
CAR T Tariff (£60,462)	• Tariff includes real world costs of all CAR-T and not representative of better safety profile with obe-cel – other uncaptured benefits of obe-cel not accounted for with tariff	• Maintains use of tariff in base case
Severity modifier (x1.2)	• 1.2 underestimates severity of disease (median life expectancy <1 year) • 1.7 should be applied in Ph- group (comparison with blinatumomab supports this)	• EAG weighted analysis resulted in 1.2 modifier

Clarity on mortality in model tunnel states - (minor impact on ICER):

- Committee preferred EAG approach to estimating post allo-SCT costs which company updated in their ACM2 base case. Company suggests costs may be slightly overestimated because mortality is only accounted for when a new follow-up period is reached instead of per cycle – EAG notes very minor impact

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Survival inputs	See appendix for all inputs	
IVIG usage	• Proportion receiving IVIG: [redacted]% [reflective of people with hypogammaglobulinaemia] of the people alive at each 6-month interval • Assumes proportion receiving IVIG reduces by 5% at months 6, 12 and 18, followed by a 2% reduction each additional 6 months over time horizon	• Proportion receiving IVIG: [redacted]% [from Feb 24 data cut off] • Assume all patients receiving IVIG have it for 12 months • Applies this as upfront cost in model
How model accounts for bridging therapies	• Applies correction factor to bridging treatment costs of <1.0	• Applies correction factor of 1

- Remaining company and EAG base case align with committee preferences from ACM1
- Scenarios requested by committee at ACM1 provided on:
  - Alternate SMR 4.0 and alternate cure point 3.5 and 4 years
  - Alternate proportions for people receiving ASCT post CAR-T treatment (5% and 2.5%)

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Abbreviations: ASCT, allogeneic stem cell transplant; CAR-T, chimeric antigen receptor -cell; SMR, standardised mortality ratio; IVIG, intravenous immunoglobulin

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Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Company and EAG base case: cPAS prices included

Comparison between obe-cel and inotuzumab, overall population	ICER (£/QALY) versus inotuzumab
Company base case	**Over £30,000**
EAG base case	**Over £30,000**

Comparison between obe-cel and comparators, Ph- population	ICER (£/QALY) versus inotuzumab	ICER (£/QALY) versus blinatumomab
Company base case	**Over £30,000**	**Over £30,000**
EAG base case	**Over £30,000**	**Over £30,000**

Comparison between obe-cel and comparators, Ph+ population	ICER (£/QALY) versus inotuzumab	ICER (£/QALY) versus ponatinib
Company base case	**Over £30,000**	**Over £30,000**
EAG base case	**Over £30,000**	**Over £30,000**

Comparison with tisa-cel provided in confidential part 2 – analysis assumes equal efficacy, resource use and cost inputs for obe-cel and tisagenlecleucel, except for the price of tisagenlecleucel

Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

- ❑ Background and ACM1 summary
- ❑ Consultation responses
- ❑ Key issues
- ❑ Cost effectiveness results
- ✓ **Other considerations**

NICE National Institute for Health and Care Excellence

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**.

Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID6347]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Draft guidance recommendation

Obecabtagene autoleucel (obe-cel) should not be used

- There is no clinical trial evidence directly comparing obe-cel with any of the usual treatments
- Indirect comparisons suggest that people who have obe-cel live longer than people who have ponatinib, inotuzumab ozogamicin or blinatumomab; but the evidence is highly uncertain
- There has also been no indirect comparison with tisagenlecleucel
- There are important uncertainties in the economic evidence; these are caused by the assumptions used in the economic model
- Because of the uncertainties in the clinical evidence and the economic model it was not possible to determine the most likely cost-effectiveness estimates for obe-cel
- So, obe-cel should not be used.

Committee's conclusions at ACM1 (1/2)

Committee conclusions ACM1 slide

RECAP

Draft guidance section	Committee's conclusion
3.5 – Comparators	Tisagenlecleucel should be included as a comparator in the 18 to 25 age group
3.6 – Obe-cel data sources	Enrolled ITT population from cohorts 1A and 2A was the most appropriate source of clinical evidence
3.8 – MAIC	Uncertainty in the company's MAIC results due to the small sample size
3.9 – Adverse events	Preferred the EAG's approach to modelling adverse events and supported the use of broader data from the larger cohort
3.11 – Preferred population and method for extrapolation	Preferred the EAG's preferred population, (enrolled ITT population from cohorts 1A and 2A)
3.12 – Inverse hazard ratio approach	Committee would like to see a more robust rationale for using the inverse hazard ratio approach
3.13 – Cure assumption	• Committee requested further clarification on the cure assumption applying to people in the post-event health state • Committee requested further evidence that it would be reasonable for people who have had events to be considered cured and have the same standardised mortality ratio as people who had no events

Abbreviations: MAIC, matching-adjusted indirect comparison; ITT, intention-to-treat

Committee's conclusions at ACM1 (2/2)

Committee conclusions ACM1 slide

RECAP

Draft guidance section	Committee's conclusion
3.14 – Hospitalisation and resource use for obe-cel	The updated tariff cost of £60,462 should be applied in the model
3.15 – Outcomes for ASCT after obe-cel	Healthcare professionals now better understand the value of CAR T-cell persistence and are less likely to offer ASCT outside a trial setting
3.16 – Costs associated with ASCT	Committee would like to see a range of scenarios on the impact of changing the proportion of people having ASCT
3.17 – Costs of follow up after ASCT	The EAG's approach was acceptable for calculating the costs of follow-up after ASCT; however, it wanted clarification from the company on how mortality had been addressed in the SCT tunnel states
3.18 – Immunoglobulin resource use	Requested updated scenarios in the model exploring higher usage and longer duration of intravenous immunoglobulin
3.19 – Discount rate	EAG's application of a per-year discount of 3.5% was acceptable for decision making
3.20 - Incorporating ASCT utility effects into the economic model	Preferred the EAG's base-case assumption that adjusted utility values in the post-event health state using time-dependent utilities from TA541
3.21 – Severity	The severity weight of 1.2 applied to the QALYs for all populations

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Abbreviations: CAR T; chimeric antigen receptor T-cell; ASCT, allogeneic stem cell transplant; SCT, stem cell transplant; TA, technology appraisal; QALYs, quality-adjusted life year

RECAP

Background on relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL)

Around 45% of ALL in adults relapses (returns) or becomes refractory (resistant) to initial treatment

Causes

- ALL is a rare, fast spreading cancer affecting blood and bone marrow caused by lymphoblast overproduction
- Relapsed/ refractory B-cell ALL returns after remission (a period of disease decline or disappearance) or doesn't respond to initial treatment

Epidemiology

- About 65% of cases of ALL diagnosed in under 25s,13% in over 60s, and it's more common in men
- 45% of ALL in adults relapses after or becomes refractory to initial treatment requiring further treatment

Diagnosis and classification

• ALL categorised by affected lymphocyte (B or T-cell; abnormally high or low) and Philadelphia (Ph) chromosome status

•Ph+ B-cell ALL more common in adults (20 – 30%) and carries a higher risk of relapse and refractory disease

Prognosis

- ALL 5-year survival outcomes vary by age (90% under in 15s, about 65% in 15-39s, about 20% in 40s and over)
- Survival rates significantly reduced following relapse (about 10- 25%)

RECAP

Patient perspectives

CAR-T should be offered earlier in the treatment pathway to prevent severe complications of stem cell transplant and chemotherapy

Submissions from 2 patient experts, Anthony Nolan and Leukaemia UK

- ALL is life threatening requiring immediate treatment with 64% as an emergency
- High rate of relapse, nearly 50% of adults, often leading to isolation and anxiety
- Extensive disruption and mental health issues to carers and family as people with ALL usually unable to work during treatment and recovery
- Stem cell transplant and chemotherapy cause major side-effects, like immunosuppression, fatigue, fevers and long hospital isolation
- Trial participants view obe-cel very positively as a potential curative therapy when other treatments have failed
- Trial results show obe-cel has fewer side effects than existing CAR-T options for people aged 26 or over
- Lower toxicity of obe-cel allows clinicians to monitor people when out of hospital, reducing the use of ICU, benefiting mental health

"If I had the choice now between a bone marrow transplant and CAR-T I would go straight to CAR-T. The transplant was so invasive and the chemotherapy and radiotherapy ahead of it has caused long term issues. I hope in the future they can give CAR-T as a first line treatment."

Abbreviations: CAR-T, chimeric antigen receptor T-cell; ALL, acute lymphoblastic leukaemia; obe-cel, obecabtagene autoleucel; ICU, intensive care unit

Clinical perspectives

Obe-cel offers a tolerable and effective CAR-T therapy for adults with R/R B-ALL

Submissions from 2 Consultant Haematologists

- Obe-cel has high complete response rates, even in high-burden B-ALL
- Obe-cel can be safely used in older people and in people with multiple medical conditions
- Obe-cel is associated with durable responses without the need for allo-SCT as consolidation therapy (further treatment after initial treatment)
- Ongoing response is associated with ongoing CAR-T persistence in the blood
- Obe-cel administration opens discussion for ambulatory (outpatient) administration of CAR-T for certain people, providing therapy that is more accessible for some

Obe-cel is safe and has low rates of severe grade CRS and ICANs, opening it up as an option for people where toxicity is a concern

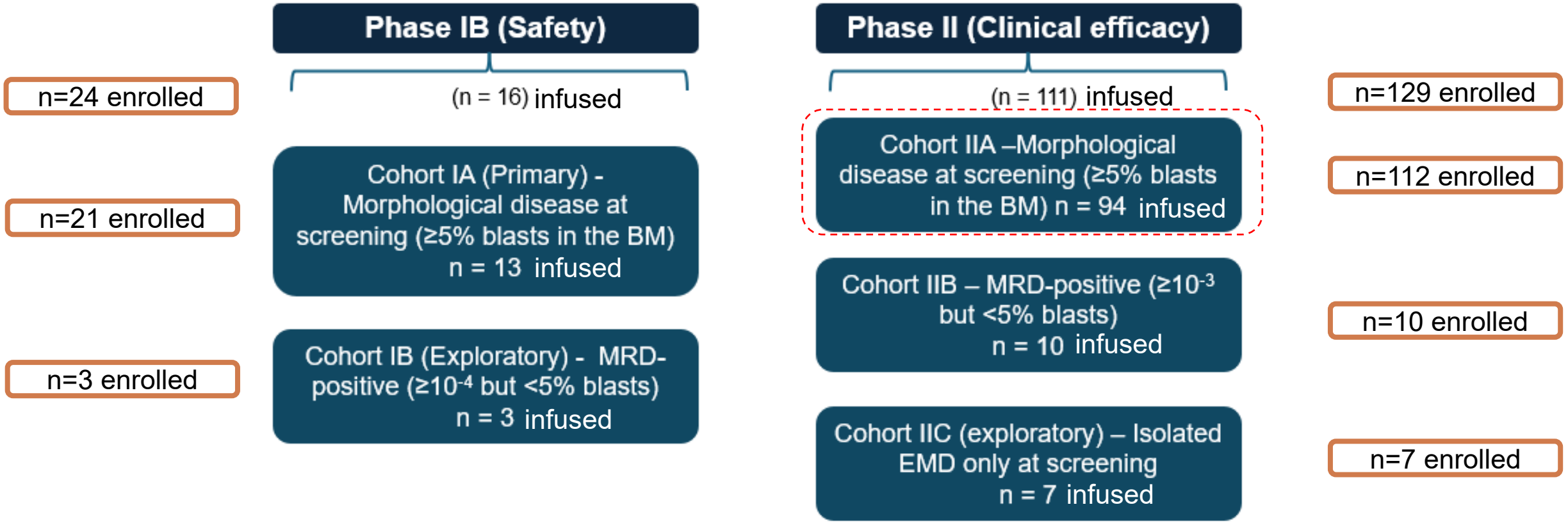
Abbreviations: CAR-T, chimeric antigen receptor T-cell; R/R relapsed or refractory; B-ALL, B-cell acute lymphoblastic leukaemia; CRS, cytokine release syndrome; ICANs, immune effector cell-associated neurotoxicity syndrome; allo-SCT, allogeneic stem cell transplant

FELIX study design

Back to slide 25

Back to Jan 2025 data cut

RECAP



- Company prefer infused patients only from cohort IIA for modelling (n=94) - mITT
- EAG considers both Cohorts IA and IIA relevant (n=133): Cohort IA includes 21 enrolled of which 13 infused and cohort IIA includes 112 enrolled of which 94 infused - ITT
- EAG suggest ITT data set more representative of what happens to people during start of CAR-T in NHS practice

Abbreviations: BM, bone marrow; EMD, extramedullary disease; MRD, minimal residual disease; mITT, modified intention-to-treat; ITT, intention-to-treat; CAR-T, chimeric antigen receptor T-cell

Back to FELIX results

Obe-cel study results: January 2025 date cut-off

	Cohorts IA and IIA – enrolled (n=133)		Cohorts IA and IIA – infused (n=107)
Source of data	(clarification response A1) February 2024	Autolus_Data on file. January 2025	Autolus_Data on file. January 2025
ORR	81 (60.9%)	[redacted]	[redacted]
CR	61 (45.9%)	[redacted]	[redacted]
CRi	20 (15.0%)	[redacted]	[redacted]
DOR	Without censoring	Without censoring	Without censoring
Median (months)	NR	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
24 months	NR	[redacted]	[redacted]
36 months	NR	[redacted]	[redacted]
48 months	NR	[redacted]	[redacted]

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Abbreviations: ORR, overall remission rate; CR, complete remission; Cri, complete remission with incomplete haematological recovery; DOR, duration of remission ;NR, not reported

Back to FELIX results

Obe-cel study results: EFS – January 2025 date cut-off

Committee conclusion at ACM1: FELIX Cohort 1A and 2A enrolled population appropriate for decision making

KM plot of EFS measured by IRRC without censoring new non-protocol anti-cancer therapies including SCT - Enrolled Set – Cohort 1A and 2A

EFS measured by IRRS without censoring – Enrolled set

	Cohort 1A and 2A (n=133)
Events, n (%)	
Median EFS, months [95% CI]	
EFS rates [95% CI]	
6 months	
12 months	

Back to Key issue-cure assumption

Abbreviations: EFS, event-free survival; IRRC, International Review and Regulatory Committee; SCT, stem cell transplant; KM, Kaplan-Meier

Back to FELIX results

Obe-cel study results: OS – January 2025 date cut-off

KM plot of OS without censoring SCT, Cohort 1A and 2A, enrolled set

	Cohort 1A and 2A(n=133)
Events, n (%)	[redacted]
Median OS, months [95% CI]	[redacted]
OS rates [95% CI]	
6 months	[redacted]
12 months	[redacted]

NICE Abbreviations: OS, overall survival; SCT, stem cell transplant; KM, Kaplan-Meier

Back to Key issue-cure assumption

Obe-cel study results – EFS

EFS considered to be equivalent to PFS in this setting

EFS measured by IRRC with or without censoring new non-protocol anti-cancer therapies including SCT (Cohort IIA, mITT) [February 2024]

EFS (Cohort IIA, mITT) with censoring for SCT and other new anti-cancer therapies

	FELIX mITT (n=94)
Events, n (%)	54 (57.4)
Median EFS, months [95% CI]	9.03 [6.14, 14.98]
EFS rates [95% CI]	
6 months	
12 months	

Abbreviations: EFS, event-free survival; PFS, Progression-free survival; IRRC, International Review and Regulatory Committee; mITT, modified intention-to-treat; SCT, stem cell transplant

Obe-cel study results – OS

OS with or without censoring post SCT (Cohort IIA, mITT) [February 2024]

OS (Cohort IIA, mITT) without censoring for SCT

	FELIX mITT (n=94)
Events, n (%)	[redacted]
Median OS, months [95% CI]	[redacted]
OS rates [95% CI]	
6 months	[redacted]
12 months	[redacted]

NICE Abbreviations: EFS, event-free survival; mITT, modified intention-to-treat

Back to FELIX results

Key clinical trial

	FELIX trial (n=127 infused)
Design	Phase Ib/II , multi-centre, single-arm open-label study
Trial phases and cohorts	• Phase IB, cohort IA: morphological disease (n=13) infused • Phase IB, cohort IB: morphological remission with minimal residual disease (n=3) infused • Phase II, cohort IIA: morphological disease (n=94) infused • Phase II, cohort IIB: morphological remission with minimal residual disease (n=10) infused • Phase II, cohort IIC: isolated extramedullary disease at screening (n=7) infused
Population	Adults (≥18 years) with R/R B-cell ALL and ECOG PS of 0 or 1
Intervention	410 x 10^6 (±25%) CD19 CAR-positive T-cells, administered as split dose on Day 1 & 10
Primary outcome	Phase IIA: ORR, CR, CRi
Key secondary outcomes	Phase IIA: MRD-negative remission, CRR within 3 months post AUTO1 infusion, DOR, Stem cell transplantation, Sustained remission, AEs and SAEs, EQ-5D
Locations	34 locations: US (n=23), Spain (n=3) , UK (n=8)
Used in model?	Cohort IIA, mITT population

Abbreviations: R/R, relapsed or refractory; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ALL, acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor; ORR, overall remission rate; CR, complete remission; Cri, complete remission with incomplete haematological recovery; DOR, duration of remission; MRD, minimal residual disease; CRR, complete remission rate; AE, adverse event; SAE, serious adverse event; EQ-5D, EuroQol Five Dimensions of Quality of Life / 5 level scale; mITT, modified intention-to-treat

Baseline characteristics

EAG: FELIX unlikely to be representative of NHS population

Baseline characteristics		Infused, Cohort IIA, mITT (N=94)
Age (years) categorised – n (%)	≥18 to ≤ 25	11 (11.7)
	>25 to < 40	20 (21.3)
	≥40 to < 65	42 (44.7)
	≥65	21 (22.3)
Sex, male – n (%)		47 (50.0)
Number of prior lines of therapy – n (%)	1	29 (30.9)
	2	36 (38.3)
	3	17 (18.1)
	≥4	12 (12.8)
Previous allogeneic SCT – n (%)		36 (38.3)
BM blasts (%) by morphology before enrolment (median)		58.9
ECOG score – n (%)	0	35 (37.2)
	1	58 (61.7)
	≥2	0
	Missing	1

EAG

- Concern with exclusion of people with ECOG PS ≥2
- Unlikely to be representative of NHS population
- Both sexes equally distributed, despite UK ALL incidences are higher in males

Abbreviations: BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; SCT, stem cell transplant

Baseline characteristics- EAG Comparison

Baseline characteristics		Infused, mITT (N=94)	FELIX UK enrolled patients in cohort IIA (n=36)	Cancer Research UK for ALL (n=282)	Kumar et.al. (2024) (n=3,526)
Age (years) categorised – n (%)	≥18 to ≤ 25	11 (11.7)	[redacted]	NA	-
	>25 to < 40	20 (21.3)	[redacted]	75 (26.6)	-
	≥40 to < 65	42 (44.7)	[redacted]	105 (37.2)	-
	≥65	21 (22.3)	[redacted]	102 (36.2)	-
Sex, male – n (%)		47 (50.0)	[redacted]	167 (59)	-
Number of prior lines of therapy – n (%)	1	29 (30.9)	[redacted]	-	-
	2	36 (38.3)	[redacted]	-	-
	3	17 (18.1)	[redacted]	-	-
	≥4	12 (12.8)	[redacted]	-	-
Previous allogeneic SCT – n (%)		36 (38.3)	[redacted]	-	-
BM blasts (%) by morphology before enrolment (median)		58.9	[redacted]	-	-
ECOG score – n (%)	0	35 (37.2)	[redacted]	-	1467 (41.6)
	1	58 (61.7)	[redacted]	-	1543 (43.8)
	≥2	0	[redacted]	-	516 (14.6)
	Missing	1	[redacted]	-	-

Abbreviations: BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; SCT, stem cell transplant

Baseline characteristics: identified indirect comparison trials

Study Arm	FELIX (Obe-cel)	INO-VATE (Inotuzumab)	PACE (Ponatinib)	TOWER (Blinatumomab)
Population (N)	mITT n = 94	ITT n=164	ITT n=32	ITT n=271
Age, Median (Range)	50 (20 - 81)	46.5 (18-78)	62 (20-80)	41.0 (18-80)
Male:Female %	50.0%:50.0%	55.5%: 44.5%	62.5%: 37.5%	59.8%: 40.2%
Previous Lines of Treatment	1: 29 (30.9%)	1: 111 (67.7%)	NR	1: 114 (42.1%)
	2: 36 (38.3%)	2: 51 (31.1%)	≥2 TKI: 26 (81.3%)	2: 91 (33.6%)
	3: 17 (18.1%)	NR	≥3 TKI: 12 (37.5%)	3: 45 (16.6%)
	≥4: 12 (12.8%)	NR	NR	≥4th: 21 (7.8%)
Refractory to 1st-line Therapy	24 (25.5%)	NR	TKI: 27 (84.4%)	115 (42.4%)
Relapse ≤12 Months	41 (43.6%)	NR	NR	76 (28.0%)
Previous SCT (%)	36 (38.3%)	29 (17.7%)	9 (28.1%)	94 (34.7%)
BM Blasts at Screening (%)	<50%: 47 (49.5%)	<50: 53 (32.3%)	NR	<50%: 69 (25.5%)
ECOG PS (%)	0: 35 (37.2%)	0: 62 (37.8%)	0: 11 (31.9%)	0: 96 (35.4%)
	1: 58 (61.7%)	1: 81 (49.4%)	1: 17 (42.6%)	1: 134 (49.4%)
	2: 0'	2: 21 (12.8%)	2: 4 (25.5%)	2: 41 (15.1%)

EAG

- FELIX may not fully reflect real-world settings due to exclusion of patients with ECOG PS ≥2
- INOVATE, PACE,TOWER include broader range of ECOG PS and treatment histories → more representative

NICE Abbreviations: ORR, overall remission rate; NR, not reported; SCT, stem cell transplant; : ECOG, Eastern Cooperative Oncology Group; PS, performance status

Unknown impact ?

Key issue: Comparison against tisa-cel

Back to key issue

Covariates before and after matching to tisa-cel

Baseline characteristic	FELIX (Cohort IIA, mITT, ages 18-25) - unweighted	Tis-t pooled analysis (ages <=25)	FELIX (Cohort IIA, mITT, ages 18-25) - matched
Age at diagnosis	[redacted]	[redacted]	[redacted]
Sex (male), %	[redacted]	[redacted]	[redacted]
Previous lines of therapy: 1, %	[redacted]	[redacted]	[redacted]
Previous lines of therapy: 2*, %	[redacted]	[redacted]	[redacted]
Prior SCT, %	[redacted]	[redacted]	[redacted]
BM blasts <50%, %	[redacted]	[redacted]	[redacted]

* Age at diagnosis presented for completeness but was not included in the matching, thus matched covariates are unavailable.
Abbreviations: BM; bone marrow; ECOG, Eastern Cooperative Oncology Group; Ph, Philadelphia Chromosome; mITT, Modified intention to treat; NA, not available; SCT, stem cell transplant

Back to Key issue

Key issue: Updated MAIC and complementary STC

EFS for FELIX versus comparators, enrolled pooled Cohort 1A and 2A population

	Overall population		Ph- population	Ph+ population
Treatment	Obe-cel	Inotuzumab	Blinatumomab	Ponatinib
Patient numbers	133	164	271	32
Patient numbers from FELIX	-	133	[redacted]	[redacted]
2025 FELIX data cut results – MAIC analysis				
Median EFS	[redacted]	5.0 months	0.0 months†	3.0 months
ESS	-	[redacted]	[redacted]	[redacted]
Unadjusted HR	-	[redacted]	[redacted]	[redacted]
Adjusted HR	-	[redacted]	[redacted]	[redacted]
2025 FELIX data cut results – STC analysis				
Median EFS	[redacted]	5.0 months	0.0 months†	3.0 months
Unadjusted HR	-	[redacted]	[redacted]	[redacted]
Adjusted HR	-	[redacted]	[redacted]	[redacted]

NICE *Statistically significant results. †Median EFS for blinatumomab unavailable. Abbreviations: EFS, event-free survival; MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison; Ph, Philadelphia chromosome; HR, hazard ratio

Back to Key issue

Key issue: Updated MAIC and complementary STC

Table 5: Overall survival for FELIX versus comparators, enrolled pooled Cohort 1A and 2A population

	Overall population		Ph- population	Ph+ population
Treatment	Obe-cel	Inotuzumab	Blinatumomab	Ponatinib
Patient numbers	133	164	271	32
Patient numbers from FELIX	-	133	[redacted]	[redacted]
2025 FELIX data cut results – MAIC analysis				
Median OS	[redacted]	7.7 months	7.7 months	8.0 months
ESS	-	[redacted]	[redacted]	[redacted]
Unadjusted HR	-	[redacted]	[redacted]	[redacted]
Adjusted HR	-	[redacted]	[redacted]	[redacted]
2025 FELIX data cut results – STC analysis				
Median OS	[redacted]	7.7 months	7.7 months	8.0 months
Unadjusted HR	-	[redacted]	[redacted]	[redacted]
Adjusted HR	-	[redacted]	[redacted]	[redacted]

NICE *Statistically significant results. Abbreviations: OS, overall survival; MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison; Ph, Philadelphia chromosome; HR, hazard ratio

Key issue: Intravenous immunoglobulin use

EAG comparison of company IVIG cost vs. modelled undiscounted IVIG cost (cohort 1A+2A)

Parameters	Cohort IA+IIA	Source
% receiving IVIG	[redacted]	Company's preferred values for using in the base case analysis
Frequency (days)	[redacted]	
Dose (g/kg)	[redacted]	
Mean weight (kg)	[redacted]	
IVIG cost per unit (g)	[redacted]	
Calculated total one-off IVIG cost	[redacted]	Product of parameters above
IVIG undiscounted cost from the model output	[redacted]	From model output
Underestimation caused by the modelling	[redacted]	EAG calculation

EAG calculated IVIG cost

Parameter	Cohort 1A+IIA
% of population with IVIG	[redacted]
Frequency (days)	[redacted]
Dose (g/kg)	[redacted]
Weight -mean (kg)	[redacted]
IVIG cost per unit (g)	[redacted]
Total one-off cost of IVIG	[redacted]

*frequency came from clinical expert estimate that average duration was 12 months (1 infusion day per month) [this duration is also assumed in TA677]

Abbreviations: ASCT, allogeneic stem cell transplant; IVIG; intravenous immunoglobulin; ASCT, allogeneic stem cell transplant; TA, technical appraisal; mITT, modified intention-to-treat

EAG's adjustments to OS and EFS in the company's base-case model: whole population after ACM1 (1/3)

= change from company base case

Assumption	Company's approach	EAG* approach
EFS Obe-cel	**Data source:** FELIX, pooled enrolled cohort IA + IIA, [redacted] **Curve selection:** Flexible - Normal - 2	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N:[redacted] **Curve selection:** Flexible - Normal - 1
EFS Inotuzumab	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** (Value based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Inotuzumab[[redacted]])	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** The company's approach
OS Obe-cel	**Data source:** Pooled enrolled cohort IA + IIA, N:[redacted] **Curve selection:** Standard – Weibull	**Data source:** Pooled enrolled cohort IA + IIA, N:[redacted] **Curve selection:** The company's approach
OS Inotuzumab	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** (Value based on obe-cel curve) ^(1/OS HR of obe-cel vs Inotuzumab[[redacted]])	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** The company's approach

*Adjusted analyses approach has been in line with the company's approach (Inverse MAIC), and the HRs come from the company's response to EAG clarification questions. Abbreviations: CS, company submission; HR, hazard ratio; mITT, modified intention to treat; ITT, intention to treat; CQs, clarification questions; OS, overall survival; EFS, event-free survival; MAIC, matching-adjusted indirect comparisons; ACM, appraisal committee meeting

EAG's adjustments to OS and EFS in the company's base-case model: Ph- population after ACM1 (2/3)

Assumption	Company's approach	EAG* approach
EFS Obe-cel	**Data source:** FELIX, pooled enrolled cohort IA + IIA, [redacted]**Curve selection:** Standard - Log-normal	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N:[redacted]**Curve selection:** Flexible - Normal – 3
EFS Blinatumomab	**Data source:** TOWER, N:271 has been used in the MAIC **Curve selection:** (Value based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Blinatumomab [redacted])	**Data source:** TOWER, N:271 has been used in the MAIC **Curve selection:** The company's approach
EFS Inotuzumab	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** (based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Inotuzumab[redacted])	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** The company's approach
OS Obe-cel	**Data source:** FELIX, pooled enrolled Cohort IA + IIA, N:[redacted]**Curve selection:** Standard - Generalised gamma	**Data source:** FELIX, pooled enrolled Cohort IA + IIA, N:[redacted]**Curve selection:** Flexible - Normal - 0
EFS Blinatumomab	**Data source:** TOWER, N:271 has been used in the MAIC **Curve selection:** (based on obe-cel curve) ^(1/HR of obe-cel vs Blinatumomab [redacted])	**Data source:** TOWER, N:271 has been used in the MAIC **Curve selection:** The company's approach
OS Inotuzumab	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** (Value based on obe-cel curve) ^(1/OS HR of obe-cel vs Inotuzumab[redacted])	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** The company's approach

*Adjusted analyses approach has been in line with the company's approach (Inverse MAIC), and the HRs come from the company's response to EAG clarification questions. Abbreviations: CS, company submission; HR, hazard ratio; mITT, modified intention to treat; ITT, intention to treat; CQs, clarification questions; OS, overall survival; EFS, event-free survival; MAIC, matching-adjusted indirect comparisons; ACM, appraisal committee meeting

EAG's adjustments to OS and EFS in the company's base-case model: Ph+ population after ACM1 (3/3)

Assumption	Company's approach	EAG* approach
Obe-cel	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N: [redacted] **Curve selection:** Flexible - Normal – 3	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N:[redacted] **Curve selection:** The company's approach
Inotuzumab	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** (Value based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Inotuzumab[0.[redacted]])	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** The company's approach
Ponatinib	**Data source:** PACE, N:32 **Curve selection:** Standard - Log-logistic	**Data source:** PACE, N:32 **Curve selection:** The company's approach
Obe-cel	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N: [redacted] **Curve selection:** Standard – Exponential	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N: [redacted] **Curve selection:** The company's approach
Inotuzumab	**Data source:** INO-VATE, N;164 has been used in the MAIC **Curve selection:** (Value based on obe-cel curve) ^(1/OS HR of obe-cel vs Inotuzumab[[redacted]])	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** The company's approach
Ponatinib	**Data source:** PACE, N:32 **Curve selection:** Standard - Log-normal	**Data source:** PACE, N:32 **Curve selection:** The company's approach

*Adjusted analyses approach has been in line with the company's approach (Inverse MAIC), and the HRs come from the company's response to EAG clarification questions. Abbreviations: CS, company submission; HR, hazard ratio; mITT, modified intention to treat; ITT, intention to treat; CQs, clarification questions; OS, overall survival; EFS, event-free survival; MAIC, matching-adjusted indirect comparisons; ACM, appraisal committee meeting

Key Issue: Costs and effects of allo-SCT for obe-cel

Background

- Company assume no allo-SCT for people in obe-cel treatment arm
- But, company include benefits of allo-SCT in OS for obe-cel but did not include associated costs
- Some people received allo-SCT in FELIX in remission, company explored including them in sensitivity analysis

Company

- OS and EFS data inherently capture effects of allo-SCT, aligning with TA893 methods
- Company's UK clinical experts confirmed no patient treated with CAR T-cell therapy would proceed onto SCT due to curative nature of CAR T-cell therapy
- OS results demonstrates observed OS benefit with obe-cel is independent of subsequent SCT

EAG comments

- Including survival benefits of allo-SCT without associated costs introduces a bias in obe-cel
- Assumes small portion of obe-cel patients proceed with allo-SCT, costs should be included in model
- EAG base case includes allo-SCT costs for obe-cel patients ([redacted]ITT population)

Could patients receiving obe-cel go on to receive an allo-SCT? If so, what proportion is appropriate to model?

Abbreviations: TA, technical appraisal; OS, overall survival; allo-SCT, allogeneic stem cell transplant; ICER, Incremental cost-effectiveness ratio

NHSE 2025/26 Financial year CAR T tariff costs

- 2025/26 financial year CAR T tariff is £60,462
- £60,462 is the annual uplift figure for 2025/26 applied to the 2024/25 figure of £58,953

Costs associated with	Included in NHS tariff?
Leukapheresis	Yes
CAR-T therapy delivery in hospital	Yes
Adverse events in hospital	Yes
Monitoring for 100 days	Yes
Training	Yes
Conditioning and bridging chemotherapy acquisition, administration and delivery	No
CAR-T product acquisition	No
Subsequent treatments	No
Subsequent allo-SCT	No

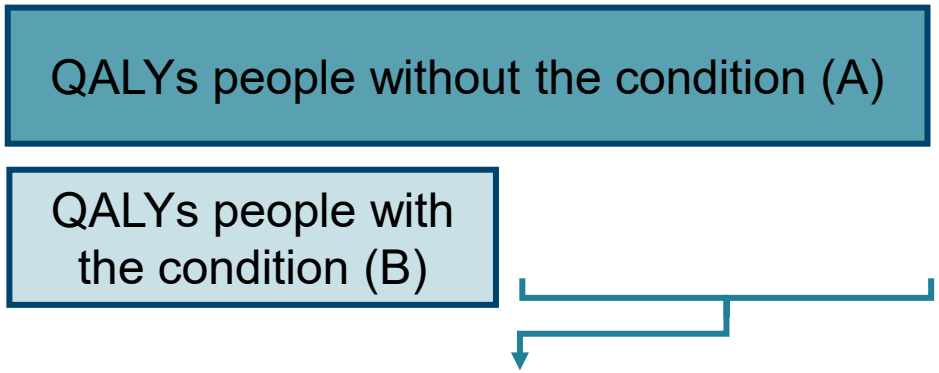
Abbreviations: CAR-T, chimeric antigen receptor T-cel; allo-SCT, allogeneic stem cell transplant l

QALY weighting for severity

NICE methods now include a QALY weighting system based on disease severity

Severity reflects future health lost by people living with a condition having current standard care

Health: length and quality of life (QALYs)



Health lost by people with the condition: QALY shortfall

Absolute shortfall: total = A – B

Proportional shortfall: fraction = (A – B) / A

NICE QALY weighting for severity used to decide whether to apply additional weight, and how much

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

- QALY weightings for severity can be applied based on whichever of absolute or proportional shortfall implies the greatest severity
- If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply
- Additional weight applied to QALYs within cost effectiveness calculation

Key Issue: Severity modifier

Background

- Company's shortfall analysis shows obe-cel meets criteria for 1.7 severity modifier vs blinatumomab, and 1.2 multiplier vs inotuzumab and ponatinib
- Company applies 1.7 multiplier for all analyses

Company

- 1.7 appropriate severity modifier as obe-cel meets criteria of 1.7 versus at least one of the comparators
- 1.7 modifier was considered for decision making in TA975 (Tisa-cel, people 25 years and under)

EAG comments

- Company approach doesn't fully account for variability in treatment outcomes across comparator populations
- Inappropriate to apply 1.7 multiplier for all analyses, regardless of population and comparator
- 1.7 multiplier potentially applicable in some parts of obe-cel pathway, but lack of evidence to justify this
- EAG conducted weighted analysis (including age, QALYs, and sex distribution):
    - if 5% Ph- population received inotuzumab, QALY shortfall analysis suggests 1.2 multiplier
    - Overall proportional shortfall supports 1.2 severity modifier for all population
- Severity modifier of 1.2 applied to EAG's preferred cost effectiveness results

What is the most appropriate severity modifier to apply?

Abbreviations: tisa-cel, tisagenlecleucel; QALY, quality-adjusted life year; TA, technical appraisal

QALY weightings for severity

- Company data inputs for QALY shortfall calculations:
  - mean age (48.3 years) and sex distribution (50% male) (based on FELIX trial, aligned with base case)

Company calculations of shortfall

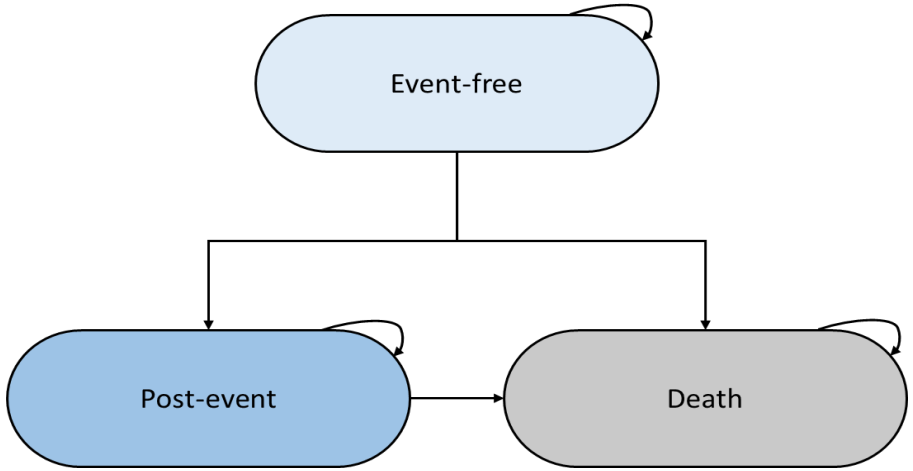
Treatment	General Population QALYs	Total QALYs for this population	Absolute shortfall	Proportional shortfall	Severity modifier
Blinatumomab (PH-)	[redacted]	[redacted]	[redacted]	[redacted]	1.7
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	1.2
Ponatinib (PH+)	[redacted]	[redacted]	[redacted]	[redacted]	1.2

Company
- 1.7 severity modifier appropriate for all comparisons based on QALY shortfall analysis

Abbreviations: QALY, quality-adjusted life year

Company's model overview

Model based on partition survival approach



Modelling assumptions with greatest effect on ICER:

- Application of costs following allo-SCT
- Choice of population and corresponding survival extrapolations
- Application of subsequent allo-SCT costs for obe-cel
- Severity modifier
- Application of CAR T tariff cost

EAG:

Overall, the technology is modelled to affect QALYs by:

- Likely increasing average duration of EFS and OS within first three years
- Likely increasing the proportion of people alive at 3 years who are assumed cured by the model

Overall, the technology is modelled to affect costs by:

- Having a large upfront cost, and different administration pattern
- Likely decreasing the need for subsequent treatments and having a different distribution of subsequent treatments

NICE

Abbreviations: allo-SCT, allogeneic stem cell transplant; ICER, incremental cost-effectiveness ratio; CAR T, chimeric antigen receptor therapy

Equality considerations

Issues raised in patient and clinical expert organisation submissions

- People from ethnic minority backgrounds are less likely to find a fully matched unrelated donor for stem cell transplant
    - Any additional options offering an alternative to an unrelated donor stem cell transplant, such as CAR-T are important

- Geographical access to CAR-T specialist centres
    - If people can afford to travel to the limited number of CAR-T specialist centres to receive treatment
    - If people and carers will be supported with travel, accommodation, and other needs related to long-term monitoring

Are there any equality issues relevant to the potential recommendations?

Abbreviations: CAR-T, chimeric antigen receptor T-cell; ALL, acute lymphoblastic leukaemia