Slides for public: confidential information redacted

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

Technology appraisal committee HST [22 May 2025]

Chair: Paul Arundel

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Company: Autolus Limited

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

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

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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%)

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

Equality considerations

Issues raised in patient and clinical expert organisation submissions

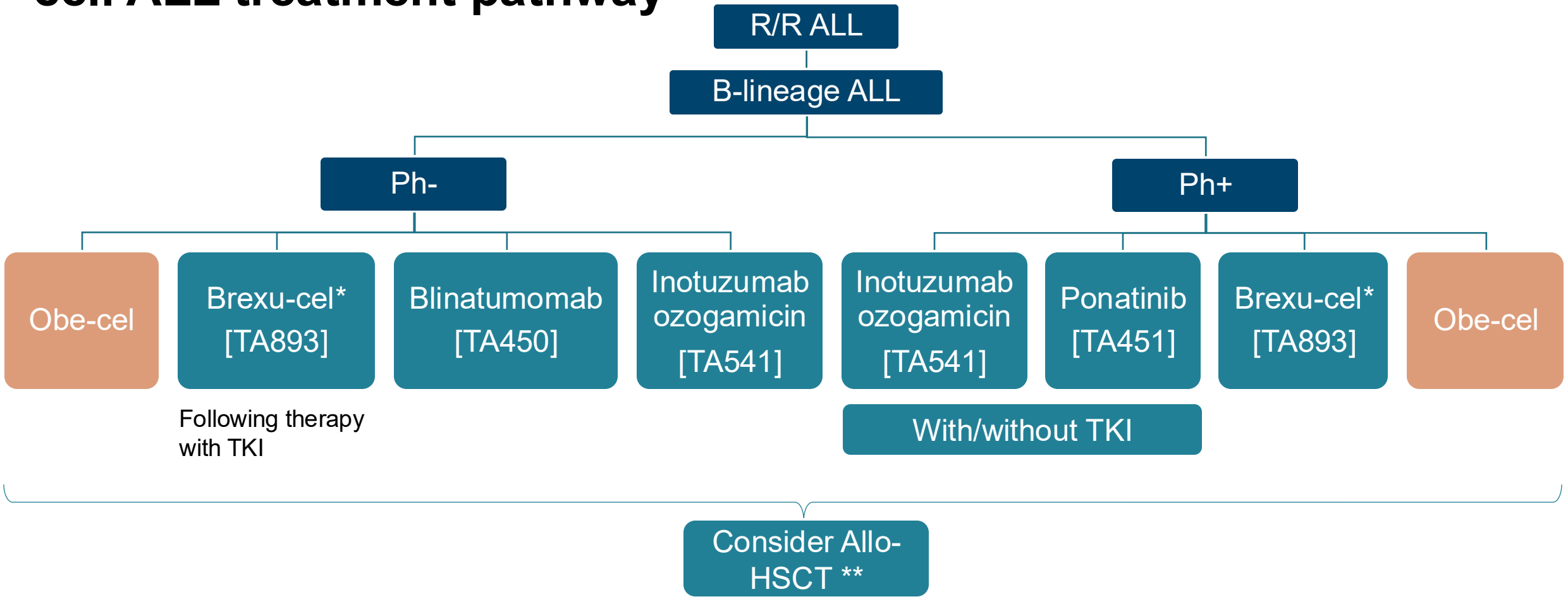
- People from ethnic minority backgrounds are less likely to find a fully matched unrelated donor for stem cell transplant
    - Any additional options offering an alternative to an unrelated donor stem cell transplant, such as CAR-T are important

- 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

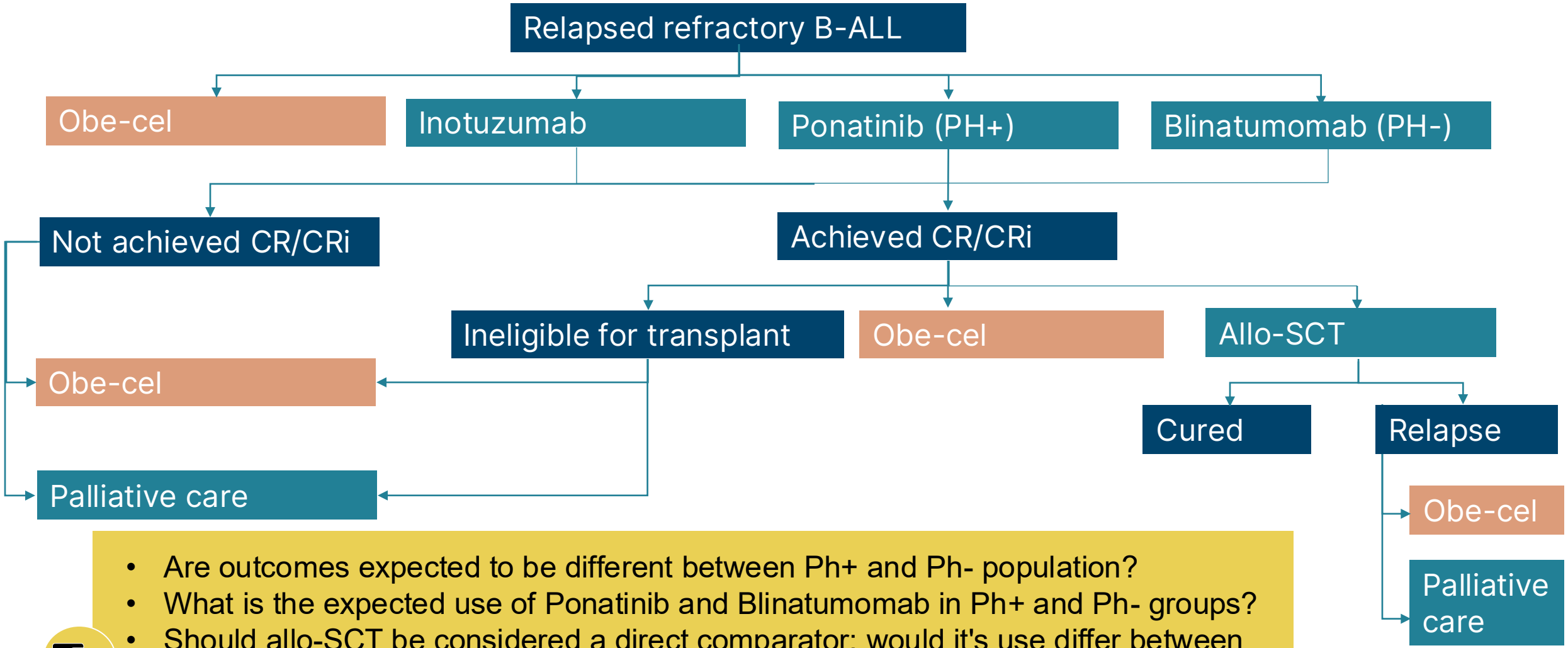
Proposed positioning of obe-cel in the relapsed/refractory B-cell ALL treatment pathway



*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

EAG updated treatment pathway

EAG updated treatment pathway based on available therapies using clinical advice



- Are outcomes expected to be different between Ph+ and Ph- population?
- What is the expected use of Ponatinib and Blinatumomab in Ph+ and Ph- groups?
- Should allo-SCT be considered a direct comparator; would it's use differ between Ph+ and Ph- groups?
- Would people receiving obe-cel bridge to allo-sct?

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Note brexu-cel not included as in CDF. ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; Ph+, Philadelphia chromosome-positive; Ph-, Philadelphia chromosome negative; CR, complete remission, CRi, complete remission with incomplete hematologic

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

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

Key Issues

Issue	ICER impact
Limitations of the FELIX trial for decision making	Unknown
Reliance on biased and highly uncertain MAIC analyses	Unknown
Adverse event reporting	Small impact on ICER
Preferred population and method for extrapolations	Moderate impact on ICER
Hospitalisation and resource use for obe-cel	Small impact on ICER
Costs and effects of allo-SCT	Moderate impact on ICER
Costs of follow-up after allo-SCT	Large impact on ICER
Allo-SCT utility effects	Small impact on ICER
Severity modifier	Large impact on ICER

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Abbreviations: MAIC, matching-adjusted indirect comparison; allo-SCT, allogeneic stem cell transplant; ICER, Incremental cost-effectiveness ratio; CSR, clinical study report

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Sources of clinical effectiveness evidence

FELIX: ongoing, single-arm, non-randomised open-label trial of obe-cel

FELIX trial: single arm phase Ib/II, open-label clinical study of **obe-cel**
International (including UK)
5 Cohorts; Cohort IIA mITT* population identified by company as relevant population
N=112 enrolled, N=94 infused
✓ in model
Median follow-up 20.25 months

Comparator studies – used in indirect treatment comparisons (naïve and MAIC)

INO-VATE phase III
N=164
✓ models overall population (R/R ALL) inotuzumab

PACE- phase II
N=32
✓ models Ph+ ponatinib

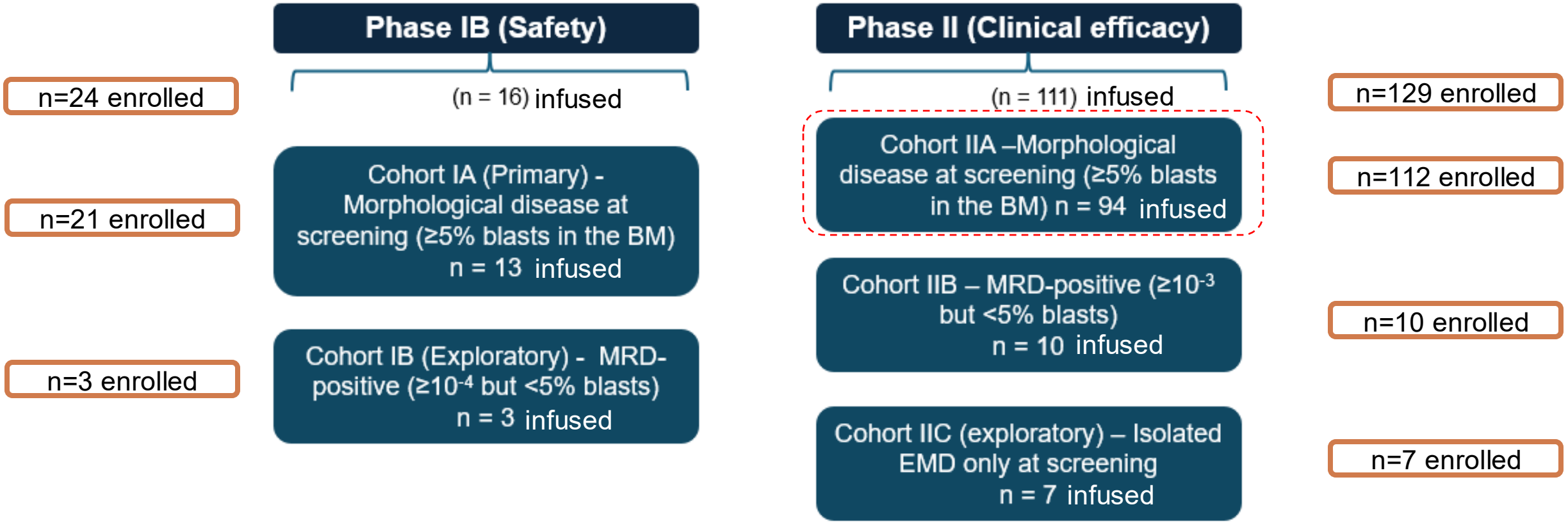
TOWER- phase III
N=271
✓ models Ph- blinatumomab

*mITT population comprises all enrolled patients who received at least one infusion of obe-cel

Abbreviations: mITT, modified intention-to-treat

FELIX study design

see appendix for baseline characteristics and baseline characteristics (EAG comparison)



- 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

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	[redacted]
12 months	[redacted]

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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]

[redacted]

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

Key issues: Limitations of the FELIX trial for decision making

Background

- FELIX is an ongoing single-arm, open-label trial with small sample size

Company

- Cohort IIA mITT population most relevant (comprises patients who received at least 1 obe-cel infusion)
- Cohort IIA best reflects anticipated licenced population
- mITT best reflects clinical practice as obe-cel will be reimbursed for patients who receive at least one dose

EAG comments

- Despite high recruitment in UK, FELIX unlikely to be representative of NHS population:
  - Lower incidence of disease in people over 65 compared to UK (Cancer Research UK for ALL)
  - Exclusion of people with ECOG PS ≥2 unlikely to be representative of NHS population
- Longer follow-up from FELIX, new head-to-head trials or real-world studies may provide more evidence of obe-cel's short and long-term efficacy

Is the FELIX trial representative of NHS practice?

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Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; mITT, modified intent-to-treat; MRD, minimal residual disease

Key issues: Reliance on biased and highly uncertain Matching-adjusted indirect comparisons (MAIC) analyses

Company

- MAIC shows obe-cel favourable effect on EFS and OS
- Acknowledge small ESS when matching to PACE (ponatinib) → indicates poor overlap and results unreliable

	Company: Cohort IIA mITT (n=94)					EAG: enrolled ITT Cohorts IA and IIA (n=[redacted])				
		EFS		OS			EFS		OS	
Treatment	ESS	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR	ESS	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
Inotuzumab (mITT)	44.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blinatumomab (Ph-)	40.99	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib (Ph+)	7.89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Comparison of FELIX post-infusion period ignores outcomes of those enrolled but not infused to follow-up from trials with no pre-infusion period
- MAICs unable to account for all known TEMS → may be biased and small ESS estimates highly uncertain
- Cohorts IA and IIA (enrolled ITT population, [redacted]) more reliable comparison (include FELIX pre-infusion period) → improves comparability of outcome data but likely violates proportional hazards assumption (also violated in company's preferred population [Cohort IIA, mITT population [n=94])

NICE Are the MAIC analyses suitable for decision making?

*statistically significant. Abbreviations: ESS, effective sample size; EFS, event-free survival; OS, overall survival; ITT, intention-to-treat; TEM, treatment effect modifier

Underreporting of adverse events (AEs) and discrepancies with the company's clinical study report (CSR)

Background

- Incidence of AEs derived from individual comparator trials
- For obe-cel, grade ≥3 AEs occurring in mITT population of FELIX included in model

EAG comments

- Company's reporting of AEs reveals inconsistencies and potential underreporting
- Feedback received from EAG's clinical advisers:
    - ICANs (critical to CAR T-cell therapies) not reported in company model - raising concerns about completeness of data
    - EAG clinical advisor notes concerns regarding probabilities of AEs included in company model:
        - probability of infection ([redacted]%), but probability of sepsis ([redacted]%)
        - probability for febrile neutropenia (26.6%), (presumed an infection), higher than probability of neutropenia (20.2%)
- Gaps and inconsistences deviate from CSR
- EAG preference: include all TEAEs (Grade ≥3) (as reported in CSR) for all infused patients across all cohorts

What clinical events are important to be included within the modelling?

Abbreviations: ICAN, immune effector cell-associated neurotoxicity syndrome, mITT, modified intention-to-treat; ITT, intention-to-treat; CAR T, CAR-T, chimeric antigen receptor T-cell; TEAE, treatment-emergent adverse event

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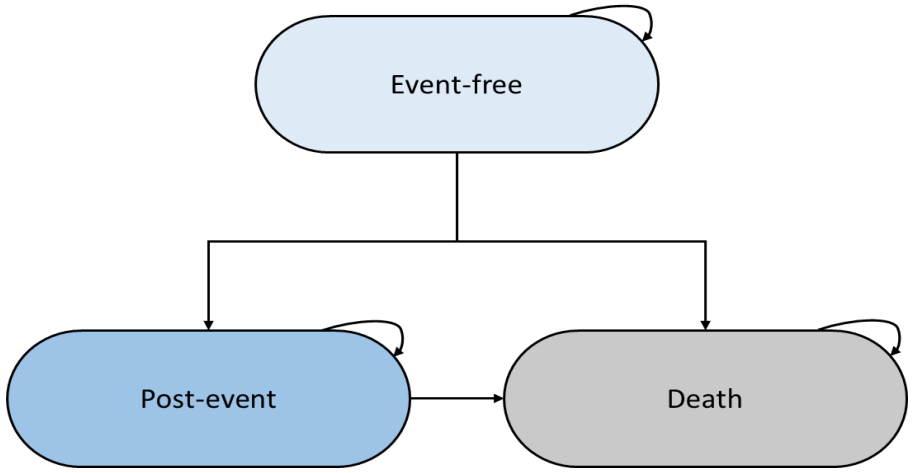
Company's model overview

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

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

Key issues: Preferred population and method for extrapolation (1/3)

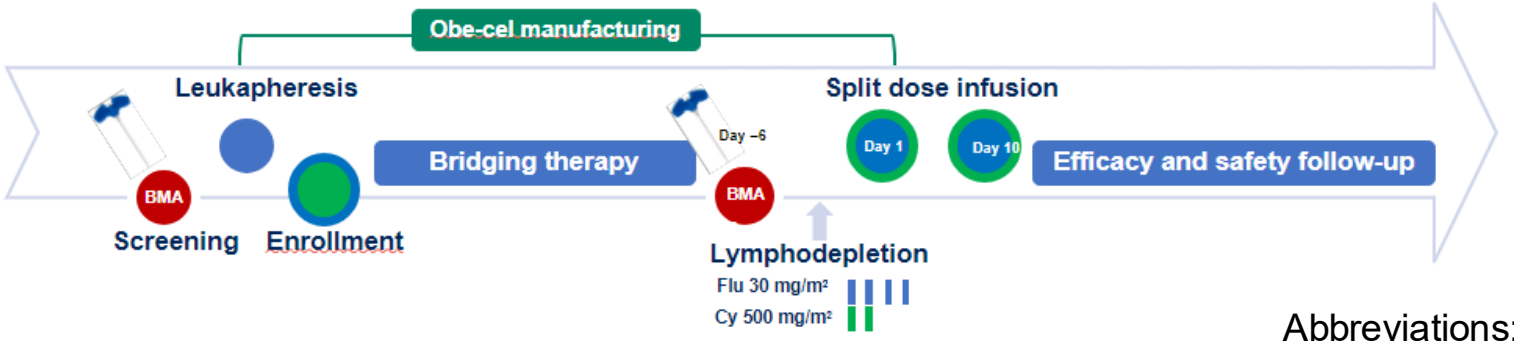
Background

- Company uses infused mITT population of FELIX cohort IIA (people who received obe-cel) for basis of all comparisons - Includes cure assumption for patients alive 3 years post treatment
- EAG prefers enrolled ITT population of cohorts IA and IIA as it includes pre-infusion period (people who underwent leukapheresis)→ bigger sample ([redacted] vs 94), more data for extrapolation, less biased estimates – also included cure assumption at 3 years

EAG comments

- Company's choice of population introduces potential bias as mITT population excludes people who stopped treatment for reasons that may influence costs and outcomes in clinical practice
- Company asserts mITT population reflects clinical practice as obe-cel will only be reimbursed for people receiving at least one infusion. EAG suggests assumption narrows the scope and may underestimate the full burden of treatment, whilst also ignoring outcomes for people who are not infused
- Obe-cel should be assessed as part of the full treatment pathway, including pretreatment period

FELIX- treatment stages



Abbreviations: mITT, modified intention-to-treat

Key Issue: Preferred population and method for extrapolation (2/3)

Company

- Applied inverse HRs from MAIC to obe-cel extrapolations for blinatumomab and inotuzumab (in line with TA893)
- Naïve ITC approach used for ponatinib, digitised curves used
- Alternative MAIC implementation and naïve analyses explored in scenario analyses → results highly varied

EAG comments

- Inverse HRs assumes hazard proportionality, which is violated, with instances of hazard curves crossing
- EAG preference of pooling cohorts relies on assumption of proportionality, (likely violated), no better alternatives
- Uncertain cure assumption at 3 years suitable for all people remaining alive, especially in post-event health state

What is the preferred population (infused modified intention-to-treat population of cohort IIA, or enrolled [underwent leukapheresis] intention-to-treat populations of cohort IA and IIA)?
Is the use of the inverse hazard ratio appropriate?

Abbreviations: mITT, modified intention-to-treat; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparisons; ITC, indirect treatment comparison; TA, technical appraisal; HR, hazard ratio

Key Issue: Preferred population and method for extrapolation (3/3)

Company and EAG choice of population lead to different extrapolations

			**EAG (Leukapheresed-ITT)		Company (Infused-mITT)	
Treatment	Outcome	Population	Base case	3Y surv	Base case	2.99Y surv
Obe-cel (FELIX trial)	EFS	Overall	Log-normal	[redacted]	3-knot normal	[redacted]
	OS		Log-normal	[redacted]	3-knot odds	[redacted]
	EFS	Ph-	Gompertz	[redacted]	Weibull	[redacted]
	OS		2-knot odds	[redacted]	Exponential	[redacted]
	EFS	Ph+	Exponential	[redacted]	1-knot hazard	[redacted]
	OS		Exponential	[redacted]	Log-normal	[redacted]
Ponatinib (PACE trial)	EFS		Log-logistic	[redacted]	1-knot odds	[redacted]
	OS		Log-normal	[redacted]	Log-normal	[redacted]

*Survival at 2.99 years (cycle 39)

Is the cure assumption at 3 years appropriate?

**Updated table from EAG addendum

Abbreviations: EFS, event-free survival; OS, overall survival; Ph, Philadelphia chromosome; MAIC, matching-adjusted indirect comparison

see appendix for EAG's adjustments to OS and EFS in company base-case model

Key issue: Hospitalisation and resource use for obe-cel

Background

- Company use bottom-up costing approach for CAR T-cell therapy infusion cost calculations
- Hospitalisation data in original CS based on TA893 (hospital length of stay, proportion requiring ICU, ICU length of stay)
- At clarification company used UK-specific data from FELIX (N=36) to estimate hospitalisation durations

Company

- Consider UK specific FELIX trial data more appropriate ([redacted] days non-ICU,[redacted] days ICU)
- Explored using approach in TA893 £41,101 tariff cost for CAR T-cell infusion cost calculations in scenario analyses

EAG comments

Identified issues with company bottom-up costing approach:

  - Length of hospital stay should reflect complete FELIX dataset in Cohort IIA ([redacted] days non-ICU,[redacted] ICU)
  - Real-world data from a sufficient sample of UK patients could enhance the estimates of these parameters
  - UK specific data from FELIX may underestimate length of hospital stay compared with broader FELIX data
- Prefers using latest tariff costs for CAR T therapy (£60,462); costs cover leukapheresis, CAR-T therapy delivery in hospital, adverse events in hospital, monitoring for 100 days and training

What is the most appropriate method for estimating hospitalisation duration and resource use?

see appendix for CAR T tariff components table

Abbreviations: CS, company submission; TA, technology appraisal; CAR-T, chimeric antigen receptor T-cell

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

Key Issue: Costs of follow-up after allo-SCT

Background

- Cost calculated as stem cell harvesting + allo-SCT procedure + follow-up costs (up to 24 months)
- EAG identified error for calculating the follow up costs in the model which overestimated the follow up costs

Company

- Recognise error in initial costing approach used in model and agree with EAG that maximum undiscounted total costs should align with proportion of patients receiving an allo-SCT
- EAG's approach does not account for mortality within follow-up period, it overestimates costs in both comparator and obe-cel arms

EAG comments

- EAG assumes that total undiscounted costs for different components of allo-SCT should not exceed the proportion of patients receiving allo-SCT multiplied by the corresponding cost
- EAG base case: patient distribution across different follow-up periods for each cycle to ensure maximum undiscounted total costs align with the proportion of patients receiving allo-SCT

How should follow-up after allo-SCT costs be incorporated into the model?

Abbreviations: allo-SCT, allogeneic stem cell transplant; TA, technical appraisal

see next slide for comparison of administration costs of allo-SCT

Comparison of administration costs of allo-SCT

Description	Cost inflated to 2024	Maximum undiscounted total costs based on Proportion of patients who receive an allo-SCT*			Undiscounted total costs from the model		
		Inotuzumab	Blinatumomab	Ponatinib	Inotuzumab	Blinatumomab	Ponatinib
Stem cell harvesting	£5,904	£1,372	£103	£1,298	[redacted]	[redacted]	[redacted]
Allo-SCT procedure	£109,688	£25,483	£1,914	£24,107	[redacted]	[redacted]	[redacted]
0-6 months follow-up	£34,347	£49,394	£3,120	£40,999	[redacted]	[redacted]	[redacted]
6-12 months follow-up	£23,594	£22,401	£917	£14,346	[redacted]	[redacted]	[redacted]
12-24 months follow-up	£17,026	£27,180	£565	£12,862	[redacted]	[redacted]	[redacted]
Total costs	£190,559	£125,830	£6,618	£93,610	[redacted]	[redacted]	[redacted]

EAG: assumes that the total undiscounted costs for different components of allo-SCT should not exceed the proportion of patients receiving allo-SCT multiplied by the corresponding cost, as shown in the columns under "Maximum undiscounted total costs based on the proportion of patients receiving an allo-SCT"

*These proportions have used in this table: Blinatumomab: 0.1321; Inotuzumab: 0.482; Ponatinib: 0.4688

Incorporating allo-SCT utility effects into the economic model

Background

- Company base case did not consider disutility post-SCT in base case analysis
- Company assumes no obe-cel patients receive subsequent allo-SCT in model

Company

- Disutility post-SCT applied to people post-SCT (in line with TA450) explored via scenario
- Using alternative utility values had negligible impact on ICER in all three modelled populations

EAG comments

- Post-event' health state ([redacted]) does not appear to reflect specific impacts of allo-SCT
- People undergoing allo-SCT experience different utility values depending on time post-transplantation (in line with TA541)
- TA541 utility values appropriate, as account for variations in HRQoL over time and include disutility associated with GvHD
- EAG preference: adjust utility values in post-event health state using time-dependent utilities from TA541 to account for proportion of people receiving allo-SCT across different treatments

Should the utility effects of allo-SCT be incorporated in the model?

see appendix for EAG adjusted utility values in post-event health state

Abbreviations: QALY, quality-adjusted life year; TA, technical appraisal; allo-SCT, allogeneic stem cell transplant; GvHD, graft versus host disease; ICER, incremental cost-effectiveness ratio

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)

QALYs people without the condition (A)

QALYs people with the condition (B)

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

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

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, isagenlecleucel; QALY, quality-adjusted life year; TA, technical appraisal

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Modelled population	Cohort IIA (mITT)	Cohorts IA and IIA (ITT)
Cure point and standardised mortality ratio (SMR)	3 years (SMR 3.0)	3 years (SMR 3.0)
Follow-up costs of allo-SCT	Costs aligning with TA893	Normalise patient distribution across follow-up periods in each cycle
Proportion of people eligible to receive allo-SCT in obe-cel	[redacted]%	[redacted]%
Approach to CAR T-cell infusion cost calculations	Bottom-up costing using UK-specific FELIX trial data	Using tariff costs for CAR T infusion and monitoring
Source of AEs incidence	Grade ≥3 AEs in FELIX mITT population	Include TEAEs (Grade ≥3) for all infused patients as reported in CSR
Allo-SCT utility effects	Exclude	Include
Discount factor (see appendix)	Per-cycle discount factor	Per-year discount factor
Severity modifier across populations	1.7	1.2

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Abbreviations: allo-SCT, allogeneic stem cell transplant; TA, technical appraisal; CAR T, CAR-T, chimeric antigen receptor T-cell; AE, adverse event; CSR, clinical study report; TEAE, treatment-emergent adverse event

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	Dominant
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	Dominant	Under £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	Dominant	Under £30,000
EAG base case	**Over £30,000**	**Over £30,000**

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

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

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

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

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Key issues

Key issue	ICER impact	Slide
Limitations of the FELIX trial for decision making	Unknown	16
Reliance on biased and highly uncertain MAIC analyses	Unknown	17
Adverse event reporting	Small	18
Preferred population and method for extrapolations	Moderate	21
Hospitalisation and resource use for obe-cel	Small	24
Costs and effects of allo-SCT	Moderate	25
Costs of follow-up after allo-SCT	Large	26
Allo-SCT utility effects	Small	28
Severity modifier	Large	31

Abbreviations: MAIC, matching-adjusted indirect comparison; allo-SCT, allogeneic stem cell transplant; ICER, Incremental cost-effectiveness ratio

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

Supplementary appendix

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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

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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

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 allogenic 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 allogenic 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

Indirect treatment comparison (ITC)

Background

- Company performed ITCs between obe-cel and comparators given single-arm nature of FELIX
- Company updated search strategy used in TA893 (considered similar indication)
- Single-arm design of FELIX means only unanchored ITCs are possible, which have a high risk of bias
- ITC methods conducted were matching-adjusted indirect comparisons and naïve comparisons

Important patient characteristics adjusted for (yes vs. no)

		FELIX (Cohort IIA, mITT)	INO-VATE (inotuzumab arm)	TOWER (blinatumomab arm)	PACE (Ph+ ALL arm)
Primary refractory, %		✓	X	✓	X
BM blasts at screening, % <50%		✓	✓	✓	X
Prior lines of therapy, %	1	✓	✓	✓	✓
	2	✓	✓	✓	✓
	≥3	✓	X	✓	✓
1st remission ≤12m, no. %		✓	✓	✓	X

EAG comments

- Comparison of prognostic factors and TEMS impact reliability of company's ITC
- Missing data on important patient characteristics in some trials introduces uncertainty

Abbreviations: BM, bone marrow; Ph, Philadelphia chromosome; TEM, treatment effect modifier; mITT, modified intent-to-treat; TA, technical appraisal

Baseline characteristics: identified indirect comparison trials

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

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

Back to key issue

Incorporating allo-SCT utility effects into the economic model

Determining the changes in basic utility due to SCT for different treatments

Treatment	Obe-cel	Blinatumomab	Inotuzumab	Ponatinib
Proportion who receive an allo-SCT in company base case	0%	13%	48%	47%
Post event-free (from FELIX trial)	[redacted]	[redacted]	[redacted]	[redacted]
Post-HSCT (from TA541)*				
Post-HSCT- <1 year post	0.59	0.59	0.59	0.59
Post-HSCT- 1–2 years' post	0.75	0.75	0.75	0.75
Post-HSCT- 3–5 years' post	0.74	0.74	0.74	0.74
Post-HSCT- >5 years post	0.76	0.76	0.76	0.76
Change in basic utility due to HCT**				
Post-HSCT- <1 year post	[redacted]	[redacted]	[redacted]	[redacted]
Post-HSCT- 1–2 years' post	[redacted]	[redacted]	[redacted]	[redacted]
Post-HSCT- 3–5 years' post	[redacted]	[redacted]	[redacted]	[redacted]
Post-HSCT- >5 years post	[redacted]	[redacted]	[redacted]	[redacted]

* Assumed that AML utilities after HSCT from Kurosawa et al. (2016) can be applied to R/R ALL patients. These include disutility for GvHD. ** Calculated by multiplying the difference between health state utility and post-HSCT utility by the proportion of individuals who undergo an allo-SCT. Abbreviations: TA, technical appraisal; allo-SCT, allogeneic stem cell transplant; GvHD, graft versus host disease; R/R relapsed or refractory; B-ALL, B-cell acute lymphoblastic leukaemia; AML, acute myeloid leukaemia

NHSE 2025/26 Financial year CAR T tariff costs

Key issue slide

- 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

Key issue

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case – whole population

Assumption	Company base case	EAG* base case
EFS Obe-cel	**Data source:** FELIX mITT- Cohort IIA, N:94, censored for subsequent therapy **Curve selection:** 3-knot normal flexible parametric spline curve (changed after CQs)	**Data source:** FELIX, ITT, Cohorts IA and IIA (n=[redacted]), not censored for subsequent therapy **Curve selection: Log-normal**
EFS Inotuzumab	**Data source:** INO-VATE, N;164 **Curve selection:** (Value based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Inotuzumab[redacted]) However in CS: 3-knot odds spline	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Inotuzumab[redacted])
OS Obe-cel	**Data source:** mITT- Cohort IIA,N:94, not censored for subsequent therapy **Curve selection:** 3-knot odds spline	**Data source:** FELIX, ITT, Cohorts IA and IIA (n=[redacted]), not censored for subsequent therapy **Curve selection:** Log-normal
OS Inotuzumab	**Data source:** INO-VATE, N;164 **Curve selection:** (Value based on obe-cel curve) ^(1/OS HR of obe-cel vs Inotuzumab[redacted]) However in CS: 2-knot hazards spline	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^(1/OS HR of obe-cel vs Inotuzumab[redacted])

*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

Summary of base case

Use of per-cycle discount rate instead of per-year discount rate

Background

- Company applied a per-cycle discount rate to calculate discount factors in model
- Cycle length 28 days, and discounting applied at end of each cycle

EAG comments

- Note discounting (3.5%) was applied on a per-cycle basis meaning it had effect in the first year
- Per-cycle discount rate deviates from NICE reference case (2023) as splits annual discount rate into smaller time intervals (28 days) → potentially leading to discounting inconsistencies across model's time horizon
- EAG used a per-year discount rate of 3.5% (which did not have any effect for the first year) ensuring costs and health effects are appropriately discounted over the time horizon