Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Autolus**
   a. Comments
   b. Cost-effectiveness results
   c. Clinical effectiveness results
   d. Survival analyses and indirect treatment comparison

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Anthony Nolan
   b. Leukaemia UK

3. **Comments on the Draft Guidance from experts:**
   a. Dr Claire Roddie – clinical expert, nominated by Autolus
   b. Dr Michelle Lannon – clinical expert, nominated by Anthony Nolan

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Consultation on the draft guidance document – deadline for comments 5pm on Friday 4 July 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Autolus Limited

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable as we are submitting company
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Executive summary	Autolus would like to thank NICE for the opportunity to respond to the draft guidance for obecabtagene autoleucel (obe-cel) for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL) [ID6347]. Autolus would like the committee to

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	consider two potential inconsistencies with recent chimeric antigen receptor (CAR) T therapy appraisals: • The dramatic 47% increase in the CAR T tariff, from £41,101 for the four CAR T appraisals in 2023 (TA872 [Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies], TA893 [Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over], TA894 [Axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma], and TA895 [Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy]), to £60,462 in 2025 for this appraisal.[1–4] • The use of the 1.2 severity modifier for this appraisal, compared to the end of life criteria (approximating the 1.7 severity modifier) for the recent TA893 appraisal, which assessed another CAR T therapy in the same indication and against the same comparators.[2] The Company hopes that the evidence presented within this response address the Committee's uncertainties regarding the clinical and economic data and also highlights the benefits that obe-cel can bring for a wide range of patients. As a new data cut became available from the pivotal clinical trial of obe-cel, FELIX, Autolus have revised their base case to incorporate this new clinical efficacy evidence. Additionally, the Company have rerun the pairwise matching-adjusted indirect comparison (MAIC) versus all comparators (inotuzumab ozogamicin [inotuzumab], blinatumomab and ponatinib) as well as conducted a simulated treatment comparison (STC) to address potential methodological uncertainties with the MAIC. Results from the 2025 data cut of FELIX are consistent with the data cut previously presented to NICE with a more pronounced plateau for both event-free survival (EFS) and overall survival (OS), highlighting the long-term benefits of obe-cel and conclusions from the original company submission (CS). Similarly, the updated MAIC results are consistent with that of the previous data cut, as well as between the MAIC and STC, which should reduce the uncertainty by supporting the reliability of the analyses. Autolus would also like to highlight the significant unmet need in this population, where over half of all patients treated with the comparators will not live past 1 year, whilst obe-cel shows a 3 year survival rate of [redacted]. . In their revised base case, Autolus have accepted all Committee preferences, but would like to highlight that the following key benefits are not considered by adopting these methods and requests that the Committee take these into account during their decision-making: • Considerably smaller proportion of patients will be pre-treated but not infused with obe-cel in real-world clinical practice, as supported by clinical experts; thereby using an enrolled population instead of an infused population is a conservative approach. • Due to the use of the NHS CAR-T tariff, several benefits of obe-cel remain uncaptured, including an improved safety profile, outpatient or ambulatory care use, United Kingdom (UK) manufacturing and a better patient management leading to the potential for better patient outcomes. • The proportion of patients who undergo subsequent allo-SCT following treatment with inotuzumab, blinatumomab and ponatinib is likely higher than

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	what is considered in the economic analysis, as clinical expert feedback indicated that these treatments are not considered to be consolidation therapies and the goal would be to try and get a patient to a curative treatment (allogeneic stem cell transplantation [allo-SCT]). Clinical efficacy evidence from the 2025 FELIX data cut, the updated MAIC, STC and survival analyses and the updated deterministic and probabilistic cost-effectiveness results have been presented in detail in separate reports. In line with the Committee's request, Autolus also present the following within this response: • 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 • Comparison using FELIX data for obe-cel alongside real-world data from National Health Service (NHS) England for tisagenlecleucel • Further evidence and justification for applying the inverse hazard ratio to blinatumomab • Further clarification on the population included in the post-event health state, and the assumption that people who have had events can be considered cured • Further evidence to support the assumption that a standardised mortality ratio (SMR) of 3 is appropriate, especially for those who have had an event • A range of scenarios exploring a proportion of less than 10% of people having allo-SCT after obe-cel in the intention to treat (ITT) population • Further clarification on how mortality was addressed in the allo-SCT tunnel states • Further evidence and justification on the proportion of people having intravenous immunoglobulin (IVIG) in the model, and the duration of treatment

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Issue 1: Comparison against tisagenlecleucel	**While comparison against tisagenlecleucel showed at least a comparable overall survival benefit for obe-cel, any comparison is characterised by high uncertainty due to poor overlap between the populations of the clinical trials.** The Company acknowledges that tisagenlecleucel (tis-t) is a relevant comparator in patients aged 18-25 years. However, due to the small patient numbers, especially for obe-cel, any indirect comparison to tis-t would be severely limited to the extent that results would not be meaningful – therefore, the Company did not conduct any indirect comparison versus tis-t prior to the appraisal committee meeting (ACM): • The 18–25-year-old population in FELIX consists of only [redacted] obe-cel patients (Cohort IIA). As only [redacted] additional patient in Cohort IA was 18-25 years old, using the pooled enrolled population was not expected to make a meaningful difference to the results. • Whilst study designs are largely comparable, almost half of the prognostic factors and treatment effect modifiers (TEMs) are not available from the tis-t trial publications, further reducing the feasibility of conducting any meaningful analysis and violating the 'conditional constancy of absolute effects' assumption required for an unanchored MAIC; the weighting model must include every effect modifier and prognostic variable.[5] Four key TEMs: Eastern Cooperative Oncology Group (ECOG) status, race, Philadelphia chromosome (Ph) and duration of 1st remission ≤12 months, could not be accounted for based on the published tis-t data, further undermining the validity of any unanchored comparison. • Additionally, published subgroup results for tis-t considering patients older than 18 is limited, rendering only comparisons with the overall tis-t population possible. It is known that younger patients do better, so this would be an overestimation of the potential outcomes in 18+ group. The primary manuscript from tis-t trial ELIANA (Maude *et al*. 2018, Supplementary Appendix[6]) includes a forest plot which shows a lower overall response rate (ORR) in patients aged 18 and above compared to younger patients and the overall population, indicating that a comparison with the overall population would be a conservative approach. Despite the severe limitations, the Company has conducted a MAIC for obe-cel patients aged 18-25 versus tis-t (all ages) based on the pooled data published by Stackelberg *et al*. 2023[7] and utilised in TA975 (Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under)[8]. Due to time constraints, the Company conducted the MAIC on FELIX Cohort IIA (infused) using the 2024 data cut as this dataset had already been prepared for previous MAICs versus other comparators. Only OS was considered for the analysis, again due to time constraints. Additionally, OS was the only Systemic Anti-Cancer Therapy (SACT) data set outcome presented for tis-t[9]. The SACT data was used to conduct further analysis in an attempt to validate the MAIC outcomes, as discussed towards the end of this issue. Refer to the CS Section B.2.9 for the full MAIC methodology. As anticipated, the analysis is highly unreliable. The substantial differences in the available TEMs between the obe-cel patients aged 18-25 and tis-t patients (aged <=25; Table 1) resulted in an extremely low effective sample size (ESS) following matching. When all available TEMs were included in the analysis, matching was not possible. Therefore "age at diagnosis" was excluded, resulting in an ESS of [redacted].

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Table 1: Prognostic factors and treatment effect modifiers for intervention and comparator trials

		FELIX (Cohort IIA, mITT, ages 18-25)	Tis-t pooled analysis (ages <=25)
Study size, N		[redacted]	[redacted]
Primary refractory, %		[redacted]	[redacted]
BM blasts at screening, % <50%		[redacted]	[redacted]
Prior lines of therapy, %	**1**	[redacted]	[redacted]
	2	[redacted]	[redacted]
	3	[redacted]	[redacted]
	≥4	[redacted]	
1st remission ≤12m, no. %		[redacted]	[redacted]
Ph chromosome, % Ph+		[redacted]	[redacted]
Age at diagnosis, Median (SD) years		[redacted]	[redacted]
Race, %	**White**	[redacted]	[redacted]
	Asian	[redacted]	[redacted]
	Black	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Prior SCT, %		[redacted]	[redacted]
ECOG status, %		[redacted]	[redacted]
Sex, Male, %		[redacted]	[redacted]

*Refractory to previous lines of therapy reported in Stackelberg et al.
BM – Bone marrow; ECOG – Eastern Cooperative Oncology Group; mITT – Modified intention to treat; Ph – Philadelphia; SCT – Stem cell transplant; SD – Standard deviation

As shown in Table 2, it was not possible to fully match the TEMs between the populations, as a result of the low number of patients and large differences in patient characteristics.

Table 2: Covariates before and after matching to tis-t

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]

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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. BM – Bone marrow; ECOG – Eastern Cooperative Oncology Group; Ph – Philadelphia; Ph – Philadelphia; mITT – Modified intention to treat; NA – Not available; SCT – Stem cell transplant

The results of the analysis show a non-significant OS benefit with obe-cel versus tis-t for the adjusted analysis. However, these results should be interpreted with extreme caution, considering the limited availability of TEMs from the tis-t trials, the considerable population differences, the wide confidence intervals (CIs), and especially the low ESS.

Table 3: Overall survival for obe-cel (age 18-25) versus tis-t (age <=25)

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

CI – Confidence interval; ESS - Effective sample size; HR - Hazard ratio; mITT - Modified intention to treat; OS – Overall survival

Plots of obe-cel unweighted, obe-cel weighted and comparator KM data for OS for obe-cel (FELIX, ages 18-25 years) versus tis-t pooled studies (ages <=25 years) are shown in Figure 1**Figure *1***.

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Figure 1: KM plot of OS, FELIX Cohort IIA mITT – ages 18-25 vs tis-t pooled analysis (ages <=25)

KM – Kaplan Meier; mITT - Modified intention to treat; OS – Overall survival

In order to mitigate these limitations as far as possible, the Company considered using real-world evidence (RWE) from SACT in tis-t patients aged 18-25 recently made available to the Company[9]. This analysis includes relevant tis-t infused patients (ages 18-25, N=36) which is an improvement compared to the previously available data from Stackelberg *et al*. 2023[7]. Whilst this mitigates the issue with the severely limited age overlap between the overall tis-t population and the obe-cel population aged 18-25, the low number of obe-cel patients remains. Additionally, the only SACT data provided was a Kaplan-Meier (KM) OS plot, as well as the gender and age bands of patients, rendering meaningful matching impossible. A naïve comparison in which the tis-t KM curve was overlayed on the obe-cel KM curve matched to the overall tis-t population (as presented in Table 2 and Figure 1) was undertaken and shows improved survival with obe-cel, but again results should be interpreted with caution (Figure 2). Whilst the weighted obe-cel population is closer to the SACT tis-t population than the unweighted in terms of age and gender, it is unknown how similar the populations are in terms of the other patient characteristics. For instance,in a publication of the overall UK population receiving tis-t from 2023, the average disease burden was bone marrow (BM) burden 2%, which is significantly lower than in the pooled analysis and FELIX, with lower BMs being associated with not only improved efficacy, but also potentially lower rates of adverse events. This publication also highlights a much higher rate of post treatment

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	allo-SCT for this overall population, with 29 out of 62 responders (46.7%) receiving an allo-SCT than seen in FELIX, which would not only impact on potential outcomes, but also would add significant cost to the use of tis-t.[10] Furthermore, as was shown in Castleton *et al.,* 2024 real-world use of CAR T in R/R B-ALL likely differs from the trial setting with more patients receiving prior allo-SCT and having a <5% BM blast in clinical practice, leading to potentially better outcomes.[11] As such, comparing trial data for obe-cel from FELIX with RWE for tis-t likely introduces an underlying bias in favour of tis-t. **Figure 2: KM plot of OS, tis-t (ages 18-25) and obe-cel (mITT - ages 18-25)**  KM – Kaplan-Meier; mITT – Modified intention to treat; OS – Overall survival Due to the notable limitations with the indirect comparisons discussed in this issue, comparison to tis-t was not assessed from an economic point of view. The analysis conducted shows that there is likely to be at least comparable efficacy outcomes between obe-cel and tis-t, with potentially significantly more post treatment allo-SCT and better pre-treatment managed patient for tis-t (in the real world).
Issue 2: Clarification on how the model accounts for ponatinib and inotuzumab being used as bridging chemotherapies to CAR-T therapy	In line with the Committee's request, the Company would like to clarify that the costs associated with bridging treatment, including bridging with inotuzumab and ponatinib, are captured in the 'Treatment Costs' sheet of the model by calculating a weighted average based on the proportion of patients who received each bridging chemotherapy from FELIX and the associated acquisition and administration costs. In the pooled Cohort IA and IIA, [redacted] ([redacted]) patients received inotuzumab and [redacted] ([redacted]) patients received ponatinib. The impact on clinical efficacy from bridging therapy is captured in the model as efficacy data for obe-cel was informed by FELIX. As it was highlighted by the clinical experts during the ACM, there is a greater understanding now in real-world clinical practice that more effective bridging chemotherapies may enhance CAR T therapy outcomes by improving disease control prior to infusion, leading to more patients being infused, further aligning the real-world population to an infused rather than an enrolled population from FELIX. It should also be noted that better disease control was associated with better outcomes in FELIX, both from an efficacy and safety for patient who had a lower burden of disease at the point of obe-cel infusion. For instance in the whole ITT for FELIX, those with a BM >20% have a median OS of 13.8 months, whilst those with lower BM have not reached a median, with a plateau of the curve at 65.4%.[12] It should however be noted that considering the washout period between receiving the last dose of the bridging therapy and CAR T infusion to mitigate any potential toxicity and preserve T-cell function, observed clinical efficacy following more aggressive bridging therapies can be attributed to CAR T-cel therapy itself rather than residual effects of the bridging regimen. There is

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	therefore the possibility that this real world management of patients could improve patient outcomes compared to the outcomes seen in FELIX.
Issue 3: Conservative clinical efficacy modelling approach	**Considering the advancements in CAR-T cell therapy delivery since the start of the pivotal FELIX trial, the Company considers it a conservative approach to use the enrolled population to inform clinical efficacy in the economic model and for decision-making.** The Company acknowledges that the Committee's preferred approach was to include a wider patient population with the inclusion of the Cohort IA population (n=21) and to inform time to event data used in the economic model for the pooled enrolled cohorts IA and IIA to capture the CAR T-cell therapy pretreatment and manufacturing period. However, during the ACM the clinician experts emphasised that considerable learnings have been implemented in delivery of CAR T products, including obe-cel, such as that the patient selection and management has been optimised since FELIX study enrolment. It should also be noted that FELIX was recruited during the COVID-19 pandemic. The clinical experts stated that in clinical practice, a lower proportion of patients who undergo pre-treatment will end up not receiving obe-cel, compared to what was observed in FELIX. Additionally, few FELIX patients ([redacted] in the pooled Cohort IA and IIA) received inotuzumab as a bridging therapy, which led to less controlled disease and to patients dying during the bridging period. The current situation is very different, the CAR T manufacturing period is considerably shorter (21-22 days, per expert opinion in the ACM), and bridging therapies are more aggressive; hence less patients will end up being pre-treated but not subsequently infused. Therefore, informing the clinical efficacy of obe-cel based on the enrolled FELIX population likely overestimates the proportion of pre-treated but not infused patients and the pre-treatment-to-infusion period, and underestimates the true efficacy of obe-cel. Considering that the proportion of patients who are pre-treated but do not undergo CAR T-cell therapy infusion will further decrease as obe-cel patient selection and delivery further improve in the UK with increased use, the infused population may be more reflective of the clinical outcomes observed in patients who receive obe-cel in clinical practice. The Company also sought further clinical opinion following the ACM to understand how reflective the FELIX population is of patients likely to receive CAR T in the UK. In the discussions held on the 26th and 27th June 2025, all three consulted experts noted that the population is "*similar*" or "*fairly representative*" of the UK population, with one clinician adding that the infused population is more aligned with UK patients.[13]
Issue 4: Updated MAIC and complementary STC results are consistent with the original MAIC	**The updated MAIC analyses and new STC analyses results conducted using the FELIX 2025 data cut are consistent with the previous MAIC results.** Autolus acknowledges the Committee's concerns regarding the uncertainty of the MAIC results. However, an unanchored MAIC was the optimal method considering the available evidence in absence of direct head-to-head trials. The low ESS is indicative of the between-trial population differences, supporting the use of the MAIC results over a naïve comparison versus blinatumomab and inotuzumab. The MAIC methodology presented in this submission aligns with established precedent set by previous CAR-T cell therapy NICE appraisals, such as TA893 (Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over)[2] and TA975 (Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under)[8]. In both these appraisals, the Committee concluded that the MAICs were appropriate for decision making, with an ESS of 37-39 and 23-24 for brexu-cel versus blinatumomab and inotuzumab in TA893, and 41.60 for tisagenlecleucel versus blinatumomab in TA975.[2,8] The ESS for obe-cel versus blinatumomab and inotuzumab in the infused Cohort IIA population were [redacted] and [redacted],

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while in the pooled enrolled Cohort IA and IIA populations were [redacted] and [redacted], respectively. Considering that these ESS are comparable or higher than those accepted in previous CAR T-cell therapy appraisals in R/R B-cell ALL, and that similar levels of follow-up and data maturity were deemed sufficient in earlier appraisals, the current concerns regarding the uncertainties of these results appear inconsistent with the approach taken in past recommendations. .

Nonetheless, to address the uncertainties in the MAIC, Autolus have updated the analysis using the most recent (January 2025) FELIX data cut to inform the obe-cel arm. Furthermore, to address potential methodological uncertainties, Autolus have conducted pairwise STCs using the January 2025 FELIX data cut to inform the obe-cel arm, and data from the same published comparator trials to inform the inotuzumab, blinatumomab and ponatinib arms that was used for the MAIC analyses.

Results of the updated and new ITC analyses

The updated MAIC and STC results for EFS and OS are presented in Table 4 and Table 5, with the detailed methodology and interpretation of the results provided in the separate ITC and survival analysis report. As shown, results from the 2024 and 2025 FELIX data cuts, as well as between the MAIC and STC are consistent, supporting the robustness of the analyses despite the limitations in the available evidence.

Table 4: Event-free survival for FELIX versus comparators, enrolled pooled Cohort IA and IIA 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]
2024 FELIX data cut results – MAIC analysis				
Median EFS	7.0 months	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 – MAIC analysis				
Median EFS	[redacted]	5.0 months	0.0 months†	3.0 months
ESS	-	[redacted]	[redacted]	[redacted]
Unadjusted HR	-	[redacted]	[redacted]	[redacted]

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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]

*Statistically significant results. †Median EFS for blinatumomab unavailable due to censoring of patients who have not achieved complete remission or complete remission with incomplete haematologic recovery. EFS – event-free survival; ESS – effective sample size; HR – hazard ratio; ITT – intention to treat; MAIC – Matching-adjusted indirect treatment comparison; Ph – Philadelphia chromosome; STC – Simulated treatment comparison

Table 5: Overall survival for FELIX versus comparators, enrolled pooled Cohort IA and IIA 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]
2024 FELIX data cut results – MAIC analysis				
Median OS	12.2 months	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 – 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]

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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]

*Statistically significant results. ESS - effective sample size; HR - hazard ratio; ITT - intention to treat; MAIC – Matching-adjusted indirect treatment comparison; OS – overall survival; Ph – Philadelphia chromosome; STC – Simulated treatment comparison

Revised base case results, incorporating the updated MAIC results

Table 6 presents the revised base case results for obe-cel versus its comparators using the 2025 MAIC results and clinical efficacy from the Committee preferred pooled enrolled Cohort IA and IIA population. Scenario analyses have been conducted to show the impact of using the STC results, with results presented in the separate cost-effectiveness results report.

With all Committee preferred changes to the cost-effectiveness analysis accepted and using the updated MAIC hazard ratios (HRs), all incremental cost-effectiveness ratios (ICERs) versus obe-cel decreased compared to the EAG ICERs presented at the post-factual accuracy stage. For consistency between the methods used for each population, the Company has used the inverse HR approach in the base case in the Ph+ population versus inotuzumab. However, it should be noted that this leads to a significant overestimation of both EFS and OS compared to the published inotuzumab KM, suggesting that a naïve approach may be more appropriate (EFS and OS KM landmark survival at last observed period, 28 months and 49 months respectively: 14.0%, 9.7%; EFS and OS extrapolated survival curve at the same timepoints: [redacted]). This overestimation of inotuzumab efficacy versus the last observed period of EFS and OS KMs persists in all comparisons when using the STC HRs as well. Results for using a naïve approach versus inotuzumab have been presented in the separate cost-effectiveness results report.

Revised deterministic and probabilistic base-case and scenario analysis results are presented in detail in the separate cost-effectiveness results report.

Table 6: Revised deterministic base case results – PAS price

Population	Incremental costs	Incremental QALYs	ICER
Overall population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Ph- population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus blinatumomab	[redacted]	[redacted]	[redacted]
Ph+ population			

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	<table><tr><td>Obe-cel versus inotuzumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Obe-cel versus ponatinib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table> ICER – Incremental cost-effectiveness ratio; Ph: Philadelphia chromosome
Issue 5: Further evidence for using the inverse hazard ratio approach for the comparison against inotuzumab and blinatumomab	**The inverse hazard ratio approach is the only method that allows for subgroup specific modelling in the economic analysis, thereby better reflecting the long-term outcomes in the Ph- patient population than a standard MAIC approach.** It should be noted that the approach suggested by the EAG of fitting separate parametric curves to each arm using the standard MAIC approach would not allow for an accurate incremental analysis in the Ph- subgroup, considering the multiple comparators. This justification was provided in Section B.3.3.1.5 of the CS (page 116) and at the factual accuracy stage. As no Ph subgroup-specific data was available from INOVATE, the HRs are based on the overall populations of inotuzumab and obe-cel. Applying this HR in the economic model to the inotuzumab curve to estimate obe-cel efficacy would, therefore, introduce bias, as neither the obe-cel or the inotuzumab curves would be representative of the Ph- subgroup. The inverse HR approach anchors the inotuzumab curve to the subgroup-specific obe-cel data, thereby minimising the bias arising from using overall population data from INOVATE. This method is in line with the Committee's preference in TA893 (Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over)[2] and was deemed appropriate for decision-making. Furthermore, as mentioned above, this approach ensures that the same baseline characteristics are assumed for all treatment arms when comparing to both inotuzumab and blinatumomab, allowing for a fair comparison. The Company acknowledges the Committee and EAG's concern with regards to the ESS being small in absolute terms when matched to inotuzumab and blinatumomab. However, this is indicative of the between trial differences and supports the use of the MAIC results over a naïve comparison, as the MAIC better aligns patient populations. While the Company acknowledges that the EAG also raised concerns regarding the underlying proportional hazards (PH) assumption, when suggesting the inverse HR approach, the EAG in TA893 noted that *"This [cure assumption] means that long-term survival extrapolations are not required, and therefore a strong-assumption of long-term PH is not necessary when using a transportable HR approach"* (EAG report, Section 3.4., page 82), further supporting the precedent of using the inverse HR approach, with similar data that was presented and used in this submission.
Issue 6: Further clarification on the cure assumption and SMR applied to patients in the post-event health state	**The plateau observed in the OS curve indicate that patients, regardless of whether they experienced an event, achieve long-term survival, supporting the use of the cure assumption in the progressive disease (PD) health state.** The Company acknowledges the Committee's request to provide 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. As seen in Figure 3 and Figure 4, the 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, including those in the PD health state. Furthermore, the lack of divergence in the difference between EFS and OS in the plateau supports the assumption that long-term mortality risk converges between the health states, indicating that using the same SMR in the event-free (EF) and PD health states is appropriate. Whilst a further small downward inflection is observed at the tail of both the EFS and OS curves, this is driven by censoring following two additional patient deaths not related

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to the disease and does not indicate a broader trend or invalidate the extrapolation assumption.

Figure 3: KM plot of EFS without censoring new non-protocol anticancer therapies including SCT - enrolled Cohort IA and IIA

EFS – Event-free survival; KM – Kaplan-Meier; SCT – Stem cell transplant

Figure 4: KM plot of OS without censoring new non-protocol anticancer therapies including SCT - enrolled Cohort IA and IIA

KM – Kaplan-Meier; OS – Overall survival; SCT – Stem cell transplant

Median EFS remained consistent at [redacted] months (95% CI: [redacted]) in both the February 2024 and January 2025 data cuts, with one additional patient experiencing an event in the latter. The EFS rates at 12, 24, and 36 months were [redacted], [redacted], and [redacted] respectively, indicating that a significant proportion of patients maintain remission over the longer term.

Median OS improved from [redacted] months (95% CI: [redacted]) in the February 2024 data cut to [redacted] months (95% CI: [redacted]) in January 2025. OS rates remained stable at [redacted] at 6 months and [redacted] at 12 months in both data sets. Importantly, 24-month OS increased from [redacted] to [redacted], with the latest data showing a 36-month OS of [redacted].

Together, these data demonstrate the sustained and durable clinical benefit of obe-cel, reducing uncertainty around long-term outcomes. This strengthens the evidence base with

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regards to obe-cel's efficacy and value for patients over time, with a clear convergence between EFS and OS at the 3 year time point.

It should also be noted that precedent exists for a similar approach in the same positioning to modelling cure assumption from TA893 (Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over)[2]. In their response to clarification question B31, the submitting company in TA893[2] clearly stated that "*our assumption is that following the cure timepoint all patients, regardless of whether they were in the EFS or PD health state, were assumed to be cured*". The Committee accepted this assumption and deemed it appropriate for decision-making.

Regarding the SMR value to apply in the economic analysis, as outlined in CS Section B.3.2.2.1 (page 105), the cure timepoint of three years was selected to align with TA893 and validated with two UK clinical experts. Both experts expressed that patients treated with obe-cel who relapse would typically do so within a year. As such, the three-year cure assumption can even be considered conservative.[14] The Company notes clinician experience with treatment with allo-SCT have likely improved since 1970 and 2002, years from which data was used in Martin *et al*. 2010[15]. As such, SMR values closer to the lower end of the range reported in this publication may be more representative of the increased risk of mortality in patients undergoing treatments with a curative potential, such as allo-SCT or CAR T therapy. Considering that only a low proportion of patients are expected to undergo allo-SCT following treatment with obe-cel, assuming a higher SMR from Martin *et al*. 2010[15] would be inappropriate.

Scenario analyses in the revised base case

While the Company maintains the appropriateness of the cure assumption to all patients who are alive at three years and using an SMR of 3 in the base case for all cured patients, in order to mitigate uncertainty scenario analyses were conducted using an SMR of 4.

Revised deterministic and probabilistic scenario analysis results are presented in detail in the separate cost-effectiveness results report.

Table 7: Deterministic scenario analyses using an SMR of 4 - PAS price

Population	Incremental costs	Incremental QALYs	ICER
Overall population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Ph- population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus blinatumomab	[redacted]	[redacted]	[redacted]
Ph+ population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus ponatinib	[redacted]	[redacted]	[redacted]

ICER – Incremental cost-effectiveness ratio; Ph: Philadelphia chromosome

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Issue 7: Using the most recent CAR T tariff	**As mentioned in the ACM by the Committee, clinician experts and patient experts, there are several considerable uncaptured benefits of obe-cel treatment which are not captured when applying the CAR-T tariff (£60,462).** Firstly, the tariff is based on costs associated with real-world CAR-T patients from UK clinical practice, i.e., not based on obe-cel patients. Therefore, it 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. The clinician experts pointed out that one key benefit of obe-cel is its ability to reduce cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANs) through a unique binder which performs differently to other CAR-Ts. In addition to the lower observed rates of grade 3+ CRS and neurotoxicity compared to currently available CAR-Ts e.g., brexu-cel, these toxicities are also highly linked to high disease burden at the point of obe-cel infusion, which as discussed in Issues 2 and 3, is likely to be better managed in real world usage. It should also allow for more efficient monitoring and earlier intervention for those patients most at risk. The favourable adverse event profile of obe-cel allows for the potential to administer and/or monitor obe-cel in an outpatient setting, making administration less costly and the product more accessible to patients across the board. Indeed, the clinician experts in the ACM noted that patients can go back to work and "*get on with their lives*" earlier compared to other treatment options, in addition to saving them the inconvenience of travelling for hours in order to reach specialist clinics. Such indirect cost benefits are likely substantial and not formally captured in the economic analysis. Furthermore, 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. Clinical experts have noted that patients with lower bone marrow blast counts are likely candidates for less intensive inpatient management, and this subgroup is expected to grow over time with better treatment delivery and supportive care. Evidence from Castleton *et al.,* 2024[11] shows that a much higher proportion of patients with R/R B-ALL are treated with CAR T in real-world UK setting than what is observed in clinical trials (67% vs 9%) further supporting the uncaptured nature of these benefits in this appraisal. These developments are directly relevant to two important considerations. Firstly, the fact that obe-cel is manufactured in the UK should allow for quicker treatment and less time in the bridging period which may reduce the requirement for or the dose of bridging therapies. These patients are not only more likely to be managed in outpatient settings, reducing the need for intensive care unit (ICU)-level monitoring and prolonged hospital stays, Secondly, while ICU costs reductions are modelled separately from the tariff, the model does not capture the improvement in health-related quality of life (HRQoL) as a result of the reduced ICU admissions. Additionally, freeing up ICU capacity could improve outcomes for other critically ill patients in the UK. In addition to the above, it should be noted that the current tariff is substantially higher than what was applied in earlier CAR T appraisals (e.g., TA893[2]). As noted by NHS England in TA893, the tariff represents the substantial costs related to the establishment of infrastructure for CAR T delivery, with economics of scale expected over time. The reduction of toxicity and intensity of monitoring was specifically pointed out as key drivers of these economics of

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scale. Therefore, a reduced tariff of £41,101 was accepted. It is therefore not appropriate to apply a substantially higher CAR T tariff to obe-cel.

It should also be noted that the CAR T tariff established during the appraisal process of TA872 (Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies)[1], and subsequently used in TA893[2], was a result of extensive discussions with NICE and NHS England with the company submitting in TA872 to ensure a cost of treatment that is fair and accurate, aligned with real-world considerations. It is concerning that the companies most recently submitting to NICE do not get a detailed outline of how this new tariff was calculated and what resource use assumption it entails. The design of the CAR T tariff does not incentivise innovation as a set tariff implies that resource use is the same over all treatments. As mentioned above, obe-cel was designed to reduce toxicity, with consequential improved rates of CRS and ICANS observed. Hence the use of the tariff in the base case means an uncaptured benefit of innovation and potentially limits patient access to new treatments that address a considerable medical unmet need.

There is precedent for NICE considering alternatives to the standard CAR T tariff where there is evidence to suggest it may not be appropriate. In the TA975 (Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under)[8] re-appraisal in 2024, for which 83% of the treated population were aged 18 or less, the Cancer Drugs Fund (CDF) lead noted that CAR T associated costs are higher in children than in adults. This led to the committee considering a weighted CAR T tariff of £95,194 for their decision making.

While in our revised base case Autolus have used the CAR T tariff to align with the Committee's preference, scenario analyses have been conducted using the bottom-up costing approach, incorporating healthcare resource use associated with obe-cel infusion from FELIX (see Table 8). The Company considers the bottom-up costing method to closer align with the real-world costs of obe-cel delivery.

Table 8: Deterministic scenario analyses using a bottom-up costing approach - PAS price

Population	Incremental costs	Incremental QALYs	ICER
Overall population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Ph- population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus blinatumomab	[redacted]	[redacted]	[redacted]
Ph+ population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus ponatinib	[redacted]	[redacted]	[redacted]

ICER – Incremental cost-effectiveness ratio; Ph: Philadelphia chromosome

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Issue 8: Appropriate costs associated with ASCT in the obe-cel arm

The original CS included allo-SCT and associated follow-up costs from TA893, which used 2014 NHS Blood and Transplant costs inflated to the 2019/2020 cost year. The Company, however, recently became aware that more recent data is available on these costs in the England in a report by Ernst & Young (EY) LLP, 2021.[16] The report describes results from the analysis of hospital activity and costs associated with patients who underwent allo-SCT one year post-discharge. Two data sources informed the analysis, NHS Digital's Secondary Uses Services to identify patients who received allo-SCT in England during 2015/2016 and track the patients' subsequent hospital activity; and data from the Royal Marsden NHS Foundation Trust's Patient Level Information and Costing Systems to estimate the costs linked to these activities. The analysis found that hospital resource use remained significant beyond 100 days, and estimated costs to be much higher than what is used in the original CS (Table 9).

Table 9: Allo-SCT costs used in the original company submission and the EY, 2021 report

Allo-SCT cost category	Original company submission (inflated to 2023 cost year)	EY report (2021 cost year)[16]
SCT costs	£115,591	£82,197
0-6 months follow-up	£34,347	£88,808*
6-12 months follow-up	£23,594	£35,963

*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]). In numerical terms: (138,935-82,197)+32,070. Allo-SCT – Allogenic stem cell transplant EY – Ernst & Young LLP

Considering that this report may provide a more up-to-date and accurate estimate of the long-term resource use and costs associated with allo-SCT, the Company has implemented these as scenario analyses to the updated economic model. Results for these scenarios are shown in Table 10.

Table 10: Deterministic scenario analyses using allo-SCT costs from EY report - PAS price

Population	Incremental costs	Incremental QALYs	ICER
Overall population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Ph- population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus blinatumomab	[redacted]	[redacted]	[redacted]
Ph+ population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus ponatinib	[redacted]	[redacted]	[redacted]

ICER – Incremental cost-effectiveness ratio; Ph: Philadelphia chromosome

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Additionally, in line with the Committee's request, the Company have conducted scenario analyses using alternative proportions of patients undergoing allo-SCT post-obe-cel (see Table 11 and Table 12). While these results better reflect real-world use of allo-SCT following obe-cel, these may continue to underestimate allo-SCT usage in the comparator arms. As was highlighted during the ACM by the clinical experts, the aim of treatment in R/R adult ALL is to get patients on to a potentially curative treatment, which for the comparators would be allo-SCT.

Table 11: Deterministic scenario analyses results using 5% post-obe-cel allo-SCT proportion - PAS price

Population	Incremental costs	Incremental QALYs	ICER
Overall population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Ph- population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus blinatumomab	[redacted]	[redacted]	[redacted]
Ph+ population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus ponatinib	[redacted]	[redacted]	[redacted]

ICER – Incremental cost-effectiveness ratio; Ph: Philadelphia chromosome

Table 12: Deterministic scenario analyses results using 2.5% post-obe-cel allo-SCT proportion - PAS price

Population	Incremental costs	Incremental QALYs	ICER
Overall population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Ph- population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus blinatumomab	[redacted]	[redacted]	[redacted]
Ph+ population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]

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	Obe-cel versus ponatinib | [redacted] | [redacted] | [redacted] ICER – Incremental cost-effectiveness ratio; Ph: Philadelphia chromosome
Issue 9: Mortality captured in the SCT tunnel states	To clarify how mortality has been addressed in the SCT tunnel states in the original company model, the tunnel states account for mortality in each model cycle. Therefore, accordingly, the original company model estimated costs using the full proportion of patients in each post allo-SCT follow-up period (0–6 months, 6–12 months, and 12–24 months) in each model cycle. In contrast, the EAG's approach uses only the first tunnel state in each 6 and 12 monthly period (e.g., at 6 and 12 months) within each cycle, meaning mortality is only accounted for when a new follow-up period is reached instead of per cycle. The Company acknowledges that allo-SCT costs in each treatment arm are however now in line with the proportion of patients receiving allo-SCT in each model arm in the EAG's model and therefore have implemented these changes in the updated company economic model.
Issue 10: Intravenous immunoglobulin use captured in the economic model	The Company acknowledges the concerns regarding the potential underestimation of IVIG use in the original economic model. However, in current UK clinical practice, IVIG is not routinely administered to all patients with low immunoglobulin levels. Instead, treatment decisions are guided by clinical presentation, specifically whether the patient experiences recurrent infections despite prophylactic antibiotics and has a serum IgG level below 3 g/L, as acknowledged by the Committee in the ACD. Clinical experts have confirmed that IVIG is typically reserved for patients with severe or repeated infections, rather than being a standard intervention for all patients with B-cell ALL. Importantly, the Company noted that in the original submission the economic model reflected this selective use of IVIG by linking its use to the incidence of grade ≥3 hypogammaglobulinaemia as reported in FELIX. This has now been updated in the model to reflect clinical expert opinion and new real-world data available from FELIX following 6-month post-obe-cel infusion, which show that long-term IVIG use is uncommon.[17] Across the infused pooled population (Cohort IA and IIA; n=104), mean IVIG use was [redacted] days (standard deviation [SD]: [redacted] days) with a median of [redacted] day (min–max: [redacted] – [redacted] days). In the UK-specific cohort (n=40), usage was slightly higher but still low overall, with a mean of [redacted] days (SD: [redacted] days) and a median of [redacted] days (min–max: [redacted] – [redacted] days). These data provide reassurance that IVIG use in the model is not underestimated and aligns with current UK clinical practice. The updated model base case incorporates the low duration of IVIG use observed in FELIX, with IVIG use reevaluated every six months throughout the entire time horizon. To address concerns that IVIG use may have been underestimated, a conservative reduction in IVIG use was applied, decreasing by 5% at months 6, 12, and 18, followed by 2% reduction every six months thereafter. To further address concerns regarding potential underestimation of IVIG costs in the model, the monthly IVIG dose was calculated using ideal body weight (IBW), in line with NHS England's *Clinical Commissioning Policy for the use of therapeutic immunoglobulin (Ig)*.[18] This ensures consistency with national prescribing guidance and provides a conservative and clinically appropriate basis for modelling IVIG usage. The model dose also not capture IVIG use for patients in the comparator arms undergoing allo-SCT, where similar doses and rates of IVIG usage may be expected.
Issue 11: Using a 1.2 severity weight for all populations	The Company acknowledges that the use of blinatumomab in the same indication as obe-cel will likely reduce following blinatumomab's approval as a first-line treatment. However, the Company would like to reiterate the importance of this comparison in decision-making; the ITC to blinatumomab provides the most robust evidence on the relative effect of obe-cel,

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given the similarity of the trial population, and so this provides the most robust estimate of treatment effect. FELIX patients were more heavily pre-treated than the comparator trial populations, with blinatumomab's TOWER study population being the one closest to FELIX baseline characteristics, including in terms of pre-treatments.

The Company believes that a 1.2 severity modifier not only under represents the severity of the disease, where median life expectancy is less than a year, but also the large degree of uncaptured benefit that has been described for obe-cel (please see Issue 7 and Issue 12). The Company feel that a 1.7 modifier would be appropriate at least for the Ph- population, hence the true appropriate value is somewhere in-between 1.2 and 1.7. Prior appraisals in this disease area have met the end-of-life criteria (such as in TA893 [Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over])[2], and it would be consistent and fair to take a comparable approach here.

While the revised base-case results have been updated to reflect a 1.2 severity modifier, scenario analyses have been conducted using the 1.7 value and are shown in Table 13.

Table 13: Deterministic scenario analyses using a 1.7 severity modifier - PAS price

Population	Incremental costs	Incremental QALYs	ICER
Overall population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Ph- population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus blinatumomab	[redacted]	[redacted]	[redacted]
Ph+ population			
Obe-cel versus inotuzumab	[redacted]	[redacted]	[redacted]
Obe-cel versus ponatinib	[redacted]	[redacted]	[redacted]

ICER – Incremental cost-effectiveness ratio; Ph: Philadelphia chromosome

Issue 12. Benefits not captured in the QALY

The Company believe that there are important elements of values that cannot be captured in the QALY. It is well recognised that this is a severe condition and for 30-40% of patients this technology may result in a curative outcome, compared to the majority of patients living less than a year. The full value of this transformation cannot be captured quantitively but is fundamentally important to patients, families and also society.

Additionally, some 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. These benefits are discussed further in Issue 7, which outlines how they contribute to improved patient experience and greater efficiency in the use of healthcare resources.

The favourable safety and toxicity profile of obe-cel is expected to lower healthcare resource utilisation by reducing the need for intensive care and enabling less complex treatment

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	delivery. These factors are also likely to enhance patient quality of life. Current curative treatment on the NHS is limited to allo-SCT, which is restricted to a generally healthier and younger population, by approving obe-cel with its safety profile, more patients may be eligible for a potentially curative treatment, including the elderly (patient aged over 70 years) and also ethnic minorities where there may be less opportunities for a match. All of these potential advantages were also considered in detail in TA1048 (Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy when a stem cell transplant is suitable)[19], where the Committee acknowledged their relevance in informing decision-making, even though they were not fully included in the economic analysis. The Company considers that similar reasoning is appropriate in this appraisal, given the emerging evidence for more streamlined and resource-efficient CAR T delivery in this population.

Insert extra rows as needed

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Consultation on the draft guidance document – deadline for comments 5pm on Friday 4 July 2025. Please submit via NICE Docs.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Cost-effectiveness results using the 2025 data cut of the pivotal FELIX trial demonstrating the efficacy and safety of obe-cel in adult acute lymphoblastic leukaemia (ALL)

July 2025

Contents

1 Introduction

This report has been produced to present the most recent cost-effectiveness results of obe-cel. Since the original submission in November 2024, a new data cut from the FELIX trial (January 2025) has become available. The longer follow-up addresses some of the Committee's uncertainties regarding the economic value of obe-cel in relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL). Additionally, the Committee preferred cost-effectiveness data based on a combination of Cohort IA and IIA over the Company's original approach of basing cost-effectiveness on Cohort IA alone (the primary efficacy population in the FELIX trial). This report presents the cost-effectiveness results from the most current FELIX data cut for:

- Pooled Cohort IA and IIA (enrolled set)

2 Base-case results

This section presents the base-case results for the economic analysis comparing obe-cel to inotuzumab, blinatumomab, and ponatinib in the population of R/R B-cell adult ALL.

The base-case results are presented using the list price for all comparators, and both the list price and confidential simple patient access scheme (PAS) discount of [redacted] for obe-cel.

2.1 Overall population

Total costs, life years gained (LYG), quality-adjusted life years (QALYs), incremental results and the incremental cost-effectiveness ratio (ICER) for obe-cel versus inotuzumab are presented in Table 1 and Table 2 using obe-cel list and PAS price, respectively.

Using the list price for obe-cel, and a severity modifier of 1.2, the ICER of obe-cel compared with inotuzumab in the overall population is [redacted] per QALY gained in the base-case. Obe-cel generates an additional 1.68 QALYs at an additional cost of [redacted]. When the PAS discount is applied, obe-cel is associated with an additional cost [redacted] versus inotuzumab, resulting in an ICER of [redacted] per QALY gained.

Table 1: Deterministic results, overall population – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years

Table 2: Deterministic results, overall population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life year

2.2 Ph- population

Total costs, LYG, QALYs, incremental results and the ICER for obe-cel versus inotuzumab and blinatumomab are presented in Table 3 and Table 4 using obe-cel list and PAS price, respectively.

Using the list price for obe-cel and a severity modifier of 1.2, the cost-effectiveness of obe-cel compared with blinatumomab is [redacted] per QALY gained. Obe-cel generates an additional [redacted] QALYs at an additional cost of [redacted]. When the PAS discount is applied, obe-cel is associated with additional costs of [redacted] versus blinatumomab, resulting in an ICER of [redacted] per QALY gained.

Using the list price for obe-cel and a severity modifier of 1.2, the cost-effectiveness of obe-cel compared with inotuzumab is [redacted] per QALY gained. Obe-cel generates an additional [redacted] QALYs at an additional cost of [redacted]. When the PAS discount is applied, obe-cel is associated with additional costs of [redacted] versus inotuzumab, resulting in an ICER of [redacted] per QALY gained.

Table 3: Deterministic results, Ph- population – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (obe-cel versus comparator)	ICER incremental
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; Ph – Philadelphia chromosome; QALYs – quality-adjusted life years

Table 4: Deterministic results, Ph- population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (obe-cel versus comparator)	ICER incremental
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; Ph – Philadelphia chromosome; QALYs – quality-adjusted life years

2.3 Ph+ population

Total costs, LYG, QALYs, incremental results and the ICER for obe-cel versus inotuzumab and ponatinib are presented in Table 5 and Table 6 using obe-cel list and PAS price, respectively.

Using the list price for obe-cel and a severity modifier of 1.2, the cost-effectiveness of obe-cel compared with inotuzumab is [redacted] per QALY gained. Obe-cel generates an additional [redacted] QALYs at an additional cost of [redacted]. When the PAS discount is applied, obe-cel is associated with an additional cost of [redacted] versus inotuzumab, resulting in and ICER of [redacted].

Using the list price for obe-cel and a severity modifier of 1.2, the cost-effectiveness of obe-cel compared with ponatinib is [redacted] per QALY gained. Obe-cel generates an additional [redacted] QALYs at an additional cost of [redacted]. When the PAS discount is applied, obe-cel is associated with additional costs of [redacted] versus ponatinib, resulting in an ICER of [redacted] per QALY gained.

Table 5: Deterministic results, Ph+ population – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (obe-cel versus comparator)	ICER incremental
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; Ph – Philadelphia chromosome; QALYs – quality-adjusted life years

Table 6: Deterministic results, Ph+ population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (obe-cel versus comparator)	ICER incremental
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; Ph – Philadelphia chromosome; QALYs – quality-adjusted life years

3 Deterministic sensitivity analyses

One-way deterministic sensitivity analysis (OWSA) involves varying one parameter at a time to assess how sensitive the model results are to different values. This is typically done by allocating a low value and high value to each parameter, where these values correspond to the lower and upper bounds of the 95% confidence interval (CI). If CI data are not available, parameters can be altered by ±20%. This approach allows for an understanding of how robust the model results are to changes in individual input parameters.

3.1 Overall population

The top ten parameters yielding the biggest impact on cost-effectiveness results for the overall population are presented in Table 7 and Figure 1. The top three most sensitive parameters were overall survival (OS) standard parametric coefficients, the proportion of inotuzumab patients receiving haematopoietic stem cell transplant (HSCT), and patient weight.

Table 7: Tabulated OWSA results - obe-cel versus inotuzumab (overall population) - ICER

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
OS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
Inotuzumab - proportion HSCT (0.39, 0.58)	[redacted]	[redacted]	[redacted]
Patient weight (63.45, 94.39)	[redacted]	[redacted]	[redacted]
Standardised mortality ratio for all long-term survivors (1.09, 4.00)	[redacted]	[redacted]	[redacted]
Infusion and monitoring costs - Obe-cel (£52,347, £77,544)	[redacted]	[redacted]	[redacted]
Patient height (135.72, 201.88)	[redacted]	[redacted]	[redacted]
Utility: Long-term survivorship (0.05, 0.07)	[redacted]	[redacted]	[redacted]
Utility: Post-event (0.55, 0.82)	[redacted]	[redacted]	[redacted]
HSCT - Initial treatment cost (£94,050, £139,321)	[redacted]	[redacted]	[redacted]
Total per cycle AE costs: Inotuzumab (£14,672, £21,734)	[redacted]	[redacted]	[redacted]

AE – Adverse event; HSCT – haematopoietic stem cell transplant; ICER – Incremental cost-effectiveness ratio; OS – Overall survival; OWSA – one-way sensitivity analysis

Figure 1: OWSA results for obe-cel versus inotuzumab (overall population) – ICER

ICER – Incremental cost-effectiveness ratio; OWSA – one-way sensitivity analysis

3.2 Ph- population

The top ten parameters yielding the biggest impact on cost-effectiveness results for the Philadelphia chromosome negative (Ph-) population versus blinatumomab are presented in Table 8 and Figure 2. The top three most sensitive parameters were the event-free survival (EFS) standard parametric coefficients, the event-free utilities, and standardised mortality ratio for long-term survivors. Results for the Ph- comparison to inotuzumab are presented in Table 9 and Figure 3. The top three most sensitive parameters were the proportion of inotuzumab patients receiving HSCT, patient weight, and patient height.

Table 8: Tabulated OWSA results - obe-cel versus blinatumomab (Ph- population) - ICER

Parameter	**Lower bound ICER (£)**	**Upper bound ICER (£)**	**Difference (£)**
EFS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
Utility: Event-free (0.59, 0.88)	[redacted]	[redacted]	[redacted]
Standardised mortality ratio for all long-term survivors (1.09, 4.00)	[redacted]	[redacted]	[redacted]
Utility: Long-term survivorship (0.05, 0.08)	[redacted]	[redacted]	[redacted]
Infusion and monitoring costs - Obe-cel (£52,347, £77,544)	[redacted]	[redacted]	[redacted]
OS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
Blinatumomab - proportion HSCT (0.11, 0.16)	[redacted]	[redacted]	[redacted]

Obe-cel - proportion HSCT (0.08, 0.12)	[redacted]	[redacted]	[redacted]
Utility: Post-event (0.55, 0.82)	[redacted]	[redacted]	[redacted]
SubTx drug costs - Blinatumomab (£16,827, £24,926)	[redacted]	[redacted]	[redacted]

EFS – Event-free survival; HSCT – haematopoietic stem cell transplant; ICER – incremental cost-effectiveness ratio; OS – Overall survival; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis; SubTX – Subsequent treatment.

Figure 2: OWSA results for obe-cel versus blinatumomab (Ph- population) - ICER

ICER – incremental cost-effectiveness ratio; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis

Table 9: Tabulated OWSA results for obe-cel versus inotuzumab (Ph- population) - ICER

Parameter	**Lower bound ICER (£)**	**Upper bound ICER (£)**	**Difference (£)**
Inotuzumab - proportion HSCT (0.39, 0.58)	[redacted]	[redacted]	[redacted]
Patient weight (65.29, 97.12)	[redacted]	[redacted]	[redacted]
Patient height (136.10, 202.46)	[redacted]	[redacted]	[redacted]
Infusion and monitoring costs - Obe-cel (£52,347, £77,544)	[redacted]	[redacted]	[redacted]
Standardised mortality ratio for all long-term survivors (1.09, 4.00)	[redacted]	[redacted]	[redacted]
HSCT - Initial treatment cost (£94,050, £139,321)	[redacted]	[redacted]	[redacted]
Utility: Long-term survivorship (0.05, 0.08)	[redacted]	[redacted]	[redacted]
Utility: Event-free (0.59, 0.88)	[redacted]	[redacted]	[redacted]
EFS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
OS Standard parametric coefficients	[redacted]	[redacted]	[redacted]

HSCT – haematopoietic stem cell transplant; ICER – Incremental cost-effectiveness ratio; OS – Overall survival; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis; SubTX – Subsequent treatment.

Figure 3: OWSA results for obe-cel versus inotuzumab (Ph- population) - ICER

NMB – net monetary benefit; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis

3.3 Ph+ population

The top ten parameters yielding the biggest impact on cost-effectiveness results for the Philadelphia chromosome positive (Ph+) comparison to inotuzumab, these are presented in Table 10 and Figure 4. The top three most sensitive parameters were the standardised mortality ratio for all long-term survivors, post-event utilities and long-term survivorship utilities. Results for the Ph+ population versus ponatinib are presented in Table 11 and Figure 5. The top three most sensitive parameters were the OS standard parametric coefficients, standardised mortality ratio for all long-term survivors, and event-free utilities.

The proportion of patients receiving HSCT is a particularly sensitive parameter across all populations, due to high HSCT-associated costs. The assumptions used in the base-case for HSCT align with TA893, to minimise decision uncertainty.[1]

Table 10: Tabulated OWSA results - obe-cel versus inotuzumab (Ph+ population) - ICER

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Standardised mortality ratio for all long-term survivors (1.09, 4.00)	[redacted]	[redacted]	[redacted]
Utility: Post-event (0.55, 0.82)	[redacted]	[redacted]	[redacted]
Utility: Long-term survivorship (0.04, 0.05)	[redacted]	[redacted]	[redacted]
OS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
Infusion and monitoring costs - Obe-cel (£52,347, £77,544)	[redacted]	[redacted]	[redacted]

Inotuzumab - proportion HSCT (0.39, 0.58)	[redacted]	[redacted]	[redacted]
Patient weight (58.15, 86.50)	[redacted]	[redacted]	[redacted]
Patient height (134.41, 199.94)	[redacted]	[redacted]	[redacted]
HSCT - Initial treatment cost (£94,050, £139,321)	[redacted]	[redacted]	[redacted]
Total one-off AE utility decrement: Obe-cel (0.255, 0.378)	[redacted]	[redacted]	[redacted]

EFS – Event-free survival; HSCT – haematopoietic stem cell transplant; ICER – Incremental cost-effectiveness ratio; OS – Overall survival; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis; SubTX – Subsequent treatment.

Figure 4: OWSA results for obe-cel versus inotuzumab (Ph+ population) - ICER

ICER – Incremental cost-effectiveness ratio; Ph – Philadelphia; OWSA – one-way sensitivity analysis

Table 11: Tabulated OWSA results - obe-cel versus ponatinib (Ph+ population) - ICER

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
OS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
Standardised mortality ratio for all long-term survivors (1.09, 4.00)	[redacted]	[redacted]	[redacted]
Utility: Event-free (0.59, 0.88)	[redacted]	[redacted]	[redacted]
Utility: Long-term survivorship (0.04, 0.05)	[redacted]	[redacted]	[redacted]
Ponatinib - proportion HSCT (0.38, 0.56)	[redacted]	[redacted]	[redacted]
Infusion and monitoring costs - Obe-cel (£52,347, £77,544)	[redacted]	[redacted]	[redacted]
EFS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
HSCT - Initial treatment cost (£94,050, £139,321)	[redacted]	[redacted]	[redacted]
EFS Flexible parametric coefficients	[redacted]	[redacted]	[redacted]
SubTx drug costs - Ponatinib (£30,978, £45,889)	[redacted]	[redacted]	[redacted]

EFS – Event-free survival; HSCT – haematopoietic stem cell transplant; ICER – incremental cost-effectiveness ratio; OS – Overall survival; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis; SubTX – Subsequent treatment.

Figure 5: OWSA results for obe-cel versus ponatinib (Ph+ population) - ICER

ICER – incremental cost-effectiveness ratio; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis.

4 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), whereby all appropriate parameters are assigned distributions and varied jointly. Parameters that deemed not appropriate for variation included structural assumptions (e.g., cell links for different modelling options, time horizon) and inputs considered to be certain (e.g., drug acquisition costs). A total of 1,000 Monte Carlo simulations were recorded and plotted over time for each model population (overall population, Ph- and Ph+ subgroups) using the PAS discount and the 1.2 severity modifier, to demonstrate the convergence of the population-specific ICERs.

Cost-effectiveness acceptability curves were generated presenting the percentage difference of simulations in which obe-cel is cost-effective over the WTP thresholds from £0-100,000 per QALY gained. Please note that the results plotted to the cost-effectiveness acceptability curves do not take the severity modifier into account.

4.1 Overall population

The mean costs and QALYs for the overall population are presented in Table 12. Results were plotted on incremental cost-effectiveness planes and cost-effectiveness acceptability curves which are presented in Figure 6 and Figure 7, respectively.

The mean PSA results for obe-cel versus inotuzumab in the overall population were comparable to the base-case, resulting in a [redacted]% difference in incremental QALYs

and a [redacted]% difference in incremental costs which translates into an ICER of [redacted].

Table 12: Probabilistic results considering PAS discount (overall population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life year gained; PAS – Patient Access Scheme; Ph – Philadelphia; QALY – quality-adjusted life year.

Figure 6: Scatterplot (overall population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 7: CEAC (overall population)

CEAC – Cost-effectiveness acceptability curve

4.2 Ph- population

The mean costs and QALYs for the Ph- population are presented in Table 13. Results were plotted on incremental cost-effectiveness planes and cost-effectiveness acceptability curves which are presented in Figure 8 and Figure 10 for obe-cel versus inotuzumab, and Figure 9 and CEAC – Cost-effectiveness acceptability curve

Figure 11 for obe-cel versus blinatumomab, respectively.

In the Ph- population, the mean probabilistic incremental QALYs and costs for obe-cel versus inotuzumab resulted in a [redacted]% and [redacted]% difference compared to the base-case, which similarly to the base-case, translates into an ICER of [redacted]. In comparison against blinatumomab, the mean PSA results for obe-cel were comparable to the base-case, resulting in a [redacted]% difference in incremental QALYs and a [redacted]% difference in incremental costs relative to the base-case, translating into a probabilistic ICER of [redacted].

Table 13: Probabilistic results considering PAS discount (Ph- population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Obe-cel (£/QALY)	ICER incremental (£/QALY)
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life year gained; PAS – Patient Access Scheme; Ph – Philadelphia; QALY – quality-adjusted life year.

Figure 8: Scatterplot, obe-cel versus inotuzumab (Ph- population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 9: Scatterplot, obe-cel versus blinatumomab (Ph- population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 10: CEAC, obe-cel versus inotuzumab (Ph- population)

CEAC – Cost-effectiveness acceptability curve

Figure 11: CEAC, obe-cel versus blinatumomab (Ph- population)

CEAC – Cost-effectiveness acceptability curve

4.3 Ph+ population

The mean costs and QALYs for the Ph+ population are presented in Table 14. Results were plotted on incremental cost-effectiveness planes and cost-effectiveness acceptability curves which are presented in Figure 12 and Figure 14 for obe-cel versus inotuzumab, and Figure 13 and Figure 15 for obe-cel versus ponatinib, respectively.

The mean PSA results for obe-cel versus inotuzumab in the Ph+ population were comparable to the base-case, resulting in a [redacted]% difference in incremental QALYs and a [redacted]% difference in incremental costs relative to the base-case, which translates into an ICER of [redacted]. In the comparison against ponatinib, the mean probabilistic incremental QALYs and costs resulted in a [redacted]% and [redacted]% difference, respectively, compared to the base-case results, translating into a probabilistic ICER of [redacted].

Table 14: Probabilistic results considering PAS discount (Ph+ population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus Obe-cel (£/QALY)	ICER incremental (£/QALY)
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life year gained; PAS – Patient Access Scheme; Ph – Philadelphia; QALY – quality-adjusted life year

Figure 12: Scatterplot, obe-cel versus inotuzumab (Ph+ population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 13: Scatterplot, obe-cel versus ponatinib (Ph+ population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 14: CEAC, obe-cel versus inotuzumab (Ph+ population)

CEAC – Cost-effectiveness acceptability curve

Figure 15: CEAC, obe-cel versus ponatinib (Ph+ population)

CEAC – Cost-effectiveness acceptability curve

5 Scenario analyses

Table 15: Scenario analyses included in the model

#	Category	Base-case	Scenario	
		Value	**Value**	**Rationale**
1	Annual discount rate for costs and QALYs	3.5%	0% for costs and outcomes	As per NICE guidelines[2]
2			6% for costs and outcomes	
3	Costs	Using tariff costing for CAR T-cell infusion cost calculations	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	Approach used in TA893[1]
4		Exclude drug wastage	Include drug wastage (for comparator therapies)	To consider the availability of vial-sharing in comparator treatments
5	Survival curve and ITC choices	Inotuzumab and blinatumomab use an inverse MAIC approach. Ponatinib use a naïve approach	Base-case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab; inverse MAIC vs. ponatinib)	Exploring combinations of alternative modelling approaches
6			Base-case ITC approach + alternative obe-cel survival curves*	
7	Subsequent allo-SCT	10% subsequent allo-SCT for obe-cel	5% subsequent allo-SCT for obe-cel	Exploring the proportion of patients with subsequent allo-SCT
8			2.5% subsequent allo-SCT for obe-cel	
9	Use allo-SCT costs from 2021 EY publication[3]	Use allo-SCT costs from TA893	Allo-SCT costs from 2021 EY publication	Exploring more recent allo-SCT cost data in the England

10	Alternative SMR	3.0	4.0	Exploratory analysis
11	Use STC results instead of MAIC	Inotuzumab and blinatumomab use an inverse MAIC approach. Ponatinib use a naïve approach	STC results for all comparators	Exploratory analysis
12	Use UK only patient population for IVIG use	Overall pooled enrolled	UK only patients	Exploratory analysis
13	Use 1.7 severity modifier	1.2 severity modifier	1.7 severity modifier	Exploratory analysis

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; EY - Ernst & Young LLP; ITC – Indirect treatment comparison; IVIG – Intravenous immunoglobulin; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMR – Standard mortality ratio; TA – Technology Appraisal; UK – United Kingdom
*Alternative survival curves used are: Overall population – EFS: Weibull; OS: Weibull; Ph- population – EFS: 3-knots normal spline curve; OS: Gompertz; Ph+ population – EFS: Gompertz; OS: Gompertz

5.1 Overall population

#	Value	Deterministic ICER	Probabilistic ICER
1	0% for costs and outcomes	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]
3	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	[redacted]	[redacted]
4	Include drug wastage (for comparator therapies)	[redacted]	[redacted]
5	Base-case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and	[redacted]	[redacted]

	blinatumomab; inverse MAIC vs. ponatinib)		
6	Base-case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]
7	5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]
8	2.5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]
9	Allo-SCT costs from 2021 EY publication	[redacted]	[redacted]
10	4.0 SMR	[redacted]	[redacted]
11	STC results for all comparators	[redacted]	[redacted]
12	UK only patients	[redacted]	[redacted]
13	1.7 severity modifier	[redacted]	[redacted]

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; EY - Ernst & Young LLP; ITC – Indirect treatment comparison; IVIG – Intravenous immunoglobulin; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMR – Standard mortality ratio; TA – Technology Appraisal; UK – United Kingdom

5.2 Ph- population

#	Scenario	Versus inotuzumab		Versus blinatumomab	
		Deterministic ICER	**Probabilistic ICER**	**Deterministic ICER**	**Probabilistic ICER**
1	0% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
3	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	[redacted]	[redacted]	[redacted]	[redacted]

4	Include drug wastage (for comparator therapies)	[redacted]	[redacted]	[redacted]	[redacted]
5	Base-case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab; inverse MAIC vs. ponatinib)	[redacted]	[redacted]	[redacted]	[redacted]
6	Base-case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]	[redacted]	[redacted]
7	5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]	[redacted]	[redacted]
8	2.5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]	[redacted]	[redacted]
9	Allo-SCT costs from 2021 EY publication	[redacted]	[redacted]	[redacted]	[redacted]
10	4.0 SMR	[redacted]	[redacted]	[redacted]	[redacted]
11	STC results for all comparators	[redacted]	[redacted]	[redacted]	[redacted]
12	UK only patients	[redacted]	[redacted]	[redacted]	[redacted]
13	1.7 severity modifier	[redacted]	[redacted]	[redacted]	[redacted]

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; EY - Ernst & Young LLP; ITC – Indirect treatment comparison; IVIG – Intravenous immunoglobulin; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMR – Standard mortality ratio; TA – Technology Appraisal; UK – United Kingdom

5.3 Ph+ population

#	Scenario	Versus inotuzumab		Versus ponatinib	
		Deterministic ICER	Probabilistic ICER	Deterministic ICER	Probabilistic ICER
1	0% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
3	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	[redacted]	[redacted]	[redacted]	[redacted]
4	Include drug wastage (for comparator therapies)	[redacted]	[redacted]	[redacted]	[redacted]
5	Base-case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab; inverse MAIC vs. ponatinib)	[redacted]	[redacted]	[redacted]	[redacted]
6	Base-case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]	[redacted]	[redacted]
7	5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]	[redacted]	[redacted]
8	2.5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]	[redacted]	[redacted]
9	Allo-SCT costs from 2021 EY publication	[redacted]	[redacted]	[redacted]	[redacted]
10	4.0 SMR	[redacted]	[redacted]	[redacted]	[redacted]
11	STC results for all comparators	[redacted]	[redacted]	[redacted]	[redacted]

12	UK only patients	[redacted]	[redacted]	[redacted]	[redacted]
13	1.7 severity modifier	[redacted]	[redacted]	[redacted]	[redacted]

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; EY - Ernst & Young LLP; ITC – Indirect treatment comparison; IVIG – Intravenous immunoglobulin; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMR – Standard mortality ratio; TA – Technology Appraisal; UK – United Kingdom

6 Interpretation and conclusions of the cost-effectiveness results

This analysis was conducted to estimate the most recent cost-effectiveness results of obe-cel in comparison with relevant comparators (inotuzumab, blinatumomab and ponatinib) for adult patients with B-cell ALL, based on updated data from the FELIX trial (January 2025 data cut), in the pooled enrolled population of Cohort IA and IIA of FELIX, as per the Committee's preference.

The results of the cost-effectiveness analysis show that the updated ICERs for obe-cel versus all comparators are either improved or consistent with the external assessment group (EAG) ICERs using the previous data cut of FELIX (February 2024) across all three populations (overall population, Ph- and Ph+ subgroups). This consistency between the new ICERs from the more recent FELIX data cut with extended follow-up, and the earlier estimates from the 2024 data reduces key clinical uncertainties. The longer follow-up period strengthens the evidence base surrounding longer-term efficacy, durability of response, and overall survival outcomes associated with obe-cel treatment. In particular, the alignment of new and previous cost-effectiveness results supports the reliability and maturity of the obe-cel clinical data, thereby enhancing confidence in the observed treatment benefits. As a result, the uncertainty associated with extrapolating long-term outcomes from immature data is significantly mitigated, providing a more robust foundation of evidence and improving the credibility of obe-cel cost-effectiveness estimates.

The Company aligned with the Committee's preferred settings in the base-case analysis. While the ICERs generated result in values above the accepted cost-effectiveness threshold in all populations other than obe-cel versus blinatumomab in the Ph- population, it is important to acknowledge that these settings do not fully capture the broader clinical and economic benefits of obe-cel, as outlined in the appraisal consultation document (ACD) response document. Scenario analyses incorporating the 1.7 severity modifier and bottom-up costing approach for CAR T-cell infusion costs demonstrate that the base-case assumptions – specifically the use of the 1.2 severity modifier and the updated tariff costing for CAR T-cell therapy infusion costs - are particularly penalising for obe-cel.

The Company believes that a 1.2 severity modifier not only underrepresents the severity of the disease, where median life expectancy is less than a year, but also the large degree of uncaptured benefit that has been described for obe-cel, including its favourable adverse event profile and treatment delivery efficiencies. The Company feel that a 1.7 modifier would be appropriate at least for the Ph- population, hence the true appropriate value is somewhere in-between 1.2 and 1.7.

While the CAR T tariff was implemented to align with the Committee's preference, scenario analyses using the bottom-up costing approach, which incorporates healthcare resource use associated with obe-cel infusion from FELIX, produced ICERs below the cost-effectiveness threshold for all comparisons other than obe-cel versus inotuzumab in the overall and Ph+ populations. There are several considerable benefits of treatment with obe-cel which remain uncaptured when applying the CAR-T tariff (£60,462). As detailed in the ACD response, the tariff does not reflect the improved safety profile and CAR persistence of obe-cel, rendering a higher cost than is likely to be observed in clinical practise for obe-cel. Therefore, the Company considers the bottom-up costing method to closer align with the real-world costs of obe-cel delivery.

It should also be noted that the comparisons that do not produce cost-effective ICERs in the highlighted scenarios for obe-cel versus inotuzumab in the overall and Ph+ populations, overestimate both EFS and OS of inotuzumab compared to the published Kaplan-Meier (KM). Therefore, the scenario exploring the alternative MAIC approach may better represent the true ICER of obe-cel versus inotuzumab in these populations.

Overall, the updated cost-effectiveness analysis of obe-cel, based on the January 2025 data cut from the FELIX trial, demonstrates consistency with previous analyses and reinforces the longer-term durability and reliability of the obe-cel clinical data. The base-case analysis reflects the Committee's preferred assumptions, which do not fully capture the clinical and economic benefits of obe-cel (for further detail, please refer to the ACD response), resulting in ICERs above the accepted cost effectiveness threshold in most comparisons. When alternative assumptions that more accurately reflect the real-world benefits of treatment with obe-cel are applied,

the resulting ICERs fall within the cost effectiveness threshold, supporting the economic value of obe-cel as a treatment for R/R B-cell ALL.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clinical effectiveness results in the 2025 data cut of the pivotal FELIX trial demonstrating the efficacy and safety of obe-cel in adult acute lymphoblastic leukaemia (ALL)

July 2025

Contents

1 Introduction

This report has been produced to present the most recent clinical efficacy results of obe-cel. Since the original submission in November 2024, a new data cut from the FELIX trial (January 2025) has become available. The longer follow-up addresses some of the Committee's uncertainties regarding the clinical value of obe-cel in relapsed/refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL). Additionally, the Committee preferred clinical data based on a combination of Cohort IA and IIA over the Company's original approach of basing efficacy on Cohort IA alone (the primary efficacy population in the FELIX trial). This report presents the clinical efficacy and safety results from the most current FELIX data cut for:

- Pooled Cohort IA and IIA (enrolled set) (Section 2.3)
- Cohort IIA (infused set) (Section 2.4)

Additionally, the most recent long-term overall survival (OS) is discussed upfront in Section 2.1, and a comparison between the previous (February 2024) and most recent (January 2025) data cut is presented in Section 2.2.

2 Clinical effectiveness results

2.1 Long-term overall survival rates – Cohort IA and IIA, enrolled set and Cohort IIA, infused set

This section highlights the most recent OS of obe-cel, considering both the pooled Cohort IA and IIA, enrolled set and the Cohort IIA, infused set. Refer to Sections 2.3.5 and 2.4.5 for full details in the respective populations.

OS Kaplan-Meier (KM) plots for pooled Cohort IA and IIA, enrolled set and Cohort IIA, infused set, respectively are shown in Figure 1 and Figure 2. In Cohort IA and IIA, enrolled set, the median OS is [redacted] months, and the % event-free probability estimate at one, two, and three years are [redacted]%, [redacted]% and [redacted]%, respectively. In Cohort IIA, infused set the corresponding is [redacted] months median OS, and [redacted]%, [redacted]% and [redacted]% event-free probability estimate at one, two, and three years.

Figure 1: KM plot of OS without censoring SCT, Cohort IA and IIA, enrolled set

Abbreviations: CI – Confidence interval; KM – Kaplan-Meier; OS – Overall survival; SCT – Stem cell transplant;
Source: Autolus Limited. Data on file. FELIX (AUTO1-AL1) Figure 14.2.16.1.10.a[1]

Figure 2: KM plot of OS without censoring SCT, Cohort IIA, infused set

Abbreviations: CI – Confidence interval; KM – Kaplan-Meier; OS – Overall survival; SCT – Stem cell transplant;
Source: Autolus Limited. Data on file. FELIX (AUTO1-AL1) Figure 14.2.16.1.1.iia[2]

2.2 Summary comparison of February 2024 and January 2025 data cuts – Cohort IIA, infused set

This section provides an overview of key outcomes compared between the February 2024 data cut informing the original company submission (CS) and the most recent January 2025 data cut. Note that this comparison is based on Cohort IIA, infused set, as this was the population for which clinical evidence was initially submitted. The new data cut solidifies earlier FELIX findings, another step in the direction of demonstrating long-term remission and cure, by showing an increase in OS at 24

and 36 months, this is aligned with clinical expectations and experiences thus far from clinicians working with obe-cel.

Overall remission rate (ORR) – Section 2.4.1

- In both the February 2024 and January 2025 data cuts, a statistically significant ORR of [redacted]% (95% CI: [redacted]) was observed.

- A deeper level of remission achieved by obe-cel is reflected in the large proportion of patients achieving minimal residual disease (MRD)-negative remission. The MRD-negative remission rate ($<10^{-4}$ level) remained at [redacted]% in both data cuts, indicating a substantially low risk of relapse in these patients.

Event-free survival (EFS) – Section 2.4.4

- In both the February 2024 and January 2025 data cuts, the median EFS was [redacted] (95% CI: [redacted]) months. [redacted] had experienced an event in the January 2025 cut compared to February 2024.The new 2025 data cut, also shows EFS at 12, 24 and 36 months of [redacted]%, [redacted]% and [redacted]% respectively.

Overall survival (OS) – Section 2.4.5

- Median OS increased from [redacted] (95% CI: [redacted]) months in the February 2024 data cut to [redacted] (95% CI: [redacted]) months in January 2025.

- OS remained at [redacted]% at Month 6 and [redacted]% at Month 12 in both data cuts. The later data cut has seen the 24 month increase from [redacted]% to [redacted]%, with the new data cut showing the 36 month OS being [redacted]%.

2.3 FELIX pooled Cohort IA and IIA, enrolled set

2.3.1 Primary endpoint: Overall remission rate

The primary efficacy endpoint, ORR (defined as complete remission [CR] or CR with incomplete haematological recovery [CRi] at any time post-infusion) as assessed by International Review and Regulatory Committee (IRRC), was met at the January

2025 data cut-off. The median follow-up at the January 2025 cut-off was [redacted] months (range: [redacted]– [redacted] months).

Results from the January 2025 data cut-off found a statistically significant ORR of [redacted]% (95% CI: [redacted] to [redacted], [redacted]) (Table 1).

Table 1: ORR measured by IRRC - Enrolled set

Parameter	Cohort IA and IIA (n=133)
ORR (CR + CRi)	
n (%) [95% CI]	[redacted]

CI – Confidence interval; CR – Complete remission; CRi – Complete remission with incomplete haematologic recovery; IRRC – International Review and Regulatory Committee; ORR – Overall remission rate.
Source: Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.2.1.2.12[3]

MRD-negative remission rate was evaluated in the pooled Cohort IA and IIA, in infused patients only. In the [redacted] patients ([redacted]% of infused set) that achieved ORR (CR or CRi), [redacted] ([redacted]%) also achieved MRD-negative remission, and [redacted] ([redacted]%) achieved MRD-positive remission to the $<10^{-4}$ level, indicating a substantially low risk of relapse.

2.3.2 Secondary endpoint: Duration of remission

Longer-term analyses of duration of remission (DOR) were conducted by including all patients in remission at any time post-infusion (CR or CRi by IRRC) and assessing the time from first onset of remission to morphological relapse or death due to any reason, without censoring of stem cell therapy (SCT) or any other new anti-cancer therapies for B-cell ALL.

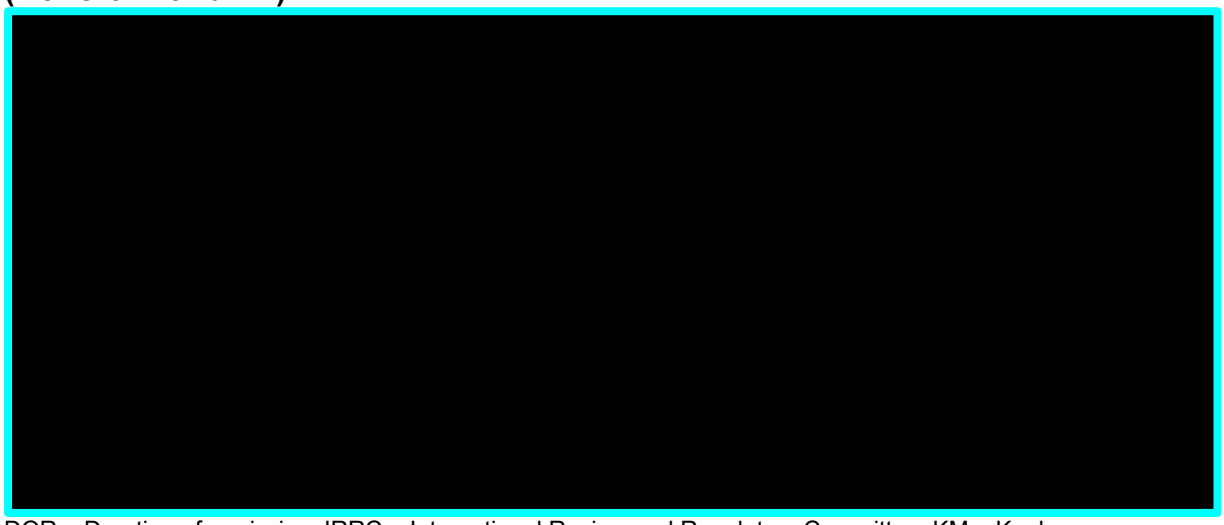
At the January 2025 data cut-off, [redacted]% of the patients who had achieved CR or CRi remained in remission without relapse or use of other anti-cancer therapies, including SCT (Table 2). The estimated median DOR was [redacted] (95% CI: [redacted] to [redacted]). At a median estimated duration of follow-up of [redacted] months, the probability of survival at 12 months after onset of remission was [redacted]% (95% CI: [redacted] to [redacted]) (Table 2). Figure 3 demonstrates that DOR begins to plateau from Month 15 onwards, with only [redacted] events occurring beyond this point.

Table 2: DOR measured by IRRC without censoring - Enrolled Set

Parameter	Cohort IA and IIA (n=133)
Number of patients in analysis	[redacted]
Number of events, n (%)	[redacted]
Morphological relapse	[redacted]
Death due to reason other than underlying cancer	[redacted]
Number of censored observations, n (%)	[redacted]
Ongoing without event	[redacted]
Maximum follow-up (months)	[redacted]
Median follow-up (months)	[redacted]
% event-free probability estimate	
At 6 months, % [95% CI]	[redacted]
At 9 months, % [95% CI]	[redacted]
At 12 months, % [95% CI]	[redacted]

CI – Confidence interval; DOR – Duration of remission; IRRC – International Review and Regulatory Committee; mITT – Modified intent-to-treat; SCT – Stem cell transplant.
Source: Autolus Limited. Data on file. FELIX (AUTO1-AL1): Table 14.2.10.5.1.a[4]

Figure 3: KM plot of DOR measured by IRRC without censoring - Enrolled Set (Cohort IA and IIA)



DOR – Duration of remission; IRRC – International Review and Regulatory Committee; KM – Kaplan-MeierSource: Autolus Limited. Data on file. FELIX (AUTO1-AL1) Figure 14.2.10.5.1.a[5]

2.3.3 Secondary endpoint: Complete remission

Complete remission rate for the pooled Cohort IA and IIA population was [redacted]% (95% CI: [redacted] to [redacted]) as of the January 2025 data cut-off.

Table 3 provides an overview of the duration of remission for the subset of patients from pooled Cohort IA and IIA that achieved CR (n=[redacted]). The estimated median

duration of remission was [redacted] months for CR (95% CI: [redacted] to [redacted]) and [redacted] months for CRi (95% CI: [redacted] to [redacted]).

Table 3: CR measured by IRRC without censoring – Enrolled set

Parameter	Cohort IA and IIA (n=133)
Number of patients in analysis	[redacted]
Number of events, n (%)	[redacted]
Morphological relapse	[redacted]
Death due to reason other than underlying cancer	[redacted]
Number of censored observations, n (%)	[redacted]
Ongoing without event	[redacted]
Maximum follow-up (months)	[redacted]
Median follow-up (months)	[redacted]
% event-free probability estimate	
At 3 months, % [95% CI]	[redacted]
At 6 months, % [95% CI]	[redacted]
At 9 months, % [95% CI]	[redacted]
At 12 months, % [95% CI]	[redacted]
At 15 months, % [95% CI]	[redacted]
At 18 months, % [95% CI]	[redacted]

CI – confidence interval; CR – Complete remission; IRRC – Independent Response Review Committee.
Source: Autolus Limited. Data on file. FELIX (AUTO1-AL1): Table 14.2.10.5.1.a[4]

2.3.4 Secondary endpoint: Event-free survival

Event-free survival (EFS) was defined as time from first obe-cel infusion to treatment failure, morphological relapse, or death, whichever occurred earliest. As of the January 2025 data cut-off, [redacted] ([redacted]%) of the [redacted] enrolled patients in pooled Cohort IA and IIA, had not experienced any event. The median EFS was [redacted] months. EFS at Month 6 post-obe-cel infusion was [redacted]% and [redacted]% at Month 12 (Table 4).

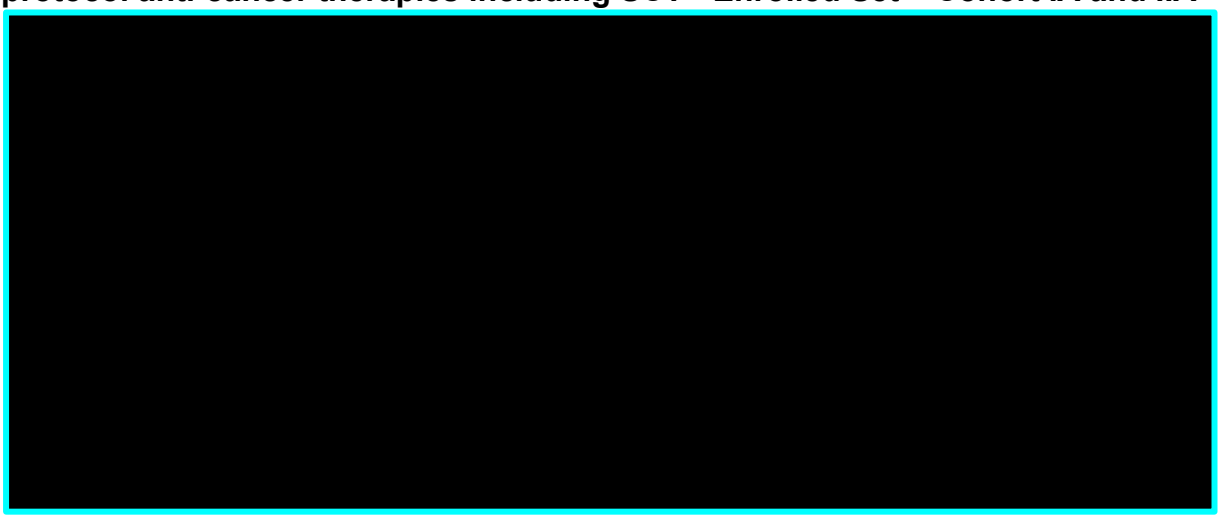
Table 4: EFS measured by IRRS without censoring – Enrolled set

Parameter	Cohort IA and IIA (n=133)
	EFS[1]
Patients with event, n (%)	[redacted]
Median EFS [95% CI]	[redacted]
EFS at 6 months [95% CI]	[redacted]
EFS at 12 months [95% CI]	[redacted]

CI – Confidence interval; EFS – Event-free survival; IRRC – International Review and Regulatory Committee.

[1]Without censoring for SCT and other new anti-cancer therapies
Source: Autolus Limited. Data on file. FELIX (AUTO1-AL1): Table 14.2.15.3.1[6]

Figure 4: KM plot of EFS measured by IRRC without censoring new non-protocol anti-cancer therapies including SCT - Enrolled Set – Cohort IA and IIA



EFS – Event-free survival; IRRC – International Review and Regulatory Committee; KM – Kaplan-Meier; SCT – Stem cell transplant.
Source: Autolus Limited. Data on file. FELIX (AUTO-AL1) Figure 14.2.15.3.1.a[7]

2.3.5 Secondary endpoint: Overall survival

As of the January 2025 data cut-off, [redacted]% of patients were alive, 92 patients from the enrolled set of pooled Cohort IA and IIA, had died. The median OS at the January 2025 data cut-off was [redacted] months (95% CI: [redacted] to [redacted]) (Table 5). At Month 6, OS for the January 2025 cut-off OS was [redacted]%, and [redacted]% for the Month 12.

Table 5: OS without censoring - Enrolled set

Parameter	Cohort IA and IIA(n=133)
	OS[1]
Patients with event, death, n (%)	[redacted]
Median OS [95% CI]	[redacted]
OS at 6 months [95% CI]	[redacted]
OS at 12 months [95% CI]	[redacted]

CI – Confidence interval; OS – Overall survival; SCT – Stem cell transplant.
[1]Without censoring for SCT
Source: Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.2.16.2.8.[8]

2.4 FELIX Cohort IIA, infused population results

2.4.1 Primary endpoint: Overall remission rate

Results from the January 2025 data cut-off found a statistically significant ORR of [redacted]% (95% CI: [redacted] to [redacted], [redacted]) (Table 6). A deeper level of remission achieved by obe-cel is reflected in the MRD-negative remission rate, which remained at a high level in both the February 2024 and January 2025 data cuts. In the February 2024 data cut, of the [redacted]% of patients who achieve ORR, [redacted] ([redacted]%) achieved MRD-negative remission, and [redacted] ([redacted]%) achieved MRD-positive remission to the $<10^{-4}$ level, indicating a substantially low risk of relapse. These rates were sustained in the January 2025 data cut.

Table 6: ORR measured by IRRC - Infused set

Parameter	mITT Cohort IIA (n=94)	
	Feb 2024	Jan 2025
ORR (CR + CRi)		
n (%) [95% CI]	[redacted]	[redacted]
MRD-negative ($<10^{-4}$) remission		
MRD-negative CR/CRi, n (%)	[redacted]	[redacted]

CI – Confidence interval; CR – Complete remission; CRi – Complete remission with incomplete haematologic recovery; IRRC – International Review and Regulatory Committee; mITT – Modified intent-to-treat; ORR – Overall remission rate.
Source: Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.2.4.4.2.iia[9,10]

2.4.2 Secondary endpoint: Duration of remission

Longer-term analyses of DOR were conducted by including all patients in remission at any time post-infusion (CR or CRi by IRRC) and assessing the time from first onset of remission to morphological relapse or death due to any reason, with censoring of SCT or any other new anti-cancer therapies.

At the January 2025 data cut-off, [redacted]% of the patients who had achieved CR or CRi remained in remission without relapse or use of other anti-cancer therapies, including SCT. For the [redacted] patients that achieved a best overall response (BOR) of CR or CRi, the estimated median DOR was [redacted] (95% CI: [redacted] to [redacted]). At a median estimated duration of follow-up of [redacted] months, the probability of survival at 12 months after onset of remission was [redacted]% ([redacted]) (Table 7).

Table 7: DOR measured by IRRC with censoring - Infused set

Parameter	mITT Cohort IIA (n=94)
Number of patients in analysis	[redacted]
Number of events, n (%)	[redacted]
Morphological relapse	[redacted]
Death due to reason other than underlying cancer	[redacted]
Number of censored observations, n (%)	[redacted]
Ongoing without event	[redacted]
SCT	[redacted]
New non-protocol anti-cancer therapies	[redacted]
Maximum follow-up (months)	[redacted]
Median follow-up (months)	[redacted]
% event-free probability estimate	
At 6 months, % [95% CI]	[redacted]
At 9 months, % [95% CI]	[redacted]
At 12 months, % [95% CI]	[redacted]

CI – Confidence interval; DOR – Duration of remission; IRRC – International Review and Regulatory Committee; SCT – Stem cell transplant.
Source: Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.2.7.3.2.iia[11]

2.4.3 Secondary endpoint: Complete remission

Complete remission for Cohort IIA was reported as [redacted]% (95% CI: [redacted] to [redacted]) as of the January 2025 data cut-off.

Table 8 provides an overview of the duration of complete remission for Cohort IIA. The estimated median duration of remission was [redacted] months for CR (95% CI: [redacted] to [redacted]) and was [redacted] months for complete remission with incomplete haematologic recovery (CRi) (95% CI: [redacted] to [redacted]) as of the January 2025 data cut-off.

Table 8: CR measured by IRRC with censoring – Infused set

Parameter	mITT Cohort IIA (n=94)
Number of patients in analysis	[redacted]
Number of events, n (%)	[redacted]
Morphological relapse	[redacted]
Death due to reason other than underlying cancer	[redacted]
Number of censored observations, n (%)	[redacted]
Ongoing without event	[redacted]
SCT	[redacted]
New non-protocol anticancer therapies other than SCT	[redacted]
Maximum follow-up (months)	[redacted]
Median follow-up (months)	[redacted]
% event-free probability estimate	
At 3 months, % [95% CI]	[redacted]
At 6 months, % [95% CI]	[redacted]
At 9 months, % [95% CI]	[redacted]
At 12 months, % [95% CI]	[redacted]
At 15 months, % [95% CI]	[redacted]
At 18 months, % [95% CI]	[redacted]

CI – confidence interval; IRRC – Independent Response Review Committee
Source: Autolus Limited. Data on file. Table 14.2.7.3.2.iia[11]

2.4.4 Secondary endpoint: Event-free survival

EFS was defined as time from first obe-cel infusion to treatment failure, morphological relapse, or death, whichever occurred earliest. As of the January 2025 data cut-off, [redacted] ([redacted]%) of the [redacted] infused patients in Cohort A, phase II population had not experienced any event. Of these, [redacted] were in ongoing remission without non-protocol therapies, including SCT. The median EFS was [redacted] months. EFS at Month 6 post-obe-cel infusion was [redacted]% and [redacted]% at Month 12 (Table 9).

Table 9: EFS measured by IRRC with censoring SCT - Infused Set

Parameter	mITT Cohort IIA (n=94)	
	EFS[1]	
	Feb 2024	**Jan 2025**
Patients with event, n (%)	[redacted]	[redacted]
Median EFS [95% CI]	[redacted]	[redacted]
EFS at 6 months [95% CI]	[redacted]	[redacted]
EFS at 12 months [95% CI]	[redacted]	[redacted]

CI – Confidence interval; EFS – Event-free survival; IRRC – International Review and Regulatory Committee

[1]With censoring for SCT and other new anti-cancer therapies
Source: Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.2.12.1.1[12]

2.4.5 Secondary endpoint: Overall survival

As of the January 2025 data cut-off, [redacted]% of patients were alive, [redacted] patients had died due to disease progression since the primary analysis data cut-off (June 2023). The median OS at January 2025 data cut-off was [redacted]months (95% CI: [redacted] to [redacted]) (Table 10). At Month 6, the OS was [redacted]%, and [redacted]% at Month 12, for the January 2025 data cut-off. OS at Month 6 was aligned between the February 2024 and January 2025 data cut-offs. At Month 12, the January 2025 OS was the same as what was reported in the February 2024 data cut ([redacted]%).

Table 10: OS without censoring SCT - Infused set

Parameter	**mITT Cohort IIA (n=94)**	
	OS[1]	
	Feb 2024	**Jan 2025**
Patients with event, death, n (%)	[redacted]	[redacted]
Median OS [95% CI]	[redacted]	[redacted]
OS at 6 months [95% CI]	[redacted]	[redacted]
OS at 12 months [95% CI]	[redacted]	[redacted]

CI – Confidence interval; OS – Overall survival; SCT – Stem cell transplant.
[1]Without censoring for SCT
Source: Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.2.16.2.9[13]

3 Adverse reactions

3.1 Common adverse events

The treatment-emergent adverse events (TEAEs) which occurred in more than 10% of patients in the safety set (defined as all infused patients in each cohort and study phase, n=[redacted]) are reported in Table 11 below. The values are taken from the January 2025 data cut-off.

The most frequently observed TEAE of any grade was cytokine release syndrome (CRS) ([redacted] patients, [redacted]%), pyrexia ([redacted] patients, [redacted]%) and anaemia ([redacted] patients, [redacted]%). The majority of all these TEAEs were low grade, with the TEAE being ≥ grade 3 in [redacted]% (CRS) and [redacted]% (Pyrexia). Grade ≥ 3 TEAEs were higher for anaemia ([redacted]%).

Table 11: TEAEs in more than 10% of patients, at any time post obe-cel infusion, regardless of relationship to obe-cel (safety set, n=127)

TEAE	All grades n (%)	Grade ≥ 3 n (%)
All	[redacted]	[redacted]
CRS	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
ICANS	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Hyperferritinaemia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]

COVID-19 – Coronavirus disease 2019; CRS – Cytokine release syndrome; ICANS – Immune cell-associated neurotoxicity syndrome; TEAE – Treatment-emergent adverse event.
Source: Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.3.1.2.29[14]

3.2 Adverse events of special interest

CAR T-cell therapy for B-cell ALL is associated with considerable and potentially life-threatening immunotoxicity (CRS and immune cell-associated neurotoxicity syndrome (ICANS)). Obe-cel was specifically designed to reduce cell-cell contact and minimise the triggering of cytokine release, and with a fractionated split dose

regimen, which positively impacted the rate of CRS and ICANS, with low rate of ≥ grade 3 events.

3.2.1 Cytokine release syndrome

In the January 2025 data cut-off, CRS was recorded in [redacted] ([redacted]%) of the patients in the safety set (n=127).[14] The majority of these patients ([redacted]) had low-grade (1 or 2) CRS, which is not life-threatening and can be managed with supportive treatment such as low-flow oxygen supplementation or antipyretics.[14] Only [redacted] patients [redacted]infused with obe-cel experienced grade 3 CRS.[14] No patient had CRS greater than grade 3, meaning no patient had life-threatening conditions requiring urgent intervention.[15]

3.2.2 Immune effector cell-associated neurotoxicity syndrome

In the January 2025 data cut-off, [redacted] included in the safety set (n=[redacted]) experienced ICANS, the majority of which were low-grade (1 or 2) ([redacted]).[14] Grade 3 ICANS occurred in [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%) experienced ICANS greater than grade 3.[14]

3.3 Safety summary

At the latest data cut-off (January 2025), all patients in the safety set (N=[redacted]) experienced at least one TEAE at some time post obe-cel infusion.[14] In total, [redacted] patients ([redacted]%) experienced a TEAE grade ≥3.[14] The adverse event (AE) profile of obe-cel at the January 2025 data cut-off remained mostly unchanged compared with the safety profile based on the February 2024 data cut-off. There were only one new type of grade 3+ TEAEs reported between February 2024 and January 2025 ([redacted]), indicating favourable long-term safety for obe-cel.

AEs of special interest include CRS and ICANS. Only [redacted] patients from all cohorts ([redacted]%) infused with obe-cel experienced ≥ grade 3 CRS and [redacted] patients ([redacted]%) experienced ≥ grade 3 ICANS.[14]

4 References

1. Autolus Limited. Data on file. FELIX (AUTO1-AL1) Figure 14.2.16.1.10.a Kaplan-Meier plot of Overall Survival (OS) Without Censoring SCT. 2025.
2. Autolus Limited. Data on file. FELIX (AUTO1-AL1) Figure 14.2.16.1.1.iia Kaplan-Meier plot of Overall Survival (OS) Without Censoring SCT. 2025.
3. Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.2.1.2.12 Overall Response with Disease Assessment by IRRC By Cohort and Study Phase. 2025.
4. Autolus Limited. Data on file. FELIX (AUTO1-AL1): Table 14.2.10.5.1.a Duration of response (DOR) by IRRC Without Censoring New Non-Protocol Anticancer Therapies Including SCT by BOR or CR vs CRi with Disease Assessment by IRRC. 2025.
5. Autolus Limited. Data on file. FELIX (AUTO1-AL1) Figure 14.2.10.5.1.a Kaplan-Meier Plot of Duration of Response (DOR) by IRRC Without Censoring New Non-Protocol Anticancer Therapies Including SCT By BOR or CR vs CRi with Disease Assessment by IRRC.
6. Autolus Limited. Data on file. FELIX (AUTO1-AL1): Table 14.2.15.3.1 Event-Free Survival (EFS) Without Censoring New Non-Protocol Anticancer Therapies Including SCT with Disease Assessment by IRRC By Cohort and Study Phase. 2025.
7. Autolus Limited. Data on file. FELIX (AUTO-AL1) Figure 14.2.15.3.1.a Kaplan-Meier plot of Event-free Survival (EFS) Without Censoring New Non-Protocol Anticancer Therapies Including SCT with Disease Assessment by IRRC. 2025.
8. Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.2.16.2.8. Overall Survival (OS) Without Censoring SCT By Cohort and Study Phase. 2025.

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13. Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.2.16.2.9 Overall Survival (OS) Without Censoring SCT By Cohort and Study Phase. 2025.
14. Autolus Limited. Data on file. FELIX (AUTO-AL1) Table 14.3.1.2.29 Treatment Emergent Adverse Events Anytime Post Obe-cel Infusion, Regardless of Relationship to Obe-cel, by Preferred Term By Cohort and Study Phase. 2025.
15. Schuster SJ, Maziarz RT, Rusch ES, *et al.* Grading and management of cytokine release syndrome in patients treated with tisagenlecleucel in the JULIET trial. *Blood Adv* 2020. 4: 1432–1439.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Survival analyses and indirect treatment comparison for obe-cel versus inotuzumab, blinatumomab and ponatinib in acute lymphoblastic leukaemia (ALL) patients, using the 2025 FELIX data cut

June 2025

Contents

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Introduction

In the original company submission, survival analyses and indirect treatment comparisons (ITCs) for obe-cel versus inotuzumab, blinatumomab and ponatinib were conducted to estimate long-term outcomes and comparative efficacy in the economic analysis. As the follow-up periods of both the intervention and comparator trials for event-free/progression-free survival (EFS/PFS) and overall survival (OS) were shorter than the model time horizon, extrapolation of the observed data was required to estimate long-term survival. ITCs were performed in the absence of head-to-head clinical trial evidence for obe-cel versus the comparators. As the pivotal clinical trial of obe-cel, FELIX, did not include a control arm, only unanchored analyses were possible; pairwise unanchored matching-adjusted indirect comparisons (MAIC) and naïve comparisons were therefore performed.

As of 2025, a new FELIX data cut with longer follow-up has become available, which could potentially address key uncertainties highlighted in the first appraisal committee meeting (ACM1), particularly those related to the robustness and uncertainty surrounding the survival and ITC analyses. The updated analyses based on this new data cut, focusing on the Committee preferred enrolled pooled Cohort IA and IIA population as well as the infused Cohort IIA population, aim to provide a more reliable foundation for decision-making. In addition to updating the survival analyses and the MAIC, a simulated treatment comparison (STC) was conducted to reduce uncertainty around the comparative efficacy findings of the previously conducted ITC.

1 Survival analysis

1.1 Methods

1.1.1 Data

Data for obe-cel were sourced from the latest 2025 data cut from the FELIX trial. FELIX is an ongoing open-label, multicentre, single-arm Phase Ib/II study designed to assess the safety and clinical efficacy of obe-cel in adult patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL). EFS and OS data were

used directly from FELIX[1] to inform clinical efficacy inputs for obe-cel in the economic analysis. Survival analyses were conducted for two populations:

- The population who successfully received CAR-T cell infusion in Cohort IIA (modified intention to treat [mITT], [redacted]), in addition to subgroup analyses for the Philadelphia chromosome negative (Ph-; [redacted]) and Philadelphia chromosome positive (Ph+; [redacted]) subgroups. This population aligns with the primary population in the original company submission.

- The total population who were enrolled to Cohort IA and IIA in FELIX, including patients who did not necessarily receive CAR-T cell infusion (intention to treat [ITT], [redacted]), in addition to subgroup analyses for the Ph- ([redacted]) and Ph+ [redacted]) subgroups. This population was identified as the Committee's preference during ACM1.

A description of the clinical data informing survival data in the model for inotuzumab, blinatumomab and ponatinib are presented in Section B.3.3.1 (pages 115-116) in the original company submission to National Institute for Health and Care Excellence (NICE).

1.1.2 Analysis methodology

Comprehensive survival analyses were conducted, covering standard parametric and flexible spline analyses in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 and TSD 21 and the original company submission.[2,3] Standard parametric models used included exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma functions. Analysis of hazard plots found the proportional hazards assumption to be violated when comparing obe-cel and each comparator, thus independent parametric models were adopted. Additionally, flexible spline models were considered to allow for time-varying hazards, therefore allowing a better fit to the observed data, exploring a range of restricted cubic spline models with one, two, and three knots using hazard, odds, and normal scales.

For completeness, the diagnostic plots for each analysis are presented throughout Section 1.2.

In line with NICE DSU TSD 14 and TSD 21, the following key criteria were considered for both treatment arms when selecting the best-fitting curves:[2,3]

- Visual inspection of survival curve fit to the KM data from the relevant clinical trials
- Inspection of log-cumulative hazard plots to assess the behaviour of the hazard over time
- Statistical model fit, as measured by the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)

All analyses were carried out in R using the 'survival' package, in RStudio version 2024.12.0.

As the outputs of the survival analysis conducted for inotuzumab, blinatumomab, and ponatinib are reported in the original company submission to NICE, the following sections present the independent standard parametric models and flexible spline survival models for obe-cel for the infused Cohort IIA and pooled enrolled Cohort IA and IIA populations of FELIX, using the 2025 data cut.

1.2 Results

1.2.1 Infused Cohort IIA

1.2.1.1 Event-free survival (EFS)

Conclusion of the diagnostic tests

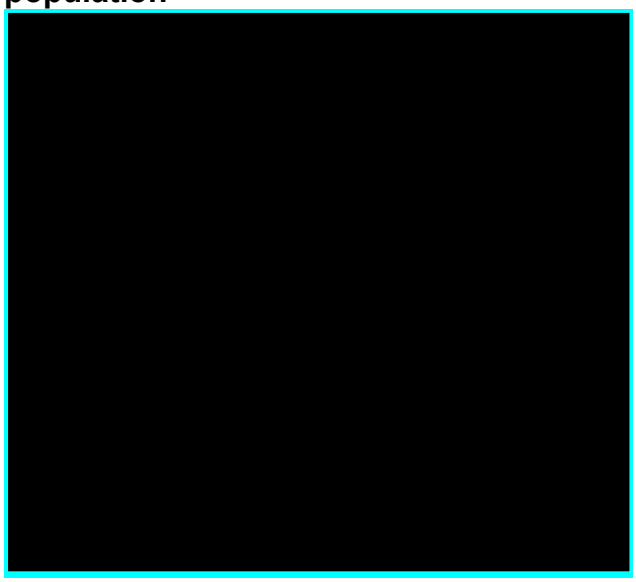
In the overall infused Cohort IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot suggest that the relative hazards are likely to vary over time, and as such, it is not possible to conclude that the proportional hazards (PH) assumption holds.

In Figure 1 the respective lines intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and inotuzumab in the infused Cohort IIA population can be rejected. The residual plot in Figure 2 shows a non-zero slope and a significant relationship between residuals and time ($p<0.05$), giving evidence that

the PH assumption does not hold, despite a random pattern. Therefore, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are monotonically decreasing (Figure 4), characterised by a lack of turning points. This indicates that monotonic models may be sufficient to capture the shape of the hazards.

Figure 1: EFS cumulative log-log plot for the overall Cohort IIA infused population

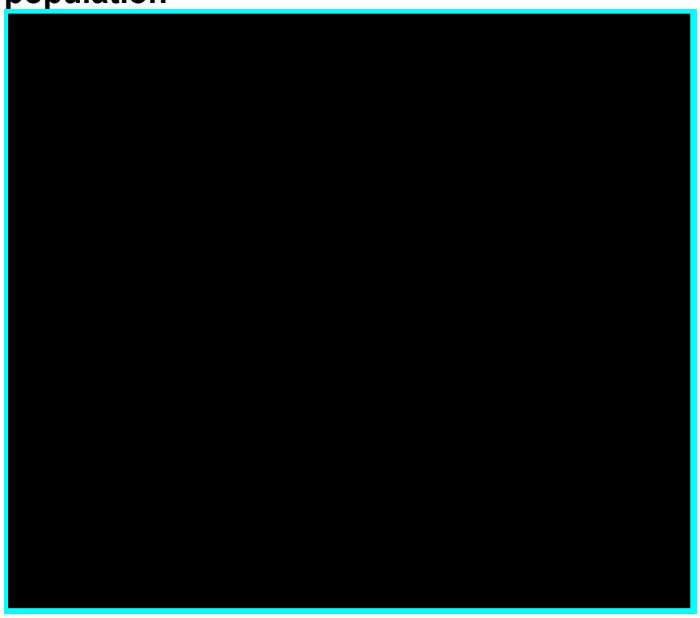


EFS - Event-free survival

Figure 2: EFS Schoenfeld residuals plot for the overall Cohort IIA infused population

EFS – Event-free survival

Figure 3: EFS quantile-quantile plot for the overall Cohort IIA infused population



EFS – Event-free survival

Figure 4: EFS hazard rate plot for the overall Cohort IIA infused population

EFS – Event-free survival

Similarly to the overall population, in the Ph- infused Cohort IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot suggest that the relative hazards are likely to vary over time, and as such, it is not possible to conclude that the PH assumption holds.

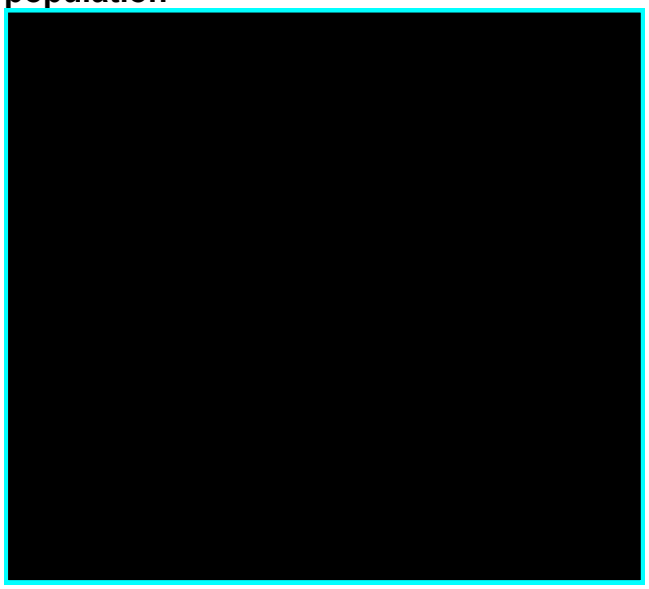
In Figure 5 the respective lines do not intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and blinatumomab cannot be rejected in the Ph-infused Cohort IIA population. However, the residual plot in Figure 6 shows a non-zero slope with a significant relationship between residuals and time ($p<0.05$), giving evidence that the PH assumption does not hold, despite a random pattern. As the quantiles in Figure 7 do not lie on a straight line, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are monotonically decreasing (Figure 8), characterised by a lack of turning points. This indicates that monotonic models may be sufficient to capture the shape of the hazards.

Figure 5: EFS cumulative log-log plot for the Ph- Cohort IIA infused population

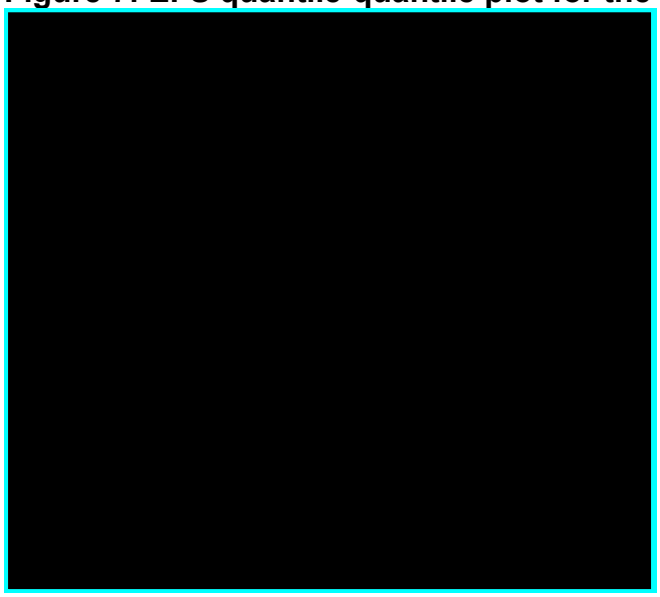
EFS - Event-free survival; Ph- - Philadelphia chromosome negative

Figure 6: EFS Schoenfeld residuals plot for the Ph- Cohort IIA infused population



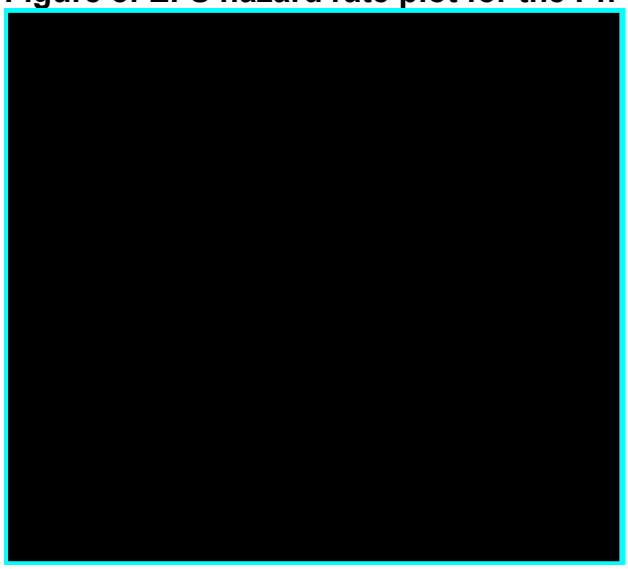
EFS – Event-free survival; Ph- - Philadelphia chromosome negative

Figure 7: EFS quantile-quantile plot for the Ph- Cohort IIA infused population



EFS – Event-free survival; Ph- - Philadelphia chromosome negative

Figure 8: EFS hazard rate plot for the Ph- Cohort IIA infused population



EFS – Event-free survival; Ph- - Philadelphia chromosome negative

In the Ph+ infused Cohort IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot suggest that the relative hazards are likely to vary over time, and as such, it is not possible to conclude that the PH assumption holds.

In Figure 9 the respective lines intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and ponatinib can be rejected. The residual plot in Figure 10 shows a random pattern and a non-significant relationship between residuals and time ([redacted]), giving evidence that the PH assumption cannot be rejected, despite the non-zero slope. Considering the log-cumulative hazard plot and that the quantiles on Figure 11 do not lie on a straight line, suggesting a non-multiplicative treatment effect, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are monotonically decreasing (Figure 12), characterised by a lack of turning points. This indicates that monotonic models may be sufficient to capture the shape of the hazards.

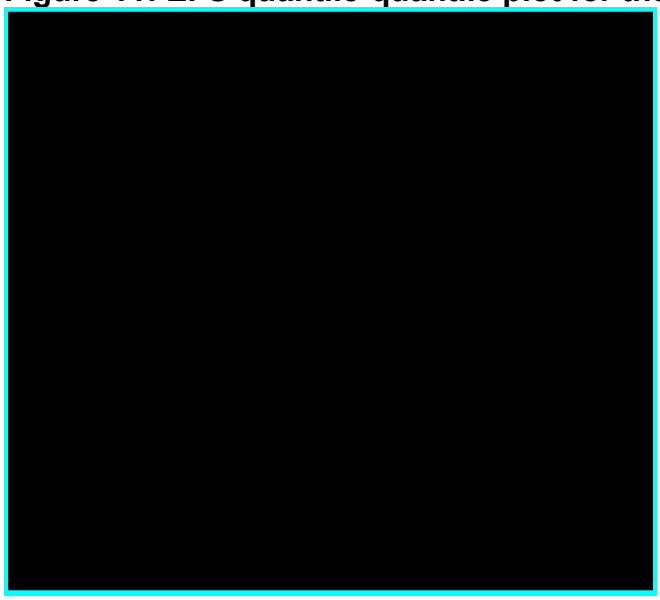
Figure 9: EFS cumulative log-log plot for the Ph+ Cohort IIA infused population

EFS - Event-free survival; Ph+ - Philadelphia chromosome positive

Figure 10: EFS Schoenfeld residuals plot for the Ph+ Cohort IIA infused population

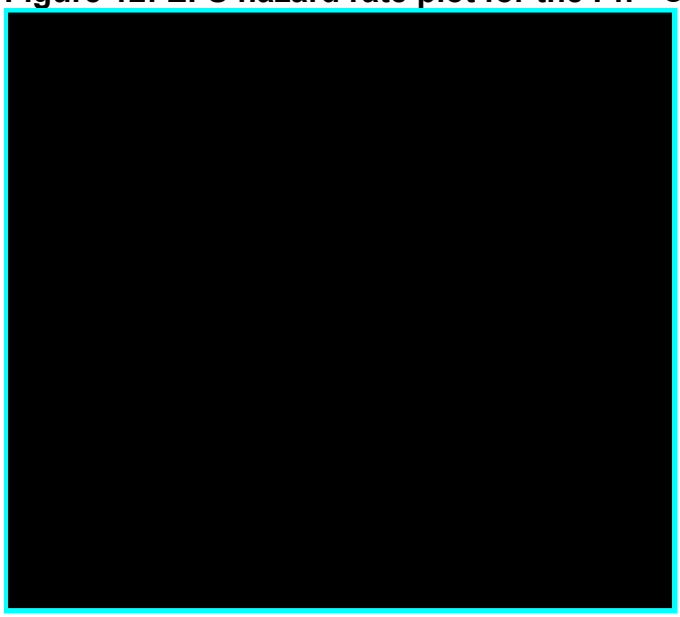
EFS – Event-free survival; Ph+ - Philadelphia chromosome positive

Figure 11: EFS quantile-quantile plot for the Ph+ Cohort IIA infused population



EFS – Event-free survival; Ph+ - Philadelphia chromosome positive

Figure 12: EFS hazard rate plot for the Ph+ Cohort IIA infused population



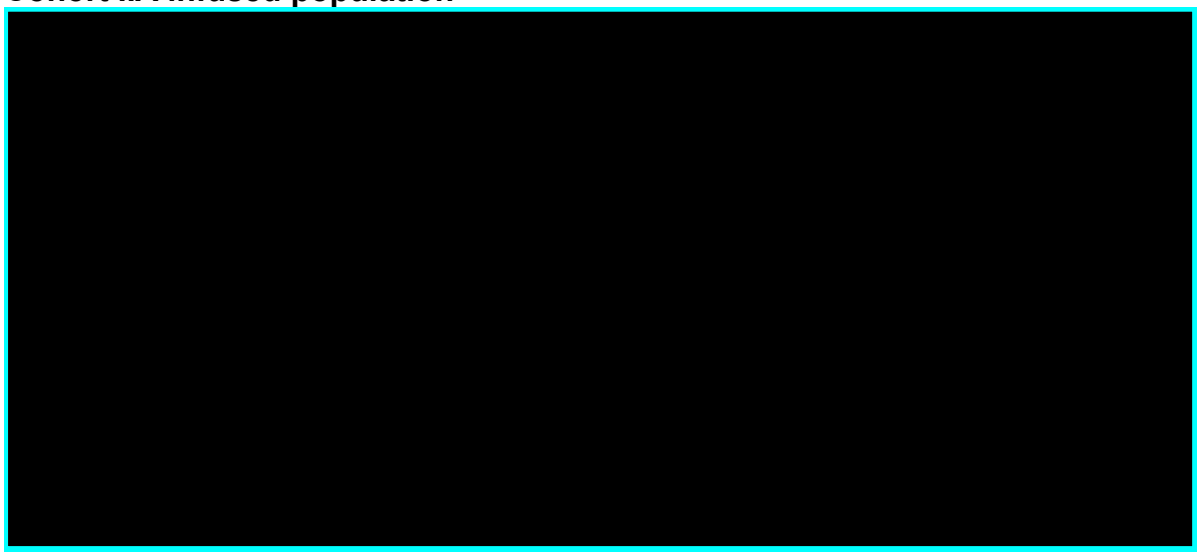
EFS – Event-free survival; Ph+ - Philadelphia chromosome positive

Independent survival curves

Six standard independent parametric models were fitted to the overall infused Cohort IIA obe-cel data: exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma. The hazard rate plots indicated that standard parametric

models may capture the shape of the hazard overtime in this population, however, for consistency between the methods used for obe-cel and inotuzumab, flexible spline models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel EFS for the overall infused Cohort IIA population are presented in Figure 13 and Figure 14, respectively.

Figure 13: EFS independent standard parametric curves for obe-cel: overall Cohort IIA infused population



EFS – Event-free survival; KM – Kaplan-Meier

Figure 14: EFS flexible parametric spline curves for obe-cel: overall infused Cohort IIA population

EFS – Event-free survival; KM – Kaplan-Meier

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 1 and Table 3 for the overall infused Cohort IIA population,

respectively. The AICs and BICs for the independent curves are similar, except for exponential which had the highest AIC and BIC indicating poor statistical fit. The lowest combined AIC and BIC for the independent curves was the Weibull, indicating the best statistical fit. However, the AIC and BIC scores for the log-logistic, log-normal, and generalised gamma curve were within three points of the Weibull distribution, meaning the models are considered of comparable fit. For the flexible spline parametric models, the 3-knot normal had the lowest AIC, with the 3-knot odds distribution providing a comparable fit. Of the five best statistically fitting models, the log-normal, 3-knot normal and the 3-knot odds distributions appear to best fit the data visually.

Table 2 and Table 4 outlines the landmark EFS rates for the obe-cel overall infused Cohort IIA population using standard parametric and flexible spline models, respectively. The estimated EFS rates at years 1-4 indicate that in general, flexible spline models provide a better fit to the data than standard parametric models, and the 3-knot normal model provides the closest estimates of all standard and flexible models tested.

Table 1: AIC and BIC statistical goodness-of-fit data for obe-cel EFS – overall infused Cohort IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; EFS – Event-free survival

Table 2: Obe-cel landmark survival rates for EFS – overall infused Cohort IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

EFS – event-free survival; KM – Kaplan-Meier

Table 3: Goodness-of-fit data for obe-cel EFS – overall infused Cohort IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; EFS – Event-free survival

Table 4: Obe-cel landmark survival rates for EFS – overall infused Cohort IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

EFS – Event-free survival; KM – Kaplan-Meier

Six standard independent parametric models were fitted to the Ph- infused Cohort IIA obe-cel data: exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma. The hazard rate plots indicated that standard parametric models may capture the shape of the hazard overtime in this population, however, for consistency between the methods used in the overall infused Cohort IIA population, flexible spline models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel EFS for the Ph- infused Cohort IIA population are presented in Figure 15 and Figure 16, respectively.

Figure 15: EFS independent standard parametric curves for obe-cel: Ph- infused Cohort IIA population

EFS – Event-free survival; KM – Kaplan-Meier; Ph- - Philadelphia chromosome negative

Figure 16: EFS flexible parametric spline curves for obe-cel: Ph- infused Cohort IIA population

EFS – Event-free survival; KM – Kaplan-Meier; Ph- - Philadelphia chromosome negative

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 13 and Table 15 for the obe-cel Ph- infused Cohort IIA population, respectively. The AICs and BICs for the independent curves are similar, with the lowest combined AIC and BIC being Weibull, indicating the best statistical fit. However, the AIC score for all curves other than Gompertz and exponential are within three points of the Weibull distribution, meaning these models are considered of comparable fit. For the flexible spline parametric models, the 2-knot normal had the lowest AIC, with the 2-knot odds distributions providing a comparable fit. Visual inspection of the curves indicate that flexible spline models provide a better fit to the data than standard parametric models, but all curves, except the 3-knot hazards, odds, and normal curves seem to either under or overpredict survival relative to the KM curve.

Table 6 and Table 8 outline the landmark EFS rates for the obe-cel Ph- infused Cohort IIA population using standard parametric and flexible spline models, respectively. The estimated EFS rates at years 1-4 indicate that in general, flexible spline models provide a better fit to the data than standard parametric models, and the 3-knot odds model provides the closest estimates of all standard and flexible models tested.

Table 5: AIC and BIC statistical goodness-of-fit data for obe-cel EFS – Ph- infused Cohort IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; OS – overall survival; Ph- - Philadelphia chromosome negative

Table 6: Obe-cel landmark survival rates for EFS – Ph- infused Cohort IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

EFS – Event-free survival; KM – Kaplan-Meier; Ph- - Philadelphia chromosome negative

Table 7: Goodness-of-fit data for obe-cel EFS – Ph- infused Cohort IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]

2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; OS – overall survival; Ph- - Philadelphia chromosome negative

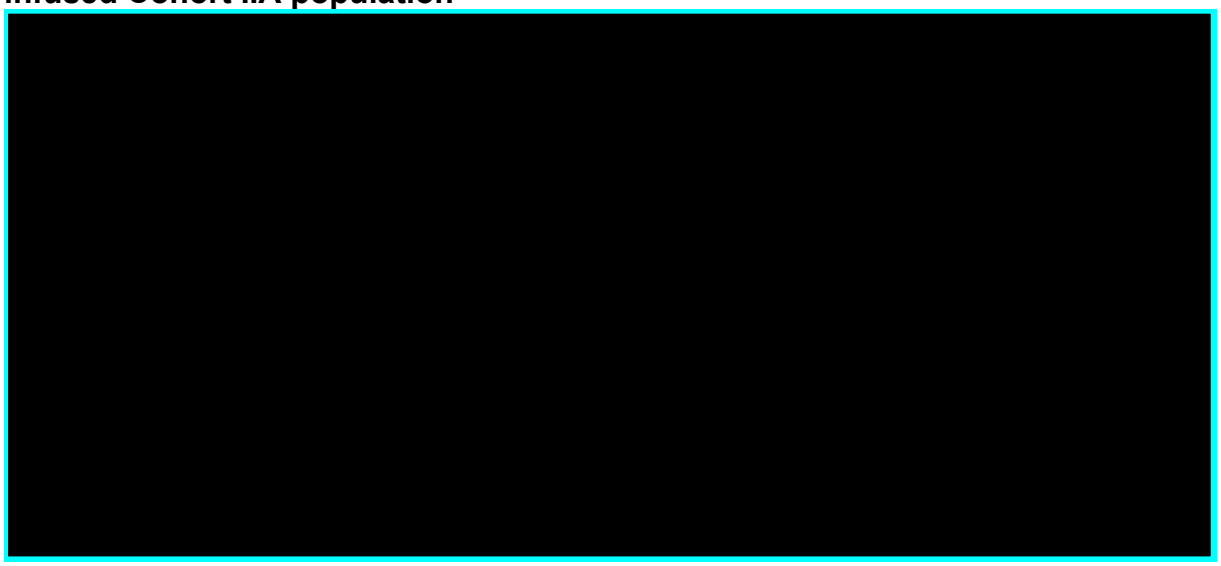
Table 8: Obe-cel landmark survival rates for EFS – Ph- infused Cohort IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

EFS – event-free survival KM – Kaplan-Meier; Ph- - Philadelphia chromosome negative

Six standard independent parametric models were fitted to the Ph+ infused Cohort IIA obe-cel data: exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma. The hazard rate plots indicated that standard parametric models may capture the shape of the hazard overtime in this population, however, for consistency between the methods used for overall and Ph- infused Cohort IIA populations, flexible spline models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel EFS for the Ph+ infused Cohort IIA population are presented in Figure 17 and Figure 18, respectively.

Figure 17: EFS independent standard parametric curves for obe-cel: Ph+ infused Cohort IIA population



EFS – Event-free survival; KM – Kaplan-Meier; Ph+ - Philadelphia chromosome positive

Figure 18: EFS flexible parametric spline curves for obe-cel: Ph+ infused Cohort IIA population

EFS – Event-free survival; KM – Kaplan-Meier; Ph+ - Philadelphia chromosome positive

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 9 and Table 11 for the Ph+ infused Cohort IIA population, respectively. The AICs and BICs for the independent curves are similar, with the lowest combined AIC and BIC being Weibull, indicating the best statistical fit. However, the AIC score for all curves other than exponential are within three points of the Weibull distribution, meaning these models are considered of comparable fit.

For the flexible spline parametric models, the 0-knot hazards had the lowest AIC, with all distributions other than 3-knot hazards, 3-knot normal and 3-knot odds providing a comparable fit. Visual inspection of the curves indicate that standard parametric models provide a better fit to the data than flexible spline models, except for the 3-knots hazards, odds, and normal distributions.

Table 10 and Table 12 outline the landmark EFS rates for the obe-cel Ph+ infused Cohort IIA population using standard parametric and flexible spline models, respectively. The estimated EFS rates at years 1-4 indicate that all standard parametric and flexible spline models provide a good fit to the data up to two years, but most models underpredict survival at 3 years relative to the KM curve.

Table 9: AIC and BIC statistical goodness-of-fit data for obe-cel EFS – Ph+ infused Cohort IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; EFS – event-free survival; Ph+ - Philadelphia chromosome positive

Table 10: Obe-cel landmark survival rates for EFS – Ph+ infused Cohort IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

EFS – event-free survival; KM – Kaplan-Meier; Ph+ - Philadelphia chromosome positive

Table 11: Goodness-of-fit data for obe-cel EFS – Ph+ Cohort IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; EFS – event-free survival; Ph+ - Philadelphia chromosome positive

Table 12: Obe-cel landmark survival rates for EFS – Ph+ infused Cohort IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

EFS – Event-free survival; KM – Kaplan-Meier; Ph+ - Philadelphia chromosome positive

1.2.1.2 Overall survival (OS)

Conclusion of the diagnostic tests

Similarly to EFS, in the overall infused Cohort IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot for OS suggest that the relative hazards are likely to vary over time, and as such, it is not possible to conclude that the PH assumption holds.

In Figure 19 the respective lines intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and inotuzumab can be rejected. The residual plot in Figure 20 shows a random pattern and a non-significant relationship between residuals and time ([redacted]), giving evidence that the PH assumption cannot be rejected, despite the non-zero slope. Considering the multiple intersection of the log-cumulative hazard curves, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted. Independent models should be selected for use in the economic analysis.

The hazard rates for obe-cel are decreasing (Figure 22) and characterised by one turning point. This indicates that flexible spline models may be more suitable to capture the shape of the hazards.

Figure 19: OS cumulative log-log plot for the obe-cel overall infused Cohort IIA population

OS – Overall survival

Figure 20: OS Schoenfeld residuals plot for the overall infused Cohort IIA population

OS – Overall survival

Figure 21: OS quantile-quantile plot for the overall infused Cohort IIA population

OS – Overall survival

Figure 22: OS hazard rate plots for the overall infused Cohort IIA population

OS – Overall survival

In the Ph- infused Cohort IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot for OS suggest that the relative hazards are proportional over time, and as such, it is possible to conclude that the PH assumption holds.

In Figure 23 the respective lines do not intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and blinatumomab cannot be rejected. The residual plot in Figure 24 shows a random pattern with a non-significant relationship between residuals and time ([redacted]), giving further evidence that the PH assumption cannot be rejected, despite a non-zero slope. As the quantiles on Figure 25 do not lie on a straight line, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are characterised by a turning point (Figure 26). This indicates that flexible spline models may be more suitable to capture the shape of the hazard.

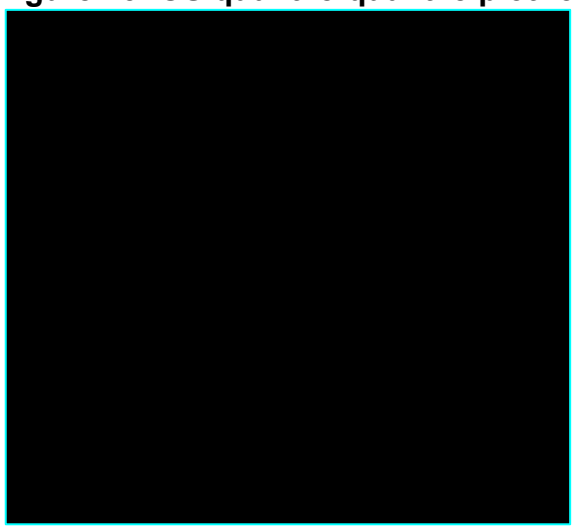
Figure 23: OS cumulative log-log plot for the obe-cel Ph- infused Cohort IIA population

OS – Overall survival; Ph- - Philadelphia chromosome negative

Figure 24: OS Schoenfeld residuals plot for the Ph- infused Cohort IIA population

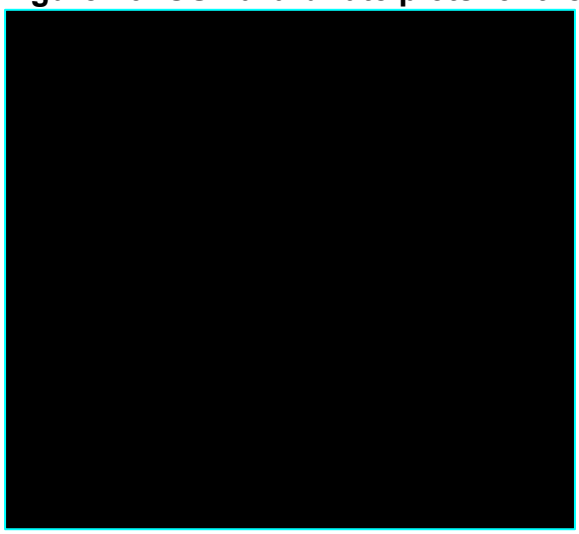
OS – Overall survival; Ph- - Philadelphia chromosome negative

Figure 25: OS quantile-quantile plot for the Ph- infused Cohort IIA population



OS – Overall survival; Ph- - Philadelphia chromosome negative

Figure 26: OS hazard rate plots for the Ph- infused Cohort IIA population



OS – Overall survival; Ph- - Philadelphia chromosome negative

In the Ph+ infused Cohort IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot for OS suggest that the relative hazards are proportional over time, and as such, it is possible to conclude that the PH assumption holds.

In Figure 27 the respective lines do not intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and ponatinib cannot be rejected. The residual plot in Figure 28 shows a random pattern and a non-significant relationship between residuals and time, giving further evidence that the PH assumption holds,

despite a non-zero slope. As the quantiles in Figure 29 do not lie on a straight line, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are constant (Figure 30), characterised by one turning point. This indicates that standard parametric and flexible spline models may both be suitable to capture the shape of the hazards.

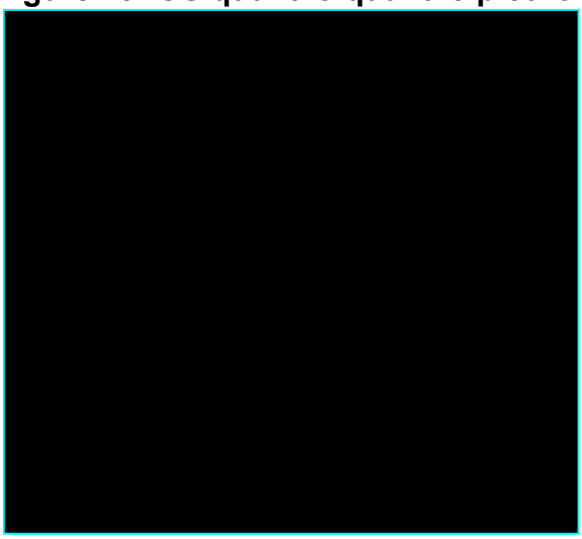
Figure 27: OS cumulative log-log plot for the obe-cel Ph+ infused Cohort IIA population

OS – Overall survival; Ph+ - Philadelphia chromosome positive

Figure 28: OS Schoenfeld residuals plot for the Ph+ infused Cohort IIA population

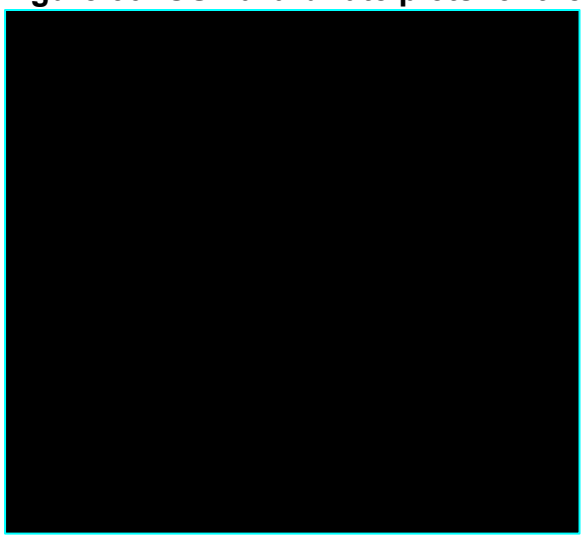
OS – overall survival; Ph+ - Philadelphia chromosome positive

Figure 29: OS quantile-quantile plot for the Ph+ infused Cohort IIA population



OS – Overall survival; Ph+ - Philadelphia chromosome positive

Figure 30: OS hazard rate plots for the Ph+ infused Cohort IIA population



OS – Overall survival; Ph+ - Philadelphia chromosome positive

Independent survival curves

Six standard independent parametric models were fitted to the overall infused Cohort IIA obe-cel data. The hazard rate plots indicate that flexible spline models may capture the shape of the hazard overtime, however, for consistency between the methods used for EFS, standard parametric models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel OS for the overall infused Cohort IIA population are presented in Figure 31 and Figure 32, respectively.

Figure 31: OS independent standard parametric curves for obe-cel: overall infused Cohort IIA population

KM – Kaplan-Meier; OS – Overall survival

Figure 32: OS flexible parametric spline curves for obe-cel: overall infused Cohort IIA population

KM – Kaplan-Meier; OS – Overall survival

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 13 and Table 15, respectively. The AICs and BICs for the independent curves are similar, with the lowest combined AIC and BIC being exponential, indicating the best statistical fit. However, the AIC score for all other curves are within three points of the exponential distribution, meaning these models are considered of comparable fit. For the flexible spline parametric models, the 0-

knot normal had the lowest AIC, with all distributions other than 2-knot hazards, 2-knot odds, and 2-knot normal distributions providing a comparable fit. Visual inspection of the curves indicate that standard parametric models provide a better fit to the data than flexible spline models.

Table 14 and Table 16 outlines the landmark OS rates for the obe-cel overall infused Cohort IIA population using standard parametric and flexible spline models, respectively. The estimated OS rates at years 1-4 indicate that most standard parametric and flexible spline models provide a good fit to the data.

Table 13: AIC and BIC statistical goodness-of-fit data for obe-cel OS – overall infused Cohort IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; OS – overall survival

Table 14: Obe-cel landmark survival rates for OS – overall infused Cohort IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival

Table 15: Goodness-of-fit data for obe-cel OS – overall Cohort IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]

1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; OS – overall survival

Table 16: Obe-cel landmark survival rates for OS – overall infused Cohort IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival

Six standard independent parametric models were fitted to the Ph- infused Cohort IIA obe-cel data. The hazard rate plots indicate that flexible spline models may capture the shape of the hazard over time, however, for consistency between the methods used for the overall infused Cohort IIA population, standard parametric models were also fitted to the data. The standard parametric and flexible spline

extrapolations of obe-cel OS for the Ph- infused Cohort IIA population are presented in Figure 33 and Figure 34, respectively.

Figure 33: OS independent standard parametric curves for obe-cel: Ph- infused Cohort IIA population

KM – Kaplan-Meier; OS – Overall survival; Ph- - Philadelphia chromosome negative

Figure 34: OS flexible parametric spline curves for obe-cel: Ph- infused Cohort IIA population

KM – Kaplan-Meier; OS – Overall survival; Ph- - Philadelphia chromosome negative

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 17 and Table 19 for the Ph- infused Cohort IIA population, respectively. The AICs and BICs for the independent curves are similar, with the

lowest combined AIC and BIC being exponential, indicating the best statistical fit. However, the AIC score for all other curves are within three points of the exponential distribution, meaning these models are considered of comparable fit. For the flexible spline parametric models, the 3-knot normal had the lowest AIC, with the 0-knot odds, 3-knot odds, 3-knot hazards, 0-knot normal, 1-knot normal distributions providing a comparable fit. Visual inspection of the curves indicate that flexible spline models provide a better fit to the data than standard parametric models.

Table 18 and Table 20 outlines the landmark OS rates for the obe-cel Ph- infused Cohort IIA population using standard parametric and flexible spline models, respectively. The estimated OS rates at years 1-4 indicate that most standard parametric and flexible spline models provide a good fit to the data.

Table 17: AIC and BIC statistical goodness-of-fit data for obe-cel OS – Ph- infused Cohort IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; OS – overall survival; Ph- - Philadelphia chromosome negative

Table 18: Obe-cel landmark survival rates for OS – Ph- infused Cohort IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival; Ph- - Philadelphia chromosome negative

Table 19: Goodness-of-fit data for obe-cel OS – Ph- Cohort IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; OS – overall survival; Ph- - Philadelphia chromosome negative

Table 20: Obe-cel landmark survival rates for OS – Ph- infused Cohort IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival; Ph- - Philadelphia chromosome negative

Six standard independent parametric models were fitted to the Ph+ infused Cohort IIA obe-cel data. The hazard rate plots indicate that flexible spline models may

capture the shape of the hazard over time, however, for consistency between the methods used for overall and Ph- infused Cohort IIA populations, standard parametric models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel OS for the Ph+ infused Cohort IIA population are presented in Figure 35 and Figure 36, respectively.

Figure 35: OS independent standard parametric curves for obe-cel: Ph+ infused Cohort IIA population

KM – Kaplan-Meier; OS – Overall survival; Ph+ - Philadelphia chromosome positive

Figure 36: OS flexible parametric spline curves for obe-cel: Ph+ infused Cohort IIA population

KM – Kaplan-Meier; OS – Overall survival; Ph+ - Philadelphia chromosome positive

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 21 and Table 23 for the Ph+ infused Cohort IIA population, respectively. The AICs and BICs for the independent curves are similar, with the lowest combined AIC and BIC being exponential, indicating the best statistical fit. However, the AIC score for all other curves are within three points of the exponential distribution, meaning these models are considered of comparable fit. For the flexible spline parametric models, the 0-knot normal had the lowest AIC, with all distributions other than 2-knot hazards, 3-knot hazards, 3-knot odds, 2-knot normal, and 3-knot normal providing a comparable fit. Visual inspection of the curves indicate that standard parametric models provide a better fit to the data than flexible spline models.

Table 22 and Table 24 outline the landmark OS rates for the obe-cel Ph+ infused Cohort IIA population using standard parametric and flexible spline models, respectively. The estimated OS rates at years 1-4 indicate that standard parametric models provide a better fit to the data, with flexible spline models underpredicting survival at 3 years.

Table 21: AIC and BIC statistical goodness-of-fit data for obe-cel OS – Ph+ infused Cohort IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; OS – overall survival; Ph+ - Philadelphia chromosome positive

Table 22: Obe-cel landmark survival rates for OS – Ph+ infused Cohort IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival; Ph+ - Philadelphia chromosome positive

Table 23: Goodness-of-fit data for obe-cel OS – Ph+ infused Cohort IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; OS – overall survival; Ph+ - Philadelphia chromosome positive

Table 24: Obe-cel landmark survival rates for OS – Ph+ infused Cohort IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival; Ph+ - Philadelphia chromosome positive

1.2.2 Pooled enrolled Cohorts IA and IIA population

1.2.2.1 Event-free survival (EFS)

Conclusion of the diagnostic tests

In the overall pooled enrolled Cohort IA and IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot suggest that the relative hazards are likely to vary over time, and as such, it is not possible to conclude that the PH assumption holds.

In Figure 37 the respective lines intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and inotuzumab can be rejected. The residual plot in Figure 38 shows a non-zero slope and a significant relationship between residuals and time ($p<0.05$), giving further evidence that the PH assumption does not hold, despite a random pattern. As the quantiles in Figure 39 do not lie on a straight line, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are non-monotonically decreasing (Figure 40). characterised by a turning point at approximately two months. This indicates that flexible spline models may be suitable to capture the shape of the hazards.

Figure 37: EFS cumulative log-log plot for the overall pooled enrolled Cohort IA and IIA population

EFS - Event-free survival

Figure 38: EFS Schoenfeld residuals plot for the overall pooled enrolled Cohort IA and IIA population

EFS – Event-free survival

Figure 39: EFS quantile-quantile plot for the overall pooled enrolled Cohort IA and IIA population

EFS – Event-free survival

Figure 40: EFS hazard rate plot for the overall pooled enrolled Cohort IA and IIA population

EFS – Event-free survival

In the Ph- pooled enrolled Cohort IA and IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot suggest that the relative hazards are likely to vary over time, and as such, it is not possible to conclude that the PH assumption holds.

In Figure 41 the respective lines do not intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and blinatumomab cannot be rejected in the Ph- pooled enrolled Cohort IA and IIA population. The residual plot in Figure 42 shows a non-zero slope alongside a significant relationship between residuals and time ($p<0.05$), giving evidence that the PH assumption does not hold, despite a random pattern. As the quantiles in Figure 43 do not lie on a straight line, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are monotonically decreasing (Figure 44), characterised by the lack of turning points. This indicates that standard parametric models may be sufficient to capture the shape of the hazards.

Figure 41: EFS cumulative log-log plot for the Ph- pooled enrolled Cohort IA and IIA population

EFS - Event-free survival; Ph- - Philadelphia chromosome negative

Figure 42: EFS Schoenfeld residuals plot for the Ph- pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; Ph- - Philadelphia chromosome negative

Figure 43: EFS quantile-quantile plot for the Ph- pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; Ph- - Philadelphia chromosome negative

Figure 44: EFS hazard rate plot for the Ph- pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; Ph- - Philadelphia chromosome negative

In the Ph+ pooled enrolled Cohort IA and IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot suggest that the relative hazards are likely to vary over time, and as such, it is not possible to conclude that the PH assumption holds.

Figure 45 the respective lines intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and ponatinib can be rejected. The residual plot in Figure 46 shows a random pattern and a non-significant relationship between residuals and time (p[redacted]), giving evidence that the PH assumption cannot be rejected, despite a non-zero slope. As the quantiles in Figure 47 do not lie on a straight line, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are monotonically decreasing (Figure 48), characterised by the lack of turning points. This indicates that standard parametric models may be sufficient to capture the shape of the hazards.

Figure 45: EFS cumulative log-log plot for the Ph+ pooled enrolled Cohort IA and IIA population

EFS - Event-free survival; Ph+ - Philadelphia chromosome positive

Figure 46: EFS Schoenfeld residuals plot for the Ph+ pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; Ph+ - Philadelphia chromosome positive

Figure 47: EFS quantile-quantile plot for the Ph+ pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; Ph+ - Philadelphia chromosome positive

Figure 48: EFS hazard rate plot for the Ph+ pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; Ph+ - Philadelphia chromosome positive

Independent survival curves

Six standard independent parametric models were fitted to the overall pooled enrolled Cohort IA and IIA obe-cel data: exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma. The hazard rate plots indicated that flexible spline models may capture the shape of the hazard overtime in this population, however, for consistency between the methods used for the infused Cohort IIA population, standard parametric models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel EFS for the pooled enrolled Cohort IA and IIA population are presented in Figure 49 and Figure 50, respectively.

Figure 49: EFS independent standard parametric curves for obe-cel: overall pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; KM – Kaplan-Meier

Figure 50: EFS flexible parametric spline curves for obe-cel: overall pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; KM – Kaplan-Meier

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 25 and Table 27 for the overall pooled enrolled Cohort IA and IIA population, respectively. The AICs and BICs for the independent curves are similar, except for exponential and Gompertz which had the highest AIC and BIC indicating poor statistical fit. The lowest combined AIC and BIC for the independent curves was the log-normal, indicating the best statistical fit. However, the AIC score for the

Weibull and generalised gamma curves were within three points of the log-normal distribution, meaning the models are considered of comparable fit. For the flexible spline parametric models, the 2-knot normal had the lowest AIC, with no other distribution providing a comparable fit. Flexible spline distributions appear to best fit the data visually.

Table 26 and Table 28 outlines the landmark EFS rates for the obe-cel overall pooled enrolled Cohort IA and IIA population using standard parametric and flexible spline models, respectively. The estimated EFS rates at years 1-4 indicate that in general, flexible spline models provide a better fit to the data than standard parametric models.

Table 25: AIC and BIC statistical goodness-of-fit data for obe-cel EFS – overall pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; EFS – event-free survival

Table 26: Obe-cel landmark survival rates for EFS – overall pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

EFS – event-free survival; KM – Kaplan-Meier

Table 27: Goodness-of-fit data for obe-cel EFS – overall pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; EFS – event-free survival

Table 28: Obe-cel landmark survival rates for EFS – overall pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

EFS – Event-free survival; KM – Kaplan-Meier

Six standard independent parametric models were fitted to the Ph- pooled enrolled Cohort IA and IIA obe-cel data: exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma. The hazard rate plots indicated that standard parametric models may capture the shape of the hazard overtime in this population, however, for consistency between the methods used for the overall pooled enrolled Cohort IA and IIA population, flexible spline models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel EFS for the Ph-pooled enrolled Cohort IA and IIA population are presented in Figure 51 and Figure 52, respectively.

Figure 51: EFS independent standard parametric curves for obe-cel: Ph-pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; KM – Kaplan-Meier

Figure 52: EFS flexible parametric spline curves for obe-cel: Ph- pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; KM – Kaplan-Meier

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in

Table **29** and Table 31 for the obe-cel Ph- pooled enrolled Cohort IA and IIA population, respectively. The AICs and BICs for the independent curves are similar, with the lowest combined AIC and BIC being log-normal, indicating the best statistical fit. However, the AIC score for Weibull and generalised gamma are within three points of the log-logistic distribution, meaning these models are considered of comparable fit. For the flexible spline parametric models, the 3-knot normal had the lowest AIC, with no other distributions providing a comparable fit. Visual inspection of the curves indicate that the log-normal curve provides the best fit to the data, with all other curves underreporting survival relative to the KM curve.

Table 30 and Table 32 outline the landmark EFS rates for the obe-cel Ph- infused Cohort IIA population using standard parametric and flexible spline models, respectively. The estimated EFS rates at years 1-4 indicate that the log-normal, 3-knot hazards, 3-knot odds, and 3-knot normal curves provide a good fit to the data.

Table 29: AIC and BIC statistical goodness-of-fit data for obe-cel EFS – Ph- pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; OS – overall survival; Ph- - Philadelphia chromosome negative

Table 30: Obe-cel landmark survival rates for EFS – Ph- pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

EFS – Event-free survival; KM – Kaplan-Meier; Ph- - Philadelphia chromosome negative

Table 31: Goodness-of-fit data for obe-cel EFS – Ph- pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]

0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; OS – overall survival; Ph- - Philadelphia chromosome negative

Table 32: Obe-cel landmark survival rates for EFS – Ph- pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

EFS – event-free survival KM – Kaplan-Meier; Ph- - Philadelphia chromosome negative

Six standard independent parametric models were fitted to the Ph+ pooled enrolled Cohort IA and IIA obe-cel data: exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma. The hazard rate plots indicated that standard parametric models may capture the shape of the hazard overtime in this population, however, for consistency between the methods used for the overall and Ph- pooled enrolled Cohort IA and IIA population, flexible spline models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel EFS for the Ph+ pooled enrolled Cohort IA and IIA population are presented in Figure 53 and Figure 54, respectively.

Figure 53: EFS independent standard parametric curves for obe-cel: Ph+ pooled enrolled Cohort IA and IIA population

EFS – event-free survival; KM – Kaplan-Meier; Ph+ - Philadelphia chromosome positive

Figure 54: EFS flexible parametric spline curves for obe-cel: Ph+ pooled enrolled Cohort IA and IIA population

EFS – Event-free survival; KM – Kaplan-Meier; Ph+ - Philadelphia chromosome positive

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 33 and Table 35 for the Ph+ pooled enrolled Cohort IIA population, respectively. The AICs and BICs for the independent curves are similar, with the lowest combined AIC and BIC being Weibull, indicating the best statistical fit. However, the AIC score for generalised gamma and log-logistic are within three points of the Weibull distribution, meaning these models are considered of

comparable fit. For the flexible spline parametric models, the 3-knot normal had the lowest AIC, with all distributions other than the 0-knot normal and 2-knot hazards distributions providing a comparable fit. Visual inspection of the curves indicate that flexible spline models provide a better fit to the data than standard parametric models.

Table 34 and Table 36 outline the landmark EFS rates for the obe-cel Ph+ enrolled Cohort IA and IIA population using standard parametric and flexible spline models, respectively. The estimated OS rates at years 1-4 indicate that the 3-knot normal distribution provides the best fit to the data, with all other curves either under-, or overpredicting survival relative to the KM curve.

Table 33: AIC and BIC statistical goodness-of-fit data for obe-cel EFS – Ph+ pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; EFS – event-free survival; Ph+ - Philadelphia chromosome positive

Table 34: Obe-cel landmark survival rates for EFS – Ph+ pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

EFS – event-free survival; KM – Kaplan-Meier; Ph+ - Philadelphia chromosome positive

Table 35: Goodness-of-fit data for obe-cel EFS – Ph+ pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; EFS – event-free survival; Ph+ - Philadelphia chromosome positive

Table 36: Obe-cel landmark survival rates for EFS – Ph+ pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

EFS – event-free survival; KM – Kaplan-Meier; Ph+ - Philadelphia chromosome positive

1.2.2.2 Overall survival (OS)

Conclusion of the diagnostic tests

Inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot for OS in the overall pooled enrolled Cohort IA and IIA suggest that the relative hazards are likely to vary over time, and as such, it is not possible to conclude that the PH assumption holds.

In Figure 55 the respective lines intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and inotuzumab can be rejected. The residual plot in Figure 56 shows a random pattern alongside a non-significant relationship between residuals and time ([redacted]), giving evidence that the PH assumption cannot be rejected, despite a non-zero slope. As the quantiles in Figure 57 do not lie on a straight line, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are monotonically decreasing (Figure 58) characterised by the lack of turning points. This indicates that standard parametric models may be sufficient to capture the shape of the hazards.

Figure 55: OS log−log transformation for the overall pooled enrolled Cohort IA and IIA population

OS – overall survival

Figure 56: OS Schoenfeld residuals plot for the overall pooled enrolled Cohort IA and IIA population

OS – overall survival

Figure 57: OS quantile-quantile plot for the overall pooled enrolled Cohort IA and IIA population

OS – overall survival

Figure 58: OS hazard rate for the overall pooled enrolled Cohort IA and IIA population

OS – overall survival

In the Ph- pooled enrolled Cohort IA and IIA population, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot for OS suggest that the relative hazards may be proportional over time, and as such, it is not possible to conclude that the PH assumption can be rejected.

In Figure 59 the respective lines do not intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and blinatumomab cannot be rejected. The residual plot in Figure 60 shows a random pattern and a non-significant relationship between residuals and time ([redacted]), giving further evidence that the PH assumption holds, despite a non-zero slope. As the quantiles in Figure 61 do not lie on a straight line, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are decreasing (Figure 62), characterised by the lack of turning points. This indicates that standard parametric models may be sufficient to capture the shape of the hazards.

Figure 59: OS cumulative log-log plot for the obe-cel Ph- pooled enrolled Cohort IA and IIA population

OS – overall survival; Ph- - Philadelphia chromosome negative

Figure 60: OS Schoenfeld residuals plot for the obe-cel Ph- pooled enrolled Cohort IA and IIA population

OS – overall survival; Ph- - Philadelphia chromosome negative

Figure 61: OS quantile-quantile plot for the obe-cel Ph- pooled enrolled Cohort IA and IIA population

OS – overall survival; Ph- - Philadelphia chromosome negative

Figure 62: OS hazard rate plots for the obe-cel Ph- pooled enrolled Cohort IA and IIA population

OS – overall survival; Ph- - Philadelphia chromosome negative

Similarly to EFS, inspection of the log-cumulative hazards, Schoenfeld residual plot, and the quantile-quantile plot for OS for the enrolled Cohort IIA and IA population suggest that the relative hazards are proportional over time, and as such, it is not possible to conclude that the PH assumption cannot be rejected.

In Figure 63 the respective lines do not intersect, therefore, the hypothesis that the PH assumption holds between obe-cel and ponatinib cannot be rejected. The residual plot in Figure 64 shows a random pattern with a non-significant relationship between residuals and time ([redacted]), giving further evidence that the PH assumption cannot be rejected, despite a non-zero slope. As the quantiles in Figure 65 do not lie on a straight line, dependent models, which assume a proportional treatment effect, were considered inappropriate and hence not attempted.

The hazard rates for obe-cel are characterised by multiple turning points (Figure 66). This indicates that flexible spline models may be sufficient to capture the shape of the hazards.

Figure 63: OS cumulative log-log plot for the obe-cel Ph+ pooled enrolled Cohort IA and IIA population

OS – overall survival; Ph+ - Philadelphia chromosome positive

Figure 64: OS Schoenfeld residuals plot for the obe-cel Ph+ pooled enrolled Cohort IA and IIA population

OS – overall survival; Ph+ - Philadelphia chromosome positive

Figure 65: OS quantile-quantile plot for the obe-cel Ph+ pooled enrolled Cohort IA and IIA population

OS – overall survival; Ph+ - Philadelphia chromosome positive

Figure 66: OS hazard rate plots for the obe-cel Ph+ pooled enrolled Cohort IA and IIA population

OS – overall survival; Ph+ - Philadelphia chromosome positive

Independent survival curves

Six standard independent parametric models were fitted to the obe-cel overall pooled enrolled Cohort IA and IIA data: exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma. The hazard rate plots indicate that standard parametric models may capture the shape of the hazard overtime, however, for consistency between the methods used for EFS, flexible spline models were also fitted to the overall pooled enrolled Cohort IA and IIA population data. The standard parametric and flexible spline extrapolations of obe-cel OS for the overall pooled enrolled Cohort IA and IIA population are presented in Figure 67 and Figure 68, respectively.

Figure 67: OS independent standard parametric curves for obe-cel: overall pooled enrolled Cohort IA and IIA population

KM – Kaplan-Meier; OS – Overall survival

Figure 68: OS flexible parametric spline curves for obe-cel: overall pooled enrolled Cohort IA and IIA population

KM – Kaplan-Meier; OS – Overall survival

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 37 and

Table 39 for the overall pooled enrolled Cohort IA and IIA population, respectively. The AICs and BICs for the independent curves are similar, except for exponential and Weibull which each had the highest AIC and BIC indicating poor statistical fit. The lowest combined AIC and BIC for the independent curves was the log-normal, indicating the best statistical fit. For the flexible spline parametric models, the 0-knot normal had the lowest AIC, the same as the log-normal AIC.

Table 37 and Table 39 outline the landmark OS rates for the obe-cel overall pooled enrolled Cohort IA and IIA population using standard parametric and flexible spline models, respectively. The estimated OS rates at years 1-4 indicate that the Weibull curve provides the best fit to the data, with all other curves overestimating survival relative to the KM curve.

Table 37: AIC and BIC statistical goodness-of-fit data for obe-cel OS – overall pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; OS – overall survival

Table 38: Obe-cel landmark survival rates for OS – overall pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival

Table 39: Goodness-of-fit data for obe-cel OS – overall pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; OS – overall survival

Table 40: Obe-cel landmark survival rates for OS – overall pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival

Six standard independent parametric models were fitted to the Ph- pooled enrolled Cohort IA and IIA population obe-cel data. The hazard rate plots indicate that standard parametric models may capture the shape of the hazard overtime, however, for consistency between the methods used for the overall pooled enrolled Cohort IA and IIA population, flexible spline models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel OS for the Ph- pooled enrolled Cohort IA and IIA population are presented in Figure 69 and Figure 70, respectively.

Figure 69: OS independent standard parametric curves for obe-cel: Ph- pooled enrolled Cohort IA and IIA population

KM – Kaplan-Meier; OS – Overall survival; Ph- - Philadelphia chromosome negative

Figure 70: OS flexible parametric spline curves for obe-cel: Ph- pooled enrolled Cohort IA and IIA population

KM – Kaplan-Meier; OS – Overall survival; Ph- - Philadelphia chromosome negative

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 41 and Table 43 for the Ph- pooled enrolled Cohort IA and IIA population, respectively. The AICs and BICs for the independent curves are similar, with the lowest combined AIC and BIC being log-normal, indicating the best statistical fit. However, the AIC score for all other curves other than exponential and Weibull are within three points of the log-normal distribution, meaning these models are considered of comparable fit. For the flexible spline parametric models, the 0-

knot normal had the lowest AIC, with the 1-knot hazards, 3-knot hazards, 0-knot odds, 1-knot odds, 2-knot odds, and 1-knot normal distributions providing a comparable fit. Visual inspection of the curves indicate that standard parametric models provide a better fit to the data than flexible spline models.

Table 42 and Table 44 outline the landmark OS rates for the obe-cel Ph- pooled enrolled Cohort IA and IIA population using standard parametric and flexible spline models, respectively. The estimated OS rates at years 1-4 indicate that standard parametric models provide a better fit to the data, with all flexible spline models underpredicting survival relative to the KM curve.

Table 41: AIC and BIC statistical goodness-of-fit data for obe-cel OS – Ph- pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; OS – overall survival; Ph- - Philadelphia chromosome negative

Table 42: Obe-cel landmark survival rates for OS – Ph- pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival; Ph- - Philadelphia chromosome negative

Table 43: Goodness-of-fit data for obe-cel OS – Ph- pooled enrolled Cohort IA and IIA population spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]
1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; OS – overall survival; Ph- - Philadelphia chromosome negative

Table 44: Obe-cel landmark survival rates for OS – Ph- pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – overall survival; Ph- - Philadelphia chromosome negative

Six standard independent parametric models were fitted to the Ph+ pooled enrolled Cohort IA and IIA obe-cel data. The hazard rate plots indicate that standard

parametric models may capture the shape of the hazard overtime, however, for consistency between the methods used for the overall and Ph- pooled enrolled Cohort IA and IIA population, flexible spline models were also fitted to the data. The standard parametric and flexible spline extrapolations of obe-cel OS for the Ph+ pooled enrolled Cohort IA and IIA population are presented in Figure 71 and Figure 72, respectively.

Figure 71: OS independent standard parametric curves for obe-cel: Ph+ pooled enrolled Cohort IA and IIA population

KM – Kaplan-Meier; OS – Overall survival; Ph+ - Philadelphia chromosome positive

Figure 72: OS flexible parametric spline curves for obe-cel: Ph+ pooled enrolled Cohort IA and IIA population

KM – Kaplan-Meier; OS – Overall survival; Ph+ - Philadelphia chromosome positive

The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 45 and Table 47 for the Ph+ pooled enrolled Cohort IA and IIA population, respectively. The AICs and BICs for the independent curves are similar, with the lowest combined AIC and BIC being exponential, indicating the best statistical fit. However, the AIC score for all other curves are within three points of the exponential distribution, meaning these models are considered of comparable fit. For the flexible spline parametric models, the 0-knot normal had the lowest AIC, with the 0-knot hazards, 1-knot hazards, 0-knot odds, 1-knot normal, and 2-knot normal distributions providing a comparable fit. Visual inspection of the curves indicate that standard parametric models provide a better fit to the data, with all flexible spline models underpredicting survival relative to the KM curve.

Table 46 and Table 48 outlines the landmark OS rates for the obe-cel Ph+ pooled enrolled Cohort IA and IIA population using standard parametric and flexible spline models, respectively. The estimated OS rates at years 1-4 indicate that all standard parametric and flexible spline models provide a good fit to the data.

Table 45: AIC and BIC statistical goodness-of-fit data for obe-cel OS – Ph+ pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC – Akaike information criterion; BIC – Bayesian information criterion; OS – Overall survival; Ph+ - Philadelphia chromosome positive

Table 46: Obe-cel landmark survival rates for OS – Ph+ pooled enrolled Cohort IA and IIA population, independent standard parametric curves

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – Overall survival; Ph+ - Philadelphia chromosome positive

Table 47: Goodness-of-fit data for obe-cel OS – Ph+ pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distributions	AIC
0-knot hazards	[redacted]
1-knot hazards	[redacted]
2-knot hazards	[redacted]
3-knot hazards	[redacted]
0-knot odds	[redacted]
1-knot odds	[redacted]
2-knot odds	[redacted]
3-knot odds	[redacted]
0-knot normal	[redacted]

1-knot normal	[redacted]
2-knot normal	[redacted]
3-knot normal	[redacted]

AIC – Akaike information criterion; OS – Overall survival; Ph+ - Philadelphia chromosome positive

Table 48: Obe-cel landmark survival rates for OS – Ph+ pooled enrolled Cohort IA and IIA population, flexible spline parametric models

Distribution	Years			
	1	2	3	4
KM	[redacted]	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

KM – Kaplan-Meier; OS – Overall survival; Ph+ - Philadelphia chromosome positive

1.3 Conclusions

Survival analyses were conducted to determine the naïve effect of obe-cel compared to inotuzumab, blinatumomab, and ponatinib on EFS and OS. Analyses demonstrated that both independent parametric and flexible spline curves are appropriate to extrapolate obe-cel EFS and OS. The base-case and scenario analysis curves selected for obe-cel for each population based on analysis of the diagnostic plots, statistical fit, visual inspection and landmark survival times, are outlined in Table 49.

Table 49: Base-case and scenario analysis curves for obe-cel in the infused Cohort IIA, and enrolled Cohort IA and IIA populations in the economic analysis

Population	Outcome	Base-case	Scenario analysis
Infused Cohort IIA population			
Overall population	EFS	3-knot normal	Weibull
	OS	3-knot normal	Log-normal
Ph- population	EFS	3-knot odds	3-knot normal
	OS	2-knot normal	3-knot normal
Ph+ population	EFS	Weibull	3-knot normal
	OS	Log-normal	Exponential
Enrolled Cohort IA and IIA population			
Overall population	EFS	2-knot normal	Weibull
	OS	Weibull	Weibull
Ph- population	EFS	Log-normal	3-knot normal
	OS	Generalised gamma	Gompertz
Ph+ population	EFS	3-knot normal	Gompertz
	OS	Exponential	Gompertz

EFS – Event-free survival; OS – Ooverall survival; Ph-/+ - Philadelphia chromosome negative/positive

2 Indirect treatment comparisons

2.1 Methods

2.1.1 Data

In the absence of head-to-head clinical trial evidence for obe-cel versus the comparators considered in this submission (inotuzumab, blinatumomab, and ponatinib), it was necessary to conduct an SLR to identify evidence for use in an ITC. Details on the methods for the SLR are presented in Appendix D of the original submission. Of the 76 publications identified in the SLR, only the pivotal trials (INO-VATE, TOWER and PACE) reported across 19 publications were deemed relevant for indirect comparison, as other studies either did not report relevant outcomes (N=11), or were undertaken in settings or populations not relevant for the

assessment (N=18). Three comparator studies were considered for inclusion in the analyses, comparing to different sub-populations of the FELIX trial, as detailed in Table 50.

As of January 2025, a new FELIX data cut with longer follow-up has become available, and this is the data cut considered throughout this NICE submission update. Two populations were of interest for the updated ITC, the infused Cohort IIA and the enrolled pooled Cohorts IA and IIA, as requested by the External Assessment Group (EAG) and committee.

Table 50: Summary of trials considered for the indirect treatment comparison

Trial	FELIX 2025 data cut[4]	INO-VATE[5]	TOWER[6]	PACE[7]
Population	R/R ALL **Analysis (Infused Cohort IIA):** Overall (N=94), Ph- ALL (N=69), Ph+ ALL (N=25) **Analysis (Enrolled pooled Cohorts IA and IIA):** Overall (N=133), Ph- ALL (N=103), Ph+ ALL (N=30)	R/R ALL **Analysis (intervention arm):** Overall (N=164)	R/R Ph- ALL **Analysis (intervention arm):** Ph- ALL (N=271)	Ph+ ALL **Analysis:** Ph+ ALL (N=32)
Intervention	Obe-cel	Inotuzumab	Blinatumomab	Ponatinib
Study design	• Phase Ib/II* • Open-label • Single arm	• Phase III • Open-label • Controlled	• Phase III • Open-label • Controlled	• Phase II • Open-label • Single arm
Outcomes	• EFS (IRRC) • OS	• PFS • OS	• EFS • OS	• PFS • OS

***Note:** Populations used for the comparisons are sourced from phase 2.*
ALL - Acute lymphoblastic leukaemia; EFS - Event-free survival; ITT - Intent-to-treat; MAIC - Matching-adjusted indirect comparison; mITT - Modified intent-to-treat; OS - Overall survival; PFS - Progression-free survival; Ph+/- - Philadelphia chromosome positive/negative; R/R - Relapsed/refractory; RFS - Relapse-free survival; STC - Simulated treatment comparis

The baseline characteristics of the FELIX trial and comparator studies were consistent with those seen in the previous data cut. Baseline characteristics are detailed in the EAG clarification questions document, with Table 48 presenting the infused Cohort IIA population and Table 10 for the enrolled pooled Cohorts IA and IIA population. Table 10 in the EAG clarification questions document also details the baseline characteristics of the comparator studies to enable comparisons.

2.1.2 Analysis methodology

Population-adjusted ITCs adjust for differences in relevant covariates and thereby improve the balance of study populations and minimise bias in the outcomes analysed. Population-adjusted ITC analyses generate controlled relative effect estimates of treatments in the absence of head-to-head trial data on the basis that the studies are sufficiently similar in terms of design, population, interventions, and outcomes. Given that individual patient data (IPD) was not available for all trials of interest, a population-adjusted ITC was conducted in the original company submission using a MAIC methodology, as described in the NICE Decision Support Unit (DSU) Technical Support Document 18: ee Section B.2.9 in the company submission). However, during ACM1 both the EAG and the Committee raised concerns about the MAIC results, particularly around the small sample sizes. To address these methodological uncertainties, pairwise STC were conducted for EFS and OS using the 2025 FELIX data cut to inform the obe-cel arm, and the same comparator trials that were used for the MAIC to inform the comparator arms.

The premise of MAIC and STC is to adjust for between-trial differences in baseline characteristics defined as prognostic factors or treatment effect modifiers (TEMs), to identify a coherent set of estimates. As outlined in Section B.2.9.2 of the company submission, there is no common treatment arm between FELIX and the identified comparator studies, therefore, all comparisons in the ITCs were unanchored.

- **MAIC:** A form of propensity score weighting, applicable where IPD is available for one population and aggregate data for another. Individuals in the IPD population are weighted by the inverse of their propensity score, to balance the covariate distribution with that of the target aggregate population.

- **STC:** A form of outcome regression, applicable where IPD are available for one population and aggregate data for another. A statistical model describing the outcomes in terms of the covariates is fitted for the IPD population and used to predict the outcomes that would have been observed in the aggregate target population.

The assumptions underlying unanchored population-adjusted ITCs were reported in Section B.2.9.2 of the original company submission. No separate feasibility assessment were conducted for the STC, as the results of the feasibility assessment for the MAIC were deemed applicable to this methodology. The same PFs and TEMs were considered for both the MAIC and the STC. One missing value for Eastern Cooperative Oncology Group (ECOG) status was present in the data in the overall and Ph- populations, and the patient was assumed to belong to the group containing the most patients in FELIX (ECOG 1) for the comparisons with inotuzumab and blinatumomab. This methodology is in line with the original company submission.

The NICE DSU Technical Support Document 18 states that all covariates identified as important should be included in the model, despite the resulting low effective sample size (ESS).[8] Therefore, all covariates which were reported in both FELIX and the comparator trials were included in the models, in line with the methods used for the MAIC in the original company submission.

2.2 Results

Comparisons were performed for each population (infused Cohort IIA and pooled enrolled Cohorts IA and IIA) of the three subgroups: overall population versus INO-VATE, Ph- population versus TOWER, and Ph+ population versus PACE for both EFS and OS.

2.2.1 Infused Cohort IIA population

2.2.1.1 Matching-adjusted indirect comparison

Event-free survival

The findings of the MAIC indicate obe-cel had a favourable effect on EFS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. A summary of the EFS findings is presented in Table 51.

All results are consistent with the findings of the previously conducted MAIC analyses, supporting the comparative efficacy of obe-cel versus its comparators.

Table 51: Event-free survival MAIC outcomes for FELIX versus comparators: Infused Cohort IIA population

Treatment	Median EFS	ESS	Unadjusted HR	Adjusted HR
Obe-cel (Overall)	[redacted]	-	-	-
Inotuzumab (Overall)	5.0 months	[redacted]	[redacted]	[redacted]
Blinatumomab (Ph-)	31% at 6 months†	[redacted]	[redacted]	[redacted]
Ponatinib (Ph+)	3.0 months	[redacted]	[redacted]	[redacted]

*Statistically significant results. †Median EFS for blinatumomab unavailable due to censoring of patients who have not achieved complete remission or complete remission with incomplete haematologic recovery.
EFS – Event-free survival; ESS – Effective sample size; HR – Hazard ratio; Ph – Philadelphia chromosome

Overall population

The estimated adjusted and unadjusted hazard ratios (HRs) for the overall population were in favour of obe-cel compared to inotuzumab. While the unadjusted HR was statistically significant in favour of obe-cel, the adjusted HR was not significant. This trend is reflected in the KM plot (Figure 73), which shows a separation in survival curves favouring obe-cel over inotuzumab, with the adjusted (obe-cel weighted) curve aligning more closely with the comparator, consistent with the non-significant adjusted HR.

Figure 73: Obe-cel versus inotuzumab MAIC EFS KM plot: Infused Cohort IIA population

EFS – Event-free survival; KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison

Ph- population

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, with both differences reaching statistical significance. This is reflected in the EFS KM plot (Figure 74), which shows a clear separation between the obe-cel and blinatumomab survival curves, indicating improved outcomes with obe-cel.

Figure 74: Obe-cel versus blinatumomab MAIC EFS KM plot: Infused Cohort IIA population

EFS – Event-free survival; KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison

Ph+ population

The estimated adjusted and unadjusted HRs for the Ph+ population were in favour of obe-cel compared to ponatinib, and these differences were statistically significant. However, there is considerable uncertainty surrounding the EFS estimates for ponatinib, as illustrated in the KM plot (Figure 75), suggesting instability in the results. This is likely attributable to the low ESS for ponatinib, as reported in Table 51.

Figure 75: Obe-cel versus ponatinib MAIC EFS KM plot: Infused Cohort IIA population

EFS – Event-free survival; KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison

Overall survival

The findings of the MAIC indicate obe-cel had a favourable effect on OS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. A summary of the OS findings is presented in Table 52.

While the unadjusted HR versus inotuzumab slightly increased compared to the previously conducted MAIC analysis using the 2024 data cut from FELIX, all other

unadjusted and adjusted results are comparable to that of the results presented in response to clarification question A29.

Table 52: Overall survival MAIC outcomes for FELIX versus comparators: Infused Cohort IIA population

Treatment	Median OS	ESS	Unadjusted HR	Adjusted HR
Obe-cel (Overall)	[redacted]	-	-	-
Inotuzumab (Overall)	7.7 months	[redacted]	[redacted]	[redacted]
Blinatumomab (Ph-)	7.7 months	[redacted]	[redacted]	[redacted]
Ponatinib (Ph+)	8.0 months	[redacted]	[redacted]	[redacted]

*Statistically significant results.
EFS – Event-free survival; ESS – Effective sample size; HR – Hazard ratio; Ph – Philadelphia chromosome

Overall population

The estimated adjusted and unadjusted HRs for the overall population were in favour of obe-cel compared to inotuzumab. While the unadjusted HR was statistically significant in favour of obe-cel, the adjusted HR was not significant. This trend is reflected in the OS KM plot (Figure 73), which shows a separation in survival curves favouring obe-cel over inotuzumab, with the adjusted (obe-cel weighted) curve aligning more closely with the comparator, consistent with the non-significant adjusted HR.

Figure 76: Obe-cel versus inotuzumab MAIC OS KM plot: Infused Cohort IIA population

KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison; OS – Overall survival

Ph- population

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, with both differences reaching statistical significance. This is reflected in the OS KM plot (Figure 77), which shows a clear separation between the obe-cel and blinatumomab survival curves, indicating improved outcomes with obe-cel.

Figure 77: Obe-cel versus blinatumomab MAIC OS KM plot: Infused Cohort IIA population

KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison; OS – Overall survival

Ph+ population

For the Ph+ population, both the adjusted and unadjusted HRs favoured obe-cel over ponatinib, with statistically significant differences observed in both cases. However, the confidence intervals around the ponatinib comparison estimates are extremely wide, reflecting a high degree of uncertainty in the OS results. This is visually apparent in the KM plot (Figure 78), where the large variability in the survival curves suggest instability in the estimates.

Figure 78: Obe-cel versus ponatinib MAIC OS KM plot: Infused Cohort IIA population

KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison; OS – Overall survival

Complete remission

There was inconsistency in how complete remission (CR) was evaluated among the key studies, therefore different comparisons were conducted for each pairwise analyses, in line with the company response to clarification question A29. CR and complete remission with incomplete response (CRi) were not reported individually in the INO-VATE trial, however, were reported as a combined endpoint. Similarly, CRi

was not reported in the PACE clinical trial, so comparison between obe-cel and ponatinib was not possible for CRi. The findings are summarised in Table 53.

In the comparison against inotuzumab using the combined CR/CRi endpoint, the unadjusted OR significantly* favoured obe-cel, while the adjusted OR favoured inotuzumab.

Adjusted and unadjusted CRi was only assessed in the TOWER study, therefore could only be evaluated versus blinatumomab. Both unadjusted and adjusted OR for CRi were significantly in favour of obe-cel compared to blinatumomab. The adjusted and unadjusted OR for CR versus blinatumomab was in favour of obe-cel, but this did not reach statistical significance.

The estimated adjusted and unadjusted CR for the Ph+ population was in favour of obe-cel compared to ponatinib, and was statistically significant.

All results are directionally in line with the findings of the MAIC conducted using the 2024 FELIX data cut.

Table 53: Complete remission outcomes for FELIX versus comparators, Infused Cohort IIA population

Treatment	Inotuzumab (Overall)	Blinatumomab (Ph-)	Ponatinib (Ph+)
Complete remission (CR)			
Unadjusted	-	[redacted]	[redacted]
Adjusted	-	[redacted]	[redacted]
Complete remission with incomplete response (CRi)			
Unadjusted	-	[redacted]	-
Adjusted	-	[redacted]	-
CR/CRi combination			
Unadjusted	[redacted]	-	-
Adjusted	[redacted]	-	-

*Statistically significant results.

Effective sample size

ESS combinations were requested by the EAG as part of the clarification questions for the 2024 data cut. As these are derived from baseline characteristics, they remain unchanged in the 2025 data cut. The cumulative ESS for each of the comparisons by order of importance of TEM or prognostic factors (PF) are presented in Tables 72, 73 and 74 in the EAG clarification questions document for inotuzumab, blinatumomab, and ponatinib, respectively. In line with NICE DSU TSD 18, all covariates identified as PFs or TEMs were included for each comparison.

2.2.1.2 Simulated treatment comparison

The findings of the STC are largely consistent with those produced by the MAIC, supporting the overall direction of treatment effect observed. While some differences in statistical significance and effect size are noted, the STC results reinforce the comparative advantage of obe-cel observed in the MAIC, particularly versus blinatumomab and ponatinib.

Event-free survival

The findings of the STC are consistent with those produced by the MAIC, indicating obe-cel had a favourable effect on EFS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. A summary of the EFS findings is presented in Table 54.

Table 54: Event-free survival STC outcomes for FELIX versus comparators: Infused Cohort IIA population

Treatment	Median EFS	Naïve HR	Adjusted HR
Obe-cel (Overall)	[redacted]	-	-
Inotuzumab (Overall)	5.0 months	[redacted]	[redacted]
Blinatumomab (Ph-)	31% at 6 months†	[redacted]	[redacted]

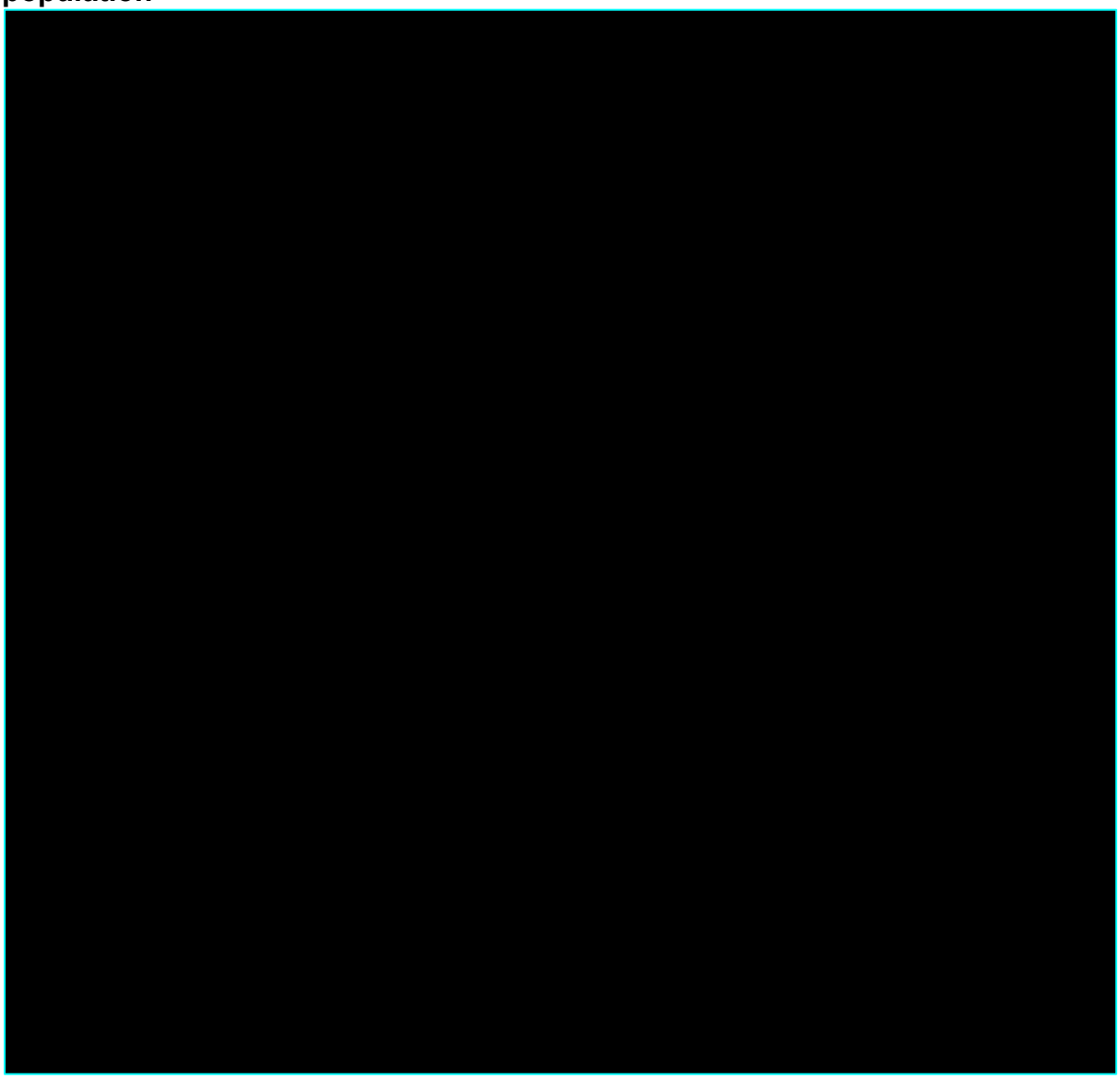
Ponatinib (Ph+)	3.0 months	[redacted]	[redacted]

*Statistically significant results.
EFS – Event-free survival; ESS – Effective sample size; HR – Hazard ratio; Ph – Philadelphia chromosome; STC – Simulated treatment comparison

Overall population

In the overall population, both the adjusted and naïve HRs favoured obe-cel over inotuzumab, with both reaching statistical significance. This pattern is illustrated in Figure 79, which displays overlap in survival curves favouring obe-cel. The key distinction between the MAIC and STC results lies in the statistical significance of the adjusted EFS HR; while the STC analysis yielded a statistically significant result, the corresponding HR from the MAIC was not significant.

Figure 79: Obe-cel versus inotuzumab STC EFS KM plot: Infused Cohort IIA population

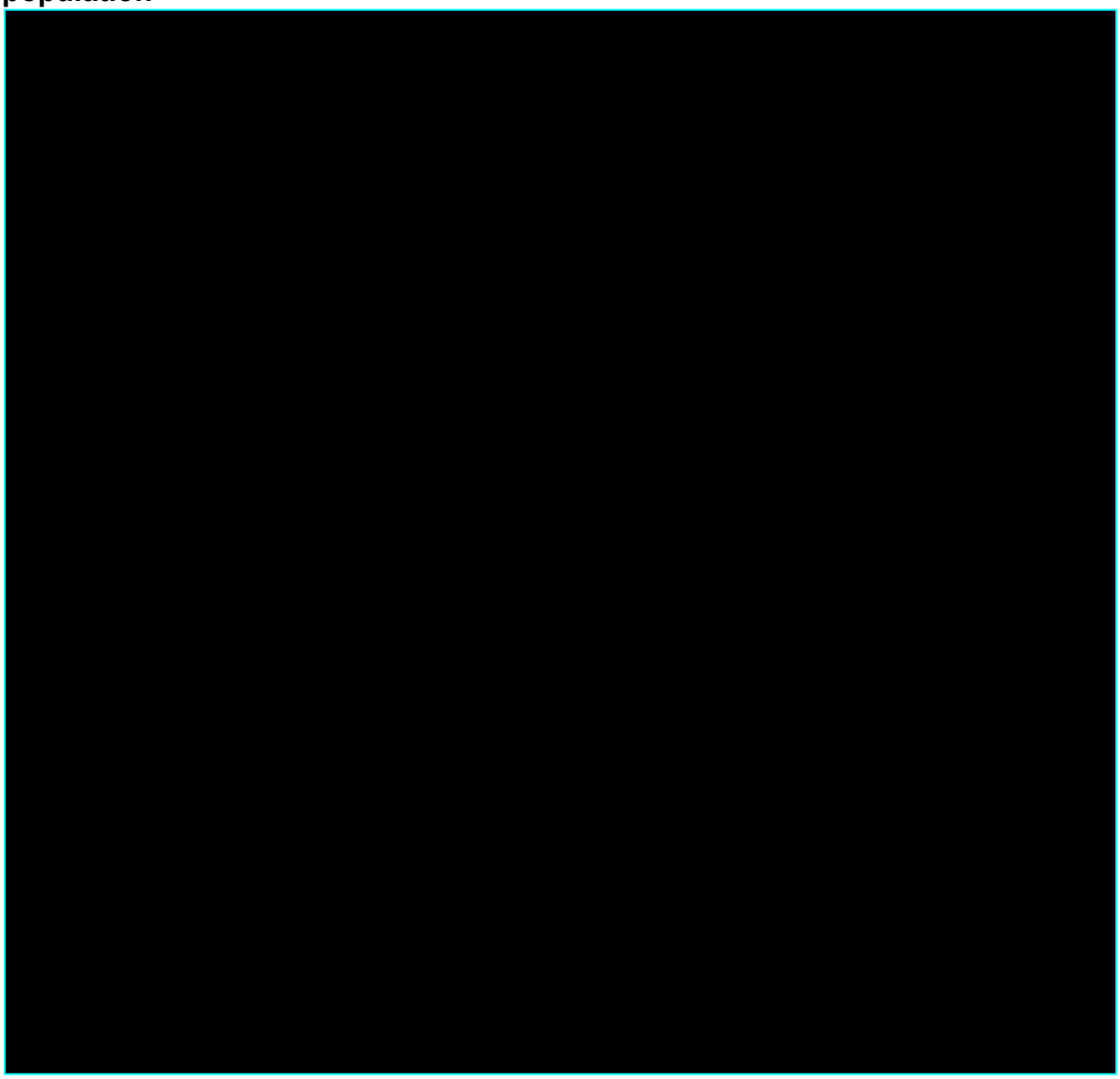


EFS – Event-free survival; KM – Kaplan-Meier; STC – Simulated treatment comparison

Ph- population

The estimated adjusted and naïve HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, with both differences reaching statistical significance. This is illustrated in the EFS KM plot (Figure 80), presenting a clear separation between the obe-cel survival curves and the lower blinatumomab curve, indicating improved outcomes with obe-cel.

Figure 80: Obe-cel versus blinatumomab STC EFS KM plot: Infused Cohort IIA population

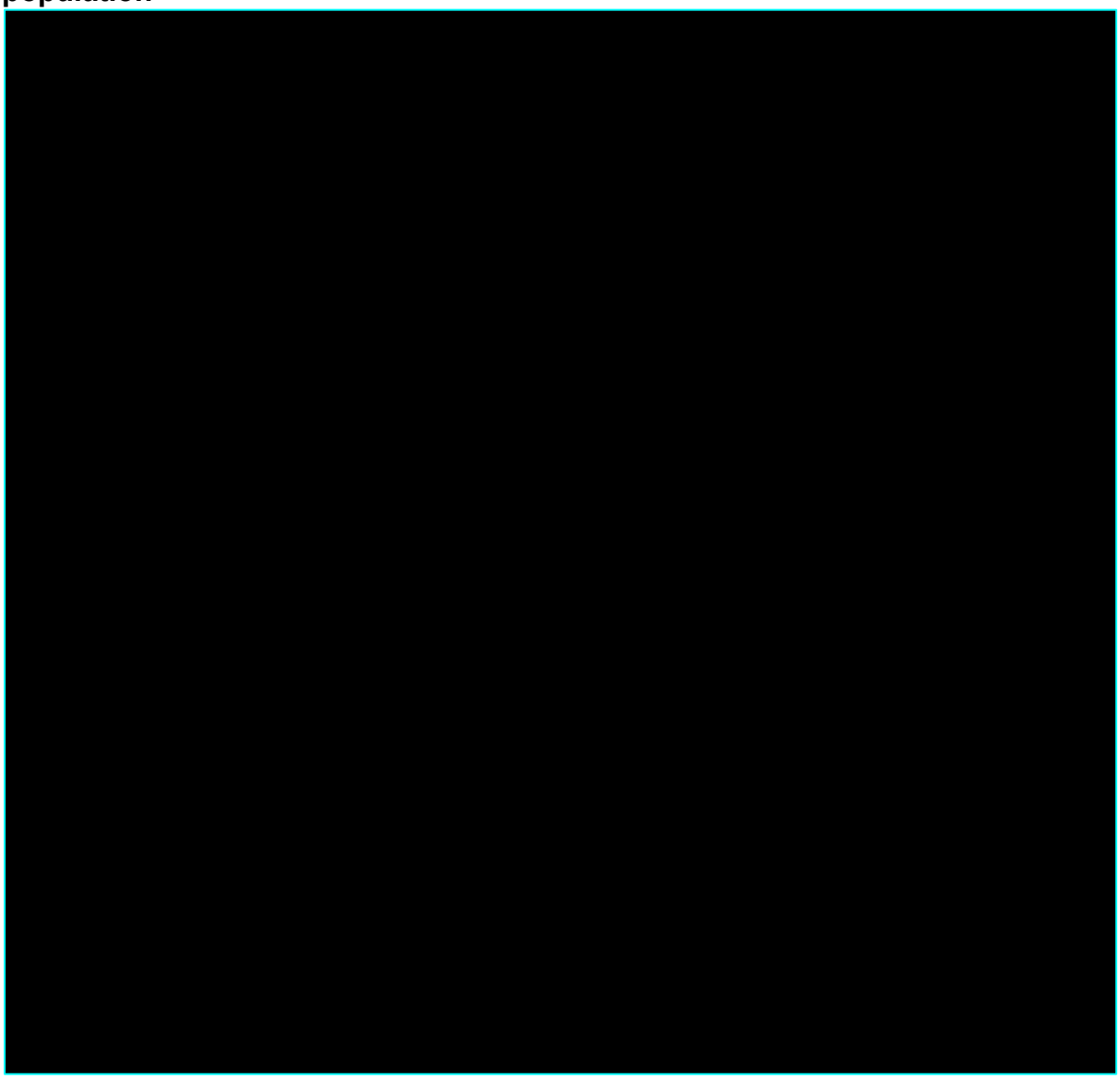


EFS – Event-free survival; KM – Kaplan-Meier; STC – Simulated treatment comparison

Ph+ population

The adjusted and naïve HRs for the Ph+ population favoured obe-cel over ponatinib, with both differences reaching statistical significance. However, there is considerable uncertainty surrounding the weighted EFS estimates for ponatinib, as shown in the KM plot (Figure 81), indicating the same limitations in results as seen in the MAIC. The ponatinib survival curve lies notably below both the adjusted and naïve obe-cel curves, with a clear separation observed, further highlighting the favourable EFS outcomes associated with obe-cel.

Figure 81: Obe-cel versus ponatinib STC EFS KM plot: Infused Cohort IIA population



EFS – Event-free survival; KM – Kaplan-Meier; STC – Simulated treatment comparison

Overall survival

The findings of the STC are consistent with those produced by the MAIC, indicating obe-cel had a favourable effect on OS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. A summary of the OS findings is presented in Table 55.

All results are aligned with the findings of the MAIC conducted using the 2024 FELIX data cut.

Table 55: Overall survival STC outcomes for FELIX versus comparators: Infused Cohort IIA population

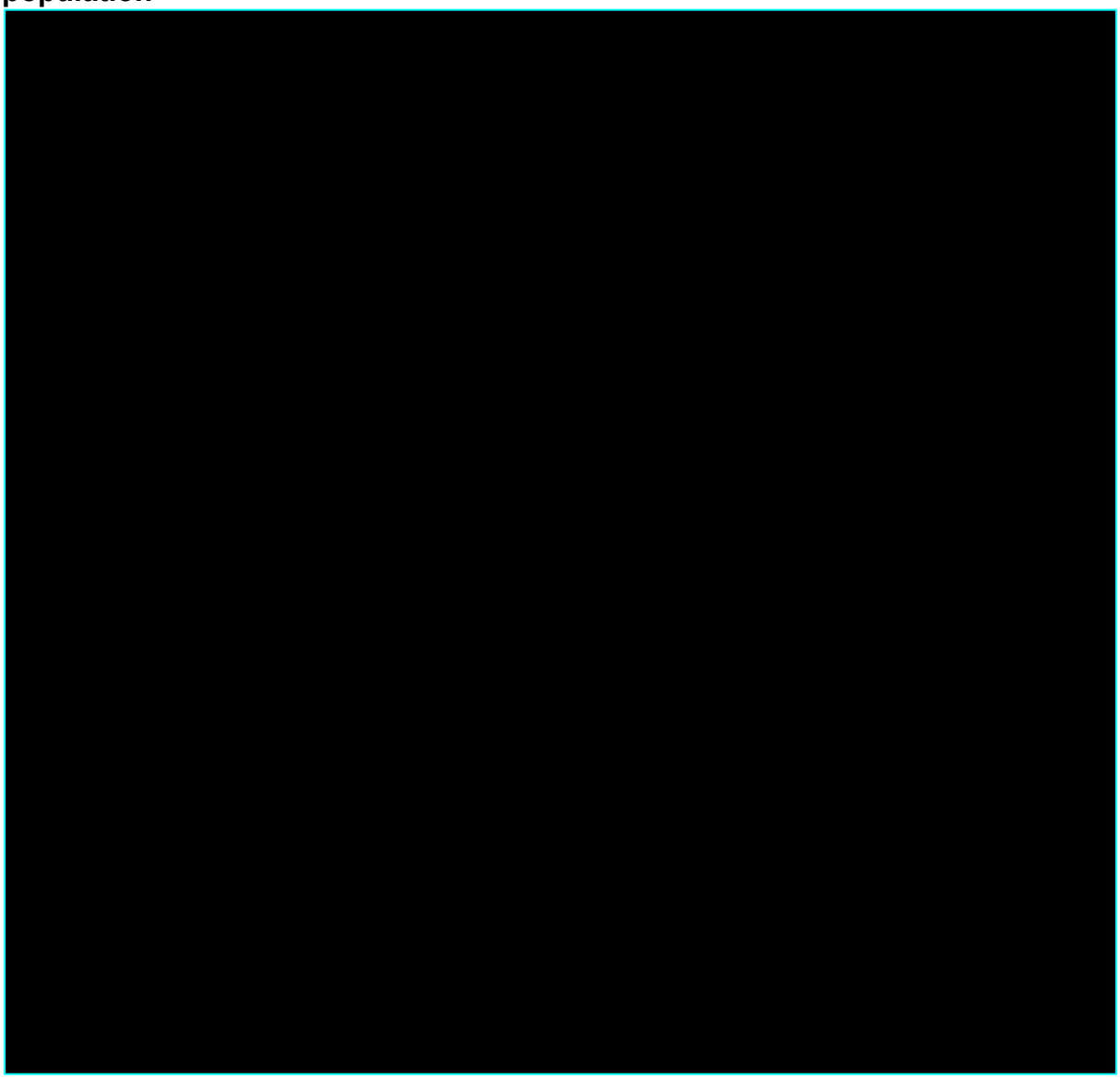
Treatment	Median OS	Naïve HR	Adjusted HR
Obe-cel (Overall)	[redacted]	-	-
Inotuzumab (Overall)	7.7 months	[redacted]	[redacted]
Blinatumomab (Ph-)	7.7 months	[redacted]	[redacted]
Ponatinib (Ph+)	8.0 months	[redacted]	[redacted]

*Statistically significant results.
HR – Hazard ratio; OS – Overall survival; Ph – Philadelphia chromosome

Overall population

The estimated adjusted and naïve HR for the overall population were in favour of obe-cel compared to inotuzumab. While the naïve HR was statistically significant in favour of obe-cel, the adjusted HR was not significant. This trend is reflected in the KM plot (Figure 82), which illustrates considerable overlap in the inotuzumab and adjusted obe-cel survival curves.

Figure 82: Obe-cel versus inotuzumab STC OS KM plot: Infused Cohort IIA population



KM – Kaplan-Meier; OS – Overall survival; STC – Simulated treatment comparison

Ph- population

The estimated adjusted and naïve HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, with both differences reaching statistical significance. This is reflected in the OS KM plot (Figure 83), which shows a clear separation between the obe-cel and blinatumomab survival curves, indicating improved outcomes with obe-cel.

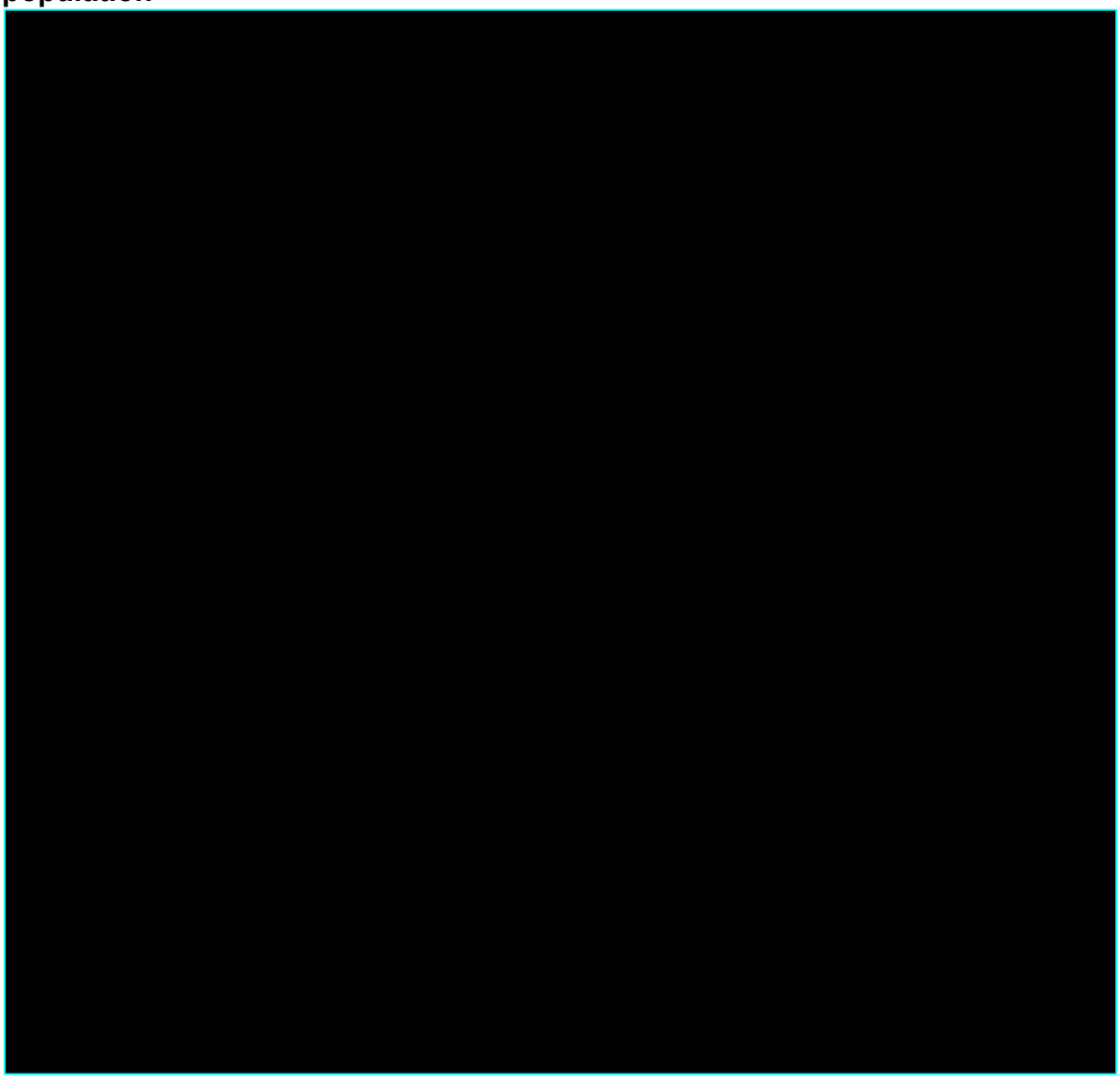
Figure 83: Obe-cel versus blinatumomab STC OS KM plot: Infused Cohort IIA population

KM – Kaplan-Meier; OS – Overall survival; STC – Simulated treatment comparison

Ph+ population

For the Ph+ population, both the adjusted and naïve HRs favoured obe-cel over ponatinib, with statistically significant differences observed in both cases. However, the confidence intervals around the ponatinib comparison estimates are extremely wide, reflecting a high degree of uncertainty in the OS results. This is visually apparent in the KM plot (Figure 84), where the large variability in the survival curves suggest instability in the estimates and the lack of overlap demonstrates the statistical significance.

Figure 84: Obe-cel versus ponatinib STC OS KM plot: Infused Cohort IIA population



KM – Kaplan-Meier; OS – Overall survival; STC – Simulated treatment comparison

2.2.2 Enrolled pooled Cohorts IA and IIA population

2.2.2.1 Matching-adjusted indirect comparison

Event-free survival

The findings of the MAIC indicate obe-cel had a favourable effect on EFS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. A summary of the EFS findings is presented in Table 56.

All results are aligned with the findings of the MAIC conducted using the 2024 FELIX data cut.

Table 56: Event-free survival MAIC outcomes for FELIX versus comparators: Pooled enrolled Cohort IA and IIA population

Treatment	Median EFS	ESS	Unadjusted HR	Adjusted HR
Obe-cel (Overall)	[redacted]	-	-	-
Inotuzumab (Overall)	5.0 months	[redacted]	[redacted]	[redacted]
Blinatumomab (Ph-)	31% at 6 months†	[redacted]	[redacted]	[redacted]
Ponatinib (Ph+)	3.0 months	[redacted]	[redacted]	[redacted]

*Statistically significant results. †Median EFS for blinatumomab unavailable due to censoring of patients who have not achieved CR or CRi haematologic recovery.
EFS – Event-free survival; ESS – Effective sample size; HR – Hazard ratio; Ph – Philadelphia chromosome

Overall population

The estimated adjusted and unadjusted HRs for the overall population were in favour of obe-cel compared to inotuzumab, however neither estimate reached statistical significance. This is reflected in the EFS KM plot (Figure 85) which shows considerable overlap between the survival curves, although with a modest trend favouring obe-cel.

Figure 85: Obe-cel versus inotuzumab MAIC EFS KM plot: Enrolled pooled Cohort IA and IIA population

EFS – Event-free survival; KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison

Ph- population

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, with both differences reaching statistical significance. This is reflected in the EFS KM plot (Figure 86), which shows a separation between the obe-cel and blinatumomab survival curves, indicating improved outcomes with obe-cel. While the direction and statistical significance is

consistent with that seen in the infused Cohort IIA population, the effect size is slightly lower.

Figure 86: Obe-cel versus blinatumomab MAIC EFS KM plot: Enrolled pooled Cohort IA and IIA population

EFS – Event-free survival; KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison

Ph+ population

The estimated adjusted and unadjusted HRs for the Ph+ population were in favour of obe-cel compared to ponatinib, and these differences were statistically significant. However, there is considerable uncertainty surrounding the adjusted EFS estimates for ponatinib, as illustrated in the KM plot (Figure 87), suggesting instability in the

results. This is likely attributable to the low ESS for ponatinib, as reported in Table 56. The findings in the enrolled pooled Cohort IA and IIA population are consistent with those in the infused Cohort IIA population.

Figure 87: Obe-cel versus ponatinib MAIC EFS KM plot: Enrolled pooled Cohort IA and IIA population

EFS – Event-free survival; KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison

Overall survival

The findings of the MAIC indicate obe-cel had a favourable effect on OS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. A summary of the OS findings is presented in Table 57.

All results are aligned with the findings of the MAIC conducted using the 2024 FELIX data cut.

Table 57: Overall survival MAIC outcomes for FELIX versus comparators: Pooled enrolled Cohort IA and IIA population

Treatment	Median OS	ESS	Unadjusted HR	Adjusted HR
Obe-cel (Overall)	[redacted]	-	-	-
Inotuzumab (Overall)	7.7 months	[redacted]	[redacted]	[redacted]
Blinatumomab (Ph-)	7.7 months	[redacted]	[redacted]	[redacted]
Ponatinib (Ph+)	8.0 months	[redacted]	[redacted]	[redacted]

*Statistically significant results.
EFS – Event-free survival; ESS – Effective sample size; HR – Hazard ratio; Ph – Philadelphia chromosome

Overall population

The estimated adjusted and unadjusted HRs for the overall population were in favour of obe-cel compared to inotuzumab. While the unadjusted HR was statistically significant in favour of obe-cel, the adjusted HR was not significant. This trend is reflected in the OS KM plot (Figure 88), which shows an overlap in survival curves for the adjusted obe-cel estimate. The findings are consistent with those found in the infused Cohort IIA population, in terms of both direction and significance.

Figure 88: Obe-cel versus inotuzumab MAIC OS KM plot: Enrolled pooled Cohort IA and IIA population

KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison; OS – Overall survival

Ph- population

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, with only the adjusted estimate reaching statistical significance. This is reflected in the OS KM plot (Figure 89), which shows greater overlap between obe-cel and blinatumomab survival curves, compared to the adjusted obe-cel estimate.

Figure 89: Obe-cel versus blinatumomab MAIC OS KM plot: Enrolled pooled Cohort IA and IIA population

KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison; OS – Overall survival

Ph+ population

For the Ph+ population, both the adjusted and unadjusted HRs favoured obe-cel over ponatinib, with statistically significant differences observed in both cases. However, the confidence intervals surrounding the adjusted estimates are extremely wide, reflecting a high degree of uncertainty in the OS results. This is visually

apparent in the KM plot (Figure 90), where the large variability in the survival curves suggest instability in the estimates.

Figure 90: Obe-cel versus ponatinib MAIC OS KM plot: Enrolled pooled Cohort IA and IIA population

KM – Kaplan-Meier; MAIC – Matching-adjusted indirect comparison; OS – Overall survival

Effective sample size

ESS combinations were requested by the EAG as part of the clarification questions for the 2024 data cut. As these are derived from baseline characteristics, they remain unchanged in the 2025 data cut. The cumulative ESS for each of the comparisons by order of importance of TEM / PF are presented in Tables 14, 15 and

16 of the EAG clarification questions document for inotuzumab, blinatumomab, and ponatinib, respectively. In line with NICE DSU TSD 18, all covariates identified as PFs or TEMs were included for each comparison.

Complete remission

There was inconsistency in how complete remission (CR) was evaluated among the key studies, therefore different comparisons were conducted for each pairwise analyses, in line with the company response to clarification question A29. CR and CRi were not reported individually in the INO-VATE trial, however, were reported as a combined endpoint. Similarly, CRi was not reported in the PACE clinical trial, so comparison between obe-cel and ponatinib was not possible for CRi. The findings are summarised in in Table 58.

In the comparison against inotuzumab using the combined CR/CRi endpoint, the unadjusted OR significantly* favoured obe-cel, while the adjusted OR favoured inotuzumab.

Adjusted and unadjusted CRi was only assessed in the TOWER study, therefore could only be evaluated versus blinatumomab. Both unadjusted and adjusted OR for CRi were significantly in favour of obe-cel compared to blinatumomab. The adjusted and unadjusted OR for CR versus blinatumomab was in favour of obe-cel, but this did not reach statistical significance.

The estimated adjusted and unadjusted CR for the Ph+ population was in favour of obe-cel compared to ponatinib, and was statistically significant.

All results are directionally in line with the findings of the MAIC conducted using the 2024 FELIX data cut.

Table 58: Complete remission outcomes for FELIX versus comparators, enrolled pooled Cohorts IA and IIA population

Treatment	Inotuzumab (Overall)	Blinatumomab (Ph-)	Ponatinib (Ph+)
Complete remission (CR)			
Unadjusted	-	[redacted]	[redacted]

Adjusted	-	[redacted]	[redacted]
Complete remission with incomplete response (CRi)			
Unadjusted	-	[redacted]	-
Adjusted	-	[redacted]	-
CR/CRi combination			
Unadjusted	[redacted]	-	-
Adjusted	[redacted]	-	-

*Statistically significant results.
CR – Complete remission; CRi – Complete remission with incomplete response; Ph – Philadelphia chromosome

2.2.2.2 Simulated treatment comparison

The findings of the STC are largely consistent with those produced by the MAIC, supporting the overall direction of treatment effect observed. While some differences in effect size are noted, the statistical significance of the adjusted estimates was aligned across both methods. The STC results reinforce the comparative advantage of obe-cel observed in the MAIC, particularly versus blinatumomab and ponatinib.

Event-free survival

The findings of the STC are consistent with those produced by the MAIC, in terms of both direction and statistical significance, indicating that obe-cel had a favourable effect on EFS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. A summary of the EFS findings is presented in Table 59.

Table 59: Event-free survival STC outcomes for FELIX versus comparators: Enrolled pooled Cohort IA and IIA population

Treatment	Median EFS	Naïve HR	Adjusted HR
Obe-cel (Overall)	[redacted]	-	-

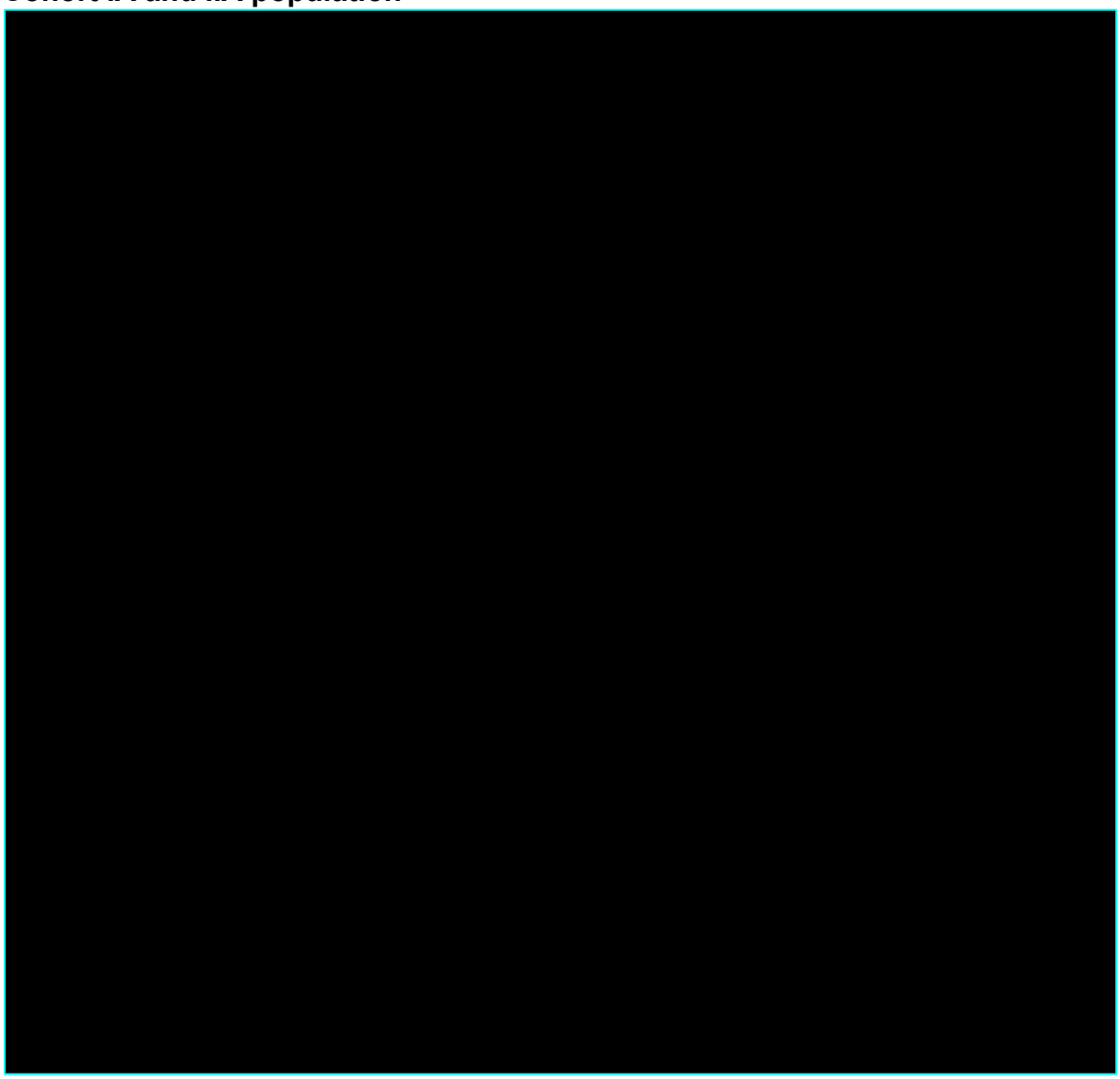
Inotuzumab (Overall)	5.0 months	[redacted]	[redacted]
Blinatumomab (Ph-)	31% at 6 months†	[redacted]	[redacted]
Ponatinib (Ph+)	3.0 months	[redacted]	[redacted]

*Statistically significant results.
EFS – Event-free survival; ESS – Effective sample size; HR – Hazard ratio; Ph – Philadelphia chromosome

Overall population

In the overall population, both the adjusted and naïve HRs favoured obe-cel over inotuzumab, but neither reached statistical significance. This pattern is illustrated in Figure 91 which, despite favouring obe-cel, displays considerable overlap in survival curves.

Figure 91: Obe-cel versus inotuzumab STC EFS KM plot: Enrolled pooled Cohort IA and IIA population

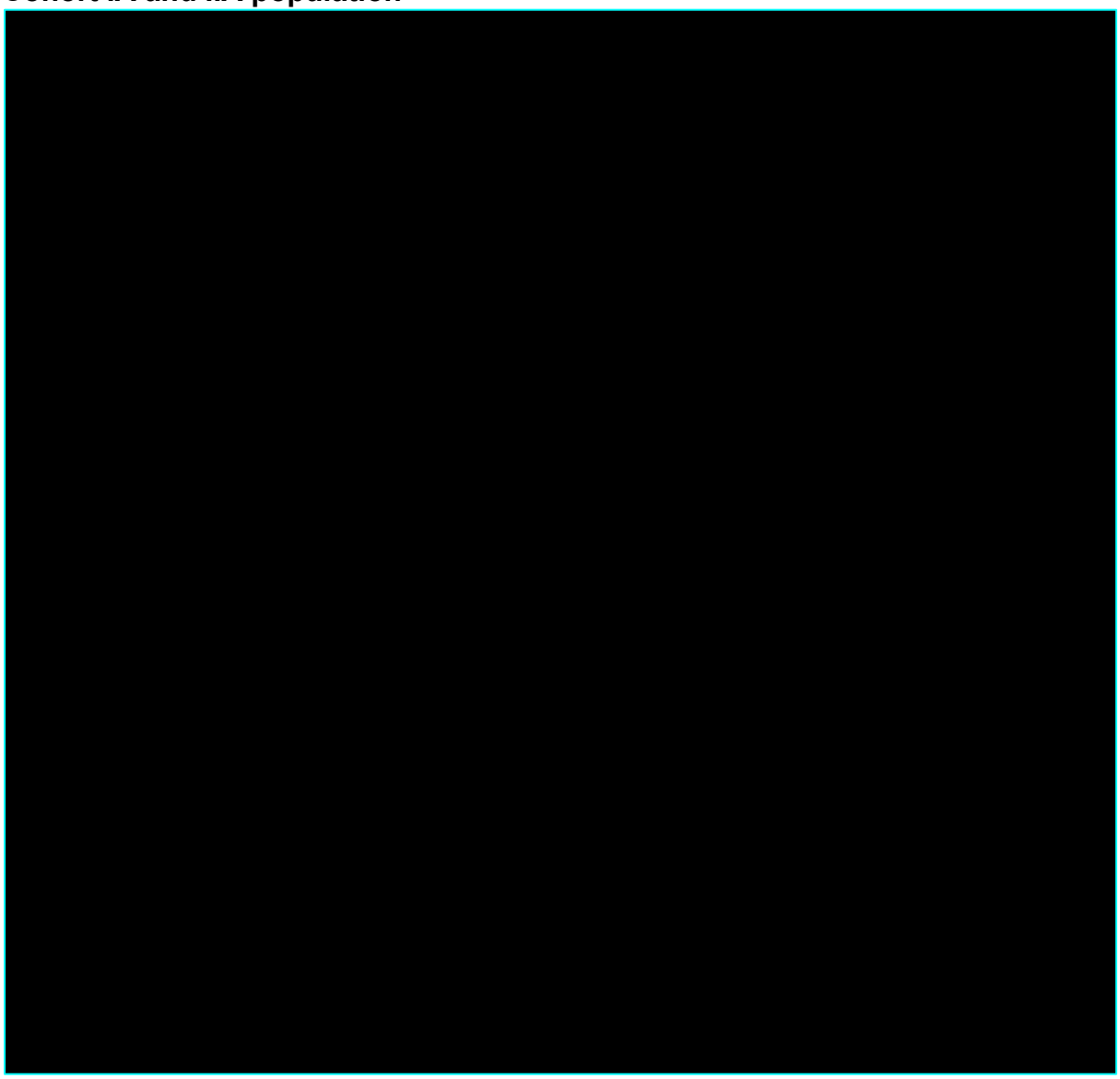


EFS – Event-free survival; KM – Kaplan-Meier; STC – Simulated treatment comparison

Ph- population

The estimated adjusted and naïve HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, with both estimates reaching statistical significance. This is illustrated in the EFS KM plot (Figure 92), with a separation between the obe-cel survival curves and the lower blinatumomab curve, indicating improved outcomes with obe-cel.

Figure 92: Obe-cel versus blinatumomab STC EFS KM plot: Enrolled pooled Cohort IA and IIA population

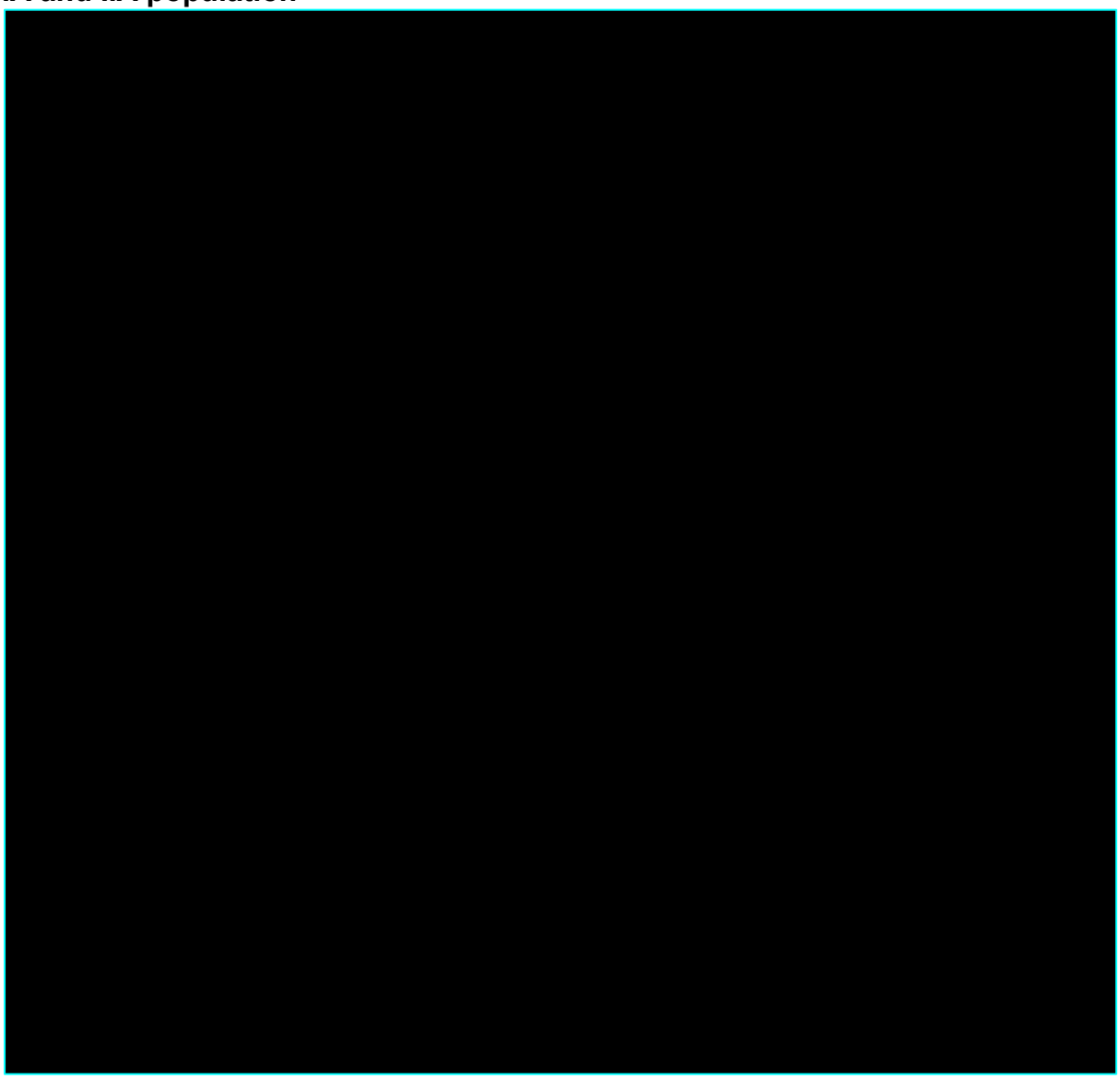


EFS – Event-free survival; KM – Kaplan-Meier; STC – Simulated treatment comparison

Ph+ population

The adjusted and naïve HRs for the Ph+ population favoured obe-cel over ponatinib, with both differences reaching statistical significance. As presented in the EFS KM (Figure 93), the ponatinib survival curve lies notably below both the adjusted and naïve obe-cel curves, with a clear separation observed, further highlighting the favourable EFS outcomes associated with obe-cel.

Figure 93: Obe-cel versus pontainib STC EFS KM plot: Enrolled pooled Cohort IA and IIA population



EFS – Event-free survival; KM – Kaplan-Meier; STC – Simulated treatment comparison

Overall survival

The findings of the STC are consistent with those produced by the MAIC in terms of direction and statistical significance, indicating obe-cel had a favourable effect on OS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. A summary of the OS findings is presented in Table 60.

Table 60: Overall survival STC outcomes for FELIX versus comparators: Enrolled pooled Cohort IA and IIA population

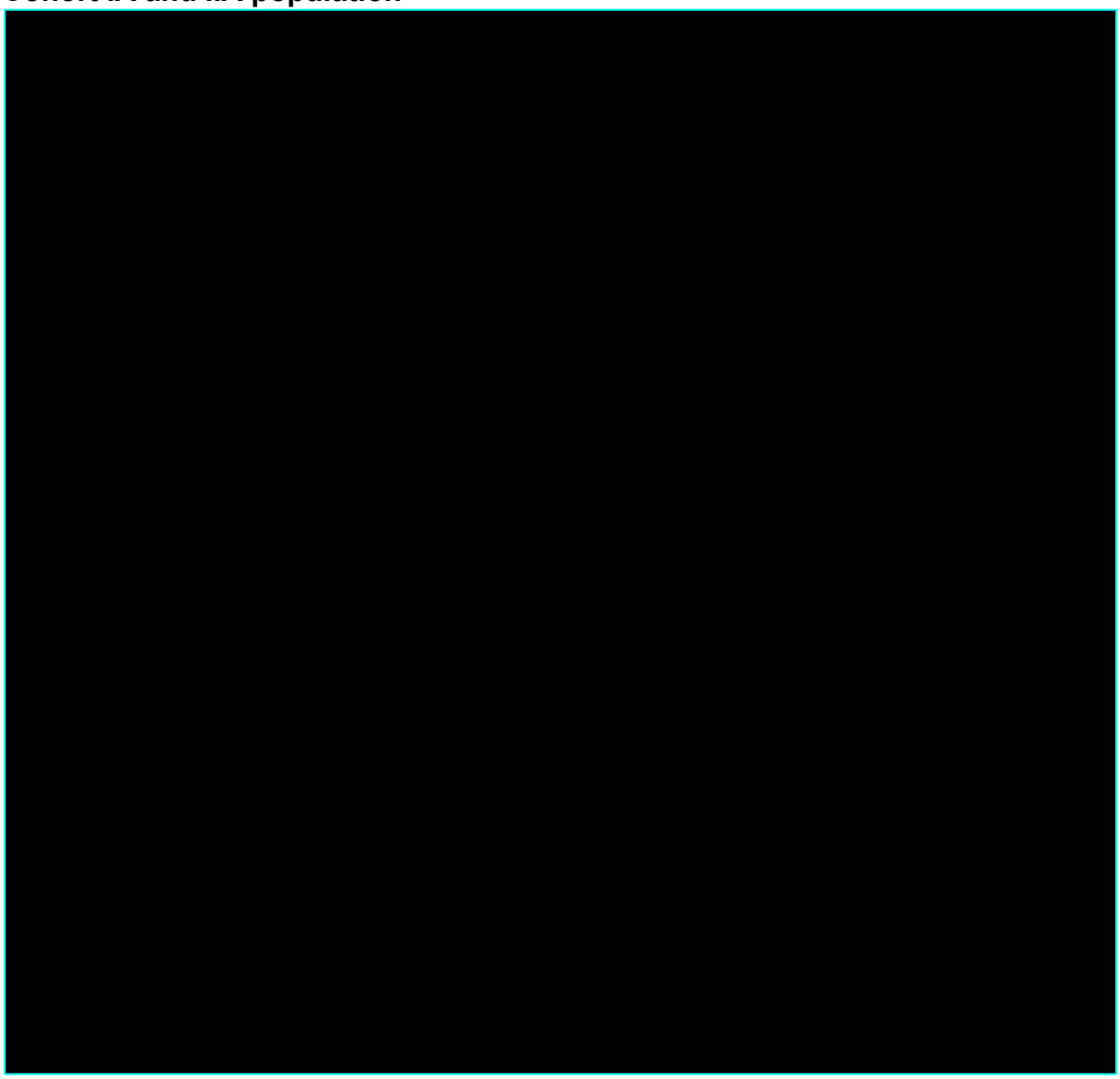
Treatment	Median OS	Naïve HR	Adjusted HR
Obe-cel (Overall)	[redacted]	-	-
Inotuzumab (Overall)	7.7 months	[redacted]	[redacted]
Blinatumomab (Ph-)	7.7 months	[redacted]	[redacted]
Ponatinib (Ph+)	8.0 months	[redacted]	[redacted]

*Statistically significant results.
; HR – Hazard ratio; OS – Overall survival; Ph – Philadelphia chromosome

Overall population

The estimated adjusted and naïve HR for the overall population were in favour of obe-cel compared to inotuzumab. While the naïve HR was statistically significant in favour of obe-cel, the adjusted HR was not significant. This trend is reflected in the KM plot (Figure 94), which illustrates notable overlap in the inotuzumab and adjusted obe-cel survival curves. Therefore, the comparative OS efficacy of obe-cel versus inotuzumab is less pronounced.

Figure 94: Obe-cel versus inotuzumab STC OS KM plot: Enrolled pooled Cohort IA and IIA population



KM – Kaplan-Meier; OS – Overall survival; STC – Simulated treatment comparison

Ph- population

The estimated adjusted and naïve HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, with only the adjusted estimate reaching statistical significance. This is reflected in the OS KM plot (Figure 95), which depicts overlap between the unadjusted obe-cel and blinatumomab survival curves. The separation between the adjusted obe-cel survival curve and blinatumomab illustrates the significantly improved outcomes with obe-cel.

Figure 95: Obe-cel versus blinatumomab STC OS KM plot: Enrolled pooled Cohort IA and IIA population

KM – Kaplan-Meier; OS – Overall survival; STC – Simulated treatment comparison

Ph+ population

For the Ph+ population, both the adjusted and naïve HRs favoured obe-cel over ponatinib, with statistically significant differences observed in both cases. However, the confidence intervals around the ponatinib comparison estimates are wide, reflecting a high degree of uncertainty in the OS results. This is visually apparent in the KM plot (Figure 96), where the large variability in the survival curves suggest instability in the estimates and the lack of overlap demonstrates the statistical significance.

Figure 96: Obe-cel versus ponatinib STC OS KM plot: Enrolled pooled Cohort IA and IIA population

KM – Kaplan-Meier; OS – Overall survival; STC – Simulated treatment comparison

2.3 Conclusions

Overall, the results of the ITCs are consistent with those observed in the previous data cut, reinforcing the robustness of the findings over time. Across both MAIC and STC methodologies, the direction and magnitude of treatment effect estimates were generally aligned, with obe-cel demonstrating a favourable profile relative to relevant comparators. While inherent limitations exist in the available evidence, the consistency in findings across approaches and data cuts supports the conclusion that obe-cel offers a clear clinical benefit.

3 References

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7. Cortes JE, Kim D-W, Pinilla-Ibarz J, *et al.* Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood* 2018. 132: 393–404.
8. Phillippo DM, Ades AE, Dias S, *et al. NICE DSU TECHNICAL SUPPORT DOCUMENT 18: METHODS FOR POPULATION-ADJUSTED INDIRECT*

COMPARISONS IN SUBMISSIONS TO NICE. 82. at

<http://www.nicedsu.org.uk>

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Anthony Nolan

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	*Committee recommendation: "Usual treatment for relapsed or refractory B-cell or B-cell precursor acute lymphoblastic leukaemia is ponatinib, inotuzumab ozogamicin, blinatumomab or tisagenlecleucel. This can be followed by an allogeneic stem cell transplant for some people. Obe-cel would be another treatment option."*

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	We believe the committee has over-simplified the treatment pathway and comparators in this recommendation, even though the full discussion has been reflected in the committee papers, as such we would like to reiterate: Tisagenlecleucel is only a comparator for people aged 25 years old and younger, and therefore is not a direct comparator for adults over 25 years old who could be treated with obecabtagene autoleucel (obe-cel). The comparator CAR-T for this indication in adults aged 26 years and older is brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over which is currently available through the Cancer Drugs Fund. However, we remain concerned that toxicity of this CAR-T is higher than that of obe-cel, and therefore obe-cel would be more suitable for patients who are older or less fit and therefore unable to tolerate brexucabtagene. In addition, it was made clear by clinical experts in the committee meeting that blinatumomab is used predominantly as a bridging therapy to either CAR-T or stem cell transplant, and not often used as a standalone therapy. Furthermore, clinical experts made clear that while an allogeneic stem cell transplant can be used as a last line therapy after a CAR-T, it is not often that this occurs in practice given the severity of treatments patients have often undertaken until this point and their diminishing fitness. Therefore, 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 allo-transplant donor.
2	*Committee recommendation: “There is no clinical trial evidence directly comparing obe-cel with any of the usual treatments.”* We believe it is understandable that there is limited or no clinical trial evidence directly comparing obe-cel with comparator treatments or CAR-T given most have only been available on the NHS for a limited time. Therefore, NICE and the company must come together to collect further data to support use through a managed access scheme before deciding to limit access altogether.
3	We believe that obe-cel should be recommended for use once the company has addressed any modelling issues as per the committee’s concerns, and if further data needs to be collected NICE and company should work together on a managed access agreement because there is clear need from patients for an additional CAR-T treatment that has shown to have a more favourable side-effect profile and increased persistence over time.
4	
5	
6	

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Leukaemia UK

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted] ([redacted] – Leukaemia UK)

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the current recommendation may not fully reflect the clinical reality faced by patients with acute lymphoblastic leukaemia (ALL). Of the approximately 1,173 people

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	diagnosed with ALL ech year in the UK, relapse rates – particularly in adults – remain high, at about 50%. These patients often endure significant physical emotional and physiological burden. For those aged 16-25, the impact is especially profoundly, with substantial disruption to education, employment and social development, we therefore believe Obe-cel could be an effective treatment for this group.
2	Most treatments for ALL are extremely toxic and require long periods of hospitalisation. The reduced toxicity of Obe-cel also allows clinicians to monitor patients out of hospital, i.e. in ambulatory care settings and reduces the use of intensive care.
3	People from ethnic minority backgrounds are significantly less likely to find a fully matched unrelated donor for an allogenic stem cell transplant (ASCT), which remains a necessary treatment option following chemotherapy, immunotherapy or even some CAR-T therapies. Obe-cel has demonstrated the potential to induce durable remissions without the need for subsequent Stem Cell Transplants (SCTs). This means that Obe-cel would bring a particularly meaningful advancement for patients from ethnic minority groups, offering a more accessible and potentially successful treatment pathway.
4	We are concerned that while CAR-T therapies are available - such as tisagenlecleucel (Kymriah) for patients under 25, and brexucabtagene autoleucel (Tecartus) for those aged 26 and over – there treatments often still require a subsequent stem cell transplant (SCT). SCT can carry severe side effects and involve prolonged recovery, which is particularly challenging for patients aged 16–25. For this age group, achieving durable remission with fewer long-term side effects is especially important to support their social, educational, and emotional development, this is why we think that Obe-cel could be a game-changing treatment for these patients.
5	We are concerned for older patients and patients with co-morbidities. There is an unmet need or treatments suitable for patients with comorbidities and reduced fitness. Since Kymriah was withdrawn from the Cancer Drugs Fund, options for adult B-cel ALL patients – especially older or less fit individuals – have significantly decreased. Clinicians are now less likely to offer CAR-T therapy to this group, the addition of another treatment such as Obe-cel could potentially change treatment decision for these patients.
6	Obe-cell has a record of less severe side effects, patients and carers feel that fewer severe side effects would greatly improve their quality of life.
7	We are concerned that treatment options for patients with co-morbidities have limited treatment options and Obe-cel represents a good treatment option for these groups.
8	We are concerned that the current inaccessibility of Obe-cel for patients aged 18 and over is limiting treatment options for this age group. Given that Obe-cel has marketing authorisation for individuals 18 and older, its availability would provide a much-needed additional option for adults with B-ALL, who currently have access to only one CAR-T therapy.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	University College London Hospitals

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	Dr Claire Roddie

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Re: Obe-cel for Relapsed/Refractory (r/r) B-cell Acute Lymphoblastic Leukaemia (B-ALL)	
1	I was very happy to participate in the Obe-cel NICE appraisal conducted in May 2025 as one of the clinical experts but was disappointed to learn of the committee's decision that current evidence does not support its clinical use in the UK. In my experience obe-cel is an extremely well-tolerated and highly effective treatment for adults with r/r B-ALL and this decision is a major blow to B-ALL patients and clinicians.
2	If cost-effectiveness is at the heart of the decision, I would like to re-iterate the point I made in the meeting that the comparator groups, namely stand-alone therapy with Inotuzumab/ Blinatumomab/ Ponatinib are an imperfect fit. When we give obe-cel as a stand-alone therapy, the intent is to achieve long-term remission without the requirement for consolidative allogeneic stem cell transplant (allo-SCT). In my experience, the comparator drugs listed can only deliver the same treatment goals i.e. long-term remission, when used as a bridge to allo-SCT in fit, transplant-naïve patients. My view is that allo-SCT should be an integral part of the Inotuzumab/ Blinatumomab/ Ponatinib cost modelling. Obviously in the case of post-allo-SCT relapse, all 3 comparator drugs are used with palliative intent to prolong life, but without prospect of long-term disease control which is a very different scenario to how we view and use obe-cel in the clinic.
3	In the US, where the FDA have approved obe-cel for adult B-ALL, clinicians are now routinely using this in preference to the other approved CD19 CAR-T product brexu-cel. The advantages of obe-cel over brexu-cel are stark. With Obe-cel, low rates of ≥Grade 3 CRS and ICANS means that ICU admissions are infrequent, and the burden of immune-modulating drugs required is low. This ultimately means that obe-cel can be safely used in older, co-morbid patients who would not be considered 'fit' enough for brexu-cel or allo-SCT. Critically, this singular feature supports equity of access to CAR-T in patients who would otherwise be denied this type of treatment.
4	The other major advantage of obe-cel for B-ALL is the prolonged CAR persistence (and resulting B-cell aplasia) observed in a substantial number of treated patients, which is significantly associated with durable remission without the requirement for allo-SCT. Even when we follow the data out to almost 3 years, 40% of infused patients maintain remission without allo-SCT[1]. This updated data was presented by Dr Jae Park at the EHA conference in June 2025.

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5	In assessing the intention-to-treat (ITT) analysis, I think it is important to recognise that the FELIX study was initiated before 2020 (running right through the COVID-19 pandemic) when our collective UK clinical experience of CAR-T for B-ALL was minimal. Clinical inexperience meant that patients received less intensive bridging therapy and anti-infection prophylaxis pre-CAR-T. We now know these factors can negatively impact the likelihood of making it to CAR-T infusion due to (a) symptomatic progressive disease from inadequate bridging, and (b) severe infection (often fungal) from inadequate prophylaxis, adversely impacting ITT. Our clinical approach in 2025 is very different to that of 2020 and is reflected in the UK real-world experience of brexu-cel for B-ALL, presented at ASH 2024[2]. Here, 94.4% of patients received bridging, of whom 53% received Inotuzumab which resulted in excellent disease control going into CAR-T. Good disease control prior to obe-cel has been shown in the FELIX study to have 2 major benefits, namely no ≥Grade 3 CRS/ICANS, and excellent event free survival (12-month EFS 65%). If obe-cel receives NICE committee approval, routine use of aggressive bridging therapy is now standard UK practice, and the attendant reduction in bone marrow disease burden pre-CAR-T would be beneficial for patients both medically (less toxicity, better outcomes) and from a QoL perspective. Further, low-burden disease pre-CAR-T has tangible benefits for healthcare providers by making obe-cel even more accessible to older patients with co-morbidities, by minimising the risks of toxicity/ICU and prolonged inpatient admission, with potential benefits in terms of healthcare-associated costs. This will also allow us to develop obe-cel for outpatient administration which would further reduce the financial toxicity of treatment.
6	The NICE committee also raised some questions regarding the use of IVIG on FELIX where around 20% of patients required IVIG post-CAR-T. Again, our clinical practice has evolved over the 2020-2025 period, and our current approach to IVIG is somewhat more stringent, reserving IVIG for those patients who fail antibiotic prophylaxis. We anticipate that this will reduce the patient numbers going on to IVIG in the future. Further, we now pro-actively interrupt IVIG ('IVIG holiday') and stop IVIG in stable patients with the goal of reducing hospital time for patients, of reducing overall costs and to preserve this precious resource.
7	In summary, obe-cel is an extremely well-tolerated and highly effective treatment which will transform outcomes for substantial numbers of UK B-ALL patients. It will replace brexu-cel forthwith and will no doubt replace allo-SCT in due course. UK patients and clinicians are desperate to be able to use it and would welcome a positive outcome from this NICE committee review.
8	Please do not hesitate to contact myself and my clinical CAR-T colleagues at UCLH Dr O'Reilly, Dr Northend and Dr Maciocia for any further information. Dr Claire Roddie

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	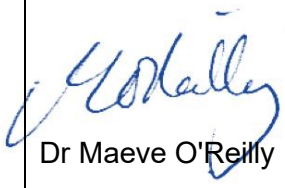 Dr Maeve O'Reilly  Dr Michael Northend  Dr Paul Maciocia
9	**References:** 1. https://library.ehaweb.org/eha/2025/eha2025-congress/4159190/jae.h.park.can.car.t-cell.therapy.be.a.definitive.treatment.for.adult.r.r.html?f=menu%3D6%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Ace_id%3D2882%2Aot_id%3D31558%2Amarker%3D5843%2Afeatured%3D19595 2. https://ashpublications.org/blood/article/144/Supplement%201/2823/532359/A-UK-Intention-to-Treat-Analysis-of-Brexucabtagene

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	Dr Michelle Lannon

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Example 1	We are concerned that this recommendation may imply that ……..
1	With regards to the comments about age and ECOG PS being representative of the UK population. The patient population to be considered must hold a god performace status in order to undergo an intensive procedure such as CAR-T cell therapy and this is not unique to this product.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 4 July 2025. Please submit via NICE Docs.

	At the ALL panel it would be seen as essentail that patients meet this criteria, not because it is mandated by the CDF but because it is only clinically approriate to proceed. As for smaller number of patients over the age of 65, this may not be representative of the UK population but only few patients are fit enough I undergo CAR-T cell therapy in this age group (25% of the UK RWD for Brexucel were over the age of 60)
2	Equality issues related to travel for thearpy need to be clarified as patients have to travel even if being treated in their own regional centre. In order for safe monitoring post CAR-T therapy then an arrangement needs to be made for patients to be within a reasonable travel distance until D28 post CAR-T due to the potnetial risk of toxicity of interest.
3	Slide 8 of the publicly available slides – this shows the EAG updated pathway of treatment. It implies that a patient who has achieved a CR/Cri after treatment with Ponatinib would receive either Obe-cel of an Allo SCT. Obe-cel should not be seen as a consolidative therapy for an established remission in the same way that Allo SCT might be used.
4	As an ALL treating clinician, I would not intend on using Obe-cel as a bridge to Allo SCT as persistence is important for the efiicacy of this CAR product and Allo SCT may wipe out the CAR. It also may not be necessary and so this should not be planned as part of the treatment. The numbers of patients who have not already had an Allo SCT are likely to be small.
5	There are a number of RWD sets which show that Philadelpia Positive B-ALL patients seem to benefitting from CAR-T and may even have superior outcomes to those who fall into other genetic risk categories. This may in some way be related to TKI consolidation post-CAR-T therapy and so this may need to be factored in.
6	There remains an error on slide 7 of the publically available slides – it states 'Following therapy with TKI' on the philadelphia negtve side of the flow chart and this should be removed.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are' not endorsed by NICE, its officers or advisory committees.

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	Cell and Gene Therapy Catapult
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Given that the company has addressed the key clinical uncertainties regarding the comparative benefit of obe-cel versus the relevant comparators, we believe that some of the uncertainties would be better addressed under a managed access agreement through the Cancer Drugs Fund (CDF) as done for brexu-cel, if agreed with company, specifically:

- Whether obe-cel can be delivered in the outpatient setting, so that when it gets reevaluated the cost effectiveness calculation is revisited accordingly and pricing for routine commissioning is established on the basis of whether it can be delivered in the outpatient setting or not
- Whether it is reasonable, under the cure assumption, to apply the same standardised mortality ratio to patients who have experienced events as to those who have not, once they are considered cured; and
- Clinical and cost-effectiveness estimates uncertainty resolution by comparing real-world data (RWD) along with trial data of obe-cel with NHS England RWD for tisagenlecleucel.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

There are issues with the CAR-T tariff cost in general which require assessment for current and future CAR-T assessments. With increasing experience of CAR-T delivery centres over time, staff training needs are expected to plateau, and monitoring processes will likely become more efficient, making off-the shelf tariff uplifts inappropriate. Additionally, the cost of managing treatment-related events is evolving, with newer CAR-T therapies like obe-cel showing fewer high-cost adverse events, reducing the burden on NHS resources (for further details, see response titled ‘uncaptured benefits’).

To address these concerns, there is need for greater visibility of how the new tariff was established due to its impact on cost-effectiveness discussions. The approach could be strengthened through a more up-to-date costing analysis, capturing the actual hospital costs incurred. There is the risk that no change may disincentivise the development of innovative

CAR-Ts that could reduce the costs to NHS England currently captured within the existing tariff.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No comments

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No comments

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

yes - absolutely

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

Absolutely - there is also some urgency behind this as its by far a more superior product than currently available

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

it should be available to all patients over the age of 18 years - no upper age limit please

Comments on the draft guidance

Through the Felix study I have gained a lot of experience with Obe-cel. It is a much safer product than those available otherwise. Compared to Tecartus

it is miles superior in terms of safety (and long-term efficacy) and even has a lower neurotoxicity rate than Kymriah. For me it is clear that this next generation CAR construct covers an unmet need that for sure Tecartus cannot cover - elderly and more frail / comorbid patients but overall its also more efficacious. There will be many patients who can benefit from this treatment

Title: *Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID6347]: EAG Response to Comments Received following Draft Guidance after AC1*

Produced by	*Birmingham Centre for Evidence and Implementation Science*
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MOR: Has attended educational events sponsored by Novartis and Autolus in the past 12 months, and was a sub-investigator and co-author of the ALLCAR19 clinical trial.

No other conflicts of interest have been declared by authors or contributors.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Please note that: Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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1 Introduction

The company's submission was divided into four documents, which the EAG responds to in turn. The first is the company's draft guidance comments document which contains responses to 12 issues raised by the company. The second document is an overview of the updated follow-up from the FELIX trial, whilst the third utilities this follow-up in survival analyses and indirect comparisons. The final document contains results from the company's updated cost-effectiveness analyses.

The EAG goes through these documents in turn, summarising and critiquing the company's submissions. The EAG also reviewed the comments received from other stakeholders, but did not identify any new evidence to inform this appraisal.

2 Summary and Critique of company comments on draft guidance.

The company's response document was structured into 12 issues, which the EAG now goes through.

2.1 *Issue 1 – Comparison against tisagenlecleucel*

During the EAG appraisal of the initial company submission, it was anticipated that the license for obe-cel would be for adults aged 25 and over. However, the license was granted for adults aged 18 and over. This extension meant for people aged 18-25 tisagenlecleucel (tisa-cel) was a potential comparator, which the company accept. The company states that only [redacted] people from the FELIX trial cohorts IA and IIA fall within this age range, and with minimal information from tisa-cel studies available specific to this age group. Furthermore, the reporting of key prognostic and effect-modifying characteristics from studies of tisa-cel are poorly reported.

The company perform an unanchored MAIC analysis, weighting data for the 18-25 subgroup from cohort IIA to the population reported by Stackelberg et al.[1] This study combined the populations of several tisa-cel studies, including a combination of trial and real-world populations. This comparison compares infused populations of both technologies. The company do not justify using only the IIA cohort, but they say that the small difference in the starting sample is unlikely to impact the analysis. The Kaplan-Meier plots from the company's MAIC analyses suggest that even a small

change to the population could be influential on the subsequent inferences. Hence, the EAG does not agree with this statement and recommends the analysis be reproduced using cohorts IA and IIA. The covariates included were sex, lines of previous therapy, prior SCT and BM blasts (<50%), however the covariates remain imperfectly balanced after the weights are applied (Company Document Table 2) meaning the analysis is at risk of bias. The resulting hazard ratio for overall survival was [redacted], which the EAG notes is larger than the effect size between inotuzumab and obe-cel raising concerns over the reliability. The effective sample size was small (n=[redacted]) for the obe-cel population after weighting, suggesting the results have considerable uncertainty associated with them. Were additional covariates available to be included in the weighting (such as age, ECOG, Philadelphia chromosome status and duration of first remission), these would likely have further increased uncertainty.

The company also compare FELIX obe-cel data with SACT data for tisa-cel provided by NHS England. Upon review, the EAG note the company have truncated the follow-up, appearing to censor participants at 35 months. The notes the SACT dataset shows a plateau out to 78 months (Figure 1), however the number of people at risk is small.

[redacted]

Figure 1: Kaplan Meier plot for overall survival of tisa-cel SACT population (taken from NHS England Report)

In their visual comparison of overall survival of obe-cel to the SACT tisa-cel population, the company uses the obe-cel population as weighted for the comparison to the Stackelberg et al. study.[1] The company prefer this to a naïve comparison stating the characteristics (age, gender) are more similar. The EAG is unclear why a separate MAIC could not be performed using characteristics specific to the SACT population.

Through comparing the figures presented by the company, a naïve comparison to the SACT follow-up would suggest that obe-cel is more likely to offer [redacted] overall survival than tisa-cel, however this is highly uncertain. This [redacted] when it is noted that this is a comparison of trial data for obe-cel to real-world data for tisa-cel, however any difference may be attributable to differences in baseline characteristics rather than treatment efficacy. The EAG understands it is not permitted to receive more than one CAR T therapy through NHS care. The EAG's clinical expert indicated a preference for obe-cel, given its perceived better CAR T persistence and reduced probability of requiring further therapy.

The EAG concludes that a reliable comparison between obe-cel and tisa-cel is unlikely to be possible based on currently reported data. However, the EAG has not had time to undertake a systematic search for additional literature.

The committee could choose to restrict access to obe-cel to people aged 25 and over if they are concerned about the cost-effectiveness versus tisa-cel. The EAG presents a limited comparison of the cost-effectiveness of the technologies in the cPAS appendix.

2.2 *Issue 2 – Clarification on how the model accounts for ponatinib and inotuzumab being used as bridging therapies to CAR-T therapy*

The EAG appreciates the company's clarification on how ponatinib and inotuzumab bridging therapy costs and effects are incorporated into the model using weighted averages from FELIX data. The EAG acknowledges that the model captures the

influence of these therapies on CAR T-cell outcomes by incorporating efficacy data from FELIX, reflecting improved disease control prior to infusion.

However, we note a potential issue with the formula using *i_FELIX_pop_name_param* (in the worksheet 'Treatment Costs', cells E203:E211), which currently only tests if the value is true rather than explicitly distinguishing between Infused Cohort IIA (code 1) and the pooled Cohort IA + IIA (code 2). This may cause the model to return a fixed value irrespective of cohort and should be corrected to ensure accurate cohort-specific results.

The next concern relates to the correction factor applied to bridging treatment costs (worksheet 'Treatment Costs', cell K218). The company estimated these costs using a frequency derived from the percentage of enrolled patients who received bridging treatment (worksheet 'Treatment Costs', cells E203:E211). However, applying this frequency alongside a correction factor of less than 1 results in a double-counting of the impact of using the ITT population in the cost calculations. The EAG considers a correction factor of 1 to be the most appropriate value to avoid this duplication.

2.3 *Issue 3 – Conservative clinical efficacy modelling approach*

In Issue 3, the company indicates that the infused population may better reflect current UK clinical practice, suggesting that reliance on the enrolled population could potentially lead to an underestimation of obe-cel's efficacy. The company originally opted to exclude [redacted] patients ([redacted]%) from cohorts IA and IIA who underwent leukapheresis but did not proceed to infusion.

The reasons for this potential underestimation are that current practice has increased use of bridging therapies, improved patient selection and faster manufacturing time compared to when the FELIX trial was conducted.

However, the company has not provided strong supporting data or references to support these statements. Consequently, the assumption that real-world infusion failure rates would be lower than those observed in FELIX may be somewhat optimistic and lacks clear evidentiary support. As is often the case when comparing clinical trials to real-world datasets, the FELIX trial was conducted under controlled

conditions and idealised procedures, which are generally associated with lower attrition rates than those typically observed in routine NHS practice.

In contrast, consistent with the committee's position, the EAG has expressed reservations about excluding non-infused patients, cautioning that such an approach may inadvertently underestimate real-world attrition and introduce selection bias. Within standard NHS care, patients would generally receive conventional treatments without the delays and risks associated with CAR T pre-infusion procedures. In the absence of robust data to validate the company's assumptions, the EAG considers the enrolled (leukapheresed) ITT population of 133 patients from cohorts IA and IIA to offer a more realistic reflection of clinical practice. This perspective aligns with the Committee's preference and provides a more comprehensive view of the patient journey, including those who do not advance to infusion.

2.4 *Issue 4 – Updated MAIC analyses*

This comment contains information the updated MAIC analyses, new STC analyses and the impact on the cost-effectiveness, which the EAG will critique in more detail using the separate documents submitted by the company, in sections 4 and 5 of this report.

2.5 *Issue 5 – Further evidence using the inverse hazard ratio for the comparison against inotuzumab and blinatumomab.*

The company have maintained their use of applying hazard ratios resulting from the MAIC to obtain ICERs which allow a fully-incremental analysis of obe-cel, inotuzumab and blinatumomab for the Ph- subgroup. The company have not implemented analyses which fit parametric models to MAIC weighted data, and to the follow-up from the respective studies of inotuzumab and blinatumomab, which would relax the assumption of proportional hazards which the company acknowledged is violated in the original submission but would not permit 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 in section 3.12 of the draft guidance.

The EAG is unable to explore alternative approaches and maintains the assumption of hazard proportionality in the comparisons to inotuzumab and blinatumomab.

2.6 *Issue 6 – Further clarification on the cure assumption and SMR applied to patients in the post-event health state*

In the original model, the company assume that all people remaining alive at 3 years revert to a mortality rate that is based on the general population, using a standardised mortality ratio of 3.0. This includes people who are alive in the post-event health state. The company state that this is supported by the plateau that emerges in the OS survival curve, more evident in their extended follow-up. The EAG considers that this point 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 has been provided to the EAG beyond this sentence to add supporting detail. Hence the EAG maintains the 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.

2.7 *Issue 7 – Using the most recent CAR T tariff*

The company consider that the application of the most recent CAR T tariff cost of £60,462 fails to capture the benefits associated with obe-cel over other CAR T therapies. The company have however used this tariff cost in their base-case analysis.

In summary, the company state that the tariff is generated from the use of older CAR T therapies with inferior safety profiles, that obe-cel is associated with delivery efficiencies, and better quality of life. The company also states there is a precedent for deviating from the tariff value, where they report that in TA975 the committee used a weighted tariff of £95,194 to reflect the higher costs associated with CAR T for children. The EAG notes that this was a deviation to a higher value, rather than lower as preferred by the company in this instance. The EAG maintains the use of the most recent CAR T tariff value its base case.

2.8 *Issue 8 – Appropriate costs associated with ASCT in the obe-cel arm*

The EAG has reviewed the company's submission on allo-SCT costs and proportions in the obe-cel arm. The company originally used a [redacted]% proportion of patients receiving allo-SCT post-CAR T treatment, while the EAG's base case, based on the intention-to-treat (ITT) population, used [redacted]%. Following Appraisal Committee (AC) discussions, the EAG accepts the company's [redacted]% proportion for the base case and supports scenario analyses with lower proportions (5% and 2.5%), as proposed by the company, to reflect the committee's view that fewer than [redacted]% of patients are likely to require allo-SCT post-obe-cel due to CAR T-cell loss without relapse.

Regarding costs, the company's base case uses the original allo-SCT costs (£115,591 for SCT, £34,347 for 0-6 months follow-up, £23,594 for 6-12 months follow-up). The EAG agrees with this approach but acknowledges the company's scenario analyses incorporating the Ernst & Young (EY) 2021 report costs (£82,197 for SCT, £88,808 for 0-6 months, £35,963 for 6-12 months), which reflect higher follow-up costs and may better represent current NHS resource use. The EAG recommends further validation of EY costs against NHS data.

2.9 *Issue 9 – Mortality captured in the SCT tunnel states*

The company appear to accept the EAG's implementation of utilising the entry point of the tunnel states to estimate the costs, but note that mortality across each period is not accounted for. The EAG accept this limitation, however consider that the impact will be minimal, and welcomes the company's acceptance of the EAG's modelling approach.

2.10 *Issue 10 – Intravenous immunoglobulin use captured in the economic model*

The EAG acknowledges the company's efforts to update the economic model to incorporate IVIG use. However, the EAG maintains several concerns regarding the modelling approach and the parameter values applied.

1. Modelling of IVIG costs: The EAG notes a structural issue within the model that results in an underestimation of IVIG costs. Specifically, the undiscounted IVIG cost output from the model should align with the total IVIG cost calculated using the company's input parameters (e.g., proportion of patients receiving IVIG, dose, frequency, weight, and unit cost). However, as shown below, the model output (£[redacted]) is notably lower than the calculated total one-off IVIG cost (£[redacted]), representing a [redacted]% underestimation. (see Table 1)

Table 1: Comparison of calculated IVIG cost vs. modelled undiscounted IVIG cost (cohort IA+IIA)

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

IVIG: Intravenous Immunoglobulin; mg: Milligram; g/kg: Grams per Kilogram; kg: Kilogram; mITT: Modified Intent-to-Treat; EAG: External Assessment Group; SCT: Stem Cell Transplant;

2. Proportion of patients receiving IVIG

The EAG also questions the assumed proportion of patients treated with IVIG. The company currently applies [redacted]%, which may reflect the proportion with hypogammaglobulinaemia, but likely underestimates the proportion requiring IVIG therapy in clinical practice.

In TA677, the company reported that 32% of patients received IVIG. In response to EAG clarification (question A14), the company stated that as of the February 2024 data cut-off, [redacted]% of patients had received IVIG. These figures are at odds with the

information supplied by the company in their submission following AC1 which suggest that the appropriate usage is [redacted]% for the cohorts IA and IIA, or [redacted]% for UK participants. Without greater clarity, the EAG uses [redacted]% in its base case.

3. IVIG dose and treatment duration

With respect to dose and treatment duration, the clinical commissioning policy for therapeutic immunoglobulin use in England (2025)[2] recommends initiating treatment at 0.4–0.6 g/kg per month for a period of 6 to 12 months. In TA677, the company used a dose of 0.5 g/kg and a duration of 12 months.

The EAG accepts the use of 0.4 g/kg as clinically reasonable, based on input from its clinical adviser. However, the assumed frequency of [redacted] days (based on the company's model, the assumed IVIG treatment duration is [redacted] months) appears underestimated. The company then re-applied their calculated costs of IVIG every 6 months, reducing the proportion receiving IVIG by 5% at months 6, 12 and 18, followed by a 2% reduction each additional 6 months. The EAG considers the company's approach confusing and likely underestimating real-world IVIG use.

The EAG's clinical expert reiterated that the majority of people will remain on IVIG for over 12 months. To reflect clinical practice more accurately and transparently, the EAG prefers to model IVIG administration over a 12-month duration applied in the first model cycle.

4. Mean weight

The EAG agrees with the use of the mean weight from the mITT population, as applied by the company, as IVIG use before infusion is uncommon.

2.11 *Issue 11 – Using a 1.2 severity modifier for all populations*

The company consider that the committee's preference for a 1.2 severity modifier does not capture the severity of the disease. The company states that the comparison to blinatumomab (which, under company assumptions, was the only analysis which supported using a 1.2 modifier) was considered the most robust. Whilst the statement may be true for a naïve comparison, the EAG is unclear why it

might hold for the MAIC analyses when weights are applied. The company states that TA893 in this area met the previously used end-of-life criteria; however, it has used the 1.2 modifier in its base-case analyses and present scenario analyses using the 1.7 modifier.

2.12 *Issue 12 – Benefits not captured in the QALY*

The company emphasises again the uncaptured benefits associated with obe-cel, stating it shares characteristics with liso-cel where these benefits were reportedly taken into consideration by the committee in TA1048. The company acknowledges these points were raised in Issue 7, and so the EAG provides no further comment.

3 Review of updated clinical follow-up

3.1 *Primary and secondary endpoints*

In the original submission, the company selectively reported outcomes based on data cut-offs from June 2023 and February 2024. The EAG focused on the most recent data cut-off available at the time—February 2024—and, where applicable, used and reported results from the Clinical Study Report (CSR) corresponding to this cut-off, which had a median follow-up of 20.2 months ([redacted]months). In response to the EAG clarification query A1, the company reported results for the cohorts IA+IIA enrolled population (leukapheresed).

In the updated submission, the company used the latest data cut-off from January 2025, which includes a median follow-up of [redacted] months ([redacted] months).

A comparison of the enrolled and infused populations in cohorts IA and IIA, based on the updated documents, has been provided. Overall, the outcomes are very similar to the previous data-cut.

Table 2: Overview of FELIX cohort IA and IIA combination for enrolled and infused patients

	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]
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]

Figure 2 and Figure 3 show the updated follow-up from FELIX for EFS and OS respectively, using the enrolled population. The Kaplan-Meier functions demonstrate that the new follow-up is very similar to the previous data-cut. The exact timing of when to apply a cure assumption remains uncertain, given the possibility of late occurring events as observed in FELIX.

Figure 2. Event-free survival for the enrolled population of FELIX

Figure 3: Overall survival for the enrolled population of FELIX

3.2 *Safety*

An updated table of treatment-emergent adverse events (TEAEs) reporting on the last data cuts has been provided. The table shows that a small number of TEAEs since the previous data-cut, the management of which may not be included in the CAR T tariff. The impact of these has not been captured in the model, however their impact is expected to be small.

Table 3: Number of patients infused in all cohorts (phase Ib/II) experienced TEAEs associated with significant safety topics*

Parameter	All Grades (N=127) n (%)		Grade ≥ 3 (N=127) n (%)	
Data cut-off	**February 2024**	**January 2025**	**February 2024**	**January 2025**
Severe infections	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine release syndrome (CRS)	87 (68.5)	[redacted]	3 (2.4)	[redacted]
Immune effector cell-associated neurotoxicity syndrome (ICANS)	29 (22.8)	[redacted]	9 (7.1)	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]	[redacted]	[redacted]
Graft versus host disease (GvHD)**	[redacted]	[redacted]	[redacted]	[redacted]
Secondary malignancies	[redacted]	[redacted]	[redacted]	[redacted]
Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)	[redacted]	[redacted]	[redacted]	[redacted]
Tumour lysis syndrome (TLS)	[redacted]	[redacted]	[redacted]	[redacted]

*The number of patients who experienced an event is reported. If a patient experienced multiple events, they are counted only once in the report; **Aggravation of GvHD, irrespective of prior history of an allogeneic SCT or receipt of an allogeneic SCT after obe-cel infusion; ***The company reports that none were considered related to obe-cel (CSR doc, page 26)

4 Review of updated survival analysis and indirect treatment comparison

For each of the three comparisons, the company updated the indirect treatment comparisons, and the survival extrapolations, performing analyses for both the infused and the enrolled populations of cohorts IA and IIA of FELIX, where no censoring was applied by subsequent alloSCT. The EAG summarises the impact of these changes for each comparison. Overall the updated datacut has minimal impact on the hazard ratios which are applied in the economic model. The EAG has no issue using revised hazard ratios. There are occasional minor differences between the MAIC and STC estimates, however the differences are not of concern to the EAG.

4.1 *Comparison of obe-cel to inotuzumab (whole population)*

This comparison utilised the full population of FELIX (n=133).

4.1.1 Indirect Treatment Comparison

Below are the outputs from the indirect comparison against inotuzumab, including the hazard ratios used to obtain EFS and OS extrapolations from the models fitted to obe-cel data from FELIX.

Table 4: Comparison of outcomes from indirect comparison to inotuzumab: Infused population

	Original Company MAIC	MAIC using updated data-cut	STC using updated data-cut
EFS Hazard Ratio	[redacted]	[redacted]	[redacted]
OS Hazard Ratio	[redacted]	[redacted]	[redacted]
CR/CRi	[redacted]	[redacted]	[redacted]

CR: complete remission; CRi: complete remission with incomplete response; EFS: event-free survival; MAIC: matching adjusted indirect comparison; OS: overall survival; STC: simulated treatment comparison

Table 5: Comparison of outcomes from indirect comparison to inotuzumab: Enrolled population

	Original Company MAIC	MAIC using updated data-cut	STC using updated data-cut
EFS Hazard Ratio	[redacted]	[redacted]	[redacted]
OS Hazard Ratio	[redacted]	[redacted]	[redacted]
CR/CRi	[redacted]	[redacted]	[redacted]

CR: complete remission; CRi: complete remission with incomplete response; EFS: event-free survival; MAIC: matching adjusted indirect comparison; OS: overall survival; STC: simulated treatment comparison

4.1.2 EFS extrapolation

For this comparison, parametric and spline survival models were fitted to the data for the whole population of FELIX. The company fitted models to both the infused and enrolled populations, but the EAG focuses their critique on the enrolled population.

The EAG presents the goodness of fit statistics and the three year survival predictions for each candidate model. It is unclear why BIC were not reported for the spline models.

The company's preferred model is the 2-knot normal, which predicts 3 year EFS to be [redacted]%. This is lower than the EAG's previously preferred model ([redacted]%) however a decrease is consistent with the extended follow-up. The goodness-of-fit statistics and visual fit indicate almost all models struggle with the unusual shape of the KM plot. The consider the company's preferred model to be too pessimistic, and opt for the 1 knot normal, as this prediction is closest to the company and EAG preferred extrapolation for OS, and hence has a much smaller post-event population subject to a cure assumption.

Table 6: Summary of EFS model characteristics for whole FELIX population.

Distributions	AIC	BIC	3 year survival prediction
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]
1-knot normal**	[redacted]	[redacted]	[redacted]
2-knot normal*	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]

*indicates company preferred model. ** indicates EAG preference

4.1.3 OS extrapolation

The company preferred extrapolation is the Weibull model which has the lowest OS prediction at 3 years ([redacted]%) of all candidate models. This is lower than the EAG's previously preferred model ([redacted]%), however it is more consistent with the new follow-up from FELIX. The EAG does not object to the choice of the Weibull model, and uses it in the EAG base case.

Table 7: Summary of OS model characteristics for whole FELIX population.

Distributions	AIC	BIC	3 year survival prediction
Exponential	[redacted]	[redacted]	[redacted]
Weibull*	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]

*indicates company preferred model.

4.2 *Comparison of obe-cel to blinatumomab (Ph- population)*

This comparison utilised the Ph- population of FELIX (n=103).

4.2.1 Indirect Treatment Comparison

Below the EAG presents the output from the indirect comparison, including the hazard ratios used by the company to obtain an extrapolation for blinatumomab from the models fitted to obe-cel data. Both company and EAG use hazard ratios coming from the enrolled population of FELIX.

Table 8: Comparison of outcomes from indirect comparison to blinatumomab: Infused population

	Original Company MAIC	MAIC using updated data-cut	STC using updated data-cut
EFS Hazard Ratio	[redacted]	[redacted]	[redacted]
OS Hazard Ratio	[redacted]	[redacted]	[redacted]
CR Odds Ratio	[redacted]	[redacted]	[redacted]
CRi Odds Ratio	[redacted]	[redacted]	[redacted]

CR: complete remission; CRi: complete remission with incomplete response; EFS: event-free survival; MAIC: matching adjusted indirect comparison; OS: overall survival; STC: simulated treatment comparison

Table 9: Comparison of outcomes from indirect comparison to blinatumomab: Enrolled population

	Original Company MAIC	MAIC using updated data-cut	STC using updated data-cut
EFS Hazard Ratio	[redacted]	[redacted]	[redacted]
OS Hazard Ratio	[redacted]	[redacted]	[redacted]
CR Odds Ratio	[redacted]	[redacted]	[redacted]
CRi Ratio	[redacted]	[redacted]	[redacted]

CR: complete remission; CRi: complete remission with incomplete response; EFS: event-free survival; MAIC: matching adjusted indirect comparison; OS: overall survival; STC: simulated treatment comparison

4.2.2 EFS extrapolation

For this comparison, parametric and spline survival models were fitted to the data for the Ph- population of FELIX. The company fitted models to both the infused and enrolled populations, but the EAG focuses their critique on the enrolled population.

The company preferred model is the log-normal which has the highest prediction for EFS at 3 years ([redacted]%). This is higher than the rate from the EAG's previously preferred model ([redacted]%), however a higher rate is supported by the extended follow-up, and reduces the size of the post-event but alive population.

The EAG notes that the company appear to have truncated the Ph- Kaplan-Meier plot to remove a final event. A late event can be seen on the whole population plot (Figure 49 and 50 of Company Survival Document), but this is not present in either Figure 51 or 52, which are stopped just before it. The EAG prefers to use the 3 knot-normal model as this has the lowest AIC, and has a 3 year prediction slightly below the KM plateau, consistent with the potential for small chance of a late EFS event as observed in FELIX.

Table 10: Summary of EFS model characteristics for Ph- FELIX population.

Distributions	AIC	BIC	3 year survival prediction
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal*	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]

2-knot hazards	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]
3-knot normal**	[redacted]	[redacted]	[redacted]

*indicates company preferred model. **indicates EAG preferred model.

4.2.3 OS extrapolation

For overall survival, the company preferred to use the generalise gamma model. This was model was the joint highest predicting model for 3 year survival ([redacted]%). This prediction is higher than the EAG's previously preferred model ([redacted]%), however the extended follow-up supports a higher rate. Again the KM plots presented by the company appear to be truncated before a final event is observed. Hence the EAG preference is to use the 0-knot normal which has the joint lowest AIC and predicts a slightly lower 3 year overall survival ([redacted]%), consistent with a small risk of late events as observed in FELIX.

Table 11: Summary of OS model characteristics for whole Ph- population.

Distributions	AIC	BIC	3 year survival prediction
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Generalised Gamma*	[redacted]	[redacted]	[redacted]
0-knot hazards	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]

0-knot odds	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]
0-knot normal**	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]

*indicates company preferred model.

4.3 *Comparison of obe-cel to ponatinib (Ph+ population)*

This comparison utilised the Ph+ population of FELIX (n=30). Note, these indirect comparisons were not used in the base case, due to the small effective sample size of the MAIC. A naïve comparison was used instead.

4.3.1 Indirect Treatment Comparison

Table 12: Comparison of outcomes from indirect comparison to ponatinib: Infused population

	Original Company MAIC	MAIC using updated data-cut	STC using updated data-cut
EFS Hazard Ratio	[redacted]	[redacted]	[redacted]
OS Hazard Ratio	[redacted]	[redacted]	[redacted]
CR Odds Ratio	[redacted]	[redacted]	[redacted]

CR: complete remission; CRi: complete remission with incomplete response; EFS: event-free survival; MAIC: matching adjusted indirect comparison; OS: overall survival; STC: simulated treatment comparison

Table 13: Comparison of outcomes from indirect comparison to ponatinib: Enrolled population

	Original Company MAIC	MAIC using updated data-cut	STC using updated data-cut
EFS Hazard Ratio	[redacted]	[redacted]	[redacted]
OS Hazard Ratio	[redacted]	[redacted]	[redacted]
CR Odds Ratio	[redacted]	[redacted]	[redacted]

CR: complete remission; CRi: complete remission with incomplete response; EFS: event-free survival; MAIC: matching adjusted indirect comparison; OS: overall survival; STC: simulated treatment comparison

4.3.2 EFS extrapolation

For this comparison, parametric and spline survival models were fitted to the data for the Ph+ population of FELIX. The company fitted models to both the infused and enrolled populations, but the EAG focuses their critique on the enrolled population.

The company's preferred model is the 3-knot normal, which has a 3-year survival rate of [redacted]%. This is one of the highest predictions made by the candidate models, and is relatively close to the company's preferred OS survival rate ([redacted]%). This is higher that the EAG's previously preferred extrapolation ([redacted]%), however it appears consistent with the follow-up from FELIX, and the EAG are content with its choice. Most spline models are reasonable fits relative to the company's preferred model, and the EAG explore the impact of using the 2-knot normal model in a scenario.

Table 14: Summary of EFS model characteristics for Ph+ FELIX population.

Distributions	**AIC**	**BIC**	**3 year survival prediction**
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]

0-knot hazards	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]
3-knot normal*	[redacted]	[redacted]	[redacted]

*indicates company preferred model.

4.3.3 OS extrapolation

The company's preferred choice of model is the exponential. It has one of the highest predictions of 3 year survival ([redacted]%), and among the lowest AIC.

This model's prediction is similar to the prediction from the EAG's previously preferred model ([redacted]%) and so the EAG maintain its use in the EAG base-case. The EAG explore the impact of using the 0-knot normal which has the lowest AIC and predicts 3 year survival to be [redacted]%.

Table 15: Summary of OS model characteristics for Ph+ FELIX population.

Distributions	AIC	BIC	3 year survival prediction
Exponential*	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]

0-knot hazards	[redacted]	[redacted]	[redacted]
1-knot hazards	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]
3-knot hazards	[redacted]	[redacted]	[redacted]
0-knot odds	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]
0-knot normal	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]

*indicates company preferred model.

5 Overview of the company's base-case and EAG's approaches (changes) in the base case after AC1

5.1 *Deterministic sensitivity analyses results*

Total costs, life years gained (LYG), quality-adjusted life years (QALYs), incremental results and the incremental cost-effectiveness ratio (ICER) for obe-cel versus comparators in the overall population, Ph- population, and Ph+ population are presented in Table 16, Table 17, and Table 18, respectively.

In the overall population (Table 16), when the PAS discount is applied, obe-cel is associated with an additional cost of [redacted] versus inotuzumab, resulting in an ICER of [redacted] per QALY gained.

In the Ph- population (Table 17), obe-cel (when the PAS discount is applied) is associated with additional costs of [redacted] versus inotuzumab, resulting in an ICER

of [redacted] per QALY gained. Obe-cel compared to blinatumomab, leads to additional costs of [redacted], resulting in an ICER of [redacted] per QALY gained.

In the Ph+ population (Table 17), when the PAS discount is applied, obe-cel is associated with an additional cost of [redacted] versus inotuzumab, resulting in [redacted]. Obe-cel compared to ponatinib, leads to additional costs of [redacted] versus ponatinib, resulting in an ICER of [redacted] per QALY gained.

Table 16: Deterministic results, overall population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life year

Table 17: Deterministic results, Ph- population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (obe-cel versus comparator)	ICER incremental
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; Ph – Philadelphia chromosome; QALYs – quality-adjusted life years

Table 18: Deterministic results, Ph+ population – PAS price

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (obe-cel versus comparator)**	**ICER incremental**
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; Ph – Philadelphia chromosome; QALYs – quality-adjusted life years

5.2 *Scenario analyses*

Table 19: Scenario analyses included in the model

#	Category	Base-case	Scenario	
		Value	**Value**	**Rationale**
1	Annual discount rate for costs and QALYs	3.5%	0% for costs and outcomes	As per NICE guidelines[2]
2			6% for costs and outcomes	
3	Costs	Using tariff costing for CAR T-cell infusion cost calculations	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	Approach used in TA893[1]
4		Exclude drug wastage	Include drug wastage (for comparator therapies)	To consider the availability of vial-sharing in comparator treatments
5	Survival curve and ITC choices	Inotuzumab and blinatumomab use an inverse MAIC approach. Ponatinib use a naïve approach	Base-case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab; inverse MAIC vs. ponatinib)	Exploring combinations of alternative modelling approaches
6			Base-case ITC approach + alternative obe-cel survival curves*	
7	Subsequent allo-SCT	10% subsequent allo-SCT for obe-cel	5% subsequent allo-SCT for obe-cel	Exploring the proportion of patients with subsequent allo-SCT
8			2.5% subsequent allo-SCT for obe-cel	
9	Use allo-SCT costs from 2021 EY publication[3]	Use allo-SCT costs from TA893	Allo-SCT costs from 2021 EY publication	Exploring more recent allo-SCT cost data in the England
10	Alternative SMR	3.0	4.0	Exploratory analysis

11	Use STC results instead of MAIC	Inotuzumab and blinatumomab use an inverse MAIC approach. Ponatinib use a naïve approach	STC results for all comparators	Exploratory analysis
12	Use UK only patient population for IVIG use	Overall pooled enrolled	UK only patients	Exploratory analysis
13	Use 1.7 severity modifier	1.2 severity modifier	1.7 severity modifier	Exploratory analysis

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; EY - Ernst & Young LLP; ITC – Indirect treatment comparison; IVIG – Intravenous immunoglobulin; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMR – Standard mortality ratio; TA – Technology Appraisal; UK – United Kingdom
*Alternative survival curves used are: Overall population – EFS: Weibull; OS: Weibull; Ph- population – EFS: 3-knots normal spline curve; OS: Gompertz; Ph+ population – EFS: Gompertz; OS: Gompertz

Table 20: Scenario analyses - Overall population

#	Value	Deterministic ICER	Probabilistic ICER
1	0% for costs and outcomes	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]
3	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	[redacted]	[redacted]
4	Include drug wastage (for comparator therapies)	[redacted]	[redacted]
5	Base-case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab; inverse MAIC vs. ponatinib)	[redacted]	[redacted]

6	Base-case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]
7	5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]
8	2.5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]
9	Allo-SCT costs from 2021 EY publication	[redacted]	[redacted]
10	4.0 SMR	[redacted]	[redacted]
11	STC results for all comparators	[redacted]	[redacted]
12	UK only patients	[redacted]	[redacted]
13	1.7 severity modifier	[redacted]	[redacted]

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; EY - Ernst & Young LLP; ITC – Indirect treatment comparison; IVIG – Intravenous immunoglobulin; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMR – Standard mortality ratio; TA – Technology Appraisal; UK – United Kingdom

Table 21: Scenario analyses - Ph- population

#	Scenario	Versus inotuzumab		Versus blinatumomab	
		Deterministic ICER	Probabilistic ICER	Deterministic ICER	Probabilistic ICER
1	0% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
3	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	[redacted]	[redacted]	[redacted]	[redacted]
4	Include drug wastage (for comparator therapies)	[redacted]	[redacted]	[redacted]	[redacted]

5	Base-case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab; inverse MAIC vs. ponatinib)	[redacted]	[redacted]	[redacted]	[redacted]
6	Base-case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]	[redacted]	[redacted]
7	5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]	[redacted]	[redacted]
8	2.5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]	[redacted]	[redacted]
9	Allo-SCT costs from 2021 EY publication	[redacted]	[redacted]	[redacted]	[redacted]
10	4.0 SMR	[redacted]	[redacted]	[redacted]	[redacted]
11	STC results for all comparators	[redacted]	[redacted]	[redacted]	[redacted]
12	UK only patients	[redacted]	[redacted]	[redacted]	[redacted]
13	1.7 severity modifier	[redacted]	[redacted]	[redacted]	[redacted]

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; EY - Ernst & Young LLP; ITC – Indirect treatment comparison; IVIG – Intravenous immunoglobulin; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMR – Standard mortality ratio; TA – Technology Appraisal; UK – United Kingdom

Table 22: Scenario analyses - Ph+ population

#	Scenario	Versus inotuzumab		Versus ponatinib	
		Deterministic ICER	Probabilistic ICER	Deterministic ICER	Probabilistic ICER

1	0% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
3	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	[redacted]	[redacted]	[redacted]	[redacted]
4	Include drug wastage (for comparator therapies)	[redacted]	[redacted]	[redacted]	[redacted]
5	Base-case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab; inverse MAIC vs. ponatinib)	[redacted]	[redacted]	[redacted]	[redacted]
6	Base-case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]	[redacted]	[redacted]
7	5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]	[redacted]	[redacted]
8	2.5% subsequent allo-SCT for obe-cel	[redacted]	[redacted]	[redacted]	[redacted]
9	Allo-SCT costs from 2021 EY publication	[redacted]	[redacted]	[redacted]	[redacted]
10	4.0 SMR	[redacted]	[redacted]	[redacted]	[redacted]
11	STC results for all comparators	[redacted]	[redacted]	[redacted]	[redacted]
12	UK only patients	[redacted]	[redacted]	[redacted]	[redacted]
13	1.7 severity modifier	[redacted]	[redacted]	[redacted]	[redacted]

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; EY - Ernst & Young LLP; ITC – Indirect treatment comparison; IVIG – Intravenous immunoglobulin; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMR – Standard mortality ratio; TA – Technology Appraisal; UK – United Kingdom

5.3 *EAG comments on company's results*

The company's deterministic results for the overall, Ph-, and Ph+ populations, as presented in Table 23, Table 24, and Table 25, aim to evaluate the cost-effectiveness of obe-cel compared to the comparator(s). It appears that the incremental costs (£), incremental life years gained (LYG), and incremental quality-adjusted life years (QALYs) were calculated as part of a fully incremental analysis by the company. However, the EAG has identified several issues in the company's methodology and results, which are discussed below.

Ph- population results

In the Ph- population, the company compares blinatumomab, inotuzumab, and obe-cel. The reported incremental values for inotuzumab versus blinatumomab (£[redacted], [redacted] LYG, [redacted] QALYs) and obe-cel versus inotuzumab (£[redacted], [redacted] LYG, [redacted] QALYs) suggest a fully incremental analysis. However, the EAG notes a discrepancy in the incremental QALYs for obe -cel versus inotuzumab. While the company reports [redacted] QALYs, the EAG's revised analysis corrects this to [redacted] QALYs, aligning with the expected difference based on total QALYs ([redacted]), adjusted by a severity modifier of 1.2.

The ICERs for pairwise comparisons of obe-cel versus inotuzumab and blinatumomab are consistent across analyses. However, the EAG's revised ICER for inotuzumab versus blinatumomab (£[redacted]) is lower than the company's estimate (£[redacted]), reflecting corrections in the QALY calculations.

Ph+ population results

For the Ph+ population, the company compares ponatinib, inotuzumab, and obe-cel. The company reports incremental QALYs for inotuzumab versus ponatinib as [redacted], without applying a severity modifier. The EAG's revised analysis adjusts this to [redacted] QALYs, incorporating a severity modifier of 1.2. While the incremental values for obe-cel versus inotuzumab and ponatinib are consistent between the company and the EAG, the EAG's revised ICER for inotuzumab versus ponatinib in the fully incremental analysis is £[redacted], compared to the company's estimate of £[redacted].

Table 23: Company's deterministic results, overall population – PAS price

Treatment	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY*	ICER	INHB (£20,000 WTP)	INHB (£30,000 WTP)
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: Life Years Gained; QALY: Quality-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio; INHB: Incremental Net Health Benefit; WTP: Willingness To Pay.
* The severity modifier of 1.2 is applied

Table 24: Company's deterministic results (revised by the EAG), Ph- population – PAS price

Treatment	Total costs (£)	Total LYG	Total QALY	Fully incremental analysis				Obe-cel versus comparator		
				Incremental costs (£)	Incremental LYG	Incremental QALY*	ICER	ICER	INHB (£20,000 WTP)	INHB (£30,000 WTP)
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: Life Years Gained; QALY: Quality-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio; INHB: Incremental Net Health Benefit; WTP: Willingness To Pay.
* The severity modifier of 1.2 is applied

Table 25: Company's deterministic results (revised by the EAG), Ph+ population – PAS price

Treatment	Total costs (£)	Total LYG	Total QALY	Fully incremental analysis				Obe-cel versus comparator		
				Incremental costs (£)	Incremental LYG	Incremental QALY*	ICER	ICER	INHB (£20,000 WTP)	INHB (£30,000 WTP)
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: Life Years Gained; QALY: Quality-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio; INHB: Incremental Net Health Benefit; WTP: Willingness To Pay.
* The severity modifier of 1.2 is applied

5.4 *Overview of the company and EAG's approaches (changes) in the base case after AC1*

Table presents an overview of the company and EAG's approaches used in the base case. The content has been informed by several sources, including:

- The draft guidance consultation
- The EAG's report
- The company's draft guidance comments document
- The company's updated model

Table 26: Overview of the company and EAG's approaches in the base case after AC1

Variable	Company's value/approach	EAG's value/approach	Reference to related section(s)
Baseline characteristic			
Main population	Originally, from infused IIA population After AC1, from pooled enrolled IA and IIA population	From pooled enrolled IA and IIA population	-
Programming adjustments and error resolution for follow-up costs of allo-SCT in the economic model			
Costs of follow-up after ASCT	Originally, the full proportion of patients in each post allo-SCT follow-up period was used in each model cycle. After AC1, the EAG approach was followed.	Using only the first tunnel state in each post allo-SCT follow-up period to ensure maximum undiscounted costs align with the proportion of patients receiving allo-SCT	-
Correcting cost and effect inconsistencies for allo-SCT in obe-cel economic modelling			
Proportion of patients eligible to receive allo-	[redacted]% After AC1: [redacted]%	In the original report: [redacted]% After AC1: [redacted]%	Section 2.8

<table>
<tr><th>Variable</th><th>Company's value/approach</th><th>EAG's value/approach</th><th>Reference to related section(s)</th></tr>
<tr><td>SCT in obe-cel</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">Revised hospitalization duration and resource use estimates post obe-cel infusion</td></tr>
<tr><td>Approach to CAR T-cell infusion cost calculations</td><td>Originally, Bottom-up costing (using UK-specific FELIX trial data: [redacted] days non-ICU, [redacted] days ICU stays, [redacted]% of patients requiring ICU care).

After AC1, using the tariff cost of £60,462 + ICU cost ([redacted]% requiring ICU from pooled enrolled cohort IA + IIA)</td><td>Originally, using the tariff costs for CAR T infusion and monitoring, valued at £58,964 + ICU cost ([redacted]% requiring ICU from Cohort IA)

After AC1, the EAG's approach was the same as the company's approach after AC1</td><td>-</td></tr>
<tr><td colspan="4">Addressing underreporting of adverse events and discrepancies with the company's clinical study report (CSR)</td></tr>
<tr><td>Source of adverse events incidence</td><td>Originally, Grade ≥3 AEs which occurred in the mITT population observed during the FELIX study

After AC1, the EAG's approach</td><td>Include treatment-emergent adverse events (Grade ≥3) for all infused patients, as reported in the CSR</td><td>-</td></tr>
<tr><td colspan="4">Addressing inconsistencies in severity modifier applications across populations</td></tr>
<tr><td>QALY weight</td><td>Originally, 1.7

After AC1, 1.2</td><td>1.2</td><td>-</td></tr>
<tr><td colspan="4">Incorporating allo-SCT utility effects into the economic model</td></tr>
<tr><td>Allo-SCT utility</td><td>Originally, no allo-SCT utility effects

After AC1, the EAG's approach</td><td><table><tr><th>Treatment</th><th>Obe-cel</th><th>Blinatumomab</th></tr><tr><td>Post-HSCT- <1 year post</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Post-HSCT- 1–2 years' post</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Post-HSCT- 3–5 years' post</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Post-HSCT- >5 years post</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>-</td></tr>
</table>

<table>
<tr><th>Variable</th><th>Company's value/approach</th><th>EAG's value/approach</th><th>Reference to related section(s)</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Treatment</th><th>Inotuzumab</th><th>Ponatinib</th></tr>
<tr><td>Post-HSCT- <1 year post</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Post-HSCT- 1–2 years' post</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Post-HSCT- 3–5 years' post</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Post-HSCT- >5 years post</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td></td></tr>
<tr><td colspan="4">Use of per-cycle discount rate instead of per-year discount rate</td></tr>
<tr><td>Discount factor</td><td>Originally, per-cycle discount factor

After AC1, the EAG's approach</td><td>Per-year discount factor</td><td>-</td></tr>
<tr><td colspan="4">Cure assumption</td></tr>
<tr><td>PSM cure time definition</td><td>3 years</td><td>Originally, 3 years

After AC1, 3 years</td><td>Section 2.6</td></tr>
<tr><td>Standardized mortality ratio for all long-term survivors</td><td>3.0</td><td>Originally, 3.0

After AC1, 3.0</td><td>Section 2.6</td></tr>
<tr><td colspan="4">Patients who have intravenous immunoglobulin and the duration of treatment</td></tr>
<tr><td>IVIG</td><td>Originally,
<table>
<tr><td>Dose (mg/kg)</td><td>0.5</td></tr>
</table>
</td><td>Originally, company's original approach

After AC1,</td><td>Section 2.10</td></tr>
</table>

<table>
<tr><th>Variable</th><th>Company's value/approach</th><th>EAG's value/approach</th><th>Reference to related section(s)</th></tr>
<tr><td></td><td>
<table>
<tr><td>Dose per day (mg)</td><td>39.365</td></tr>
<tr><td>Frequency (weeks)</td><td>4</td></tr>
<tr><td>Duration (weeks)</td><td>52</td></tr>
<tr><td>% of pop needs IVIG</td><td>[redacted]%</td></tr>
</table>
After AC1,
<table>
<tr><td>Dose (g/kg)</td><td>0.4</td></tr>
<tr><td>Dose per month (g)</td><td>25.15</td></tr>
<tr><td>Frequency (days)</td><td>[redacted]</td></tr>
<tr><td>% of pop need IVIG</td><td>[redacted]%</td></tr>
</table>
</td><td>
<table>
<tr><td>Dose (g/kg)</td><td>0.4</td></tr>
<tr><td>Dose per month (g)</td><td>25.15</td></tr>
<tr><td>Frequency (days) (Use UK only cohort IA + IIA FELIX patients for duration of IVIG)</td><td>[redacted]</td></tr>
<tr><td>Proportion with hypogammaglobulinaemia</td><td>[redacted]%</td></tr>
<tr><td>% of pop needs IVIG (sourced from the company's response to CQ A14 for cohort IIA)</td><td>[redacted]%</td></tr>
</table>
</td><td></td></tr>
<tr><td>Bridging therapy costs calculations and adjustment of ITT correction factor</td><td>There were some errors in worksheet 'Treatment Costs', cells E203:E211 and double counting of correction factor</td><td>Correction of cohort-specific bridging costs calculations and adjustment of ITT correction factor</td><td>Section 2.2</td></tr>
</table>

Table 27 - Table 29 outline the EAG's adjustments to OS and EFS in the company's base-case model for different patient populations, following AC1 and incorporating new evidence submitted by the company.

Table 27: EAG's adjustments to OS and EFS in the company's base-case model - Whole population after AC1

Parameters	Company's approach	EAG approach*	Reference to related section(s)
EFS			
Obe-cel	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N:[redacted] **Curve selection:** Flexible - Normal - 2	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N:[redacted] **Curve selection:** Flexible - Normal - 1	Section 4
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	Section 4
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	Section 4
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	Section 4

HR: Hazard ratio; mITT: Modified intention to treat; ITT: Intention to treat; CQs: Clarification questions; OS: Overall survival; EFS: Event-free survival
*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.

Table 28: EAG's adjustments to OS and EFS in the company's base-case model: Ph- population- after AC1

Parameters	Company's approach	EAG approach*	Reference to related section(s)
EFS			
Obe-cel	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N:[redacted] **Curve selection:** Standard - Log-normal	**Data source:** FELIX, pooled enrolled Cohort IA + IIA, N:[redacted] **Curve selection:** Flexible - Normal - 3	Section 4
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	Section 4
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	Section 4
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	Section 4
Blinatumomab	**Data source:** TOWER, N:271 has been used in the MAIC **Curve selection:** (Value 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	Section 4
Inotuzumab	**Data source:** INO-VATE, N:164 has been used in the MAIC	**Data source:** INO-VATE, N:164 has been used in the MAIC	Section 4

Parameters	Company's approach	EAG approach*	Reference to related section(s)
	Curve selection: (Value based on obe-cel curve) ^(1/OS HR of obe-cel vs Inotuzumab[ ])	**Curve selection:** The company's approach	

HR: Hazard ratio; mITT: Modified intention to treat; ITT: Intention to treat; CQs: Clarification questions; OS: Overall survival; EFS: Event-free survival
*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.

Table 29: EAG's adjustments to OS and EFS in the company's base-case model- Ph+ population- after AC1

Parameters	Company's approach	EAG approach*	Reference to related section(s)
EFS			
Obe-cel	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N: **Curve selection:** Flexible - Normal - 3	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N: **Curve selection:** The company's approach	Section 4
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.])	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** The company's approach	Section 4
Ponatinib	**Data source:** PACE, N:32 **Curve selection:** Standard - Log-logistic	**Data source:** PACE, N:32 **Curve selection:** The company's approach	Section 4
OS			
Obe-cel	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N: **Curve selection:** Standard – Exponential	**Data source:** FELIX, pooled enrolled cohort IA + IIA, N: **Curve selection:** The company's approach	Section 4

Parameters	Company's approach	EAG approach*	Reference to related section(s)
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[ ])	**Data source:** INO-VATE, N:164 has been used in the MAIC **Curve selection:** The company's approach	Section 4
Ponatinib	**Data source:** PACE, N:32 **Curve selection:** Standard - Log-normal	**Data source:** PACE, N:32 **Curve selection:** The company's approach	Section 4

HR: Hazard ratio; mITT: Modified intention to treat; ITT: Intention to treat; CQs: Clarification questions; OS: Overall survival; EFS: Event-free survival
*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.

5.5 *Impact of EAG changes on the company's base-case results*

Table 30, Table 31, and Table 32 present the results of the EAG's exploratory analyses comparing obe-cel with relevant comparators across different populations.

In the overall population, the EAG's preferred assumptions and modelling approach for IVIG usage led to a [redacted]% increase in the company's base case ICER. All changes applied in this population result in a combined increase of [redacted]% in the ICER relative to the company's base case.

In the Ph- population, the use of alternative curves for PFS and OS leads to a [redacted]% increase in the ICER for obe-cel versus inotuzumab, and a [redacted]% decrease in the ICER for obe-cel versus blinatumomab. Incorporating the EAG's approach to IVIG use results in a [redacted]% increase in the ICER for obe-cel versus inotuzumab and a [redacted]% increase in the comparison with blinatumomab. Overall, the EAG base case results in a [redacted]% higher ICER for obe-cel versus inotuzumab and a [redacted]% increase in the ICER for obe-cel versus blinatumomab, compared with the company's base case.

In the Ph+ population, only two changes were made to the company's model. The EAG's adjustments to IVIG usage result in a [redacted]% increase in the ICER for obe-cel versus ponatinib and a [redacted]% increase in the comparison with inotuzumab. Overall, the EAG base case results in a [redacted]% higher ICER for obe-cel versus inotuzumab and a [redacted]% increase in the ICER for obe-cel versus ponatinib, compared with the company's base case.

Table 30: Results of EAG's exploratory analysis, overall population- after AC1

EAG's preferred assumption based on issues		Incremental costs (£)	Incremental QALY	ICER (£/QALY)	Impact
Company's Base Case – Post AC1		[redacted]	[redacted]	[redacted]	[redacted]
1	Survival inputs: EFS: Switch to 1 knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2	IVIG usage	[redacted]	[redacted]	[redacted]	[redacted]
3	Correction of cohort-specific bridging cost calculations and adjustment of ITT correction factor	[redacted]	[redacted]	[redacted]	[redacted]
1 - 3 combined (EAG base case)		[redacted]	[redacted]	[redacted]	[redacted]

EAG: External Assessment Group; AC: Appraisal Committee; IVIG: Intravenous Immunoglobulin; ITT: Intention-To-Treat; EFS: Event-Free Survival; QALY: Quality-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio

Table 31: Results of EAG's exploratory analysis, Ph- population after AC1

EAG's preferred assumption based on issues		Obe-cel vs inotuzumab				Obe-cel vs blinatumomab			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Impact	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Impact
Company's Base Case – Post AC1		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	Survival inputs: EFS: Switch to 3 knot normal OS: Switch to 0 knot normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	IVIG usage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Correction of cohort-specific bridging cost calculations and adjustment of ITT correction factor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 - 3 combined (EAG base case)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG: External Assessment Group; AC: Appraisal Committee; IVIG: Intravenous Immunoglobulin; ITT: Intention-To-Treat; EFS: Event-Free Survival; QALY: Quality-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio

Table 32: Results of EAG's exploratory analysis, Ph+ population after AC1

EAG's preferred assumption based on issues		Obe-cel vs inotuzumab				Obe-cel vs ponatinib			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Impact	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Impact
Company's Base Case – Post AC1		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	IVIG usage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Correction of cohort-specific bridging cost calculations and adjustment of ITT correction factor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 and 2 combined (EAG base case)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG: External Assessment Group; AC: Appraisal Committee; IVIG: Intravenous Immunoglobulin; ITT: Intention-To-Treat; EFS: Event-Free Survival; QALY: Quality-Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio

6 EAG additional cost-effectiveness analyses

6.1 *Results of EAG base-case analysis*

6.1.1 Deterministic base-case results

The following tables summarise the deterministic cost-effectiveness results provided by the EAG for obe-cel compared with relevant comparators across three populations: the overall population (Table 33), Ph− population (Table 34), and Ph+ population (Table 35).

Key results include:

- In the overall population, obe-cel was associated with [redacted] additional QALYs compared to inotuzumab but incurred £[redacted] higher costs, resulting in an ICER of £[redacted].
- In the Ph- population, obe-cel showed [redacted] additional QALYs versus inotuzumab with an ICER of £[redacted].
- In the Ph+ population, obe-cel achieved the [redacted] QALYs ([redacted]) among all treatments but came at a [redacted] cost (£[redacted]), resulting in an ICER of £[redacted] when compared to inotuzumab.

Table 33: EAG deterministic results, overall population – PAS price

Treatment	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY*	ICER	INHB (£20,000 WTP)	INHB (£30,000 WTP)
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years
*The severity modifier of 1.2 is applied to incremental QALYs.

Table 34: EAG deterministic results, Ph- population – PAS price

Treatment	Total costs (£)	Total LYG	Total QALY	Fully incremental analysis				Obe-cel versus comparator		
				Incremental costs (£)	Incremental LYG	Incremental QALY*	ICER	ICER	INHB (£20,000 WTP)	INHB (£30,000 WTP)
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years
*The severity modifier of 1.2 is applied to incremental QALYs.

Table 35: EAG deterministic results, Ph+ population – PAS price

Treatment	Total costs (£)	Total LYG	Total QALY	Fully incremental analysis				Obe-cel versus comparator		
				Incremental costs (£)	Incremental LYG	Incremental QALY*	ICER	ICER	INHB (£20,000 WTP)	INHB (£30,000 WTP)
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years
*The severity modifier of 1.2 is applied to incremental QALYs.

6.1.2 Probabilistic sensitivity analysis (PSA) results

The following tables and figures present the results of the probabilistic sensitivity analysis (PSA) conducted for the different patient populations.

Overall population: The probabilistic ICER is estimated at £[redacted] (Table 36), which is slightly higher than the deterministic result. The associated cost-effectiveness scatter plot indicates that all iterations fall within the [redacted] quadrant. This positioning suggests that, compared to inotuzumab, obe-cel is consistently both [redacted] (Figure 4). The cost-effectiveness acceptability curve (CEAC) (Figure 5) further illustrates that at a WTP threshold of £30,000 per QALY, the probability of obe-cel being cost-effective is [redacted]%.

Ph- population: In the Ph- subgroup, the probabilistic results are broadly consistent with the deterministic estimates, albeit marginally higher. The fully incremental analysis yields ICERs of £[redacted] for obe-cel versus inotuzumab which is cost-effective versus blinatumomab. Pairwise comparisons provide ICERs versus inotuzumab and blinatumomab of £[redacted] and £[redacted], respectively (Table 37). The scatter plots for both comparisons (Figure 6 and Figure 7) demonstrate that all iterations fall within the [redacted] quadrant, indicating that obe-cel is [redacted]. According to the CEAC, the probability of obe-cel being cost-effective versus inotuzumab at a £30,000 per QALY threshold is [redacted]%, while the probability increases to approximately [redacted]% when compared with blinatumomab.

Ph+ population: In the Ph+ subgroup, the probabilistic results are closely aligned with the deterministic estimates. The fully incremental analysis (Table 38) reports ICERs of £[redacted] for obe-cel versus inotuzumab which was cost-effective versus ponatinib. Pairwise analyses yield ICERs versus inotuzumab and ponatinib of £[redacted] and £[redacted], respectively. As with the other populations, the scatter plots (Figure 10 and Figure 11) show all iterations residing in the [redacted] quadrant, again indicating that obe-cel is both [redacted]. The CEAC demonstrates a [redacted]% probability of obe-cel being cost-effective compared with inotuzumab at the £30,000 threshold, and approximately [redacted]% for the comparison with ponatinib.

Table 36: EAG probabilistic results considering PAS discount (overall population)

Treatment	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY*	ICER	INHB (£20,000 WTP)	INHB (£30,000 WTP)
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel									

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years
*The severity modifier of 1.2 is applied to incremental QALYs.

Table 37: EAG probabilistic results considering PAS discount (Ph- population)

Treatment	Total costs (£)	Total LYG	Total QALY	Fully incremental analysis				Obe-cel versus comparator		
				Incremental costs (£)	Incremental LYG	Incremental QALY*	ICER	ICER	INHB (£20,000 WTP)	INHB (£30,000 WTP)
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel										

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years
*The severity modifier of 1.2 is applied to incremental QALYs.

Table 38: EAG probabilistic results considering PAS discount (Ph+ population)

Treatment	Total costs (£)	Total LYG	Total QALY	Fully incremental analysis				Obe-cel versus comparator		
				Incremental costs (£)	Incremental LYG	Incremental QALY*	ICER	ICER	INHB (£20,000 WTP)	INHB (£30,000 WTP)
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obe-cel										

ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years
*The severity modifier of 1.2 is applied to incremental QALYs.

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 4: EAG scatterplot (overall population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 5: EAG CEAC (overall population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 6: EAG scatterplot, obe-cel versus inotuzumab (Ph- population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 7: EAG scatterplot, obe-cel versus blinatumomab (Ph- population)

CEAC – Cost-effectiveness acceptability curve

Figure 8: EAG CEAC, obe-cel versus blinatumomab (Ph- population)

CEAC – Cost-effectiveness acceptability curve

Figure 9: EAGCEAC, obe-cel versus inotuzumab (Ph- population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 10: EAG scatterplot, obe-cel versus inotuzumab (Ph+ population)

ICEP – Incremental cost-effectiveness plane; WTP – Willingness-to-pay

Figure 11: EAG scatterplot, obe-cel versus ponatinib (Ph+ population)

CEAC – Cost-effectiveness acceptability curve

Figure 12: EAG CEAC, obe-cel versus inotuzumab (Ph+ population)

CEAC – Cost-effectiveness acceptability curve

Figure 13: EAG CEAC, obe-cel versus ponatinib (Ph+ population)

6.1.3 One-way sensitivity analysis results

The following figures present the results of a one-way sensitivity analysis (OWSA) conducted across various population subgroups.

Overall population: Within the overall population, analysis based on net monetary benefit (NMB) indicates that [redacted], exert the greatest influence on the NMB outcomes. (see Figure 14)

Ph- population: As shown in Figure 15, for the comparison between obe-cel and blinatumomab, the parameters with the most notable effect on NMB are the [redacted]. For the comparison between obe-cel and inotuzumab (Figure 16), [redacted] emerge as the key drivers of NMB.

Ph+ population: In the comparison of obe-cel versus inotuzumab within the Ph+ population (Figure 17), [redacted], are identified as the most influential factors affecting NMB. In the comparison between obe-cel and ponatinib (Figure 18), the most critical determinants of NMB are the [redacted].

NMB – net monetary benefit; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis

Figure 14: EAG OWSA results for obe-cel versus inotuzumab (overall population) - NMB

NMB – net monetary benefit; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis

Figure 15: EAG OWSA results for obe-cel versus blinatumomab- (Ph- population) NMB

NMB – net monetary benefit; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis

Figure 16: EAG OWSA results for obe-cel versus inotuzumab (Ph- population) – NMB

NMB – net monetary benefit; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis

Figure 17: EAG OWSA results for obe-cel versus inotuzumab (Ph+ population) - NMB

NMB – net monetary benefit; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis

Figure 18: EAG OWSA results for obe-cel versus ponatinib (Ph+ population) - NMB

6.1.4 Scenario analysis results

The following tables present the results of the EAG scenario analyses. These analyses evaluate the cost-effectiveness of obe-cel under various scenarios for the different populations. The analyses report incremental costs, incremental QALYs, ICERs, and the percentage impact on the ICER relative to the EAG's base case post-AC1.

Overall population: Table 39 outlines the scenario analysis results for the overall population. Among the scenarios tested, the application of a QALY weight of 1.7 results in the [redacted] in the ICER (by [redacted]% to £[redacted] per QALY). Conversely, the assumption of a 4-year cure time point [redacted] the ICER by [redacted]% to £[redacted] per QALY.

Ph- population: Table 40 compares obe-cel against inotuzumab and blinatumomab in the Ph- population. For obe-cel versus inotuzumab, the [redacted] was observed when using a bottom-up costing approach for CAR T-cell infusion costs, [redacted] the ICER by [redacted]% to £[redacted] per QALY. The 4-year cure time point scenario [redacted] the ICER by [redacted]% to £[redacted] per QALY. For obe-cel versus blinatumomab, the [redacted] comes from applying a QALY weight of 1.7.

Ph+ population: Table 41 evaluates obe-cel against inotuzumab and ponatinib. For both comparisons, the [redacted] comes from applying a QALY weight of 1.7. In contrast, the MAIC increases the ICER by [redacted]% to £[redacted] per QALY. For obe-cel versus ponatinib, the [redacted] stems from the QALY weight of 1.7.

Summary: Across all populations, the application of a QALY weight of 1.7 consistently produces the [redacted] in cost-effectiveness by notably [redacted] ICERs, underscoring the importance of QALY adjustments in economic evaluations. Conversely, assumptions such as extended cure time points or specific survival model choices frequently result in increased ICERs, highlighting the sensitivity of cost-effectiveness outcomes to these parameters.

Table 39: EAG's Scenario analysis results, overall population

Scenarios		Incremental costs (£)	Incremental QALY	ICER (£/QALY)	Impact
EAG's base case – Post AC1		[redacted]	[redacted]	[redacted]	[redacted]
% subsequent allo-SCT for obe-cel	5%	[redacted]	[redacted]	[redacted]	[redacted]
	2.5%	[redacted]	[redacted]	[redacted]	[redacted]
CAR T-cell infusion cost	Use a bottom-up costing approach	[redacted]	[redacted]	[redacted]	[redacted]
Cure time point assumption	3.5 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
SMR for all long-term survivors	4.0 SMR	[redacted]	[redacted]	[redacted]	[redacted]
Drug wastage	Include drug wastage (for comparators)	[redacted]	[redacted]	[redacted]	[redacted]
IVIG usage	12% as % of pop need IVIG	[redacted]	[redacted]	[redacted]	[redacted]
	32% as % of pop need IVIG	[redacted]	[redacted]	[redacted]	[redacted]
	2.8 days as frequency	[redacted]	[redacted]	[redacted]	[redacted]
	6.7 days as frequency	[redacted]	[redacted]	[redacted]	[redacted]
Survival model choices	EFS: 2 knot normal OS: 0 knot hazard spline	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted analyses approach	Using MAIC	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT costs	Source from 2021 EY publication	[redacted]	[redacted]	[redacted]	[redacted]
QALY weight	1.7	[redacted]	[redacted]	[redacted]	[redacted]

CAR: Chimeric antigen receptor; AC: appraisal committee; EFS: Event-free survival; EY: Ernst & Young LLP; ITC: Indirect treatment comparison; IVIG: Intravenous immunoglobulin; MAIC: Match-adjusted indirect treatment comparison; QALY: Quality-adjusted life year; SCT: Stem cell transplant; SMR: Standard mortality ratio; TA – Technology Appraisal; UK: United Kingdom

Table 40: EAG's scenario analysis results, Ph- population

scenarios		Obe-cel vs inotuzumab				Obe-cel vs blinatumomab			
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Impact	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Impact
EAG's Base Case – Post AC1		[redacted]							
% subsequent allo-SCT for obe-cel	5%								
	2.5%								
CAR T-cell infusion cost	Use a bottom-up costing approach								
Cure time point assumption	3.5 years								
	4 years								
SMR for all long-term survivors	4.0 SMR								
Drug wastage	Include drug wastage (for comparators)								
IVIG usage	12% as % of pop need IVIG								
	32% as % of pop need IVIG								
	2.8 days as frequency								
	6.7 days as frequency								
Survival model choices	EFS: 3 knot odds OS: log-normal								

Adjusted analyses approach	Using MAIC	[redacted]							
Allo-SCT costs	Source from 2021 EY publication	[redacted]							
QALY weight	1.7	[redacted]							

CAR: Chimeric antigen receptor; AC: appraisal committee; EFS: Event-free survival; EY: Ernst & Young LLP; ITC: Indirect treatment comparison; IVIG: Intravenous immunoglobulin; MAIC: Match-adjusted indirect treatment comparison; QALY: Quality-adjusted life year; SCT: Stem cell transplant; SMR: Standard mortality ratio; TA – Technology Appraisal; UK: United Kingdom

Table 41: EAG's scenario analysis results, Ph+ population

Scenarios		**Obe-cel vs inotuzumab**				**Obe-cel vs ponatinib**			
		Inc. Costs (£)	**Inc. QALYs**	**ICER (£/QALY)**	**Impact**	**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**	**Impact**
EAG's Base Case – Post AC1		[redacted]							
% subsequent allo-SCT for obe-cel	5%								
	2.5%								
CAR T-cell infusion cost	Use a bottom-up costing approach								
Cure time point assumption	3.5 years								
	4 years								
SMR for all long-term survivors	4.0 SMR								
Drug wastage	Include drug wastage (for comparators)								
IVIG usage	12% as % of pop need IVIG								
	32% as % of pop need IVIG								
	2.8 days as frequency								
	6.7 days as frequency								

Survival Model Choices	EFS: 2 knot normal OS: 0 knot normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted analyses approach	Using MAIC (vs inotuzumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT costs	Source from 2021 EY publication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY weight	1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CAR: Chimeric antigen receptor; AC: appraisal committee; EFS: Event-free survival; EY: Ernst & Young LLP; ITC: Indirect treatment comparison; IVIG: Intravenous immunoglobulin; MAIC: Match-adjusted indirect treatment comparison; QALY: Quality-adjusted life year; SCT: Stem cell transplant; SMR: Standard mortality ratio; TA – Technology Appraisal; UK: United Kingdom

6.2 *Conclusions of the cost effectiveness analysis*

Following discussions at AC1, the company submitted a revised base case for evaluation.

In the overall population, the comparison of obe-cel with inotuzumab yielded an ICER of £[redacted] per QALY gained.

In the Ph- population, obe-cel compared with inotuzumab resulted in an ICER of £[redacted] per QALY, while obe-cel versus blinatumomab produced a more favourable ICER of £[redacted] per QALY.

In the Ph+ population, obe-cel versus inotuzumab generated an ICER of £[redacted] per QALY, and compared with ponatinib, an ICER of £[redacted] per QALY was observed.

As part of the fully incremental analysis submitted by the company, several technical and methodological errors were identified. Upon correction, the results showed that in the Ph- population, inotuzumab compared to blinatumomab resulted in an ICER of £[redacted] per QALY. In the Ph+ population, inotuzumab compared to ponatinib generated an ICER of £[redacted] per QALY.

The EAG identified two key improvements to the company's base case: the modelling of IVIG usage and correction of cohort-specific bridging cost calculations, including adjustment of the ITT correction factor, across all populations. An additional charge related to survival input assumptions was applied to the overall and Ph- populations. Among these, IVIG usage had the greatest impact on ICER outcomes, followed by survival modelling assumptions.

The EAG's deterministic base case produced the following results:

- In the overall population, obe-cel was associated with [redacted] additional QALYs compared to inotuzumab, at an incremental cost of £[redacted], yielding an ICER of £[redacted] per QALY, which exceeds standard UK WTP thresholds.
- In the Ph- subgroup, obe-cel achieved [redacted] additional QALYs versus inotuzumab, with an ICER of £[redacted] per QALY, also above typical WTP thresholds.
- In the Ph+ population, obe-cel delivered the highest total QALYs ([redacted]) among comparators but incurred the highest costs (£[redacted]), leading to an ICER of £[redacted] per QALY, which is substantially above accepted thresholds.

Scenario analyses based on the EAG base case and post-committee preferences revealed that applying a QALY weighting of 1.7 consistently resulted in notable [redacted] cost-effectiveness across all populations by reducing ICERs. In contrast, assumptions such as extended cure time points or alternative survival modelling approaches generally [redacted] ICERs, emphasising the sensitivity of the economic results to such parameters.

References

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