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

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Autolus:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions from**:
   a. Anthony Nolan & Leukaemia UK
   b. NHSE

4. **External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science
   a. Addendum

5. **External Assessment Report – factual accuracy check**
   a. Additional factual accuracy check

6. **Statements from experts:**
   a. Michelle Lannon – clinical expert, nominated by Anthony Nolan
   b. Claire Roddie – clinical expert, nominated by Autolus (company)
   c. Harry Brown – patient expert, nominated by Anthony Nolan
   d. Elizabeth Spear – patient expert, nominated by Leukaemia UK

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

November 2024

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[ID6347]_Obe cel_Company evidence submission_Document B_7Nov24_CIC FINAL	Final	Yes	7th November 2024

Contents

Tables and figures

List of tables

List of figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The decision problem addressed in this submission is presented in Table 1.

This submission appraises the clinical and cost-effectiveness of obecabtagene autoleucel (obe-cel) within its expected marketing authorisation for treating relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL) in adults ([redacted]).

The submission covers the full expected marketing authorisation for obe-cel.

The decision problem and rationale for any deviations from the NICE final scope are outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with R/R B-precursor ALL	Adults ([redacted]) with R/R B-cell ALL.	The anticipated marketing authorisation for obe-cel will be for [redacted].
Intervention	Obe-cel	In line with scope	NA
Comparator(s)	• Tisagenlecleucel (for adults aged 25 years and under) • Inotuzumab ozogamicin (CD22-positive B-precursor ALL) • Fludarabine, cytarabine and granulocyte colony stimulating factor (FLAG)-based combination chemotherapy • Blinatumomab (Philadelphia-chromosome-negative ALL) • Tyrosine kinase inhibitor (such as imatinib, dasatinib or ponatinib), alone or in combination with FLAG-based combination chemotherapy (Philadelphia chromosome-positive ALL) • Best supportive care (including palliative care)	According to the anticipated place of obe-cel in the treatment pathway, the appropriate comparators are as follows: • Inotuzumab ozogamicin • Blinatumomab (Ph-) • Ponatinib (Ph+)	The following therapies should not be in scope based on the final licence wording for obe-cel: • Tisagenlecleucel • Clofarabine The expected indication for obe-cel is [redacted] years. Tisagenlecleucel is recommended as an option for people 25 years and under, and clofarabine is not recommended but possibly used off-label in young adults. FLAG-based chemotherapy lies within the licence of obe-cel, however is not considered a comparator due to the positioning of obe-cel alongside clinical feedback and committee preferences expressed in TA893 ([brexucabtagene autoleucel for treating R/R B-cell ALL in people 26

			years and over]). In TA893, the committee had concerns of the toxicity associated with FLAG-IDA, and noted limited use in clinical practice. The patients anticipated to receive obe-cel are equally fragile than those receiving brexu-cel. Therefore, it is unlikely that the population eligible for obe-cel would be eligible for FLAG-IDA. This view was shared by two clinical experts interviewed as part of this submission. Imatinib should not be included as comparator in the scope as it is for an earlier line of treatment not included within the licence. Imatinib is used earlier in the treatment pathway and is therefore not a relevant comparator to obe-cel. Dasatinib should not be included as comparator in the scope as it is not reimbursed in the UK and not used in clinical practice. Best supportive care (palliative care) lies within the licence of obe-cel, would be given to patients who cannot tolerate chemotherapies or targeted treatments. These patients

			would not be eligible for CAR T-cell therapy and therefore best supportive care is not a relevant comparator to obe-cel
Outcomes	• Overall survival • Progression-free survival (including relapse-free survival and event-free survival) • Treatment response rate (including minimal residual disease, haematologic responses and complete remission) • Rate of allogenic stem cell transplant • Adverse effects of treatment • Health-related quality of life	In line with scope	NA
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes	In line with scope	NA

	between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.		
Subgroups to be considered	Not specified	• Ph+ • Ph-	Some of the comparators included in this appraisal are available within the Ph+ and Ph- subgroups. To allow comparison with blinatumomab (Ph-) and ponatinib (Ph+), the model distinguishes between these subgroups.
Perspective for outcomes	All direct health effects for patients	In line with scope	NA
Perspective for costs	NHS and PSS	In line with scope	NA
Time horizon	Lifetime horizon, long enough to reflect all important differences in costs or outcomes between the technologies being compared	In line with scope	NA
Synthesis of evidence on health effects	Based on systematic review	In line with scope	NA

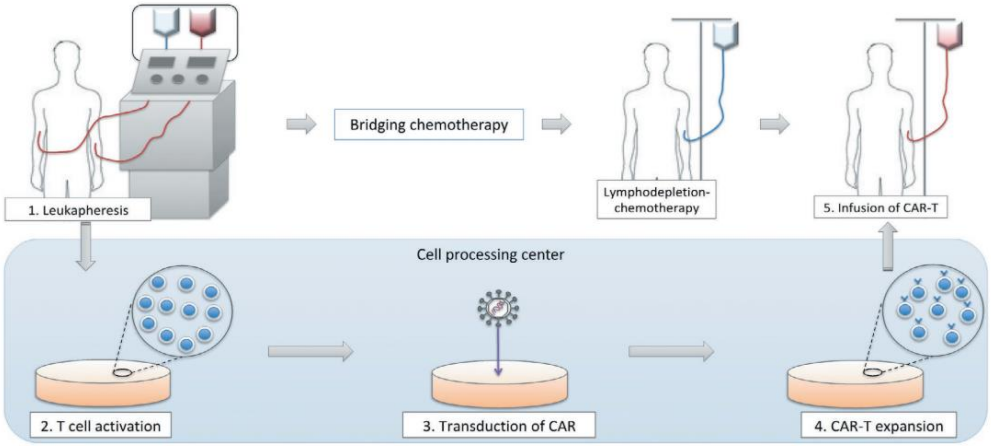
Measuring and valuing health effects	Health effects should be expressed in quality-adjusted life years (QALYs). The EQ-5D is the preferred measure of health-related quality of life in adults.	In line with scope	NA
Source of data for measurement of health-related quality of life	Reported directly by patients or carers, or both.	FELIX clinical trial reported directly by patients.	NA
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	In line with reference case	NA
Equity considerations	None	In line with scope	NA
Evidence on resource use and costs	Costs relate to NHS and PSS resources and are sourced from the NHS reference costs.	In line with scope	NA
Discounting	3.5%	In line with scope	NA

AE – Adverse event; ALL – Acute lymphoblastic leukaemia; Brexu-cel – brexucabtagene autoleucel; HRQoL – Health-related quality of life; NA – Not applicable; Obe-cel – obecabtagene autoleucel; OS – Overall survival; PFS – Progression-free survival; Ph+ – Philadelphia chromosome-positive; Ph- – Philadelphia chromosome negative; R/R – Relapsed/Refractory

B.1.2 Description of the technology being evaluated

Table 2 summarises the technology being appraised in this submission. The draft Summary of Product Characteristics (SmPC) is presented in Appendix C.

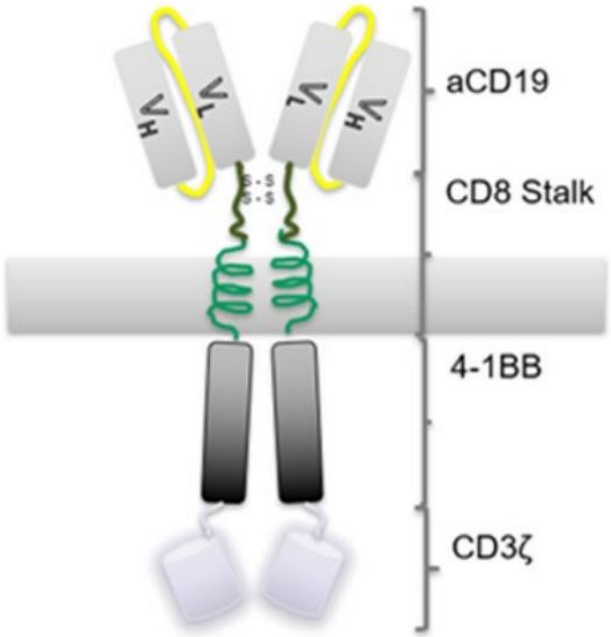
Table 2: Technology being evaluated

UK approved name and brand name	UK approved named: obecabtagene autoleucel Brand name: Aucatzyl®
Mechanism of action	**Chimeric antigen receptor (CAR) T-cell therapy** Obe-cel is a CAR T-cell therapy. CAR T-cells are manufactured through leukapheresis, i.e., the collection of T-cells from patients' blood through separating and collecting white blood cells (leukocytes). Once collected, the T-cells are modified to become CAR T-cells, through being activated and genetically engineered to express the CAR. The modified cells are multiplied before being transferred to a drip to infuse back into the patient's bloodstream. Before patients receive the infusion of CAR T-cells, they receive lymphodepleting chemotherapy. Lymphodepleting chemotherapy decreases the number of T-cells and as a result, the body reacts by increasing cytokine signals that encourage T-cells to grow and multiply. Therefore, the CAR T-cells which are infused back into the patient can grow and become more active, and the modifications to the cells allow them to recognise and attack cancer cells (Figure 1). **Figure 1: CAR T-cell therapy process**  CAR – Chimeric antigen receptor **Source:** Makita *et al.*[1]

Obe-cel mechanism of action

Obe-cel specifically targets cluster of differentiation 19 (CD19) cells, which are found on the surface of B-cells (a type of white blood cell that produce antibodies, developed from stem cells in the bone marrow, which can be cancerous or non-cancerous).[2] Obe-cel's unique CD19 CAR is designed to have a "fast-off" kinetic property mimicking physiological T-cell receptor interactions (Figure 2), which results in increased T-cell persistence, high levels of durable remission and low levels of CRS.[3]

Figure 2: Structure of obe-cel



4-1BB – Tumour necrosis factor ligand superfamily member 9; CD – Cluster of differentiation.
Source: FELIX study protocol[4]

	Obe-cel is a CD19-directed genetically modified autologous T-cell immunotherapy consisting of the patient's own T-cells expressing an anti-CD19 CAR. Engagement of anti-CD19 CAR-positive T-cells with CD19 expressed on target cells, such as cancer cells and normal B-cells, leads to activation of the anti-CD19 CAR-positive T-cells and downstream signalling through the CD3-zeta domain. Proliferation and persistence by the anti-CD19 CAR-positive T-cells following activation are enhanced by the presence of the 4-1BB co-stimulatory domain. This binding to CD19 results in anti-tumour activity and killing of CD19-expressing target cells.
Marketing authorisation/CE mark status	Obe-cel does not currently have marketing authorisation in the UK as the MHRA procedure is under assessment. The GB National Marketing Authorisation application submission occurred on July 29th, 2024. The CHM meeting following the initial D89 assessment will occur November 21st, 2024, followed by a two month clock stop.
Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)	Obe-cel is indicated for the treatment of adult patients (≥18 years) with R/R B-cell ALL.[5]
Method of administration and dosage	**Administration** Treatment with obe-cel consists of a split dose IV infusion, administered on Day 1 and Day 10 (±2 days). The target dose of obe-cel is 410 x 10^6 CD19 CAR-positive viable T-cells supplied in three or more infusion bags. The doses are personalised to individual tumour burden, assessed by BM blast percentage from a sample obtained within 7 days prior to the start of lymphodepletion. Patients can either receive the high tumour burden dosage regimen if the blast percentage is >20% or low tumour dosage regimen if the blast percentage is ≤20% (Table 3). Obe-cel must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with the medicinal product. Before administering obe-cel, patients receive lymphodepleting chemotherapy which includes fludarabine 30 mg/m^2/day IV and cyclophosphamide 500mg/m^2/day IV.

<table>
<tr><td></td><td>Fludarabine and cyclophosphamide will be given together for two days and fludarabine alone on the 3rd and 4th day (total dose: fludarabine 120 mg/m^2; cyclophosphamide 1000 mg/m^2). Obe-cel is infused three days after completion of lymphodepleting chemotherapy.

Table 3: Obe-cel split dosing regimens
<table>
<tr><th>Dosage regimen</th><th>Day 1</th><th>Day 10</th></tr>
<tr><td>High tumour burden</td><td>• 10x10^6 dose administered via a syringe</td><td>• 100x10^6 dose administered via bag infusion and,
• 300x10^6 dose administered via bag infusion.</td></tr>
<tr><td>Low tumour burden</td><td>• 100x10^6 dose administered via bag infusion</td><td>• 10x10^6 dose administered via bag infusion and,
• 300x10^6 dose administered via bag infusion</td></tr>
</table>
Monitoring

Patients should be monitored daily for 14 days after the first infusion for signs and symptoms of potential CRS, ICANS and other toxicities. Frequency of monitoring after the first 14 days should be carried out at the physician’s discretion and should be continued for at least four weeks after. Patients should be instructed to remain within proximity of the qualified treatment centre for at least 4 weeks following the first infusion.</td></tr>
<tr><td>Additional tests or investigations</td><td>No additional tests or investigations, beyond clinical practise, is expected in order to identify patients eligible for obe-cel.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>List price (cost per pack): £372,000
The average cost of a course of treatment with PAS applied is: [redacted].
The total cost of treatment including leukapheresis, bridging therapy, conditioning chemotherapy and administration is: [redacted].</td></tr>
</table>

Patient access scheme (if applicable)	A patient access scheme has been submitted to PASLU for NHS England, comprising a simple [redacted]% discount from list price.

ALL – Acute lymphoblastic leukaemia; BM – bone marrow; CAR – Chimeric antigen receptor; CHM – Commission on Human Medicines; CRS – Cytokine release syndrome; CY – cyclophosphamide; EMA – European Medicines Agency; FLU – fludarabine; GB – Great Britian; ICANS – Immune effector cell-associated neurotoxicity syndrome; IV – Intravenous; MHRA – Medicines and Healthcare products Regulatory Agency; NHS – National Health Service; PAS – Patient access scheme; PASLU – Patient Access Schemes Liaison Unit; UK – United Kingdom.

B.1.3 Health condition and position of the technology in the treatment pathway

Table 4: Overview of ALL, clinical pathway and obe-cel

Overview of ALL, epidemiology, humanistic and economic burden
• ALL is a rare, aggressive blood cancer caused by a build-up of leukaemia cells in the bone marrow.[6] • UK incidence is 1.1 per 100,000 people, with 40% of cases in adults aged 20 or older.[7] • Survival outcomes differ substantially based on age, genetic factors and treatment response, with poorer survival rates observed in older adult and relapsed patients. Five-year UK survival rates are 57% for patients aged 15-39 at diagnosis and as low as 28% in patients older than 40 at diagnosis.[8] • Survival rates following relapse range from <10% to circa 25%, and 40% of adult ALL patients relapse following treatment.[9] • ALL patients face a tremendous emotional and mental burden, often resulting in depression and anxiety.[10] • International studies indicate that ALL is associated with large productivity losses, incurring a substantial societal impact.[11,12]
Current clinical pathway
• Upon initial diagnosis, patients are immediately put on a chemotherapy regimen, with the aim of achieving CR. • B-cell ALL adults who face relapse receive immunotherapy (Ph- patients) or TKI-immunotherapy + chemotherapy (Ph+ patients).[13] • Allo-HSCT is recommended as subsequent treatment if MRD has been achieved.[13] • Current treatments for adult R/R B-cell ALL include brexu-cel (via the CDF), tisagenlecleucel (for patients aged < 26 years), blinatumomab (for Ph- patients), ponatinib (for Ph+ patients) and inotuzumab ozogamicin.[14–18] • Current treatment options such as chemotherapy add to patient burden due to invasiveness and cumbersome side effects.[11,19] • Available CAR T-cell treatments are associated with high rates of severe, potentially life-threatening adverse events (CRS and ICANS).[20]
Obe-cel
• Obe-cel is an autologous CD19 CAR T-cell therapy designed to improve CAR T-cell activity and persistence, demonstrating low levels of toxicity. • The efficacy of obe-cel is in line with existing CAR T-cell therapy, brexu-cel, with a superior safety profile and considerably lower rates of CRS and ICANS.[21,22]

ALL – Acute lymphoblastic leukaemia; allo-HSCT – Allogeneic haematopoietic stem cell transplantation; CAR – Chimeric antigen receptor; CR – Complete remission; CRi – Complete remission with incomplete haematological recover; CDF – Cancer Drugs Fund; CRS – Cytokine release syndrome; ICANS – Immune effector cell-associated neurotoxicity syndrome; MRD – Minimal residual disease; Ph+ - Philadelphia chromosome-positive; Ph- – Philadelphia chromosome negative; R/R – relapsed/refractory; TKI – tyrosine kinase inhibitor; UK – United Kingdom; VOD – Veno-occlusive disease.

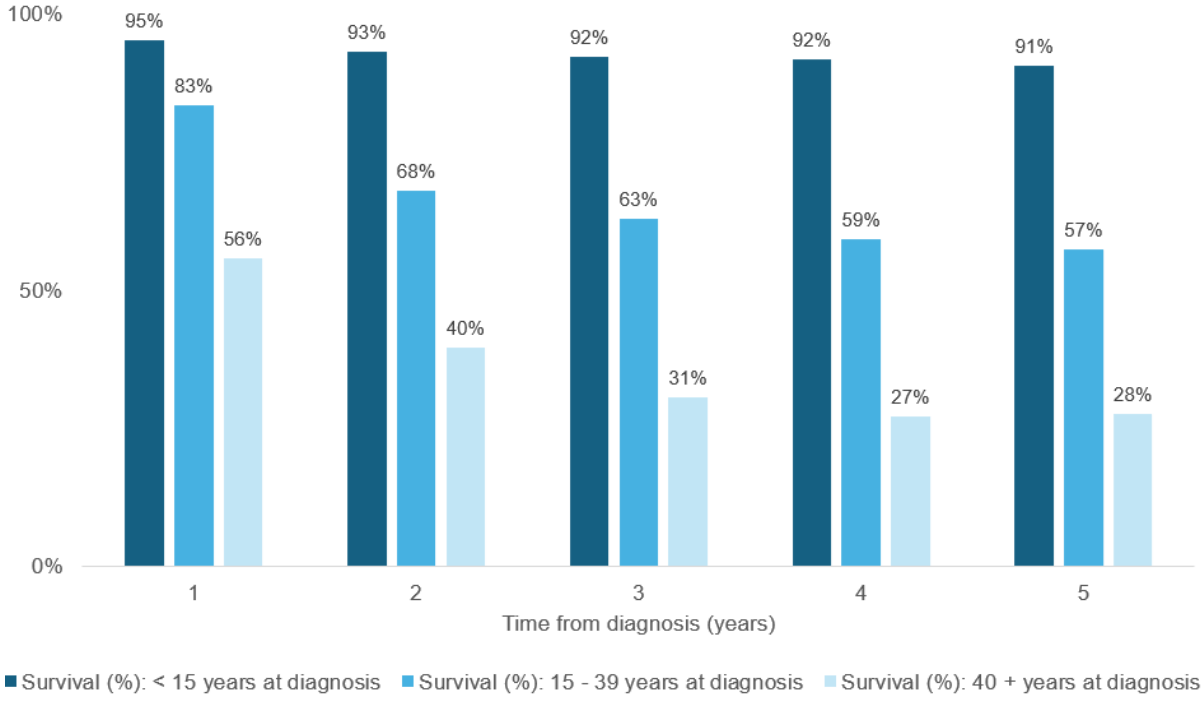
B.1.3.1 Disease overview

ALL is a rare, aggressive blood cancer which arises from a build-up of abnormal lymphoblasts in the bone marrow.[6] Lymphoblasts are immature cells which fail to develop correctly into white blood cells (lymphocytes). The lymphoblasts accumulate in the bone marrow, and may spread to the central nervous system (CNS), liver, lymph nodes, spleen and other organs.[23,24] ALL most commonly affects B-lymphocytes, accounting for 75% of cases. B-cells produce infection-fighting antibodies. Abnormal cells failing to develop into functional B-lymphocytes interfere with the production of normal blood cells, weaken the immune system, and increase risk of infection.[23,25]

Survival outcomes in ALL differ substantially based on age, genetic factors and treatment response. The approval of recent technologies including immunotherapy (blinatumomab), anti-body conjugates (inotuzumab ozogamicin [hereafter inotuzumab]), and chimeric antigen receptor (CAR) T-cell therapies (brexu-cel and tisagenlecleucel) have dramatically improved prognosis in younger populations.[26]

Overall survival (OS) for children and adolescent young adults (aged ≤25) are 90% and 70-80% at 5 years, respectively. By contrast, five-year United Kingdom (UK) survival rates for patients aged 15-39 at diagnosis is 57%, and as low as 28% in patients older than 40 at diagnosis (Figure 3).[8] Furthermore, 40% of adult ALL patients relapse following treatment. Survival rates following relapse ranges from <10% to circa 25%.[9]

Figure 3: Net survival by age of diagnosis



Adapted from HMRN.[8]
HMRN – Haematological Malignancy Research Network

Philadelphia chromosome (Ph) status in ALL refers to whether the Philadelphia chromosome is present, an abnormality resulting from a t(9;22) (q34;q11) translocation which results in a Breakpoint Cluster Region-Abelson Murine Leukaemia (BCR-ABL) 1 fusion gene.[27] Ph status impacts characteristics, treatment strategy, and prognosis of ALL.[27,28]

Absence of the Philadelphia chromosome (Ph-) is more common than Philadelphia chromosome-positive (Ph+) ALL, especially in younger populations. Ph+ accounts for circa 20-30% of adult ALL, with increased frequency in older populations, representing up to 50% of ALL cases in patients aged 50 and older.[28] Ph+ ALL patients are at greater risk of CNS involvement and a more aggressive clinical course.[28] Ph+ ALL have historically had a considerably worse prognosis than Ph- ALL, although this has improved with the emergence of TKIs.[28]

There is no standard numbered staging system for adult ALL. The disease is described in stages based on treatment response: untreated, in remission or recurrent.[23]

- **Untreated:** Newly diagnosed disease, with no treatment given except symptom relieving, and either an abnormal complete blood count (CBC), ≥5% bone marrow (BM) blasts (leukaemia cells), or signs and symptoms of leukaemia.[23]
- **Remission:** CBC deemed normal, ≤5% BM blasts, and no signs of leukaemia except for in the bone marrow.[23]
- **Recurrent:** Leukaemia cells reappearing in the blood, BM, or other parts of the body following a period of remission.[23]

Relapsed ALL is when the ongoing disease returns after an initial remission/suppression of symptoms,[29] and refractory ALL is when remission is not achieved following treatment. Only 30-40% of adult patients achieve long-term remission.[24,25,30]

B.1.3.2 Epidemiology

In the UK, the incidence of ALL is 1.1 per 100,000 people. Between 2016 and 2018, there were an average of 791 new UK ALL cases each year. ALL accounts for 10% of all leukaemia cases.[7]

While ALL is more common in children, around 40% of cases in the UK occur in adults aged 20 or older. A total of 6% of all cases diagnosed in the UK are in people aged 75 and over and around 60% of all ALL diagnoses are male.[7]

B.1.3.3 Clinical presentation, diagnosis and treatment outcomes

The clinical presentation of ALL is characterised by symptoms caused by a lack of platelets, commonly including fatigue, pale skin, fever, swelling of lymph nodes, joint pain, bleeding and bruising.[31] Patients may also present signs of bone marrow failure including anaemia, thrombocytopenia and leukopenia, with 20% of patients experiencing involvement of extramedullary sites such as lymphadenopathy, splenomegaly and hepatomegaly.[25]

In the UK, patients displaying any of these symptoms receive initial blood tests and a physical examination from a general practitioner (GP).[6] Further tests are conducted by a haematologist to confirm the diagnosis, e.g., bone marrow testing,

immunophenotyping, lumbar puncture, scans including computer tomography (CT), magnetic resonance imaging (MRI) and X-ray, and tissue typing tests.[6] Diagnosis with ALL is established by ≥20% lymphoblast presence in the blood or bone marrow.[25]

Following diagnosis, tests such as CT scans, MRIs, chest x-rays and lumbar puncture to sample cerebrospinal fluid (CSF) are conducted to assess whether the ALL has spread to the CNS or other parts of the body.[23] Symptoms indicating that ALL has spread to the CNS are most commonly cranial nerve deficits or meningismus.[25]

The aim of treating ALL is to extend a patient's life, while preserving quality of life (QoL) and minimising the invasiveness and toxicity of treatment. Treatment response is defined in terms of prolonged survival, complete remission (CR) and complete remission with incomplete haematological recovery (CRi). CR is defined as meeting the following within the same disease assessment:

- **Bone marrow:** <5% BM blasts and trilineage haematopoiesis.
- **Peripheral blood:** no lymphoblasts in peripheral blood, absolute neutrophil count (ANC) >1000/μL, platelet count >100,000/μL, no platelet transfusions in the last seven days, and no administration of short- or long- acting Granulocyte colony stimulating factor in the last three or 14 days respectively.
- **Extramedullary disease**: no extramedullary disease.[4]

CRi is defined as meeting all criteria for CR, except platelet count or ANC.[4]

B.1.3.4 Clinical pathway in B-cell ALL

B.1.3.4.1 First line ALL

B-cell ALL treatment is initiated rapidly after diagnosis and generally takes two to three years to complete.[32] First line patients receive initial treatment with chemotherapy drugs which can include vincristine, doxorubicin, cyclophosphamide, cytarabine, asparaginase and/or methotrexate. If B-cell ALL has spread to the CNS, patients will be treated with extra intrathecal chemotherapy, and those who are Ph+ receive a tyrosine kinase inhibitor (TKI) alongside treatment (commonly imatinib).[33]

Following CR, to prevent disease recurrence, patients receive consolidation and intensification phases with stronger treatment, commonly chemotherapy, including doxorubicin, asparaginase, methotrexate, cytarabine, etoposide, daunorubicin, cyclophosphamide and mercaptopurine. Some patients have an allogeneic haematopoietic stem cell transplantation (allo-SCT) or a BM transplant, each of which requires myeloablative or reduced intensity conditioning therapy.[33]

Finally, patients spend approximately two years on maintenance therapy, with the aim of keeping the leukaemia in remission. Maintenance therapies include short steroid courses, with methotrexate, vincristine, mercaptopurine and prednisolone, and weaker chemotherapy injections.[33]

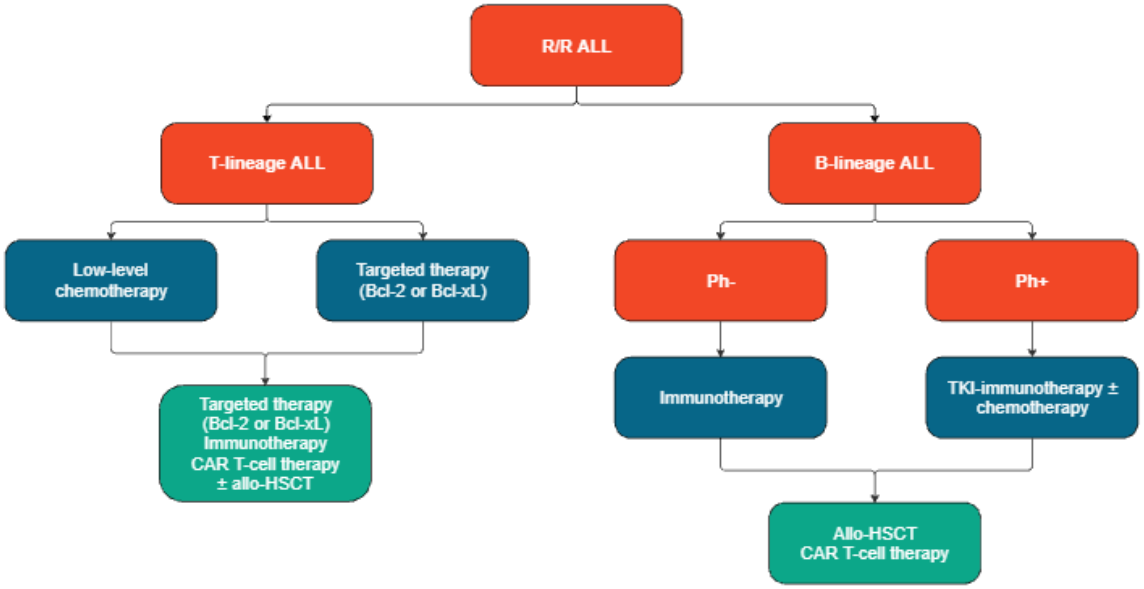
B.1.3.4.2 Relapsed/refractory ALL

There are no UK specific guidelines for the treatment of adults with relapsed/refractory (R/R) B-cell ALL. In general, treatment of R/R B-cell ALL is independent of treatments received for first line B-cell ALL. An overview of the European Society for Medical Oncology (ESMO) R/R B-cell ALL treatment guidelines are summarised below:[13]

- Immunotherapy (blinatumomab or inotuzumab) is recommended as first-line treatment and considered superior to standard chemotherapy. Tumour burden reduction should be considered before initiating blinatumomab. Inotuzumab is preferred in patients with no prior liver disease.[13]
- Allo-HSCT is recommended as a subsequent treatment, if sufficient reduction in minimal residual disease (MRD) has been achieved by bridging therapy. Immunotherapy in combination with a potent TKI (ponatinib) can reduce the need for allo-HSCT.[13] Allo-HSCT is a potentially curative treatment option, however, a number of factors that affect eligibility of receiving allo-HSCT. Donor availability, remission status, depth of remission and comorbidities can all influence whether a patient is eligible for allo-HSCT.[13]
- CAR T-cell therapy is recommended following immunotherapy. Bridging with blinatumomab is not recommended due to a lower CR rate seen in trials.[13]

- As CAR T-cell therapy for B-cell ALL is typically associated with considerable and potentially life-threatening immunotoxicity (cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)), ESMO recommends strategies to prevent CAR T-cell associated immunotoxicity. Strategies include pre-emptive use of immune modulators (tocilizumab, corticosteroids), fractionated CAR T-cell dosing, and modified CAR T-cell design, e.g., fast-off-rate CD19 binding elements.

Figure 4: Treatment algorithm for R/R ALL based on ESMO guidelines



Adapted from ESMO.[13] **Orange:** general categories or stratification; **blue:** systemic anti-cancer therapy; **turquoise:** combination of treatments or other systemic treatments.
ALL – Acute lymphoblastic leukaemia; allo-HSCT – allogeneic haematopoietic stem cell transplantation; Bcl – B-cell lymphoma; CAR – chimeric antigen receptor; ESMO - European Society for Medical Oncology; Ph+ - Philadelphia chromosome-positive; Ph- - Philadelphia chromosome negative; R/R – relapsed/refractory; TKI – tyrosine kinase inhibitor

Table 5 provides an overview of R/R B-cell ALL treatments recommended by NICE to date. Tisagenlecleucel is not deemed a relevant comparator to obe-cel as it is only eligible for patients aged 25 or younger.[14] Blinatumomab is only recommended for Ph- patients while ponatinib is only recommended for Ph+ patients.[15,16]

Table 5: NICE guidance for the treatment of R/R adult ALL

NICE submission	Recommendations
TA893[17]	Brexu-cel is recommended for use within the CDF for treated R/R B-cell ALL patients who are 26 years or older.

Company evidence submission template for obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID6347]

TA450[15]	Blinatumomab is recommended for adults with Ph- R/R B-cell ALL.
TA451[16]	Ponatinib is recommended for patients with Ph+ ALL who are resistant to dasatinib or the T315I gene is present.
TA541[18]	Inotuzumab is recommended for the treatment of CD22-positive R/R B-cell ALL. Ph+ patients should have been treated with at least one TKI.
TA975[14]	Tisagenlecleucel is recommended for the treatment of B-cell ALL for patients 25 years or younger.

ALL – Acute lymphoblastic leukaemia; CDF – Cancer Drugs Fund; NICE – National Institute for Health and Care Excellence; Ph+ - Philadelphia chromosome-positive; Ph- - Philadelphia chromosome negative; R/R – Relapsed/refractory; TA – Technology appraisal; TKI – Tyrosine kinase inhibitor.

B.1.3.5 Humanistic burden of ALL

As ALL is a life-threatening disease, patients face a tremendous emotional and mental burden, often resulting in depression and anxiety.[10] Patients' QoL is heavily impacted physically, mentally and emotionally, through debilitating symptoms, invasive treatment and extended hospital stays.[19] A global study conducted in 2019 by the Acute Leukaemia Advocates Network (ALAN) showed that 21% and 26% of patients had been diagnosed with depression or anxiety, respectively, since their diagnosis with ALL.[10] In a qualitative study assessing information shared in social media by 41 adult ALL patients (Crawford *et al.* 2023) 27% reported impact on their usual daily activities (e.g. difficulty with basic self-care [10%], chores and shopping [22%] and hobbies and leisure activities [7%]).[11]

Treatment options such as chemotherapy, BM- and stem cell transplants (SCTs) are invasive, associated with cumbersome side effects and may require inpatient stays. Adverse events associated with these treatments included fatigue (27%), hair loss (27%) and nausea (22%).[11] As such, the burden of treatment is substantial to patients: "*the treatment made me feel worse than the cancer ever did*"[11], and their families: "*wife took time off work and stayed with me most days and overnight.…when I got home, I struggled. I expected to go back to normal but I found it hard to even walk upstairs*".[34]

Treatment with immunotherapy is also associated with a suboptimal safety profile. Inotuzumab is linked with veno-occulsive disease (VOD), a blockage of small blood vessels which can lead to liver failure. In the INO-VATE clinical trial, 9% of patients

experienced grade 3 or higher VOD with two treatment-related deaths occurring.[35] In the TOWER study, 5% of patients on blinatumomab experienced grade 3 or higher CRS.[36] A post-hoc analysis of the efficacy and safety of blinatumomab (TOWER) reported that five deaths occurred due to adverse events, including due to acute respiratory failure, pneumonitis, and tumour lysis syndrome.[37]

Current CAR T treatments are associated with severe, sometimes life-threatening adverse events (AEs) – most commonly CRS and ICANS. Brexu-cel, the only currently available CAR T for adult R/R B-cell ALL patients in the UK (via the Cancer Drugs Fund [CDF]), is associated with very high levels of CRS (89%) and neurological events associated with ICANS (60%).[20,22] Additionally, few patients were in ongoing remission without subsequent therapies such as allo-HSCT at long-term follow-up, suggesting brexu-cel is frequently used as a bridge to SCT.[38]

- **CRS** is a systemic inflammatory response caused by cytokines released by infused CAR T-cells and can lead to widespread organ disfunction.[39]
- **ICANS** initially presents as confusion and impaired motor skills and may progress to seizures and in severe cases, cerebral edema.[40]

In the ZUMA-3 clinical trial, brexu-cel was shown to have a suboptimal safety profile with grade 3 or 4 CRS occurring in 24% of patients and grade 3 or higher neurological events occurring in 25% of patients.[22,41] Two patients died due to complications, including one due to a brain herniation and one to septic shock.[22] This issue is exacerbated in older patient populations; a review of CAR T-cell therapies for the treatment of R/R diffuse large B-cell lymphoma found evidence which suggests higher toxicity in patients aged 65 years and older. The review reported that the rate of grade ≥3 neurotoxicity was 44% and 28% for patients aged ≥65 years and younger patients respectively. The rate of grade ≥3 CRS in the older population was 12% compared to 8% in the younger population.[42]

B.1.3.6 Economic burden of ALL

ALL is associated with substantial resource use and high costs. Healthcare costs associated with blood cancers are approximately twice the average cost per patient across all cancers.[43] Primary cost drivers in ALL include expensive treatments

regimens, often requiring extended hospital stays and follow-up care for treating associated toxicities.

Two health care resource use (HCRU) studies undertaken in the UK, France, Germany, Italy, and Spain independently identified substantial HCRU attributed to R/R ALL, and a need for novel therapies reducing the HCRU burden.[44,45] Key cost drivers include hospitalisations and intensive care unit (ICU) stays. Zhang *et al.*, a Delphi-based study in adults with Ph+ R/R ALL found that the UK mean inpatient stays for patients receiving chemotherapy were 31 days (induction) and 23 days (consolidation treatment).[45] Cool *et al.*,a retrospective chart review of R/R ALL patients found that the proportion hospitalised over the duration of treatment ranged from 27% (primary refractory) to 40% (relapsed, post-SCT) in second line patients, and from 34% (primary refractory) to 48% (relapsed, post-SCT) in third line patients. Mean length of stay was 15 days in second line patients, and 14 days in third line patients. On average, 34% and 35% of patients required ICU stays in first- and second line.[44] Hospitalisations, particularly ICU stays, incur high costs. ICU stays have a cost of £2,412 per day, using NHS reference costs 2022/2023.[46]

An ongoing HCRU study conducted in FELIX trial patients from the US, Spain and the UK is the first to estimate care costs for B-cell ALL patients following CAR T-cell therapy.[47] Findings to date suggest that costs and HCRU following treatment with obe-cel are substantially reduced in the long term, with only 8% of costs incurred after month 3. Only 11% of patients required ICU stays, with a mean length of stay of 9 days.[47]

While UK specific information on the indirect costs of ALL are scarce, international studies suggest a considerable impact on productivity. A qualitative social media review by Crawford *et al*. found that 39% of adult ALL patients reported impact on their ability to work.[11] As 34% of new ALL cases in the UK occur in working age population, there are likely substantial productivity losses due to the disease.[7] A Danish nationwide cohort study by Maksten *et al*. found that only 42%, 66% and 61% of ALL patients working prior to diagnosis returned to work one, three, and five years after treatment, respectively.[12]

B.1.3.7 Unmet need

Despite improvements to the ALL treatment landscape, survival rates in adult R/R B-cell ALL remain low and treatment-associated morbidity remains high.[26] Currently available CD19 targeting CAR T-cell therapies have improved outcomes for patients who historically have had poor results to therapy; however, the severe and sometimes life-threatening toxicities associated with current options render them unsuitable for older and fragile patients.[48–50]

The need for a safe and effective treatment option is further exacerbated by the large HCRU and cost burden incurred by ALL patients. Firstly, the condition itself requires vast amounts of costly and life-interrupting resources such as specialist appointments, hospitalisations, ICU stays and emergency room (ER) visits.[19,43] The costs and resource use required to mitigate and treat therapy-related side effects, notably CRS and ICANS, result in a large humanistic and economic burden.[19,43] Furthermore, treatment-related symptoms reduces patients' productivity, and render a large proportion of patients unable to return to work.[11]

Taking the above into consideration, there is a clear unmet need for an effective treatment which reduces resource use and patient burden via an improved safety profile. There is particular unmet need for older and relapsed and refractory ALL patients who are ineligible for current CAR T-cell therapies.

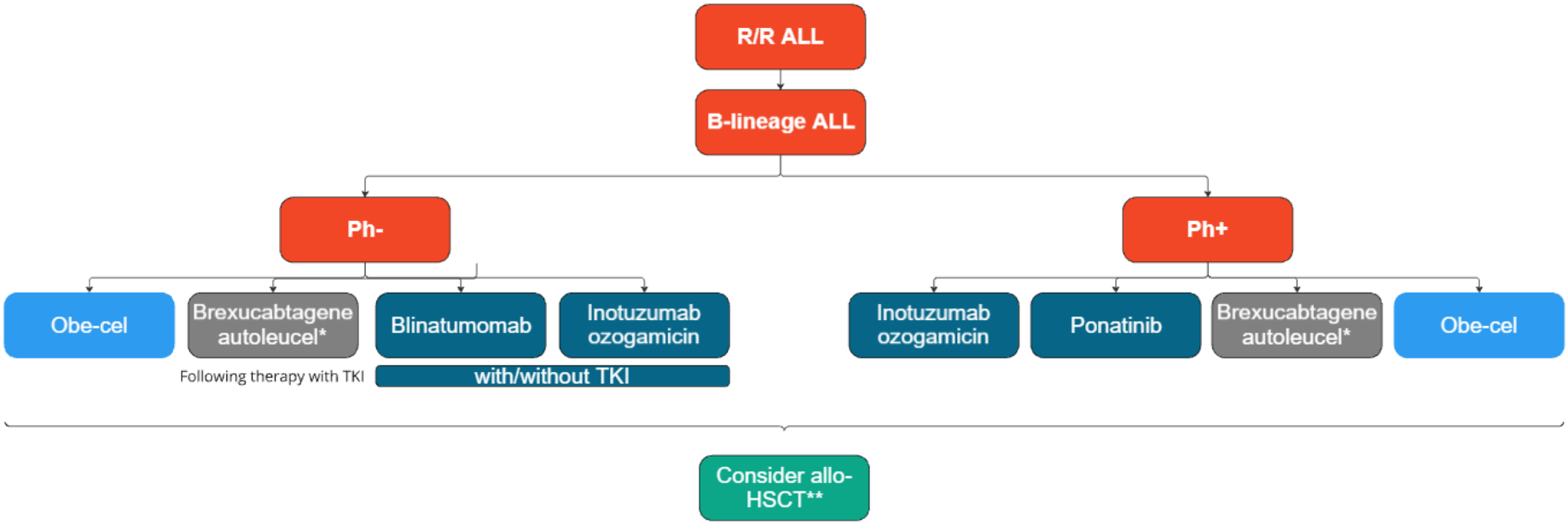
B.1.3.8 Place of obe-cel in therapy of ALL

Obe-cel is a novel autologous CD19 CAR T-cell therapy, binding to and eliminating CD19 expressing B-cells. Obe-cel is designed with a low-affinity CD19 bunder to improve CAR T activity and persistence. The safety and efficacy of obe-cel is currently being investigated in pivotal, open-label, single-arm Phase Ib/II study FELIX. Results to date indicate comparable or improved efficacy outcomes to those observed for brexu-cel in ZUMA-3, and a lower proportion of CRS and ICANS, indicating an improved safety profile. At latest data cut-off (7th February 2024, median follow-up 20.25 months), the overall remission rate (ORR, defined as CR + CRi) for infused patients in FELIX was 77%. This is in line with the 71% brexu-cel ORR in ZUMA-3.[21,22] To date, only 2% of all treated patients in FELIX experienced grade ≥3 CRS and 7% experienced grade ≥3 ICANS, In contrast, 24% and 26%

patients treated with brexu-cel in the ZUMA-3 trial experienced grade ≥3 CRS and grade ≥3 ICANS, respectively.[22]

The proposed positioning of obe-cel in the treatment pathway is displayed in Figure 5.

Figure 5: Proposed positioning of obe-cel in the R/R B-cell ALL treatment pathway



ALL – acute lymphoblastic leukaemia; allo-HSCT – allogeneic haematopoietic stem cell transplantation; Ph+ - Philadelphia chromosome-positive; Ph- - Philadelphia chromosome negative; R/R – relapsed/refractory; TKI – tyrosine kinase inhibitor
Note: The TA893 NICE recommendation for brexu-cel differs from ESMO guidelines presented in Figure 4 in that it does not restrict brexu-cel to 2L+ in the Ph+ population.

*Brexucabtagene autoleucel is available through the Cancer Drugs Fund and is not considered a comparator in this appraisal.
**Allo-HSCT is part of the treatment pathway, however, is not considered a comparator, but rather an outcome.

B.1.4 Equality considerations

There are no known equality issues relating to the use of obe-cel in patients with B-cell ALL.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

An update to the SLR conducted for TA893 was undertaken, aiming to capture evidence published after the TA893 study period (September 2021). The rationale for conducting an update rather than a *de-novo* SLR was to leverage findings from a recent SLR focused on a similar indication which adhered to NICE guidance and met NICE standards.

A detailed description of the SLR update methods is provided in Appendix D.

To meet the study objective for the cost-effectiveness SLR, the following research question was addressed:

- What is the efficacy and safety reported in clinical studies for treating adult patients with R/R ALL?

A total of 29 clinical references, reporting four clinical trials (NCT04521231, INO-VATE, ZUMA-3 and FELIX), 10 observational studies, and five pooled analyses (TOWER and Study 265; TOWER, NCT01209286 and NCT01466179; NCT01209286 and NCT01466179; INO-VATE and Study 1010; and FELIX and ALLCAR19) met the criteria for inclusion (Table 6). Three interventions were assessed as part of these trials (obe-cel, blinatumomab, inotuzumab, and brexu-cel). The clinical trials were based across a range of countries.

Table 6: Summary of clinical studies (n=29)

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
Clinical trials						
NCT04521231	Jabbour *et al*. 2024[51]	Blinatumomab	Adult patients with R/R B-cell ALL	Multicentre, single-arm, open-label, phase Ib trial	CR/CRh within two cycles MRD-negative Safety	Age Sex Race ECOG PS Prior LOT Refractory to first-line therapy Previous allogeneic stem cell transplantation Previous anti-CD19 CAR T-cell therapy Previous cIV blinatumomab Maximum bone marrow blasts
INO-VATE	Kayser *et al*. 2023[52]	Inotuzumab, SoC	Adult patients with R/R B-cell ALL	Multicentre, global, open-label, randomised, phase III trial	CR Partial remission Refractory disease MRD OS	Age Sex Median WBC x109 /L Median platelets x10^9 /L Median haemoglobin, g/dL Median LDH, U/L Median BM blasts, % ECOG PS

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
						Cytogenetics
	Kantarjian *et al.* 2021[53]	Inotuzumab, SoC	Adult patients with R/R CD22-positive B-cell ALL	Multicentre, global, open-label, randomised, phase III trial	OS CR/CRi MRD rate duration of remission (DoR) Duration of CR PFS Patient-reported outcomes	Median leukemic blast CD22 positivity
ZUMA-3	Shah *et al.* 2023[54]	Brexu-cel	Adult patients with R/R B-cell ALL	Single-arm, multicentre, phase I/II	CR/CRi DoR Relapse-free survival OS Safety	Gender Age ECOG PS Philadelphia chromosome-positive Extramedullary disease at screening CNS-1 disease at baseline Bone marrow blasts at baseline CD19 lymphoblast baseline category per central laboratory

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
						Number of prior therapies Prior blinatumomab Prior inotuzumab Prior allo-SCT Prior radiotherapy Primary refractory Relapsed or refractory to second or greater line of therapy First relapse with remission ≤12.0 months Relapsed or refractory postalloSCT Response to the last prior therapy
	Shah *et al.* 2023[55]	Brexu-cel	Adult patients with R/R B-cell ALL	Single-arm, multicentre, phase I/II	CR/CRi DoR Relapse-free survival OS Safety	Age Bone marrow blasts
	Shah *et al.* 2023[56]	Brexu-cel	Adult patients with R/R B-cell ALL	Single-arm, multicentre, phase I/II	CR/CRi DoR Relapse-free survival	Prior LOT

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
					OS Safety	
	Hadjivassileva *et al.* 2023[57]	Brexu-cel	Adult patients with R/R B-cell ALL	Single-arm, multicentre, phase I/II	CR/CRi DoR Relapse-free survival OS Safety	Prior LOT
	Shah *et al.* 2022[58]	Brexu-cel	Adult patients with R/R B-cell ALL	Single-arm, multicentre, registrational, phase I/II	CR/CRi DoR Relapse-free survival OS Safety	Age Baseline BM blasts
	Bouchkouj *et al.* 2022[59]	Brexu-cel	Adult patients with R/R B-cell ALL	Single-arm, multicentre, registrational, phase I/II	CR/CRi Safety	Age Gender Race Ethnicity Baseline ECOG status Disease characteristics Disease status at enrolment
	Shah *et al.* 2021[22]	Brexu-cel	Adult patients with R/R B-cell ALL	Phase I/II, single-arm, open-label study	CR/CRi MRD- DoR Relapse-free survival	Gender Age Race ECOG PS

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
					OS Allo-SCT rate Safety	Philadelphia chromosome-positive Extramedullary disease at screening CNS-1 disease at baseline Number of previous therapies Relapsed or refractory Bone marrow blasts at screening Bone marrow blasts at baseline Bone marrow blasts at pre-conditioning after bridging chemotherapy
	Shah *et al.* 2021[60]	Brexu-cel	Adult patients with R/R B-cell ALL	Phase I/II, single-arm, open-label study	CR/CRi DoR Relapse-free survival OS Safety	Gender Age ECOG PS Philadelphia chromosome-positive Extramedullary disease CNS disease at screening Previous regimens Prior blinatumomab Prior inotuzumab Refractory status

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
						Percentage of BM blasts
FELIX	Roddie *et al.* 2024[61]	Obe-cel	Adult patients with R/R B-cell ALL	Open-label, multicentre, global, single-arm Phase Ib/II study	CR/CRi MRD-	NR
	Roddie *et al.* 2023[62]	Obe-cel	Adult patients with R/R B-cell ALL	Open-label, multicentre, global, single-arm Phase Ib/II study	CR/CRi Safety	Age Median prior LOT
	Jabbour *et al.* 2024[63]	Obe-cel	Adult patients with R/R B-cell ALL	Open-label, multicentre, global, single-arm Phase Ib/II study	CR/CRi MRD- EFS OS	Age Prior LOT
Pooled analyses						
TOWER and Study 265	Kobayashi *et al.* 2021[37]	Blinatumomab	Asian adult patients with R/R B-cell ALL	Post-hoc pooled analysis	CR OS Duration of relapse-free survival Safety	Gender Age ECOG PS B-ALL subtype Prior allo-HSCT Number of relapses Number of salvage therapies
TOWER, NCT01209286	Topp *et al.* 2021[64]	Blinatumomab	Adult patients with R/R B-cell ALL	Pooled analysis	OS Relapse-free survival	Age Gender Race

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
and NCT01466179					MRD CR/CRi Safety	ECOG PS Prior allo-HSCT Bone marrow blasts
NCT01209286 and NCT01466179	Topp *et al.* 2021[65]	Blinatumomab	Adult patients with R/R B-cell ALL	Pooled analysis	OS Relapse-free survival	Age Gender Race Primary refractory Prior relapses Prior HSCT Bone marrow blasts Cytogenetic factors, ECOG PS
INO-VATE and Study 1010	Chen *et al.* 2021[66]	Inotuzumab	Adult patients with R/R B-cell ALL	Pooled analysis	CR/CRi MRD-	Age Gender Race ECOG PS CD22-positivity Salvage therapy Cytogenetics
FELIX and ALLCAR19	Roddie *et al.* 2024[61]	Obecabtagene autoleucel	Adult patients with R/R B-cell ALL	Pooled analysis	CR/CRi MRD-	Age Gender Race Ph status Prior therapies

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
						Prior SCT BM blasts at screening EMD at screening
Observational studies						
Torrent 2023	Torrent *et al.* 2023[67]	Inotuzumab	Adult patients with R/R B-cell ALL	Observational, retrospective, multicentre study	Early death CR/CRi CR duration PFS OS Performance of allo-HSCT after IO	Gender Age ECOG PS Median WBC x10^9 /L BM blasts Extranodal involvement Immunophenotype Karyotype before IO No. of prior treatment lines Allo-HSCT prior to IO Duration of 1st CR prior to IO Response to line before IO
Ribera 2021	Ribera *et al.* 2021[68]	Inotuzumab	Adult patients with R/R B-cell ALL	Observational, retrospective, multicentre study	DoR PFS OS CR/Cri	Gender Age ECOG PS Median WBC x10^9 /L BM blasts Prior LOT

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
ROCCA	Roloff *et al.* 2023[69]	Brexu-cel	Adult patients with R/R B-cell ALL	Observational, real-world, multicentre study	CR MRD- DoR PFS OS	Age Gender Race Prior LOT
Sartor 2022	Sartor 2022[70]	Inotuzumab	Adult patients with R/R B-cell ALL	Retrospective, single-centre	CR PR MRD DoR OS	Age Gender Disease Duration of 1st remission Previous blinatumomab Previous HSCT Salvage treatment phase BM blasts FDG-PET scan Karyotype
Aldoss 2021	Aldoss *et al.* 2021[71]	Blinatumomab	Adult patients with R/R B-cell ALL	Retrospective study	ORR MRD-	Gender Age Response to blinatumomab Prior allo-HCT History of EMD Disease setting Blast % before blinatumomab Prior lines of therapy

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
						CD19 expression at progression or relapse
Badar 2021	Badar *et al.* 2021[72]	Blinatumomab, inotuzumab		Multicentre, retrospective cohort analysis	DoR OS CR/CRi DDTAE Safety	Year of start of first drug Age Gender WBC $\times 10^9$ /L Peripheral blasts BM blasts No. of therapies before first novel agent Extramedullary disease, Time to first progression No. of therapies before first novel agent No. of cycles of first novel agent Novel agents given in combination with TKI and/or chemo
Radhakrishnan 2021	Radhakrishnan *et al.* 2021[73]	Inotuzumab	Adult patients with R/R B-cell ALL	Real-world, observational study	MRD- Allo-HCT rate Safety	Age Gender Prior regimens Significant comorbidities DS pre-IO

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
						Line of therapy with inotuzumab CD22 expression Karyotype High-risk cytogenetic/molecular markers Number of inotuzumab cycles
Açar 2023	Açar *et al.* 2023[74]	Blinatumomab	R/R B-cell ALL	Retrospective, single-centre, observational study	Adverse events ORR CR MRD- OS	NR
Papayannidis 2021	Papayannidis *et al.* 2021[75]	Inotuzumab	Adult patients with R/R B-cell ALL	Real-world, observational study	CR/CRi OS PFS Safety	Age Gender Prior LOT
Aldoss 2023	Aldoss *et al.* 2023[76]	Blinatumomab, inotuzumab	R/R Ph-negative B-ALL	Retrospective study	ORR MRD-	Gender Age Response to blinatumomab Prior allo-HCT History of EMD

Study	Reference	Intervention(s)	Population	Study design	Endpoints	Baseline characteristics reported
						Disease setting Blast % before blinatumomab Prior lines of therapy CD19 expression at progression or relapse

AE – Adverse Event; ALL – Acute Lymphoblastic Leukaemia; Allo-HSCT – Allogeneic Haematopoietic Stem Cell Transplantation; BM – Bone Marrow; CAR – Chimeric Antigen Receptor; CNS – Central Nervous System; CR – Complete Remission; CRh – Complete Remission with Partial Haematologic Recovery; CRi – Complete Remission with incomplete haematologic recovery; DDTAE – Duration of Deepening or Deepening to Any Extent; DoR – Duration of Response; ECOG PS – Eastern Cooperative Oncology Group Performance Status; EGIL – European Group for the Immunological Characterisation of Leukaemias; EFS – Event-Free Survival; EMD – Extramedullary Disease; ESMO – European Society for Medical Oncology; FDG-PET – Fluorodeoxyglucose-Positron Emission Tomography; inotuzumab – Inotuzumab Ozogamicin; IO – Inotuzumab Ozogamicin; LOT – Line of Therapy; MRD – Minimal Residual Disease; NA – Novel Agent; NCT – National Clinical Trial; NTC – Non-Tumour Cells; ORR – Overall Remission Rate; OS – Overall Survival; PFS – Progression-Free Survival; PR – Partial Remission; RR – Relapsed or Refractory; SoC – Standard of Care; TKI – Tyrosine Kinase Inhibitor; WBC – White Blood Cell.

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 FELIX (NCT04404660)

The safety and efficacy of obe-cel is being assessed in ongoing open-label, multicentre, single-arm Phase IB/II study FELIX. An overview of the FELIX clinical trial is presented in Table 7, with outcomes used in the economic model in bold.

Table 7: Clinical effectiveness evidence

Study	**FELIX (NCT04404660)**
Study design	An open-label, multicentre, single-arm Phase IB/II study designed to assess the safety and clinical efficacy of obe-cel in adult patients with R/R B-cell ALL
Population	Adults (>18 years) with R/R B-cell ALL
Intervention(s)	Obecabtagene autoleucel (obe-cel)
Comparator(s)	None (FELIX is a single-arm trial)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	• Overall survival • Progression-free survival (including relapse-free survival and event-free survival) • Treatment response rate (including minimal residual disease, haematologic responses and complete remission) • Rate of allogenic stem cell transplant • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• Duration of remission • Proportion of patients undergoing SCT prior to leukaemia relapse* • Proportion of patients in CR/CRi without SCT or other subsequent therapies at 6, 12 and 24 months following obe-cel infusion • Depletion of circulating B ells assessed by flow cytometry in the peripheral blood • Frequency and duration of hospitalisation and/or critical care support to manage obe-cel related toxicity

ALL – Acute lymphoblastic leukaemia; CR – Complete remission; CRi – Complete remission with incomplete haematologic recovery; N/A – Not applicable; R/R – Relapsed/refractory; SCT – Stem cell transplant
*This outcome was only used in a scenario

B.2.2.2 ALLCAR19

ALLCAR19 is an ongoing phase I, open-label study conducted in three UK centres, measuring the safety and efficacy of obe-cel in 20 treated patients. The latest data cut of ALLCAR19 includes up to 60 months of follow-up. Data from ALLCAR19 are presented in Section B.3.3.1 and B.3.3.2, to demonstrate long-term outcomes in a relevant cohort of patients treated with obe-cel.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

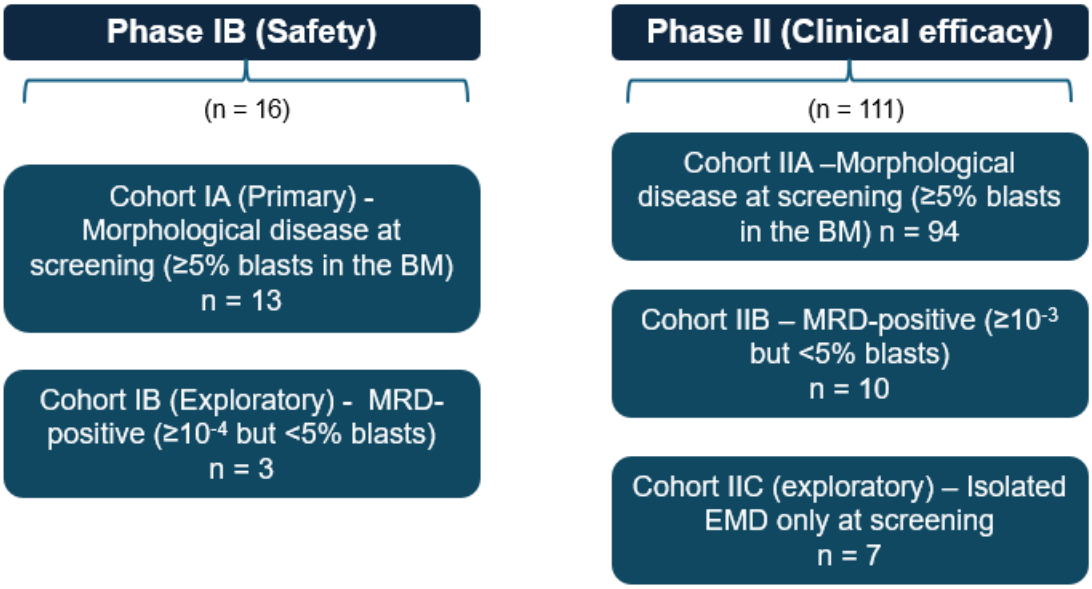
FELIX is an ongoing open-label, multicentre, single-arm Phase IB/II study designed to assess the safety and clinical efficacy of obe-cel in adult patients with R/R B-cell ALL. Considering the aggressive and life-threatening nature of R/R ALL, randomising patients to a control arm that may not receive a potentially life-saving therapy would have been unethical.

The FELIX trial consists of two phases (Figure 6):

- **Phase IB:** Designed to evaluate the safety of obe-cel and the manufacturing and dosing of the product in a multicentre setting. In Cohort IA, 21 patients with morphological disease (≥5% blasts in the BM at screening) were enrolled and 13 patients were treated with obe-cel. In Cohort IB, three patients in morphological remission with MRD-positive disease (≥ 10^{-4} and < 5% blasts in the BM at screening) received treatment. A total of 16 patients were infused with obe-cel in phase IB. Once at least six patients had been treated with obe-cel and monitored for four weeks, the safety data were evaluated and it was decided whether it was appropriate to continue with Phase II of the study.
- **Phase II:** Designed to evaluate the efficacy of obe-cel by determining the overall remission rate (ORR). ORR is defined as complete remission (CR) or complete remission with incomplete haematologic recovery (CRi). The Phase II part of the trial (129 enrolled patients, of which 111 were infused) consists of three cohorts:

- **Cohort IIA:** Adults with R/R B-cell ALL who have ≥5% blasts in the BM at screening (112 enrolled patients, whereof 94 were infused).
- **Cohort IIB:** Adults with R/R B-cell ALL in morphological remission with minimal residual disease at screening (10 enrolled patients, all infused).
- **Cohort IIC (exploratory cohort):** Adults with R/R B-cell ALL with isolated extramedullary disease at screening (seven enrolled patients, all infused).

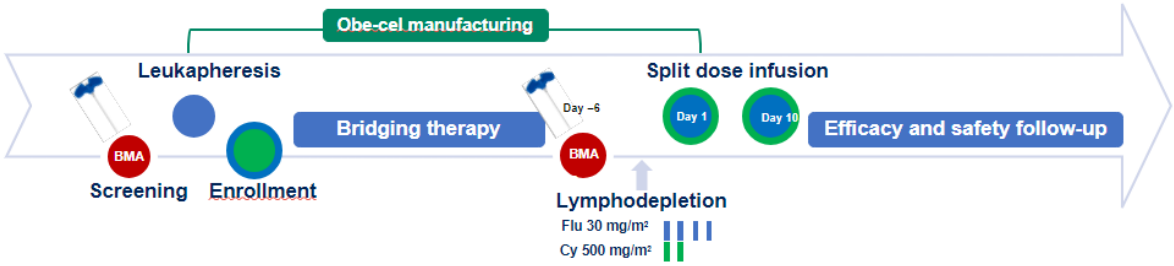
Figure 6: FELIX study design



BM – Bone marrow; EMD – Extramedullary disease; MRD – Minimal residual disease

In both Phase IB and Phase II, patients underwent five sequential stages: screening, leukaperesis, lymphodepletion, treatment and follow-up (Figure 7 with further detail in Appendix N).

Figure 7: FELIX subject treatment stages



BMA – bone marrow analysis, cy – cyclophosphamide, flu – fludarabine, m – meter; mg – milligram

The cohort relevant for this submission is the Cohort IIA modified intent-to-treat (mITT) population (highlighted in red in Figure 8), which comprises patients who received at least one obe-cel infusion (N=94). Cohort IIA best reflects the anticipated licenced population, and mITT best reflects clinical practice given that obe-cel will only be reimbursed for patients who receive at least one dose. Of the 112 patients enrolled in the cohort, 94 received at least one obe-cel dose. The remaining 18 patients either died (n=[redacted]), experienced an adverse event (n=[redacted]), experienced disease progression (n=[redacted]) or did not receive obe-cel due to manufacturing related reasons (n=[redacted]) (Figure 8).

The latest FELIX data available at the time of submission is the February 2024 data cut.[3] This is the data cut used throughout this submission, except where explicitly stated otherwise.

Figure 8: Patient cohorts and participant flow in FELIX

The red line indicates the infused Cohort IIA set, which is the patient cohort of interest for this submission.

B.2.3.2 Trial methodology

Table 8 provides an overview of the trial methodology for FELIX.

Table 8: FELIX trial methodology

Location	FELIX was conducted across 34 study centres across North America, Spain, and the United Kingdom (8 sites in the UK).
Trial design	An open-label, multicentre, single-arm Phase Ib/II study designed to assess the safety and clinical efficacy of obe-cel in adult patients with R/R B-cell ALL
Eligibility criteria for participants	**Inclusion criteria:** • Age 18 years or older • ECOG performance status of 0 or 1 • Relapsed or refractory B-cell ALL • Patients with Ph+ ALL were eligible if intolerant to TKI, failed two lines of any TKI, or failed one line of second-generation TKI, or if TKI is contraindicated • Documented CD19 positivity within 1 month of screening • Phase Ib: Primary Cohort IA: Presence of ≥5% blasts in BM at screening • Phase Ib: Exploratory Cohort IB: MRD-positive defined as ≥ 1e-4 and <5% blasts in the BM at screening • Phase II: Primary Cohort IIA: Presence of ≥5% blasts in BM at screening • Phase II: Cohort IIB: ≥2nd CR or CRi with MRD-positive defined as ≥1e-3 by central ClonoSEQ® NGS testing and <5% blasts in the BM at screening • Adequate renal, hepatic, pulmonary, and cardiac function **Exclusion criteria** • Phase Ib (Cohort IA and Cohort IB) and Phase II (Cohort IIA and Cohort IIB) B-cell ALL with isolated EM disease • Diagnosis of Burkitt's leukaemia/lymphoma or CML lymphoid in blast crisis • History or presence of clinically relevant CNS pathology • Presence of CNS-3 disease or CNS-2 disease with neurological changes • Presence of active or uncontrolled fungal, bacterial, viral, or other infection requiring systemic antimicrobials for management • Active or latent Hepatitis B virus or active Hepatitis C virus • Human Immunodeficiency Virus (HIV), HTLV-1, HTLV-2, syphilis positive test • Prior CD19 targeted therapy other than blinatumomab. Patients who have experienced Grade 3 or higher neurotoxicity following blinatumomab treatment.

Settings and locations where data were collected	**Clinical sites:** 34 locations in the US (n=23), Spain (n=3) and the UK (n=8)
Study periods and trial drugs	The patients in the trial went through five sequential periods described in Section B.2.3.1, Figure 7.
Prior and concomitant medication	Bridging chemotherapy between leukapheresis and one week prior to start of lymphodepleting treatment. The choice of bridging therapy was based on the investigator's choice and local practice. In Ph+ patients who achieved CR after obe-cel infusion, treatment with a TKI could be resumed no earlier than two months after obe-cel infusion and after discussions with the medical monitor. Intrathecal therapies for CNS prophylaxis could be given post obe-cel infusion per Investigator discretion in accordance with institutional guidelines but should be avoided for at least eight weeks after obe-cel infusion.
Primary outcome	**Phase IB:** To evaluate the safety of obe-cel. Frequency and severity of AEs and SAEs occurring after obe-cel infusion. **Phase II:** To evaluate the clinical efficacy of obe-cel. **Cohort IIA:** ORR defined as the proportion of patients achieving CR or CRi as assessed by IRRC. **Cohort IIB:** Proportion of patients achieving MRD-negative remission by central ClonoSEQ NGS testing ($<10^{-4}$ leukemic cells)
Secondary outcomes used in the model/specified in the scope	DOR OS EFS MRD
Pre-planned subgroups	**Efficacy subgroup analysis:** • CNS status at screening (CNS1 / CNS2) • Karyotype at pre-conditioning (normal / abnormal / unknown) **Safety subgroup analysis:** • Prior blinatumomab and inotuzumab **Efficacy and Safety subgroup analyses included:** • Sex (male / female) • Age groups (≥18 to ≤25 / >25 to <40 / ≥40 to <65 / ≥65) • Race (Asian / black or African American / White / unknown) • Ethnicity (Hispanic or Latino / Not Hispanic or Latino / unknown) • EMD at screening (absent / present) • EMD at LD (absent / present) • Blasts in BM at screening (≥5% to ≤20% / >20% to ≤75% / >75%)

	• Blasts in BM at LD (<5% / ≥5% to ≤20% / >20% to ≤75% / >75%) • Ph chromosome/BCR-ABL status (positive / negative) • Prior lines of therapy (1 / 2 / 3 / ≥4) • Prior allogenic SCT therapy (yes / no) • Prior blinatumomab (yes / no) • Prior inotuzumab (yes / no) • Refractory to all prior lines of therapy (yes / no) • Refractory to 1st prior line of therapy (yes / no) • Refractory to last prior line of therapy (yes / no) • Relapsed to 1st prior line of therapy within 12 months (yes / no)

AE – Adverse event; ALL – Acute lymphoblastic leukaemia; BM – Bone Marrow; CNS – Central nervous system; CR – Complete response; DOR – Duration of remission; EMD – Extramedullary disease; IRRC – International Review and Regulatory Committee; LD – Lymphodepletion; MRD – Minimal residual disease; ORR – Overall remission rate; OS – Overall survival; Ph – Philadelphia chromosome; R/R – Relapsed/refractory; SCT – Stem cell transplant

B.2.3.3 Baseline characteristics

Table 9 and Table 10 present the demographics and disease characteristics for the Cohort IIA mITT population. The majority were aged 25 or older (88.3%), with 74.5% white, 10.6% Asian and 2.1% black patients, and an equal amount of male and female participants (50%). A total of 38.3% of the patients are from the UK.

The population consists of heavily pre-treated patients, a group associated with poor outcomes and a high unmet need. There are indications that patients who failed treatment with blinatumomab have poor response in later lines of therapy,[77] and a higher number of previous treatments is associated with inferior outcomes.[78] Approximately half of the Cohort IIA mITT patients have previously been treated with blinatumomab or inotuzumab (51.1%). All enrolled patients had received at least one prior line of therapy and a majority of the patients (69.2%) had received two or more prior lines of therapy (Table 10). Additionally, all patients had ≥5% BM blasts prior to enrolment; 29.9% had up to 20%, 34.0% had up to 75% and 36.2% had >75%. The percentage of BM blasts is an important early prognostic indicator, with a higher percentage associated with poorer outcomes.[79] The majority of patients, 79.8%, had extramedullary disease (EMD) prior to enrolment, another disease characteristic associated with poor outcomes.[80]

In order to test the generalisability of FELIX to the UK target population, post-hoc subgroup analyses were undertaken in UK patients and in patients aged [redacted] (Section B.2.6.2).

Table 9: Demographics in the FELIX trial (Cohort IIA, mITT)

Demographic		**Infused, mITT (N=94)**
Age (years)	Mean (SD)	48.3 (17.12)
	Median	50.0
Age (years) categorised – n (%)	≥18 to ≤ 25	11 (11.7)
	>25 to < 40	20 (21.3)
	≥40 to < 65	42 (44.7)
	≥65	21 (22.3)
Sex, male – n (%)		47 (50.0)
Race – n (%)	Asian	10 (10.6)
	Black or African American	2 (2.1)
	White	70 (74.5)
	Unknown	12 (12.8)
Country – n (%)	United States	47 (50.0)
	United Kingdom	36 (38.3)
	Spain	11 (11.7)

mITT – Modified intention-to-treat; SD – Standard deviation

Table 10: Disease characteristics in the FELIX trial (Cohort IIA, mITT)

Disease characteristic		**Infused, mITT (N=94)**
Number of prior lines of therapy – n (%)	1	29 (30.9)
	2	36 (38.3)
	3	17 (18.1)
	≥4	12 (12.8)
Refractory to all prior lines of anti-cancer therapy – n (%)		12 (12.8)
Refractory to first-line therapy – n (%)		24 (25.5)
Refractory to last prior line of therapy – n (%)		51 (54.3)
Relapsed to first-line therapy within 12 months – n (%)		41 (43.6)
Previous blinatumomab – n (%)		33 (35.1)
Previous inotuzumab – n (%)		30 (31.9)
Previous blinatumomab and inotuzumab – n (%)		15 (16.0)
Previous blinatumomab or inotuzumab – n (%)		48 (51.1)
Previous allogenic SCT – n (%)		36 (38.3)
Disease status at screening		
BM blasts (%) by morphology prior to enrolment (median)		58.9
BM blasts by morphology prior to enrolment categorised – n (%)	>75%	34 (36.2)
	>20% to ≤75%	32 (34.0)
	≥5% to ≤20%	28 (29.9)
	<5%	0
EMD status prior to enrolment – n (%)	Absent	75 (79.8)
	Present	19 (20.2)
ECOG score – n (%)	0	35 (37.2)
	1	58 (61.7)
	≥2	0
	Missing	1
CD19 status at screening – n (%)	Positive	94 (100)
	Negative	0
	Mixed population (positive+negative)	0
CNS disease history – n (%)	CNS1	81 (86.2)
	CNS2	2 (2.1)
	CNS3	0
	Unknown	11 (11.7)

BM – Bone marrow; CD – Cluster of differentiation; CNS – Central nervous system; ECOG – Eastern Cooperative Oncology Group; EMD – Extramedullary disease; mITT – Modified intent-to-treat; SCT – Stem cell transplant

B.2.3.4 Discontinuation

The majority of infused patients in Cohort IIA ([redacted] of 94, [redacted]) were followed for ≥6 months. The remaining [redacted] discontinued prior to six months. The reasons for

discontinuation were: AEs (3), manufacturing related issues (1), death (1), progressive disease (1) and [redacted]. More than half of the patients ([redacted] of 94, [redacted]) were followed up for ≥12 months.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis population (Cohort IIA)

Intention-to-treat (ITT) population

The ITT population comprises all patients who were enrolled in the study (N=112).

mITT population

The mITT population comprises all enrolled patients who received at least one infusion of obe-cel (N=94), which is the population used for the main efficacy analyses. The main analysis was performed regardless of whether the target dose of obe-cel (410 x 10^6 total CAR-positive T-cells) was received. In total, 85 out of 94 patients received the target dose.

B.2.4.2 Sample size and statistical power

Primary endpoint

The primary endpoint in Cohort IIA was ORR, defined as the proportion of patients achieving CR or CRi.

The primary efficacy analysis tested whether ORR was ≤40% against the alternative hypothesis that ORR was >40% at a one-sided 2.5% level of significance.

The null hypothesis that the true remission rate with obe-cel was 40% was considered reasonable based on the following:

At the start of the FELIX study, blinatumomab had recently received regulatory approval for R/R B-cell ALL.[15] In the phase III TOWER study, the ORR within three months of starting treatment was 42% [95% CI: 37 to 49] for blinatumomab versus 20% [95% CI: 14 to 28] for standard of care (SoC) chemotherapy.[81]

Enrolled patients in FELIX had either already relapsed following blinatumomab treatment, or were blinatumomab naïve. For the relapsed patients, chemotherapy

would be an option for subsequent treatment, and the blinatumomab naïve patients would be eligible for blinatumomab. The expected ORR with these treatments would be in the range of 20% to 42%, making an ORR of 40% a reasonable comparison for obe-cel versus prior treatment.

A sample size of at least 90 infused patients was assessed to provide >94% power to demonstrate statistical significance at one-sided 2.5% level of significance, if the underlying ORR was 60%.

Key secondary endpoint

The key secondary efficacy analysis for Cohort IIA tested whether the CR rate post obe-cel infusion was ≤20% against the alternative hypothesis that the CR was >20% at an overall one-sided 2.5% level of significance.

A CR threshold of 20% was considered to be clinically meaningful as it is between the CR of blinatumomab (34%) and SoC chemotherapy (16%) for patients treated in the TOWER study.[36]

The FELIX study included a broad range of R/R B-cell ALL patients in first, second or later salvage therapy as well as primary refractory patients and post-SCT patients. It was anticipated that approximately 40% of the patients would have been previously treated with either blinatumomab, inotuzumab or both, in addition to various chemotherapeutic regimens. Furthermore, adult patients with high-risk prognostic features such as Ph+ ALL and patients with complex karyotypes were enrolled, ensuring a heterogenous and heavily pretreated patient population. Therefore, a CR of 20% is a reasonable assumption for obe-cel versus SoC.

It should be noted that all patients in the TOWER study were blinatumomab and inotuzumab naïve, and hence had a better prognosis than patients enrolled in the FELIX study.

It was assessed that a sample size of at least 90 infused patients would provide 88% power to demonstrate statistical significance with an overall one-sided 2.5% level of significance, if the underlying CR rate was 35%.

B.2.4.3 Statistical analysis

Primary efficacy endpoint

The primary efficacy endpoint (ORR by IRRC, defined as CR or CRi) was planned to be analysed when at least 90 patients had received infusion with obe-cel and had completed at least six months follow-up post-infusion or discontinued treatment.

A summary of the statistical analysis is presented in Table 11.

Table 11: Statistical analysis performed to analyse the primary efficacy endpoint

Population	**Cohort IIA, mITT (N=94)**
Hypothesis	Whether the ORR with obe-cel was ≤40% against the alternative hypothesis that ORR was >40% at a one-sided 2.5% level of significance.
Statistical analysis	The hypothesis is tested according to the O'Brien-Fleming type alpha spending function. A one-sided p-value from the exact binominal test <0.0026 implies that the ORR of obe-cel treatment is higher than 40%. Conversely, a p-value >0.0026 would imply there is not enough evidence to claim superiority of obe-cel from the efficacy interim analysis. If this had been the case, the primary endpoint would have been continued to be tested during the final analysis at the one-sided 0.0242 significance level. In addition, exact 95% CIs are provided together with the point estimate.
Sample size and power calculation	A sample size of at least 90 infused patients would provide >94% power to demonstrate statistical significance at one-sided 2.5% level of significance, with an underlying ORR of 60%.
Handling of intercurrent events	The following potential intercurrent events were identified, with the corresponding handling strategy described below. **Patients achieve <5% blasts in BM prior to pre-conditioning** • Main analysis to be performed regardless of whether patient had ≥5% or <5% blasts in the BM prior to pre-conditioning (i.e., infused set analysis) • Supplementary analysis to be performed among patients who had ≥5% blasts in the BM regardless of EMD status prior to pre-conditioning • Additional supplementary analysis to be performed among patients who had <5% blasts in BM without EMD prior to pre-conditioning, and who had <5% blasts in BM with EMD prior to pre-conditioning **Patients discontinue treatment without obe-cel infusion** • The main analysis to be performed among patients who receive at least one obe-cel dose (i.e., infused set analysis) • Supplementary analysis to be performed among patients who enrolled in the study, i.e., the patient meets all inclusion/exclusion criteria, and the patient's leukapheresate is accepted for manufacturing (enrolled set analysis) **Did not receive the target CAR T-cell dose** • The main analysis to be performed regardless of whether the target dose is received (i.e., infused set analysis)

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	Discontinued treatment prior to achieving CR or CRi • The main analysis to be performed regardless of whether the 2nd obe-cel infusion is received (infused set analysis) • Supplementary analysis to be performed by whether patients received only one obe-cel infusion or both obe-cel infusions **Initiation of any non-protocol anti-cancer therapy (including HSCT) prior to achieving CR or CRi** • These patients to be considered as not achieving CR or CRi per variable definition. • For patients who achieve CR or CRi after initiation of protocol specified anti-cancer therapies, the response after such therapies will be considered for analysis **Death prior to achieving CR or CRi** • These patients to be considered as not achieving CR or CRi per variable definition.

BM – bone marrow; CAR - Chimeric antigen receptor; CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematological recovery; EMD – extramedullary disease; HSCT - haematopoietic stem cell transplantation; ORR – overall remission rate.

Secondary efficacy endpoints

The key secondary efficacy analysis was conducted only when the primary efficacy endpoint was met, in order to avoid an increased risk of error from performing multiple tests simultaneously. The key secondary endpoint is the CR rate as assessed by the International Review and Regulatory Committee (IRRC), defined as the proportion of patients who achieve a best overall response of CR without initiation of any non-protocol anti-cancer therapies. The analyses of the CR rate follow similar principles as for the ORR endpoint: one-sided binomial testing whether the CR rate is less than or equal to 20% against the alternative hypothesis that the CR rate is greater than 20%.

Other secondary and exploratory efficacy endpoints include:

- **Complete remission within 3 months post obe-cel infusion:** measured using the same methods as for the key secondary efficacy endpoint, except those patients who received CR beyond Month 3 were not counted as meeting the endpoint.
- **MRD-negative remission rate:** analysis performed on the proportion of patients receiving MRD-negative remission by central assessment.
- **Duration of remission:** estimated using the Kaplan-Meier (KM) method among patients who achieved remission after receiving at least one

administration of obe-cel treatment. DOR is defined as the time from CR or CRi to the earliest disease relapse or death.

- **Duration of complete remission:** estimated using the KM method and defined as time from first documented CR to the earliest disease relapse or death. Only patients achieving CR after infusion with obe-cel are included in the analysis.
- **Event-free survival:** estimated using the KM method, performed on the infused dataset and defined as the time from treatment initiation to the earliest of either treatment failure, disease relapse or death.
- **Progression-free survival:** considered equivalent to EFS in this disease setting.
- **Overall survival:** measured using the KM method, performed on the infused dataset and defined as the time from the date of first infusion to the date of death.
- **Incidence of CD19 negative relapse:** summarised descriptively among patients who achieved CR or CRi after infusion with obe-cel.

Safety analysis

Safety analyses, including AE rates and laboratory data, were performed in all patients infused with at least one dose of obe-cel from all cohorts and phases of the study. Safety was assessed by physical examination, vital signs, oxygen saturation and weight, neurocognitive assessment, Eastern Cooperative Oncology Group (ECOG) performance status, clinical laboratory tests, AE and serious adverse event (SAE) monitoring, and concomitant medication usage.

The severity of AEs was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0. CRS and neurological toxicity were graded according to the American Society for Transplantation and Cellular Therapy/American Society for Blood and Marrow Transplantation (ASTCT/ASBMT) consensus grading.[82]

As CRS and ICANS can present with multiple signs and symptoms, such events were recorded with the appropriate grading in the concomitant medication electronic case report form (eCRF). In addition, AEs associated with CRS were collected and

AEs associated with ICANS were recorded separately. Both CRS and ICANS associated AEs were recorded with appropriate NCI CTCAE grading as applicable.

Quality of life analysis

Health-related quality of life (HRQoL) was measured prior- and periodically after infusion with obe-cel. The instruments used for the analysis were the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30), the EuroQol-5 dimension 5 level (EQ-5D-5L) and visual analogue scale (VAS). HRQoL was categorised as having improved, deteriorated or by having no change following treatment with obe-cel.

Subgroup analysis

Key subgroups were based on patients' disease status at screening. Efficacy analyses of the primary endpoint were performed in a broad range of patient subgroups, including those typically associated with a poor prognosis or poorer outcome with other treatments for B-cell ALL (e.g., older age, Ph+, high disease burden based on blasts in BM, and presence of EMD). Refer to Table 8 for a complete list of the pre-planned subgroups.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The quality assessment of FELIX was conducted using the Downs and Black checklist, shown in Appendix N, Table 68.

The overall risk of bias of FELIX is deemed to be low. The primary endpoint of ORR and the key secondary endpoint of CR were assessed by an IRRC, and tested for statistical significance using thresholds set according to those observed for SoC, providing an assessment that is reflective of clinical practice.

The administration of obe-cel was conducted in accordance with local clinical guidelines, and the target dose was equivalent to that of the anticipated marketing authorisation.

Patients enrolled in the study reflect clinical practice in England, including a mixture of patients who had received bridging therapy either with blinatumomab (42%) and

inotuzumab (32%), both of which are recommended treatments for adults with R/R B-cell ALL.

Given single-arm nature of FELIX, an indirect treatment comparison (ITC) was required to provide relative outcome estimates for decision making, as explored in Section B.2.9.

B.2.6 Clinical effectiveness results of the relevant studies

Summary of clinical effectiveness results

- The efficacy and safety of obe-cel has been demonstrated in the open label, multicentre, Phase Ib/II FELIX trial.
- The primary endpoint (>40% achieving ORR defined as CR or CRi at any time post-infusion) was met at the February 2024 data cut-off: 76.6% achieved ORR (95% CI: 66.7 to 84.7, p<0.0001, at a median follow-up of 20.25 months.
- The estimated median DOR increased from [redacted] (95% CI: [redacted] to not estimable) months as of the June 2023 data cut-off to 14.06 (95% CI: 8.18 to not estimable) months as of February 2024.KM estimates of EFS at 6 and 12 months were [redacted] and [redacted].
- KM estimates of OS at 6 and 12 months were [redacted] and [redacted].

B.2.6.1 FELIX Phase II mITT results

To demonstrate the consistency of findings, results from the FELIX trial are presented using two data cut-offs:

- **June 2023:** Data cut-off used for the primary analysis, ≥90 patients with at least 6 months follow-up post obe-cel infusion.
- **February 2024:** The most recent data cut-off

No further patients were enrolled in the FELIX study or treated with obe-cel since the June 2023 data cut-off.

B.2.6.1.1 Primary endpoint: Overall remission rate

The primary efficacy endpoint, ORR (CR or CRi at any time post-infusion) as assessed by IRRC, was met at the February 2024 data cut-off. The median follow-up at the February 2024 cut-off was 20.25 months (range: [redacted] months).

Results from the February 2024 data cut-off found a statistically significant ORR of 76.6% (95% CI: 66.7 to 84.7, p<0.0001).

CR was achieved in a majority of the mITT patients (55.3%). 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 data cut-offs. In the February 2024 data cut, of the 76.6% of patients who achieve ORR, [redacted]% achieved MRD-negative remission to the $<10^{-4}$ level, indicating a substantially low risk of relapse. A summary of ORR outcomes is presented in Table 12.

Table 12: ORR measured by IRRC (Cohort IIA, mITT)

Parameter	**mITT population (n=94)**	
	Jun 2023	**Feb 2024**
ORR (CR + CRi)		
n (%) [95% CI]	72 (76.6) [66.7, 84.7]	72 (76.6) [66.7, 84.7]
CR		
n (%) [95% CI]	52 (55.3) [44.7, 65.6]	52 (55.3) [44.7, 65.6]
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, Data on file[3]

B.2.6.1.2 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, with or without censoring of SCT or any other new anti-cancer therapies for B-cell ALL.

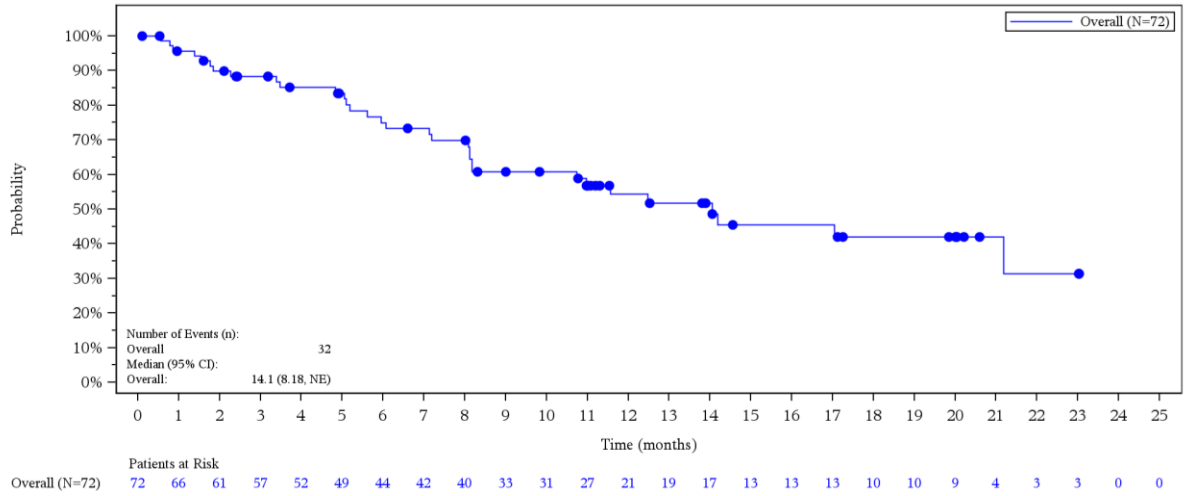
At the February 2024 data cut-off, [redacted]% of the patients who had achieved CR or CRi remained in remission without relapse or use of other anti-cancer therapies, including SCT (Table 12). The estimated median DOR increased from [redacted] (95% CI: [redacted] to not estimable) months as of the June 2023 data cut-off to 14.06 (95% CI: 8.18 to not estimable) months as of February 2024. At a median estimated duration of follow-up of 14.1 months, the probability of survival at 12 months after onset of remission was [redacted]% ([redacted]) (Table 13). Figure 9 demonstrates a plateauing of DOR from Month 15 onwards, with only two events occurring beyond this point.

Table 13: DOR measured by IRRC (Cohort IIA, mITT)

Parameter	mITT population (n=94)	
	Jun 2023	Feb 2024
Number of patients in analysis	[redacted]	72
Number of events, n (%)	[redacted]	32 (44.4)
Morphological relapse	[redacted]	[redacted]
Death due to reason other than underlying cancer	[redacted]	[redacted]
Number of censored observations, n (%)	[redacted]	[redacted]
Ongoing without event	[redacted]	[redacted]
SCT	[redacted]	[redacted]
New non-protocol anti-cancer therapies	[redacted]	[redacted]
Maximum follow-up (months)	[redacted]	[redacted]
Median follow-up (months)	[redacted]	[redacted]
% event-free probability estimate		
At 6 months, % [95% CI]	[redacted]	[redacted]
At 9 months, % [95% CI]	[redacted]	[redacted]
At 12 months, % [95% CI]	[redacted]	[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, Data on file[3]

Figure 9: KM plot of DOR measured by IRRC with censoring [February 2024]



DOR – Duration of remission; IRRC – International Review and Regulatory Committee; KM – Kaplan-Meier
Source: Roddie et al. 2024 (supplementary appendix)[1]

B.2.6.1.3 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 February 2024 data cut-off, 40 (42.6%) of the 94 infused patients in Cohort IIA had not

experienced any event. Of these, 26 were in ongoing remission without non-protocol therapies, including SCT. The median EFS was 9.03 months (unchanged from the June 2023 data cut-off). EFS at Month 6 post-obe-cel infusion was [redacted]% and [redacted]% at Month 12 (Table 14). When evaluated without censoring for SCT, median EFS was [redacted] months, highlighting that obe-cel treatment resulted in sustained EFS without consolidation SCT (Figure 10).

Table 14: EFS (Cohort IIA, mITT)

Parameter	**mITT population (n=94)**	
	EFS[1]	
	Jun 2023	**Feb 2024**
Patients with event, n (%)	[redacted]	54 (57.4)
Median EFS [95% CI]	9.03 [6.01, 14.32]	9.03 [6.14, 14.98]
EFS at 6 months [95% CI]	[redacted]	[redacted]
EFS at 12 months [95% CI]	[redacted]	[redacted]

CI – Confidence interval; EFS – Event-free survival; mITT – Modified intent-to-treat.
[1] With censoring for SCT and other new anti-cancer therapies
Source: Autolus, Data on file[3]

Figure 10: KM plot of EFS measured by IRRC with or without censoring new non-protocol anti-cancer therapies including SCT (Cohort IIA, mITT) [February 2024]

EFS – Event-free survival; IRRC – International Review and Regulatory Committee; KM – Kaplan-Meier; mITT – Modified intent-to-treat.
Source: Autolus, Data on file[3]

B.2.6.1.4 Secondary endpoint: Overall survival

As of the February 2024 data cut-off, [redacted] of patients were alive, 11 patients had died due to disease progression since the primary analysis data cut-off (June 2023). The median OS at February 2024 data cut-off was [redacted] months (95% CI: [redacted]

[redacted]), and OS without censoring was [redacted]% at Month 6 and [redacted]% at Month 12, highlighting that obe-cel treatment resulted in sustained OS without consolidation SCT (Table 15,). OS at Month 6 was aligned between the June 2023 and February 2024 data cut-offs. At Month 12, the February 2024 OS was almost [redacted]% higher compared to the June 2023 estimate. Figure 11 shows that from Month 18, only one event occurred when censoring for SCT and when not censoring, highlighting the sustained effect of obe-cel on OS, irrespective of SCT.

Table 15: OS (Cohort IIA, mITT)

Parameter	**mITT population (n=94)**	
	OS[1]	
	Jun 2023	**Feb 2024**
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; mITT – Modified intent-to-treat; OS – Overall survival.
[1] Without censoring for SCT
Source: Autolus, Data on file[3]

Figure 11: KM plot of OS (Cohort IIA, mITT) [February 2024]

[redacted]

KM – Kaplan-Meier; mITT – Modified intent-to-treat; OS – Overall survival.
Source: Autolus, Data on file[3]

B.2.6.1.5 Health-related quality of life

Of the 94 patients in the Cohort IIA mITT population, EQ-5D-5L and EORTC-QLQ C30 data were available for 70 and 71 patients, respectively. Patient-reported

outcomes (PROs) were collected prior to obe-cel infusion (baseline) and at 28±2 days and 3, 6, 9, 12 and 18 months post-first infusion.

B.2.6.1.5.1 EuroQol Five Dimensions of Quality of Life (EQ-5D-5L)

The EQ-5D-5L mean score at baseline ([redacted]) increased by [redacted] to [redacted] by Month 24, as presented in Table 16. This highlights how obe-cel maintains and improves patients' HRQoL in the longer term, as visualised in Figure 12. From three months onwards, the EQ-5D-5L scores are consistently higher than prior to treatment with obe-cel (baseline), following an initial small decrease at day 28.

Table 16: EQ-5D-5L Index score results, February 2024

Timepoint	EQ-5D-5L Index mean score (SD)
Baseline*	[redacted]
Day 28	[redacted]
Month 3	[redacted]
Month 6	[redacted]
Month 9	[redacted]
Month 12	[redacted]
Month 18	[redacted]
Month 24	[redacted]

EQ-5D-5L – EuroQol Five Dimensions of Quality of Life; SD – Standard deviation.
*Prior to treatment with obe-cel.
Source: Autolus, Data on file[3]

Figure 12: EQ-5D-5L Index score results

EQ-5D-5L – EuroQol Five Dimensions of Quality of Life.
Error bars show the standard deviations.
Source: Sandhu *et al.* 2024[83]

B.2.6.1.5.2 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)

The EORTC-QLQ-C30 mean score at baseline ([redacted]) increased by [redacted] to [redacted] by Month 24 as presented in Table 17. These results are consistent with the EQ-5D-5L data, further demonstrating the effect of obe-cel in improving patients' HRQoL as defined by multiple endpoints.

Table 17: EORTC-QLQ-C30 Global health status, February 2024

Timepoint	EORTC-QLQ-C30 mean Global health status score (SD)
Baseline*	[redacted]
Day 28	[redacted]
Month 3	[redacted]
Month 6	[redacted]
Month 9	[redacted]
Month 12	[redacted]
Month 18	[redacted]
Month 24	[redacted]

EORTC-QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of life Questionnaire; SD – Standard deviation.
*Prior to treatment with obe-cel.
Source: Autolus, Data on file[3]

B.2.6.2 Supportive long-term efficacy data (FELIX and ALLCAR19)

Long-term EFS and OS from FELIX cohort IA, FELIX Cohort IIA and patients from ALLCAR19 with ≥5% BM blasts at screening were compared, to provide long-term estimates in comparable patient cohorts. A comparison of EFS across the cohorts censoring for new non-protocol cancer therapies including SCT is presented in

Figure 13. A comparison of OS without censoring for SCT is presented in Figure 14.

Results show that FELIX Cohort IIA and ALLCAR19 were well-aligned at all timepoints. Long-term ALLCAR19 data indicate a plateau for EFS from 12 months, and a plateau for OS from approximately 18 months, with only one OS event occurring between 18 and 60 months.

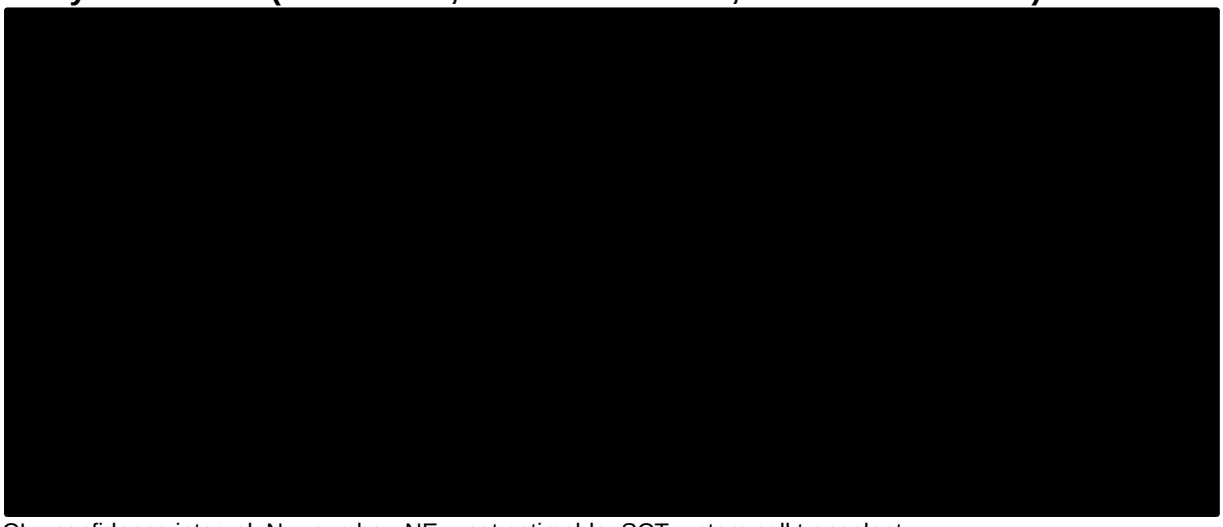
A pooled analysis of the three cohorts was also conducted, with results indicating durable long-term responses. The pooled EFS analysis with censoring new non-

protocol anti-cancer therapies including SCT indicates a plateau from around 15 months (Figure 15). The pooled OS analysis without censoring for SCT indicates a plateau from approximately 18 months (Figure 16). Landmark survival results in the pooled analysis are in line with that of the February 2024 data cut of FELIX (Table 14 and Table 15), with [redacted] and [redacted] of patients event-free, and [redacted] and [redacted] alive at months 6 and 12, respectively.

Figure 13: Event-free survival censoring new non-protocol anti-cancer therapies including SCT by study and cohort (Infused set, FELIX Cohort IA, Cohort IIA, and ALLCAR19 ALL patients with BM blasts ≥5% at screening)

CI – confidence interval; N – number; NE – not estimable; SCT – stem cell transplant
Data cut-off: 07-Feb-2024.
Source: Autolus Data on File – Clinical Overview Addendum[84]

Figure 14: Kaplan-Meier plot of overall survival without censoring SCT, by study and cohort (infused set, FELIX Cohorts IA, IIA and ALLCAR19)

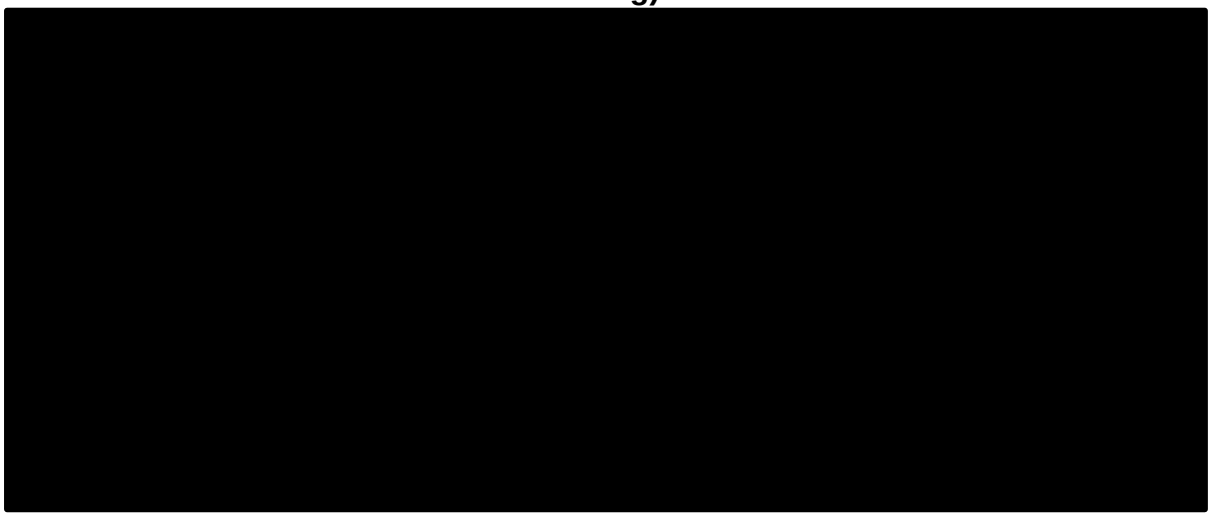


CI – confidence interval; N – number; NE – not estimable; SCT – stem cell transplant
Data cut-off: 07-Feb-2024.
Source: Autolus Data on File – Clinical Overview Addendum[84]

Figure 15: Kaplan-Meier plot of event-free survival (EFS) censoring new non-protocol anti-cancer therapies including SCT (Infused set, FELIX Phase Ib Cohort A, Phase II Cohort A, and ALLCAR19 ALL patients with bone marrow blast >=5% at screening)

ALL – adult lymphoblastic leukaemia; CI – confidence interval; N – number; SCT – stem cell transplant
Data cut-off: 23-Jul-2024.
Source: Autolus Data on File – Clinical Overview Addendum[84]

Figure 16: Kaplan-Meier plot of overall survival without censoring SCT (Infused set, FELIX Phase Ib Cohort A, Phase II Cohort A, and ALLCAR19 ALL patients with bone marrow blast >=5% at screening)



ALL – adult lymphoblastic leukaemia; CI – confidence interval; N – number; SCT – stem cell transplant
Data cut-off: 23-Jul-2024.
Source: Autolus Data on File – Clinical Overview Addendum[84]

B.2.7 Subgroup analysis

Planned subgroup analyses were conducted for selected efficacy and safety covariates. Pre-planned subgroups are listed in Section B.2.3.2, Table 8.

A wide range of pre-planned subgroups analyses were undertaken, including in subgroups typically associated with poor prognosis or poorer outcomes with other treatments for B-cell ALL (e.g., older age, Ph+, high disease burden based on blasts in BM, and presence of EMD). The impact of prior allo-SCT was also examined.

The ORR (primary endpoint) with 95% confidence intervals was measured for all pre-specified subgroups.

In addition to the pre-planned analyses which demonstrated consistency of effect across all pre-specified subgroups, post-hoc subgroup analyses were undertaken, with the purpose of testing the generalisability of FELIX outcomes to the target UK population. Analyses were undertaken in patients [redacted] (N=[redacted]) given that the expected indication of obe-cel is in this age group, and in the [redacted] patients who were from the UK. As discussed in Section B.1.3.7, currently available CAR T-cell therapy for R/R B-cell ALL (brexu-cel, available through the CDF), is frequently used as a bridge to SCT, as few patients have been observed remaining in long-term remission without subsequent therapies, e.g., SCT. As subsequent use of SCT is not expected in clinical practice with obe-cel, a final post-hoc analysis was undertaken with and without censoring for SCT.

B.2.7.1 Results of subgroup analyses

B.2.7.1.1 Results of pre-planned subgroup analyses

All subgroups achieved an estimated ORR of >[redacted]%, indicating a meaningful clinical benefit of obe-cel in R/R B-cell ALL patients. A forest plot of the subgroup analyses is presented in Appendix E, Figure 8.

Patients with particularly poor prognosis responded well to obe-cel and achieved remission including:

- [redacted] of [redacted] patients with Ph+ disease (ORR: [redacted]%),
- [redacted] of [redacted] patients who relapsed to first-line therapy within 12 months (ORR: [redacted]),
- [redacted] of [redacted] patients refractory to first-line therapy (ORR: [redacted]%).

In patients with no prior allo-SCT, the ORR response rate [redacted] (95% CI[redacted]) and the CR response rate [redacted] (95% CI: [redacted]) were both close to the respective mITT rates ([redacted] and [redacted]), indicating that obe-cel efficacy is independent of prior allo-SCT status.

Overall, these subgroup analyses support the use of obe-cel in a large variety of patients and support that obe-cel is an effective treatment for patients who typically face a poor prognosis with current treatments.

B.2.7.1.2 Results of post-hoc subgroup analyses

Particularly positive results were observed in the post-hoc subgroup analyses of patients [redacted] years or older and in UK patients (Table 18).

- In the [redacted] years or older subgroup, ORR was achieved in [redacted] patients ([redacted]%) (95% CI: [redacted]), which is a higher proportion than in the mITT population (Table 18).
- In the UK subgroup analysis, ORR was achieved in [redacted] patients ([redacted]%), which is a considerably higher proportion than in the mITT population, supporting the generalisability of the FELIX results to the UK population (Table 18).

Table 18: Outcomes of post-hoc subgroup analyses compared to mITT

	Cohort IIA, mITT (N=94)	Patients aged [redacted] and older (N=[redacted])	UK patients (N=[redacted])
CR, N (%)	52 (55.3)	[redacted]	[redacted]
CRi, N (%)	20 (21.3)	[redacted]	[redacted]
ORR, N (%) [95%CI]	72 (76.6) [66.7, 84.7]	[redacted]	[redacted]

CI – confidence interval; CR – complete remission; mITT – modified intention-to-treat; UK – United Kingdom
Source: Autolus Data on file[85]

Additionally, a post-hoc analysis was conducted comparing outcomes in Cohort IIA in FELIX with and without censoring for consolidative allo-SCT. The analysis included all patients in Cohort IIA in FELIX (N=94) who achieved best overall response of CR/CRi post obe-cel infusion (N=[redacted]). Among the [redacted] responders, [redacted] patients received SCT during remission, and [redacted] patients received non-protocol anti-cancer therapy other than SCT.

- When censoring for SCT, [redacted]% of patients were still in remission at the time of the data cut-off at February 2024, which is similar to [redacted]% of patients in remission without censoring for SCT (Table 19).
- Similarly, the proportion of patients who relapsed ([redacted]% vs [redacted]%) and the proportion of patients who died ([redacted]% vs [redacted]%) were closely aligned between analyses with and without censoring.
- EFS landmark estimates were comparable between groups at Month 6 and 12, suggesting that obe-cel treatment resulted in sustained EFS benefit without consolidation SCT.

Table 19: Outcomes of post-hoc subgroup analyses with and without censoring for SCT

	Patients with CR/CRi from Cohort IIA, mITT – censoring for SCT (N=[redacted])	Patients with CR/CRi from Cohort IIA, mITT – without censoring for SCT (N=[redacted])
Ongoing without an event, N (%)	[redacted]	[redacted]
Morphological relapse, N (%)	[redacted]	[redacted]
Death, N (%)	[redacted]	[redacted]
% event-free probability estimate		
At 6 months, % [95% CI]	[redacted]	[redacted]
At 12 months, % [95% CI]	[redacted]	[redacted]

CI – confidence interval; CR – complete remission; mITT – modified intention-to-treat; SCT – stem cell transplant
Source: Autolus Data on file[86]

B.2.8 Meta-analysis

As the outcomes are sourced from one single, robust trial with sufficient statistical power it is neither necessary nor possible to perform a meta-analysis.

B.2.9 Indirect and mixed treatment comparisons

In the absence of head-to-head clinical trial evidence for FELIX versus the comparators considered in this appraisal (inotuzumab, blinatumomab, and ponatinib), it was necessary to conduct an SLR to identify evidence for use in an ITC. As NICE recently published TA893 for brexu-cel for the treatment of R/R B-cell ALL in people 26 years and over, an update to the TA893 clinical SLR was conducted. TA893 considered a similar indication to the expected indication of obe-cel, and the SLR met NICE standards. Therefore, an update was considered more

efficient than a *de-novo* SLR for the purpose of this ITC. Details on the methods for the SLR update are presented Section B.2.1 and in Appendix D.

The studies selected for inclusion in the ITC were based on TA893 and clinical expert input. Of the 29 publications identified in the SLR update, 18 related to relevant comparators (inotuzumab and blinatumomab). None of the publications were deemed relevant for indirect comparison, as they either did not report relevant outcomes (N=11), or were undertaken in settings or populations not relevant for the assessment (N=18). The key pivotal trial publications for the comparator studies (already identified in TA893) were selected for inclusion in the analyses (Table 20).

Table 20: Summary of trials considered for the indirect treatment comparison

Trial	FELIX[62]	INO-VATE[87]	TOWER[36]	PACE[88]
Population	R/R ALL **Analysis:** mITT (N=94), mITT Ph- (N=69), mITT Ph+ (N=25)	R/R ALL **Analysis (intervention arm):** ITT (N=164)	R/R Ph- ALL **Analysis (intervention arm):** mITT (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 • OS	• PFS • OS	• EFS • OS	• PFS • OS

***Note:** Populations used for the comparisons are sourced from phase 2. **Note:** Each reference represents the pivotal trial publication.*
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

B.2.9.1 Overview of population-adjusted indirect comparisons

Due to absence of individual patient data (IPD) in the comparator studies and as FELIX is a single-arm study, only unanchored population-adjusted indirect comparisons were feasible.

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. The ITC methods conducted were matching-adjusted indirect comparisons (MAICs) and naïve comparisons, in line with NICE Decision Support Unit (DSU) Technical Support Document 18.[89]

A MAIC is 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.

The premise of MAIC 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. Prognostic factors are covariates that are predictive of outcomes regardless of treatment, whereas TEMs are predictive of outcomes and influences treatment effect. As there is no common treatment arm between FELIX and the identified comparator studies, all comparisons in the ITC will be unanchored.

B.2.9.2 Unanchored population-adjusted ITC assumptions

When studies in a population-adjusted ITC share common treatment arms, an anchored comparison can be used to predict relative effects between treatment arms in the trials. For disconnected treatment networks or single-arm trials, unanchored comparisons must be applied to assess the absolute effects. Anchored comparisons relax the treatment effect constancy assumptions from unconditional to conditional, requiring only all TEMs to be known and adjusted for, as opposed to all prognostic

variables and TEMs. Whilst anchored comparisons are preferable due to their reduced assumptions, since no common comparator arms are present in this assessment, only an unanchored population ITC were assessed for feasibility. For an unanchored population-adjusted ITC to be feasible and to generate unbiased results, there must be adequate data on relevant prognostic factors and TEMs in both the intervention and comparator studies. Whilst appropriate use of a population-adjusted ITC can substantially reduce the systematic error associated with an unanchored estimate, residual systematic error is highly likely to remain. Figure 17 presents diagrams showing the difference between an anchored and unanchored ITC.

Figure 17: Anchored and unanchored ITCs

Anchored: Common comparator treatment; adjustment should be performed on TEMs only. **Unanchored:** no common comparator treatment; adjustment should be performed on TEMs and prognostic variables.
ITC – Indirect treatment comparison; TEM – treatment effect modifier.

The four key assumptions required to conduct an unanchored population-adjusted ITC outlined in the NICE DSU TSD 18 are listed below:[89]

- Homogeneity of outcomes on each treatment: outcomes on treatment and control are the same whether the individual is assigned to the trial or not. This refers to the trial population and target population in practice. In general, it is assumed that this assumption is valid since trial data is used (or ITC results based on trial data) as if it was tested on the target population in practice, but there may be some differences in the trial setting and real clinical practice.
- Stable unit treatment value: the outcomes of one individual are not affected by any other individuals.
- Conditional constancy of absolute effects: this means that the absolute treatment effects are assumed constant at any given level of the TEM and prognostic variables, and all TEM and prognostic variables are required to be

known. This is a far more demanding assumption, and it is widely accepted that it is very hard to meet. For this assumption to be considered sufficient, other assumptions are required. Either the true outcome model is independent of the correlations between covariates, or the missing correlations in the trial being compared may be imputed from those observed in the FELIX trial.

- Model specification: MAIC weighting models must include every effect modifier and prognostic variable.

B.2.9.3 Feasibility assessment

B.2.9.3.1 Methodology

To assess the suitability of trials for inclusion in the MAIC, trials were assessed for whether they can be considered sufficiently homogenous. Study features were selected based on recommendations in the Cochrane handbook for Systematic Reviews of Interventions and TA893.[17][1,2] The availability of data from each trial was reviewed to ensure that sufficient data are available to perform a MAIC.

Unanchored population-adjusted ITCs require the conditional constancy of absolute effects to hold. This entails that all potential TEMs and prognostic variables must be included in the adjustment model. Unanchored ITCs must adjust for prognostic variables since absolute outcomes are to be predicted. In practice, it is rare to fulfil the criteria. Perfect knowledge of all prognostic variables and TEMs cannot be empirically tested. Consequently, unanchored population-adjusted ITCs should be interpreted with caution. In order to minimise the risk of bias, TEMs and prognostic variables should be identified in advance, e.g., through literature review or clinical expert opinion. Interviews with two clinical experts were undertaken to validate the selection of TEMs and prognostic variables for this feasibility assessment.[92]

A logistic propensity score model was created including relevant TEMs and PFs, following which weights for the IPD were estimated such that the weighted mean baseline characteristics of interest for the population in FELIX was aligned with that reported in the comparator trials, using method of moments. Based on the clinical validation, the final list of prognostic factors and TEMs included in the feasibility assessment and subsequent ITC, in order of priority, is reported below:

- Primary refractory disease
- % Bone marrow blasts at screening
- Prior lines of therapy
- Extramedullary disease prior to lymphodepletion
- Duration of 1st remission ≤12 months
- Philadelphia chromosome
- Age at baseline
- Bridging chemotherapy
- Race
- Prior SCT
- ECOG status
- Sex

This order of priority considers the absolute ranking from each clinician as well as the magnitude of difference between clinician opinion.

B.2.9.3.2 Results

Table 21 outlines the study features across INO-VATE, TOWER and PACE which were considered in the feasibility assessment.

Table 21: Study features considered in the feasibility assessment

Study feature	Factors assessed	Assessment outcome
Study design	Study design, randomisation, blinding, loss to follow-up, and study duration and follow-up.	The FELIX trial was deemed sufficiently similar to each of the comparator trials to not warrant the exclusion of any study based on study design. All trials are open-label. The comparator trials have control arms and were randomised in contrast to single-arm study FELIX. However, this did not introduce bias as only the active arms of the controlled trials were used. One of the studies, INO-VATE, had longer median follow-up compared to FELIX. As this cannot be adjusted for, the analyses consider different time points, which introduces bias.
Patient population	Eligibility criteria and population characteristics were assessed to ensure that the populations enrolled in the studies were suitably similar. The baseline characteristics age, sex, race, duration of first remission <12 months, prior stem cell transplant (SCT), Eastern Cooperative Oncology Group (ECOG) status, bone marrow blast at screening, Philadelphia chromosome status, bridging chemotherapy, number of prior lines of therapy and primary refractory patients were assessed to identify whether there were any outliers in the studies.	**INO-VATE:** The inclusion criteria were similar to those of FELIX. However, the study included patients with ECOG status 2, which results in overlap issues. To mitigate these, matching was done using categories of ECOG status 0, and ECOG status 1 or 2. Additionally, information on the proportion of primary refractory patients, extramedullary disease prior to lymphodepletion, and bridging chemotherapy was not reported. There is variation in the patient characteristics compared to FELIX. **TOWER:** The key differences in inclusion criteria were that TOWER included ECOG 2 patients, and only Philadelphia chromosome negative patients. The difference in ECOG criteria resulted in overlap issues, whereas Philadelphia status was adjusted for. To mitigate the overlap issues, matching was done using categories of ECOG status 0, and ECOG status 1 or 2. Extramedullary disease prior to lymphodepletion, and bridging chemotherapy were not reported. There is variation in the reported patient characteristics compared to FELIX. **PACE:** The key differences in inclusion criteria were that PACE included ECOG 2 patients, and only included Ph+ patients. The difference in ECOG criteria resulted in overlap issues, whereas Ph status was adjusted for. To mitigate the overlap issues, matching was done using categories of ECOG status 0, and ECOG status 1 or 2. Primary refractory status, BM blasts at screening, extramedullary disease prior to lymphodepletion, proportion with duration of 1st remission <12 months, and bridging chemotherapy were not reported. There is

		variation in the reported patient characteristics compared to FELIX.
Treatment arms	For all treatments, the method of administration, design of the treatment phases and timing of treatment were assessed.	The dose and administration between FELIX and the other trials was inconsistent, which is unsurprising given that the other treatments are not CAR T-cell therapies, and as such their optimal dosing regimens are likely to differ. These differences are not likely to introduce bias.
Outcomes	In order to perform an unanchored population-adjusted ITC, trials for comparator treatments must: • Report similar or comparable definitions and assessments of outcomes, as differences in how outcomes are defined may introduce bias. • Measure similar aspects – i.e., outcomes should capture the same underlying treatment effect. • Report similar timing and duration of outcome assessment, as differences in follow-up time can lead to biased comparisons. The outcomes across FELIX and the three comparator studies considered for the MAIC were: • PFS • OS	The definitions of EFS and OS were similar over the trials. However, INO-VATE and TOWER reported PFS. This measurement was defined similarly to EFS.

ECOG – Eastern Cooperative Oncology Group; EFS – event-free survival; ITC – indirect treatment comparison; MAIC – matching-adjusted indirect comparison; OS – overall survival; PFS – progression-free survival; SCT – stem cell transplan

B.2.9.3.3 Conclusions

INO-VATE (inotuzumab)

The median length of follow-up in INO-VATE is considerably longer than in FELIX, meaning the outcomes were assessed at different time points, introducing bias, and possibly underestimating the comparative efficacy of obe-cel. As unlike FELIX, INO-VATE includes ECOG 2 patients, therefore matching was done using categories of ECOG status 0, and ECOG status 1 or 2 to mitigate overlap issues. There was one patient in FELIX for whom ECOG status was not reported. For this patient, an ECOG status of 1 was assumed based on the higher proportion of patients with ECOG status of 1 than 0 in FELIX (see Section B.2.3.3). There were notable differences in population characteristics between INO-VATE and FELIX, such as a lower proportion of patients with <50% bone marrow blasts at screening, a larger proportion who only had one previous treatment, a higher proportion with duration of first remission <12 months, and a lower proportion who received prior SCT (See Appendix N, Table 69). Furthermore, important patient characteristics such as proportion of primary refractory patients, extramedullary disease prior to lymphodepletion and bridging chemotherapy were not reported and could not be adjusted for. INO-VATE did not evaluate EFS, however PFS is defined in a similar way in the study. Based on the assumptions listed in Section B.2.9.2, it was deemed feasible to conduct a MAIC between INO-VATE and FELIX, however it was considered that results would yield moderate to high uncertainty.

TOWER (blinatumomab)

All patients in TOWER were Philadelphia chromosome negative, which required adjustment. As similarly to INO-VATE, TOWER includes ECOG 2 patients, the same methodology was applied when matching on ECOG as for in the ITC of obe-cel versus inotuzumab ITC to mitigate overlap issues. Compared to FELIX, there was a lower proportion of patients with <50% bone marrow blasts at screening. Patient characteristics extramedullary disease prior to lymphodepletion and bridging chemotherapy were not reported and could not be adjusted for. Based on the assumptions listed in Section B.2.9.2, it was deemed feasible to conduct a MAIC

between TOWER and FELIX, however it was considered that results would yield moderate to high uncertainty.

PACE (ponatinib)

All patients in PACE were Philadelphia chromosome-positive, which required adjustment. As PACE includes ECOG 2 patients, the same methodology was applied when matching on ECOG as for in the ITC of obe-cel versus inotuzumab, and blinatumomab to mitigate overlap issues. Compared to FELIX, patients had a higher mean age, and there was a larger proportion of men. The main issue was that many prognostic factors and TEMs were missing and could not be adjusted for: proportion primary refractory, <50% bone marrow blasts at screening, extramedullary disease prior to lymphodepletion, proportion with duration of first remission <12 months, and bridging chemotherapy. Due to the large number of TEMs not reported in the primary PACE publication, data from the clinicaltrials.gov entry[93] reported for Cohort E was used for ponatinib baseline characteristics of ECOG status, race and prior SCT, which is a further limiting assumption of the analysis. PACE did not evaluate EFS, however PFS is defined in a similar way. For PFS, patients were censored at the last response assessment (for which events are not detailed in the publications available), whereas in FELIX, patients were censored when receiving a new therapy. Therefore, bias was potentially introduced in favour of ponatinib. Based on the assumptions listed in Section B.2.9.2 and the above, it was considered feasible to conduct a MAIC between PACE and FELIX with the caveat that results would be highly uncertain due to the bias introduced above.

Overall conclusions

The assessment concluded it was feasible to conduct MAICs between FELIX and INO-VATE and TOWER, with the caveat that comparison likely would have moderate to high uncertainty. It was found that a MAIC between FELIX and PACE was feasible but likely highly biased, to the extent that naïve comparison may be preferred. Following NICE DSU Technical Support Document 18, all covariates identified as important should be included in the model, despite the resulting low effective sample size (ESS).[89] Therefore, all covariates which were reported in both FELIX and the comparator trials were included in the models.

B.2.9.4 ITC results

Comparisons were performed for each of the three populations: mITT with INO-VATE, Ph- with TOWER, and Ph+ with PACE for both EFS and OS. Given the small sample size in FELIX, the matched comparisons to INO-VATE, TOWER, and PACE resulted in a small ESS meaning the results of the comparisons may not be robust and should be interpreted with caution.

B.2.9.4.1 Event-free survival

EFS results are presented in Table 22.

mITT

The estimated adjusted and unadjusted hazard ratios (HRs) for the mITT 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.

Ph-

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, and these differences were statistically significant.

Ph+

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.

Table 22: Event-free survival for FELIX versus comparator trials

Population	Treatment	Median EFS	ESS	Unadjusted HR	Adjusted HR
mITT	Obe-cel	[redacted]	-	-	-
	Inotuzumab	5.0 months	[redacted]	[redacted]	[redacted]
Ph-	Blinatumomab	0.0 months†	[redacted]	[redacted]	[redacted]
Ph+	Ponatinib	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; mITT – Modified intention-to-treat; Ph – Philadelphia chromosome

B.2.9.4.2 Overall survival

OS results are presented in Table 23.

mITT

The estimated adjusted and unadjusted HRs for the mITT 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.

Ph-

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, and these differences were statistically significant.

Ph+

The estimated adjusted and unadjusted HRs for the Ph+ population were in favour of obe-cel compared to ponatinib. While the unadjusted HR was statistically significant in favour of obe-cel, the adjusted HR was not significant.

Table 23: Overall survival for FELIX versus comparator trials

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

*Statistically significant results
ESS – Effective sample size; HR – Hazard ratio; mITT – Modified intention-to-treat; OS – Overall survival; Ph – Philadelphia chromosome

B.2.9.4.3 Conclusions of the MAIC

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

However, the small ESS when matched to ponatinib indicates poor overlap between the two studies, as identified in the feasibility assessment, and suggests the results are unstable. The ESS when matched to inotuzumab and blinatumomab are small in absolute terms but indicate a better overlap of trial populations and stabler results.

Given the issues identified with matching to ponatinib, a naïve comparison is used to for the comparative effectiveness of obe-cel versus ponatinib in the Ph+ population used for economic model presented in Section B.3, while a MAIC is used for comparisons to inotuzumab and blinatumomab in the mITT and Ph- populations, respectively.

The methods used for the MAIC align with recommendations for population-adjusted indirect comparisons from NICE DSU Technical Support Document 18.[89]

B.2.10 Adverse reactions

The safety and tolerability of obe-cel for the treatment of adult R/R B-cell ALL patients was the primary outcome of phase IB and a secondary endpoint of Phase II of the FELIX trial. All safety analyses are undertaken in the safety set, defined as all infused patients in each cohort and study phase (N=[redacted], Figure 18).

Figure 18: FELIX safety set

AE – adverse event

The number of TEAEs experienced in patients who received the target dose of obe-cel were reported as supportive analyses. Further subgroup analysis was conducted for obe-cel responders only (defined as those who received CR or CRi at any point post obe-cel infusion) for certain safety outcomes, e.g., rate of infection.

Results are presented from the February 2024 data cut-off when available, otherwise from the June 2023 data cut-off.

Exposure to obe-cel

The target dose for patients in the FELIX trial were 410 x 10^6 total CD19 CAR-positive T-cells as a split dose. The dosing schedule was based on BM blast count.

Patients with a low disease burden (≤20% blasts) received:

- Dose 1: 100 x 10^6 CD19 CAR-positive T-cells
- Dose 2: 320 x 10^6 CD19 CAR-positive T-cells

Patients with a high disease burden (>20% blasts) received:

- Dose 1: 10 x 10^6 CD19 CAR-positive T-cells
- Dose 2: 400 x 10^6 CD19 CAR-positive T-cells

The second dose was only administered if no ≥ grade 3 CRS and/or ≥ grade 2 ICANS or ≥ grade 3 pulmonary or cardiac toxicities were observed following the first dose. Of the 11 patients in the safety set who did not receive the target dose, seven were due to safety events and four were due to manufacturing reasons (section B.2.10.3).

A patient was considered to have received the target dose if the total received dose was within ±25% of 410 x 10^6 total CD19 CAR-positive T-cells.

B.2.10.1 Duration of hospital for obe-cel infusion

All patients were hospitalised for obe-cel infusion for at least ten days. The median total duration of hospital stay following obe-cel infusion for mITT patients was [redacted].

B.2.10.2 Common adverse events

The treatment-emergent adverse events (TEAEs) which occurred in more than 10% of patients in the safety set at any time up to 6 months post obe-cel infusion are reported in Table 24 below. The values are taken from the February 2024 data cut-off.

The most frequently observed TEAE of any grade was CRS (87 patients, 68.5%), pyrexia (37 patients, 29.1%) and nausea (33 patients, 26.0%). The majority of all these TEAEs were low grade, with the TEAE being ≥ grade 3 in 2.4%, 1.6% and 2.4% of patients respectively.

Table 24: Treatment-emergent adverse events in more than 10% of patients, at any time post obe-cel infusion, regardless of relationship to obe-cel (Phase IB and Phase II, safety set, N=127)

TEAE	All grades n (%)	Grade ≥ 3 n (%)

Any	127 (100.0)	104 (81.9)
Cytokine release syndrome	87 (68.5)	3 (2.4)
Pyrexia	37 (29.1)	2 (1.6)
Nausea	33 (26.0)	3 (2.4)
Diarrhoea	32 (25.2)	2 (1.6)
Febrile neutropenia	31 (24.4)	30 (23.6)
Anaemia	30 (23.6)	26 (20.5)
Headache	30 (23.6)	0 (0.0)
Immune effector cell-associated neurotoxicity syndrome	29 (22.8)	9 (7.1)
Neutropenia	29 (22.8)	26 (20.5)
Hypotension	28 (22.0)	6 (4.7)
Hypokalaemia	27 (21.3)	8 (6.3)
Neutrophil count decreased	25 (19.7)	25 (19.7)
Fatigue	24 (18.9)	2 (1.6)
COVID-19	23 (18.1)	8 (6.3)
Vomiting	21 (16.5)	1 (0.8)
Platelet count decreased	18 (14.2)	16 (12.6)
Thrombocytopenia	18 (14.2)	16 (12.6)
Hyperferritinaemia	17 (13.4)	13 (10.2)
Abdominal pain	16 (12.6)	2 (1.6)
Confusional state	16 (12.6)	3 (2.4)
Alanine aminotransferase increased	15 (11.8)	6 (4.7)
Cough	15 (11.8)	0 (0.0)
Decreased appetite	15 (11.8)	4 (3.1)
Hypomagnesaemia	14 (11.0)	0 (0.0)
Arthralgia	13 (10.2)	0 (0.0)
Weight decreased	13 (10.2)	2 (1.6)

TEAE – treatment-emergent adverse event.

B.2.10.3 Adverse events of special interest

CAR T-cell therapy for B-cell ALL is associated with considerable and potentially life-threatening immunotoxicity (CRS and 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.

B.2.10.3.1 Cytokine release syndrome

In the February 2024 data cut-off87 patients (68.5%) in the safety set experienced CRS. The majority of these patients (84 patients, 96.6%) 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. Only three patients (2.4%) infused with obe-cel experienced grade 3 CRS. No patient had CRS greater than grade 3, meaning no patient had life-threatening conditions requiring urgent intervention.[94]

Among the patients who experienced CRS, the median time to onset was was 8 days (range: 1-23 days) after the first infusion. A total of [redacted] had onset after the second obe-cel infusion compared with [redacted] between the first and second. The median time to onset for grade ≥3 CRS was slightly later post obe-cel infusion at [redacted].

The median duration of CRS was [redacted]. Systemic anti-cytokine therapy was given to [redacted], most commonly tocilizumab (66 patients, 52.0%) but also corticosteroids (20 patients, 15.7%) and other anti-cytokine therapies [redacted]. Vasopressors with or without vasopressins were required in 3 patients (2.4%).

B.2.10.3.2 ICANS

In the February 2024 data cut-off, 29 patients (22.8%) included in the safety set (N=127) experienced ICANS, the majority of which were low-grade (1 or 2) (20 patients, 70.0%). Grade 3 ICANS occurred in seven patients (5.5%) and two patients (1.6%) experienced ICANS greater than grade 3.

The time to onset was 12 days (range: 1-31) after the first infusion, with onset occurring after the 2nd infusion in [redacted] of the 29 patients. For grade ≥3 ICANS, the time to onset was slightly later at [redacted].

The median duration of ICANS was 8 days (range: 1-53) with 24 patients receiving therapy for ICANS. Therapy options included corticosteroids (24 patients, 100.0%) and anti-epileptics [redacted], with [redacted] patients receiving another therapy option.

B.2.10.4 Safety summary (February 2024 data cut-off)

At the latest data cut-off (February 2024), all patients in the safety set (N=127) experienced at least one TEAE at some time post obe-cel infusion. In total, 104 patients (81.9%) experienced a TEAE grade ≥3. The AE profile of obe-cel at the February 2024 data cut-off remained mostly unchanged compared with the safety profile based on the June 2023 primary analysis. There were only [redacted] additional grade 3 TEAEs reported between June 2023 and February 2024, indicating favourable long-term safety for obe-cel.

Obe-cel related TEAEs occurred in [redacted], of which [redacted] experienced a grade ≥3 or higher. Serious TEAEs occurred in [redacted] at some time post obe-cel infusion. A total of [redacted] patients experienced serious TEAEs suspected to be associated with obe-cel treatment.

Adverse events of special interest include CRS and ICANS. Only three patients (2.4%) infused with obe-cel experienced ≥ grade 3 CRS and nine patients (7.1%) experienced ≥ grade 3 ICANS.[21] Two patients died due to AEs considered to be related to treatment with obe-cel, one patient due to ICANS and acute respiratory distress syndrome and one due to neutropenic sepsis.

Overall, obe-cel has an improved safety profile over existing CAR-Ts and immunotherapies in ALL. Brexu-cel is currently the only CAR T-cell therapy available to the target population of this submission (through the CDF) and, as shown in Table 25**,** the rate of CRS and ICANS is considerably lower for obe-cel compared to that of brexu-cel:

- **CRS:** In brexu-cel Phase I/II trial ZUMA-3, grade 3/4 CRS occurred in 24% of participants,[22] in contrast to in 2.4% of patients treated with obe-cel in FELIX.
- **ICANS:** The percentage of patients experiencing grade ≥3 neurological events associated with ICANS was substantially higher for brexu-cel than obe-cel: 25.5% in ZUMA-3 as compared to 7.1% in FELIX.

Table 25: Key safety data for obe-cel and brexu-cel

Intervention	Any TEAE all	Any TEAE grade ≥ 3, n (%)	CRS all grades, n (%)	CRS grade ≥ 3, n (%)	ICANS all grades, n (%)	ICANS grade ≥ 3, n (%)

Company evidence submission template for obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID6347]

	grades, n (%)					
Obe-cel (N=127)	127 (100)	104 (81.9)	87 (68.5)	3 (2.4)	29 (22.8)	9 (7.1)
Brexu-cel (N=55)	55 (100)	52 (94.5)	49 (89.1)	11 (23.6)	33 (60.0)	14 (25.5)

CRS – cytokine release syndrome; ICANS – immune effector cell-associated neurotoxicity syndrome; TEAE – treatment-emergent adverse event

Immunotherapies, including inotuzumab and blinatumomab, also have suboptimal safety profiles. Inotuzumab is associated with VOD, with 9% of patients in the INO-VATE clinical trial experiencing grade 3 or higher.[87] In the TOWER study, 5% of patients treated with blinatumomab experienced grade 3 or higher CRS.[36]

B.2.11 Ongoing studies

The FELIX study is an ongoing trial and will provide additional evidence for obe-cel in adults with R/R B-cell ALL. No additional data cut-offs are planned during the timeframe of this evaluation.

B.2.12 Interpretation of clinical effectiveness and safety evidence

The efficacy and safety of obe-cel in the treatment of adults with R/R B-cell ALL has been demonstrated in the open-label, multicentre Phase IB/II FELIX trial. The overall risk of bias of FELIX was deemed low (Section B.2.5).

The primary endpoint of the FELIX trial was met, with a statistically significant ORR amongst mITT patients of 76.6% (95% CI: 66.7 to 84.7 p<0.0001). Of the 76.6%, [redacted]% achieved MRD-negative remission to the $<10^{-4}$ level, highlighting the low risk levels of relapse for patients receiving obe-cel. These results demonstrate compelling efficacy for obe-cel in the context of approved R/R ALL therapies; for instance, ORR observed in the pivotal trial for blinatumomab was 44% (TOWER).[36] The ORR of the only currently available CAR T-cell therapy, brexu-cel (available through the CDF), was 71% (ZUMA-3).[22]

The generalisability of results from the FELIX trial to the population being appraised (UK adults [redacted] with R/R B-cell ALL) was examined and supported by subgroup analyses in the relevant age group ([redacted] years old) and in UK patients (Section B.2.7.1.2). Response rates to obe-cel in patients older than [redacted] were slightly higher than those observed in the mITT analysis. Response rates for UK patients were considerably higher than the mITT rates, with [redacted]% achieving ORR as compared to 76.6% in the mITT population. While there is limited literature detailing the characteristics of the UK R/R B-cell ALL population, pre-specified subgroup analyses showed consistently strong results over a wide range of patient characteristics, including those traditionally associated with poor prognosis (Section B.2.7.1.1). Finally, the FELIX trial included patients with and without prior SCT, which is reflective of the anticipated place of obe-cel in the treatment pathway. In both subgroups, response rates were close to those observed in the mITT population, mitigating concerns related to previous CAR T-cell therapy assessments that efficacy may partially be attributed to the SCT (Section B.2.7.1.1).

The survival of patients was assessed by median EFS and OS, with 12-month probability estimates being [redacted]% and [redacted]%, respectively. The robustness of obe-cel outcomes was further demonstrated through well-aligned outcomes between the June 2023 and February 2024 data cuts. At the latest data cut, [redacted] patients had not experienced an EFS event and [redacted] patients were still alive, indicating potential for median EFS and OS to improve with further data cuts. Long-term ALLCAR19 data demonstrated a plateau for EFS from 12 months, and a plateau for OS from approximately 18 months, with [redacted] occurring between 18 and 60 months. These results support UK clinical expert opinion suggesting that patients treated with obe-cel who relapse would typically do so within a year of infusion.[92]

Only [redacted]% of patients received new anti-cancer therapies and [redacted]% received SCT within the timeframe of the latest FELIX data cut. Censoring analyses showed that subsequent SCT did not impact treatment outcomes (see Section B.2.7.1.2). These results indicate that the efficacy observed in FELIX is attributed to obe-cel, rather than subsequent SCT.

The severe and sometimes life-threatening toxicities associated with currently available treatments underscores the need for a safe and effective option. Obe-cel has a compelling safety profile; to date, only 2% of all treated patients in FELIX experienced grade ≥3 CRS and 7% experienced grade ≥3 ICANS. The efficacy of obe-cel is largely comparable to that observed for brexu-cel, the only currently available CAR T-cell therapy for adult R/R B-cell ALL patients in the UK (via the CDF). Results to date show a lower proportion of CRS and ICANS observed with obe-cel in FELIX than with brexu-cel in ZUMA-3, indicating an improved safety profile. Out of the 68.5% and 22.8% of patients in FELIX experiencing CRS or ICANS, respectively, the vast majority had low grade events: three (2.4%) patients experienced grade 3 CRS, and nine (7.1%) experienced grade 3 or higher ICANS. In contrast, brexu-cel is associated with very high levels of CRS (89.1%) and neurological events associated with ICANS (60.0%).[20,22] The rate of ≥ grade 3 CRS following brexu-cel treatment is almost 10-fold higher (23.6%) than that of obe-cel. Furthermore, ≥ grade 3 ICANS associated neurological events occurred in 25.5% or patients treated with brexu-cel (Section B.2.10, Table 25). Inotuzumab and

blinatumomab also have suboptimal safety profiles. Inotuzumab is associated with VOD, with 9% of patients in the INO-VATE clinical trial experiencing grade 3 or higher.[87] In the TOWER study, 5% of patients treated with blinatumomab experienced grade 3 or higher CRS.[36]

As discussed in Section B.1.3.5, ZUMA-3 indicated brexu-cel was frequently used as a bridging therapy to SCT as few patients in the long-term follow-up were in ongoing remission without subsequent therapies including allogeneic SCT.[38] In contrast, obe-cel provides a potentially curative treatment without consolidative SCT in a meaningful percentage of patients ([redacted]%; see Section B.2.7.1.2), thus reducing the need for this resource- and cost-intensive procedure and minimising patient burden.

In the absence of head-to-head trials, an ITC was necessary to estimate the comparative efficacy of obe-cel versus the comparators. The ITC methodology adhered to recommendations for population-adjusted indirect comparisons from NICE DSU Technical Support Document 18[89], and the methods and outcomes were thoroughly validated with an external statistical expert. TEMs and PFs for inclusion in the adjustment were selected and ranked in collaboration with two UK clinical experts, and the thorough feasibility assessment underwent review by an external statistical expert.[92]

B.2.12.1 Limitations of evidence

Considering the aggressive and life-threatening nature of R/R ALL, and the lack of efficacious licenced comparators at the time of running the trial, a single-arm study design was the only feasible option for FELIX. Randomising patients to a control arm that may not receive a potentially life-saving therapy would have been unethical. For this reason, single-arm trials are common in later-line oncology.

As FELIX did not include a control arm, only unanchored analyses were possible; an unanchored MAIC and naïve comparison were therefore conducted. The potential uncertainty introduced by unanchored methods was mitigated to an as far extent as possible, through careful adjustment to TEMs identified in close collaboration with clinical experts.

The latest available data cut from FELIX has a median follow-up of 20.25 months, however some uncertainty related to long-term outcomes remains and [redacted]% of patients are censored in the latest analysis.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

As discussed in Section B.2.1, an update to the SLR conducted for TA893 was undertaken, aiming to capture evidence published after the TA893 study period (September 2021). An update was conducted rather than a *de-novo* SLR to leverage findings from TA893, and the update adhered to NICE guidance and met NICE standards and identified recent updates which add to the body of available evidence. A detailed description of the SLR update methods is provided in Appendix G.

To meet the study objective for the cost-effectiveness SLR, the following research question was addressed:

- Which are the published cost-effectiveness studies of treatments for patients who have R/R ALL?

A total of three cost-effectiveness studies were identified (Table 26). The studies were conducted in the UK (Spousta et al), the US (Shah et al) and Norway/Sweden (van Oostrum et al).[95–97] All studies utilised partitioned survival models, with lifetime time horizons. Two studies evaluated brexu-cel vs blinatumomab, inotuzumab and salvage chemotherapy, and one evaluated inotuzumab versus SoC chemotherapy.

Table 26: Summary list of published cost-effectiveness studies (N=3)

Study	Year	Summary of model	Perspective	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Spousta *et al.* 2023[97]	2023	Partitioned survival model Health states included: EFS, progressed disease and death	UK NHS and PSS	R/R B-cell ALL in patients aged 26 years and older	**Brexu-cel vs. blinatumomab:** Brexu-cel 6.53 Blinatumomab 2.24 **Brexu-cel vs. inotuzumab:** Brexu-cel 6.03 Inotuzumab 2.38 **Brexu-cel vs. chemotherapy:** Brexu-cel 5.83 Chemotherapy 1.21	**Brexu-cel vs. blinatumomab:** Brexu-cel £368,223 Blinatumomab £273,789 **Brexu-cel vs. inotuzumab:** Brexu-cel £370,274 Inotuzumab £214,657 **Brexu-cel vs. chemotherapy:** Brexu-cel £369,420 Chemotherapy £97,197	**Brexu-cel vs. blinatumomab:** £22,011 **Brexu-cel vs. inotuzumab:** £42,623 **Brexu-cel vs. chemotherapy:** £58,897

Shah *et al.* 2022[95]	2022	Decision tree prior to entry into a partitioned survival analysis. Health states included: pre-progression survival, progressed disease and death	US payer perspective	R/R ALL	**Brexu-cel vs. blinatumomab:** Brexu-cel 7.75 Blinatumomab 4.92 **Brexu-cel vs. inotuzumab:** Brexu-cel 7.75 Inotuzumab 3.79 **Brexu-cel vs. chemotherapy** Brexu-cel 7.75 Chemotherapy 2.17	**Brexu-cel vs. blinatumomab:** Brexu-cel $776,320 Blinatumomab $725,407 **Brexu-cel vs. inotuzumab:** Brexu-cel $776,320 Inotuzumab $524,789 **Brexu-cel vs. chemotherapy** Brexu-cel $776,320 Chemotherapy $344,293	**Brexu-cel vs. blinatumomab:** $20,843 **Brexu-cel vs. inotuzumab:** $77,271 **Brexu-cel vs. chemotherapy:** $93,768
Van Oostrum *et al.* 2022[96]	2022	Time-dependent partitioned survival model	**Sweden** Societal **Norway** Societal	R/R ALL	**Sweden** Inotuzumab vs. SoC 1.613* **Norway**	**Sweden** Inotuzumab vs. SoC €26,163* **Norway**	**Sweden** €16,219** **Norway** €44,405

		Health states included: Stable, CR/CRi, post-HSCT, progression and death			Inotuzumab vs. SoC 1.424*	Inotuzumab vs. SoC €63,220*	

ALL – Acute lymphoblastic leukaemia; CR – Complete remission; CRi – Complete remission with incomplete haematologic recovery; EFS – Event-free survival; HSCT – Haematopoietic Stem Cell Transplant; ICER – Incremental cost-effectiveness ratio; NHS – National Health Service; PSS – Personal Social Services; R/R – Relapsed/refractory; QALYs – Quality-adjusted life years; SoC – Standard of care; UK – United Kingdom; US – United States

*Incremental costs and QALYs presented

**The base case ICER for Sweden was lower compared to Norway mainly due to the inclusion of productivity costs. With these costs excluded, the Swedish ICER was more comparable, at €50,361 per QALY gained vs SoC

B.3.2 Economic analysis

None of the identified cost-effectiveness studies addressed the decision problem relevant to this appraisal. Therefore, a *de-novo* cost-effectiveness model was developed to evaluate the clinical and cost-effectiveness of obe-cel in alignment with the final scope.

B.3.2.1 Patient population

The population evaluated is adult patients with R/R B-cell ALL [redacted] years or older, in alignment with the licenced wording and anticipated positioning of obe-cel, and the final scope and decision problem of this evaluation (Section B.1.1). Data from the whole FELIX Cohort IIA (including patients under the age of 26) is used to inform the analysis, given the relatively small starting sample size. Based on subgroup analysis presented in Section B.2.7.1.2 demonstrating slightly increased obe-cel efficacy in patients [redacted] years, it is anticipated that use of the whole FELIX Cohort IIA is conservative.

As availability of comparator treatments differs by Ph expression (as presented in Figure 5, Section B.1.3.7), the economic analysis considered three populations:

- Overall population (inclusive of both Ph- and Ph+ patients)
- Ph- subgroup, and
- Ph+ subgroup.

Baseline patient characteristics used in the economic model were informed by the FELIX study and are presented for the mITT, Ph- and Ph+ populations in Table 27.

Table 27: Baseline patient characteristics in the model (mITT population)

Patient characteristics	Value, mITT	Value, Ph-	Value, Ph+	Source
Age (years)	48.30	45.62	55.60	FELIX[3]
Male (%)	50%	56%	32%	FELIX[3]
Average patient weight, kg	78.73	80.90	72.59	FELIX[3]

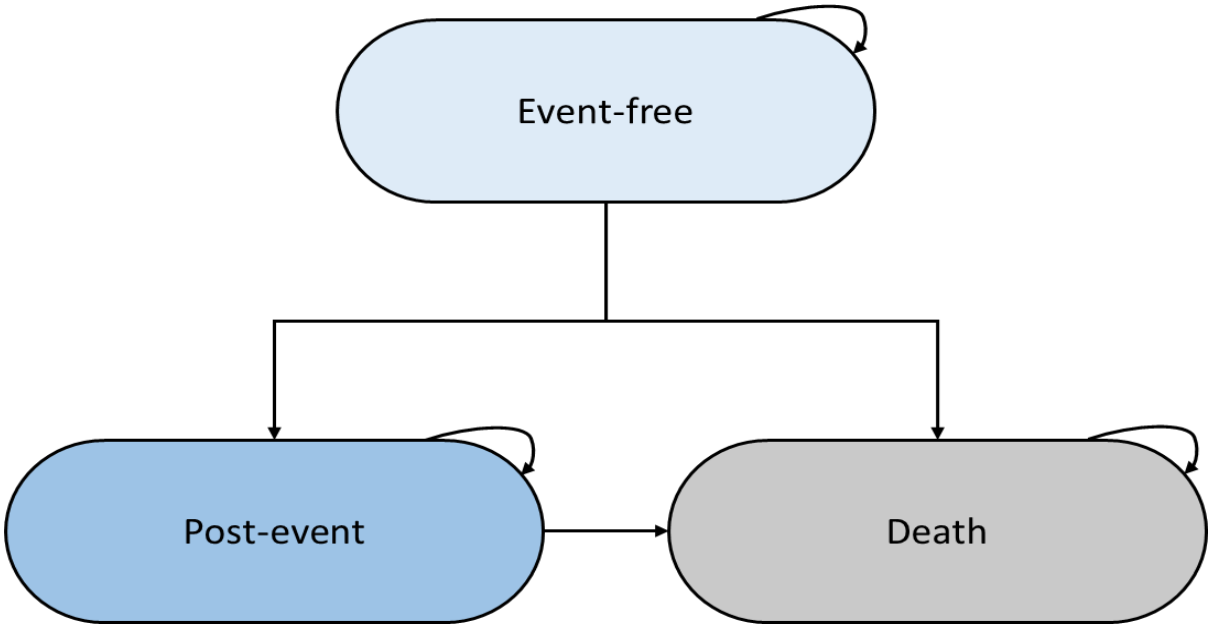
Average patient BSA (m^2)	1.89	1.91	1.81	FELIX[3]
Proportion of ALL patients with Ph+ mutation (mITT population) [%]	26.6	-	-	FELIX[3]

ALL – Acute lymphoblastic leukaemia; BSA – Body surface area; kg – kilogram; Ph+ – Philadelphia chromosome-positive; SE – Standard error.

B.3.2.2 Model structure

A partitioned survival model (PSM) was developed which captures patients' disease course with R/R adult ALL using three mutually exclusive health states: event-free, post-event and death. The three states are fully exhaustive, meaning that patients must occupy one of the states at any given time. The model structure is presented in Figure 19.

Figure 19: Model structure



All patients enter the model in the Event-free state and transition to the Post-event or the Death state upon disease progression. The Event-free state captures the time from which patients first receive treatment to the time at which one of the following events occurs: treatment failure, morphological relapse or death due to any cause, at which point patients progress to the Post-event or Death health state.[3] The structure of the PSM is reflective of the pathway of ALL in that patients who progress to the post-event state cannot return to the event-free state. The clinical effectiveness of treatment with obe-cel and comparators is captured by the proportion of patients occupying the three health states over the modelled time horizon. State membership to the Event-free state is estimated from the extrapolated EFS KM curve. State membership of the Death state is estimated using the extrapolated OS KM curve

(Death=1-OS) and the Post-event state membership is estimated to be the difference between the state occupancy of the other two health states. The model was structured such that EFS cannot exceed OS to ensure that the proportion of patients who are event-free is always less than or equal to the proportion of patients who are alive.

This structure is aligned with the findings in the SLR update, in which all three identified studies utilised a PSM (see Section B.3.1); the SLR conducted for TA893 in which five of 14 studies used a PSM; and the economic model developed for TA893, which was considered appropriate for decision making by the committee.[17]

B.3.2.2.1 Cure assumption

In the economic analysis, patients in any treatment arm who are alive at three years are assumed to be cured, and as such considered to be long-term survivors. The possibility of achieving cure in ALL is supported by available literature.[92,98] Obe-cel OS data from FELIX Cohort IIA is presented in Section B.2.6.1, Figure 11 and shows that from Month 17 onwards there is a plateau with only one event occurring between 17 and 30 months. While the comparators included in this analysis are not considered standalone curative treatments, they can be utilised as bridging therapies to allo-SCT, a well-established therapy with a curative intent in ALL.[92] A cure assumption was therefore applied for all treatment arms in the model.

The cure timepoint of three years was selected to align with TA893 and validated with two UK clinical experts who both expressed that patients treated with obe-cel who relapse would typically do so within a year. As such, the three-year cure assumption is considered conservative.[92] Exploratory scenarios have been conducted (presented in Section 0) considering one- and two-year cure assumptions. The use of a cure assumption has further precedence in NICE appraisals of CAR T-cell therapies for R/R mantle cell lymphoma (MCL) (TA559, TA567 and TA677).[99–101]

In line with TA893, TA559, TA567 and TA677, cured patients were assumed to have lower resource use and improved HRQoL compared to non-cured patients. Cured patients were also assumed to have improved survival outcomes compared to non-cured patients but excess mortality compared to the age-equivalent general

population in the economic analysis. To reflect this excess mortality, a standardised mortality ratio (SMR) is applied to the age- and gender- matched general population mortality of patients alive beyond three years. The base case utilises an SMR of three, reflecting a threefold increased risk of death compared to the general population, in line with the committee's preference in TA893. Notably, brexu-cel long-term OS evidence published after the TA893 final appraisal document (FAD) indicates that an SMR of three may be conservative: the latest brexu-cel long-term OS data published at ASCO May 2024 presents a median follow-up of 25.6 months for the mITT ZUMA-3 population[38], compared to median OS of 22.4 months for phase 1 and 18.2 months for phase 2 in the ZUMA-3 trial at the point of TA893 company submission.[17] These data are supportive of a cure assumption in the long-term, indicating that survival outcomes improve as more mature data becomes available. A similar observation is expected with obe-cel. While the OS data for obe-cel are still immature, high response rates and EFS are promising and indicate the potential for improved OS with longer follow-up.

B.3.2.2.2 Allogeneic stem cell transplant

The economic analysis adopts the same approach as TA893, whereby the survival impact of subsequent allo-SCT is not directly modelled, but rather captured by cost and utility impact. For the comparators, this was estimated by weighting the cost and QoL impact associated with allo-SCT by the proportion of patients undergoing the procedure, informed by the pivotal trials (INO-VATE, TOWER, PACE). In the FELIX trial, [redacted] patients in the mITT population received allo-SCT. This was part of the study design as specified in the FELIX study protocol.[4] Based on UK expert clinician feedback, no obe-cel patients are assumed to receive subsequent allo-SCT in NHS practice, as CAR T therapy is an option when SCT is not recommended or if the patient has relapsed following SCT. Given that [redacted] patients did receive SCT in FELIX while in remission, sensitivity analyses are presented in Section 0 that explore the impact of including these patients on the results. Section B.2.6.1 presents censored results for PFS and OS for patients who did/did not receive SCT following obe-cel treatment. The analysis demonstrates that the observed OS benefit with obe-cel is independent of subsequent SCT.

B.3.2.2.3 Patients undergoing leukapheresis, conditioning, and bridging therapy but not receiving obe-cel

A total of 112 patients were enrolled in FELIX Cohort IIA, of which 94 received at least one obe-cel infusion (mITT). While the cost-effectiveness model (CEM) population is reflective of the infused patients, the analysis accounts for the costs of leukapheresis, conditioning, and bridging chemotherapies for the patients who ultimately did not receive obe-cel by the use of cost multipliers. This approach is consistent with TA893. The cost multipliers applied are presented in Section B.3.5.1.

B.3.2.3 Analysis features

The model takes an NHS England and Personal Social Services (PSS) perspective, considering direct healthcare costs, as per the NICE reference case.[102] The cycle length is 28 days, and the model adopts a lifetime time horizon, defined as 100 years minus the baseline age of the cohort. Half-cycle correction is applied in the model base case. Costs and outcomes are discounted at an annual rate of 3.5%.

Table 28 summarises the key features of the current analysis alongside the economic models of previous NICE appraisals in R/R ALL.

Table 28: Features of the economic analysis

	Previous evaluations					Current evaluation	
Factor	**TA450 Blinatumomab**[15]	**TA541 Inotuzumab**[18]	**TA451 Ponatinib**[16]	**TA554 Tisagenlecleucel**[14]	**TA893 Brexucel**[17]	**Chosen values**	**Justification**
Time horizon	50 years (lifetime horizon)	60 years (lifetime horizon)	47 years (lifetime)	88 years (lifetime horizon)	57 years (lifetime horizon)	51.7 years (lifetime horizon [100-baseline age])	Covers period over which all important differences in costs and outcomes between the treatments being compared would be observed. The time horizon was defined as [100 years – baseline age], considering the cohort mean age of 48.3 years at baseline.
Treatment waning effect?	Applied	Not applied	Not applied	Not applied	Not applied	Not applied	Lack of data to support a treatment waning effect; consistency with previous appraisals.

Source of utilities	Mapped from EORTC-QLQ-C30 to EQ-5D data collected in the TOWER study.	CR/CRi health states and no HSCT: INO-VATE HSCT and post-HSCT states: time-dependent utilities based on Kurosawa *et al.* 2015. Progressed disease: Aristides *et al.* 2015.	Company assumed that utilities for BP-CML reported in Szabo *et al.* were applicable for patients with Ph+ ALL.	Company used Kelly et al (2015) data, and mapped SF-36 and CHRIs to iHUI2 and EQ-5D).	EQ-5D values collected prospectively in the ZUMA-3 study.	EQ-5D-5L values from FELIX mapped to EQ-5D-3L.	The EQ-5D-5L data is from the pivotal FELIX trial and is in line with the approach used in NICE TA893.
Source of costs	Dosing regimens from TOWER; NHS reference costs 2014/2015; UK oncology nurses; British National Formulary (BNF) 2016; NHS Generic	NHS blood and transplant 2014 [uplifted from 2012/2013 to 2015/2016 prices using PSSRU inflation indices]; NHS	Expert survey conducted to provide HCRU estimates; NHS Reference Costs 2014/2015; Palliative care costs	eMIT 2017; NHS Reference Costs 2016/2017	Electronic market information tool (eMIT), NHS Reference Costs 2019/2020, PSSRU 2020, TA554.	eMIT,British National Formulary (BNF) 2023/2024, NHS Reference Costs 2021/2022, PSSRU 2023, TA893.	Generic drug costs were sourced from eMIT, while all other drug costs were sourced from the BNF. Other cost inputs were sourced from the most recent NHS Reference Costs, PSSRU, NICE TA893 and published literature.

	Pharmaceuticals eMit 2015; UK Stem Cell Strategy Oversight Committee 2014; Kings Fund 2008; Marie Curie 2012	reference costs 2015/2016.	sourced from Marie Curie Cancer Care.				HCRU frequencies were based on TA893, as it was deemed the most appropriate source due to the similarities in the patient population and model structure.

BP-CML – Blast Phase Chronic Myeloid Leukaemia; BNF – British National Formulary; CHRIs – Child Health Ratings Inventories; CR/CRi – Complete Response/Complete Response with incomplete haematologic recovery; eMIT – Electronic Market Information Tool; EORTC-QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D – EuroQol 5 Dimensions; HCRU – Healthcare Resource Utilisation; HSCT – Haematopoietic Stem Cell Transplantation; iHUI2 – Indirect Health Utility Index 2; NICE – National Institute for Health and Care Excellence; NHS – National Health Service; PSSRU – Personal Social Services Research Unit; SF-36 – Short Form (36) Health Survey; TA – Technology Appraisal; UK – United Kingdom.

B.3.2.4 Intervention technology and comparators

B.3.2.4.1 Intervention: obe-cel

The intervention for this appraisal is obe-cel. As outlined in Section B.1.2, obe-cel is a CAR T-cell therapy administered at a target dose of $410x10^6$ CD19 CAR-positive viable T-cells supplied in three or more infusion bags. Prior to receiving obe-cel patients receive conditioning therapy, consisting of lymphodepletion comprising of intravenous (IV) fludarabine 30mg/m^2 over 30 minutes on days -6, -5, -4, and -3 (total dose 120 mg/m^2) and cyclophosphamide IV 500 mg/m^2 over 30 minutes on days -6 and -5 (total dose 1000 mg/m^2). Bridging chemotherapy (administered after leukapheresis and before lymphodepleting treatment) is recommended for all patients.[5]

Dosing for the pre-infusion conditioning therapy, bridging chemotherapy and obe-cel in the model are informed by FELIX.

B.3.2.4.2 Comparators

The comparators included in the model are reflective of the current SoC for patients with R/R ALL in the UK and are in line with clinical opinion[92]:

- Overall population: inotuzumab
- Ph+: ponatinib
- Ph-: blinatumomab

The final scope for this appraisal included additional comparators, which were not considered appropriate for inclusion. The reasons these were not considered appropriate are described in Section B.1.1 and summarised below:

- Tisagenlecleucel: Obe-cel's expected indication is adults [redacted]. Tisagenlecleucel is recommended for people [redacted] and under.
- Clofarabine: Not recommended but possible used off-label in young adults and obe-cel's expected indication is adults [redacted].

- FLAG-based chemotherapy: Based on clinical feedback, ESMO guidelines, and committee preference in TA893, FLAG-IDA is not relevant in this population.
- Imatinib: Used as an earlier line of treatment no included within the license.
- Dasatinib: Not reimbursed in the UK and not used in clinical practise.
- SCT: Considered an outcome following therapeutic treatment.
- Best supportive care (palliative care): Patients receiving palliative care cannot tolerate treatments such as chemotherapy and CAR T-cell therapy and therefore it is not a relevant comparator for obe-cel.

Inotuzumab

Inotuzumab is recommended for treating R/R CD22-positive B-cell precursor ALL in adults (TA541).[18] The recommended dose of inotuzumab was based on the SmPC and is in line with the INO-VATE study. Inotuzumab is administered IV at a dose of 0.8 mg/m^2 on day 1, and 0.5mg/m^2 on day 8 and day 15 in cycle 1 in a 21-day cycle. From cycle 2 onwards it is administered 0.5 mg/m^2 or 0.8 mg/m^2 on day 1 to patients who have and have not achieved CR or CRi respectively, and 0.5 mg/m^2 on day 8 and day 15 in 28-day cycles for up to six cycles. The model assumes that patients with CR/CRi receive six treatment cycles, while patients with no CR/CRi receive three cycles.

Blinatumomab

Blinatumomab is recommended for treating Ph- R/R B-cell ALL in adults (TA450).[15] The recommended dose of blinatumomab was based on the SmPC and is in line with the TOWER study. Blinatumomab is administered IV at a dose of 9 µg/day during week 1 of cycle 1, then 28 µg/day for the remainder of the cycle and during subsequent cycles followed by a treatment-free interval of two weeks. The model assumes that all patients receive two cycles of treatments, with patients who achieve CR/CRi receiving an additional three cycles of blinatumomab as consolidation treatment.

Ponatinib

Ponatinib is recommended for treating Ph+ R/R ALL when either the patient is resistant or intolerant to dasatinib, when subsequent treatment with imatinib is not clinically appropriate, or when a T315I mutation is present (TA451).[16] The recommended dose of ponatinib was based on the SmPC and is in line with the PACE study. Ponatinib is administered orally at a dose of 45 mg/day. The model assumes that patients would be treated for a maximum of three months, in line with the SmPC.

B.3.3 Clinical parameters and variables

A summary of the populations considered, the comparators by subgroup, the corresponding FELIX datasets by subgroup and the types of ITC and survival analyses available in the model is provided in Table 29.

Table 29: Summary of approach to modelling of clinical parameters

Comparator	Population	Type of ITC	FELIX dataset	Comparator data set	Survival analyses
Inotuzumab	• Overall • Ph- ALL • Ph+ ALL	• Naïve ITC (base case, ponatinib) • Inverse MAIC (base case, inotuzumab and blinatumomab)	Cohort IIA, mITT (N=94)	INO-VATE[35] ITT (N=164)	• Spline models with three-year cure assumption (base case) • SPM with three-year cure assumption
Blinatumomab	• Ph- ALL		Cohort IIA, mITT Ph- (N=69)	TOWER[36] ITT (N=271, Ph- ALL)*	
Ponatinib	• Ph+ ALL		Cohort IIA, mITT Ph+ (N=25)	PACE[88] Ph+ ALL (N=32)	

*Less than 1% of patients in the blinatumomab arm of TOWER withdrew consent before receiving treatment. Since time-to-event data were reported for the entire study population (N=271) these data were used in the ITC and to estimate survival outcomes for patients assumed to receive blinatumomab in the economic model.
EFS – event-free survival; ITC – indirect treatment comparison; mITT – modified intention-to-treat; OS – overall survival; Ph – Philadelphia chromosome; SPM – standard parametric model

B.3.3.1 Clinical efficacy inputs

A description of the clinical data informing clinical efficacy in the model for each modelled treatment arm is presented below.

B.3.3.1.1 Obe-cel

EFS and OS data were used directly from FELIX[3] to inform clinical efficacy inputs for obe-cel in the analysis. To extrapolate survival over the model time horizon, data for the population who successfully received CAR T-cell infusion (Cohort IIA mITT, N=94) was used, in addition to subgroup analyses for the Ph- (N=69) and Ph+ (N=25) subgroups.

B.3.3.1.2 Inotuzumab

Published KM curves for PFS (proxy for EFS) and OS from the INO-VATE[35] study were used to construct pseudo-IPD to inform clinical efficacy inputs in the economic model. While INO-VATE did not evaluate EFS, PFS was defined in a similar way and censoring occurred in both FELIX and INO-VATE if patients received a SCT (see Section B.2.9.3). PFS was therefore considered an appropriate proxy for EFS in the economic analysis. Both Ph+ and Ph- patients were enrolled in INO-VATE, however disaggregated efficacy results by Ph subgroup were not reported. Results for the overall population (N=164) in INO-VATE were therefore used to model EFS and OS outcomes across all three populations in the analysis.

B.3.3.1.3 Blinatumomab

Published KM curves for EFS and OS from the TOWER[36] study were used to construct pseudo-IPD to inform clinical efficacy inputs in the economic model. As TOWER only enrolled R/R ALL patients who were Ph-, data for the overall study population was used for the Ph- subgroup. As patients who did not achieve complete remission with full, partial or incomplete haematologic recovery were assigned an event-free duration of one day in TOWER, the extrapolated curves for blinatumomab were fitted to the proportion of patients who achieved CR/CRi to avoid convergence issues. Those patients who did not achieve CR/CRi were assumed to transition to the progressive-disease (PD) health state in the first cycle of the model. Four patients (less than 1%) in the blinatumomab arm of the study withdrew consent.

However, EFS and OS data were reported for the entire study population (N=271). Given the small differences in sample size (267 vs. 271) data from the entire study population was considered appropriate to estimate survival outcomes within the economic model.

B.3.3.1.4 Ponatinib

Published KM curves for PFS (proxy for EFS) and OS from the PACE study[88] were used to construct pseudo-IPD to inform clinical efficacy inputs in the economic model. PACE did not evaluate EFS, but PFS was defined in a similar way to FELIX (see Section B.2.9.3), therefore, it was considered an appropriate proxy in the economic model. PACE enrolled R/R ALL patients who were Ph+ only, thus, the overall study population was used for the Ph+ subgroup.

B.3.3.1.5 Comparative effectiveness

As described in Section B.2.9.4.3, comparative effectiveness estimates generated by the MAIC were selected for comparisons to inotuzumab and blinatumomab in the economic model, while naïve comparison was selected for the comparison versus ponatinib given the issues identified with matching. In accordance with committee preference from TA893, the application of the MAIC outputs versus inotuzumab and blinatumomab are applied inversely, given the requirement to compare to multiple comparators, and that the FELIX cohort better reflects the UK population. Multiple scenarios are explored in the analysis, namely standard MAIC application and naïve comparisons versus inotuzumab and blinatumomab, and the use of inverse MAIC versus ponatinib. Results of these scenarios are presented in Section 0.

B.3.3.2 Survival analysis inputs and assumptions

The follow-up periods of both the intervention and comparator trials for EFS/PFS and OS were shorter than the model time horizon, therefore extrapolation of the observed data was required to estimate long-term survival in the economic analysis. Based on the mechanism of action of CAR T-cell therapies and precedent from previous NICE appraisals in R/R adult ALL (TA893), parametric and flexible spline models were fit to the intervention and comparator data for EFS/PFS and OS in line with NICE DSU TSD 14[103] and TSD 21[104].

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 (results presented in Appendix M), 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.

In line with NICE DSU TSD 14[103] and TSD 21[104], the following key criteria were considered for all treatment arms when selecting the base-case curves:

- Statistical model fit, as measured by the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)
- Inspection of log-cumulative hazard plots to assess the behaviour of the hazard over time
- Visual inspection of survival curve fit to the KM data from the relevant clinical trials
- Clinical plausibility of long-term extrapolation beyond the trial period, based on expert feedback from two UK clinical experts[92]

Given the curative potential of obe-cel, mixture cure and non-mixture cure models were considered, however, EFS and OS data from FELIX were deemed too immature to yield reliable results ([redacted] and [redacted] had not experienced an event for EFS and OS, respectively, at the time of data cut-off; see Section B.2.6). A similar data maturity in TA893 resulted in widely varying cure rates, leading the External Assessment group (EAG) and committee to consider cure models to be inappropriate for the economic analysis. Given the precedent for the use of a cure timepoint assumption in TA893, this was therefore considered a more appropriate approach (see Section B.3.2.2.1 and below).

As outlined in Section B.3.2.2.1, to capture the potential curative effect of obe-cel and the potential use of comparators as bridging therapies to allo-SCT, the analysis adopts a cure assumption. The model allows for the use of a selected parametric

model (standard or flexible spline) until a user-defined period or percentage of patients remaining event-free/alive, followed by general population mortality adjusted by a SMR. This approach is in line with the committee-preferred assumptions in TA893 and was considered a suitable alternative to fitting mixture cure models and estimating a proportion of cured patients from immature data.[17] In the base case, patients who are event-free at three years are assumed to be cured with an SMR value of three, consistent with committee preference in TA893[17]. Full details and rationale of the methodology are discussed in Section B.3.2.2.1.

B.3.3.2.1 Summary of curve selection

A summary of the parametric distributions used in the base case for each comparator until the cure timepoint (three years in the model base case) is provided in Table 30. For each comparator, the most appropriate standard parametric and flexible spline models were identified based on visual fit, goodness-of-fit statistics and UK clinical expert opinion.

Table 30: Summary of curve selection - base case

Subgroup	Treatment arm	EFS	OS
Overall	Obe-cel	0-knot normal spline	3-knot odds spline
	Inotuzumab	3-knot odds spline	2-knot hazards spline
Ph-	Obe-cel	Weibull	Exponential
	Inotuzumab	***Same as overall subgroup***	
	Blinatumomab	0-knot hazards spline	Log-normal
Ph+	Obe-cel	1-knot hazards spline	Log-normal
	Inotuzumab	***Same as overall subgroup***	
	Ponatinib	1-knot odds spline	Log-normal

EFS – event-free survival; OS – overall survival

B.3.3.2.2 Overall R/R B-cell ALL population

For the overall population comparison versus inotuzumab, unadjusted EFS and OS curves were used from FELIX to inform the obe-cel arm for the economic analysis.

The unadjusted PFS and OS curves from INO-VATE were used to reconstruct pseudo-IPD for the inotuzumab arm in the model.

B.3.3.2.2.1 Obe-cel

The standard parametric and flexible spline extrapolations of obe-cel EFS are presented in Figure 24 and Figure 25 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 39 and Table 40 of Appendix M, respectively.

As the UK clinical expert felt that all flexible spline curves provided plausible survival estimates, the model that provided the best statistical fit, the 0-knot normal curve, was deemed the most appropriate parametric curve to model obe-cel EFS until the three-year cure timepoint in the base case. The selected base case curve for obe-cel is presented in Figure 20.

Figure 20: Modelled obe-cel EFS for overall population, cure assumption at 3 years – 0-knot normal

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

The standard parametric and flexible spline extrapolations of obe-cel OS are presented in Figure 26 and Figure 27 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 41 and Table 42 of Appendix M, respectively.

The 3-knot normal and exponential distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for obe-cel, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the 3-knot odds curve aligned closest to clinical opinion and provided a comparable statistical fit to the best-fitting 3-knot normal curve, it was deemed the most appropriate parametric curve to model obe-cel OS until the three-year cure timepoint in the base case. The selected base case curve for obe-cel is presented in Figure 21.

Figure 21: Modelled obe-cel OS for overall population, cure assumption at 3 years – 3-knot odds

KM – Kaplan-Meier; OS – overall survival

The long-term outcomes of the survival analysis for obe-cel are supported by the five-year outcomes of the ALLCAR19 study (Section B.2.6.2). As shown in Table 31, the proportion of patients event-free and alive at months 24 and 36 in the economic model closely align with the pooled analysis, slightly underestimating both EFS and OS for obe-cel. Therefore, the curves selected for use in the base case according to clinical opinion can be considered a conservative estimate of obe-cel outcomes.

Table 31: EFS and OS outcomes in the pooled FELIX and ALLCAR19 analysis, and the economic model

	Pooled FELIX Cohort IA, IIA and ALLCAR19 (N=123)	Modelled outcomes for FELIX Cohort IIA, mITT (N=94)
% event-free probability estimate		
At 24 months, %	[redacted]	[redacted]
At 36 months, %	[redacted]	[redacted]
% alive probability estimate		
At 24 months, %	[redacted]	[redacted]
At 36 months, %	[redacted]	[redacted]

EFS – event-free survival; mITT – modifier intetion-to-treat; OS – overall survival

B.3.3.2.2.2 Inotuzumab

The standard parametric and flexible spline extrapolations of inotuzumab EFS are presented in Figure 28 and Figure 29 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 43 and Table 44 of Appendix M, respectively.

The 3-knot hazards and log-logistic distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for inotuzumab, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the flexible 3-knot odds curve aligned closest to clinical opinion and provided a comparable fit to the best-fitting 3-knot hazards curve, it was deemed the most appropriate parametric curve to model inotuzumab EFS until the three-year cure timepoint in the base case. The selected base case curve for inotuzumab is presented in Figure 22.

Figure 22: Modelled inotuzumab EFS for overall population, cure assumption at 3 years – 3-knot odds

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

The standard parametric and flexible spline extrapolations of inotuzumab OS are presented in Figure 30 and Figure 31 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 45 and Table 46 of Appendix M, respectively.

The 1-knot normal and generalised gamma distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for inotuzumab, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the 2-knot hazards curve aligned closest to clinical opinion and provided a comparable fit to the best-fitting 1-knot normal curve, it was deemed the most appropriate parametric curve to model inotuzumab OS until the three-year cure timepoint in the base case. The selected base case curve for inotuzumab is presented in Figure 23.

Figure 23: Modelled inotuzumab OS, cure assumption at 3 years – 2-knot hazards

KM – Kaplan-Meier; OS – overall survival

B.3.3.2.3 Ph- population

For the Ph- population, unadjusted EFS and OS curves were used from the Ph- subgroup of FELIX (N=69) to inform the obe-cel arm for the comparison versus inotuzumab and blinatumomab in the economic analysis. As the INO-VATE study did not report disaggregated outcomes by Ph expression, the same data and curve choices were used as for the overall population (see Section B.3.3.2.2.2). For the blinatumomab arm, the unadjusted EFS and OS curves from TOWER were used to reconstruct pseudo-IPD.

B.3.3.2.3.1 Obe-cel

The standard parametric and flexible spline extrapolations of obe-cel EFS are presented in Figure 40 and Figure 41 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 47 and Table 48 of Appendix M, respectively.

The 2-knot normal and the Weibull distributions were the best-fitting flexible spline and standard parametric models, respectively, for obe-cel, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the Weibull curve aligned closest to clinical opinion, it was deemed the most appropriate to model obe-

cel EFS until the three-year cure timepoint in the base case. The selected base case curve for obe-cel is presented in Figure 24.

Figure 24: Modelled obe-cel EFS for Ph- population, cure assumption at 3 years – Weibull

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

The standard parametric and flexible spline extrapolations of obe-cel OS are presented in Figure 42 and Figure 43 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 49 and Table 50 of Appendix M, respectively.

The 2-knot normal and exponential distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for obe-cel, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the exponential curve aligned closer to clinical opinion, it was deemed the most appropriate parametric curve to model obe-cel OS until the three-year cure timepoint in the base case. The selected base case curve for obe-cel is presented in Figure 25.

It should be noted that the OS hazard rate for obe-cel in the Ph- population demonstrates evidence of varying over time, suggesting the constant hazard function of the exponential distribution may not reflect the underlying hazard of the data (see Appendix M.3.2). This is a limitation of using the exponential curve, however on

balance it was considered appropriate to retain the exponential curve in the base case to align with UK clinical expert OS estimates for obe-cel in the Ph- population.

Figure 25: Modelled obe-cel OS for Ph- population, cure assumption at 3 years – exponential

KM – Kaplan-Meier; OS – overall survival

B.3.3.2.3.2 Blinatumomab

The standard parametric and flexible spline extrapolations of blinatumomab EFS are presented in Figure 44 and Figure 45 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 51 and Table 52 of Appendix M, respectively.

The 0-knot hazards and log-logistic distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for blinatumomab, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the flexible 0-knot hazards curve aligned closest to clinical opinion and provided a comparable fit to the best-fitting 0-knot odds curve, it was deemed the most appropriate parametric curve to model blinatumomab EFS until the three-year cure timepoint in the base case. The selected base case curve for blinatumomab is presented in Figure 26.

Figure 26: Modelled blinatumomab EFS for Ph- population, cure assumption at 3 years – 0-knot hazards

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

The standard parametric and flexible spline extrapolations of blinatumomab OS are presented in Figure 48 and Figure 49 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 53 and Table 54 of Appendix M, respectively.

The 3-knot normal and lognormal distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for blinatumomab, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the lognormal curve aligned closest to clinical opinion and provided the best statistical fit to the data, it was deemed the most appropriate parametric curve to model blinatumomab OS until the three-year cure timepoint in the base case. The selected base case curve for blinatumomab is presented in Figure 27.

Figure 27: Modelled blinatumomab OS for Ph- population, cure assumption at 3 years – lognormal

KM – Kaplan-Meier; OS – overall survival

B.3.3.2.4 Ph+ population

For the Ph+ population, unadjusted EFS and OS curves were used from the Ph+ subgroup of FELIX (N=25) to inform the obe-cel arm for the comparison versus inotuzumab and ponatinib in the economic analysis. Similarly to the Ph- subgroup, as the INO-VATE study did not report disaggregated outcomes by Ph expression, the same data and curve choices were used as for the overall population (see Section B.3.3.2.2.2). For the ponatinib arm, the unadjusted EFS and OS curves from PACE were used to reconstruct pseudo-IPD.

B.3.3.2.4.1 Obe-cel

The standard parametric and flexible spline extrapolations of obe-cel EFS are presented in Figure 58 and Figure 59 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 55 and Table 56 of Appendix M, respectively.

The 0-knot hazards and Weibull distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for obe-cel, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the second best-fitting 1-knot hazards curve aligned closest to clinical opinion and

provided a comparable fit to the best-fitting 0-knot hazards curve, it was deemed the most appropriate parametric curve to model obe-cel EFS until the three-year cure timepoint in the base case. The selected base case curve for obe-cel is presented in Figure 28.

Figure 28: Modelled obe-cel EFS for Ph+ population, cure assumption at 3 years – 1-knot hazards

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

The standard parametric and flexible spline extrapolations of obe-cel OS are presented in Figure 60 and Figure 61 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 57 and Table 58 of Appendix M, respectively.

The 0-knot normal and exponential distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for obe-cel, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the second best-fitting lognormal curve aligned closest to clinical opinion and provided a comparable fit to the best-fitting exponential curve, it was deemed the most appropriate parametric curve to model obe-cel OS until the three-year cure timepoint in the base case. The selected base case curve for obe-cel is presented in Figure 29.

Figure 29: Modelled obe-cel OS for Ph+ population, cure assumption at 3 years – lognormal

KM – Kaplan-Meier; OS – overall survival

B.3.3.2.4.2 Ponatinib

The standard parametric and flexible spline extrapolations of ponatinib EFS are presented in Figure 62 and Figure 63 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 59 and Table 60 of Appendix M, respectively.

The 0-knot odds and log-logistic distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for ponatinib, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the flexible 1-knot odds curve aligned closest to clinical opinion and provided a comparable fit to the best-fitting 0-knot odds curve, it was deemed the most appropriate parametric curve to model ponatinib EFS until the three-year cure timepoint in the base case. The selected base case curve for ponatinib is presented in Figure 30.

Figure 30: Modelled ponatinib EFS for Ph+ population, cure assumption at 3 years – 1-knot odds

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

The standard parametric and flexible spline extrapolations of ponatinib OS are presented in Figure 64 and Figure 65 of Appendix M, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 61 and Table 62 of Appendix M, respectively.

The 0-knot normal and lognormal distributions were identified as the best-fitting flexible spline and standard parametric models, respectively, for ponatinib, as indicated by the AIC and BIC goodness-of-fit statistics. As the survival estimates of the lognormal curve aligned closest to clinical opinion and provided a comparable fit to the best-fitting exponential curve, it was deemed the most appropriate parametric curve to model ponatinib OS until the three-year cure timepoint in the base case. The selected base case curve for ponatinib is presented in Figure 31.

Figure 31: Modelled ponatinib OS for Ph+ population, cure assumption at 3 years – lognormal

KM –Kaplan-Meier; OS – overall survival

B.3.3.3 Adverse events

The incidence of AEs was derived from individual comparator trials. Grade ≥3 AEs which occurred in ≥3% of the population in any arm were included in the model, except for CRS, for which the proportion of patients with grade ≥2, and grade ≥3 were included, given the importance of this AE for CAR T-cell therapies. All patients with grade ≥2 CRS were assumed to be treated with tocilizumab, while patients with grade ≥3 CRS to require hospitalisation. For obe-cel, grade ≥3 AEs which occurred in the mITT population observed during the FELIX study were used in the model.[3] For blinatumomab, grade ≥3 AEs which occurred in the total infused population observed during the TOWER study were included in the model.[105] For inotuzumab, grade ≥3 AEs which occurred in the safety population observed during the INO-VATE study were included in the model.[35] For ponatinib, grade ≥3 treatment-emergent AEs which occurred in ≥20% of the total population were included in the model, as this was the threshold for reporting in publications of PACE data.[88] AE rates for each treatment arm are reported in Table 32.

Table 32: Adverse event rates included in the model

Adverse event	Obe-cel	Blinatumomab	Inotuzumab	Ponatinib
CRS (Grade 2+, treated with tocilizumab)	[redacted]	0.0%	NR	NR
CRS (Grade 3+)	3.2%	4.9%	NR	NR
Neurological event	[redacted]	9.4%	NR	NR
Neutropenia	20.2%	37.8%	36.0%	21.9%
Infection	[redacted]	34.1%	1.2%	NR
Elevated liver enzyme	[redacted]	12.7%	NR	NR
Decrease in platelet count	12.8%	6.4%	NR	NR
Decrease in white-cell count	8.5%	5.2%	NR	NR
VOD	[redacted]	NR	10.4%	NR
Infusion reaction	0.0%	3.4%	NR	NR
Lymphopenia	1.1%	1.5%	11.6%	NR
Thrombocytopenia	14.9%	0.0%	24.4%	18.8%
Pyrexia	1.1%	0.0%	1.8%	0.0%
Hypotension	4.3%	0.0%	0.0%	NR
Anaemia	20.2%	0.0%	12.2%	18.8%
Sinus tachycardia	0.0%	0.0%	NR	NR
Hypoxia	2.1%	0.0%	NR	NR
Hypokalaemia	7.4%	0.0%	1.2%	0.0 NR
Hypophosphatemia	1.1%	0.0%	NR	NR
Neutrophil count decreased	20.2%	3.7%	NR	NR
Alanine aminotransferase increased	4.3%	5.6%	1.2%	NR
Diarrhoea	0.0%	0.0%	0.0%	3.1%
Encephalopathy	0.0%	1.5%	NR	NR
Febrile neutropenia	26.6%	21.3%	14.0%	NR
Pneumonia	6.4%	0.0%	0.0%	NR
Respiratory failure	5.3%	0.0%	0.0%	NR
Abdominal pain	[redacted]	0.0%	1.8%	6.3%
Sepsis	[redacted]	0.0%	0.0%	NR
Renal failure	[redacted]	NR	NR	NR
Hypogammaglobulinaemia	[redacted]	NR	NR	NR

CRS – cytokine release syndrome; NR, – not reported; VOD – veno-occlusive disease.

B.3.4 Measurement and valuation of health effects

Each health state in the model is associated with a specific utility weight. In the base case, utility values for the health states 'event-free' and 'post-event' were sourced from the pivotal FELIX clinical trial.

B.3.4.1 Health-related quality-of-life data from clinical trials

The FELIX clinical trial collected HRQoL data using EQ-5D-5L and EORTC-QLQ C30. Scores were collected prior to obe-cel infusion (at baseline), 28±2 days and 3, 6, 9, 12 and 18 months post-first infusion.

Of the 94 infused patients in Cohort IIA, 70 and 71 patients reported baseline scores for the EQ-5D-5L and EORTC-QLQ C30, respectively.

B.3.4.2 Mapping

In line with the NICE reference case, the EQ-5D-5L scores were mapped to EQ-5D-3L using the algorithm published by Hernández Alava et al (2017), which uses a UK tariff developed from a UK general population.[102] The NICE methods guide recommends to use EQ-5D to measure utilities unless there is evidence that QoL would be inaccurately captured in the target population, which was found to not be the case in a study looking into the validity of using the EQ-5D in patients with ALL by van Dongen-Leunis *et al* (2016).[102,106]

The mapped utility values were pooled onto the following categories, which aligned with TA893[17] and corresponded to the model health states:

- Baseline: any utility score collected prior to obe-cel infusion (day 1), which served as a reference category.
- Event-free: any utility score collected after infusion and prior to an event occurring. If the patient did not experience an event, all scores collected would fall into this category. If a patient never responded to treatment, all scores were included in the post-event category.
- Post-event: all scores collected post-event. This also included all scores of patients who failed to respond to treatment.

No imputation of missing data was performed to avoid bias, as missing observations could not be guaranteed to be missing at random. As patients reported multiple scores within each health state, mean estimates of utility index scores were calculated using a linear mixed-effects model which included the 'event-free' and 'post-event' health states as independent variables and patient ID as a mixed effect. A linear mixed-effects model is considered the most appropriate model for utility analysis as it allows for repeated measures and does not assume normality.[107] Clinical plausibility of the health-state utility value (HSUV) results were explored by ensuring the HSUV did not exceed that of the general population. The resulting health state utility values demonstrate a decrease in utility post-event (Table 33).

Table 33: EQ-5D-3L health-state utility values utilised in the economic model

Health state	Utility value
Event-free	[redacted]
Post-event	[redacted]

Source: FELIX data on file.
EQ-5D-3L – European Quality of Life Dimensions 3 level version

B.3.4.3 Long-term utility

A long-term survivorship utility increment is applied to patients alive at the 3-year time-point in the model, as they are assumed to be cured. It was assumed that the utility of long-term survivors would be halfway between that of the general population at the base case cure time (3 years) and the 'event-free' HSUV. As such a value of [redacted] is applied on top of the 'event-free' utility value to demonstrate the improved utility of patients deemed to be long-term survivors. This is applied in both the base case and the scenario using TA450 to source HSUVs. A scenario using values from blinatumomab SMC2234 is explored (discussed in Section B.3.4.7) and uses a different assumption around long-term utility, therefore the long-term utility increment is not applied for this scenario[108].

B.3.4.4 General population utility

In the base case, age and gender matched general population utility adjustment is applied, as when patients grow older, HRQoL declines in line with population norms.

A utility adjustment, calculated as the change in general population utility respective to baseline (cycle 0), is applied to the HSUVs.

General population utility values were calculated modelled using the ordinary least squares regression described by Ara and Brazier *et al*. (2010)[109], which accounts for age and gender:

$$EQ - 5D = \alpha + \beta_1 Male + \beta_2 Age + \beta_3 Age^2$$

The coefficients, α, β_1, β_2, and β_3, were sourced from Ara and Brazier *et al*. (2010)[109], with the age and proportion male being informed by the FELIX clinical trial.

B.3.4.5 Health-related quality-of-life studies

As described in Section B.2.1, an update to the SLR conducted for TA893 was undertaken, aiming to capture HRQoL evidence published after the TA893 SLR period (September 2021). A detailed description of the SLR update methods is provided in Appendix H. In TA893, 10 publications were identified which reported HRQoL or utilities.[17] One new study was identified in the SLR update, Sandhu *et al.* (2024), which reported EQ-5D-5L and EORTC-QLQ-C30 values from the FELIX clinical trial. EQ-5D-5L mapped to EQ-5D-3L from FELIX are used in the model base case.

B.3.4.6 Adverse reactions

Utility decrements associated with adverse events were incorporated in the cost-effectiveness model and are presented in Table 34. Utility decrements were applied as a one-off at the model start. This approach to modelling the utility decrements of adverse events is generally consistent with the committee-preferred assumptions in TA893.[17]In the base case, the utility value of CRS is assumed to be zero, therefore a decrement equivalent to the event-free health state utility value is applied. This approach to modelling the utility value for CRS is in line with the approach used in TA893.[17] An alternative utility decrement of 0.23 sourced from Howell et al (2022)[110] was explored as a scenario.

Table 34: Utility decrements associated with adverse events included in the model

Adverse event	Utility decrement	Source
Cytokine release syndrome (CRS)	[redacted]	Equal to a utility value of zero
Neurological event	0.220	TA893, assumed the same as encephalopathy [17]
Neutropenia	0.090	TA893, Nafees *et al.*, (2008) [17,111]
Infection	0.200	TA893, Tolley *et al.*, (2013), assumed the same as sepsis. [17,112]
Elevated liver enzyme	0.000	Assumed the same as alanine aminotransferase increased.
Decrease in platelet count	0.050	TA893, TA416 [17,113]
Decrease in white-cell count	0.050	TA893, TA520 [17,114]
VOD	0.104	TA893 [17]
Infusion reaction	0.050	TA520, Assumed the same as device related infection [114]
Lymphopenia	0.070	TA893, TA510 [17,115]
Thrombocytopenia	0.090	TA893, Nafees *et al.*, (2008) [17,111]
Pyrexia	0.110	TA893, Beusterien *et al.*, (2010) [17,116]
Hypotension	0.070	TA893, TA510 [17,115]
Anaemia	0.120	TA893, Swinburn *et al.*, (2010) [17,117]
Sinus tachycardia	0.150	TA677 [101]
Hypoxia	0.220	TA893, Lachaine *et al.*, (2015) [17,118]
Hypokalaemia	0.200	TA893, Beusterien *et al.*, (2008) [17,116]
Hypophosphatemia	0.070	TA893, TA511 [17,119]
Neutrophil count decreased	0.000	TA893, TA520 [17,114]
Alanine aminotransferase increased	0.000	TA893 [17]
Diarrhoea	0.050	TA893, Nafees *et al.*, (2008) [17,111]
Encephalopathy	0.220	TA893, TA416 [17,113]
Febrile neutropenia	0.090	TA893, Nafees *et al.*, (2008) [17,111]
Pneumonia	0.220	TA893, Stein *et al.*, (2018) [17,120]
Respiratory failure	0.220	TA893, assumed the same as pneumonia. [17]
Abdominal pain	0.050	TA893, assumed the same as diarrhoea. [17]
Sepsis	0.200	TA893, Tolley *et al.*, (2013) [17,112]
Renal failure	0.150	TA677[101]
Hypogammaglobulinaemia	0.000	TA893 [17]

CRS – Cytokine release syndrome; TA – technology appraisal; VOD – veno-occlusive disease.

B.3.4.7 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the utility values used in the cost-effective analysis is presented in the Table 35 below.

Table 35: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission	Justification
Event-free	[redacted]	[redacted]	Section B.3.4.2, Table 33	Prospective utility data measured in trial population of interest
Post event-free	[redacted]	[redacted]	Section B.3.4.2, Table 33	Prospective utility data measured in trial population of interest
Adverse event utility decrements				
Cytokine release syndrome (CRS)	[redacted]	NA – total AE utility decrement varied	Section B.3.4.6, Table 34	Equal to a utility value of zero
Neurological event	0.220			Assumed the same as encephalopathy
Neutropenia	0.090			Precedent from TA893
Infection	0.200			Assumed the same as sepsis
Elevated liver enzyme	0.000			Assumed the same as alanine aminotransferase increased
Decrease in platelet count	0.050			Precedent from TA893
Decrease in white-cell count	0.050			Precedent from TA893
VOD	0.104			Precedent from TA893
Infusion reaction	0.050			Assumed the same as device related infection
Lymphopenia	0.070			Precedent from TA893
Thrombocytopenia	0.090			Precedent from TA893
Pyrexia	0.110			Precedent from TA893
Hypotension	0.070			Precedent from TA893
Anaemia	0.120			Precedent from TA893
Sinus tachycardia	0.150			Precedent from TA667
Hypoxia	0.220			Precedent from TA893

Hypokalaemia	0.200			Precedent from TA893
Hypophosphatemia	0.070			Precedent from TA893
Neutrophil count decreased	0.000			Assumed no disutility due to the very mild nature of this event
Alanine aminotransferase increased	0.000			Assumed no disutility due to the very mild nature of this event
Diarrhoea	0.050			Precedent from TA893
Encephalopathy	0.220			Precedent from TA893
Febrile neutropenia	0.090			Precedent from TA893
Pneumonia	0.220			Precedent from TA893
Respiratory failure	0.220			Assumed to be the same as pneumonia
Abdominal pain	0.050			Assumed the same as diarrhoea
Sepsis	0.200			Precedent from TA893
Renal failure	0.150			Precedent from TA667
Hypogammaglobulinaemia	0.000			Precedent from TA893

CRS – Cytokine release syndrome; VOD – veno-occlusive disease.

In addition to the base case HSUVs from FELIX, two other utility scenarios were explored in the model:

- **HSUVs from TA450**, which were EORTC-QLQ-C30 values collected from TOWER and mapped to EQ-5D.[15] These HSUVs are slightly higher than the FELIX values but show a similar drop in utility for patients in the 'post-event' health state respective to those in the 'event-free' health state (see Table 36). In addition, a disutility post-SCT is applied to patients post-SCT as per TA450, whichis not considered in the base case (see Table 37).
- **HSUVs from Scottish Medicines Consortium (SMC) submission no. 1145/16 (blinatumomab).**[121] The other scenario considered applied health state utilities used in the SMC submission of blinatumomab (no. 1145/16), as reported in NICE TA541. EQ-5D utility values were derived from a time-trade off (TTO) utility elicitation study and combined with the response rates from the blinatumomab study. Similarly to the base case, this scenario also considers that patients who remain alive beyond the cure

time (3 years in the model base case) have a slightly higher utility value (see Table 38).

- Instead of a utility increment, however, the HSUV assumed for patients who remained event-free beyond 60 months in the blinatumomab SMC submission is used for patients who remain alive beyond the cure time.

Table 36: EQ-5D health state utility values (TA450 scenario) [15]

Health state	Utility value
Event-free	0.802
Post-event	0.692

EQ-5D – EuroQoL 5 dimension; TA – technology appraisal.

Table 37: Disutility post SCT (TA450 scenario)[121]

Criteria	Decrement
< 1 year	0.170
1-2 years	0.010
3-5 years	0.020
> 5 years	0.000

EQ-5D – EuroQoL 5 dimension; SCT – stem cell transplant; TA – technology appraisal.

Table 38: EQ-5D health state utility values (SMC no. 1145/16 scenario)

Health state	Utility value
Event-free	0.840
Post-event	0.350
Event-free (> cure time [3 years in base case])	0.860

EQ-5D – EuroQoL 5 dimension; SMC – Scottish Medicines Consortium.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An update to the SLR conducted for TA893 was undertaken, aiming to capture cost and healthcare resource use data published after the TA893 SLR period (September 2021).[17] A detailed description of the SLR update methods is provided in Appendix I.

Overall, six references met the selection criteria following first and second pass. None of the studies were deemed relevant. Only one study included UK data but

reported results on a multinational level. The remaining five studies were all based in the US. Therefore, cost and healthcare resource use in this analysis is aligned with TA893.[17] As the economic analysis was conducted from the perspective of the NHS and PSS, only direct healthcare costs were considered in the model base case.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Obe-cel treatment costs

The acquisition, administration and pre-treatment costs associated with obe-cel treatment are described in turn, below.

B.3.5.1.1.1 Obe-cel acquisition cost

The cost of a single, one-time i nfusion of obe-cel is £372,000. The proposed simple PAS of [redacted] is applied in the base case, providing a discounted price of [redacted].

B.3.5.1.1.2 Administration costs

Bottom-up administration cost (base case)

The base case uses the bottom-up costing approach, where the obe-cel treatment costs, including administration, acquisition and adverse event costs, are calculated from predicted resource use from the FELIX clinical trial and previous technology appraisals (TAs), is included in the model.

The calculated administration cost of obe-cel can be seen in Table 39 and consists of hospitalisation and ICU costs.

Table 39: Obe-cel administration cost for bottom-up costing

Input	Cost	Source
Mean daily hospital cost for administration and CAR T-cell therapy pre-treatment	£621.42	Acute lymphoblastic leukaemia with CC score 0-5+, reference codes SA24G-J. Weighted average of day case. National Schedule of NHS Costs - Year 2022/23.[46]
Length of hospital stay	24	Based on TA893[17]

Weighted average daily ICU cost	£2,203.31	Non-specific, general adult critical care with 0-6 or more organs supported, reference codes XC01Z-XC07Z. Weighted average of critical care. National Schedule of NHS Costs - Year 2022/23.[46]
Length of ICU stay	4	Based on TA893[17]
Proportion of patients requiring ICU	0.54	Based on TA893[17]
Infusion and monitoring cost bottom-up costing	£5,988.49	Calculation

CAR – chimeric antigen receptor; CC – complications and comorbidities ICU – intensive care unit; NHS – National Health Service.

For the administration of obe-cel, a 24-day hospital stay as well as a 4-day ICU stay for 54% of patients is expected, in line with TA893.[17] The daily hospital and ICU costs were sourced from the NHS 2022/23 reference costs, using the Healthcare Resource Group (HRG) codes SA24G-J and XC01Z-XC07Z respectively.[46]

Using bottom-up costing results in an infusion and monitoring cost of £5,988.49.

Tariff cost (scenario)

As a scenario, a tariff cost for the infusion and monitoring of CAR-Ts of £41,101.00, equivalent to the cost applied in TA893, is used and assumed to cover the cost of leukapheresis, CAR T-cell administration, CAR T-cell therapy associated AEs, and monitoring, treatment administration and delivery of CAR T-cell therapy. As per committee preference in TA893, the tariff cost does not cover conditioning and bridging chemotherapy.[17] Instead, these cost items are modelled as per the base case.

B.3.5.1.1.3 Pre-treatment costs

CAR T-cell therapies are also associated with costs prior to receiving treatment, therefore the following pre-treatment costs were applied in the first cycle of the model for patients receiving obe-cel.

Leukapheresis

It was assumed that all patients would receive leukapheresis prior to infusion with obe-cel. Leukapheresis is required to manufacture CAR T-cells and involves the collection of T-cells from patients' blood through separating and collecting white blood cells (leukocytes).

Using 'bottom-up' costing, the cost of leukapheresis is included in the model as a pre-treatment cost which can be seen in Table 40.

In this scenario, the cost of leukapheresis was calculated as a weighted average of the NHS reference cost HRG codes SA34Z and SA18Z, as in TA893.[17,122,123]

In the tariff costing scenario, the cost of leukapheresis is assumed to be £0 as it is accounted for within the one-off infusion and monitoring tariff cost.

Table 40: Cost of leukapheresis

Leukapheresis costs	Unit cost (inflated to 2024)	Source
Peripheral Blood Stem Cell Harvest	£1,592.98	Reference code SA34Z. National Schedule of NHS Costs - Year 2022/23.[46]
Bone Marrow Harvest	£5,006.35	Reference code SA18Z. National Schedule of NHS Costs - Year 2022/23.[46]
Weighted average unit cost	£1,651.95	Calculation.

NHS – National Health Service

A correcting factor (cost multiplier) was applied to the weighted average unit cost to account for patients who received leukapheresis but ultimately did not receive an obe-cel infusion. In FELIX, [redacted] patients were enrolled in Cohort IIA and underwent leukapheresis (the ITT population) with 94 receiving treatment (mITT population). Please note that one patient in Cohort IIA underwent leukapheresis but was not accepted for CAR T manufacturing. Dividing the ITT population by the mITT population resulted in a cost multiplier of [redacted]. Applying the multiplier increased the cost of leukapheresis from £1,651.95 to [redacted].

Bridging chemotherapy

During the FELIX clinical trial, some patients awaiting obe-cel treatment received bridging therapy, depending on investigator choice and local practice. One week of bridging therapy was assumed, with treatment regimens and proportions sourced from FELIX and dosing schedule from TA893[17] (Table 41 and Table 42).

Table 41: Cost of bridging chemotherapy

Drug	Formulation	Dose per unit (mg)	Unit cost	Pack size	Cost per mg	Dosing schedule per week	Dose (mg/m^2)	mg per dose	Drug cost per week	Admin cost per week	Source
Vincristine	Solution for injection vials	1	£9	1	£9	1	1	2	£19	£393	eMIT.[124] Dosing schedule assumed a maximum of 2 mg IV/week, based on TA893.[17]
		2	£11	1	£5	1	1	2	£11	£393	
Cyclo-phosphamide	Powder for solution for injection vials	500	£8	1	£0	3	150	283	£14	£1,179	eMIT.[124] BNF.[125] Dosing schedule assumed 150 mg/m^2 for 3 days, based on TA893.[17]
		1	£13	1	£0	3	150	283	£11	£1,179	
		2	£27	1	£0	3	150	283	£12	£1,179	
Methotrexate	Solution for infusion	500	£12	1	£0	1	250	472	£12	£393	eMIT.[124] Dosing schedule assumed 250 mg/m^2 for day 1, based on TA893.[17]
Mercaptopurine	Oral suspension	20	£170	1	£9	7	63	118	£7,017	£2,245	BNF.[125] Dosing schedule assumed

											62.5 mg/m^2/day, based on TA893.[17]
Cytarabine	Solution for injection vials	100	£14	5	£0	8	500	944	£209	£3,144	eMIT[124] Dosing schedule assumed 500 mg/m IV in 4 doses on days 2 and 3, based on TA893.[17]
		1	£8	1	£0	8	500	944	£59	£3,144	
		2	£15	1	£0	8	500	944	£56	£3,144	
		500	£31	5	£0	8	500	944	£93	£3,144	
Fludarabine	Solution for injection vials	50	£106	1	£2	2	30	57	£240	£786	eMIT[124] Dosing schedule assumed 30 mg/m2 IV on days 1-2, based on TA893.[17]
Ponatinib	Tablets	45	£4,116	30	£3	7	45	85	£1,812	£2,245	BNF.[125] Assumed 1 week administration.
Inotuzumab	Powder for solution for injection vials	1	£8,048	1	£8,048	1	1	2	£12,150	£459	BNF.[125] Assumed 1 week administration.
Dexamethasone		3	£17	10	£1	3	20	20	£31	£1,179	

	Solution for injection vials	7	£24	5	£1	3	20	20	£44	£1,179	BNF.[125] Dosing schedule assumed 20 mg IV 3 days per week, based on TA893.[17]

BNF – British National Formulary; IV – Intravenous; Mg – Milligram; eMIT – Electronic market information tool; TA – Technology appraisal

Table 42: Obe-cel frequency of use - bridging chemotherapy drugs

Drug	Obe-cel frequency
Vincristine	[redacted]
Cyclophosphamide	[redacted]
Methotrexate	[redacted]
Mercaptopurine	[redacted]
Cytarabine	[redacted]
Fludarabine	[redacted]
Ponatinib	[redacted]
Inotuzumab	[redacted]
Dexamethasone	[redacted]

In Cohort IIA, [redacted] patients of the ITT population and 88 patients in the mITT population received bridging therapy after leukapheresis and so a correcting factor of [redacted] was applied to the costs to account for patients who received bridging therapy but who did not receive obe-cel. When applying the correcting factor, the total bridging chemotherapy costs were [redacted].

Conditioning chemotherapy

In FELIX, patients received conditioning chemotherapy in preparation for obe-cel infusion. Conditioning therapy included:

- Fludarabine: 30mg/m^2 on days -6, -5, -4 and -3, resulting in a total dose of 120 mg/m^2.
- Cyclophosphamide: 500mg/m^2 on days -6 and -5, resulting in a total dose of 1000mg/m^2.

Table 43: Acquisition cost of conditioning chemotherapy

Drug	Dosing schedule	Dose (mg/m^2)	mg per dose	Drug cost	Source
Fludarabine	4	30	54	£847	FELIX clinical trial
Cyclophosphamide	2	500	906	£33	
Total				**£880**	Calculation

m – meter; mg – milligram.

Aligned with TA893, it was assumed that 66% of patients received conditioning chemotherapy in the inpatient setting, with the remaining receiving treatment in the outpatient setting.[17]

Table 44: Administration cost of conditioning chemotherapy

Hospital setting	Cost inflated to 2024	Proportion	Number of days	Total cost	Source
Inpatient	£59.17	66%	7	£273.38	Reference codes SA24G-J, total cost. National Schedule of NHS Costs - Year 2022/23.[46]
Outpatient	£354.00	34%	3	£379.58	Reference code SB13Z, weighted

					average of day case. National Schedule of NHS Costs - Year 2022/23.[46]
Total				**£652.96**	Calculation

NHS – National Health Service.

A correcting factor of [redacted] was applied to the total acquisition and administration costs to account for the patients who received conditioning chemotherapy but failed to receive infusion with obe-cel. The value of [redacted] was derived by dividing the number of patients in the ITT population (n=[redacted]) by the number of patients in the mITT population (n=94). With the inclusion of the correcting factor, the total cost of conditioning chemotherapy for obe-cel was [redacted].

B.3.5.1.2 Comparator treatment costs

B.3.5.1.2.1 Blinatumomab

Blinatumomab costs £2,017 per 38.5 µg vial, taken from the BNF.[125] An infusion of 9 µg is administered for the first 7 days of cycle 1, followed by 28 µg/day for the remainder of the cycle and 28 µg/day for all subsequent cycles as seen in Table 45.[126] Each cycle lasts for a total of 28 days, and there is a 14-day treatment-free interval at the end of every cycle.

In alignment with TA893, patients who have CR/CRi following two cycles of treatment with blinatumomab will continue to receive blinatumomab for three subsequent cycles (treated for five cycles in total).[17] Those patients who do not achieve CR/CRi will end treatment after two cycles.

Table 45: Acquisition cost of blinatumomab

Cycle	Number of days	Dose per day (µg)	Number of vials	Total cost
Cycle 1, days 1-7	7	9	7	£14,119.00
Cycle 1, days 8-28	21	28	21	£42,357.00
Cycle 2+, days 1-28	28	28	28	£56,476.00

µg – microgram.

Patients are assumed to be administered on an inpatient basis for the first 10 days of cycle 1. The mean daily hospital cost was sourced from the NHS 2022/23 reference costs using the codes SA24G-J, resulting in a daily cost of £621 and a total hospitalisation cost of £6,214.[46,122,123]

Following the first 10 days of inpatient administration in cycle 1, blinatumomab is administered intravenously on an outpatient basis via a pump, for which a new bag is required every three days. Intravenous infusion costs are therefore applied for six days in cycle 1 and for a total of 9.3 days per subsequent 28-day cycle. The outpatient costs were sourced from NHS 2022/23 reference costs, equalling £459.45 for the first outpatient infusion (model day 11) and £374.60 thereafter, using HRG codes SB13Z and SB15Z respectively.[46,122,123] The cost of a home infusion pump aligns with TA450 and equates to £125.36 per 28-day cycle.

Total administration costs are therefore calculated as £8,922 in cycle 1 (a sum of outpatient and hospitalisation costs) and £3,622 per remaining 28-day treatment cycle.

The drug administration and hospitalisation costs are presented in Table 46.

Table 46: Administration cost inputs for blinatumomab

Input	Cost	Source
Mean daily hospital cost	£621.42	Acute lymphoblastic leukaemia with CC score 0-5+, reference codes SA24G-J. Weighted average of day case. National Schedule of NHS Costs - Year 2022/23.[46]
Intravenous infusion (first attendance)	£459.45	Deliver complex chemotherapy, including prolonged infusion, at first attendance reference code SB13Z. Weighted average of day case, outpatient and other services. National Schedule of NHS Costs - Year 2022/23.[46]
Intravenous infusion (subsequent)	£374.60	Deliver subsequent elements of a chemotherapy cycle reference code SB15Z. Weighted average of day case, outpatient and other services. National Schedule of NHS Costs - Year 2022/23.[46]
Home infusion pump costs	£125.36	NICE TA450.[15]

B.3.5.1.2.2 Inotuzumab

The list price for inotuzumab is £8,048 per 1 mg vial, taken from the BNF.[125] Inotuzumab is infused intravenously at a dose of 0.8mg/m^2 on day one of treatment followed by a dose of 0.5mg/m^2 on days 8 and 15.[127] The treatment cycles are 28 days in length, with day 22 having no infusion to allow recovery from toxicity. For subsequent cycles, the dosing regimen depends on response to treatment, with patients with CR/CRi receiving a dose of 0.5 mg/m^2 on days 1, 8 and 15 and patients with no CR/CRi continuing to receive 0.8mg/m^2, 0.5 mg/m^2 and 0.5 mg/m^2 on days 1,8 and 15, respectively (Table 47). This aligns with TA541 (inotuzumab for treating R/R B-cell acute lymphoblastic leukaemia).[18] The number of vials required for treatment was calculated by multiplying the dose required by the average patient BSA in the model (1.89m^2), sourced from FELIX (as presented in B.3.2.1).

In the base case, responders receive six cycles of treatment with inotuzumab while non-responders are treated for three cycles, aligning with the SmPC.[126]

Table 47: Acquisition cost of inotuzumab

Cycle	Dose (mg/m²)	Dose per day (mg/m²)	Number of vials	Total cost	Total cost (per cycle)
Cycle 1, day 1	0.8	1.512	2	£16,069.00	£32,192.00
Cycle 1, day 8	0.5	0.945	1	£8,048.00	
Cycle 1, day 15	0.5	0.945	1	£8,048.00	
Patients with CR/CRi					
Cycle 2+, day 1	0.5	0.945	1	£8,048.00	£24,144.00
Cycle 2+, day 8	0.5	0.945	1	£8,048.00	
Cycle 2+, day 15	0.5	0.945	1	£8,048.00	
Patients with no CR/CRi					
Cycle 2+, day 1	0.8	1.512	2	£16,069.00	£32,192.00
Cycle 2+, day 8	0.5	0.945	1	£8,048.00	
Cycle 2+, day 15	0.5	0.945	1	£8,048.00	

CR – complete response; CRi – complete response with incomplete haematologic recovery; m – meter; mg – milligram.

Inotuzumab is administered on an inpatient basis for CR/CRi patients for the first two infusions in cycle 1, equating to 9.5 inpatient days, and then on an outpatient basis for the remainder of the treatment duration, aligning with TA893 and TA541.[17,18] Inpatient and outpatient infusions were costed from 2022/23,using codes SA24G-J

and SB13Z, respectively (Table 48).[46,122,123] As it is assumed that patients receive three infusions per 28-day treatment cycle, the acquisition cost of inotuzumab was calculated as £5,552.96 (£459.45 in outpatient and £5,093.51 in hospitalisation costs) in cycle 1 and £1,378.35 for subsequent treatment cycles.

Table 48: Administration cost inputs of inotuzumab

Input	Cost	Source
Mean daily hospital cost	£621.42	Acute lymphoblastic leukaemia with CC score 0-5+, reference codes SA24G-J. Weighted average of day case. National Schedule of NHS Costs - Year 2022/23.[46]
Intravenous infusion (first attendance)	£459.45	Deliver complex chemotherapy, including prolonged infusion, at first attendance reference code SB13Z. Weighted average of day case, outpatient and other services. National Schedule of NHS Costs - Year 2022/23.[46]

CC – complications and comorbidities; NHS – National Health Service.

B.3.5.1.2.3 Ponatinib

The cost per pack of ponatinib is £4,116 which consists of 30x 45mg tablets, indicating that the cost per 45mg table is £137.19 Patients are given a dose of 45mg per day for each day of a 28-day cycle. Patients receive treatment for a total of 3 cycles.

Ponatinib is administered orally, but supervision and monitoring costs still apply. An administration cost of £320.04 is applied once per treatment cycle to account for this, based on the weighted average of day case, outpatient and other costs from the NHS reference costs 2021/22 code SB11Z (Table 49).[46,122,123]

Table 49: Administration cost of ponatinib

Input	Cost	Source
Administration cost	£320.67	Deliver exclusively oral chemotherapy, reference code SB11Z. Weighted average of day case, outpatient and other. National Schedule of NHS Costs - 2022/23.[46]

NHS – National Health Service.

B.3.5.2 Health state unit costs and resource use

In the model, resource use is dependent on health state and treatment arm, with obe-cel assumed to have a higher resource use. Healthcare resource use frequencies and unit costs were aligned with TA893 and are presented in Table 50,

Table 51 and Table 52 for the event-free health state for obe-cel, event-free health state for blinatumomab, inotuzumab and ponatinib and for all patients in the post-event health state, respectively.[17] HCRU for cured patients is presented in the long-term survival columns of Table 50 and Table 51. Resulting health state costs are presented in Table 53.[17] All unit costs were derived from NHS reference costs 2022/23.[46,122,123]

Table 50: Obe-cel resource use for patients in the 'event-free' health state

Resource use	Cost	Annual frequency - Year 1	Annual frequency - Year 2	Annual frequency - Year 3	Annual frequency - Long-term survival	Source
Bone marrow biopsy	£487.01	3	0	0	0	Diagnostic bone marrow extraction - Outpatient procedures, clinical haematology, reference code SA33Z. National Schedule of NHS Costs - Year 2022/23.[46]
Chemistry panel	£1.61	16	4	2	0	Directly accessed pathology services - Clinical biochemistry, reference code DAPS04. National Schedule of NHS Costs - Year 2022/23.[46]
Coagulation panel	£2.43	3	0	0	0	Directly accessed pathology services - Integrated blood services, reference code DAPS03. National Schedule of NHS Costs - Year 2022/23.[46]
ECG	£378.44	1	0	0	0	Electrocardiogram Monitoring or Stress Testing, clinical haematology services, reference code EY51Z. National Schedule of NHS Costs - Year 2022/23.[46]
Consultant visit	£224.06	12	4	2	1	Non-admitted face-to-face attendance, follow-up - Consultant led, medical oncology, reference code WF01D. National Schedule of NHS Costs - Year 2022/23.[46]
Haematology panel	£5.09	16	4	2	0	Directly accessed pathology services - Haematology, reference code DAPS05.

						National Schedule of NHS Costs - Year 2022/23.[46]
Serum test	£2.43	5	0	0	0	Directly accessed pathology services - Integrated blood services, reference code DAPS03. National Schedule of NHS Costs - Year 2022/23.[46]
CSF	£830.19	1	0	0	0	Diagnostic spinal puncture, 19 years and over (outpatient services, 303), reference code HC72A. National Schedule of NHS Costs - Year 2022/23.[46]
Bone marrow aspirate	£487.31	3	0	0	0	Diagnostic bone marrow extraction - Outpatient procedures, clinical haematology, reference code SA33Z. National Schedule of NHS Costs - Year 2022/23.[46]

CSF – cerebrospinal fluid; ECG – electrocardiography; NHS – National Health Service.

Table 51: Blinatumomab, inotuzumab and ponatinib resource use for patients in the 'event-free' health state

Resource use	Cost	Annual frequency - Year 1	Annual frequency - Year 2	Annual frequency - Year 3	Annual frequency - Long-term survival	Source
ECG	£378.44	1	0	0	0	Electrocardiogram Monitoring or Stress Testing, clinical haematology services, reference code EY51Z. National Schedule of NHS Costs - Year 2022/23.[46]
Consultant visit	£244.06	6	4	2	1	Non-admitted face-to-face attendance, follow-up - Consultant led, medical oncology,

						reference code WF01D. National Schedule of NHS Costs - Year 2022/23.[46]
Haematology panel	£5.09	6	4	2	0	Directly accessed pathology services - Haematology, reference code DAPS05. National Schedule of NHS Costs - Year 2022/23.[46]
CSF	£830.19	1	0	0	0	Diagnostic spinal puncture, 19 years and over (outpatient services, 303), reference code HC72A. National Schedule of NHS Costs - Year 2022/23.[46]
Bone marrow aspirate	£487.31	3	0	0	0	Diagnostic bone marrow extraction - Outpatient procedures, clinical haematology, reference code SA33Z. National Schedule of NHS Costs - Year 2022/23.[46]
Echocardiogram	£539.78	1	0	0	0	Complex Echocardiogram - Outpatient procedures, clinical haematology, reference code EY50Z. National Schedule of NHS Costs - Year 2022/23.[46]
Liver function test	£1.61	6	0	0	0	Clinical biochemistry - directly accessed patient services, reference code DAPS04. National Schedule of NHS Costs - Year 2022/23.[46]

CSF – cerebrospinal fluid; ECG – electrocardiography; NHS – National Health Service.

Table 52: Resource use for all patients in the 'post-event' health state

Resource use	Cost	Annual frequency	Source
Consultant visit	£224.06	6	Non-admitted face-to-face attendance, follow-up - Consultant led, medical oncology, reference code WF01D. National Schedule of NHS Costs - Year 2022/23.[46]
Haematology panel	£5.09	6	Directly accessed pathology services - Haematology, reference code DAPS05. National Schedule of NHS Costs - Year 2022/23.[46]
CSF	£830.19	1	Diagnostic spinal puncture, 19 years and over (outpatient services, 303), reference code HC72A. National Schedule of NHS Costs - Year 2022/23.[46]
Bone marrow aspirate	£487.31	1	Diagnostic bone marrow extraction - Outpatient procedures, clinical haematology, reference code SA33Z. National Schedule of NHS Costs - Year 2022/23.[46]
Echocardiogram	£539.78	1	Complex Echocardiogram - Outpatient procedures, clinical haematology, reference code EY50Z. National Schedule of NHS Costs - Year 2022/23.[46]
Liver function test	£1.61	6	Clinical biochemistry - directly accessed patient services, reference code DAPS04. National Schedule of NHS Costs - Year 2022/23.[46]

CSF – cerebrospinal fluid; NHS – National Health Service.

Table 53: Health state resource use costs per health state and treatment

Health state	Year	Cost – obe-cel	Cost – non-CAR T-cell therapy	Source
Event-free	1	£564.93	£367.16	Calculation
	2	£80.24	£79.73	
	3+	£40.12	£39.86	
Post-event		£272.18		
Long-term survival	Cured patients (survival at the 3 year time-point in the base case)	£19.52		

CAR – chimeric antigen receptor.

B.3.5.3 Adverse reaction unit costs and resource use

Unit costs of adverse events were sourced from NHS reference costs 2022/23.[46,122,123] Unit costs were multiplied by the AE rates of each intervention (see Section B.3.4.6) and applied as a one-off cost. A summary of costs per AE is presented in Table 54; the resulting one-off costs applied per treatment arm are shown in Table 55.

In the base case, the bottom-up costing approach is used (see Section B.3.5.1). Adverse event costs are calculated from predicted resource use from the FELIX clinical trial and previous TAs.

Table 54: Adverse event costs

Adverse event	Event cost	Source
Cytokine release syndrome (CRS) (Grade 2+, treated with tocilizumab)	£2,982	MIMS (2024), FDA Tecartus Clinical Review and Evaluation (2021)[128,129]
Cytokine release syndrome (CRS) (Grade 3+)	£16,525	NHS 2022/23 National Cost Collection. Weighted average of Adult critical care per day multiplied by estimated length of hospital stay, XC01Z-07Z.[46]
Neurological event	£1,982	NHS 2022/23 National Cost Collection. Weighted average of Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, AA26C-26H.[46]
Neutropenia	£0	NHS 2022/23 National Cost Collection. Weighted average of Other Haematological or Splenic Disorders (all grades) - Day case, SA35A-E.[46]
Infection	£4,088	NHS 2022/23 National Cost Collection. Weighted average of Infections or Other Complications of Procedures (all grades) - Elective, WH07A-G.[46]
Elevated liver enzyme	£2,647	NHS 2022/23 National Cost Collection. Weighted average of Non-Malignant, Hepatobiliary or Pancreatic Disorders (all grades) - Elective, GC17A-K.[46]
Decrease in platelet count	£0	NHS 2022/23 National Cost Collection. Weighted average of Other Haematological or Splenic Disorders (all grades) - Day case.[46]
Decrease in white-cell count	£0	NHS 2022/23 National Cost Collection. Weighted average of Other Haematological or Splenic Disorders (all grades) - Day case.[46]

VOD	£171,553	TA541. Consists of hospital costs and treatment costs (defirotide).[46]
Infusion reaction	£1,372	NHS 2022/23 National Cost Collection. Allergy or Adverse Allergic Reaction - Elective, WH05Z.[46]
Lymphopenia	£0	NHS 2022/23 National Cost Collection. Weighted average of Other Haematological or Splenic Disorders (all grades) - Day case, SA08G-J.[46]
Thrombocytopenia	£0	NHS 2022/23 National Cost Collection. Weighted average of Thrombocytopenia (all grades) - Elective, SA12G-K.[46]
Pyrexia	£610	NHS 2022/23 National Cost Collection. Weighted average of Fever of Unknown Origin with Interventions (all grades) - Elective, WJ07B-C.[46]
Hypotension	£2,019	NHS 2022/23 National Cost Collection. Elective, EB04Z.[46]
Anaemia	£396	NHS 2022/23 National Cost Collection. Weighted average of Other Haematological or Splenic Disorders (all grades) - Elective, SA01G-K, SA03G-H, SA04G-L, SA05G-J.[46]
Sinus tachycardia	£1,952	NHS 2022/23 National Cost Collection. Weighted average of Arrhythmia or Conduction Disorders (all grades) - Elective, EB07A-E.[46]
Hypoxia	£0	Placeholder
Hypokalaemia	£540	NHS 2022/23 National Cost Collection. Electrolyte Disorders (all grades) - Elective, KC05G-N.[46]
Hypophosphatemia	£540	NHS 2022/23 National Cost Collection. Weighted average of Fluid or Electrolyte Disorders (all grades) - Elective, KC05G-N.[46]
Neutrophil count decreased	£0	NHS 2022/23 National Cost Collection. Weighted average of Other Haematological or Splenic Disorders (all grades) - Elective, SA35A-E.[46]
Alanine aminotransferase increased	£2,647	NHS 2022/23 National Cost Collection. Weighted average of Non-Malignant, Hepatobiliary or Pancreatic Disorders (all grades) - Elective, GC17A-K.[46]
Diarrhoea	£564	NHS 2022/23 National Cost Collection. Weighted average of Non-Malignant Gastrointestinal Tract Disorders without Interventions (all grades) - Elective, FD10D-M.[46]
Encephalopathy	£3,651	NHS 2022/23 National Cost Collection. Weighted average of Cerebrovascular Accident, Nervous System Infections or Encephalopathy (all grades) - Elective, AA22C-G.[46]

Febrile neutropenia	£1,921	NHS 2022/23 National Cost Collection. Weighted average of Other Haematological or Splenic Disorders (all grades) - Elective, SA08G-J.[46]
Pneumonia	£635	NHS 2022/23 National Cost Collection. Weighted average of Lobar, Atypical or Viral Pneumonia, with Multiple Interventions (all grades) - Elective stay, DZ11K-V.[46]
Respiratory failure	£507	NHS 2022/23 National Cost Collection. Weighted average of Other Respiratory Disorders, with Multiple or Single Interventions (all grades) - Elective stay, DZ27N-U.[46]
Abdominal pain	£4,648	NHS 2022/23 National Cost Collection. Abdominal Pain with Interventions - Elective, FD05A.[46]
Sepsis	£480	NHS 2022/23 National Cost Collection. Weighted average of Sepsis (all grades) - Elective stay, WH07D.[46]
Renal failure	£3,564	NHS 2022/23 National Cost Collection. Weighted average of General Renal Disorders (all grades) - Elective, LA09J-Q.[46]
Hypogammaglobulinemia	£3,324	TA677, NHS 2022/23 National Cost Collection. Deliver Simple Parenteral chemotherapy at first attendance, weighted average of day case, outpatient and other, SA12Z.[46]

CRS – Cytokine release syndrome; NHS – National Health Service; VOD – Veno-occlusive disease.

Table 55: One-off total AE costs applied to treatment arms

Treatment	Cost
Obe-cel	[redacted]
Blinatumomab	£3,380
Inotuzumab	£18,013
Ponatinib	£382

AE – Adverse event

B.3.5.4 Subsequent treatment costs

B.3.5.4.1 Haematopoietic stem cell transplant costs

The analysis assumed that patients in comparator arms who have an event following treatment initiation are eligible to receive a subsequent allo-SCT.

The proportion of patients receiving subsequent allo-SCT is presented by initial treatment arm in Table 56. The rate of subsequent allo-SCT for patients post-treatment with blinatumomab, inotuzumab and ponatinib were aligned with TA893.

No allo-SCT was assumed for patients in the obe-cel treatment arm, in line with TA893 and clinical opinion; UK clinical experts confirmed that no patient treated with a CAR T-cell therapy would proceed onto SCT due to the curative nature of a CAR T-cell therapy.[17] A scenario analysis explores the inclusion of allo-SCT as a subsequent treatment option for patients in the obe-cel treatment arm, based on the FELIX clinical trial.

Table 56: Proportion of patients who receive an allo-SCT, by initial treatment

Treatment	Proportion who receive an allo-SCT	Source
Obe-cel	0%	Clinical opinion and in line with TA893[17]
Blinatumomab	13%	TA893[17]
Inotuzumab	48%	TA893[17]
Ponatinib	47%	TA893[17]

Allo-SCT – allogenic stem cell transplant; TA – Technology Appraisal.

The cost of allo-SCT was calculated as a sum of stem cell harvesting and the allo-SCT procedure, in addition to follow-up costs for a duration of 24 months (Table 57). The allo-SCT costs align with those used in TA893.[17,122,123]

Table 57: Administration cost of allo-SCT

Description	Cost inflated to 2024	Source
Stem cell harvesting	£5,903.60	Weighted average of reference codes SA18Z, SA34Z, elective inpatient costs. National Schedule of NHS Costs - Year 2022/23.[46]
Allo-SCT procedure	£109,687.69	Weighted average of reference codes SA20B - SA23B, S38B, SA39B, elective inpatient costs. National Schedule of NHS Costs - Year 2022/23.[46]
0-6 months follow-up	£34,347.14	TA893[17]
6-12 months follow-up	£23,594.15	TA893[17]
12-24 months follow-up	£17,025.97	TA893[17]

Allo-SCT – allogenic stem cell transplant; NHS – National Health Service; TA – Technology Appraisal.

B.3.5.4.2 Subsequent treatment drug costs

Patients who have an event but who do not receive an allo-SCT are assumed to be eligible to receive a subsequent treatment. The interventions assumed to be offered as subsequent treatments were validated with UK clinical experts, and consist of inotuzumab + ponatinib, inotuzumab, cyclophosphamide + dexamethasone, or

blinatumomab.[92] The proportion of patients who receive each subsequent treatment is presented in Table 58, and was also based on clinical opinion, with patients assumed to not be re-treated with their initial therapy. In the base case, CAR T-cell therapy is not assumed to be offered as a subsequent treatment, but this was included as a scenario in the model.

Table 58: Proportion of patients receiving subsequent treatment, by initial treatment

Treatment	Inotuzumab + ponatinib	Inotuzumab	Cyclophosphamide + dexamethasone	Blinatumomab	Source
Obe-cel	5%	45%	30%	20%	Clinical opinion[92]
Blinatumomab	5%	55%	40%	0%	
Inotuzumab	0%	0%	50%	50%	
Ponatinib	0%	50%	20%	30%	

Subsequent treatment costs were applied as a one-off cost upon entry to the post-event health state. The dosing schedule of cyclophosphamide + dexamethasone was aligned with the bridging therapy regimen in TA893, which assumed 150mg/m^2 of cyclophosphamide for 3 days and 20 mg IV of dexamethasone for 3-4 days.[17] Both drugs were assumed to be administered intravenously on an inpatient basis on each day of treatment. A cost of £393.00 per administration was used, based on the weighted average of day case, outpatient and other appointments of the NHS reference code SB12Z.[46] Unit costs for these drugs were sourced from the BNF.[125] See section B.3.5.1.2 for the acquisition and administration costs of other treatments.

Table 59 shows the total acquisition and administration costs of each subsequent treatment, assuming 2 cycles of treatment for blinatumomab and 1 cycle for other interventions. The cost shown for obe-cel administration includes infusion and monitoring costs, as well as the associated correcting factor-adjusted pre-treatment costs.

Table 59: Subsequent treatment costs, by initial treatment

Treatment	Total acquisition costs	Total administration costs

Inotuzumab + ponatinib	£36,033.37	£6,683.63
Inotuzumab	£32,192.00	£6,362.96
Cyclophosphamide + dexamethasone	£5,102.56	£2,751.00
Blinatumomab	£84,714.00	£10,795.26
Obe-cel (scenario only)	[redacted]	[redacted]

B.3.5.5 Terminal care costs

Terminal care costs have been applied as composite costs for the last three months of life based on Georgiou and Bardsley (2014), in line with TA893.[17,130] These costs comprise of a district nurse, nursing and residential care, inpatient care, the final three months of life hospital care, and end-of-life at home nurse care from the Marie Curie nursing service (Table 60). Each cost component was adjusted for inflation from 2009-2011 to 2023 prices, using the PSSRU inflation index.[122,123] The total terminal care cost of £8,586.57 was applied as a one-off cost to patients upon entry into the death health state.

Table 60: Terminal care costs

Resource use	Cost inflated to 2024	Source
District nurse	£346.42	Georghiou and Bardsley, 2014[130]
Nursing and residential care	£1,253.60	
Hospital care – inpatient	£689.48	
Hospital care – final 3 months of life	£5,607.57	
Marie Curie nursing service	£689.48	
Total one-off terminal care cost	**£8,586.57**	Calculation

B.3.6 Severity

Based on the undertaken analysis outlined in this section, obe-cel meets the criteria to be assessed using a 1.7 severity modifier, reflecting the severity of adult R/R ALL. Five-year UK survival rates for patients older than 40 at diagnosis are as low as 28%[8], and 40% of adult patients relapse following treatment, facing survival rates ranging from <10% to circa 25%.[9] Existing treatment options in routine commissioning offer limited survival and QoL gain, especially in relapsed patients.

The remaining life expectancy and QoL of UK R/R ALL patients under current care was compared with that of an age- and sex-matched general population in line with the NICE reference case using the approach and references from Schneider *et al*.

(2022)[131]. Life expectancy for the general population was based on ONS UK life tables (2017-2019)[132], and quality-adjusted using EQ-5D UK population norm values from Hernández Alava *et al*. (2022)[133]. A discount rate of 3.5% was applied.

The base case starting age and sex distribution, based on the FELIX trial and aligned with the base case, is reported in Table 61. A breakdown of health state benefits and utility values used in the analysis is presented in Table 62. The QALY shortfall analysis is presented in Table 63 and demonstrates obe-cel meets the criteria for a 1.7 severity modifier versus blinatumomab, and a 1.2 severity modifier versus inotuzumab and ponatinib.

Table 61: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	50% (Table 27)	Section B.3.2.1
Starting age	48.30 (Table 27)	

QALY – quality-adjusted life year

Table 62: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years		
		Inotuzumab	Blinatumomab	Ponatinib
Event-free	[redacted]	[redacted]	[redacted]	[redacted]
Post-event	[redacted]	[redacted]	[redacted]	[redacted]

QALY – quality-adjusted life year

Table 63: Summary of QALY shortfall analysis

Treatment	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute shortfall	Proportional shortfall	Severity modifier versus comparator

Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	1.7
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	1.2
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	1.2

QALY – quality-adjusted life year

To contextualise the outcomes of this analysis to previous appraisals in R/R ALL, Table 64 summarises the outcomes of TA975. All other TAs in R/R ALL (presented in Table 2, Section B.1.2) were undertaken prior to the introduction of the severity modifier. Although the population considered in TA975 was patients 25 years and younger, and therefore does not overlap with the anticipated population for this appraisal, it represents the only appraisal in R/R ALL following the introduction of the severity modifier. The committee for TA975 utilised a severity modifier of 1.7 for decision making. Similarly, the committee for TA893 considered that brexu-cel met the end-of-life criteria, and therefore a willingness-to-pay (WTP) threshold of £50,000 was considered suitable for decision making, equivalent to the use of a 1.7 severity modifier.[17]

Table 64: Summary list of QALY shortfall from previous evaluations

TA	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
TA975	23.79	**Blinatumomab:** 3.06 **Salvage chemotherapy:** 2.22	**Blinatumomab** Absolute shortfall: 20.73 Proportional shortfall: 0.87 **Salvage chemotherapy** Absolute shortfall: 21.56 Proportional shortfall: 0.91

QALY – quality-adjusted life year; TA – Technology assessment

Given that obe-cel meets the criteria for a 1.7 severity modifier versus at least one of the comparators in this appraisal, and in the context of the 1.7 modifier being considered for decision making in TA975 and a WTP threshold of £50,000 being considered for decision making in TA893, the company consider 1.7 to be the appropriate severity modifier to use for decision making in this appraisal.

B.3.7 Uncertainty

From the perspective of economic modelling, and the need to estimate clinical outcomes over a lifetime horizon, the limited follow-up of the FELIX trial and availability of long-term data introduces uncertainty. This uncertainty has been minimised through the comprehensive survival analyses presented in Section B.3.3, and scenario analyses discussed in further detail in Section 0.

Furthermore, there are no randomised studies comparing obe-cel with the identified relevant comparators leading to uncertainty in the clinical inputs informing the economic model. To estimate the efficacy of obe-cel compared with relevant comparators, ITCs, including naïve and MAICs were conducted as discussed in Section B.2.9, and scenario analyses tested, discussed in Section 0.

Wherever possible, the model aligns with committee preference from TA893 given the extensive review of materials that occurred as part of the appraisal and the recency of the appraisal, to minimise uncertainty and ensure consistency of decision making.[17] For other model inputs and assumptions, extensive clinical validation was conducted to minimise clinical uncertainty (described in full detail in Section B.3.13).

The uncertainty in the model is explored through extensive deterministic sensitivity analyses, probabilistic sensitivity analyses and scenario analyses, with results for these presented in Section B.3.10.1.

B.3.8 Summary of base case analysis inputs and assumptions

B.3.8.1 Summary of base case analysis inputs

A summary of the inputs used in the base case of the economic model is provided in Table 65.

Table 65: Summary of variables applied in the economic model

Parameter	Included in PSA?	Value	OWSA			Within PSA varied by	Reference to section in submission
			SE	Lower bound	Upper bound		
Time horizon (years)	No	51.7	-	-	-	-	B.3.2.3
Discount rate (costs)	No	3.50%	-	-	-	-	B.3.6
Discount rate (LYs)	No	0.00%	-	-	-	-	
Discount rate (QALYs)	No	3.50%	-	-	-	-	
Starting age	No	48.30	-	-	-	-	
Proportion male	No	50%	5.0%	40%	100%	Beta	B.3.2.1
Patient BSA	No	1.89	0.019	1.52	2.26	Normal	
Patient weight	Yes	78.73	7.87	63.60	94.16	Normal	
Obe-cel – EFS KM adjustment	No	1.00	-	-	-	-	-
Blinatumomab – EFS KM adjustment	No	0.44	-	-	-	-	-
Inotuzumab – EFS KM adjustment	No	1.00	-	-	-	-	-
Ponatinib – EFS KM adjustment	No	1.00	-	-	-	-	-
Utility: Event-free	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta	B.3.4.2
Utility: Post-event	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta	
Utility: Alive >60m scenario	Yes	0.860	0.086	0.65	0.98	Beta	
Utility: long-term survivorship	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta	B.3.4.3

Utility decrement: Post-HSCT < 1 year	Yes	0.170	0.017	0.14	0.20	Beta	B.3.4.2
Utility decrement: Post-HSCT 1-2 years	Yes	0.010	0.001	0.01	0.01	Beta	
Utility decrement: Post-HSCT 3-5 years	Yes	0.020	0.002	0.02	0.02	Beta	
Utility decrement: Post-HSCT >5 years	Yes	0.000	0.000	0.00	0.00	Beta	
GP Utility – constant	Yes	0.951	-	-	-	-	B.3.4.4
GP Utility – age	Yes	0.000	-	-	-	-	
GP Utility – age^2	Yes	0.000	-	-	-	-	
GP Utility - gender	Yes	0.021	-	-	-	-	
Obe-cel acquisition cost (£)	No	[redacted]	-	-	-	-	B.3.5.1.1.1
Blinatumomab acquisition cost (£)	No	2,017	-	-	-	-	B.3.5.1.2.1
Inotuzumab acquisition cost (£)	No	8,048	-	-	-	-	B.3.5.1.2.2
Ponatinib acquisition cost (£)	No	4,116	-	-	-	-	B.3.5.1.2.3
Oral (£)	Yes	321	32	261	387	Gamma	B.3.5
Subcutaneous (£)	Yes	34	3	28	41	Gamma	
Intravenous (first attendance) (£)	Yes	393	39	320	474	Gamma	
Intravenous (first attendance – complex chemotherapy) (£)	Yes	459	46	374	554	Gamma	
Intravenous infusion (subsequent) (£)	Yes	375	37	305	452	Gamma	
Home infusion pump costs (£)	Yes	125	13	102	151	Gamma	
Mean daily hospital cost (£)	Yes	621	62	506	749	Gamma	
Leukapheresis cost (£)	Yes	1,652	165	1,344	1.991	Gamma	B.3.5.1.1.3

Leukapheresis correcting factor	No	[redacted]	-	-	-	-	
Bridging chemotherapy costs (£)	Yes	5,094	509	4,145	6.140	Gamma	
Bridging chemotherapy correcting factor	No	[redacted]	-	-	-	-	
Conditioning chemotherapy costs (£)	Yes	1,533	153	1,248	1,848	Gamma	
Conditioning chemotherapy correcting factor	No	[redacted]	-	-	-	-	
HSCT – initial cost (£)	Yes	115,591	11,559	94,050	139,321	Gamma	B.3.5.4.2
HSCT – per cycle cost (<6 months post-HSCT)	Yes	34,347	3,435	27,946	41,398	Gamma	
HSCT – per cycle cost (6-12 months post-HSCT)	Yes	23,594	2,359	19,197	28,438	Gamma	
HSCT – per cycle cost (12-24 months post-HSCT)	Yes	17,026	1,703	13,853	20,521	Gamma	
Obe-cel – proportion HSCT	Yes	0.00	0.00	0.00	0.00	Beta	
Blinatumomab – proportion HSCT	Yes	0.13	0.01	0.11	0.16	Beta	
Intozumomab – proportion HSCT	Yes	0.48	0.05	0.39	0.58	Beta	
Ponatinib – proportion HSCT	Yes	0.47	0.05	0.38	0.56	Beta	
Obe-cel – SubTx drug costs (£)	Yes	34,111	3,411	27,754	41,114	Gamma	
Blinatumomab – SubTx drug costs (£)	Yes	20,681	2,068	16,827	24,926	Gamma	
Inotuzumab – SubTx drug costs (£)	Yes	43,824	4,382	35,657	52,820	Gamma	
Ponatinib – SubTx drug costs (£)	Yes	42,097	4,210	34,252	50,739	Gamma	
Obe-cel – SubTx admin costs (£)	Yes	6,182	618	5,030	7,451	Gamma	

Blinatumomab – SubTx admin costs (£)	Yes	4,934	493	4,015	5,947	Gamma	
Inotuzumab – SubTx admin costs (£)	Yes	6,773	677	5,511	8,164	Gamma	
Ponatinib – SubTx admin costs (£)	Yes	6,970	697	5,671	8,401	Gamma	
Obe-cel: total per cycle AE costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma	B.3.5.3
Blinatumomab: total per cycle AE costs (£)	Yes	3,380	338	2,750	4,074	Gamma	
Inotuzumab: per cycle AE costs (£)	Yes	18,013	1,801	14,656	21,711	Gamma	
Ponatinib: total per cycle AE costs (£)	Yes	382	38	311	461	Gamma	
Obe-cel: total AE utility decrement	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta	
Blinatumomab: total AE utility decrement	Yes	0.190	0.019	0.154	0.229	Beta	
Inotuzumab: total AE utility decrement	Yes	0.108	0.011	0.087	0.130	Beta	
Ponatinib: total AE utility decrement	Yes	0.064	0.006	0.052	0.077	Beta	
HCRU costs: event-free – year 1 – CAR T (£)	Yes	565	56	460	681	Gamma	B.3.5.2
HCRU costs: event-free – year 2 – CAR T (£)	Yes	80	8	65	97	Gamma	
HCRU costs: event-free – year 3+ – CAR T (£)	Yes	40	4	33	48	Gamma	
HCRU costs: event-free – year 1 – non-CAR T (£)	Yes	367	37	299	443	Gamma	
HCRU costs: event-free – year 2 – non-CAR T (£)	Yes	80	8	65	97	Gamma	

HCRU costs: event-free – year 3+ – non-CAR T (£)	Yes	40	4	32	48	Gamma	
HCRU costs: event-free – long-term survival (£)	Yes	20	2	16	24	Gamma	
HCRU costs: post-event (£)	Yes	272	27	221	328	Gamma	
Terminal care cost (£)	Yes	8,587	859	6986	10,349	Normal	B.3.5.5
Standardised mortality ratio for long-term survivors	Yes	3	0.30	1.09	4	Normal	B.3.2.2.1

AE – Adverse event; BSA – Body surface area; EFS – Event-free survival; GP – General Practitioner; HCRU – Health care resource use; HSCT – Haematopoietic stem cell transplant; IVIG – Intravenous immunoglobin; KM – Kaplan-Meier; LY – Life year; OS – Obe-cel; PSA – Probabilistic sensitivity analyses; SubTx – Subsequent treatment; QALY – Quality-adjusted life year.

B.3.8.2 Assumptions

A summary of assumptions applied in the model is presented in Table 66.

Table 66: Assumptions applied in the model

Aspect	Assumption	Justification	Source/Exploration in scenario analysis
Patient population	Cohort IIA patients from the FELIX trial are representative of the patient population expected to receive obe-cel in NHS practice.	A diverse group of adult R/R B-cell ALL patients were included in the trial, with a number of subgroups that are prognostically considered to be difficult to treat.	See Section B.2.3.3
	Clinical efficacy of patients who failed to receive obe-cel infusion in FELIX is not included in the economic analysis.	Patients who fail to receive CAR T-cell therapy infusion following leukapheresis, bridging chemotherapy or conditioning therapy are assumed to receive salvage chemotherapy.	In line with TA893[17].
Clinical efficacy	An inverse MAIC approach is used in the base case for inotuzumab and blinatumomab. A naïve ITC approach is used in the base case for ponatinib.	The MAIC analyses versus inotuzumab and blinatumomab yielded a reasonable ESS and plausible results. Implementing a MAIC inversely was preferred by EAG in TA893. The MAIC results are limited by poor population overlap between FELIX and PACE.	In line with TA893[17]. Alternative MAIC implementation and naïve analyses were explored in scenario analyses (see Section 0).
	Independent survival curve modelling is used in the model base case for all comparisons.	Analysis of the standard parametric models found the proportional hazards assumption to be violated when comparing obe-cel and each comparator.	See Appendix M.
Mortality	Patients who are alive after three years in the model are assumed	Based on precedent from previous NICE TAs and UK clinician feedback[92], patients who are	In line with TA893[17].

	to be cured, and as such have a heightened risk of mortality relative to the general population.	alive after three years can be considered cured but still have an increased risk of death compared to the general population.	Alternative SMR values were explored in scenario analyses (see Section 0).
HRQoL inputs	Health state utility values from FELIX are representative of the UK population.	[redacted] of patients in FELIX were from the UK.	See Section B.2.4.1.
	Patients who are alive after three years in the model are assumed to be cured, and as such incur a utility increment in addition to their health state utility.	Based on precedent from previous NICE TAs and UK clinician feedback[92], patients who are alive after three years can be considered cured but still have a slightly lower QoL than the general population.	In line with TA893[17]. Alternative utility values for long-term survivors were explored in scenario analyses (see Section 0).
	CRS disutility is assumed equal to the utility of the EFS health state.	CRS is a severe and potentially life-threatening toxicity associated with CAR T-cel therapies.	In line with TA893[17]. An alternative CRS disutility value was explored in scenario analyses (see Section 0).
Cost inputs	CAR T-cell therapy bottom-up costing approach is used for treatment administration costs associated with obe-cel.	Obe-cel is associated with substantially lower rates of CRS and ICANS than other approved CAR-Ts such as brexu-cel, therefore using data from the FELIX trial to inform predicted resource use appropriately captures the lower rates of CRS and ICANS.	Using CAR T-cell therapy tariff costs for the treatment administration costs associated with obe-cel were explored in scenario analyses (see Section 0).

Subsequent treatment	A proportion of patients who progress are assumed to receive subsequent treatments, other than their initial therapy.	Based on UK clinician feedback[92], patients would receive subsequent therapies upon disease progression.	In line with TA893[17].
	Patients are not assumed to receive subsequent allo-SCT following obe-cel infusion.	Based on UK clinician feedback[92], patients whose disease progressed following CAR T-cell therapy would not be treated with allo-SCT.	Assuming subsequent allo-SCT for patients in the obe-cel arm was explored in scenario analyses (see Section 0).

Allo-SCT – allogeneic stem cell transplantation; AE – adverse event; CAR T-cell – chimeric antigen receptor T-cell; CRS – cytokine release syndrome; HR – hazard ratio; ICANS – immune effector cell-associated neurotoxicity syndrome; MAIC – matching-adjusted indirect comparison; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; QoL – quality of life; SMR – standardised mortality ratio; TA – technology appraisal; UK – United Kingdom

B.3.9 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 PAS discount of [redacted] for obe-cel.

B.3.9.1 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 67 and Table 68 using obe-cel list and PAS price, respectively.

Using the list price for obe-cel, and a severity modifier of 1.7, 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 2.88 QALYs at an additional cost of £[redacted]. When the PAS discount is applied, obe-cel is associated with costs savings of £[redacted] versus inotuzumab, resulting in [redacted]. Disaggregated base case results are presented in Appendix J.

Table 67: 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.88	[redacted]

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

Table 68: Deterministic results, overall population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.88	[redacted]

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

B.3.9.2 Ph- population

Total costs, LYG, QALYs, incremental results and the ICER for obe-cel versus inotuzumab and blinatumomab are presented in Table 69 and Table 70 using obe-cel list and PAS price, respectively.

Using the list price for obe-cel and a severity modifier of 1.7, the cost-effectiveness of obe-cel compared with blinatumomab is £[redacted] per QALY gained. Obe-cel generates an additional 5.08 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 1.7, the cost-effectiveness of obe-cel compared with inotuzumab is £[redacted] per QALY gained. Obe-cel generates an additional 2.15 QALYs at an additional cost of £[redacted]. When the PAS discount is applied, obe-cel is associated with cost savings of £[redacted] versus inotuzumab, [redacted]

Disaggregated base case results are presented in Appendix J.

Table 69: 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]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.72	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.15	[redacted]	[redacted]

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

Table 70: 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.08	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.15	[redacted]	[redacted]

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

B.3.9.3 Ph+ population

Total costs, LYG, QALYs, incremental results and the ICER for obe-cel versus inotuzumab and ponatinib are presented in Table 71 and Table 72 using obe-cel list and PAS price, respectively.

Using the list price for obe-cel and a severity modifier of 1.7, the cost-effectiveness of obe-cel compared with inotuzumab [redacted]. Obe-cel generates an additional [redacted] QALYs with cost savings of £[redacted]. When the PAS discount is applied, obe-cel is associated with cost savings of £[redacted] versus ponatinib, resulting in [redacted].

Using the list price for obe-cel and a severity modifier of 1.7, the cost-effectiveness of obe-cel compared with ponatinib is £[redacted] per QALY gained. Obe-cel generates an additional 11.04 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.

Disaggregated base case results are presented in Appendix J.

Table 71: 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.04	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.54	[redacted]	[redacted]

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

Table 72: 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.04	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.54	[redacted]	[redacted]

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

B.3.10 Exploring uncertainty

B.3.10.1 Deterministic sensitivity analysis

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.

The top ten parameters yielding the biggest impact on cost-effectiveness results for the overall population are presented in Table 73 and Figure 32. The top three most sensitive parameters were the proportion of inotuzumab patients receiving HSCT, the inotuzumab HSCT per cycle cost and the HSCT initial treatment cost.

The top ten parameters yielding the biggest impact on cost-effectiveness results for the Ph- population versus blinatumomab are presented in Table 74 and Figure 33. The top three most sensitive parameters were the OS standard parametric coefficients, EFS standard parametric coefficients and the SMR. Results for the Ph- comparison to inotuzumab are presented in Table 75 and Figure 34. The top three most sensitive parameters were the OS standard parametric coefficients, the proportion of inotuzumab patients receiving HSCT and the HSCT per cycle cost.

The top ten parameters yielding the biggest impact on cost-effectiveness results for the Ph+ comparison to inotuzumab, these are presented in Table 76 and Figure 35. The top three most sensitive parameters were the OS standard parametric coefficients, the proportion of inotuzumab patients receiving HSCT and the EFS flexible parametric coefficients. Results for the Ph+ population versus ponatinib are presented in Table 77 and Figure 36. The top three most sensitive parameters were the OS standard parametric coefficients, the proportion of ponatinib patients receiving HSCT and the EFS flexible parametric coefficients.

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.[17]

Table 73: Tabulated OWSA results - obe-cel versus inotuzumab (overall population) - NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Inotuzumab - proportion HSCT (0.39, 0.58)	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (<6 months post-HSCT) (£27,946, £41,398)	[redacted]	[redacted]	[redacted]
HSCT - Initial treatment cost (£94,050, £139,321)	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (12-24 months post-HSCT) (£13,853, £20,521)	[redacted]	[redacted]	[redacted]
Utility: Long-term survivorship (0.05, 0.07)	[redacted]	[redacted]	[redacted]
OS Flexible parametric coefficients	[redacted]	[redacted]	[redacted]
Standardised mortality ratio for all long-term survivors (1.09, 4.00)	[redacted]	[redacted]	[redacted]
Patient weight (63.30, 94.16)	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (6-12 months post-HSCT) (£19,197, £28,438)	[redacted]	[redacted]	[redacted]
Patient height (135.16, 201.06)	[redacted]	[redacted]	[redacted]

HSCT – haematopoietic stem cell transplant; NMB – Net monetary benefit; OS – Overall survival; OWSA – one-way sensitivity analysis; SubTX – Subsequent treatment.

Figure 32: OWSA results for obe-cel versus inotuzumab (overall population) - NMB

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

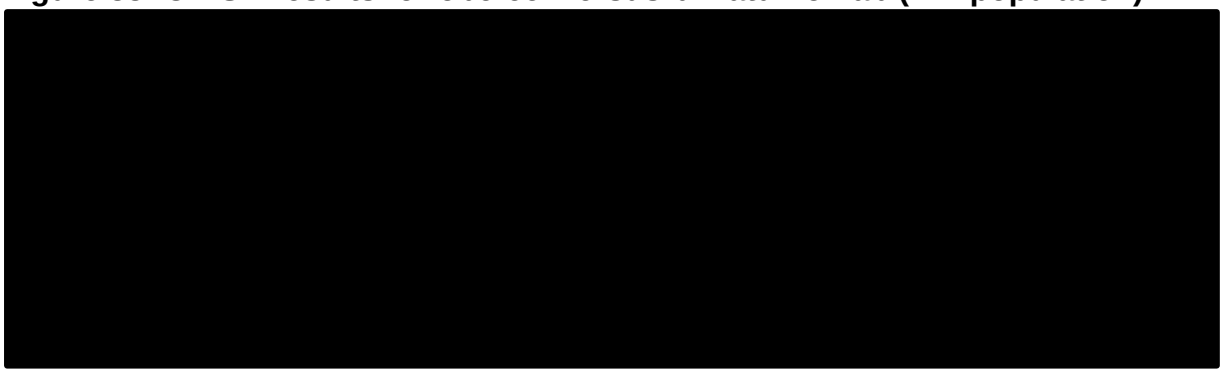
Company evidence submission template for obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID6347]

Table 74: Tabulated OWSA results - obe-cel versus blinatumomab (Ph- population) - ICER

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
OS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
EFS 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 (0.05, 0.08)	[redacted]	[redacted]	[redacted]
Blinatumomab - proportion HSCT (0.11, 0.16)	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (<6 months post-HSCT) (£27,946, £41,398)	[redacted]	[redacted]	[redacted]
SubTx drug costs - Blinatumomab (£16,827, £24,926)	[redacted]	[redacted]	[redacted]
Patient weight (65.04, 96.76)	[redacted]	[redacted]	[redacted]
HSCT - Initial treatment cost (£94,050, £139,321)	[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 33: OWSA results for obe-cel versus blinatumomab (Ph- population)



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

Table 75: Tabulated OWSA results for obe-cel versus inotuzumab (Ph- population) - NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
OS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
Inotuzumab - proportion HSCT (0.39, 0.58)	[redacted]	[redacted]	[redacted]

Company evidence submission template for obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID6347]

HSCT - per cycle cost (<6 months post-HSCT) (£27,946, £41,398)	[redacted]	[redacted]	[redacted]
Patient weight (65.04, 96.76)	[redacted]	[redacted]	[redacted]
HSCT - Initial treatment cost (£94,050, £139,321)	[redacted]	[redacted]	[redacted]
Patient height (135.16, 201.06)	[redacted]	[redacted]	[redacted]
Standardised mortality ratio for all long-term survivors (1.09, 4.00)	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (6-12 months post-HSCT) (£19,197, £28,438)	[redacted]	[redacted]	[redacted]
Utility: Long-term survivorship (0.05, 0.08)	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (12-24 months post-HSCT) (£13,853, £20,521)	[redacted]	[redacted]	[redacted]

HSCT – haematopoietic stem cell transplant; NMB – Net monetary benefit; OS – Overall survival; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis; SubTX – Subsequent treatment.

Figure 34: OWSA results for obe-cel versus inotuzumab (Ph- population) - NMB

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

Table 76: Tabulated OWSA results - obe-cel versus inotuzumab (Ph+ population) - NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
OS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
Inotuzumab - proportion HSCT (0.39, 0.58)	[redacted]	[redacted]	[redacted]
EFS Flexible parametric coefficients	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (<6 months post-HSCT) (£27,946, £41,398)	[redacted]	[redacted]	[redacted]

HSCT - per cycle cost (12-24 months post-HSCT) (£13,853, £20,521)	[redacted]	[redacted]	[redacted]
HSCT - Initial treatment cost (£94,050, £139,321)	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (6-12 months post-HSCT) (£19,197, £28,438)	[redacted]	[redacted]	[redacted]
Patient weight (58.36, 86.82)	[redacted]	[redacted]	[redacted]
Patient height (133.96, 199.28)	[redacted]	[redacted]	[redacted]
Utility: Long-term survivorship (0.03, 0.05)	[redacted]	[redacted]	[redacted]

EFS – Event-free survival; HSCT – haematopoietic stem cell transplant; NMB – Net monetary benefit; OS – Overall survival; Ph – Philadelphia chromosome; OWSA – one-way sensitivity analysis; SubTX – Subsequent treatment.

Figure 35: OWSA results for obe-cel versus inotuzumab (Ph+ population) - NMB

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

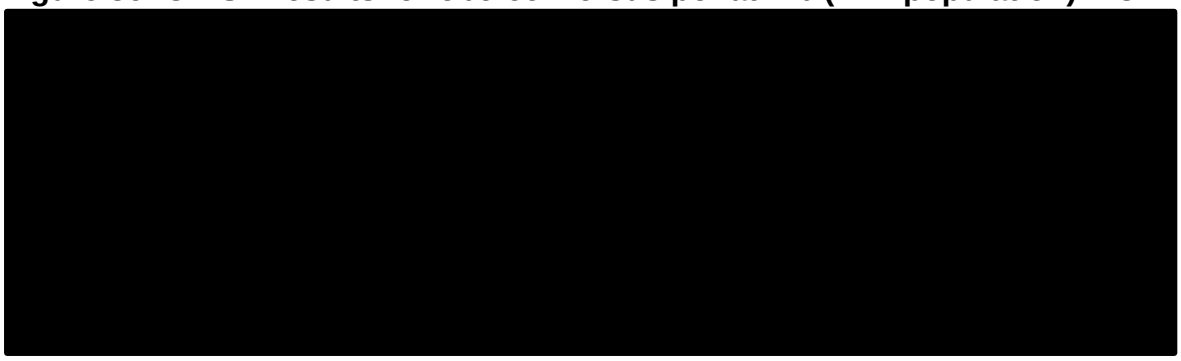
Table 77: Tabulated OWSA results - obe-cel versus ponatinib (Ph+ population) - ICER

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
OS Standard parametric coefficients	[redacted]	[redacted]	[redacted]
Ponatinib - proportion HSCT (0.38, 0.56)	[redacted]	[redacted]	[redacted]
EFS Flexible parametric coefficients	[redacted]	[redacted]	[redacted]
Standardised mortality ratio for all long-term survivors (1.09, 4.00)	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (<6 months post-HSCT) (£27,946, £41,398)	[redacted]	[redacted]	[redacted]
HSCT - Initial treatment cost (£94,050, £139,321)	[redacted]	[redacted]	[redacted]

Utility: Event-free (0.59, 0.88)	[redacted]	[redacted]	[redacted]
Utility: Long-term survivorship (0.03, 0.05)	[redacted]	[redacted]	[redacted]
SubTx drug costs - Ponatinib (£30,978, £45,889)	[redacted]	[redacted]	[redacted]
HSCT - per cycle cost (6-12 months post-HSCT) (£19,197, £28,438)	[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 36: OWSA results for obe-cel versus ponatinib (Ph+ population) - ICER



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

B.3.10.2 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 1.7 severity modifier, to demonstrate the convergence of the population-specific ICERs.

The mean costs and QALYs for the overall, Ph- and Ph+ populations are presented in Table 78 to Table 80, respectively. Results were plotted on incremental cost-effectiveness planes which are presented in Figure 37 for the overall population, Figure 39 and Figure 40 for the Ph- population and Figure 43 and Figure 44 for the Ph+ population. 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. Cost-effectiveness acceptability curves are presented in Figure 38 for the overall population, Figure 41 and Figure 42 for the Ph- population and Figure 45 and Figure 46 for the Ph+ populations.

The mean PSA results for obe-cel versus inotuzumab in the overall population were comparable to the base case, resulting in a 2.4% difference in incremental QALYs and a [redacted] difference in incremental costs which translates into [redacted].

In the Ph- population, the mean probabilistic incremental QALYs and costs for obe-cel versus inotuzumab resulted in a 0.8% and [redacted] difference compared to the base case, which similarly to the base case, translates into [redacted]. In comparison against blinatumomab, the mean PSA results for obe-cel were comparable to the base case, resulting in a 2.4% difference in incremental QALYs and a [redacted] difference in incremental costs relative to the base case, translating into a probabilistic ICER of [redacted].

The mean PSA results for obe-cel versus inotuzumab in the Ph+ population were comparable to the base case, resulting in a 4.3% difference in incremental QALYs and a [redacted] difference in incremental costs relative to the base case, which translates into [redacted]. In the comparison against ponatinib, the mean probabilistic incremental QALYs and costs resulted in a -3.1% and [redacted] difference, respectively, compared to the base case results, translating into a probabilistic ICER of [redacted].

Table 78: Probabilistic results considering PAS discount (overall population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.81	[redacted]

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

Table 79: 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.21	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.17	[redacted]	[redacted]

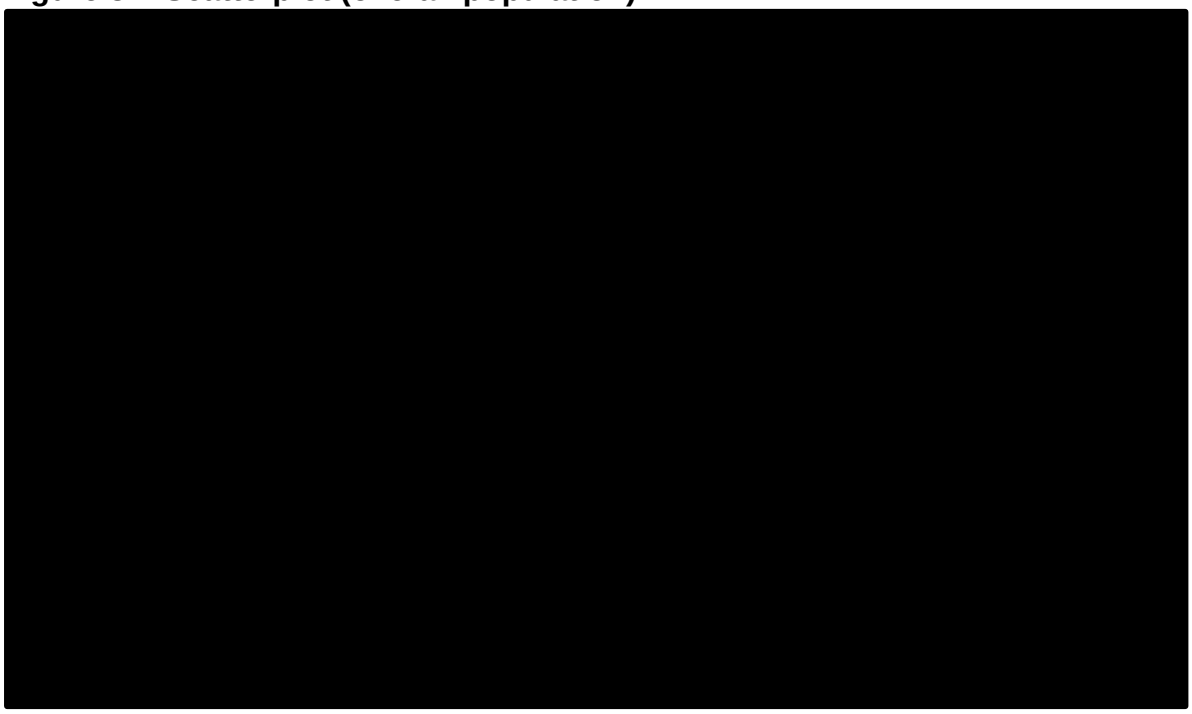
ICER – incremental cost-effectiveness ratio; LYG – life year gained; PAS – Patient Access Scheme; Ph – Philadelphia; QALY – quality-adjusted life year.

Table 80: 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.70	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.43	[redacted]	[redacted]

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

Figure 37: Scatterplot (overall population)



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

Figure 38: CEAC (overall population)

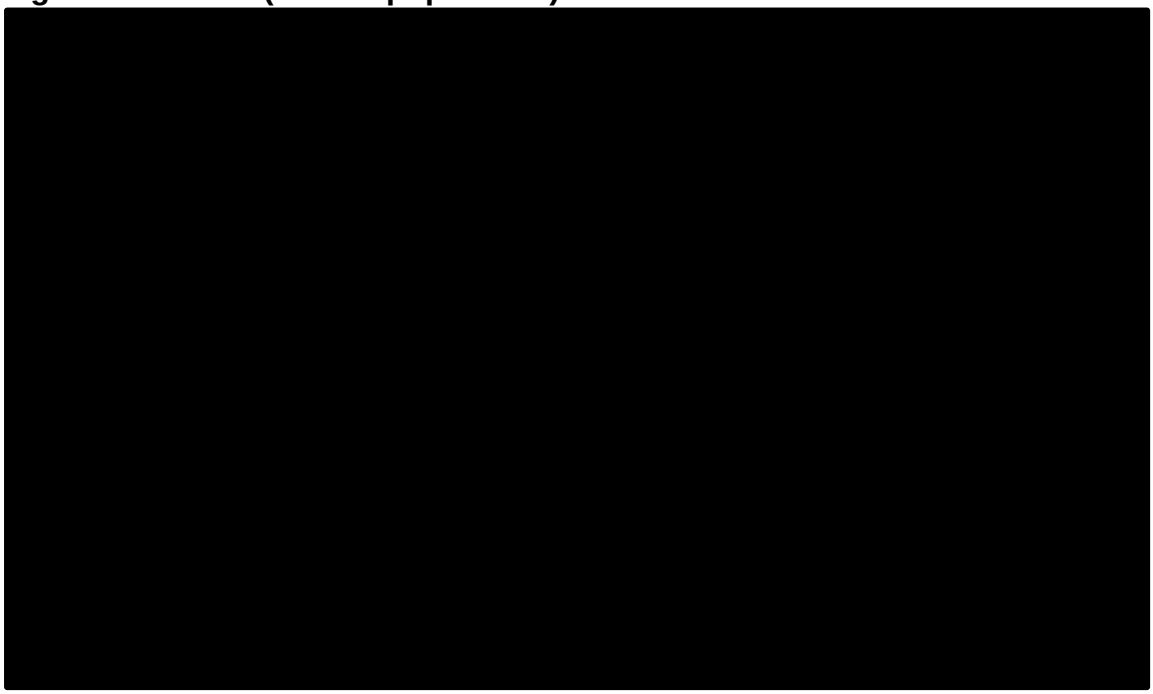
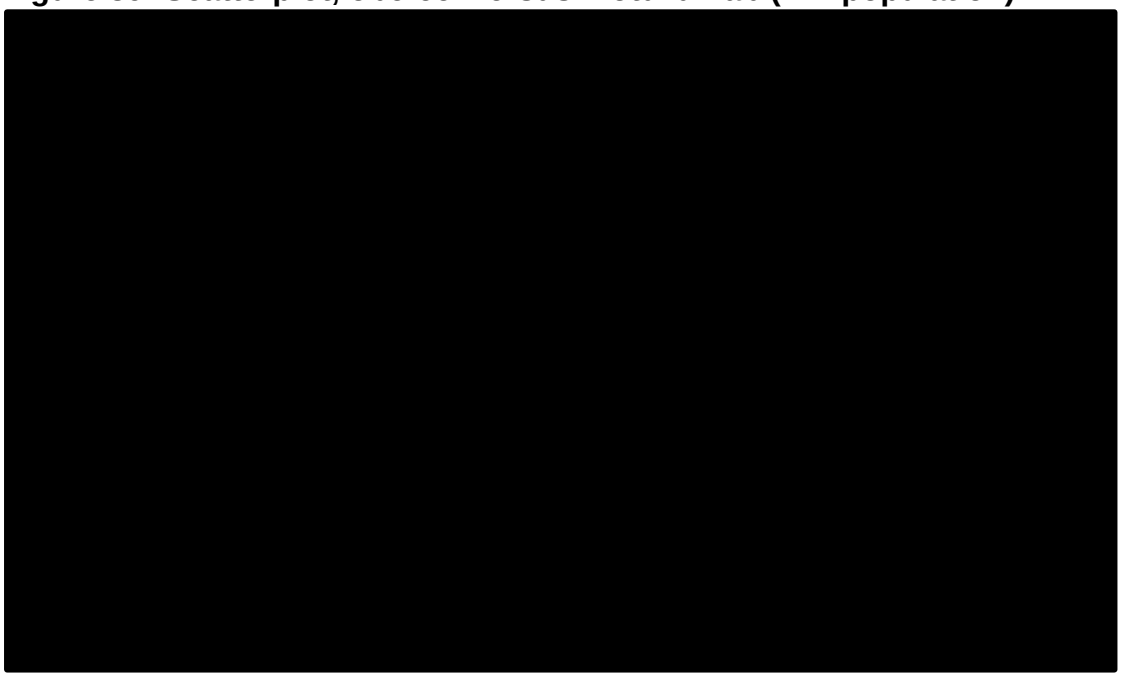
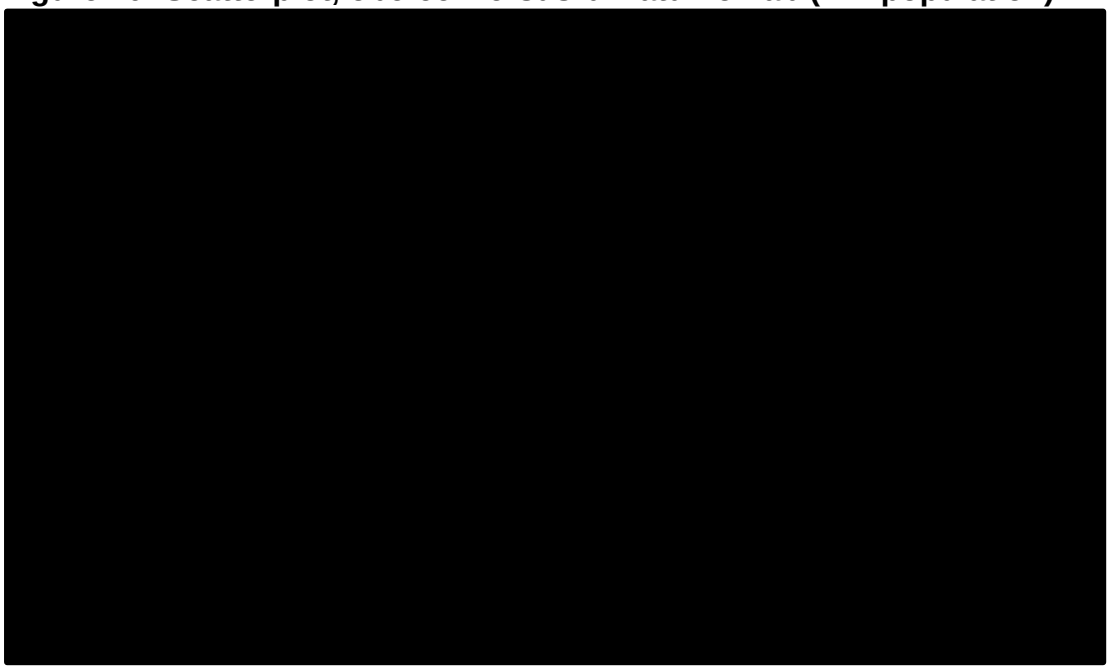


Figure 39: Scatterplot, obe-cel versus inotuzumab (Ph- population)



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

Figure 40: Scatterplot, obe-cel versus blinatumomab (Ph- population)



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

Figure 41: CEAC, obe-cel versus blinatumomab (Ph- population)

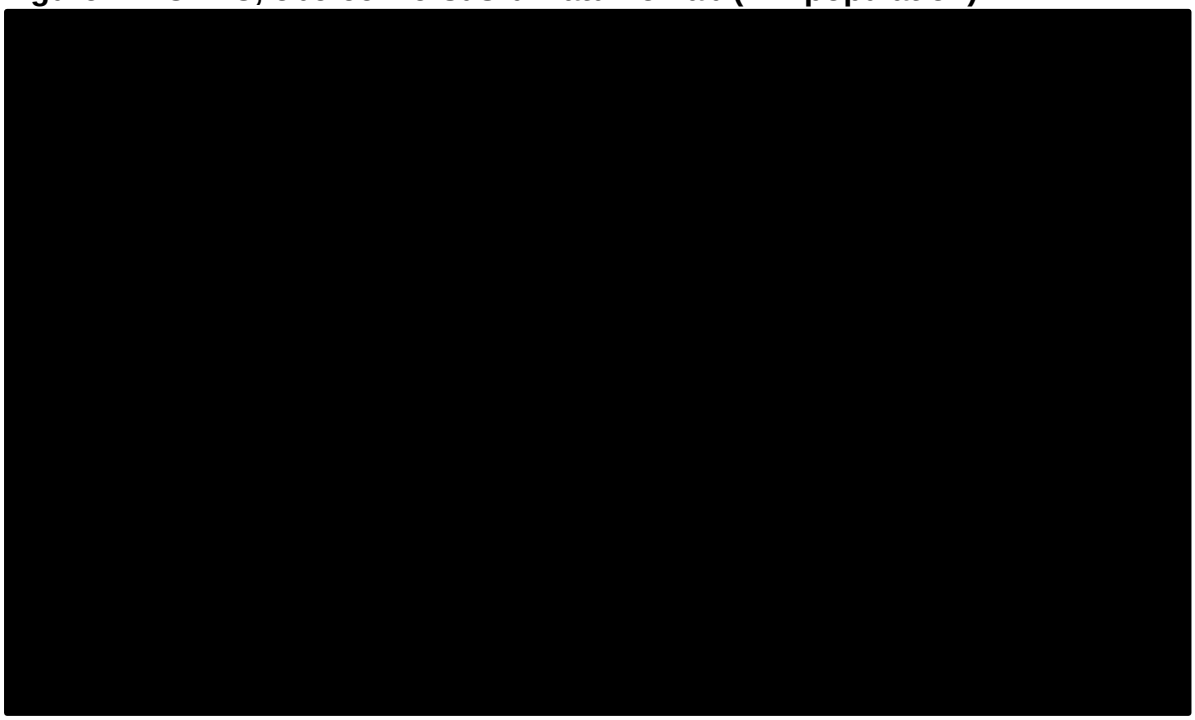


Figure 42: CEAC, obe-cel versus inotuzumab (Ph- population)

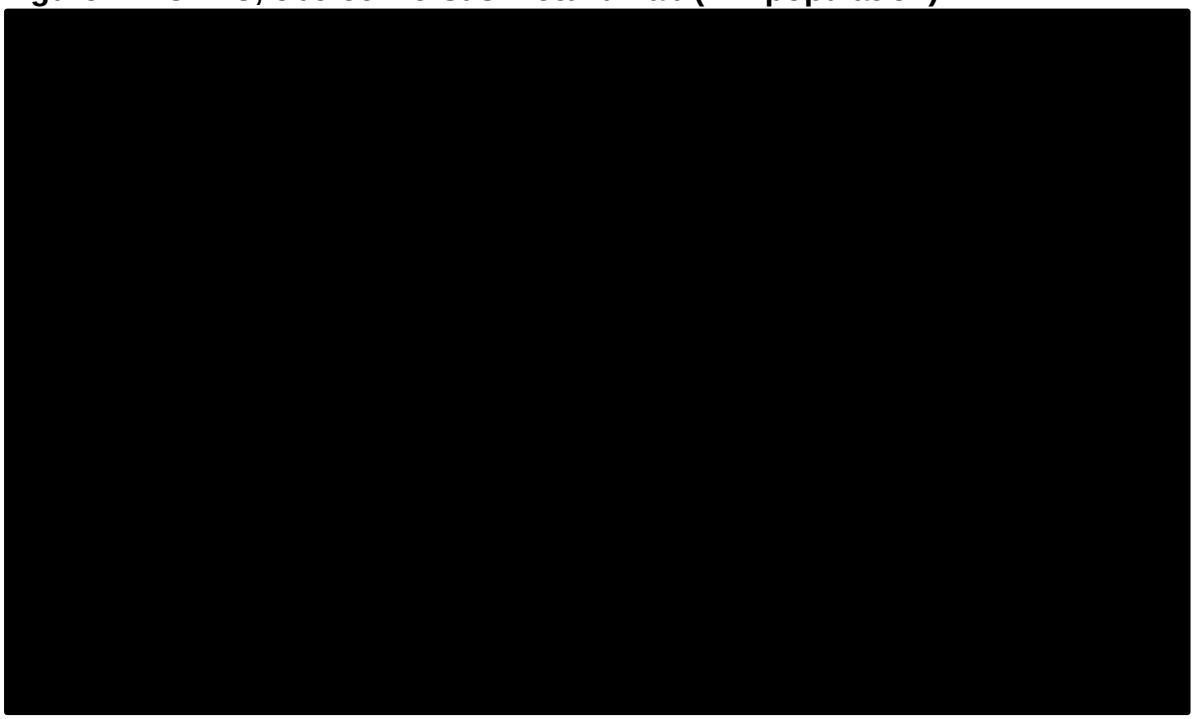
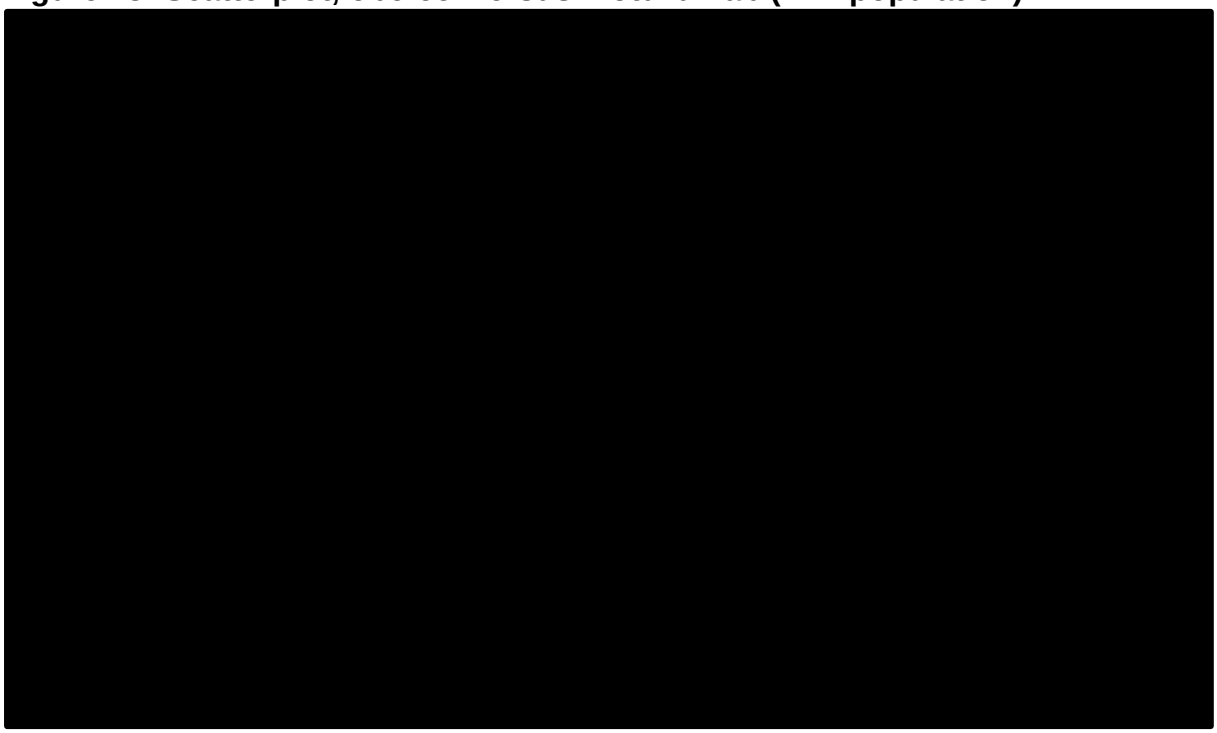


Figure 43: Scatterplot, obe-cel versus inotuzumab (Ph+ population)



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

Figure 44: Scatterplot, obe-cel versus ponatinib (Ph+ population)

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

Figure 45: CEAC, obe-cel versus inotuzumab (Ph+ population)

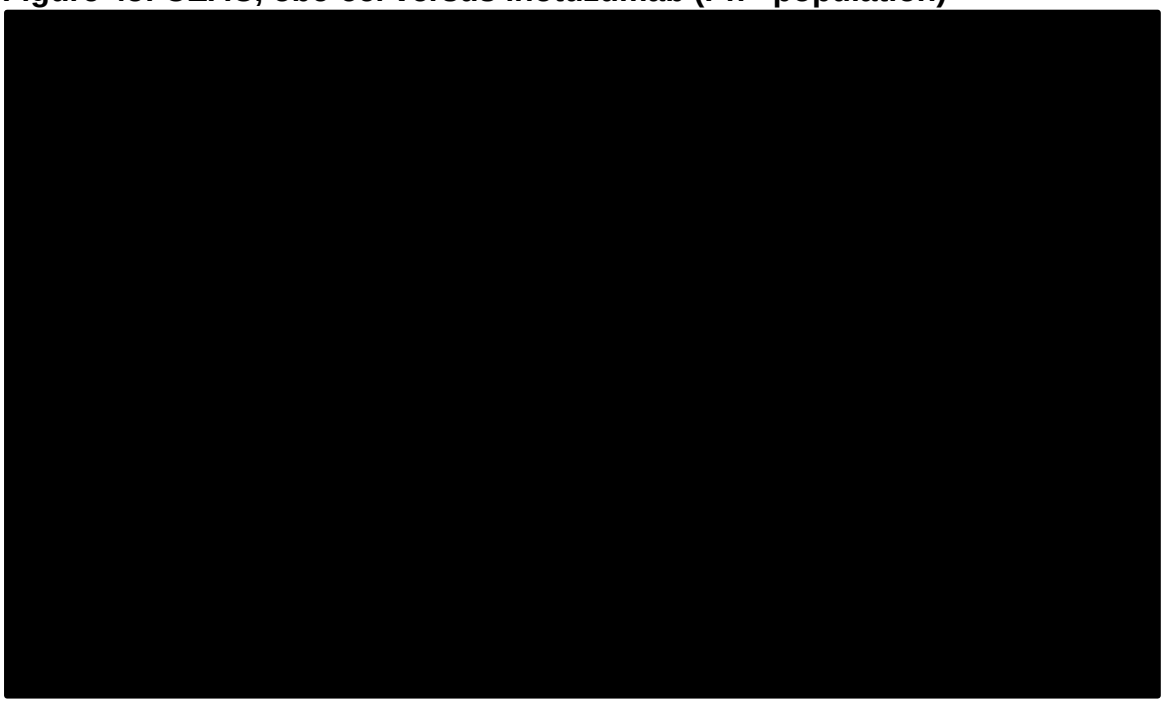
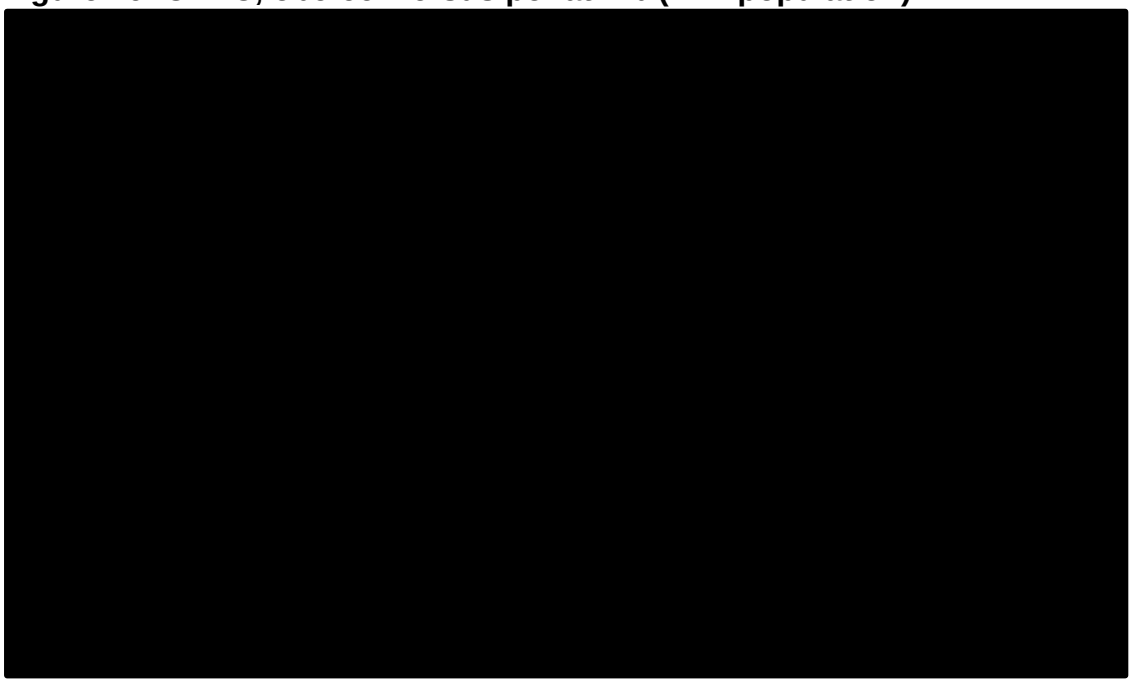


Figure 46: CEAC, obe-cel versus ponatinib (Ph+ population)



CEAC – Cost-effectiveness acceptability curve

B.3.10.3 Scenario analysis

Table 81 presents the scenario analyses conducted in the model for the overall population, Ph- population and Ph+ population. Table 82, Table 83, and Table 84 present the results of these scenario analyses.

In the overall population, scenario results remain stable, and obe-cel [redacted] in all scenarios.

In the Ph- population, scenario results remain stable for inotuzumab, and in a majority of scenarios [redacted]. [redacted] in all but two scenarios. Scenario results for blinatumomab vary, [redacted] in all but three scenarios. Two of the scenarios were the scenarios using utility values from the SMC appraisal of blinatumomab and including subsequent SCT after CAR T-cell therapy. The resulting ICERs versus blinatumomab in the Ph- population for these scenarios were [redacted] and [redacted] respectively.

[redacted] was the scenario exploring the naïve approach for comparative effectiveness (scenario 6). The EFS and OS for blinatumomab relative to obe-cel in this scenario underestimates the survival benefit of obe-cel as captured by the HRs produced by the MAIC and naïve comparison (see Section B.2.9.4). The counterintuitive result observed can partly be explained by the OS curve choices for obe-cel and blinatumomab using differing hazard functions, with the OS curve for blinatumomab having more of a plateau when not applying the inverse MAIC, which is unlikely to reflect real-world outcomes.

In the Ph+ population, obe-cel [redacted] versus inotuzumab in all scenarios. Obe-cel remained [redacted] in all scenarios versus ponatinib.

Table 81: 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[102]
2			6% for costs and outcomes	
3	Costs	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	Using tariff costing for CAR T-cell infusion cost calculations	Approach used in TA893[17]
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 + non-inverse MAIC	Exploring combinations of alternative modelling approaches
6			Base case ITC approach + alternative obe-cel survival curves*	
7			Base case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab; inverse MAIC vs. ponatinib)	
8	Subsequent treatment costs	No CAR T-cell therapy as subsequent treatment	Include CAR T-cell therapy as subsequent treatment	CAR T-cell therapies as a subsequent treatment have been observed in clinical practise with the current treatment available.
9	Subsequent SCT	No subsequent SCT after CAR T-cell therapy	Include subsequent SCT after CAR T-cell therapy	This shows that even if patients go onto receive SCT, the observed effects of obe-cel are the same
10	Utilities	FELIX clinical trial	Health state utility source TA450	Exploratory analysis

11			Blinatumomab SMC utility values	Exploratory analysis
12		Utility decrement of EFS health state	CRS disutility based on Howell *et al.*	Exploratory analysis
13	Mortality	SMR of 3	Alternative SMR 1.09	Exploratory analysis

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; ITC – Indirect treatment comparison; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMC – Scottish Medicines Consortium; SMR – Standard mortality ratio; TA – Technology Appraisal.
*Alternative survival curves used are: Overall population – EFS: 0-knots odds spline curve; OS: 3-knots normal spline curve; Ph- population – EFS: generalised gamma curve; OS: Weibull curve; Ph+ population – EFS: Weibull; OS: Exponential

Table 82: Scenario analysis results, overall population

#	Scenario	Deterministic ICER	Probabilistic ICER
0	Base case	[redacted]	[redacted]
1	0% for costs and outcomes	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]
3	Using tariff costing for CAR T-cell infusion cost calculations	[redacted]	[redacted]
4	Include drug wastage (for comparator therapies)	[redacted]	[redacted]
5	Base case survival curves + non-inverse MAIC	[redacted]	[redacted]
6	Base case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]
7	Base case survival curves + alternative ITC approach (naïve approach vs. inotuzumab)	[redacted]	[redacted]
8	Include CAR T-cell therapy as subsequent treatment	[redacted]	[redacted]
9	Include subsequent SCT after CAR T-cell therapy	[redacted]	[redacted]
10	Health state utility source TA450	[redacted]	[redacted]

11	Blinatumomab SMC utility values	[redacted]	[redacted]
12	CRS disutility based on Howell *et al.*	[redacted]	[redacted]
13	Alternative SMR 1.09	[redacted]	[redacted]

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; ICER – Incremental cost-effectiveness ratio; ITC – Indirect treatment comparison; MAIC – Match-adjusted indirect treatment comparison; SCT – Stem cell transplant; SMC – Scottish Medicines Consortium; SMR – Standard mortality ratio; TA – Technology Appraisal.

Table 83: Scenario analysis results, Ph- population

#	Scenario	Versus inotuzumab		Versus blinatumomab	
		Deterministic ICER	Probabilistic ICER	Deterministic ICER	Probabilistic ICER
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]
1	0% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
3	Using tariff costing 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 + non-inverse MAIC	[redacted]	[redacted]	[redacted]	[redacted]
6	Base case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]	[redacted]	[redacted]
7	Base case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab)	[redacted]	[redacted]	[redacted]	[redacted]
8	Include CAR T-cell therapy as subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]

9	Include subsequent SCT after CAR T-cell therapy	[redacted]	[redacted]	[redacted]	[redacted]
10	Health state utility source TA450	[redacted]	[redacted]	[redacted]	[redacted]
11	Blinatumomab SMC utility values	[redacted]	[redacted]	[redacted]	[redacted]
12	CRS disutility based on Howell *et al.*	[redacted]	[redacted]	[redacted]	[redacted]
13	Alternative SMR 1.09	[redacted]	[redacted]	[redacted]	[redacted]

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; ICER – Incremental cost-effectiveness ratio; ITC – Indirect treatment comparison; MAIC – Match-adjusted indirect treatment comparison; SCT – Stem cell transplant; SMC – Scottish Medicines Consortium; SMR – Standard mortality ratio; TA – Technology Appraisal.

Table 84: Scenario analysis results, Ph+ population

#	Scenario	Versus inotuzumab		Versus ponatinib	
		Deterministic ICER	Probabilistic ICER	Deterministic ICER	Probabilistic ICER
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]
1	0% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
3	Using tariff costing 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 + non-inverse MAIC	[redacted]	[redacted]	[redacted]	[redacted]
6	Base case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]	[redacted]	[redacted]
7	Base case survival curves + alternative ITC approach (naïve approach vs. inotuzumab; inverse MAIC vs. ponatinib)	[redacted]	[redacted]	[redacted]	[redacted]

8	Include CAR T-cell therapy as subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]
9	Include subsequent SCT after CAR T-cell therapy	[redacted]	[redacted]	[redacted]	[redacted]
10	Health state utility source TA450	[redacted]	[redacted]	[redacted]	[redacted]
11	Blinatumomab SMC utility values	[redacted]	[redacted]	[redacted]	[redacted]
12	CRS disutility based on Howell *et al.*	[redacted]	[redacted]	[redacted]	[redacted]
13	Alternative SMR 1.09	[redacted]	[redacted]	[redacted]	[redacted]

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; ICER – Incremental cost-effectiveness ratio; ITC – Indirect treatment comparison; MAIC – Match-adjusted indirect treatment comparison; SCT – Stem cell transplant; SMC – Scottish Medicines Consortium; SMR – Standard mortality ratio; TA – Technology Appraisal.

B.3.11 Subgroup analysis

The results for subgroup analyses for Ph- and Ph+ patients are presented above in Section B.3.9.2 and Section B.3.9.3, respectively.

B.3.12 Benefits not captured in the QALY calculation

As discussed in Section B.1.3.5, the currently approved treatment options for R/R B-cell ALL are associated with severe and potentially life-threatening toxicities, such as CRS and ICANS, that require substantial resource use. In contrast to currently approved CAR T-cell therapies, obe-cel is associated with considerably lower rates of these debilitating AEs indicating that its introduction to the NHS will reduce resource use, translating into increased service capacity. This would not only allow for the optimisation of care provision to patients with R/R B-cell ALL but with other conditions as well. However, as the current economic analysis only considers direct healthcare costs and outcomes and does not compare to brexu-cel, this benefit to the broader UK population is not reflected in the model.

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

B.3.13.1.1 Internal validation

Internal validation of the economic model was conducted by the primary modellers and another modeller external to the project, using an extensive quality control checklist that included the following:

- Cell-by-cell check of formulae
- Adaptations of key sections of the model
- Logical tests
- A full audit of model inputs

Any issues were addressed within the analysis.

B.3.13.1.2 Expert validation

Expert validation of clinical and technical assumptions was conducted with two UK clinicians over a series of interviews to ensure the inputs and assumptions in the economic model are clinically valid and plausible.[92] The topics covered included:

- Place of obe-cel in the clinical pathway
- Identification and validation of treatment effect modifiers and prognostic factors
- Validation of ITC methods
- Validation of survival curves
- Identification and validation of subsequent treatment regimens, including subsequent allo-SCT following CAR T-cell therapy

B.3.13.1.3 Alignment with previous NICE appraisals

Although not a comparator in this appraisal, the brexu-cel submission (TA893[17]) constitutes a recent appraisal in the same indication as obe-cel for a treatment with a similar mechanism of action, and therefore was considered to be highly relevant for the appraisal of obe-cel. Throughout this submission, many of the base case model choices and settings are aligned with the committee preference of TA893[17], including:

- Survival approach of using standard parametric or flexible spline models for each treatment arm until cure timepoint of three years
- SMR value of 3
- Acquisition, administration, HCRU, AE, subsequent treatment and terminal care unit costs
- Applying a correcting factor for bridging chemotherapy, leukapheresis and conditioning therapy costs to account for the patients who fail to receive CAR T-cell therapy
- HCRU frequencies
- Assuming no vial-sharing for blinatumomab and inotuzumab

- Disutilities associated with AEs, including assuming CRS disutility is equal to the utility decrement of the EFS health state

B.3.14 Interpretation and conclusions of economic evidence

This analysis was conducted in order to estimate the cost-effectiveness of obe-cel in comparison with SoC for adult patients [redacted] with B-cell ALL. Various sources were used to inform this analysis, including data from FELIX and TA893.[3,17]

The results of the cost-effectiveness analysis show that obe-cel is associated with higher QALYs and is [redacted] versus all comparators across all populations in the base case analysis when considering the proposed PAS.

PSA, OWSA and extensive scenario analyses were conducted to assess areas of uncertainty in the analysis, and all mean probabilistic ICERs were comparable to the associated deterministic ICER, highlighting that results are robust to parameter uncertainty. In the OWSA, the parameters yielding the biggest ICER impact were inputs associated with HSCT, survival analysis, and the SMR for long-term survivors. In all scenario analyses tested for the overall and Ph+ populations, [redacted]. In the Ph- population, obe-cel was [redacted] versus inotuzumab in all but one scenario, and [redacted] versus blinatumomab in all but three scenarios. One of these scenarios explored the naïve approach for comparative effectiveness in the Ph- population. This scenario is unlikely to reflect real-world outcomes, considering the obe-cel benefit observed in the unadjusted HRs compared to these treatments (see Section B.2.9.4).

Some data gaps remain, notably EFS and OS data from the ongoing FELIX study are circa 40% incomplete at the latest available data cut-off (median follow-up [redacted] months). Comparison to data from the ALLCAR19 study, with up to five years of follow-up, demonstrated that obe-cel remains efficacious in the longer-term. ALLCAR19 data indicate a plateau for EFS from 12 months, and a plateau for OS from approximately 18 months, with only one OS event occurring between 18 and 60 months. Additionally, landmark survival results in the pooled analysis of FELIX and ALLCAR19 are in line with that of the February 2024 data cut of FELIX further

supporting the durability of long-term responses observed in the Phase II trial and the cure assumption applied in the economic model. As outlined in Section B.3.3.2.2.1, long-term OS and EFS extrapolations used in the economic model align with the results of the pooled analysis and indicate the modelled OS and EFS benefit of obe-cel can be considered conservative.

Overall, this cost-effectiveness analysis demonstrates that obe-cel can benefit patients in comparison to treatments currently available in clinical practice due to its improved safety profile, providing the high efficacy associated with CAR T therapies without associated high toxicity. Additionally, obe-cel is expected to generate benefits that are not captured in the QALY framework, including considerably lower rates of debilitating AEs, indicating that its introduction to the NHS will reduce resource use, translating into increased service capacity.

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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]

Summary of Information for Patients (SIP)

November 2024

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6347_Obecel_Summary of information for patients_Final_07Nov24	Final	No	7th November 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response: Brand name: Aucatzyl Drug name: Obecabtagene Autoleucel (obe-cel, AUTO1). Referred to as "obe-cel" hereafter for ease of reading.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response: Adult patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: Medicines and Healthcare products Regulatory Agency (MHRA) authorisation pending. See Document B, Section B.1.2, Table 2 for anticipated date of approval.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response: Autolus has engaged with Blood Cancer UK and Leukaemia Care to better understand the patient perspective, including unmet need, and to provide information and support for their educational initiatives for patients and caregivers. Autolus has not provided any financial support to these patient groups during 2024.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

Indication:

NICE is assessing obe-cel to treat adult patients diagnosed with R/R B-cell ALL.

About B-cell acute lymphoblastic leukaemia:

B-cells are white blood cells that produce antibodies. Antibodies recognise foreign substances (such as bacteria) in the body and mark them for destruction by the immune system. In B-cell ALL, too many B-cells are produced in the bone marrow. These B-cells are immature and abnormally shaped. They are called 'leukaemia cells' or 'blasts' and do not fight infections properly. These large numbers of B-cells prevent you from making the other blood cells you need.(1)

As an acute leukaemia, B-ALL is a serious and life-threatening disease and will progress rapidly if left untreated. B-ALL occurs in both children and adults. Approximately 60% of all B-ALL newly diagnosed patients are younger than 20 years of age; most of them are between 2 and 5 years old. The other 40% of patients with newly diagnosed B ALL are adults, and most of these patients are older than 50 years of age.

In England, 765 patients are diagnosed with B-ALL and 253 die per year.(2)

Treatment and prognosis:

Despite recent advances in treating this disease, the general prognosis remains poor. In adults, people will receive chemotherapy treatment.

<u>Newly diagnosed B-CELL ALL:</u>

Approximately 90% of treated patients will be free of disease at the end of treatment; this is called Complete Response. However, in the long term, only 40% of the people treated with chemotherapy will remain free of disease, while the majority will see the disease coming back (relapsing). In England the UKLL12 study showed that the proportion of people who relapsed following initial chemotherapy alive at five years is 7% (3).

Some patients are described as having refractory disease, this means that their B-cell ALL did not respond to treatment, being resistant at the start of treatment, or becoming resistant during treatment.

<u>Relapsed or refractory (R/R) B-cell ALL:</u>

People who see their disease relapse will experience the original symptoms coming back. They may experience fever, fatigue, profuse sweating during sleep, pallor due to decreased red blood cells, petechiae and ecchymosis small red or purple spots and larger bruises on the skin, mucosal bleeding and bone pain. People may also experience headaches and neurological symptoms such as changes in vision, nausea, vomiting.

The only curative option for people with R/R disease consists of being treated with chemotherapy or a combination of chemo and immunotherapy to be free of disease (complete response) and then receive a bone marrow transplant. However, less than 50% of people achieve a complete response after chemotherapy treatment; thus, only a fraction of patients could receive a transplant. Less than one-third of the patients treated with transplants will obtain long-term benefits. In addition, transplant is associated with severe adverse effects and significant mortality rates.(3)

Impact of the diagnosis on people's life:
People diagnosed with B-cell ALL see their quality of life severely affected in several areas of their life.

- Physically, they experience fatigue, fever and infections since the immune system cannot defend the body from infections. The treatment causes nausea, hair loss, and another debilitating side effects that affect the day-to-day life.
- Emotionally, the diagnosis can lead to anxiety and depression since people are afraid of relapse, feeling of loneliness and social isolation.
- Financially: People may not be able to work, leading to financial stress and their social life being affected by their health.
- Family: Family members often take on caregiving roles, which can strain relationships and impact their quality of life.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:
Once a relapse is suspected, the treating physician will request a series of laboratory and imaging analysis to confirm the relapse. The treating physician will request a bone marrow biopsy to confirm that the disease has came back. Other test will also be performed before a new course of treatment can start. The treating physician may order scans to evaluate if the disease has extended to the brain, a full set of blood test will be done including molecular analysis to characterize the disease, x-chest ray, electrocardiogram, evaluation of cardiac function and other analysis considered necessary by the physician.
In addition, before treating with obe-cel, a second bone marrow biopsy/aspiration will be needed to determine the dose to treat.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:
See Figure 1

Figure 1: B-cell ALL Treatment Flow (4,5)

B-cell ALL diagnosis

Treatment will start straight away.
You may need to stay in hospital for several weeks.

Induction therapy

Induction is the 1st treatment given. It aims to induce complete remission.
Available options:

- Chemotherapy
- Tyrosine Kinase Inhibitors (TKI) for patients with Philadelphia Chromosome positive (Ph +) disease
- Antibodies drug conjugates
- Intrathecal chemotherapy to prevent the disease spreading to the central nervous system

Consolidation

Consist of the same treatment but at higher dose.
Normally outpatient (it does not require hospitalization)

- Chemotherapy
- TKIs for Ph + disease
- Antibodies drug conjugates
- Bone Marrow transplant

Maintenance

Consist of the same treatment but at lower doses
The aim is to kill the remaining leukemic cells.

- Same as above
- Pulse steroids

Aucatzyl will be indicated in this setting

At progression or lack or response to induction:

Clinical progression at any time since diagnosis (refractory or relapsed disease)

The objective is to prolong life and reduce symptoms

- **CAR T therapy: Aucatzyl**
- Chemotherapy
- Targeted therapies
- Antibodies
- Bone Marrow Transplant

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

ALL can bring many changes to the daily life of patients. Patients face a heavy physical, emotional and mental burden which often result in depression and anxiety.(6) Debilitating symptoms, invasive treatment and extended hospital stays puts a heavy strain on the physical, mental and emotional wellbeing of patients.(7) A global survey study conducted in 2019 by the Acute Leukaemia Advocates Network (ALAN) found that following ALL diagnosis, 21% of respondents suffer from depression and 26% from anxiety.(6) A qualitative study which assessed information shared on social media by adult ALL patients found that 27% report impact on their usual daily activities. Of these, 10% reported difficulty with basic self-care, 22% with chores and shopping and 7% with hobbies and leisure activities.(8)

Treatment options such as chemotherapy, bone marrow- and stem cell transplants are invasive, can lead to difficult and potentially dangerous side effects and may require extended stay at the hospital. Patients have reported side effects including fatigue (27%), hair loss (27%) and nausea (22%) associated with these treatments.(8) Testimonies illustrate the substantial burden to patients: "*the treatment made me feel worse than the cancer ever did*"(8), and their families: "*wife took time off work and stayed with me most days and overnight.…when I got home, I struggled. I expected to go back to normal but I found it hard to even walk upstairs*".(9)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Obe-cel is a type of treatment that uses the patient's own immune cells to fight cancer. These immune cells, called T-cells, are taken from the patient's blood and modified in a lab to better recognize and attack cancer cells. This modification involves adding a special receptor to the T-cells that targets a protein called CD19 found on cancer cells. The modified T-cells will help to fight cancer.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:

No

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

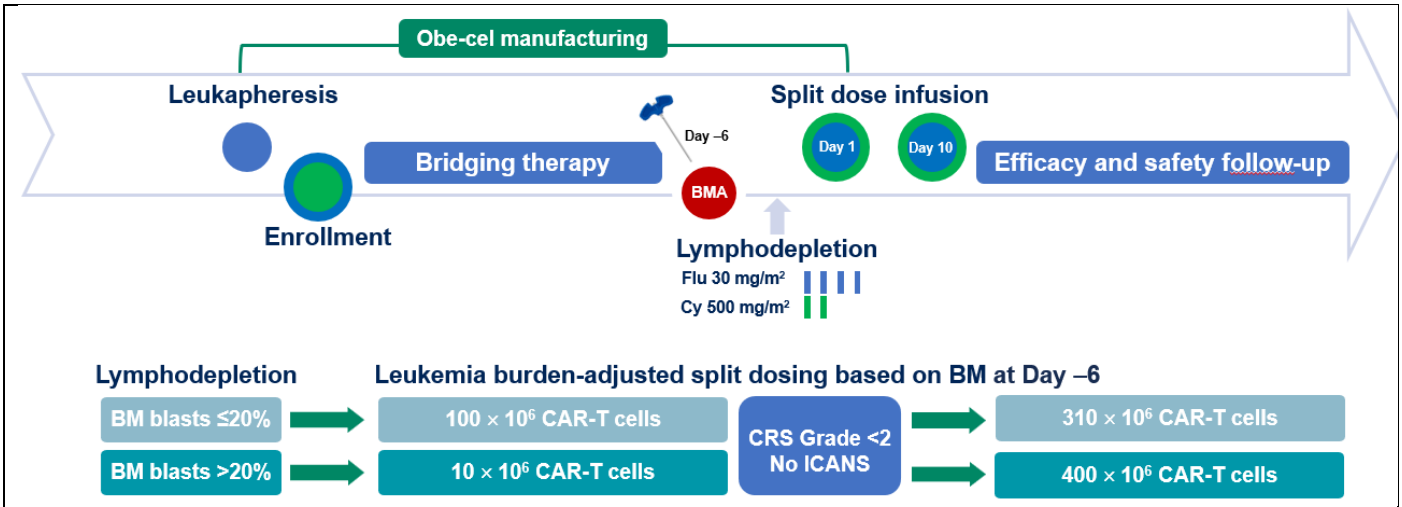
Response:

Obe-cel is given once intravenously (into a vein). The treatment is given in two infusions separated by 10 days. The total dose of 410 x 10^6 CAR T-cells will be the same to all patients(10).

Administration:

The way of administration will depend on the number of cancer cells in the bone marrow at the time of lymphodepletion, this is called tumour burden. The cancer cells present in the bone marrow are called “blasts”. Lymphodepletion involves the patient receiving a short course of chemotherapy to kill their T-cells.

- If the tumour burden is <20%, the first dose given on day 1 will be a higher dose then a lower dose on day 10.
- If the tumour burden is >20%, the first dose given on day 1 will be a lower dose and a higher dose on day 10. This is done to reduce the chances of observing adverse events.



Abbreviations: B-ALL – B-cell acute lymphoblastic leukemia; BM – bone marrow; BMA – bone marrow analysis; CAR-T – chimeric antigen receptor T-cell; CRS – cytokine release syndrome; cy – cyclophosphamide; flu – fludarabine; ICANS – immune effector cell-associated neurotoxicity syndrome; obe-cel – obecabtagene autoleucel; R/R – relapsed/refractory
Source: Roddie *et al*. 2023 (10)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

The table below reports the clinical trials of obe-cel that are being conducted. This information was taken from Clinicaltrials.gov website (www.clinicaltrials.gov) on 29th October, 2024.

Study name	Phase	Location	Patient group	N	Treatments studied	Expected completion date
NCT04404660 (FELIX)	Ib/II	Spain, UK, US	Adult (age ≥18) R/R B-cell ALL	153	Obe-cel	May 2025
NCT06333483 (CARLYSLE)	I	Spain, UK	Severe, Refractory Systemic Lupus Erythematosus	12	Obe-cel	Oct 2025
NCT06173518 (AUTO1-PY1)	Ib	Spain, UK, US	Paediatric R/R B-cell ALL & paediatric R/R aggressive mature B-NHL	24	Obe-cel	Nov 2027
NCT04443829 (CAROUSEL)	I	UK	Adult (age ≥16) R/R Primary CNS lymphoma	12	Obe-cel	Dec 2032
NCT02935257 (ALLCAR19)	I	UK	B-NHL, B-CLL, B-cell ALL.	60	Obe-cel	Dec 2033

Abbreviations: ALL – Acute lymphoblastic leukaemia; B-NHL – B-cell non-Hodgkin lymphoma; CNS – Central nervous system; R/R – Relapsed or refractory

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

The efficacy and safety of obe-cel for treating adult R/R B-cell ALL patients is being studied in an ongoing open-label, single-arm trial (FELIX, NCT04404660). In the study, a total of 127 patients were infused with obe-cel. The efficacy results reported below refer to results from February 2024, which is the most recent published data.

The primary measure of efficacy in FELIX is the proportion of patients who achieve overall remission (overall remission rate, ORR), indicating minimal levels of leukaemia cells in the blood and bone marrow. FELIX met its primary endpoint. The results demonstrated that 78% of patients treated with obe-cel achieved overall remission, at a median follow up of 21.5 months.(11)

Event-free survival (EFS)

At 12 months, 49.5% (95% CI: 39.6, 58.6%) of patients had not experienced any of the pre-defined events (treatment failure, morphological relapse, or death). Median EFS was 11.9 months (95% CI: 7.98, 22.11).(11)

Overall survival (OS)

At 12 months, 61.1% (95% CI: 52, 69) of patients were still alive. Median OS was 15.6 months (95% CI: 12.91, NE).(11)

Duration of remission

At a median follow up of 21.5 months, 40% of responders were in ongoing remission, without subsequent treatments (including stem cell transplants).(11)

Additional results from FELIX are presented in Document B2, Section B.2.6.

Limitations

Considering the aggressive and life-threatening nature of R/R B-cell ALL, a single arm study design was the only feasible option for FELIX. Randomizing patients to a control arm that may not receive a potentially life-saving therapy would have been unethical. For this reason, single arm trials are common in advanced cancers.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

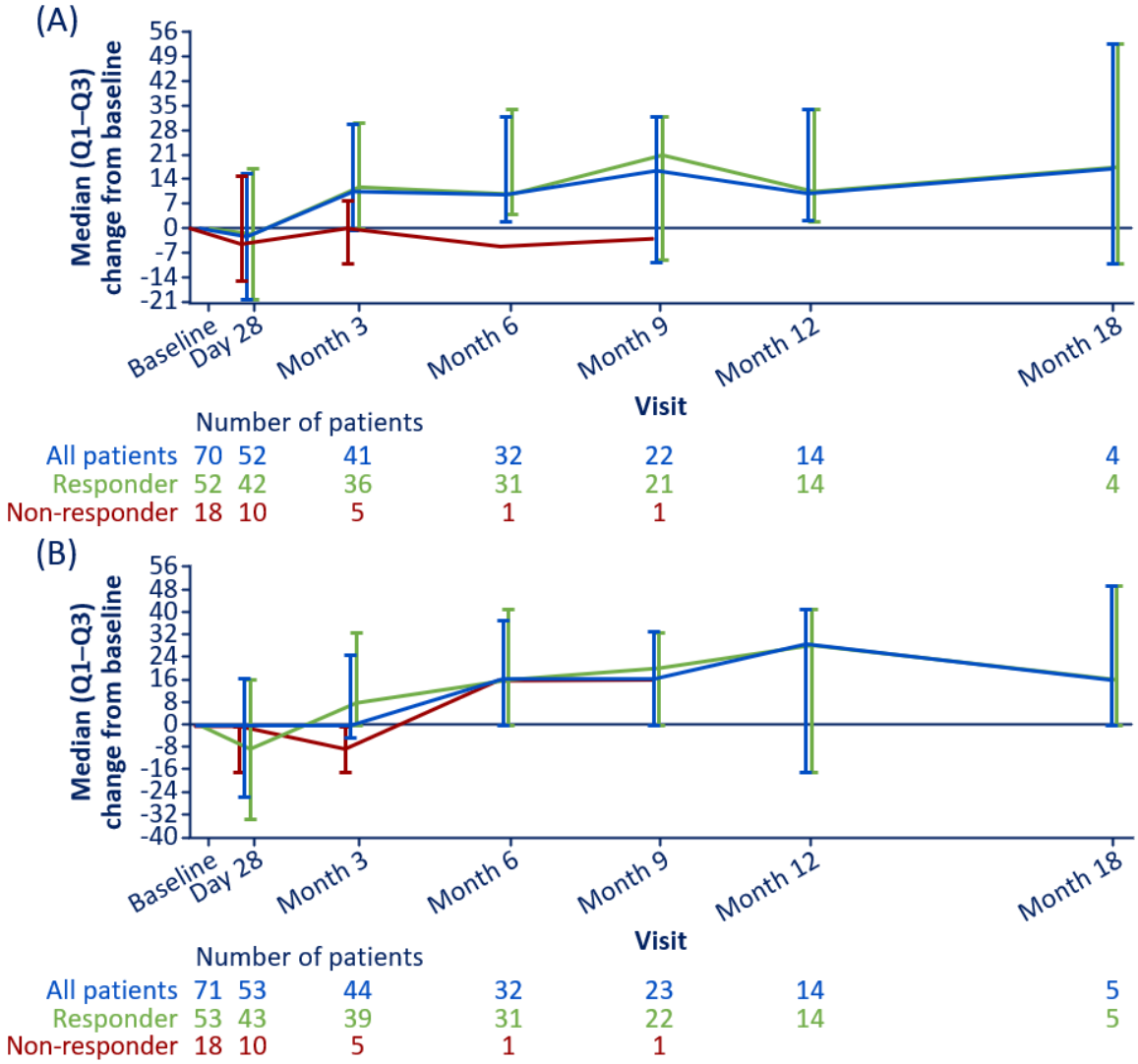
Response:

The FELIX trial assesses the impact of obe-cel on patients' health-related quality of life (HRQoL) using two patient reported outcome (PRO) instruments:

- **EQ-5D-5L**, a standardized measure of HRQoL. The visual analogue scale (VAS) score of EQ-5D ranges from 0 to 100, where 100 represents the best possible health status.
- **European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30**, a widely used 30-item questionnaire designed to measure cancer patients' physical, psychological and social functions. The global health status (GHS) score of EORTC QLQ-C30 ranges from 0 to 100, where 100 represents the best possible health status.

HRQoL data was collected at baseline (prior to obe-cel infusion), at first assessment (Day 28), and at 3, 6, 9, 12, and 18 months after the first infusion. The Company has published HRQoL results from Phase II of FELIX (Cohort IIA). Cohort IIA enrolled 112 patients with ≥5% blasts in the bone marrow (BM) at screening, a clinical characteristic associated with worse outcomes in ALL. In total, 94 patients in Cohort IIA were infused with obe-cel. Baseline EQ-5D-5L and EORTC QLQ-C30 data were available for 70 and 71 patients, respectively. After an initial small decline in both scores following obe-cel infusion, patients recovered to and later exceeded baseline status in overall HRQoL.(12)

Patients started at a baseline EQ-5D score of 67 and EORTC QLQ-C30 of 58. At Day 28, a small decline was observed, which was not considered clinically meaningful. As shown in the figure below, starting at three months after obe-cel treatment for EQ-5D (A) and at six months for EORTC QLQ-C30 (B), the scores exceeded the baseline values, indicating that the patients' HRQoL improved compared to before treatment. The largest improvement from baseline values occurred at Month 18 for EQ-5D-5L VAS (median change from baseline 17.50) and at Month 12 for EORTC QLQ-C30 (median change from baseline 29.17). This demonstrates that obe-cel therapy is associated with a meaningful improvement in HRQoL by three months post-infusion.(12)



Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L VAS, EQ-5D-5L visual analog scale; GHS, global health status; Q, quartile.

Source: Sandhu *et al.* 2024 (12)

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

CAR T therapies are associated with cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) adverse events in ALL patients (13). Cytokines are a type of protein involved in the regulation of the immune system. CAR T therapy stimulates the production of cytokines. The Cancer Research UK and Macmillan Cancer Support websites (see links below) provide information on CRS and neurological side effects for CAR T therapies.

Obe-cel utilises a fast off-rate CD19 binding domain designed to reduce toxicity and improve persistence. Obe-cel treatment resulted in very low rates of grade >=3 CRS (2.4%) and low rates of grade >=3 ICANs (7.1%) in the FELIX trial.(10) The most common grade >=3 treatment emergent adverse events observed in FELIX were febrile neutropenia (24%), neutropenia (21%), anemia (21%), and decreased neutrophil count (20%).(10) Neutrophils are a type of white blood cell that helps the body fight infections. Neutropenia is the presence of lower than normal levels of neutrophils in the blood. Febrile neutropenia is a fever that occurs during a period of neutropenia. Anemia is the presence of lower than normal levels of red blood cells in the blood.

FELIX: Safety - TEAEs

TEAEs that occurred in >=20% of patients regardless of causality	**All infused patients (n=127)**	
	Any grade, %	**Grade >=3, %**
Patients with any TEAE	100	81
CRS	69	2
Pyrexia	29	2
Nausea	26	2
Diarrhea	25	2
Febrile neutropenia	24	24
Anemia	24	21
Headache	24	0
Neutropenia	23	21
ICANS	23	7
Hypotension	22	5
Hypokalemia	21	6
Neutrophil count decreased	20	20

Abbreviations: CRS – Cytokine release syndrome; ICANS – Immune effector cell-associated neurotoxicity syndrome; TEAE – treatment emergent adverse event
Source: Roddie *et al*. 2023 (10)

Managing side effects:

Please visit the Cancer Research UK and Macmillan Cancer Support website sections on CAR T-cell therapy (https://www.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/CAR-T-cell-therapy and https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/car-t-cell-therapy) for information on the potential side effects of having CAR T-cell therapy, and how these are treated.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Response:

Despite improvements to the ALL treatment landscape, many adult R/R B-cell ALL patients face poor chances of long-term survival and often suffer from severe side effects from available treatments.(14) Currently available CAR T-cell therapies are associated with severe, sometimes life-threatening adverse events – most commonly CRS and ICANS. These toxicities render current options unsuitable for many older and fragile patients.(15–17)
Currently available immunotherapies, including inotuzumab and blinatumomab, also have suboptimal safety profiles. Inotuzumab is associated with veno-occulsive disease (VOD), a blockage of small blood vessels which can lead to liver failure.(18) In the pivotal blinatumomab trial, 5% of patients experienced grade 3 or higher CRS.(19)

The key benefits of obe-cel to adult R/R B-cell ALL patients, caregivers and society include:

- Obe-cel is a CAR T treatment which has demonstrated high rates of complete remission and durable response.
    - Overall remission rate of 78% and 40% of responders in ongoing remission without subsequent stem cell transplant or other therapy, at a median follow-up of 21.5 months.(11)
    - 12-month EFS and OS rates 49.5% and 61.1%, respectively.(11)
- Obe-cel has an improved safety profile over existing CAR Ts and immunotherapies in ALL.
    - Obe-cel has demonstrated very low rates of grade >=3 CRS (2.4%) and low rates of grade >=3 ICANS (7.1%) AEs.(10)
- Meaningful improvement in HRQoL from three months after treatment.(12)

All in all, obe-cel is an effective treatment which reduces resource use and patient burden via an improved safety profile.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

CAR T treatments are associated with a number of procedures which are cumbersome to patients. CAR T-cells are manufactured through leukapheresis, i.e., the collection of T-cells from patients' blood through separating and collecting white blood cells (leukocytes). Once collected, the T-cells are modified to become CAR T-cells, through being activated and genetically engineered to express the CAR. The modified cells are multiplied before being transferred to a drip to infuse back into the patient's bloodstream. Before patients receive the infusion of CAR T-cells, they receive lymphodepleting chemotherapy. Lymphodepleting chemotherapy decreases the number of T-cells and as a result, the body reacts by increasing cytokine signals that encourage T-cells to grow and multiply. Therefore, the CAR T-cells which are infused back into the patient can grow and become more active, and the modifications to the cells allow them to recognise and attack cancer cells. Prior to infusion with obe-cel, patients have a bone marrow biopsy to inform leukemia burden-adjusted dosing (10).

The waiting time from CAR T prescription to the date of infusion may patients may distress patients. Treatment is also associated with extended hospitalisation.

As discussed in 3h, currently available CAR T treatments are associated with severe and potentially life-threathening AEs. This however applies less to obe-cel, thanks to its improved safety profile.

Please visit the Cancer Research UK and Macmillan Cancer Support website sections on CAR T-cell therapy (https://www.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/CAR-T-cell-therapy and https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/car-t-cell-therapy) for practical information on the process of having CAR T-cell therapy.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

Obe-cel represents an new treatment option for adult R/R B-cell ALL patients who currently face poor prognosis and cumbersome and potentially dangerous side-effects with available treatments. The comparable efficacy of obe-cel versus routinely commissioned current treatment options (inotuzumab, blinatumomab and ponatinib) indicates that obe-cel has the potential to improve survival outcomes in this patient population.

The Company has undertaken an economic analysis to assess the cost-effectiveness of obe-cel versus inotuzumab, blinatumomab and ponatinib in adult patients with R/R B-cell ALL. The results confirmed that obe-cel represents good value for money for the NHS, at a willingness to pay threshold of £30,000 per quality adjusted life-year (QALY) gained and when considering the severity of the condition.

The full results of the cost-effectiveness analysis are presented in Document B3, Section B.3.9.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Obe-cel utilises a novel CD19-directed chimeric antigen receptor with a “fast-off” kinetic property mimicking physiological T-cell receptor interactions, which results in increased T-cell persistence, high levels of durable remission and low levels of CRS and ICANS adverse events.(20)

Furthermore, obe-cel is administered in two doses at separate occasions, titrated to pre-lyphodepletion bone marrow disease burden. This dosing approach is intended to mitigate toxicities, specifically CRS and ICANS through a more controlled expansion of CAR T-cells, resulting in lower peaks of inflammatory cytokines.(21,22)

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Response: There are no known equality issues relating to the use of obe-cel in patients with B-cell ALL.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

Patient groups and charities in the UK:

- Cancer Research UK - Acute Lymphoblastic Leukaemia
- Cancer Research UK – CAR T therapy
- Macmillan Cancer Support – Acute Lymphoblastic Leukaemia
- Macmillan Cancer Support – CAR T therapy
- Leukaemia UK – Acute Lymphoblastic Leukaemia
- Leukaemia Care
- Blood Cancer UK

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Adverse event (AE) – An adverse event is an unintended negative medical event in a patient receiving a medical treatment, which may or may not be caused by the treatment. Adverse events reported for clinical trials are graded on a scale of 1 to 5, based on their severity. Grade 1 is mild, grade 2 is moderate, grade 3 is severe, grade 4 is life-threatening or disabling, and grade 5 is fatal.

Acute Lymphoblastic Leukaemia (ALL) – A type of fast-growing leukemia that affects white blood cells.

B-cell – A type of white blood cell (or lymphocyte) that makes antibodies to fight infection. Like all other cells in the body, B-cells can become cancerous.

Bone Marrow biopsy – A procedure that takes a sample of bone marrow by inserting a hollow needle through the bone (usually the hip bone) and into the bone marrow.

Bridging therapy – Therapy that is meant to control cancer during the time between leukapheresis and CAR T-cell infusion.

Chimeric antigen receptor (CAR) – A protein created in a laboratory that is designed to recognise an antigen (or marker) on cancer cells. When added to T-cells, CARs give T-cells (now called “CAR T-cells”) the ability to identify and destroy cancer cells.

CD19 – A protein on the surface of B-cells, used as a target for some B-cell ALL therapies, including obe-cel.

Cytokines – Small proteins that regulate the immune system. Cytokines are released by certain immune system cells. They can stimulate the immune system to attack cancer and also cause the production of more cytokines.

Cytokine Release Syndrome (CRS) – A common side effect of CAR T-cell therapy. CRS occurs when many cytokines are released by immune cells during immunotherapy. Some symptoms are nausea, fever, headache, rapid heartbeat, low blood pressure, rash and trouble breathing. CRS can be mild or moderate. CRS can feel like a very bad case of the flu, and it can be severe or life-threatening.

Event-free survival (EFS) – is used as a measure of the efficacy of a treatment (how well it works) in clinical trials. For the FELIX trial, EFS is the time from the first obe-cel infusion until the earliest of the following events: treatment failure, relapse or death (for any reason).

Immune effector Cell-associated Neurotoxicity Syndrome (ICANS) – A severe side effect of CAR T-cell therapy in which the immune response can produce a toxic effect on the nervous system. Patients may suffer headaches, confusion, seizures, loss of speech and loss of motor skills. ICANS can range from very mild to quite severe and life-threatening.

Leukapheresis – A procedure that involves removing blood from the body, delivering it to a machine that separates and collects white blood cells and then returning the remaining blood components to the body.

Lymphodepletion – Chemotherapy given before CAR T-cell infusion in order to decrease the number of white blood cells (including T-cells) in the body. CAR T-cells grow and expand better if there are not as many of the patient's own T-cells present.

Overall Remission Rate (ORR) – Is a measure of the efficacy of a treatment (how well it works). The ORR for a treatment is the proportion of patients who experience either a complete remission, or a complete remission with incomplete blood count recovery.

Overall Survival (OS) – is used as a measure of the efficacy of a treatment (how well it works) in clinical trials. For the FELIX trial, OS is the time from the first obe-cel infusion until death (for any reason).

Patient-reported outcomes (PROs) – are used as a measure of the efficacy of a treatment (how well it works) in clinical trials. PROs are based on questionnaires that are completed by patients themselves and therefore represent the patient perspective. The questions in PROs are concerned with aspects of health-related quality of life (HRQoL) that may be impacted by disease (and thus helped by treatment), such as mobility, self-care, ability to conduct usual activities, pain/discomfort and anxiety/depression. The PRO questionnaires used in the FELIX trial of obe-cel in B-cell ALL are the EQ-5D-5L and the EORTC QLQ-C30.

Philadelphia Chromosome positive (Ph+) ALL – Some B-cell ALL patients have the Ph+ form of the disease. This means that their leukaemia cells have a genetic change called the Philadelphia chromosome. Ph+ B-cell ALL patients can be treated with tyrosine kinase inhibitor drugs, which targets an abnormal protein produced by the genetic change in the Philadelphia chromosome.

Refractory – Patients that did not respond to a therapy, or became resistant to a therapy during treatment, are described as having refractory disease.

Relapsed – Patients that responded to a therapy and were disease-free at the end of the treatment course, but eventually saw the disease return, are described as having relapsed disease.

T-cell – A type of white blood cell that travels throughout the body and destroys damaged or infected cells.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

Provided throughout the text.

1. Leukaemia Care [Internet]. [cited 2024 Nov 6]. B-cell acute lymphoblastic leukaemia (B-cell ALL). Available from: https://www.leukaemiacare.org.uk/support-and-information/information-about-blood-cancer/blood-cancer-information/leukaemia/acute-lymphoblastic-leukaemia/b-cell-acute-lymphoblastic-leukaemia-b-cell-all/

2. Cancer Research UK [Internet]. 2015 [cited 2024 Nov 6]. Acute lymphoblastic leukaemia (ALL) statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all

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5. Leukaemia Care. Relapsed and refractory acute lymphoblastic leukaemia (ALL) [Internet]. [Internet]. Available from: https://www.leukaemiacare.org.uk/support-and-information/information-about-blood-cancer/blood-cancer-information/leukaemia/acute-lymphoblastic-leukaemia/relapsed-and-refractory-acute-lymphoblastic-leukaemia-all/

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7. Bryant AL, Walton AL, Shaw-Kokot J, Mayer DK, Reeve BB. Patient-Reported Symptoms and Quality of Life in Adults With Acute Leukemia: A Systematic Review. Oncol Nurs Forum. 2015 Mar;42(2):E91–101.

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10. Roddie C, Sandhu K, Tholouli E, Shaughnessy P, Barba P. OBECABTAGENE AUTOLEUCEL (OBE-CEL, AUTO1) FOR RELAPSED/REFRACTORY ADULT B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (R/R B-ALL): POOLED ANALYSIS OF THE ONGOING FELIX PHASE IB/II STUDY. 704Cellular Immunotherapies: Early Phase and Investigational Therapies. 2023;

11. Jabbour E, Tholouli E, Sandhu KS, Shaughnessy P, Barba P, Guerreiro M. Obecabtagene autoleucel (obe-cel, AUTO1) in adults with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL): Overall survival (OS), event-free survival (EFS) and the potential impact of chimeric antigen receptor (CAR)-T cell persistency and consolidative stem cell transplantation (SCT) in the open-label, single-arm FELIX phase Ib/II study. J Clin Oncol. 2024;Jun;42(16_suppl):6504–6504.

12. Sandhu KS, Yared JA, Logan AC, Park JH, Shang J, Patel D, et al. Quality of Life in Adult Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia Treated with Obecabtagene Autoleucel (obe-cel) in the Pivotal Phase 2 Felix Study. Transplantation and Cellular Therapy. 2024 Feb 1;30(2, Supplement):S200.

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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]

Clarification questions

December 2024

File name	Version	Contains confidential information	Date
[ID6347]_Obe-cel_Clarification questions response_16Dec24	V1.0	Yes	Monday 16th December 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. PRIORITY QUESTION: Please combine the FELIX enrolled cohorts IA and IIA and present all primary and secondary outcomes described in the protocol, and repeat the indirect comparisons using this pooled population, without censoring for subsequent treatment. Please also perform these analyses excluding people aged below 26.

Primary and secondary outcomes for combined enrolled Cohorts IA and IIA

Pooled results for enrolled Cohorts IA and IIA are provided below. The results presented are without censoring for stem cell transplantation (SCT).[1]

Results from the February 2024 data cut-off, for pooled Cohort IA and IIA found a statistically significant overall remission rate (ORR) of [redacted]% (95% confidence interval (CI): [redacted] to [redacted], [redacted]).[1]

Complete remission (CR) was achieved in nearly [redacted] of patients ([redacted]%). The minimal residual disease (MRD)-negative remission rate reflects the deep level of remission achieved by obe-cel (Table 1).

Table 1: ORR, CR and MRD-negativity by IRRC (pooled Cohort IA and IIA)

Parameter	Cohort IA and IIA (n=133)
ORR (CR + CRi)	
n (%) [95% CI]	[redacted]
CR	
n (%)	[redacted]
MRD-negative ($<10^{-4}$) remission	
MRD-negative CR/CRi, n (%)	[redacted]

CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematologic recovery; IRRC – Independent Response Review Committee; MRD – minimal residual disease; ORR – overall remission rate
Source: Autolus, Data on file[1]

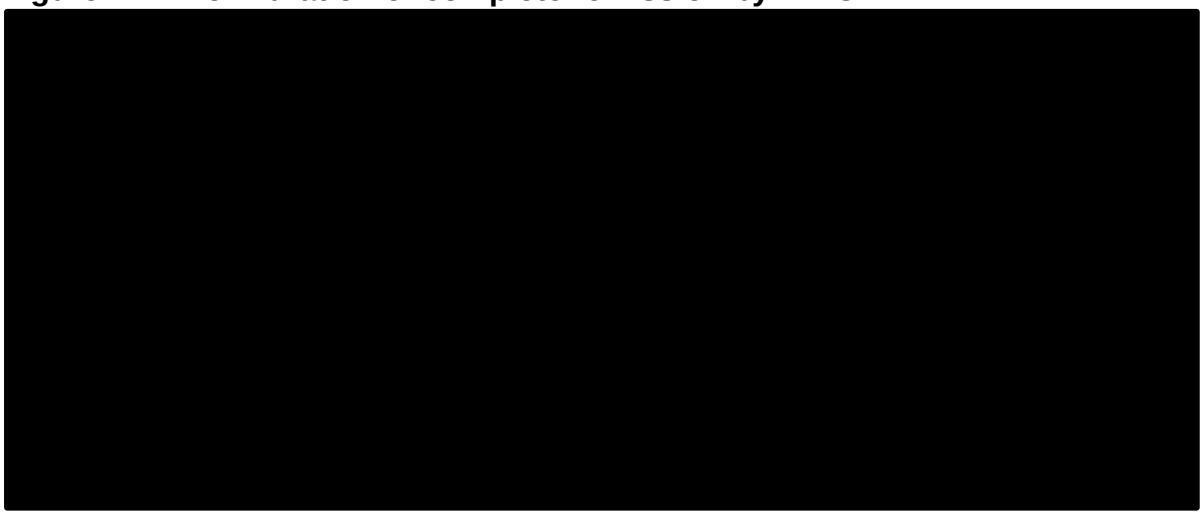
At a median estimated duration of follow-up of [redacted] months, the probability of being in remission at 12 months after onset of remission was [redacted]% (95% CI: [redacted]) (Table 2). Figure 1 demonstrates a plateauing of duration of remission (DOR) for patients achieving CR from Month [redacted] onwards, with only [redacted] occurring beyond this point.[1]

Table 2: DOR by IRRC (pooled Cohort IA and IIA)

Parameter	Pooled 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 – Independent Response Review Committee
Source: Autolus, Data on file[1]

Figure 1: KM of Duration of complete remission by IRRC



CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematologic recovery; IRRC – Independent Response Review Committee; KM – Kaplan-Meier
Source: Autolus, Data on file[1]

Of the 133 patients in pooled Cohort IA and IIA, [redacted] out of 133 had not experienced any event. The median event-free survival (EFS) was [redacted] months (Table **3**, Figure 2).[1]

Table 3: EFS by IRRC (pooled Cohort IA and IIA)

Parameter	Pooled Cohort IA and IIA (n=133)
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 – Independent Response Review Committee; mITT – modified intent-to-treat.
Source: Autolus, Data on file[1]

Figure 2: KM curve for EFS by IRRC (pooled Cohort IA and IIA)

CI – confidence interval; EFS – event-free survival; IRRC – Independent Response Review Committee
Source: Autolus, Data on file[1]

The number of patients who were alive in pooled Cohort IA and IIA was [redacted] ([redacted]%), and [redacted] ([redacted]%) had died due to disease progression. The median overall survival (OS) was [redacted] (95% CI: [redacted]), and OS was [redacted]% at Month 6 and [redacted]% at Month 12 (Table 4, Figure 3). Figure 3 shows that from Month [redacted], only [redacted] occurred.[1]

Table 4: OS by IRRC (Cohort IA)

Parameter	Pooled Cohort IA and IIA (n=133)
Patients with event, 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; IRRC – Independent Response Review Committee
Source: Autolus, Data on file[1]

Figure 3: KM curve for OS by IRRC (pooled Cohort IA and IIA)

[redacted]

OS – overall survival; IRRC – Independent Response Review Committee; KM – Kaplan-Meier
Source: Autolus, Data on file[1]

Data not presented in company submission (CS)

The following data was not presented in the CS and is presented for pooled Cohort IA and IIA below.[1]

Table 5 provides an overview of the duration of complete remission for pooled Cohort IA and IIA. The estimated median duration of remission was [redacted] months for CR (95% CI: [redacted]) and was [redacted] months for complete remission with incomplete haematologic recovery (CRi) (95% CI: [redacted]) as of the February 2024 data cut-off for Cohort IA. The KM plot for duration of complete remission for the pooled cohort is presented in Figure 1.[1]

Table 5: Duration of complete remission by IRRC

Parameter	Pooled Cohort IA and IIA (n=133)
Number of patients in analysis	[redacted]
Number of events, n (%)	[redacted]
Morphological relapse	[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; IRRC – Independent Response Review Committee
Source: Autolus, Data on file[1]

Results for CR within 3 months post obe-cel infusion were not feasible to generate within the timeframe of this response.

MRD by ClonoSEQ results were not feasible to generate within the timeframe of this response.

Safety and tolerability of obe-cel

The safety data reported below is for the pooled infused cohort (n=107), as the safety analysis set comprised of enrolled patients who received an infusion of obe-cel. Therefore, the safety set is equivalent to the infused set and is the main analysis set. Adverse event (AE) data for Cohort IA and IIA is presented in response to question A6, Table 42.[1]

The laboratory abnormalities experienced by patients in pooled Cohort IA and IIA are presented in Table 6.

Table 6: Laboratory abnormalities experienced by patients in pooled Cohort IA and IIA

Laboratory abnormality	Pooled Cohort IA and IIA (n=107)

Haemoglobin (g/L) (Decreased)	
Any grade	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Lymphocytes (10^9/L) (Decreased)	
Any grade	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Neutrophils (10^9/L) (Decreased)	
Any grade	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Platelets (10^9/L) (Decreased)	
Any grade	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Leukocytes (10^9/L) (Decreased)	
Any grade	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]

g – grams; L – litre
Source: Autolus, Data on file[1]

Expansion and persistence of obe-cel

Table 7 and Table 8 present the expansion and persistence of obe-cel over time through ddPCR levels in the peripheral blood and bone marrow, respectively.[1]

Table 7: Concentration of obe-cel transgene level (copies/ug DNA) by ddPCR in peripheral blood, pooled Cohort IA and IIA

Obe-cel transgene – blood (Copies/ug DNA)	**Pooled Cohort IA and IIA (n=107)**
Baseline	
N	[redacted]
Mean (SD)	[redacted]
Day 3	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Day 6	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Day 9	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Day 12	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Day 15	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Day 22	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Day 28	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 2	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 3	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 4	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]

Month 6	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 9	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 12	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 15	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 18	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 21	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 24	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 30	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 36	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]

*N is the number of patients with available data, and M is the number of patients with non-zero values.
ddPCR – digital droplet polymerase chain reaction; SD – standard deviation
Source: Autolus, Data on file[1]

Table 8: Concentration of obe-cel transgene level (copies/ug DNA) by ddPCR in bone marrow, pooled Cohort IA and IIA

Obe-cel transgene – bone marrow (copies/ug DNA)	Pooled Cohort IA and IIA (n=107)
Day 28	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 3	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 6	

N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 12	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 18	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]
Month 24	
N*	[redacted]
M*	[redacted]
Mean (SD)	[redacted]

*N is the number of patients with available data, and M is the number of patients with non-zero values.
ddPCR – digital droplet polymerase chain reaction; SD – standard deviation
Source: Autolus, Data on file[1]

Duration of B-cell aplasia

B-cell aplasia was not reported in Cohort IA and therefore results are not available for pooled Cohort IA and IIA.

Health care resource utilisation for the management of obe-cel related toxicity

The resource use data reported below is for the pooled infused cohort (n=107), as this data was only collected for the safety analysis set. Table 9 provides the frequency and duration of hospitalisation and intensive care unit (ICU) stays to support patients who experience obe-cel related toxicity in Cohort IA and IIA. In pooled Cohort IA and IIA, [redacted] patients were admitted to ICU for a mean duration of [redacted] days.[1]

Table 9: Frequency and duration of hospitalisation and/or critical care support to manage obe-cel related toxicity, pooled Cohort IA and IIA

	Pooled Cohort IA and IIA (n=107)
Duration of hospitalisation within 28 days post obe-cel infusion	
N	107
Mean (SD)	[redacted]
Median	[redacted]
Patients admitted to ICU, n(%)	[redacted]
Total duration of ICU stays (days)	
N	[redacted]
Mean (SD)	[redacted]
Median	[redacted]

Reason for ICU	
Adverse event other than CRS/ICANS	[redacted]
ICANS	[redacted]
CRS	[redacted]
Technical/Social/Practical reasons	[redacted]
Disease progression	[redacted]

CRS – cytokine release syndrome; ICANS – immune effector cell-associated neurotoxicity syndrome; ICU – intensive care unit; SD – standard deviation
Source: Autolus, Data on file[1]

Indirect comparisons combining enrolled patients in Cohorts IA and IIA

Comparisons were performed on the pooled IA and IIA enrolled cohort for each of the three relevant populations: ITT versus INO-VATE, Ph- versus TOWER, and Ph+ versus PACE.[2–4] Matching for each population was performed using the same list of TEMs as outlined in the CS. Table 10 presents baseline characteristics for the ITT population of FELIX (considering all enrolled patients in Cohorts IA and IIA) compared to the ITT populations of comparator studies.[1]

Table 10: Comparison of baseline characteristics across trials (pooled Cohort IA and IIA enrolled patients)

		FELIX (Pooled Cohort IA and IIA, ITT)[5]	**INO-VATE (inotuzumab arm)**[2]	**TOWER (blinatumomab arm)**[3]	**PACE (Ph+ ALL arm)**[4]
Study size, N		133	164	271	32
Primary refractory, %		[redacted]	NR	42.4	NR
BM blasts at screening, % <50%		[redacted]	32.3	25.5	NR
Prior lines of therapy, %	1	[redacted]	67.7*	42.1**	19.0
	2	[redacted]	32.3*	33.6**	44.0
	3	[redacted]	0.0*	16.6**	≥3**:** 37.0
	≥4	[redacted]	0.0*	7.8**	
1st remission ≤12m, no. %		[redacted]	58.5	28.0	NR
Ph chromosome, % Ph+		[redacted]	13.0	0.0	100
Age at baseline, Median (SD) years		[redacted]	46.5 (15)	40.8 (17.1)	62.0 (15)
Race, %	White	[redacted]	68.3	84.1	81.3
	Asian	[redacted]	18.9	7.0	16.7
	Black	[redacted]	2.4	1.8	2.1
	Other	[redacted]	10.4	7.0	0.0

Prior SCT, %	[redacted]	17.7	34.7	23
ECOG status, %	[redacted]	0: 37.8 1: 49.4 2: 12.8	0: 35.4 1: 49.4 2: 15.1	0: 31.9 1: 42.6 2: 25.5
Sex, Male, %	[redacted]	55.5	59.8	62.0

*Prior induction therapy; ** Salvage-treatment phase
BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; ITT – intention to treat; NR – not reported; Ph – Philadelphia chromosome; SCT – stem cell transplant; SD – standard deviation
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

Covariate balance for obe-cel before and after matching to inotuzumab, blinatumomab, and ponatinib are presented in Table 11, Table 12 and Table 13, respectively. Covariates are well-balanced for all comparisons after matching.[1]

Table 11: Covariates before and after matching to inotuzumab (pooled Cohort IA and IIA enrolled patients)

	Obe-cel ITT (unweighted)[5]	**Inotuzumab**[2]	**Obe-cel matched to inotuzumab**
N	133.00	164.00	[redacted]
Age	[redacted]	46.50	46.50
Sex (male), %	[redacted]	55.49	55.49
ECOG: 0*, %	[redacted]	37.80	37.80
ECOG: 1 or 2, %	[redacted]	62.20	62.20
Previous lines of therapy: 1, %	[redacted]	67.68	67.68
Previous lines of therapy: 2*, %	[redacted]	32.32	32.32
Race: White, %	[redacted]	68.29	68.29
Prior SCT, %	[redacted]	17.68	17.68
Duration of remission <12 months, %	[redacted]	58.54	58.54
BM blasts <50%, %	[redacted]	32.32	32.32
Ph+, %	[redacted]	13.41	13.41

*Treated as baseline.
BM - bone marrow; ECOG – Eastern Cooperative Oncology Group; ITT – intention to treat; Ph – Philadelphia chromosome; SCT – stem cell transplant
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2019)[2]

Table 12: Covariates before and after matching to blinatumomab (pooled Cohort IA and IIA enrolled patients)

	Obe-cel (Ph-)[5]	Blinatumomab[3]	Obe-cel matched to blinatumomab
N	[redacted]	271.00	[redacted]
Age	[redacted]	40.80	40.80
Sex (male), %	[redacted]	59.78	59.78
ECOG: 0*, %	[redacted]	35.50	35.50
ECOG: 1 or 2, %	[redacted]	64.50	64.50
Previous lines of therapy: 1, %	[redacted]	42.07	42.07
Previous lines of therapy: 2, %	[redacted]	33.58	33.58
Previous lines of therapy: ≥3*, %	[redacted]	24.35	24.35
Race: White, %	[redacted]	84.13	84.13
Prior SCT, %	[redacted]	34.69	34.69
Duration of remission <12 months, %	[redacted]	28.00	28.00
BM blasts <50%, %	[redacted]	25.46	25.46
Primary refractory, %	[redacted]	42.44	42.44

*Treated as baseline.
BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; Ph – Philadelphia chromosome; SCT – stem cell transplant
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]

Table 13: Covariates before and after matching to ponatinib (pooled Cohort IA and IIA enrolled patients)

	Obe-cel (Ph+)[5]	Ponatinib[4]	Obe-cel matched to ponatinib
N	[redacted]	32	[redacted]
Age	[redacted]	62.00	62.00
Sex (male), %	[redacted]	62.50	62.50
ECOG: 0*, %	[redacted]	31.90	31.90
ECOG: 1 or 2, %	[redacted]	68.10	68.10
Previous lines of therapy: 1, %	[redacted]	19.00	19.00

Previous lines of therapy: 2, %	[redacted]	44.00	44.00
Previous lines of therapy: ≥3*, %	[redacted]	37.00	37.00
Race: White, %	[redacted]	81.30	81.30
Prior SCT, %	[redacted]	23.00	23.00

*Treated as baseline.
ECOG – Eastern Cooperative Oncology Group; Ph – Philadelphia chromosome; SCT – stem cell transplant
Source: Autolus. Data on file (2024)[5]; Cortes et al. (2018)[4]

The outcomes considered in the analysis were EFS, OS, CR, and CRi, by IRRC assessment. As per the EAG request, all analyses were performed without censoring for subsequent treatment.

The cumulative effective sample size (ESS) for each of the comparisons by order of importance of treatment effect modifier (TEM)/prognostic factors (PF) are presented in Table 14, Table 15, and Table 16 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.

Table 14: ESS combinations, obe-cel matched to inotuzumab, pooled Cohort IA and IIA enrolled patients

Covariate	ESS
BM blasts at screening	[redacted]
Prior lines of therapy	[redacted]
Duration of remission <12 months	[redacted]
Ph chromosome	[redacted]
Age	[redacted]
Race	[redacted]
Prior SCT	[redacted]
ECOG	[redacted]
Sex	[redacted]

BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; ESS – effective sample size; ITT – intention to treat; Ph - Philadelphia chromosome; SCT - stem cell transplant

Table 15: ESS combinations, obe-cel matched to blinatumomab, pooled Cohort IA and IIA enrolled patients

Covariate	ESS
Primary refractory	[redacted]
BM blasts at screening	[redacted]
Prior lines of therapy	[redacted]
Duration of remission <12 months	[redacted]
Age	[redacted]
Race	[redacted]

Prior SCT	[redacted]
ECOG	[redacted]
Sex	[redacted]

BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; ESS – effective sample size; Ph - Philadelphia chromosome; SCT - stem cell transplant

Table 16: ESS combinations, obe-cel matched to ponatinib, pooled Cohort IA and IIA enrolled patients

Covariate	ESS
Prior lines of therapy	[redacted]
Age	[redacted]
Race	[redacted]
Prior SCT	[redacted]
ECOG	[redacted]
Sex	[redacted]

ECOG – Eastern Cooperative Oncology Group; ESS – effective sample size; SCT – stem cell transplant

EFS

EFS for FELIX versus comparator trials is presented in Table 17.

ITT

The estimated adjusted and unadjusted HRs for the ITT population were in favour of obe-cel compared to inotuzumab, however these were not statistically significant.

Ph-

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, and these differences were statistically significant.

Ph+

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.

Table 17: Event-free survival for FELIX versus comparator trials, all enrolled patients

Population	Treatment	Median EFS	ESS	Unadjusted HR	Adjusted HR
ITT	Obe-cel	[redacted]	-	-	-
	Inotuzumab	5.0 months	[redacted]	[redacted]	[redacted]
Ph-	Blinatumomab	0.0 months†	[redacted]	[redacted]	[redacted]
Ph+	Ponatinib	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; ITT – intention to treat; Ph – Philadelphia chromosome

Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

OS

OS for FELIX versus comparator trials is presented in Table 18.

ITT

The estimated adjusted and unadjusted hazard ratios (HRs) for the ITT population were in favour of obe-cel compared to inotuzumab, however only the unadjusted HR was statistically significant.

Ph-

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, and the adjusted HR was statistically significant.

Ph+

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.

Table 18: Overall survival for FELIX versus comparator trials, all enrolled patients

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

*Statistically significant results. ESS - effective sample size; HR - hazard ratio; ITT - intention to treat; OS – overall survival; Ph – Philadelphia chromosome

Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

CR

CR for FELIX versus comparator trials is presented in Table 19.

ITT

CR was not reported in INO-VATE, so comparison between obe-cel and inotuzumab was not possible for CR.

Ph-

The estimated adjusted and unadjusted odds ratios (ORs) for the Ph- population were in favour of obe-cel compared to blinatumomab, however these were not statistically significant.

Ph+

The estimated adjusted and unadjusted ORs for the Ph+ population were in favour of obe-cel compared to ponatinib, and these differences were statistically significant.

Table 19: Complete remission for FELIX versus comparator trials, all enrolled patients

Population	Treatment	Mean CR (%)	Obe-cel weighted mean CR (%)	ESS	Unadjusted OR	Adjusted OR
ITT	Obe-cel	[redacted]	-	-	-	-
Ph-	Blinatumomab	0.34	[redacted]	[redacted]	[redacted]	[redacted]
Ph+	Ponatinib	0.41	[redacted]	[redacted]	[redacted]	[redacted]

*Statistically significant results. CI – confidence interval; CRi – complete remission with incomplete haematologic recovery; ESS - effective sample size; ITT - intention to treat; OR – odds ratio; Ph – Philadelphia chromosome
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]; Cortes et al. (2018)[4]

CRi

CRi for FELIX versus comparator trials is presented in Table 20.

ITT

CRi was not reported in INO-VATE, so comparison between obe-cel and inotuzumab was not possible for CRi.

Ph-

The estimated adjusted and unadjusted ORs for the Ph- population were in favour of obe-cel compared to blinatumomab, and these were statistically significant.

Ph+

CRi was not reported in PACE, so the comparison between obe-cel and ponatinib was not possible for CRi.

Table 20: Complete remission with incomplete haematologic recovery for FELIX versus comparator trials, all enrolled patients

Population	Treatment	Mean CRi (%)	Obe-cel weighted mean CRi (%)	ESS	Unadjusted OR	Adjusted OR
ITT	Obe-cel	[redacted]	-	-	-	-
Ph-	Blinatumomab	0.01	[redacted]	[redacted]	[redacted]	[redacted]

*Statistically significant results. CI – confidence interval; CRi – complete remission with incomplete haematologic recovery; ESS - effective sample size; ITT - intention to treat; OR – odds ratio; Ph – Philadelphia chromosome
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]

CR/CRi

CR/CRi for FELIX versus comparator trials is presented in Table 21.

ITT

CR and CRi were not reported separately in INO-VATE, thus CR/CRi was used in the comparison between FELIX and INO-VATE. The unadjusted and adjusted ORs were in favour of inotuzumab compared to obe-cel.

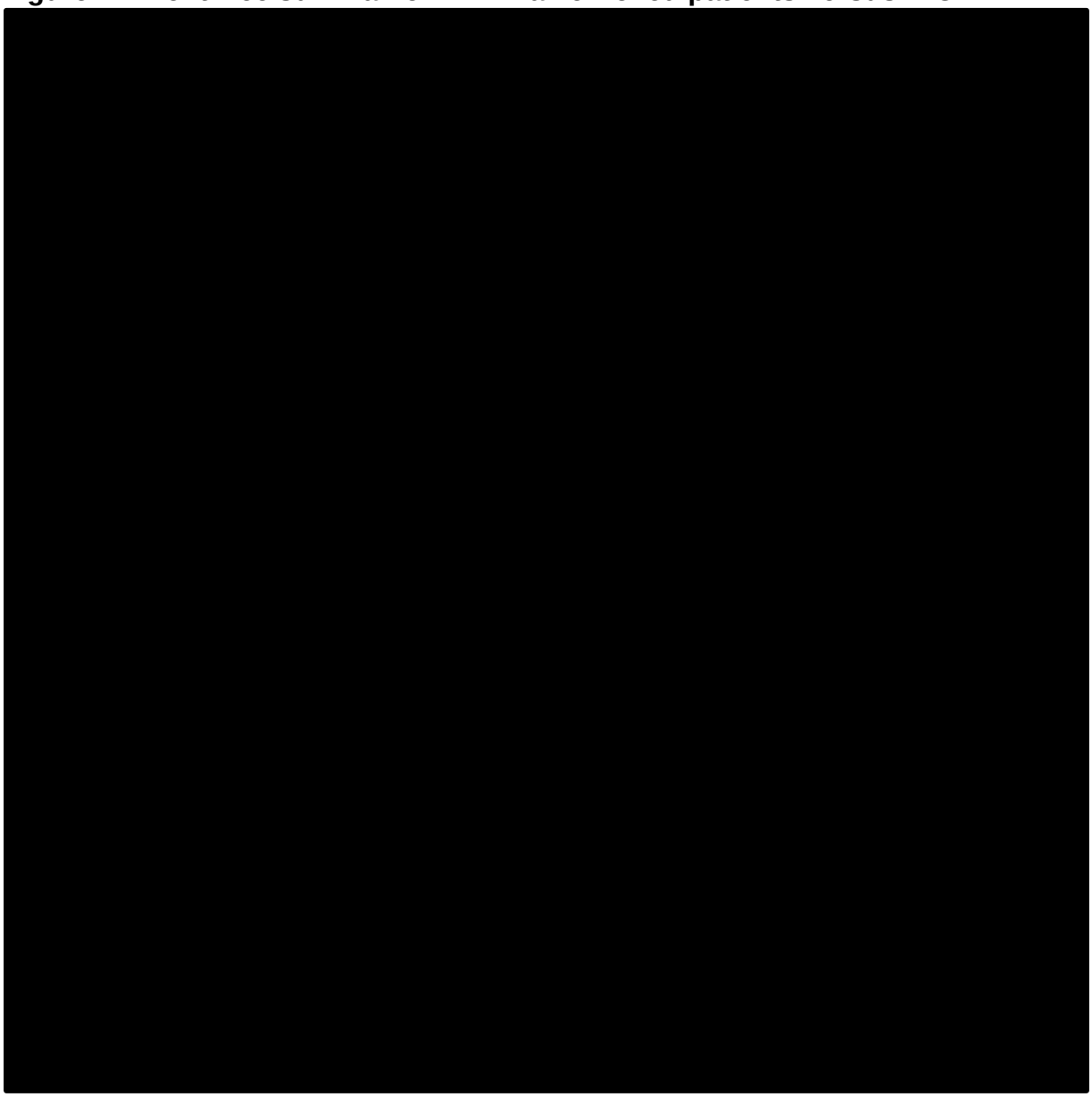
Table 21: Complete remission or complete remission with incomplete haematologic recovery for FELIX versus INO-VATE, all enrolled patients

Population	Treatment	Mean CR/CRi (%)	Obe-cel weighted mean CR/CRi (%)	ESS	Unadjusted OR	Adjusted OR
ITT	Obe-cel	[redacted]	-	-	-	-
	Inotuzumab	0.74	[redacted]	[redacted]	[redacted]	[redacted]

*Statistically significant results. CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematologic recovery; ESS - effective sample size; ITT - intention to treat; OR – odds ratio
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2019)[2]

Plots of obe-cel unweighted, obe-cel weighted and comparator KM data for EFS and OS for FELIX versus inotuzumab, blinatumomab and ponatinib are shown in Figure 4 to Figure 9, respectively.

Figure 4: Event-free survival for FELIX all enrolled patients versus INO-VATE

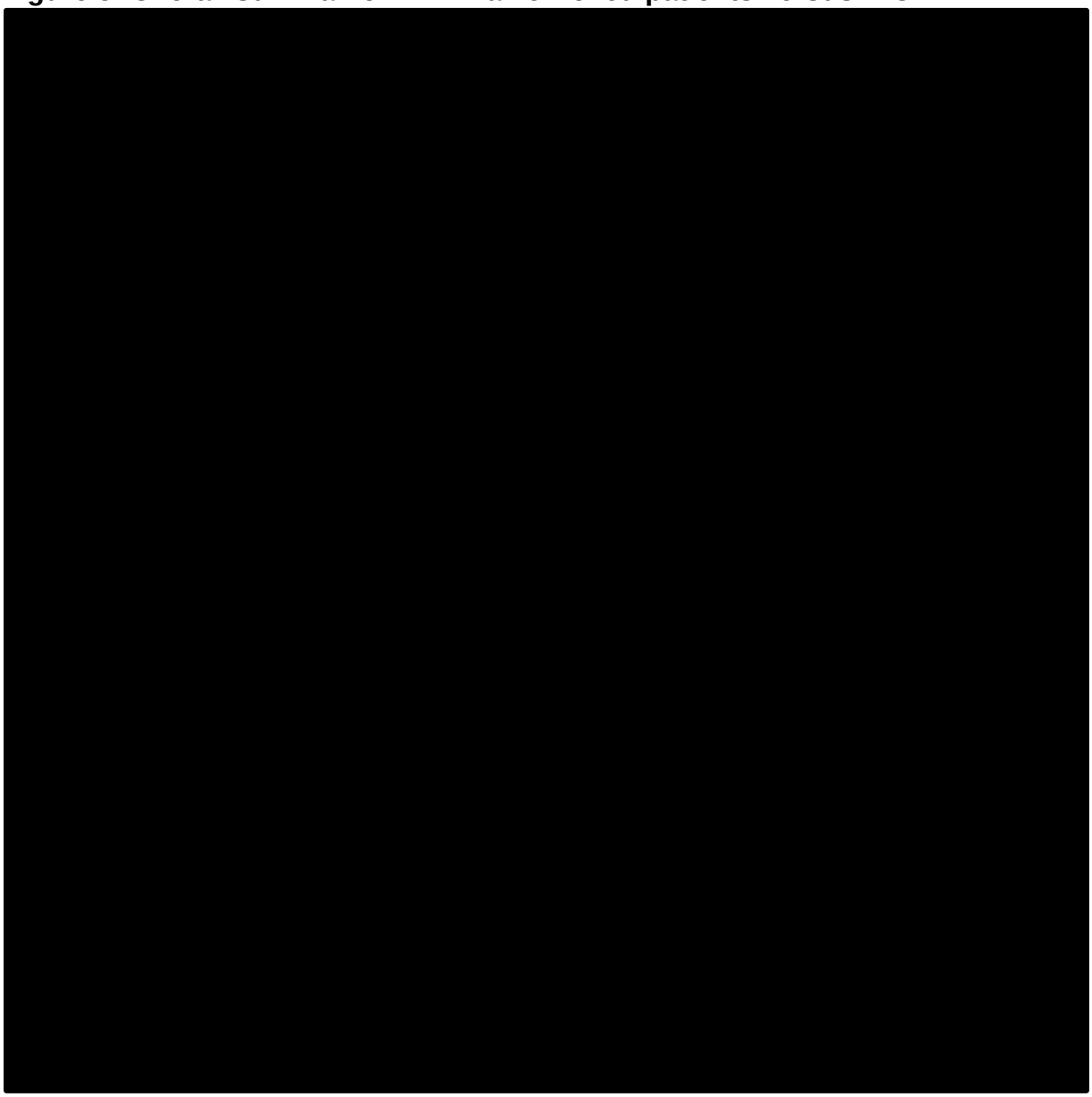


EFS – event-free survival

Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2019)[2]

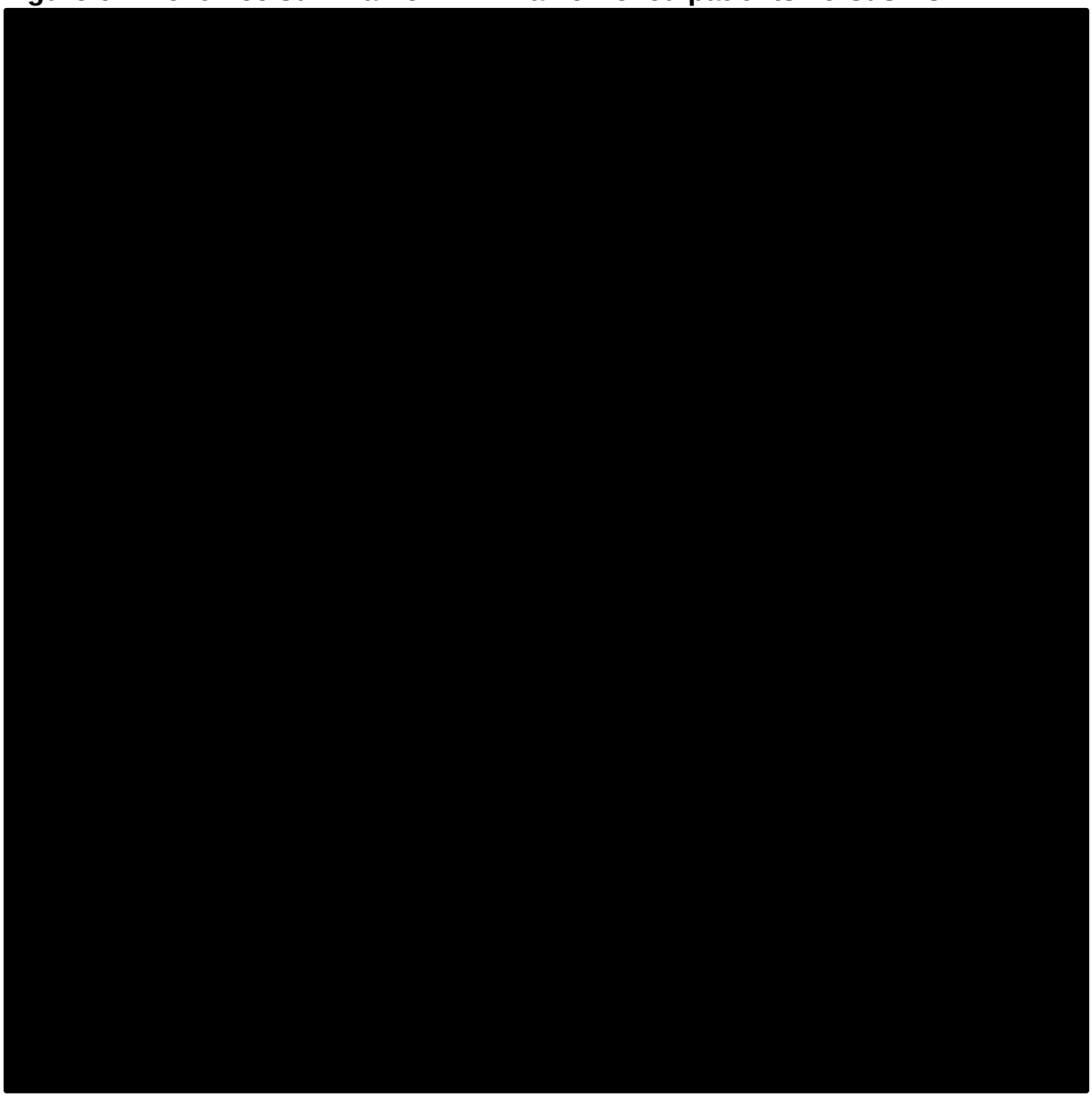
N.B. Number at risk in the weighted population is not equal to ESS as ESS considers the weights assigned to each patient after matching. This is the same for all MAIC-adjusted KM curves.

Figure 5: Overall survival for FELIX all enrolled patients versus INO-VATE



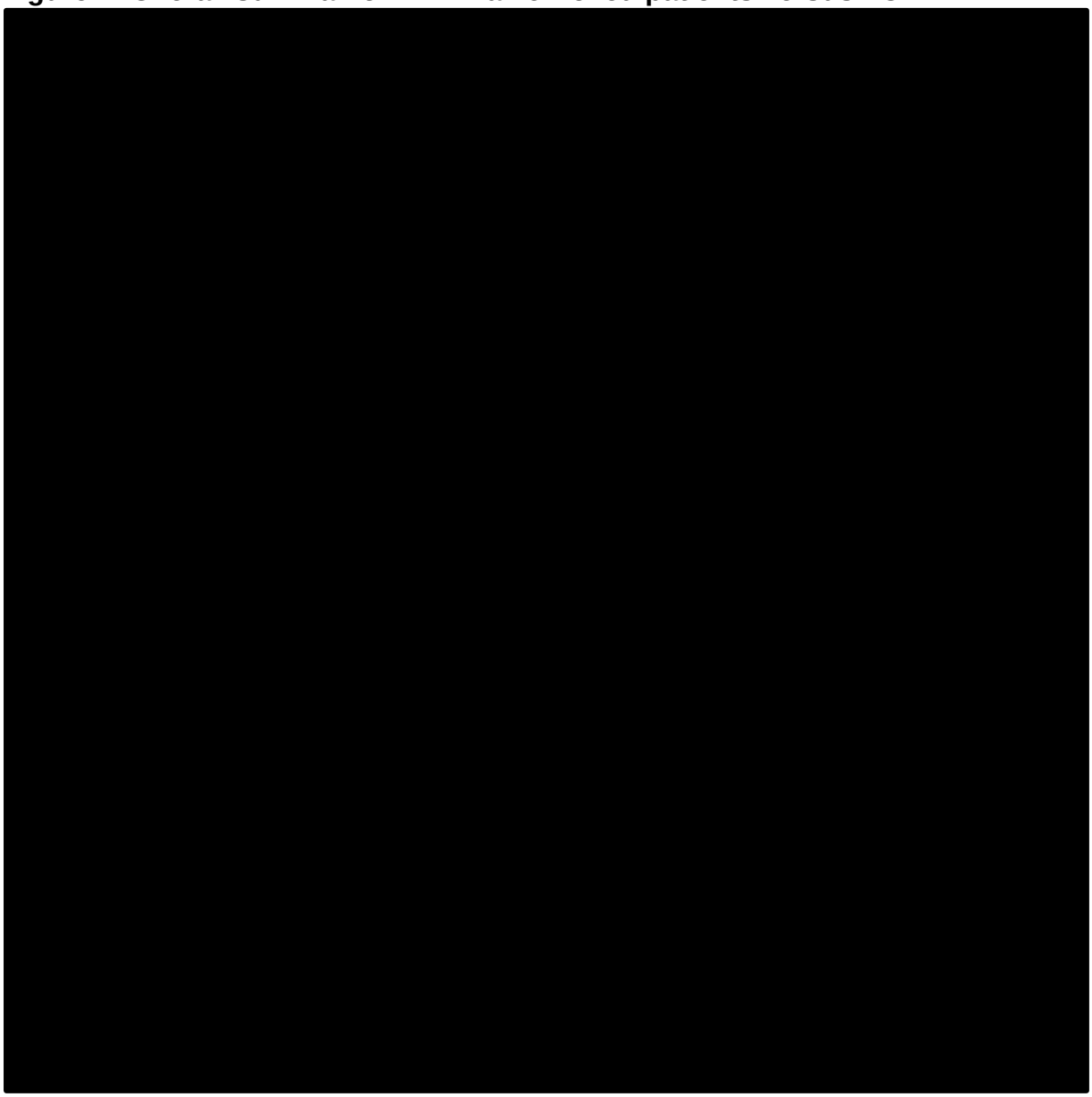
OS – overall survival
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2019)[2]

Figure 6: Event-free survival for FELIX all enrolled patients versus TOWER



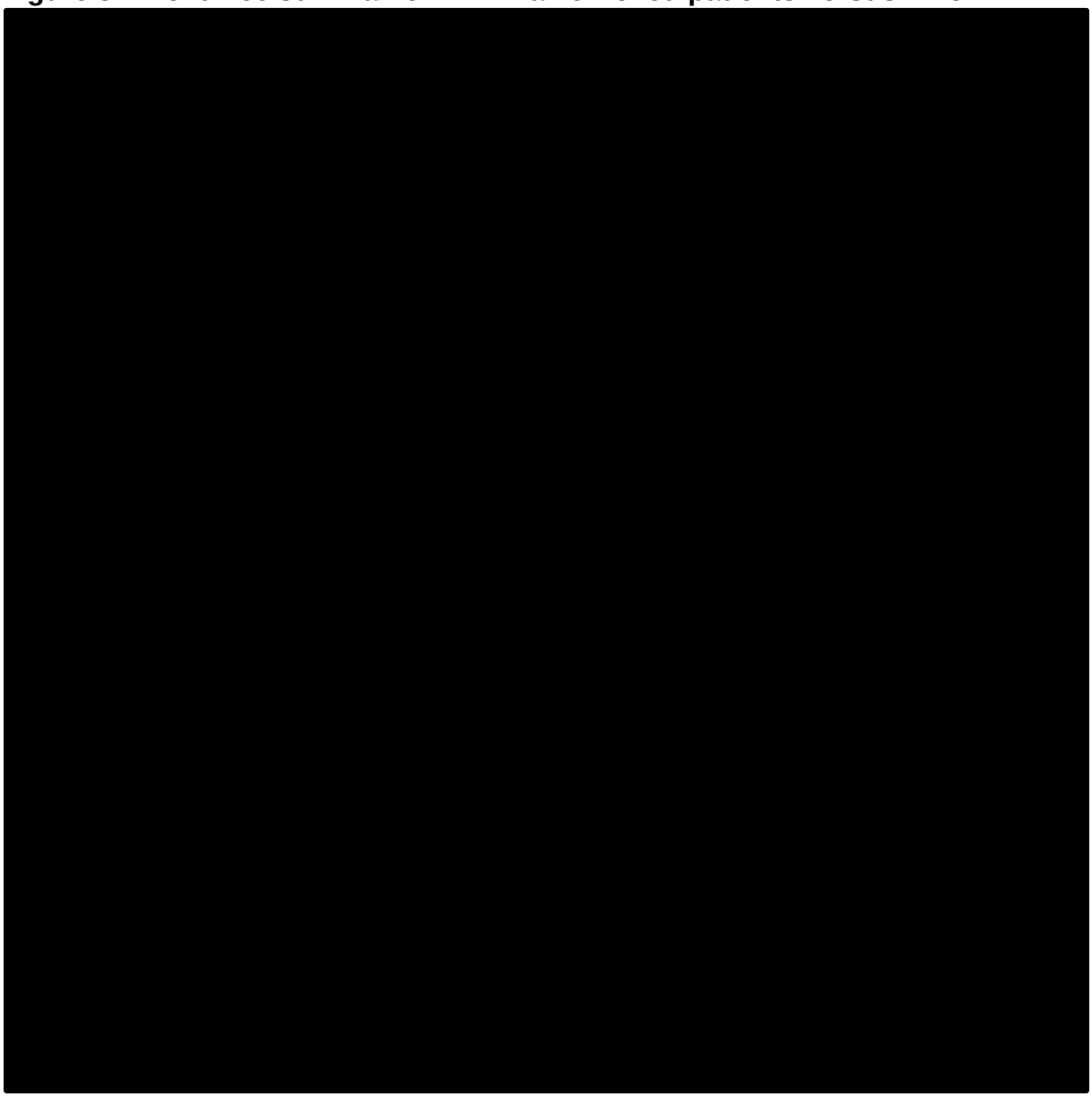
EFS – event-free survival
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]

Figure 7: Overall survival for FELIX all enrolled patients versus TOWER



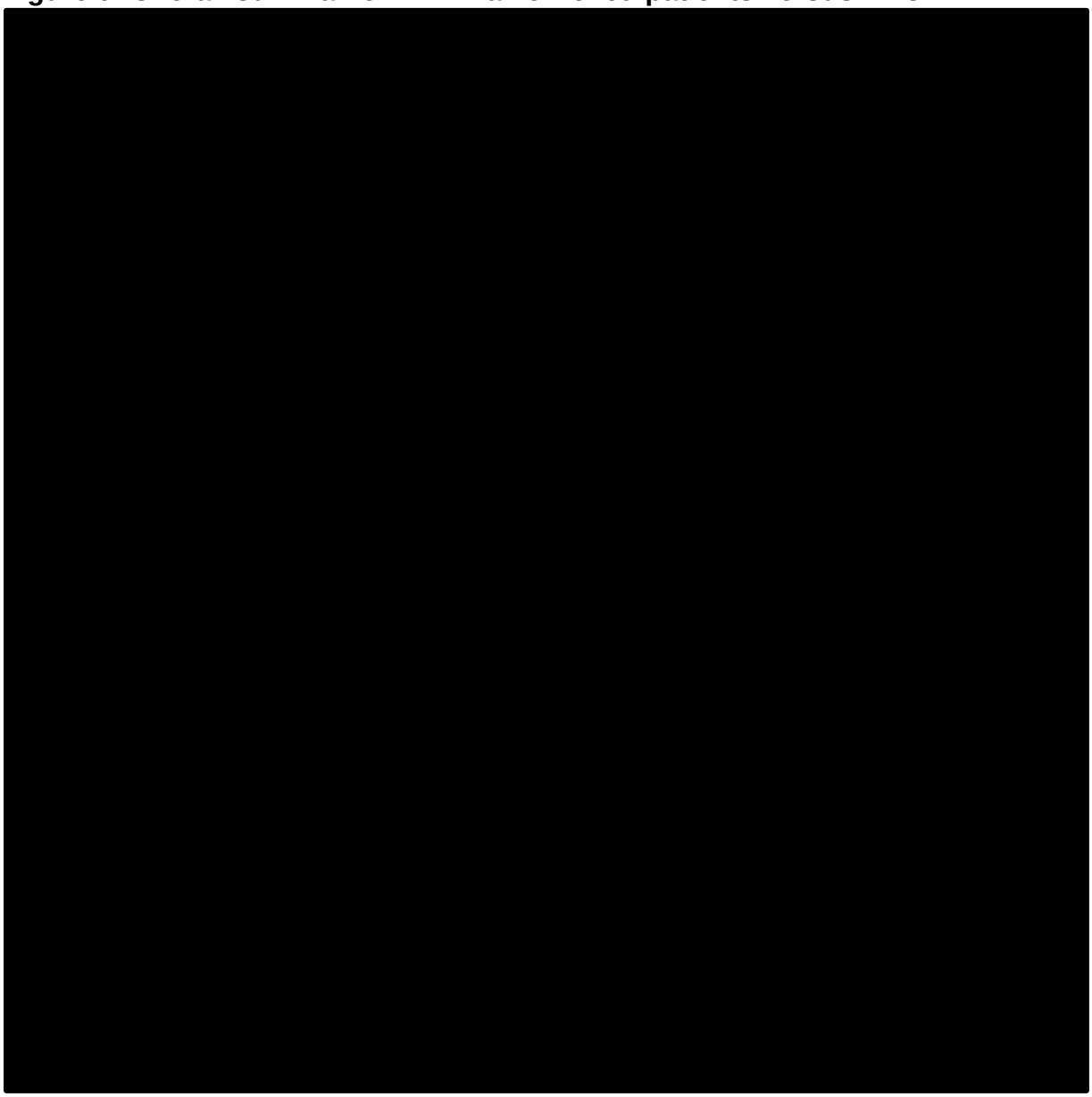
OS – overall survival
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]

Figure 8: Event-free survival for FELIX all enrolled patients versus PACE



EFS – event-free survival
Source: Autolus. Data on file (2024)[1]; Cortes et al. (2018)[4]

Figure 9: Overall survival for FELIX all enrolled patients versus PACE



OS – overall survival
Source: Autolus. Data on file (2024)[1]; Cortes et al. (2018)[4]

Indirect comparisons combining enrolled patients in Cohorts IA and IIA over the age of 26

Comparisons were performed on patients in the pooled IA and IIA enrolled cohort over the age of 26 for each of the three relevant populations: ITT versus INO-VATE, Ph- versus TOWER, and Ph+ versus PACE. [2–4] Similarly to the pooled analysis on the full enrolled cohort, matching for each population was performed using the same list of TEMs as outlined in the CS. Baseline characteristics before and after matching to inotuzumab, blinatumomab and ponatinib are presented in Table 22, Table 23 and Table 24, respectively.

Table 22: Covariates before and after matching to inotuzumab (pooled Cohort IA and IIA enrolled patients over the age of 26)

	Obe-cel ITT (unweighted)	Inotuzumab	Obe-cel matched to inotuzumab
N	[redacted]	164.00	[redacted]
Age	[redacted]	46.50	46.50
Sex (male), %	[redacted]	55.49	55.49
ECOG: 0*, %	[redacted]	37.80	37.80
ECOG: 1 or 2, %	[redacted]	62.20	62.20
Previous lines of therapy: 1, %	[redacted]	67.68	67.68
Previous lines of therapy: 2*, %	[redacted]	32.32	32.32
Race: White, %	[redacted]	68.29	68.29
Prior SCT, %	[redacted]	17.68	17.68
Duration of remission <12 months, %	[redacted]	58.54	58.54
BM blasts <50%, %	[redacted]	32.32	32.32
Ph+, %	[redacted]	13.41	13.41

*Treated as baseline.
BM - bone marrow; ECOG - Eastern Cooperative Oncology Group; ITT - intention to treat; Ph - Philadelphia chromosome; SCT - stem cell transplantation
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2019)[2]

Table 23: Covariates before and after matching to blinatumomab (pooled Cohort IA and IIA enrolled patients over the age of 26)

	Obe-cel (Ph-)	Blinatumomab	Obe-cel matched to blinatumomab
N	[redacted]	271.00	[redacted]
Age	[redacted]	40.80	40.80
Sex (male), %	[redacted]	59.78	59.78
ECOG: 0*, %	[redacted]	35.50	35.50
ECOG: 1 or 2, %	[redacted]	64.50	64.50
Previous lines of therapy: 1, %	[redacted]	42.07	42.07
Previous lines of therapy: 2, %	[redacted]	33.58	33.58

Previous lines of therapy: ≥3*, %	[redacted]	24.35	24.35
Race: White, %	[redacted]	84.13	84.13
Prior SCT, %	[redacted]	34.69	34.69
Duration of remission <12 months, %	[redacted]	28.00	28.00
BM blasts <50%, %	[redacted]	25.46	25.46
Primary refractory, %	[redacted]	42.44	42.44

*Treated as baseline.
BM - bone marrow; ECOG - Eastern Cooperative Oncology Group; Ph - Philadelphia chromosome; SCT - stem cell transplant
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]

Table 24: Covariates before and after matching to ponatinib (pooled Cohort IA and IIA enrolled patients over the age of 26)

	Obe-cel (Ph+)	Ponatinib	Obe-cel matched to ponatinib
N	[redacted]	32.00	[redacted]
Age	[redacted]	62.00	62.00
Sex (male), %	[redacted]	62.50	62.50
ECOG: 0*, %	[redacted]	31.9	31.9
ECOG: 1 or 2, %	[redacted]	68.10	68.10
Previous lines of therapy: 1, %	[redacted]	19.00	19.00
Previous lines of therapy: 2, %	[redacted]	44.00	44.00
Previous lines of therapy: ≥3*, %	[redacted]	37.00	37.00
Race: White, %	[redacted]	81.30	81.30
Prior SCT, %	[redacted]	23.00	23.00

*Treated as baseline.
ECOG - Eastern Cooperative Oncology Group; Ph - Philadelphia chromosome; SCT - stem cell transplant
Source: Autolus. Data on file (2024)[5]; Cortes et al. (2018)[4]

An analysis of all enrolled patients over the age of 26 years was conducted on the following outcomes: EFS, OS, CR, and CRi by IRRC. As per the EAG request, all analyses were performed without censoring for subsequent treatment.

The cumulative ESS for each of the comparisons by order of importance of TEM/PF are presented in Table 25, Table 26, and Table 27 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 as per the analysis on the full enrolled cohorts.[6]

Table 25: ESS combinations, obe-cel matched to inotuzumab, pooled Cohort IA and IIA enrolled patients aged over 26 years

Covariate	ESS
BM blasts at screening	[redacted]
Prior lines of therapy	[redacted]
Duration of remission <12 months	[redacted]
Ph chromosome	[redacted]
Age	[redacted]
Race	[redacted]
Prior SCT	[redacted]
ECOG	[redacted]
Sex	[redacted]

BM - bone marrow; ECOG - Eastern Cooperative Oncology Group; ESS – effective sample size; ITT - intention to treat; Ph - Philadelphia chromosome; SCT - stem cell transplantation

Table 26: ESS combinations, obe-cel matched to blinatumomab, pooled Cohort IA and IIA enrolled patients aged over 26 years

Covariate	ESS
Primary refractory	[redacted]
BM blasts at screening	[redacted]
Prior lines of therapy	[redacted]
Duration of remission <12 months	[redacted]
Age	[redacted]
Race	[redacted]
Prior SCT	[redacted]
ECOG	[redacted]
Sex	[redacted]

BM - bone marrow; ECOG - Eastern Cooperative Oncology Group; ESS – effective sample size; Ph - Philadelphia chromosome; SCT - stem cell transplant

Table 27: ESS combinations, obe-cel matched to ponatinib, pooled Cohort IA and IIA enrolled patients aged over 26 years

Covariate	ESS
Prior lines of therapy	[redacted]
Age	[redacted]
Race	[redacted]
Prior SCT	[redacted]
ECOG	[redacted]
Sex	[redacted]

ECOG - Eastern Cooperative Oncology Group; ESS – effective sample size; Ph - Philadelphia chromosome; SCT - stem cell transplant

Results for EFS and OS are shown in Table 28 and Table 29, respectively.

EFS

EFS for FELIX versus comparator trials is presented in Table 28. The efficacy of obe-cel in patients aged over 26 years compared to inotuzumab, blinatumomab, and ponatinib are consistent with the results of the overall enrolled population. The results in the ITT population versus inotuzumab indicate that the efficacy of obe-cel is improved compared to the overall population.

Table 28: Event-free survival for FELIX versus comparator trials, enrolled patients aged over 26 years

Population	Treatment	Median EFS	ESS	Unadjusted HR	Adjusted HR
ITT	Obe-cel	[redacted]	-	-	-
	Inotuzumab	5.0 months	[redacted]	[redacted]	[redacted]
Ph-	Blinatumomab	0.0 months†	[redacted]	[redacted]	[redacted]
Ph+	Ponatinib	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; mITT - modified intention to treat; Ph - Philadelphia chromosome

Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

OS

OS for FELIX versus comparator trials is presented in Table 29. The efficacy of obe-cel in patients aged over 26 years compared to inotuzumab, blinatumomab, and ponatinib are consistent with the results of the overall enrolled population.

Table 29: Overall survival for FELIX versus comparator trials, enrolled patients aged over 26 years

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

*Statistically significant results. ESS - effective sample size; HR - hazard ratio; ITT - intention to treat; OS – overall survival; Ph – Philadelphia chromosome

Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

CR

CR for FELIX versus comparator trials is presented in Table 30. The efficacy of obe-cel in patients aged over 26 years compared blinatumomab and ponatinib are consistent with the results of the overall enrolled population.

Table 30: Complete remission for FELIX versus comparator trials, enrolled patients aged over 26 years

Population	Treatment	Mean CR (%)	Obe-cel weighted mean CR (%)	ESS	Unadjusted OR	Adjusted OR
ITT	Obe-cel	[redacted]	-	-	-	-
Ph-	Blinatumomab	0.34	[redacted]	[redacted]	[redacted]	[redacted]
Ph+	Ponatinib	0.41	[redacted]	[redacted]	[redacted]	[redacted]

*Statistically significant results. CI – confidence interval; CRi – complete remission with incomplete haematologic recovery; ESS - effective sample size; ITT - intention to treat; OR – odds ratio; Ph – Philadelphia chromosome
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]; Cortes et al. (2018)[4]

CRi

CRi for FELIX versus comparator trials is presented in Table 31. The efficacy of obe-cel in patients aged over 26 years compared to blinatumomab are consistent with the results of the overall enrolled population. CRi was not reported in PACE, so the comparison between obe-cel and ponatinib was not possible for CRi.

Table 31: Complete remission with incomplete haematologic response for FELIX versus comparator trials, enrolled patients aged over 26 years

Population	Treatment	Mean CRi	Obe-cel weighted mean CRi (%)	ESS	Unadjusted OR	Adjusted OR
ITT	Obe-cel	[redacted]		-	-	-
Ph-	Blinatumomab	0.01	[redacted]	[redacted]	[redacted]	[redacted]

*Statistically significant results. CI – confidence interval; CRi – complete remission with incomplete haematologic recovery; ESS – effective sample size; ITT – intention to treat; OR – odds ratio; Ph – Philadelphia chromosome
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]

CR/CRi

CR/CRi for FELIX versus comparator trials is presented in Table 32. The efficacy of obe-cel in patients aged over 26 years compared to inotuzumab is improved versus the results of the overall enrolled population.

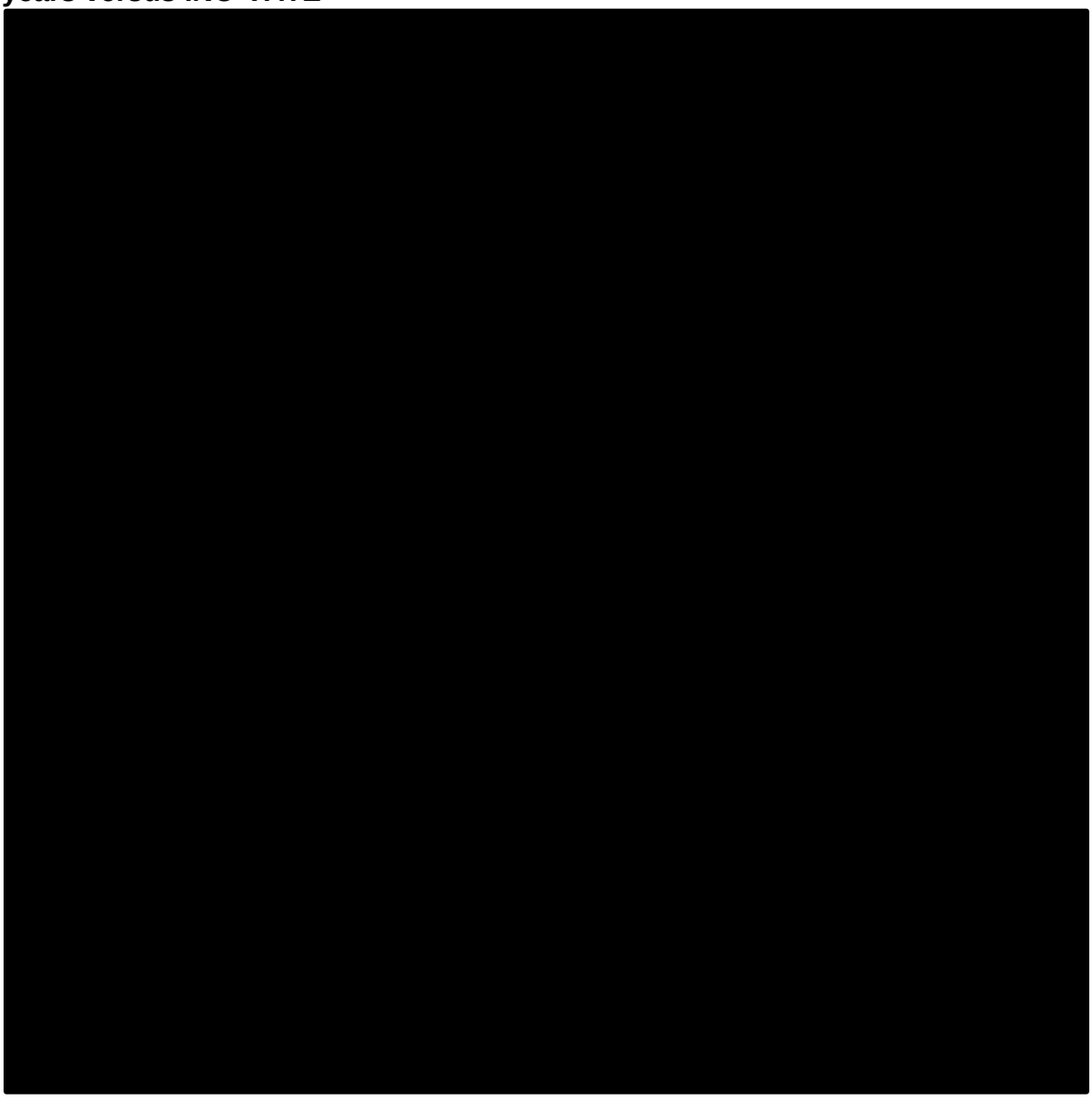
Table 32: Complete remission or complete remission with incomplete haematologic response for FELIX versus INO-VATE, enrolled patients aged over 26 years

Population	Treatment	Mean CR/CRi	Obe-cel weighted mean CR/CRi (%)	ESS	Unadjusted OR	Adjusted OR
ITT	Obe-cel	[redacted]	-	-	-	-
	Inotuzumab	0.74	[redacted]	[redacted]	[redacted]	[redacted]

CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematologic recovery; ESS - effective sample size; ITT - intention to treat; OR – odds ratio
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2019)[2]

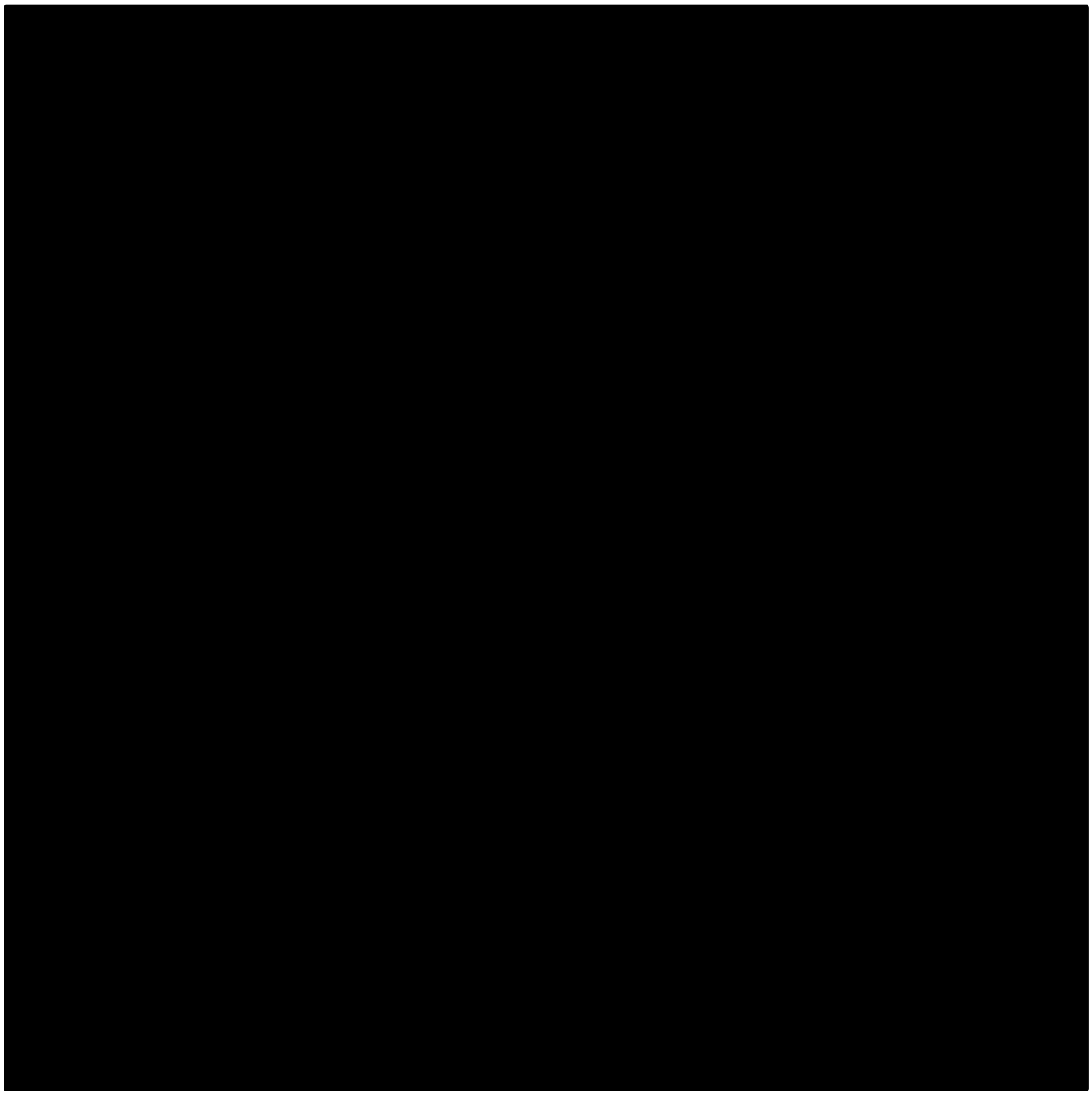
Plots of obe-cel unweighted, obe-cel weighted and comparator KM data for EFS and OS for FELIX versus inotuzumab, blinatumomab and ponatinib are shown in Figure 10 to Figure 15, respectively.

Figure 10: Event-free survival for FELIX all enrolled patients over aged 26 years versus INO-VATE



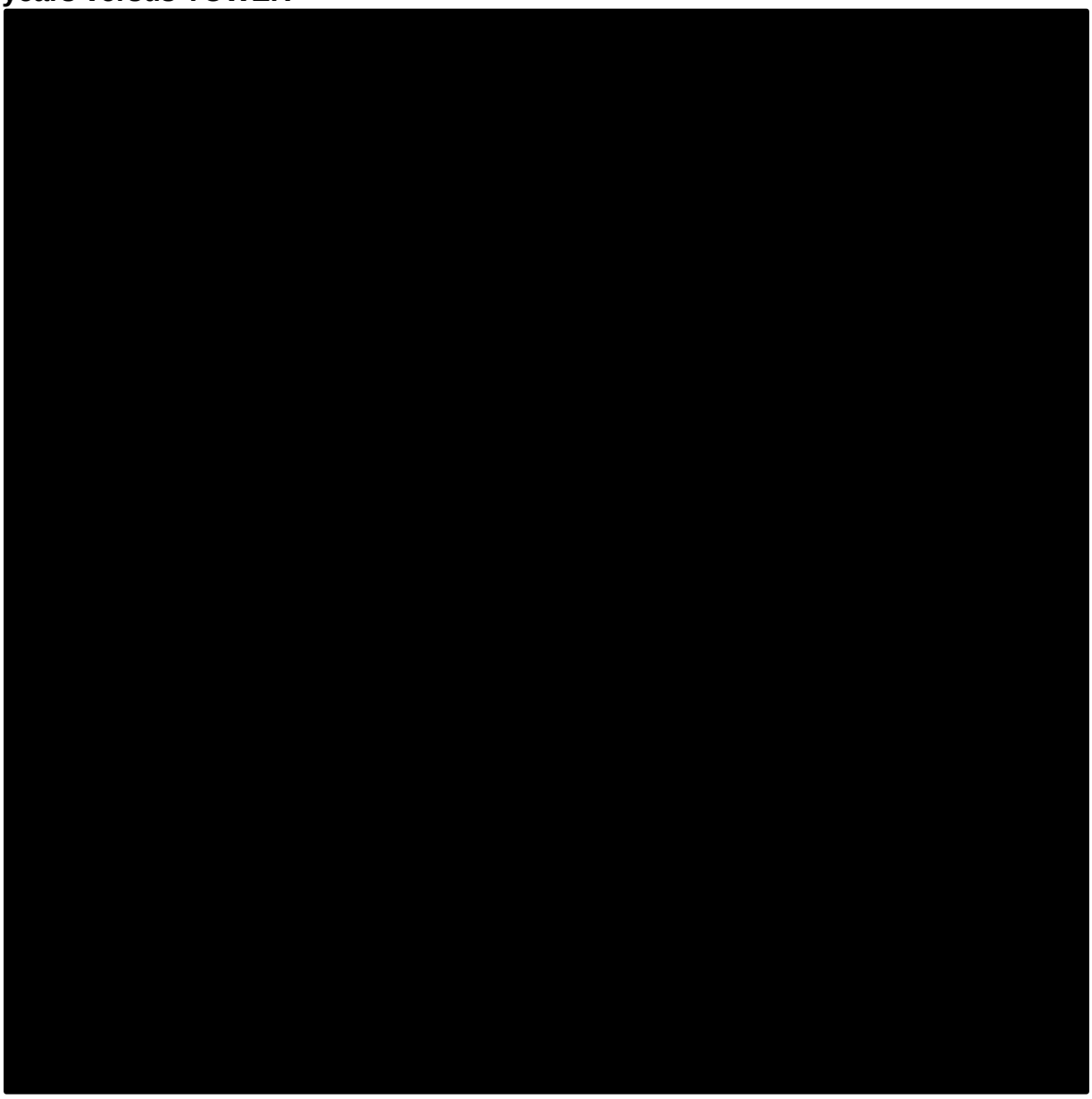
EFS – event-free survival
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2019)[2]

Figure 11: Overall survival for FELIX all enrolled patients over aged 26 years versus INO-VATE



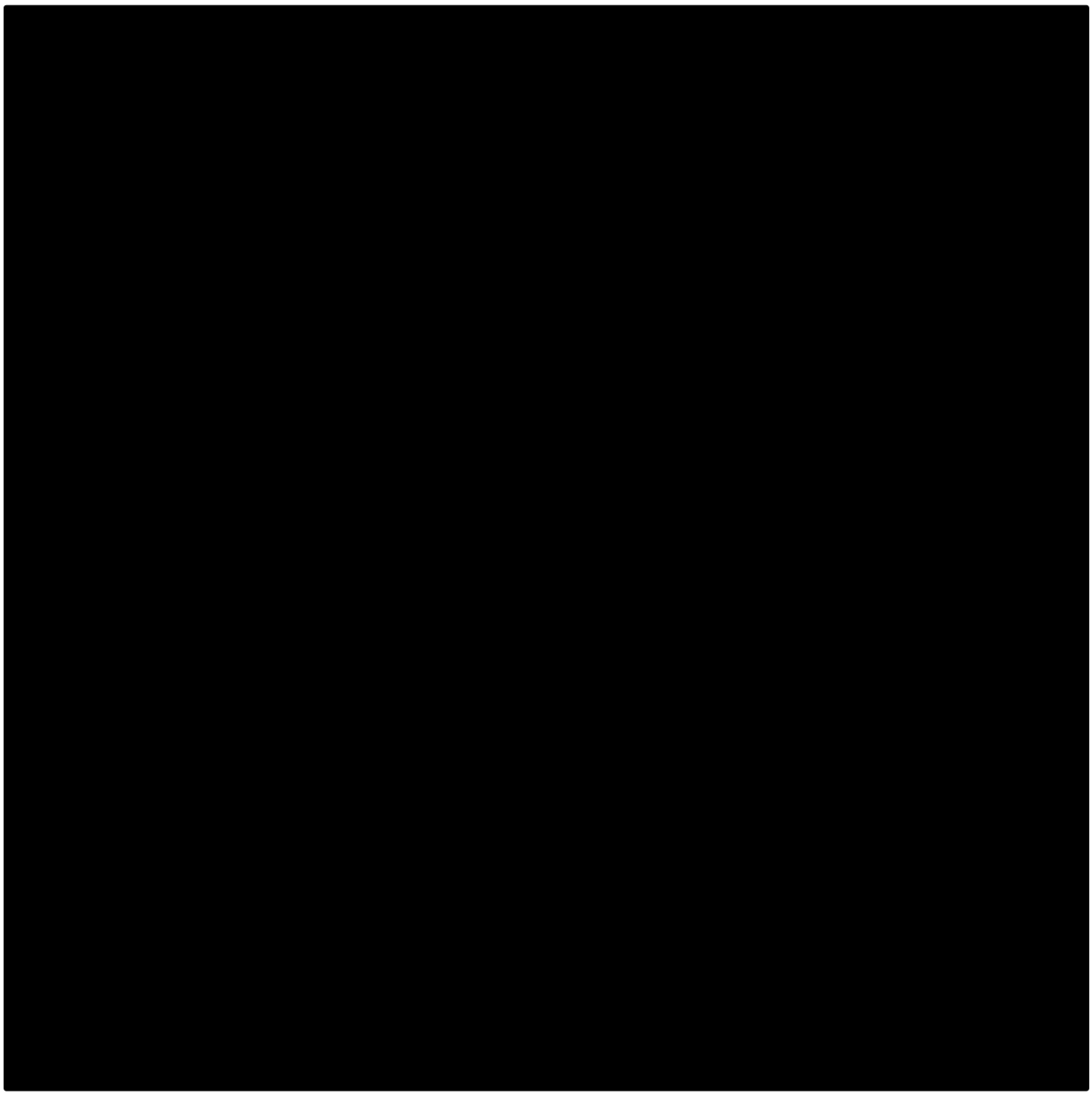
OS – overall survival
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2019)[2]

Figure 12: Event-free survival for FELIX all enrolled patients over aged 26 years versus TOWER



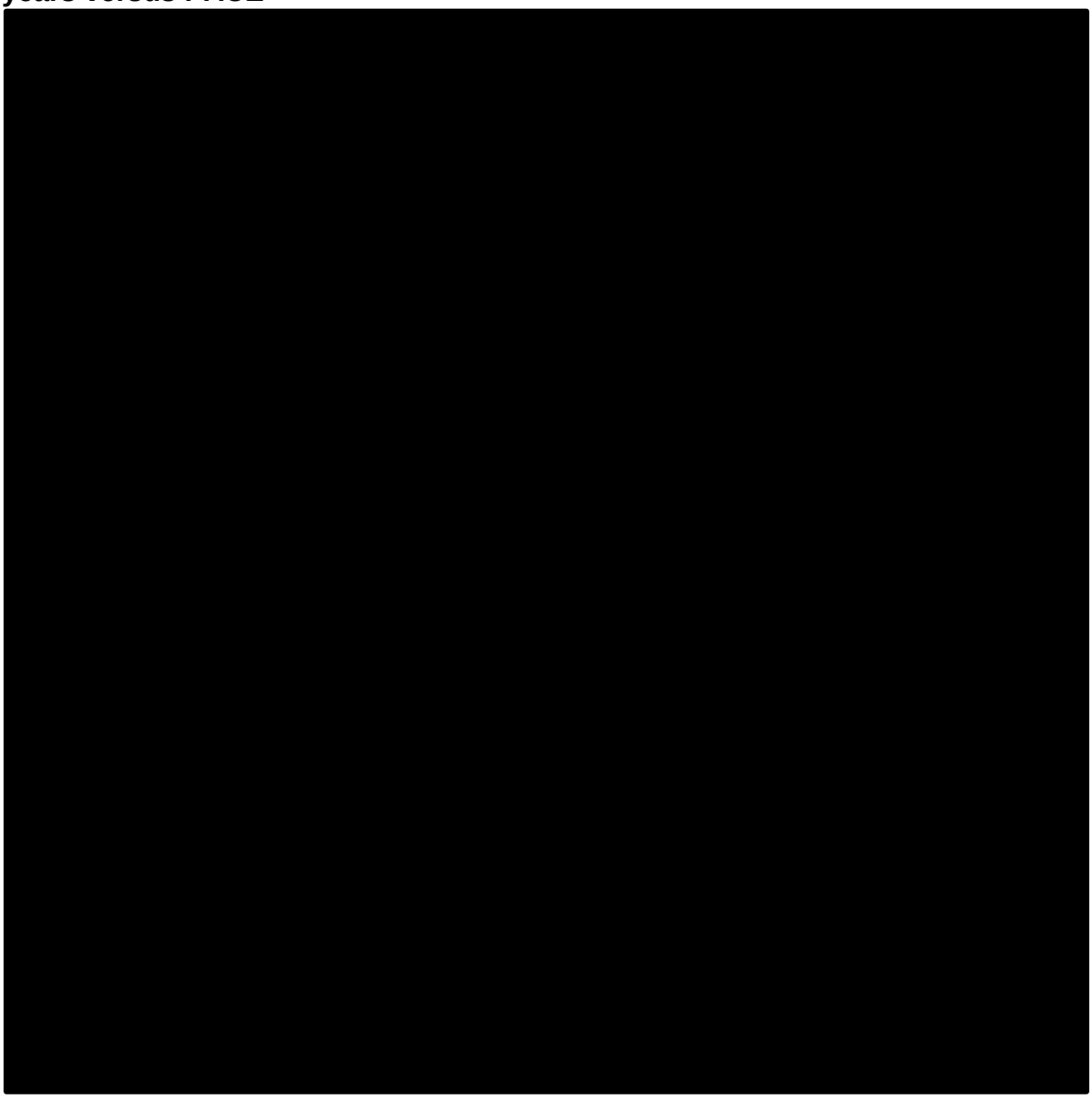
EFS – event-free survival
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]

Figure 13: Overall survival for FELIX all enrolled patients over aged 26 years versus TOWER



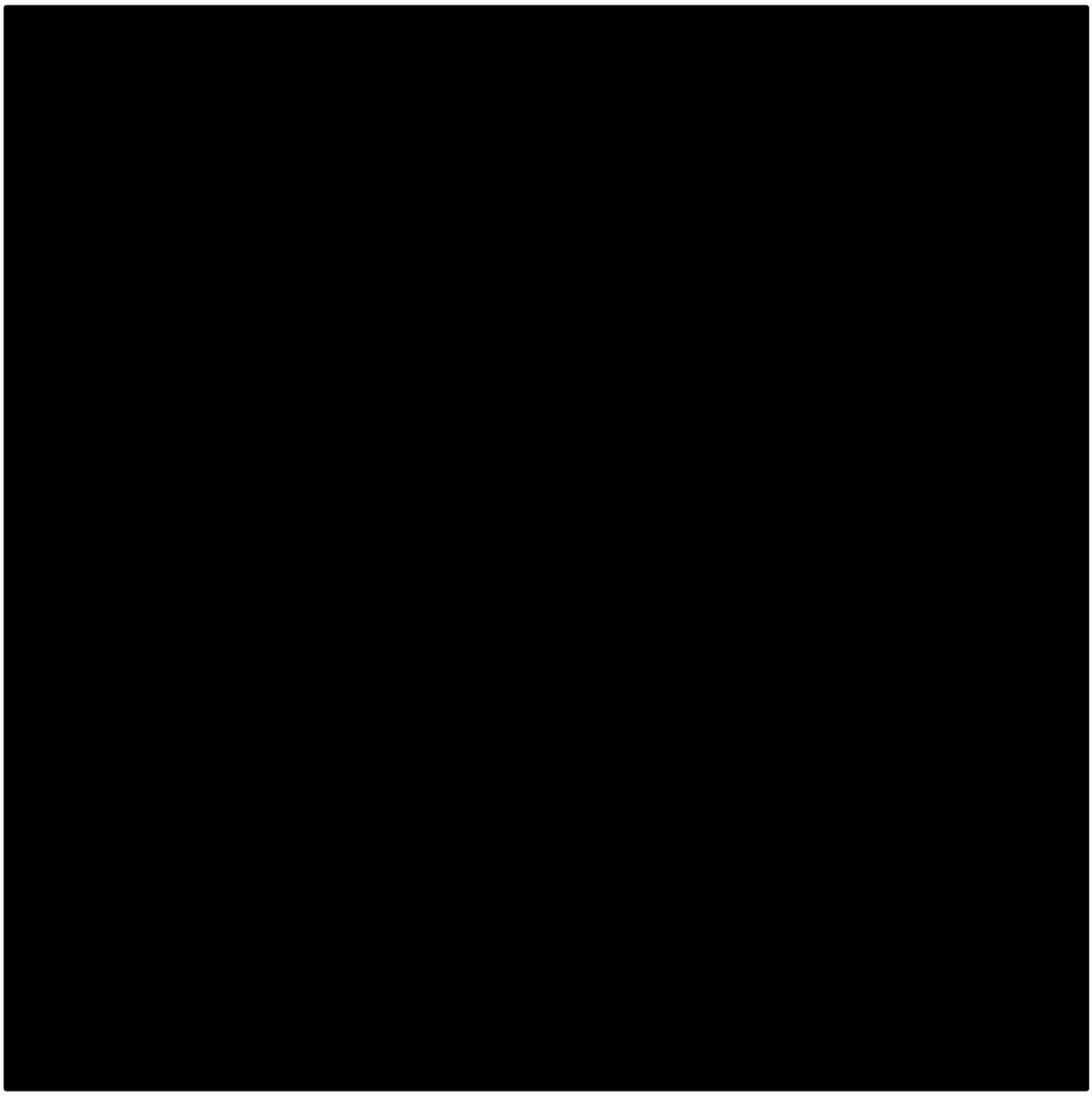
OS – overall survival
Source: Autolus. Data on file (2024)[1]; Kantarjian et al. (2017)[3]

Figure 14: Event-free survival for FELIX all enrolled patients over aged 26 years versus PACE



EFS – event-free survival
Source: Autolus. Data on file (2024)[1]; Cortes et al. (2018)[4]

Figure 15: Overall survival for FELIX all enrolled patients over aged 26 years versus PACE



OS – overall survival
Source: Autolus. Data on file (2024)[1]; Cortes et al. (2018)[4]

Conclusion

The findings of the MAIC indicate obe-cel has a favourable effect on EFS and OS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. the MAIC also indicates that obe-cel has a favourable effect on CR and CRi compared to blinatumomab and ponatinib. The findings of the subgroup of patients aged over 26 years are consistent with the overall population.

A2. In CS, Appendix C, Table 5. The following percentages of prior therapies are reported: 35.1% had prior blinatumomab, 31.9% had prior inotuzumab, and 16% had both. Please clarify at what point in the patients treatment pathways these treatments were given, whether any other treatments were given to these or other patients, and the number of treatment-naïve patients. Please clarify how treatment-naïve is defined and how many of them had prior treatments. Please provide detail on patient response to previous these therapies.

In this context, treatment-naïve is defined as patients who did not receive any treatment with blinatumomab and/or inotuzumab. It should be noted that no patients in the FELIX trial were treatment-naïve *per se*, as all patients had relapsed or refractory (R/R) disease to meet the trial inclusion criteria.

The FELIX trial did not collect the requested details regarding timepoints at which patients received prior inotuzumab and/or blinatumomab and any treatments prior to this, or responses to previous therapies. However, subgroup analyses of patients receiving bridging therapy with/without inotuzumab are presented in the Company response to question A15. Additionally, outcomes for patients who were enrolled but ultimately did not receive obe-cel are presented in the Company response to question A19, including patients who received inotuzumab as bridging therapy.

A3. Please clarify how many enrolled patients were ineligible for stem cell transplant before receiving CAR T-cell therapy and the reasons for their ineligibility.

The number of patients who were ineligible for SCT in the FELIX clinical trial and the reasons for ineligibility are not available to provide here, as these data were not collected. The decision to perform an SCT prior to receiving CAR T was made by the treating physician. Normally, allo-SCT is offered to patients below 55 years of age while patients >55 years of age are considered ineligible for SCT, either e.g. for no donor availability, patient's preference, contraindication to receiving SCT, and not in MRD-negative CR.

A4. Please report the incidence of CD19-negative relapses in the FELIX trial.

In Cohort IIA, [redacted] patients ([redacted]%) had CD19-negative relapse. In Cohort IA, [redacted] ([redacted]%) experienced CD19-negative relapse.[1]

A5. Please provide information on duration of complete remission for FELIX IA and IIA, including a Kaplan-Meier plot.

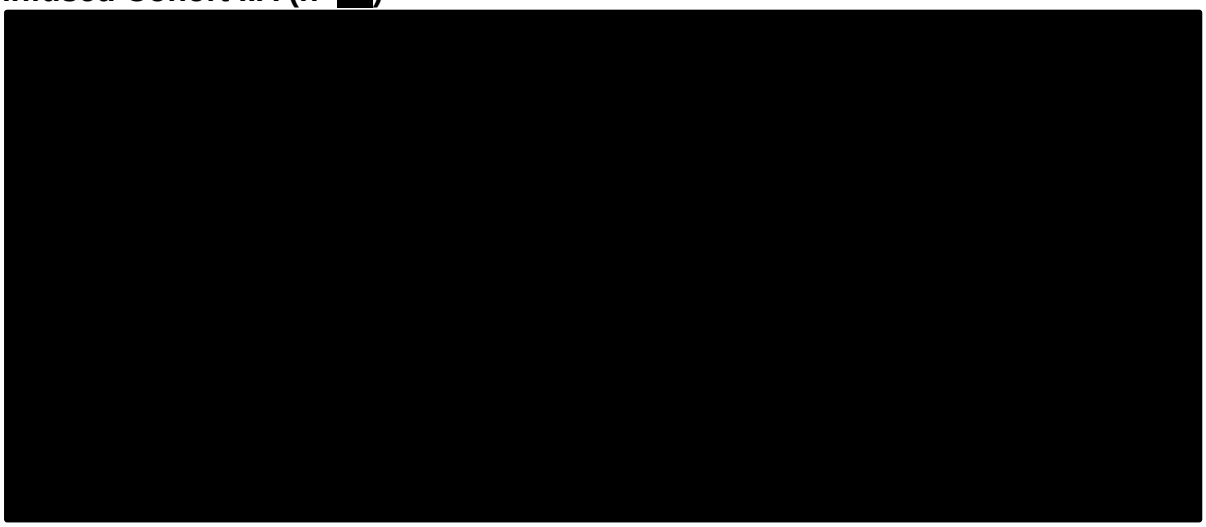
Table 33 provides an overview of the duration of complete remission in Cohort IA and Cohort IIA. The estimated median duration of complete remission was not estimable as of the February 2024 data cut-off for Cohort IA. The estimated median duration of complete remission was [redacted] (95% CI: [redacted]) months as of the February 2024 data cut-off for Cohort IIA. The KM plot for duration of complete remission for Cohort IIA is presented in Figure 16.[1]

Table 33: Duration of complete remission by IRRC, infused Cohorts IA and IIA

Parameter	Cohort IA (n=13)	Cohort IIA (n=94)
Number of patients in analysis	[redacted]	[redacted]
Number of events, n (%)	[redacted]	[redacted]
Morphological relapse	[redacted]	[redacted]
Number of censored observations, n (%)	[redacted]	[redacted]
Maximum follow-up (months)	[redacted]	[redacted]
Median follow-up (months)	[redacted]	[redacted]
% event-free probability estimate		
At 3 months, % [95% CI]	[redacted]	[redacted]
At 6 months, % [95% CI]	[redacted]	[redacted]
At 9 months, % [95% CI]	[redacted]	[redacted]
At 12 months, % [95% CI]	[redacted]	[redacted]
At 15 months, % [95% CI]	[redacted]	[redacted]
At 18 months, % [95% CI]	[redacted]	[redacted]

CI – confidence interval; IRRC – Independent Response Review Committee; NE – not estimable; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Figure 16: KM of duration of complete remission by IRRC for patients in FELIX infused Cohort IIA (n=[redacted])



CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematologic recovery; IRRC – Independent Response Review Committee; KM – Kaplan-Meier
Source: Autolus, Data on file[1]

A6. Please provide information on complete remission within 3 months for FELIX IA and IIA, and PFS and any other outcomes listed in the protocol but that are not available in the CSR.

Data for Cohort IA

Presented below are the results which were included in the CS, repeated for Cohort IA. Results presented are without censoring for SCT. KM curves have not been presented for Cohort IA due to the low number of patients in the cohort. KM curves are presented for the pooled Cohort IA and IIA in response A1.[1]

Progression-free survival (PFS) was not analysed in the CSR, as the definition of PFS was identical to EFS in the FELIX clinical trial. Therefore, PFS results are not presented below.

Results from the February 2024 data cut-off, for Cohort IA found a statistically significant ORR of [redacted]% (95% CI: [redacted] to [redacted], p<[redacted]). CR was achieved in nearly [redacted] of patients ([redacted]%). The MRD-negative remission rate reflects a deep level of remission achieved by obe-cel (Table 34).[1]

Table 34: ORR by IRRC (Cohort IA)

Parameter	Cohort IA (n=13)
ORR (CR + CRi)	
n (%) [95% CI]	[redacted]
CR	
n (%)	[redacted]
MRD-negative ($<10^{-4}$) remission	
MRD-negative CR/CRi, n (%)	[redacted]

CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematologic recovery; IRRC – Independent Response Review Committee; MRD – minimal residual disease; ORR – overall remission rate
Source: Autolus, Data on file[1]

At a median estimated duration of follow-up of [redacted] months, the estimated DOR was [redacted] months, and the probability of survival at 12 months after onset of remission was [redacted]% (95% CI: [redacted]) (Table 35).[1]

Table 35: DOR by IRRC (Cohort IA)

Parameter	Cohort IA (n=13)
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]
Estimated median DOR (months) [95% CI]	[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 – Independent Response Review Committee; NE – not estimable
Source: Autolus, Data on file[1]

Of the 13 patients in Cohort IA, [redacted] had not experienced any event. The median EFS was [redacted] (95% CI: [redacted]) months (Table 36).[1]

Table 36: EFS by IRRC (Cohort IA)

Parameter	Cohort IA (n=13)
Patients with event, n (%)	[redacted]
Median EFS, months [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 – Independent Response Review Committee; mITT – modified intent-to-treat; NE – not estimable
Source: Autolus, Data on file[1]

Of the 13 patients Cohort IA, [redacted] had died due to disease progression. The median OS was [redacted] (95% CI: [redacted]) months (Table 37).[1]

Table 37: OS by IRRC (Cohort IA)

Parameter	Cohort IA (n=13)
Patients with event, n (%)	[redacted]
Median OS, months [95% CI]	[redacted]
OS at 6 months, % [95% CI]	[redacted]
OS at 12 months, % [95% CI]	[redacted]

CI – confidence interval; mITT – modified intent-to-treat; IRRC – Independent Response Review Committee; NE – not estimable; OS – overall survival
Source: Autolus, Data on file[1]

Data not presented in CS

The following data were not presented in the CS and is therefore presented for both Cohorts IA and IIA below.

CR within 3 months post obe-cel infusion was achieved in [redacted] ([redacted]%) patients in Cohort IA and [redacted] ([redacted]%) patients in Cohort IIA, presented in Table 38.[1]

Table 38: CR by IRRC within 3 months post obe-cel infusion (Cohort IA)

Parameter	Cohort IA (n=13)	Cohort IIA (n=94)
CRR within 3 months		
n (%)	[redacted]	[redacted]
[95% CI]	[redacted]	[redacted]

CI – confidence interval; CR – complete remission; CRR – complete remission rate; IRRC – Independent Response Review Committee
Source: Autolus, Data on file[1]

Of the patients who achieved CR in Cohort IA, [redacted] ([redacted]%) patients were MRD-negative, [redacted] patients were MRD-positive, and [redacted] ([redacted]%) patients were not evaluable. Of the patients who achieved CR in Cohort IIA, [redacted] ([redacted]%) patients were

MRD-negative, [redacted] ([redacted]%) patients were MRD-positive and [redacted] ([redacted]%) patients were not evaluable (Table 39).[1]

Table 39: MRD by ClonoSEQ NGS/Flow/qPCR by IRRC (Cohort IA)

Parameter	Cohort IA (n=13)	Cohort IIA (n=94)
Patients who achieved CR or CRi – n (%)	[redacted]	[redacted]
MRD-negative CR/CRi	[redacted]	[redacted]
MRD-positive CR/CRi	[redacted]	[redacted]
MRD-unknown CR/CRi	[redacted]	[redacted]

CR – complete remission; CRi – complete remission with incomplete haematologic recovery; MRD – minimal residual disease; NGS – next-generation sequencing; IRRC – Independent Response Review Committee
Source: Autolus, Data on file[1]

ORR split by whether patients received SCT in remission is presented in Table 40 below. In Cohort IIA, the ORR was [redacted]% despite not receiving an SCT in remission.[1] Results for Cohort IA were not feasible to generate within the timeframe of this response.

Table 40: ORR by whether patients received post SCT in remission

	Cohort IIA (n=94)			
	CR/CRi then SCT in remission (n=12)	**CR/CRi without SCT in remission (n=60)**	**No CR/CRi (n=22)**	**Total (n=94)**
N (%)	[redacted]	[redacted]	[redacted]	[redacted]
[95% CI]	[redacted]	[redacted]	[redacted]	[redacted]

CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematologic recovery; ORR – overall remission rate; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Safety and tolerability of obe-cel

The laboratory abnormalities experienced by patients in Cohorts IA and IIA are presented in Table 41.[1]

Table 41: Laboratory abnormalities experienced by patients in pooled Cohort IA and IIA

Laboratory abnormality	Cohort IA (n=13)	Cohort IIA (N=94)
Haemoglobin (g/L) (Decreased)		
Any grade	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]

Lymphocytes (10^9/L) (Decreased)		
Any grade	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Neutrophils (10^9/L) (Decreased)		
Any grade	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Platelets (10^9/L) (Decreased)		
Any grade	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Leukocytes (10^9/L) (Decreased)		
Any grade	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]

g – grams; L – litre
Source: Autolus, Data on file[1]

Table 42 gives an overview of the frequency and grade of the most common treatment-related adverse events (TEAEs) patients experienced post obe-cel in Cohort IA and IIA.[1]

Table 42: TEAEs post obe-cel infusion, frequency and grade, in Cohort IA and IIA

	Cohort IA (n=13)						Cohort IIA (n=94)					
TEAE	**All grades n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Grade ≥ 3 n (%)**
Any	[redacted]											
CRS												
Pyrexia												
Diarrhoea												
Febrile neutropenia												
Anaemia												
Headache												
ICANS												
Neutropenia												
Hypotension												
Hyperferritinaemia												
Neutrophil count decreased												
COVID-19												
Vomiting												
Platelet count decreased												
Thrombocytopenia												
Abdominal pain												
Confusional state												

CRS – cytokine release syndrome; ICANS – immune effector cell-associated neurotoxicity syndrome; TEAE – treatment emergent adverse event
Source: Autolus, Data on file[1]

Health-related quality of life (HRQoL) data

The observed change over time and change from baseline scores for the European Quality of Life 5 Dimensions 5 Level Version Visual Analogue Scale (EQ-5D-5L VAS) are presented in Table 43 for Cohort IIA. These data were not collected for Cohort IA. The observed change over time and change from baseline scores for the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) are presented in Table 44.[1]

Table 43: Change over time in EQ-5D-5L VAS

Parameter visit, EQ VAS score	Cohort IIA (n=94)	
	Observed	Change from baseline
Baseline	[redacted]	-
	[redacted]	-
	[redacted]	-
Day 28	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Month 3	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Month 6	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Month 9	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

EQ-5D-5L – European Quality of Life 5 Dimensions 5 Level Version; VAS – visual analogue score
Source: Autolus, Data on file[1]

Table 44: Change over time in EORTC-QLQ-C30 score

Parameter visit, Global health, QoL		Cohort IIA (n=94)	
		Observed	Change from baseline
Baseline	N	[redacted]	-
	Mean (SD)	[redacted]	-

	Median	[redacted]	-
Day 28	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
Month 3	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
Month 6	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
Month 9	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
Month 12	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
Month 18	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
Month 24	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]

EORTC-QLQ-C30 – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QoL – quality of life; SD – standard deviation
Source: Autolus, Data on file[1]

Expansion and persistence of obe-cel

Table 45 and Table 46 present the expansion and persistence of obe-cel over time through droplet digital PCR (ddPCR) levels in the peripheral blood and bone marrow, respectively.[1]

Table 45: Concentration of obe-cel transgene level (copies/ug DNA) by ddPCR in peripheral blood, Cohort IA and Cohort IIA

Obe-cel transgene – blood (copies/ug DNA)	Cohort IA (n=13)	Cohort IIA (N=94)
Baseline		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Day 3		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Day 6		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]

Mean (SD)	[redacted]	[redacted]
Day 9		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Day 12		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Day 15		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Day 22		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Day 28		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 2		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 3		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 4		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 6		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 9		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 12		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 15		

N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 18		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 21		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 24		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 30		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 36		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

*N is the number of patients with available data, and M is the number of patients with non-zero values.
ddPCR – droplet digital polymerase chain reaction; DNA – deoxyribonucleic acid; N/A – not available; SD – standard deviation
Source: Autolus, Data on file[1]

Table 46: Concentration of obe-cel transgene level (copies/ug DNA) by ddPCR in bone marrow, Cohort IA and Cohort IIA

Obe-cel transgene – bone marrow (copies/ug DNA)	Cohort IA (n=13)	Cohort IIA (n=93)
Day 28		
N	[redacted]	[redacted]
m	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 3		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 6		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 12		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]

Mean (SD)	[redacted]	[redacted]
Month 18		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Month 24		
N*	[redacted]	[redacted]
M*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

*N is the number of patients with available data, and M is the number of patients with non-zero values.
ddPCR – droplet digital polymerase chain reaction; DNA – deoxyribonucleic acid; N/A – not available; NE – not estimable; SD – standard deviation
Source: Autolus, Data on file[1]

Of the 94 patients in Cohort IIA, [redacted] ([redacted]%) had ongoing B-cell aplasia. Ongoing B-cell aplasia results for Cohort IA was not feasible to generate within the timeframe of this response.[1]

Health care resource utilisation for the management of obe-cel related toxicity

Table 47 provides the frequency and duration of hospitalisation and ICU stays to support patients who experience obe-cel related toxicity in Cohort IA and IIA. In Cohort IA, [redacted] ([redacted]%) patients were admitted to ICU and in Cohort IIA, [redacted] patients ([redacted]%) were admitted. The mean duration of stay in Cohort IA was [redacted] days, and [redacted] days in Cohort IIA.[1]

Table 47: Frequency and duration of hospitalisation and/or critical care support to manage obe-cel related toxicity

	Cohort IA (n=13)	**Cohort IIA (n=94)**
Duration of hospitalisation within 28 days post obe-cel infusion		
N	13	94
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Patients admitted to ICU, n(%)	[redacted]	[redacted]
Total duration of ICU stays (days)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Reason for ICU		
Adverse event other than CRS/ICANS	[redacted]	[redacted]
ICANS	[redacted]	[redacted]
CRS	[redacted]	[redacted]

Technical/Social/Practical reasons	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]

CRS – cytokine release syndrome; ICANS – immune effector cell-associated neurotoxicity syndrome; ICU – intensive care unit; SD – standard deviation
Source: Autolus, Data on file[1]

A7. Please report the baseline characteristics table for both enrolled and infused UK patients in FELIX IA and IIA.

Table 48 and Table 49 present the baseline demographics and disease characteristics of UK patients in the FELIX trial Cohorts IA and IIA, respectively.[1]

Table 48: Demographics in the UK population in the FELIX clinical trial

Demographic		**Enrolled**		**Infused**	
		Cohort IA (n=5)	**Cohort IIA (n=42)**	**Cohort IA (n=4)**	**Cohort IIA (n=36)**
Age (years)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
Age (years) categorised – n (%)	≥18 to ≤ 25	[redacted]	[redacted]	[redacted]	[redacted]
	>25 to < 40	[redacted]	[redacted]	[redacted]	[redacted]
	≥40 to < 65	[redacted]	[redacted]	[redacted]	[redacted]
	≥65	[redacted]	[redacted]	[redacted]	[redacted]
Sex, male – n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Race – n (%)	Asian	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]
	White	[redacted]	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]	[redacted]

SD – standard deviation; UK – United Kingdom
Source: Autolus, Data on file[1]

Table 49: Disease characteristics in the UK population in the FELIX clinical trial

Disease characteristic		Enrolled		Infused	
		Cohort IA (n=5)	Cohort IIA (n=42)	Cohort IA (n=4)	Cohort IIA (n=36)
Number of prior lines of therapy – n (%)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2				
	3				
	≥4				
Refractory to all prior lines of anticancer therapy – n (%)					
Refractory to first-line therapy – n (%)					
Refractory to last prior line of therapy – n (%)					
Relapsed to first-line therapy within 12 months – n (%)					
Previous blinatumomab – n (%)					
Previous inotuzumab – n (%)					
Previous blinatumomab and inotuzumab – n (%)					
Previous blinatumomab or inotuzumab – n (%)					
Previous allogenic SCT – n (%)					
Disease status at screening					
BM blasts (%) by morphology prior to enrolment (median)					
BM blasts by morphology prior to enrolment categorised – n (%)	>75%				
	>20% to ≤75%				
	≥5% to ≤20%				
	<5%				
EMD status prior to enrolment – n (%)	Absent				
	Present				
ECOG score – n (%)	0				
	1				
	≥2				
	Missing				
CD19 status at screening – n (%)	Positive				
	Negative				
	Mixed population (positive+negative)				
CNS disease history – n (%)	CNS1				
	CNS2				
	CNS3				
	Unknown				

BM – bone marrow; CD – cluster of differentiation; CNS – central nervous system; ECOG – Eastern Cooperative Oncology Group; EMD – extramedullary disease; SCT – stem cell transplant; UK – United Kingdom
Source: Autolus, Data on file[1]

A8. Protocol doc, page 64. states

"[redacted]

[redacted]

[redacted]

[redacted]**." Please clarify how many patients have been eligible under this protocol statement.**

Across Cohort IA and IIA, a total of [redacted] patients received two obe-cel infusions with a reduced total dose due to less than the target dose being manufactured, and a further [redacted] patients did not receive their second dose of obe-cel due to less than the target dose being manufactured. Further details on these patients are provided in the Company response to EAG Question A9.[7]

A9. Protocol doc, section 4.3, page 64 states:

"[redacted]

[redacted]

[redacted]

[redacted]**." Considering this statement, please clarify the following questions:**

a) How many patients failed to generate enough cells for the prescribed dose?

b) How many of these patients have been treated with a low dose and what were the outcomes?

c) How many patients were not treated?

Company response to a) and b):

A total of [redacted] patients failed to generate enough cells for the prescribed dose:

- [redacted] patients received only the first obe-cel infusion. [redacted] due to less than the target dose being manufactured as the sole reason, and t[redacted] due to both [redacted] and having less than the target dose manufactured. Please refer to Table 50 for response outcomes for these patients.[7]

- [redacted] received two obe-cel infusions with a reduced total dose due to less than the target dose being manufactured. Please refer to Table 51 for response outcomes for these patients.[7]

Table 50: Outcomes for patients who did not receive the second dose of obe-cel due to less than target dose manufactured

Reason for not receiving the second dose	Best overall response per IRRC
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CRi – complete remission with incomplete haematological recovery; IRRC - Independent Response Review Committee
Source: Autolus, Data on file[7]

Table 51: Overview of patients who received two obe-cel infusions with a reduced total dose due to less than target dose manufactured

Reason for receiving total dose different to the target dose	Best overall response per IRRC
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CR – complete remission; CRi – complete remission with incomplete haematological recovery; IRRC - Independent Response Review Committee
Source: Autolus, Data on file[7]

Company response to c):

[redacted] failed to generate enough cells and were not treated in on study.[7]

A10. Please clarify and report all immune-related adverse effects over time from the first infusion to the latest follow-up.

The immune-related AEs which occurred in the infused population in the safety set prior and post obe-cel infusion are reported in Table 52 below.

The only immune-related AE which occurred after enrolment and prior to obe-cel infusion was [redacted] of which [redacted] reported low grade cases (grade ≤3).[8]

At the June 2023 data cut-off, [redacted] patients in the safety set experienced an immune-related event, with [redacted] patients reporting events of grade ≥3.[7] The longer-term follow-up demonstrated minimal additional immune-related AEs, indicating a favourable

long-term safety profile for obe-cel. By February 2024, the number of reported immune-related events of all grades and of grade ≥3 were [redacted] and [redacted], respectively.[9]

The most frequently reported immune-related AEs of any grade by the February 2024 data cut were [redacted] ([redacted] patients, [redacted]%) and [redacted] ([redacted] patients, [redacted]%).[9] The majority of these were low grade, with the events being ≥ grade 3 in [redacted]% and [redacted]% of cases respectively.[9]

Table 52: Immune-related adverse events from prior to post obe-cel infusion, February 2024 (Phase Ib and II, mITT)

Immune-related adverse event	After enrolment and prior to obe-cel infusion (Phase Ib and II, n=127)		Post obe-cel infusion, June 2023 data cut (Phase Ib and II, n=127)		Post obe-cel infusion, February 2024 data cut (Phase Ib and II, n=127)	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine release syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Graft versus host disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Graft versus host disease in skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Graft versus host disease in gastrointestinal tract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemophagocytic lymphohistiocytosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute graft versus host disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Graft versus host disease in liver	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overlap syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

mITT – modified Intention to treat; NR – not reported
Source: FELIX, data on file[7–9]

A11. Please report Infusion-related Reactions post-day 1 and day 10 based on their severity for all FELIX cohorts.

No infusion-related reactions (IRR) were experienced by patients' post-Day 1 and Day 10 who had received treatment with obe-cel.[1]

A12. Please provide details on patient comorbidities for enrolled and infused populations of FELIX cohorts IA and IIA.

The data for patient comorbidities are not readily available. If the EAG consider this a priority, the Company can provide this at a later date and request the EAG to clarify what information on comorbidities they would like to be provided.

A13. PRIORITY QUESTION: Did any patients in the trial receive more administrations of obe-cel (or non conforming product) beyond the two planned administrations? If so please, give details such as whether re-harvesting was required, number and timing and dosage of additional doses. Please provide details of any other deviation from the day 1/10 administration schedule.

No patient received obe-cel beyond the two planned administrations on Day 1 and Day 10 +/-, the respective window as outlined in the protocol. In particular, no patient received the second administration later than 21 days after the first infusion.

A14. Protocol doc, page 93, reports monitoring of immunoglobulin (IgG) levels within FELIX. Please clarify how many patients and to what extent patients' IgG levels decreased from the first day of infusion to the latest data cutoff and how many patients received IV IgG post-infusion.

Patients' immunoglobulin levels in the FELIX trial from pre-conditioning to latest data cut-off (February 2024) are reported in Table 53 below. Values were shown to decrease over time, with means of [redacted] and [redacted] reported at pre-conditioning and baseline, respectively and a mean value of [redacted] at Month 24.[1]

As of the February 2024 data cut-off, [redacted] of patients had received intravenous immunoglobin (IVIG).[1]

Table 53: Immunoglobulin levels reported in FELIX over time, Cohort IIA (N=94)

Immunoglobulin levels (umol/L)	Number observed	Mean (SD)

Prior to pre-conditioning	[redacted]	[redacted]
Baseline	[redacted]	[redacted]
Day 28	[redacted]	[redacted]
Month 3	[redacted]	[redacted]
Month 6	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]

SD – standard deviation
Source: Autolus, Data on file[1]

A15. In Doc B, Table 8, the company has stated that the bridging therapies were decided by investigators.

a. **Please clarify what criteria were used to make treatment choices at this stage.**
b. **Please provide the proportions receiving each bridging therapy in the FELIX cohorts IA and IIA.**
c. **Please provide subgroup analysis for different bridging therapies that have been used for different outcomes such as OS, PFS, and ORR.**

Company response to a):

As stated in CS Document B, Table 8, the choice of bridging therapy was based on investigators' choice and local practice, meaning the criteria was up to clinician discretion. Bridging therapy primarily included chemotherapy alone or chemotherapy with a tyrosine kinase inhibitor (TKI).

Company response to b):

The proportions receiving each bridging therapy in Cohorts IA and IIA are presented in Table 54:

- In Cohort IA, [redacted] patients [redacted] received bridging therapy after leukapheresis until one week prior to lymphodepletion. [redacted] received chemotherapy alone ([redacted] patients, [redacted]%) or in combination with TKI ([redacted] patients, [redacted]%). [redacted] patients received inotuzumab.[1]

- In Cohort IIA, [redacted] of 94 patients ([redacted]%) received bridging therapy after leukapheresis until one week prior to lymphodepletion. The majority received chemotherapy alone ([redacted] patients, [redacted]%) or in combination with TKI ([redacted] patients, [redacted]%). Inotuzumab alone or in combination with chemotherapy was administered to [redacted] patients ([redacted]%).[1]

Table 54: Bridging medications by regimen (Cohorts IA and IIA, infused set)

	Cohort	
	IA (N=13) n (%)	**IIA (N=94) n (%)**
Number of patients with any bridging medication	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Chemotherapy + TKI	[redacted]	[redacted]
Chemotherapy + inotuzumab	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]
TKI	[redacted]	[redacted]
Steroids	[redacted]	[redacted]
Other*	[redacted]	[redacted]

TKI – tyrosine kinase inhibitor
* Patient received rituximab
Source: FELIX clinical study report[7]

Company response to c):

The Company has undertaken subgroup analyses in Cohort IIA in patients who received bridging therapy with (N=[redacted]) and without (N=[redacted]) inotuzumab, and in patients who did not receive bridging therapy (N=[redacted]). All analyses are based on the February 2024 data cut-off.[1]

With the exception for baseline tumour burden, the bridging subgroups were comparable in terms of patient and disease characteristics (Table 55), and had similar length of follow-up. Best observed response (BOR), overall response, complete response, and median EFS and OS for the respective subgroups are presented in Table 56. KM plots of DOR, EFS and OS are presented in Figure 17, Figure 18, and Figure 19.[1]

Acknowledging that the subgroup of patients who received bridging therapy with inotuzumab was considerably [redacted] than the subgroup that did not, results were relatively comparable across subgroups. The subgroup of patients who received bridging therapy with inotuzumab had below [redacted] patients at risk for DOR and EFS

beyond [redacted] months, and beyond [redacted] months for OS, hampering meaningful comparison. Persistence was comparable between the two groups, with ongoing persistence observed beyond Month 12 in both. The presented data therefore suggest that long-term persistence of obe-cel is possible, irrespective of the type of bridging therapy used.[1]

ORR was notably [redacted] in patients who did not receive bridging therapy; however, since this subgroup consisted of only [redacted] patients, no reliable conclusions can be drawn.[1]

Table 55: Patient and disease characteristics by bridging therapy (with or without inotuzumab) (Cohort IIA, infused set)

	Bridging with inotuzumab (N-17)	Bridging without inotuzumab (N=71)	No bridging (N=6)	Total (N=94)
Median number of prior lines of therapy	[redacted]	[redacted]	[redacted]	2
Number of prior lines of therapy categorised - n (%)				
1	[redacted]	[redacted]	[redacted]	29 (30.9)
2	[redacted]	[redacted]	[redacted]	36 (38.3)
3	[redacted]	[redacted]	[redacted]	17 (18.1)
≥4	[redacted]	[redacted]	[redacted]	12. (12.8)
R/R status - n (%)				
Refractory to all prior lines of anticancer therapy	[redacted]	[redacted]	[redacted]	12. (12.8)
Refractory to first-line therapy	[redacted]	[redacted]	[redacted]	24 (25.5)
Refractory to last prior line of therapy	[redacted]	[redacted]	[redacted]	51 (54.3)
Relapsed to first-line therapy within 12. months	[redacted]	[redacted]	[redacted]	41 (43.6)
Previous therapy - n (%)				
Allo-SCT	[redacted]	[redacted]	[redacted]	3.6 (38.3)
Blinatumomab	[redacted]	[redacted]	[redacted]	3.3 (35.1)
Inotuzumab	[redacted]	[redacted]	[redacted]	30 (31.9)
Blinatumomab and inotuzumab	[redacted]	[redacted]	[redacted]	15 (16.0)
Blinatumomab or inotuzumab	[redacted]	[redacted]	[redacted]	48 (51.1)
Bone marrow blasts (%) by morphology prior to enrolment				
Median	[redacted]	[redacted]	[redacted]	58.9
>75%	[redacted]	[redacted]	[redacted]	34 (36.2)

20% ≤75%	[redacted]	[redacted]	[redacted]	3.2 (34.0)
≥5% ≤20%	[redacted]	[redacted]	[redacted]	28 (29.8)
< 5%	[redacted]	[redacted]	[redacted]	0
Extramedullary disease status prior to enrolment - n (%)				
Absent	[redacted]	[redacted]	[redacted]	75 (79.8)
Present	[redacted]	[redacted]	[redacted]	19 (20.2)
Philadelphia chromosome-positive	[redacted]	[redacted]	[redacted]	25 (26.6)
ECOG score - n (%)				
0	[redacted]	[redacted]	[redacted]	3.5 (37.2)
1	[redacted]	[redacted]	[redacted]	58 (61.7)
Missing	[redacted]	[redacted]	[redacted]	1

ECOG – Eastern Cooperative Oncology Group; R/R – relapsed/refractory; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Table 56: Overall response with disease assessment by IRRC by bridging therapy (with or without inotuzumab) (Cohort IIA, infused set)

	Bridging with inotuzumab (N=17)	Bridging without inotuzumab (N=71)	No bridging (N=6)	Total (N=94)
BOR, n (%)				
CR	[redacted]	[redacted]	[redacted]	52 (55.3)
CRi	[redacted]	[redacted]	[redacted]	20 (21.3)
ORR (CR or CRi)				
n (%)	[redacted]	[redacted]	[redacted]	72 (76.6)
95% CI	[redacted]	[redacted]	[redacted]	66.7, 84.7
CR rate				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
EFS				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]		[redacted]
OS				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]		[redacted]

BOR – best overall response; CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematologic recovery; EFS – event-free survival; IRRC – Independent Response Review Committee; NE – not estimable; OS – overall survival
Source: Autolus, Data on file[1]

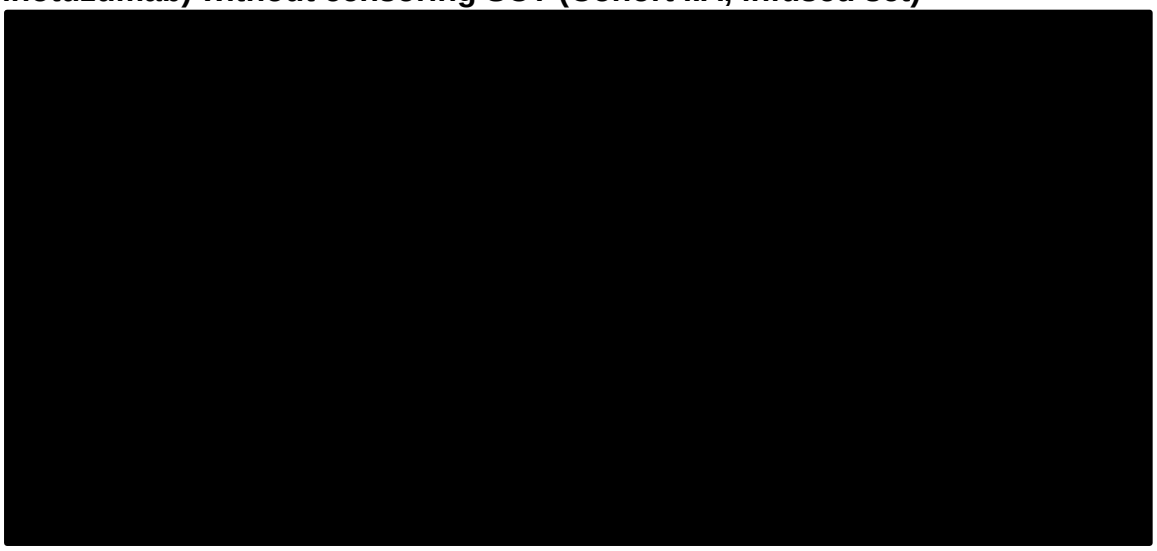
Figure 17: Kaplan-Meier plot of DOR by IRRC by bridging therapy (with or without inotuzumab) censoring new non-protocol anticancer therapies including SCT (Cohort IIA, infused set)

DOR – duration of response; IRRC – Independent Response Review Committee; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Figure 18: Kaplan-Meier plot of EFS by IRRC by bridging therapy (with or without inotuzumab) censoring new non-protocol anticancer therapies including SCT (Cohort IIA, infused set)

EFS – event-free survival; IRRC – Independent Response Review Committee; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Figure 19: Kaplan-Meier plot of OS by bridging therapy (with or without inotuzumab) without censoring SCT (Cohort IIA, infused set)



IRRC – Independent Response Review Committee; OS – overall survival; SCT – stem cell transplant
Source: Autolus, Data on file[1]

A16. The FELIX protocol mentions assessing the CD19 expression levels at different time points. Please report the changes in CD19 expression levels from the enrolment date to 24 months or preferably, the latest available data cutoff.

CD19 status prior to enrolment (by flow cytometry) was positive in all infused patients in all cohorts.[9] Of the 112 enrolled patients in Cohort IIA, [redacted] patient ([redacted]) had a mixed positive + negative status.[9]

Time of B-cell recovery, defined as the days between the first obe-cel infusion and the first time at which ≥20 cells/uL in CD19 positive cells in lymphocytes in blood is achieved, is presented in Figure 20, for Cohort IA and IIA.

At the February 2024 data cut-off, of the [redacted] infused patients in Cohort IA, [redacted] ([redacted]%) achieved B-cell recovery. A total of [redacted] patients ([redacted]%) had been censored:[9]

- [redacted] patients ([redacted]%) due to ongoing B-cell aplasia
- [redacted] patients ([redacted]%) died
- [redacted] patients ([redacted]%) due to no evaluable results post infusion

At the February 2024 data cut-off, of the 94 infused patients in Cohort IIA, [redacted] ([redacted]%) achieved B-cell recovery. A total of [redacted] patients ([redacted]%) had been censored:

- [redacted] patients ([redacted]%) due to ongoing B-cell aplasia
- [redacted] patients ([redacted]%) died
- [redacted] patients ([redacted]%) received SCT
- [redacted] patients ([redacted]%) due to no evaluable results post infusion
- [redacted] patients ([redacted]%) withdrew consent

Figure 20: Kaplan-Meier analysis of time of B-cell recovery pooled Cohort IA and IIA (infused set)

[redacted]

Source: Autolus, Data on file[9]

A17. Protocol doc, page 71.

"[redacted]" Please provide the CD19 expression data cutoff for patients at the screening level for inclusion.

CD19 positivity was based on local assessment (and therefore the cut-off is not available).

A18. Table 14.1.1.1.1 of FELIX CSR document reports that some patients were not infused due to manufacturing-related issues. Please clarify the reasons behind the issues mentioned.

[redacted] patients did not receive obe-cel due to manufacturing-related issues. The reasons for these manufacturing issues are presented in Table 57 below.[7]

Table 57: Manufacturing-related issues associated with no infusion

Manufacturing-related issue(s)	Number of patients
Low potency	[redacted]
Low dose	[redacted]
Batch terminated due to low T cells	[redacted]
Leukapheresis sterility and low T cells	[redacted]
Sterility	[redacted]

Source: Autolus, data on file[7]

A19. PRIORITY QUESTION: For all patients who enrolled but were not infused within cohorts IA and IAA, please provide details on their treatment journey and health outcomes. (treatments received, duration of therapy, EFS, OS outcomes).

Table 58 presents the treatment journey and outcomes of the patients in Cohort IA and IIA who were enrolled but not infused, based on the February 2024 data cut-off. The Company would like to caveat that these data were not systematically collected and should be interpreted with caution. While the survival outcomes are reliable, the dataset of received treatments is incomplete. The Company apologises for this.

The vast majority of the patients experienced notably short EFS and OS. The median EFS and OS was [redacted] and [redacted] months, respectively in Cohort IA. In Cohort IIA, the EFS and OS was [redacted] and [redacted] months.[1]

Of the [redacted] patients in Cohort IA, [redacted] were alive at the cut-off. [redacted] patients were ongoing without an event, [redacted] patients had experienced treatment failure and [redacted] had died due to other reasons than the underlying cancer. Of the [redacted] patients in Cohort IIA, [redacted] patients were alive at the cut-off. [redacted] patient was ongoing without an event, [redacted] patients had experienced treatment failure and [redacted] died due to other reasons than the underlying cancer.[1]

Table 58: Survival outcomes and treatments in patients who were enrolled but not infused (Cohorts IA and IIA)

	Cohort IA	Cohort IIA
N	[redacted]	[redacted]
Event description		
Ongoing without event	[redacted]	[redacted]
Treatment failure	[redacted]	[redacted]
Death due to reason other than underlying cancer	[redacted]	[redacted]
Survival (months)		
EFS	[redacted]	[redacted]
OS	[redacted]	[redacted]
Bridging therapies (n)		
Bosutinib	[redacted]	[redacted]
Clofarabine	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Cytarabine	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]
Fludarabine	[redacted]	[redacted]
Hydrocortisone	[redacted]	[redacted]
Hydroxycarbamide	[redacted]	[redacted]
Idarubicin	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]
Inotuzumab ozogamicin	[redacted]	[redacted]
Mercaptopurine	[redacted]	[redacted]
Mesna	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]
Pegfilgrastim	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]
Vincristine	[redacted]	[redacted]
Post anticancer therapies (n)		
Bosutinib	[redacted]	[redacted]
CAR T cells nos	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Fludarabine	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]

CAR – chimeric antigen receptor; EFS – event-free survival; OS – overall survival
Source: Autolus Data on file[1]

A20. Please confirm characteristics listed in B2.9.3.1 are included in every ITC conducted. If not, please state clearly which characteristics were used in each ITC.

Table 59 provides an overview of the availability of baseline characteristics reported for each comparator. Where baseline characteristics were not reported for comparators, they could not be included in the analyses. Aside from this, the ITCs were conducted using all categories presented in the table for all comparators, except for the comparison to inotuzumab which categorised 1 vs ≥2 prior lines of therapy.

Table 59: Overview of baseline characteristics used in ITCs

		FELIX (Cohort IIA, mITT)[5]	INO-VATE (inotuzumab arm)[2]	TOWER (blinatumomab arm)[3]	PACE (Ph+ ALL arm)[4]
Study size, N		94	164	271	32
Primary refractory, %		✓	X	✓	X
BM blasts at screening, % <50%		✓	✓	✓	X
Prior lines of therapy, %	1	✓	✓	✓	✓
	2	✓	✓	✓	✓
	≥3	✓	X	✓	✓
Extramedullary disease prior to lymphodepletion, %		✓	X	X	X
1st remission ≤12m, no. %		✓	✓	✓	X
Ph chromosome, % Ph+		✓	✓	✓	✓
Age at baseline, Median (SD) years		✓	✓	✓	✓
Bridging chemotherapy, %		✓	X	X	X
Race, %	White	✓	✓	✓	✓
	Non-White	✓	✓	✓	✓
Prior SCT, %		✓	✓	✓	✓
	0	✓	✓	✓	✓

		FELIX (Cohort IIA, mITT)[5]	INO-VATE (inotuzumab arm)[2]	TOWER (blinatumomab arm)[3]	PACE (Ph+ ALL arm)[4]
ECOG status, %	1 or 2	✓	✓	✓	✓
Sex, Male, %		✓	✓	✓	✓

BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; MAIC – matching adjusted indirect comparison; NICE – National Institute of Health and Care Excellence; Ph – Philadelphia chromosome; SCT – stem cell transplant; TEM – Treatment effect modifier

Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

A21. Doc B, Table 7. Please report relapse-free survival from day 1 infusion to the February 2024 data cutoff. Additionally, please list the relapses that have occurred and their frequency during the ALLCAR19 and FELIX trials.

The Company would like to clarify that relapse-free survival (RFS) was removed as an outcome of the FELIX clinical trial following regulatory feedback (US Food and Drugs Administration [FDA] in 2022). The change was applied in October 2022, prior to the pre-specified interim analysis being performed. Therefore, it is not possible to report RFS here.[7]

At the latest FELIX data cut-off (February 2024), [redacted]/94 ([redacted]%) patients had relapsed, and in the ALLCAR19 trial, [redacted] relapses occurred.[9]

A22. Given that FELIX is an ongoing trial, when are future data-cuts anticipated to be available?

There are no planned data cut-offs that will be available within the timeframe of this appraisal. The February 2024 is the latest available data cut-off for the FELIX clinical trial. There is a planned data cut-off to be available in approximately [redacted]

A23. Section B.2.6.2. the company compares data from their trial to the Phase I ALLCAR19 study (Rhoddie et al., 2023) and asserts that Obe-cel remains efficacious in the longer term (Document A, section A.9). Could you provide a summary of the findings from the Phase I ALLCAR19 study and explain how these findings are consistent with the results of the FELIX trial?

As outlined in Section B.2.2.2 in the CS, ALLCAR19 is an ongoing phase I, open-label, multicentre study evaluating the safety and efficacy of obe-cel in 20 patients with R/R B-ALL. The primary endpoints were the safety and feasibility of CAR T-cell manufacturing, while secondary endpoints included CAR T-cell persistence, incidence and duration of B-cell aplasia and hypogammaglobulinemia, EFS and OS at 1 and 2 years.[10]

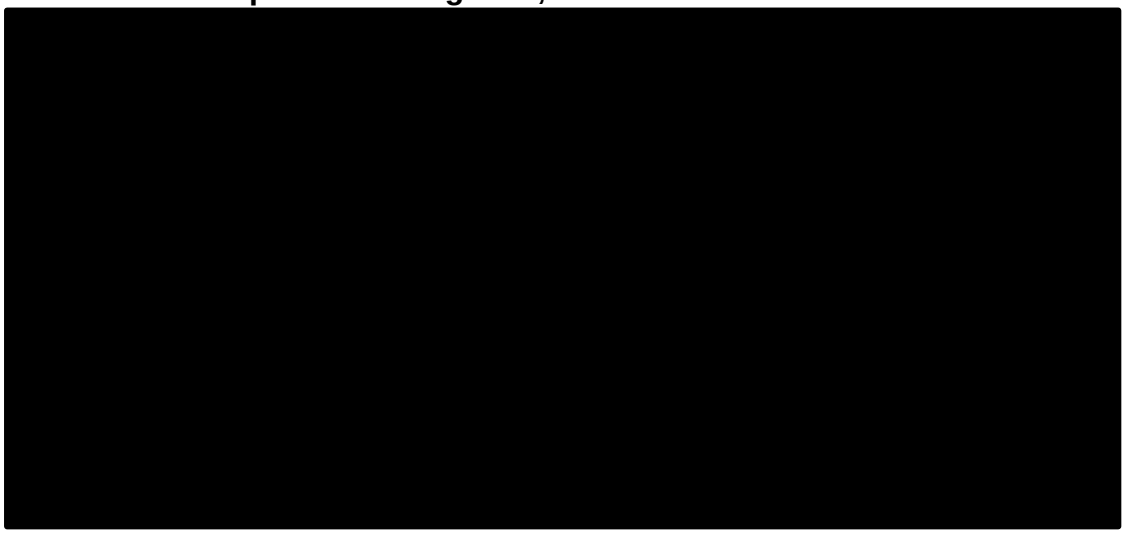
ALLCAR19 results for infused patients indicate that obe-cel was well tolerated, with no patients experiencing grade ≥3 CRS and 15% (3/20) experiencing ICANS, which was resolved to grade ≤1 within 24-72 hours with corticosteroids.[10] MRD-negative CR was achieved in 85% (17/20) and 70% (14/20) of patients at Month 1 and Month

3, respectively.[10] EFS at 6, 12, and 24 months was 68.3%, 48.3%, and 48.3% by morphologic relapse criteria, respectively; and 68.8%, 43.6%, and 43.6% by MRD relapse criteria.[10] OS at 6, 12, and 24 months was 69.1%, 63.8%, and 58%, respectively. OS and EFS were not significantly different between patients with and without previous allo-SCT.[10]

These results are consistent with the findings of FELIX presented in Section B.2 in the CS, with only three and nine patients experiencing ≥ grade 3 CRS (2.4%) and ICANS (7.1%), respectively. MRD-negative CR was achieved in [redacted] of patients in Cohort IIA of FELIX at the time of the February 2024 data cut-off (median follow-up 20.25 months), which closely align with the results of ALLCAR19. The EFS at Month 6 and 12 by morphological relapse criteria was [redacted] and [redacted], respectively, in FELIX Cohort IIA which further supports alignment with ALLCAR19. Similarly, OS at Month 6 and 12 in Cohort IIA was [redacted] and [redacted], respectively.

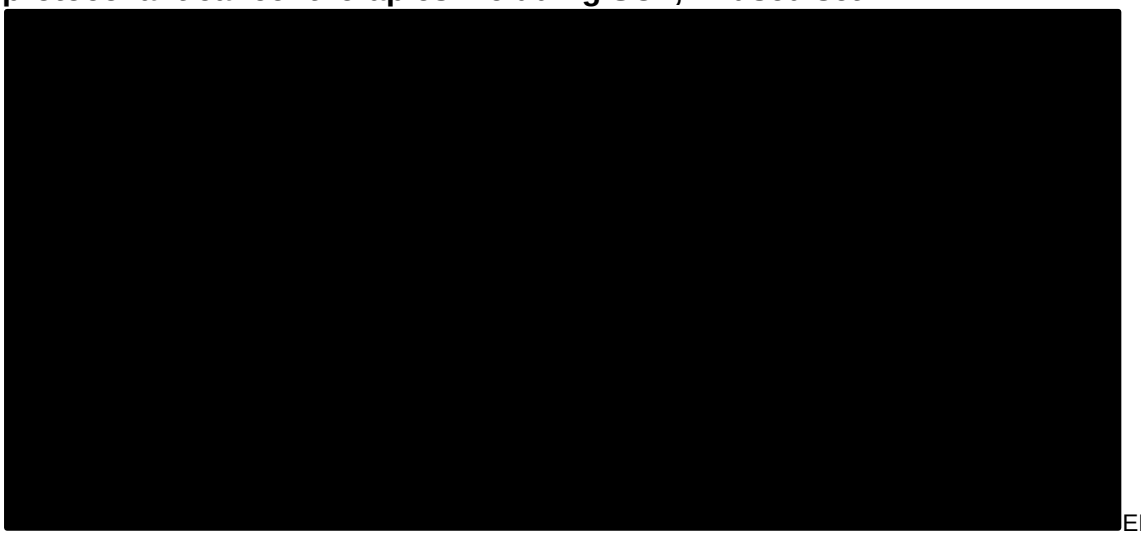
DOR, EFS and OS results from an ad-hoc November 2024 data cut-off for ALLCAR19 recently became available and are presented in Figure 21, Figure 22 and Figure 23, indicating a clear and sustained plateau for all endpoints. The strong alignment of results between FELIX Cohort IIA and ALLCAR19 at all timepoints as demonstrated above supports that obe-cel remains efficacious in the longer-term.

Figure 21: Ad-hoc Kaplan-Meier plot of DOR - censoring new non-protocol anticancer therapies including SCT, infused set



DOR – duration of response; SCT – stem cell transplant
Source: Autolus. Data on file (2024)[1]

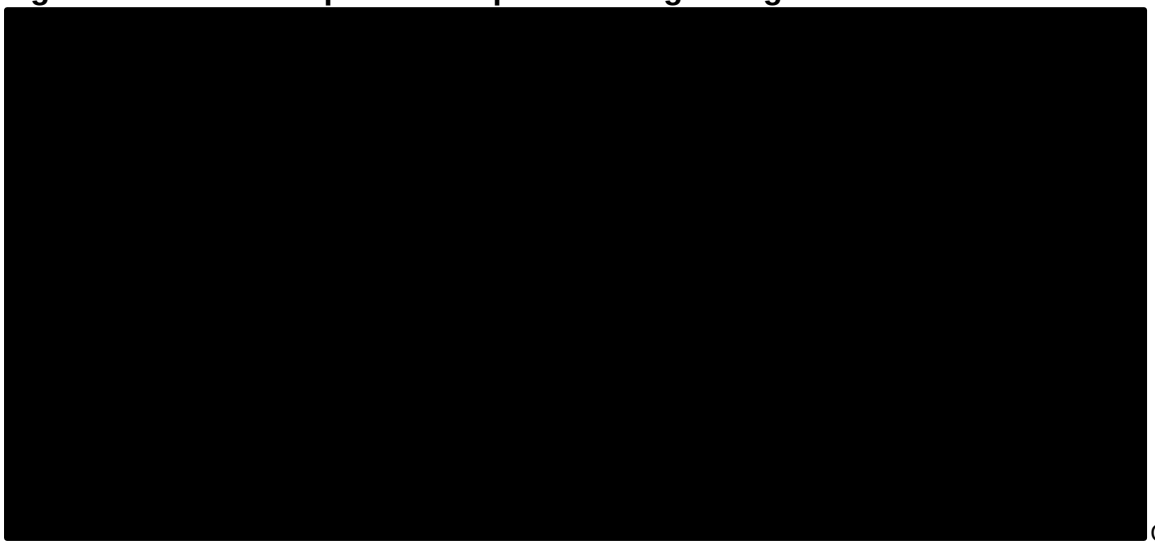
Figure 22: Ad-hoc Kaplan-Meier plot of EFS by IRRC - censoring new non-protocol anticancer therapies including SCT, infused set



EFS – event-free survival; IRRC – Independent Response Review Committee; SCT – stem cell transplant

Source: Autolus. Data on file (2024)[1]

Figure 23: Ad-hoc Kaplan-Meier plot of OS ignoring SCT - infused set



OS – overall survival; SCT – stem cell transplant

Source: Autolus. Data on file (2024)[1]

A24. Section B.2.7.1.2, Table 18. Please report the baseline characteristics for patients under 25 years in the mITT, ITT, and UK populations.

The baseline and disease characteristics of patients under 25 years in the mITT, ITT and UK populations are reported in Table 60 and Table 61, respectively.[1]

Table 60: Baseline characteristics of patients under 25 years

Demographic		ITT population, Cohort IIA (n=13)	mITT population, Cohort IIA (n=11)	mITT, UK population, Cohort IIA (n=1)
Age (years)	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
Sex, male – n (%)		[redacted]	[redacted]	[redacted]
Race – n (%)	Asian	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]
	White	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]
Country – n (%)	United Kingdom	[redacted]	[redacted]	[redacted]

ITT – intention to treat; mITT – modified intention to treat; SD – standard deviation; UK – United Kingdom
Source: Autolus, Data on file[1]

Table 61: Disease characteristics of patients under 25 years

Disease characteristic		ITT population, Cohort IIA (n=13)	mITT population, Cohort IIA (n=11)	mITT, UK population, Cohort IIA (n=1)
Number of prior lines of therapy – n (%)	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]
	≥4	[redacted]	[redacted]	[redacted]
Refractory to all prior lines of anticancer therapy – n (%)		[redacted]	[redacted]	[redacted]
Refractory to first-line therapy – n (%)		[redacted]	[redacted]	[redacted]
Refractory to last prior line of therapy – n (%)		[redacted]	[redacted]	[redacted]
Relapsed to first-line therapy within 12 months – n (%)		[redacted]	[redacted]	[redacted]
Previous blinatumomab – n (%)		[redacted]	[redacted]	[redacted]
Previous inotuzumab – n (%)		[redacted]	[redacted]	[redacted]
Previous blinatumomab and inotuzumab – n (%)		[redacted]	[redacted]	[redacted]
Previous blinatumomab or inotuzumab – n (%)		[redacted]	[redacted]	[redacted]
Previous allogenic SCT – n (%)		[redacted]	[redacted]	[redacted]
Disease status at screening				
BM blasts (%) by morphology prior to enrolment (median)		[redacted]	[redacted]	[redacted]
BM blasts by morphology prior to enrolment categorised – n (%)	>75%	[redacted]	[redacted]	[redacted]
	>20% to ≤75%	[redacted]	[redacted]	[redacted]
	≥5% to ≤20%	[redacted]	[redacted]	[redacted]
	<5%	[redacted]	[redacted]	[redacted]
EMD status prior to enrolment – n (%)	Absent	[redacted]	[redacted]	[redacted]
	Present	[redacted]	[redacted]	[redacted]
ECOG score – n (%)	0	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]
	≥2	[redacted]	[redacted]	[redacted]
CD19 status at screening – n (%)	Positive	[redacted]	[redacted]	[redacted]
	Negative	[redacted]	[redacted]	[redacted]
	Mixed population (positive+negative)	[redacted]	[redacted]	[redacted]
CNS disease history – n (%)	CNS1	[redacted]	[redacted]	[redacted]
	CNS2	[redacted]	[redacted]	[redacted]
	CNS3	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]

BM – bone marrow; CD – cluster of differentiation; CNS – central nervous system; ECOG – Eastern Cooperative Oncology Group; EMD – extramedullary disease; ITT – intention to treat; mITT – modified intention to treat; SCT – stem cell transplant; SD – standard deviation; UK – United Kingdom
Source: Autolus, Data on file[1]

A25. CSR Table 3, please explain how there were more people achieving CR in the enrolled cohort than there were in the infused cohort, despite no difference in the number achieving any response.

[redacted] patients included in the enrolled and the infused set achieved CR whilst receiving bridging therapy waiting for obe-cel to be manufactured (Table 62). Following obe-cel infusion, all these [redacted] patients achieved a BOR of CRi. Overall, these [redacted] patients were included in the enrolled set and achieved BOR of CR after enrolment (N=55). However, post obe-cel infusion, BOR achieved for these patients was CRi, and therefore they were not included in the infused set for the CR parameter calculation (N=52).[1]

Table 62: ORR by IRRC

Parameter	Infused set (N=94)	Enrolled set (N=112)
ORR (CR or CRi)	72 (76.6)	72 (64.3)
CR	52 (55.3)	[redacted]
CRi	20 (44.7)	[redacted]

CR – complete remission; CRi – complete remission with incomplete haematologic recovery; IRRC – Independent Response Review Committee; ORR – overall remission rate
Source: Autolus, Data on file[7]

A26. Doc B, Table 24: Please provide definitions for the classification for neutropenia, neutrophil count decreased, thrombocytopenia and platelet cells decreased.

The severity of AEs (including neutropenia, neutrophil count decreased, thrombocytopenia and platelet cells decreased) is assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0.[11] While neutropenia/neutrophil count decreased and thrombocytopenia/platelet cells decreased were reported as separate events by sites, these terms are equivalent. Neutropenia/neutrophil count decreased is defined as "A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen" and Thrombocytopenia/platelet cells decreased is defined as "A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen" (NCI CTCAE V5.0).[11]

A27. CSR section 3.1.4.3: The company has referenced observed cytopenia as part of lymphodepletion therapy. Please report the total percentages of

cytopenia, mean, median, and CI over time from screening to the latest follow-up.

The percentages of patients with neutrophil count decreased (neutropenia), platelet count decreased (thrombocytopenia) and haemoglobin decreased (anaemia) are reported in Table 63. A [redacted] proportion of patients experienced early cytopenia, which is expected and typically attributed to lymphodepletion therapy.[7]

Table 63: Observed cytopenia in terms of neutrophil count, platelet count and haemoglobin decreased over time from screening to the latest follow-up, safety set (n=127)

	Prior to enrolment *	Prior to lympho-depletion	After lympho-depletion and prior obe-cel infusion	30 days post obe-cel infusion	June 2023 data cut-off	February 2024 data cut-off
Neutrophil count decreased ≥ grade 3 – n (%)	[redacted]					
Platelet count decreased ≥ grade 3 – n (%)	[redacted]					
Haemoglobin decreased ≥ grade 3 – n (%)	[redacted]					
Neutrophil/ platelet/ haemoglobin decreased ≥ grade 3 – n (%)	[redacted]					

*"Prior to enrolment" was defined as the last available measurement prior to enrolment.
NR – not reported
Source: Autolus, Data on file[7]

Due to limited data availability, neutrophil, platelet and haemoglobin count for patients in the safety set has also been included from prior to enrolment to Month 36 (Table 64).

Table 64: Neutrophil, platelet and haemoglobin count over time of patients in the safety set (n=127)

	Neutrophil count (10^9/L)			Platelet count (10^9/L)			Haemoglobin (g/L)		
	N	Mean (SD)	Median	N	Mean (SD)	Median	N	Mean (SD)	Median
Prior to enrolment	[redacted]								
Prior to pre-conditioning	[redacted]								
Baseline	[redacted]								
Day 28	[redacted]								
Month 3	[redacted]								
Month 6	[redacted]								
Month 12	[redacted]								
Month 18	[redacted]								
Month 24	[redacted]								
Month 36	[redacted]								

g – gram; L – litre; SD – standard deviation
Source: Autolus, Data on file[7]

A28. Please provide the baseline characteristics for FELIX split by Ph chromosome expression (Ph+ and Ph-).

The baseline characteristics for the FELIX enrolled trial population split by Ph- and Ph+ chromosome are presented in Table 65 and Table 66 below.[1]

Table 65: Demographics in the FELIX clinical trial

Demographic		**Ph- chromosome (n=91)**	**Ph+ chromosome (n=36)**
Age (years)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
Age (years) categorised – n (%)	≥18 to ≤ 25	[redacted]	[redacted]
	>25 to < 40	[redacted]	[redacted]
	≥40 to < 65	[redacted]	[redacted]
	≥65	[redacted]	[redacted]
Sex, male – n (%)		[redacted]	[redacted]
Race – n (%)	Asian	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]
	White	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]
Country – n (%)	United States	[redacted]	[redacted]
	United Kingdom	[redacted]	[redacted]
	Spain	[redacted]	[redacted]

mITT – modified intention to treat; Ph – Philadelphia chromosome; SD – standard deviation
Source: Autolus, Data on file[1]

Table 66: Disease characteristics in the FELIX clinical trial

Disease characteristic		Ph- chromosome (n=91)	Ph+ chromosome (n=36)
Number of prior lines of therapy – n (%)	1	[redacted]	[redacted]
	2	[redacted]	[redacted]
	3	[redacted]	[redacted]
	≥4	[redacted]	[redacted]
Refractory to all prior lines of anticancer therapy – n (%)		[redacted]	[redacted]
Refractory to first-line therapy – n (%)		[redacted]	[redacted]
Refractory to last prior line of therapy – n (%)		[redacted]	[redacted]
Relapsed to first-line therapy within 12 months – n (%)		[redacted]	[redacted]
Previous blinatumomab – n (%)		[redacted]	[redacted]
Previous inotuzumab – n (%)		[redacted]	[redacted]
Previous blinatumomab and inotuzumab – n (%)		[redacted]	[redacted]
Previous blinatumomab or inotuzumab – n (%)		[redacted]	[redacted]
Previous allogenic SCT – n (%)		[redacted]	[redacted]
Disease status at screening			
BM blasts (%) by morphology prior to enrolment (median)		[redacted]	[redacted]
BM blasts by morphology prior to enrolment categorised – n (%)	>75%	[redacted]	[redacted]
	>20% to ≤75%	[redacted]	[redacted]
	≥5% to ≤20%	[redacted]	[redacted]
	<5%	[redacted]	[redacted]
EMD status prior to enrolment – n (%)	Absent	[redacted]	[redacted]
	Present	[redacted]	[redacted]
ECOG score – n (%)	0	[redacted]	[redacted]
	1	[redacted]	[redacted]
	≥2	[redacted]	[redacted]
	Missing	[redacted]	[redacted]
CD19 status at screening – n (%)	Positive	[redacted]	[redacted]
	Negative	[redacted]	[redacted]
	Mixed population (positive+negative)	[redacted]	[redacted]
CNS disease history – n (%)	CNS1	[redacted]	[redacted]
	CNS2	[redacted]	[redacted]
	CNS3	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]

BM – bone marrow; CD – cluster of differentiation; CNS – central nervous system; ECOG – Eastern Cooperative Oncology Group; EMD – extramedullary disease; mITT – modified intent-to-treat; Ph – Philadelphia chromosome; SCT – stem cell transplant. Source: Autolus, Data on file[1]

A29. PRIORITY QUESTION: The current reporting of the indirect treatment comparisons is unsatisfactory.
INPUT: Please present a table comparing the prognostic and effect modifiers (as reported in CS document B page 80) for the studies included in the ITC, by treatment group where appropriate and include all arms from the studies. Also include study design features such as follow-up length, timepoints analysed, outcome definitions.

METHOD: Present how the ESS is affected after the inclusion of each TEM for adjustment, How were missing data handled in the MAIC? Present a table of covariate balance after trimming and before and after matching the FELIX study to each relevant comparator study. Please confirm that inverse MAIC refers to inversing the output only, and no change to the underlying estimation of weights.

RESULTS: Please provide comprehensive results including Kaplan-Meier plots, risk tables, and confidence intervals around effect estimates. Please compare PFS from FELIX to PFS of other studies if they do not report EFS, and also present all possible outcomes (e.g. ORR, CR, DOR). Where comparator trials include multiple arms, please conduct the indirect comparison against all arms and present results to support validation of the analysis.

As discussed in the EAG clarification call on the 2nd December 2024, the additional comparators are of lower priority and has therefore not been provided as part of this response, in order to meet the timelines.

PFs and TEMs for patients in the ITT populations of FELIX and comparator trials are presented in Table 67 (PFs and TEMs for appropriate Ph subgroups are provided in Table 70 and Table 71). PFs and TEMs are generally well-balanced between FELIX and comparator trials, with some notable differences: ECOG, bone marrow blast at lymphodepletion, and prior lines of therapy. Additionally, not all PFs and TEMs are reported across all trials with poor reporting of several factors for PACE.[4]

Table 67: Prognostic factors and treatment effect modifiers for intervention and comparator trials

		FELIX (Cohort IIA, mITT)[5]	INO-VATE (treatment arm)[2]	TOWER (treatment arm)[3]	PACE (Ph+ ALL arm)[4]
Study size, N		94	164	271	32
Primary refractory, %		[redacted]	NR	42.4	NR
BM blasts at screening, % <50%		[redacted]	32.3	25.5	NR
Prior lines of therapy, %	**1**	[redacted]	67.7*	42.1**	19.0
	2	[redacted]	32.3*	33.6**	44.0
	3	[redacted]	0.0*	16.6**	≥3: 37.0
	≥4	[redacted]	0.0*	7.8**	
1st remission ≤12m, no. %		[redacted]	58.5	28.0	NR
Ph chromosome, % Ph+		[redacted]	13.0	0.0	100
Age at baseline, Median (SD) years		[redacted]	46.5 (15)	40.8 (17.1)	62.0 (15)
Race, %	**White**	[redacted]	68.3	84.1	81.3
	Asian	[redacted]	18.9	7.0	16.7
	Black	[redacted]	2.4	1.8	2.1
	Other	[redacted]	10.4	7.0	0.0
Prior SCT, %		[redacted]	17.7	34.7	23
ECOG status, %		[redacted]	0: 37.8 1: 49.4 2: 12.8	0: 35.5 1: 49.4 2: 15.1	0: 31.9 1: 42.6 2: 25.5
Sex, Male, %		[redacted]	55.5	59.8	62.0

*Prior induction therapy; ** Salvage-treatment phase

BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; NR – not reported; Ph – Philadelphia; SCT – stem cell transplant; SD – standard deviation

Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

A summary of the study design in FELIX and comparator trials is presented in Table 68. The study design was generally consistent across trials, however FELIX was a phase 1b/2 single arm trial. As the MAICs are unanchored, these differences were not expected to bias results. Differences also exist in follow-up period between trials.

Table 68: Comparison of study design

	FELIX (Cohort IIA)[7]	INO-VATE (treatment arm)[2]	TOWER (treatment arm)[3]	PACE (Ph+ ALL)[4]
Intervention	Obe-cel	Inotuzumab	Blinatumomab	Ponatinib
Study design	• Phase 1b/2 • Open-label • Single arm	• Phase 3 • Open-label • Controlled	• Phase 3 • Open-label • Controlled	• Phase 2 • Open-label • Single arm
Study duration	62 months March 2020 – May 2025	53 months August 2012 – January 2017	38 months January 2014 – March 2017	100 months September 2010 – January 2019

Follow-up, median (range) [IQR]	11.8 months (0–22.1) at February 7, 2024 data cut-off	29.6 months (1.7-49.7)	11.7 months	5.4 months (0.1–59.6)
EFS outcome definition	The time from the first obe-cel infusion to the earliest of the following events: treatment failure, morphological relapse, or death due to any cause.	Progression-free survival (PFS) defined as time from date of randomization to earliest date of the following events: death, progressive disease (objective progression, relapse from CR/CRi or treatment discontinuation due to global deterioration of health status) and starting new induction therapy or post-therapy SCT without achieving CR/CRi.	Time from randomization until relapse after achieving a complete remission with full, partial, or incomplete haematologic recovery within 12 weeks after initiation with treatment, or death.	PFS defined as the interval from the first dose of study treatment until the criteria for progression or death are met.
OS outcome definition	Calculated from the date of first obe-cel infusion to the date of death. Patients still alive were censored at the date of last contact.	The time from randomization to death due to any cause.	Time from randomization to death from any cause.	The interval from the first dose of study treatment until death.

ALL – acute lymphoblastic leukaemia; CR – complete remission; CRi – complete remission with incomplete haematalogic response; EFS – event-free survival; IQR – interquartile range; OS - overall survival; PFS – progression-free survival; Ph – Philadelphia chromosome

Source: Autolus. Clinical Study Protocol: FELIX. (2023)[7]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

Covariate balance for obe-cel before and after matching to inotuzumab, blinatumomab, and ponatinib are presented in Table 69, Table 70, and Table 71, respectively. Covariates are well-balanced for all comparisons after matching.

Table 69: Covariates before and after matching to inotuzumab (Cohort IIA)

	Obe-cel ITT (unweighted)[5]	Inotuzumab[2]	Obe-cel matched to inotuzumab
N	94.00	164.00	[redacted]
Age	[redacted]	46.50	46.50
Sex (male), %	[redacted]	55.49	55.49
ECOG: 0*, %	[redacted]	37.80	37.80
ECOG: 1 or 2, %	[redacted]	62.20	62.20
Previous lines of therapy: 1, %	[redacted]	67.68	67.68
Previous lines of therapy: 2*, %	[redacted]	32.32	32.32
Race: White, %	[redacted]	68.29	68.29
Prior SCT, %	[redacted]	17.68	17.68
Duration of remission <12 months, %	[redacted]	58.54	58.54
BM blasts <50%, %	[redacted]	32.32	32.32
Ph+, %	[redacted]	13.41	13.41

*Treated as baseline.
BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; ITT – intention to treat; Ph – Philadelphia chromosome; SCT – stem cell transplant
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2019)[2]

Table 70: Covariates before and after matching to blinatumomab (Cohort IIA)

	Obe-cel (Ph-)[5]	Blinatumomab[3]	Obe-cel matched to blinatumomab
N	[redacted]	271.00	[redacted]
Age	[redacted]	40.80	40.80
Sex (male), %	[redacted]	59.78	59.78
ECOG: 0*, %	[redacted]	35.50	35.50
ECOG: 1 or 2, %	[redacted]	64.50	64.50
Previous lines of therapy: 1, %	[redacted]	42.07	42.07
Previous lines of therapy: 2, %	[redacted]	33.58	33.58
Previous lines of therapy: ≥3*, %	[redacted]	24.35	24.35
Race: White, %	[redacted]	84.13	84.13
Prior SCT, %	[redacted]	34.69	34.69

Duration of remission <12 months, %	[redacted]	28.00	28.00
BM blasts <50%, %	[redacted]	25.46	25.46
Primary refractory, %	[redacted]	42.44	42.44

*Treated as baseline.
BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; Ph – Philadelphia chromosome; SCT – stem cell transplant
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]

Table 71: Covariates before and after matching to ponatinib (Cohort IIA)

	Obe-cel (Ph+)[5]	**Ponatinib**[4]	**Obe-cel matched to ponatinib**
N	[redacted]	32.00	[redacted]
Age	[redacted]	62.00	62.00
Sex (male), %	[redacted]	62.50	62.50
ECOG: 0*, %	[redacted]	31.9	31.9
ECOG: 1 or 2, %	[redacted]	68.10	68.10
Previous lines of therapy: 1, %	[redacted]	19.00	19.00
Previous lines of therapy: 2, %	[redacted]	44.00	44.00
Previous lines of therapy: ≥3*, %	[redacted]	37.00	37.00
Race: White, %	[redacted]	81.30	81.30
Prior SCT, %	[redacted]	23.00	23.00

*Treated as baseline.
ECOG – Eastern Cooperative Oncology Group; Ph – Philadelphia chromosome; SCT – stem cell transplant
Source: Autolus. Data on file (2024)[5]; Cortes et al. (2018)[4]

Methods

The Company confirms that the inverse MAIC approach used in the cost-effectiveness model (CEM) relates to the use of the inverse of the HR. The Company confirms this does not affect the methodology of the MAIC or underlying weight estimation. One missing value for ECOG was present in the data in the mITT 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.

The cumulative ESS for each of the comparisons by order of importance of TEM/PF are presented in Table 72, Table 73, and Table 74 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.[6]

Table 72: ESS combinations, obe-cel matched to inotuzumab, mITT

Covariate	ESS
BM blasts at screening	[redacted]
Prior lines of therapy	[redacted]
Duration of remission <12 months	[redacted]
Ph chromosome	[redacted]
Age	[redacted]
Race	[redacted]
Prior SCT	[redacted]
ECOG	[redacted]
Sex	[redacted]

BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; ESS – effective sample size; Ph – Philadelphia chromosome; SCT – stem cell transplant

Table 73: ESS combinations, obe-cel matched to blinatumomab, Ph-

Covariate	ESS
Primary refractory	[redacted]
BM blasts at screening	[redacted]
Prior lines of therapy	[redacted]
Duration of remission <12 months	[redacted]
Age	[redacted]
Race	[redacted]
Prior SCT	[redacted]
ECOG	[redacted]
Sex	[redacted]

BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; ESS – effective sample size; Ph – Philadelphia chromosome; SCT – stem cell transplant

Table 74: ESS combinations, obe-cel matched to ponatinib, Ph+

Covariate	ESS
Prior lines of therapy	[redacted]
Age	[redacted]
Race	[redacted]
Prior SCT	[redacted]
ECOG	[redacted]
Sex	[redacted]

ECOG – Eastern Cooperative Oncology Group; ESS – effective sample size; Ph – Philadelphia chromosome; SCT – stem cell transplant

EFS

EFS for FELIX versus comparator trials is presented in Table 75. The Company would like to clarify that the comparisons between FELIX and comparator studies in the original company submission used EFS outcomes assessed by local investigator. To align with the primary definition of EFS used in FELIX, the Company considers EFS as assessed by the Independent Response Review Committee (IRRC) preferable to use for the MAIC. Accordingly, the Company has re-ran the EFS analysis using IRRC outcomes, results of which are presented below alongside the investigator-assessed analysis presented in the CS. Results are consistent between both efficacy outcome criteria. The Company apologise that this was not conducted in the original CS or made clear in reporting.

To ensure consistency within the appraisal, the Company have updated the EFS survival analysis used within the CEM to use IRRC outcomes. Updated survival analysis and revised base case cost-effectiveness results are presented at the end of this document.

mITT

The estimated adjusted and unadjusted HRs for the mITT population were in favour of obe-cel compared to inotuzumab, and the unadjusted HR was statistically significant.

Ph-

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, and these differences were statistically significant.

Ph+

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.

Table 75: Event-free survival for FELIX versus comparator trials, infused patients

Population	Treatment	Median EFS	ESS	Unadjusted HR (95% CI)	Adjusted HR IRRC (95% CI)	Adjusted HR INV (95% CI)
mITT	Obe-cel	[redacted]	-	-	-	-
	Inotuzumab	5.0 months	44.14	[redacted]	[redacted]	[redacted]
Ph-	Blinatumomab	0.0 months†	40.99			
Ph+	Ponatinib	3.0 months	7.89			

*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; INV – investigator-assessed; IRRC – Independent Response Review Committee; mITT – modified intention to treat; Ph – Philadelphia chromosome
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

OS

OS for FELIX versus comparator trials is presented in Table 76.

mITT

The estimated adjusted and unadjusted HRs for the mITT population were in favour of obe-cel compared to inotuzumab, however only the unadjusted HR was statistically significant.

Ph-

The estimated adjusted and unadjusted HRs for the Ph- population were in favour of obe-cel compared to blinatumomab, and these differences were statistically significant.

Ph+

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.

Table 76: Overall survival for FELIX versus comparator trials, infused patients

Population	Treatment	Median OS	ESS	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
mITT	Obe-cel	[redacted]	-	-	-
	Inotuzumab	7.7 months	44.14	[redacted]	[redacted]

Ph-	Blinatumomab	7.7 months	40.99	[redacted]	[redacted]
Ph+	Ponatinib	8.0 months	7.89	[redacted]	[redacted]

*Statistically significant results. CI – confidence interval; ESS – effective sample size; HR – hazard ratio; mITT – modified intention to treat; OS – overall survival; Ph – Philadelphia chromosome
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

CR

CR for FELIX versus blinatumomab and ponatinib are presented in Table 77. All CR analyses and all subsequent binary outcomes are presented using IRRC assessment. Note, CR was not reported for INO-VATE.

Ph-

The estimated adjusted and unadjusted ORs for the Ph- population were in favour of obe-cel compared to blinatumomab, and these differences were statistically significant.

Ph+

The estimated adjusted and unadjusted ORs for the Ph+ population were in favour of obe-cel compared to ponatinib, and these differences were statistically significant.

Table 77: Complete remission for FELIX and comparator trials, infused patients

Population	**Treatment**	**Mean CR (%)**	**Obe-cel weighted mean CR (%)**	**ESS**	**Unadjusted OR**	**Adjusted OR**
mITT	Obe-cel	[redacted]	-	-	-	-
Ph-	Blinatumomab	0.34	[redacted]	[redacted]	[redacted]	[redacted]
Ph+	Ponatinib	0.41	[redacted]	[redacted]	[redacted]	[redacted]

*Statistically significant results. CI – confidence interval; CR – complete remission; ESS – effective sample size; mITT – modified intention to treat; OR – odds ratio; Ph – Philadelphia chromosome
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]; Cortes et al. (2018)[4]

CRi

CRi for FELIX versus blinatumomab is presented in Table 78.

Ph-

The estimated adjusted and unadjusted ORs for the Ph- population were in favour of obe-cel compared to blinatumomab, and these were statistically significant.

Ph+

CRi was not reported in PACE, so the comparison between obe-cel and ponatinib was not possible for CRi.

Table 78: Complete remission with incomplete haematologic response for FELIX versus comparator trials, infused patients

Population	Treatment	Mean CRi (%)	Obe-cel weighted mean CRi (%)	ESS	Unadjusted OR	Adjusted OR
mITT	Obe-cel	[redacted]	-	-	-	-
Ph-	Blinatumomab	0.01	[redacted]	[redacted]	[redacted]	[redacted]

*Statistically significant results. CI – confidence interval; CRi – complete remission with incomplete haematologic recovery; ESS - effective sample size; mITT – modified intention to treat; OR – odds ratio; Ph – Philadelphia chromosome

Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]

CR/Cri

CR/CRi for FELIX versus inotuzumab is presented in Table 79.

mITT

CR and CRi were not reported separately in INO-VATE, thus CR/CRi used in the comparison between FELIX and INO-VATE. The unadjusted OR was in favour of obe-cel compared to inotuzumab, while the adjusted OR was in favour of inotuzumab compared to obe-cel. Neither OR was statistically significant.

Table 79: Complete remission/Complete remission with incomplete haematologic recovery for FELIX versus INO-VATE, infused patients

Population	Treatment	Mean CR/CRi (%)	Obe-cel weighted mean CRi (%)	ESS	Unadjusted OR	Adjusted OR
mITT	Obe-cel	[redacted]	-	-	-	-

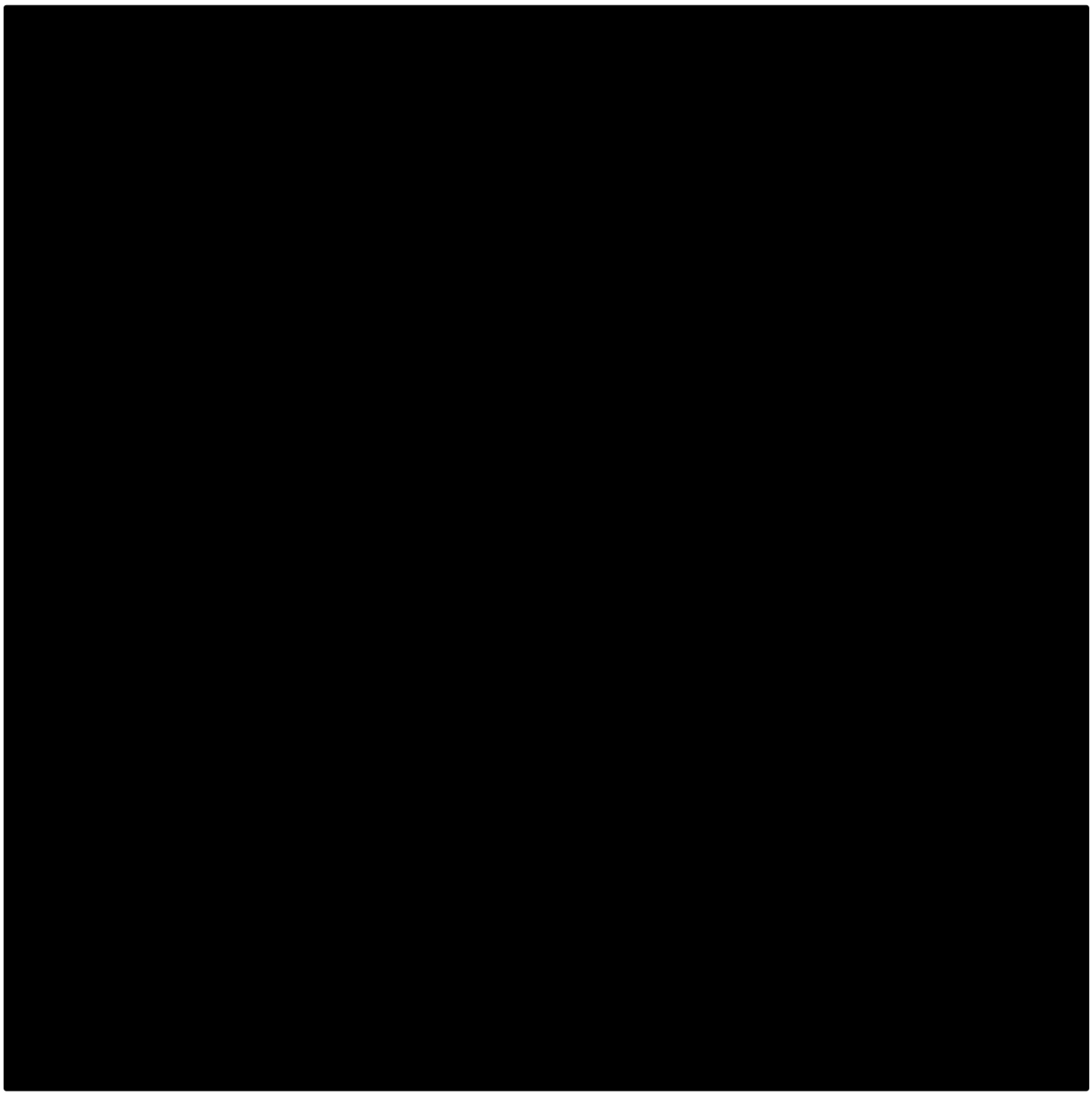
	Inotuzumab	0.74	[redacted]	[redacted]	[redacted]	[redacted]

*Statistically significant results. CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete haematologic recovery; ESS - effective sample size; mITT – modified intention to treat; OR – odds ratio; Ph – Philadelphia chromosome

Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2019)[2]

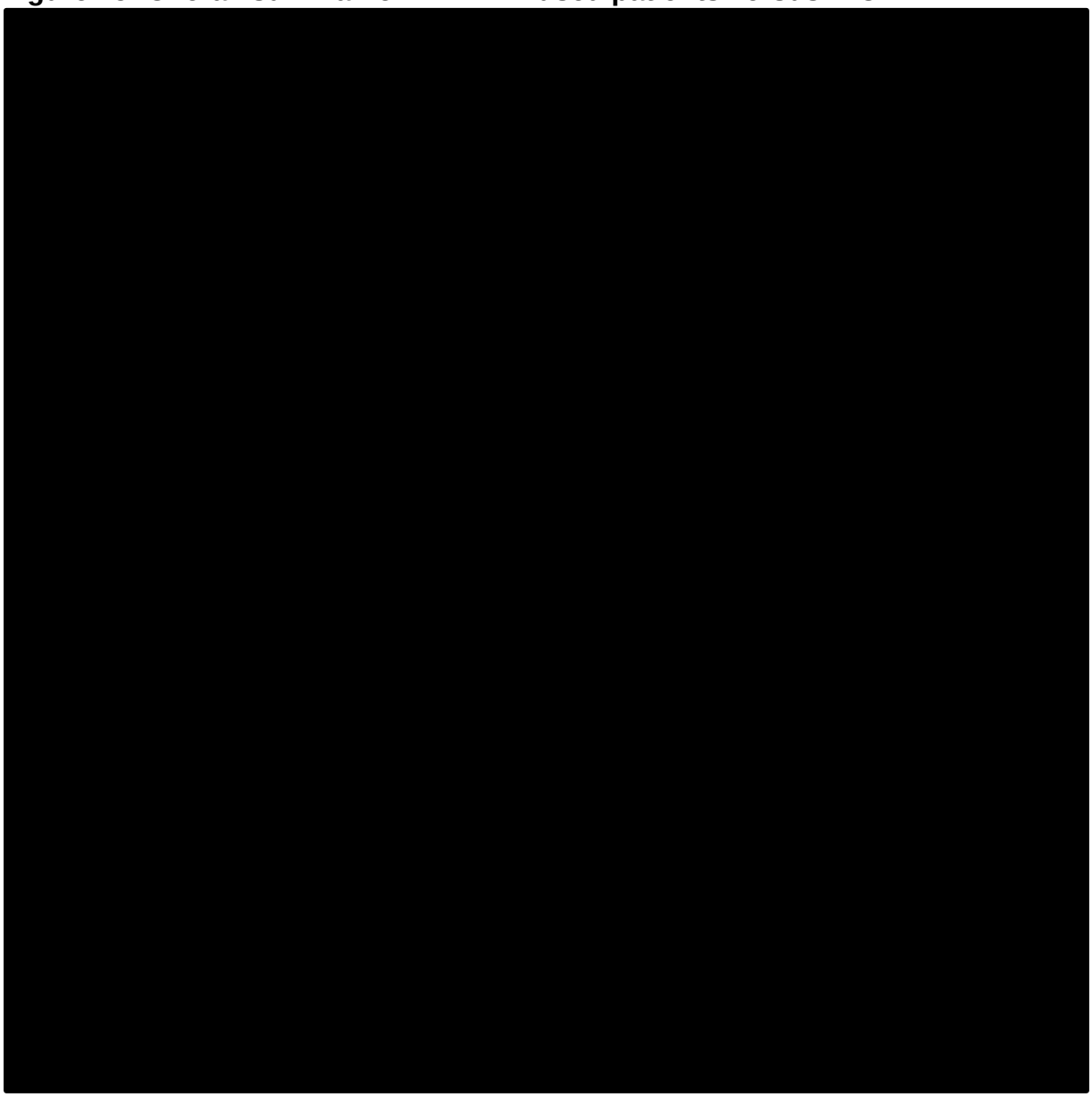
Plots of obe-cel unweighted, obe-cel weighted and comparator KM data for EFS and OS for FELIX versus inotuzumab, blinatumomab and ponatinib are shown in Figure 24 to Figure 29. For completeness, the accompanying plots for the originally submitted analysis using investigator-assessed EFS are presented in Figure 30 to Figure 32, respectively.

Figure 24: Event-free survival for FELIX infused patients versus INO-VATE, IRRC-assessed



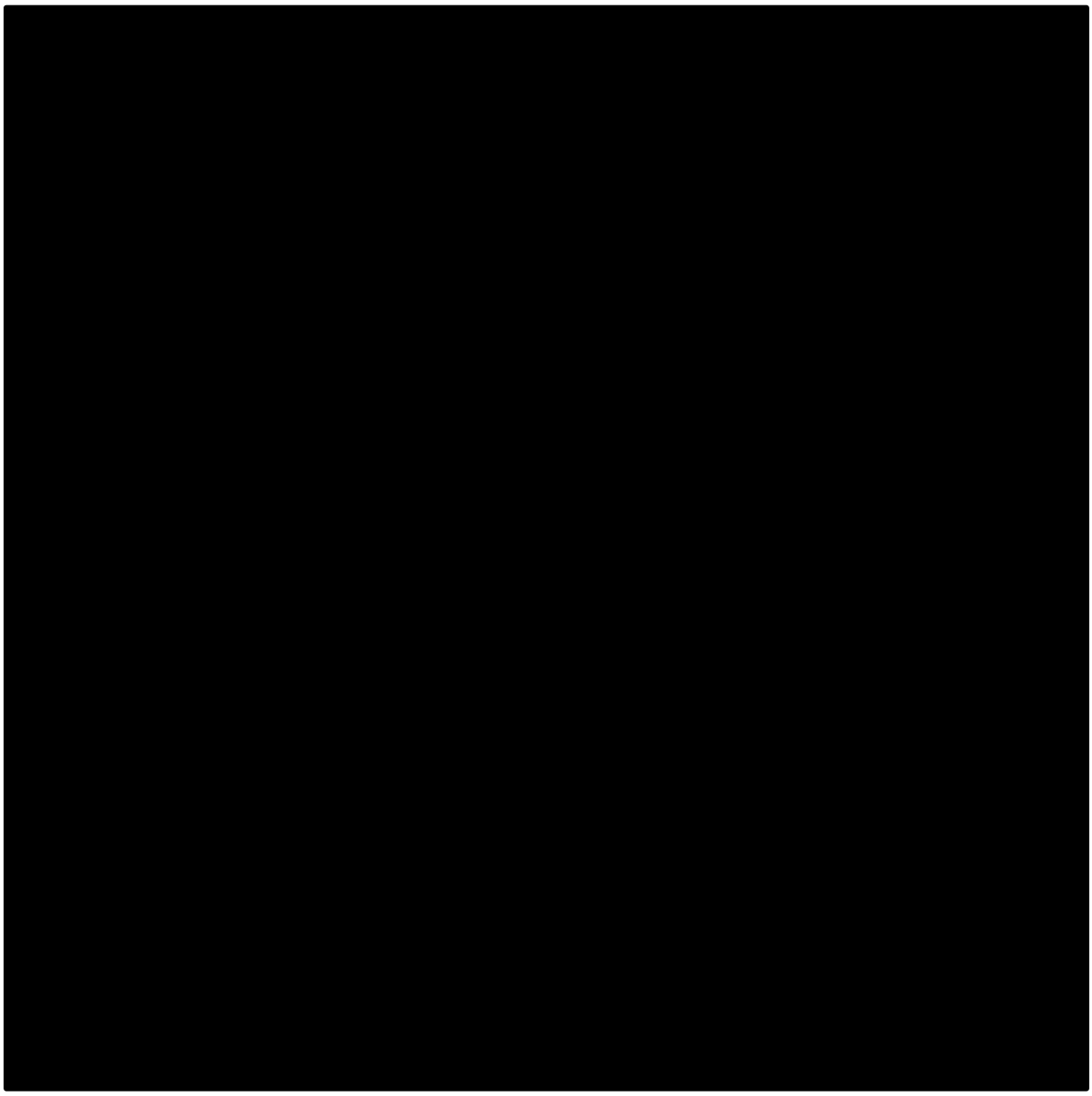
EFS – event-free survival; IRRC - Independent Response Review Committee
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2019)[2]

Figure 25: Overall survival for FELIX infused patients versus INO-VATE



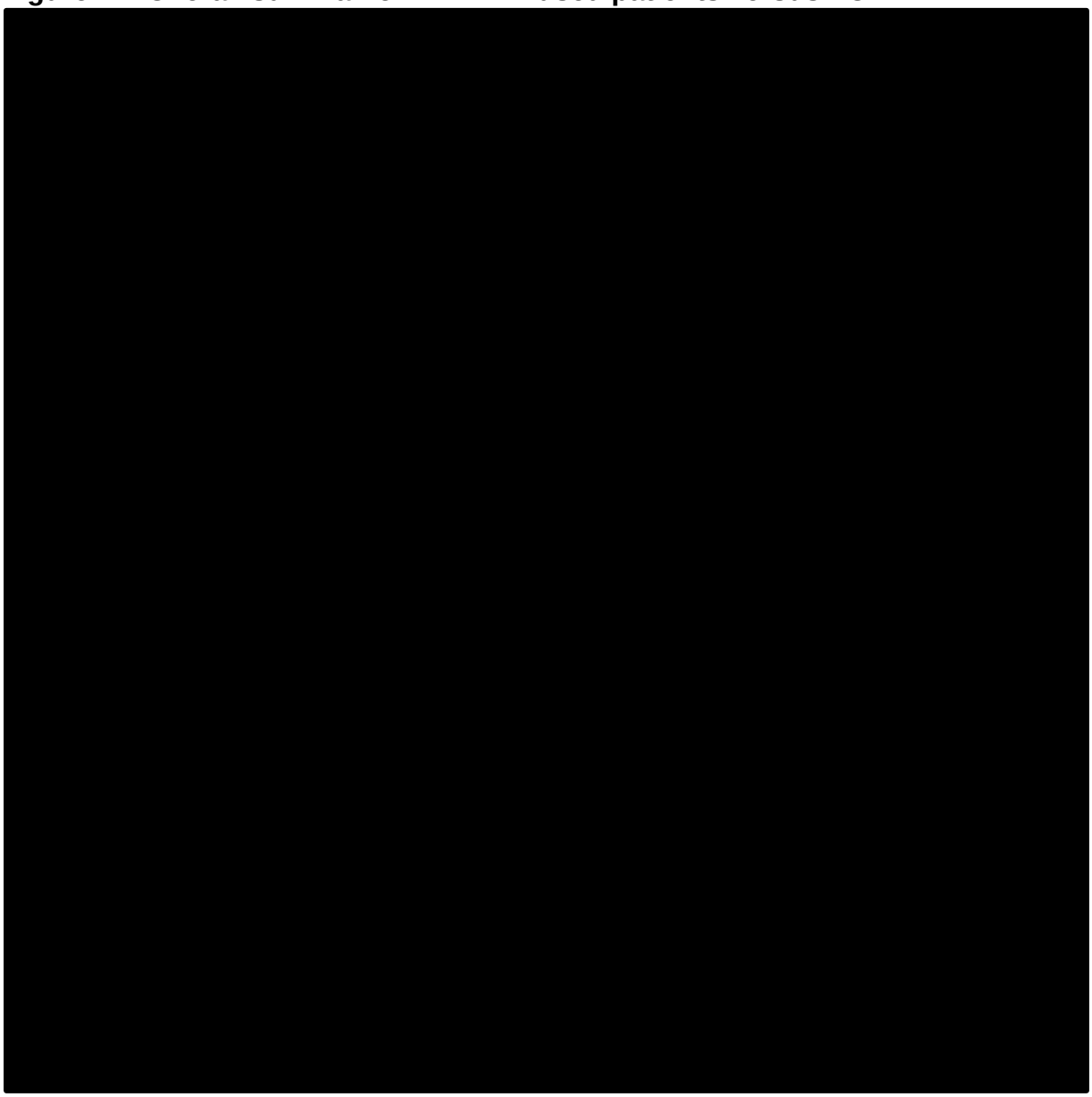
OS – overall survival
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2019)[2]

Figure 26: Event-free survival for FELIX infused patients versus TOWER, IRRC-assessed



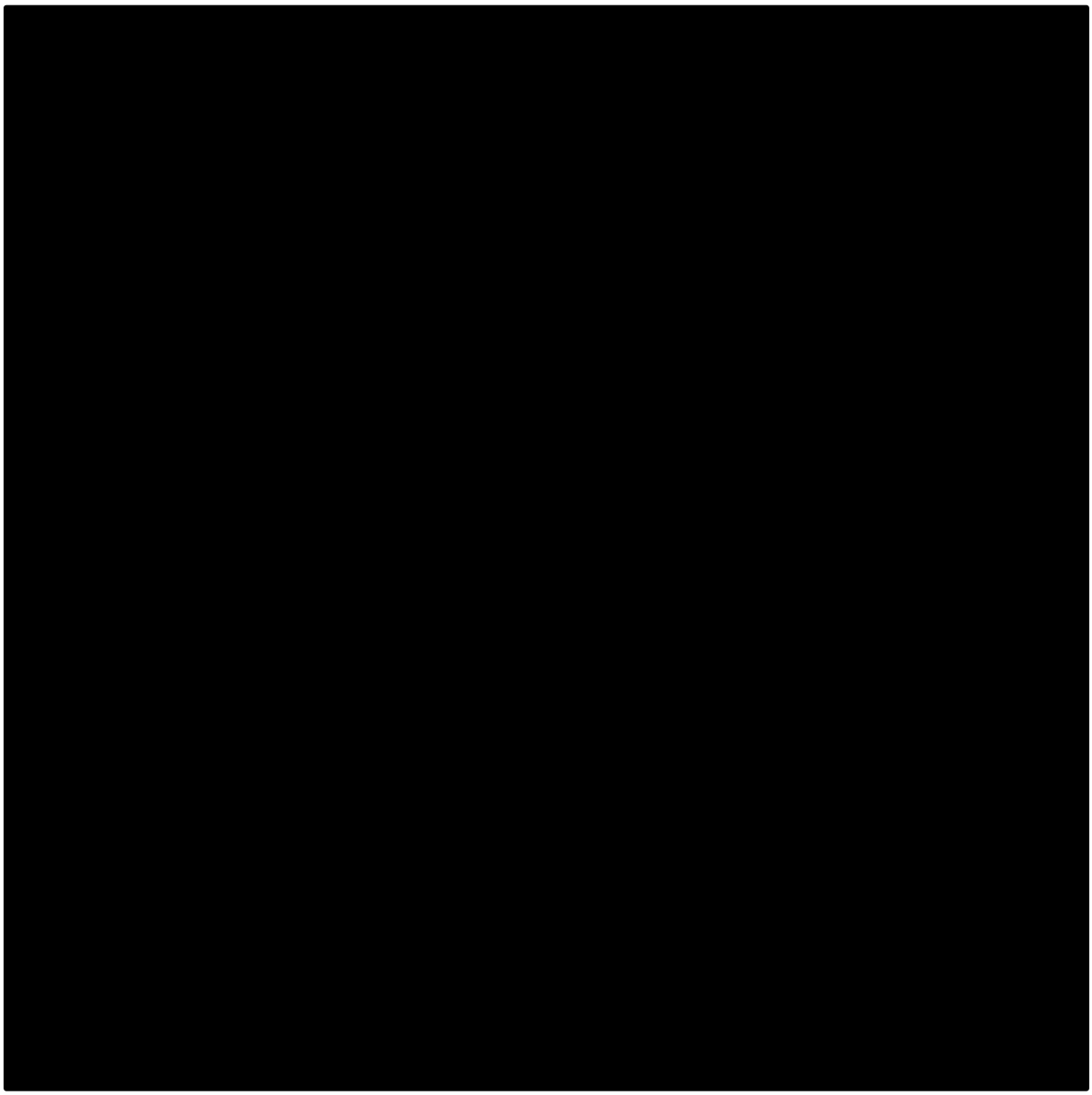
EFS – event-free survival; IRRC - Independent Response Review Committee
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]

Figure 27: Overall survival for FELIX infused patients versus TOWER



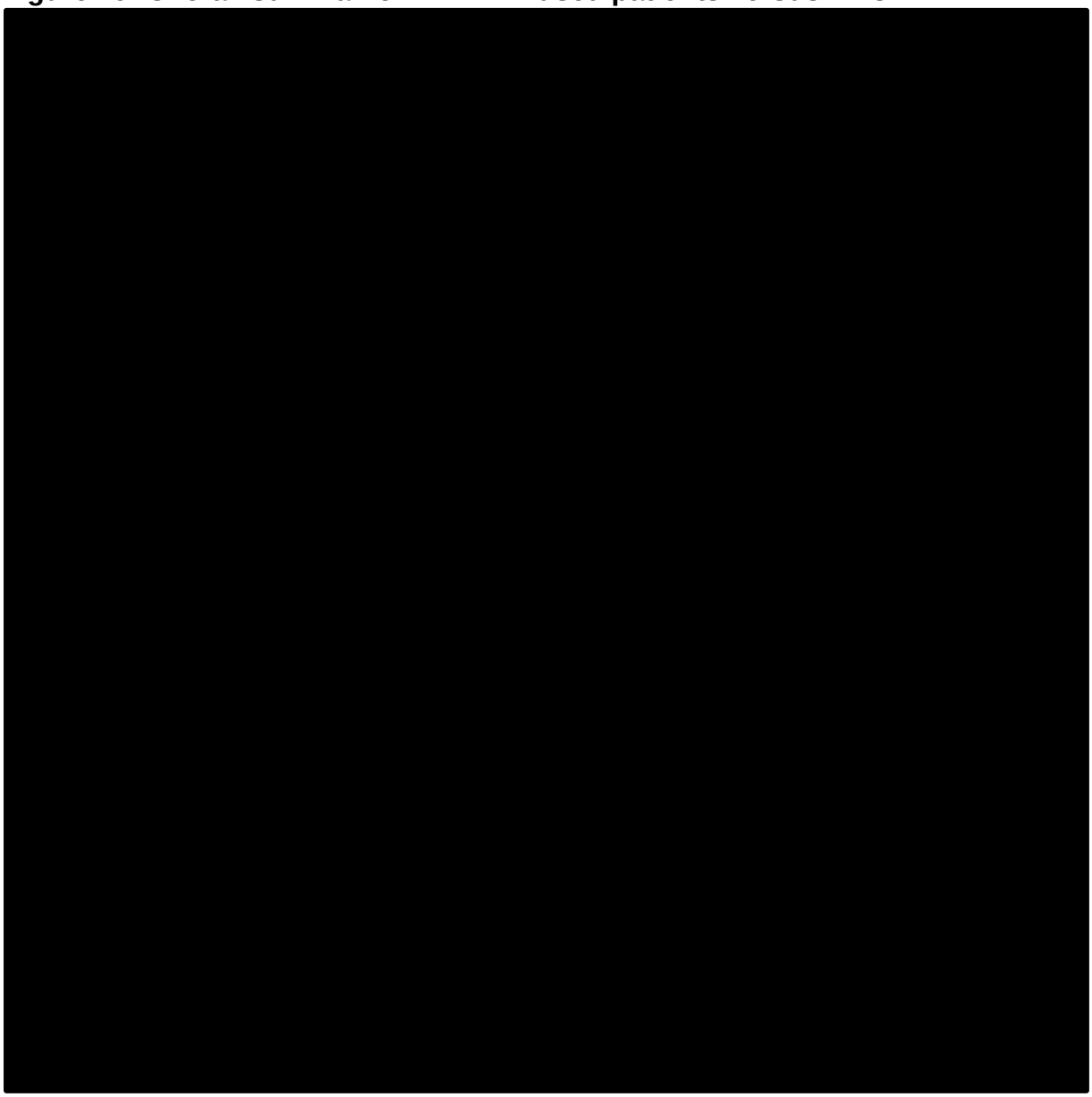
OS – overall survival
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]

Figure 28: Event-free survival for FELIX infused patients versus PACE, IRRC-assessed



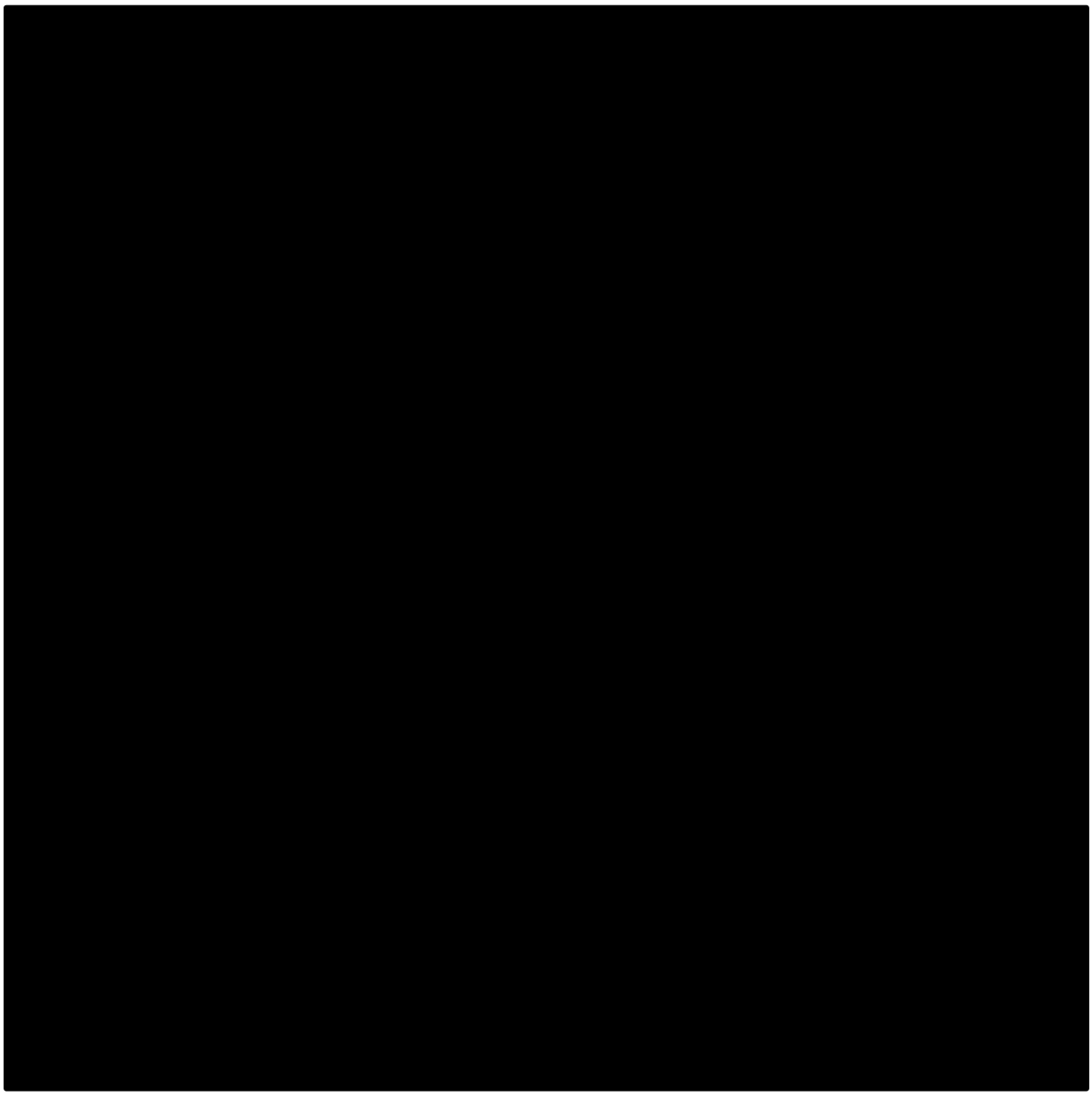
EFS – event-free survival; IRRC - Independent Response Review Committee
Source: Autolus. Data on file (2024)[5]; Cortes et al. (2018)[4]

Figure 29: Overall survival for FELIX infused patients versus PACE



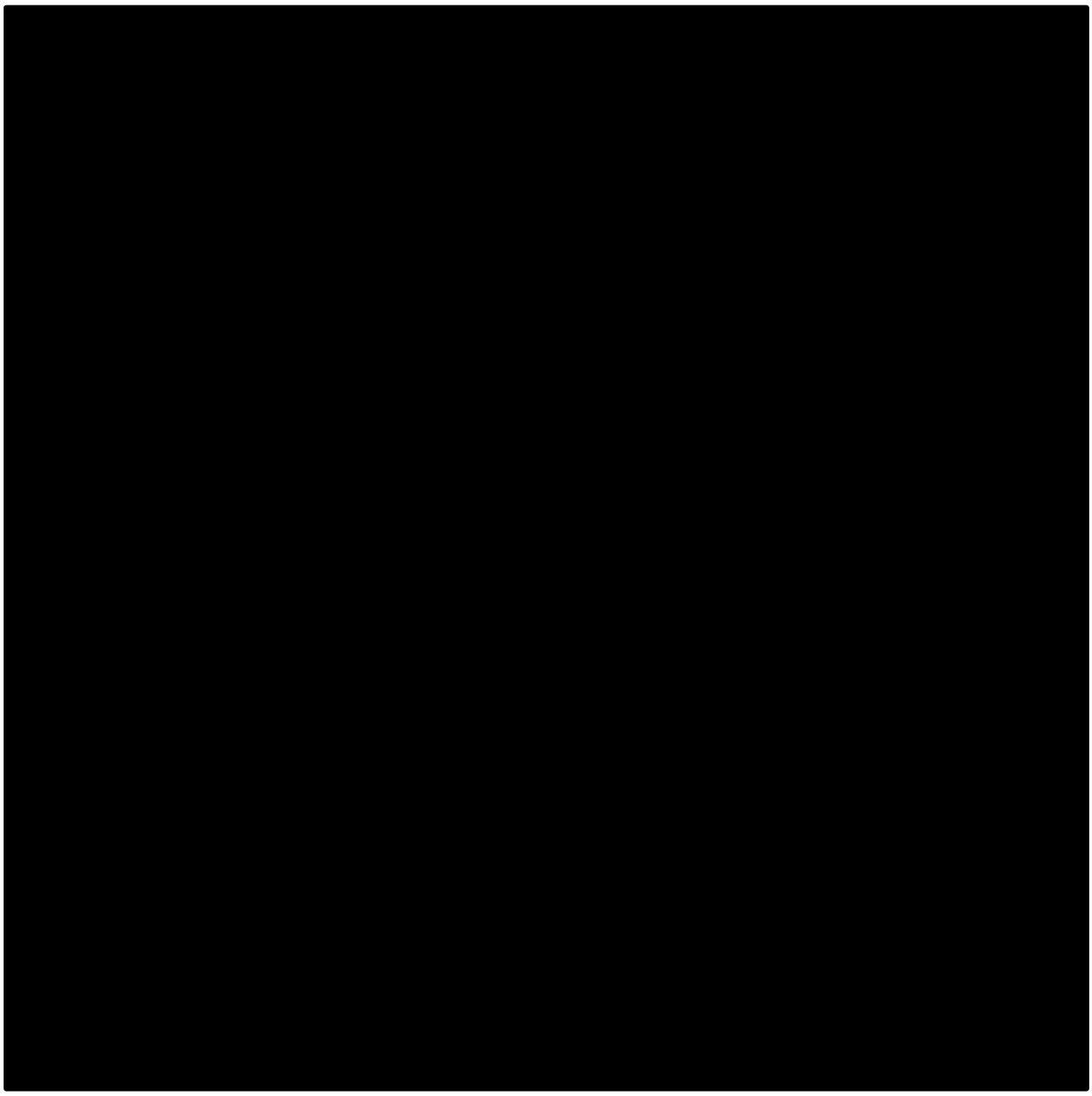
OS – overall survival
Source: Autolus. Data on file (2024)[5]; Cortes et al. (2018)[4]

Figure 30: Event-free survival for FELIX infused patients versus INO-VATE, INV assessed



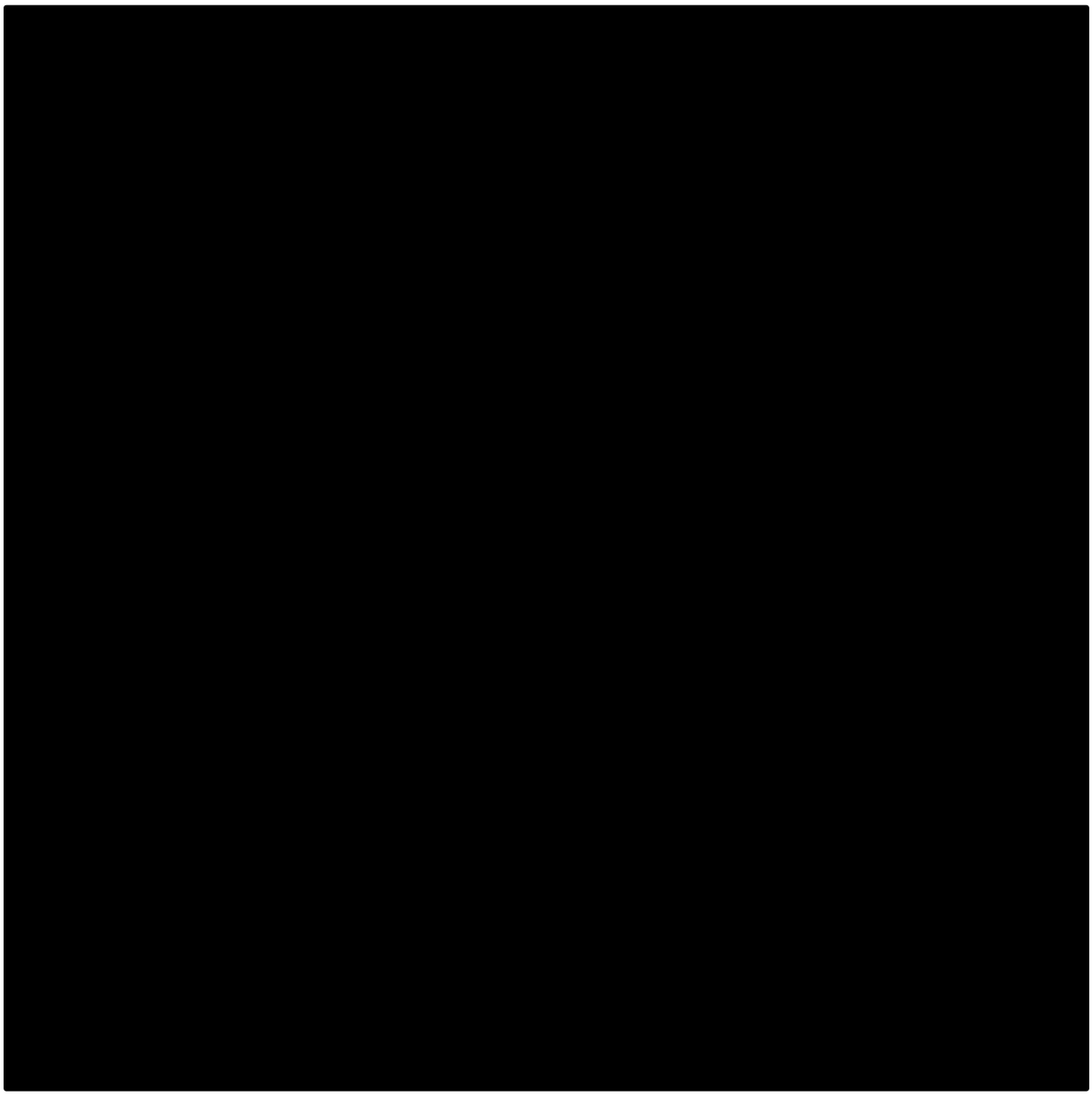
EFS – event-free survival; INV – investigator
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2019)[2]

Figure 31: Event-free survival for FELIX infused patients versus TOWER, INV assessed



EFS – event-free survival; INV – investigator
Source: Autolus. Data on file (2024)[5]; Kantarjian et al. (2017)[3]

Figure 32: Event-free survival for FELIX infused patients versus PACE, INV assessed



EFS – event-free survival; INV – investigator
Source: Autolus. Data on file (2024)[5]; Cortes et al. (2018)[4]

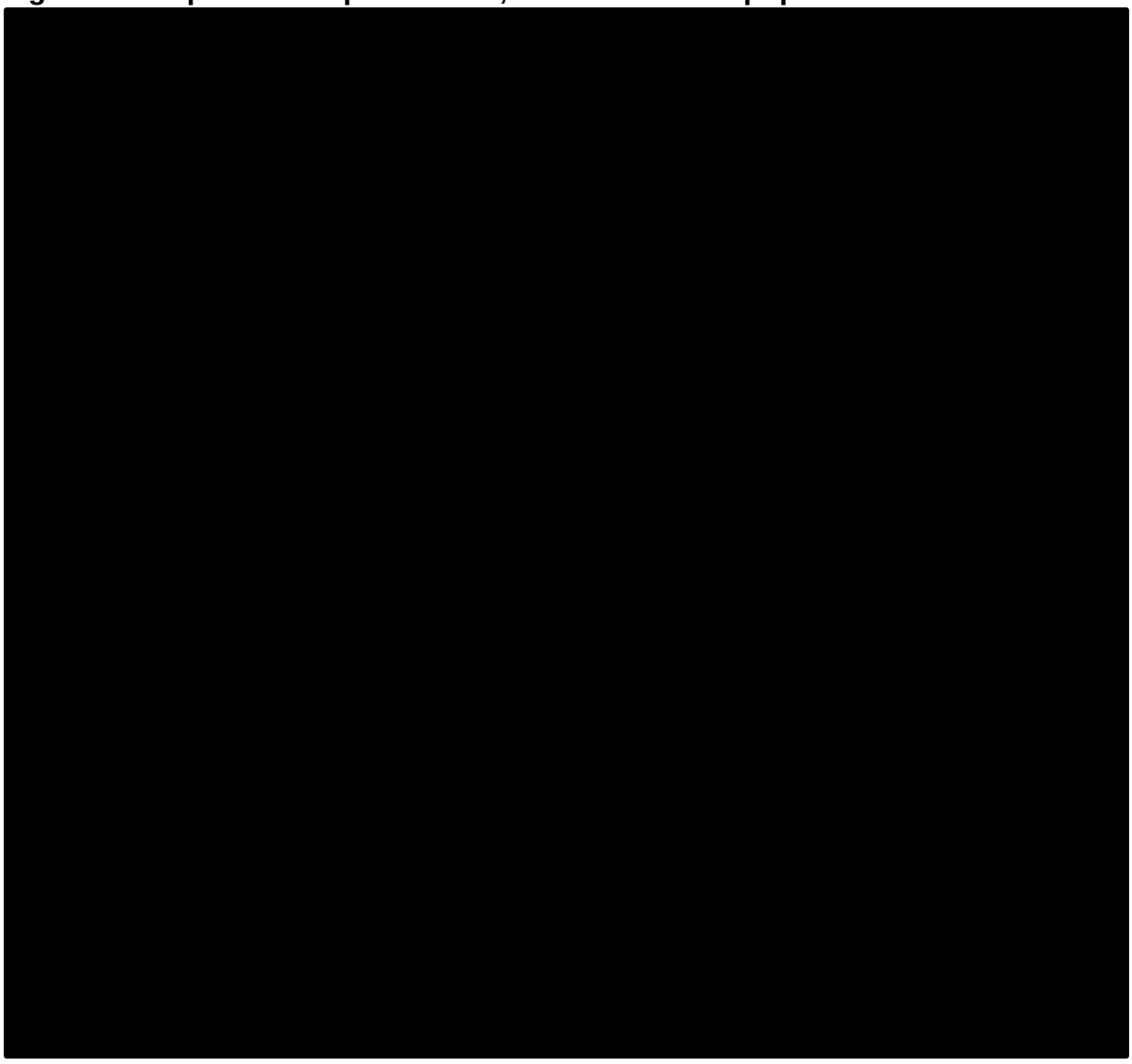
Conclusion

The findings of the MAIC indicate obe-cel had a favourable effect on EFS and OS compared to inotuzumab, blinatumomab and ponatinib in patients with R/R ALL. The MAIC also indicates that obe-cel had a favourable effect on CR and CRi compared to blinatumomab and ponatinib. The results of the updated analysis using IRRC-assessed EFS is consistent with the original MAIC conducted using local investigator-assessed outcomes.

A30. Please provide the Kaplan-Meier plots with the number at risk, including markers for censoring, for the FELIX mITT Ph- and Ph+ populations for both EFS and OS (4 plots in total).

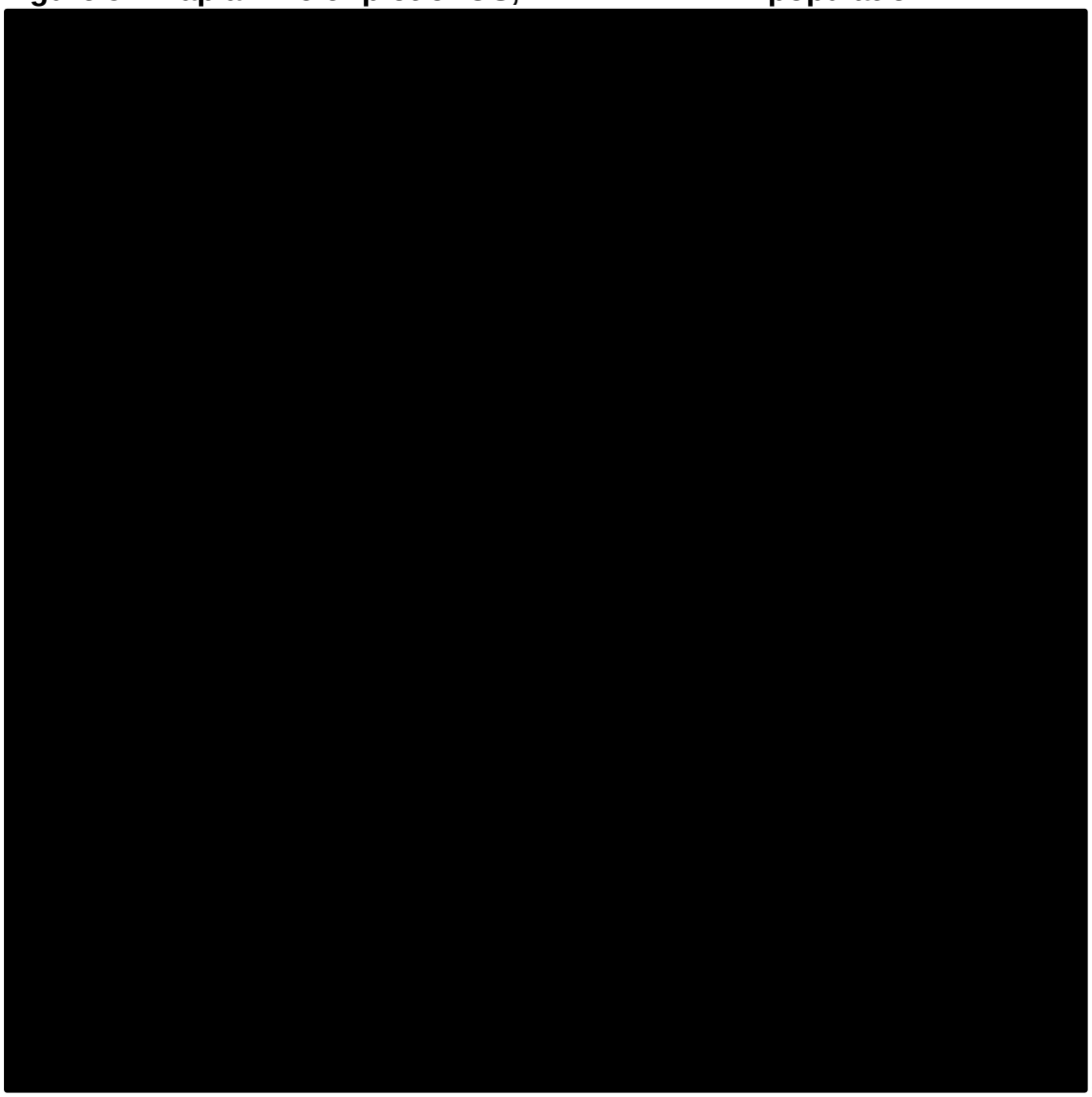
Please find the requested EFS and OS Kaplan-Meier plots in Figure 33 to Figure 36 for the FELIX mITT, Ph-, and Ph+ populations, respectively.[1]

Figure 33: Kaplan-Meier plot of EFS, FELIX mITT Ph- population



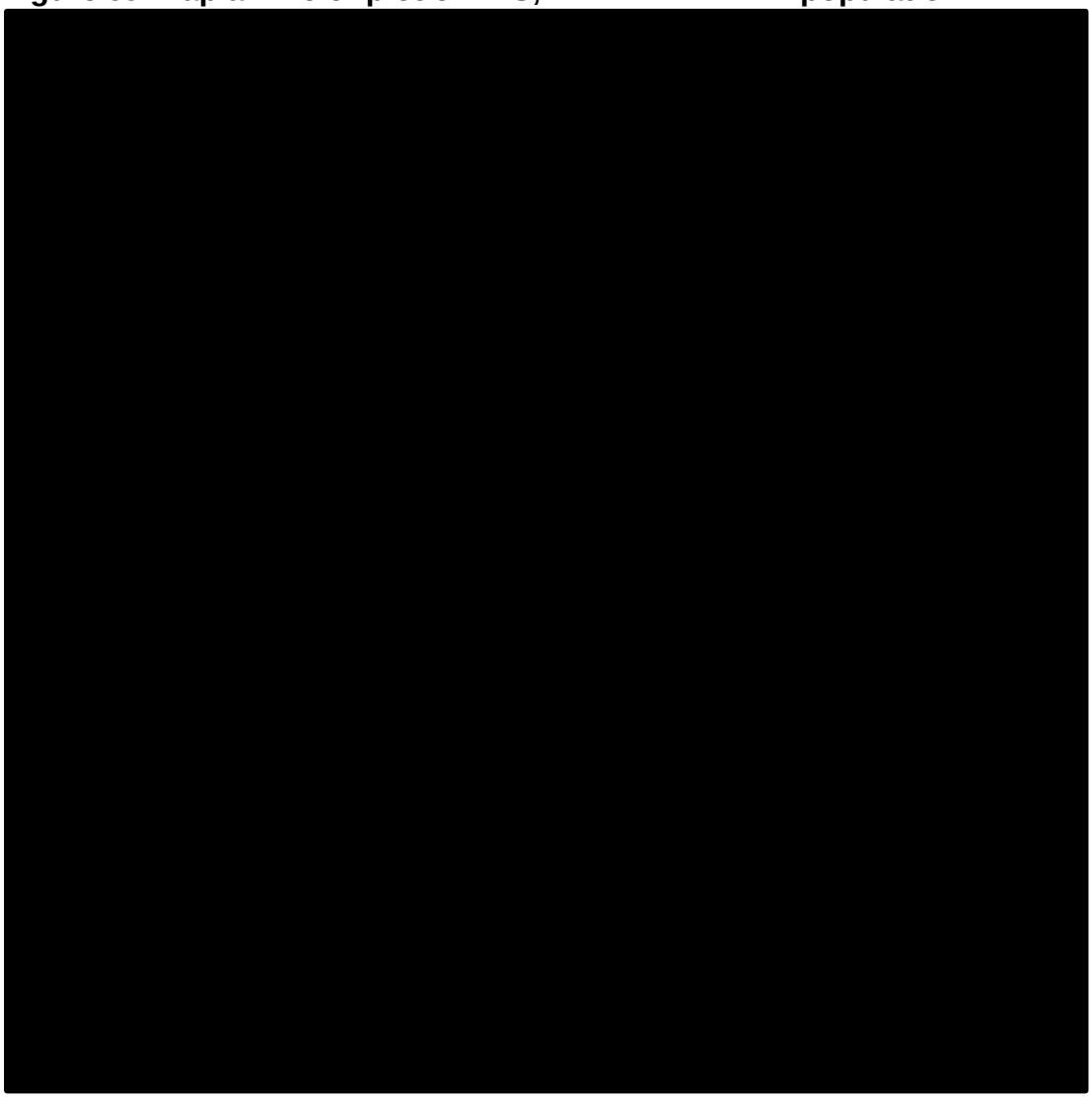
EFS – event-free survival; mITT – modified intention to treat; Ph – Philadelphia chromosome
Source: Autolus, Data on file[1]

Figure 34: Kaplan-Meier plot of OS, FELIX mITT Ph- population



OS – overall survival; mITT – modified intention to treat; Ph – Philadelphia chromosome
Source: Autolus, Data on file[1]

Figure 35: Kaplan-Meier plot of EFS, FELIX mITT Ph+ population



EFS – event-free survival; mITT – modified intention to treat; Ph – Philadelphia chromosome
Source: Autolus, Data on file[1]

Figure 36: Kaplan-Meier plot of OS, FELIX mITT Ph+ population

OS – overall survival; mITT – modified intention to treat; Ph – Philadelphia chromosome
Source: Autolus, Data on file[1]

A31. Please provide the number of EFS and OS events identified after reconstructing the Kaplan-Meier plots from the comparator studies in one table, and how/if they differ to the published results. Please share the output from your reconstructed data (i.e. patient event/censoring times) in .csv format

Please see the number of EFS and OS events identified after the reconstruction of the relevant Kaplan-Meier plots from INO-VATE, TOWER and PACE for inotuzumab, blinatumomab and ponatinib, respectively, along with the number of events reported in the trial publications in Table 80.[2–4] Note, publications for TOWER and PACE did

not report the number of events observed. The number of events for INO-VATE is broadly consistent across the reconstructed and published data.[2–4]

Table 80: Number of EFS and OS events identified in the reconstructed KM plots from INO-VATE, TOWER and PACE and published values

	Number of EFS events		Number of OS events	
	Reconstructed KM	**Published KM**	**Reconstructed KM**	**Published KM**
Inotuzumab (INO-VATE)[2]	126	129	129	131
Blinatumomab (TOWER)[3]	207	NR	165	NR
Ponatinib (PACE)[4]	31	NR	26	NR

EFS – event-free survival; KM – Kaplan-Meier; NR – not reported; OS – overall survival
Source: Kantarjian et al. (2017)[3]; Kantarjian et al. (2019)[2]; Cortes et al. (2018)[4]

Although the number of EFS and OS events were not reported for TOWER and PACE, the numbers at risk were available for each outcome.[3,4] Please see Table 81 and Table 82 for the comparison of the number of patients at risk between the reconstructed and the published Kaplan-Meier plots for TOWER and PACE, respectively. Numbers at risk are consistent for most timepoints, and only diverge at later timepoints when numbers at risk are below 10 in the published KMs.

Table 81: Number of patients at risk for EFS and OS identified in the reconstructed KM plots from TOWER and published values

Time	**Number of patients at risk**			
	Reconstructed EFS KM	**Published EFS KM**	**Reconstructed OS KM**	**Published OS KM**
Month 0	271	271	271	271
Month 3	95	95	176	176
Month 6	55	55	124	124
Month 9	25	25	79	79
Month 12	11	11	45	45
Month 15	1	7	27	27
Month 18	1	2	4	9
Month 21	1	1	4	4
Month 24	0	0	0	0

EFS – event-free survival; KM – Kaplan-Meier; OS – overall survival
Source: Kantarjian et al. (2017)[3]

Table 82: Number of patients at risk for EFS and OS identified in the reconstructed KM plots from PACE and published values

Time	**Number of patients at risk**			
	Reconstructed EFS KM	**Published EFS KM**	**Reconstructed OS KM**	**Published OS KM**

Month 0	32	32	32	32
Month 12	2	2	10	10
Month 24	0	0	4	4
Month 36	0	0	0	3
Month 48	0	0	0	2
Month 60	0	0	0	0
Month 72	0	0	0	0

EFS – event-free survival; KM – Kaplan-Meier; OS – overall survival
Source: Cortes et al. (2018)[4]

A32. Please can the company offer an interpretation of CSR Appendix 1 Table 1. Additionally, please report the BM blasts (%) by morphology median, min-max for screening, bridge therapy, lymphodepletion, day 1, day 10, day 28, 09-Jun-2023 Cut-off, and 07-Feb-2024 Cut-off for enrolled and infused in cohorts IA and IIA.

The Company would like to clarify that the percentage of BM blasts was only collected at screening; the distribution of BM blasts was not collected over time within the FELIX trial.[7]

A33. Please provide a breakdown of patients in FELIX enrolled cohorts IA and IIA who received subsequent allo-SCT by their initial response to obe-cel.

The best BOR for patients in Cohorts IA and IIA who received SCT subsequent to obe-cel is reported in Table 83 below. [redacted] patients across Cohorts IA and IIA achieved CR or CRi with obe-cel before receiving subsequent SCT therapy. CR and CRi were achieved in [redacted]% and [redacted]% of patients, respectively.[1]

Table 83: Initial response to obe-cel for patients who received subsequent SCT

	CR/CRi then SCT in remission, Cohort IA (n=[redacted])	**CR/CRi then SCT in remission, Cohort IIA (n=[redacted])**	**CR/CRi then SCT in remission, Cohort IA and IIA (n=[redacted])**
Best overall response – n (%)			
CR	[redacted]	[redacted]	[redacted]
CRi	[redacted]	[redacted]	[redacted]
No response	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Overall remission rate (ORR = CR + CRi) – n (%)			

n (%)	[redacted]	[redacted]	[redacted]
95% CI (%)	[redacted]	[redacted]	[redacted]

CI – confidence interval; CR – complete remission; CRi – complete remission with incomplete recovery of counts; ORR – overall response rate; SCT – stem cell transplant
Source: Autolus, Data on file[1]

A34. Please perform and present results of exploratory analyses for the following subgroups for the pooled population of FELIX cohorts IA and IIA, without censoring for subsequent therapy: previous SCT – yes/no, subsequent SCT – yes/no, age – over/under 60.

Desired results include odds/hazard ratio, confidence interval, and Kaplan-Meier output for ORR, CR, DoR, EFS and OS.

The results of the requested exploratory subgroup analyses for patients with and without prior allo-SCT are provided in Table 84 and Table 85, and Figure 37 to Figure 39.[1] The CIs for the ORs for ORR and CR [redacted], suggesting that there is [redacted] in overall response outcomes between participants with and without prior allo-SCT. The HRs for DOR, EFS and OS suggest that patients with prior allo-SCT have [redacted] time to event (TTE) outcomes, however, this finding should be interpreted with caution, as the analysis did not account for key confounding factors, such as disease severity. Patients who did not undergo allo-SCT prior to entering the FELIX trial were likely deemed ineligible due to their disease severity. As outlined in Table 86, patients who did not undergo allo-SCT prior to obe-cel infusion were characterised by substantially [redacted] BM blast counts, [redacted] refractory disease, and a [redacted] proportion of patients with extramedullary disease (EMD) and an ECOG score of 1. Consequently, this population was inherently [redacted], and therefore, more likely to experience [redacted] TTE outcomes.

Table 84: Overall response with disease assessment by IRRC with prior allo-SCT vs. without – infused set, phase IA and IIA

With prior allo-SCT vs. Without	Odds Ratio (95% CI)
Overall Remission	[redacted]
Complete Remission	[redacted]

CI – confidence interval; IRRC – Independent Response Review Committee; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Table 85: Time-to-event outcomes by IRRC with prior allo-SCT vs. without - infused set, phase IA and IIA

With prior allo-SCT vs. Without	HR (95% CI)

DOR (ignoring SCT ignoring other anticancer therapies for ALL post obe-cel infusion)	[redacted]
EFS starting from obe-cel infusion (ignoring SCT ignoring other anticancer therapies for ALL post obe-cel infusion)	[redacted]
Overall survival starting from obe-cel infusion (ignoring SCT)	[redacted]

CI – confidence interval; DOR – duration of response; EFS – event-free survival; HR – hazard ratio; IRRC – Independent Response Review Committee; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Table 86: Disease characteristics at screening by prior allo-SCT at screening - infused set, phase IA and IIA

Disease characteristics		**With prior allo-SCT (N=43)**	**Without prior allo-SCT (N=64)**
Prior lines of therapy – n (%)	1	[redacted]	[redacted]
	2	[redacted]	[redacted]
	3	[redacted]	[redacted]
	≥4	[redacted]	[redacted]
Refractory to all prior line of anticancer therapy – n (%)		[redacted]	[redacted]
Refractory to 1st line therapy – n (%)		[redacted]	[redacted]
Refractory to last prior line therapy – n (%)		[redacted]	[redacted]
Relapsed to 1st line therapy within 12 months – n (%)		[redacted]	[redacted]
BM blast (%) by morphology prior to enrolment*			
N		[redacted]	[redacted]
Mean (SD)		[redacted]	[redacted]
Median		[redacted]	[redacted]
BM blast (%) by morphology prior to enrolment categorised* – n (%)			
>75%		[redacted]	[redacted]
>20% - ≤75%		[redacted]	[redacted]
≥5% - ≤20%		[redacted]	[redacted]
<5%		[redacted]	[redacted]
Missing		[redacted]	[redacted]
Extramedullary disease status prior to enrolment – n (%)			
Absent		[redacted]	[redacted]
Present		[redacted]	[redacted]
ECOG score** – n (%)			
0		[redacted]	[redacted]
1		[redacted]	[redacted]
Missing		[redacted]	[redacted]

* Bone marrow blast (%) was determined by morphology as the highest value from bone marrow aspirate and trephine at screening. ** ECOG based on last non-missing value from screening period prior to leukapheresis.
BM – bone marrow; ECOG – Eastern Cooperative Oncology Group; SCT – stem cell transplant; SD – standard deviation
Source: Autolus, Data on file[1]

Figure 37: Kaplan-Meier plot of DOR by IRRC without censoring new non-protocol anticancer therapies including SCT by prior allo-SCT at screening - infused set, phase IA and IIA

DOR – duration of response; IRRC – Independent Response Review Committee; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Figure 38: Kaplan-Meier plot of EFS by IRRC without censoring new non-protocol anticancer therapies including SCT by prior allo-SCT at screening - infused set, phase IA and IIA

EFS – event-free survival; IRRC – Independent Response Review Committee; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Figure 39: Kaplan-Meier plot of OS without censoring new non-protocol anticancer therapies including SCT by prior allo-SCT at screening - infused set, phase IA and IIA

IRRC – Independent Response Review Committee; OS – overall survival; SCT – stem cell transplant
Source: Autolus, Data on file[1]

The results of the requested exploratory subgroup analyses by patients with and without subsequent allo-SCT are provided in Table 87 and Table 88. While the HRs for DOR, EFS and OS suggest that patients who underwent allo-SCT post obe-cel infusion have more [redacted] TTE outcomes, these results should be interpreted with caution as subsequent SCT is a post-baseline, time-dependent variable. As such, subgrouping based on this single criteria fails to account for other covariates, such as disease severity, response to obe-cel treatment, and AEs, that can independently affect TTE outcomes, and therefore introduce bias. Due to these limitations, KM plots for this subgroup analyses are not provided.

As shown in Table 88 and Section B.2.7.1.2 of the CS, results for CR/CRi and TTE outcomes suggest that there is [redacted] between patients who underwent subsequent allo-SCT and those who did not.

Table 87: Time-to-event outcomes by IRRC with subsequent allo-SCT vs. without - infused set, phase IA and IIA

With post SCT vs. Without post SCT	HR (95% CI)
DOR (Ignoring SCT ignoring other anticancer therapies for ALL post obe-cel infusion)	[redacted]
EFS starting from obe-cel infusion (Ignoring SCT ignoring other anticancer therapies for ALL post obe-cel infusion)	[redacted]
Overall survival starting from obe-cel infusion (ignoring SCT)	[redacted]

CI – confidence interval; DOR – duration of response; EFS – event-free survival; HR – hazard ratio; IRRC – Independent Response Review Committee; SCT – stem cell transplant

Source: Autolus, Data on file[1]

Table 88: Overall response with disease assessment by IRRC by whether patients received post SCT in remission - infused set, phase IA and IIA

	CR/CRi then SCT in remission (N=14)	CR/CRi without SCT in remission (N=67)	No CR/CRi (N=26)
Best overall response – n (%)			
CR	[redacted]	[redacted]	[redacted]
CRi	[redacted]	[redacted]	[redacted]
No response	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]

CR – complete remission; CRi – complete remission with incomplete recovery of counts; IRRC – Independent Response Review Committee; SCT – stem cell transplant
Source: Autolus, Data on file[1]

The results of the requested exploratory subgroup analyses by patients over and under 60 years are provided in Table 89 and Table 90, and Figure 40 to Figure 42. The CIs for all ORs and HRs [redacted], suggesting that there is [redacted] in overall response and TTE outcomes between participants aged over and under 60 years in the FELIX trial. Similarly, KM curves for all TTE endpoints [redacted] for the duration of the study indicating [redacted].

Table 89: Overall response with disease assessment by IRRC with age ≥60 vs. age <60 – infused set, phase IA and IIA

Age >=60 vs. Age <60	Odds Ratio (95% CI)
Overall Remission	[redacted]
Complete Remission	[redacted]

CI – confidence interval; IRRC – Independent Response Review Committee
Source: Autolus, Data on file[1]

Table 90: Time-to-event outcomes by IRRC with age ≥60 vs. age <60 - infused set, phase IA and IIA

Age >=60 vs. Age <60	HR (95% CI)
DOR (Ignoring SCT ignoring other anticancer therapies for ALL post obe-cel infusion)	[redacted]
EFS starting from obe-cel infusion (Ignoring SCT ignoring other anticancer therapies for ALL post obe-cel infusion)	[redacted]
Overall survival starting from obe-cel infusion (ignoring SCT)	[redacted]

CI – confidence interval; DOR – duration of response; EFS – event-free survival; HR – hazard ratio; IRRC – Independent Response Review Committee
Source: Autolus, Data on file[1]

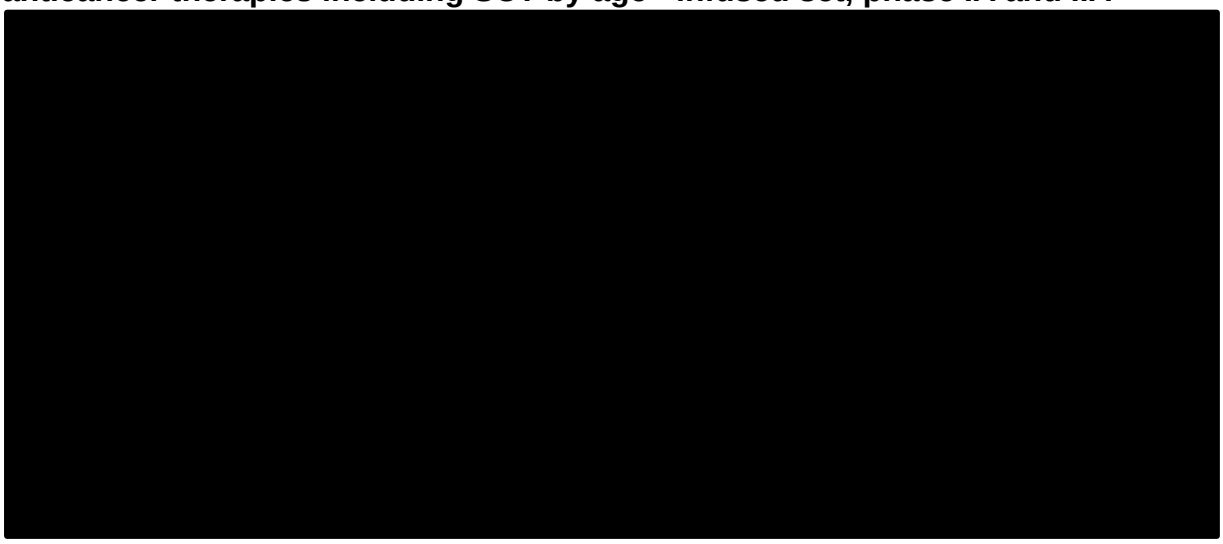
Figure 40: Kaplan-Meier plot of DOR by IRRC without censoring new non-protocol anticancer therapies including SCT by age - infused set, phase IA and IIA

DOR – duration of response; IRRC – Independent Response Review Committee; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Figure 41: Kaplan-Meier plot of EFS by IRRC without censoring new non-protocol anticancer therapies including SCT by age - infused set, phase IA and IIA

EFS – event-free survival; IRRC – Independent Response Review Committee; SCT – stem cell transplant
Source: Autolus, Data on file[1]

Figure 42: Kaplan-Meier plot of OS without censoring new non-protocol anticancer therapies including SCT by age - infused set, phase IA and IIA



IRRC – Independent Response Review Committee; OS – overall survival; SCT – stem cell transplant
Source: Autolus, Data on file[1]

A35. PRIORITY QUESTION: The EAG remain unclear about the positioning of obe-cel in the treatment pathway. The company's proposed positioning of obe-cel appears to come before allo-SCT (Doc B Figure 5), however the EAG's clinical experts stated that patients eligible for allo-SCT would receive this ahead of CAR T therapy due to the greater potential benefit. The EAG understands that people most likely to receive CAR T are those who have not responded sufficiently well to inotuzumab/ponatinib/blinatumomab, which are given as bridging therapies with the aim of getting patients to allo-SCT, or who have had an unsuccessful allo-SCT. The EAG is concerned that this population may not be reflected in the company's trial or the indirect comparisons. Furthermore, the EAG notes a potential difference in the positioning of obe-cel in the treatment pathway, compared with that of brexu-cel (NICE TA893 Doc B Figure 7). Please could the company provide additional clarity on the expected positioning of obe-cel and confirm whether they envisage any difference in positioning in the treatment pathway of brexu-cel.

As highlighted in Section B.1.3 of the CS, there are no UK specific guidelines for the treatment of adults with relapsed/refractory (R/R) B-cell ALL. Based on the European Society for Medical Oncology (ESMO) treatment guidelines, immunotherapy (blinatumomab or inotuzumab) is recommended as treatment for patients with R/R B-cell ALL. After achieving a subsequent complete remission the recommendation is

to consider this as a bridging therapy to allo-HSCT.[12] Allo-HSCT is a potentially curative option, however a number of factors affect a patient's eligibility of receiving allo-HSCT including if sufficient reduction in MRD has been achieved by bridging therapy, as well as donor availability, remission status, depth of remission and comorbidities.[12] The Company agree with the EAG that some patients will receive allo-SCT ahead of CAR T treatment, particularly high-risk patients in first complete remission[12], as highlighted in Section B.1.3.4.1 of the CS.

Brexu-cel, the only CAR T-cell therapy currently available to the target population, is recommended for use within the Cancer Drugs Fund (CDF) for patients who have relapsed following an allo-SCT, who are ineligible for an allo-SCT or who are unlikely to be eligible for an allo-SCT via current bridging therapies.[13] The NICE committee acknowledged that use of allo-SCT may decrease in favour of CAR T-cell therapy, as allo-SCT is a highly toxic treatment.[13] However, brexu-cel is associated with very high levels of CRS (89%) and neurological events associated with ICANS (60%).[14]

Obe-cel is a novel autologous CD19 CAR T-cell therapy, binding to and eliminating CD19 expressing B-cells. In contrast to brexu-cel, obe-cel demonstrates a much lower proportion of CRS and ICANS, indicating an improved safety profile.[7,14] Aligning with the positioning of brexu-cel in the treatment pathway, obe-cel is offered as an alternative treatment to therapies such as inotuzumab, blinatumomab and/or ponatinib for patients who are ineligible to receive an allo-SCT, as a replacement for allo-SCT in a subset of patients, or unlikely to be eligible with current bridging therapies for allo-SCT.[13] The anticipated positioning of obe-cel in the treatment pathway is presented in CS Figure 5 of the CS.

While patients may receive blinatumomab, inotuzumab or ponatinib prior to treatment with obe-cel, it is not a requirement for patients to receive these prior to commencing treatment with obe-cel. Rather these treatments are considered comparators to obe-cel, aligning with the conclusion of the final appraisal document for brexu-cel in TA893 (brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over) that “The relevant comparators are inotuzumab, blinatumomab and ponatinib” and with the NICE final scope for this appraisal.[13] In the FELIX clinical trial, 51.1% of patients in Cohort IIA

received prior blinatumomab or inotuzumab and therefore the proportion of patients who do experience initial treatment with immunotherapy are accounted for in the trial.[7] Pre-specified subgroup analysis showed obe-cel achieved ORR and CR well in excess of the pre-specified threshold of 40% (CS Appendix E).[13]

The FELIX clinical trial included patients both with and without prior SCT, aligning with the proposed positioning of obe-cel, and pre-specified analyses of patients without prior SCT showed similar response rates relative to the overall population. In patients with no prior allo-SCT, the ORR response rate was [redacted] and the CR response rate [redacted], aligning with the respective mITT rates ([redacted] and [redacted]), and indicating that obe-cel efficacy is independent of prior allo-SCT.[15] Additionally, obe-cel provides a potentially curative treatment without consolidative SCT in a meaningful percentage of patients ([redacted]%) and based on clinical opinion, it is anticipated that patients treated with obe-cel would not receive a subsequent SCT.[16–18]

Section B: Clarification on cost-effectiveness data

B1. Please explain how the outcomes for people who enrolled in FELIX but did not receive a transfusion are included in the model. Please confirm all associated costs for these people are captured in the model.

The economic model is reflective of the infused patient population in FELIX (mITT, N=94) and therefore, does not account for clinical or quality of life outcomes for patients who were enrolled but ultimately did not receive obe-cel infusion. Considering the mITT patient population ensures that the analysis captures the direct clinical and economic impacts of receiving obe-cel and does not include costs and outcomes unrelated to the intervention itself.

The model does consider costs for patients who receive obe-cel pretreatments but do not proceed to infusion, ensuring a comprehensive evaluation of the total costs to the NHS associated with providing access to obe-cel. As detailed in Section B.3.5.1.1.3 of the CS, separate cost multipliers were applied to the weighted average unit costs of leukapheresis, bridging chemotherapy and conditioning treatments. The multipliers were calculated as the ratio of patients in the enrolled population (ITT)

who received these treatments to those in the infused population (mITT). This method is consistent with the approach used in TA893 and reflects the analysis used for decision making from this appraisal.[13]

As outlined in Section B.3.5.1.1.3 in the CS, in FELIX enrolled Cohort IIA, [redacted] patients underwent leukapheresis, [redacted] patients received bridging therapy and [redacted] patients underwent conditioning therapy.[9] As noted in Section B.3.5.1.1.3 of the CS, one patient in Cohort IIA underwent leukapheresis but was not accepted for CAR T manufacturing, hence the figure for leukapheresis ([redacted]) exceeds the enrolled Cohort IIA total (112). In the infused Cohort IIA, 94 patients received leukapheresis, 88 patients received bridging therapy and 94 patients received conditioning chemotherapy, which led to cost multipliers of [redacted], [redacted] and [redacted], respectively.[9] The total costs for each pretreatment category with and without the multipliers applied are presented in Table 91.

Table 91: Comparison of pretreatment costs with and without multipliers

Pretreatment	Multiplier	Cost without multiplier	Cost with multiplier	Cost difference
Leukapheresis	[redacted]	£1,651.95	[redacted]	[redacted]
Bridging therapy	[redacted]	£5,214.82	[redacted]	[redacted]
Conditioning chemotherapy	[redacted]	£1,533.24	[redacted]	[redacted]

B2. Please explain why cure models were not used despite the assumption of a cure in the economic model. If cure models were considered and fitted, pleased provide detail on their output.

The Company considered the use of mixture and non-mixture cure models (MCMs and non-MCMs), as per NICE DSU TSD 21[19], considering the curative potential of obe-cel. As discussed in CS Document A Section A.11.2, EFS and OS data from FELIX were deemed too immature to yield reliable results. Figure 43 and Figure 44 present the KM plots curves of OS and EFS for obe-cel using the February 2024 data cut-off. While the KM plots indicate a plateau, particularly for OS, at the data cut-off [redacted]% of patients had not experienced an EFS event, and [redacted]% had not experienced an OS event; accordingly, the tails of the Kaplan-Meier curves have very low numbers at risk. TSD 21[19] highlights that while cure modelling can be

suitable if a proportion treated with the intervention can be considered cured, issues can arise from small datasets and low numbers at risk in the tail of the data.

Since the time point of submission, the Company has ran MCMs and non-MCMs in order to further explore the viability of cure modelling. The outcomes of the analyses are presented in Table 92 and Table 93 for the MCMs for OS and EFS, and Table 94 and Table 95 for non-MCMs for OS and EFS, respectively. As anticipated, the analyses resulted in implausibly wide variation in cure rates, indicating highly uncertain results from which no conclusions can be drawn. Additionally, the cure fraction tended to zero for the log-normal curves, indicating that the immaturity of the data rendered the package unable to separate hazards trending to general population (i.e., cure) from falling hazards, due to a turning point as could be represented by a log-normal distribution. The MCMs and non-MCMs resulted in OS cure fractions for obe-cel ranging from close to [redacted] up until [redacted]% and [redacted]%, respectively, despite similar Akaike information criterion (AIC) for the various curve choices. The EFS cure fractions ranged from close to [redacted] up until [redacted]% and [redacted]%, also despite similar AICs. A similar data maturity was observed for OS and RFS in TA893[13], rendering the EAG to consider cure models inappropriate.

Figure 43: Kaplan-Meier plot of overall survival with obe-cel, Cohort IIA mITT

mITT – modified intention to treat; OS – overall survival

Figure 44: Kaplan-Meier plot of event-free survival with obe-cel, Cohort IIA mITT

EFS – event-free survival; mITT – modified intention to treat

Table 92: Mixture cure models, obe-cel overall survival

Curve	Cure fraction (%, probit/logit)	AIC (probit/logit)
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]

AIC – Akaike information criterion

Table 93: Mixture cure models, obe-cel event-free survival

Curve	Cure fraction (%, probit/logit)	AIC (probit/logit)
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]

AIC – Akaike information criterion

Table 94: Non-mixture cure models, obe-cel overall survival

Curve	Cure fraction (%, probit/logit)	AIC (probit/logit)
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]

AIC – Akaike information criterion

Table 95: Non-mixture cure models, obe-cel event-free survival

Curve	Cure fraction (%, probit/logit)	AIC (probit/logit)
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]

AIC – Akaike information criterion

B3. Please provide the EFS and OS survival curves, goodness of fit statistics, and comparison to KM data for the MAIC-adjusted obe-cel analyses.

Please find the requested MAIC-adjusted results for EFS and OS in the tables and figures below.

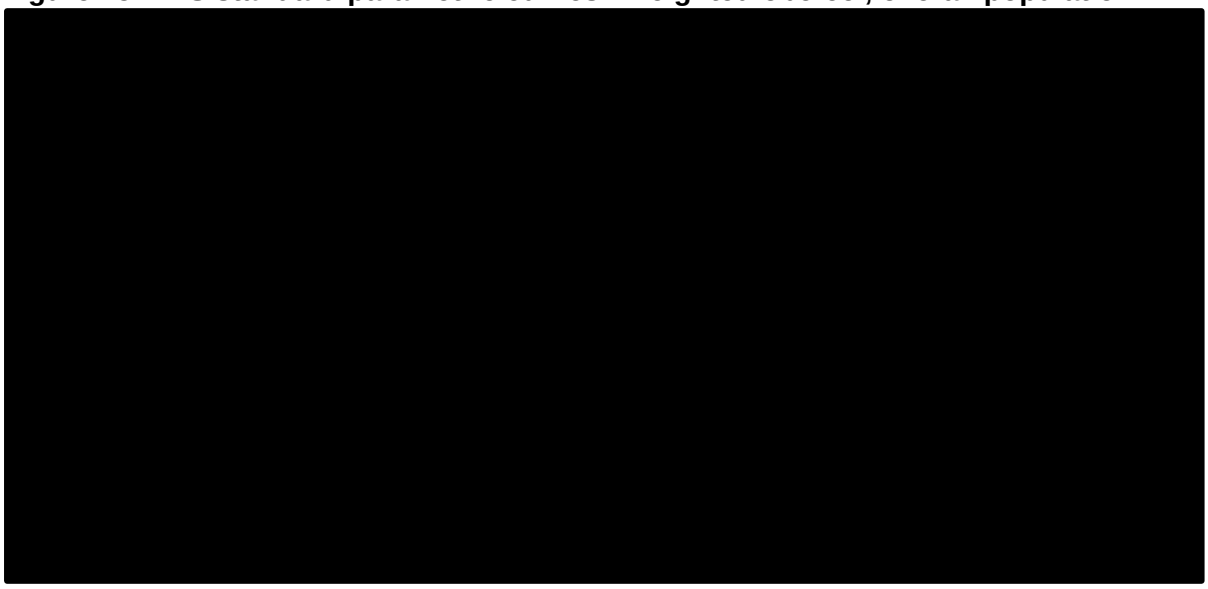
- Overall population
    - Standard parametric extrapolations for EFS and OS presented in Figure 45 and Figure 46, respectively. Goodness-of-fit statistics outlined in Table 96 and Table 97.
    - Flexible parametric extrapolations for EFS and OS presented in Figure 47 and Figure 48, respectively. Goodness-of-fit statistics outlined in Table 98 and Table 99.
- Ph+ population
    - Standard parametric extrapolations for EFS and OS presented in Figure 49 and Figure 50, respectively. Goodness-of-fit statistics outlined in Table 100 and Table 101.
- Ph- population
    - Standard parametric extrapolations for EFS and OS presented in Figure 51 and Figure 52, respectively. Goodness-of-fit statistics outlined in Table 102 and Table 103.

- Flexible parametric extrapolations for EFS and OS presented in Figure 53 and Figure 54, respectively. Goodness-of-fit statistics outlined in Table 104 and Table 105.

Please note that these analyses have been performed for the purposes of the above request, as the economic model does not use these outcomes. When the ‘MAIC’ approach is selected in the CEM, the selected curve for the comparators is adjusted by the relevant HRs obtained from the MAIC to generate the obe-cel survival estimates. Furthermore, please note that the below EFS curves use the IRRC data and MAIC outputs, in alignment with the response to question A29.

Visual inspection indicates that flexible models provide a better fit to both OS and EFS for the MAIC-adjusted obe-cel data for the overall population.

Figure 45: EFS standard parametric curves - weighted obe-cel, overall population



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

Figure 46: OS standard parametric curves - weighted obe-cel, overall population

KM – Kaplan-Meier; OS – overall survival

Table 96: AIC and BIC statistical goodness-of-fit data for the weighted obe-cel EFS – overall 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 97: AIC and BIC statistical goodness-of-fit data for the weighted obe-cel OS – overall population, independent standard parametric curves

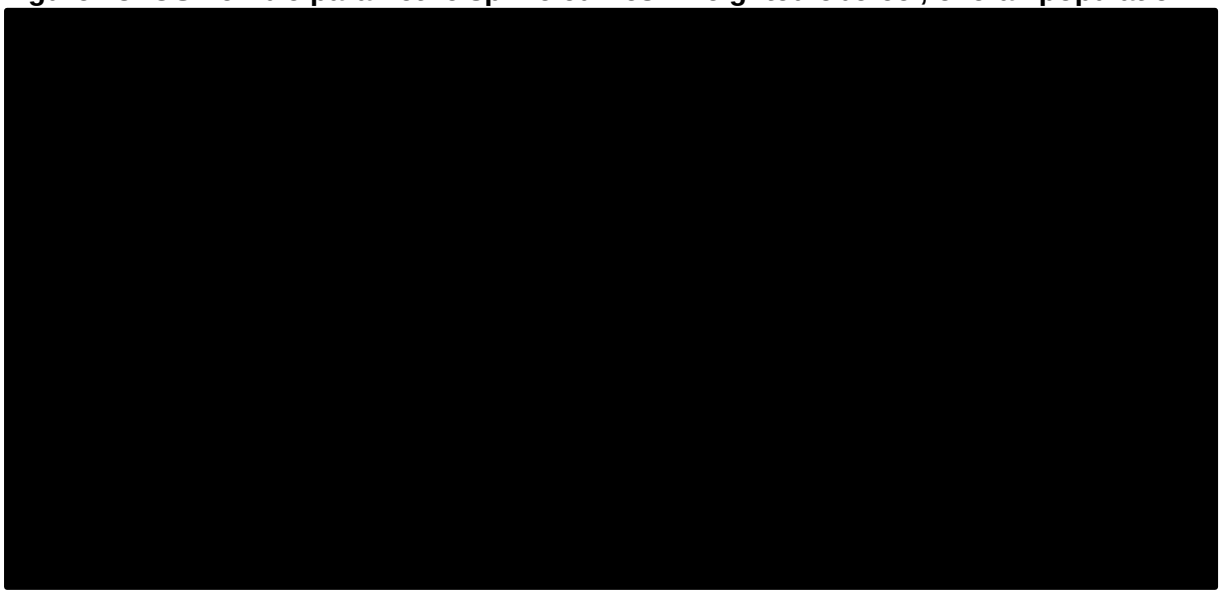
Distributions	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

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

Figure 47: EFS flexible parametric spline curves - weighted obe-cel, overall population

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

Figure 48: OS flexible parametric spline curves - weighted obe-cel, overall population



KM – Kaplan-Meier; OS – overall survival

Table 98: Goodness-of-fit data for weighted obe-cel EFS – overall 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

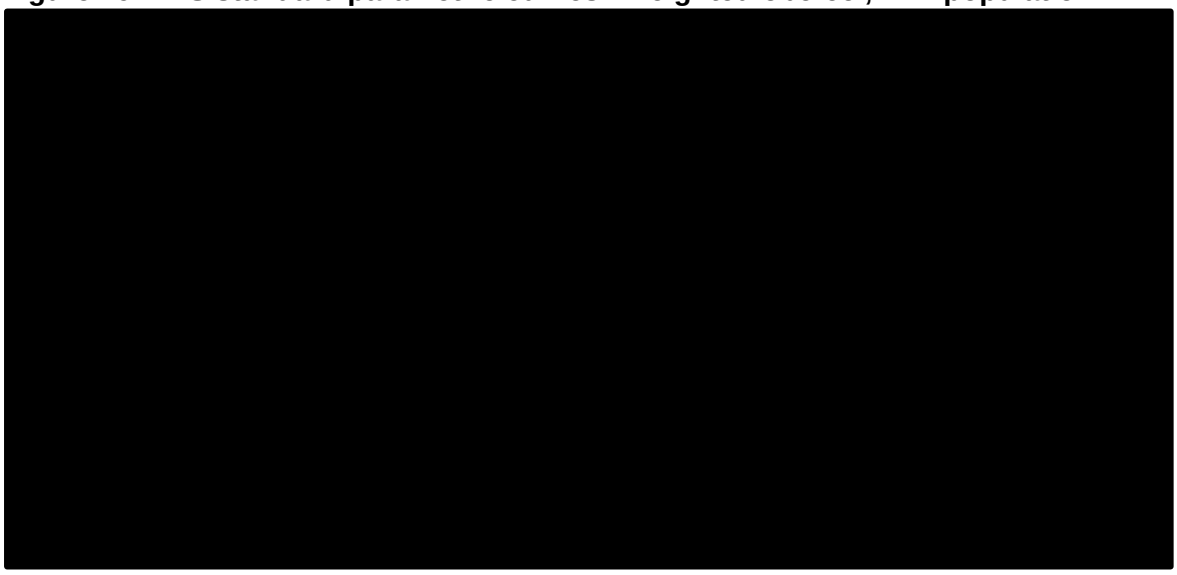
Table 99: Goodness-of-fit data for weighted obe-cel OS – overall population, flexible spline parametric models

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

Due to the small ESS in the Ph+ population ([redacted] patients, see Table 75), only standard parametric models could be fitted to the MAIC-adjusted obe-cel EFS and OS data.

Figure 49: EFS standard parametric curves - weighted obe-cel, Ph+ population



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

Figure 50: OS standard parametric curves - weighted obe-cel, Ph+ population

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

Table 100: AIC and BIC statistical goodness-of-fit data for the weighted obe-cel EFS – Ph+ 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

Table 101: AIC and BIC statistical goodness-of-fit data for the weighted obe-cel OS – Ph+ 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]

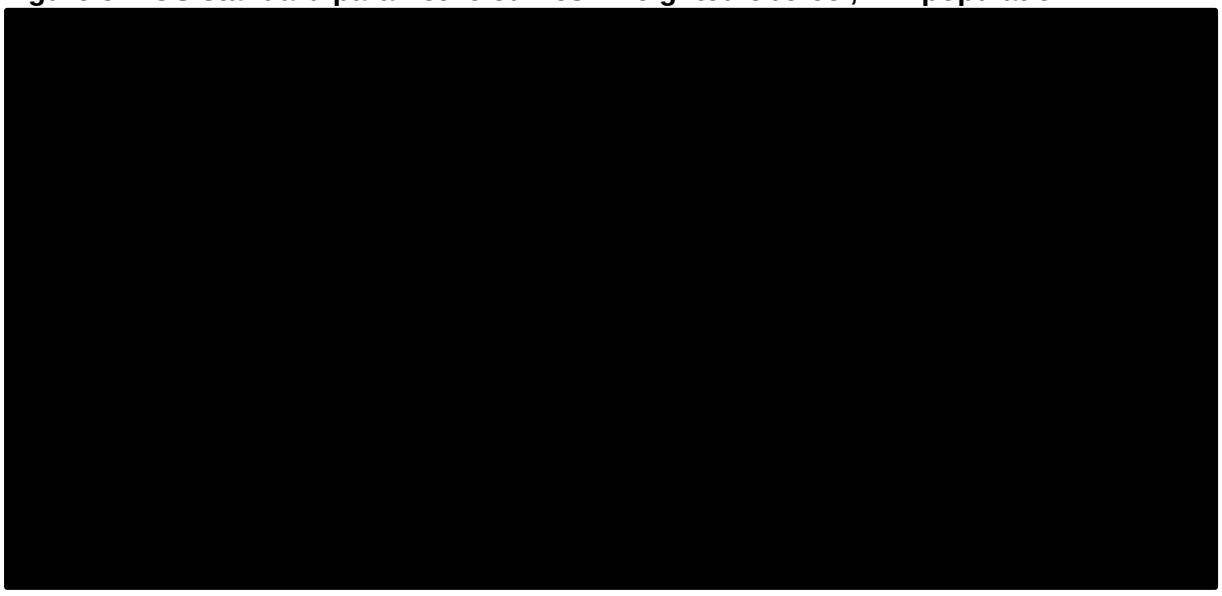
AIC – Akaike information criterion; BIC – Bayesian information criterion; OS – overall survival; Ph – Philadelphia chromosome

Visual inspection indicates that flexible models provide a better fit to both OS and EFS MAIC-adjusted data for the Ph- population.

Figure 51: EFS standard parametric curves - weighted obe-cel, Ph- population

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

Figure 52: OS standard parametric curves - weighted obe-cel, Ph- population



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

Table 102: AIC and BIC statistical goodness-of-fit data for the weighted obe-cel EFS – Ph- population, independent standard parametric curves

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

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

Table 103: AIC and BIC statistical goodness-of-fit data for the weighted obe-cel OS – Ph- 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

Figure 53: EFS flexible parametric spline curves - weighted obe-cel, Ph- population

[redacted]

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

Figure 54: OS flexible parametric spline curves - weighted obe-cel, Ph- population

[redacted]

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

Table 104: Goodness-of-fit data for weighted obe-cel EFS – Ph- 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

Table 105: Goodness-of-fit data for weighted obe-cel OS – Ph- 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

B4. Please justify using the same cure timepoint for all populations and confirm whether any other cure timepoints were considered.

A three-year cure time was considered across all populations, including the mITT, Ph- and Ph+ populations. No other cure time points were considered in the analysis. The cure timepoint of three years was initially selected to align with TA893, whereby it was used across all three populations (overall, Ph- and Ph+). The three-year time point was validated with two UK clinical experts who both expressed that this was reasonable but possibly conservative, and they expected that patients treated with obe-cel who relapse would typically do so within a year.[13,17]

Obe-cel OS data from FELIX Cohort IIA (mITT) shows the beginning of a plateau from Month 17 onwards (question A29 response, Figure 25), indicating that cure can be achieved from this time point. Furthermore, obe-cel OS data in the Ph- and Ph+ populations plateau at 17-months and 14-months, respectively (question A29 response, Figure 27 and Figure 29). Table 106 explores the incremental cost-effectiveness ratio (ICER) impact of reducing the cure time point to reflect the time at which OS Kaplan-Meier curves plateau in each population, plus the clinician's alternative timepoint of one year, relative to the revised Company base case. All scenarios tested reduce the ICERs.

Table 106: Scenario analysis of cure time points in mITT, Ph- and Ph+ population

Population	Cure time	ICER	
mITT		**Versus inotuzumab**	
	1 year	[redacted]	
	17-months	[redacted]	
	3 years	[redacted]	
Ph- population		**Versus inotuzumab**	**Versus blinatumomab**
	1 year	[redacted]	[redacted]
	17-months	[redacted]	[redacted]
	3 years	[redacted]	[redacted]
Ph+ population		**Versus inotuzumab**	**Versus ponatinib**
	1 year	[redacted]	[redacted]
	14-months	[redacted]	[redacted]
	3 years	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; mITT – modified intention to treat; Ph- – Philadelphia chromosome negative; Ph+ – Philadelphia chromosome-positive

B5. Please confirm if any attempt to explore uncertainty around Ph chromosome subgroups was undertaken for comparison to inotuzumab.

As KM data stratified by Ph chromosome status are not reported in publications for the pivotal inotuzumab trial (INO-VATE), no analyses could be undertaken to explore this uncertainty.[2]

B6. The company states that for the comparators, the costs and utilities impact of allo-SCT were estimated by weighting the costs and outcomes by the proportion of patients undergoing the procedure, informed by pivotal trials

(INO-VATE, TOWER, PACE) (CS, document B, page 106). Could the company clarify the assumptions and justifications behind this approach, particularly regarding the effect of allo-SCT on utility values, overall survival, and event-free survival?

The Company would like to clarify that only the cost impact of allo-SCT was estimated by weighting the costs by the proportion of patients undergoing allo-SCT for each comparator (CS Table 57). The proportions were informed by the respective pivotal comparator trials (see CS Table 56).

As outlined in Section B.3.2.2.2 of the CS, the CEM does not model the impact of subsequent allo-SCT on survival explicitly, however, the EFS and OS Kaplan-Meier curves reconstructed from the comparator trials and subsequently used in the economic analysis do not censor patients receiving allo-SCT. Therefore, the effect of allo-SCT on survival is inherently captured within these curves, and subsequently on patient QoL. This approach is further supported by precedent from TA893, as not directly modelling the impact of subsequent allo-SCT aligns with the methods accepted by the EAG and Committee.

It should be noted that scenario 10 (health state utility sourced from TA450) presented in the CS considers separate utility decrements associated with allo-SCT in addition to alternative health state utility values (HSUVs), in line with TA450. As shown in Section B.3.10.3 of the CS, using these alternative utility values had a negligible impact on the ICER in all three modelled populations (overall population, Ph+ and Ph-).

B7. The company has stated that "CRS disutility is assumed to equal the utility of the EFS health state," and appears to justify this assumption by defining CRS as “a severe and potentially life-threatening toxicity associated with CAR T-cell therapies.” Please could the company provide a rationale for this assumption, and clarify how the uncertainty, particularly its effect on utility, due to this assumption, has been addressed?

CRS is the most considerable treatment-related toxicity associated with CAR T-cell therapies, resulting from a strong immune activation triggered by treatment. CRS typically manifests within the first week post-therapy, with onset and peak severity

during this period. While mild cases may present with flu-like symptoms such as fatigue, rash, arthralgia, and myalgia, severe cases can escalate to life-threatening multiorgan failure due to an uncontrolled inflammatory response.[20]

Fever, often exceeding 40.5°C, is the first clinical sign of CRS and is observed in most patients.[20,21] The condition can progress to life-threatening complications, including vasodilatory shock and capillary leak syndrome, leading to hypoxic respiratory failure.[22] Depending on its severity, CRS may resolve on its own with supportive care or require targeted anticytokine therapy.[21] However, the majority of patients with grade 3 CRS require an ICU admission.[23] Severe hypoxia may necessitate ventilator support, and in some cases, CRS induces cardiac dysfunction, presenting as rapidly progressing cardiomyopathy with features resembling stress cardiomyopathy.[20,22]

The disutility associated with CRS was assumed to match the utility of the 'event-free' health state given its above mentioned profound impact on patients, i.e. patients experiencing CRS in the CEM have a utility value of zero for the duration of the event. This method aligns with precedent set in TA975 and TA893.[13,24] The uncertainty associated with this assumption was tested in scenario 12 presented in Section B.3.10.3 in the CS, which applied an alternative CRS disutility value based on Howell et al. (2022), a study exploring the utilities for AEs associated with CAR T-cell therapy, particularly CRS and neurological events.[25] The results of the scenario analysis showed that the ICER was robust to changes in the CRS disutility value in all three modelled populations, with all ICERs showing minimal change from the Company base case.

B8. The EAG understands that typically CAR T product costs are only incurred when treatment is infused. Please confirm what would happen in cases where patients receive only one dose of obe-cel.

The Company anticipates that patients receiving obe-cel would incur the same costs regardless of the number of doses they receive, given that all patients who reach the point of obe-cel infusion are expected to undergo the same procedures associated with CAR T delivery (i.e., pretreatments, infusion, monitoring). As obe-cel has a flat acquisition cost, the full acquisition cost would apply in these cases which is

reflected in the CEM. The clinical data used for the CEM also reflect this, as efficacy data are based on the infused Cohort IIA of FELIX (all 94 patients who received at least one infusion of obe-cel). The unit costs for each CAR T-related cost category used in the CEM are outlined in Table 107.

Table 107: CAR T-cell therapy related costs

Cost category	Unit cost
Drug acquisition costs (with [redacted] PAS discount)	[redacted]
Infusion and monitoring costs	[redacted]
Leukapheresis costs	[redacted]
Bridging therapy costs	[redacted]
Conditioning treatment costs	[redacted]

CAR – chimeric antigen receptor; PAS – Patient Access Scheme

B9. Please explain why a 28 day cycle length was used, rather than a 7 day cycle length.

The 28-day cycle length was chosen to align with the duration of the obe-cel treatment phase, defined as Day 28 after the first obe-cel infusion in the FELIX trial protocol.[7] Additionally, this cycle length aligns with the complete treatment cycle of blinatumomab and the dosing regimen of subsequent cycles (following Cycle 1) for inotuzumab, as outlined in the respective SmPCs for each treatment.[26,27]

B10. In Doc B, Table 29, please confirm that estimates for the relative effect between inotuzumab and obe-cel for two Ph chromosome subgroups are obtained from the analysis of the overall population.

The Company confirms that the EAG's interpretation is correct. The estimates for the relative effect between obe-cel and inotuzumab for the two Ph chromosome subgroups were obtained from the analysis of the overall population, in absence of reported Kaplan-Meier plots stratified by Ph chromosome status for the INO-VATE trial.[2] The Company would like to note that HRs for OS based on Ph status are provided in Figure 5 in Kantarjian et al., (2019).[2] However, these were not considered for the analysis, as equivalent HRs were not reported for EFS and adjusting for OS only would have led to inconsistency between the handling of these outcomes.

B11. Please clarify how missing data for EQ-5D responses were addressed when calculating utility values, particularly since missing data are unlikely to be missing at random? Please provide more detailed information about the linear mixed-effects model used for the utility analysis, particularly the estimates (including standard errors), p-values, and any other relevant statistical outputs?

As the model contains both fixed and random effects, a linear mixed-effects model (LMEM) was deemed appropriate. The LMEM was developed in R using the 'lme4' package, with health states as independent variables and patient ID as a random effect. This function ignores missing observations and uses maximum likelihood estimation to estimate parameters, which will be unbiased assuming the missingness is missing-at-random.

Missing values in the individual patient data (IPD) were due to death or a lack of measurement during patient visit due to a patient not returning for assessment or a site failing to report a visit. A similar level of missingness occurred for visits in both health states and at base case (see Table 108) indicating it is plausible for data to be considered missing-at-random. In the base case missing data points were removed and no imputation was performed as no bias is expected for missing-at-random data.

Table 108: Extent of missingness of EQ-5D-5L data in each health state

Health state	Missing data (%)
Baseline	[redacted]
Event-free	[redacted]
Post-event	[redacted]

EQ-5D-5L – EuroQol 5-dimension 5-level

The change in utility from being in the 'event-free' or 'post-event' health states compared to baseline utility was not statistically significant (Table 109**Error! Reference source not found.**). This is not surprising due to the small number of non-responders from which the calculations were based.

To ensure validity of results, a manual check was conducted to compare results of the LMEM versus descriptive HRQoL outputs from FELIX (Figure 55). Results were consistent thus confirming the validity of the analysis. Additionally, utility values were

broadly consistent with those used in TA540. However, to account for the uncertainty in the calculated utility values, two scenario analyses were conducted using different HSUVs to assess ICER impact (see CS Section B.3.10.3).

Table 109: Results from the linear mixed-effects model

	Estimate	Standard error	P-value	HSUV
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Event-free	[redacted]	[redacted]	[redacted]	[redacted]
Post-event	[redacted]	[redacted]	[redacted]	[redacted]

HSUV – health state utility value; P-value – probability value

Figure 55: Change in EQ-5D-5L index score over time, Cohort IIA

[redacted]

EQ-5D-5L – EuroQol-5 Dimensions-5 Levels; SE – standard error
Source : FELIX, data on file[28]

To explore uncertainty around the missing data, the Company has performed multiple imputation and re-ran the analysis. Multiple imputation with chained equations (MICE) was performed in R after removing missing data from death and patients who did not report EQ-5D-5L values at any time point. Multiple imputation is an effective method when data is missing-at-random in multiple variables and reduces the risk of underestimating variance. Resulting HSUV using imputed data are shown in Table 110. The ICER impact of using the HSUV using imputed data in the CEM are presented in Table 111, Table 112 and Table 113 for the overall, Ph- and Ph+ populations, respectively.

Table 110: Health state utility values using multiple imputation

Health state	Estimate	Standard error	P-value	HSUV

Baseline	[redacted]	[redacted]	[redacted]	
Event-free	[redacted]	[redacted]	[redacted]	[redacted]
Post-event	[redacted]	[redacted]	[redacted]	[redacted]

HSUV – health state utility value; P-value – probability value

Table 111: Deterministic alternative HSUV scenario results, overall population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.76	[redacted]

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

Table 112: Deterministic alternative HSUV scenario 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.16	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.07	[redacted]	[redacted]

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

Table 113: Deterministic alternative HSUV scenario 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.81	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.41	[redacted]	[redacted]

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

B12. Please provide justification for applying the selected utility increment for long-term survivors within the economic model. Please clarify why this increment was not applied for scenario 11 (Blinatumomab SMC utility values).

As outlined in Section B.3.2.2.1 and Table 66 in the CS, the assumption that long-term survivors have an improved HRQoL compared to non-cured patients but a lower HRQoL than that of the general population is in line with EAG and Committee preference in previous NICE appraisals of CAR T therapies, including TA893.[13,24,29,30] In the model base case, the estimated utility increment is applied on top of the 'event-free' utility value. In contrast, in scenario 11, the long-term survivorship utility value used in the blinatumomab SMC dossier is applied from the cure timepoint onwards, replacing the use of an increment on top of the HSUV. Applying a utility increment on top of the long-term survivorship utility for this scenario would lead to double-counting the QoL benefit associated with long-term survivorship.

B13. Doc B, Table 44, please can the company confirm the column with name "Cost inflated to 2024" in this table refers to unit cost? Additionally, can company confirm these costs are align with National Schedule of NHS Costs - Year 2022/23 and model in worksheet 'Treatment Costs'?

At the point of model development, functionality was included for a 2024 cost year. However, at the time of submission, 2022/23 was the most recent NHS reference cost available, hence the 2023 cost year was used. Therefore, any reference to a 2024 cost year is redundant; the Company apologises that these were not removed from the model.

B14. Doc B, Table 55: We have identified an inconsistency between the cost values for obe-cel and inotuzumab listed in Table 55 and those used in the company's model (specifically, in the "Adverse Events" worksheet). Could you please clarify which of these values—those in Table 55 or those in the model worksheet—represents the most current and accurate data? Additionally, if similar inconsistencies are found elsewhere, please confirm which data should be considered authoritative.

As some of the AE-related treatments use weight-based dosing and the baseline patient weight is dependent on the selected model population, the one-off total AE

costs applied to each treatment arm varies between the overall, Ph+ and Ph- populations. Therefore, the costs used within the model represent the most accurate data. The costs presented in CS Table 55 are reflective of the overall population, however, the Company acknowledges that considering the differences in baseline characteristics across populations, presenting these one-off costs separately for each population would have been clearer. Therefore, please see the AE costs per population in Table 114 to Table 116 for the overall, Ph+ and Ph- populations, respectively, aligning with the values in the CEM.

Table 114: One-off total AE costs applied to treatment arms - overall population

Treatment	Cost
Obe-cel	[redacted]
Inotuzumab	£18,013

AE – adverse event

Table 115: One-off total AE costs applied to treatment arms - Ph+ population

Treatment	Cost
Obe-cel	[redacted]
Inotuzumab	£17,403
Ponatinib	£382

AE – adverse event; Ph – Philadelphia chromosome

Table 116: One-off total AE costs applied to treatment arms - Ph- population

Treatment	Cost
Obe-cel	[redacted]
Inotuzumab	£18,229
Blinatumomab	£3,380

AE – adverse event; Ph – Philadelphia chromosome

B15. Doc B, Table 65, page 167, it appears that the data presented in Table 65 relates to the overall population (obe-cel vs. inotuzumab). Could the company kindly provide the following tables for clarification:

- Table A: Summary of common variables applied within the economic model for all population

- Table B: Summary of variables applied within the economic model, specifically for the overall population

- Table C: Summary of variables applied within the economic model, specifically for the Ph+ population

- Table D: Summary of variables applied within the economic model, specifically for the Ph- population

Please see the requested tables below. The content of

Table 117, Table 118, Table 119 and Table 120 corresponds to the requested Table A, Table B, Table C and Table D, respectively.

The values presented in the CS are relevant for the overall population. Due to weight-based dosing for some of the bridging chemotherapies and long-term utility being calculated based on age and gender-matched utility, the varying baseline characteristics between the patient populations mean these values are dependent on patient population.

Table 117: Summary of common variables applied within the economic model for all populations

Parameter	Included in PSA?	Value	OWSA			Within SA varied by
			SE	Lower bound	Upper bound	
Time horizon (years)	No	51.7	-	-	-	-
Discount rate (costs)	No	3.50%	-	-	-	-
Discount rate (LYs)	No	0.00%	-	-	-	-
Discount rate (QALYs)	No	3.50%	-	-	-	-
Utility: Event-free	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Utility: Post-event	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Utility: Alive >60m scenario	Yes	0.860	0.086	0.65	0.98	Beta
Utility decrement: Post-HSCT < 1 year	Yes	0.170	0.017	0.14	0.20	Beta
Utility decrement: Post-HSCT 1-2 years	Yes	0.010	0.001	0.01	0.01	Beta
Utility decrement: Post-HSCT 3-5 years	Yes	0.020	0.002	0.02	0.02	Beta
Utility decrement: Post-HSCT >5 years	Yes	0.000	0.000	0.00	0.00	Beta

GP Utility – constant	Yes	0.951	-	-	-	-
GP Utility – age	Yes	0.000	-	-	-	-
GP Utility – age^2	Yes	0.000	-	-	-	-
GP Utility - gender	Yes	0.021	-	-	-	-
Obe-cel acquisition cost (£)	No	[redacted]	-	-	-	-
Oral (£)	Yes	321	32	261	387	Gamma
Subcutaneous (£)	Yes	34	3	28	41	Gamma
Intravenous (first attendance) (£)	Yes	393	39	320	474	Gamma
Intravenous (first attendance – complex chemotherapy) (£)	Yes	459	46	374	554	Gamma
Intravenous infusion (subsequent) (£)	Yes	375	37	305	452	Gamma
Home infusion pump costs (£)	Yes	125	13	102	151	Gamma
Mean daily hospital cost (£)	Yes	621	62	506	749	Gamma
Leukapheresis cost (£)	Yes	1,652	165	1,344	1.991	Gamma
Leukapheresis correcting factor	No	[redacted]	-	-	-	-
Bridging chemotherapy correcting factor	No	[redacted]	-	-	-	-
Conditioning chemotherapy costs (£)	Yes	1,533	153	1,248	1,848	Gamma
Conditioning chemotherapy correcting factor	No	[redacted]	-	-	-	-
Infusion and monitoring costs - Obe-cel (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
HSCT – initial cost (£)	Yes	115,591	11,559	94,050	139,321	Gamma
HSCT – per cycle cost (<6 months post-HSCT)	Yes	34,347	3,435	27,946	41,398	Gamma
HSCT – per cycle cost (6-12	Yes	23,594	2,359	19,197	28,438	Gamma

months post-HSCT)						
HSCT – per cycle cost (12-24 months post-HSCT)	Yes	17,026	1,703	13,853	20,521	Gamma
Obe-cel – proportion HSCT	Yes	0.00	0.00	0.00	0.00	Beta
HCRU costs: event-free – year 1 – CAR T (£)	Yes	565	56	460	681	Gamma
HCRU costs: event-free – year 2 – CAR T (£)	Yes	80	8	65	97	Gamma
HCRU costs: event-free – year 3+ – CAR T (£)	Yes	40	4	33	48	Gamma
HCRU costs: event-free – year 1 – non-CAR T (£)	Yes	367	37	299	443	Gamma
HCRU costs: event-free – year 2 – non-CAR T (£)	Yes	80	8	65	97	Gamma
HCRU costs: event-free – year 3+ – non-CAR T (£)	Yes	40	4	32	48	Gamma
HCRU costs: event-free – long-term survival (£)	Yes	20	2	16	24	Gamma
HCRU costs: post-event (£)	Yes	272	27	221	328	Gamma
Terminal care cost (£)	Yes	8,587	859	6986	10,349	Normal
Standardised mortality ratio for long-term survivors	Yes	3	0.30	1.09	4	Normal

AE – adverse event; BSA – body surface area; EFS – event-free survival; GP – general Practitioner; HCRU – health care resource use; HSCT – haematopoietic stem cell transplant; KM – Kaplan-Meier; LY – life year; OS – overall survival; OWSA – one-way sensitivity analyses; PSA – probabilistic sensitivity analyses; SA – sensitivity analysis; SE – standard error; SubTx – subsequent treatment; QALY – quality-adjusted life year

Table 118: Summary of variables applied within the economic model, specifically for the overall population

Parameter	Included in PSA?	Value	OWSA			Within SA varied by
			SE	Lower bound	Upper bound	

Starting age	No	48.30	4.83	38.82	57.74	Normal
Proportion male	No	50%	5.0%	40%	100%	Beta
Patient BSA	No	1.89	0.19	1.52	2.26	Normal
Patient weight	Yes	78.73	7.87	63.60	94.16	Normal
Inotuzumab – EFS KM adjustment	No	1.00	-	-	-	-
Inotuzumab acquisition cost (£)	No	8,048	-	-	-	-
Obe-cel bridging costs (£)	Yes	5,214	521	4,242	6,284	Gamma
Utility: Long-term survivorship	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Intozumomab – proportion HSCT	Yes	0.48	0.05	0.39	0.58	Beta
Obe-cel – SubTx drug costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Inotuzumab – SubTx drug costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Obe-cel – SubTx admin costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Inotuzumab – SubTx admin costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Obe-cel: total one-off AE costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Inotuzumab: one-off AE costs (£)	Yes	18,013	1,801	14,656	21,711	Gamma
Obe-cel: total AE utility decrement	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Inotuzumab: total AE utility decrement	Yes	0.108	0.011	0.087	0.130	Beta

AE – adverse event; BSA – body surface area; EFS – event-free survival; HSCT – haematopoietic stem cell transplant; KM – Kaplan-Meier; Ph – Philadelphia chromosome; PSA – probabilistic sensitivity analyses; SA – sensitivity analysis; SE – standard error; SubTx – subsequent treatment

Table 119: Summary of variables applied within the economic model, specifically for the Ph+ population

Parameter	Included in PSA?	Value	OWSA			Within SA varied by
			SE	Lower bound	Upper bound	
Starting age	No	55.60	5.56	44.70	66.50	Normal
Proportion male	No	32%	3.2%	0.26	1.00	Beta

Patient BSA	No	1.81	0.18	1.46	2.17	Normal
Patient weight	Yes	166.62	16.66	133.96	199.28	Normal
Ponatinib – EFS KM adjustment	No	1.00	-	-	-	-
Inotuzumab – EFS KM adjustment	No	1.00	-	-	-	-
Ponatinib acquisition cost (£)	No	4,116	-	-	-	-
Inotuzumab acquisition cost (£)	No	8,048	-	-	-	-
Obe-cel bridging costs (£)	Yes	5,094	509	4,145	6,140	Gamma
Utility: Long-term survivorship	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Ponatinib – proportion HSCT	Yes	0.47	0.05	0.38	0.56	Beta
Intozumomab – proportion HSCT	Yes	0.48	0.05	0.39	0.58	Beta
Obe-cel SubTx drug costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Ponatinib – SubTx drug costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Inotuzumab – SubTx drug costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Obe-cel SubTx admin costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Ponatinib – SubTx admin costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Inotuzumab – SubTx admin costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Obe-cel: total one-off AE costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Ponatinib: total one-off AE costs (£)	Yes	382	38	311	461	Gamma
Inotuzumab: total one-off AE costs (£)	Yes	17,403	1,740	14,160	20,976	Gamma
Obe-cel: total AE utility decrement	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta

Ponatinib: total AE utility decrement	Yes	0.064	0.006	0.052	0.077	Beta
Inotuzumab: total AE utility decrement	Yes	0.108	0.011	0.087	0.130	Beta

AE – Adverse event; BSA – Body surface area; EFS – Event-free survival; HSCT – Haematopoietic stem cell transplant; KM – Kaplan-Meier; OWSA – one-way sensitivity analyses; Ph – Philadelphia chromosome; PSA – Probabilistic sensitivity analyses; SA – Sensitivity analysis; SE – Standard error; SubTx – Subsequent treatment

Table 120: Summary of variables applied within the economic model, specifically for the Ph- population

Parameter	Included in PSA?	Value	OWSA			Within SA varied by
			SE	Lower bound	Upper bound	
Starting age	No	45.62	4.56	36.68	54.56	Normal
Proportion male	No	56%	5.6%	0.45	1.00	Beta
Patient BSA	No	1.91	0.19	1.53	2.28	Normal
Patient weight	Yes	168.11	16.81	135.16	201.06	Normal
Blinatumomab – EFS KM adjustment	No	0.44	-	-	-	-
Inotuzumab – EFS KM adjustment	No	1.00	-	-	-	-
Blinatumomab acquisition cost (£)	No	2,017	-	-	-	-
Inotuzumab acquisition cost (£)	No	8,048	-	-	-	-
Obe-cel bridging costs (£)	Yes	5,249	525	4,270	6,326	Gamma
Utility: Long-term survivorship	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Blinatumomab – proportion HSCT	Yes	0.13	0.01	0.11	0.16	Beta
Intozumomab – proportion HSCT	Yes	0.48	0.05	0.39	0.58	Beta
Obe-cel – SubTx drug costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Blinatumomab – SubTx drug costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Inotuzumab – SubTx drug costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma

Obe-cel – SubTx admin costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Blinatumomab – SubTx admin costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Inotuzumab – SubTx admin costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Obe-cel: total one-off AE costs (£)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Gamma
Blinatumomab: total one-off AE costs (£)	Yes	3,380	338	2,750	4,074	Gamma
Inotuzumab: total one-off AE costs (£)	Yes	18,229	1,823	14,832	21,971	Gamma
Obe-cel: total AE utility decrement	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Beta
Blinatumomab: total AE utility decrement	Yes	0.190	0.019	0.154	0.229	Beta
Inotuzumab: total AE utility decrement	Yes	0.108	0.011	0.087	0.130	Beta

AE – adverse event; BSA – body surface area; EFS – event-free survival; HSCT – haematopoietic stem cell transplant; KM – Kaplan-Meier; OWSA – one-way sensitivity analyses; Ph – Philadelphia chromosome; PSA – probabilistic sensitivity analyses; SA – sensitivity analysis; SE – standard error; SubTx – subsequent treatment

B16. In Doc B, Table 39 (page 140), data for hospital stay and ICU stay appears to be drawn from TA893 (These data were reduced from TA893 committee papers' report). However, in CS, Document B, page 89, the company stated, "All patients were hospitalised for obe-cel infusion for at least ten days. The median total duration of hospital stay following obe-cel infusion for mITT patients was 28.0 days (range: 4.0-118.0)." Could the company please provide data from the FELIX clinical trial specifically regarding hospital and ICU stays, as outlined in the table below? Additionally, could the company explain the rationale for using data from TA893 instead of FELIX trial data in this instance?

The median total duration of hospital stay reported in the CS was based on the June 2023 data cut-off. The Company has since recalculated the total duration of hospitalisation, with a mean total duration of hospital stay for patients in Cohort IIA of [redacted] days (range: [redacted]) including the 10-day hospital stay required to administer treatment with obe-cel. Table 121 outlines the hospital and ICU stays reported for patients in infused Cohort IIA in the February 2024 data cut-off of FELIX.

Table 121: Hospitalisation post obe-cel infusion of patients in Cohort IIA, February 2024 data cut-off

Hospitalisations		Mean (SD), Cohort IIA	Min - max, Cohort IIA
Hospital stay except ICU	Length of hospital stay (day)	[redacted]	[redacted]
ICU stay	Length of ICU stay (day)	[redacted]	[redacted]
	Proportion of patients requiring ICU – n (%)	[redacted]	

ICU – intensive care unit; SD – standard deviation
Source: Autolus, Data on file[1]

The Company has also calculated UK specific hospitalisation data from FELIX as of the February 2024 data cut-off, outlined in Table 122. Hospitalisation data were based on TA893 in the original CS as the FELIX trial was not UK specific, however on reflection the Company consider that the UK specific FELIX trial data would be more appropriate to use and have revised the Company base case.

Table 122: Hospitalisation post obe-cel infusion of patients in Cohort IIA, February 2024 data cut-off - UK sites (N=36)

Hospitalisations		Mean (SD), Cohort IIA	Min - max, Cohort IIA
Hospital stay except ICU	Length of hospital stay (day)	[redacted]	[redacted]
ICU stay	Length of ICU stay (day)	[redacted]	[redacted]
	Proportion of patients requiring ICU – n (%)	[redacted]	

ICU – intensive care unit; SD – standard deviation
Source: Autolus, Data on file[1]

When applying these values in the CEM, the administration cost of obe-cel decreases from £[redacted] (CS page 140-141) to £[redacted] due to a smaller proportion of patients required to stay in the ICU in comparison to TA893 data. Revised base case results inclusive of the FELIX UK hospitalisation data are presented in Table 129, Table 130, and Table 131 for the mITT, Ph- and Ph+ populations, respectively.

Section C: Textual clarification and additional points

C1. Please clarify the correct number from the following related to OS events: CS Table 15 states [redacted] patients died in the OS outcome, meaning [redacted] are alive, whilst Section B.3.3.2 (page 117) states [redacted] had not experienced an OS event.

The number of patients who did not experience an OS event prior to the February 2024 data cut-off is [redacted]. The number reported in Section B.3.3.2 (page 117) was a typographical error; the Company thanks the EAG for noting this.

Revised Company base case analysis

EFS IRRC survival analysis

The standard parametric and flexible spline extrapolations of the overall population for obe-cel EFS are presented in Figure 56 and Figure 57, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 123 and Table 124, respectively.

Figure 56: Standard parametric extrapolations for obe-cel EFS by IRRC - overall population

EFS – event-free survival; IRRC – Independent Response Review Committee; KM – Kaplan-Meier

Figure 57: Flexible parametric spline extrapolations for obe-cel EFS by IRRC - overall population

IRRC – Independent Response Review Committee; KM – Kaplan-Meier; OS – overall survival

Table 123: AIC and BIC statistical goodness-of-fit data for the obe-cel EFS by IRRC – overall population

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; IRRC – Independent Response Review Committee

Table 124: Goodness-of-fit data for obe-cel EFS by IRRC – overall 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; IRRC – Independent Response Review Committee

The standard parametric and flexible spline extrapolations of the Ph+ population for obe-cel EFS are presented in Figure 58 and Figure 59, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 125 and Table 126, respectively.

Figure 58: Standard parametric extrapolations for obe-cel EFS by IRRC – Ph+ population

[redacted]

EFS – event-free survival; IRRC – Independent Response Review Committee; KM – Kaplan-Meier

Figure 59: Flexible parametric spline extrapolations for obe-cel EFS by IRRC – Ph+ population

IRRC – Independent Response Review Committee; KM – Kaplan-Meier; OS – overall survival

Table 125: AIC and BIC statistical goodness-of-fit data for the obe-cel EFS by IRRC – Ph+ population

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; IRRC – Independent Response Review Committee

Table 126: Goodness-of-fit data for obe-cel EFS by IRRC – Ph+ 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; IRRC – Independent Response Review Committee

The standard parametric and flexible spline extrapolations of the Ph- population for obe-cel EFS are presented in Figure 60 and Figure 61, respectively. The AIC/BIC goodness-of-fit statistics for the standard and flexible spline models are presented in Table 127 and Table 128, respectively.

Figure 60: Standard parametric extrapolations for obe-cel EFS by IRRC – Ph- population

EFS – event-free survival; IRRC – Independent Response Review Committee; KM – Kaplan-Meier; Ph – Philadelphia chromosome

Figure 61: Flexible parametric spline extrapolations for obe-cel EFS by IRRC – Ph- population

IRRC – Independent Response Review Committee; KM – Kaplan-Meier; OS – overall survival; Ph – Philadelphia chromosome

Table 127: AIC and BIC statistical goodness-of-fit data for the obe-cel EFS by IRRC – Ph- population, standard parametric models

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

AIC – Akaike information criterion; BIC – Bayesian information criterion; EFS – event-free survival; IRRC – Independent Response Review Committee; Ph – Philadelphia chromosome

Table 128: Goodness-of-fit data for obe-cel EFS by IRRC – Ph- population, flexible spline parametric models

Distributions	AIC
0-knot hazards	
1-knot hazards	
2-knot hazards	
3-knot hazards	
0-knot odds	
1-knot odds	
2-knot odds	
3-knot odds	
0-knot normal	
1-knot normal	
2-knot normal	

3-knot normal	[redacted]

AIC – Akaike information criterion; EFS – event-free survival; IRRC – Independent Response Review Committee; Ph – Philadelphia chromosome

Revised base case cost-effectiveness results

As described in response to questions A29 and B16, the Company base case has been revised to include FELIX hospitalisation rates and EFS MAIC HRs and survival analyses using IRRC assessment.

For the overall population, the third best-fitting 3-knot normal flexible parametric spline curve was used as it aligned the closest to the survival estimates validated by UK clinicians at the time of the submission and provided a comparable statistical fit to the best-fitting 2-knot normal curve. For the Ph- population, the best-fitting standard parametric Weibull curve was used as indicated by the AIC and BIC goodness-of-fit statistics, consistent with the original submission. For the Ph+ population, the second best-fitting 1-knot hazards curve was selected, consistent to the original submission, as it provided an almost identical statistical fit to the best-fitting 0-knot hazards curve. Similarly to the curve selection for the overall population, the curves for the Ph- and Ph+ populations were chosen to align with the survival estimates of the curves identified as most appropriate by UK clinical experts as outlined in Section B.3.3.2 in the CS. All other CEM settings are as per the original Company base case in Section B.3.8 in the CS.

Results are presented in Table 129, Table 130, and Table 131 for mITT, Ph- and Ph+ populations, respectively. Results are well-aligned with the original Company base case.

Table 129: Deterministic results, overall population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.85	[redacted]

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

Table 130: 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.07	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.14	[redacted]	[redacted]

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

Table 131: 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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.00	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.51	[redacted]	[redacted]

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

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Anthony Nolan & Leukaemia UK
3. Job title or position	Anthony Nolan: [redacted] Leukaemia UK: [redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Anthony Nolan:** Anthony Nolan is a charity with 50 years of expertise in uniting science and people to push the boundaries of what can be achieved for blood cancer and blood disorder patients. Our stem cell register matches potential donors to patients in need of transplants. We carry out cell and gene therapy research to improve the outcomes from cell therapy and support patients through their treatment journeys. We are funded by a combination of income sources as detailed in our annual report. **Leukaemia UK:** Leukaemia UK is a leading leukaemia research and advocacy charity, that believes research has the power to stop leukaemia devastating lives. We bring together the leukaemia community—patients, families, researchers, and advocates—to fund and drive the life-saving breakthroughs that matter most to those affected. We campaign for change, pushing for earlier diagnosis, better treatment options, improved care, and more investment in research to represent the nearly 60,000 people living with leukaemia in the UK and to make sure that the next person with leukaemia has the best possible experience and outcomes of diagnosis, treatment and care. Leukaemia UK receives income from a variety of sources (as detailed in the charity's 2023 Annual Report).
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the	**Anthony Nolan:** • **Autolus Therapeutics:** ○ £50,000 commercial income for the provision of cord blood for cell and gene therapy research and development in immunotherapy/oncology

comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	○ £10,000 donation towards Anthony Nolan's CAR-T CNS • **Kite, Gilead:** £18,200 research grant towards the Anthony Nolan CAR-T Patient Experience Study • **Sanofi:** £20,000 grant to support the development of a report highlighting the psychological impact of stem cell transplant and CAR-T on patients and families **<u>Leukaemia UK:</u>** • **Novartis** funding of £20,000 for a policy research project
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We spoke directly to patients and family members, including a patient who had received obe-cel as part of a clinical trial, and other patients who had been treated for B-cell ALL with a stem cell transplant and other therapies. In addition we drew on insights from our regular patient surveys and wider engagement with patients and families affected by leukaemia. We also spoke to clinical experts about their experiences of treating patients with ALL.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Acute lymphoblastic leukaemia (ALL) is a rapidly progressing form of leukaemia (a type of blood cancer). It is life threatening and requires immediate treatment. In 2022, 1,173 people were diagnosed with ALL (men / women / children of all ages). Symptoms experienced prior to diagnosis for adults include fatigue, fever or night sweats, bruising or bleeding, pain in bones or joints, and unexplained weight loss. The NDRS 'Routes to Diagnosis' report shows that 64% of ALL patients are diagnosed via emergency presentation (42% via A&E and 27% via emergency GP referral). This compares to a cancer average of 22% and is the highest of any cancer type in the report. The rapidly progressing nature of the condition means that 86% of ALL patients start treatment within a week of diagnosis. Being diagnosed with ALL can also have a huge emotional impact, prompting patients (and their families) to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. The high rates of diagnosis in an emergency setting and the need to rapidly begin treatment contribute to the severe emotional toll of diagnosis. There is a high rate of relapse in ALL patients - nearly 50% of adults with ALL will relapse. Evidence indicates that having relapsed from initial treatment worsens a patient's quality of life further. Relapsed patients are more likely to feel isolated all of the time, they are also the most likely group to experience anxiety. In addition, relapsed patients are less satisfied with their healthcare teams' support for depression and anxiety. Carers and family members also experience extensive disruption to their lives and there is a considerable mental health impact on them too. Patients with ALL are usually unable to work during their treatment and recovery and require frequent visits to hospital, so it is often the carer who takes on responsibility for the household finances, providing transport and emotional support, and caring for the rest of the family. Often the patient is too ill to grasp the treatment pathway and or engage with their medical team, and so this also falls to their carers/family members.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Current treatment**
	Without treatment, relapsed and refractory B-cell ALL is incurable. Treatment is necessary to provide the chance of remission or at the very least to improve quality of life and extend survival. Current treatment options for relapsed or refractory B-ALL include:
	• Chemotherapy
	• Targeted immunotherapy (usually blinatumomab)
	• Donor stem cell transplant, which requires conditioning using high dose-chemo and possibly radiation therapy (if an appropriate match can be found and the patient is fit enough to tolerate transplant)
	• CAR-T therapy (patients under the age of 25 years old can access tisagenlecleucel (Kymriah), or those aged 26 years and over can access brexucabtagene autoleucel (Tecartus).
	
	Patient insights into current treatment
	Patients with relapsed or refractory B-cell ALL feel that current options are important but with several key limitations:
	• The severe and potentially long term side effects of treatment, including:
	  ○ the impact of high dose chemo, and total body irradiation (TBI) prior to stem cell transplant, including on fertility and in increasing the risk of secondary cancer
	  ○ the risk of Graft vs Host disease
	  ○ the risk of being immunocompromised over the long term
	• Negative impacts on work, social and family life
	
	Experiences of chemotherapy and stem cell transplant
	• Induction chemotherapy can result in fevers, diarrhoea, nausea, vomiting, complete lack of energy.
	• Patients often feel a lot of uncertainty about whether existing treatments will work and whether or not they will be well enough to get to a stem cell transplant. A patient told us they initially undertook chemotherapy which was ineffective, and then began treatment with blinatumomab with the intention to proceed to transplant. However, the leukaemia spread, and they were getting an increasing number of infections which meant they were then unable to have a stem cell transplant. This was challenging for them emotionally and physically.
	• Patients feel that stem cell transplant is an incredibly difficult treatment to go through, for themselves and their families. It requires intensive conditioning with high-dose chemotherapy and potentially TBI, long spells in hospital isolation, and has significant long term side effects and risks including Graft versus Host disease and infection. They would prefer to have effective options that have fewer physical and

	psychological side effects and long-term impacts on their health. In addition to the treatment itself, there is the mental health impact of waiting to find a donor match which can be stressful, and there are patient subgroup populations that are less likely to find a suitable donor match. • Experience of TBI: "*I had to have an NG tube inserted, because my throat blistered up fully from the radiation, so I wasn't able to swallow, I wasn't able to eat, so I was fed through an NG tube.*" • Conditioning regimens can lead to extreme tiredness, and lots of pain. One patient told us, "*I got all the side effects from the chemo because it's part of the conditioning process. I had chemotherapy and radiotherapy side effects back-to-back. They hit me, kind of a week later as well, so that two-to-three-week period immediately after the transplant was very challenging.*" • Patient/carer views of stem cell transplant vs CAR-T: *"If I had the choice now between a bone marrow transplant and CAR-T I would go straight to CAR-T. The transplant was so invasive and the chemotherapy and radiotherapy ahead of it has caused long term issues. I hope in the future they can give CAR-T as a first line treatment. If it wasn't for that she wouldn't be here."* **Patient and carer experiences of currently available CAR-T** There is very limited choice in the B-ALL pathway after someone has relapsed or is refractory to prior treatment. Patients feel that although the currently available CAR-T is very important, they would like to see more CAR-T options that are effective but with fewer side effects such as cytokine release syndrome and immune effector cell associated neurotoxicity syndrome (ICANS). These side effects can have very significant impacts on the quality of life and wellbeing of patients and families. Patients feel that ideally CAR-T should be offered earlier in the pathway to avoid the more severe complications of stem cell transplant and chemotherapy.
8. Is there an unmet need for patients with this condition?	There is an unmet need for treatments that can be tolerated by people with co-morbidities and reduced fitness. There has been a loss in access to additional CAR-T treatments in the adult B-cell ALL population since Kymriah was withdrawn from the Cancer Drugs Fund and not submitted for approval via the NICE technology appraisal process. Kymriah was being used by clinical team for patients who had comorbidities and could not withstand more toxic treatments, usually older patients. Currently, their choices have been greatly reduced, and clinical teams are less likely to start them for a CAR-T therapy as a result.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients who have received obe-cel as part of a clinical trial are very positive about its potential as a curative therapy where other treatments have failed. B-ALL patients would greatly welcome the availability of obe-cel as an additional CAR-T option. Clinical trial results indicate that obe-cel is much less likely to lead to severe side effects than the existing CAR-T option for people aged 26 and over (Tecartus). Patients and carers feel that fewer severe side effects would greatly improve their quality of life. They also feel that it is very important to have CAR-T options that could be suitable for a wider range of patients, such as older patients or those who have experienced significant side effects from prior stem cell transplant that would make them unable to tolerate the existing CAR-T. Reduced toxicity also allows clinicians to monitor patients out of hospital, i.e. in ambulatory care settings and reduces the use of intensive care. This is hugely beneficial for the mental health of patients and carers. We also feel that the UK-based manufacturing of obe-cel is likely to help improve outcomes for B-ALL patients as the product can be delivered in a shorter time frame, meaning there is less chance that a patient's condition could deteriorate to a point where CAR-T is no longer an option. Finally, as obe-cel's marketing authorisation is for patients 18 and older, there would be a much-needed additional option for people with B-ALL aged 18 and over who at present can only be offered one CAR-T product.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients and carers often need to travel long distances to receive CAR-T as this treatment is offered at a relatively small number of sites. They also need to remain within close distance of the treating hospital following the procedure for at least month. Although patients and carers appreciate the opportunity to receive CAR-T, they would welcome improved support with travel and accommodation costs.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Older patients and those with comorbidities will greatly benefit from the added option of obe-cel. Clinicians are more likely to see obe-cel as viable for these patients.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We know that minority ethnic patients are less likely to find a fully matched unrelated donor for stem cell transplant. As such, any additional options that can offer an alternative to an unrelated donor stem cell transplant, such as CAR-T, are important. Another potential equality issue is whether patients can afford to travel to CAR-T specialist centres in order to receive treatment, and whether they and their carers will be supported with travel, accommodation, and other needs related to long-term monitoring. Finally, there are the geographical inequalities that can have a negative mental health impact on patients. By the time patients have r/r B-ALL, they are usually aware of the international B-ALL community. A patient said that knowing a treatment is available somewhere else, but not to them, simply because of the country they live in can have a negative mental health impact because they become stressed and worried about why they cannot have access to another potentially curative option, and whether they should travel abroad to try to access this option. The patient noted, that regardless of the effectiveness of the treatment, or whether it was right for the person, knowing another option is available but not having access was overall a negative experience for patients. Conversely, there is a positive mental health impact of knowing you are receiving the right, personalised treatment tailored for your needs out of multiple options versus just the treatment that is available due to external constraints.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• **Obe-cel can help to meet a clear unmet need for additional CAR-T options**: There's a need for treatments with fewer severe side effects and that older and less fit patients can tolerate. The removal of certain CAR-T options (e.g., Kymriah) has left some patients with fewer choices, especially those with comorbidities. • **Obe-cel can help to improve the quality of life of patients receiving CAR-T**: Obe-cel offers a promising option due to its lower toxicity and quicker treatment delivery via UK-based manufacturing.

Thank you for your time.

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NHSE submission for obecabtagene autoleucel for relapsed/refractory acute lymphoblastic leukaemia ID6347

1. The base CAR T tariff excluding Market Forces Factor and overheads @ 24/25 prices was £58,953.
2. Each year, such tariffs are adjusted according to a composite figure of the following: the NHS Payment Scheme Cost Uplift Factor, the NHS Payment Scheme Efficiency Factor, any additional uplift for prices subject to the Market Forces Factor and any additional uplift to prices for Agenda for Change and medical pay awards. The pay award figure for 25/26 is not yet known and so the current uplift percentage is 2.56%.
3. The cost uplift and efficiency factors are published as part of the overall NHS Payment Scheme: NHS England » 2025/26 NHS Payment Scheme section 3.2 and 3.2. The CAR-T tariff itself is not published as this is classified as a local tariff and as such is only formally notified to the affected providers.
4. The base CAR T tariff excluding Market Forces Factor and overheads @ 24/25 prices is currently £60,462.
5. The costs included in the CAR T tariff are as shown below:

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

Prof Peter Clark
National Clinical Lead for cancer drugs and the Cancer Drugs Fund
NHS England
May 2025

Title: *Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID6347]: EAG Report*

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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.
RB: Has contributed to a press release for Amgen of the results from E1910 study (blinatumomab) in the past 12 months.
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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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Contributions of authors
MY led the summary and critique of the cost-effectiveness section. AMe led the summary and critique of the clinical effectiveness section. AMw, IK and KY contributed to the clinical effectiveness review. MP led the statistical critique throughout the report. RB contributed to the background section. DG led the project. All authors read the final report.

Please note that: Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

Table of Contents

Table of Tables

Table of Issues

Table of Figures

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report (starting at section 2).

All issues identified represent the EAG's view, not the opinion of National Institute for Health and Care Excellence (NICE).

1.1 *Overview of the EAG's key issues*

Table 1: Summary of key issues

ID6347	Summary of issue	Report sections
Key Issue 1	Limitations of the FELIX trial for decision making	2.2.2, 3.2.1
Key Issue 2	Reliance on biased and highly uncertain MAIC analyses	3.3, 3.4
Key Issue 3	Preferred population and method for extrapolations	4.2.3, 4.2.6
Key Issue 4	Hospitalisation and resource use for obe-cel	4.2.8.1
Key Issue 5	Costs of follow-up after allo-SCT	4.2.8.5
Key Issue 6	Costs and effects of allo-SCT	4.2.8.5
Key Issue 7	Most suitable severity modifier to apply	4.2.9

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The choice of population, influencing preferred MAIC outputs and survival extrapolations
- The method of calculation of follow-up costs after Allogeneic Stem Cell Transplant (allo-SCT)
- The severity modifier deemed most suitable
- Whether to apply the CAR T tariff for costs associated with obe-cel

Additional changes made by the EAG, with a non-trivial effect, relate to the source of adverse events (AEs) used in the modelling, and an annual discount rate.

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

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

Overall, the technology is modelled to affect costs by:

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

The modelling assumptions that have the greatest effect on the ICER are:

- The application of costs following allo-SCT
- The choice of population and corresponding survival extrapolations
- The application of subsequent allo-SCT costs for obe-cel
- The severity modifier
- The application of the CAR T tariff cost

1.3 *The decision problem: summary of the EAG's key issues*

No key issues related to the decision problem were identified by the EAG.

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 1: Limitations of the FELIX trial for decision making

Report section	2.2.2, 3.2.1
Description of issue and why the EAG has identified it as important	If approved, obe-cel appears to be accessible at several points in the B-ALL treatment pathway. The EAG understands that most or all of the identified points have some representation in the FELIX trial, however there may be differences in their expected outcomes. Analyses are largely presented for a whole FELIX population, combining these different points. This single-arm trial has a small sample size and limited follow-up. The EAG has concerns around approaches to censoring, and the exclusion of people with Eastern Cooperative Oncology Group (ECOG) ≥2 among other concerns that despite its high recruitment within the UK, is unlikely to be representative of the NHS population.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up from FELIX, and new head-to-head trials or real-world studies could provide more certainty of the short and long-term efficacy of obe-cel.

Issue 2: Reliance on biased and highly uncertain Matching-adjusted indirect comparisons (MAIC) analyses

Report section	3.3, 3.4
Description of issue and why the EAG has identified it as important	The EAG is concerned by the comparison of the post-infusion period of FELIX which ignores the outcomes of people who were enrolled but not infused, to follow-up from other trials that do not have a pre-infusion period. The MAICs are not able to account for all known treatment effect modifiers and may be biased. The effective sample sizes are small and estimates highly uncertain. There is the potential for unmeasured differences across the trials such as for previous and subsequent therapies received.
What alternative approach has the EAG suggested?	The EAG considers using the enrolled (intention-to-treat, ITT) population of cohorts IA and IIA to be a fairer and more reliable comparison, though it likely still violates the assumption of proportional hazards and is subject to many of the same limitations. However, the EAG considers it the best available option at this stage.
What is the expected effect on the cost-effectiveness estimates?	It is unclear how close to a true and fair comparison current analyses are.

What additional evidence or analyses might help to resolve this key issue?	Head-to-head trial evidence would reduce reliance on indirect comparisons.

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

Issue 3: Preferred population and method for extrapolation

Report section	4.2.3, 4.2.6
Description of issue and why the EAG has identified it as important	The company uses the infused mITT population of FELIX cohort IIA for the basis of all comparisons, whilst the EAG prefers the enrolled ITT population of cohorts IA and IIA. This choice of population affects the choice of extrapolation for obe-cel plus the hazard ratio and reference extrapolation for inotuzumab and blinatumomab. Using hazard ratios for the comparisons to inotuzumab and blinatumomab assumes proportionality which does not hold. It is uncertain whether the assumption of cure at 3 years is suitable for all people remaining alive, especially those in the post-event health state.
What alternative approach has the EAG suggested?	The EAG preference of using the pooled cohorts results in a bigger sample and more information to extrapolate from, and less biased estimates of relative efficacy. This approach still relies on the assumption of proportionality, which is likely violated, however no better options are available.
What is the expected effect on the cost-effectiveness estimates?	This has a moderate effect on the ICER.
What additional evidence or analyses might help to resolve this key issue?	The ability to implement MAIC weighted extrapolations for the ITT/enrolled population would allow relaxing the proportional hazards (PH) assumption but will be based on the characteristics of the trial populations of the comparator treatments.

Issue 4: Hospitalisation and resource use for obe-cel

Report section	4.2.8.1
Description of issue and why the EAG has identified it as important	The company has used data from FELIX to derive model inputs around length of stay in hospital, proportion requiring intensive care unit (ICU) and duration of ICU stay, but these come from the UK-specific subgroup of FELIX and were lower than the broader FELIX population.
What alternative approach has the EAG suggested?	The EAG prefers to use the CAR T tariff cost to account for hospitalisation costs of obe-cel. The EAG also explores a scenario applying ICU costs in addition to the CAR T tariff cost.
What is the expected effect on the cost-effectiveness estimates?	This has a small impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Real-world data from a sufficient sample of UK patients could enhance the estimates of these parameters.

Issue 5: Costs of follow-up after allo-SCT

Report section	4.2.8.5
Description of issue and why the EAG has identified it as important	The EAG noticed an error in the company's application of costs of follow-up after allo-SCT. For example, the follow-up costs applied for the ~50% people receiving allo-SCT after inotuzumab greatly exceeded the EAG's estimated follow-up costs for if all people had received allo-SCT. These costs are substantial.
What alternative approach has the EAG suggested?	The EAG has altered how these costs are calculated and applied within the model, resulting in a much lower cost of follow-up after allo-SCT.
What is the expected effect on the cost-effectiveness estimates?	This has a large impact on the cost-effectiveness results.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers this issue resolved.

Issue 6: Costs and effects of allo-SCT for obe-cel

Report section	4.2.8.5
Description of issue and why the EAG has identified it as important	The company base case analyses use data from FELIX that is not censored for receiving subsequent allo-SCT (i.e. includes the effect), but do not capture the costs associated with this allo-SCT use.
What alternative approach has the EAG suggested?	The EAG implements where the costs of this subsequent allo-SCT are included in the model.
What is the expected effect on the cost-effectiveness estimates?	This has a moderate effect on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Real-world time-to-event data from a sufficient sample of UK patients including information on subsequent allo-SCT may be an improved source of efficacy and cost data.

1.6 *Other key issues: summary of the EAG's view*

Issue 7: Most suitable severity modifier to apply

Report section	4.2.9
Description of issue and why the EAG has identified it as important	The company's analysis identifies that a 1.7 severity multiplier may be appropriate based on their extrapolation of blinatumomab in the Philadelphia chromosome-negative (Ph-) population. A 1.2 multiplier was calculated as appropriate for inotuzumab and ponatinib based on the pooled and Philadelphia chromosome-positive (Ph+) populations respectively. The company applies the 1.7 multiplier for all analyses, regardless of the population and comparator, which the EAG considers inappropriate. The EAG accepts it is possible that for some placements of obe-cel in the treatment pathway, a 1.7 multiplier may be applicable, but there is insufficient evidence to justify this at present.
What alternative approach has the EAG suggested?	The EAG has conducted a weighted analysis to show that if just 5% of people with Ph- disease received inotuzumab, a QALY shortfall analysis suggests the 1.2 multiplier is correct. The EAG base case analysis involving blinatumomab also supports using a 1.2 multiplier for this comparison.
What is the expected effect on the cost-effectiveness estimates?	This has a large impact on the ICER when other corrections and changes are made.
What additional evidence or analyses might help to resolve this key issue?	Evidence from subgroups of patients at later points in the treatment pathway may justify the higher threshold, however may require a narrowing of the eligibility criteria for obe-cel (i.e. an optimised recommendation).

1.7 *Summary of EAG's preferred assumptions and resulting ICER*

Table 2 contains the changes to get to the EAG base-case ICERs for the pooled population vs inotuzumab, implemented one at a time, showing the impact of each on the company's base case ICER.

Table 2: Summary of EAG's preferred assumptions and ICER

EAG's preferred assumption based on issues		Obe-cel vs inotuzumab		
		Inc. Costs (£)	**Inc. QALYs**	**ICER (£/QALY)**
Company's base case		[redacted]	2.85	[redacted]
1	Programming and implementation errors related to incorporating follow-up costs of allo-SCT in the economic model	[redacted]	2.85	[redacted]
2	Inappropriate ITC approach and narrowed population	[redacted]	2.27	[redacted]
3	Inconsistent Inclusion of Costs and effects of allo-SCT for obe-cel in the Economic Model	[redacted]	2.85	[redacted]
4	Underestimating Hospitalization Durations and Resource Use Post obe-cel Infusion	[redacted]	2.85	[redacted]
5	Underreporting of adverse events and discrepancies with the company's clinical study report (CSR)	[redacted]	2.68	[redacted]
6	Inconsistencies in severity modifier application across comparator populations	[redacted]	2.01	[redacted]
7	Excluding allo-SCT utility effects from the economic model	[redacted]	2.83	[redacted]
8	Use of per-cycle discount rate instead of per-year discount rate	[redacted]	2.91	[redacted]
9	EAG Base Case (Changes 1-8)	[redacted]	1.51	[redacted]
ITC – Indirect treatment comparison; QALY – Quality-adjusted life year; SCT – Stem cell transplant; EAG-External assessment group;				

Acronyms Table

Abbreviation	Description
AE	Adverse event
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
Allo-SCT	Allogeneic Stem Cell Transplant
AML	Acute Myeloid Leukaemia
B-ALL	B cell precursor acute lymphoblastic leukaemia
BCR / ABL	Breakpoint Cluster Region / Abelson Murine Leukaemia
BIC	Bayesian information criterion
BM	Bone marrow
Brexu-cel	Brexucabtagene autoleucel
BSA	Body surface area
BSC	Best supportive care
CAR	Chimeric antigen receptor
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CNS	Central nervous system
CO	Clinical Overview
CQ	Clarification questions
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery
CRR	Complete Remission Rate
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of remission
EAG	External Assessment Group
ECOG/ PS	Eastern Cooperative Oncology Group/ Performance status
EFS	Event-free survival
EM	Erythema multiforme
EMD	Extramedullary disease
EQ-5D/ 5L	EuroQol Five Dimensions of Quality of Life / 5 level scale

EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire - Core 30-item version
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FDA	Food Drug Administration
FLAG	Fludarabine, cytarabine, and granulocyte colony-stimulating factor
FLAG-IDA	Fludarabine, cytarabine, and granulocyte colony-stimulating factor, Idarubicin
GvHD	Graft versus host disease
HCRU	Healthcare resource use
HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic Stem Cell Transplantation
HR	Hazard ratio
HRG	Health Resource Group.
HRQoL	Health-related quality of life
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Individual patient data
IQR	Inter-quartile range
IRRC	Independent Response Review Committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
Kg	Kilogram
KM	Kaplan-Meier
LD	Lymphodepletion
LYG	Life years gained
MAIC	Matching-adjusted indirect comparisons
MAS	Macrophage activation syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified Intention-to-treat
MRD	Minimal residual disease
NA	Not applicable
NE	Not estimable

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
Obe-cel	Obecabtagene autoleucel
ORR	Overall remission rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
PFS	Progression-free survival
Ph-	Philadelphia chromosome-negative
Ph+	Philadelphia chromosome-positive
PH	Proportional hazards
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal social services
PT	Preferred term
QALY	Quality-adjusted life years
R/R	Relapsed or refractory
RoB	Risk of bias
ROBINS-E	Risk Of Bias in Non-randomized Studies - of Exposures
ROBINS-I	Risk Of Bias in Non-randomized Studies - of Interventions
ROBIS	Risk Of Bias in Systematic Reviews
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMR	Standard mortality ratio
SoC	Standard of care
STA	Single Technology Appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TEMs	Treatment effect modifiers

TKI	Tyrosine kinase inhibitors
TLS	Tumour lysis syndrome
VOD	Veno-occlusive disease
WTP	Willingness-to-pay

External Assessment Group Report

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction*

The EAG has reviewed the company submission (CS) from Autolus Limited to NICE on the clinical- and cost-effectiveness of obecabtagene autoleucel (obe-cel) for treating relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (B-ALL) in adults.

The company states that [redacted] (CS Document B, Section B. 1.1 and 1.2 Table 2). The CS did not state when it expects anticipated the marketing authorisation.

2.2 *Background*

The company provides a description of obe-cel and of the relevant health condition in sections B. 1.2 and 1.3 of the CS. The EAG provides a critique of the company overview of the disease, the technology, the positioning of obe-cel in the treatment pathway and additional input has been provided by the EAG clinical advisors.

2.2.1 Condition, epidemiology and symptoms

The CS cited relevant references in their description of the health condition (CS, doc B, section 1.3.1). However, the EAG noted that this appraisal lacked detailed evidence specific to R/R B-ALL. R/R B-ALL is a blood cancer where the disease returns after remission or does not respond to initial treatment.[1] This condition is a subtype of acute lymphoblastic leukaemia (ALL), a fast-progressing bone marrow cancer characterised by excessive production of immature lymphocytes (blast cells), which crowd out normal blood cells and impair their function.[2]

In the UK, ALL is most common in individuals under 25 (65% of cases), and cases over 60 years account for 13% of ALL cases. The incidence of ALL is higher in men than women.[3] However, B-ALL is the most common subtype of ALL in adults,

accounting for approximately 75% of ALL cases, with the remainder predominantly being T-cell ALL. [4, 5]

In addition to being classified as either B-cell or T-cell ALL, the condition can also be categorised based on chromosome and genetic changes, such as the presence of the Philadelphia chromosome (Ph+). Ph+ ALL occurs when the ABL1 (Abelson Murine Leukemia) gene on chromosome 9 fuses with the BCR (Breakpoint Cluster Region) gene on chromosome 22, forming the BCR-ABL fusion gene, which produces an abnormal tyrosine kinase protein that drives leukaemia cell growth.[6] Ph+ B-ALL is more common in older people (affects 20 – 30% of adults).[7-9]

Patients with R/R B-ALL often present symptoms similar to those seen at the ALL diagnosis, including cytopenia-related issues like anaemia, fatigue, easy bruising, fever, and recurrent infections.[6, 9] Additional symptoms may include bone and joint pain, abdominal pain, swollen lymph nodes and dyspnoea.[6, 9-12]

In the R/R B-ALL, adults have a higher relapse rate after achieving remission (50–70%) compared to children (15–20%).[13] General risk factors associated with R/R B-ALL that lead to poor prognosis include age, initial white blood cell count (>50 x 10^9 cells/L), and genetic and chromosomal abnormalities, such as Ph status or other genetic mutations like Down syndrome.[3, 14, 15]

The EAG clinical advisors also noted that Ph+ B-ALL patients were historically associated with a poor prognosis but improved since the advent of tyrosine kinase inhibitors (TKI).

The CS in section B.1.3.6 states that "*ALL is associated with substantial resource use and high costs"*. However, the EAG notes that the evidence cited broadly to all blood cancer types and is not specific to R/R B-ALL.[16] Additionally, the CS cites R/R B-ALL specific data on two health care resource use (HCRU) studies conducted in the UK.[17, 18] While the EAG acknowledges the need for novel therapies to reduce the HCRU burden associated with R/R B-ALL, it highlights limitations in the cited studies. Both studies[17, 18] rely on indirect data collection methods rather than real-world patient-level data and do not provide a detailed cost analysis to quantify the HCRU impact. The CS also reports HCRU outcomes for the FELIX trial as the only study that explores these outcomes specifically for R/R B-ALL in a UK setting. The EAG further discusses the FELIX trail in the clinical effectiveness section 3 of this report.

2.2.2 Clinical treatment pathway

2.2.2.1 Initial treatment

The initial diagnosis and treatment of ALL involve blood and bone marrow tests, genetic testing, and further assessments.[2, 19] The bone marrow and blood sampling results stratify risk, inform prognosis, and set treatment targets. Treatment varies by patient characteristics including Ph status (Ph+/-), age, and health, and typically includes four phases. The CS summarises these phases while citing relevant sources.[2, 20-22] These phases may vary in duration based on the patient's response to treatment and overall risk factors.[2, 20-22] The phases include:

- Pre-phase & Supportive Care: Steroids, chemotherapy, and medications to prevent tumour lysis syndrome (TLS) risk, whereby cancer cells' rapid destruction leads to complications including renal failure.[2]
- Induction (1-2 months): Combination chemotherapy to achieve remission.
- Consolidation (6-8 months): High-dose chemotherapy targeting hidden disease.
- Maintenance (2-3 years): Low-dose chemotherapy with regular monitoring.

Stem cell transplant (SCT) is an option post-induction or consolidation for high-risk patients or those with minimal residual disease (MRD) patients.[2, 23]

2.2.2.2 Position of Obe-cel in the clinical treatment pathway

The CS states that no UK-specific guidelines exist for R/R B-ALL in adults. Still, the European Society for Medical Oncology (ESMO) provides guidance.[22, 24, 25] These treatment options include salvage chemotherapy, immunotherapy and chimeric antigen receptor T-cell (CAR-T). Although no universally accepted salvage therapy exists, treatment generally aims to achieve remission followed by SCT. The choice of treatment is tailored to patient-specific factors, such as performance status, comorbidities, transplant eligibility, and the duration of the first response.[2]

The ESMO guidelines recommends stratifying treatment for R/R ALL based on Ph status:

- Ph+ Patients: Initial therapy TKI combined with chemotherapy, transitioning to immunotherapy if necessary (e.g., ponatinib or inotuzumab)

- Ph- Patients: Immunotherapy (e.g., inotuzumab or blinatumomab) is typically first-line.

In the UK, Immunotherapy options include inotuzumab and blinatumomab, targeting CD22 and CD19, respectively. For Ph+ patients, ponatinib is recommended while inotuzumab is recommended only after TKI failure.[26] Blinatumomab is currently recommended by NICE for Ph- patients and approved for MRD+ R/R B-ALL, with NICE evaluations ongoing for its use in MRD-negative cases.[20, 21].

Role of CAR-T therapy

An emerging option is chimeric antigen receptor T-cell (CAR-T) therapy, such as obe-cel.[27] Obe-cel is positioned as a CD19 CAR-T therapy in the CS, designed to reprogram T-cells to target and destroy CD19-expressing malignant and normal B-cells.[28] The CS provides a treatment algorithm for R/R B-ALL based on ESMO guidelines (CS, section B.1.3.4.2, Figure 4).

Updated treatment pathway based on EAG advice

Based on EAG clinical expert advice, the EAG has mapped where Obe-cel might fit in the NHS treatment pathway (Figure 1). As a first-line therapy, Obe-cel can be considered alongside ponatinib, inotuzumab, and blinatumomab. For patients ineligible for allo-SCT due to persistent disease, advanced age, or lack of a suitable donor (e.g., in minority ethnic groups), obe-cel or palliative care is preferred. Patients achieving complete remission (CR/CRi) proceed to allo-SCT or obe-cel. Those in remission and eligible for CAR T with a reasonable chance of durable remission are often directed to the less toxic CAR T option instead of allo-SCT. Patients not achieving CR/CRi with first-line therapies are directed to obe-cel or palliative care. For patients refractory to or relapsing after obe-cel, palliative care becomes the primary pathway, though allo-SCT could be considered for very fit and young patients. Patients at high relapse risk without active disease may undergo clinical observation (or allo-SCT for a few numbers). It is uncommon to start other therapies in these cases, as they do not have active disease, and hence palliative care is not considered.

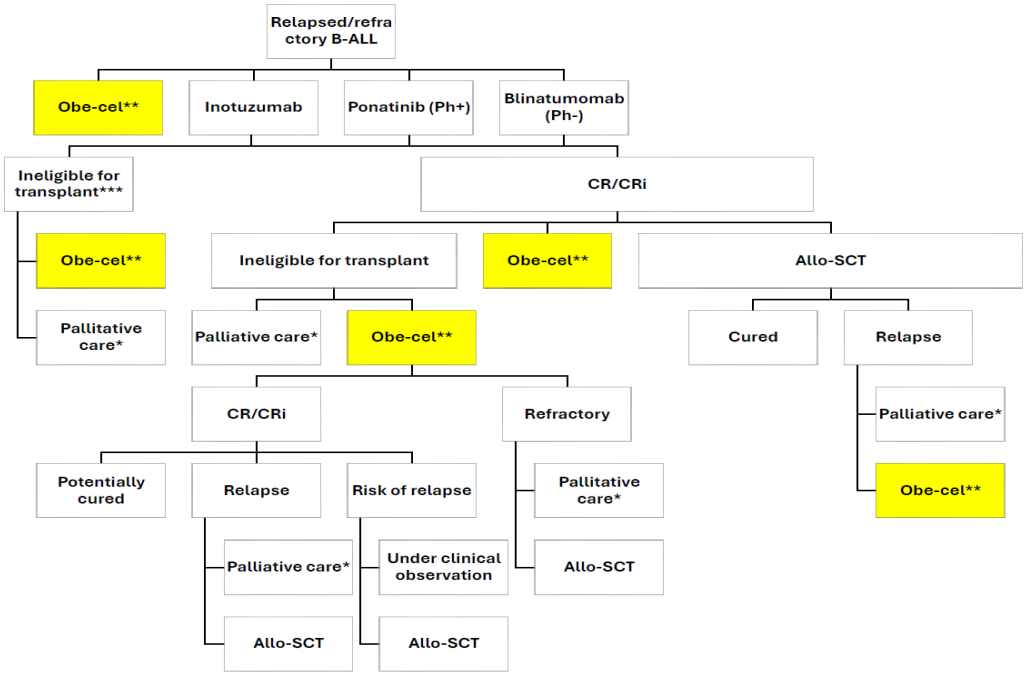

Figure 1: Position of Obe-cel in the clinical treatment pathway for R/R B-ALL

*Inotuzumab, blinatumomab, and ponatinib may replace palliative care if beneficial; **The EAG considers that the post-obe-cel treatment pathway, as shown on the bottom left, applies regardless of where in the pathway obe-cel is used. Note that obe-cel is often used alongside bridging therapies (not shown); ***Ineligible for an allo-SCT due to persistent disease/fitness/other factors.

2.3 *Unmet need*

The company suggests that there is an unmet need. CS Section B.1.3.8 states that current CD 19 CAR-T cell therapies are associated with life-threatening toxicities thus being unsuitable for older and fragile patients.[29-31] The CS also highlights the economic burden incurred by ALL patients in terms of HCRU and cost burden. While the cited sources are relevant to ALL, the EAG notes that none of these pertain to R/R B-ALL as noted earlier in section 2.2.1 of this report.

2.4 *Critique of company's definition of decision problem*

The EAG comments on the company's decision problem are in Table 3. There are differences between the company decision problem and the final NICE scope,[32] but the EAG has no major concerns. The evidence provided in the CS is largely aligned with the decision population. Key differences include:

- The FELIX trial includes adult patients aged 18 years and older with R/R B-cell ALL are included in the FELIX trial.

- The comparator in NICE's scope includes tisagenlecleucel, inotuzumab ozogamicin, fludarabine, cytarabine, and granulocyte colony-stimulating factor (FLAG)-based chemotherapy, blinatumomab, TKI (e.g., imatinib, dasatinib, ponatinib), and best supportive care. However, the CS is limited to blinatumomab, inotuzumab, and ponatinib which are narrower than the NICE final scope.[32] The EAG finds the company's justifications for these comparators sufficient.
- The company presents subgroup analyses across various patient characteristics. The EAG notes that these subgroup analyses have not been considered in the NICE final scope.[32]

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with R/R B-precursor ALL	Adults ([redacted] with R/R B-cell ALL.	The anticipated marketing authorisation for obe-cel will be for [redacted].	The EAG agrees that the population is in line with the NICE scope. However, adult patients who are 18 years and older are included in the FELIX trial. As a rationale for this narrower population, the company states "the anticipated marketing authorisation for obe-cel will be for [redacted]". However, at the time of the EAG submission of this report (24th January 2025, no marketing authorization approval has been granted for the company submission. Therefore, the company's evidence is for a narrower population than NICE's final scope.
Intervention	Obe-cel	In line with scope	NA	The EAG agrees that the intervention aligns with NICE final scope. The company also describes the technology and obe-cel mechanism of action (CS Document B, Section B.1.2, Table 2), which is consistent with the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				summary of product characteristics (SmPC).[33]
Comparator(s)	Tisagenlecleucel (for adults aged 25 years and under) Inotuzumab ozogamicin (CD22-positive B-precursor ALL) Fludarabine, cytarabine and granulocyte colony stimulating factor (FLAG)-based combination chemotherapy Blinatumomab (Philadelphia-chromosome-negative ALL) Tyrosine kinase inhibitor (such as imatinib, dasatinib or ponatinib), alone or in combination with FLAG-based combination chemotherapy (Philadelphia chromosome-positive ALL) Best supportive care (including palliative care)	According to the anticipated place of obe-cel in the treatment pathway, the appropriate comparators are as follows: Inotuzumab ozogamicin Blinatumomab (Ph-) Ponatinib (Ph+)	The following therapies should not be in scope based on the final licence wording for obe-cel: Tisagenlecleucel Clofarabine The expected indication for obe-cel is [redacted] years. Tisagenlecleucel is recommended as an option for people 25 years and under, and clofarabine is not recommended but possibly used off-label in young adults. FLAG-based chemotherapy lies within the licence of obe-cel, however, is not considered a comparator due to the positioning of obe-cel alongside clinical feedback and committee preferences expressed in TA893 ([brexucabtagene autoleucel for treating R/R B-cell ALL in people 26 years and over]). In TA893, the committee had concerns of the toxicity associated with	The company only includes inotuzumab ozogamicin, blinatumomab for negative Philadelphia chromosome (Ph-), and ponatinib for positive Philadelphia chromosome (Ph+) (CS Document B, Table 1) while highlighting this as a treatment pathway that has been considered for obe-cel. The company provides their rationale for the exclusion of other comparators listed in the NICE final scope. The EAG has checked the validity of these rationales with the EAG clinical advisors and highlights the following: Tisagenlecleucel: The EAG agree it is recommended only within the Cancer Drugs Fund (CDF) for patients ≤25 years, under managed access conditions.[34]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			FLAG-IDA and noted limited use in clinical practice. The patients anticipated to receive obe-cel are equally fragile as those receiving brexu-cel. Therefore, it is unlikely that the population eligible for obe-cel would be eligible for FLAG-IDA. This view was shared by two clinical experts interviewed as part of this submission. Imatinib should not be included as comparator in the scope as it is for an earlier line of treatment not included within the licence. Imatinib is used earlier in the treatment pathway and is therefore not a relevant comparator to obe-cel. Dasatinib should not be included as comparator in the scope as it is not reimbursed in the UK and not used in clinical practice. Best supportive care (palliative care) lies within the licence of obe-cel, would be given to patients who cannot tolerate chemotherapies or targeted treatments. These patients would not be eligible for CAR T-cell	FLAG- based chemotherapy (fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin): The EAG agree that FLAG-IDA is toxic (per TA893) Clofarabine: The EAG agrees it is used “off-label” in the paediatric/young adult setting as part of the CDF.[35] Imatinib and Dasatinib: The EAG agrees imatinib should be excluded, as it is used earlier in the pathway and outside the licence.[36] Dasatinib should also be excluded, as it is not reimbursed in the UK or used in practice.[37] Best supportive care: The EAG agrees it is irrelevant as a comparator, as it applies to patient’s ineligible for CAR T-cell therapy. Additionally, all patients as part of NHS care will receive it regardless of their treatment options.

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**	**EAG comment**
			therapy and therefore best supportive care is not a relevant comparator to obe-cel	
Outcomes	Overall survival Progression-free survival (including relapse-free survival and event-free survival) Treatment response rate (including minimal residual disease, haematologic responses and complete remission) Rate of allogenic stem cell transplant Adverse effects of treatment Health-related quality of life	In line with scope	NA	The EAG notes that the company has not reported relapse-free survival and upon clarification, the company stated that "*Relapse-free survival was removed as an outcome of the FELIX clinical trial following regulatory feedback (US Food and Drugs Administration [FDA] in 2022).Therefore, it is unavailable and has been replaced by event free survival due to the FDA's suggestion*" (clarification question A21). The EAG clinical advisors agree that they would consider EFS to be equivalent to PFS in this setting
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time	In line with scope	NA	The economic modelling was broadly in line with the NICE reference case, however the EAG noted that discounting was applied on a per-cycle basis meaning it had effect in the first year. The EAG used an annual approach which did not have any effect for the first year.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups	Not specified	Ph+ Ph-	Some of the comparators included in this appraisal are available within the Ph+ and Ph- subgroups. To allow comparison with blinatumomab (Ph-) and ponatinib (Ph+), the model distinguishes between these subgroups.	NICE has not specified any subgroups for this appraisal. However, the company has included Ph+ and Ph- subgroups into the economic model (CS, doc B, Table 1, page 12). Additionally, the company has provided a more extensive list of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				subgroups in the CS, Appendix E which includes: Sex Age Race Ethnicity CNS status at screening Extramedullary (EM) disease presence at screening and pre-conditioning Blasts in bone marrow (%) at screening and pre-conditioning Karyotype at pre-conditioning Refractory to all prior lines of anti-cancer therapy, to first-line treatment, to last previous lines of therapy Relapsed to first-line therapy within 12 months Number of previous lines of therapy Previous allogeneic SCT (allo-SCT), blinatumomab, and inotuzumab The EAG and the clinical advisors accepts the subgroups suggested by the company. The EAG clinical

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				advisors also note that among the suggested subgroups, the key effect modifiers are ECOG status above 2 (associated with poor outcomes compared to ECOG status 0 or 1), age, disease burden – specifically blasts in bone marrow (%) and extramedullary disease at screening and pre-conditioning. However, sex and Philadelphia chromosome status are less significant modifiers.
Special considerations including issues related to equity or equality	NA	NA	NA	NA

CAR T-cell therapy, Chimeric antigen receptor T-cell therapy; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; HRQoL, health-related quality of life; Ph+, Philadelphia chromosome-positive; Ph-, Philadelphia chromosome-negative; r/r B-ALL, relapse or refractory B-cell Acute lymphoblastic leukaemia

3 CLINICAL EFFECTIVENESS

3.1 *Summary and critique of the methods of review(s)*

The CS presents a systematic literature review (SLR) of clinical trials on patients with r/r B-ALL. The company's SLR has been a replication and update of TA893.[38]

3.1.1 Search strategy

Searches in a relevant set of bibliographic databases were undertaken in May 2024 (CS Appendix D.2). The company reports to have carried out an update of the search strategy for the SLR of the STA for brexucabtagene autoleucel (brexu-cel) for treating R/R B-cell ALL in people 26 years and over, TA893.[38] The most recent search strategy for TA893 was carried out in September 2021; thereby, the company limited the searches for this update to studies published after 2021. The full search strategies for TA893 are not publicly available. The available data for the TA893 search strategies consists of the numbers of search results, as reported in the clarification responses (A14, A17, Figure 4: Clinical SLR PRISMA flow chart).[27] Therefore, the company was not able to rerun the exact search strategy using the same search terms. The company reported the methods used to test and 'validate' their search strategy was to develop a broad search 'with the aim of capturing the studies included in the TA893 SLR' and to compare the overall number of hits for each database search for their search (limited to studies published up to November 2020) against the overall number from the original searches for TA893 (CS Appendix D.3 Table 10). The company report that the search results from their searches were larger and could thus conclude that their searches were broader. The EAG notes that the necessitated changes to the search terms and syntax means that the search carried out by the company are not a true update of the search for TA893. The company tested whether their search retrieved all included studies for TA893 to the extent possible based on available information. The EAG notes that the company's approach of developing and testing their search to ensure that a broader search was conducted would be a reasonable approach if the inclusion and exclusion criteria was the same for this submission as TA893 or if the search included search terms for the population only, as the EAG critique of the search strategy for TA893 did not identify any significant issues.[27] The EAG note that as the inclusion and exclusion criteria for this submission differs from TA893, as outlined in Table 4 and the EAG

assessment of risks of bias of the CS systematic review about the scope of the appraisal (modified ROBIS), they cannot conclude with certainty that their updated search is sufficiently comprehensive to ensure that all relevant studies for the intervention and comparators would be retrieved. To ensure that a thorough and comprehensive search is carried out, the EAG would recommend that the search strategy only include search terms for the population/ condition only and limited the results published after 2021 or that a new search strategy for population and all relevant intervention and comparator terms is run that is not restricted by date.

Notably, obecabtagene autoleucel was not listed as a comparator in the TA893 submission, therefore was unlikely to have been included in the original search strategy. This means that the company's search strategy has restricted the date range for this specific therapy and that older potentially relevant results would be missed.

The company searched Embase, Medline and PubMed simultaneously via Embase.com (CS Appendix D.2, Table 8). The combined search contains Emtree (Embase subject headings) terms for the condition, which is appropriate as Emtree terms automatically include all the relevant MeSH (Medical Subject Headings – used in Medline) terms as MeSH terms are mapped to Emtree terms in Embase. It should be noted that the Emtree indexing terms for the drug terms are missing from the search, for example 'obecabtagene autoleucel/' (CS Appendix D.2, Table 8). The free text term searches do not contain information as to which fields were searched, for example title and abstract or title and abstract and keyword. Searching for title and abstract and keyword would be optimal (CS Appendix D.2, Table 8). The comparator search terms for 'Car T' are not sufficiently comprehensive as that single term is searched as a phrase and related terms such as 'Chimeric Antigen Receptor T-cell therapy', 'Chimeric Antigen Receptor therapy' or 'T-Cell' are not included. The drug search terms do not include all trade names, for example, 'AUCATZYL' is not included as a search term for obecabtagene autoleucel or 'Sprycel' for dasatinib or 'Besponsa' for inotuzumab ozogamicin. No language restrictions or study design filters were applied, which increases the sensitivity of the searches.

The Cochrane Library search, carried out via Wiley does not contain any indexing/ MeSH terms for the condition or intervention and the American spelling of 'leukemia'

is also missing (CS Appendix D.2 Table 9), which could reduce the sensitivity of this search.

The company searched five relevant cancer and haematology conferences over a two-year period. They also searched for grey literature via Google Scholar, manufacturers websites and the NICE website. Three clinical trial registries were searched including ClinicalTrials.Gov, the EU Clinical Trials Register and the World Health Organisation International Clinical Trials Registry Platform (ICTRP). The search terms and numbers of results are not reported for any of the non-database searches (CS Appendix D.2). Backwards citation searches of SLRs identified were carried out. The company do not report which SLRs had reference checks carried out on. The PRISMA flow diagram reports that four studies were retrieved from 'the grey literature'. Despite a broad and comprehensive range of non-database sources being searched, it is not clear whether comprehensive searches were carried out as the terms applied and numbers retrieved in the search are not fully reported (CS Appendix D.6).

The search results are reported in the PRISMA flowchart and do not contain any errors in the reporting of database search results (CS Appendix D.6, Figure 5).

Despite concerns about the literature search methodology, the EAG considers it unlikely that the company missed any relevant clinical studies due to their knowledge of the research on treatment of adults with R/R B-precursor ALL.

Systematic literature review (SLR) methods

A summary of the EAG critique for each step of the SLR and cross-references to the relevant section in the CS is presented in Table 4.

The full EAG assessment using the modified ROBIS[39] can be found in Table 63. Overall, the EAG found the risk of bias in the company's SLR to be high.

Table 4: Summary of the EAG's critique of the company SLR

Method step	Section(s) of CS of relevance	EAG overall assessment
Eligibility criteria	CS Appendix D, sections D.1-D.3, D.8 and D.9	High concern
Searches and selection of studies	CS Appendix D, Sections D.1.1-D1.3 CS document B, section B.2.9	Low concern
Data extraction and risk of bias assessment	CS Appendix D, Sections D.5 and D.12.	Unclear concern
Evidence synthesis	CS document B, section B.2.9 CS Appendix D, Sections D.9-D.11	High concern

The review aimed to update the NICE STA for brexu-cel but faced inconsistencies and ambiguities in criteria application, particularly regarding age, based on the EAG's ROBIS conclusion (section 8.1). Exclusions of prior CAR T-cell therapy and allo-SCT patients, despite their inclusion in related trials, limited the review's comprehensiveness. The company inconsistently reported and justified the inclusion and exclusion of studies, such as brexu-cel and ponatinib, indicating potential bias and deviations from pre-defined objectives and criteria.

Two reviewers independently assessed study relevance, with a third resolving disagreements.

Data were extracted by one reviewer and checked by a second for accuracy and consistency. The company used Cochrane's RoB2 for RCTs and Downs and Black for non-randomised trials.[40, 41] While comprehensive, Downs and Black is not recommended by NICE's methodologies.[42] ROBINS[43] tool is suggested as a more valid and comprehensive assessment tool, focusing on potential biases common in non-randomised trials. It is unclear to the EAG whether two reviewers independently conducted the risk of bias assessment.

3.2 *Summary and critique of trials of the technology of interest, the company's analysis and interpretation*

3.2.1 FELIX trial design

The EAG's summary of the key features of FELIX, based on the company' submitted information, is summarised in Table 5.

Table 5: EAG Summary of FELIX design

Method step	Summary of the approach used
Method of randomisation	FELIX trial is a multi-centre (8 centres in the UK and 26 in the US and Spain), single-arm, open-label study without randomisation.
Eligibility criteria	Participants must be 18 or older with an ECOG performance status of 0 or 1 and have relapsed or refractory CD19-positive B-ALL. Specific criteria include primary refractory disease, first relapse within 12 months, or relapse after multiple therapies or allogeneic transplant. Ph+ ALL patients are eligible under certain conditions, and CD19 expression must be confirmed post-blinatumomab treatment. Adequate renal, hepatic, pulmonary, and cardiac function is required. Exclusions were certain types of leukaemia, pregnancy, significant CNS pathology, uncontrolled heart disease, recent pulmonary embolism, active gastrointestinal bleeding, uncontrolled infections, specific viral infections, recent malignancies, autoimmune diseases, specific genetic syndromes, recent stem cell transplants, prior CD19 therapy (except blinatumomab), specific medications, and inability to tolerate leukapheresis or comply with study requirements. A complete list of exclusion criteria is reported in the CS, protocol, sections 6.3-6.4.
Treatment stages	All patients went through the following stages: 1. Screening (Day -84); 2. Leukapheresis and the start of obe-cel manufacturing; 3. Then enrolment, and bridging therapy; 4. Lymphodepletion or pre-conditioning (Days -6, -5, -4, -3 ± 1day); 5. Obe-cel split dose infusion (Day 1 and 10); 6. Follow-up and assessment on day 28, months 2, 3, 4, 6, 9, 12, 15, 18, 21, 24 (±7days), then every 6 months (±4weeks).

Dose	The target dose for patients in the FELIX trial was 410 x 10^6 (±25%) total CD19 CAR-positive T-cells, administered as a split dose on Day 1 and Day 10. The dosing schedule was based on bone marrow (BM) blast count (%) before the start of lymphodepletion or preconditioning (Day -6). Then classified as: Patients with a low disease burden (≤20% blasts) received: Dose 1: 100 x 10^6 CD19 CAR-positive T-cells Dose 2: 320 x 10^6 CD19 CAR-positive T-cells Patients with a high disease burden (>20% blasts) received: Dose 1: 10 x 10^6 CD19 CAR-positive T-cells Dose 2: 400 x 10^6 CD19 CAR-positive T-cells
Trial phases and cohorts	The FELIX trial has evaluated the safety and efficacy of obe-cel in phases IB/II through five cohorts in total: **Phase IB, cohort IA**: 21 patients with morphological disease (≥5% blasts in the bone marrow) were enrolled, and 13 were infused. **Phase IB, cohort IB**: Three patients in morphological remission but with minimal residual disease (MRD ≥10^-4 and <5% blasts) were enrolled, and all of whom were infused. **Phase II, cohort IIA**: 112 patients with morphological disease (≥5% blasts in the bone marrow) were enrolled, and 94 were infused. **Phase II, cohort IIB**: 10 patients in morphological remission but with minimal residual disease (MRD ≥10^-4 and <5% blasts) were enrolled, and all of whom were infused. **Phase II, cohort IIC**: Seven patients with isolated extramedullary disease at screening, were enrolled all of whom were infused.
Measured outcomes	Primary Outcomes in Phase IIA Overall complete remission rate (ORR): Complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) Secondary Outcomes in Phase IIA Minimal residual disease (MRD)-negative remission Complete Remission Rate (CRR) within 3 months post obe-cel infusion.

	Duration of complete remission (DOR). Stem cell transplantation: Proportion of patients undergoing stem cell transplantation before leukaemia relapse. Sustained remission: Proportion of patients in CR/CRi without stem cell transplants or other subsequent therapies at 6, 12, and 24 months following AUTO1 infusion. Adverse events (AEs) and serious adverse events (SAEs) Quality of life (QoL): scores of the EQ-5D and the EORTC instruments.
Statistical analysis	Hypothesis On treatment with obe-cel: H0: Objective response rate ≤40% at a one-sided significance of 2.5%. H1: Objective response rate >40% at a one-sided significance of 2.5%. The 40% was based on results from the phase III TOWER study investigating the efficacy of blinatumomab versus standard of care (SOC) chemotherapy for R/R B-cell ALL. The ORR within three months of starting treatment on blinatumomab was 42% versus 20% for SOC. Using the O'Brien-Fleming type alpha spending function, a one-sided p-value <0.0026 implies the ORR of obe-cel is higher than 40%. Sample size Assuming an underlying ORR of 60%, a sample size of at least 90 infused patients would provide over 94% power to detect a significant difference at a one-sided significance of 2.5%.

The FELIX trial was a single-arm, non-randomised, open-label trial. In the CS, doc B, section B.2.3.1, the company states that "*randomising patients to a control arm that may not receive a potentially life-saving therapy would have been unethical*". The EAG notes that this is the case where patients have limited treatment options. Using an active comparator like inotuzumab ozogamicin instead of a placebo or any other

relevant comparators can be a more ethical approach with a limited risk of bias. The suggested approach helps ensure that all patients receive a potentially beneficial treatment, addressing ethical concerns while still allowing for a rigorous comparison of the new therapy's effectiveness.[44, 45]

Out of 217 screened patients, nearly 30% (64 patients) were excluded due to screening failure (84%), death (7.8%), physician's decision (3%), progression (3%), and other reasons (1.6%).[46] The specific details and justifications were not reported, especially for screening failure.

Patient numbers in each cohort presented as infused/enrolled are as follows: IA [redacted]

In total, of the 153 patients enrolled, only 127 were infused, meaning 26/153 were not infused (17%), for which the main reasons were death and manufacturing issues.[46] Based on the ALLCAR19 results,[47] the company stated, "*We lost patients during the manufacturing period to infections and disease progression. In the future, improved logistics and rapid release testing should improve vein-to-delivery times to 14 days*". The manufacturing process concerns addressed in the ALLCAR19 study were not reported in the FELIX study.

For those not infused within cohorts IA and IIA, [redacted] died due to reasons other than underlying cancer, and [redacted] had treatment failure. At the latest data cutoff, only [redacted] non-infused patients were alive.

The EAG considers both mITT (infused) and ITT (enrolled) data sets relevant. The EAG found the ITT to be more representative of what happens to patients during the start of CAR T-cell therapy in NHS practice and more suitable for comparing the efficacy against other treatments.

Six patients (6.4%) from cohort IIA received only the first dose (10 x 10^6 cells).[46]

Table 6 presents the EAGs summary of the company's stated key endpoints for FELIX based on submitted information (CS doc B, Appendices, and CSR doc).

Table 6: EAG summary of key endpoints of FELIX

Objectives	Endpoint Description	Assessment	Reported assessment time points	Incorporated into the

				economic analyses
Primary	ORR (CR+CRi)	Assessed by an Independent Response Review Committee (IRRC)	6, 12 and 24 months	No
Secondary: Efficacy	To assess the efficacy of obe-cel: OS, DOR, EFS, OS, ORR [CR+CRi], MRD-negative CR, or CRi response	OS was measured from IPD. DOR, EFS, measured by IRRC. ORR assessed by the Investigator.	3, 6, 9, 12, 15, 18, 21 and 24 months	Yes – EFS and OS only.
Secondary: PROs	To evaluate Patient Reported Outcomes and Quality of Life (QoL).	Changes over time in symptom, functioning, and quality of life scores of the EQ-5D-5L and the EORTC instruments.	Patient-reported outcomes (PROs) were collected before obe-cel infusion (baseline) and at 28±2 days and 3, 6, 9, 12, and 18 months±7days post-first infusion.	Yes – through health state utility values derived from FELIX EQ-5D-5L data by mapping to EQ-5D-3L.
Safety	To assess the safety and	Frequency and severity of AEs and SAEs.	At all visits (at screening, leukapheresis, pre-conditioning,	Yes

	tolerability of obe-cel	Incidence and duration of severe hypogammaglobulinemia.	days 1, 3±1, 6±1, 8±1, 9±1, 10±2, 12±1, 15±2, 22±2, 28±2 and then months 2, 3, 6, 9, 12, 24±7days)	

AE, Adverse event; CR, Complete remission; DOR, Duration of remission; EMD, Extramedullary disease; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol Five Dimensions of Quality of Life; IRRC, International Review and Regulatory Committee; IPD, individual patient data; MRD, Minimal residual disease; ORR, Overall remission rate; OS, Overall survival; PRO, Patient-reported outcomes; QoL, Quality of life.

3.2.2 Critique of patients' characteristics

In this section, the EAG compares the FELIX cohort IIA-infused patients (n=94) (CS, doc B, section B.2.3.3) with both the cohort IIA-infused UK patients (n=36; from eight UK centres) (Clarification question A7) and Real-world data were obtained from age-specific incidence rates reported by Cancer Research UK (2017-2019; 282 ALL patients),[48] and Kumar et al. (2024)[49] for the Kaiser Permanente Northern California data source (3526 patients with haematological diseases). An overview is provided in Table 7.

The EAG notes that 11 (11.7%) of FELIX cohort IIA-infused patients were under 25 years old, with a median age of [redacted] years (clarification question A24; Table 60), and are out-of-scope for this STA. The EAG compared the characteristics of cohorts IA and IIA and found no differences of concern.

Table 7: Comparison of baseline characteristics between FELIX-infused cohort IIA, UK-infused in FELIX, and other real-world references.

Baseline characteristics		Infused, mITT (N=94)	FELIX UK enrolled patients in cohort IIA (n=36)	Cancer Research UK for ALL; n=282 (%).[48]	Kumar et.al. (2024) for haematologic malignancies; n=3526 patients (%).[49]
Age (years) categorised – n (%)	≥18 to ≤ 25	11 (11.7)	[redacted]	NA	-
	>25 to < 40	20 (21.3)	[redacted]	75 (26.6)	-
	≥40 to < 65	42 (44.7)	[redacted]	105 (37.2)	-
	≥65	21 (22.3)	[redacted]	102 (36.2)	-
Sex, male – n (%)		47 (50.0)	[redacted]	167 (59)	-
Race – n (%)	Asian	10 (10.6)	[redacted]	-	-
	Black or African American	2 (2.1)	[redacted]	-	-
	White	70 (74.5)	[redacted]	-	-
	Unknown	12 (12.8)	[redacted]	-	-
Number of prior lines of therapy – n (%)	1	29 (30.9)	[redacted]	-	-
	2	36 (38.3)	[redacted]	-	-
	3	17 (18.1)	[redacted]	-	-
	≥4	12 (12.8)	[redacted]	-	-
Previous allogenic SCT – n (%)		36 (38.3)	[redacted]	-	-
BM blasts (%) by morphology before enrolment (median)		58.9	[redacted]	-	-
ECOG score – n (%)	0	35 (37.2)	[redacted]	-	1467 (41.6)
	1	58 (61.7)	[redacted]	-	1543 (43.8)
	≥2	0	[redacted]	-	516 (14.6)
	Missing	1	[redacted]	-	-

BM – Bone marrow; ECOG – Eastern Cooperative Oncology Group; EMD – Extramedullary disease; mITT – Modified intent-to-treat; SCT – Stem cell transplant

Demographics

In the FELIX cohort IIA, both sexes were equally distributed (47/94; 50%), despite the UK ALL incidences are higher in males than females. The UK ALL annual death rate is 1.5 times higher in males than in females.[48] The EAG suspects that the FELIX population is likely to be on average younger than UK ALL patients. The EAG notes that among the anticipated licensed population ([redacted]), 36.2% of UK patients have disease incidence aged over 65, compared to 22.3% in this age group

at the start of the FELIX trial.[48] Therefore, the generalisability of FELIX to the UK population is of concern.

Prior treatment

Although the company claims in CS document B, section B.2.3.3, that FELIX patients were heavily pre-treated, the EAG notes that only 30.9% had 3 or more previous therapies, whilst the same proportion had just 1 prior therapy.

EMD

The company claims that 79.8% of patients had extramedullary disease (EMD) before enrolment (CS, doc B, section B.2.3.3). However, CS, doc B, Table 10 and the CSR document show only 20.2% in cohort IIA, revealing a discrepancy and undermining the company's statements credibility about poor prognosis at baseline. The presence of EMD is significantly associated with poor prognosis, as highlighted by the EAG's advisor.[50]

ECOG-PS

No patients with an ECOG performance status (PS) ≥2 were included in FELIX. Most FELIX patients from UK centres compared to the whole cohort IIA ECOG PS scored zero ([redacted] vs. 37.2%). Kumar et. al. (2024) shows that 15% of patients (516 out of 3526 patients) with haematological cancers were treated.[49] The presence of ECOG PS ≥2 in the real-world context was also supported by EAG's advisors. On this matter, the EAG concludes that FELIX is not wholly representative of the UK context.

BM blast

The company reports on BM blasts (%) by morphology before enrolment (09-Jun-2023; CS, doc B, Table 10), while it is not the updated version (CSR doc, section 2.2, page 11). According to the latest data source, Appendix 1 Table 1, in cohort IIA, the median BM blast (%) by morphology was 58.9 (6-100), reducing to [redacted] after bridging therapy before the infusion (Day -6). The patients with less than 5% BM blasts increased to 24.5% (23/94), compared to zero at screening. Other percentages similarly reduced in favour of obe-cel.

Ph+/Ph- baseline characteristics (FELIX infused patients; n=127)

Both EMD and BM blasts significantly negatively impact patient outcomes post-infusion, as noted by the company's advisors and confirmed by EAG experts. A [redacted] proportion of Philadelphia-[redacted] patients had ≥20% BM blasts at screening compared to [redacted] indicating a [redacted] disease burden in the [redacted] group. Similarly, [redacted]patients with EMD were in the [redacted] subgroup compared to the [redacted]subgroup [redacted] (Clarification question A28, Table 66). The EAG is unsure whether these differences are representative of the UK B-ALL population.

3.2.3 Clinical effectiveness results of FELIX trial

The company identified cohort IIA as the relevant population, but the EAG argued that both cohort IA and IIA patients had similar morphological diseases (>5% BM blasts) at screening and that both cohorts should be considered, a view supported by the EAG's clinical advisors. In response to CQ A1, the company provided an overview of outcomes for these combined cohorts. The EAG considered the characteristics of cohorts IA and IIA and, considering the number of patients in each cohort, found that combining the populations would not alter the concerns previously identified. Where possible, the EAG used information for this combined group, however, the details on some information were only reported for cohort IIA.

At the data cut-off in February 2024 (latest data cut-off with a median follow-up of 20.2 months [[redacted]]), [redacted]/94 of cohort IIA were alive.

Nearly [redacted]of the patients were followed for less than [redacted] months, potentially missing late-occurring events like delayed relapses or long-term side effects. Long-term follow-up is crucial for accurately reporting outcomes such as OS, immune-related adverse events, and long-term relapse rates, and for establishing the curative potential of obe-cel.

An overview of the results is shown in Table 8.

Table 8: Overview of results from FELIX.

	Cohort IIA – infused (n=94) (CS B.2.6; CS B.3.3.2; CSR 14.2.30; CSR 14.2.12; CSR 14.2.15)	**Cohort IIA – enrolled (n=112)** (CSR 2.4)	**Cohorts IA and IIA – enrolled (n=133)** (clarification response A1)
Overall Remission Rate	72 (76.6%)	[redacted]	[redacted]
CR	52 (72.2%)	[redacted]	[redacted]
CRi	20 (27.8%)	[redacted]	[redacted]
Duration of Remission	Without | with censoring for SCT	With censoring for SCT	Without censoring for SCT
Median (months)	[redacted] | 14.06	[redacted]	NR
12 months	NR | [redacted]	[redacted]	[redacted]
24 months	NR | [redacted]	NR	NR
Event-Free Survival	Without | with censoring for SCT	With censoring for SCT	Without censoring for SCT
Median (months)	[redacted] | 9.03	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	NR	NR
Overall Survival	Without | with censoring for SCT	Without censoring for SCT	Without censoring for SCT
Median (months)	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	NR	NR

CR- complete remission; CRi- complete remission with incomplete haematological recovery; ITT- intention-to-treat; NE- not estimated; NR- not reported; SCT- stem cell transplant.

3.2.3.1 Primary outcome (infused cohort IIA (n=94); infused with ≥5% blast after bridging therapy(n=71))

3.2.3.1.1 Overall remission rate (ORR)

The overall complete remission rate (ORR) is the proportion of patients achieving complete remission (CR) or complete remission with incomplete recovery of counts (CRi). CR is defined as <5% blasts in bone marrow, while CRi includes <5% blasts but with incomplete platelet and/or neutrophil count recovery.

According to Appendix 1, Table 1 of the CSR document, the median bone marrow (BM) blast percentage in cohort IIA during the screening phase was 58.9% (range: 6%-100%). This was reduced to [redacted] before lymphodepletion or pre-conditioning, indicating the benefits of bridging therapy before infusion. Therefore, the ORR results and benefits attributed to obe-cel reflect the combined impact of bridging therapy and obe-cel, rather than obe-cel alone.(Roddie.et.al, 2024, Figure S7).[46] The results in CS doc B, Table 12, do not distinguish whether ORR was achieved before or after obe-cel infusion. Only 71 patients (reducing 23 with less than 5% blasts from 94 cohort IIA patients) had morphological disease at the time of obe-cel infusion.

Out of 71 patients with more than 5% BM blasts before infusion out of 94 infusions in cohort IIA, [redacted] achieved CR/CRi ([redacted]. Among these, [redacted] patients were in complete remission ([redacted]).

Out of 94 cohort IIA-infused patients, 72 achieved CR/CRi (76.6%; 95% CI [66.7-84.7], p < .0001). Among these, 52 patients were in complete remission (55.3%; 95% CI [44.7-65.6]).

Of the total remissions, 20/72 (27.8%) patients from cohort IIA-infused patients reached CRi. Those patients had a shorter remission duration [redacted] (clarification question A1, cohort IA).

According to the CSR document (Appendix 2, page 56), [redacted] patients have died between the primary analysis (data cut-off on June 9, 2023) and the latest cut-off date (February 7, 2024). Of these, [redacted] died due to [redacted].

Based on the CSR doc, Table 14.2.4.4.1, [redacted] of patients reached MRD negative with CR or CRi.

3.2.3.2 Secondary outcomes

3.2.3.2.1 Duration of remission (DOR) (infused cohort IIA (n=94); infused with ≥5% blast after bridging therapy in cohort IIA (n=71))

The FELIX protocol (page 132) defines duration of remission (DOR) as "*measured by the time from the first achievement of CR or CRi to relapse or death due to any reason*". Based on the number of patients in the DOR analyses, out of 94 patients who achieved CR/CRi in cohort IIA, 72 were included in the analysis (CS, doc B,

Table 12). Of these 72 patients, [redacted] remained in remission without relapse or subsequent treatments (CS, doc B, section B.2.6.1.2).

When comparing the protocol's definition of death for EFS and DOR ("*death due to any reason*") and then the company reporting "*death due to reasons other than underlying cancer*" for DOR and EFS (CSR, Table 14.2.10.2.2.iia and 14.2.7.2.1.iia) the EAG notes a potential inconsistency.

According to CSR doc, Table 14.2.16.2.1.iia, [redacted] out of 71 infused patients with ≥5% blast after bridging therapy have died without/with censoring for subsequent SCT, respectively. Since the company has not reported the number of deaths defined in the protocol for CR/CRi patients ([redacted]/71 patients) for this subgroup, the actual DOR is unclear to the EAG. Considering the total number of deaths and the protocol's definition of death, the EAG notes that the percentage of patients maintaining a response would be considerably less than [redacted].

The company's reported follow-up durations for DOR range from [redacted] months, with a median of [redacted] months. Nearly [redacted] of the patients were followed for less than [redacted] months, [redacted]. This variability may affect results, as shorter follow-up times may not capture long-term DOR, particularly for patients with an aggressive nature of relapsed/refractory B-ALL. EAG notes that longer and more consistent follow-ups are required for a more accurate assessment of the treatment's long-term efficacy, especially DOR.

3.2.3.2.2 Event-free survival (EFS) (infused cohort IIA (n=94); infused with ≥5% blast after bridging therapy in cohort IIA (n=71); infused phase Ib/II (all cohorts, n=127))

The company defined EFS and PFS in the protocol on page 133, reporting EFS as a surrogate for PFS. Events were defined as treatment failure, relapses, or any cause of death. Our advisor indicated that relapses are treatment failures. Other treatment failures were not considered by the company like the emergence of minimal residual disease (MRD). In addition, the literature suggests including disease progression as an event for the EFS, which the company has not considered.[51, 52]

Based on the CSR doc, Table 14.2.12.2.2.iia and Roddie et.al. (2024)[46], the results reported do not reflect the protocol. To be more precise, the company only has reported morphological relapses (vs all relapses), treatment failures (vs progression

and failure), and deaths from any cause other than underlying cancer (vs any cause) (CSR doc, Table 14.2.12.2.2.iia).

The company suggests that EFS and PFS are identical (clarification question A6). The EAG can only accept the surrogacy offered if the company has reported all progressions, death due to any cause, and all relapses, as is defined in the protocol and indicated by literature.[51, 52] In the phase Ib and phase II infused patients (127 patients), [redacted] has been the main cause of death ([redacted]) but not considered as an event in the EFS results (CSR doc, Table 14.3.3.1.3). Death due to progression shows a lack of effectiveness in controlling disease progression.

According to CSR, Table 14.2.12.2.2.iia EFS events with censoring anticancer therapies, the company reported that only [redacted]/94[redacted] of infused patients) and [redacted]/71 [redacted] of infused with morphological disease (BM blasts ≥5%) after bridging) remained event-free. The subsequent treatment impact on the obe-cel results is considerable and therefore, the reported EFS may not accurately represent the obe-cel efficacy.

The event-free probability was [redacted] after 24 months and will decrease further by three years (not reported) (CSR doc, Table 14.2.15.2.2.iia).

The long-term EFS percentages have been reported briefly in CS, doc B, Table 14 to a maximum of 12 months. The EAG found the CSR doc, Table 14.2.12.2.2.iia more informative on long-term EFS from months [redacted]. Starting at [redacted] for patients with >5% blasts after bridging therapy (71 patients), the EFS drops sharply to [redacted]. [redacted]). Therefore, a high degree of uncertainty undermines the results' reliability and robustness.

In the CSR document (Table 14.2.27.2.2), 99 out of 127 infused patients (phase Ib/II) achieved CR or CRi. However, 15 received TKIs and 3 received intrathecal chemotherapy with unblinded investigators' decision, and were not censored in the analyses.[46] Excluding subsequent treatments and the TKI administrations, less than [redacted] patients remained in remission ([redacted] out of 99 in remission for phase Ib/II; less than [redacted]), raising concerns about the efficacy of obe-cel.

3.2.3.2.3 Overall survival (OS) (infused cohort IIA (n=94); ITT cohort IIA (enrolled set, n=112); infused with ≥5% blast after bridging therapy cohort IIA (n=71))

Based on the CSR doc, Table 14.2.16.2.1.iia, out of 71 patients with BM blasts >5% post bridging, [redacted] were deceased. Of the cohort IIA ITT population (enrolled set; n=112), [redacted] were deceased before infusion (CSR doc, Figure 1) while the bridging therapy positively has improved patients' prognosis and outcomes by reducing the BM blasts (CSR doc, Appendix 1 Table 1; see section 3.2.2).

[redacted]

In the protocol on page 52, the company states that the 3 to 5-year OS of patients is less than 10% to 15% and therefore, enrolment to a trial with obe-cel is justified. Considering the KM plot reported in Figure 11 CS document B, the OS after 24 months and later (3-5 years) seems to be [redacted]

3.2.3.2.4 Health-related quality of life (HRQoL) for infused cohort IIA (70 infused cohort IIA patients)

The company has captured HRQoL and PRO (patient-reported outcomes) at baseline (before lymphodepletion; day -6), day 28, and other time points up to 24 months (11 measurements over 24 months). However, the first HRQoL measurement for the FELIX trial post-infusion is scheduled for day 28, which, as reported in the safety results (see section 3.2.5), fails to account for the immediate impact of lymphodepletion and the infusion. The serious adverse events (AEs) such as CRS and ICANS, along with the hospitalization required for infusion impact have not been captured, casting significant doubt on the reliability of the HRQoL outcomes. More accurate assessments should have been conducted at closer intervals to the infusions. This oversight raises serious concerns and undermines the reported HRQoL, making it appear unreliable. The following Table 9 is copied from the CS, doc B, Tables 16 and Table 17.

Table 9: EQ-5D-5L and EORTC-QLQ-C30 results, February 2024

Timepoint	EQ-5D-5L Index mean score (SD); n=70	EORTC-QLQ-C30 mean Global health status score (SD); n=71
Baseline*	[redacted]	[redacted]
Day 28	[redacted]	[redacted]
Month 3	[redacted]	[redacted]
Month 6	[redacted]	[redacted]
Month 9	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]

EQ-5D-5L, EuroQol Five Dimensions of Quality of Life; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of life Questionnaire; SD, Standard deviation.

*Prior to treatment with obe-cel.

The EQ-5D-5L and EORTC-QLQ-C30 mean were reported with [redacted] standard deviations (SDs), which further questions the results' variability, consistency, and overall reliability.

Since the baseline is set before receiving obe-cel (day -6), the EAG cannot determine if any improvements have been reported based on the mean compared to the start of CAR T-cell therapy. The HRQoL measurements were scheduled at long and infrequent intervals (monthly for only four months, then at 2, 3, and every 6 months; only 7 measurements in the first year and 6 in the second year), failing to capture relapses, and progressions, and the high rate of AEs in earlier times post-infusion and long-term.

Additionally, based on the number of patients after 6 months reported in Figure 12 of CS document B, the results lack sufficient power to be considered reliable.

3.2.4 Subgroup analysis (infused Cohort IIA; n=94)

The company has presented the subgroup analysis in CS, doc B, section B.2.7, and in CS, Appendix E. The Figure 2 forest plot is copied from the CS, appendix E, Figure 8. It shows that most subgroups had an ORR where the lower 95% confidence interval was >40%. Confidence intervals are wide due to the small sample size of the subgroups, however, the EAG notes the potential for reduced obe-cel efficacy for people with high disease burden (BM blasts >75%), EMD, and ≥4 prior lines of therapy.

Figure 2: Subgroup analyses of overall remission rate
CI – confidence interval; CNS – central nervous system; EM – erythema multiforme; n – number; SCT – stem cell transplant

3.2.5 Overview of safety and adverse effects (Phase Ib/II infused patients; n=127)

The company has reported the safety and adverse effects of obe-cel in the CS document B, section 2.2.7, with additional details in the CSR document for EAG's consideration. According to CS appendix F, no studies other than FELIX have reported obe-cel adverse reactions. The phase I ALLCAR19 study assessed grade 3-5 toxicity in 20 patients aged 16+ with r/r B-ALL. No patients had grade 3+ CRS, but 3 (15%) had grade 3 neurotoxicity. The EAG notes the small sample size may be insufficient to fully capture obe-cel's safety.

Recurrent events do not appear to be counted. Overall, 218 adverse events of any grade have occurred, with 173 being Grade 3 or higher. Major events include severe infection, CRS, and cytopenia.

3.2.5.1 Hospitalisation

The company states that patients should be hospitalised for "*at least ten days*" after their first infusion (CS, protocol doc, page 52), but the actual range of hospitalisation spans starts from [redacted] days to more than [redacted] (CSR doc, section 3.1.5). This wide range [redacted] indicates significant variability in patient responses to the treatment, likely due to differences in patient health, severity of side effects, or complications arising from the treatment. A median of [redacted] days means that [redacted], which can be burdensome both physically and emotionally.

It has been noted that 15.7% (20/127) of patients have required intensive care unit (ICU) admission post-infusion, with [redacted]. The EAG did not find any data for the number of ICU admissions per patient. The main reason for ICU admission was [redacted].

Notably, over [redacted] required more than [redacted] hospitalization incident (CSR doc, Table 8), raising further concerns.

Long hospital stays are resource-intensive, requiring significant medical staff, facilities, and financial resources. They can negatively impact patients' quality of life, leading to hospital-acquired infections, decreased mobility, and mental health challenges. The study protocol (page 17) shows that HRQoL was not assessed until day 28, potentially missing the most hospitalization periods (e.g. between days 1 and 10) when AEs (such as CRS and ICANS) are most likely.

3.2.5.2 Treatment-emergent adverse events (TEAEs) (safety set; infused phase Ib/II; n=127)

In CS document B, Table 24, the company reports only TEAEs that occurred in more than 10% of patients in the safety set up to 6 months post-obe-cel infusion (June 2023 data cut-off). The latest data cutoff events (February 2024) were reported in the CSR and used by EAG.

Based on Table 24 of CS document B and CRS document section 3.1, all patients experienced at least one TEAE. According to CS, doc B, Table 25, all patients experienced any grade AE(s), with nearly 82% (104 out of 127) being Grade 3, 4, or 5.

The TEAEs associated with significant safety concerns for all infused patients, based on the latest data cut-off (February 2024), are reported in Table 10 (adapted from CSR doc, Table 6, page 26).

Table 10: 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 (%)
Severe infections	[redacted]	[redacted]
Cytokine release syndrome (CRS)	87 (68.5)	3 (2.4)
Immune effector cell-associated neurotoxicity syndrome (ICANS)	29 (22.8)	9 (7.1)
Hypogammaglobulinemia	[redacted]	[redacted]
Graft versus host disease (GvHD)**	[redacted]	[redacted]
Secondary malignancies	[redacted]	[redacted]
Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)	[redacted]	[redacted]
Tumour lysis syndrome (TLS)	[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)

3.2.5.2.1 Severe infections

In the CS, doc B, section B.2.10.2, the company states "*The most common TEAE was CRS*". In the CS document B, the company has not reported the severe infection events. Based on the CSR doc, the [redacted] had experienced severe infections with [redacted]. The EAG notes that the company has not reported the severity and hazardous impact of the infection on patients who received infusions, as documented in CS doc B and the Appendices.

Additionally, out of 31 events of any grade (24.4% total all grade events), 30 were ≥Grade 3 febrile neutropenia. The high rates and severity of these events raise concerns about the increased risk of infections (CS, doc B, Table 24). The EAG notes that all 25 cases of febrile neutropenia in cohort IIA were ≥Grade 3.[46]

3.2.5.2.2 Cytopenia (Safety Set, infused Phase Ib and Phase II; n=127)

The company reported that neutropenia and neutrophil decrease were defined equivalently according to the clarification response A26. However, they report differing frequencies of these events in the CS, doc B, Table 24 (29 vs. 25 events).

The company has not explicitly discussed prolonged cytopenia (neutropenia, thrombocytopenia, and anaemia) in the CS, doc B, and Appendices for obe-cel, but it is reported in the CSR section 3.1.4.3.

In CSR Table 14.3.5.1.1, the company reported ≥ grade 3 cytopenia for the safety set (127 patients), summarised by EAG in Table 11. The decrease in blood cell counts, particularly cytopenia and total ≥ grade 3 events, shows potential haematologic concerns.

Table 11: Grade 3 or 4 Cytopenia changes between lymphodepletion and 30-days post-obe-cel infusion

Grade 3 or 4 Cytopenia (February 2024 data cutoff)	Before infusion and after lymphodepletion n (%)	30 days post-infusion n (%)	Changes in cytopenia between post-obe-cel infusion n (%)
Neutrophil count decreased ≥grade 3	[redacted]	[redacted]	[redacted]
Platelet count decreased ≥grade 3	[redacted]	[redacted]	[redacted]
Haemoglobin decreased ≥grade 3	[redacted]	[redacted]	[redacted]
Neutrophil/Platelet/Haemoglobin decreased ≥grade 3	[redacted]	[redacted]	[redacted]

3.2.5.2.3 Cytokine release syndrome (CRS)

With 68.5% of patients experiencing CRS in all cohorts and 75.5% in cohort IIA (94 patients), a significant proportion of patients are affected by this AE.[46]

According to the CRS doc, Appendix 1 Table 5, [redacted] of patients with CRS had ≥ Grade 2 CRS ([redacted]). All ≥ grade 3 CRS events of all cohorts occurred in cohort IIA.[46]

The median time to onset of CRS was 8 days, with some cases occurring as late as 23 days after infusion. Some patients experienced symptoms for up to 21 days (CS, doc B, section B.2.10.3.1).

3.2.5.2.4 Immune effector cell-associated neurotoxicity syndrome (ICANS)

Nearly a quarter of the patients (22.8%) experienced ICANS, which is significant. This suggests that the treatment has a notable risk of neurotoxicity.

Although most cases were low-grade, 7 patients (5.5%) experienced Grade 3 ICANS, and 2 patients (1.6%) had even more severe reactions.

The onset of ICANS occurred up to 31 days after the first infusion, with a median onset of 12 days. This delayed onset means that patients need prolonged monitoring, increasing the burden on healthcare resources and the patients themselves. Some patients experienced symptoms for up to 53 days.

Overall, while the majority of ICANS cases were low-grade, the significant proportion of patients experiencing this condition, the severity of some cases, and the need for intensive and prolonged treatment raise concerns over the safety profile of this treatment.

3.2.5.2.5 Comparing brexu-cel and obe-cel

In CS, doc B, section B.2.10.4, the company compares to brexu-cel. Although not a formal comparator, EAG notes company's comments about improved safety align with current data. Both treatments show high adverse events, but brexu-cel has a higher rate of severe events (≥Grade 3), CRS, and ICANS.[38] No statistical analysis confirms the significance of these differences. Blinatumomab has a similar incidence of severe CRS (5%) compared to obe-cel, but the company hasn't compared obe-cel with blinatumomab.

3.2.6 FELIX risk of bias

The company has used Down and Black (CS, appendix N.2, Table 68) to assess the risk of bias for the FELIX trial and found it with a low risk of bias.[41] The EAG used ROBINS-E (Table 64) as the FELIX trial is a single-arm open-label uncontrolled study with no randomisation. The Down and Black is useful, but it falls short in critical areas such as blinding and confounding.[41] Additionally, it only reviews the quality of the study rather than reporting on the degree of bias. Furthermore, the EAG has replicated the Down and Black risk of bias in Table 65.

3.3 *Summary and critique of the indirect comparison and/or multiple treatment comparison*

3.3.1 Company's ITC approach

Given the single-arm nature of the FELIX trial, the company performed indirect treatment comparisons (ITCs) between obe-cel and the three comparators identified in Table 1 of CS Doc B: inotuzumab, blinatumomab, and ponatinib. Matching adjusted indirect comparisons (MAICs) were used to account for the differences in baseline characteristics of the trials.

3.3.1.1 Company's search strategy

The company opted to update the search strategy used in the recently published TA893 for brexucabtagene autoleucel for the treatment of R/R B-cell ALL in people 26 years and older. This appraisal was published on the NICE website on 07 June 2023, and the search for TA893 was conducted up to November 2020 (Table 10 in Appendix D.4). The company conducted an update between January 2021 to May 2024 and identified a further 29 publications which were included in the review. Of these 29, none of them were included in the ITC due to either not reporting relevant outcomes (N=11) or being undertaken on irrelevant settings or populations (N=18). Thus, the studies that were included in the ITC were FELIX for obe-cel, INO-VATE for inotuzumab, TOWER for blinatumomab, and PACE for ponatinib.

3.3.1.2 Comparison of identified studies/trials

The EAG presents a summary of the trials identified and included in the indirect comparisons: PACE[53], INOVATE[54] and TOWER[55]; covering their baseline characteristics.

Table 12: Baseline characteristics of identified indirect comparison trials

Study Arm	**FELIX (Obe-cel)**[56]	**INO-VATE (Inotuzumab)**[54]	**PACE (Ponatinib)**[53]	**TOWER (Blinatumomab)**[55]
Population (N)	[redacted]	ITT n=164	ITT n=32	ITT n=271
Age, Median (Range)	[redacted]	46.5 (18-78)	62 (20-80)	41.0 (18-80)
Male:Female	[redacted]	91:73 (55.5%: 44.5%)	20:12 (62.5%: 37.5%)	162:109 (59.8%: 40.2%)

Race	[redacted]	White: 112 (68.3%)	White: 81.3%	White: 228 (84.1%)
	[redacted]	Other: 52 (31.7%)	Other: 18.7%	Other: 43 (15.9%)
Previous Lines of Treatment	[redacted]	1: 111 (67.7%)	NR	1: 114 (42.1%)
	[redacted]	2: 51 (31.1%)	≥2 TKI: 26 (81.3%)	2: 91 (33.6%)
	[redacted]	NR	≥3 TKI: 12 (37.5%)	3: 45 (16.6%)
	[redacted]	NR	NR	≥4th: 21 (7.8%)
Refractory to First-line Therapy	[redacted]	NR	TKI: 27 (84.4%)	115 (42.4%)
Relapse ≤12 Months	[redacted]	NR	NR	76 (28.0%)
Response to Last Line	NR	Complete response: 121 (73.7%)	Major hematologic response: 13 (40.6%)	NR
Previous SCT (%)	[redacted]	29 (17.7%)	9 (28.1%)	94 (34.7%)
BM Blasts at Screening (%)	[redacted]	<50: 53 (32.3%)	NR	<50%: 69 (25.5%)
Peripheral Blasts (x10^9/L)	NR	107.6 (0-42,660) cells/µL	NR	4.4 ± 15.5
ECOG PS (%)	[redacted]	0: 62 (37.8%)	0: 11 (31.9%)	0: 96 (35.4%)
	[redacted]	1: 81 (49.4%)	1: 17 (42.6%)	1: 134 (49.4%)
	[redacted]	2: 21 (12.8%)	2: 4 (25.5%)	2: 41 (15.1%)

Prior treatments

- In the FELIX trial, a higher proportion of patients [redacted] had one or two prior treatments.
- INO-VATE had 98.8% of patients with 1 or 2 prior lines of treatment, representing the least heavily treated population of the considered trials.
- PACE patients were the most heavily pre-treated, with 81% having received ≥2 TKIs.

- TOWER had 75.6% with 1 or 2 prior lines, representing a slightly less pre-treated cohort than FELIX.

Stem cell transplantation (SCT)

- In the FELIX trial, a higher proportion of patients ([redacted]) had previous SCT before enrolment in comparison to the other trials.
- INO-VATE and PACE reported 17.7% and 28.1% of participants with prior SCT, indicating less prior SCT exposure in their cohorts.
- TOWER included 34.7% of patients with prior SCT, closely aligning with FELIX.
- While FELIX's high proportion of prior SCT patients demonstrates its inclusion of heavily pre-treated individuals, differences in SCT history impact trial comparability, as patients with prior SCT generally have a worse prognosis.

Performance status (ECOG PS)

- The FELIX trial excluded patients with an ECOG performance status (PS) ≥2
- Similarly, INO-VATE had 86.1% of patients with ECOG 0–1, while TOWER had 84.8%. PACE also reported a majority (87.5%) in this category
- FELIX's absence of ECOG 2 patients may indicate a slightly less severely ill cohort.
- A broader analysis of 3,526 haematological cancer cases found a similar ECOG PS distribution to that of the comparator trials, with approximately 15% of patients having an ECOG PS ≥2.[49]

Generalisability and representativeness

The FELIX trial population, while well-defined and homogenous, may not fully reflect real-world settings due to the exclusion of patients with ECOG PS ≥2. In contrast, INOVATE, TOWER, and PACE included more diverse populations, with a broader range of performance statuses and treatment histories. These characteristics make these trials more representative of the heterogeneity observed in clinical practice.

In Table 13, the EAG presents an overview of the main clinical outcomes from each trial.

Table 13: Clinical Outcomes of trials included in indirect comparison

Outcome	FELIX (Cohort IIA – Obe-cel arm)[56]	INO-VATE (Inotuzumab)[54, 57]	PACE (Ponatinib)[53, 58]	TOWER (Blinatumomab)[55]
Population Size	[redacted]	ITT n=164	ITT n=32	ITT n=271
Overall remission rate	[redacted]	NR	NR	NR
Overall survival (OS)	[redacted]	Median: 7.7 months (95% CI: 6.0- 9.2) 24-month: 22.8% (95% CI: 16.7-29.6)	Median: 8 months 24-month: 40% (Cortes 2013)	Median: 7.7 months (95% CI: 5.6 - 9.6)
Progression-Free Survival (PFS)	NR	Median: 5 months (95% CI, 3.9-5.8)	Median: 3 months (95% CI, 1.8 - 3.9) (Cortes 2018) 12-month: 7% (Cortes 2013)	NR
Event-Free Survival (EFS)	[redacted]	NR	NR	6-month: 31%
Duration of remission (DOR)	[redacted]	Median: 5.4-months (95% CI, 4.2 - 7.0)	NR	NR
Minimal Residual Disease (MRD)	NR	71% MRD negativity	NR	NR
Haematologic Responses	NR	NR	NR	NR
Complete Remission	[redacted]	NR	NR	NR
Rate of Allo-SCT	NR	NR	NR	NR
Adverse Effects (AE)	NR	Any AE: 99% (Gr 3-4: 90%; Gr 5: 16%). Treatment-related AE: Gr 3-4: 70%; Gr 5: 6%.	NR	NR

AE: Adverse Effects, Allo-SCT: Allogeneic Stem Cell Transplantation, AS: Age-Standardised, CI: Confidence Interval, DOR: Duration of Remission, EFS: Event-Free Survival, ITT: Intention to Treat, mITT: Modified Intention to Treat, MRD: Minimal Residual Disease, NR: Not Reported, OS: Overall Survival, PFS: Progression-Free Survival

3.3.1.3 Variables used in indirect comparisons

The company provided a comparison of the prognostic factors and treatment effect modifiers (TEMs) in their response to clarification question A29. Table 14, taken from the company's responses to CQ A20 shows the TEMs provided in each study, indicating which TEMs could be adjusted for in the ITC.

Table 14: Overview of baseline characteristics used in ITCs (taken from CQ Responses Table 59 for question A20)

		FELIX (Cohort IIA, mITT)[5]	INO-VATE (inotuzumab arm)[2]	TOWER (blinatumomab arm)[3]	PACE (Ph+ ALL arm)[4,59]
Study size, N		94	164	271	32
Primary refractory, %		✓	X	✓	✓
BM blasts at screening, % <50%		✓	✓	✓	X
Prior lines of therapy, %	1	✓	✓	✓	✓
	2	✓	✓	✓	✓
	≥3	✓	X	✓	✓
Extramedullary disease prior to lymphodepletion, %		✓	X	X	X
1st remission ≤12m, no. %		✓	✓	✓	X
Ph chromosome, % Ph+		✓	✓	✓	✓
Age at baseline, Median (SD) years		✓	✓	✓	✓
Bridging chemotherapy, %		✓	X	X	X
Race, %	White	✓	✓	✓	✓
	Non-White	✓	✓	✓	✓
Prior SCT, %		✓	✓	✓	✓
ECOG status, %	0	✓	✓	✓	✓
	1 or 2	✓	✓	✓	✓
Sex, Male, %		✓	✓	✓	✓

INO-VATE and PACE did not report the proportion of patients with primary refractory disease, which, according to the company's experts', is the most important prognostic factor in the feasibility assessment. Without this information, it is unclear whether the populations in FELIX and comparable to those in INO-VATE or PACE, introducing uncertainty into the ITC and weakens the reliability of the matching MAIC and naïve comparison.

PACE also did not report the bone marrow blast data which leaves additional uncertainty for the naïve comparison to ponatinib since this means that the comparability between FELIX and PACE cannot be judged based on the two most important TEMs.

INO-VATE's trial population predominantly had fewer lines of prior therapy, about two-thirds having one line, and the remaining having two lines, while the patients in TOWER were more closely aligned to FELIX, though FELIX had a higher proportion of patients with >3 lines of therapy ([redacted]% vs. 7.8%). The difference between FELIX and TOWER is less pronounced and causes less concern for adjustment compared to INO-VATE which did not include patients with three or more lines of prior therapy. In PACE, only 19% had one line compared to [redacted] in FELIX and 37% with more than two lines, compared to [redacted] in FELIX. Furthermore, the trial phases differ slightly. INO-VATE involves a population earlier in the treatment pathway (prior induction), while TOWER is focused on salvage therapy, more aligned with FELIX.

INO-VATE had a higher proportion of patients with first remission ≤12 months compared to FELIX, suggesting that its population may have a worse prognosis compared to FELIX, while TOWER has a lower proportion, implying a less aggressive disease profile compared to FELIX. The imbalances may bias the results in favour of TOWER unless it is adequately adjusted for in the MAIC. The lack of data for PACE on this factor creates even more uncertainty about the comparability of the populations in the naïve comparison.

INO-VATE has a much lower proportion of Ph+ patients compared to FELIX, suggesting that the INO-VATE population may differ in prognosis and responsiveness to treatment. TOWER excludes Ph+ patients entirely while PACE recruits Ph+ patients only. Since only the relevant Ph subgroup from FELIX will be

used in the ITC, this should not be an issue but reduces the ESS and increases imprecision and uncertainty.

The median ages of the patients in FELIX and INO-VATE are [redacted]. Patients in TOWER are [redacted] and patients in PACE are [redacted]. In Table 67 of CQ responses, the company reported the medians and standard deviations (SDs) of age, which is unusual reporting.

The prevalence in prior SCT in FELIX is substantially higher than INO-VATE, higher than PACE, and comparable to TOWER. The wide disparity between FELIX and INO-VATE suggests that adjustments in the MAIC may face challenges due to limited overlap.

FELIX had [redacted] in ECOG 2, while the other trials reported ECOG 2 patients, with TOWER having the highest proportion (15.1%).

The comparison of prognostic factors and TEMs reveals several key issues that impact the reliability of the company's ITC. Notably, missing data on primary refractory disease, bone marrow blasts, and remission status in some trials introduces uncertainty. The naïve comparison to ponatinib is limited by imbalances in prior lines of therapy, Ph+ status, and prior stem cell therapy further complicate the analyses. Additionally, differences in age, race, ECOG status, and sex distributions may affect the comparability of populations and introduce potential biases.

3.3.1.4 Methods used

Disconnected network

Since the pivotal obe-cel trial, FELIX, was a single-arm study the network of the four treatments were disconnected, a network meta-analysis or anchored analysis was not feasible.

MAIC

Matching-adjusted indirect comparisons involve reweighting individual patient data (IPD) from one study to match the baseline characteristics of a comparator study, enabling a fairer comparison between treatments. In this case, IPD was used from FELIX to reweight the mITT population of FELIX to match important treatment effect modifiers from INO-VATE and TOWER. The quality of the results depends on the overlap between populations, indicated by the effective sample size (ESS) and the

choice of variables for matching. MAIC was performed to compare to ponatinib, however the results were deemed unreliable.

Naïve comparison

A naïve comparison is an unadjusted analysis comparing outcomes between treatments without accounting for potential confounding factors or differences in baseline characteristics between the study populations. This type of comparison assumes that the populations are sufficiently similar to allow direct comparison of outcomes, but it is prone to bias if this assumption does not hold. This method was used to compare obe-cel to ponatinib in the company base case.

3.3.1.5 Results

Table 22 of CS Doc B presented the unadjusted and adjusted hazard ratios (HRs) for EFS, and Table 23 for OS. [redacted]

[redacted]

However, these results were based on EFS as assessed by local investigator. The company updated these results at the clarification stage to include EFS as assessed by the Independent Response Review Committee. The results of which are presented in Table 15.

Table 15: Results of the company's ITC analyses as presented in response to CQ A29 based on patients from the mITT population

			EFS		OS	
Population	**Treatment**	**ESS**	**Unadjusted HR**	**Adjusted HR**	**Unadjusted HR**	**Adjusted HR**
mITT	Obe-cel	-	-	-	-	-
	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ph-	Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ph+	Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3.1.5.1 Analyses requested at CQ stage

The EAG requested further analyses from the company in clarification question A1. The EAG asked the company to present the primary and secondary outcomes on the FELIX enrolled cohorts IA and IIA, and asked to rerun the ITC on this population. The company was also asked to perform these analyses excluding people ages below 26 years. These were provided by the company in response to CQ A1.

The company's approach was the same as the original ITC presented in the original submission. However, with 133 participants instead of [redacted], the ESS was [redacted] in the new analyses. These analyses include the pre-infusion period from FELIX, which the EAG consider to improve the comparability of the outcome data.

The results of this ITC is presented in Table 16. Compared to the results of the ITC in the infused population, the results of the enrolled ITC were [redacted] favourable to obe-cel for the comparison to inotuzumab and blinatumomab. However, there were [redacted].

Table 16: Results of the company's ITC analyses as presented in response to CQ A1 based on patients from the ITT (all enrolled) population

			EFS		OS	
Population	**Treatment**	**ESS**	**Unadjusted HR**	**Adjusted HR**	**Unadjusted HR**	**Adjusted HR**
ITT	Obe-cel	-	-	-	-	-
	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ph-	Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ph+	Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For the analyses when excluding patients under 26 years of age, the results, in terms of direction and statistical significance, were [redacted] to the infused and enrolled results, see Table 17.

Table 17: Results of the company's ITC analyses as presented in response to CQ A1 based on patients from the ITT (all enrolled) population excluding patients aged 25 years or younger

			EFS		OS	
Population	**Treatment**	**ESS**	**Unadjusted HR**	**Adjusted HR**	**Unadjusted HR**	**Adjusted HR**
ITT	Obe-cel	-	-	-	-	-
	Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ph-	Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ph+	Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3.1.6 Company's conclusions

The company noted the favourable effect that obe-cel had on EFS and OS compared to the other treatments using the results from the ITC. They acknowledge the very small ESS when matching to PACE, making the results unreliable. They also acknowledge the small ESS when matching the obe-cel group to the inotuzumab and blinatumomab groups.

3.4 *EAG's critique to company's ITC*

3.4.1 Search strategy

There are potential issues which could arise when updating an existing SLR, particularly for a treatment not included in the company's decision problem. It runs the risk of unintentionally excluding relevant studies published before the original search data if the initial search strategy was not exhaustive. Furthermore, as all 29 newly identified studies from the update were excluded from the ITC, it could raise questions the completeness of the search in identifying relevant studies.

3.4.2 Feasibility assessment

3.4.2.1 Study characteristics

The study duration of FELIX is longer than INO-VATE and TOWER, but shorter than PACE. However, median follow-up of PACE is the shortest at 5.4 months, and that of

INO-VATE was the longest at 29.6 months. The median follow-up between FELIX, was 20.3 months, longer than that of TOWER (11.7 months). Longer follow-up, even beyond that of INO-VATE, may allow for a more comprehensive assessment of long-term outcomes, potentially introducing bias if not properly adjusted for. In contrast, the shorter follow-up in PACE increases the uncertainty of the results, particularly when comparing with FELIX, which may lead to imbalances in observed survival outcomes or treatment effects due to the varying durations of data collection.

FELIX and TOWER define EFS similarly, though there are slight nuances in their event definitions. FELIX includes treatment failure, relapse, or death, while TOWER includes relapse after achieving remission. INO-VATE and PACE include PFS as an outcome, not EFS. The company stated these outcomes are similar, however there are differences in how they are defined compared to EFS from FELIX. INO-VATE has a broader definition of PFS, including not only relapse and progression but also treatment discontinuation or post-therapy SCT without achieving remission, which may lead to different interpretation of progression events compared to FELIX and TOWER. PACE uses a more general definition of PFS, encompassing progression or death but does not include health status deterioration or treatment discontinuation, leading to potentially fewer progression events being captured. Definitions for OS are more aligned across the studies, measuring the time from treatment initiation to death.

The differences in follow-up duration and outcome definitions introduce some uncertainty in the comparisons between FELIX and the other trials. While the matching process in the MAIC for TOWER and INO-VATE may help reduce biases, the varying study designs and definitions of EFS/PFS could still affect the robustness of the results. The naïve comparison between FELIX and PACE, without the benefit of matching or randomisation, is particularly susceptible to confounding, further amplifying the uncertainty in the ITC.

3.4.2.2 Information not presented pre-clarification

Overall, the information provided by the company in the CS pre-clarification was minimal and unsatisfactory. There was a myriad of things that were not presented which was requested at the clarification stage. Confidence intervals were not provided for the hazard ratios of the results, which are essential to evaluate the

precision of the estimates, which could have been provided in a forest plot. Neither was how EFS and PFS was defined in each study. Furthermore, the direct reporting of observed outcomes across studies were not reported, which is important for contextualising the relative effects and understanding the magnitude of benefit across treatments.

While the CS listed the TEMs that were used in the matching procedure, the company did not provide a comparison of how TEMs differed across studies, including any significant differences. The impact of adding each TEM on the ESS was not reported. The submission also lacked details on whether the TEMs were adequately balanced across comparator populations after reweighting.

The company did not specify the statistical method or algorithm used for reweighting (for example inverse probability weighting or another approach). This is a critical methodological detail necessary to assess its validity.

3.4.2.3 Effective sample size pre- and post-matching

Tables 69, 70, and 71 of CQ responses A29 presents the covariate balance between the post-matched obe-cel group and the inotuzumab, blinatumomab, and ponatinib groups, respectively. In each case, the covariates in the adjusted-obe-cel group matches the target group to two decimal places. However, specifically for race, only the post-adjustment proportion of White patients were presented. This omission in the CQ responses could potentially obscure residual imbalances for these subgroups, especially since they had small proportions to begin with, which may affect the validity of the matching.

3.4.3 Results

The company presents the point estimate, median EFS or OS, and ESS of the unadjusted and adjusted results of the ITCs for EFS and OS in the CS, Tables 22 and 23. The EAG requested the confidence intervals of the HRs for EFS and OS, and requested further ITCs for other outcomes. These were provided by the company in response to CQ A29. These were put into forest plots by the EAG and presented in Figure 3 and

Figure 4.

Compared to the other treatments, the unadjusted hazard ratios were significantly in favour of obe-cel while the adjusted HRs for the comparison to blinatumomab and ponatinib were statistically significantly in favour of obe-cel, across both EFS and OS. There was no statistically significant difference between obe-cel and inotuzumab when considering the adjusted HRs. The company assessed the validity of the proportional hazards (PH) assumption for obe-cel vs all comparators across EFS and OS outcomes. For all treatments, the PH assumption was found not be hold, so separate models were fit for each treatment, by the company and EAG. The use of both parametric and spline models reflects an effort to address the violations of the PH assumption. While splines can enhance the robustness of survival estimates, the inconsistent application of inverse-MAIC and naïve hazard ratios across comparators increases uncertainty in the results.

For the CR, CRi, and CR/CRi outcomes, results significantly favoured obe-cel except for the following. In the unadjusted CR comparison to ponatinib, and the unadjusted and adjusted comparison to inotuzumab for the CR/CRi outcome.

Figure 3: Results of the company's ITC analyses for EFS and OS

Figure 4: Results of the company's ITC analyses for CR, CRi, and CR/Cri

3.4.4 EAG's conclusion

The EAG identified several limitations in the company's ITC methodology, including potential issues with the search strategy, lack of transparency in statistical methods, and missing details on TEM balance across studies. The absence of randomisation in the single-arm studies (FELIX and PACE) introduces the risk of confounding, while differences in study durations and endpoint definitions add further uncertainty to the comparisons.

Despite these concerns, the ITC results consistently favoured obe-cel in comparisons to blinatumomab and ponatinib for EFS and OS, with statistical significance in adjusted analyses. However, there was no significant difference versus inotuzumab. While the findings suggest potential efficacy benefits for obe-cel, the methodological uncertainties, particularly around residual confounding and generalisability, limit the confidence in the results. The ITC is sufficient to indicate a trend but may not fully establish comparative effectiveness without further robust validation.

This will have implications on the economic modelling presented by the company. The use of the inverse-MAIC HRs (1/HR) in the economic model assumes that the ITC results are robust, the PH assumption holds and accurately reflects the relative efficacy of obe-cel compared to inotuzumab, blinatumomab, and ponatinib.

3.5 *Ongoing trial*

In response to the EAG's clarification question A22, the company has confirmed that [redacted] will be the next data cutoff of the FELIX trial. This timeframe will not be captured within the timeframe of this appraisal.

3.6 *Additional work on clinical effectiveness undertaken by the EAG*

The EAG has not undertaken any further work on the clinical effectiveness beyond what has already been presented in terms of extracting and compiling relevant information on obe-cel from a range of sources.

3.7 *Conclusions of the clinical effectiveness section*

The FELIX trial, a single-arm phase Ib/II study, is subject to several limitations including small sample size, short follow-up, and mixed cohort in terms of previous and subsequent therapies which hinder its suitability to contribute evidence for decision-making. Considerable uncertainty remains around long-term efficacy. The reliance on MAICs limited by un-adjustable population differences and small effective sample sizes, or even a naïve comparison, to estimate the relative efficacy of obe-cel against the comparators is a major concern. Furthermore, the assumptions around the hazard ratios are likely violated, meaning the effect estimates may not represent the true relative efficacy.

4 COST EFFECTIVENESS

4.1 *EAG comment on company's review of cost-effectiveness evidence*

4.1.1 Searches

The company searched relevant electronic bibliographic databases in May 2024 to identify cost-effectiveness (CS Appendix G.4), health-related quality of life (HRQoL) (CS Appendix H.13) and costs and resource use (CS Appendix I.2) evidence. The EAG note an error in the reporting of the HRQoL and cost and resource use search strategies which are entitled 'May 2021' and should be 'May 2024' (CS Appendix H.13 Table 21, I.2 Table 25). The search methods sections for the cost-effectiveness, HRQoL or costs and resource searches do not list the Cochrane Library as a source that was searched (CS Appendix G.4, H.13 and I.2); however, the search strategy reported in the clinical SLR section (CS Appendix D.2 Table 9) includes search terms to identify costs and quality of life studies (CS Appendix D.2 Table 9, lines 10-12). The search results for the Cochrane Library are reported in the clinical SLR PRISMA flow-diagram only (CS Appendix D.6 Figure 5). This may be due to no studies being included; however not reporting it is a limitation of the recording.

The company have limited their search results to studies published after the search strategy was ran for TA893.[38] The EAG commented on the approach for updating the search strategy used for TA893 at Section 4.1.1.

The searches were carried out via MEDLINE and EMBASE simultaneously via Embase.com, the Cochrane Library (via Wiley) and the International Network of Agencies for Health Technology Assessment (INAHTA). Relevant study filters are applied to capture results relevant to the review questions. References for the study filters are not reported but the search terms include a relevant and broad range of indexing and free text terms (CS Appendix G.4 Table 16, H.13 Table 21 and I.2 Table 25).

Additional searches were carried out on five relevant cancer and haematology conferences and three clinical trials registries for the years 2022-2024. Additional searches were carried out on manufacturers websites, Google Scholar and the NICE

website. Reference checking of SLRs was carried out. The search terms and numbers of results of the non-database searches are not reported (CS Appendix G.4, H.13 and I.2). The SLRs that reference checking was carried out on are not provided. The lack of information regarding the non-database searches reduces the transparency and reproducibility of these searches and the EAG has concerns over the methods used to update the TA893 search strategy, outlined in Section 3.1.1.

4.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

The EAG conducted a review of the company's economic evaluation model to ensure alignment with NICE standards. A de novo cost-effectiveness model was constructed to evaluate the cost-effectiveness of obe-cel for the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia (B-cell ALL). This evaluation was based on the FELIX clinical trial population, the licensing criteria, and the decision problem outlined in the submission. The EAG provided a summary of the model's structure and critically appraised the clinical evidence (e.g., efficacy, treatment pathway, and mortality) and economic evidence (e.g., drug costs, health state resource use and costs, and utility values). The EAG critiqued the methods and inputs used in the analysis.

4.2.1 NICE reference case checklist

The EAG undertook an evaluation of the company's submission against the NICE reference case. Findings are summarised in the Table 18.

Table 18: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In general, all relevant health effects occurring after treatment have been accounted for in the economic analysis, except those from the pretreatment period.

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on costs	NHS and PSS	Resource use and costs are considered from the NHS and PSS perspective, with the exception of allo-SCT for patients undergoing their first allo-SCT.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-effectiveness analysis. The company reported pairwise comparisons as well as fully incremental results.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	It is sufficient, as the company used 100 years minus the baseline age of the FELIX trial cohort.
Synthesis of evidence on health effects	Based on systematic review	ITC suggests efficacy benefits for obe-cel, but violated assumptions and potential for confounding risks undermine confidence in the output.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The company's preferred measure is in line with the NICE final scope.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L utility data were collected in the FELIX clinical trial using EQ-5D-5L tool.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The EQ-5D-5L health utility values were mapped to EQ-5D-3L using a UK-based algorithm published by Hernández Alava et al. (2017).[60]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The company has incorporated the QALY weight into the model.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use clearly reported and valued appropriately using current prices and is in line with the NHS and PSS perspective.

Element of health technology assessment	Reference case	EAG comment on company's submission
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The discount rate is based on 3.5% per annum, but applies per cycle for both costs and benefits. The EAG's preferred approach is to use the per-year discount factor.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company adapted a partitioned survival model (PSM) to estimate the long-term costs and outcomes of treatments for relapsed/refractory (R/R) adult acute lymphoblastic leukaemia (ALL) using EFS and OS clinical outcomes to obtain three mutually exclusive health states:

1. Event-Free State: Captures the period from treatment initiation until the occurrence of key events: treatment failure, morphological relapse, or death.

2. Post-Event State: Includes patients who experience disease progression or treatment failure.

3. Death: Accounts for patients who die due to any cause (see Figure 5).

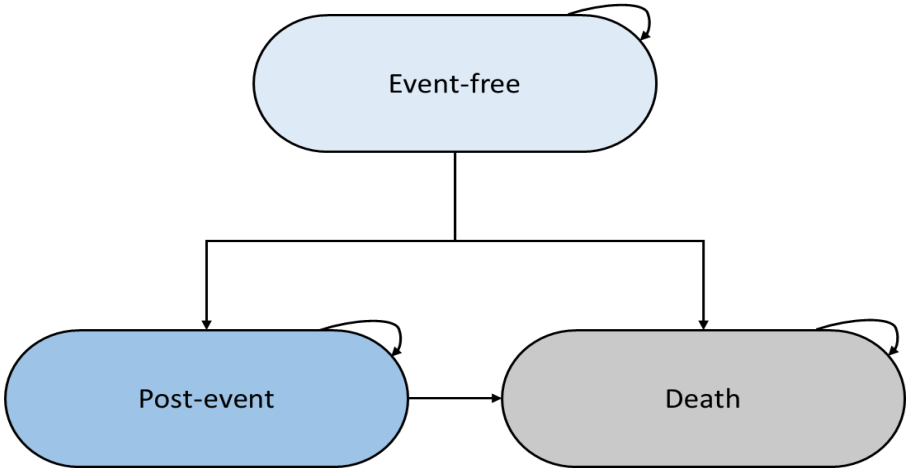

Figure 5: Model structure(obtained from CS, document B, section B.3.2.2, figure 19)

The company stated that this structure aligns with established clinical pathways in ALL and adheres to recognized best practices in health economic modelling, as demonstrated in systematic literature reviews (SLRs) and prior NICE appraisals (e.g., TA893 and TA559).

The company's model incorporates a cure assumption for patients who remain alive three years post-treatment, grounded in expert validation, data from the Obe-cel FELIX trial (Cohort IIA), and precedents in other NICE appraisals of CAR T-cell therapies, such as TA893. Cured patients are modelled with improved survival and health-related quality of life (HRQoL) compared to non-cured patients. Cured patients are also modelled with lower resource utilization but higher mortality compared to the age-matched general population.

The company stated that, in line with TA893, the model accounts for costs associated with patients who undergo leukapheresis, conditioning, or bridging therapies but do not ultimately receive obe-cel infusion.

EAG comment:

Whilst the company's approach is broadly in-line with previous appraisals, the EAG notes some areas of concern in relation to the Post-Event state and allo-SCT.

The definition of the Post-Event state focuses on patients who experience disease progression or treatment failure, but this does not fully reflect clinical practice. Comparator treatments, such as blinatumomab, are primarily used with the aim of permitting patients access to subsequent allo-SCT. In contrast, the company's model does not explicitly include allo-SCT in the Post-Event state, which limits its ability to accurately capture real-world outcomes associated with SCT. For example, in previous NICE appraisals like TA541 for inotuzumab, a considerable proportion of patients move to SCT (48% with CR/CRi conditions).

Additionally, the company asserts that the effect of allo-SCT on survival is captured within Kaplan-Meier curves that do not censor patients receiving SCT. However, the exclusion of explicit utility modelling for SCT creates a critical gap. In comparison, for other treatments, such as those used in NICE appraisals, SCT costs and utility adjustments are included, resulting in a more comprehensive assessment of patient

outcomes post-SCT. This inconsistency means the true economic and clinical burden associated with SCT is not fully captured in the company's model structure.

These inconsistencies suggest that amendments are needed to ensure a fair and accurate comparison across treatment pathways (see sections 4.2.4, 4.2.7, and 4.2.8).

4.2.3 Population

The company's analysis focuses on adult patients aged [redacted] with R/R B-ALL, adhering to the licensed indication and the anticipated therapeutic positioning of obe-cel. The inclusion of data from the FELIX Cohort IIA, encompassing patients [redacted], addresses the relatively small sample size while maintaining alignment with the evaluation's decision problem and the final scope. Subgroup analysis of FELIX data indicated slightly improved obe-cel efficacy in patients aged [redacted], suggesting that utilizing the entire cohort for analysis may be a conservative approach, whilst maximising the sample size. However, it may affect the applicability of the model to the licensed population.

To account for variability in comparator treatments based on Philadelphia chromosome (Ph) expression, the economic analysis distinguishes three populations: the overall cohort, Ph-negative (Ph-) patients, and Ph-positive (Ph+) patients. Baseline characteristics, such as age, gender distribution, weight, and body surface area, were derived from the FELIX study cohort IIA related to mITT population (N=94) and combined with efficacy data also from mITT data, from the point of infusion (Table 19). This approach excludes patients who were not infused.

Table 19: Baseline patient characteristics in the model (mITT population)
(Obtained from CS, Document B, Section B.3.2.1, Table 27)

Patient characteristics	Value, mITT	Value, Ph-	Value, Ph+
Age (years)	48.30	45.62	55.60
Male (%)	50%	56%	32%
Average patient weight, kg	78.73	80.90	72.59
Average patient BSA (m^2)	1.89	1.91	1.81
Proportion of ALL patients with Ph+ mutation (mITT population) [%]	26.6%	0%	100%

ALL – Acute lymphoblastic leukaemia; BSA – Body surface area; kg – kilogram; Ph+ – Philadelphia chromosome-positive; SE – Standard

The EAG had a concern about the company's choice of population.

EAG Concern 1 (Key Issue 3): Choice of population to model

The main EAG concern arises from the company's focus on the mITT population of Cohort IIA. Of the 112 patients initially enrolled, only 94 received at least one obe-cel infusion. The remaining [redacted] patients were excluded due to [redacted]

While the company has opted to use the modified intention-to-treat (mITT) population for its analysis—comprising only those who received at least one obe-cel infusion (N=94)—this decision introduces potential biases. The mITT population excludes patients who discontinued treatment for reasons that may influence both costs and outcomes in real-world clinical practice. The company asserts that the mITT population reflects clinical practice since obe-cel will only be reimbursed for patients receiving at least one infusion. However, this assumption narrows the scope and may underestimate the full burden of treatment, whilst also ignores the outcomes for patients who are not infused. Therefore, the evaluation of obe-cel should consider the entire treatment package, including the pretreatment period, encompassing any positive or negative effects associated with the treatment regimen.

To enhance the robustness of the analysis and increase sample size, the EAG suggests combining data from Cohorts IA and IIA. This approach would yield a more comprehensive population of 133 patients, providing a broader basis for evaluation. Key characteristics of this expanded cohort are summarized in Table 20

Table 20: Baseline patient characteristics in the model (ITT population from cohort IA and IIA) (Obtained from company's response to EAG clarification questions)

Patient characteristics	Value, Whole population	Value, Ph-	Value, Ph+
Number of patients (ITT)*	133	[redacted]	[redacted]
Number of infused patients	[redacted]	[redacted]	[redacted]
Age (years)	[redacted]	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]	[redacted]

Ph: Philadelphia chromosome; mITT: modified intention-to-treat; ITT: intention-to-treat
* Values in this table are based on data prior to matching with other comparators.

EAG Solution:

Base-case analysis: Use all ITT patients from Cohorts IA and IIA in the evaluation.

Scenario analysis: Use the mITT population, consistent with the company's proposed approach.

4.2.4 Interventions and comparators

Obe-cel is administered at a target dose of 410x10⁶ CD19 CAR-positive viable T-cells, and includes pre-treatment with lymphodepletion using fludarabine and cyclophosphamide and often involves bridging chemotherapy prior to infusion. The dosing regimens for obe-cel and associated therapies in the economic model are informed by the FELIX study.

The comparators in the model reflect the current standard of care (SoC) in the UK for R/R ALL and align with expert clinical opinion. For the overall population, inotuzumab ozogamicin is the primary comparator. For Philadelphia chromosome-negative (Ph-) patients, blinatumomab is used, while ponatinib is the comparator for Philadelphia chromosome-positive (Ph+) patients. These comparators were chosen based on their alignment with clinical practice and regulatory approval. After consulting with their clinical experts, the EAG accepts these are the most relevant comparators.

EAG comment:

In this evaluation, there is the possibility of inconsistency in the placement of obe-cel and the comparators (inotuzumab, ponatinib, blinatumomab) in the treatment

pathway. Clinicians may prefer to give obe-cel following a CR or CRi from one of the comparators, meaning the true comparator to obe-cel should be allo-SCT. However, allo-SCT is considered in this appraisal as a subsequent therapy. Alternatively, obe-cel use may be predominantly in people who have not responded to one of the comparators, and who may have little chance of going onto receive allo-SCT on the current treatment pathway. It is unclear how these different placements of obe-cel affects the most likely comparator and efficacy of the comparator.

The EAG notes that in FELIX, [redacted] out of [redacted] responders to obe-cel (achieving complete remission in cohort IIA) underwent allo-SCT during remission. This highlights obe-cel's dual role as both a curative therapy and as a potential route to allo-SCT.

Hence, the EAG assumes that all treatments under evaluation aim to achieve a cure for patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL), whilst the standalone ability of obe-cel to cure patients remains unknown.

4.2.5 Perspective, time horizon and discounting

The company stated that the economic model adopts the perspective of NHS England and Personal Social Services (PSS), in alignment with the NICE reference case, by considering direct healthcare costs.

The company further stated that the model employs a lifetime time horizon, defined as 100 years minus the baseline age of the cohort (see Table 20), to comprehensively capture all significant differences in costs and outcomes between the technologies under comparison. A cycle length of 28 days is utilized, with half-cycle corrections applied in the base case to enhance the precision of the analysis.

Additionally, the company stated that costs and outcomes are discounted at an annual rate of 3.5%, consistent with NICE guidelines.

The EAG has identified one concern with regarding the discounting applied within the company's modelling.

EAG Concern 2: Use of per-cycle discount rate instead of per-year discount rate

Company's Approach: The company applied a per-cycle discount rate to calculate discount factors in their economic model. The cycle length is 28 days, and the discounting is applied at the end of each cycle.

EAG comments: According to NICE reference case (2023), Section 4.5.1,[61] cost-effectiveness results should reflect the present value of costs and benefits over the analysis time horizon. The reference case specifically states: “For the reference case, costs and health effects should be discounted at the same rate of 3.5% per year.”

Using a Per-Cycle Discount Rate deviates from the guideline as it splits the annual discount rate into smaller time intervals (28 days), potentially leading to inconsistencies in discounting across the model's time horizon.

EAG's Solution:
Base-case: The EAG recommended revising the model to use a per-year discount rate of 3.5% as specified in nice guidelines. this ensures that both costs and health effects are appropriately discounted over the time horizon, maintaining consistency with the reference case and improving the accuracy of the cost-effectiveness results.

4.2.6 Treatment effectiveness and extrapolation

Section B.3.3.2 of the CS details the survival analysis approach taken by the company for EFS (or PFS where reported) and OS for obe-cel and the three comparator treatments: inotuzumab, blinatumomab and ponatinib. Table 30 of CS Doc B summarised the selected model for teach treatment, by outcome and subgroup (overall, Ph-, and Ph+).

4.2.6.1 Survival analysis methods

The company used the patient-level data from the FELIX study to extrapolate EFS (with censoring post-SCT and other new therapies) and OS (without censoring post-SCT) beyond the time of the study. The inclusion of censoring post-allo-SCT and other therapies in EFS, but its exclusion in OS, introduces a discrepancy that may impact the interpretation of treatment efficacy. Typically, allo-SCT is expected to improve outcomes like OS, as it is often considered curative in some patients,

according to EAG clinical advisors. However, the worser OS outcomes observed without censoring could suggest that patients who undergo allo-SCT are inherently at higher risk or experience complications that offset its benefits. As hypothesized by the company in the CSR document (page 63), subsequent allo-SCT may lead to a [redacted].

Despite stating in the CS that for the three comparators, the company used the same approach to extrapolate their digitised data, the EAG understands that for the company base case analyses for blinatumomab and inotuzumab, the company instead applied inverted hazard ratios from their MAIC to the obe-cel extrapolations. The inverse MAIC approach was consistent with the committee's preferred assumptions in TA893. For ponatinib (PACE; N=32), digitised curves for PFS and OS were used. The company employed the use of standard parametric models and restricted cubic splines in their survival modelling.

For the comparisons to inotuzumab and blinatumomab, the company has inverted the hazard ratios and applies them to the extrapolations of obe-cel from FELIX, which is considered to be more representative of the NHS population than the other trials. This approach assumes hazard proportionality, which appears violated based on evidence provided by the company, with instances of hazard curves crossing. While some hazard rates were reasonably proportional during certain trial periods, the differences in follow-up lengths across the studies further complicate the long-term validity of the PH assumption. It also assumes that the relative treatment effect does not change across the populations, which is not clearly supported.

Standard parametric models were fit to the observed KM data. These are fit from time zero until the end of the study and beyond. The parametric models fitted were the exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, and gamma models.

Restricted cubic splines were also used. Analyses were performed using 0, 1, 2, and 3-knot spline models on three different scales: normal, odds and hazards.

Knots are the points along the timeline where the behaviour of the data can change, with more knots indicating greater flexibility.

The company considered using mixture and non-mixture cure models due to the curative potential of obe-cel. Cure models are used to analyse survival data when a part of the people is considered 'cured' and will never experience the disease again.. However, cure models were not used since the raw EFS and OS data from FELIX were deemed too immature with [redacted] and [redacted] experiencing events, respectively.

Since the assumption of a cure timepoint was used in TA893 (brexu-cel), the company used the same approach in their modelling, using a cure timepoint of three years. This means that after three years, it is assumed that no more patients have an OS or EFS/PFS event. After this point, the survival of the remaining 'cured' participants are adjusted by a standardised mortality ratio of 3.00 so that the hazards of the remaining participants do not fall below that of the general population.

All the models were fit to unadjusted curves. This can potentially be misleading if important confounders influence the outcome alongside the treatment. Though no subgroup analyses were presented for EFS and OS in FELIX, the subgroup analyses for ORR and CR in cohort IIA show [redacted] between subgroups. The EAG considers that the company's use of mITT population for obe-cel introduces bias, as patients not making it to infusion are not accounted for in the FELIX follow-up, but equivalent patients are likely represented in the follow-up of the other trials.

4.2.6.2 Assumptions and model fit

Model fit was based on criteria in line with NICE Decision Support Unit Technical Support Documents 14 and 21 and were considered for all curves. This included an assessment of proportional hazards using Schoenfeld's residuals, time-dependent hazard ratio and cumulative hazard plots, visual fit to the Kaplan-Meier plot, and goodness-of-fit statistics (Akaike information criterion (AIC) and Bayesian information criterion (BIC)). Additionally, the underlying hazard functions and the clinical plausibility of the extrapolated outcomes were evaluated. Other good-fitting models were included in scenario analyses.

4.2.6.3 Company's chosen model

Models were fitted for EFS (or PFS) and OS in three different populations: overall, Ph-, and Ph+. Each model used for the company's economic base case was chosen

based on visual fit, goodness-of-fit statistics, and the opinion of the company's clinical experts.

4.2.6.3.1 Overall R/R B-cell ALL population

In this population, curves were fitted to the unadjusted EFS and OS curves from FELIX for obe-cel, and the unadjusted PFS and OS curves from INO-VATE for inotuzumab. After testing the proportional hazards assumption, the company concluded that is does not hold. Therefore, independent models were selected.

Obe-cel EFS

The company states that their experts felt that all the spline models provided plausible EFS estimates. Therefore, they chose the 0-knot normal spline as it had the lowest AIC. However, when assessing the visual fit of the spline models (Figure 25 in CS appendix M.3.1.1), they are a poor visual fit to the KM data, overestimating EFS up to around 1.5 years. The EAG considers it possible that the models were fitted to the wrong data-set.

In response to CQ A29, the company altered their definition of EFS from being assessed by a local investigator to an Independent Response Review Committee. This altered EFS results and also changed the company's preferred EFS plot from the 0-knot normal spline to the 3-knot normal spline, the results of which were presented at the end of the CQ responses in the revised company base case analysis section. As with the original EFS curves for obe-cel that were presented in CS Document B, the new curves presented in the CQ responses largely have poor visual fit. The parametric models in Figure 56 of CQ responses are mostly poor visual fits to the observed KM data up to one year and the three-year EFS estimates differ widely between the different models. The spline models in Figure 57 of CQ response look to be a better visual fit compared to the parametric model

Obe-cel OS

For OS, both the 3-knot normal spline and the exponential had the best fit while the 3-knot normal spline gave the most plausible OS estimates, therefore this model was chosen by the company. Visually, both the parametric curves and the splines provided good fit to the KM data.

Inotuzumab EFS and OS

For inotuzumab, the company did not use their preferred extrapolations from INO-VATE, but applied the inverse hazard ratios from their MAIC to the obe-cel EFS and OS extrapolations.

4.2.6.3.2 Ph- population

The company fitted models to the Ph- subgroup of obe-cel and the blinatumomab group of TOWER which was a Ph- population by design. Again, the PH assumption was violated.

Obe-cel EFS

For the EFS outcome in the obe-cel Ph- subgroup, the company chose the Weibull model due to it being the best statistically fitting model from the parametric models and having more plausible EFS estimates compared to the best-fitting spline model, the 2-knot normal spline. When assessing their visual fits, the Weibull conforms to the KM data well, while the spline models all underestimate EFS.

Obe-cel OS

For OS, the company chose the exponential over the 2-knot normal model, with both being the best fitting models. Both the parametric and spline models looked to have good visual fit to the KM data. The company also noted that “the OS hazard rate for obe-cel in the Ph- population demonstrates evidence of varying over time, suggesting the constant hazard function of the exponential distribution may not reflect the underlying hazard of the data (see Appendix M.3.2). This is a limitation of using the exponential curve, however on balance it was considered appropriate to retain the exponential curve in the base case to align with UK clinical expert OS estimates for obe-cel in the Ph- population.”

Blinatumomab EFS and OS

As for the comparison to inotuzumab, the company did not use their preferred extrapolations as described in their submission, but used the inverse MAIC approach to apply the hazard ratios to their preferred obe-cel extrapolations.

4.2.6.3.3 Ph+ population

The company fitted models to the Ph+ subgroup of obe-cel and the ponatinib group of PACE which was a Ph+ population by design. Again, the PH assumption was violated. There was no adjustment for differences in trial populations.

For the EFS curves in the obe-cel Ph+ population, the chosen 1-knot hazards spline was the second best-fitting model but had the most plausible EFS estimates, as chosen by the company's clinical experts. Visually, the spline models seem to underestimate EFS in this group. Similarly, the selected log-normal model was the second-best fitting model form the parametric curves but had what was deemed to be the most plausible OS estimates. Visually, these curves all fit well until around one year into FELIX where is there a large step in the KM curve.

For the EFS outcome in PACE, the company chose the 1-knot odds spline which was the best fitting splines curve, and for OS the company selected the log-normal model, the best-fitting parametric curve. For both outcomes, the chosen model fit well with the observed KM data.

The base case models selected by the company were the following:

- Obe-cel
    - EFS: 1-knot hazards spline
    - OS: log-normal
- Ponatinib
    - EFS: 1-knot odds spline
    - OS: Log-normal

4.2.6.3.4 Scenario analysis models

The company explored the following models in scenario analyses, varying the choice of extrapolation for obe-cel.

- Overall population:
    - EFS: 0-knot odds spline
    - OS: 3-knot normal spline
- Ph- population:
    - EFS: Generalised gamma curve
    - OS: Weibull parametric curve

- Ph+ population:
    - EFS: Weibull parametric curve
    - OS: Exponential parametric curve

Additional scenario analyses were performed based on direct extrapolation of the comparator treatments (i.e. naïve comparisons) for inotuzumab and blinatumomab, and on an inverse MAIC approach for ponatinib. The EAG did not consider these useful for decision-making given their major limitations.

4.2.6.4 EAG's survival modelling

In the absence of readily available Kaplan-Meier IPD for any of the treatments, the EAG digitised the EFS (or PFS where appropriate) and OS KM plots from the key trials of obe-cel, inotuzumab, blinatumomab, and ponatinib to generate pseudo-IPD. The EAG also requested the KM plots for the obe-cel Ph- and Ph+ populations during the clarification stage which was provided the company in response to CQ A30. Furthermore, the EAG also requested the KM plots for the FELIX ITT population, which were the all-enrolled cohorts IA and IIA. These were provided in response to CQ A1.

The EAG's preferred sources of data for inotuzumab, ponatinib, and blinatumomab were the same as the company. For obe-cel, the EAG uses the FELIX ITT population cohorts IA + IIA, while the company used the FELIX mITT population cohort IIA. The EAG preferred dataset increases the sample size (133 vs 94) and reduces likely bias from the company's approach of excluding the pre-infusion period of the trial.

To reconstruct the IPD, the EAG used the 'ipdfc' package in STATA SE 18 (64-bit) to reconstruct the pseudo-IPD and fit the parametric and spline models in R version 4.1.0 using the 'flexsurv' package.

4.2.6.4.1 Reconstruction accuracy

It should be noted that reconstructed KM pseudo-IPD may vary slightly between individuals due to differences in digitisation precision, software packages, and reconstruction methods, resulting in similar but not identical outcomes compared to the results presented. The optimum method would be to use the observed KM IPD, however this was not available to the EAG for any of the four treatments and was

only available to the company for obe-cel. Any impact on the extrapolations is likely to be minimal.

4.2.6.4.2 EAG preferred models fitted to reconstructed IPD

This section presents the EAG's preferred base case and scenario analyses models. These models were chosen based on statistical fit, visual it, and plausibility of survival extrapolations up to and at the company's base case cure timepoint of three years.

Table 21 presents the EAG's and company's chosen models, alongside some of the scenarios considered. The differences between the EAG's and company's obe-cel preferred models were due to the populations modelled. [redacted]

In the FELIX ITT Ph- subgroup population, [redacted].

In the FELIX ITT Ph+ subgroup population, [redacted].

In PACE, which featured the Ph+ subgroup, [redacted]

[redacted].

Table 21: EAG's and company's preferred survival plots

			EAG				Company			
Treatment	**Outcome**	**Population**	**Base case**	**3Y surv**	**Scenario**	**3Y surv**	**Base case**	**2.99Y surv**	**Scenario**	**2.99Y surv**
Obe-cel EAG: ITT Company: mITT	EFS	Overall	Log-normal	[redacted]			3-knot normal	[redacted]	0-knot odds	[redacted]
	OS		Log-normal	[redacted]	Gen Gamma	[redacted]	3-knot odds	[redacted]	3-knot normal	[redacted]
	EFS	Ph-	Gompertz	[redacted]	Gen Gamma	[redacted]	Weibull	[redacted]	Gen Gamma	[redacted]
	OS		2-knot odds	[redacted]	1-knot odds	[redacted]	Exponential	[redacted]	Weibull	[redacted]
	EFS	Ph+	Exponential	[redacted]			1-knot hazard	[redacted]	Weibull	[redacted]
	OS		Exponential	[redacted]	Gen Gamma	[redacted]	Log-normal	[redacted]	Exponential	[redacted]
Ponatinib	EFS		Log-logistic	[redacted]	1-knot odds	[redacted]	1-knot odds	[redacted]	Inverse MAIC	[redacted]
	OS		Log-normal	[redacted]	0-knot odds	[redacted]	Log-normal	[redacted]	Inverse MAIC	[redacted]

*Survival at 2.99 years (cycle 39)

4.2.7 Health related quality of life

The company assesses health effects through utility weights for different health states, derived primarily from the FELIX clinical trial using EQ-5D-5L and EORTC-QLQ-C30 tools using mITT population of cohort IIA. Baseline health-related quality of life (HRQoL) data and post-treatment outcomes were collected at multiple intervals (prior to obe-cel infusion (at baseline), 28±2 days, and 3, 6, 9, 12, and 18 months post-first infusion), showing consistent improvements in patients' HRQoL post-infusion. Out of the 94 infused patients, 70 provided baseline scores for the EQ-5D-5L. Utility values for the "event-free" ([redacted]) and "post-event" ([redacted]) states were mapped to EQ-5D-3L using a UK-based algorithm published by Hernández Alava et al. (2017)[60], in line with NICE guidelines.[62]

For the base case analysis, missing data were not imputed, and utility estimates were calculated using linear mixed-effects models. An analysis using multiple imputation for missing values reported event-free and post-event utilities of [redacted] and [redacted] respectively. A long-term survivorship increment was applied to cured patients after three years. This utility was calculated such that the health state utility of long-term survivors would be halfway between that of the general population at 3 years (base-case cure assumption) and the event-free utility. As general population utility is age-dependent, the long-term utility values differed between the modelled populations due to variations in baseline characteristics ([redacted], [redacted] and [redacted] in the overall, Ph- and Ph+ populations, respectively). General population utility values were modelled using the ordinary least squares regression described by Ara and Brazier et al. (2010).[63] Utility decrements for adverse events were incorporated into the post-event-free health state for base case analysis. Overall, the company has stated that the methodology ensures robust, patient-centred valuation aligned with clinical data and health economic guidelines.

A summary of the utility values used in the cost-effectiveness analysis is presented in

Table 22.

Table 22: Summary of utility values for cost-effectiveness analysis (Obtained from CS, Document B, Section B.3.4, Tables 33 and 34, and economic model)

State	Utility value: mean (95% confidence interval)	Justification
Health state utility (base-case)		
Event-free	[redacted]	Prospective utility data measured in trial population of interest
Post event-free	[redacted]	Prospective utility data measured in trial population of interest
Long-term survivorship utility	[redacted]	Assumed such that the health state utility of long-term survivors will be halfway between that of the age/sex matched general population at 3 years (base-case cure time assumption) and the event-free utility.
Health state utility (Scenario analysis)		
Event-free	0.802	NICE TA450: Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia
Post event-free	0.692	
Long-term survivorship utility	0.860	

Table 23: Proportion and utility decrements associated with adverse events included in the model (Obtained from CS, Document B, Section B.3.4, and Economic model)

Adverse event (≥ Grade 3)	Disutility	Proportion with event*			
		Obe-cel	Blinatumomab	Inotuzumab	Ponatinib
Cytokine release syndrome (CRS) (Grade 2+, treated with tocilizumab)	-	[redacted]	0.00%	0.00%	0.00%
Cytokine release syndrome (CRS) (Grade 3+)	[redacted]	[redacted]	4.87%	0.00%	0.00%
Neurological event	0.220	[redacted]	9.36%	0.00%	0.00%
Neutropenia	0.090	[redacted]	37.83%	35.98%	21.88%
Infection	0.200	[redacted]	34.08%	1.22%	0.00%
Elevated liver enzyme	0.000	[redacted]	12.73%	0.00%	0.00%
Decrease in platelet count	0.050	[redacted]	6.37%	0.00%	0.00%
Decrease in white-cell count	0.050	[redacted]	5.24%	0.00%	0.00%
VOD	0.104	[redacted]	0.00%	10.37%	0.00%
Infusion reaction	0.050	[redacted]	3.37%	0.00%	0.00%
Lymphopenia	0.070	[redacted]	1.50%	11.59%	0.00%
Thrombocytopenia	0.090	[redacted]	0.00%	24.39%	18.75%
Pyrexia	0.110	[redacted]	0.00%	1.83%	0.00%

Hypotension	0.070	[redacted]	0.00%	0.00%	0.00%
Anaemia	0.120	[redacted]	0.00%	12.20%	18.75%
Sinus tachycardia	0.150	[redacted]	0.00%	0.00%	0.00%
Hypoxia	0.220	[redacted]	0.00%	0.00%	0.00%
Hypokalaemia	0.200	[redacted]	0.00%	1.22%	0.00%
Hypophosphatemia	0.070	[redacted]	0.00%	0.00%	0.00%
Neutrophil count decreased	0.000	[redacted]	3.75%	0.00%	0.00%
Alanine aminotransferase increased	0.000	[redacted]	5.62%	1.22%	0.00%
Diarrhoea	0.050	[redacted]	0.00%	0.00%	3.13%
Encephalopathy	0.220	[redacted]	1.50%	0.00%	0.00%
Febrile neutropenia	0.090	[redacted]	21.35%	14.02%	0.00%
Pneumonia	0.220	[redacted]	0.00%	0.00%	0.00%
Respiratory failure	0.220	[redacted]	0.00%	0.00%	0.00%
Abdominal pain	0.050	[redacted]	0.00%	0.61%	6.25%
Sepsis	0.200	[redacted]	0.00%	0.00%	0.00%
Renal failure	0.150	[redacted]	0.00%	0.00%	0.00%
Hypogammaglobulinaemia	0.000	[redacted]	0.00%	0.00%	0.00%
Total One-off disutility	-	[redacted]	0.190	0.108	0.064

CRS – Cytokine release syndrome; TA – technology appraisal; VOD – veno-occlusive disease.

EAG Concern 3: allo-SCT utility effects.

The EAG has identified one concern with the company's implementation of quality of life in the economic model, around the exclusion of utility effects from allo-SCT.

Company's approach: The company base case analysis has excluded the specific utility effects of allo-SCT from the economic model for all comparators. Additionally, for obe-cel, the company assumes no patients undergo allo-SCT in the base-case analysis and does not model separate utility values for patients receiving allo-SCT. A scenario analysis was performed which considered the disutility associated with allo-SCT, but not any incremental utility.

EAG Critiques and Assumptions: The utility value applied for the 'post-event' health state ([redacted]) does not appear to reflect the specific impacts of allo-SCT. Evidence from TA541 and related studies[64, 65] indicates varying utility values across

post-HSCT periods, with including SCT related complications like graft-versus-host disease (GvHD).

Moreover, comparators like inotuzumab, blinatumomab, and ponatinib primarily function as bridging therapies to allo-SCT. A significant proportion of patients treated with inotuzumab (48%) and ponatinib (47%) proceed to allo-SCT. Despite this, the model assigns a uniform utility value to all patients in the post-event health state, disregarding distinct post-SCT conditions such as complete remission (CR/CRi).

Assuming equivalence between the well-being of post-SCT patients and the broader post-event population contradicts clinical evidence. For example, TA541 reports that post-SCT utility values are 0.59 during the first year and 0.75 in years 1–2, underscoring the variability in health-related quality of life over time (see **Table 25**).

Table 24: Proportion of patients who receive an allo-SCT, by initial treatment (Obtained from CS, Document B, Section B.3.5.4, Table 56)

Treatment	Proportion who receive an allo-SCT	Source
Obe-cel	0%	Clinical opinion and in line with TA893[17]
Blinatumomab	13%	TA893[17]
Inotuzumab	48%	TA893[17]
Ponatinib	47%	TA893[17]

Allo-SCT – allogenic stem cell transplant; TA – Technology Appraisal.

Regarding this concern, EAG makes the following assumptions:

• that the utilities derived from the FELIX trial for the post-event health state do not reflect the utility impacts of allo-SCT.

• in line with TA541, that patients undergoing allo-SCT experience different utility values depending on the time period post-transplantation.

• that TA541 utility values are applicable, as they account for variations in HRQoL over time and include disutility associated with GvHD.

EAG Solution:

Base Case: Adjusting utility values in the post-event health state using time-dependent utilities from TA541 to capture variations in post-HSCT HRQoL and account for the proportion of patients receiving allo-SCT across different treatments (see Table 25).

Table 25: Determining the Changes in basic utility due to SCT for different treatments

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

* Assumed that AML utilities after HSCT from Kurosawa et al. (2016) can be applied to R/R ALL patients. These include the disutility for GvHD
** Calculated by multiplying the difference between health state utility and post-HSCT utility by the proportion of individuals who undergo an allo-SCT. For example, [redacted] = (0.59 - [redacted]) × 13%.

Scenario Analysis: The company's original approach.

Justification for Adjusted Model: The adjusted model better aligns with real-world evidence and clinical data, addressing the significant differences in HRQoL across health states and treatments. It also adheres to NICE guidelines and reflects patient experiences more accurately. By incorporating these solutions, the EAG provides a more robust framework for evaluating the impact of allo-SCT on HRQoL. This approach ensures a fair comparison of the intervention and comparators in health economic evaluations.

4.2.8 Resources and costs

The company stated that the cost and resource use analysis for obe-cel and comparators (blinatumomab, inotuzumab, and ponatinib) encompass drug acquisition, administration, pre-treatment costs, health state costs, adverse events, subsequent treatment costs, and terminal care costs. These were modelled using a bottom-up costing approach, leveraging data from the FELIX clinical trial and previous technology appraisals (such as TA893). The company has focused on direct healthcare costs from the NHS and Personal Social Services (PSS) perspective. The company has conducted an updated SLR, building on TA893, captured healthcare resource use and cost data published post-September 2021. The company stated that, despite six references meeting inclusion criteria, none were deemed relevant, with only one providing UK-based multinational data. Consequently, the analysis adheres to the assumptions and cost inputs from TA893.

ITT and mITT Populations: Costs in the model account for both the intention-to-treat (ITT) population (patients who underwent leukapheresis) and the modified intention-to-treat (mITT) population (patients who received obe-cel). The company stated a cost multiplier derived from the ratio of ITT to mITT populations was applied to ensure accurate adjustment for patients who initiated but did not complete therapy due to factors like manufacturing failure. For more information and details regarding EAG concerns related to the population, please refer to section 4.2.3.

4.2.8.1 Drug acquisition and administration

Obe-cel: The acquisition cost for a single obe-cel infusion is £372,000, discounted to [redacted] under the proposed PAS (discount of [redacted]). This one-time infusion cost reflects the upfront nature of CAR-T therapies. The company stated that administration costs for obe-cel (using bottom-up costing) include a 24-day hospital stay, with 54% of patients spending 4 of those days in the ICU, aligning with TA893. Daily costs were derived from NHS 2022/23 reference costs using HRG codes SA24G-J and XC01Z-XC07Z. These resulted in a total administration cost of £5,989.

Blinatumomab: The company has conducted calculations of acquisition cost based on an NHS reference cost of £2,017 per 38.5-mcg vial. For administration, the first treatment cycle includes hospitalization for seven days to monitor for cytokine

release syndrome (CRS), followed by outpatient care, totalling £8,922 per cycle. Subsequent cycles involve outpatient administration costs of £3,622 each.

Inotuzumab: The company stated that inotuzumab's cost per 1-mg vial is £8,048, with dose administration based on patient weight (average of 70 kg). For the first cycle, the cost totals £32,192. As it is assumed that patients receive three infusions per 28-day treatment cycle, the acquisition cost of inotuzumab was calculated as £5,552.96 (£459.45 in outpatient and £5,093.51 in hospitalisation costs) in cycle 1 and £1,378.35 for subsequent treatment cycles.

Ponatinib: Ponatinib is an oral therapy, and the company stated that it incurs lower administration costs compared to infusion therapies. Drug acquisition costs are based on a 45-mg daily dose, amounting to £4,116 per 28-day cycle. Monitoring costs, including outpatient visits, blood tests, and imaging, total £321 per cycle.

The EAG had a concern with the approach employed by the company.

EAG Concern 4 (Key Issue 4): Underestimating Hospitalization Durations and Resource Use Post obe-cel Infusion

Company's Approach: The company utilized UK-specific data from the FELIX trial to estimate hospitalization durations. They reported a revised mean hospitalization duration of [redacted] days (excluding ICU), with a range of [redacted] days. For ICU stays, the mean was [redacted] days (range: [redacted] days), and [redacted] of patients were assumed to require ICU care. The company has used the cost of [redacted] as mean daily hospital cost for administration and CAR T pre-treatment.

EAG Critique and Assumptions: The most recent FELIX trial data (February 2024 cut-off provided in response to clarification questions) shows a mean total hospital stay (excluding ICU) of [redacted] days (range: [redacted] days). ICU stays demonstrated considerable variability, with a mean duration of [redacted] days (range: [redacted] days), and [redacted] of patients required ICU care. The EAG considers that the company's revised estimates may underestimate hospitalization durations compared with the broader FELIX trial data, which suggests substantially longer hospital stays. Furthermore, the company's approach for calculating the obe-cel infusion and monitoring costs involves the formula:

((1-I143)*I133*K105+I143*((I133-I138)*K105+I138*K118))

Here, K105 represents the mean daily hospital cost for administration that has been used by the company ([redacted]), I143 is the proportion of patients requiring ICU ([redacted]), I133 is the length of hospital stay per infusion, I138 is the length of ICU stay, and K118 is the weighted average daily ICU cost [redacted]).

Critically, the company's use of [redacted] as the mean daily hospital cost in this calculation underestimates costs, as the comparators use [redacted], leading to inconsistencies. Additionally, the coefficient (1−I143), used to account for patients requiring hospitalization, is not justified and is unsupported by the clarification data provided by the company (Table 26). The EAG's opinion is that a more reasonable approach is to use the summary tariff costs for CAR T infusion and monitoring and in line with the TA893, which better reflects the actual costs.

Table 26: Hospitalisation post obe-cel infusion of patients in Cohort IIA, February 2024 data cut-off (Obtained from company's response to EAG clarification questions)

Hospitalisations		Mean (SD), Cohort IIA	Min - max, Cohort IIA
Hospital stay except ICU	Length of hospital stay (day)	[redacted]	[redacted]
ICU stay	Length of ICU stay (day)	[redacted]	[redacted]
	Proportion of patients requiring ICU – n (%)	[redacted]	

ICU – intensive care unit; SD – standard deviation
Source: Autolus, Data on file[1]

EAG assumes that hospitalization durations should reflect the complete FELIX trial dataset in Cohort IIA. This includes a mean non-ICU hospital stay of [redacted] days (SD: [redacted]), a mean ICU stay of [redacted] days (SD: [redacted]), and [redacted] of patients requiring ICU care.

EAG Solution:

Base-Case Analysis: Using the tariff costs for CAR T infusion and monitoring, valued at £58,964,[66] in line with approach followed by the TA893.

Scenario Analysis: Scenario 1: Use the full FELIX trial dataset in Cohort IIA to estimate hospitalization durations: [redacted] days for non-ICU hospital stays, [redacted] days for ICU stays, and include ICU costs for [redacted] of patients. Scenario 2: Incorporate UK-specific FELIX trial data, using a mean of [redacted] days for non-ICU stays, [redacted] days for ICU stays, and [redacted] of patients requiring ICU care. For both scenarios, the related formula is amended as follows: (((1-I143)*I133*K106)+(I143*I138*K118)).

4.2.8.2 Pre-Treatment Costs (required for CAR T-cell manufacturing)

Leukapheresis: Pre-treatment costs such as leukapheresis, required for CAR T-cell manufacturing, were also included. The company has conducted detailed calculations using NHS reference costs (HRG codes SA34Z and SA18Z) and applied a cost multiplier of [redacted] to account for patients who underwent leukapheresis but did not proceed to infusion. This adjustment increased the leukapheresis cost from £1,651.95 to [redacted].

Bridging chemotherapy: Bridging chemotherapy costs were calculated based on investigator choice in the FELIX trial, incorporating a correcting factor of [redacted] to account for patients who received bridging therapy but not obe-cel, resulting in a total cost of [redacted].

Conditioning chemotherapy: Patients in the FELIX trial received conditioning chemotherapy, with the company stating that costs were adjusted using a factor of [redacted] to reflect those who did not proceed to infusion. Conditioning regimens included fludarabine (120 mg/m²) and cyclophosphamide (1,000 mg/m²). Costs were split between inpatient and outpatient settings, resulting in a total of [redacted].

4.2.8.3 Health State resource use and costs

The company stated that health state resource use and costs depend on the treatment arm. The model assumes higher resource use for obe-cel in the event-free health state compared to comparators. Frequencies and unit costs were aligned with TA893 and derived from NHS 2022/23 reference costs. The company stated that these inputs ensured accurate health state costs across treatment arms.

4.2.8.4 Adverse event resource use and costs

Adverse event costs were modelled as one-off costs based on AE rates from the FELIX trial and prior STAs (such as TA893). Unit costs for each AE were derived from NHS 2022/23 reference costs and adjusted for the frequency and severity of events observed. The EAG has one concern over the implementation of AE costs.

EAG Concern 5: Underreporting of adverse events and discrepancies with the company's clinical study report (CSR)

Company's Inputs: The incidence of each adverse event, based on the company's approach, is provided in Table 22.

EAG Critique and Assumptions: The company's reporting of adverse events (AEs) reveals inconsistencies and potential underreporting. EAG received feedback from clinical advisers regarding the events and rates presented by the company in its

submission. For instance, immune effector cell-associated neurotoxicity syndrome (ICANS), which is critical to CAR T-cell therapies, was not reported, raising concerns about the completeness of the data. One of EAG's clinical advisers noted some inconsistencies including the probability of infection being [redacted].%, but probability of sepsis was [redacted]%. Similarly, the probability for febrile neutropenia was [redacted]%, which is typically presumed to be an infection, was higher than the reported neutropenia probability of [redacted]%. These gaps and inconsistencies diverge from the Clinical Study Report (CSR), which should include all treatment-emergent AEs (Grade ≥3) for infused patients across all cohorts.

EAG Solution:

Base-Case Analysis: Include treatment-emergent adverse events (Grade ≥3) for all infused patients, as reported in the Clinical Study Report (CSR), within the model (see Table 27).

Table 27: Adverse event rates included in the model (Obtained from CSR report for all Infused Patients (n=127), section 14.3.1)

Adverse event (≥ Grade 3)	Total number of events	Proportion with event
Cytokine release syndrome (CRS) (Grade 2+, treated with tocilizumab)	[redacted]	[redacted]
Cytokine release syndrome (CRS) (Grade 3+)	[redacted]	[redacted]
Neurological event and ICANS	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Elevated liver enzyme	[redacted]	[redacted]
Decrease in platelet count	[redacted]	[redacted]
Decrease in white-cell count	[redacted]	[redacted]
VOD	[redacted]	[redacted]
Infusion reaction	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]

Diarrhoea	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]
CSR: Clinical Study Report; ICANS: Immune effector cell-associated neurotoxicity syndrome; VOD: Veno-occlusive disease		

Scenario Analysis: Using the company's original table of adverse events

4.2.8.5 Subsequent Treatment Costs

Allo-SCT: The company stated that, allo-SCT were modelled for comparator arms but not for obe-cel due to its curative nature. SCT costs included harvesting, the procedure itself, and follow-up care over 24 months, sourced from TA893 data.

Alternative Subsequent Treatments: The company stated that, patients ineligible for allo-SCT were assumed to receive subsequent treatments validated by clinical experts, such as inotuzumab + ponatinib or cyclophosphamide + dexamethasone, with administration costs adjusted accordingly.

The EAG has two concerns relating to the company's implementation of subsequent treatment costs.

EAG Concern 6 (Key Issue 5): Programming and implementation errors related to incorporating follow-up costs of allo-SCT in the economic model (in all treatments)

Company's Approach: The company calculated the cost of allo-SCT as a combination of stem cell harvesting, the procedure itself, and 24 months of follow-up. The costs for stem cell harvesting and the allo-SCT procedure were derived from NHS 2022/23 reference costs, while follow-up costs were calculated based on TA893 (see columns under "Undiscounted total costs from the model" in Table 28).

EAG Critique and assumption: NHS 2022/23 reference costs values[67] for different components of allo-SCT appear to represent total costs, consistent with the

methodology used in TA893.[38] According to TA893, "*The costs associated with allo-SCT included stem cell harvesting, the procedure itself, and long-term follow-up (up to 24 months). The total cost of allo-SCT was estimated at £117,751 and applied as a one-off cost in the first cycle of the model."*

While the company appropriately followed this approach for stem cell harvesting and the allo-SCT procedure, it overestimated follow-up costs due to a lack of an appropriate method for normalizing patient distribution across different follow-up periods for each cycle. EAG assumes that the total undiscounted costs for different components of allo-SCT should not exceed the proportion of patients receiving allo-SCT multiplied by the corresponding cost, as shown in the columns under "Maximum undiscounted total costs based on the proportion of patients receiving an allo-SCT" in Table 28.

Table 28: Administration cost of allo-SCT (Obtained from CS, document B, table 57 and economic model)

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

Allo-SCT – allogenic stem cell transplant; NHS – National Health Service; TA – Technology Appraisal.
*These proportions have used in this table: Blinatumomab: 0.1321; Inotuzumab: 0.482; Ponatinib: 0.4688

EAG Solution:

Base-case analysis: Normalize patient distribution across different follow-up periods for each cycle to ensure the Maximum Undiscounted Total Costs align with the proportion of patients receiving an allo-SCT.

EAG Concern 7 (Key Issue 6): Inconsistent inclusion of costs and effects of allo-SCT for obe-cel in the economic model

Company's Approach: The company included the benefits of allo-SCT in the overall survival (OS) for obe-cel without incorporating in the associated costs. The company argued that OS and EFS data inherently capture the effects of allo-SCT, aligning with the methodology outlined in TA893.

EAG Critique and assumption: As mentioned in section 4.2.4, obe-cel, as a CAR T-cell therapy, has the dual potential to function as a curative therapy or as a bridging therapy to allo-SCT. Based on insights from EAG clinical advisers, only a small proportion of patients (around 10%) are expected to receive obe-cel as a bridging therapy to subsequent allo-SCT. Including the survival benefits of allo-SCT without accounting for associated costs introduces a bias in obe-cel. As of the February 2024 data cut-off, 133 patients in cohort IA and IIA had received infusions, among whom [redacted] patients ([redacted]) underwent allo-SCT, as stated by the company in response to clarification questions and Clinical Study Report (CSR). Based on Roddie et al. (2024),[46] 66% of these SCT procedures were first allo-SCT, equating to approximately [redacted] of the 133 patients ([redacted] × 66% = [redacted]).

EAG assumes that a small portion of obe-cel patients, would proceed with allo-SCT, and these associated costs must be incorporated into the economic model.

EAG Solution:

Base-case analysis: Include allo-SCT costs for obe-cel patients ([redacted] of the ITT population).

Scenario analysis: 1- Including the allo-SCT costs for obe-cel patients without a previous allo-SCT ([redacted] of the ITT population). 2- Excluding the allo-SCT of obe-cel treatment pathway.

4.2.8.6 Terminal Care Costs

Costs associated with the last three months of life were derived from Georgiou and Bardsley (2014), adjusted to 2023 prices using the PSSRU inflation index. The total one-off cost was £8,586.57, reflecting a combination of inpatient, residential, and home-based care components.

The tables below outline resource utilization and associated costs by health state and treatment for different populations: the overall population (Table 29), the Ph- population (Table 30), and the Ph+ population (Table 31).

Table 29: Resource use and costs per health state and treatment, whole population (Obtained from the model)

Health state	Cost items	Obe-cel (whole population)		Inotuzumab (whole population)	
		Cost	%	Cost	%
Event-free	Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
	Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
	Pre-treatment	[redacted]	[redacted]	[redacted]	[redacted]
	Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
	HCRU-Event-free	[redacted]	[redacted]	[redacted]	[redacted]
	Total cost of Event-free	[redacted]	[redacted]	[redacted]	[redacted]
Post-event	Sub. Tx. drug costs	[redacted]	[redacted]	[redacted]	[redacted]
	Sub. Tx admin costs	[redacted]	[redacted]	[redacted]	[redacted]
	HSCT	[redacted]	[redacted]	[redacted]	[redacted]
	HCRU-Post-event	[redacted]	[redacted]	[redacted]	[redacted]
	End of life	[redacted]	[redacted]	[redacted]	[redacted]
	Total cost of Post-event	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]

Table 30: Resource use and costs per health state and treatment, Ph- population (Obtained from the model)

Health state	Cost items	Obe-cel		Inotuzumab		Blinatumomab	
		Cost	%	Cost	%	Cost	%
Event-free	Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pre-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HCRU-Event-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total cost of Event-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-event	Sub. Tx. drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Sub. Tx admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HSCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	HCRU-Post-event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End of life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total cost of Post-event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 31: Resource use and costs per health state and treatment, Ph+ population (Obtained from the model)

Health state	**Cost items**	**Obe-cel**		**Inotuzumab**		**Ponatinib**	
		Cost	**%**	**Cost**	**%**	**Cost**	**%**
Event-free	**Drug acquisition**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pre-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HCRU-Event-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total cost of Event-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-event	**Sub. Tx. drug costs**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Sub. Tx admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HSCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HCRU-Post-event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End of life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total cost of Post-event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.2.9 Severity modifier

The company stated that this appraisal meets the criteria for a 1.7 severity modifier, reflecting the severity of adult relapsed or refractory (R/R) B-ALL.

Life expectancy for the general population was derived from ONS UK life tables (2017–2019)[68] and adjusted using EQ-5D UK population norm values from Hernández Alava *et al*. (2022).[69] A discount rate of 3.5% was applied, ensuring consistency with established economic evaluation standards. The analysis incorporated a base-case starting age and sex distribution informed by the FELIX trial.

The QALY shortfall analysis demonstrates that people receiving blinatumomab have a shortfall of [redacted] compared to the general population, qualifying for a 1.7 severity modifier. While comparisons with inotuzumab and ponatinib yield a 1.2 modifier, the company considers the 1.7 severity modifier appropriate for decision-making, supported by precedents set in previous NICE appraisals and should apply for all comparisons (Table 32). The EAG has a concern with this conclusion.

Table 32: Summary of QALY shortfall analysis (Obtained from CS, Document B, Section B.3.6, Table 63)

Treatment	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute shortfall	Proportional shortfall	Severity modifier versus comparator
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	1.7
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	1.2
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	1.2

QALY – quality-adjusted life year

EAG Concern 8 (Key Issue 7): Appropriate Severity Modifier

The company asserts that obe-cel meets the criteria for a 1.7 severity modifier, supported by a proportional shortfall of [redacted] when compared to blinatumomab. However, this approach does not fully account for variability in treatment outcomes across different comparator populations.

The company considers three distinct populations: the overall cohort, Philadelphia chromosome-negative (Ph-) patients, and Philadelphia chromosome-positive (Ph+) patients. Only for Ph- patients, blinatumomab serves as the comparator, leading to a 1.7 severity modifier based on a proportional shortfall of [redacted] In contrast, when

compared to inotuzumab and ponatinib, the proportional shortfalls are lower ([redacted] respectively), which corresponds to a 1.2 severity modifier. These inconsistencies suggest that the use of a 1.7 severity modifier may overestimate the severity adjustment for the entire population.

The EAG assumes that inotuzumab is utilized by at least 5% of patients with relapsed or refractory B-cell acute lymphoblastic leukaemia, while the remaining patients are treated with blinatumomab and ponatinib based on the proportion of Philadelphia chromosome-positive (22%) and Philadelphia chromosome-negative (78%) disease in England and Wales, as referenced in TA450.[70] According to this assumption and based on utility values from the company's base-case analysis, the weighted analysis includes age, QALYs, and sex distribution, resulting in an overall proportional shortfall of [redacted], supporting a 1.2 severity modifier for all population (Table 33). Furthermore, under the EAG base case, blinatumomab has a 92.6% QALY shortfall, supporting the 1.2 multiplier.

Table 33: Summary of QALY shortfall analysis based on EAG's assumption

Treatment	**Blinatumomab**	**Inotuzumab**	**Ponatinib**
Age (year)	46	48	56
Total QALYs that people living with a condition would be expected to have with current treatment	0.65	4.36	1.80
Sex distribution (female %)	44%	50%	68%
Treatments use by patients (%)	74%	5%	21%
weighted age	48		
weighted utility	1.08		
weighted sex distribution (female %)	49%		
Expected total QALYs for the general population	16.50		
Absolute shortfall	15.42		
Proportional shortfall	93%		
Severity modifier	1.2		

The EAG performed a scenario analysis where a 1.7 severity modifier is applied for all population.

5 COST EFFECTIVENESS RESULTS

5.1 *Company's cost effectiveness results*

The deterministic analysis evaluates the cost-effectiveness of technologies for the overall, Ph-, and Ph+ populations using Obe-cel PAS pricing. Table 34, Table 35 and Table 36 summarize the company's cost-effectiveness results for obe-cel versus inotuzumab, blinatumomab, and ponatinib using PAS prices. In the overall population, obe-cel [redacted] and 2.88 additional QALYs. Within the Ph- population, obe-cel is associated with [redacted] and 2.15 additional QALYs compared to inotuzumab. Against blinatumomab in the same population, obe-cel provides 5.08 incremental QALYs at an additional cost of [redacted] per QALY. In the Ph+ population, obe-cel dominates inotuzumab with [redacted] and 2.54 additional QALYs. When compared directly to ponatinib in this population, obe-cel generates 11.04 additional QALYs at an incremental cost of [redacted] per QALY.

Table 34: Deterministic results, overall population – PAS price (results from CS, document B)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.88	[redacted]

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

Table 35: Deterministic results, Ph- population – PAS price (results from CS, document B)

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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.08	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.15	[redacted]	[redacted]

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

Table 36: Deterministic results, Ph+ population – PAS price (results from CS, document B)

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]
Obe-cel						11.04		
Inotuzumab						-2.54		

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

The company revised its base case based on responses to clarification questions (A29 and B16), incorporating FELIX hospitalisation rates, EFS MAIC HRs, and survival analyses using IRRC assessments.

[redacted]

Table 37: Deterministic results, overall population – PAS price (results from responses to EAG clarification questions)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.85	[redacted]
ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; QALYs – quality-adjusted life years							

Table 38: Deterministic results, Ph- population – PAS price (results from responses to EAG clarification questions)

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]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.07	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.14	[redacted]	[redacted]
ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; Ph – Philadelphia chromosome; QALYs – quality-adjusted life years								

Table 39: Deterministic results, Ph+ population – PAS price (results from responses to EAG clarification questions)

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]
Obe-cel	[redacted]	[redacted]			[redacted]	11.00	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]			[redacted]	-2.51	[redacted]	[redacted]
ICER – incremental cost-effectiveness ratio; LYG – life years gained; PAS – patient access scheme; Ph – Philadelphia chromosome; QALYs – quality-adjusted life year								

5.2 *Company's sensitivity analyses*

5.2.1 Company's deterministic sensitivity analysis

One way sensitivity analysis (OWSA) assesses model sensitivity by varying one parameter at a time, typically within the 95% confidence interval (CI) or ±20% if CI data are unavailable. The company stated that this method evaluates the robustness of model results to changes in individual input parameters.

For the overall population, the top ten parameters with the greatest impact on cost-effectiveness are detailed in Figure 6. The most sensitive parameters are the proportion of inotuzumab patients receiving HSCT, the HSCT per cycle cost for inotuzumab, and the HSCT initial treatment cost.

In the Ph- population, key results are shown in Figure 7 and Figure 8. Against blinatumomab, the most sensitive parameters include OS and EFS parametric coefficients and the SMR. Against inotuzumab, they are the OS parametric coefficients, HSCT proportion, and HSCT per cycle cost.

For the Ph+ population, results are presented in Figure 9 and Figure 10. Compared to inotuzumab, the most sensitive parameters are OS parametric coefficients, HSCT proportion, and EFS flexible coefficients. Versus ponatinib, these are OS parametric coefficients, HSCT proportion, and EFS flexible coefficients.

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

Figure 6: OWSA results for obe-cel vs inotuzumab (overall population) - NMB

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

Figure 7: OWSA results for obe-cel vs blinatumomab (Ph- population) ICER

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

Figure 8: OWSA results for obe-cel vs inotuzumab (Ph- population) – NMB

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

Figure 9: OWSA results for obe-cel versus inotuzumab (Ph+ population) - ICER

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

Figure 10: OWSA results for obe-cel versus ponatinib (Ph+ population) – ICER

5.2.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to explore joint parameter uncertainty by assigning appropriate distributions to parameters and varying them simultaneously. Parameters deemed unsuitable for variation, such as structural assumptions (e.g., time horizon) and certain inputs (e.g., drug acquisition costs), were excluded. Using the PAS discount and 1.7 severity modifier, 1,000 Monte Carlo simulations were performed for the overall, Ph-, and Ph+ populations, demonstrating ICER convergence over time.

In the overall population, PSA results for obe-cel versus inotuzumab align closely with the base case, showing a 2.4% difference in incremental QALYs and a [redacted] difference in costs, [redacted]. [redacted], with a 0.8% QALY and [redacted] cost difference versus

inotuzumab. Against blinatumomab, the ICER was [redacted]. For the Ph+ population, obe-cel [redacted] versus inotuzumab, and against ponatinib, the ICER was [redacted]

Table 40: Probabilistic results considering PAS discount (overall population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.81	[redacted]

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

Table 41: Probabilistic results considering PAS discount (Ph- population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER versus Obe-cel (£/QALY)
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.21	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.17	[redacted]	[redacted]

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

Table 42: Probabilistic results considering PAS discount (Ph+ population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER versus Obe-cel (£/QALY)
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.70	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2.43	[redacted]	[redacted]

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

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

Figure 11: Scatterplot (overall population)

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

Figure 12: CEAC (overall population)

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

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

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

Figure 14: Scatterplot, obe-cel versus blinatumomab (Ph- population)

CEAC – Cost-effectiveness acceptability curve

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

CEAC – Cost-effectiveness acceptability curve

Figure 16: CEAC, obe-cel versus inotuzumab (Ph- population)

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

Figure 17: Scatterplot, obe-cel versus inotuzumab (Ph+ population)

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

Figure 18: Scatterplot, obe-cel versus ponatinib (Ph+ population)

CEAC – Cost-effectiveness acceptability curve

Figure 19: CEAC, obe-cel versus inotuzumab (Ph+ population)

CEAC – Cost-effectiveness acceptability curve

Figure 20: CEAC, obe-cel versus ponatinib (Ph+ population)

5.2.3 Scenario analysis

Scenario analyses for the overall, Ph-, and Ph+ populations are detailed in Table 44, Table 45, and Table 46. In the overall population, [redacted]

For the Ph- population, results were stable for inotuzumab, with obe-cel [redacted]. In the few scenarios where obe-cel [redacted]. Against blinatumomab, obe-cel was [redacted]. These included the use of utility values from the SMC appraisal of blinatumomab (ICER: [redacted]) and the inclusion of subsequent SCT after CAR T-cell therapy (ICER: [redacted]). In the naïve approach for comparative effectiveness (Scenario 6), obe-cel [redacted]. This counterintuitive outcome is partly attributed to differing hazard functions for OS curves, leading to an artificial plateau for blinatumomab.

In the Ph+ population, obe-cel [redacted] inotuzumab across all scenarios and was either [redacted] in all comparisons with ponatinib.

Table 43: 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[102]
2			6% for costs and outcomes	
3	Costs	Use a bottom-up costing approach for CAR T-cell infusion cost calculations	Using tariff costing for CAR T-cell infusion cost calculations	Approach used in TA893[17]
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 + non-inverse MAIC	Exploring combinations of alternative modelling approaches
6			Base case ITC approach + alternative obe-cel survival curves*	
7			Base case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab; inverse MAIC vs. ponatinib)	
8	Subsequent treatment costs	No CAR T-cell therapy as subsequent treatment	Include CAR T-cell therapy as subsequent treatment	CAR T-cell therapies as a subsequent treatment have been observed in clinical practise with the current treatment available.
9	Subsequent SCT	No subsequent SCT after CAR T-cell therapy	Include subsequent SCT after CAR T-cell therapy	This shows that even if patients go onto receive SCT, the observed effects of obe-cel are the same
10	Utilities	FELIX clinical trial	Health state utility source TA450	Exploratory analysis
11			Blinatumomab SMC utility values	Exploratory analysis

12		Utility decrement of EFS health state	CRS disutility based on Howell *et al.*	Exploratory analysis
13	Mortality	SMR of 3	Alternative SMR 1.09	Exploratory analysis

CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; ITC – Indirect treatment comparison; MAIC – Match-adjusted indirect treatment comparison; NICE – National Institute for Health and Care Excellence; QALY – Quality-adjusted life year; SCT – Stem cell transplant; SMC – Scottish Medicines Consortium; SMR – Standard mortality ratio; TA – Technology Appraisal.
*Alternative survival curves used are: Overall population – EFS: 0-knots odds spline curve; OS: 3-knots normal spline curve; Ph- population – EFS: generalised gamma curve; OS: Weibull curve; Ph+ population – EFS: Weibull; OS: Exponential

Table 44: Scenario analysis results, overall population

#	Scenario	Deterministic ICER	Probabilistic ICER
0	Base case	[redacted]	[redacted]
1	0% for costs and outcomes	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]
3	Using tariff costing for CAR T-cell infusion cost calculations	[redacted]	[redacted]
4	Include drug wastage (for comparator therapies)	[redacted]	[redacted]
5	Base case survival curves + non-inverse MAIC	[redacted]	[redacted]
6	Base case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]
7	Base case survival curves + alternative ITC approach (naïve approach vs. inotuzumab)	[redacted]	[redacted]
8	Include CAR T-cell therapy as subsequent treatment	[redacted]	[redacted]
9	Include subsequent SCT after CAR T-cell therapy	[redacted]	[redacted]
10	Health state utility source TA450	[redacted]	[redacted]
11	Blinatumomab SMC utility values	[redacted]	[redacted]

12	CRS disutility based on Howell *et al.*	[redacted]	[redacted]
13	Alternative SMR 1.09	[redacted]	[redacted]
CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; ICER – Incremental cost-effectiveness ratio; ITC – Indirect treatment comparison; MAIC – Match-adjusted indirect treatment comparison; SCT – Stem cell transplant; SMC – Scottish Medicines Consortium; SMR – Standard mortality ratio; TA – Technology Appraisal.			

Table 45: Scenario analysis results, Ph- population

#	Scenario	Versus inotuzumab		Versus blinatumomab	
		Deterministic ICER	Probabilistic ICER	Deterministic ICER	Probabilistic ICER
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]
1	0% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
3	Using tariff costing 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 + non-inverse MAIC	[redacted]	[redacted]	[redacted]	[redacted]
6	Base case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]	[redacted]	[redacted]
7	Base case survival curves + alternative ITC approach (naïve approach vs. inotuzumab and blinatumomab)	[redacted]	[redacted]	[redacted]	[redacted]
8	Include CAR T-cell therapy as subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]
9	Include subsequent SCT after CAR T-cell therapy	[redacted]	[redacted]	[redacted]	[redacted]

10	Health state utility source TA450	[redacted]	[redacted]	[redacted]	[redacted]
11	Blinatumomab SMC utility values	[redacted]	[redacted]	[redacted]	[redacted]
12	CRS disutility based on Howell *et al.*	[redacted]	[redacted]	[redacted]	[redacted]
13	Alternative SMR 1.09	[redacted]	[redacted]	[redacted]	[redacted]
CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; ICER – Incremental cost-effectiveness ratio; ITC – Indirect treatment comparison; MAIC – Match-adjusted indirect treatment comparison; SCT – Stem cell transplant; SMC – Scottish Medicines Consortium; SMR – Standard mortality ratio; TA – Technology Appraisal.					

Table 46: Scenario analysis results, Ph+ population

#	Scenario	Versus inotuzumab		Versus ponatinib	
		Deterministic ICER	Probabilistic ICER	Deterministic ICER	Probabilistic ICER
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]
1	0% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
2	6% for costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
3	Using tariff costing 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 + non-inverse MAIC	[redacted]	[redacted]	[redacted]	[redacted]
6	Base case ITC approach + alternative obe-cel survival curves	[redacted]	[redacted]	[redacted]	[redacted]

7	Base case survival curves + alternative ITC approach (naïve approach vs. inotuzumab; inverse MAIC vs. ponatinib)	[redacted]	[redacted]	[redacted]	[redacted]
8	Include CAR T-cell therapy as subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]
9	Include subsequent SCT after CAR T-cell therapy	[redacted]	[redacted]	[redacted]	[redacted]
10	Health state utility source TA450	[redacted]	[redacted]	[redacted]	[redacted]
11	Blinatumomab SMC utility values	[redacted]	[redacted]	[redacted]	[redacted]
12	CRS disutility based on Howell *et al.*	[redacted]	[redacted]	[redacted]	[redacted]
13	Alternative SMR 1.09	[redacted]	[redacted]	[redacted]	[redacted]
CAR – Chimeric antigen receptor; CRS – Cytokine release syndrome; EFS – Event-free survival; ICER – Incremental cost-effectiveness ratio; ITC – Indirect treatment comparison; MAIC – Match-adjusted indirect treatment comparison; SCT – Stem cell transplant; SMC – Scottish Medicines Consortium; SMR – Standard mortality ratio; TA – Technology Appraisal.					

5.3 *Model validation and face validity check*

The validation process of the cost-effectiveness model for obe-cel was conducted by the company to ensure its accuracy and clinical relevance.

Internal validation was stated to have been carried out by both the primary modellers and an external modeller. This included a cell-by-cell check of formulae, adaptations of key sections, logical testing, and a comprehensive audit of model inputs. Any issues identified were systematically addressed to maintain the model's integrity.

Expert validation was stated to have been performed by two UK clinicians who reviewed the clinical and technical assumptions through a series of interviews. The company covered topics such as obe-cel's role in the clinical pathway, treatment effect modifiers, ITC methods, survival curves, and subsequent treatment regimens like allo-SCT. These steps ensured that the assumptions were clinically valid and aligned with current best practices.

Additionally, the company stated that the model was aligned with previous NICE appraisals, particularly the brexu-cel submission (TA893), to enhance its consistency and relevance.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 *EAG's changes made to the company's base-case model*

Table 47 and Table 48 presents the company data used in the company's base case for certain parameters, along with new values derived from the EAG concerns outlined in Section 4.2. For further details and justifications, please refer to the associated sections listed in the last column of

Table 47 and Table 48. The tables include the EAG's preferred assumptions, which will be used in the forthcoming sections.

Table 47: EAG's changes made to the company's base-case model- across all population models

Variable	Company's Value/approach	EAG's value/approach	Reference to related section(s)
Programming adjustments and error resolution for follow-up costs of allo-SCT in the economic model			
Follow-up costs of allo-SCT	There is no suitable method to normalize patient distributions across different follow-up periods within each cycle	Normalize patient distribution across follow-up periods in each cycle to ensure maximum undiscounted costs align with the proportion of patients receiving allo-SCT	Section 4.2.8 and appendices 8.3
Correcting cost and effect inconsistencies for allo-SCT in obe-cel economic modelling			
Proportion of patients eligible to receive allo-SCT in obe-cel	[redacted]%	[redacted]%	Section 4.2.8 and appendices 8.3
Revised hospitalization duration and resource use estimates post obe-cel infusion			
Approach to CAR T-cell infusion cost calculations	Bottom-up costing (using UK-specific FELIX trial data: [redacted] days non-ICU, [redacted] days ICU stays, [redacted]% of patients requiring ICU care.)	Using the tariff costs for CAR T infusion and monitoring, valued at £58,964 (which includes related costs such as adverse event costs and leukapheresis)	Section 4.2.8 and appendices 8.3
Addressing underreporting of adverse events and discrepancies with the company's clinical study report (CSR)			
Source of adverse events incidence	Grade ≥3 AEs which occurred in the mITT population observed during the FELIX study	Include treatment-emergent adverse events (Grade ≥3) for all infused patients, as reported in the Clinical Study Report (CSR)	Section 4.2.8 and appendices 8.3
Addressing inconsistencies in severity modifier applications across populations			

<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>QALY weight</td><td>1.7</td><td>1.2</td><td>Section 4.2.9 and appendices 8.3</td></tr>
<tr><td colspan="4">Incorporating allo-SCT utility effects into the economic model</td></tr>
<tr><td>allo-SCT utility</td><td>No allo-SCT utility effects</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>
<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>Section 4.2.7 and appendices 8.3</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>Per-cycle discount factor</td><td>Per-year discount factor</td><td>Section 4.2.5 and appendices 8.3</td></tr>
</table>

Table 48: EAG's adjustments to OS and EFS in the company's base-case model - Whole population

Parameters	Company's approach	EAG approach*	Reference to related section(s)
EFS			
Obe-cel	**Data source:** mITT-Cohort IIA, N:94, censored for subsequent therapy **Curve selection:** 3-knot normal flexible parametric spline curve (changed after CQs)	**Data source:** FELIX, ITT, Cohorts IA and IIA (n=133), not censored for subsequent therapy **Curve selection: Log-normal**	Sections 4.2.6, 4.2.3 and appendices 8.3
Inotuzumab	**Data source:** INO-VATE, N;164 **Curve selection:** (Value based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Inotuzumab[0.[redacted]]) While in the CS, page 118 we have: Flexible Parametric Survival (3-knot odds spline)	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Inotuzumab[[redacted]])	Sections 4.2.6 and appendices 8.3
OS			
Obe-cel	**Data source:** mITT-CohortIIA,N:94, not censored for subsequent therapy **Curve selection:** Flexible Parametric Survival (3-knot odds spline)	**Data source:** FELIX, ITT, Cohorts IA and IIA (n=133), not censored for subsequent therapy **Curve selection:** Log-normal	Sections 4.2.6, 4.2.3 and appendices 8.3
Inotuzumab	**Data source:** INO-VATE, N;164 **Curve selection:** (Value based on obe-cel curve) ^(1/OS HR of obe-cel vs Inotuzumab[[redacted]]) While in the CS, page 118 we have: Flexible Survival Analysis (2-knot hazards spline)	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^(1/OS HR of obe-cel vs Inotuzumab[[redacted]])	Sections 4.2.6 and appendices 8.3

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 49: EAG's adjustments to OS and EFS in the company's base-case model - Ph- population

Parameters	Company's approach	EAG approach*	Reference to related section(s)
EFS			
Obe-cel	**Data source:** mITT-Cohort IIA, N:[redacted] **Curve selection:** Standard Parametric Survival Model (Weibull)	**Data source:** FELIX, ITT, Cohorts IA and IIA- Ph-population (n=[redacted]) **Curve selection:** Gompertz	Sections 4.2.6, 4.2.3 and appendices 8.3
Blinatumomab	**Data source:** TOWER, N:271 **Curve selection:** (Value based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Blinatumomab [[redacted]]) While in CS, page 118 we have: 0-knot hazards spline	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^ (1/EFS HR of obe-cel vs Blinatumomab [[redacted]])	Sections 4.2.6 and appendices 8.3
Inotuzumab	**Data source:** INO-VATE, N;164 **Curve selection:** (Value based on obe-cel curve) ^(1/HR of obe-cel vs Inotuzumab[[redacted]]) While in CS, page 118 we have: ***Same as overall subgroup***	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^(1/HR of obe-cel vs Inotuzumab[[redacted]])	Sections 4.2.6 and appendices 8.3
OS			
Obe-cel	**Data source:** mITT-Cohort IIA, N:[redacted] **Curve selection:** Standard Parametric Survival Model (Exponential)	**Data source:** FELIX, ITT, Cohorts IA and IIA- Ph-population (n=[redacted]) **Curve selection: 2-**knot odds	Sections 4.2.6, 4.2.3 and appendices 8.3
Blinatumomab	**Data source:** TOWER, N:271 **Curve selection:** (Value based on obe-cel curve) ^(1/HR of obe-cel vs Blinatumomab [0.49]) This is not Log-normal as company stated in CS page 118	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^(1/HR of obe-cel vs Blinatumomab [[redacted]])	Sections 4.2.6 and appendices 8.3

Parameters	Company's approach	EAG approach*	Reference to related section(s)
Inotuzumab	**Data source:** INO-VATE, N;164 **Curve selection:** (Value based on obe-cel curve) ^(1/HR of obe-cel vs Inotuzumab[redacted]) It is not the Same as overall subgroup (CS PAGE 118)	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^(1/HR of obe-cel vs Inotuzumab[redacted])	Sections 4.2.6 and appendices 8.3
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 50: EAG's adjustments to OS and EFS in the company's base-case model- Ph+ population

Parameters	Company's approach	EAG approach*	Reference to related section(s)
EFS			
Obe-cel	**Data source:** mITT-Cohort IIA, N:[redacted] **Curve selection:** Flexible Parametric Survival (Hazard-1) While in the CS, page 118 we have: 1-knot hazards spline	**Data source:** FELIX, ITT, Cohorts IA and IIA- Ph+ population (n=[redacted]) **Curve selection:** Exponential	Sections 4.2.6, 4.2.3 and appendices 8.3
Inotuzumab	**Data source:** INO-VATE, N;164 **Curve selection:** Flexible Parametric Survival for obe-cel EFS (Hazard-1) ^ (1/EFS HR of obe-cel vs Inotuzumab[redacted]) While in the CS, page 118 we have: *Same as overall subgroup*	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^(1/HR of obe-cel vs Inotuzumab[redacted])	Sections 4.2.6 and appendices 8.3
Ponatinib	**Data source:** PACE, N:32 **Curve selection:** Flexible Parametric	**Data source:** PACE, N:32 **Curve selection:** Log-logistic	Sections 4.2.6 and appendices 8.3

Parameters	Company's approach	EAG approach*	Reference to related section(s)
	Survival (1-knot odds spline)		
OS			
Obe-cel	**Data source:** mITT-CohortIIA,N:25 **Curve selection:** Standard Parametric Survival Model (Log-normal)	**Data source:** FELIX, ITT, Cohorts IA and IIA- Ph+ population (n=[redacted]) **Curve selection:** Exponential	Sections 4.2.6, 4.2.3 and appendices 8.3
Inotuzumab	**Data source:** INO-VATE, N;164 **Curve selection:** Standard Parametric Survival Model for obe-cel (Log-normal)^ (1/OS HR of obe-cel vs Inotuzumab[redacted]) It is not the Same as overall subgroup (CS PAGE 118)	**Data source:** Based on obe-cel selected curve **Curve selection:** (Value based on obe-cel curve) ^(1/HR of obe-cel vs Inotuzumab[redacted])	Sections 4.2.6 and appendices 8.3
Ponatinib	**Data source:** PACE, N:32 **Curve selection:** Standard Parametric Survival Model (Log-normal)	**Data source:** PACE, N:32 **Curve selection:** Log-normal	Sections 4.2.6 and appendices 8.3
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.			

6.2 *Impact of EAG changes on the company's base-case results*

Table 51, Table 52, and Table 53 illustrate the results of EAG's exploratory analysis for the comparison between obe-cel and comparator in different population. The two primary determinants of the ICER across all analysed populations (overall, Ph-, and Ph+) in the comparison of obe-cel with blinatumomab, inotuzumab, and ponatinib are:

1. **Programming and Implementation Errors Related to Follow-Up Costs of Allo-SCT**

   Adjustments for incorporating follow-up costs of allo-SCT into the economic model markedly influenced the ICER results across all populations. In the overall population, this correction led to incremental costs of [redacted], yielding an ICER of [redacted] per QALY compared to inotuzumab. Similarly, in the Ph- population, this adjustment resulted in an ICER of [redacted] per QALY (vs. inotuzumab) and [redacted] per QALY (vs. blinatumomab). For the Ph+ population, the impact was also pronounced, with ICERs of [redacted] (vs. inotuzumab) and [redacted] (vs. ponatinib). These findings underscore the critical importance of accurately integrating follow-up costs associated with allo-SCT, as this element substantially influences the economic evaluation's validity and robustness.

2. **Inconsistent Inclusion of Allo-SCT Costs and Effects for Obe-cel**

   The inclusion (or omission) of allo-SCT-related costs and clinical effects introduced substantial variations in the ICER outcomes. For the overall population, ensuring consistent treatment of these inputs resulted in an incremental cost of [redacted] and a corresponding ICER of [redacted] per QALY. In the Ph- population, this adjustment generated ICERs of [redacted] (vs. inotuzumab) and [redacted] (vs. blinatumomab), reflecting the significance of addressing such inconsistencies. For the Ph+ population, consistent handling of allo-SCT inputs resulted in ICERs of [redacted] (vs. ponatinib) and [redacted] vs inotuzumab.

Table 51: Results of EAG's exploratory analysis for the comparison between obe-cel and comparator, overall population

EAG's preferred assumption based on issues		Obe-cel vs inotuzumab		
		Inc. Costs (£)	**Inc. QALYs**	**ICER (£/QALY)**
Company's base case		[redacted]	2.85	[redacted]
1	Programming and implementation errors related to incorporating follow-up costs of allo-SCT in the economic model	[redacted]	2.85	[redacted]
2	Inappropriate ITC approach and narrowed population	[redacted]	2.27	[redacted]
3	Inconsistent Inclusion of Costs and effects of allo-SCT for obe-cel in the Economic Model	[redacted]	2.85	[redacted]
4	Underestimating Hospitalization Durations and Resource Use Post obe-cel Infusion	[redacted]	2.85	[redacted]
5	Underreporting of adverse events and discrepancies with the company's clinical study report (CSR)	[redacted]	2.68	[redacted]
6	Inconsistencies in severity modifier application across comparator populations	[redacted]	2.01	[redacted]
7	Excluding allo-SCT utility effects from the economic model	[redacted]	2.83	[redacted]
8	Use of per-cycle discount rate instead of per-year discount rate	[redacted]	2.91	[redacted]
ITC – Indirect treatment comparison; QALY – Quality-adjusted life year; SCT – Stem cell transplant; EAG-External assessment group;				

Table 52: Results of EAG's exploratory analysis for the comparison between obe-cel and comparators, Ph- population

EAG's preferred assumption based on issues		Obe-cel vs inotuzumab			Obe-cel vs blinatumomab		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Company's base case		[redacted]	2.14	[redacted]	[redacted]	5.07	[redacted]
1	Programming and implementation errors related to incorporating follow-up costs of allo-SCT in the economic model	[redacted]	2.14	[redacted]	[redacted]	5.07	[redacted]
2	Inappropriate ITC approach and narrowed population	[redacted]	1.65	[redacted]	[redacted]	3.61	[redacted]
3	Inconsistent Inclusion of Costs and effects of allo-SCT for obe-cel in the Economic Model	[redacted]	2.14	[redacted]	[redacted]	5.07	[redacted]
4	Underestimating Hospitalization Durations and Resource Use Post obe-cel Infusion	[redacted]	2.14	[redacted]	[redacted]	5.07	[redacted]
5	Underreporting of adverse events and discrepancies with the company's clinical study report (CSR)	[redacted]	1.96	[redacted]	[redacted]	4.90	[redacted]
6	Inconsistencies in severity modifier application across comparator populations	[redacted]	1.51	[redacted]	[redacted]	3.58	[redacted]
7	Excluding allo-SCT utility effects from the economic model	[redacted]	2.14	[redacted]	[redacted]	5.07	[redacted]
8	Use of per-cycle discount rate instead of per-year discount rate	[redacted]	2.18	[redacted]	[redacted]	5.16	[redacted]

ITC – Indirect treatment comparison; QALY – Quality-adjusted life year; SCT – Stem cell transplant; EAG-External assessment group;

Table 53: Results of EAG's exploratory analysis for the comparison between obe-cel and comparators, Ph+ population

EAG's preferred assumption based on issues		Obe-cel vs inotuzumab			Obe-cel vs ponatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Company's base case		[redacted]	2.51	[redacted]	[redacted]	11.00	[redacted]
1	Programming and implementation errors related to incorporating follow-up costs of allo-SCT in the economic model	[redacted]	2.51	[redacted]	[redacted]	11.00	[redacted]
2	Inappropriate ITC approach and narrowed population	[redacted]	2.10	[redacted]	[redacted]	10.50	[redacted]
3	Inconsistent Inclusion of Costs and effects of allo-SCT for obe-cel in the Economic Model	[redacted]	2.51	[redacted]	[redacted]	11.00	[redacted]
4	Underestimating Hospitalization Durations and Resource Use Post obe-cel Infusion	[redacted]	2.51	[redacted]	[redacted]	11.00	[redacted]
5	Underreporting of adverse events and discrepancies with the company's clinical study report (CSR)	[redacted]	2.34	[redacted]	[redacted]	10.83	[redacted]
6	Inconsistencies in severity modifier application across comparator populations	[redacted]	1.77	[redacted]	[redacted]	7.77	[redacted]
7	Excluding allo-SCT utility effects from the economic model	[redacted]	2.43	[redacted]	[redacted]	11.01	[redacted]
8	Use of per-cycle discount rate instead of per-year discount rate	[redacted]	2.56	[redacted]	[redacted]	11.20	[redacted]
ITC – Indirect treatment comparison; QALY – Quality-adjusted life year; SCT – Stem cell transplant; EAG-External assessment group;							

6.3 *Results of EAG base-case analysis*

6.3.1 EAG cost-effectiveness results

The EAG's base-case analysis compares obe-cel versus all comparators, using the PAS agreement in place for obe-cel and list or eMIT/PAS prices for the comparators (see Appendix 8.4 for list of analyses applying confidential prices when in place for comparator treatments and their source of prices) (results presented in a separate confidential appendix document). The EAG's preferred base-case includes all changes listed in

Table 47, Table 48, Table 49, and Table 50. In appendix 8.3 we provide details of the changes made in the spreadsheets used to amend the company's economic model, which formed the basis of the EAG model.

6.3.1.1 Deterministic base-case results

In Table 54, the EAG deterministic results for the overall population using PAS prices demonstrate that treatment with obe-cel is [redacted] but also [redacted] compared to inotuzumab, which has a total cost of [redacted] and provides [redacted] QALYs. This results in an ICER of [redacted] per QALY for obe-cel compared to inotuzumab.

Table 55 presents fully incremental and pairwise analysis results for the Ph- population. Based on fully incremental analysis, blinatumomab is the [redacted] costly option ([redacted]). Inotuzumab, though [redacted] than blinatumomab, is [redacted]. The comparison between inotuzumab and obe-cel results in an ICER of [redacted] per QALY for obe-cel. Pairwise analysis confirms these findings, with the same ICER for obe-cel versus inotuzumab and [redacted] for obe-cel versus blinatumomab.

Table 56 presents results for the Ph+ population. Ponatinib is [redacted] option [redacted] QALYs ([redacted]). Inotuzumab, while [redacted] [redacted] QALYs), incurs additional costs, resulting in an ICER of [redacted] per QALY compared to ponatinib. Obe-cel [redacted]

[redacted]

Table 54: EAG Deterministic results, overall population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.51	[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 55: EAG Deterministic results, Ph- population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER incremental	ICER (obe-cel versus comparator)
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.42	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.09	[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 56: EAG Deterministic results, Ph+ population – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs*	ICER incremental	ICER (obe-cel versus comparator)
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.09	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.33	[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.

6.3.1.2 Probabilistic sensitivity analysis (PSA) results

Table 57 presents the EAG probabilistic results for the overall population considering PAS discounts. [redacted] incremental QALY of 1.505 [redacted]

Table 58 presents probabilistic results for the Ph- population. Based on the fully incremental analysis, [redacted]

Table 59 presents results for the Ph+ population. [redacted]

Table 57: EAG Probabilistic results considering PAS discount (overall population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.505	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life year gained; PAS – Patient Access Scheme; Ph – Philadelphia; QALY – quality-adjusted life year.
The severity modifier of 1.2 is applied to incremental QALYs.

Table 58: EAG probabilistic results considering PAS discount (Ph- population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental	ICER (obe-cel versus comparator)
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.426	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.097	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life year gained; PAS – Patient Access Scheme; Ph – Philadelphia; QALY – quality-adjusted life year.
The severity modifier of 1.2 is applied to incremental QALYs.

Table 59: EAG probabilistic results considering PAS discount (Ph+ population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental	ICER (obe-cel versus comparator)
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.349	[redacted]	[redacted]
Obe-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.289	[redacted]	[redacted]

ICER – incremental cost-effectiveness ratio; LYG – life year gained; PAS – Patient Access Scheme; Ph – Philadelphia; QALY – quality-adjusted life year.
The severity modifier of 1.2 is applied to incremental QALYs.

The figures presented below illustrate the probabilistic sensitivity analysis (PSA) results comparing obe-cel with alternative treatments across different populations.

Figure 21 and Figure 22 focus on the overall population. Figure 21, an incremental cost-effectiveness plane (ICEP) scatterplot, shows that [redacted] Figure 22, the cost-effectiveness acceptability curve (CEAC), demonstrates that at a willingness-to-pay (WTP) threshold of £30,000 per QALY, [redacted]

Figure 23, Figure 24, Figure 25, and Figure 26 examine the Ph- population. Figure 23 and Figure 24, ICEP scatterplots, indicate that [redacted]. Figure 25 shows that for obe-cel versus blinatumomab, [redacted]. Figure 26, reveal that at a WTP threshold of £30,000 per QALY, [redacted].

Figure 27, Figure 28, Figure 29, and Figure 30 depict the results for the Ph+ population. Figure 27 and Figure 28 present ICEP scatterplots for obe-cel versus inotuzumab and ponatinib, respectively. In both comparisons, [redacted] Figure 30, the CEAC, [redacted]

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

Figure 21: EAG scatterplot (overall population)

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

Figure 22: EAG CEAC (overall population)

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

Figure 23: EAG scatterplot, obe-cel versus inotuzumab (Ph- population)

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

Figure 24: EAG scatterplot, obe-cel versus blinatumomab (Ph- population)

CEAC – Cost-effectiveness acceptability curve

Figure 25: EAG CEAC, obe-cel versus blinatumomab (Ph- population)

CEAC – Cost-effectiveness acceptability curve

Figure 26: EAGCEAC, obe-cel versus inotuzumab (Ph- population)

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

Figure 27: EAG scatterplot, obe-cel versus inotuzumab (Ph+ population)

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

Figure 28: EAG scatterplot, obe-cel versus ponatinib (Ph+ population)

CEAC – Cost-effectiveness acceptability curve

Figure 29: EAG CEAC, obe-cel versus inotuzumab (Ph+ population)

CEAC – Cost-effectiveness acceptability curve

Figure 30: EAG CEAC, obe-cel versus ponatinib (Ph+ population)

6.3.1.3 One-way sensitivity analysis results

The following figures summarize the one-way sensitivity analysis (OWSA) results in terms of net monetary benefit (NMB), highlighting several influential parameters affecting cost-effectiveness outcomes.

Figure 31 presents OWSA results for obe-cel versus inotuzumab in the overall population. The most influential parameters include proportion of HSCT in inotuzumab arm, [redacted]

Figure 32 and Figure 33 detail OWSA results for the Ph- population. In Figure 32, the comparison between obe-cel and blinatumomab identifies [redacted] Similarly, Figure 33 highlights that for obe-cel versus inotuzumab, [redacted]

Figure 34 and Figure 35 focus on the Ph+ population. In Figure 34, comparing obe-cel to inotuzumab, the key drivers include [redacted] For Figure 35, which compares obe-cel to ponatinib, [redacted]

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

Figure 31: EAG OWSA results for obe-cel versus inotuzumab (overall population) - NMB

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

Figure 32: EAG OWSA results for obe-cel versus blinatumomab- (Ph-population) NMB

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

Figure 33: EAG OWSA results for obe-cel versus inotuzumab (Ph- population) – NMB

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

Figure 34: EAG OWSA results for obe-cel versus inotuzumab (Ph+ population) - NMB

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

Figure 35: EAG OWSA results for obe-cel versus ponatinib (Ph+ population) - NMB

6.3.1.4 Scenario analysis results

Table 60 presents the results of various scenario analyses comparing obe-cel to inotuzumab across different assumptions in the overall population. The [redacted] in ICER is observed in Scenario 10, where the use of Blinatumomab SMC utility values reduces QALYs to [redacted], leading to the highest ICER of [redacted]/QALY. Conversely, Scenario 3, using a bottom-up costing approach for CAR T-cell infusion cost calculations (with using the UK-specific FELIX trial data in Cohort IIA to estimate hospitalization durations), results in the [redacted] ICER of [redacted]/QALY.

In terms of incremental costs, Scenario 5, which uses data from the mITT population with company preferences, yields the [redacted] incremental cost of [redacted]. Meanwhile, Scenario 3 demonstrates the [redacted] incremental cost of [redacted], reinforcing the cost-saving potential when allo-SCT is excluded.

Regarding QALYs, Scenario 13, which incorporates a severity modifier of 1.7, results in the [redacted] QALYs of [redacted]. Conversely, Scenario 10 yields the [redacted] QALYs ([redacted]) due to the use of blinatumomab SMC utility values.

Table 60: EAG's Scenario analysis results, overall population

Scenario		Obe-cel vs inotuzumab		
		Inc. Costs (£)	**Inc. QALYs**	**ICER (£/QALY)**
EAG base case		[redacted]	1.51	[redacted]
1	Using 1.5% as the annual discount rate for costs and QALYs	[redacted]	2.04	[redacted]
2	Using a bottom-up costing approach for CAR T-cell infusion cost calculations (with using the full FELIX trial dataset in Cohort IIA to estimate hospitalization durations)	[redacted]	1.51	[redacted]
3	Using a bottom-up costing approach for CAR T-cell infusion cost calculations (with using the UK-specific FELIX trial data in Cohort IIA to estimate hospitalization durations)	[redacted]	1.51	[redacted]
4	Considering the availability of vial sharing in comparator treatments	[redacted]	1.51	[redacted]
5	Using data from the mITT population with all company preferences regarding OS and EFS curves	[redacted]	1.91	[redacted]
6	Excluding allo-SCT as a subsequent treatment for obe-cel	[redacted]	1.51	[redacted]
7	Excluding the utility effects of allo-SCT	[redacted]	1.54	[redacted]
8	Using the alternative SMR of 1.09 in mortality	[redacted]	1.79	[redacted]
9	Health state utility source: TA450	[redacted]	1.18	[redacted]
10	Blinatumomab SMC utility values	[redacted]	0.80	[redacted]
11	Including allo-SCT costs for obe-cel patients without a previous allo-SCT ([redacted])	[redacted]	1.51	[redacted]
12	Using the company's original table of adverse events	[redacted]	1.61	[redacted]
13	Using the severity modifier of 1.7 in the model	[redacted]	2.14	[redacted]
ITC – Indirect treatment comparison; QALY – Quality-adjusted life year; SCT – Stem cell transplant; EAG-External assessment group;				

Table 61 presents the results of various scenario analyses comparing obe-cel to inotuzumab and blinatumomab for the Ph- population. For ICER values, Scenario 10, which utilizes blinatumomab SMC utility values, results in the [redacted] ICER for both obe-cel versus inotuzumab (£[redacted]) and obe-cel versus blinatumomab (£[redacted]). Conversely, Scenario 3, using a bottom-up costing method to estimate the cost of CAR T-cell infusion, relying on UK-specific FELIX trial data, results in the [redacted] ICER of £[redacted] for obe-cel versus inotuzumab and £[redacted] for obe-cel versus blinatumomab.

In terms of incremental costs, Scenario 5, which uses data from the mITT population with company preferences regarding OS and EFS curves, yields the [redacted] incremental cost of £[redacted] for obe-cel versus inotuzumab and £[redacted] for obe-cel versus blinatumomab.

Regarding QALYs, Scenario 13, using the severity modifier of 1.7 in the model, results in the [redacted] QALYs for both obe-cel versus inotuzumab and blinatumomab. Meanwhile, Scenario 10, using blinatumomab SMC utility values again yields the [redacted] QALYs.

Table 61: EAG's Scenario analysis results, Ph- population

Scenario		Obe-cel vs inotuzumab			Obe-cel vs blinatumomab		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
EAG base case		[redacted]	1.09	[redacted]	[redacted]	2.50	[redacted]
1	Using 1.5% as the annual discount rate for costs and QALYs	[redacted]	1.47	[redacted]	[redacted]	3.25	[redacted]
2	Using a bottom-up costing approach for CAR T-cell infusion cost calculations (with using the full FELIX trial dataset in Cohort IIA to estimate	[redacted]	1.09	[redacted]	[redacted]	2.50	[redacted]

Scenario		Obe-cel vs inotuzumab			Obe-cel vs blinatumomab		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
	hospitalization durations)						
3	Using a bottom-up costing approach for CAR T-cell infusion cost calculations (with using the UK-specific FELIX trial data in Cohort IIA to estimate hospitalization durations)	[redacted]	1.09	[redacted]	[redacted]	2.50	[redacted]
4	Considering the availability of vial sharing in comparator treatments	[redacted]	1.09	[redacted]	[redacted]	2.50	[redacted]
5	Using data from the mITT population with all company preferences regarding OS and EFS curves	[redacted]	1.41	[redacted]	[redacted]	3.52	[redacted]
6	Excluding allo-SCT as a subsequent treatment for obe-cel	[redacted]	1.09	[redacted]	[redacted]	2.50	[redacted]
7	Excluding the utility effects of allo-SCT	[redacted]	1.09	[redacted]	[redacted]	2.50	[redacted]
8	Using the alternative SMR of 1.09 in mortality	[redacted]	1.29	[redacted]	[redacted]	2.94	[redacted]
9	Health state utility source: TA450	[redacted]	0.83	[redacted]	[redacted]	2.08	[redacted]
10	Blinatumomab SMC utility values	[redacted]	0.32	[redacted]	[redacted]	1.60	[redacted]
11	Including allo-SCT costs for	[redacted]	1.09	[redacted]	[redacted]	2.50	[redacted]

Scenario		Obe-cel vs inotuzumab			Obe-cel vs blinatumomab		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
	obe-cel patients without a previous allo-SCT ([redacted]						
12	Using the company's original table of adverse events	[redacted]	1.18	[redacted]	[redacted]	2.59	[redacted]
13	Using the severity modifier of 1.7 in the model	[redacted]	1.54	[redacted]	[redacted]	3.55	[redacted]
ITC – Indirect treatment comparison; QALY – Quality-adjusted life year; SCT – Stem cell transplant; EAG-External assessment group;							

Table 62 presents the results of various scenario analyses comparing obe-cel to inotuzumab and ponatinib for the Ph+ population. For ICER values, Scenario 10, which utilizes blinatumomab SMC utility values, results in the [redacted] ICER for obe-cel versus inotuzumab (£[redacted]) and obe-cel versus ponatinib (£[redacted]). Conversely, Scenario 13, Using the severity modifier of 1.7 in the model, yields the [redacted] ICER of £[redacted] for obe-cel versus inotuzumab and £[redacted] for obe-cel versus ponatinib.

In terms of incremental costs, Scenario 5, which uses data from the mITT population with company preferences regarding OS and EFS curves, yields [redacted] incremental cost of £[redacted] for obe-cel versus inotuzumab and £[redacted] for obe-cel versus ponatinib.

Regarding QALYs, Scenario 13, using the severity modifier of 1.7 in the model, results in the [redacted] QALYs for both obe-cel versus inotuzumab and ponatinib. Meanwhile, Scenario 10, which uses blinatumomab SMC utility values, again results in the [redacted] QALYs.

Table 62: EAG's Scenario analysis results, Ph+ population

Scenario		Obe-cel vs inotuzumab			Obe-cel vs ponatinib		
		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
EAG base case		[redacted]	1.33	[redacted]	[redacted]	7.42	[redacted]
1	Using 1.5% as the annual discount rate for costs and QALYs	[redacted]	1.78	[redacted]	[redacted]	9.24	[redacted]
2	Using a bottom-up costing approach for CAR T-cell infusion cost calculations (with using the full FELIX trial dataset in Cohort IIA to estimate hospitalization durations)	[redacted]	1.33	[redacted]	[redacted]	7.42	[redacted]
3	Using a bottom-up costing approach for CAR T-cell infusion cost calculations (with using the UK-specific FELIX trial data in Cohort IIA to estimate hospitalization durations)	[redacted]	1.33	[redacted]	[redacted]	7.42	[redacted]
4	Considering the availability of vial sharing in comparator treatments	[redacted]	1.33	[redacted]	[redacted]	7.42	[redacted]
5	Using data from the mITT population with all company preferences regarding OS and EFS curves	[redacted]	1.62	[redacted]	[redacted]	7.78	[redacted]

Scenario		Obe-cel vs inotuzumab			Obe-cel vs ponatinib		
		Inc. Costs (£)	**Inc. QALYs**	**ICER (£/QALY)**	**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
6	Excluding allo-SCT as a subsequent treatment for obe-cel	[redacted]	1.33	[redacted]	[redacted]	7.42	[redacted]
7	Excluding the utility effects of allo-SCT	[redacted]	1.39	[redacted]	[redacted]	7.42	[redacted]
8	Using the alternative SMR of 1.09 in mortality	[redacted]	1.58	[redacted]	[redacted]	9.29	[redacted]
9	Health state utility source: TA450	[redacted]	0.89	[redacted]	[redacted]	5.65	[redacted]
10	Blinatumomab SMC utility values	[redacted]	0.30	[redacted]	[redacted]	3.89	[redacted]
11	Including allo-SCT costs for obe-cel patients without a previous allo-SCT ([redacted])	[redacted]	1.33	[redacted]	[redacted]	7.42	[redacted]
12	Using the company's original table of adverse events	[redacted]	1.45	[redacted]	[redacted]	7.54	[redacted]
13	Using the severity modifier of 1.7 in the model	[redacted]	1.88	[redacted]	[redacted]	10.52	[redacted]
ITC – Indirect treatment comparison; QALY – Quality-adjusted life year; SCT – Stem cell transplant; EAG-External assessment group;							

6.4 *EAG's model validation*

The internal validation of the economic model was conducted to ensure accuracy and reliability. All changes implemented in the model were thoroughly discussed within the team. The final validation process included:

- Cell-by-cell verification of formulae to confirm accuracy.
- Logical testing to ensure consistency in model calculations.

- Input validation to identify and resolve any discrepancies.

Expert validation was carried out to confirm the clinical and technical assumptions underlying the economic model. This process involved consultation with three clinical advisors to ensure that the model's inputs and assumptions were clinically valid and plausible. The key areas of focus during the expert validation process included:

- Incorporation of costs associated with allo-SCT for obe-cel.
- Hospitalization durations, including both ICU and non-ICU stays.
- Inclusion of adverse event incidences
- Utilization rates of inotuzumab and other treatments for RR-ALL, including considerations of proportional shortfall and severity modifiers.
- Placement of obe-cel within the clinical treatment pathway.
- Utility adjustments reflecting subsequent allo-SCT
- Validation of survival curves.

The EAG reviewed prior NICE appraisals to ensure consistency and alignment with established methodologies and assumptions. This review included appraisals for: TA450 (blinatumomab), TA541(inotuzumab), TA451 (ponatinib), TA554 (tisagenlecleucel), and TA893 (brexucabtagene autoleucel). The review emphasised:

- Survival modelling approaches.
- Costs associated with acquisition, administration, healthcare resource utilization (HCRU), adverse events (AEs), subsequent treatments, and end life care.
- Adjustments for bridging chemotherapy, leukapheresis, and conditioning therapy costs for patients who do not proceed to CAR T-cell therapy.
- HCRU frequencies and the assumption of no vial-sharing for certain treatments.
- Disutilities associated with AEs, including cytokine release syndrome (CRS) and its impact on utility.

These processes ensured that the EAG's modifications to the company's economic model aligned with clinical evidence, adhered to methodological rigor, and complied with NICE standards.

6.5 *Conclusions of the cost effectiveness section*

The general approach taken by the company is consistent with other appraisals. The EAG identified several concerns in the economic model, the most influential being a considerable overestimation of follow-up costs for allo-SCT, which was rectified by the EAG. Another involved the exclusion of allo-SCT costs for obe-cel while including its survival effects, which introduced bias, again removed in the EAG base case.

Considerable uncertainty remains in the long-term efficacy of obe-cel, and there is no data to support claims of potential cure. Other EAG changes relate to the starting population (infused vs enrolled), and hospitalisation following obe-cel infusion.

Additionally, the company underestimated hospitalization durations and resource use following obe-cel infusion. The EAG suggested using complete trial data and appropriate tariff costs.

Uncertainty around the MAIC analyses mean all relative efficacy estimates (and corresponding economic analyses) are unreliable and may not be fit for decision-making, particularly those based on a naïve comparison (vs ponatinib).

Deterministic results reveal that for the overall population, obe-cel is [redacted] However, at a willingness-to-pay (WTP) threshold of £30,000 per QALY, [redacted]

In the Ph- population, obe-cel is compared with inotuzumab and blinatumomab. Against inotuzumab, obe-cel achieves an ICER of [redacted] At a WTP threshold of £30,000 per QALY, the probability of obe-cel being cost-effective is [redacted].

For the Ph+ population, [redacted] but [redacted]

[redacted]The probability of obe-cel being cost-effective at a WTP threshold of £30,000 per QALY [redacted]

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8 Appendices

8.1 *EAG assessment of risks of bias of the CS systematic review about the scope of the appraisal (modified ROBIS)*

Table 63: EAG ROBIS evaluation of the company's SLR

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably no	The review aimed to update the NICE STA for brexu-cel. However, the limited publicly available information on the original SLR methods (CS, appendix D.3) suggests potential deviations from pre-defined objectives and criteria. The criteria applied were inconsistent across different stages of the review.
1.2 Were the eligibility criteria appropriate for the review question?	Probably no	The population is defined as adults [redacted] (CS, doc B, Table 1), but the inclusion criteria specify patients ≥26 years old. This inconsistency could lead to the inclusion of studies with different age ranges, affecting the review's relevance and accuracy. Excluding patients with prior CAR T-cell therapy or other genetically modified T-cell therapy limits the comprehensiveness of the review, as these therapies are relevant to the treatment landscape of R/R ALL. These populations have also been included in the FELIX and ALLCAR19 trials.
1.3 Were eligibility criteria unambiguous?	No	The criteria contain ambiguities, particularly regarding age range, leading to inconsistent application and interpretation. In CS, appendix D.7, Table 11, the company included ZUMA3 trial results (brexu-cel) but later stated in CS, appendix D.9 that only INO-VATE and TOWER were relevant for indirect comparison, excluding brexu-cel data without proper justification. Appendix D is based on TA893 and brexu-cel, yet all brexu-cel data were excluded due to improper outcomes or populations. The EAG wonders why the company chose to replicate these studies if they were deemed inappropriate. In Appendix D.8, the company reports no publication of ponatinib as a main comparator but includes PACE trial (ponatinib) results in section D.9. This indicates inconsistencies, ambiguity, and potential bias in the company's approach.

1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably no	The company excluded populations reporting on "Prior CAR T-cell therapy or other genetically modified T-cell therapy" (CS, Appendix D.2, Table 7). Publications with data on patients with previous allo-SCT therapy were excluded from this SLR, despite such patients being included in the company's ALLCAR19 and FELIX trials.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably no	The company has not explicitly defined exclusion criteria but has imposed them on some comparators and their related studies. For example, ponatinib was listed as a comparator in Appendix D.2, Table 7, but no related studies were reported in the summary of clinical publications (Appendix D.7, Table 11). However, it was later considered in section D.9. Brexu-cel was included in the SLR results (Appendix D.7, Table 11), but it was excluded from the ITC and subsequent analysis (CS, doc B, Table 20) without clear justification or exclusion criteria.
Concerns regarding specification of study eligibility criteria	**High concern**	The EAG has some concerns about the adherence to the eligibility criteria and the rationale and justification behind inclusion/exclusions.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	Yes	Databases: Medline, Embase, PubMed, Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) Grey literature was sought via: - Google Scholar - NICE website - 3 clinical trial registries (clinicaltrials.gov, the EU Clinical Trials Register, the World Health Organisation International Clinical Trials Registry Platform) - Manufacturer's repository of evidence and websites of manufacturers of comparator products - Backwards citation searching of SLRs carried out - 5 broad cancer and specific haematology conferences hand searched from 2022 to 2024 (American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Society of Medical Oncology (ESMO), European Hematology Association (EHA) and The Professional Society for Health Economics and Outcomes Research (ISPOR))

2.2 Were methods additional to database searching used to identify relevant reports?	Probably yes	Google searches, NICE website, clinical trials registries, and conferences (see above) were searched but search details not reported.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no	The company report that this search is an update of the search strategy used to inform the SLR for TA893. As the inclusion/ exclusion criteria differs relevant search terms for this SLR were not searched for beyond the date restriction of 2021 as they wouldn't have been included in the search for TA893 (see section 2.4) **General:** Free text searches don't include search field information so not clear if searched in title, abstract and/ or keyword. **Population terms:** the Medline/ Embase/ PubMed search used appropriate indexing and free text terms. The Cochrane Library searches are missing the Cochrane Library/ MeSH indexing terms, e.g. Precursor Cell Lymphoblastic Leukemia-Lymphoma' used for Acute lymphoblastic leukaemia. The Cochrane Library search also does not include the American spelling of 'leukemia' **Intervention terms:** Includes relevant indexing and free text terms for the comparators, including 'Tisagenlecleucel'. The intervention search terms could be broadened. 'Car T' is searched as a phrase but doesn't include related terms such as Chimeric Antigen Receptor T-cell therapy, Chimeric Antigen Receptor therapy or T-Cell. The drug terms do not include all trade names, e.g. 'Tecartus' is not included as a search term for Brexucabtagene autoleucel. The Emtree (Embase indexing terms) drug terms are also not included.
2.4 Were restrictions based on date, publication format, or language appropriate?	No	The search was limited to studies published between 2021-2024 as the search strategy for TA893 SLR was carried out in 2021. The company did not have access to the full search strategy for TA893 but had access to the EAG critique and numbers of search results (available in the clarification responses (A14, A17, Figure 4: Clinical SLR PRISMA flow chart). The company compared their search results figures limited to 2020 (the date that the TA893 search was carried out) against the numbers of results for TA893. Their results were slightly larger and thus conclude that their search is broader (Embase, Medline and PubMed search results, TA893: 10,719, their search: 12,948) Not having the full search strategy to replicate, means that it is not a true update of the search strategy from TA893. If the inclusion/ exclusion criteria were

		the same this would be a reasonable approach to take. However, as the inclusion and exclusion criteria differs (see sections 1.1-1.5) the company should have either carried out a search strategy for the population/ condition only and not included any terms for the intervention and limited it to studies published after 2021 or developed a new strategy which includes search terms for the population and intervention and not restricted by date to ensure that all of the terms related to their inclusion criteria were included to ensure that a thorough and comprehensive search was carried out. No language restrictions or study design filters were applied, which increases the sensitivity of the searches.
2.5 Were efforts made to minimise errors in selection of studies?	No	Efforts were made to minimize errors in the selection of studies, but the process has notable shortcomings. While two independent reviewers assessed the relevance of the studies and a third reviewer arbitrated discrepancies, the approach of aligning reviewers only after 20% of the studies had been reviewed (CS, Appendix D.4), has a potential risk of bias. Detecting inconsistencies at this stage means that any initial biases or errors are likely to influence subsequent selections. Although this early alignment aims to correct discrepancies, it inadvertently introduces a new bias: reviewers might adjust their selections to achieve consensus rather than independently applying the criteria. This leads to a convergence of decisions, where the emphasis shifts from objective assessment to agreement, potentially compromising the review's integrity. As a result, the remaining 80% of the study selection is influenced not only by initial biases but also by the reviewers' efforts to align their judgments, which could affect the overall reliability and validity of the study selection process.
Concerns regarding methods used to identify and/or select studies	**Low concern**	
3: Data collection and study appraisal sections		
3.1 Were efforts made to minimise error in data collection?	Unclear	The data were extracted by one reviewer and checked by a second reviewer for accuracy and consistency. It is unclear whether the second reviewer captured and added any information that may have been missed by the first reviewer. Additionally, it is unclear if the second reviewer read the paper in detail to not only check the extracted data for accuracy but also to ensure that no relevant information was missed.

3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Probably yes	Sufficient study characteristics for all studies, including those in the SLR, were reported in Table 69 of the CS Appendices.
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes	Relevant study results were reported in CS, doc B, Tables 20-23.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably no	The company has used Cochrane's risk of bias tool for RCTs (RoB2) and Downs and Black for non-randomised trials. While the Downs and Black is comprehensive, ROBINS-I[43] is considered a more valid tool according to NICE's methodologies. NICE does not recommend Down and Black for non-randomised clinical trials.[42] ROBINS-I allows for a more comprehensive assessment of bias, considering the entire study process from design to reporting. It focuses specifically on bias domains relevant to non-randomized studies, such as confounding, selection bias, and measurement bias. It provides detailed guidance and a structured approach to assess the risk of bias, which helps ensure consistency and thoroughness. Downs and Black scoring could be subjective and complicated, it lacks comprehensive guidance and may not adequately address issues related to blinding and confounding.
3.5 Were efforts made to minimise error in risk of bias assessment?	Unclear	The company has not provided any information regarding two independent reviewers who have conducted the risk of bias assessment.
Concerns regarding methods used to collect data and appraise studies	**Unclear concern**	
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	Probably no	The EAG had concerns over the methodology of this search and the methods used to update the search for TA893. The search is limited to studies published after 2021. The company did not have access to the search terms used for TA893. TA893 did not include obe-cel as a comparator so is unlikely to have been included in this search. The search strategy incorporated a broad range of indexing and free-text terms for the population and condition. A relevant and comprehensive range of databases and sources were searched. The search strategy was an update of the SLR searches carried out for TA893.
4.2 Were all predefined analyses followed or departures explained?	Probably yes	The company followed pre-planned population-adjusted analyses and only departed from that for the PACE trials given the heterogeneity issues.

4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Probably yes	The comparator studies didn't report some of the important TEMs, but otherwise, MAIC/naïve comparisons were appropriate.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Probably no	The EAG notes that heterogeneity issues were not discussed, and no steps were taken to address these problems in the synthesis. This suggests that between-study variation was not adequately addressed.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	No	The EAG indicates the absence of funnel plots and sensitivity analyses. It also points out the lack of robustness in the ITC results due to large CRD intervals, indicating low precision. This suggests that the findings are not robust.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably no	Sensitivity analyses or adjustment approaches were not employed. There were methodological inadequacies.
Concerns regarding the synthesis and findings	**High concern**	Heterogeneity between studies not addressed, lack of funnel plots/sensitivity analyses
Risk of bias	**High risk of bias**	More than one domain raised high concerns.

8.2 *Risk of bias for FELIX trial*

The EAG used a modified Risk of Bias in Non-randomised Studies - of Exposure (ROBINS-E) tool to assess the FELIX trial.

Confounding and Selection Bias

In CS appendix N, Table 68, the company mentions performing extensive subgroup analyses on potential confounders (baseline characteristics). However, their response fails to address residual confounding and lacks additional statistical adjustments for the FELIX trial. Relying solely on subgroup analyses is insufficient, and no extra control, stratifications, or adjustments were implemented.

The selection of participants is of concern, with evidence (e.g. changing the recruiting criteria for ≥65 years patients) indicating that patients were chosen based on their fitness and baseline characteristics, rather than being broadly recruited to represent the real-world population.

Measurement of Exposure and Outcomes

Both tools identified issues with measuring exposure and outcomes. Follow-up assessments potentially missed early patient-reported quality-of-life data and late adverse events (long-term), leading to underreporting or delayed reporting. Additionally, infrequent assessments due to cost and design caused post-infusion events to be captured late, resulting in inaccurate and overestimated EFS and DOR outcomes. The unblinded structure biased patient-reported outcomes, HRQoL, and adverse events in favour of obe-cel. Timings and assessments lacked consistency.

Missing Data

No missing data, loss to follow-up, or clear statements were reported. Additionally, there was no information on the extent of missing data or any imputation methods used.

Post-Exposure Interventions

The comorbidities and concomitant medications (drug-drug interactions, etc) that patients received before and after infusion are unclear. Therefore, the association and the impact on effectiveness cannot be determined.

Reporting Bias

The results were not reported under a pre-determined analysis plan, and there have been changes to the definition of death defined as an event. not all actual probability values were reported, and the company failed to report all defined outcomes in the protocol (e.g. the feasibility of manufacturing and administering, different types of relapses such as molecular, MRD, CNS, EMD type relapses, etc.).

Overall Risk of Bias

Overall, both the ROBINS-E tool and the Down and Black checklist indicated a high risk of bias in the FELIX trial due to no adjustments for confounders, issues with exposure and outcome measurement, inadequate reporting, and selection bias. All of which, contribute to significant concerns about the reliability and generalisability of the trial's findings. These limitations must be carefully considered when interpreting the results of the study.

Table 64: FELIX trial ROBINS-E assessment

ROBINS-E domain, and signalling questions	EAG's rating	Reasoning

1: Bias due to confounding		
1.1 Did the authors control for all the important confounding factors for which this was necessary?	**No information**	The company has reported baseline characteristics and subgroup analysis although no approach has been taken controlling for confounders.
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	**NA**	
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	**NA**	
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	**Probably yes**	FELIX only included patients with an ECOG score of 0 or 1, while INO-VATE, TOWER and PACE also included those with an ECOG score of 2.[55, 57, 59] For the FELIX trial, no patients with an ECOG PS score of 2 were included, although the company has merged them with score 1 patients despite their different prognoses to reduce the impact. Other factors such as the proportion of Ph+ patients, prior SCTs, gender, and age also varied and needed consideration (CS, appendix N, Table 69).
Risk of bias judgement	**High risk of bias**	
2: Risk of bias arising from measurement of the exposure		

2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study?	**Weak no**	In the company reports patients have been assessed according to the protocol document, Tables 1-4. Ten times at the first month, six times till month 12 and only four measurements till the second year (final data cutoff for this submission). In the protocol section 8.10.2, company specifies that the first follow-up assessment occurs at the next planned visit, which could be as late as two months after a significant event (e.g., relapse at Month 10, first follow-up at Month 12). This delay can lead to missing critical early data on adverse events or survival outcomes, introducing bias due to the exclusion of follow-up immediately after the exposure window. In the protocol section 8.10.4, company states that the long-term follow-up protocol aims to assess delayed consequences of using a lentiviral vector in AUTO1 manufacture, with semi-annual and annual evaluations. Patients will undergo yearly clinic visits for physical exams and medical history reviews, focusing on potential lentiviral-related events. The EAG notes that the semi-annual and annual evaluations might miss important changes or events that occur between these intervals, leading to underreporting or delayed reporting of adverse events or other
2.2 Was the exposure likely to be measured with error, or misclassified?	**Weak yes**	

		outcomes. This inconsistency can introduce bias in the estimated effect of the exposure.
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	**Strong yes**	As the FELIX trial was an open-label study, and the assessors had knowledge of the risk of the outcome, patients, and risk of the outcome could have affected exposure measurements. This could have affected the reported AE and HRQoL outcomes. The participants were unblinded, therefore, EAG considers systematic differences in the way individuals remember or report their HRQoL outcomes.
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	**NA**	
Risk of bias judgement	**High risk of bias**	
3: Risk of bias in selection of participants into the study (or into the analysis)		
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	**Probably no**	In the protocol (page 87), the company states that if a patient relapses at Month 10, the first safety and survival follow-up visit will occur at Month 12. Additionally, patients who have completed the 24-month follow-up period will be monitored every 6 months until the end of the study (EoS) as per the Schedule of Assessments (protocol section 8.10.2). Despite the company's acknowledgment in section 8.10.4 of the protocol regarding potential

		delayed consequences from the lentiviral vector used in AUTO1, the EAG cannot verify that all expected adverse events (AEs) are fully captured by these follow-up assessments due to the intervals between visits.
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	**Probably no**	The company's acknowledgment of potential delayed consequences from the lentiviral vector suggests that the effects of the exposure may change over time. Monitoring patients only four times in the second year and then semi-year or yearly, is not comprehensive to report all possible AE, progression, relapses, health states that patients would have experienced.
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	**Yes**	The demographic characteristics were assessed at the screening timepoint (CS protocol, Table 1). Considering that FELIX has been an uncontrolled, open-label, non-randomised trial, and both patients and assessors were unblinded, it is likely that patients were selectively picked during the screening process and prior to enrolment, as 64 out of 217 screened patients were discontinued (30%). It is unclear to the EAG whether this approach was due to not matching the eligibility criteria or an attempt to select fit, young patients with minimal poor prognosis (*see* Critique of patients' characteristics).

		Selection based on characteristics observed before the start of the exposure window that are predictive of the results could have been addressed by controlling for these characteristics in the analysis (analogous to baseline confounding, addressed in domain 1), which the company has not done.
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	**NA**	
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	**NA**	
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	**No**	The EAG found no approaches been taken by company in this regard.
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	**Probably no**	The EAG found no sensitivity analysis reported.
Risk of bias judgement	**High risk of bias**	
4: Risk of bias due to post-exposure interventions		
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	**Probably yes**	The supportive care and treatments that patients received post-infusion are considered in this context for the management of AE(s) and

4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	**NA**	contaminant treatments modifications for comorbidities. The company has not reported comorbidities and concomitant medications that patients received before and after infusion. However, the EAG believes that, based on the list of adverse events (AEs) reported in the CS, document B, Table 24, and CS, protocol, section 10 about management of AE(s), there have been modifications in the concomitant treatments for pre-existing comorbid conditions and their exacerbations following the mentioned AEs. Patients likely had treatment adjustments, as discussed, and modifications to the supportive drugs they received for their severe AEs (CS, doc protocol, Table 15). The company has not provided any information in this regard. The EAG cannot determine the impact this might have on the effectiveness outcomes, discontinuations and patients HRQoL outcomes.
Risk of bias judgement	**Some concerns**	
5: Risk of bias due to missing data		
5.1 Were complete data on exposure status available for all, or nearly all, participants?	**No**	The company's documents provide no information about the extent of missing data. The number of missing data is not reported by company. The

5.2 Were complete data on the outcome available for all, or nearly all, participants?	**Probably no**	EAG notes that almost [redacted] of patients in cohorts IA and IIA have been reported dead in the CSR, Table 14.2.30.3.3. The EAG assumes that the number of missing data by 24 months will be considerable and concerning. The company has only reported the mITT and ITT. The EAG found no data of complete case analysis.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	**Probably no**	
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	**No**	The company has reported the ITT (enrolled patients) in the CSR document. No analysis on complete case analysis has been reported.
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	**NA**	
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	**NA**	
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	**No information**	The company has not reported any imputation of missing values.
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	**NA**	
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	**No**	The company has not reported or conducted any information about complete case analysis nor based on imputing missing values. No inverse probability weighting and full

		information maximum likelihood have been undertaken.
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	**No**	No sensitivity analysis or any other analyses have been undertaken to assess plausible relationships between the missing values and the likelihood that data are missing. The company should have provided further justification for the assumption of missing not at random (MNAR) and conducted additional analyses to explore the robustness of their results to missing data. This would ensure the validity of the utility estimates and their alignment with real-world data.
Risk of bias judgement	**High risk of bias**	
6: Risk of bias arising from measurement of the outcome		
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	**Yes**	For the HRQoL outcomes, the company captured patients' HRQoL outcomes only before day one and no HRQoL assessments were conducted (CS, protocol Table 1) until day 28. In the CS, document B, section B.2.10, the company reports an average hospitalization duration of [redacted] The time to onset of CRS and ICANS was reported as [redacted] respectively, after the first infusion with lower dose. The timing schedule for PRO assessments appears to have been chosen (CS, protocol, Table 1) to ensure that the serious adverse events occurring within the first 28

		days would not impact the HRQoL results. When patients have been assessed at day 28, their serious AE have been resolved (median duration of CRS was [redacted]). The EAG notes that this approach raises the risk of bias and results in overly optimistic HRQoL outcomes due to missing data. Furthermore, the schedule of assessments has been reduced over time, despite ongoing concerns about the occurrence of adverse events in the long term (discussed in domain 2).
6.2 Were outcome assessors aware of study participants' exposure history?	**Yes**	Both assessors and patients were unblinded. In the CS document B, the company reports IRRC assessment results for DOR, ORR, and EFS measured by IRRC. All remaining outcomes are assumed to be assessed, collected, analysed, and reported by the unblinded investigators, which raises the risk of biases. According to the protocol, disease progression and the determination of the causal relationship between treatment with the study medication, AEs and SAEs, and their relationship to the treatment, as well as blast count percentages at different stages from patient screening to the last dose delays,
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	**Yes**	

		have been measured by investigators. The HRQoL is assessed and reported by unblinded patients, which might not capture the true values of health states that patients will experience in the real world.
Risk of bias judgement	**High risk of bias**	
7: Risk of bias in selection of the reported result		
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	**No**	In the protocol page 128, company states: “Further details of the statistical analysis of all the endpoints will be included in a separate Statistical Analysis Plan (SAP). Any analysis that deviates from the SAP will be documented and justified in the Clinical Study Report (CSR)”. No SAP or pre-defined analysis plan has been reported in the CSR, CS document B and appendices.
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	**Probably yes**	The EAG raises concerns about the completeness and reliability of the reported effect estimates. This suggests that the effect estimate might have not been comprehensively reported. All exposure measurements within the domain should have been reported. Given this context, it is likely that the reported effect estimate has a risk of bias (e.g. different types of relapses such as molecular, MRD, CNS, EMD type relapses, etc.).
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome	**Probably yes**	

measurements within the outcome domain?		
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	**No**	The use of predefined data cut-offs and the consistency which outcomes are being analysed indicates adherence to the trial protocol. There is no direct evidence of bias, however the presentation of statistically significant results indicates a focus on favourable findings. Nevertheless, this is standard procedure to support the efficacy of the treatment in question.
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different subgroups?	**Probably no**	The reported subgroup results are not likely to be selected solely based on desirability as results are consistent across the pre-planned and post-hoc analyses. However, the emphasis on favourable outcomes in target populations, such as the UK population, suggests an effort was made to align findings to the strategic goals of the submission.
Risk of bias judgement	**Some concerns**	
Overall risk of bias		
Overall risk of bias	**High risk of bias**	

Table 65: EAG replicated Down and Black risk of bias assessment for FELIX trial

	Company's response	EAG's comment
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes CS, doc B, section B.2.3.1
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes CS, protocol, page 6

Are the characteristics of the subjects included in the study clearly described?	Yes	Yes CS, CSR, section 14.1.2.
Are the interventions of interest clearly described?	Yes	Yes CS, doc B, Table 1
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes	No, the company has not clearly defined or reported the confounders. While some baseline characteristics and subgroup analysis (which is based on the patient's baseline status) have been reported and then claimed to be the whole confounders, but the EAG does not accept. There should have been controlling and adjustments based on confounders. The EAG finds the information provided by the company to be insufficient and inaccurate.
Are the main findings of the study clearly described?	Yes	Yes CS, doc B, section B.2.6.1
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes, For studies in which statistical analysis has been conducted, the 95% confidence interval has been reported.
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes, CSR doc, section 14.3
Have the characteristics of subjects lost to follow-up been described?	No	No The company has not reported missing data, loss to follow-up over time and in different timepoints.
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes	No Not all actual values are reported. CS, doc B, Table 12
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes	No There are differences in the baseline characteristics of patients that were screened and enrolled compared to the real-world population.
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	No	No Not information has been reported in this regard. The company has defined eligibility criteria that do not include severe conditions. The patients appear to be young and fit, with only ECOG PS scores of 0 and 1 (mainly score 0). Patients mostly have had one or

		two prior treatments. There is no information about patients' comorbidities. This suggests that the population was selected to likely respond favourably to obe-cel.
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes	Unable to determine No information about the centres, staff, and facilities that delivered the treatment has been reported. Therefore, the EAG cannot determine whether they were similar to NHS practice.
Was an attempt made to blind study subjects to the intervention they have received?	N/A	No All subjects, staff, investigators were unblinded. The company could have used other comparators but has not.
Was an attempt made to blind those measuring the main outcomes of the intervention?	N/A	No The investigators were not blinded.
If any of the results of the study were based on “data dredging”, was this made clear?	Yes	Yes The EAG found no data dredging.
In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	Yes
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes
Was compliance with the intervention/s reliable?	N/A	Unable to determine No information in this regard has been reported.
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes
Were the subjects in different intervention groups or were they recruited from the same population?	N/A	Probably no Patients were included from 34 study centres across the US, Spain, and the UK (8 centres) based on specific eligibility criteria. The EAG notes that it appears patients were selectively picked by the company rather than being broadly recruited. FELIX trial was an open label uncontrolled single arm study.
Were study subjects in different intervention groups or were they recruited over the same period of time?	N/A	Unable to determine No information was provided about the timing of recruitment. Given that this was a single-arm, open-label trial, it is likely that patients were

		selected based on their fitness and baseline characteristics at different time points.
Were study subjects randomised to intervention groups?	N/A	No FELIX was a single arm non-randomised open label study.
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A	No The company has not reported any information about the recruitment process and its validity. All patients, assessors, analysers and investigators were unblinded.
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes	No No adjustments were conducted for the confounders.
Were losses of subjects to follow-up taken into account?	Yes	No The company reports that "patients who were lost to follow-up were censored". The company doesn't report the exact number of patients who were loss to follow-up. The reasons were provided but the details and the impact has not been considered.
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes	Yes, the company has considered at least 90 infused patients to be powered enough. 43 patients were considered as possible dropouts (133 patients cohort IA/IIA). However, the details on dropouts and withdrawal expectations were not provided.

8.3 *EAG changes to model (base-case)*

In Table 66, we present the technical details of the changes made to the company model that formed the basis of the EAG analyses.

Table 66: EAG changes to the company model

EAG's issues	Technical report of changes in the company's model
Programming and implementation errors related to incorporating follow-up costs of allo-SCT in the economic model (in all treatments)	For all 'Trace' worksheets: - Cell DG22, the formula changed to "AQ22" - Cell DH22, the formula changed to "AX22" - Cell DI22, the formula changed to "BD22" In all above items, the amendments for subsequent cells have been applied accordingly. In worksheets "Trace - Obe-cel vs …) - Cell AP23, The formula changed to (AG23-AG24)*p_i_SCT_int

Inconsistent Inclusion of Costs and effects of allo-SCT for obe-cel in the Economic Model	In the 'Subsequent Tx Costs' worksheet, cell F12 change to [redacted] In the 'Settings' worksheet, Cell F52 change to 'Yes'
Underestimating Hospitalization Durations and Resource Use Post obe-cel Infusion	- In the 'Settings' worksheet: Cell F38 change to 'Tariff costs' -In the 'Treatment Costs' worksheet, changes below are applied (general amendments that affect the scenarios): Cell of I133: value change to [redacted] Cell of I138: value change to [redacted] Cell of I143: value change to [redacted] Cell of I128: the formula changed as follow: - Worksheet "Treatment Costs", formula in cell I128 changed to CHOOSE(i_infusion_cost_approach,(((1-I143)*I133*K106)+(I143*I138*K118)),(I149+(I143*I138*K118))) - Cell I148: The value changed to £58,964
Underreporting of Adverse Events and Discrepancies with the Company's Clinical Study Report (CSR)	In 'Adverse Events' worksheet: - Cells F86:F115 replaced with new values from CSR. - Cell D38: replaced with Neurological event and ICANS - Cell G75 changed to 127
Inconsistencies in severity modifier application across comparator populations	In 'Settings' worksheet: Cell F18 changed to 'Yes - 1.2'
Excluding allo-SCT utility effects from the economic model	- In the 'Settings' worksheet (cells D189:G191): Add a combo box for selecting either the EAG approach or the company approach. - In the 'Quality of Life Inputs' worksheet (cells C109:I126): Create the table to determine changes in basic utility due to SCT for various treatments. - For all 'Trace' worksheets (Cells DR11:DV11): Modify the formula to perform actions based on the selected approach and retrieve the value from the new table.
Use of per-cycle discount rate instead of per-year discount rate	Worksheets 'Trace-…' : - Cell FA22: The formula has been changed to 1/(1+p_i_disc_QALYs)^ROUNDDOWN($M22,0) and amendments for subsequent cells have been applied accordingly - Cell FB22: The formula has been changed to 1/(1+p_i_disc_costs)^ROUNDDOWN($M22,0) and amendments for subsequent cells have been applied accordingly
Inappropriate ITC approach and narrowed population	Worksheet 'Lists', cells B22:E28 , Baseline characteristics for all populations are updated based on ITT populations

	Worksheet 'Extrapolation Inputs': - The mITT Event-free survival parameters (standard parametric), in LOC assessed section, replaced with ITT-EFS parameters - The mITT OS parameters (standard parametric and Flexible parametric), in LOC assessed section, replaced with ITT-OS parameters - Company's parametric curves for ponatinib EFS and OS replaced with EAG preferred parametric curves - Hazard ratios in cells EH13:EI20 replaced with new values from ITT population. Worksheets 'Trace-…' : - Cell T22: The value has been changed to EFS!(related cell)76, and amendments for subsequent cells have been applied accordingly. - Cell U22: The value has been changed to OS!(related cell)78, and amendments for subsequent cells have been applied accordingly. - Cell O22: The formula has been changed to misc_cycleLength/misc_daysPerYear and amendments for subsequent cells have been applied accordingly Worksheet 'Trace – Blina' : - Cell AB22: The formula has been changed to IF(AND(J22<=6,J22>=0),1,0) - Cell AC22: The formula has been changed to IF(AND(J22<=2,J22>=0),1,0) Worksheet 'Trace - Ino' : - Cell AB22: The formula has been changed to IF(AND(J22<=5,J22>=0),1,0) - Cell AC22: The formula has been changed to IF(AND(J22<=3,J22>=1),1,0) Worksheet 'Trace - Ponatinib' : - Cell AB22: The formula has been changed to IF(AND(J22<=2,J22>=0),1,0) Worksheets 'Trace-Obe-cel vs …' : - Cell EH22: The formula has been changed to AG22*AM23*(live_i_c_TxLeukapheresis_int+live_i_c_TxBridging_int+live_i_c_TxCondit_int) and amendments for subsequent cells have been applied accordingly.

	- Cell AG22: The formula has been changed to CHOOSE(misc_HCC,W22,AVERAGE(W21:W22)) Worksheet 'Treatment Costs': Tables with name 'Summary per cycle drug acquisition costs' and 'Summary per cycle drug administration costs' were updated for starting the treatment at new cycle Worksheet 'Subsequent Tx Costs': - Cell F86: The formula has been changed to SUM(OFFSET('Treatment Costs'!$F$9,1,0):OFFSET('Treatment Costs'!$F$9,E86,0)) - Cell F84: The formula has been changed to SUM(OFFSET('Treatment Costs'!$G$9,1,0):OFFSET('Treatment Costs'!$G$9,E84,0)) - Cell F83: The formula has been changed to SUM(OFFSET('Treatment Costs'!$G$9,1,0):OFFSET('Treatment Costs'!$G$9,E83,0))+SUM(OFFSET('Treatment Costs'!$I$9,1,0):OFFSET('Treatment Costs'!$I$9,E83,0)) - Cell G83: The formula has been changed to SUM(OFFSET('Treatment Costs'!$G$50,1,0):OFFSET('Treatment Costs'!$G$50,E83,0))+SUM(OFFSET('Treatment Costs'!$H$50,1,0):OFFSET('Treatment Costs'!$H$50,E83,0))+SUM(OFFSET('Treatment Costs'!$G$31,1,0):OFFSET('Treatment Costs'!$G$30,E83,0))+SUM(OFFSET('Treatment Costs'!$H$30,1,0):OFFSET('Treatment Costs'!$H$30,E83,0)) - Cell G84: The formula has been changed to SUM(OFFSET('Treatment Costs'!$G$50,1,0):OFFSET('Treatment Costs'!$G$50,E84,0))+SUM(OFFSET('Treatment Costs'!$G$31,1,0):OFFSET('Treatment Costs'!$G$31,E84,0)) - Cell G86: The formula has been changed to SUM(OFFSET('Treatment Costs'!$F$50,1,0):OFFSET('Treatment Costs'!$F$50,E86,0))+SUM(OFFSET('Treatment Costs'!$F$31,1,0):OFFSET('Treatment Costs'!$F$31,E86,0)) Worksheet 'Lists' cell C18 and Worksheet 'Settings' cell F23 mITT changed to ITT

	Worksheet 'Lists', Cells I5:K12: New table of Baseline characteristics (Cohort IA and IIA) Worksheet 'Treatment Costs' (model start at start point of pretreatment then we need some justifications) - Cell G174: The formula has been changed to E175/F175 And E175 = 133 , F175=[redacted] (based on cohort IA and IIA) - Cell H156: The formula has been changed to IF(i_infusion_cost_approach=1,p_i_c_TxLeukapheresis *p_i_c_CorFactLeukapheresis_int,p_i_c_TxLeukapheresis*(1-p_i_c_CorFactLeukapheresis_int)) - Cell I214: The formula has been changed to H215/G215 And H215=[redacted], G215=[redacted] - Cell I238: The formula has been changed to H239/G239 And H239=[redacted], G239=[redacted] Worksheet 'Trace - Obe-cel vs Blina': - Cell EC22: The formula has been changed to (AG22+(Infused_Ph_Nega_P/ITT_Ph_Nega_P)-AG22)*AM22*$EC$7 - Cell ED22: The formula has been changed to (AG22+(Infused_Ph_Nega_P/ITT_Ph_Nega_P)-AG22)*AM22*$ED$7 - Cell DW22: The formula has been changed to IF(J22=1,((AG22+AH22)+(Infused_Ph_Nega_P/ITT_Ph_Nega_P)-(AG22+AH22))*$DW$7,0) and amendments for subsequent cells have been applied accordingly Worksheet 'Trace - Obe-cel vs Ino': - Cell EC22: The formula has been changed to (AG22+(Infused_Whole_P/ ITT_Whole_P)-AG22)*AM22*$EC$7 - Cell ED22: The formula has been changed to (AG22+(Infused_Whole_P/ ITT_Whole_P)-AG22)*AM22*$ED$7 - Cell DW22: The formula has been changed to IF(J22=1,((AG22+AH22)+(Infused_Whole_P/ ITT_Whole_P)-(AG22+AH22))*$DW$7,0) and amendments for subsequent cells have been applied accordingly Worksheet 'Trace - Obe-cel vs Pon':

	- Cell EC22: The formula has been changed to (AG22+(Infused_Ph_Posi_P/ ITT_Ph_Posi_P)-AG22)*AM22*$EC$7 - Cell ED22: The formula has been changed to (AG22+(Infused_Ph_Posi_P/ ITT_Ph_Posi_P)-AG22)*AM22*$ED$7 - Cell DW22: The formula has been changed to IF(J22=1,((AG22+AH22)+(Infused_Ph_Posi_P/ ITT_Ph_Posi_P)-(AG22+AH22))*$DW$7,0) and amendments for subsequent cells have been applied accordingly

8.4 *List of company and EAG cost-effectiveness analyses (applying confidential prices) and source of prices*

The EAG re-ran the company's base-case analysis and conducted its own base-case analysis to compare obe-cel versus all comparators, using the available PAS discounts for treatments. This report is provided separately in the document titled "EAG Confidential Appendix." In Table 67, we present the sources of the prices used in the analyses in the EAG Confidential Appendix document.

The EAG confidential appendix report includes the following analyses:

- Company's cost-effectiveness results applying confidential prices for comparator treatments
    - Deterministic base-case results,
    - Probabilistic sensitivity analysis results
    - Scenario analysis results
- EAG cost-effectiveness results applying confidential prices for comparator treatments
    - Deterministic base-case results,
    - Probabilistic sensitivity analysis results
    - Scenario analysis results

Table 67: Sources of prices used in EAG confidential appendix (provided separately)

Name	Dose per unit	Pack size	Source

Obecabtagene autoleucel	Target dose: 410 x 10^6 CD19 CAR-positive viable T-cells	1	PAS
Blinatumomab	38.5 µg	1	PAS
Inotuzumab	1 mg	1	PAS
Ponatinib	45 mg	30 tablets	PAS
Vincristine	1 mg/1ml	5 vials	eMIT July 23 – Jun 24
Vincristine	2mg/2ml	5 vials	eMIT July 23 – Jun 24
Cyclo-phosphamide	500mg	1	eMIT July 23 – Jun 24
Cyclo-phosphamide	1000mg	1	eMIT July 23 – Jun 24
Cyclo-phosphamide	2000mg	1	eMIT July 23 – Jun 24
Methotrexate	500mg/20ml	1	eMIT July 23 – Jun 24
Mercaptopurine	20mg/1ml	100ml	MPSC
Cytarabine	100mg/1ml	1	eMIT July 23 – Jun 24
Cytarabine	1000mg/10ml	1	eMIT July 23 – Jun 24
Cytarabine	2000mg/10ml	1	eMIT July 23 – Jun 24
Cytarabine	500mg/5ml	5	eMIT July 23 – Jun 24
Fludarabine	50mg/2ml	1	eMIT July 23 – Jun 24
Dexamethasone	3.3mg/1ml	10	eMIT July 23 – Jun 24
Dexamethasone	6.6mg/2ml	10	eMIT July 23 – Jun 24

Note: Costs for tisa-cel were also provided to the EAG, however this technology was not used in the economic model.

8.5 *EAG changes to model (scenario analysis)*

Table 68: Technical report of changes (related to EAG's Scenario analysis) in the EAG's model

EAG's Scenario analysis		**Technical report of changes in the EAG's model**
1	Using 1.5% as the annual discount rate for costs and QALYs	Worksheet "Settings", cells F14 and F16 changed to "1.5%"
2	Using a bottom-up costing approach for CAR T-cell infusion cost calculations (with using the full FELIX trial dataset in Cohort IIA to estimate hospitalization durations)	Worksheet "Settings", cell F38 changed to "bottom-up costing"
3	Using a bottom-up costing approach for CAR T-cell infusion cost calculations (with using the UK-specific FELIX trial data in Cohort IIA to estimate hospitalization durations)	Worksheet "Settings", cell F38 changed to "bottom-up costing" -In the 'Treatment Costs' worksheet, changes below are applied (general amendments that affect the scenarios): Cell of I133: value change to [redacted] Cell of I138: value change to Cell of I143: value change to

EAG's Scenario analysis		**Technical report of changes in the EAG's model**
4	Considering the availability of vial sharing in comparator treatments	Worksheet "Settings", cells F48 changed to "Yes"
5	Using data from the mITT population with all company preferences regarding OS and EFS curves	In the company's model (the most updated version that EAG has received with the company's response to EAG's clarification questions), all the changes in this table have been applied.
6	Excluding allo-SCT as a subsequent treatment for obe-cel	Worksheet "Settings", cells F52 changed to "No"
7	Excluding the utility effects of allo-SCT	Worksheet "Settings", cells E190 changed to "Company's approach"
8	Using the alternative SMR of 1.09 in mortality	Worksheet "Settings", cells I154 changed to "1.09"
9	Health state utility source: TA450	Worksheet "Settings", cells F62 changed to "TA450"
10	Blinatumomab SMC utility values	Worksheet "Settings", cells F62 changed to "Blinatumomab-SMC"
11	Including allo-SCT costs for obe-cel patients without a previous allo-SCT ([redacted])	Worksheet "Subsequent Tx Costs", cells F1 changed to "[redacted]"
12	Using the company's original table of adverse events	Worksheet "Subsequent Tx Costs", cells E86:E115 changed to original values in company's submission model Worksheet "Subsequent Tx Costs", cell G75 changed to "94"
13	Using the severity modifier of 1.7 in the model	Worksheet "Settings", cells F18 changed to "1.7"

8.6 *EAG Survival Extrapolations*

[redacted]

Figure 36: OS for FELIX ITT (cohort IA and IIA) whole population

Figure 37: EFS for FELIX ITT (cohort IA and IIA) whole population

Figure 38: OS for FELIX ITT (cohort IA and IIA) Ph+ population

Figure 39: EFS for FELIX ITT (cohort IA and IIA) Ph+ population

Figure 40: OS for FELIX ITT (cohort IA and IIA) Ph- population

Figure 41: EFS for FELIX ITT (cohort IA and IIA) Ph- population

Title: *Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID6347]: Addendum to the EAG Report*

Produced by	*Birmingham Centre for Evidence and Implementation Science*
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Date	*08/05/2025*

In this addendum to the EAG report, the EAG provides an updated version of Table 21. Previously, this table contained estimates of various extrapolations at 3 years, but were based on the raw extrapolation, before adjustments were made (i.e. limiting PFS so that it could not exceed OS).

The EAG now presents an updated table where these estimates correspond to the values use in the economic model for the company and EAG base cases, with relevant adjustments applied. The EAG considers that this version of the table will better assist committee with their decision-making. Note that the differences in models (and predictions of survival at 3 years) are largely attributable to the choice of population (leukapheresed vs infused), rather than outright disagreement of the efficacy of obe-cel among people infused with product, though this remains highly uncertain. EAG-preferred 3 year estimates for obe-cel are in the region of 10-20% lower than the company's, reflecting the different starting size of the leukapheresed and infused populations.

Table 1: EAG's and company's preferred survival plots

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

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 4 February 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Generalisability of the FELIX trial for decision making

Description of problem	Description of proposed amendment	Justification for amendment	
The External Assessment group (EAG) expressed concerns regarding the generalisability of the FELIX trial to the relevant UK population and perceived limitations with FELIX study design. As detailed in the rows below, there are several instances in which the EAG base these concerns on an incorrect understanding of the FELIX population which the Company wishes to clarify.			
Page 11 states: "This single-arm trial has a small sample size and limited follow-up."	This text should be amended to: "Characteristically for later-line trials in aggressive oncology indications, FELIX is a single-arm trial. While the small sample size and relatively short follow-up (median: 20.3 months) pose limitations, this is typical data maturity of oncology trials at the point of submission to NICE."	It is misleading to not acknowledge that the single-arm trials are common for late-stage oncology. Additionally, the data maturity of FELIX is typical for oncology submissions to NICE: a systematic review of oncology NICE single technology appraisals published between 2018 and 2022 found 57% of relied on immature data, typically defined as fewer than 50% of events having occurred. The follow-up of FELIX is therefore typical of oncology appraisals submitted to NICE.(1)	Not a factual error.

Page 21 states: "The CS did not state the expected marketing authorisation"	This text should be removed.	The Company stated that the marketing authorisation is anticipated to be in patients aged [redacted] (Company submission [CS] page 1, page 9; Table 1, page 72).	The EAG has amended the text to clarify it meant about when the anticipated marketing authorisation is expected.
Page 25 states: "Only adult patients aged [redacted] with R/R B-cell ALL are included in the FELIX trial" Page 27; Table 3 states: "Adults ([redacted]) with R/R B-cell ALL."	This text should be amended to: Page 25: "Adults patients aged 18 and older with R/R B-cell ALL are included in the FELIX trial" Page 27; Table 3: "Adults (18 years and older) with R/R B-cell ALL"	Patients 18 and older were included in the FELIX clinical trial.	The EAG has amended the flagged text to better reflect the population of FELIX.
Page 44 states: "In the FELIX cohort IIA, both sexes were equally distributed (47/94; 50%), despite the UK ALL incidences are higher in makes than females."	This text should be amended to: "In FELIX cohort IIA, both sexes were equally distributed (47/49; 50%), broadly in line with the UK ALL incidence."	A statement from Cancer Research UK shows that incidence of acute lymphoblastic leukaemia (ALL) in the UK is 41% female and 59% male.(2) The equal split between females and males in FELIX is therefore broadly in line with that observed in the UK.	Not a factual error.

Page 44 states: "While 20% of incidences are in those aged 75 and over, their mortality is highest, the FELIX trial has 1.6 times fewer patients aged 65 and over compared to Cancer Research UK. Therefore, the generalisability of FELIX to the UK population is of concern"	This text should be amended to: "While 20% of incidences are in those aged 75 and over, their mortality is highest. Cancer Research UK data shows that 13.3% of new ALL cases are in patients aged 65 and older, whereas FELIX Cohort IIA mITT included 22.3% of patients aged 65 years and older.(2) The proportion of patients aged 65 and over in FELIX is 1.7 higher compared to Cancer Research UK. The efficacy observed in FELIX is therefore likely a conservative estimate of the true efficacy of obe-cel in UK practice."	The statement is factually incorrect. As per Cancer Research UK data, the proportion of FELIX patients aged 65 years and older is 1.7 times higher than the UK population (22.3% versus 13.3%). Therefore, the slight difference observed indicates that if anything, FELIX data would underestimate the true obe-cel efficacy likely to be observed in UK practice.	The EAG has amended the text to clarify the point being made.
Page 45 states: "Although the company claims in CS document B, section B.2.3.3, that FELIX patients were heavily pre-treated, the data shows that 69.2% (65 out of 94) had only one or two prior lines of therapy"	This text should be amended to: "FELIX patients were heavily pre-treated: [redacted]% (65 out of 94) had two or more prior lines of therapy"	The text is misleading and does not acknowledge that only [redacted] of FELIX patients had one prior line of therapy. Additionally, typographical error corrected in the proposed amendment.	The EAG has amended this text to clarify the information being communicated.
Page 46 states:	This text should be removed or the EAG should add justification to the text	The EAG does not justify this statement by offering any comparison to the	The EAG has amended this text to clarify the uncertainty around the

“The EAG concludes that the characteristics of the Ph+ subgroup might not be generalisable to real-world patients”		characteristics of UK ALL patients in the Philadelphia chromosome (Ph)+ subgroup. If the EAG cannot justify this statement, this should be removed.	differences in the baseline characteristics in the Ph subgroups.
Page 60 states: “The FELIX trial population, while well-defined and homogenous, may not fully reflect real-world settings due to the exclusion of patients with ECOG PS ≥2 and a focus on less heavily pretreated individuals”	This text should be amended to: “The FELIX trial population was well-defined and homogenous, and included heavily pretreated individuals”	Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 is a common eligibility criteria for Chimeric Antigen Receptor T-cell (CAR T) therapy and is aligned with other CAR-T trials, e.g., ZUMA-3(3). Furthermore, analysis of UK National Health System (NHS) patients treated with brexu-cel via the Cancer drug fund (CDF) indicated 44% of patients had an ECOG score of 0, and 56% of patients had a score of 1. These scores show the strong prevalence of patients eligible for CAR-T with an ECOG score of 0 or 1.(4) It is incorrect to state that FELIX focused on less	The EAG has removed part of the sentence referring to the focus on less heavily pre-treated individuals.

		heavily pretreated individuals than comparator studies, as FELIX had fewer patients with one prior line of therapy versus each comparator study in the relevant patient population, as presented in the Company clarification questions response, in response to question A29: For the modified intention to treat (mITT) population, substantially fewer patients with one prior line of therapy in FELIX compared to INO-VATE ([redacted]% vs 67.7%, respectively). In the Ph- subgroup, fewer patients with one prior line of therapy in FELIX compared to TOWER ([redacted]% vs 42.1%, respectively) In the Ph+ subgroup, fewer patients with one prior line of therapy in FELIX compared to PACE ([redacted]% vs 19%, respectively)	

		Furthermore, in the aforementioned analysis of patients treated with brexu-cel via the CDF, 31% of infused patients received three or more prior lines of therapy, the same as the proportion observed in FELIX (31%) indicating that FELIX is likely to reflect UK practice.(4) Since FELIX did not enrol patients with fewer prior treatments than in the comparator studies, obe-cel outcomes were not favoured based on prior treatments.	
Page 59-60 states: "• PACE patients were heavily pre-treated, with 81% having received ≥2 TKIs. • TOWER, with 42.1% of patients treated in 1st-line and 50.2% in ≥2nd-line settings, represents a slightly less pre-treated cohort than FELIX.	This text should be amended to: " • In the Ph+ subgroup, there were fewer patients with one prior line of therapy in FELIX compared to PACE (12% vs 19%, respectively)" • In the Ph- subgroup, there were fewer patients with one prior line of therapy in FELIX compared to TOWER (37.7% vs 42.1%, respectively) • The comparison indicates that FELIX data are comparable to	As per the above row, these statements do not take into account that in each relevant population, the FELIX population was more heavily pre-treated than the comparator studies. This is particularly true for the comparison with INO-VATE. In the INO-VATE trial, 67.7% of patients only had one prior	The EAG has amended this text to better communicate the EAG's point. Note that the EAG is comparing the trials generally, and not the subgroups, meaning the values suggested by the company are not required and there was no factual error.

• This disparity favours the outcomes of obe-cel in the FELIX trial, as patients with fewer prior treatments generally have a better prognosis.”	comparator studies and in some instances has a more heavily pretreated population than the comparators. This disparity biases outcomes against FELIX, as patients with fewer prior treatments generally have a better prognosis”	line of therapy, and 99% one or two prior lines. In FELIX Cohort IIA mITT, 69.1% of patients had received one or two prior lines of therapy. A total of 18.1% of FELIX Cohort IIA mITT patients had received three prior lines of therapy, and 12.8% four or more.	

Issue 2 Reliance on biased and highly uncertain MAIC and preferred population and method for extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	
The EAG prefers to use all enrolled patients from the FELIX trial (ITT) regardless of whether they were infused with obe-cel for the indirect treatment comparison (ITC) (matching-adjusted indirect comparison, MAIC) and cost-effectiveness analyses. Additionally, the EAG express a number of methodological concerns with the analyses. As detailed in the rows below, there are a number of misconceptions behind the EAG's concerns as well as issues with their proposed alternative approaches.			
The EAG expressed a preference for using the ITT population (cohort IA and IIA) in the ITC and cost-effectiveness model (CEM). Page 11 states: "The EAG is concerned by the comparison of the post-infusion period of FELIX which ignores the outcomes of people who were enrolled but not infused, to follow-up from other trials that do not have a pre-infusion period."	This statement should be removed.	The efficacy estimates presented throughout the CS are based on the infused mITT population as this reflects the efficacy of obe-cel in patients who actually received obe-cel. Whilst patients would incur certain costs regardless of whether they are ultimately infused (e.g., pre-infusion regimens), obe-cel would only be reimbursed by the NHS for patients who receive at least one dose. The economic model includes pre-infusion costs for all enrolled patients,	Not a factual error.

		regardless if they subsequently were infused with obe-cel. Therefore, it is misleading to state that the comparison ignores the outcomes of those who were enrolled but not infused. This approach for the ITC and economic model analyses is in line with the data accepted for decision making in NICE Technology assessment (TA) 893 (Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over).(5)	
Pages 58-59; Table 12 details the baseline characteristics for obe-cel and comparators. A considerable number of values reported in the table are incorrect.	The table should be revised to report the correct values per the FELIX clinical study report (CSR)(6) and comparator study publications(7–9). Appendix 1, Table 1 in this document reports the correct values next to the values reported in the EAG report. Please note that some of these erroneous values are referred to later in the EAG report; all instances where	Reporting errors.	The EAG acknowledge the discrepancy in values between the CSR and CS, and also of the values in Table 12. The EAG has amended the values in Table 12, but notes that on cross-checking, some values provided

	an incorrect value is reported should be updated to refer to the correct value. See the rows below for further detail.		by the company were not correct.
Page 60 states: "While FELIX's high proportion of prior SCT patients shows its focus in assessing outcomes in heavily pre-treated individuals, differences in SCT history impact comparability, as patients with prior SCT generally have a worse prognosis, which could influence outcomes in comparator trials"	This text should be amended to: "While FELIX's high proportion of prior SCT patients shows its focus in assessing outcomes in heavily pre-treated individuals, differences in SCT history impact comparability, as patients with prior SCT generally have a worse prognosis, which may favour outcomes in comparator trials"	The higher proportion of patients with prior stem cell transplantation (SCT) in FELIX favours outcomes for the comparators over obe-cel. The word 'influence' does not capture this and is thus misleading.	The EAG has removed the ending of this sentence, and made minor amendments to the text related to this point to simplify the comparisons of trials.
Page 60 states: "Similarly, INO-VATE had 85% of patients with ECOG 0–1, while TOWER had 84.8%. PACE also reported a majority (87%) in this category"	This text should be amended to: "Similarly, INO-VATE had 87% of patients with ECOG 0–1, while TOWER had 84.8%. PACE also reported a majority (87%) in this category"	Reporting error. Per the INO-VATE study(7), 87% of patients had ECOG 0-1.	The EAG has amended this in the report.

Page 64 states: "INO-VATE has a significantly lower proportion of Ph+ patients compared to FELIX, suggesting that the INO-VATE population may differ in prognosis and responsiveness to treatment"	This text should be amended to: "INO-VATE has a lower proportion of Ph+ patients compared to FELIX, suggesting that the INO-VATE population may differ in prognosis and responsiveness to treatment"	It is misleading to use the word "significant" here, as it implies statistical significance – no statistical analysis was undertaken on the difference in the proportion of Ph+ patients in INO-VATE and FELIX.	The EAG has reworded this statement.
Page 65 states: "This method was used to compare obe-cel to ponatinib"	This text should be amended to: "Both MAIC and naïve comparison were used to compare obe-cel to ponatinib. The naïve comparison is used in the CEM base case"	This statement is misleading as it does not reflect that both naïve and adjusted analyses were provided for the comparison between obe-cel and ponatinib; it reads as if only naïve comparison was undertaken.	Not a factual error. The text in the previous "MAIC" section acknowledges a MAIC was performed for the comparison to ponatinib.
Page 68 states: "The study duration of FELIX is longer than INO-VATE and TOWER, but shorter than PACE. However, median follow-up of PACE is the shortest at 5.4 months, and that of INO-VATE was the longest at 29.6 months. The median follow-up between FELIX and TOWER were	This text should be amended to: "The study duration of FELIX is longer than INO-VATE and TOWER, but shorter than PACE. However, median follow-up of PACE is the shortest at 5.4 months, and that of INO-VATE was the longest at 29.6 months. The median follow up in FELIX was 20.3 months. Longer follow-up, such as in FELIX and INO-VATE, may allow for a more comprehensive assessment of	Correction of reporting error and conclusions drawn from incorrect value. The median follow-up of FELIX is 20.3 months, which is not similar to TOWER.	The EAG has amended the text to correctly reflect the duration of follow-up of FELIX.

similar (11.8 months and 11.7 months, respectively). Longer follow-up, such as in INO-VATE, may allow for a more comprehensive assessment of long-term outcomes, potentially introducing bias if not properly adjusted for. In contrast, the shorter follow-up in PACE increases the uncertainty of the results, particularly when comparing with FELIX, which may lead to imbalances in observed survival outcomes or treatment effects due to the varying durations of data collection."	long-term outcomes, potentially introducing bias if not properly adjusted for. In contrast, the shorter follow-up in PACE increases the uncertainty of the results, particularly when comparing with FELIX, which may lead to imbalances in observed survival outcomes or treatment effects due to the varying durations of data collection."		
The EAG expresses a number of concerns with the systematic literature review (SLR). These concerns were not raised at the clarification stage, meaning the Company did not have an opportunity to mitigate them. Page 34 states:	The text on page 34 should be amended to: "The company tested whether their search retrieved all included studies for TA893 to the extent possible based on available information." "The full search strategies for TA893 are not publicly available"	The Company did report the method of testing whether the search retrieved all studies included in TA893 (CS Appendix D, page 50: "Additionally, to the extent it was possible to establish which studies TA893 extracted, they were checked against the search strategy presented in Section D.2	The EAG has amended the text on page 34 and 74 as suggested. The EAG has also revised the text on page 76 for clarity, however does not consider this a factual error.

“The company do not report whether they tested whether their search retrieved all included studies for TA893” “The company reports that the full search strategies for TA893 are not publicly available (CS Appendix D.3)” Page 37 states: “The review aimed to update the NICE STA for brexu-cel but faced inconsistencies and ambiguities in criteria application, particularly regarding age and disease definitions. Exclusions of prior CAR T-cell therapy and allo-SCT patients, despite their inclusion in related trials, limited the review's comprehensiveness. The company inconsistently reported and justified the inclusion and exclusion of studies, such as brexu-cel and ponatinib, indicating potential bias and deviations	This text on page 37, page 74 and page 76, Table 18 should be removed.	(applying the search dates from TA893), to ensure that all relevant papers would have been captured by our searches”). Furthermore, since the full search strategies are not publicly available, it is misleading to present this as a claim from the Company when it is an objective fact. The Embase interface used for the searches comprises Embase, Medline and PubMed. Given the lack of detail in the EAG report, the factual accuracy of the statements on pages 37 and 74 cannot be assessed properly. As the Company were not informed of EAG’s concerns at clarification questions, the Company was not given an opportunity to mitigate any concerns the EAG had regarding the SLR.	The EAG has amended the text on page 37 to make clear that it is based on the ROBIS risk of bias conclusion, where the points are discussed in suitable detail.

from pre-defined objectives and criteria." Page 74 states: "The search methods sections for the cost-effectiveness, HRQoL and costs and resource use SLRs, list Medline and Embase as the sources searched but the headings for each search strategy also list PubMed (CS Appendix G.4. Table 16, H.13 Table 21, I.2 Table 25)." Page 76; Table 18 states: "ITC suggests efficacy benefits for obe-cel, but significant methodological flaws, transparency issues, and confounding risks undermine confidence in the ITC conclusions."		As the ITC ultimately utilised findings from the TA893 SLR, the statement on page 76 is misleading.(5)	
Page 69 states: "Overall, the information provided by the company in the CS pre-clarification was minimal and unsatisfactory"	This text should be amended to: "Overall, the information provided by the company in the CS pre-clarification was unsatisfactory,	The current text is misleading as it omits that the Company provided all requested information at the clarification stage.	Not a factual error. The fact that this information was provided at clarification stage to the EAG meant the EAG had considerably less

	however this was corrected at the clarification stage”		time to critique the company’s methods.
Page 70 states: “Compared to the other treatments, the unadjusted hazard ratios were significantly in favour of obe-cel while the adjusted HRs for the comparison to blinatumomab and ponatinib were statistically significantly in favour of obe-cel”	This text should be amended to: “Compared to all other treatments, the unadjusted hazard ratios were significantly in favour of obe-cel, while the adjusted HRs for the comparison to blinatumomab and ponatinib were statistically significantly in favour of obe-cel”	The current text is misleading as it does not explicitly state that obe-cel is favourable to all comparator treatments in the unadjusted analyses.	Not a factual error.

Issue 3 Hospitalisation and resource use for obe-cel

Description of problem	Description of proposed amendment	Justification for amendment	
The EAG disagrees with the Company's utilisation of UK-specific data from the FELIX trial to estimate hospitalization durations, noting that the durations are longer in the overall FELIX population. Page 99, paragraph two states: "The company's revised estimates underestimate hospitalization durations, leading to an understated resource use for obe-cel." Page 99, paragraph four states: "A more reasonable approach would be to use the summary tariff costs for CAR T infusion and monitoring and in line with the TA893, which better reflects the actual costs". Page 100 states:	The text on page 99, paragraph two should be amended to: "The company's revised estimates reflect the hospitalization durations for UK patients, reflecting resource use for obe-cel patients in UK practice." The text on page 99, paragraph four should be amended to: "The summary tariff costs for CAR T infusion and monitoring are likely to overestimate the actual resource use associated with obe-cel UK usage". The text on page 100 should be amended to: "EAG assumes that hospitalization durations should reflect the complete FELIX trial dataset in Cohort IIA. This includes a mean non-ICU hospital stay of [redacted] days (SD: [redacted]), a mean ICU stay of [redacted] days (SD: [redacted]), and [redacted]% of	[redacted] ([redacted]%) of the patients in FELIX are from the US, and [redacted]% are from Spain. Resource use estimates based on the [redacted] ([redacted]%) patients from the UK are more representative of UK clinical practise than estimates inclusive of patients from other countries. The EAG suggest that UK real-world evidence relating to resource use would strengthen their trust in the estimates, acknowledging the value of using UK patient data. The TA893 CAR T tariff cost was suitable to cost brexu-cel	Page 99 paragraph 2 – The EAG has amended this text to clarify that this is the opinion of the EAG. Page 99 paragraph 4 – The EAG has amended this text to clarify that this is the opinion of the EAG. Related to these points, the EAG raised further concerns as to how costs were incorporated into the model, leading to an unrealistically low estimated cost of £3,201 for obe-cel infusion and monitoring. The method used to integrate mean daily hospital costs appears flawed, and it is unclear whether the company acknowledges this issue.

“EAG assumes that hospitalization durations should reflect the complete FELIX trial dataset in Cohort IIA. This includes a mean non-ICU hospital stay of [redacted] days (SD: [redacted]), a mean ICU stay of [redacted] days (SD: [redacted]), and [redacted]% of patients requiring ICU care.”	patients requiring ICU care. These durations are longer than those observed for the FELIX UK cohort.”	hospitalisations; however it would be inappropriate to apply the tariff to obe-cel as the cost calculates adverse event-related intensive care unit (ICU) stays based on previous CAR T therapies.(5) As discussed in CS Section B.1.3.5, page 28, currently available CAR T treatments are associated with considerable rates of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). For example, brexu-cel is associated with very high levels of CRS (89%) and neurological events associated with ICANS (60%)(3,10), with grade 3 or 4 CRS	

		occurring in 24% of patients and grade 3 or higher neurological events occurring in 25% of patients.(3,11). By contrast, obe-cel has demonstrated substantially lower rates of grade ≥3 CRS (2.4%) and ≥3 ICANS (7.1%), which is the level that generally requires ICU admission. The tariff is therefore not reflective of obe-cel's safety profile. It would be misrepresentative to apply this cost to obe-cel. The Company maintain that basing resource use on the subset of UK patients from the FELIX trial is the most appropriate approach.	

Page 54 states: "The study protocol (page 17) shows that HRQoL was not assessed during most hospitalization periods particularly between days 1 and 10, and day 28, potentially missing valuable data."	This text should be removed.	The EAG points out on page 54 that the median length of hospital stay for obe-cel patients is [redacted] days. This means that the assessment at day 28 would have captured health-related quality of life (HRQoL) during a hospital stay for the majority of patients, i.e., mitigating the EAG's concern that 'valuable data' was missed.	The EAG has amended the text to clarify the key point being made.
There are issues with the EAGs implementation into the cost-effectiveness model. The implementation double-counts ICU costs. Page 100 states: "For both scenarios, the related formula is amended as follows: (I133*K106)+(I143*I138*K118)"	If the EAG wishes to explore the application of the tariff cost, the formula should be amended to: (((1-I143)*I133*K106)+(I143*I138*K118))	The update to the formula that the EAG proposed was incorrect. I143 is the proportion who stayed in ICU. Therefore, it would be incorrect to count the hospitalization costs for these patients, as the ICU costs are already included in the	The EAG acknowledges the company's proposed amendments. In response, the two EAG scenario analyses (scenarios 2 and 3) concerning the "bottom-up costing approach for CAR T-cell infusion cost calculations" have been revised.

		overall hospitalisation incidence. Therefore, hospitalization costs only need to be applied to 1-I143 (i.e. those in hospital but not ICU).	
The cost of leukapheresis is double counted in the EAG's base case.	The cost of leukapheresis (sheet 'Treatment Costs', cell 'H156') should be set to zero in the model.	In the EAG model, the cost of leukapheresis is considered in addition to the tariff cost. The tariff includes the costs of leukapheresis, therefore the EAG's approach double counts this cost. The EAG base case should have the cost of leukapheresis set to zero, and the results presented throughout section 6 of the EAG report should be amended to reflect this. After this change is applied, the company estimate that the EAG base	This is not a factual error, as per below: - As outlined in Table 66, the formula used by the EAG in Cell H156 (Worksheet 'Treatment Costs') is: IF(i_infusion_cost_approach=1, p_i_c_TxLeukapheresis * p_i_c_CorFactLeukapheresis_int, p_i_c_TxLeukapheresis * (1 - p_i_c_CorFactLeukapheresis_int)) - According to the company's original model, all ITT patients underwent leukapheresis, as reflected in the correction factor of [redacted] (derived from ITT population: 113 / modified ITT (mITT) population: [redacted]). - The CAR T-cell therapy tariff covers the cost of leukapheresis

		case incremental cost-effectiveness ratio (ICER) versus inotuzumab in the overall population should be £[redacted].	for infused patients. However, a correction factor is still required for ITT patients who did not receive obe-cel (ITT – mITT). - The formula component (1 - p_i_c_CorFactLeukapheresis_int) accounts for this adjustment, ensuring that the leukapheresis cost for the [redacted] of ITT patients in cohorts IA and IIA who did not receive obe-cel is appropriately considered. Thus, the EAG maintains that the current approach is methodologically sound and does not result in double counting.
Page 98 states: "Administration costs for obe-cel (with using bottom-up costing) include a 24-day hospital stay, of which 4 days are spent in the ICU for 54% of patients"	This text should be amended to: "Administration costs for obe-cel (with using bottom-up costing) include a 24-day hospital stay, of which 4 days are spent in the ICU for 54% of patients, aligning with TA893"	Administration costs for obe-cel are aligned to brexu-cel in TA893 including length of stay in hospital and ICU; the current text does not acknowledge this.(5)	While the EAG does not consider this text to be a FAC, the EAG has incorporated the company's preference: "The company stated that administration costs for obe-cel (using bottom-up costing) include a 24-day hospital stay, with 54% of patients spending 4 of those days in the ICU, aligning with TA893."

Page 98 states: “Monitoring costs, including outpatient visits, blood tests, and imaging, total £320 per cycle”	This text should be amended to: “Monitoring costs, including outpatient visits, blood tests, and imaging, total £321 per cycle”	The exact monitoring cost for ponatinib is £320.67.	This text has been amended to: “Monitoring costs, including outpatient visits, blood tests, and imaging, total £321 per cycle”

Issue 4 Costs and effects of allo-SCT

Description of problem	Description of proposed amendment	Justification for amendment	
Page 14 states: "The company base case analyses use data from FELIX that is not censored for receiving subsequent allo-SCT (i.e. includes the effect), but do not capture the costs associated with this allo-SCT use." Page 106 states: "As of the February 2024 data cut-off, [redacted] patients in cohort IA and IIA had received infusions, among whom [redacted] patients ([redacted]) underwent allo-SCT, as stated by the company in response to clarification questions and Clinical Study Report (CSR). Based on Roddie et al. (2024),66% of these SCT procedures were first allo-SCT, equating to approximately [redacted] of the	This text should be amended to: Page 14: "The company base case analyses use data from FELIX that is not censored for receiving subsequent allo-SCT (i.e. includes the effect), but analyses that censor for allo-SCT have been provided in the CS, showing comparable results between the analyses. The base case economic analysis does not consider allo-SCT following obe-cel." Page 106: The Company request that the EAG present the results of the post-hoc analysis conducted to compare outcomes in Cohort IIA in FELIX with and without censoring for consolidative allo-SCT, as presented in	The omission of the post-hoc analysis results from the EAG report, despite these being provided in the CS (Section B.2.7.1.2 [page 73-74; Table 19]), gives the impression that no evidence has been submitted to demonstrate the standalone curative potential of obe-cel and justify the Company's approach to not include allogeneic (allo)-SCT costs for obe-cel patients. This is misleading, as the text suggests that the Company made an arbitrary assumption to exclude allo-SCT costs for the obe-cel arm in the economic analysis, rather than basing this on clinical evidence. The results of this post-hoc analysis indicated that outcomes are comparable with and without censoring for	Page 14: Not a factual error. This text is clearly referring to the company base case. The justification for the company's exclusion of allo-SCT costs for obe-cel was not considered strong. Note, the EAG clinical experts could not rule out the possibility of a subsequent allo-SCT after obe-cel for a small number of patients, and this reflects what occurred in FELIX. Page 106: The EAG do not consider the company's suggestion appropriate as page 106 is a summary of a one of the EAG concerns relating to the economic modelling, whist the company refer to a section of their clinical results which focuses on people with CR/CRi. Given that

[redacted] patients ([redacted] × 66% = [redacted]).”	Section B.2.7.1.2 of the CS (page 73-74; Table 19).	subsequent SCT. Therefore, this analysis provides important evidence on the potential curative treatment effect of obe-cel and supports the Company’s base case analysis.	the company and EAG agree on the preferred source of OS data, the EAG did not consider this issue worth dwelling on.
Page 82 states: “Hence, the EAG assumes that all treatments under evaluation aim to achieve a cure for patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL), whilst the standalone ability of obe-cel to cure patients remains unknown.”	The Company request that the EAG remove the following text: “…whilst the standalone ability of obe-cel to cure patients remains unknown.” Additionally, the Company that the EAG present or acknowledge the results of the post-hoc analysis conducted to compare outcomes in Cohort IIA in FELIX with and without censoring for consolidative allo-SCT, as presented in Section B.2.7.1.2 of the CS (page 73-74; Table 19).	The omission of the post-hoc analysis results from the EAG report, despite these being provided in the CS, along with the phrasing of the sentence, give the impression that no evidence was submitted to demonstrate the standalone curative potential of obe-cel and is therefore misleading. Furthermore, as stated above the results of the post-hoc analysis indicated that the outcomes are comparable with and without censoring for subsequent SCT. Omitting this analysis ignores important evidence on the potential curative treatment effect of obe-cel.	Not a factual error.

Page 95 states: “The company has excluded the specific utility effects of allo-SCT from the economic model for all comparators.”	The text should be amended to: “The company has excluded the specific utility effects of allo-SCT from the economic model for all comparators in the base case. A scenario analysis explored the impact of using health state utility values from TA450 and applying post-SCT disutility values to patients post-SCT, as outlined in TA450.”	The Company outlined two scenarios for exploring alternative utility values in Section B.3.4.7 (page 138) and in Table 81 of the CS (page 197; Section B.3.10.3), one of which considered health state utilities and post-SCT disutilities from TA450 (Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia).(12) Results for this scenario were reported for all three populations in Tables 82-84 (page 198-201) of the CS.	The EAG does not consider this a factual error, however the EAG has amended this comment so that it refers to company base case, and acknowledges the scenario analysis. As stated in the EAG report, it is essential to capture all utility effects of SCT in the model, not just the associated disutilities. In the company’s model, patients who undergo SCT transition to the post-event health state, meaning that a considerable proportion of patients in complete remission who receive SCT are assigned a specific utility value for this health state. However, the EAG does not believe that this utility value fully captures the effects of SCT, particularly for comparators where a high proportion of patients undergo transplantation. To address this, the EAG applied an alternative approach, drawing from previous STA, to adjust the company’s utility estimates for patients who receive SCT, ensuring a more comprehensive

			representation of post-SCT health outcomes.
The EAG disagrees with the Company's approach to use a uniform utility value to all patients in the post-event health state and suggest using utility values from TA541 to include distinct post-SCT conditions in the economic analysis. Page 96 states: "Adjusting utility values in the post-event health state using time-dependent utilities from TA541 to capture variations in post-HSCT HRQoL and account for the proportion of patients receiving allo-SCT across different treatments."	The Company requests that the EAG acknowledge that using values from TA541 (Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia) overestimate the post allo-SCT utilities as TA541 included a 0.3 utility for patients who progress following allo-SCT.(13)	The approach proposed by the EAG ignores that the TA541 economic model had a separate progressed-disease health state with a much lower health state utility value (0.30) than the progression-free time-varying utilities.(13) This progressed-disease utility was applied to all patients who progressed, including those progressing post allo-SCT. By not accounting for the utility of disease progression following allo-SCT, the EAG's approach may over-estimate long-term HRQoL post allo-SCT, disproportionally favouring comparator arms with a higher proportion of patients undergoing allo-SCT.	The EAG does not consider this a factual error, and believes that the company's rationale actually supports the EAG's approach for the following reason: **- Utility value discrepancies**: The company mentions that TA541 uses a much lower health state utility value (0.30) for patients with disease progression, compared to the utility range values of 0.56-0.76 for post-HSCT patients. If the company concurs with this, it highlights that using a uniform utility value for all patients in the post-event health state is not appropriate, as it does not account for the variability in post-SCT conditions. The EAG notes that, as shown in Tables 51, 52, and 53 of the EAG report, the amendments to the company's utility values did not lead to substantial changes in utility estimates, resulting in only a

			small effect on the incremental cost-effectiveness ratio (ICER).
Pages 96-97 Obe-cel column in Table 25	The Company requests that the EAG clarify their proposed approach regarding the inclusion of the proportion of patients who underwent subsequent allo-SCT in the FELIX trial.	The proportion of patients who receive allo-SCT is set to 0% in Table 25, however, in Section 4.2.8.5 of the EAG report (page 105) the EAG propose to set this proportion to [redacted] based on the ITT population of the FELIX trial. Since the table otherwise reflects the EAG base case, this should be clarified.	It appears that the company has misunderstood the purpose of Table 25. This table was intended to illustrate the EAG's approach to incorporating the proposed amendment into the model. The use of 0% in this table reflects a specific focus on addressing the current approach of utility values. It is not representative of the final value for the proportion of patients undergoing allo-SCT, as this is discussed in a later section. In the updated model, the updated SCT rate for obe-cel and subsequent utility adjustments for obe-cel and the comparators has been applied.
Page 79 states: "the company asserts that the effect of allo-SCT on survival is captured within Kaplan-Meier curves that do not censor patients receiving SCT. However, the exclusion of explicit	The Company request that the EAG clarify their position on whether they consider that the survival curves used for obe-cel in the economic analysis capture the effect of allo-SCT.	Given that obe-cel survival data and utility data in the economic model are both taken from FELIX, it is inconsistent for the EAG to state that obe-cel survival modelling does account for the impact of allo-SCT, but the	The EAG does not consider this a factual error. For obe-cel survival the EAG maintains its preference for the use of survival data that has not been censored for allo-SCT. However, it is possible that quality of life associated with allo-SCT is

utility modelling for SCT creates a critical gap." Page 106 states: "Including the survival benefits of allo-SCT without accounting for associated costs introduces a bias in obe-cel."		utility values do not. This presents an inconsistency in how the EAG interprets whether the potential benefits of allo-SCT are captured. The Company request that the EAG acknowledge or address this inconsistency.	not accurately captured in the FELIX data due to the pattern of collection. However, the EAG's primary concern is that the company should adopt a consistent methodology for incorporating both utility and cost associated with allo-SCT, similar to the approach applied to the costs of SCT. The EAG identifies an inconsistency in how the company has integrated the costs and utility of SCT into the model. While the company provides specific cost data for SCT and applies it based on the proportion of patients receiving SCT across different treatment arms, the company uses a uniform utility value to all patients in the post-event health state, without accounting for the varying proportions of patients receiving SCT across arms. The EAG believes this approach is not appropriate given the substantial differences in the proportion of patients receiving SCT between treatments. To address this issue, the EAG has proposed a more

			accurate methodology to account for these variations and ensure a fair representation of the impact of SCT on utility.

Issue 5 Most suitable severity modifier to apply

Description of problem	Description of proposed amendment	Justification for amendment	
Pages 108-109 state: "Only for Ph- patients, blinatumomab serves as the comparator, leading to a 1.7 severity modifier based on a proportional shortfall of [redacted] In contrast, when compared to inotuzumab and ponatinib, the proportional shortfalls are lower ([redacted] respectively), which corresponds to a 1.2 severity modifier. These inconsistencies suggest that the use of a 1.7 severity modifier may overestimate the severity adjustment for the entire population."	The text should be amended to: "Only for Ph- patients, blinatumomab serves as the comparator, leading to a 1.7 severity modifier based on a proportional shortfall of [redacted] In contrast, when compared to inotuzumab and ponatinib, the proportional shortfalls are lower ([redacted] respectively), which corresponds to a 1.2 severity modifier. As inotuzumab data are only available for the overall population, conclusions for the appropriate severity modifiers for the Ph- and Ph+ subgroups are best made using data for blinatumomab and ponatinib, respectively."	As described in the CS, Section B.3.3.2.3; page 123 and Section B.3.3.2.4; page 127, efficacy data for inotuzumab were only available for the mITT population. The EAG's current wording does not reflect that conclusions for the subgroups based on this data may not reflect the true severity and unmet need for patients in each subgroup.	Not a factual error. The EAG maintains that the EAG's methodological approach remains valid: 1- In its submission, the company applied a severity modifier of 1.7 (based on blinatumomab) across all populations. However, the company appears to acknowledge that blinatumomab QALYs cannot be utilized for the overall and Ph+ populations due to the absence of blinatumomab in these groups. 2- The reported shortfall of 96.19% is derived from the company's base-case QALYs for

			blinatumomab. However, if the EAG's base-case QALYs for blinatumomab are applied, the severity modifier would be 1.2. 3- Assuming that at least 6% of the Ph- population receives inotuzumab (and 94% blinatumomab), the severity modifier remains at 1.2 even when using the company's base-case QALYs for blinatumomab. These considerations indicate that a severity modifier of 1.2 is the most appropriate option for all populations.

Issue 6 Survival modelling

Description of problem	Description of proposed amendment	Justification for amendment	
Page 90 states: "These models were chosen based on statistical fit, visual it, and plausibility of survival extrapolations up to and at the company's base case cure timepoint of three years."	The Company request the EAG provide further clarification on the rationale behind their preferred curve selection, including results of the visual fit to Kaplan-Meier (KM) data and assessment of clinical plausibility. Additionally, the Company request the EAG provide coefficients for all extrapolations for all populations.	As the EAG only provided the coefficients for their selected curves and the Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit statistics for the Ph- and Ph+ subgroups in the updated economic model, the Company was unable to accurately assess whether there are any errors in the EAG's methods. Based on the updated AIC/BIC tables, it appears that the event free-survival (EFS) and OS curve choices for the Ph- population and the OS curve choice for the Ph+ population were not the best-fitting models, raising questions around the rationale of choosing these curves.	Not a factual inaccuracy. The EAG has rightfully not relied solely on goodness-of-fit statistics to selected its preferred curves, in line with NICE TSD 14. In terms of model LYs and QALYs, these are most heavily informed by the survival rate at 3 years, due to the assumption of cure beyond this. Hence, the EAG considers the most relevant piece of information for selecting a model is the survival estimate at 3 years. Ultimately the long term efficacy remains highly uncertain, and the EAG has selected models which are similar to the

		Additionally, the lack of updated KM data digitized by the EAG in the EAG model limited the Company's ability to assess how well the models fit the source data overall.	company's preferred models, but accounting for the switch from mITT to ITT data, where the 3 year survival rates are expected to be ~20% lower due to the proportion of people not receiving obe-cel infusion. However, the EAG has appended figures to its report showing the fit of candidate models to obe-cel EFS and OS for each ITT population.
Page 12 states: "The ability to implement MAIC weighted extrapolations for the ITT/enrolled population would allow relaxing the proportional hazards (PH) assumption but will be based on the characteristics of the trial populations of the comparator treatments."	The text should be amended to: "The ability to implement MAIC weighted extrapolations for the ITT/enrolled population would allow relaxing the proportional hazards (PH) assumption but will be based on the characteristics of the trial populations of the comparator treatments. However, this method would not allow to perform accurate incremental analyses in the Ph- and Ph+ subgroups."	It is misleading to not acknowledge the need to present an incremental analysis in the Ph- and Ph+ subgroups. Using the MAIC-adjusted obe-cel curves for the Ph- and Ph+ subgroups would not allow for an accurate incremental analysis in either subgroup since the obe-cel MAIC-weighted extrapolations would be adjusted to match	Not a factual error.

		blinatumomab and ponatinib, respectively, not inotuzumab. This justification was provided in Section B.3.3.1.5 of the CS (page 116).	
Page 84, paragraph 2 states: "Despite stating in the CS that for the three comparators, the company used the same approach to extrapolate their digitised data, the EAG understands that for the company base case analyses for blinatumomab and inotuzumab, the company instead applied inverted hazard ratios from their MAIC to the obe-cel extrapolations." Page 84, paragraph 3 states: "For the comparisons to inotuzumab and blinatumomab, the company	The text should be amended to: "The company used the same approach to extrapolate the digitised data for each comparator for a naïve analysis. However, in the base case of the economic analyses, the Company applied inverted hazard ratios from their MAIC to adjust the obe-cel extrapolations and used these to model comparator time-to-event outcomes for the comparison against blinatumomab and inotuzumab. This method is in line with the Committee's preference in TA893." The text should be amended to: "For the comparisons to inotuzumab and blinatumomab, the company has inverted the hazard ratios and applies them to the extrapolations of obe-cel from FELIX, which is considered to be more representative of the NHS	The Company was not able to find the sentence that the EAG was referring to regarding suggesting that the same extrapolation methods have been used for all comparators. The Company clarified in Section B.3.3.1.5 of the CS the different extrapolation methods used in the economic analysis for the three comparisons. However, the company acknowledge that Section B.3.3.2.1 could have re-stated the base case approach. Additionally, it should also be noted that this approach is consistent with the precedent set in TA893, where the same method was accepted by the	Not a factual error.

has inverted the hazard ratios and applies them to the extrapolations of obe-cel from FELIX, which is considered to be more representative of the NHS population than the other trials."	population than the other trials. This method is in line with the Committee's preference in TA893."	Committee for decision-making. (5)	
Page 84 states: "This approach assumes hazard proportionality, which appears violated based on evidence provided by the company, with instances of hazard curves crossing. While some hazard rates were reasonably proportional during certain trial periods, the differences in follow-up lengths across the studies further complicate the long-term validity of the PH assumption. It also assumes that the relative treatment effect does not change across the populations,	The Company request that the EAG clarify that the same method was used for the EAG's extrapolations and that this method satisfied the requirement for an incremental analysis between multiple comparators.	It is misleading to discredit the inverse hazard ratio approach used by the Company but to fail to mention that the EAG did not present an alternative to this method in their preferred base case. Additionally, using the MAIC-adjusted obe-cel curves for the Ph- and Ph+ subgroups does not allow for an accurate incremental analysis between multiple comparators. This justification was provided in Section B.3.3.1.5 of the CS (page 116).	Not a factual error.

which is not clearly supported.”			
Page 85 states: “However, cure models were not used since the raw EFS and OS data from FELIX were deemed too immature with [redacted] and [redacted] experiencing events, respectively.”	The text should be amended to: “However, cure models were not used since the raw EFS and OS data from FELIX were deemed too immature with [redacted] and [redacted] experiencing events, respectively.”	Typographical error. The Company reported in Table 14 in the CS (page 66; Section B.2.6.1.3) that [redacted] of the infused patients in Cohort IIA of FELIX experienced an EFS event as of the February 2024 data cut-off.	Thank you this has been amended.
Page 89 states: “The company explored the following models in scenario analyses, varying only the choice of extrapolation for obe-cel. No scenario analysis models were explored for inotuzumab, blinatumomab, or ponatinib.”	The text should be amended to: “The company explored the following alternative obe-cel models with the base case ITC approach for each comparison (Scenario 6). Additionally, the company explored using the selected best-fitting inotuzumab and blinatumomab curves in a naïve comparison, and an inverse MAIC approach for the ponatinib comparison (Scenario 7).”	The current text is misleading. The Company explored three scenarios with different combinations of modelling approaches in Table 81 of the CS (page 197; Section B.3.10.3) and reported results for all three populations in Tables 82-84 (page 198-201).	The EAG has amended the text to acknowledge these alternative scenarios.
Page 92, Table 21 (Scenario columns) details the EAG’s preferred survival plots. Key information is missing, rendering it impossible to	The Company request the EAG clarify why there are scenarios missing for the EFS curve choice for obe-cel for	Missing information for EAG scenarios. The CS explored using the inverse hazard ratio or non-	It is unclear what information the company considers missing, and

undertake a proper factual inaccuracy check.	the overall and Ph+ populations in the 'EAG' column. Additionally, the Company request the 'Company' column ponatinib rows are updated to include at least one of the scenarios explored in the CS.	inverse hazard ratio adjusted obe-cel curves as alternative scenarios in the CS; this is not reflected currently.	so the EAG is not able to address this concern. The EAG can confirm that it did not consider any scenario analysis where the cells are empty, due to either alternatives being very similar or implausible. The EAG has added information from the inverse MAIC ponatinib scenario to Table 21.
Page 93, Table 21 EAG base case 3Y surv column, ponatinib Ph+ EFS and OS rows state: Log-logistic: [redacted] Log-normal: [redacted] Additionally, the EAG scenario 3Y surv column, OS row states: 0-knot odds: [redacted]	This value does not reflect the value in the ponatinib trace in the EAG Ph+ model. The values should be updated to: Log-logistic: [redacted] Log-normal: [redacted] 0-knot odds: [redacted]	Typographical error.	Thank you this has been amended.
Page 194, Table 66 (Inappropriate ITC approach	The text should be amended to:	The current text is misleading as it suggests that the	The EAG has amended its base case to use

and narrowed population row) states that the EAG made the following adjustment in the economic model: “Worksheet ‘Lists’, cells B22:E28 , Baseline characteristics for all populations are updated based on ITT populations” However, it is not clarified in the table that only the age and proportion of male characteristics have been updated.	”Worksheet ‘Lists’, cells B22:E28 , age and proportion male/female for all populations are updated based on matched ITT baseline characteristics for all three modelled populations” Additionally, the company request that the EAG update the height and weight baseline characteristics across all three populations to reflect the increased proportion of males in the comparator populations.	baseline characteristics have been updated in line with Table 20 of the EAG report (page 81) detailing the baseline characteristics of the pooled IA and IIA ITT cohort of FELIX. However, cells G23:G25 on the ‘Lists’ worksheet in the EAG model indicate that the baseline characteristics have been updated as per the matched obe-cel characteristics for the ITT population, and as such align with the comparator trial populations. The Company considers this method inappropriate, particularly for the Ph+ subgroup as both the Company and the EAG base case use the unadjusted obe-cel data and use a naïve comparison against ponatinib. It should also be noted that the average patient weight and height inputs, informing the body surface area (BSA) values, have not been	baseline characteristics from the respective population of FELIX. Where possible, estimates were taken for the ITT IA and IIA cohorts (age, sex), or otherwise mITT IIA estimates were used (height, weight)

		updated by the EAG to match the comparator populations, therefore the baseline characteristics in the EAG model currently represent a mix of the FELIX and relevant comparator trials which is not appropriate. Since the adjustments made by the EAG would increase height and weight of patients in each subgroup, which factors into comparator treatment costs, the EAG's current approach underestimates comparator costs.	

Issue 7 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	
Page 53 states: "According to CS appendix F, no studies other than FELIX have reported obe-cel adverse reactions, although the ALLCAR19 study included safety analyses but was not considered for this submission, which EAG finds unfavourable."	This text should be amended to: "According to CS appendix F, no studies other than FELIX have reported obe-cel adverse reactions. However, the phase I ALLCAR19 study evaluated incidence of grade 3-5 toxicity causally related to obe-cel and reported a tolerable safety profile consistent with what was found in the FELIX study."	It is misleading to suggest that the Company is trying to obscure obe-cel safety evidence. If the EAG had requested safety analyses from the ALLCAR19 study as part of the clarification questions, the Company would have reported the toxicity endpoint outcomes. It should be noted that ALLCAR19 demonstrated a tolerable obe-cel safety profile, aligned with the rate and severity of adverse reactions observed in FELIX. None of the 20 ALLCAR19 participants infused with obe-cel experienced ≥ grade 3 CRS, three (15%) experienced grade 3 neurotoxicity which resolved to ≤ grade 1 within 72h with steroids.(14)	The EAG acknowledges the concerns raised by the company. Based on the ALLCAR-19 protocol and the company's suggestion, the EAG has amended the sentence to: "According to CS appendix F, no studies other than FELIX have reported obe-cel adverse reactions. The phase I ALLCAR19 study assessed grade 3-5 toxicity in 20 patients aged 16+ with r/r B-ALL. No patients had grade 3+ CRS, but 3 (15%) had grade 3 neurotoxicity. The EAG notes the small sample size may not fully

			represent obe-cel's safety.”
Page 55 states: “The company reported that neutropenia and neutrophil decrease were defined equivalently according to the clarification response A26. However, they report differing frequencies of these events in the CS, doc B, Table 24 (29 vs. 25 events).	This text should be removed.	The EAGs statement is untrue. In the clarification document A26, rates of neutrophil count decrease are not reported. Neutrophil count decrease is reported in clarification question A27, which is 25 events, and it is line with what was reported in the CS, Table 24.	The EAG does not consider this a factual error. The EAG notes that in response to clarification question A26, the company stated that “*while neutropenia/neutrophil count decreased and thrombocytopenia/platelet cells decreased were reported as separate events by sites, these terms are equivalent.*”
Page 102 states: “For instance, immune effector cell-associated neurotoxicity syndrome (ICANS), which is critical to CAR T-cell therapies, was not reported, raising concerns about the completeness of the data. One of EAG’s clinical advisers noted some inconsistencies including the probability of infection being	The company request the EAG clarify that ICANS is included as a neurological event, thus is included in the reporting. Furthermore, AEs for obe-cel are aligned with FELIX CSR(6) for infused patients (mITT cohort IIA), which aligns with the modelled population. The Company also request that the EAG update the AE table in the updated model to have whole numbers in the total number of events	AEs included in the model are specific to the Company’s modelled population (mITT cohort IIA). It is therefore not appropriate to report AEs across all cohorts. However, the Company acknowledges that the model should have explicitly stated that ICANS was categorised under neurological events.	Not a factual error. The EAG finds the safety set to be a more accurate representation of the safety margins of obe-cel. As acknowledged by the company in their justification, the EAG could not identify the source of the reported AE for the economic analysis. Therefore, the EAG considers the safety

1.1%, but probability of sepsis was 7.4%. Similarly, the probability for febrile neutropenia was 26.6%, which is typically presumed to be an infection, was higher than the reported neutropenia probability of 20.2%. These gaps and inconsistencies diverge from the Clinical Study Report (CSR), which should include all treatment-emergent AEs (Grade ≥3) for infused patients across all cohorts.”	column (sheet ‘Adverse Events’, cells E86:115).	With regards to the number of event values used in the EAG model for obe-cel, the Company does not understand how the EAG obtained these values as there are no calculations provided, however, was able to match the rounded values to the CSR for adverse events observed across all cohorts.	set reported in the CSR document on page 167.

Issue 8 Health related quality of life

Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Page 76 states: “EQ-5D-5L utility data were collected in the FELIX clinical trial using EQ-5D-5L tool.”	The text should be amended to: “In line with the NICE scope. The company used utilities derived from EQ-5D-5L responses collected from patients in the FELIX clinical trial.”	The text should reflect that data was collected directly from patients in the FELIX trial.	Not a factual error.

Page 93 states: "Missing data were not imputed, and utility estimates were calculated using linear mixed-effects models."	The text should be amended to: "In response to CQ B11, the Company performed multiple imputations with chained equations in R after removing missing data from death and patients who did not report EQ-5D-5L values at any time point. The Company presented deterministic incremental results for all three patient populations using these alternative imputed health state utilities, demonstrating that the ICER results were not sensitive to these changes."	The statement should reflect that the utility analyses were rerun by the Company to explore uncertainty around the missing data, and the impact of these alternative utility values on the ICER results.	The EAG has amended the text to clarify it is referring to the base case analysis, and now mentions this alternative analysis using multiple imputation.
Page 93 states: "A long-term survivorship increment ([redacted]) was applied to cured patients after three years."	The text should be amended to: "A long-term survivorship increment was applied to cured patients after three years. This utility was calculated such that the health state utility of long-term survivors would be halfway between that of the general population at 3 years (base-case cure assumption) and the event-free utility. As general population utility is age-dependent, the long-term utility values differed between the modelled populations due to variations in baseline characteristics ([redacted], [redacted]	In Clarification questions (response to Question B21) the Company provided the population-specific long-term survivorship increments applied for each population. The current text reports the long-term survivorship increment used for the Ph-population while Table 22 of the EAG report (page 93) presents that of the overall population, additional clarification would help avoid	The EAG has amended this text and also Table 22 to reflect the range of values used by the company, however the EAG notes that CS Doc B only referred to the value of [redacted].

	and [redacted] in the overall, Ph- and Ph+ populations, respectively)." Additionally, Table 22 should be updated to reflect the differing values for each population.	potential confusion regarding this discrepancy.	

Issue 9 Typographical errors

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG Response</th></tr>
<tr>
<td>Page 47; Table 8 states that the CR for the infused Cohort IIA is [redacted] and the CRi is [redacted]

Table 8 states that the CR for the enrolled Cohort IIA is [redacted] and the CRi is [redacted]

Table 8 states that CR for the pooled FELIX Cohorts IA and IIA is [redacted] and the CRi is [redacted].

Page 48, paragraph 4 has a reporting error.</td>
<td>The values in Table 8 should be amended to:
<table>
<tr><th></th><th>Cohort IIA – infused (n=94)
(CS B.2.6; CS B.3.3.2; CSR 14.2.30; CSR 14.2.12; CSR 14.2.15)</th><th>Cohort IIA – enrolled (n=112)
(CSR 2.4)</th><th>Cohorts IA and IIA – enrolled (n=133)
(clarification response A1)</th></tr>
<tr><td>ORR
CR
CRi</td><td>72 (76.6%)
52 (55.3%)</td><td>[redacted]
[redacted]</td><td>[redacted]
[redacted]</td></tr>
</table>
</td>
<td>Reporting error. Overall response rate (ORR) is equal to complete response (CR) + complete response with incomplete blood count recovery (CRi), however results for patients with no response or unknown response are included in the ORR calculation, therefore meaning that CR+CRi does not necessarily add to 100%.</td>
<td>This is not a factual error, but a differing perspective of reporting the outcomes.

The EAG has added confidential marking for the ORR, CR and CRi outcomes for the enrolled populations.

Regarding the company's suggestion on page 48, the EAG does not find any issues with the provided sentence. It clearly states that the CRi numbers are calculated from total remissions, resulting in approximately 28%.</td>
</tr>
</table>

	<table><tr><td></td><td>20 (21.3%)</td><td>[redacted]</td><td>[redacted]</td></tr></table> The text on page 48 should be amended to: “Of the total remissions, 20/72 (21%) patients for cohort IIA-infused patients reached Cri”		
Page 60 states: “INO-VATE reported 16% of participants with prior SCT, indicating a less pre-treated cohort overall”	The statement should be amended to: “INO-VATE reported 18% of participants with prior SCT, indicating a less pre-treated cohort overall”.	Reporting error. Per the INO-VATE study, 18% of patients had prior SCT.(7)	This text has been amended to reflect 17.7% of INO-VATE participants had prior SCT.
Page 49 states: “This variability skews results, as shorter follow-up times may not capture long-term DOR, particularly for patients with an aggressive nature of relapsed/refractory B-ALL”	This text should be amended to: “This variability may mean the efficacy of obe-cel is not fully reflected at the current data-cut, as shorter follow-up times may not capture long-term DOR, particularly for patients with an aggressive nature of relapsed/refractory B-ALL”	This is misleading as variability is likely to under-represent efficacy; ‘skew’ does not give any indication of the direction of bias.	Not a factual error. It is not appropriate to speculate over the future efficacy of the technology, however the EAG has replaced the word ‘skew’ with ‘affect’.
Page 49 states:	This text should be removed.	Factually incorrect. EFS and duration of response	The EAG has not stated that the company defined the DOR and

“When comparing the protocol's definition of death for EFS and DOR ("death due to any reason") and then the company reporting "death due to reasons other than underlying cancer" for DOR and EFS (CSR, Table 14.2.10.2.2.iia and 14.2.7.2.1.iia) the EAG notes an inconsistency”		(DOR) was not defined as death due to reasons other than underlying cancer by the Company.	EFS death events as due to reasons other than underlying cancer. The EAG has clearly quoted the company’s protocol definitions as death due to any cause. However, in the CSR and CS, death has been reported differently, which may under-represent the death events and favour obe-cel EFS and DOR results. The EAG has amended this text to describe this as a “potential inconsistency”.
Page 52 states: “It shows that most subgroups had an ORR of >40%”	This text should be amended to: “It shows that all subgroups had an ORR of [redacted]%”	Factually incorrect. Figure 2 shows that all subgroups had an ORR of [redacted].	The EAG has amended this sentence to clarify it was referring to the confidence intervals rather than the point-estimates.
Throughout the document, CS is mistakenly referred to as CSR	Replace CSR with CS when referring to company submission.	Spelling error.	The EAG has used FELIX CSR as a distinct source from the CS. The EAG is not aware of any mis-references, and to maintain accuracy for

			readers, the EAG prefers to keep CSR referencing where it is used.
Page 57 states: "Furthermore, the EAG has replicated the Down and Black risk of bias in Table"	The company requests that the table number that this text is referring to is added to the text.	Referencing error.	This has been amended, however the EAG has encountered a formatting issue related to the large document size where cross-references disappear, and apologies if any others go missing.
Page 39 states: "Complete Remission Rate (CRR) within 3 months post AUTO1 infusion"	This text should be amended to: "Complete Remission Rate (CRR) within 3 months post obe-cel infusion"	Incorrect referencing to obe-cel.	This has been amended.
Page 106 states: "As mentioned in section 4.2.4, Obe-cel, as a CAR T-cell therapy, has the dual potential to function as a curative therapy or as a bridging therapy to allo-SCT."	This text should be amended to: "As mentioned in section 4.2.4, obe-cel, as a CAR T-cell therapy, has the dual potential to function as a curative therapy or as a bridging therapy to allo-SCT."	Case error, obe-cel should not be capitalised.	This has been amended.
Page 112 states: " [redacted]	This text should be amended to: " [redacted]	Case error, obe-cel, inotuzumab, blinatumomab	This has been amended.

[redacted]	[redacted]”	and ponatinib should not be capitalised.	
Table 60, Scenario 2, 3, 5, 12	The company are unable to replicate results for these scenarios and request that the EAG revise the values in the table or provide additional information for how these scenarios were implemented. This will allow	Reporting error.	The EAG has included a new table in the appendix (Table 68), which outlines all the technical amendments

	the company to review implementation and check results are correct.		made to the model in relation to the various scenarios.
Table 61, Scenario 2, 3, 5, 12, 14	The company are unable to replicate results for these scenarios and request that the EAG revise the values in the table or provide additional information for how these scenarios were implemented. This will allow the company to review implementation and check results are correct.	Reporting error.	The EAG has included a new table in the appendix (Table 68), which outlines all the technical amendments made to the model in relation to the various scenarios.
Table 62, Scenario 2,3, 5,12, 14	The company are unable to replicate results for these scenarios and request that the EAG revise the values in the table or provide additional information for how these scenarios were implemented. This will allow the company to review implementation and check results are correct.	Reporting error.	The EAG has included a new table in the appendix (Table 68), which outlines all the technical amendments made to the model in relation to the various scenarios.

Issue 10 Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response

<table>
<tr>
<td>Page 47</td>
<td>As per clarification response A1 and the pooled cohort data being unpublished, the ORR data should be marked up.</td>
<td>
<table>
<tr><td></td><td>Cohort IIA – infused (n=94)
(CS B.2.6; CS B.3.3.2; CSR 14.2.30; CSR 14.2.12; CSR 14.2.15)</td><td>Cohort IIA – enrolled (n=112)
(CSR 2.4)</td><td>Cohorts IA and IIA – enrolled (n=133)
(clarification response A1)</td></tr>
<tr><td>ORR
CR
CRi</td><td>72 (76.6%)
52 (55.3%)
20 (21.3%)</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Although the CSR document and clarification responses were used to derive the data, the EAG also found them published in the company's recent publication (Roddie et al., 2024, Table S14). Therefore, no changes in marking are considered necessary.</td>
</tr>
<tr>
<td>Page 48</td>
<td>The bone marrow (BM) blasts by morphology prior to pre-conditioning presented in the CSR are not available in published literature, therefore should be marked up.</td>
<td colspan="2">Only [redacted] patients (reducing [redacted] with less than 5% blasts from 94 cohort IIA patients) had morphological disease at the time of obe-cel infusion.</td>
<td>In Roddie et al. (2024), page 6, it is reported that "23 of 94 patients (24%) in cohort 2A (>5% bone marrow blasts at enrollment) had less than 5% bone marrow blasts before lymphodepletion."</td>
</tr>
<tr>
<td>Page 48</td>
<td>The number of patients achieving CRi in the mITT cohort of FELIX are confidential and not available in published literature, therefore should be marked up.</td>
<td colspan="2">"Of the total remissions, [redacted] patients for cohort IIA-infused patients reached Cri"</td>
<td>As mentioned above, this has been reported in Roddie et al., Table 2. The EAG has amended the percentage to 27.8%.</td>
</tr>
</table>

Page 50	The number of patients achieving CR or CRi in the full infused cohort of FELIX are confidential and not available in published literature, therefore should be marked up.	“In the CSR document (Table 14.2.27.2.2), [redacted] out of 127 infused patients (phase Ib/II) achieved CR or CRi”	As mentioned above, this has been reported in Roddie et al., Table S14.
Page 52	The results of the subgroup analysis for ORR in FELIX are not available in published literature and therefore should be marked up	“It shows that all subgroups had an ORR of [redacted]%”	As mentioned above, this has been reported in Roddie et al., 2024.
Page 54	The resource use of FELIX patients have not been published and therefore should be marked up.	“It has been noted that [redacted] of patients have required intensive care unit (ICU) admission post-infusion, with [redacted].”	As mentioned above, this has been reported in Roddie et al., 2024.
Page 65	The details of investigator assessment in the FELIX clinical trial are publicly available, and therefore text should not be marked up.	Unmark the following text: “However, these results were based on EFS as assessed by local investigator.“	This marking has been removed.

<table>
<tr><td>Page 80</td><td>Patient numbers of the enrolled and infused set of Cohort IIA in FELIX are not confidential.</td><td>Unmark the following bolded text: “Of the 112 patients initially enrolled, only 94 received at least one obe-cel infusion.” Similarly: “While the company has opted to use the modified intention-to-treat (mITT) population for its analysis—comprising only those who received at least one obe-cel infusion (N=94)—this decision introduces potential biases.”</td><td>This marking has been removed.</td></tr>
<tr><td>Page 84</td><td>The impact of allo-SCT on the efficacy of obe-cel is not available in published literature, and therefore should be marked up.</td><td>“As hypothesized by the company in the CSR document (page 63), subsequent allo-SCT may lead [redacted]</td><td>The EAG has added the marking as requested, but notes this does not refer to data but a hypothesis, so queries this request.</td></tr>
<tr><td>Page 89</td><td>Patient numbers of the enrolled and infused set of Cohort IIA in FELIX are not confidential.</td><td>Unmark the following bolded text “The EAG preferred dataset increases the sample size ([redacted] vs 94) and reduces likely bias from the company’s approach of excluding the pre-infusion period of the trial.”</td><td>This marking has been removed.</td></tr>
<tr><td>Page 94 (Table 23)</td><td>Proportion of patients experiencing grade 3+ CRS in the blinatumomab, inotuzumab and ponatinib arms of the economic analyses are not confidential as have been</td><td><table><tr><td>Blinatumomab</td><td>Inotuzumab</td><td>Ponatinib</td></tr><tr><td>4.87%</td><td>0.00%</td><td>0.00%</td></tr></table></td><td>This marking has been removed.</td></tr>
</table>

	sourced from the relevant comparator trial publications.		

References

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10. Jain MD, Smith M, Shah NN. How I treat refractory CRS and ICANS after CAR T-cell therapy. Blood. 2023 May 18;141(20):2430–42.

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Appendix 1

Table 1: Incorrect values reported by the EAG in "Table 12: Baseline characteristics of identified indirect comparison trials"

	Values currently in EAG report	Corrected values	Values currently in EAG report	Corrected values	Values currently in EAG report	Corrected values	Values currently in EAG report	Corrected values
Study Arm	**FELIX (Obe-cel)[56]**	**FELIX (Obe-cel)[56]**	**INO-VATE (Inotuzumab)[54]**	**INO-VATE (Inotuzumab)[54]**	**PACE (Ponatinib)[53]**	***PACE (Ponatinib)[53]**	**TOWER (Blinatumomab)[55]**	**TOWER (Blinatumomab)[55]**
Population (N)	[redacted]	[redacted]	ITT n=164	ITT n=164	ITT n=32	ITT n=32	ITT n=271	ITT n=271
Age, Median (Range)	[redacted]	[redacted]	46.5 (18-78)	46.5 (18-78)	62 (20-80)	62 (20-80)	40.8 (25-54)	41 (18-80)
Male:Female	[redacted]	[redacted]	91:73 (55%:45%)	91:73 (55%:45%)	NR (20:12, Cortes)	20:12 (62%:38%)	162:109	162:109 (60%:40%)
Race	[redacted]	[redacted]	White: 112 (68.3%)	White: 112 (68.3%)	NR	White: 81.3%	White: 228 (84.1%)	White: 228 (84.1%)
	[redacted]	[redacted]	Other: 53 (31.7%)	Other: 52 (31.7%)	NR	Other: 18.7%	Other: 43 (15.9%)	Other: 43 (15.9%)

Previous Lines of Treatment	[redacted]	[redacted]	1st: 111 (67.7%)	1st: 111 (67.7%)	NR	NR	1st: 114 (42.1%)	1st: 114 (42.1%)
	[redacted]	[redacted]	2nd: 51 (31.1%)	2nd: 51 (31.1%)	≥2 TKI: 26 (81%)	≥2 TKI: 26 (81%)	2nd: 91 (33.6%)	2nd: 91 (33.6%)
	[redacted]	[redacted]	NR	NR	≥3 TKI: 37 (60%)	≥3 TKI: 37 (60%)	3rd: 45 (16.6%)	3rd: 45 (16.6%)
	[redacted]	[redacted]	[redacted]	NR	[redacted]	NR	[redacted]	≥4th: 21 (7.8%)
Refractory to First-line Therapy	[redacted]	[redacted]	NR	NR	NR	NR	114 (42.1%)	115 (42.4%)
Relapse ≤12 Months	[redacted]	[redacted]	NR	96 (58.5%)	NR	NR	76 (28.0%)	76 (28.0%)
Response to Last Line	NR	NR	Complete response: 87 (72%)	Complete response: 121 (74%)	Major hematologic response: 13 (43%)	Major hematologic response: 13 (43%)	NR	NR
Previous SCT (%)	[redacted]	[redacted]	17 (16%)	29 (17.7%)	NR	7 (23%)	94 (34.7%)	94 (34.7%)

BM Blasts at Screening (%)	[redacted]	[redacted]	<50: 30 (28%)	<50%: 53 (32.3)	NR	NR	≥50%: 201 (74.1%)	<50%: 69 (25.5%)
Peripheral Blasts (x10^9/L)	NR	NR	175.4 (0-42,660) cells/µL	107.6 (0-42,660) cells/µL	NR	NR	4.4 ± 15.5	4.4 ± 15.5 ($X10^{-9}$/L)
ECOG PS (%)	[redacted]	[redacted]	0: 43 (39%)	0: 62 (37.8%)	0: 11 (34%)	0: 11 (31.9%)	0: 96 (35.4%)	0: 96 (35.4%)
	[redacted]	[redacted]	1: 50 (46%)	81 (49.4%)	1: 17 (53%)	1: 17 (42.6%)	1: 134 (49.4%)	1: 134 (49.4%)
	[redacted]	[redacted]	2: 15 (14%)	21 (12.8%)	2: 4 (13%)	2: 4 (25.5%)	2: 41 (15.1%)	2: 41 (15.1%)

BM, Bone marrow; EAG, External assessment group; ECOG PS, Eastern Cooperative Oncology Group performance status; SCT, Stem cell transplantation

Note: Cells with incorrect values from the EAG report are highlighted in red.

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 24 March 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal Committee and will subsequently be published on the NICE website with the Committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Generalisability of the FELIX trial for decision making

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The following issues were raised in the first factual accuracy check, however have not been addressed by the EAG.			
Page 11 states: "This single-arm trial has a small sample size and limited follow-up."	As per what was requested in the previous FAC, this text should be amended to: "Characteristically for later-line trials in aggressive oncology indications, FELIX is a single-arm trial. While the small sample size and relatively short follow-up (median: 20.3 months) pose limitations, this is typical data maturity of oncology trials at the point of submission to NICE."	It is misleading to not acknowledge that the single-arm trials are common for late-stage oncology. Additionally, the data maturity of FELIX is typical for oncology submissions to NICE: a systematic review of oncology NICE single technology appraisals published between 2018 and 2022 found 57% relied on immature data, typically defined as fewer than 50% of events having occurred. The follow-up of FELIX is therefore typical of oncology appraisals submitted to NICE.(1)	Not a factual error. The EAG does not consider the current text misleading. The company's response acknowledges that this appraisal is reliant on immature data, which agrees with the EAG's description.
Page 44 states: "In the FELIX Cohort IIA, both sexes were equally distributed (47/94; 50%), despite the UK ALL incidences are higher in	As per what was requested in the previous FAC, this text should be amended to: "In FELIX Cohort IIA, both sexes were equally distributed (47/49; 50%),	A statement from Cancer Research UK shows that incidence of acute lymphoblastic leukaemia (ALL) in the UK is 41% female and 59% male.(2) The	Not a factual error. The EAG considers the company's text to be subjective.

makes than females."	broadly in line with the UK ALL incidence."	equal split between females and males in FELIX is therefore broadly in line with that observed in the UK.	
Page 44 states: "The EAG suspects that the FELIX population is likely to be on average younger than UK ALL patients. The EAG notes that among the anticipated licensed population [redacted] 36.2% of UK patients have disease incidence aged over 65, compared with 22.3% in this age group at the start of the FELIX trial.[48] Therefore, the generalisability of FELIX to the UK population is of concern."	As per what was requested in the previous FAC, this text should be amended to: "While 20% of incidences are in those aged 75 and over, their mortality is highest. Cancer Research UK data shows that 13.3% of new ALL cases are in patients aged 65 and older, whereas FELIX Cohort IIA mITT included 22.3% of patients aged 65 years and older.(2) The proportion of patients aged 65 and over in FELIX is 1.7 higher compared with Cancer Research UK. The efficacy observed in FELIX is therefore likely a conservative estimate of the true efficacy of obe-cel in UK practice."	The statement is factually incorrect. As per Cancer Research UK data, the proportion of FELIX patients aged 65 years and older is 1.7 times higher than the UK population (22.3% versus 13.3%). Therefore, the slight difference observed indicates that if anything, FELIX data would underestimate the true obe-cel efficacy likely to be observed in UK practice.	Not a factual error. The EAG's percentages are correct as they are based on the population that is consistent with this appraisal ([redacted]) and excludes incidences from the Cancer Research UK data for people who are [redacted]. The company's calculations include this population, which the EAG considers less relevant to this appraisal.
Page 60 states: "The FELIX trial population, while well-defined and homogenous, may not fully reflect real-world settings due to the exclusion of patients with ECOG PS ≥2 and a focus on less heavily	The EAG have added new text regarding "less heavily pretreated individuals" without justification and have not addressed comments from the previous FAC regarding ECOG scores. This text should be amended to: "The FELIX trial population was well-	Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 is a common eligibility criteria for Chimeric Antigen Receptor T-cell (CAR T) therapy and is aligned with other CAR T trials, e.g.,	Not a factual error. This sentence refers to a comparison between FELIX and the real-world patient population, and not the comparator trials.

pretreated individuals”	defined and homogenous, excluded patients with ECOG PS ≥2 aligning with previous CAR T trials, and patients had similar pretreatment to comparator studies.”	ZUMA-3(3). Furthermore, analysis of UK National Health System (NHS) patients treated with brexu-cel via the Cancer drug fund (CDF) indicated 44% of patients had an ECOG score of 0, and 56% of patients had a score of 1. These scores show the strong prevalence of patients eligible for CAR T with an ECOG score of 0 or 1.(4) It is incorrect to state that FELIX focused on less heavily pretreated individuals than comparator studies, as FELIX had fewer patients with one prior line of therapy versus each comparator study in the relevant patient population, as presented in the Company clarification questions response, in response to question A29: • For the modified intention to treat (mITT) population, substantially fewer patients with one prior line	The EAG is unable to verify the ECOG percentages provided by the company for UK real-world use of brexu-cel, as this information is not contained in the reference provided. O’Reilly et al. (10.1002/hem3.87) reports that 6% patients infused with brexu-cel in the UK for Mantle Cell Lymphoma had ECOG >1 at point of infusion. These people were associated with inferior outcomes, and the EAG predicts that if equivalent people were able to receive obe-cel for B-ALL this would likely decrease the average cost-effectiveness of obe-cel.

		of therapy in FELIX compared to INO-VATE ([redacted]. % vs 67.7%, respectively) • In the Ph- subgroup, fewer patients with one prior line of therapy in FELIX compared to TOWER ([redacted]% vs 42.1%, respectively) • In the Ph+ subgroup, fewer patients with one prior line of therapy in FELIX compared to PACE ([redacted]% vs 19%, respectively) Furthermore, in the aforementioned analysis of patients treated with brexu-cel via the CDF, 31% of infused patients received three or more prior lines of therapy, the same as the proportion observed in FELIX (31%) indicating that FELIX is likely to reflect UK practice.(4) Since FELIX did not enroll patients with fewer prior	

		treatments than in the comparator studies, obe-cel outcomes were not favoured based on prior treatments.	
Pages 59-60 state: "• PACE patients were the most heavily pretreated, with 81% having received ≥2 TKIs. • TOWER had 75.6% with 1 or 2 prior lines, representing a slightly less pretreated cohort than FELIX."	As per what was requested in the previous FAC, this text should be amended to: " • In the Ph+ subgroup, there were fewer patients with one prior line of therapy in FELIX compared to PACE ([redacted]% vs 19%, respectively)" • In the Ph- subgroup, there were fewer patients with one prior line of therapy in FELIX compared to TOWER ([redacted]% vs 42.1%, respectively) • The comparison indicates that FELIX data are comparable to comparator studies and in some instances has a more heavily pretreated population than the comparators. This disparity biases outcomes against FELIX, as patients with fewer prior treatments generally have a better prognosis."	As per the above row, these statements do not take into account that in each relevant population, the FELIX population was more heavily pretreated than the comparator studies. In FELIX Cohort IIA mITT, 69.1% of patients had received one or two prior lines of therapy. A total of 18.1% of FELIX Cohort IIA mITT patients had received three prior lines of therapy, and 12.8% four or more.	Not a factual error. The company's reporting is based on a comparison of people with one prior line of therapy, whilst the EAG's comparison is based on a broader consideration of the distribution of the number of therapies received for people who received more than one prior line of therapy.

Issue 2 Reliance on biased and highly uncertain MAIC and preferred population and method for extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 12 states: "It is uncertain whether the assumption of cure at 3 years is suitable for all people when remaining alive, especially those in the post-event health state."	This statement should be removed.	The text does not reflect that the cure timepoint of three years was validated with two UK clinical experts who both expressed that patients treated with obe-cel who relapse would typically do so within a year (and hence three years is conservative), and that the timepoint was selected to align with TA893 for which it was accepted by the Committee. (5)	Not a factual error. The EAG does not consider the assumption to be well supported by clinical data and hence this remains a point of uncertainty. The EAG have matched the assumption as it was made in TA893, however considers that the committee may wish to explore alternative assumptions.
Tables 51-53 on pages 140-142 state the following results for the "Inappropriate ITC approach and narrowed population" update: **Whole population:** Incremental costs: [redacted]	The Company request that the EAG revise and update their list of changes in Appendix 8.5 to clarify which inputs, settings and calculations need changing from the Company's cost-effectiveness model to replicate these results.	The Company was able to replicate all EAG results detailed in Tables 51-53 by following the model updates in Appendix 8.5, except those detailed for the "Inappropriate ITC approach and narrowed population" update.	The EAG considers that this has been addressed in subsequent documentation, including updated results, provided to the company by the EAG. The EAG has updated the results in the EAG

Incremental QALYs: 2.27 ICER: [redacted] **Ph- population:** Incremental costs: [redacted] versus inotuzumab; [redacted] versus blinatumomab Incremental QALYs: 1.65 versus inotuzumab; 3.61 versus blinatumomab ICER: [redacted] versus inotuzumab; [redacted] versus blinatumomab **Ph+ population:** Incremental costs: [redacted] versus inotuzumab; [redacted] versus ponatinib Incremental QALYs: 2.10 versus inotuzumab; 10.50 versus ponatinib ICER: [redacted] versus inotuzumab; [redacted] versus ponatinib			report for the EAG Change 2 to match the recent documentation.

The following issues were raised in the first factual accuracy check, however have not been addressed by the EAG.			
Page 68 states: "Overall, the information provided by the Company in the CS pre-clarification was minimal and unsatisfactory"	As per what was requested in the previous FAC, this text should be amended to: "Overall, the information provided by the Company in the CS pre-clarification was unsatisfactory, however this was corrected and provided at the clarification stage"	The current text is misleading as it omits that the Company provided all requested information at the clarification stage.	Not a factual error. As stated in the original FAC response, this led to the EAG having considerably less time to critique the company's approach.

Issue 3 Hospitalisation and resource use for obe-cel

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
There are issues with the EAG's implementation of tariff costs into the cost-effectiveness model. Page 102 states: "**Base-Case Analysis:** Using the tariff costs for CAR T infusion and monitoring, valued at £58,964,66 in line with approach followed by the TA893."	The Company request that if the EAG wishes to explore the application of the tariff cost, the formula in cell I128 on the 'Treatment Costs' sheet should be amended to: =CHOOSE(i_infusion_cost_approach,(((1-I143)*I133*K106)+(I143*I138*K118)),I149)	The text in the EAG report does not reflect the formula used in the EAG's cost-effectiveness model and no rationale is provided in the report for including ICU costs in addition to the tariff costs.	Not a factual error. The EAG notes that in the final appraisal document of TA1048, point 3.18 states that "NHS England confirmed that costs associated with ICU admission are not included in the CAR-T or stem

"For both scenarios, the related formula is amended as follows: (((1-I143)*I133*K106)+(I143*I138*K118))." However, when the tariff cost option is selected in the cost-effectiveness model, the following formula is used: (I149+(I143*I138*K118)). Here I149 represents the tariff cost, I143 the proportion of patients requiring ICU post obe-cel infusion, I138 the length of ICU stay and K118 the unit cost of ICU stay.		All hospitalisation costs associated with CAR T treatment are already captured in the CAR T-cell tariff cost. It is therefore inappropriate to include ICU costs in addition to the tariff costs, as payment for ICU costs would be factored into the tariff paid to providers.	cell transplant tariffs".
Page 199-200 states: "- Cell G174: The formula has been changed to E175/F175 And E175 = [redacted] , F175=[redacted] (based on cohort IA and IIA)" "- Cell I214: The formula has been changed to H215/G215 And H215=[redacted], G215=[redacted] - Cell I238: The formula has been changed to H239/G239 And H239=[redacted], G239=[redacted]"	The text should be updated to the following to align with the formula used in the cost-effectiveness model: "- Cell G174: The formula has been changed to F175/E175 And E175 = [redacted] , F175=[redacted] (based on cohort IA and IIA)" "- Cell I214: The formula has been changed to H215/G215 And H215=[redacted], G215=[redacted] - Cell I238: The formula has been changed to H239/G239 And H239=[redacted], G239=[redacted]"	Misalignment between the EAG report and the EAG cost-effectiveness model.	The EAG considers that this has been addressed in subsequent documentation provided to the company by the EAG.

The following issues were raised in the first factual accuracy check, however have not been addressed by the EAG.			
Page 100 states: "The EAG considers that the Company's revised estimates may underestimate hospitalisation durations compared with the broader FELIX trial data, which suggests substantially longer hospital stays." Page 101 states: "The EAG's opinion that a more reasonable approach is to use the summary tariff costs for CAR T infusion and monitoring and in line with TA893, which better reflects the actual costs" Page 102 states: "EAG assumes that hospitalisation durations should reflect the complete FELIX trial dataset in Cohort IIA. This includes a mean non-ICU hospital stay of [redacted]days (SD: [redacted]), a mean ICU stay of [redacted] days (SD: [redacted]), and [redacted]% of patients requiring ICU care."	As per what was requested in the previous FAC, the text on Page 100 should be amended to: "The Company's revised estimates reflect the hospitalisation durations for UK patients, reflecting resource use for obe-cel patients in UK practice" As per what was requested in the previous FAC, the text on page 101, should be amended to: "The summary tariff costs for CAR T infusion and monitoring are likely to overestimate the actual resource use associated with obe-cel UK usage". As per what was requested in the previous FAC, the text on page 102 should be amended to: "EAG assumes that hospitalisation durations should reflect the complete FELIX trial dataset in Cohort IIA. This includes a mean non-ICU hospital stay of [redacted] days (SD: [redacted]), a mean ICU stay of	[redacted] ([redacted]%) of the patients in FELIX are from the US, and [redacted]% are from Spain. Resource use estimates based on the [redacted] ([redacted]%) patients from the UK are more representative of UK clinical practice than estimates inclusive of patients from other countries. The use of the EAG proposed tariff cost for obe-cel is misrepresentative for two reasons. Firstly, the TA893 CAR T tariff cost was suitable to cost brexu-cel hospitalisations; however it would be	Not a factual error. This represents a difference of opinion to be considered by the appraisal committee, the EAG considers that applying the CAR-T tariff cost is the most appropriate option, which resolves this query. The EAG considers that the reduced sample size of the UK specific population may not capture the impact of less common outcomes.

	[redacted]days (SD: [redacted]), and [redacted]% of patients requiring ICU care. These durations are longer than those observed for the FELIX UK cohort.”	inappropriate to apply the tariff to obe-cel as the cost calculates adverse event-related intensive care unit (ICU) stays based on previous CAR T therapies.(6) As discussed in CS Section B.1.3.5, page 28, currently available CAR T treatments are associated with considerable rates of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). For example, brexu-cel is associated with very high levels of CRS (89%) and neurological events associated with ICANS (60%)(3,7), with grade 3 or 4	

		CRS occurring in 24% of patients and grade 3 or higher neurological events occurring in 25% of patients.(3,8). By contrast, obe-cel has demonstrated substantially lower rates of grade ≥3 CRS (2.4%) and ≥3 ICANS (7.1%), which is the level that generally requires ICU admission. The tariff is therefore not reflective of obe-cel's safety profile. Secondly, the EAG use a higher tariff than was used in TA893 and in the Company's cost-effectiveness model (£58,964 versus £41,101), contrary to the reasoning given in the EAG report. Using this higher tariff exacerbates the	

		overinflated costs applied to obe-cel. The Company maintain that basing resource use on the subset of UK patients from the FELIX trial is the most appropriate approach.	

Issue 4 Costs and effects of allo-SCT

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
There are issues with the EAG's implementation of follow-up costs of allo-SCT into the cost-effectiveness model. Page 107 states: "**Base-case analysis**: Normalize patient distribution across different follow-up periods for each cycle to ensure the Maximum Undiscounted Total Costs align with the	The Company request that the EAG revert to the original approach to calculating post allo-SCT costs in the traces of the cost-effectiveness model but update the costs in cells G61:G63 on the 'Subsequent Tx Costs' sheet to per cycle costs by adding the following updates to the existing formula: To cells G61:G62: /6*(misc_daysPerMonth/misc_cycleLength) To cell G63: /12*(misc_daysPerMonth/misc_cycleLength)	The Company recognize that there was an error in the initial costing approach used in the cost-effectiveness model and agree with the EAG that the maximum undiscounted total costs should align with the proportion of patients receiving an allo-SCT. However, as the EAG's normalization approach does not account for	The EAG welcomes the company's acknowledgement of an error in the company's modelling of post-alloSCT, however has not received any updated model or analyses from the company. The EAG does not consider the

proportion of patients receiving an allo-SCT.“ The EAG’s normalization approach used in columns DG:DI in the traces of the cost-effectiveness model (i.e., linking these columns to columns AQ, AX, BD) does not account for mortality within the follow-up period post allo-SCT.		mortality within the follow-up period, it overestimates costs in both the comparator and obe-cel arms.	company’s suggested revision to be a meaningful improvement, or possibly any improvement, over the EAG’s current implementation, due to uncertainty of when within each period the relevant costs are incurred. The EAG considers the two approaches to be closely aligned. As the frequency of SCT is higher for the comparators, any reduction in these costs would work against obe-cel.
Page 196 state: “In worksheets “Trace - Obe-cel vs …) - Cell AP23, The formula changed to (AG23-	The text should be updated to the following to align with the formula used in the cost-effectiveness model: “In worksheets “Trace - Obe-cel vs …) - Cell AP23, The formula changed to (AG22-	Misalignment between the EAG report and the EAG cost-effectiveness model.	The EAG considers that this has been addressed in subsequent documentation

AG24)*p_i_SCT_int”	AG23)*p_i_SCT_int”		provided to the company by the EAG.
The following issues were raised in the first factual accuracy check, however have not been addressed by the EAG.			
Page 14 states: “The Company base-case analyses use data from FELIX that is not censored for receiving subsequent allo-SCT (i.e. includes the effect), but do not capture the costs associated with this allo-SCT use.” Page 107 states: “As of the February 2024 data cut-off, [redacted] patients in cohort IA and IIA had received infusions, among whom [redacted] patients ([redacted]) underwent allo-SCT, as stated by the Company in response to clarification questions and Clinical Study Report (CSR). Based on Roddie et al. (2024),66% of these SCT procedures were first allo-SCT,	As per what was requested in the previous FAC, these texts should be amended to: Page 14: “The Company base-case analyses use data from FELIX that is not censored for receiving subsequent allo-SCT (i.e. includes the effect), but analyses that censor for allo-SCT have been provided in the CS, showing comparable results between the analyses. The base-case economic analysis does not consider allo-SCT following obe-cel.” Page 107: The Company request that the EAG present the results of the post-hoc analysis conducted to compare outcomes in Cohort IIA in FELIX with and without censoring for consolidative allo-SCT, as presented in Section B.2.7.1.2 of the CS (page 73-74; Table 19).	The omission of the post-hoc analysis results from the EAG report, despite these being provided in the CS (Section B.2.7.1.2 [page 73-74; Table 19]), gives the impression that no evidence has been submitted to demonstrate the standalone curative potential of obe-cel and justify the Company’s approach to not include allogeneic (allo)-SCT costs for obe-cel patients. This is misleading, as the text suggests that the Company made an arbitrary assumption to exclude allo-SCT costs for the obe-cel arm in the economic analysis, rather than basing this on clinical evidence.	Not a factual error. Given the potential for informative censoring in the analyses described by the company where people are censored at the point of receiving subsequent allo-SCT and possibly other select treatments, the EAG has concerns over their reliability.

equating to approximately [redacted] of the [redacted] patients ([redacted] × 66% = [redacted]).”		The results of this post-hoc analysis indicated that outcomes are comparable with and without censoring for subsequent SCT. Therefore, this analysis provides important evidence on the potential curative treatment effect of obe-cel and supports the Company’s base-case analysis.	
Page 82 states: “Hence, the EAG assumes that all treatments under evaluation aim to achieve a cure for patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukaemia (ALL), while the standalone ability of obe-cel to cure patients remains unknown.”	As per what was requested in the previous FAC, the Company request that the EAG remove the following text: “…while the standalone ability of obe-cel to cure patients remains unknown.” Additionally, the Company request that the EAG present or acknowledge the results of the post-hoc analysis conducted to compare outcomes in Cohort IIA in FELIX with and without censoring for consolidative allo-SCT, as presented in Section B.2.7.1.2 of the CS (page 73-74; Table 19).	The omission of the post-hoc analysis results from the EAG report, despite these being provided in the CS, along with the phrasing of the sentence, give the impression that no evidence was submitted to demonstrate the standalone curative potential of obe-cel and is therefore misleading. Furthermore, as stated above the results of the post-hoc analysis indicated that the outcomes are comparable with and	Not a factual error. The EAG considers this to suitably reflect the current data available for obe-cel, where uncertainty remains in the long-term efficacy, regardless of the effect of subsequent allo-SCT.

		without censoring for subsequent SCT. Omitting this analysis ignores important evidence on the potential curative treatment effect of obe-cel.	
The EAG disagrees with the Company's approach to use a uniform utility value to all patients in the post-event health state and suggest using utility values from TA451 to include distinct post-SCT conditions in the economic analysis. Page 98 states: "Adjusting utility values in the post-event health state using time-dependent utilities from TA541 to capture variations in post-HSCT HRQoL and account for the proportion of patients receiving allo-SCT across different treatments."	As per what was requested in the previous FAC, the Company requests that the EAG acknowledge that using values from TA541 (Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia) overestimate the post allo-SCT utilities as TA541 included a 0.3 utility for patients who progress following allo-SCT.(9)	The approach proposed by the EAG ignores that the TA541 economic model had a separate progressed-disease health state with a much lower health state utility value (0.30) than the progression-free time-varying utilities.(9) This progressed-disease utility was applied to all patients who progressed, including those progressing post allo-SCT. By not accounting for the utility of disease progression following allo-SCT, the EAG's approach may overestimate long-term HRQoL post allo-SCT, disproportionally favouring comparator arms with a higher proportion of	Not a factual error. The model provided to the EAG did not contain this functionality and so was not incorporated by the EAG. However, the EAG considers that any impact of this additional health-state would be minimal given the cure assumption beyond 3 years and that outcomes for people progressing after allo-SCT are poor.

		patients undergoing allo-SCT.	

Issue 5 Most suitable severity modifier to apply

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The following issues were raised in the first factual accuracy check, however have not been addressed by the EAG.			
Pages 110-111 state: "Only for Ph- patients, blinatumomab serves as the comparator, leading to a 1.7 severity modifier based on a proportional shortfall of [redacted] In contrast, when compared to inotuzumab and ponatinib, the proportional shortfalls are lower ([redacted] respectively), which corresponds to a 1.2 severity modifier. These inconsistencies suggest that the use of a 1.7 severity modifier may overestimate the severity adjustment for the entire population."	As per what was requested in the previous FAC, this text should be amended to: "Only for Ph- patients, blinatumomab serves as the comparator, leading to a 1.7 severity modifier based on a proportional shortfall of [redacted] In contrast, when compared to inotuzumab and ponatinib, the proportional shortfalls are lower ([redacted] respectively), which corresponds to a 1.2 severity modifier. As inotuzumab data are only available for the overall population, conclusions for the appropriate severity modifiers for the Ph- and Ph+ subgroups are best made using data for blinatumomab and ponatinib, respectively."	As described in the CS, Section B.3.3.2.3; page 123 and Section B.3.3.2.4; page 127, efficacy data for inotuzumab were only available for the mITT population. The EAG's current wording does not reflect that conclusions for the subgroups based on this data may not reflect the true severity and unmet need for patients in each subgroup.	Not a factual error.

Issue 6 Survival modelling

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The following issues were raised in the first factual accuracy check, however have not been addressed by the EAG.			
Page 12 states: "The ability to implement MAIC weighted extrapolations for the ITT/enrolled population would allow relaxing the proportional hazards (PH) assumption but will be based on the characteristics of the trial populations of the comparator treatments."	As per what was requested in the previous FAC, the text should be amended to: "The ability to implement MAIC weighted extrapolations for the ITT/enrolled population would allow relaxing the proportional hazards (PH) assumption but will be based on the characteristics of the trial populations of the comparator treatments. However, this method would not allow an accurate incremental analyses in the Ph- and Ph+ subgroups."	It is misleading to not acknowledge the need to present an incremental analysis in the Ph- and Ph+ subgroups. Using the MAIC-adjusted obe-cel curves for the Ph- and Ph+ subgroups would not allow an accurate incremental analysis in either subgroup since the obe-cel MAIC-weighted extrapolations would be adjusted to match blinatumomab and ponatinib, respectively, not inotuzumab. This justification was provided in Section B.3.3.1.5 of the CS (page 116).	Not a factual error. The EAG considers the benefits of this approach that would yield potentially improved pair-wise analyses to outweigh the limitations associated with an incremental analysis.
Page 84, paragraph 2 states: "Despite stating in the CS that for the three comparators, the Company used the same approach to extrapolate their digitised	As per what was requested in the previous FAC, the text should be amended to: "The Company used the same approach to extrapolate the digitised data for each comparator for a naïve analysis. However, in the base-case of	The Company was not able to find the sentence that the EAG was referring to regarding suggesting that the same extrapolation methods have been used for all comparators.	Not a factual error. The EAG is referring to the text across section B.3.3.2.

data, the EAG understands that for the Company base-case analyses for blinatumomab and inotuzumab, the Company instead applied inverted hazard ratios from their MAIC to the obe-cel extrapolations." Page 84, paragraph 3 states: "For the comparisons to inotuzumab and blinatumomab, the Company has inverted the hazard ratios and applies them to the extrapolations of obe-cel from FELIX, which is considered to be more representative of the NHS population than the other trials."	the economic analyses, the Company applied inverted hazard ratios from their MAIC to adjust the obe-cel extrapolations and used these to model comparator time-to-event outcomes for the comparison against blinatumomab and inotuzumab. This method is in line with the Committee's preference in TA893." The text should be amended to: "For the comparisons to inotuzumab and blinatumomab, the Company has inverted the hazard ratios and applies them to the extrapolations of obe-cel from FELIX, which is considered to be more representative of the NHS population than the other trials. This method is in line with the Committee's preference in TA893."	The Company clarified in Section B.3.3.1.5 of the CS the different extrapolation methods used in the economic analysis for the three comparisons. However, the Company acknowledge that Section B.3.3.2.1 could have re-stated the base-case approach. Additionally, it should also be noted that this approach is consistent with the precedent set in TA893, where the same method was accepted by the Committee for decision making.(6)	The EAG acknowledges that the inverse MAIC approach is consistent with TA893, and has added text to this effect to page 84.
Page 84 states: "This approach assumes hazard proportionality, which appears violated based on evidence provided by the	As per what was requested in the previous FAC, the Company request that the EAG clarify that the same method was used for the EAG's extrapolations and that this method satisfied the requirement for an	It is misleading to discredit the inverse hazard ratio approach used by the Company but to fail to mention that the EAG did not present an alternative to this	Not a factual error. The EAG is obliged to highlight limitations it identifies with any

Company, with instances of hazard curves crossing. While some hazard rates were reasonably proportional during certain trial periods, the differences in follow-up lengths across the studies further complicate the long-term validity of the PH assumption. It also assumes that the relative treatment effect does not change across the populations, which is not clearly supported.”	incremental analysis between multiple comparators.	method in their preferred base-case. Additionally, using the MAIC-adjusted obe-cel curves for the Ph- and Ph+ subgroups does not allow for an accurate incremental analysis between multiple comparators. This justification was provided in Section B.3.3.1.5 of the CS (page 116).	analyses provided.

Issue 7 Adverse events

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
The following issues were raised in the first factual accuracy check, however have not been addressed by the EAG.			
Page 53 states: “The EAG notes the small sample size may be	As per what was requested in the previous FAC, the text regarding sample size should be removed.	As noted in the previous FAC, while the small sample size poses limitations, late-stage oncology submissions	Not a factual error.

insufficient to fully capture obe-cel's safety"		to NICE are often based on smaller Phase II studies. Therefore, it is inappropriate to deem the sample size insufficient in this context when interpreting results.	It is well established that a trial with a small sample size may fail to observe rare safety events.
Page 56 states: "The Company reported that neutropenia and neutrophil decrease were defined equivalently according to the clarification response A26. However, they report differing frequencies of these events in the CS, doc B, Table 24 (29 vs. 25 events)."	As per what was requested in the previous FAC, this text should be removed.	This statement is untrue. In the response to clarification question A26, rates of neutrophil count decrease were not reported. Neutrophil count decrease were reported in the response to clarification question A27, which is 25 events, and it is line with what was reported in the CS, Table 24.	Not a factual error. The EAG obtained the frequencies for neutropenia and neutrophil decrease from Table 24 of the CS.
Page 104 states: "For instance, immune effector cell-associated neurotoxicity syndrome (ICANS), which is critical to CAR T-cell therapies, was not reported, raising concerns about the completeness of the data. One of EAG's clinical advisers noted some inconsistencies including the	As per what was requested in the previous FAC, the Company request the EAG clarify that ICANS is included as a neurological event, thus is included in the reporting. Furthermore, the Company request that the EAG acknowledge AEs for obe-cel used in the Company model are aligned with the FELIX CSR (12) for infused patients (mITT Cohort IIA),	The Company acknowledge that the model should have explicitly stated that ICANS was categorised under neurological events and thank the EAG for flagging this concern. AEs included in the Company model are specific to the Company's modelled population (mITT Cohort IIA).	Not a factual error. The EAG is unable to verify the accuracy of the company's statement that ICANS was included within neurological events within the model, as the CS states that the number of ICANS events of grade 3 or higher in the safety population

probability of infection being [redacted]%, but probability of sepsis was [redacted]%. Similarly, the probability for febrile neutropenia was [redacted]%, which is typically presumed to be an infection, was higher than the reported neutropenia probability of [redacted]%. These gaps and inconsistencies diverge from the Clinical Study Report (CSR), which should include all treatment-emergent AEs (Grade ≥3) for infused patients across all cohorts."	which aligns with the Company's modelled population.	It is not appropriate to report AEs across all cohorts.	(n=127) to be 9, but the modelled number of neurological events for obe-cel was [redacted] (out of 94 people). Whether it is appropriate to combine cohorts IA and IIA who received the same dose for the same disease is difference of opinions.
There are issues with the EAG's implementation of the AE rates into the cost-effectiveness model. In Table 27 on page 104-105 of the EAG report the total number of events reported as integer values. However, in cells E86:E115 on the 'Adverse Events' sheet in the cost-effectiveness model	The Company request the EAG to update the values in the cost-effectiveness model to match those reported in Table 27, ensuring the model only uses integer values for AE inputs.	Using non-integer values to report the total number of AEs does not reflect the event data from FELIX or real-world clinical practice, as adverse events are discrete occurrences, and partial events have no clinical meaning.	The EAG considers that this has been addressed in subsequent documentation provided to the company by the EAG.

numbers with varying decimal places are used.			

Issue 8 Health related quality of life

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The following issues were raised in the first factual accuracy check, however have not been addressed by the EAG.			
Page 76 states: "EQ-5D-5L utility data were collected in the FELIX clinical trial using EQ-5D-5L tool."	As per what was requested in the previous FAC, the text should be amended to: "In line with the NICE scope, the Company used utilities derived from EQ-5D-5L responses collected from patients in the FELIX clinical trial."	The text should reflect that data were collected directly from patients in the FELIX trial.	Not a factual error.
Page 93 states: "Missing data were not imputed, and utility estimates were calculated using linear mixed-effects models."	As per what was requested in the previous FAC, the text should be amended to: "In response to CQ B11, the Company performed multiple imputations with chained equations in R after removing missing data from death and patients who did not report EQ-5D-5L values at any time point. The Company presented deterministic incremental	The statement should reflect that the utility analyses were rerun by the Company to explore uncertainty around the missing data, and that the impact of these alternative utility values on the ICER results was minimal.	Not a factual error. The company appears to be quoting text from the pre-FAC EAG report. This text was revised following the original FAC.

	results for all three patient populations using these alternative imputed health state utilities, demonstrating that the ICER results were not sensitive to these changes."		

Issue 9 Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Figures 36-41 on pages 203-206	As the pooled cohort data are unpublished, the KM plots detailing the EAG survival extrapolations should be redacted.	Figures 36-41 in the EAG report should be redacted.	The EAG has added confidential marking to these figures as requested.
Page 80	Patient numbers of the enrolled set of Cohort IIA in FELIX are not confidential.	"This approach would yield a more comprehensive population of [redacted] patients, providing a broader basis for evaluation."	The number indicated by the company relates to the enrolled set across cohorts IA and IIA which the EAG understand to be confidential.
The following issues were raised in the first factual accuracy check, however have not been addressed by the EAG.			
Page 48	As per what was requested in the previous FAC, the bone marrow (BM) blasts by morphology prior to pre-conditioning presented in the CSR are	"Only [redacted] patients (reducing [redacted] with less than 5% blasts from 94 Cohort IIA patients) had	Not a factual error. As already stated, this information is reported by

	not available in published literature, therefore should be redacted.	morphological disease at the time of obe-cel infusion."	or can be inferred from Roddie et al (2024).
Page 48	As per what was requested in the previous FAC, the number of patients achieving CRi in the mITT cohort of FELIX are confidential and not available in published literature, therefore should be redacted.	"Of the total remissions, [redacted] patients for Cohort IIA-infused patients reached Cri"	Not a factual error. As already stated, this information is reported by Roddie et al (2024) [Table 2].
Page 50	As per what was requested in the previous FAC, the number of patients achieving CR or CRi in the full infused cohort of FELIX are confidential and not available in published literature, therefore should be redacted.	"In the CSR document (Table 14.2.27.2.2), [redacted] out of 127 infused patients (phase Ib/II) achieved CR or CRi"	Not a factual error. As already stated, this information is reported by Roddie et al (2024). [Table S14]
Page 52	As per what was requested in the previous FAC, the results of the subgroup analysis for ORR in FELIX are not available in published literature and therefore should be redacted.	"It shows that all subgroups had an ORR of [redacted]%"	Not a factual error. As already stated, this information is reported by Roddie et al (2024). [Figure S6]
Page 54	As per what was requested in the previous FAC, the resource use of FELIX patients have not been published and therefore should be redacted.	"It has been noted that [redacted] of patients have required intensive care unit (ICU) admission post-infusion, with [redacted]."	Not a factual error. As already stated, this information is reported by Roddie et al (2024). [Page 9]
Page 80	As per what was requested in the previous FAC, patient numbers of the	"While the Company has opted to use the modified intention to treat (mITT)	The EAG has removed the marking from this number.

	enrolled and infused set of Cohort IIA in FELIX are not confidential.	population for its analysis—comprising only those who received at least one obe-cel infusion (N=94)—this decision introduces potential biases.”	
Page 89	As per what was requested in the previous FAC, patient numbers of the enrolled and infused set of Cohort IIA in FELIX are not confidential.	“The EAG preferred dataset increases the sample size ([redacted] vs 94) and reduces likely bias from the Company’s approach of excluding the pre-infusion period of the trial.”	In the post-FAC version of the EAG report, the EAG has already removed the marking for n=94.

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Single Technology Appraisal

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

Clinical expert statement

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The deadline for your response is **5:00pm** on **Monday 17 February.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating B-cell acute lymphoblastic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Michelle Lannon
2. Name of organisation	Newcastle Upon Tyne Hospitals NHS Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with B-cell acute lymphoblastic leukaemia? ☐ A specialist in the clinical evidence base for B-cell acute lymphoblastic leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for B-cell acute lymphoblastic leukaemia?	To cure the condition

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	An MRD negative bone marrow remission and a durable progression free survival
10. In your view, is there an unmet need for patients and healthcare professionals in B-cell acute lymphoblastic leukaemia?	Yes. The ideal treatment for relapsed disease needs to be effective AND have a more tolerable toxicity profile with fewer late effects.
11. How is B-cell acute lymphoblastic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	In the NHS, a new diagnosis of B-ALL is treated following active or prior clinical trial protocols which are age dependent. The patients are enrolled on a first line ALL study, where available (e.g. ALL Together in TYA age patients) or following the protocol of the most recent adult B-ALL studies (e.g. UKALL14 or UKALL 60+). The UK national ALL treating community have devised interim guideline as more data has become available between trials in order to manage some of the areas of need in upfront therapy. In the upfront therapy, other guidelines are used to assist with decision making around transplant and the appropriate next line of therapy, e.g. EBMT, ELN. For those patient who relapse, there are options for treatment and some of those options are restricted by the diseases expression of certain immunotherapy targets (e.g. CD19 expression for Blinatumomab or CAR-T, CD22 expression for Inotuzumab or Philadelphia positivity for selecting TKI therapy) as well as the appropriateness of the treatment based on prior lines of therapy, patients fitness for therapy and meeting CDF criteria for therapy. There is a UK National Expert Panel providing support for complex cases, relapsed patient care and those who are potential CAR-T candidates (for formal approval). This panel is there by design to ensure equity of options to patients across the country, to share uptodate information and evidence and for discussion where a difference of opinion can be heard with evidence to back treatment planning.

	Relapsed disease is usually treated with immunotherapy (e.g. Blinatumomab or Inotuzumab) but mostly as a bridge to another treatment to consolidate, e.g. Allogeneic stem cell transplant or CAR-T cell therapy, or CAR-T cell therapy alone. Chemotherapy alone is recommended in certain situations but this is less common in the era of more targeted therapies. The pathway of care to receiving immunotherapy or CAR-T cell therapy is governed by the CDF and so this helps define the pathways but there remain options about sequencing of these treatments. This technology opens the option of another CAR-T cell product with promising response rates and event free survival for relapsed/refractory B-ALL patients. In trials, this technology shows a very tolerable toxicity profile with low rates of grade 3 or greater Cytokine Release Syndrome (CRS) or Immune Effector Cell Associated Neurotoxicity (ICANs). The hope, therefore, is that fewer patients will require lengthy inpatient care and delivery of care in an intensive care setting. The tolerability of this technology may also assist with patient selection for this type of therapy, e.g. those with advancing age and comorbidities.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	• CAR-T cell therapy for B-ALL is already in use for relapsed and refractory disease as per the CDF. This new technology will give the option of an alternative to the existing CDF approved CAR-T cell products. • This new technology will only be given in existing specially commissioned, JACIE accredited centres in the UK who are already setup for the delivery of CAR-T cell therapy. • These centres will already have ALL and CAR-T cell specialists delivering this care within a structure which provides apheresis, bridging therapy, lymphodepleting chemotherapy and administration of CAR-T cell therapy with management of the immediate toxicities as well as the late toxicities and follow up. These centres should also have access to co-located services to provide support in managing the potential toxicities e.g. CRS and ICANs • It is likely that these treating centres have everything already in place to deliver this therapy and that additional considerations are centred around patient selection for the appropriate CAR-T cell product.

	• Investment will be needed for training within those centres on the individual protocol for this technology as well as updates to pharmacy protocols and scripts and potentially investment in time from the stem cell lab due to the method of reinfusion. • There is consideration that this treatment may be able to be delivered in an ambulatory unit in those with a low disease burden. If this were to be the case, then consideration of the additional ambulatory space should be factored in for each individual treating centre.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	• When compared to other immunotherapy options (e.g. Blinatumomab or Inotuzumab alone), this technology has an EFS and OS advantage making this a more definitive treatment? • When compared with the existing adult approved CAR-T product (Tecartus), the outcomes in terms of EFS and OS are comparable (although clearly this is not in a head-to-head study). • In clinical trials, the lower rates of measured severe toxicity (grade 3 or more) compared with those seen in the FELIX study would be expected to benefit patients quality of life due to less time in hospital, better tolerability with the hope of reduced psychological impact.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• Given the tolerable toxicity profile of obe-cel in clinical trials, it may be that patients who are transplant ineligible due to age or comorbidity can be considered for this treatment. Heavily pre-treated patients also benefitted from obe-cel with a favourable toxicity profile based on data from the FELIX study • It also opens up a potentially curative option for patients where a donor for allogeneic stem cell transplant is not available due to lack of ethnic diversity on donor registries • Clearly Obe-cel and other CD19 targeted CAR-T cell products are only effective for those with CD19 expressing disease and so will only benefit those where this is demonstrated

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	• This technology opens options for healthcare professionals to offer to patients with difficult relapsed/refractory B-ALL • Obe-cel, if approved, will only be approved for use in existing, experienced CAR-T cell treating centres. This technology is administered in a different way based on marrow blast percentage and so this may take training and education in the CAR-T teams in order to adapt to this way of treating. • These centres should already have experience of managing patients prior to apheresis, in the bridging period and in the immediate and longer term after CAR-T infusion. • These centres will be administering therapy with the support and backing of the National ALL panel where shared experience can support ongoing treatment
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• Patients will still need to be discussed and have approvals met at the National ALL Complex Cases and CAR-T Expert Panel, as mandated for other CAR-T cell technologies. • Based on current practice, referring clinicians will have to demonstrate CD19 expression on relapsed disease for patients to receive this technology as well as other stipulations. This is not done by additional testing as flow cytometry to assess for CD19 status would be considered a standard of good clinical care in the relapse setting
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	• It is clear from the information submitted by the patient organisations that patients value treatments that involve shorted inpatient bed days and those with lesser toxicity due to the physical and psychological impact. • From the clinical trial data, Obe-cel has the potential to reduce time in hospital with less severe grade toxicities and with the potential for ambulatory protocols.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	• Obe-cel is a targeted form of therapy and is another stepwise change in the management of relapsed B-ALL which would have traditionally been treated

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	with intensive chemotherapy regimens with poor outcomes in terms of toxicity as well as disease related outcomes. CAR-T cell therapy has changed the landscape of this disease for patients with difficult disease and where options are limited due to the lack of appropriate other therapies, toxicity of other treatments, age of the patient or the lack of a stem cell donor • Obe-cel has a tolerable toxicity profile with low rates of grade 3 or greater CRS 2.4% and ICANS 7.1% in the FELIX study with infection rates which are comparable to other targeted agents, 24.4% all grades • Obe-cel in the FELIX study also demonstrated overall response rates of 77% with a median EFS of 11.9 months with 12-month event-free and overall survival of 49.5% and 61.1%, respectively. Whilst this is comparable to the Brexu-cel outcomes in Zuma-3, the FELIX study showed clear benefit in terms of responses and toxicity in those patients with lower disease burden. • Obe-cel is UK manufactured and so this innovation will hopefully allow for quicker treatment and less time in the bridging period which may reduce the need for or the dosing of bridging therapies
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	• The major toxicity from any therapy which would limit management of B-ALL is the risk of infection (24.4% of patients had neutropenic sepsis of all grades in the FELIX study with five deaths from infection). • Cytopenias after therapy may also impact on the longer-term management of patients with B-ALL and impact on the quality of life due to the need for ongoing transfusion support and management of infections.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	• Largely, the FELIX study used similar patient selection criteria to that of the criteria used for patient approvals for CAR-T cell therapy in the UK • This study had a subset of patients who were studied separately who had MRD disease or isolated extramedullary disease and this does not currently reflect selection and approvals in the UK. This is another subset of patients where there is an unmet need but I am not clear if this will be taken into account for this appraisal

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• In addition, the other difference is in the administration of the CAR-T cell technology. Obe-cel is administered in a split dose dependent on blast percentage. Although this is different to the current experience in the UK (off trial), I do not foresee that this should cause any issues with administration of the technology or in the care of the patients, once training has taken place • Otherwise, the clinical trials reflect current UK practice • In this type of trial in R/R B-ALL, the most crucial factors for outcome and for the patients in the short and longer term is EFS, OS and Toxicity. These were adequately measured in the FELIX study and predict for a more durable response than other immunotherapy agents if not consolidated with Allogeneic stem cell transplant or CAR-T cell therapy. • These are adequately measured and are reflected upon in the available data • I am not aware of any adverse effects that have come to light since the FELIX study was published
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA975]?	Yes. There has been published updates on this therapy as well as the publication of real-world data confirming its tolerability and efficacy. In addition, there has been the NICE technology appraisal guidance for Tecartus (TA893) which would be the main comparator in adults (26 years and older)
23. How do data on real-world experience compare with the trial data?	I am not aware of any significant real-world data for Obe-cel use due to the short duration between license. • There is extensive Real-World Data for other CAR-T products used in the management of R/R B-ALL.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	B-ALL affects' adults of all ages and conditions. Age inequality is a major consideration as an other CAR-T ell therapy agent, Kymriah, can be selected for younger patients (25 years and under). This has a more tolerable toxicity profile in terms of CRS and ICANs. Unfortunately, this product is not currently available in the UK for those aged 26 years or older. The CAR-T product of choice is

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Tecartus. This brings into question that older patients, many of whom are comorbid, do not have access to a more tolerable CAR-T cell therapy product for the management of relapsed/refractory disease. In addition, a large issue in many areas of the UK is the geography of the region and the distance from a CAR-T treating centre. Patients may be required to travel long distances for this treatment and for their visitors to accompany them on this journey, both when receiving treatment as an outpatient and when inpatients. This comes at considerable cost and so one of the factors to consider is the cost of this in a geographically expanse region. For some patients, this treatment may be able to be delivered in an ambulatory setting and so this may benefit those who are travelling away from their support network to have this therapy. I do not believe that this evaluation would exclude anyone protected by the equality legislation although we should be mindful of the access to this treatment for those of advancing age or those with comorbidities as well as those on a low income where travel for treatment is expected.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Obe-cel offers a tolerable and effective CAR-T product for adults with Relapsed/ Refractory B-ALL

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

Obe-cel is given in such a way that it opens up the discussion for ambulatory administration of CAR-T for certain groups of patients therefore providing therapy in a way that is more accessible for some and more compatible with Quality of life standards

Click or tap here to enter text.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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Part 1: Treating B-cell acute lymphoblastic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Claire Roddie
2. Name of organisation	University College London Hospital
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with B-cell acute lymphoblastic leukaemia? ☐ A specialist in the clinical evidence base for B-cell acute lymphoblastic leukaemia or technology? ☒ Other (please specify): specialist in CART cell therapy
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for B-cell acute lymphoblastic leukaemia?	**The main aims of treatment are to** (1) eradicate the leukaemia clones, (2) without substantial side effects/toxicity and (3) prevent the disease from coming back.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	**A clinically significant treatment response would be:** 1. Complete Remission with achievement measurable residual disease status (MRD) negativity 2. Durable ongoing response beyond 6 months without further therapy
10. In your view, is there an unmet need for patients and healthcare professionals in B-cell acute lymphoblastic leukaemia?	**Yes, there is an unmet need for patients/physicians in B-ALL.** For adult patients we need a treatment for relapsed/refractory(r/r) disease that is: 1. **Less toxic** (so accessibility of treatment is enhanced, particularly to older patients with co-morbidities) 2. **A stand-alone treatment** (i.e. does not need consolidation with allogeneic stem cell transplant (allo-SCT) to maintain response, as many patients are ineligible for allo-SCT.
11. How is B-cell acute lymphoblastic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	1. **Clinical guidelines:** First line management is protocolised. Nil UK-specific guidance for relapsed/refractory (r/r) B-ALL other than some limited ESMO guidance (D. Hoelzer et al.2023. PMID: 37832649 DOI: 10.1016/j.annonc.2023.09.3112). 2. **Pathway of Care:** This varies between centres/specialists and depends on patient demographics/fitness and stage/risk/burden/responsiveness of disease to salvage therapies. In the majority of cases of allo-SCT naïve relapse, patients will be 'bridged' to allo-SCT if eligible. However, given many patients do not have a donor/do not achieve complete response (CR) to proceed to allo-SCT/are not eligible due to age/comorbidity/other, allo-SCT is not feasible for many, thus an alternative 'stand-alone' therapy is required. My experience is from within the UK. 3. **What impact would the technology have on pathway:** The availability of obe-cel would (a) make CART for r/r adult B-ALL much more accessible as it (b) is clearly a low toxicity CAR which can be used safely in older and comorbid patients, and (c) has the potential to give rise to durable responses in a proportion of patients without the requirement for further therapy

	including allo-SCT (C Roddie et al.N Engl J Med. 2024 Dec 12;391(23):2219-2230.PMID: 39602653). 4. **We would expect obe-cel to replace brexu-cel in the current treatment pathway** and lead to a higher proportion of patients achieving durable remission without further therapy. Notably in real-world US experience with brexu-cel published in 2024, multivariate analysis showed superior progression free survival (PFS) post-brexu-cel when patients received consolidative allo-SCT (US Rocca experience, G Roloff et al. https://doi.org/10.1200/JCO.24.00321). Notably on the FELIX study, durable remission was observed without allo-SCT consolidation and was associated with durable (>6months) CAR-T persistence in the blood (https://doi.org/10.1200/JCO.2024.42.16_suppl.65). One of the problems with allo-SCT is that it can eradicate CAR-T immunosurveillance and may not be appropriate for obe-cel patients with ongoing CAR-T persistence. Secondly, we might expect that obe-cel may be used in preference to allo-SCT in some patients with r/r disease as the treatment-related mortality (TRM) of Obe-cel is substantially lower than that of allo-SCT.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	1. **How does resource use differ with current care:** Compared with Brexu-cel (Tecartus) the resource use of obe-cel is likely to be lower particularly in relation to high-dependency unit (HDU) and intensive care unit (ICU) management of high grade neurotoxicity which despite good disease control following bridging therapy pre-CART seems to still affect around 30% of B-ALL patients receiving Brexu-cel in the real-world (**UK experience**, A Castleton et al. https://doi.org/10.1182/blood-2024-199287; **US Rocca experience**, G Roloff et al. https://doi.org/10.1200/JCO.24.00321) 2. **In what clinical setting would this be used:** Specialist tertiary CAR-T centres will deliver this product. 3. **What investment needed for the technology:** Everything that would be required for clinical delivery of obe-cel is already in situ in UK CAR-T centres. Nothing special required beyond what is used for other CART products. Training will be required for site on-boarding, but this is very similar to what is required for other CART products.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	1. **Will the technology increase length of life in remission more than current care:** (a) Yes compared to the bispecific T-cell engager Blinatumomab or the ADC Inotuzumab Ozogamicin which do not induce durable responses and are generally considered more as a 'bridge' to allo-SCT; and (b) Yes compared to Brexu-cel with the caveat that the follow-up for patients treated with Obe-cel on the Phase II FELIX study is shorter than that of Brexu-cel treated patients on ZUMA 3/Phase II. That said, durable responses without further therapy were very infrequent on ZUMA-3. A poster presentation from T Hadjivassileva et al at the 2023 EHA/EBMT CART meeting indicates that of 55 patients infused in Phase II on ZUMA-3, only 4/55 (7%) were in ongoing remission without further therapy at a median of 38.8 months. If we look at extended follow up on the Phase I data of B-ALL patients treated with obe-cel on the ALLCAR19 study, 8/20 (40%) of patients were in ongoing remission at 36 months without further therapy with the exception of one patient in whom allo-SCT consolidation was given due to investigator preference. 7/8 ongoing responders (those not consolidated with allo-SCT) had ongoing CAR-T persistence in the blood (C Roddie et al; ASH 2022). 2. **Will the technology increase health-related QoL more than current care:** Obe-cel has a low immunotoxicity profile and thus patients are less likely to be debilitated by treatment which is likely to improve QoL scoring. Further, durable anti-leukaemia response to obe-cel without a requirement for further therapy will also likely improve QoL outcomes.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• As per the NEJM paper (PMID: 39602653) overall all patient subgroups responded to treatment with obe-cel, but patients with more than 75% bone marrow (BM) blasts pre-treatment were less likely than those with <75% BM blasts to achieve durable event free survival (EFS) and may be a subgroup in whom we would proactively consider post-CART consolidation approaches such as allo-SCT for those who are eligible, particularly in the event of loss of CAR-T persistence in the blood. • The role of post-CAR-T consolidation remains a subject of ongoing significant debate in the adult ALL community.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	1. **Obe-cel will be easier to use than Blinatumomab and allo-SCT** as obe-cel requires a single inpatient admission and a single 2-dose treatment schedule administered over 10 days i.e. 'one and done' therapy. Blinatumomab requires continuous infusion and often several cycles of treatment prior to allo-SCT consolidation. Allo-SCT is associated with high treatment related mortality and morbidity and is a high intensity inpatient admission for 1 month followed by very close monitoring for complications (and not infrequent re-admissions to hospital) for at least the first 3-12 months post-treatment. 2. **Obe-cel will be easier to use than Brexu-cel** as the immunotoxicity profile is much better and thus hospital stays and requirement for ICU admission will be lower.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• Obe-cel is administered as a single split-dose treatment (day 1 and day 10) with no further doses required. • Starting treatment with CAR-T requires for the patient to be free of clinically significant infection and with good organ function. • Stopping treatment (i.e. not administering day 10 obe-cel dose) would be in the event of immunotoxicity following day 1 cells that had not settled by day 10. • Otherwise there should be no other starting/stopping rules.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	• QALYs must take into account the substantially lower ≥Grade 3 CRS and ICANS rates observed with obe-cel (2.4%/7.1%; PMID:39602653) compared to brexu-cel (25%/25%; PMID: 34097852). • Bijal Shah et al presented an abstract at ASH 2024 showing that adverse event management costs generally increase with event severity, and that the key drivers of cost are medication and ICU usage. • The low incidence of Grade ≥3 CRS/ICANS in patients receiving obe-cel (2.4%/7.1%) indicates its potential to reduce healthcare resource utilization and costs.

	• Further, QALY calculations must additionally consider data from the FELIX trial which demonstrates durable remissions and CART persistence in a substantial proportion of patients without a requirement for allo-SCT consolidation. • Real-world US brexu-cel data indicates that allo-SCT post-brexu-cel is associated with better PFS (US Rocca experience, G Roloff et al. https://doi.org/10.1200/JCO.24.00321). Allo-SCT as consolidation post-CAR-T is undesirable for many reasons, briefly outlined in question 15.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any need of the patient population?	**Is the technology a 'step-change' in the management of the condition?** **Yes:** obe-cel is a step change for adult B-ALL in that it is safe and well-tolerated even in comorbid and older patients for whom treatment with other CAR products may not be feasible. Further, due to its persistence profile in the blood obe-cel is associated with durable responses without further therapy in a substantial proportion of patients. This has not been observed for patients receiving blinatumomab or brexu-cel. **Does this technology address unmet needs of the patient population?** **Yes:** due to the safety profile, obe-cel allows us to offer CAR-T therapy to substantially more patients than we currently can with brexu-cel. Further, due to the durable responses observed on ALLCAR19 (PMID: 34464155) and FELIX, obe-cel is likely to be the only therapy required for management of r/r ALL for a large number of infused patients i.e. no further salvage or consolidation may be required.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	• The immediate post CAR-T side effects (within 28 days), namely CRS/ICANS are managed in hospital with immune-modulating drugs. The incidence of these side-effects is much lower with obe-cel than with brexu-cel as outlined above. • The longer term side effects of CD19 CAR-T therapy include increased risk of infection in some patients from hypogammaglobuliemia. In this setting, patients with recurrent infections will often receive immunoglobulin replacement therapy administered monthly. This necessitates hospital visits,

	although some centres offer this therapy as home treatment if administered subcutaneously.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• The FELIX trial reflects UK approaches to management of adult ALL. • Most important outcomes were low toxicity and event free survival (with the latter having a strong association with ongoing CAR-T persistence in the blood). • No surrogate outcomes. • No other side effects that have come to light.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not aware of this.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA975]?	Not aware.
23. How do data on real-world experience compare with the trial data?	No real world evidence with obe-cel in adult ALL yet.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	If anything, obe-cel opens up the opportunity to receive CAR-T to more ALL patients due to its tolerable safety profile.

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Obe-cel is safe with a low incidence of ≥Grade 3 CRS and ICANS.

Obe-cel can be safely used in older and comorbid patients.

Obe-cel has high complete response rates, even in high-burden B-ALL.

Obe-cel is associated with durable responses without allo-SCT consolidation.

Ongoing response is associated with ongoing CAR-T persistence in the blood.

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Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with B-cell acute lymphoblastic leukaemia

Table 1 About you, B-cell acute lymphoblastic leukaemia, current treatments and equality

1. Your name	Harry Robert Brown
2. Are you (please tick all that apply)	☒ A patient with B-cell acute lymphoblastic leukaemia? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with B-cell acute lymphoblastic leukaemia? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Anthony Nolan
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement

6. What is your experience of living with B-cell acute lymphoblastic leukaemia? **If you are a carer (for someone with B-cell acute lymphoblastic leukaemia) please share your experience of caring for them**	I was diagnosed aged 17 with B-cell ALL in July 2023. Before my diagnosis I had very few symptoms. I was diagnosed in A&E with ALL and a brain haemorrhage after being taken there by an out-of-hours GP. Having presented with leukostasis, I required 2 cycles of leukapheresis to reduce my white cell count (845) which was the highest my consultant had ever seen. Right from the start I was warned my disease would take a while to treat. I was treated for 70 days on the ALLtogether 1 trial following the high-risk arm. During this time, I remained in hospital in Leeds and despite my treatment being escalated 4 times, chemo failed to get me into remission (still had 3% blasts). After consultation with my medical team and specialists from The Christie and GOSH and my parents, I decided to start Blinatumomab with the aim of having an allogenic stem cell transplant from an unrelated donor when I was in a secure remission. After tolerating the first 2 weeks of treatment I was allowed home. This was a great relief after spending 90 days in hospital. After my second cycle of blina I achieved a MRD negative remission for the 1st time. At this time, I was severely neutropenic and required regular blood transfusions. I was started on a 3rd month long blina cycle whilst my transplant was organised. During this time, I came down with Covid. Just before Christmas 2023 I had a seizure and I was taken back into hospital where the disease was found to have returned and spread to my spinal fluid and brain. At this point my doctors told me that they felt a stem cell transplant was unlikely to be successful. This was an extremely challenging time for my family and me. At this point I was having 3 times a week intrathecal chemo to try and get my disease under control. I also came down with a severe flu infection which hospitalised me for 1 month. At this point I was made aware of a clinical trial (AUTO1-PY1) that had just opened at GOSH for obe-cel. As I was told I was no longer eligible for standard NHS CAR-T, I felt that I had no other choice other than enrol. I firmly believe that this trial saved my life. I had my t cells harnessed through apheresis and was put on holding chemo. In early March I went down to London to start conditioning chemo. On the 13th of March I received my modified cells. Although my neutrophil count dropped to 0, I tolerated the cells well. I had regular neurological assessments and after 1 month in hospital I was allowed home. At my subsequent bone marrow biopsies, I was found to be in a secure remission. For 9 months I was severely neutropenic. The CAR-T has also left me with b cell Aplasia, so I now receive monthly immunoglobulin top-ups. I am

	now seen monthly at the Great North Children's hospital, and I have been able to get back to a normal life and am approaching 12 months in remission.
7a. What do you think of the current treatments and care available for B-cell acute lymphoblastic leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Current treatment is challenging both for the patient and their family. This is particularly the case for older people or those with existing health conditions. Treatment paths last for many years and are intense. Treatment is mainly centred around chemotherapy and very few people are able to access advanced cellular therapies. Care is centred around specialist hospitals often far from home with very little care available in the community. This is particularly significant for people on maintenance treatment which can last years. My views are very similar to others I have met, particularly children and their parents who really struggle through current treatment.
8. If there are disadvantages for patients of current NHS treatments for B-cell acute lymphoblastic leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Treatment schedules are intense and long. This requires large amounts of time off school and work. High strength chemo is also very damaging for the body with bone pain, mouth soreness and bowel problems common. Neutropenia is also a major problem which is very hard to manage in winter. Large amounts of blood product transfusions are also required. I had over 50 red cell and 70 platelet transfusions. This brings challenges with tiredness and bruising. It can be very difficult to return to normal life after these experiences. Currently kinder treatments such as advanced cellular therapies are only available to a very small number people. Other options such as stem cell transplants rely on suitable donors which can be hard to find and is a very stressful experience for patients and families.

9a. If there are advantages of obecabtagene autoleucel over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does obecabtagene autoleucel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	After having obe-cel I was able to return to school after 6 months. This would have been unlikely if I had a stem cell transplant. This means my normal life has been impacted less. Without obe-cel I would have had few other options. It can offer a final chance to patients who haven't responded to standard treatment. From speaking to my medical team, the prevalence of severe side effects such as neurological toxicity are far lower than standard CAR-T with patients generally tolerating it well. It also can shorten the cancer journey substantially by removing the need for maintenance chemo. In my case the treatment didn't dramatically reduce my blood counts either. I felt by far my best when receiving CAR-T compared to any other cancer treatment I have experienced. After speaking to another patient on my trial, their experience is similar. The biggest advantage is the lower prevalence of severe side effects as this is one of the most challenging problems with CAR-T and could allow it to be used more widely safely. Obe-cel has far fewer side effects which make you feel unwell. Blood counts don't drop as far, and it doesn't cause sickness. Far less disruption is felt on day-to-day life.
10. If there are disadvantages of obecabtagene autoleucel over current treatments on the NHS please describe these. For example, are there any risks with obecabtagene autoleucel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Little information is known about the possible side effects or long-term success of the treatment. It is also expensive and must be used in specialist centres in a controlled way. This might make it hard to scale up its use. It also had to know how different patients will react. There have still been some instances of severe side effects. I have also suffered from prolonged low neutrophils after obe-cel which have taken over 9 months to recover with help from GCSF. It has also caused me b cell aplasia which requires regular immunoglobulin to-ups. I am unaware whether this is a case with standard car-t.

11. Are there any groups of patients who might benefit more from obecabtagene autoleucel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Obe-cel would be good for any groups who would struggle to tolerate high intensity chemotherapy because of the lower prevalence of side effects and less disruption to normal life. Patients who have not responded to other treatment may greatly benefit from having obe-cel as an option. Obe-cel would be good for any groups who would struggle to Less well-educated groups and minorities may not be able to access information about the treatment. Those who live far away from specialist centres may also find it harder to access the treatment. Overall, I feel everyone will benefit from obe-cel.
12. Are there any potential equality issues that should be taken into account when considering B-cell acute lymphoblastic leukaemia and obecabtagene autoleucel? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	The geographical location of treatment centres and the availability of clear information about the product that all groups can understand. Some groups, particularly ethnic minorities sometimes distrust complex medical treatments like this or might have religious objections due to the genetic modification involved.
13. Are there any other issues that you would like the committee to consider?	I would like the benefit this treatment could bring to young people and the low prevalence of side effects to be closely considered.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Obe-cel got me into remission when all other treatment failed.
- Obe-cel caused me prolonged neutropenia
- The prevalence of severe side effects is reduced
- Particularly benefit could be felt by children
- Click or tap here to enter text.

Thank you for your time.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with B-cell acute lymphoblastic leukaemia

Table 1 About you, B-cell acute lymphoblastic leukaemia, current treatments and equality

NICE National Institute for Health and Care Excellence

1. Your name	ELIZABETH (LIZZIE) SPEAR
2. Are you (please tick all that apply)	☐✓ A patient with B-cell acute lymphoblastic leukaemia? ☐✓ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with B-cell acute lymphoblastic leukaemia? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	LEUKAEMIA UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐✓No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐✓I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement

6. What is your experience of living with B-cell acute lymphoblastic leukaemia? **If you are a carer (for someone with B-cell acute lymphoblastic leukaemia) please share your experience of caring for them**	LIZZIE SPEAR DOB 28.04.68 - February 2021: reluctantly made a GP appointment as my daughter Lowri (who was studying from home due to Covid preventing her from attending in person at Oxford Uni) said I was unusually unwell. (I was always unwell as I was already immunocompromised thanks to a lack of Spleen and had recently been diagnosed with Fibromyalgia) - GP assumed it was an allergic reaction to the morphine patches he had recently prescribed but ordered blood tests nonetheless - March 2021: called by local hospital (Burton) to say there was an anomaly with my blood tests and to expect a call from Derby Royal Infirmary - Same day: call from DRI to say I needed an urgent BMB - Same day: attended DRI to be told I either had ALL or AML and that they couldn't treat me and I was going to be admitted to Nottingham City Hospital the next day - March 3rd 2021: admitted and chemotherapy started. Diagnosed with ALL. I was an inpatient for 8 weeks. Chemo failed! - May 2021: Started Blinotumamab 2 x 4 week cycles to prep for SCT No match could be found for me and as an only child I had no siblings so my only hope was my only child - my daughter Lowri. (Back story….Lowri was born 9 weeks premature in 1999 after I had lost 6 babies before that. I was told she may have developmental problems and possible brain damage but she actually excelled at school and gained a place at Oxford Uni to study English!) - August 2021: admitted for pre-SCT chemo, total body irradiation and brain radiotherapy. - September 2021: 7th: Lowri donated her stem cells (via her femoral vein!) & 8th: I received Lowri's cells. Haploidentical Transplant. - March 2022: Lowri had to donate stem cells again for me to have a DLI as my chimerism numbers were dropping. - In remission for 18 months - November 2023: Routine FBC test at NCH revealed 80% blasts in my blood and was told that my only chance of survival was if I had CAR-T but that it would depend on my being accepted for treatment by the Cancer Drugs Fund panel - Outpatient chemo started again (infusions in Day Case Clinic) - February 2024: CAR-T authorised and consent signed but by this time I was REALLY unwell. I had lost my sight in one eye, was having regular falls, couldn't write my name on the consent form. Peripheral neuropathy in lower limbs and feet made mobility impossible so needed a wheelchair. Admitted to hospital and diagnosed with severe reaction to intrathecal methotrexate. - 23rd February 2024: T cell collection via apherisis - 30th March 2024: did the Blood Cancer UK Walk of Light with friends and family around my local village with me in a wheelchair! - 10th April 2024: admitted for pre CAR-T chemo - 15th April 2024: Received my CAR-T cells (Nottingham's 1st ever adult relapsed ALL CAR-T patient) - 2 more weeks as an inpatient until end of April (including my 56th birthday!)

	- May 2024: 1 month as an outpatient staying in a lovely dog friendly hotel near the hospital thanks to the generosity of Leukaemia Care. - I have progressed from wheelchair to rollator to just a stick now despite still having peripheral neuropathy! - I have managed to do a few gigs over the summer (I'm a pro cellist) - Remission confirmed 1st August 2024 WATCH THIS SPACE! -

7a. What do you think of the current treatments and care available for B-cell acute lymphoblastic leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The treatments I have had have been gruelling, if I'm honest. It has been a 4 year journey filled with chemotherapy, immunotherapy, lumbar punctures, bone marrow biopsies, total body irradiation etc etc. My immune system has been severely compromised so I'm now having IVIG infusions monthly and handfuls of medication 3 times a day! I feel brutalised! The IT MTX has left me with permanent spinal damage which has given me significant mobility issues. I can only speak of my own experiences.
8. If there are disadvantages for patients of current NHS treatments for B-cell acute lymphoblastic leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The initial courses of intensive chemotherapy as an inpatient were very tough. I felt so isolated and scared (due to Covid restrictions) The side effects were awful. Constant sickness, unable to eat, losing all my hair. My Blinatumomab 24/7 infusion was much more tolerable although the rucksack provided was a bit cumbersome to live with/shower with/sleep with! The stem cell transplant that followed was so ridden with anxiety and having to have all the chemotherapy once again to prepare for it plus the added trauma of total body and brain irradiation just added to this. Intrathecal chemotherapy is particularly unpleasant (understatement!) Hair loss and GVHD symptoms due to chemo and SCT were upsetting and worrying.

9a. If there are advantages of obecabtagene autoleucel over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does obecabtagene autoleucel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	If I'm correct I believe that I had Tisagenlecleucel (Kymriah) when I relapsed last year. I was the first patient in Nottingham City Hospital to receive this treatment for adult ALL relapse. The whole process was much more tolerable than the SCT. My initial chemotherapy was all done as an outpatient rather than having a lengthy stay in hospital and I didn't lose my hair this time, which was a blessing. I was able to work a couple of months after my CAR-T treatment and have continued to do so on a part-time basis ever since. Being able to play my cello again professionally has definitely been the biggest advantage! CAR-T is MUCH less distressing than the chemotherapy, immunotherapy and SCT options I've had previously.
10. If there are disadvantages of obecabtagene autoleucel over current treatments on the NHS please describe these. For example, are there any risks with obecabtagene autoleucel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	All potential side effects were clearly explained to me by the team at NCH and fortunately I was only mildly affected.
11. Are there any groups of patients who might benefit more from obecabtagene autoleucel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I can't really comment on this I'm afraid. The only disadvantage I can think of is the distances needed to travel to the few specialist centres that offer it.

12. Are there any potential equality issues that should be taken into account when considering B-cell acute lymphoblastic leukaemia and obecabtagene autoleucel? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I wouldn't know, I'm afraid. I have been left with mobility issues and ongoing fatigue but I don't think that is necessarily an equality issue.
13. Are there any other issues that you would like the committee to consider?	Nothing I can think of.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- ALL is brutal and life changing
- Chemotherapy and Radiotherapy have awful side effects
- **Finding a suitable match for SCT isn't always an option**
- CAR-T gave me hope for the future
- Without CAR-T I wouldn't be alive writing this!

Thank you for your time.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Monday 17 February.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with B-cell acute lymphoblastic leukaemia

Table 1 About you, B-cell acute lymphoblastic leukaemia, current treatments and equality

1. Your name	Harry Robert Brown
2. Are you (please tick all that apply)	☒ A patient with B-cell acute lymphoblastic leukaemia? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with B-cell acute lymphoblastic leukaemia? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Anthony Nolan
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement

6. What is your experience of living with B-cell acute lymphoblastic leukaemia? **If you are a carer (for someone with B-cell acute lymphoblastic leukaemia) please share your experience of caring for them**	I was diagnosed aged 17 with B-cell ALL in July 2023. Before my diagnosis I had very few symptoms. I was diagnosed in A&E with ALL and a brain haemorrhage after being taken there by an out-of-hours GP. Having presented with leukostasis, I required 2 cycles of leukapheresis to reduce my white cell count (845) which was the highest my consultant had ever seen. Right from the start I was warned my disease would take a while to treat. I was treated for 70 days on the ALLtogether 1 trial following the high-risk arm. During this time, I remained in hospital in Leeds and despite my treatment being escalated 4 times, chemo failed to get me into remission (still had 3% blasts). After consultation with my medical team and specialists from The Christie and GOSH and my parents, I decided to start Blinatumomab with the aim of having an allogenic stem cell transplant from an unrelated donor when I was in a secure remission. After tolerating the first 2 weeks of treatment I was allowed home. This was a great relief after spending 90 days in hospital. After my second cycle of blina I achieved a MRD negative remission for the 1st time. At this time, I was severely neutropenic and required regular blood transfusions. I was started on a 3rd month long blina cycle whilst my transplant was organised. During this time, I came down with Covid. Just before Christmas 2023 I had a seizure and I was taken back into hospital where the disease was found to have returned and spread to my spinal fluid and brain. At this point my doctors told me that they felt a stem cell transplant was unlikely to be successful. This was an extremely challenging time for my family and me. At this point I was having 3 times a week intrathecal chemo to try and get my disease under control. I also came down with a severe flu infection which hospitalised me for 1 month. At this point I was made aware of a clinical trial (AUTO1-PY1) that had just opened at GOSH for obe-cel. As I was told I was no longer eligible for standard NHS CAR-T, I felt that I had no other choice other than enrol. I firmly believe that this trial saved my life. I had my t cells harnessed through apheresis and was put on holding chemo. In early March I went down to London to start conditioning chemo. On the 13th of March I received my modified cells. Although my neutrophil count dropped to 0, I tolerated the cells well. I had regular neurological assessments and after 1 month in hospital I was allowed home. At my subsequent bone marrow biopsies, I was found to be in a secure remission. For 9 months I was severely neutropenic. The CAR-T has also left me with b cell Aplasia, so I now receive monthly immunoglobulin top-ups. I am

	now seen monthly at the Great North Children's hospital, and I have been able to get back to a normal life and am approaching 12 months in remission.
7a. What do you think of the current treatments and care available for B-cell acute lymphoblastic leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Current treatment is challenging both for the patient and their family. This is particularly the case for older people or those with existing health conditions. Treatment paths last for many years and are intense. Treatment is mainly centred around chemotherapy and very few people are able to access advanced cellular therapies. Care is centred around specialist hospitals often far from home with very little care available in the community. This is particularly significant for people on maintenance treatment which can last years. My views are very similar to others I have met, particularly children and their parents who really struggle through current treatment.
8. If there are disadvantages for patients of current NHS treatments for B-cell acute lymphoblastic leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Treatment schedules are intense and long. This requires large amounts of time off school and work. High strength chemo is also very damaging for the body with bone pain, mouth soreness and bowel problems common. Neutropenia is also a major problem which is very hard to manage in winter. Large amounts of blood product transfusions are also required. I had over 50 red cell and 70 platelet transfusions. This brings challenges with tiredness and bruising. It can be very difficult to return to normal life after these experiences. Currently kinder treatments such as advanced cellular therapies are only available to a very small number people. Other options such as stem cell transplants rely on suitable donors which can be hard to find and is a very stressful experience for patients and families.

9a. If there are advantages of obecabtagene autoleucel over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does obecabtagene autoleucel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	After having obe-cel I was able to return to school after 6 months. This would have been unlikely if I had a stem cell transplant. This means my normal life has been impacted less. Without obe-cel I would have had few other options. It can offer a final chance to patients who haven't responded to standard treatment. From speaking to my medical team, the prevalence of severe side effects such as neurological toxicity are far lower than standard CAR-T with patients generally tolerating it well. It also can shorten the cancer journey substantially by removing the need for maintenance chemo. In my case the treatment didn't dramatically reduce my blood counts either. I felt by far my best when receiving CAR-T compared to any other cancer treatment I have experienced. After speaking to another patient on my trial, their experience is similar. The biggest advantage is the lower prevalence of severe side effects as this is one of the most challenging problems with CAR-T and could allow it to be used more widely safely. Obe-cel has far fewer side effects which make you feel unwell. Blood counts don't drop as far, and it doesn't cause sickness. Far less disruption is felt on day-to-day life.
10. If there are disadvantages of obecabtagene autoleucel over current treatments on the NHS please describe these. For example, are there any risks with obecabtagene autoleucel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Little information is known about the possible side effects or long-term success of the treatment. It is also expensive and must be used in specialist centres in a controlled way. This might make it hard to scale up its use. It also had to know how different patients will react. There have still been some instances of severe side effects. I have also suffered from prolonged low neutrophils after obe-cel which have taken over 9 months to recover with help from GCSF. It has also caused me b cell aplasia which requires regular immunoglobulin to-ups. I am unaware whether this is a case with standard car-t.

11. Are there any groups of patients who might benefit more from obecabtagene autoleucel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Obe-cel would be good for any groups who would struggle to tolerate high intensity chemotherapy because of the lower prevalence of side effects and less disruption to normal life. Patients who have not responded to other treatment may greatly benefit from having obe-cel as an option. Obe-cel would be good for any groups who would struggle to Less well-educated groups and minorities may not be able to access information about the treatment. Those who live far away from specialist centres may also find it harder to access the treatment. Overall, I feel everyone will benefit from obe-cel.
12. Are there any potential equality issues that should be taken into account when considering B-cell acute lymphoblastic leukaemia and obecabtagene autoleucel? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	The geographical location of treatment centres and the availability of clear information about the product that all groups can understand. Some groups, particularly ethnic minorities sometimes distrust complex medical treatments like this or might have religious objections due to the genetic modification involved.
13. Are there any other issues that you would like the committee to consider?	I would like the benefit this treatment could bring to young people and the low prevalence of side effects to be closely considered.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Obe-cel got me into remission when all other treatment failed.
- Obe-cel caused me prolonged neutropenia
- The prevalence of severe side effects is reduced
- Particularly benefit could be felt by children
- Click or tap here to enter text.

Thank you for your time.

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