

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1723.1 – Brexucabtagene autoleucel for adult relapsed or refractory B-precursor acute lymphoblastic leukaemia

Applicant: Gilead Sciences Pty Ltd

Date of MSAC consideration: 23-24 November 2023

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

A re-application requesting public funding through the National Health Reform Agreement (NHRA) of TECARTUS (brexucabtagene autoleucel, also identified as KTE-X19 and abbreviated herein as brexu-cel) for adult patients (≥ 26 years of age) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (R/R B-ALL) was received from Gilead Sciences Pty Limited by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported public funding of brexu-cel for adult patients (aged 26 years or older) with R/R B-ALL. MSAC considered there was significant unmet clinical need in this group of patients and an equity of access issue as patients under 26-year-old are able to access an alternative chimeric antigen receptor T-cell (CAR-T) therapy for the same indication. MSAC noted that uncertainty remained regarding the clinical place of brexu-cel, in particular with regards to subsequent allogeneic stem cell transplant (allo-SCT). However, MSAC considered that the updated clinical evidence provided some certainty for the clinical effectiveness of brexu-cel for the treatment of R/R B-ALL in the proposed patient population. MSAC considered that the uncertainty and limitations with the economic evaluation remained and as such did not demonstrate the cost-effectiveness of brexu-cel at a price of **\$redacted**. MSAC noted the subsequent average price of **\$redacted** submitted by the applicant in a subsequent pricing proposal was consistent with the price supported for other publicly funded CAR-T therapies, that it considered to be acceptable for funding. Based on the outcomes of pay for performance (PfP) arrangements implemented for CAR-T therapies to date, MSAC considered that if a similar PfP arrangement was also implemented for R/R B-ALL, it would likely result in a higher average price than **\$redacted** per patient being paid in practice, due to the confounding introduced by subsequent allo-SCT use in this population. Therefore, MSAC considered that the PfP arrangement proposed by the applicant would not adequately manage uncertainty.

Therefore, MSAC support for public funding was contingent on a risk sharing arrangement that includes the following requirements:

- single payment of **\$redacted** paid per successfully infused patient
- limit of one successful CAR-T infusion per lifetime

- annual patient caps of **redacted** patients in Year 1, 2 and 3 respectively with **redacted** payment made for patients exceeding the annual caps
- review of the data to be conducted by MSAC no later than 3 years post the commencement of public subsidy of brexu-cel for R/R B-ALL for the purposes of understanding the clinical place, utilisation, equity of access and budget impact of brexu-cel for R/R B-ALL in Australian clinical practice. Subsequent to an initial review, MSAC may advise whether further review of the clinical effectiveness and cost-effectiveness is warranted.

As highlighted by the July 2023 review of tisagenlecleucel (tisa-cel) for the treatment of relapsed or refractory acute lymphoblastic leukaemia in paediatric and young adult patients (pALL) aged up to 25 years (MSAC application 1748), MSAC noted the challenges associated with reducing the price of already funded therapies through conducting a cost-effectiveness review informed by registry data. MSAC reiterated the need for data collection, however, did not consider that collection of additional data points for the specific purpose of informing MSAC were required. MSAC also reiterated that the Commonwealth and jurisdictions, along with other relevant stakeholders, work together to determine what the most appropriate data collection mechanism is for highly specialised therapies (HSTs).

Consumer summary

This is an application from Gilead Sciences Pty Ltd requesting public funding through the National Health Reform Agreement of brexucabtagene autoleucel (brexu-cel) to treat adults aged 26 years and over who have relapsed or refractory B-precursor acute lymphoblastic leukaemia (shortened to R/R B-ALL). MSAC first considered this application in November 2022.

Leukaemia is a type of blood cancer. B-precursor lymphoblastic leukaemia (B-ALL) is a fast-growing type of blood cancer in which too many B-cell lymphoblasts (immature forms of a certain type of white blood cell) are found in the bone marrow and blood. These abnormal B-cell lymphoblasts interfere with the production of normal blood cells, which can cause anaemia, recurring infections, bruising and bleeding.

Sometimes, B-ALL doesn't respond (is refractory) to treatment or comes back (relapses) after treatment. This is known as relapsed or refractory B-precursor acute lymphoblastic leukaemia (R/R B-ALL).

T cells are a part of a person's immune system, and are important in responding to infection. CAR-T cell therapy involves taking some of the patient's own blood and sending it to a laboratory. The T cells are then removed from the blood and genetically altered so that they can attack cancer cells. The patient's altered T cells are infused back into them so that they can target and kill the cancer cells. Brexu-cel is a type of CAR T-cell therapy that has been tested in patients with R/R B-ALL.

MSAC noted that a different CAR-T therapy is publicly funded to treat younger patients (aged 25 years or younger) with relapsed or refractory ALL but that patients aged 26 years or older with R/R B-ALL are not currently able to access a CAR-T therapy.

MSAC noted the evidence on the effectiveness of brexu-cel in comparison to other treatments currently available for patients with R/R B-ALL was uncertain and that new information provided by the applicant had not resolved these uncertainties. However, based on the evidence available, MSAC had moderate confidence that brexu-cel was effective but was less confident of how effective brexu-cel is compared to other available treatments. MSAC also noted that after brexu-cel treatment, other treatments (including stem cell [bone marrow] transplants) may be used and these subsequent treatments may be used more often in Australia than was seen in the clinical study with brexu-cel. These subsequent treatments may improve a patient's response but make it hard to know how effective brexu-cel will be on its

Consumer summary

own in Australian clinical practice. MSAC considered the higher price for brexu-cel in the applicant's submission was not cost-effective. However, MSAC noted that the lower price proposed by the applicant was similar to other funded CAR-T therapies and could represent value for money due to the unmet clinical need for patients aged 26 years or older with R/R B-ALL and if certain risk sharing arrangements were put in place. This included collecting and reviewing data on brexu-cel for R/R B-ALL no later than 3 years post the commencement of public funding to understand the actual clinical place, utilisation, equity of access and budget impact of brexu-cel for R/R B-ALL in Australia.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported public funding of brexu-cel for the treatment of patients (aged 26 years or older) with R/R B-ALL through the National Health Reform Agreement. MSAC had moderate confidence that brexu-cel was effective and considered brexu-cel would address a clinical need for a group of patients who currently do not have access to CAR-T therapies. MSAC also noted that the lower price proposed by the applicant was consistent with other publicly funded CAR-T therapies. However, MSAC recommended that a review of brexu-cel be undertaken after 3 years to assess its use and costs.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that Gilead Sciences Pty Ltd had resubmitted an application requesting public funding, through the NHRA, of brexu-cel for the treatment of adult patients (≥ 26 years of age) with R/R B-ALL. Additionally, after the resubmission of the applicant-developed assessment report (ADAR), the applicant submitted an updated pricing proposal with a PfP arrangement for brexu-cel. MSAC recalled that it had considered and not supported the original application for brexu-cel for treatment of adults with R/R B-ALL ([MSAC application 1723](#)) at its November 2022 meeting, due to several uncertainties, including the place of brexu-cel in clinical practice, its clinical effectiveness and its price. MSAC also recalled that the original application had proposed brexu-cel for adult patients aged ≥ 18 years.

MSAC recalled that it had previously supported several CAR-T therapies, including tisa-cel for the treatment of patients aged up to 25 years with R/R paediatric ALL ([MSAC application 1519](#)) and had reviewed all matters related to the public funding of tisa-cel for the treatment of pALL at its July 2023 meeting ([MSAC application 1748](#)).

MSAC noted that the resubmission had increased the eligible patient age for brexu-cel to ≥ 26 years of age. MSAC acknowledged that there was a significant unmet clinical need for adult patients (≥ 26 years of age) with R/R B-ALL and an equity of access issue as patients under 26-years-old are able to access an alternative CAR-T therapy (i.e., tisa-cel) for the same indication.

MSAC welcomed the consultation feedback received from four state and territory health authorities, noting the jurisdictions agreed that there is an unmet clinical need for adult patients (≥ 26 years of age) with R/R B-ALL. However, the state and territory submissions remained unsupportive of the application due to concerns there was limited evidence of clinical effects, the costing inputs were understated, and the clinical effects and benefits were overestimated (considering the use of brexu-cel as a bridge to allo-SCT in some patients). The state and territory submissions were supportive of a PfP arrangement.

MSAC noted that the clinical criteria in the resubmission were unchanged compared to the original submission. MSAC noted the complex clinical management algorithm and the outstanding uncertainties regarding the place of brexu-cel, including in relation to how brexu-cel may replace allo-SCT (i.e. potential comparator) and/or be used prior to allo-SCT (i.e. as a bridge to allo-SCT or allo-SCT to consolidate response), along with other uncertainties previously raised in the [public summary document \(PSD\) for MSAC application 1723](#) (pp 7–8). MSAC noted the applicant's pre-MSAC response stated that the algorithm was necessarily complex and was consistent with stakeholder input and the National Comprehensive Cancer Network (NCCN) 2023 guidelines for ALL (version 3.2023). The applicant's pre-MSAC response highlighted that the decision to pursue allo-SCT depends on the patient, their disease, and donor factors including availability of stem cells and noted that, in the ZUMA-3 study, 18% of patients in the all-ages population and 22% of patients aged ≥ 26 years had allo-SCT after brexu-cel treatment. The applicant therefore believed that the incidence of consolidating brexu-cel treatment with allo-SCT was likely to be low in Australia. However, MSAC was not convinced by this assertion and recalled a recent learning from the review of tisa-cel for R/R pALL was that the rate of allo-SCT after tisa-cel was higher in Australian clinical practice (31%) than expected from study data (19%).

MSAC noted that the clinical evidence for brexu-cel treatment of B-ALL was mostly unchanged from the original submission, but that the resubmission included updated 33 month follow-up data from the ZUMA-3 study, an updated naïve comparison and retrospective cohort matched indirect comparison (SCHOLAR-3) of brexu-cel versus the nominated comparators (blinatumomab, inotuzumab ozogamicin and chemotherapy), and a new matched-adjusted indirect comparison (MAIC) of brexu-cel (ZUMA-3) versus blinatumomab (TOWER) and inotuzumab ozogamicin (INO-VATE).

MSAC noted that the clinical effectiveness claim in the resubmission was also consistent with the original submission: that brexu-cel has superior efficacy compared with blinatumomab, inotuzumab ozogamicin, ponatinib and salvage chemotherapy in adult (≥ 26 years of age) patients with R/R B-ALL.

MSAC noted from the ZUMA-3 study that the complete remission (CR) rate was 62.8% (49/78) for brexu-cel in the modified intention-to-treat (mITT) (all ages) group. This compared to 24–48% (5/21 to 15/36) for the blinatumomab group and 32–35.8% (23/72 to 39/109) for the inotuzumab ozogamicin group. The observed 62.8% CR rate in the brexu-cel mITT (all ages) group was similar to the 61.9% CR rate reported for brexu-cel in the proposed population (≥ 26 years). MSAC noted that both overall survival (OS) and relapse-free survival (RFS) for brexu-cel in the proposed population progressively declined over time, including well past 12 months (which is the timepoint for measuring clinical response in the proposed PfP arrangement).

Overall, MSAC considered that the concerns previously raised regarding the certainty of the evidence remain. MSAC noted the applicant's pre-MSAC response regarding these concerns, but MSAC remained concerned about the non-randomised comparison, use of mITT instead of intention-to-treat (ITT) analysis, imprecision (small numbers) and short follow-up of the studies, transitivity issues for indirect comparison (baseline characteristics, cointerventions), and exclusion of allo-SCT as a comparator (stand alone or in combination with other comparator therapies). However, MSAC also acknowledged that it was unlikely to have significantly more confidence in the data within the next 2–3 years due to the limited prospect of additional relevant studies. Therefore, based on the evidence available, MSAC concluded that it was moderately certain of the clinical effectiveness of brexu-cel but was less confident of the relative effectiveness of brexu-cel compared to blinatumomab, inotuzumab ozogamicin, ponatinib and salvage chemotherapy.

MSAC noted that several aspects of the economic analysis had been revised since the original submission, including a lower price for brexu-cel (using the **\$redacted** price proposed in the ADAR), a more conservative cure point of 5 years, updated estimates for OS and event-free survival (EFS) (based on 33-month follow-up data from the ZUMA-3 study), and updated hospital and healthcare unit costs. MSAC noted that the base case incremental cost-effectiveness ratio (ICER) was **\$redacted** per quality-adjusted life year (QALY), with incremental QALYs of 2.53. The key drivers of the model included the 5-year cure point assumption, 52-year lifetime horizon, assumption that 22.2% of patients (based on the ZUMA-3 study) received subsequent allo-SCT, use of a progressive health state utility source (ZUMA-3), use of standardised mortality ratio (SMR) of 2, the choice of a parameterised survival curve and the “adjustment” procedure for extrapolations. MSAC acknowledged that other CAR-T therapies that had been approved for funding also had some uncertainties. However, MSAC considered that the uncertainty and limitations with the economic evaluation remained high and as such did not demonstrate the cost-effectiveness of brexu-cel at a price of **\$redacted**.

MSAC noted the financial analysis in the resubmission ADAR estimated the net financial impact to government ranged from **\$redacted** million in year 1 to **\$redacted** million in year 6, based on an estimated **redacted** patients in year 1 increasing to **redacted** patients in year 6 and applying an average brexu-cel price of **\$redacted**. Using the lower average price from the applicant’s proposed PfP arrangement of **\$redacted**, the estimated cost to the government ranged from **\$redacted** million in year 1 to **\$redacted** million in year 6. MSAC noted the applicant’s pre-ESC response made corrections to the estimated growth rate, which increased the estimated patient population to **redacted** patients in year 1 increasing to **redacted** patients in year 6, and increased the estimated net cost to government ranging from **\$redacted** million in year 1 to **\$redacted** million in year 6 (using an average brexu-cel price of **\$redacted**).

MSAC noted that the applicant’s updated pricing proposal included a 2-payment PfP arrangement that proposed to achieve an average price of **\$redacted** paid per successfully infused patient based on an assumed 12-month CR rate of 46%. MSAC noted that the proposed average price of **\$redacted** was consistent with the proposed average price of other funded CAR-T therapies. MSAC noted the assumed 46% CR rate was estimated from the RFS analysis from the ZUMA-3 trial, which censored patients who received subsequent allo-SCT and new anti-cancer therapies. However, MSAC noted that under the proposed PfP arrangement these patients would not be excluded, and that subsequent therapies introduces confounding when determining the response to brexu-cel and may result in a higher 12-month CR rate in the Australian setting.

MSAC noted that for funded CAR-T therapies with actual utilisation data available to the department, the response rate in Australian clinical practice was higher **redacted**. MSAC recalled from the tisa-cel for R/R pALL review, **redacted** was likely due to the higher-than-expected utilisation of allo-SCT post-tisa-cel treatment (predicted 19% vs actual 31%). MSAC considered that the CR rate in Australian clinical practice for brexu-cel for R/R B-ALL was likely to be higher than estimated from the RFS analysis because the PfP arrangement would include patients who received subsequent allo-SCT and the rate of subsequent allo-SCT is likely to be higher than observed in the ZUMA-3 study. MSAC noted a higher CR rate for brexu-cel for R/R B-ALL would lead to a higher average price per successfully infused patient based on the proposed PfP arrangements.

MSAC noted that the PfP arrangement proposed measuring clinical response at 12 months based on morphologic characteristics of leukaemia. MSAC advised that the response criteria

should include measurable residual disease (MRD)¹ negativity (ideally morphological CR and MRD negativity). MSAC considered MRD negativity to be a more clinically relevant and rigorous health outcome that may represent more contemporary clinical care, is accepted to correlate with prognosis and patient quality of life, and would align with relevant PBS listings which includes MRD thresholds to specify eligibility for access to blinatumomab².

MSAC noted that the applicant also proposed annual patient caps, ranging from **redacted** patients in year 1 to **redacted** patients in year 3 (a cap of **redacted** patients in total). The proposed amount payable upon successful infusion for patients in excess of the annual cap was **\$redacted**. MSAC considered that there should be no payment made if the use of brexu-cel exceeds the proposed annual patient caps and that the proposed caps should be adjusted to match the updated population estimates in the applicant's pre-ESC response (i.e., **redacted**, **redacted** and **redacted** patients in Year 1, 2 and 3, respectively). MSAC considered it was unlikely that the proposed patient caps would be exceeded, noting that the actual utilisation of tisa-cel in the R/R pALL population was lower than predicted.

MSAC noted the merits for a 2-payment PfP arrangement but considered that there was a high risk that a 2-payment PfP arrangement for brexu-cel for R/R B-ALL would result in a higher than expected average price paid. This is due to the high potential for the estimated CR rate and rate of allo-SCT use post-brexu-cel treatment for R/R B-ALL to be higher in the Australian setting than that observed in the ZUMA-3 study. MSAC also noted that there remained uncertainty regarding the comparative longer-term effectiveness of brexu-cel but that assessing CR at 12-month was not able to adequately address this uncertainty, given relapse observed beyond 1 year and rationale for the cure point in the model being set at a later time point (i.e., 2 to 5 years). MSAC considered that if a 2-payment PfP arrangement was pursued then the outcome measure should be morphological CR and MRD negativity measured at 2 years but noted this did not address the uncertainty in the CR rate proposed in the PfP arrangement and considered there was a reasonable risk that a higher average price would be paid in practice. Because of this risk, MSAC considered that a fixed payment of **\$redacted** for a successful infusion may be more appropriate than a 2-payment PfP arrangement. MSAC noted this is not consistent with other funded CART therapies, but it would provide several benefits, including addressing the real risk for a higher average price in practice, acknowledgement of the evolving therapeutic pathway, specifically the increased use of allo-SCT leading to a higher CR and less administrative burden for both state and territory health authorities and the Department.

MSAC recommended that Australian data be collected and reviewed by MSAC no later than 3 years post the commencement of public subsidy of brexu-cel for R/R B-ALL. MSAC noted the challenges associated with reducing the price of already funded therapies through conducting a cost-effectiveness review informed by registry data. MSAC considered Australian data collection on brexu-cel for R/R B-ALL was required and should be reviewed. However, MSAC did not consider that collection of additional data points for the specific purpose of informing MSAC were required. MSAC considered the data collection should be for the purposes of understanding the clinical place, utilisation, equity of access and budget impact of brexu-cel for R/R B-ALL in Australian clinical practice. Subsequent to an initial review, MSAC may advise whether further review of the clinical effectiveness and cost-effectiveness is warranted. MSAC reiterated that the

¹ Formerly known as 'minimal residual disease'.

² For example, the clinical criteria for the PBS listing for Blinatumomab ([11850Q](#)) includes (amongst other things) 'Patient must have achieved a complete remission, AND Patient must be minimal residual disease negative, defined as either undetectable using the same method used to determine original eligibility or less than 10⁻⁴ (0.01%) blasts based on measurement in bone marrow'.

Commonwealth and jurisdictions, along with other relevant stakeholders, work together to determine what the most appropriate data collection mechanism is for HSTs.

Overall, MSAC supported public funding through the NHRA of brexu-cel for the treatment of adult patients (≥ 26 years of age) with R/R B-ALL based on the significant unmet clinical need for this population and contingent on a risk sharing arrangement that include the following requirements:

- single payment of \$**redacted** paid per successfully infused patient
- limit of one successful CAR-T infusion per lifetime
- annual patient caps of **redacted**, **redacted** and **redacted** patients in Year 1, 2 and 3 respectively with **redacted** payment made for patients exceeding the annual caps
- review of the data to be conducted by MSAC no later than 3 years post the commencement of public subsidy of brexu-cel for R/R B-ALL for the purposes of understanding the clinical place, utilisation, equity of access and budget impact of brexu-cel for R/R B-ALL in Australian clinical practice. Subsequent to an initial review, MSAC may advise whether further review of the clinical effectiveness and cost-effectiveness is warranted.

4. Background

In November 2022, MSAC considered and did not support MSAC application 1723 which sought public funding of brexu-cel for the treatment of adult patients (≥ 18 years of age) with R/R B-ALL. MSAC considered that it was uncertain whether brexu-cel demonstrated superior efficacy in terms of durable survival outcomes compared with contemporary Australian practice because of low certainty of the evidence presented. In addition, MSAC considered that there was significant uncertainty around the place of brexu-cel in clinical practice and that brexu-cel had an inferior safety profile compared with other therapies. Based on these factors, MSAC considered that the incremental clinical value of brexu-cel had not been sufficiently demonstrated, especially in a context where other treatment options are available. MSAC also considered that the incremental cost-effectiveness ratio was highly uncertain and was likely underestimated due to the optimistic extrapolation of survival favouring brexu-cel. MSAC also noted that the states and territories were not supportive of the application as joint funders of this highly specialised therapy via the NHRA ([MSAC 1723 Public Summary Document](#) [PSD]).

Table 1 presents a summary of key matters of concern that were raised when MSAC considered MSAC application 1723.

Table 1 Summary of key matters of concern identified for MSAC application 1723

Key issues identified	Revisions made in resubmission ADAR (MSAC 1723.1) to address the issues	Commentary assessment
Requested patient population	The resubmission ADAR limited brexu-cel to eligible patients aged 26 years or above as proposed in the November 2022 pre-MSAC response. This change resulted in the exclusion of the 18-25 year old cohort from the request for public funding.	Commentary considered issue addressed given the change in the requested indication. However, the commentary also suggests that exclusion of those aged 18-25 requires consideration.
Tisa-cel as a comparator. MSAC requested more detailed comparative data on the efficacy and safety of tisa-cel and brexu-cel for the 18–25 years age group	As per the November 2022 pre-MSAC response and the resubmission ADAR, the applicant has withdrawn the request for funding brexu-cel in the 18-25 age group. Tisa-cel is no longer a relevant comparator and detailed comparative data on the efficacy and safety of tisa-cel and brexu-cel for the 18–25 year age group is not presented.	Commentary considered issue addressed given the change in the requested indication. However, the commentary also suggests that exclusion of those aged 18-25 requires consideration.

Key issues identified	Revisions made in resubmission ADAR (MSAC 1723.1) to address the issues	Commentary assessment
MSAC noted in the MSAC 1723 ADAR that the proposed clinical criteria for usage were not well-defined, but additional clinical criteria were included in the applicant's November 2022 pre-MSAC response.	Further details on the additional clinical criteria provided in the November 2022 pre-MSAC response such as central nervous system (CNS) involvement, ECOG performance status, thresholds for specific organ functions (renal, cardiac and pulmonary) and infection status are provided in the resubmission ADAR based on clinicians' feedback.	Commentary considered issue addressed.
Proposed criteria for funding – A once per lifetime limit on any CAR-T cell therapy, not just brexu-cel, should be considered due to the potential for more than one CAR-T cell therapy being available to a single patient population, and the insufficient clinical evidence for re-treatment.	As per the November 2022 pre-MSAC response and the resubmission ADAR, the funding exclusion of brexu-cel in 18 to 25-year-olds would also mean that the implementation of the criteria that any CAR-T therapy use should be once per lifetime is applied to the following situations – (a) an individual who had met the paediatric and young adult criteria up to the age of 25 years old and received treatment with a funded CAR-T therapy such as tisa-cel would not be eligible to receive subsequent treatment with a second funded CAR-T therapy such as brexu-cel when that individual has reached 26 years of age or older for this indication, and (b) an individual who had met the adult criteria aged 26 years of age or older and received treatment with funded brexu-cel would not be eligible to receive a second funded brexu-cel treatment for this indication. In short, Gilead is revising its request such that there is no overlap on the patient populations being funded between tisa-cel and brexu-cel, and (c) an individual who has not received prior therapy with an anti-CD19 targeted CAR-T therapy for this indication	Commentary considered issue addressed.
Evidence is based on naïve indirect comparisons that have a high risk of bias	The resubmission ADAR presented an (a) updated naïve comparison with updated ZUMA-3 data with 33-month follow-up data for all treated patients as well as patients ≥ 26 years of age and (b) New SCHOLAR-3 analysis matched comparison across 3 synthetic control arms with historical clinical studies in patients matched for key baseline and disease characteristics (indirect comparison). (c) New MAIC versus the pivotal comparator studies for blinatumomab and inotuzumab (TOWER and INO-VATE), providing additional support for the clinical benefits of brexu-cel (indirect comparison).	Although the resubmission ADAR presented new data and new comparisons, the commentary considered the analyses still have a high risk of bias. The economic model still used a naïve comparison in the base case. The SCHOLAR-3 analysis was used as a scenario analysis and the MAIC analysis was not utilised.
MSAC noted target population and place in clinical algorithm could be refined – the algorithm is complex	A simplified and concise current (without brexu-cel) and proposed (with brexu-cel) treatment algorithm is presented based on internal and external to Gilead advice.	While the flow diagram of the current and proposed algorithms were modified in the resubmission ADAR, the resubmission ADAR did not provide additional clarity to the algorithm. No meeting minutes or transcribed interviews were provided indicating the nature of the expert advice given.
MSAC noted that the impact of consolidation allo-SCT was being excluded as a comparator	The proposed funding population is consistent with the eligibility criteria for ZUMA-3 i.e. (i) primary refractory (ii) first relapse if remission was 12 months or less, (iii) relapsed or refractory after two or more lines of	The resubmission ADAR claimed that MSAC accepted the tisa-cel submission's comparators which did not include allo-SCT. The commentary

Key issues identified	Revisions made in resubmission ADAR (MSAC 1723.1) to address the issues	Commentary assessment
	<p>systemic therapy and (iv) relapsed or refractory after allogeneic stem-cell transplant. As described in the clinical algorithm, allo-SCT is not a comparator for brexu-cel.</p> <p>In addition, the resubmission ADAR claimed MSAC accepted the Kymriah submission's comparators which did not include allo-SCT^a</p>	<p>noted that this is not completely accurate as the ratified PICO for tisa-cel indicated that in relevant populations comparators were included "with the intention to proceed to allogenic SCT." (Tisagenlecleucel 1519 PICO Confirmation; May 2018). Additionally, tisa-cel was approved for ALL under a managed entry scheme, through which all details used to manage clinical uncertainty are not publicly available and, therefore, may not be relevant. The resubmission ADAR did not address use of allo-SCT and how it may be replaced in practice and how it could be considered as a comparator (standalone or in combination with other comparators).</p>
<p>MSAC considered that it was uncertain whether brexu-cel demonstrated superior efficacy in terms of durable survival outcomes compared with contemporary Australian practice because of low certainty of the evidence presented.</p>	<p>The resubmission ADAR provided the following:</p> <ul style="list-style-type: none"> (a) updated naïve comparison with updated ZUMA-3 data with 33-month follow-up data for all treated patients as well as patients ≥ 26 years of age and (b) New SCHOLAR-3 analysis matched comparison across 3 synthetic control arms with historical clinical studies in patients matched for key baseline and disease characteristics (indirect comparison). (c) New MAIC versus the pivotal comparator studies for blinatumomab and inotuzumab (TOWER and INO-VATE), providing additional support for the clinical benefits of brexu-cel (indirect comparison) <ul style="list-style-type: none"> • A 5-year update of ZUMA-1 study (axi-cel) that confirms the continued benefit of axi-cel beyond the study duration of 3 years. • As of January 2023, there are 81 patients who had received a successful infusion of axi-cel in Australia. (d) Real world evidence from axi-cel use in Australia showing the continued benefit of CAR-T therapy beyond the study duration. 	<p>As noted above, the updated clinical data for brexu-cel and the new indirect comparisons may not reduce the clinical uncertainty previously raised by MSAC. The commentary also noted that axi-cel is a treatment approved for autologous anti-CD19 CAR T-cell therapies for relapsed/refractory aggressive B-cell non-Hodgkin lymphoma in the third line and beyond. Also for relapsed or refractory large B-cell lymphoma. It is not clear to what degree the long-term survival of these different populations is applicable to brexu-cel.</p>
<p>MSAC noted the price for brexu-cel has not been justified.</p>	<p>Gilead has revised the brexu-cel price to \$redacted, a redacted% reduction from the price proposed in ADAR (\$redacted) and demonstrated to be cost effective.</p>	<p>The \$redacted price for brexu-cel in the ADAR remains to be justified.</p> <p>Noting that, the applicant subsequently submitted an updated pricing proposal that proposed an average price of \$redacted. Further, the price will be subject to a PfP arrangement, which remains to be negotiated.</p>
<p>MSAC noted the structural assumption of cure point at 2 years (base case) – The evidence of cure at 2 years is uncertain and overly favours brexu-cel. The ICER is likely underestimated, largely due to long term survival plateaus modelled</p>	<p>As per the pre-MSAC response the result of the revised base case is presented using</p> <ul style="list-style-type: none"> (a) Updated clinical evidence in the defined indication (b) 5-year cure point, (c) Weighted analysis approach of 'cured' and 'non-cured' cohorts, (d) Using the revised price for brexu-cel of \$redacted (redacted% reduction from the previous proposed price of \$redacted) 	<p>The economic model has been updated to reflect this revised base case. The assumed 5-year cure point is less favourable to brexu-cel in comparison to 2-year cure assumption, however the change in cure assumptions has brought about additional sources of uncertainty and the ICER remains high and likely underestimated.</p>

Key issues identified	Revisions made in resubmission ADAR (MSAC 1723.1) to address the issues	Commentary assessment
through the use of highly optimistic cure assumptions, which was not supported by relevant external evidence.		
MSAC noted the financial estimates were acknowledged by the applicant to be an overestimate and revised in the October 2022 pre-ESC response; however, there is some uncertainty in these estimates due to the assumed uptake rate (redacted % from Year 1 to 6).	As per the pre-MSAC response the estimated number of patients that may be eligible has been revised as follows: (a) Removing the total number of patients 18-25 years of age diagnosed with R/R B-ALL (b) Note the AIHW data is presented in 5-year age groups. There is the 18-19yo group, and then 20-24, 25-29, 30-34 etc to 85-89 and then 90+. (c) Adjusted the 25-29 year age group to exclude the 25 year old cohort, to align with the revised restriction discussed above. (d) Using the proposed effective price for brexu-cel of \$redacted (redacted % reduction from the previous proposed price of \$redacted)	Addressed in terms of only considering those aged 26 and older and the revised requested price. The resubmission ADAR continues to apply same uptake rates, stating it considers them reasonable for the base case, and provides scenario analyses altering the rates \pm 10%. Cost-off-sets are considered to be overestimated.
MSAC previously noted that the states and territories also did not support the application because of the uncertainty around the effectiveness of the treatment, the high and uncertain cost-effectiveness, and that the cost of delivery of the treatment was likely underestimated	In response to States' feedback previously provided the Nov 2022 MSAC consideration, the resubmission ADAR has revised the hospitalization cost associated with brexu-cel infusion based on weighted average cost of three relevant AR-DRG codes- R60A, R01A, and R61A. As per the original ADAR, the costs of pre-treatment include leukapheresis, conditioning therapy, and bridging therapy.	The original ADAR used DRG R632 (subtracted pharmacy cost to + ICU) to estimate a day cost of \$redacted . The revised hospitalisation (in-patient stay) cost using weighted DRG (previously suggested by states and territories) increased the hospitalisation cost to \$redacted (excludes pharmacy +ICU). This increased the overall infusion admission cost to \$redacted , which is still well below the \$redacted based on one jurisdiction's experience. Other instances where the costs are underestimated have not been addressed. As such, the cost of delivery of the treatment is still likely underestimated.
MSAC noted risk sharing agreement or PfP arrangements have not been proposed.	In the resubmission ADAR, the applicant stated it recognises the need for a PfP to be negotiated following MSAC support as a part of the public funding for brexu-cel. Further details of the proposal were received during the evaluation and are discussed under "Proposal for public funding".	Considered addressed, requires negotiation and agreement

Abbreviations: MSAC, Medical Services Advisory Committee; MAIC, Matched Adjusted Indirect Comparison; ECOG, Eastern Cooperative Oncology Group; ALL, Acute Lymphoblastic Leukaemia; AIHW, Australian Institute of Health and Welfare; ESC, Evaluation Sub-Committee; PfP, Pay for performance; r/r, relapsed/refractory; NCCN, National Comprehensive Cancer Network; ADAR, Applicant Developed Assessment Report; axi-cel, Axicabtagene ciloleucel; CAR-T, Chimeric antigen receptor – therapy; ICER, Incremental Cost-Effectiveness Ratio

^a Kymriah MSAC 1519.1 PSD – <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519.1-public>

The November 2022 pre-MSAC response was provided prior to the November MSAC consideration of the previous application MSAC 1723

The October 2022 pre-ESC response was provided prior to the October ESC consideration of the previous application MSAC 1723

Source: Table 1 of MSAC 1723.1 ADAR with commentary assessment

5. Prerequisites to implementation of any funding advice

Brexu-cel is included on the Australian Register of Therapeutic Goods (ARTG) for the following therapeutic indications:

TECARTUS is a genetically modified autologous immunocellular therapy for the treatment of

- patients greater than or equal to 18 years of age with R/R B-ALL ([ARTG 396794](#)); and
- patients with relapsed or refractory mantle cell lymphoma, who have received two or more lines of therapy, including a BTK inhibitor (unless ineligible or intolerant to treatment with a BTK inhibitor ([ARTG 371431](#))).

6. Proposal for public funding

Public funding for brexu-cel for adult patients (≥ 26 years of age) with R/R B-ALL is requested through the NHRA, as has been the case for brexu-cel for the treatment of mantle cell lymphoma (see [MSAC application 1647](#)). Tisa-cel, another CAR-T cell therapy, is currently jointly funded under the NHRA for treating patients (aged up to 25 years old) with R/R pALL ([MSAC application 1519](#)).

The NHRA includes funding from both the Commonwealth Government (50%) and the governments of the relevant states and territories (50%; Addendum to the National Health Reform Agreement 2020-2025).

The resubmission ADAR proposed clinical, treatment and funding criteria for brexu-cel for treating adult patients (≥ 26 years of age) with R/R B-ALL, see Table 2.

The main changes from the original ADAR (MSAC 1723) are:

- restricting the patient population to those aged ≥ 26 years (≥ 18 years previously); and
- wording limiting CAR-T therapy to once per lifetime.

Table 2 ADAR proposed clinical, treatment and public funding criteria for brexu-cel

Brexu-cel	Description
Indication:	Relapsed or refractory CD-19-positive B-precursor acute lymphoblastic leukaemia in a patient aged 26 years or above.
Clinical criteria	<p>Relapsed or refractory disease is defined as one of the following:</p> <ul style="list-style-type: none"> • Primary refractory • First relapse if remission was 12 months or less • Relapsed or refractory after two or more lines of systemic therapy • Relapsed or refractory after allogeneic stem-cell transplant <p>AND</p> <p>Patient must have more than 5% blasts in the bone marrow,</p> <p>AND</p> <p>Patient must have a ECOG performance status of less than 2,</p> <p>AND</p> <p>Patient must have sufficient organ function to tolerate treatment with brexucabtagene autoleucel,</p> <p>AND</p> <p>Patient must not have uncontrolled infection, including uncontrolled HIV or active hepatitis B or C infection.</p> <p>AND</p> <p>The treatment team must consider the patient's condition can be effectively managed during lymphocyte collection and manufacturing, to allow for the absence of rapidly progressive disease at the time of lymphocyte infusion.</p>

Brexu-cel	Description
Treatment criteria:	Patient must be treated in a tertiary public hospital with appropriate credentials AND Patient must be treated by a haematologist working in a multi-disciplinary team specialising in the provision of CAR-T cell therapy
Administrative Note	A once per lifetime limit on any CAR-T cell therapy applies for this indication as follows: (a) an individual who had met the paediatric and young adult criteria up to the age of 25 years old and received treatment with a funded CAR-T therapy, (such as tisa-cel currently) would not be eligible to receive subsequent treatment with a second funded CAR-T therapy (such as brexucabtagene autoleucl) when that individual has reached 26 years of age or older, and (b) an individual who had met the adult criteria aged 26 years of age or older and received treatment with funded brexucabtagene autoleucl, would not be eligible to receive a second funded CAR-T therapy, such as brexucabtagene autoleucl treatment.
Pay for Performance (PfP)	Redacted

Abbreviations: MSAC, Medical Services Advisory Committee; MAIC, Matched Adjusted Indirect Comparison; ECOG, Eastern Cooperative Oncology Group; ALL, Acute Lymphoblastic Leukaemia; AIHW, Australian Institute of Health and Welfare; ESC, Evaluation Sub-Committee; PfP, Pay for performance; r/r, relapsed/refractory; NCCN, National Comprehensive Cancer Network; ADAR, Applicant Developed Assessment Report; axi-cel, Axicabtagene ciloleucl; CAR-T, Chimeric antigen receptor – therapy; ICER, Incremental Cost-Effectiveness Ratio; brexu-cel, Brexucabtagene autoleucl

Source: Table ES-2 of the MSAC 1723.1 ADAR+in-line commentary

6.1 Pay for Performance (PfP)

Further detail on the proposed PfP and annual patient caps were provided by the applicant after lodging the resubmission ADAR, see Table 3 and Table 4, respectively.

Table 3 Proposal for brexu-cel based on pay for performance

Redacted

The updated pricing proposal from the applicant stated that **redacted**.

The commentary noted that the reported **redacted**.

The commentary also questioned whether MRD should also be considered **redacted**.

The applicant's annual patient cap proposal included annual patient caps **redacted**; the patient caps are derived from Section 4 estimates. For each patient treated in excess of a cap for that year, an amount of \$**redacted** is payable upon successful infusion for that year (see Table 4).

Redacted).

Table 4 Proposed annual patient cap and payable amount for each patient treated with brexu-cel in excess of the cap

	Year 1	Year 2	Year 3	Total
R/R adult ≥26 years ALL ^a	redacted	redacted	redacted	redacted
Payable amount upon successful infusion in excess of annual cap ^b	\$redacted			

^a see Table 125, MSAC 1723.1 ADAR+in-line commentary

^b derived using **redacted**

The commentary noted that the estimated number of patients receiving an infusion of brexu-cel estimated by the resubmission ADAR is likely an underestimate due to the assumption of decreasing annual age-related incidence.

7. Population

The proposed population in the resubmission ADAR is adult patients (≥ 26 years of age) with R/R B-ALL. The population in the original application (MSAC 1723) included patients aged ≥ 18 years.

The definition of relapsed or refractory (R/R) disease is unchanged from the original ADAR and is defined as one of the following:

- primary refractory
- first relapse if remission was 12 months or less
- relapsed or refractory after two or more lines of systemic therapy
- relapsed or refractory after allogeneic stem-cell transplant.

The resubmission ADAR continued to state that the earliest patients can receive brexu-cel will be as a second-line or third-line therapy. Prior to the second-line or third-line setting, patients will have typically received regimens which include induction, consolidation and maintenance chemotherapy and allo-SCT, tyrosine kinase inhibitor [TKI] (Philadelphia Chromosome positive [Ph+] only) maintenance in Australian clinical practice.

ALL is a haematologic malignancy propagated by impaired differentiation, proliferation, and accumulation of lymphoid progenitor cells in the bone marrow and/or extramedullary sites.

The resubmission ADAR, like the original ADAR stated that in Australia, approximately 446 diagnoses (in both children and adults) and 109 deaths from ALL were estimated in 2021 (AIHW 2021). ALL is mainly considered a paediatric leukaemia with 80% of cases occurring in children and 20% occurring in adults. The median age at diagnosis for ALL is 17 years and the median age of adults diagnosed with ALL is 38 years and most patients relapse within 2 years of first remission.

The 5-year overall survival (OS) is approximately 90% in children but only 20% to 40% in adults and elderly patients. Adult and paediatric ALL have distinct disease prognoses; adult patients have worse prognosis, partially driven by a higher incidence of poor outcome markers, such as Ph+/Ph-like and lysine methyltransferase 2A (*KMT2A*) rearrangement (previously known as mixed-lineage leukaemia rearrangement).

Adult ALL cases normally develop from precursors of the B-cell lineage with ~75% of adults diagnosed with B-cell ALL; T-cell ALL comprises the remaining cases. The focus of the resubmission ADAR remains B-cell ALL, specifically B-precursor ALL (as opposed to mature B-cell ALL also known as Burkitt leukaemia).

8. Comparator

Consistent with the original ADAR, blinatumomab and inotuzumab ozogamicin remain the primary clinical and cost-effectiveness comparators in the resubmission ADAR. Both drugs are PBS-listed for the treatment of adult R/R B-ALL patients who failed first line of therapy and are also recommended by National Comprehensive Cancer Network (NCCN) in R/R B-ALL. The place in therapy of brexu-cel is similar to that of blinatumomab and inotuzumab ozogamicin. The resubmission ADAR states both blinatumomab and inotuzumab ozogamicin are the medicines most likely to be replaced by brexu-cel in clinical practice.

Also unchanged, the resubmission ADAR also nominated TKI inhibitors such as ponatinib and dasatinib (if not received in first line) as potential comparators for Ph+ ALL (which accounts for ~30% of adult ALL and <5% in paediatric ALL patients) and salvage therapy as secondary

comparators. The commentary considered insufficient information was provided in the ADAR regarding what treatments salvage therapy may include.

The commentary noted that when MSAC considered the original ADAR (MSAC 1723 PSD, p3):

“MSAC noted that the comparators in the ADAR included blinatumomab and inotuzumab ozogamicin (primary comparators) and ponatinib, dasatinib and salvage chemotherapy (secondary comparators). MSAC noted that allo-SCT is recommended as consolidation therapy in high-risk patients, following treatment with the comparator therapies and could be considered as a possible comparator to brexu-cel, (either as a stand-alone comparator or in combination with one of the existing comparator therapies). MSAC noted that the exclusion of allo-SCT as a comparator was not addressed in the ADAR or in the pre-MSAC response, and the impact of this omission remained unclear (particularly as the use of allo-SCT differed across the studies)”.

The commentary noted that the resubmission ADAR reiterated claims for excluding allo-SCT as a comparator and considered the resubmission ADAR had not adequately addressed this issue (see earlier comments in Table 1).

9. Summary of public consultation input

A summary of previous consultation feedback received for MSAC Application 1723 is available in the Public Summary Document:

<http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1723-public>

Consultation input further to this resubmission was received from one consumer organisation, five health professional organisations and one individual medical professional. The six organisations that submitted input were:

- The Leukaemia Foundation
- Australasian Leukaemia and Lymphoma Group (ALLG)
- Australia and New Zealand Transplant Cellular Therapies (ANZTCT)
- Haematology Society of Australia and New Zealand (HSANZ)
- Peter MacCallum Cancer Centre - Centre of Excellence for Cellular Immunotherapy
- Westmead Hospital - Blood Transplant and Cell Therapies.

Of the 7 consultation comments received, all indicated support for the proposal to fund brexu-cel for the treatment of adult patients (≥ 26 years of age) with relapsed or refractory B-precursor adult acute lymphoblastic leukaemia (R/R B-ALL).

Benefits

The feedback indicated the main benefits include:

- Brexu-cel has the potential to provide a new treatment option to address an unmet clinical need for adult patients with R/R B-ALL who typically have poor long-term outcomes despite the current available therapies.
- Brexu-cel has the potential to offer adult patients with R/R B-ALL prolonged survival and improved quality of life with no need for ongoing therapy for the duration of treatment response.
- ANZTCT considered that the data from the ZUMA-3 study demonstrated a relative improvement in toxicity with brexu-cel compared to available therapies and may achieve

a durable response without requiring allo-SCT consolidation (although further follow up required to confirm this).

Disadvantages /Implementation Issues

- Brexu-cel is a specialised treatment and the number of sites and the capacity of those sites to deliver CAR-T therapy is limited. Further, access may be difficult for patients who have to travel from place of residence to treatment site (although this is often the case for patients to access therapies for ALL).
- Feedback highlighted the significant cost of the treatment as a disadvantage. Further, as brexu-cel for R/R B-ALL is not currently publicly funded, the significant cost of brexu-cel is prohibitively expensive for most patients creating a health equity issue (i.e., only some patients can afford to pay for the treatment locally or overseas).
- The acute toxicities associated with brexu-cel treatment (including cytokine release syndrome, neurotoxicity, infection and cytopenias) were noted as a disadvantage. Although feedback also highlighted that better preventative and management strategies have reduced the incidence and severity such that these are manageable.

Other

The feedback from HSANZ clarified that currently, Australia does not have national consensus guidelines recommending treatment choices for adult patients with ALL. ANZTCT and HSANZ noted most Australian clinicians would follow international guidelines, including the US National Comprehensive Cancer Network (NCCN) Guidelines for Adult ALL version 2.2023 which include CAR-T therapy for relapsed and refractory disease.

Regarding the position of allo-SCT in clinical practice in Australia, ANZTCT and HSANZ noted that there is no finite consensus on the role of allo-SCT for Adult ALL in Australia, particularly noting that a decision to pursue allo-SCT needs to be made on an individualised bases that depends on patient, disease and donor factors. Feedback also noted that:

- Allo-SCT use is considered earlier in treatment pathways for adult patients with ALL than it is in paediatric, adolescent and young adult patients with ALL.
- Allo-SCT may also be considered for a consolidative strategy even for patients achieving MRD negativity after induction therapy, given the generally poorer outcomes for ALL in adults compared to paediatric populations.
- CAR-T may be used as a bridge to allo-SCT in a subset of patients but that based on the data published on the brexu-cel (ZUMA-3 study, Shah et al 2021), HSANZ did not consider brexu-cel as only a bridge to allo-SCT
- The rates of allo-SCT following CAR-T are variable (13-88%³).
- Due to transplant related toxicity and morbidity seen in adult patients with ALL, only a very small number of adult patients with ALL would be considered suitable to receive a second allo-SCT.
- As more study follow up becomes available, the position of brexu-cel as a definitive therapy will be clarified and that it is likely that MRD negative patients will not undergo all-SCT.

HSANZ noted that the curative paradigm in aggressive haematological malignancies is difficult to define and that overall survival rates from clinical trials do not necessarily equal disease cure.

³ Cappell KM, Kochenderfer JN (2023) Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol* 20, 359–371. <https://doi.org/10.1038/s41571-023-00754-1>

Both ANZTCT and HSA NZ considered that measurement of MRD negativity more accurately reflects disease control and suggested that ongoing MRD negativity at 2 years post-therapy could be considered an appropriate surrogate marker for cure. However, HSA NZ noted that patients in this scenario may not achieve a life expectancy equivalent to the general population, as the effects of high dose therapy in induction will be associated with long term toxicity and increased rates of secondary malignancy, nevertheless, ongoing relapse free survival remains the primary goal of therapy. In contrast, ANZTCT considered that, to date there are no significant long term consequences of CAR-T cell therapy and patients cured can be expected to have a life expectancy similar to the normal population without the quality of life limitations seen in the post allo-SCT setting.

10. Characteristics of the evidence base

The comparative evidence base for brexu-cel presented in the resubmission ADAR is summarised in Table 5. The studies included in the evidence base has not changed from the evidence presented in the original ADAR, however data from the latest data cut of the brexu-cel study ZUMA-3 (i.e., 33-month follow-up analysis, 23 July 2022 data cut-off) for Phase 1 and 2 combined in the mITT/all-treated population and from the subgroup of patients aged ≥ 26 years is presented. The original ADAR (MSAC 1723) presented data from the ZUMA-3 study from the 21-month follow-up analysis (i.e., 23 July 2021 data cut-off) that was presented in.

According to the ZUMA-3 CSRs, the median (range) actual follow-up was 11.4 months (3.4 to 47.0 months) and 23.5 months (7.6 to 35.5 months) for Phase 1 and 2 patients, respectively, in the resubmission ADAR (33-month follow-up analysis CSR, p18).

Like the original ADAR, the resubmission ADAR presented comparisons of brexu-cel versus blinatumomab, inotuzumab ozogamicin and chemotherapy via (1) naïve comparisons; and (2) a retrospective cohort matched comparison (SCHOLAR-3).

In an attempt to address MSAC's previous concerns regarding naïve indirect comparisons that have a high risk of bias, the resubmission ADAR also presented a new matched adjusted indirect comparison (MAIC) of brexu-cel (ZUMA-3) versus blinatumomab (TOWER) and inotuzumab ozogamicin (INO-VATE). The methods of the MAIC were discussed in the resubmission ADAR, however the commentary considered the analyses to have a high risk of bias and as such may not sufficiently address clinical uncertainty for MSAC. The commentary raised the following uncertainties/concerns for the MAIC analysis:

- Although the MAIC adjusted for multiple baseline characteristics across ZUMA-3, TOWER and INO-VATE, it was not clear that all known predictors of benefit were accounted for and the MAIC could not adjust for unknown predictors of benefit.
- In ZUMA-3, patients were only enrolled if they had undergone leukapheresis, this suggests that there may be some risk of patient selection which was not accounted for in the MAIC analysis, and likely constitutes a trial design difference that cannot be adjusted for.
- After adjusting, the effective sample size (ESS) for each comparison for the ≥ 26 year old subgroup ranged from 12.33 to 40.65 with sample size reductions ranging from 52.73% to 74.72%.
- The results of the MAIC did not consistently indicate larger improvements than the naïve estimates and the adjusted hazard ratios (HRs) were associated with wide confidence intervals.

Overall, the commentary considered that the MAIC did not provide any greater clinical certainty regarding the clinical value of brexu-cel versus blinatumomab and inotuzumab ozogamicin.

Table 5 Characteristics of the included studies

	ZUMA-3	INO-VATE Kantarjian et al 2019	DeAngelo et al 2017	TOWER Kantarjian et al 2017	Kiyoi et al 2020	Topp et al 2014	Stein et al 2019	Martinelli et al 2017	PACE Cortes et al 2018	
Study design	Phase I/II, open-label, single-arm multicentre study	Phase 3, open label, randomised	Prospective, open label, phase 1/2	Prospective, randomized, phase 3	Phase 1b/2 single arm study	Open-label, multicentre, exploratory, single-arm, phase II	Open-label, single-arm, phase II	Open-label, single-arm, multicenter, phase II study	Single arm study	
Patients (n)	ITT	Phase 1 (54)	InO arm (164)	Phase I (37)	Blin arm (271)	36	64	45	32	
		Phase 2 (71)	SoC arm (162)	Phase II (35)	SoC arm (134)					Phase I (5)
	mITT	Phase 1 (23/45)*	InO arm (164)	n/a	n/a	n/a	n/a	n/a	n/a	n/a
		Phase 2I (55)	SoC arm (143)							
		Phase 1 (20)	n/a	n/a	n/a					
Phase 2 (43)										
Intervention	Brexu-cel	InO	InO	Blinatumomab	Blinatumomab	Blinatumomab	Blinatumomab	Blinatumomab	Ponatinib	
Comparator	n/a	SoC	n/a	SoC	n/a	n/a	n/a	n/a	n/a	
Actual follow-up (months) median (range) [95% CI]	Phase 1 11.4 (3.4, 47.0)	29.6 (1.7-49.7)	23.7 (6.8-29.8)	Blin arm 11.7 (n/s)	6.3 (n/s)	12.1 (n/s)	16.6 [12.4, 23.3]	8.8 (n/s)	5.4 (0.1-59.6)	
	Phase 2 23.5 (7.6, 35.5)			SoC arm 11.8 (n/s)						
Primary outcomes	Phase 1 (DLTs)	CR/CRi *** OS	Phase I (DLTs)	OS	Phase I (DLTs)	CR, CRh	CR, CRh	CR, CRh	MaHR	
	Phase 2 (OCR, CRi, CR) **		Phase II (CR/CRi)		Phase II (CR/CRh)					
Secondary outcomes	Phase 1 (OCR, CRi, CR, DOR, RFS, OS, MRD)	DOR, RFS, MRD, HSCT rate	Phase I (n/s)	CR, CRh, CRi, DOR, RFS, MRD, allo-SCT.	Phase I (CR/CRh)	DOR, RFS, MRD, allo-SCT	DOR, RFS, OS, allo-SCT	DOR, RFS, OS, allo-SCT	MMR, DOR, RFS, OS	
	Phase 2 (DOR, RFS, OS, MRD, allo-SCT rate, OCR & CRi) ***		Phase II (DOR, RFS, OS, MRD)		Phase II (RFS, OS, MRD)					
Population description	R/R B-precursor ALL	R/R B-cell precursor (BCP) ALL	CD22-positive R/R ALL	CD19-positive Ph-negative B-cell precursor ALL	R/R B-cell precursor (BCP) ALL	R/R B-cell precursor (BCP) ALL	R/R ALL with previous alloHSCT	R/R Ph-positive ALL	Refractory Ph-positive ALL	
Risk of bias	Low to moderate	High	Moderate	High	Moderate	Moderate	Moderate	Moderate	Low to moderate	

Abbreviations: ALL, acute lymphoblastic leukemia; Blin, Blinatumomab; CR, complete remission; CRh, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; DLTs dose-limiting toxicities; DOR, duration of remission; HSCT, Hematopoietic Stem-Cell Transplant; InO, Inotuzumab ozogamicin; ITT, intention-to-treat; mITT modified intention-to-treat, MaHR, major hematologic response; MMR, major molecular response; MRD, measurable residual disease MRD; n/a, not applicable; n/s, not specified; OCR, overall complete remission; OS, overall survival; Ph, Philadelphia; RFS relapse-free survival; R/R, relapsed/refractory; SoC, standard-of-care

*23 of 45 patients received target dose of 1×10^6 CAR T cells per kg bodyweight, ** per central assessment, *** per investigator assessment

Source: Table 2, p11 of the MSAC 1723 PSD and updated to include details of extended follow-up for ZUMA-3 and the ≥ 26 year old subgroup

11. Comparative safety

The resubmission ADAR presented only updated safety information relating to deaths and cause of deaths reported in the 33-month follow up analysis CSR. Adverse events (AE), other than deaths, had not changed from the 21-month follow up analysis CSR presented in the original ADAR. These data are not specific to the ≥ 26 year old subgroup, although specific data for this subgroup of Phase 2 patients are available (p154 of the 33-month follow-up analysis CSR). The applicant is requested to address whether the reported AEs in the ≥ 26 year old subgroup were consistent with whole population in its pre-ESC response.

Summary of unchanged AE as noted in the MSAC 1723 PSD (pp12-13) for the original ADAR:

- Based on a naïve comparison of brexu-cel vs inotuzumab ozogamicin, overall, a lower proportion of serious adverse events (SAEs) were reported in INO-VATE compared to ZUMA-3 (85/164 [51.8%] vs 80/100 [80.0%]). However, there were differences in the nature and frequency of specific adverse events (AEs), and Grade 3 or 4 treatment-emergent adverse events (TEAEs). A fatal study treatment toxicity was reported in 8/164 inotuzumab ozogamicin patients (4.9%).
- In the naïve comparison between brexu-cel and blinatumomab, it was observed that a similar proportion of patients in ZUMA-3 (97 patients; 97%) reported TEAEs when compared to Kiyoi et al 2020 (21 patients; 100%) and Martinelli et al 2017 (45 patients; 100%). A similar proportion of patients reported TEAEs in TOWER versus ZUMA-3 (263/267 [98.5%] vs 100/100 [100%]) as well as serious adverse events (SAEs; 165/267 [61.8%] vs 63/100 [63%]). There were 51 (19.1%) fatal adverse events in TOWER which was slightly higher than in ZUMA-3 (14%). Investigator assessment of these deaths reported that 8/267 (3%) were attributable to blinatumomab.
- A naïve comparison was performed to provide an overall comparative safety assessment of ZUMA-3 against the salvage chemotherapy arm of the INO-VATE and TOWER studies. Overall, a lower proportion of patients experienced serious TEAEs and AEs in salvage chemotherapy arm of INO-VATE and TOWER compared to ZUMA-3.
- Comparing brexu-cel with ponatinib monotherapy, a higher proportion of patients in ZUMA-3 who received brexu-cel infusion experienced pyrexia (92%), anaemia (50%), headache (39%), nausea (36%) and diarrhea (32%). The majority of TEAEs were reported in 20-25% of those in the PACE study. Ponatinib is associated with cardiac toxicity.

In summary, brexu-cel is associated with different adverse events compared with current second-line+ B-ALL therapies (including inotuzumab ozogamicin, blinatumomab, salvage chemotherapy and ponatinib monotherapy) and also a different safety profile in that the adverse events may occur during the initial period of therapy compared with an ongoing and cumulative basis with current second-line or later B-ALL therapies.

Table 6 presents the comparative analysis of the number of deaths based on the mITT population for Phases 1 (all brexu-cel doses) and II and in total in the resubmission (data cut off 23 July 2022) and original (data cut off 23 July 2021) ADAR. Overall, the deaths in ZUMA-3 remained lower compared to the comparator studies except for Kiyoi et al 2020 and PACE, 9.5% and 16%, respectively and similar compared with blinatumomab in the TOWER study. These differences may be explained by differences in median follow-up (see Table 5).

Table 6 Deaths: ZUMA-3 vs comparator studies

	Deaths, n(%)
ZUMA-3 resubmission ADAR	Phase 1: 30/45 (66.7); Phase 2: 29/55 (52.7); Total: 59/100 (59.0)
ZUMA-3 original ADAR	Phase 1: 29/45 (66.7); Phase 2: 25/55 (45.5); Total: 54/100 (54.0)
INO-VATE (inotuzumab ozogamicin, N= 164; salvage chemotherapy ^a , N= 143)	Inotuzumab ozogamicin: 131/164 (79.9) Salvage chemotherapy: 126/143 (88.1)
DeAngelo et al., 2017 (N= 72)	54 (75.0)
Kiyoi et al., 2020 (N= 21)	2 (9.5)
Stein et al., 2019 (N= 64)	47 (73)
Topp et al., 2014 (N= 36)	22 (61)
PACE (N= 32)	5 (16.0)
TOWER (Blinatumomab, N= 267; chemotherapy, N= 109)	Blinatumomab: 160/267 (59) Chemotherapy: 85/109 (63.4)

Abbreviations: N, number treated; SCA, synthetic control arm

Notes: a, FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor)/HIDAC (high-dose cytarabine)/ MXN/Ara-C (mitoxantrone and cytarabine); Data cut-offs: ZUMA-3: 23 July 2022 and 23 July 2021; INO-VATE: 8 March 2016; DeAngelo et al., 2017: 30 January 2015; Kiyoi et al., 2020: 24 August 2017; Stein et al., 2019: 20 June 2014; Topp et al., 2014: NR; SCHOLAR-3: NR; PACE: 6 February 2017

Source: Table 29 of MSAC 1723.1 ADAR and Table 3, p13 and p13 of MSAC 1723 PSD

The commentary considered that in terms of safety, as stated in the ADAR, the safety profile of brexu-cel is different, however, based on the naïve comparison brexu-cel is most likely inferior with respect to AEs of special interest and non-inferior with respect to all other AEs. A significant proportion of patients with adverse events of special interest associated with brexu-cel were observed, including cytokine release syndrome (CRS), neurological events, and cytopenia.

12. Comparative effectiveness

The resubmission ADAR presented where available, data from the latest data cut of ZUMA-3 (i.e., 33-month follow-up analysis; 23 July 2022 data cut-off) for Phase 1 and 2 combined in the mITT/all-treated population and from the subgroup of patients aged ≥ 26 years. The results of those aged ≥ 26 years were generally consistent with the mITT study population. The commentary considered that because this analysis includes fewer patients (n=63 for those aged ≥ 26 years compared with n=78 for mITT) and is post-hoc, while informative, may not necessarily be definitive.

The resubmission ADAR claimed that brexu-cel is superior to the comparators in the treatment of R/R B-ALL with markedly improved response rates, RFS and OS compared with the outcomes achieved with inotuzumab ozogamicin, blinatumomab, salvage chemotherapy and ponatinib.

Figure 1 and Figure 2 present the K-M curve for OS in the combined Phase 1 and 2 mITT population and those aged ≥ 26 years of ZUMA-3, respectively.

Figure 3 presents the K-M curve for OS in the combined Phase 1 and 2 mITT population by age category. Notably, overall survival among those aged 18-25 years (median survival of 23.2 months; 95% CI: 9.0, not estimable) is similar to that reported for those aged ≥ 26 years (median survival of 26.0 months; 95% CI: 15.9, 60.4), albeit with wider confidence intervals, likely due to the small sample size (n=15). On this basis, the commentary considers there may not be sufficient justification to exclude those aged 18-25 years from treatment with brexu-cel. Although it is noted that the availability of tisa-cel for patients aged 18-25 years old with ALL means there is no unmet need for this population. Further, while the OS results are similar in patients aged 18-25 years old and aged ≥ 26 years, this should also be considered in the context that OS tends to be worse with increasing age, i.e., younger people tend to do better (including, younger adults tend to do better than older adults).

Figure 4 and Figure 5 present the K-M curve for RFS in the combined Phase 1 and 2 mITT population and those aged ≥ 26 years of ZUMA-3, respectively. RFS was defined as the time from the brexu-cel

infusion date to the date of disease relapse or death from any cause (patients who did not achieve complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) were evaluated as having an RFS event at Day 0). RFS was to be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (excluding resumption of a TKI) or allo-SCT. In subjects who resumed TKI therapy, disease assessments obtained after resumption of TKI therapy were to contribute to the derivation of RFS.

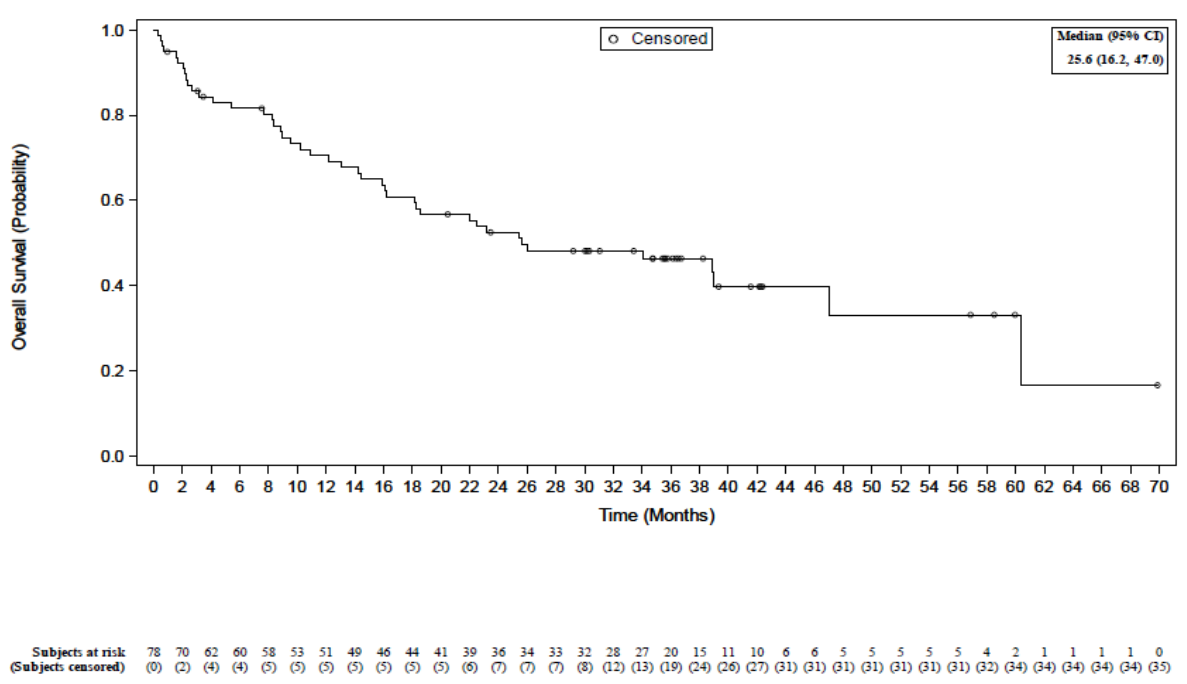
The commentary noted that Table 22 of the resubmission ADAR, reported that 24 (38.1%) of the 63 patients in the ≥ 26 -year-old subgroup analysis were censored in the RFS analysis at the 33-month follow-up. The censoring reasons included:

- ongoing remission (n=9, 14.3%)
- allo-SCT (n=10, 15.9%)
- started new anti-cancer therapy (n=2, 3.2%)
- lost to follow-up (n=2, 3.2%)
- withdrawal of consent (n=1, 1.6%).

The KM plot of RFS (Figure 5 below) indicates that at 12 months 13 of the 63 patients in the ≥ 26 -year-old subgroup analysis were censored (the timepoint used to estimate the CR rate of 46% for the PfP). However, it is unclear from the information provided, how many of these patients were censored due to receiving allo-SCT or starting a new anti-cancer therapy.

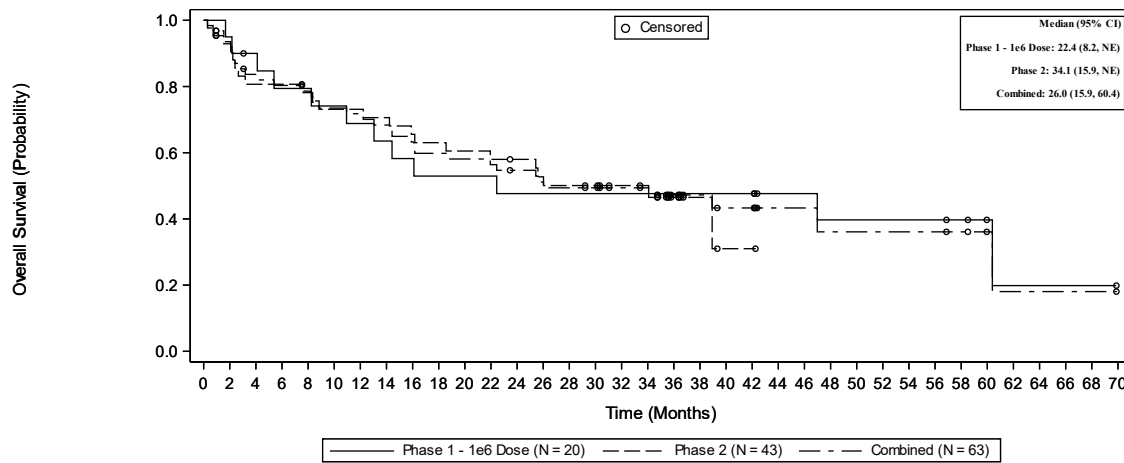
A summary of the median OS and RFS for the mITT population (in the resubmission and original ADAR, if changed) and the ≥ 26 year old age group (resubmission ADAR) are presented in Table 7, along with results for the comparator therapies.

Figure 1 Kaplan–Meier plot of overall survival (Phase 1 and 2, mITT population): ZUMA-3



Source: Figure 13 of the MSAC 1723.1 ADAR+in-line commentary

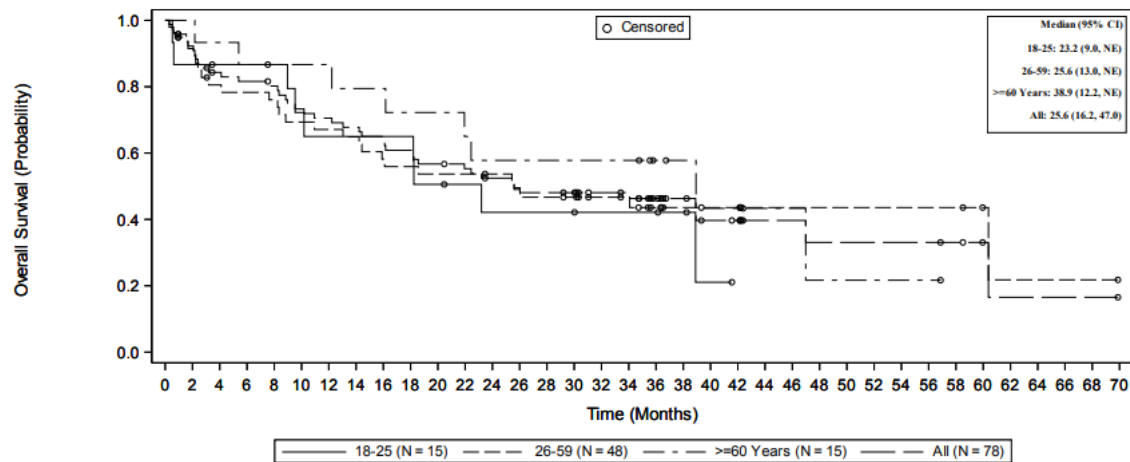
Figure 2 Kaplan–Meier plot of overall survival according to patient age ≥26 years using investigator assessment (Phase 1 and 2 combined, all dosed subjects): ZUMA-3



Phase 1 - 1e6 Dose at risk	20	19	17	15	14	13	12	11	10	10	9	9	9	9	9	9	9	9	9	6	6	5	5	5	5	5	4	2	1	1	1	0						
(Phase 1 - 1e6 Dose censored)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(5)	(7)	(7)	(7)	(8)
Phase 2 at risk	43	38	33	33	31	29	29	28	26	25	24	23	22	20	19	18	15	14	7	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0				
(Phase 2 censored)	(0)	(2)	(2)	(2)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(4)	(4)	(4)	(4)	(5)	(8)	(9)	(15)	(19)	(20)	(20)	(21)	(21)	(21)	(21)	(21)	(21)	(21)	(21)	(21)	(21)	(21)	(21)		
Combined at risk	63	57	50	48	46	43	42	40	37	35	34	33	31	29	28	27	24	23	16	12	10	10	6	6	5	5	5	5	4	2	1	1	1	0				
(Combined censored)	(0)	(2)	(3)	(3)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(5)	(5)	(5)	(6)	(9)	(10)	(16)	(20)	(21)	(21)	(25)	(25)	(25)	(25)	(25)	(25)	(25)	(26)	(28)	(28)	(28)	(28)	(28)		

Source: Figure 12 of the MSAC 1723.1 ADAR+in-line commentary
 Note: 1e6 dose = ARTG-approved dose

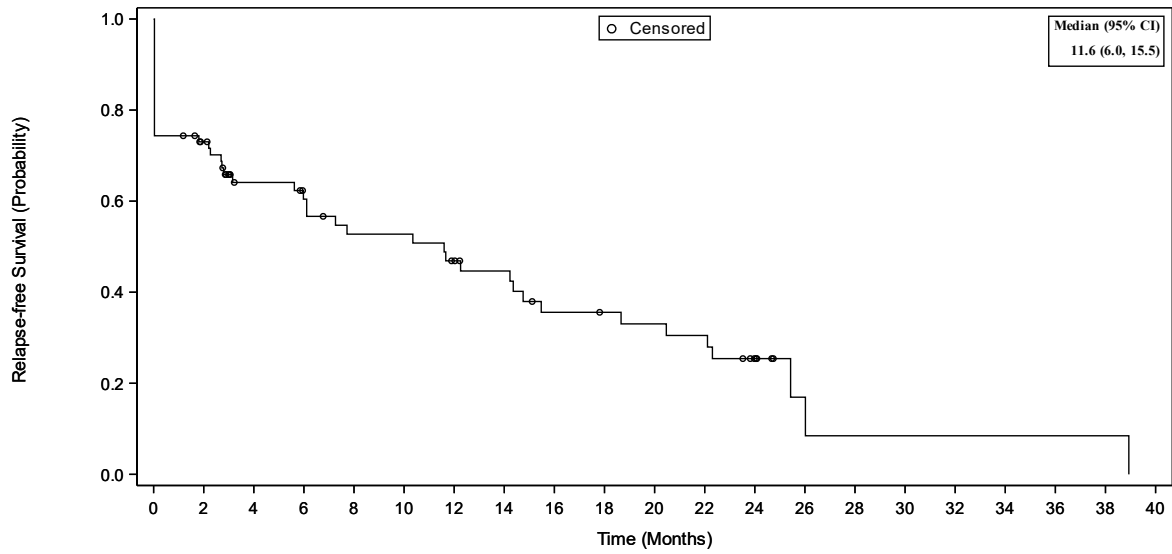
Figure 3 Kaplan–Meier plot of overall survival according to age category (Phase 1 and 2 combined, all dosed subjects): ZUMA-3



18-25 at risk	15	13	12	12	12	10	9	9	9	9	7	6	5	5	5	5	4	4	4	3	1	0	0	0	0	0	0	0	0	0	0	0	0			
(18-25 censored)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(3)	(3)	(3)	(4)	(5)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)
26-59 at risk	48	42	36	35	34	31	30	29	26	25	24	23	21	20	19	16	15	11	8	7	7	4	4	4	4	4	4	2	1	1	1	1	0			
(26-59 censored)	(0)	(2)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(4)	(4)	(4)	(5)	(8)	(9)	(12)	(15)	(16)	(16)	(19)	(19)	(19)	(19)	(19)	(19)	(19)	(19)	(19)	(19)	(19)	(19)	(19)	
>=60 Years at risk	15	15	14	13	12	12	11	11	10	10	9	8	8	8	8	8	5	4	3	3	2	2	1	1	1	1	1	0	0	0	0	0	0			
(>=60 Years censored)	(0)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(4)	(5)	(5)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(6)	(7)	(7)	(7)	(7)	(7)	(7)	(7)		
All at risk	78	70	62	60	58	53	51	49	46	44	41	39	36	34	33	32	28	27	20	15	11	10	6	6	5	5	5	4	2	1	1	1	0			
(All censored)	(0)	(2)	(4)	(4)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(7)	(7)	(7)	(8)	(12)	(13)	(19)	(24)	(26)	(27)	(31)	(31)	(31)	(31)	(31)	(31)	(31)	(31)	(32)	(34)	(34)	(34)	(34)	

Source: Figure 25, p96 of the 33-month follow-up analysis ZUMA-3 CSR

Figure 4 Kaplan–Meier plot of relapse-free survival (Phase 1 and 2, mITT population): ZUMA-3

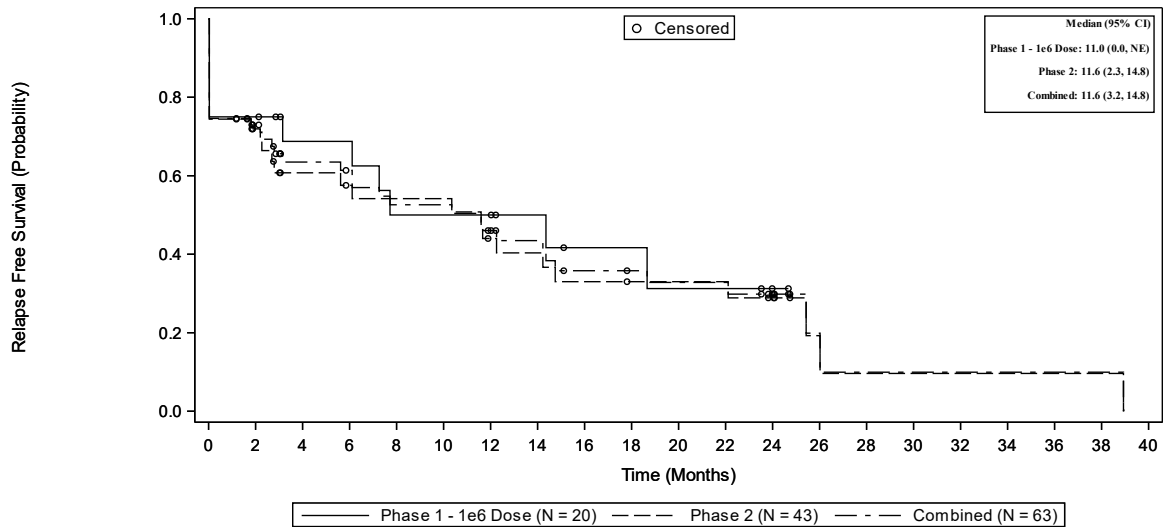


Subjects at risk	78	52	36	32	27	27	23	20	15	14	13	12	7	2	1	1	1	1	1	0
(Subjects censored)	(0)	(5)	(15)	(17)	(18)	(18)	(19)	(21)	(22)	(23)	(23)	(23)	(26)	(30)	(30)	(30)	(30)	(30)	(30)	(30)

Source: Figure 21 of the MSAC 1723.1 ADAR+in-line commentary

Note: As per Table 21 of MSAC 1723.1 ADAR+in-line commentary, 30 subjects were censored for the following reasons: ongoing remission (n=9), allo-SCT (n=14), 4 started new anticancer therapy (n=4), lost to follow up (n=2) and withdrew consent (n=1).

Figure 5 Kaplan–Meier plot of relapse-free survival according to patient age ≥26 years using investigator assessment (Phase 1 and 2 combined, all dosed subjects): ZUMA-3



Phase 1 - 1e6 Dose at risk	20	15	11	11	8	8	8	6	4	4	3	3	1	0	0	0	0	0	0	0
(Phase 1 - 1e6 Dose censored)	(0)	(0)	(3)	(3)	(3)	(3)	(3)	(5)	(6)	(6)	(6)	(6)	(8)	(9)	(9)	(9)	(9)	(9)	(9)	(9)
Phase 2 at risk	43	26	19	17	16	16	12	11	9	8	8	8	6	2	1	1	1	1	1	1
(Phase 2 censored)	(0)	(5)	(8)	(9)	(9)	(9)	(10)	(10)	(10)	(11)	(11)	(11)	(12)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
Combined at risk	63	41	30	28	24	24	20	17	13	12	11	11	7	2	1	1	1	1	1	1
(Combined censored)	(0)	(5)	(11)	(12)	(12)	(12)	(13)	(15)	(16)	(17)	(17)	(17)	(20)	(24)	(24)	(24)	(24)	(24)	(24)	(24)

Source: Figure 22 of the MSAC 1723.1 ADAR+in-line commentary

Note: 1e6 dose = ARTG-approved dose

Note: As per Table 22 of MSAC 1723.1 ADAR+in-line commentary, 24 subjects were censored for the following reasons: ongoing remission (n=9), allo-SCT (n=10), started new anticancer therapy (n=2), lost to follow up (n=2) and withdrew consent (n=1).

The original ADAR presented sub-group analyses for the four populations specified as meeting the definition of R/R B-ALL indicated similar efficacy in terms of overall complete remission (OCR), RFS at 6 months and OS at 12 months among those who were (i) primary refractory (n=24); (ii) having their first relapse within 12 months (n=22); (iii) relapsed/refractory after two or more lines of therapy (n=50) and (iv) relapsed/refractory after allogeneic stem cell transplant (n=30) among the mITT population (see Figure 3 and Figure 4 of MSAC 1723 PSD). Among patients in the mITT group, 29 had prior allogeneic stem cell transplant (which is odd given 30 had a relapse/were refractory after allogeneic stem cell transplant).

The commentary noted that no such subgroup analyses were presented for those aged ≥ 26 years, which may be of interest. However, the numbers of patients among those aged 25-59 years and ≥ 60 years were reported in the 33-month follow-up analysis CSR (p20) and were as follows: (i) primary refractory (n=17); (ii) having their first relapse within 12 months (n=20); (iii) relapsed/refractory after two or more lines of therapy (n=49) and (iv) relapsed/refractory after allogeneic stem cell transplant (n=25). Among those aged ≥ 26 years, 24 had a prior allogeneic stem cell transplant.

Table 7 provides a comparison of the efficacy results reported for the mITT and ≥ 26 year old subgroup in ZUMA-3 and the comparator studies. The ADAR reported results from Phase 1 patients treated with the ARTG-approved dose and Phase 2, combined based on the mITT population (only subjects infused with brexu-cel; 78 of 99) and those aged ≥ 26 years versus the ITT population from the comparator studies, this approach is favourable to brexu-cel (see discussion on p16 of MSAC 1723 PSD).

Table 7 Comparison of mITT and ≥ 26 year old subgroup from ZUMA-3, Phase 1 ARTG-approved dose and Phase 2, combined with comparator studies

Outcomes	mITT (n=78) per investigator	≥ 26 years (n=63) per investigator	Inotuzumab, range (n=72-164)	Blinatumomab, range (n=21 -271)	Ponatinib monotherapy PACE, Cortes et al 2018 (n=32)
CR %, n	62.8% (49/78)	61.9% (39/63)	32% (23/72) to 35.8% (39/109)	24% (5/21) to 42% (15/36)	N/A
OCR (CR+CRi/CRh) %, n	74.4% (58/78)	74.6% (47/63)	68% (49/72) to 80.7% (88/109)	36% (16/45) to 69% (25/36)	41% (13/32)
DOR, months (95% CI) for OCR	14.6 (9.4, 23.6)	20.0 (9.4, 24.1)	4.6 (3.8-6.6) to 5.4 (4.2, 7.0)	7.3 (5.8 to 9.9)	3.2 (1.8-12.8)
KM median (95% CI) OS (months)	25.6 (16.2, 47.0) ^a	26.0 (15.9, 60.4)	7.4 (5.7, 9.2) to 7.7 (6.0, 9.2)	7.1 (5.6, NE) to 9.8 (8.5 to 14.9)	12% at 3 years
KM median (95% CI) RFS (months)	11.6 (6.0, 15.5) ^b	11.6 (3.2, 14.8)	3.9 (2.9, 5.4) to 5.0 (3.7, 5.6]	5.0 (3.5, 6.4) to 7.6 (4.5, 9.5)	3 (NR)

Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CRh, complete remission with partial hematologic recovery; DOR duration of remission; NR, not reported; OCR, overall complete remission rate, OS overall survival, RFS relapse free survival.;

^a 25.4 (16.2, not estimable) in original ADAR

^b 11.6 (6.0, 15.5) in original ADAR

Source: Table 12, Table 13, Table 14, Table 15, Table 16, Table 18, Table 19, Table 21, Table 22, of MSAC 1723.1 ADAR+in-line commentary and Table 4, p17 of MSAC 1732 PSD

Compared with the comparator studies, ZUMA-3 reported the highest RFS and OS. The commentary considered that given the apparent difference in baseline characteristics between ZUMA-3 and patients in the comparator studies, ZUMA-3 results for OS and RFS should be interpreted with caution and the direction of bias is uncertain.

As noted in the MSAC 1723 PSD (pp17-18), and still relevant to this consideration:

- There was a significant difference between studies in terms of how OCR was defined. For instance, Kiyoi et al 2020, Topp et al 2014, Stein et al 2019 and Martinelli et al 2017 included CR + complete remission with partial hematologic recovery (CRh) in OCR whereas TOWER included all three definitions, CR+CRi+CRh. Cortes et al 2018 (PACE) presented OCR as Major Hematologic Response (MaHR). Only two studies, INO-VATE and DeAngelo et al 2017, reported OCR similar to ZUMA-3 (CR+CRi). Given the differences in the OCR definition, a naïve comparison of OCR rates between ZUMA-3 and comparator studies could produce biased estimates of the clinical superiority of brexu-cel.
- The applicant stated that the incidence rate of allo-SCT is relatively low across all comparators. However, some comparator studies reported the incidence rate of allo-SCT among all patients whereas others among patients only in remission.
 - Allo-SCT among all patients: In the studies conducted by Kantarjian et al 2017 (TOWER), DeAngelo et al 2017 and Kiyoi et al 2020, the incidence rate of allo-SCT among all patients was 24%, 33% (24/72) and 67% (14/21) respectively compared to 18% (14/78) in the mITT population and 17.4% (11/63) in the ≥26 year old subgroup population in ZUMA-3.
 - Allo-SCT among patients in remission: In the studies conducted by Martinelli et al., 2017, Topp et al., 2014 and Kantarjian et al 2019 (INO-VATE), the incidence rate of allo-SCT among patients with CR/CRi was 44% (7/16), 52% (14/25) and 48% (79/164) respectively compared to 24% in ZUMA-3. Also,
- There is a difference in DOR definition among TOWER and ZUMA-3 with respect to CR or CRi. For instance, TOWER defined DOR only for participants who achieved a CR, was calculated from the date a CR was first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurred first with a median observation time of 7.0 months in the blinatumomab group and 10.8 months in the SOC group (<https://clinicaltrials.gov/ct2/show/NCT02013167>). On the other hand, ZUMA-3 defined DOR as the time from first CR or CRi to relapse or any death in the absence of documented relapse. Participants who did not have a relapse event were censored on their last disease assessment date (<https://clinicaltrials.gov/ct2/show/NCT02614066>). Therefore, comparison with TOWER will produce biased estimates of DOR favouring brexu-cel.

The ADAR supplemented the naïve indirect comparisons with:

- A matched indirect comparison of ZUMA-3 versus SCHOLAR-3:
 - (i) SCA-1: patients in SCHOLAR-3 who were previously naïve to blinatumomab or inotuzumab ozogamicin matched to patients in ZUMA-3 who were previously naïve to blinatumomab or inotuzumab ozogamicin;
 - (ii) patients in SCHOLAR-3 who had previously relapsed after blinatumomab or inotuzumab ozogamicin therapy matched to patients in ZUMA-3 who had previously relapsed after blinatumomab or inotuzumab ozogamicin therapy; and
 - (iii) SCA-3: all patients from ZUMA-3, irrespective if they had previously been pre-treated with blinatumomab or inotuzumab ozogamicin therapy, were matched to patients from historical clinical studies who had not previously been treated with blinatumomab or inotuzumab ozogamicin.

The commentary considered that it was unclear what the SCHOLAR-3 matched analysis contributed to the MSAC consideration, as the sample sizes in each arm were small - never above 9 in the blinatumomab or inotuzumab ozogamicin arms.

- A matched indirect comparison versus blinatumomab, inotuzumab and chemotherapy using the pivotal comparator studies (INO-VATE and TOWER). The commentary noted that after matching, the effective sample sizes (ESS) for each comparison for the ≥26 year old subgroup ranged from

12.33 to 40.65 with sample size reductions ranging from 52.73% to 74.72%. The methods and justifications are discussed at length in the resubmission ADAR but still may not sufficiently address clinical uncertainty for MSAC. Additionally, in ZUMA-3, patients were only included in the ITT set if they had undergone leukapheresis. This suggests that there may be some risk of patient selection even in the ITT set. This was not accounted for in the MAIC analysis, and likely constitutes a trial design difference that cannot be adjusted for. The results of the MAIC did not consistently indicate larger improvements than the naïve estimates. The adjusted HRs were associated with wide CIs. Overall, it was unclear how much more clinical certainty the MAICs presented. One key issue with unanchored population-adjusted indirect comparisons is that they are only valid if all effect modifiers and prognostic variables are known and adjusted for.

Overall, the commentary considered that the updated evidence for brexu-cel did not increase the quality or quantity of evidence available for MSAC deliberations. Further, because of the lack of direct comparison with blinatumomab, or of a control group in the ZUMA-3 study, the magnitude of benefit remains highly uncertain.

As also noted in the MSAC 1723 PSD and still considered relevant to this consideration by the commentary, in ZUMA-3, Phase 2 subjects with any bridging chemotherapy were 51 (93%) out of 55 and in Phase 1, 22 (96%) out of 23. Bridging therapy in ZUMA-3 Phase 2 included cytarabine in 17 patients (31%), and fludarabine in 9 (16%), among other therapies. Similarly, in ZUMA-3 Phase 1, bridging therapy included but was not limited to cytarabine n=5 (22%), fludarabine n=3 (13%), and granulocyte-colony stimulating factor (G-CSF) n=3 (13%). Many of these therapies (namely cytarabine, fludarabine and G-CSF) were similarly used as chemotherapies in the standard care arms of the INO-VATE (inotuzumab ozogamicin) and TOWER (blinatumomab) studies. Given the high proportion of subjects that received bridging therapy and noting that the median time from leukapheresis to KTE-X19 manufacturing release is 13 days (IQR 11–14) for US patients and 14–5 days (13–19) for European patients, there is significant uncertainty around the OCR endpoints. In particular, the degree to which the remission rates can be purely attributed to brexu-cel or, to some degree, bridging therapy, remains unclear (Shah et al 2021, Phase 2).

Overall, the commentary considered the magnitude of the benefit of brexu-cel is highly uncertain and possibly overestimated due to the following identified issues:

- significant variability in baseline characteristics including proportion of patients with Ph+ disease, *KMT2A*-rearrangement, ECOG status, bone marrow blasts $\geq 50\%$, R/R post allogeneic SCT, and prior therapy including salvage therapy; the match adjusted indirect comparison considered most but not all of these, and the MAIC could not adjust for unknown predictors of benefit,
- lack of direct comparison with blinatumomab, or of a control group in the ZUMA-3 study,
- dissimilarity in OCR definition between ZUMA-3 and comparator studies,
- use of mITT instead of ITT for comparative analysis,
- the presence of bridging therapy that may contribute to the clinical outcomes to some degree,
- the comparative analysis of MRD between ZUMA-3 and comparator studies was not presented.

13. Economic evaluation

The resubmission ADAR presented a cost-utility analysis based on a clinical claim of superiority of brexu-cel to blinatumomab, with comparisons to inotuzumab ozogamicin, salvage chemotherapy, and ponatinib in scenario analyses. The clinical and, by implication, cost-effectiveness claim of brexu-cel for treatment of R/R B-ALL in adults ≥ 26 years of age, effectively relies on the assumption of cure, namely that after a certain period in relapse-free survival (a cure point) a certain proportion of patients (a cure fraction) would be in sustained remission. Previously, ESC considered that it may be reasonable to expect long-term survivorship but noted that data on the long-term survivors for brexu-cel are absent. Therefore, the original ADAR likely underestimated the ICER, largely due to the

key clinical evidence being too immature to justify long-term survival plateaus in the cost-utility model (MSAC 1723 PSD, p.36)⁴.

Table 8 presents a summary of changes in economic evaluation in the resubmission ADAR.

Table 8 Summary of the economic evaluation

Component	Description	Change or Update in Current Submission*
Perspective	Health care system perspective	No change
Population	Adult patients with R/R B-ALL, whose disease is refractory to or has relapsed following standard chemotherapy or hematopoietic stem cell transplantation as per the ZUMA-3 inclusion criteria. (Sample size is 78 infused patients)	The definition of the target population was altered to justify the exclusion of tisa-cel previously identified as a relevant comparator for the subgroup of patients in the 18-25 age group. The eligible patient population is restricted to adult patients ≥ 26 years of age with R/R B-ALL, whose disease is refractory to or has relapsed following standard chemotherapy or hematopoietic stem cell transplantation as per ZUMA-3 inclusion criteria. (Sample size is 63 infused patients)
Comparator	Blinatumomab in the base-case analysis Inotuzumab ozogamicin, salvage chemotherapy, and ponatinib in scenario analysis	No change
Duration of follow-up	ZUMA-3 observation data cut off: July 2021; 21-month follow-up analysis. Median (range) actual follow-up of 11.4 months (0.2 to 58.6 months) and 20.5 months (0.3 to 32.6 months) for Phase 1 and 2 patients, respectively.	ZUMA-3 observation data cut off: July 2022; 33-month follow-up analysis (approximately one extra year of observations). Median (range) actual follow-up was 11.4 months (3.4 to 42.0 months) and 23.5 months (7.6 to 35.5 months) for Phase 1 and 2 patients, respectively.
Type(s) of analysis	Cost-utility analysis	No change
Outcomes	<ul style="list-style-type: none"> Quality-adjusted life-years (QALYs) Life-years (LYs) 	A 'weighted analysis' approach was used where costs, LYs and QALYs are first calculated separately for the 'cured' and 'non-cured' cohorts and then aggregated into a weighted ICER
Time horizon	Lifetime horizon (defined as 57 years) in base-case	Lifetime horizon (defined as 52 years) in base-case (updated horizon to reflect the older population)
Computational method	Hybrid model (Decision tree + Partitioned survival model) adapted to curative intent by explicitly modelling the cure fraction (proportion of EFS patients at a cure point that was set at 2 years)	The cure assumptions include a cure point and a cure fraction. A cure point was set at 2 years in the original ADAR and revised to 5 years, first in the pre-MSAC response and subsequently, in the resubmission ADAR.
Extrapolation method: criteria for a switch from the K-M data to parametric extrapolations	<p>Patient progression is modelled with K-M data up to the time point when approximately 20% of patients remained at risk.</p> <p>20% of EFS patients in the brexu-cel arm remained at risk after 69 weeks (1.32 years).</p> <p>Time interval modelled with parametric functions: 2-1.32=0.68 years (8 months).</p>	<p>No change</p> <p>20% EFS patients in the brexu-cel arm remained at risk at 78 weeks (1.49 years).</p> <p>Time interval modelled with parametric functions: 5-1.49=3.51 years (42 months).</p>
Health states	<p>Partition survival model has following health states:</p> <ul style="list-style-type: none"> Event-free survival 	No change

⁴MSAC 1723 Brexucabtagene autoleucel for adult relapsed or refractory B-precursor acute lymphoblastic leukaemia. 2022 [https://www1.health.gov.au/internet/msac/publishing.nsf/Content/0C9197DC317F49F2CA258856001CDFC8/\\$File/1723%20Final%20PSD-%20Nov%202022_redacted.pdf](https://www1.health.gov.au/internet/msac/publishing.nsf/Content/0C9197DC317F49F2CA258856001CDFC8/$File/1723%20Final%20PSD-%20Nov%202022_redacted.pdf)

Component	Description	Change or Update in Current Submission*
	<ul style="list-style-type: none"> Progressed disease Death 	
Cycle length	1 week	No change
Transition probabilities	Primary data source: <ul style="list-style-type: none"> ZUMA-3 (<i>updated to include extended follow-up</i>) Other data source for base-case comparator arm: <ul style="list-style-type: none"> TOWER 	No change
Discount rate	5% for both costs and outcomes	No change
Software	Microsoft excel 2016	No change

Abbreviations: B-ALL; B-cell precursor acute lymphoblastic leukaemia; R/R, relapsed or refractory, EFS – event-free survival, K-M Kaplan-Meier

*Includes the changes previously presented to MSAC in the pre-ESC and pre-MSAC responses.

As in the original ADAR, the economic evaluation in the resubmission ADAR relied on a hybrid model approach which included a decision tree and partitioned survival model (PSM) component. The decision tree differentiated patients between those who receive brexu-cel infusion and those who discontinued prior to infusion. The structure of the model and the calculation algorithms remain essentially the same as in the original ADAR, but include a weighted analysis approach, explained below. In the original ADAR, the modelled economic evaluation assumed a 2-year cure point, which was previously considered unjustified and highly favourable to brexu-cel (MSAC 1723 PSD). In the resubmission ADAR, the cure point assumption is set at 5 years. This is a more conservative assumption. The resubmission ADAR also reference advice within the Pharmaceutical Benefits Advisory Committee (PBAC) Public Summary Document for Gilteritinib, which stated that “...in clinical practice, 5 years disease free is generally a more accepted definition of a cure...” (Gilteritinib, PSD November 2021, p.5)⁵.

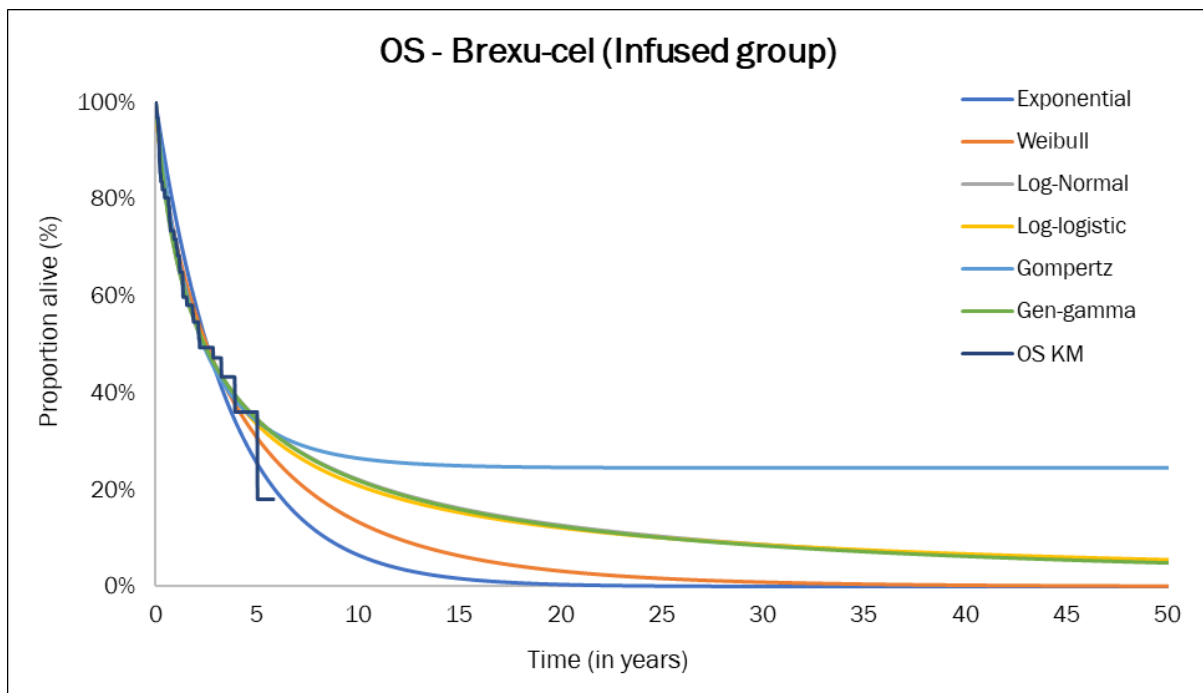
As in the original ADAR, long-term survival is modelled through parametric extrapolation of the K-M observations starting from the point where 20% of patients remain at risk (the switch point). In the original ADAR, the 2-year cure point assumption and the 69-week (1.32 years) switch translated into 0.68 years (8 months) of parametric extrapolation of event-free progression in the brexu-cel arm. K-M data in resubmission ADAR were based on the 33-month follow-up in the subgroup of ≥26 year olds, which resulted in a different 20% cut-off point, that corresponds to about 12 patients remaining at risk at approximately 18 months (78 weeks, see Figure 5). In the revised model, this 78-week (1.49 years) switch point together with the 5-year cure point assumption resulted in 3.51 years of EFS progression being extrapolated with a fitted parametric curve. In the updated OS K-M data the 20% switch point occurred at 166 weeks (3.2 years) with parametric modelling covering 1.8 years. Standard parametric functions were fitted and used to extrapolate OS and EFS K-M data beginning from the switch point and up to the 5-year cure point, when all surviving patients would be presumed cured and would revert to the general population mortality with a standardised mortality ratio (SMR) of 2 applied in the base case.

In the original ADAR, the choice of parametric curve had a limited effect on the model, because they were relied on for only a short time in the model given the assumption of cure at 2 years. However, the longer the time to cure is assumed, the longer the survival curves are based on parametric survival functions fitted to the clinical data, so the modelled results became very sensitive to the choice of a parametric curve in the revised model. Based on goodness-of-fit statistics, the

⁵ Public Summary Document – March 2022 PBAC Meeting. GILTERITINIB, Tablet 40 mg (as fumarate), Xospata®, Astellas Pharma Australia Pty Ltd. 2022. <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/files/gilteritinib-psd-march-2022.pdf>.

resubmission ADAR chose a log-normal function for extrapolation of OS in the brexu-cel arm (Figure 6). The commentary noted that, setting the goodness-of-fit statistics aside, visual inspection of Figure 6 did not suggest the log-normal curve demonstrated the best fit for the K-M survival data. There is an evident 20% drop in OS at the lower end of the K-M curve, which is inconsistent with the choice of the lognormal extrapolation model being the best fit. The commentary considered that there is a high degree of uncertainty in selecting one of the parametric curves over another for modelling overall survival.

Figure 6 Standard parametric extrapolation, OS of brexu-cel (infused group)- ZUMA-3 mITT Phase 1/2; ≥26 years



Source: Fig. 46 of the ADAR.

OS=overall survival

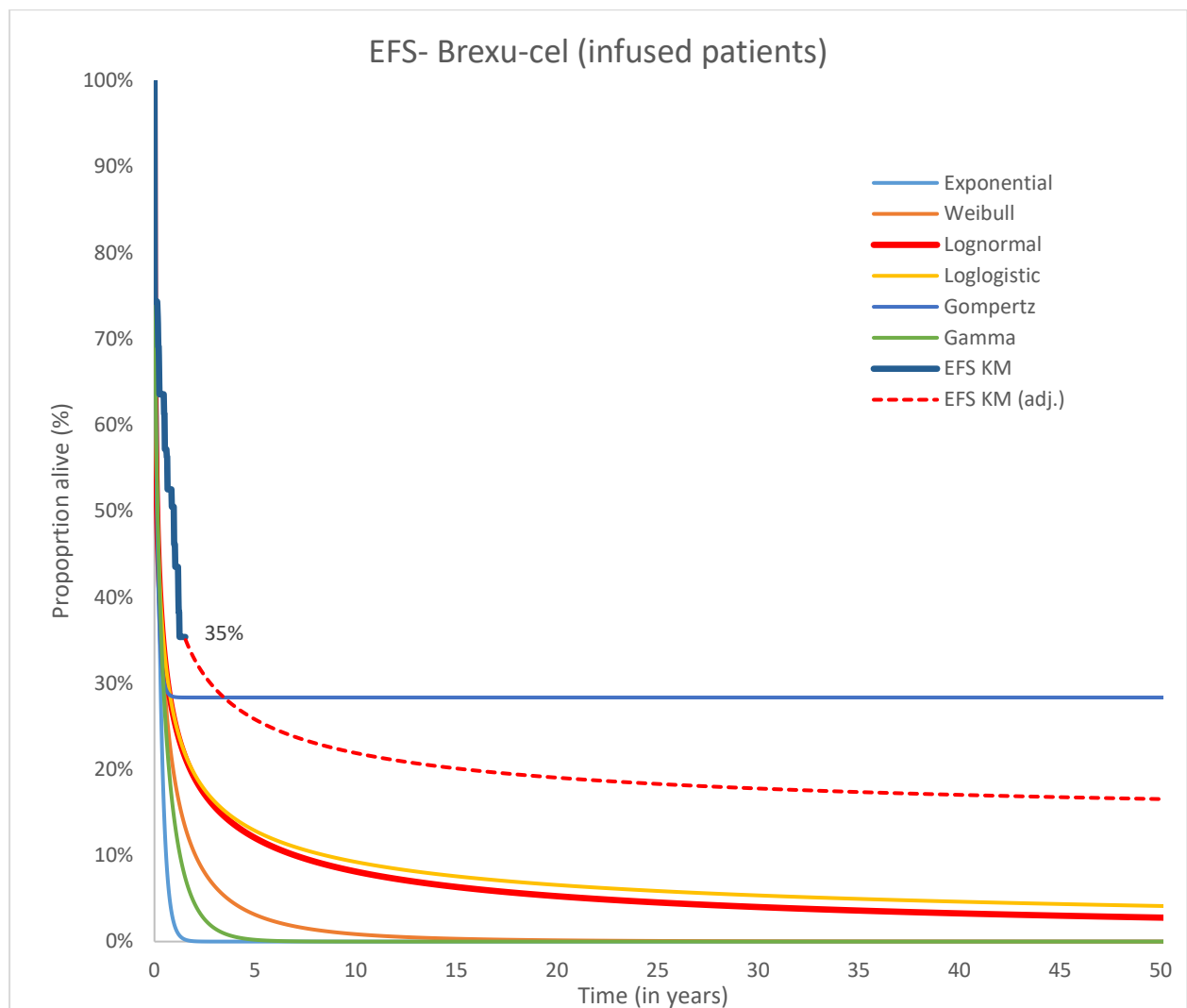
For the illustrative purposes, parametric curves are extended for the time horizon of 50 years but in the model the parametric curve was used from the 166 weeks (3.2 years) KM switch point up to the 5-year cure point.

Figure 7 illustrates the approach to extrapolation of the EFS K-M observations for the brexu-cel arm. Based on goodness-of-fit statistics, the resubmission ADAR again chose a log-normal function to predict event-free survival (the solid red line in Figure 7). The commentary noted that in the model, three out of six standard parametric curves (Log-normal, Log-logistic, and Gompertz) plateaued survival irrespective of the assumed transition to population-based mortality at the cure point. In contrast, three other parametric extrapolations (Exponential, Weibull, and Generalized Gamma) corresponded to a much shorter life expectancy. Variability is likely to relate to the smaller sample of 63 patients (in comparison to 78 in the original ADAR). Based on visual inspection of Figure 7, the commentary is not confident that the lognormal curve demonstrated the best fit for the K-M survival data. At the switch point of 78 weeks, there is a gap of about 14% between the proportion of EFS patients according to the lognormal extrapolation (21%) and the observed 35%. The resubmission ADAR used an adjustment procedure, which realigns the parametric curve with the K-M data at the switch point (the dotted red line depicts the lognormal adjustment in Figure 7). In the base case, the adjustment was applied only to EFS and may have been reasonable if there was certainty in a cure, i.e. some evidence of the K-M data plateauing around the switch point. The commentary noted that in Figure 5, the EFS K-M data depicts a sharp decline between 18 and 26 months, i.e. immediately after the switch point. While longer-term OS K-M data was included in the EXCEL attachment, the EFS K-M observations were not made available beyond the switch point of 78 weeks. The

commentary considered that, in the absence of more reliable data, the ‘adjustment’ is likely to be biasing the outcomes in favour of brexu-cel.

The adjustment procedure also applied to the comparator arms to realign parametric extrapolations with observations in the respective studies. In relation to blinatumomab, the discrepancies between the observed and predicted EFS values from the TOWER study were less pronounced (see sensitivity analyses in Table 15). In relation to the salvage chemotherapy (the control arm of the INO-VATE study) the adjustment procedure (including an additional manual adjustment of 5%) was applied to lower the parametric curve to align it with the observe data. In this case, the adjustment procedure corresponds to more conservative estimates of a cure fraction, which favours the comparator.

Figure 7 Standard parametric extrapolation, EFS of brexu-cel (infused group) ZUMA-3 mITT Phase 1/2; ≥26 years



Source: Fig. 48, of the ADAR. Reproduced with inclusion of the dotted line to provide a representative illustration of how the KM curve was adjusted, during the evaluation from the data in attached EXCEL spreadsheet.

EFS = event-free survival.

For the illustrative purposes, parametric curves are extended for the time horizon of 50 years but in the model the parametric curve was used from 78-week (1.49 years) KM switch point up to the 5-year cure point.

Although the parametric extrapolations in the resubmission ADAR are based on extended follow-up, it remains uncertain whether an extra year of observation produced data sufficiently mature for decision making. It can be argued whether it is appropriate to base the selection of extrapolation curves solely on the goodness-of-fit statistics without consideration of plausibility of extrapolations. Plausibility would usually be assessed through a comparison of predictions of the percentage of

patients who remain event free following a certain length of follow-up. Ideally, these assessments of plausibility are made comparing to relevant studies with longer observed follow-up⁶. Such studies, should they become available, may also support the cure claim, which does not seem to be adequately supported by the relevant external evidence presented in the resubmission ADAR.

The resubmission ADAR claimed that in the past, MSAC have considered implicit or explicit cure assumptions (Kymriah MSAC 1519.1 PSD⁷, Yescarta MSAC 1587 PSD)⁸. However, the original ADAR commentary's review of MSAC submission of tisagenlecleucel in paediatric and young adult R/R B-cell ALL (1519 and 1519.1 PSDs) indicated that an explicit cure assumption was not modelled in that case. Nevertheless, the resubmission ADAR still used paediatric longer-term follow-up data as an external validation of the 5-year cure assumption. In the ELIANA study⁹ the 5-year RFS rate was 49%. However, while prognosis in children with ALL is relatively favourable, survival is particularly poor among adults. The 5-year OS is approximately 90% in children but only 20% to 40% in adults and elderly patients (NCCN 2021¹⁰, Paul et al., 2016¹¹). Therefore, it does not appear reasonable to validate the suggested brexu-cel cure fraction in adults with the long-term tisa-cel observations, given that only a small proportion of the tisa-cel study population was in the young adult (18-25 age category). A review of the Yescarta (axicabtagene ciloleucel CAR-T therapy) submission also failed to identify any support for the claim of the long-term survivorship of the patients undergoing CAR-T therapies. In fact, based on the evidence presented at the time, MSAC continued to have some concerns about the durability of benefit of axicabtagene ciloleucel (MSAC 1587 PSD, p.5)⁷.

Justification of the cure assumption at two years in the original ADAR was based on a study conducted in Australia and New Zealand (Kliman, 2020)¹², which included observational data for survival after allogeneic hematopoietic cell transplant (allo-HCT), including ALL patients. The original ADAR claimed that this data reflected the impact of sustained remission on survival risk and is informative for the model. After 2 years in remission the ALL cohort in the Kliman (2020) study had survival at 10 years, close to that of the age matched general population. The resubmission ADAR again cited Kliman (2020) claiming that post-transplant survival after 2 years in remission is appropriate to estimate long-term survival risk and to be used as a proxy for sustained remission.

MSAC previously considered that the original ADAR did not justify why a study detailing long term survival in SCT patients would be applicable to brexu-cel patients and blinatumomab patients (MSAC 1723 PSD, p.21). Only a small proportion of R/R B-ALL patients (22.2% in ZUMA-3; 24% in TOWER) received a subsequent allo-SCT. Also, in the pre-ESC response the applicant stated that the ZUMA-3 study demonstrated that OS is independent of whether patients received consolidation allo-SCT (n = 13) or not (n = 45). There does not appear to be a consensus on the position of brexu-cel in

⁶ Gallacher D, Kimani P, Stallard N. *Extrapolating Parametric Survival Models in Health Technology Assessment: A Simulation Study*. *Med Decis Making*. 2021 Jan;41(1):37-50.

⁷ MSAC 1519.1 Tisagenlecleucel (CTL019) for treatment of relapsed or refractory diffuse large B-cell lymphoma (Kymriah).- November 2019. <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519.1-public>

⁸ MSAC. 1587 Axicabtagene ciloleucel for the treatment of refractory or relapsed CD19-positive lymphoma (Yescarta). 2019 [http://www.msac.gov.au/internet/msac/publishing.nsf/Content/B5B780278B3A4B48CA2583C9001B80BB/\\$File/1587%20Final%20PSD%20Nov%2019_redacted.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/B5B780278B3A4B48CA2583C9001B80BB/$File/1587%20Final%20PSD%20Nov%2019_redacted.pdf)

⁹ Rives S, et al. S112: TISAGENLECLEUCEL IN PEDIATRIC AND YOUNG ADULT PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL): FINAL ANALYSES FROM THE ELIANA STUDY. *HemaSphere*. 2022;6, p.13-14.

¹⁰ NCCN. Acute Lymphoblastic Leukemia: NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. 2021;Version 4.2021.

¹¹ Paul S, Kantarjian H, Jabbour EJ. Adult Acute Lymphoblastic Leukemia. *Mayo Clin Proc*. 2016;91(11):1645-66.

¹² Kliman D, Nivison-Smith I, Gottlieb D, Hamad N, Kerridge I, Purtill D, et al. Hematopoietic Stem Cell Transplant Recipients Surviving at Least 2 Years from Transplant Have Survival Rates Approaching Population Levels in the Modern Era of Transplantation. *Biol Blood Marrow Transplant*. 2020;26(9):1711-8.

relation to allo-SCT in the clinical pathway, and MSAC previously commented that the contribution of allo-SCT to outcomes, when used with brexu-cel and the comparators, is uncertain (MSAC 1723 PSD, p.34). Nevertheless, the applicant's statement invalidates the relevance of the Kliman (2020) study for the intended purpose.

The resubmission ADAR used a 'weighted analysis' approach to calculate the modelled outcomes. This procedure adjusts the outcomes to mitigate the inherent limitation of PSM where the cure assumption applies to all alive patients instead of only to event-free survivors. The PBAC have previously considered this kind of additional analysis in the context of the gilteritinib submission (Gilteritinib PBAC, March 2022)⁴. The weighting procedure (explained below) relies on the ratio of the percentage of patients in EFS health state to the percentage of the overall survivors at the cure point (5 years in the base case). In the 'weighted analysis' this ratio was applied to the estimates of costs, LYs and QALYs calculated separately for the 'cured' and 'non-cured' cohorts to obtain a weighted ICER. The 'cured cohort' is the population in the model with cure assumptions (as in the original ADAR). The term "not-cured cohort" is misleading and merely refers to the outcomes of the model based only on the trial K-M data and parametric extrapolations and not using the cure assumption of surviving patients having an [adjusted] general population mortality risk (i.e. a conventional PSM).

The 'weighted analysis' approach was first presented in the October 2022 pre-ESC response for MSAC 1723 with the 2-year cure assumption. However, ESC (October 2022) considered that this approach still deviated from standard practice of using parametric extrapolations fitted to the observed clinical data. In the November 2022 pre-MSAC-response the cure assumption in the model with 'weighted analysis' was further amended to 5 years. MSAC (November 2022) still considered that there was insufficient observed data to support the amended analysis and the cure assumption at five years was still highly optimistic in favour of brexu-cel and was not supported by the evidence presented (MSAC 1723 PSD. p.4).

The commentary noted that it appears, that in their 2022 consideration of the original ADAR, ESC and MSAC were discussing two distinctly different sources of bias, although both were referred to as "structural". One issue relates to the original ICER being underestimated, largely due to long term survival plateaus modelled through the use of highly optimistic cure assumptions (MSAC 1723 PSD. p.32). The second related to the known limitations of PSM due to the lack of structural link between the health states, which resulted in the cure-fraction applied to all alive patients (both EFS and PD) at a cure point. This would result in a proportion of patients in the PD health state attributed long-term survival, which is not compatible with disease pathology.

By introducing the weighted approach in the November 2022 pre-ESC response, the applicant addressed the second issue, while retaining a 2-year cure assumption. ESC (October 2022) noted this additional analysis but found that applying the cure assumption to patients in EFS only had a moderate impact on the base case ICER (10% increase) and still questioned the 2-year cure point assumption (MSAC 1723 PSD. p.37). The applicant addressed the second issue in the November 2022 pre-MSAC response by setting a cure point at 5 years in the amended ICER. The combined effect of both issues on the resubmission base-case analysis are addressed in the present Commentary.

Table 9 presents the algorithm for calculating 'weights' used for adjustment of the outcomes calculated with and without the 5-year cure assumption, i.e. for the 'cured' and 'non-cured' cohorts respectively.

Table 9 Derivation of ‘cured’ and ‘non-cured’ cohort weights with and without an assumption of a 5-year cure point

	Brexu-cel	Blinatumomab
% OS at cure point	28.6%	7.9%
% EFS at cure point	21.7% (cure fraction)*	7.3% (cure fraction)*
‘Cured cohort’ weight	75.8% (=21.7%/28.6%)	92.4% (=7.3%/7.9%)
‘Non-cured cohort’ weight	24.2% (=100%-75.8%)	7.6% (=100%-92.4%)

Source: Table 111 in the resubmission ADAR

Abbreviations: EFS, event-free survival; OS, overall survival

* Added by the evaluators

The ‘weights’ assigned to the outcomes in the ‘cured’ cohort are the ratios of the proportions of EFS to OS patients for brexu-cel and blinatumomab, 75.8% and 92.4% respectively, estimated at the cure point (5 years in the base-case). Their compliments, 24.2% and 7.6% for brexu-cel and blinatumomab respectively, were assigned to the outcomes in the ‘non-cured’ cohort, as explained below.

Table 10 presents the base case costs for the ‘cured’ and ‘non-cured’ cohort.

Table 10 Base case costs for the ‘cured’ and ‘non-cured’ cohort using the \$redacted brexu-cel price in the resubmission ADAR

Type of Costs	Costs for brexu-cel	Costs for blinatumomab	Incremental Cost
Cured cohort, i.e. the cure point of 5 years applied and the adjusted by SMR general population mortality applied to all surviving patients			
Total cost (discounted)	\$redacted	\$redacted	\$redacted
Non-cured cohort, i.e. no patients was switched to the general population mortality			
Total cost (discounted)	\$redacted	\$redacted	\$redacted
Weighted costs	\$redacted	\$redacted	\$redacted

Source: Table112, of the ADAR. EXCEL Worksheet “weighted analysis”.

The weighted cost estimate of **\$redacted** (brexu-cel) was obtained by firstly applying the ratio of the proportion of patients in the EFS health state to the proportion of patients in the OS state at the cure point of 5 years (75.8% in the base case, Table 9) to the total cost of brexu-cel in ‘cured’ patients (**\$redacted**). Secondly, the compliment of the ratio (1-75.8%=24.2%) was applied to the total cost of brexu-cel in ‘non-cured’ patients (**\$redacted**). Summation of these products produced **\$redacted**. Using the corresponding ratio of 92.4% for blinatumomab EFS and OS proportions and its compliment of 7.6% (Table 9), the calculations were repeated with respect to the total cost of blinatumomab in ‘cured’ patients (**\$redacted**) and the total cost of blinatumomab in ‘non-cured’ patients (**\$redacted**) to obtain a weighted sum of **\$redacted** used in the base case ICER. The corresponding incremental cost is **\$redacted**.

The algorithm for assigning costs to the patients in each cycle of the model is based on the proportion of patients in each health state and included a 5-year inflection point, after which the proportion of surviving patients is calculated using the different formulae, based on general population mortality. The small difference between the costs of ‘cured’ and ‘non-cured’ patients is explained by the bulk of the costs occurring before the 5 year cure point. Table 11 presents the base case LY and QALY outcomes for the ‘cured’ and ‘non-cured’ cohort.

Table 11 Base case LY and QALY for the ‘cured’ and ‘non-cured’ cohort

Parameters	Brexu-cel	Blinatumomab	Incremental outcome
Cured cohort, i.e. the cure point of 5 years applied and the surviving patients switch to the general population mortality adjusted by SMR			
Total LYs (discounted)	5.48	2.07	3.41
Total QALYs (discounted)	4.28	1.51	2.77
Non-cured cohort, i.e. no patients was switched to the general population mortality			
Total LYs (discounted)	4.09	1.48	2.61
Total QALYs (discounted)	3.15	1.02	2.13
Combined results for cured and non-cured cohorts using weights from Table 9			
Total weighted LYs	5.14	2.02	3.12
Total weighted QALYs	4.01	1.47	2.53

Source: Table 112, of the ADAR. EXCEL Worksheet “weighted analysis”.

Abbreviations: LY, life-year; ICER: incremental cost-effectiveness ratio; QALY, quality-adjusted life-year, SMR, standardised mortality ratio

The same calculation method as in the total weighted cost also applied to obtain a weighted estimate of total LYs and QALYs. The weighted ICER was \$redacted per LY gained and \$redacted per QALY gained, as shown in the step four in the table below.

Note, while Table 10 and Table 11 show brexu-cel and blinatumomab calculations separately for the ‘cured’ and ‘non-cured’ cohorts before aggregating them into the weighted costs and QALYs, only the ‘weighted analysis’ results were presented for the alternative comparators inotuzumab ozogamicin, salvage chemotherapy, and ponatinib (not replicated).

Table 12 presents the results of the stepped economic analysis. The ‘weighted analysis’ approach applied to steps 3 and 4.

Table 12 Results of the stepped economic analysis using a ‘weighted analysis’ approach and the \$redacted brexu-cel price in the resubmission ADAR

Steps	Costs			Health Outcomes			Incremental Cost-Effectiveness Ratios
	Brexu-cel	Blinatumomab	Incremental Costs	Brexu-cel	Blinatumomab	Incremental Health Outcomes	
Step 1: Incremental cost per EFLY gained, over 1 year time horizon							
Step 1	\$redacted	\$redacted	\$redacted	EFLYs: 0.55	EFLYs: 0.32	PFLYs: 0.24	\$redacted [\$ per EFLY gained]
Step 2: Incremental cost per LY gained, over 2 years’ time horizon							
Step 2	\$redacted	\$redacted	\$redacted	LYs: 0.78	LYs: 0.59	LYs: 0.19	\$redacted [\$ per LY gained]
Step 3: Incremental cost per LY gained, over a lifetime horizon of 52 years							
Step 3a*	\$redacted	\$redacted	\$redacted	5.48	2.07	3.41	\$redacted
Step 3b^	\$redacted	\$redacted	\$redacted	4.09	1.48	2.61	\$redacted
Step 3**	\$redacted	\$redacted	\$redacted	LYs: 5.14	LYs: 2.02	LYs: 3.12	\$redacted [\$ per LY gained]
Step 4 (Base-case): Incremental cost per QALY gained, over a lifetime horizon of 52 years							
Step 4a*	\$redacted	\$redacted	\$redacted	4.28	1.51	2.77	\$redacted
Step 4b^	\$redacted	\$redacted	\$redacted	3.15	1.02	2.13	\$redacted
Step 4**	\$redacted	\$redacted	\$redacted	QALYs: 4.01	QALYs: 1.47	QALYs: 2.53	\$redacted [\$ per QALY gained]

*Base case analysis for cured cohort (5 year cure point applied to all alive patients)

^ Base case analysis for non-cured cohort (model used only K-M data and parametric extrapolation over the time horizon of 52 years)

**weighted analysis results of ‘cured’ and ‘non-cured’ cohorts

EFLY = event free life year; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year.

Note: Multiple outcomes may be informative for MSAC decision-making within each step.

Source: Tables 104, 112 of the ADAR.

In the base case of the model, relying on the 5 year cure assumption (“cured cohort”), the ICER is estimated at \$redacted per QALY. In the base case of the conventional PSM (“non-cured cohort”), the estimated ICER is \$redacted per QALY, the most conservative estimate, which is inconsistent with a curative intent. The 5 year cure assumption increased the ICER by \$redacted per QALY gained (\$redacted- \$redacted). Setting the plausibility of the cure assumption aside, this is, as discussed above, is an underestimation, because all patients, including those in the progressed disease state, would attract a general population mortality risk (adjusted by SMR) at achieving the cure point. However, the weighted approach mitigated this systematic bias. For example, by applying a ratio of 75.8% (Table 9) to costs and, more importantly, to the outcomes in the brexu-cel arm, the health gains become applicable only to the proportion of the surviving patients. The weighted ICER increased by 9.5% per QALY gained (\$redacted- \$redacted=\$redacted). It is important to note that this ratio is specifically calculated using EFS and OS point estimates at the cure point (5 years in the base case) and varies significantly not just with variations of the cure point assumptions, but also with the methods used for extrapolation (extrapolation uncertainty), e.g. depending on how the K-M data is parameterised and how the K-M observations are aligned with the parametric curves (see Table 15).

Under the base case assumption, the weighted ICER is \$redacted per QALY (Table 12). This is likely to be an underestimation, although it is 6% lower than the base case ICER in the original ADAR

(\$redacted per QALY using a 2-year cure point and a previous brexu-cel price of \$redacted). The reduction is mainly due to the reduced acquisition cost for brexu-cel.

To demonstrate the model's operational validity, the resubmission ADAR produced two graphical representations of the proportion of patients (traces) in the EFS, PD, and death health states in each weekly cycle of the model (Figure 8 and Figure 9).

Figure 8 Graph of full model traces- Brexu-cel

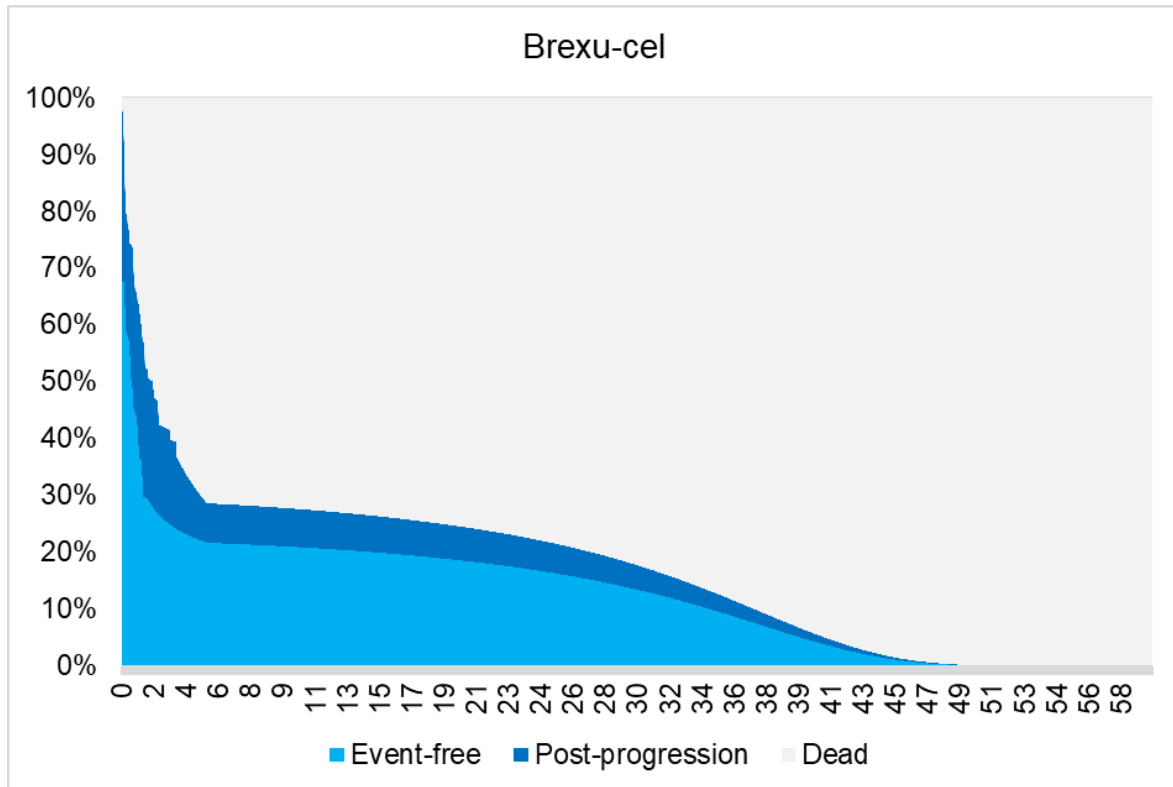
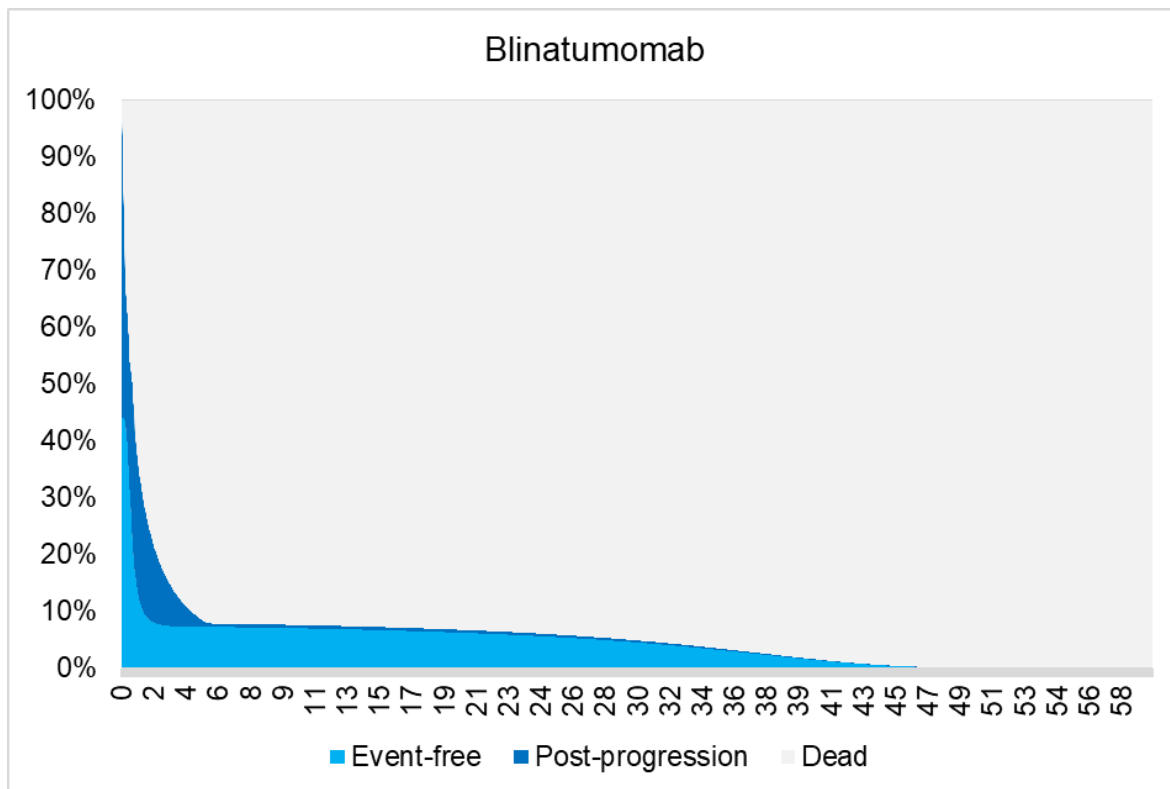


Figure 9 Graph of full model traces- Blinatumomab



The resubmission ADAR stated that it is evident from Figure 8 and Figure 9 that a) both the overall (EFS+ PD) and EFS survival are greater in brexu-cel treatment arm in comparison to blinatumomab arm; and b) OS is greater than EFS at any time point of the model for both brexu-cel and blinatumomab arm. The 5-year inflexion point where patients switch to the general population mortality is also evident on both graphs.

Sensitivity analyses presented in the resubmission ADAR show that the model, as for the original model, was most sensitive to the variations in the discount rate, time horizon, cure point, and proportion of patients receiving subsequent allo-SCT. The resubmission model remained moderately sensitive to the selected utility for patients in the progressive disease state, however it became less sensitive to an increase in the standardised mortality ratio applied to cured patients.

During the evaluation, additional univariate sensitivity analyses were conducted to replicate the commentary to the original ADAR, however the weighted approach format was used in this instance (Table 13). In addition, variation in the drug acquisition cost were tested in the sensitivity analyses, including the average net price from the applicant's updated pricing proposal that was submitted after the ADAR was lodged.

Table 13 Sensitivity analyses of the updated model with weighted analysis results conducted by the commentary and by ESC

Base case setting	Scenario setting	Incremental cost	Incremental QALYs	ICER	% change from Base case
Base case	-	\$redacted	2.53	\$redacted	-
Sensitivity analyses conducted for the commentary					
Cure point: 5 years Lognormal OS and EFS extrapolation; KM+parametric adjustment for EFS extrapolations applied in both arms;	Cure point: 10 years	\$redacted	2.36	\$redacted	6%
	Cure point: 20 years	\$redacted	2.13	\$redacted	16%
	Cure point 52 years	\$redacted	2.13	\$redacted	16%
Drug acquisition cost					
average price from the proposed PfP	\$redacted	\$redacted	2.53	\$redacted	-30%
KTE-X19 Acquisition cost (+/- 20%)	\$redacted	\$redacted	2.53	\$redacted	31%
	\$redacted	\$redacted	2.53	\$redacted	-31%
Sensitivity analyses conducted by ESC					
52 year time horizon SMR 2.0 Utilities for PD and cured	20 year time horizon	\$redacted	2.09	\$redacted	
	20 year time horizon SMR 3.0	\$redacted	2.07	\$redacted	
	20 year time horizon SMR 3.0 Utilities for PD and cured based on Aristides et al. 2015	\$redacted	1.81	\$redacted	

Source: Compiled during the assessment.

EFS= event-free survival; OS = overall survival; KM =Kaplan-Meier

The key drivers of the model are presented in Table 14.

Table 14 Key drivers of the model

Description	Method/Value	Impact Base case: \$85,054/QALY gained (weighting approach)
Cure assumption	The revised cure point assumption of 5 years, results became less sensitive to this assumption in comparison to the original ADAR	High. ICER varied from \$redacted (3 years, favouring brexu-cel) to \$redacted (20 years, favouring the comparator)
Time horizon	Lifetime horizon (52 years in the base case)	High favours brexu-cel. Use of a 20-year time horizon increased the ICER to \$redacted per QALY gained
Inclusion of allo-SCT	In the base-case 22.2% of patients (based on ZUMA-3) received subsequent allo-SCT in brexu-cel arm.	High favours brexu-cel. Assuming that 0% patients received subsequent allo-SCT in brexu-cel arm reduced ICER to \$redacted
Discount rate	5% in the base case	Moderate, favours brexu-cel when reduced to 3% (ICER=\$redacted)
Utilities	Base case progressive health state utility source: ZUMA-3	Moderate, favours brexu-cel

		Use of PD health state utility from Aristides (2015) increased the ICER to \$redacted per QALY gained.
SMR	SMR applied to cured patients in the base case was 2, based on Kliman (2020)	Moderate, favours brexu-cel Use of SMR 4 from Martin (2010) increases the ICER to \$redacted/QALY gained
Extrapolation assumptions	Choice of a parameterised survival curve and the 'adjustment' procedure. Lognormal curve with 'adjustment' to ensure its best fit to the EFS KM data was used in the base case.	High, favours brexu-cel. Removing the "adjustment" (that biases the results in favour of brexu-cel) increases the weighted ICER from 6% to 49% depending on the choice of the parametric curve.

Source: Table 115 and the evaluators' calculations ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year. PD=progressed disease; SMR=standardised mortality ratio

In comparison to the original ADAR, the updated 5 year cure point version is less sensitive to variations in the cure point assumptions. However, assuming a longer time to cure still increased the weighted ICER.

The weighted ICER in the updated model is moderately sensitive to an increase in SMR from 2 to 4. The PBAC ESC previously advised that the patients' morbidity and mortality will be greater than the general population due to their exposure to previous treatments (Gilteritinib PSD November 2021). However, the appropriate SMR value remains a source of uncertainty, with the UK clinical advice suggesting that SMR above 3 is more appropriate and may be even closer to 4 (NICE brexu-cel submission, April 2023)¹³.

The resubmission model remained moderately sensitive to the variations in the time horizon. MSAC (November 2022) already questioned a life-time horizon given that there was less than three years of observed clinical data at the time of the original ADAR (MSAC 1723 PSD, p.4). Since the original ADAR, the duration of follow-up of ZUMA-3 was extended by approximately one year, while the time horizon reduced from 57 to 52 years. On the other hand, MSAC (November 2022) previously considered that the ADAR's specification of a lifetime horizon may be reasonable and was consistent with the time horizon used in MSAC 1519.1 for tisa-cel in relapsed or refractory diffuse large B-cell lymphoma (DLBCL). It was noted, however, that MSAC 1519.1 had modelled survival convergence after 20 years (MSAC, 1723 PSD, p.20). The model in the resubmission ADAR (consistent with the original ADAR) does not assume convergence of survival over the 52 years, favouring brexu-cel. Therefore, given the limited ZUMA-3 follow-up, this approach in the updated model may not be reasonable unless the 5-year cure assumption is supported by relevant evidence.

Unlike the original model, where the choice of the parametric extrapolation did not have a significant effect on the ICER, the resubmission model is highly sensitive to extrapolation assumptions, namely the choice of an extrapolation curve, and the application of the adjustment procedure to the EFS extrapolations in the brexu-cel arm. As explained above, the latter involves realignment of the chosen parametric curve with the K-M data at the switch point (where 20% of patients still remain at risk).

Every combination of extrapolation assumptions produced new estimates of the proportions of patients in the EFS health state and the proportion of overall survivors at the cure point (5 years). The weighted ICER is very sensitive to the variations in these proportions. This is because the weighting procedure relies on the ratio of the proportions of patients in the EFS health state to the proportion of overall survivors (Table 9).

Table 15 shows results of the extensive sensitivity analyses conducted during the evaluation where different combinations of the extrapolation assumptions were tested. For each of the standard

¹³ NICE submission "Brexucabtagene autoleucl for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over" NICE, April 2023. <https://www.nice.org.uk/guidance/ta893/documents/final-appraisal-determination-document>

parametric extrapolations the “adjustment” procedure (bringing the extrapolation curve upward to realign with the K-M data at the switch point) is firstly removed from the brexu-cel arm and then from both the intervention and comparator arms.

For illustrative purposes the proportions of brexu-cel patients in EFS (cure fraction) and in OS health state at the cure point were included along with the corresponding values of the ratio, which was added to the results of the sensitivity analysis.

Table 15 Sensitivity analyses of the updated model with weighted analysis results conducted during the evaluation

	Incremental cost	Incremental QALYs	Weighted ICER	% change from Base case	Proportion of brexu-cel EFS patients [^]	Proportion of brexu-cel OS patients [^]	Ratio %ES to %OS at cure point [*]
Base case Lognormal OS and EFS extrapolations for both arms; KM+parametric adjustment for EFS extrapolations for both arms;	\$redacted	2.53	\$redacted	-	22%	29%	75.8%
Multivariate analyses (Cure point = 5 years)							
Lognormal OS and EFS extrapolations for both arms; EFS parametric adjustment removed for the brexu-cel arm	\$redacted	2.00	\$redacted	23%	11%	29%	38.4%
Lognormal OS and EFS extrapolations for both arms; EFS parametric adjustment removed for both arms	\$redacted	2.42	\$redacted	6%	9%	29%	32.7%
Exponential OS and EFS extrapolations for both arms; EFS parametric adjustment removed for the brexu-cel arm	\$redacted	1.33	\$redacted	49%	0%	20%	0%
Exponential OS and EFS extrapolations for both arms; EFS parametric adjustment removed for both arms	\$redacted	1.33	\$redacted	49%	0%	20%	0%
Gompertz OS and EFS extrapolations for both arms; EFS parametric adjustment removed for the brexu-cel arm	\$redacted	2.10	\$redacted	15%	22%	30%	73.9%
Gompertz OS and EFS extrapolations for both arms; EFS parametric adjustment removed for both arms	\$redacted	2.10	\$redacted	15%	22%	30%	73.9%
Log logistic OS and EFS extrapolations for both arms; EFS parametric adjustment removed for the brexu-cel arm	\$redacted	1.90	\$redacted	27%	12%	28%	42.6%
Log logistic OS and EFS extrapolations for both arms; EFS parametric adjustment removed for both arms	\$redacted	2.31	\$redacted	10%	10%	28%	36.1%
Weibull OS and EFS extrapolations for both arms; EFS parametric adjustment removed for the brexu-cel arm	\$redacted	1.65	\$redacted	37%	3%	24%	11.5%
Weibull OS and EFS extrapolations for both arms; EFS parametric adjustment removed for both arms	\$redacted	1.77	\$redacted	32%	2%	24%	10.1%

^{*}the 'cured cohort' weight in the brexu-cel arm, see Table 9; [^]at the base-case cure point of 5 years
Source: compiled during the evaluation

Removing this adjustment (that biases the results in favour of the brexu-cel as it brings the curve upward) increases the weighted ICER by 6% - 49% from the base-case value of \$redacted (see Figure 6 and Table 15). The effect holds for each choice of a parametric function, but for the lognormal and loglogistic functions, it can be weakened if the same adjustment procedure is not made for the EFS extrapolation in the comparator arm.

The modelled economic evaluation is highly sensitive to the choice of a parametric curve and the application of the “adjustment” procedure, that translates in variations of the cure fraction. As in the original ADAR, the clinical data, although updated for the one extra year of brexu-cel observations, had generally short follow-up and neither ZUMA-3 (brexu-cel) nor TOWER (blinatumomab) showed a clear signal of long-term cure. Because of the lack of direct comparison with blinatumomab, or of a control group in the ZUMA-3 study, the magnitude of benefit remained highly uncertain. The resubmission ADAR applied a weighted approach, which added an extra layer of complexity while compensating to some degree for the systematic underestimation of ICER associated with the structural composition of PSM.

The acceptability of the ICER estimate in the resubmission model would depend on whether MSAC considered the updated survival data in ZUMA-3 study being consistent with a curative intent and supportive of the assumption of the 5 year cure point. Also, whether the approach to extrapolation of the EFS K-M data is justified to produce a reliable estimate of a cure fraction (in the brexu-cel base case analysis using lognormal model the cure fraction is estimated at 21.7%, Table 9). The extrapolation uncertainty relates to the choice of a parameterised survival curve and ensuring its best data fit by bringing it upward to meet the ZUMA-3 EFS KM data at the switch point (the ‘adjustment’, discussed above).

At the tail end of the survival curve, the K-M algorithm is highly sensitive to the occurrence of each subsequent event. However, assumptions about the value of the cure fraction need to be tested at this part of the survival curve, where it presumably plateaued. With a reduced sample size of only 63 patients at baseline and the ever-decreasing number of surviving patients at the tail end of the K-M data, there is unlikely to be sufficient validity to support the cure assumption. The ICER estimate is highly uncertain and likely to be underestimated mainly due to the extrapolation uncertainty, but also due to the unsupported cure assumptions. The resubmission model (as in the original ADAR) does not assume convergence of survival at any point over the 52 year time horizon, therefore favouring brexu-cel and making it different from MSAC 1519.1 where survival convergence was modelled after 20 years (MSAC, 1723 PSD. p.20).

14. Financial/budgetary impacts

There were no changes proposed to the administration of brexu-cel, it will be administered in an inpatient tertiary public hospital setting. Block funding under the National Health Reform Agreement is requested, consistent with the mechanism agreed for funding of other CAR-T therapies.

The ADAR has used a mixed model (epidemiological and market share) approach to estimate the financial implications of funding brexu-cel for the treatment of adult patients with relapsed or refractory B-ALL.

The financial implications to the National Health Reform Agreement (NHRA) resulting from the proposed listing of brexu-cel for adult (≥ 26 -year-old) relapsed or refractory B-ALL over 6 years are summarised in Table 16.

Table 16 Net financial implications of brexu-cel to the National Health Reform Agreement (NHRA)

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of the proposed health technology						
Number of people eligible for brexu-cel infusion	redacted	redacted	redacted	redacted	redacted	redacted
Number of people who receive brexu-cel infusion	redacted	redacted	redacted	redacted	redacted	redacted
Number of services of brexu-cel (one per person/lifetime)	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the Government using the ADAR proposed brexu-cel price (\$redacted)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost to the Government using the PpP proposed average brexu-cel price (\$redacted)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Change in use and cost of other health technologies						
Change in use of comparators (PBS/RPBS)	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted
Net cost to PBS/RPBS [¥]	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted
Change in use of other affected health technologies**	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Decrease in use of other affected health technologies***	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted
Net financial impact to the Government using the ADAR proposed brexu-cel price (\$redacted)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net financial impact to the Government using the PpP proposed average brexu-cel price (\$redacted)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

**Refers to pre-transfusion costs and administration, monitoring and adverse events management costs.

***Refers to the administration and monitoring costs associated with blinatumomab or inotuzumab chemotherapy and adverse events management for blinatumomab, inotuzumab, asatinib and ponatinib.

¥Commentary analysis - Adjustment of the Net cost to the PBS/RPBS by adjusting the proportion of the PBS codes that is for a cohort who would receive brexu-cel (adjusted down from 31% of the population to 16%).

The net financial impact to the Government in the resubmission ADAR estimated **\$redacted** in Year 1 and **\$redacted** in Year 6, which is lower compared to the original ADAR. This reduction is due to:

- The eligible population has changed to adult patients ≥ 26 years of age with R/R B-ALL as compared to adult patients ≥ 18 years of age with R/R B-ALL in the original ADAR. This has resulted in a reduction in the number of patients estimated to receive brexu-cel. The resubmission ADAR proposed that an individual who met the new eligible population (adult patients ≥ 26 years of age with R/R B-ALL) who had previously received funded CAR-T therapy (currently tisa-cel) would not be eligible for receive a second funded CAR-T therapy. However, the resubmission ADAR did not attempt to estimate this population.
- A reduction in the cost of brexu-cel from **\$redacted** in the original ADAR to **\$redacted** in the resubmission ADAR.

An average price of **\$redacted** was proposed in the PfP arrangement subsequently submitted by the applicant. Using this lower average price, the net financial impact to the Government reduced to **\$redacted** in Year 1 and **\$redacted** in Year 6 (Table 16).

Issues noted with the estimated financial impacts are:

- The use of different assumptions about the annual change in the incidence of ALL between the estimated eligible population (-0.8%) and that used to estimate the substituted PBS/RPBS scripts for the comparator (2.6%). This underestimates the eligible population and favours the intervention.
- The resubmission ADAR uses a methodology of estimating the proportion of the estimated population with R/R B-ALL who receive a brexu-cel infusion (31%) and applying this proportion to the total dollar amount of the PBS scripts for the comparators. However, this results in an overestimate of the substitution, as the PBS codes are not just for R/R B-ALL but for ALL. The proportion of ALL patients who go on to receive brexu-cel is 16%. This reduces the estimated net cost to PBS/RPBS by approximately 50%, see Table 16.
- PBS items for the comparators blinatumomab and inotuzumab ozogamicin are different according to whether treatment occurs in a public hospital or a private hospital. The resubmission ADAR assumes 100% substitution of the PBS items, for the same proportion assumed to uptake brexu-cel. The commentary considered this to be a confusing approach as it appears to double count for the same cohort, induction and ongoing treatment in a private hospital and induction and ongoing treatment in a public hospital, but it may have been an attempt to capture all script costs for blinatumomab to be able to apportion them via the assumed proportion who receive brexu-cel. However, it is doubtful that this is the appropriate approach as in this instance the PBS code for induction of blinatumomab, which requires hospitalisation, does not subsidise in-patient blinatumomab so these costs are unlikely to be captured by the PBS statistics. It is not possible to estimate the likely underestimate of these costs without a breakdown of the public/private hospital use within this cohort.
- Within the comparator cohort, the resubmission ADAR assumes that in a 12-month period, 100% of the cohort will use all the nominated comparators. The resubmission ADAR does not attempt to separate out the cohort into patients initiating second-line therapy or third-line therapy (even though these numbers are available in the resubmission ADAR) and providing a likely treatment regimen separately for each. By doing this, the resubmission ADAR overestimates the likely use of the comparators. For example, no more than 50% of second-line patients will proceed to sequential treatment with either blinatumomab or inotuzumab (third-line) and not the 100% assumed.
- The in-patient hospital costs estimated in the original ADAR were noted to be inadequate. The resubmission ADAR has substantially increased these costs from ~\$19,400 (\$898.15 per day) to \$28,583 per admission. These costs still exclude all pharmacy costs that are included with the DRGs as costs of the intervention, comparators, and treatment of adverse events are estimated

separately. This is likely to underestimate pharmaceutical costs. However, the degree to which this new cost approximates the in-patient costs of brexu-cel patients requires clinical advice.

In summary

- The average cost of the proposed technology per patient is \$redacted per course per infused patient in Year 1 (to \$redacted per course per infused patient in Year 6). This is the cost of infusion plus pre-transfusion costs, administration, monitoring, and treatment of adverse events costs.
- The average frequency of use of the proposed technology is: once per lifetime.
- The average out-of-pocket cost per patient per course is: \$0.

The applicant’s pre-ESC response acknowledged and agreed with the commentary the estimated the annual growth in the incidence of ALL applied in the resubmission ADAR underestimated the likely population for the intervention. The applicant pre-ESC response presented the below updated financial analysis that applied a 2% growth rate to age specific rate for calculating incident patients.

Table 17- Applicant pre-ESC response: Updated financial estimates

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of the proposed health technology						
Number of people who receive brexucabtagene autoleucel (ADAR 1732.1)	redacted	redacted	redacted	redacted	redacted	redacted
Number of services of brexucabtagene autoleucel (ADAR 1732.1 pre-ESC) 2% growth rate applied to age specific rate for calculating incident patients	redacted	redacted	redacted	redacted	redacted	redacted
Total Cost Brexu-cel (ADAR 1732.1 pre-ESC) Brexu-cel = \$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Change in use and cost of other health technologies						
Change in use of comparators	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted
Increase in use of other affected health technologies	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Decrease in use of other affected health technologies	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted
Net financial impact to the Government (Pre-ESC revised base case)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Scenario Analysis						
Net financial impact to the Government (Fixed cost)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Source: Table 3 of MSAC 1723.1 Applicant Pre-ESC response

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The updated clinical data indicate a higher median and long-term survival than the previous ADAR providing some additional certainty regarding longer-term efficacy of brexu-cel.
- The previous concerns raised by MSAC regarding the reliability of the estimated magnitude of benefit remain. The evidence base has not changed, and the naïve and indirect (SCHOLAR-3) comparisons are fundamentally the same (and still have a high risk of bias), with some updated clinical results from the ZUMA-3 study. The matched analyses are limited by the large reductions in sample sizes and small effective sample sizes. There is a substantial risk of observed and unobserved effect modifiers.
- The new matched adjusted indirect comparison (MAIC) of brexu-cel (ZUMA-3) versus blinatumomab (TOWER) and inotuzumab ozogamicin (INO-VATE) may not reduce the clinical uncertainty about whether brexu-cel demonstrated superior efficacy to the comparators.
- The clinical management algorithm is still complex, and there is still uncertainty about where brexu-cel fits in the treatment pathway. The resubmission ADAR did not address the use of allo-SCT and how it may be replaced in practice. It is likely that brexu-cel will be a bridge to allo-SCT for some patients.

Economic issues:

- Although the price of brexu-cel was lowered by **redacted**% in the resubmission ADAR, the proposed cost is still high and has not been adequately justified nor broken down into components.
- The extrapolation methods used for long-term survival have a major impact on the ICER, but their suitability remains unclear.
- The assumption of the cure point is not well justified in the absence of survival data beyond the 33 months follow-up.
- The use of a partitioned survival model and its associated limitations, while practical in oncology, are highly uncertain. Different models can give very different economic outcomes, as previously shown in other CAR-T therapy evaluations. This uncertainty could be tested in additional scenario analyses using different types of models.

Financial issues:

- The uptake rate assumptions are still uncertain, and small changes in these significantly affect the financial estimates.

Other relevant information:

- The proposed two-payment pay-for-performance (PfP) arrangement, particularly the second payment at 12 months, is problematic, as patients may receive subsequent therapies (allogeneic stem-cell transplant [allo-SCT] or new-anti cancer therapies) after brexu-cel, confounding the response rate. Reasonable payment amounts and time points should be considered which mitigates this concern regarding duration of response.
- A summary of key matters of concern raised MSAC application 1723, and responses in this resubmission are presented in Table 1 and the key changes to the economic analysis are summarised in Table 8.

ESC discussion

ESC noted that Gilead Sciences Pty Ltd had resubmitted an application requesting public funding through the National Health Reform Agreement (NHRA) of brexucabtagene autoleucel (brexu-cel) for the treatment of adult patients (≥ 26 years of age) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (R/R B-ALL). In addition, subsequent to the resubmission of the applicant-developed assessment report (ADAR), the applicant submitted an updated pricing proposal for the proposed pay for performance (PfP) arrangement for brexu-cel.

ESC noted that the original [MSAC application 1723](#) was considered by MSAC at its meeting on 24–25 November 2022, and that the original application had proposed brexu-cel for adult patients ≥ 18 years of age. ESC noted that the proposed eligible patient age had since changed to ≥ 26 years in the resubmission ADAR. The applicant's pre-ESC response stated that the exclusion of patients aged 18–25 years was due to a paucity of data and very low expected patient numbers for this cohort (6 patients in year 1 to 16 patients in year 6). ESC noted that, based on the very limited data available in the ZUMA-3 study, the 18-25 year old patient cohort appeared to have similar clinical outcomes to patients aged ≥ 26 years. As such, ESC considered that the exclusion of the 18-25 year old patient cohort did not appear to be based on clinical outcomes. However, ESC noted that patients aged 18-25 years are able to access an alternative CAR-T therapy (i.e., tisagenlecleucel [tisa-cel]). As such, ESC considered the change to the eligible patient age to ≥ 26 years for brexu-cel did not create any equity issues for patients aged 18-25 years.

ESC noted that while the clinical criteria were unchanged, the resubmission ADAR had presented updated clinical management algorithms. ESC noted that relapsed or refractory disease was defined as one of the following:

- primary refractory (defined as refractory to first-line therapy in the ZUMA-3 study)
- first relapse if remission was 12 months or less
- relapsed or refractory after two or more lines of systemic therapy
- relapsed or refractory after allogeneic stem-cell transplant (defined as ≥ 100 days before enrolment and off immunosuppressive medications for at least 4 weeks before enrolment in the ZUMA-3 study).

ESC agreed with the commentary that the place of brexu-cel in the revised treatment pathway remains uncertain and considered that the revised clinical management algorithms did not resolve the issues previously raised by MSAC that stem from the complex nature of depicting patient management for the four subpopulations of patients with R/R B-ALL. ESC considered it was important to clearly define what is considered first-line therapy and when patients are considered to be refractory to first-line therapy. That is, ESC noted that first-line therapy for B-ALL is often considered to include all treatments up to the patient's first relapse, including blinatumomab for measurable residual disease (MRD)¹⁴ positivity (accessed through the Pharmaceutical Benefits Scheme [PBS]) and allogeneic stem-cell transplant (allo-SCT) although, appropriately, relapse post-allo-SCT is also a separate inclusion criterion. However, some clinicians may define first-line therapy as chemotherapy only. Therefore, ESC considered that clearly defined restrictions would be required in any deed of agreement for brexu-cel for B-ALL, for the benefit of both patients and service providers. These restrictions should include biopsy-proven extramedullary disease, and that CAR-T therapy can be given once per lifetime.

ESC noted that the comparators were unchanged from the original submission. ESC noted it is unclear whether brexu-cel will be used earlier or later in the management algorithm and therefore,

¹⁴ formerly known as 'minimal residual disease'

there remains uncertainty regarding the comparator therapies that brexu-cel may replace. ESC noted the pre-ESC response in which the applicant stated that brexu-cel was not intended as a treatment to induce remission to allow for subsequent allo-SCT, nor was it a substitute for allo-SCT. Rather, brexu-cel, is intended to be used most commonly to substitute for, or post, blinatumomab or inotumumab ozogamicin relapse. However, ESC considered that in the first relapse/refractory setting, patients would proceed to allo-SCT after receiving blinatumomab as part of second line therapy. Therefore, ESC considered that allo-SCT should be included as a comparator to brexu-cel. ESC also noted that 18% of patients subsequently received allo-SCT in the ZUMA-3 study and considered that, based on learnings from the recent review of CAR-T use in the paediatric R/R ALL population, the rate of subsequent allo-SCT following brexu-cel for R/R B-ALL is likely to be higher in the Australian clinical setting than in the ZUMA-3 clinical study. ESC considered that brexu-cel will likely be a bridging therapy to allo-SCT for a sub-group of patients.

ESC noted from the commentary that patients treated with brexu-cel in the ZUMA-3 study received bridging chemotherapy treatment similar to standard treatment in the INO-VATE and TOWER studies, so the rationale to select these studies for comparative effectiveness for salvage treatment was not justified. Further, ESC noted that depending on the line of therapy where brexu-cel is used, some patients may require access to PBS listed medicines as bridging therapies to brexu-cel but that if these therapies had been used in previous line(s) of therapy the patient may not be able to access the PBS listed medicine again. ESC noted that if any changes to PBS listings were required to address this issue, then this would need to be considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

ESC noted that updated consumer feedback was not received prior to the meeting. ESC recalled previous consultation feedback received in 2022 from the Leukaemia Foundation and Rare Cancers Australia, both of which were supportive of funding because of poor outcomes with current treatments and an unmet need in some patients. ESC also noted that the 2022 response from the Leukaemia Foundation acknowledged the adverse events and side effects related to brexu-cel, but that the Leukaemia Foundation response considered that the benefits of treatment would outweigh these negatives.

ESC noted the submissions from four state and territory health authorities, which acknowledged there is an unmet clinical need for adult patients (≥ 26 years of age) with R/R B-ALL. However, the state and territory submissions remained unsupportive of the application, expressing strong concerns regarding the validity of the clinical evidence, lack of value-based healthcare measures such as patient-reported outcomes in the PfP payment criteria, and the proposed price and cost of the intervention. The state and territory health authorities provided specific feedback that costing inputs were understated, assumptions about treatment effectiveness were too optimistic (especially when compared to actual reported outcomes for chimeric antigen receptor [CAR] T-cell therapy), evidence was limited and inadequate (especially for a very expensive cell-based therapy that may cause significant harm), and that brexu-cel was an experimental, rather than proven, therapy for R/R B-ALL.

ESC noted that the evidence base consisted of the same studies previously considered by MSAC but that the resubmission ADAR also presented updated 33-month follow-up data from the brexu-cel (ZUMA-3) study. The primary endpoint in Phase 1 of ZUMA-3 ($n = 54$ enrolled, $n = 45$ treated; $n = 20$ treated ≥ 26 years old) was dose limiting toxicities, while the primary endpoint in Phase 2 ($n = 71$ enrolled, $n = 55$ treated, $n = 43$ treated ≥ 26 years old) was overall complete remission rate (OCR, calculated as complete remission [CR] + complete remission with incomplete haematologic response [Cri]).

ESC noted the resubmission ADAR presented the same (but updated) naïve comparison and retrospective cohort matched indirect comparison (SCHOLAR-3) of brexu-cel versus the nominated

comparators (blinatumomab, inotuzumab ozogamicin and chemotherapy) that were previously considered by MSAC. In addition, the resubmission ADAR presented a new matched adjusted indirect comparison (MAIC) of brexu-cel (ZUMA-3) versus blinatumomab (TOWER) and inotuzumab ozogamicin (INO-VATE). ESC noted the issues with the naïve and indirect comparisons previously raised by MSAC remained (e.g., high risk of bias, small patient numbers in SCHOLAR-3 comparator arms, etc). ESC also agreed with the commentary that it was unclear how much additional certainty the MAIC could provide MSAC, given that adjusting for baseline characteristics reduced the sample sizes by over half (52.73%–74.72%), the risk of patient selection bias in the ZUMA-3 study (patients were only enrolled if they had undergone leukapheresis), the results not consistently indicating larger improvements than the naïve estimates, and the methodological literature not necessarily supporting the conclusions.

Regarding comparative safety, ESC noted that, consistent with the original submission, the resubmission ADAR claimed that brexu-cel is associated with different adverse events (AEs) than the comparators, and a different safety profile as AEs may occur during the initial period of brexu-cel therapy whereas AEs are likely to occur on an ongoing and cumulative basis for the primary and secondary comparators. ESC also noted that MSAC previously concluded that, in terms of comparative safety, brexu-cel is most likely inferior with respect to AEs known to be associated with brexu-cel, including cytokine release syndrome (CRS), neurological events, and cytopenia (pg 3, MSAC 1723 PSD). ESC noted that the ZUMA-3 33-month follow-up data did not report any new AEs but did report four new deaths in Phase II and one new death in Phase I (Table 6). ESC considered the safety concerns are unchanged since MSAC's previous consideration.

Regarding comparative effectiveness, ESC noted that, consistent with the original submission, the resubmission ADAR claimed that brexu-cel has superior efficacy compared with blinatumomab, inotuzumab ozogamicin, ponatinib or salvage chemotherapy in adult (≥ 26 years of age) R/R B-ALL patients. This claim was based on improved rates of remission, duration of remission (DOR), relapse-free survival (RFS) and overall survival (OS).

ESC noted that CR rate was 62.8% (49/78) for brexu-cel in the modified intention to treat (mITT) (all ages) group compared to 33.6% (91/271) in the blinatumomab group (TOWER) and 35.8% (39/109) in the inotuzumab ozogamicin group (INO-VATE). The observed 62.8% CR rate in the brexu-cel mITT (all ages) group was similar to the 61.9% CR rate reported for brexu-cel in the ≥ 26 years mITT subgroup (the revised proposed population). However, ESC noted this was based on *post hoc* subgroup analyses. ESC also noted that the OCR rate for brexu-cel was 74.4% in the mITT (all ages) group and 74.6% in ≥ 26 years mITT subgroup. This was comparable to inotuzumab ozogamicin (68–80.7%), and was higher than for blinatumomab (35%–45%), except for Topp et al. 2014 where the OCR rate (69%) for blinatumomab was similar to brexu-cel. ESC noted that there was essentially no new information presented with regard to OCR and as outlined in the previous consideration (MSAC 1723 PSD), the differences in definitions of OCR and the use of mITT results could produce biased estimates of the clinical superiority of brexu-cel (i.e., overestimate the survival benefits of brexu-cel compared with comparator).

ESC noted that the median DOR for brexu-cel was 14.6 months in the mITT (all ages) group and 20.0 months in ≥ 26 years mITT subgroup. This was higher than inotuzumab ozogamicin (4.6–5.4 months), blinatumomab (7.3 months) and salvage chemotherapy (4.2–4.6 months). However, it was unclear if this was independent of allo-SCT. That is, patients were censored at the time of allo-SCT in the ZUMA-3 study, whereas the analysis may not have excluded the allo-SCT outcomes for inotuzumab ozogamicin and blinatumomab. This makes the outcome potentially biased against brexu-cel. ESC again noted that essentially no new information was presented for DOR outcomes. ESC noted that while the resubmission ADAR presented updated data (up to 36 months for DOR compared to 24 months in the previous submission) and the longer-term estimates of DOR were

higher than in the previous submission, as highlighted by the commentary this would be expected as censored patients were estimated to be alive in the longer follow-up.

ESC noted that the median OS for brexu-cel was 25.6 months for the mITT (all ages) population (after a median potential follow-up of 36.4 months) and 26.0 months for the ≥ 26 years mITT subgroup. This is higher than the median OS reported for the comparators which ranged from 4.0 to 9.8 months. ESC noted that the updated median OS for brexu-cel was higher in the resubmission ADAR (compared to the previous ADAR) which was expected given the previously censored patients remaining alive. ESC noted that OS at 24 months increased from 17.2% in the previous ADAR to 52.4% in the resubmission ADAR, which does suggest improved longer-term survival.

ESC noted that the median RFS for brexu-cel was 11.6 months for both the mITT (all ages) population and ≥ 26 years mITT subgroup, whereas the median RFS ranged from 3 to 7.6 months for the comparators. Again, for the RFS analysis, patients who received allo-SCT post brexu-cel treatment were censored. The ADAR presented an additional analysis for the mITT (all ages) population to re-introduce allo-SCT patients for RFS analysis, as transplant may be used to consolidate remission. This indicated that 18-month RFS rates, for brexu-cel in the mITT (all ages) population, were 35% (95% CI: 20.5, 50.6) and 42% (95% CI: 28.0, 55.0), censored at subsequent allo-SCT or not, respectively. Overall, ESC agreed with the commentary that the updated RFS data did not indicate a difference at 24 months, being 25.4% in this resubmission ADAR versus 25.2% in the previous ADAR.

ESC noted that 18% ($n = 14/78$) of patients in the mITT (all ages) population and 17% ($n = 11/63$) of patients in the ≥ 26 years mITT subgroup had allo-SCT post-brexu-cel treatment. The resubmission ADAR reported that in comparison, the rate of subsequent allo-SCT was higher following inotuzumab ozogamicin (48%) in the INO-VATE study and following blinatumomab (24%) in the TOWER study. ESC noted that, overall, the rate of subsequent allo-SCT following brexu-cel treatment had not changed substantially. However, as noted earlier, ESC considered that brexu-cel will likely be a bridging therapy to allo-SCT for a sub-group of patients and that the rate of allo-SCT post-brexu-cel treatment is likely to be higher in the Australian clinical setting based on recent Australian experience on CAR-T use in the paediatric R/R ALL population.

ESC noted that no new health-related quality of life data had been presented in the resubmission ADAR.

ESC noted that MSAC had previously raised concerns that the certainty of the evidence was low, that the evidence was insufficient to determine if brexu-cel was superior to the comparators and that the incremental clinical value of brexu-cel had not been sufficiently demonstrated in a context where other treatment options are available (pg 4, MSAC 1723 PSD). ESC noted that while the evidence base in the resubmission ADAR included additional follow-up for brexu-cel that indicated higher median and long-term survival overall, the evidence base was essentially unchanged. As such, ESC considered that the uncertainty regarding the reliability of the evidence and the magnitude of the comparative efficacy of brexu-cel to the comparators remained.

ESC noted that similar to the previous ADAR, the resubmission ADAR presented a cost-utility analysis based on a clinical claim of superiority although, several aspects of economic analysis had been revised since MSAC's previous consideration. ESC noted the economic analysis had been updated to:

- reflect the revised proposed population, i.e., patients aged ≥ 26 years, $n=63$ (previously patients aged ≥ 18 years, $n=78$)
- reduce the brexu-cel price to **\$redacted** per patient (previously **\$redacted** per patient).
- use estimates for overall survival (OS) and event-free survival (EFS) based on the 33-month follow-up data from the ZUMA-3 study for brexu-cel

- amend the hospital costs to apply a weighted average of three Australian Refined Diagnosis Related Groups (AR-DRGs) that were suggested in submissions from state and territory health authorities (previous used 1 AR-DRG)
- revise the healthcare unit costs to reflect MBS/PBS/AR-DRGs costs as of June 2023.

ESC noted that, like the previous model, long-term survival (patient progression) was modelled through uncertain parametric extrapolation of the KM data starting from the point where 20% of patients remain at risk until the nominated cure point. ESC noted that although 33-month follow up data was available from the ZUMA-3 study, the point where 20% of patients remain at risk is considerably shorter. For example, for EFS in the revised economic model, observed KM data was used up until 1.49 years (previously 1.3 years) at which point the model switched to parametric extrapolation until the nominated cure point at 5 years (previously 2 years). In addition, to address limitations of the partitioned survival model (PSM) to track EFS and progressed disease that was previously raised by ESC, at the 5 year cure point the model applied a ‘weighted cured and non-cured cohort’ analysis so that the cure assumption is applied to patients who are alive and event free at 5 years (previously applied to all alive patients at the 2 year cure point due to limitation of the PSM). The resubmission justified this approach by referencing a previous PBAC application using the same method (Gilteritinib PBAC, March 2022).

Regarding the 5-year model cure point, ESC also noted that consultation feedback from the Haematology Society of Australia and New Zealand suggested that ongoing MRD negativity at 2 years post-therapy could be considered an appropriate surrogate marker for cure. A cure point at 2 years based on MRD negativity has also been accepted in published literature.¹⁵ ESC considered that the appropriate cure point definition remained difficult to define. More importantly, ESC considered that the issue remained that the evidence for brexu-cel is essentially unchanged and does not demonstrate that brexu-cel is curative given the short-term follow-up of trial data (<5 years) and in some patients brexu-cel is likely to be a bridge to allo-SCT.

ESC noted that while log-normal parametric curves were selected for extrapolation of the OS and EFS KM data based on the Akaike and Bayesian Information Criteria (AIC and BIC) goodness-of-fit statistics, ESC noted that the parametric curves were not a good fit based on visual inspection of the KM data and parametric curves (see Figure 6 and Figure 7). Consequently, model adjustments were made in the resubmission ADAR to align the parametric curve to the KM data. ESC also noted that the ICER is highly sensitive to the choice of extrapolation method and the model adjustments to align the parametric curve to the KM data (see Table 15). ESC considered the choice of the PSM approach and its associated limitations, while practical in oncology, to still be highly uncertain, also noting that it was based on a naïve comparison that included a small ($n = 63$) single-arm study data with no Australian patients. ESC noted that the choice of model is an important consideration, as different models can give very different outcomes¹⁶. ESC considered a way to address this uncertainty would be for additional scenario analyses to be undertaken using different types of models.

ESC also noted that the time horizon for the model remained a lifetime horizon but had been changed to 52 years, reflecting the change to an older eligible population (the model previously applied a lifetime horizon of 57 years). ESC noted that the [MSAC Guidelines](#) state that “Where there is evidence that a health technology affects mortality or long-term/ongoing quality of life, then a lifetime time horizon is appropriate.” ESC considered that patients with R/R B-ALL have poor outcomes, with a very low 5-year survival rate, and the longer-term survival effects of brexu-cel are

¹⁵ Bassan R, Hoelzer D, Thomas X, Montesinos P, et al. (2019). [Clinician concepts of cure in adult relapsed and refractory Philadelphia-negative B cell precursor acute lymphoblastic leukemia: a Delphi study](#). *Adv Ther* 36(4):870–9.

¹⁶ Whittington MD, McQueen RB, Ollendorf DA, et al. (2019). Long-term Survival and Cost-effectiveness Associated With Axicabtagene Ciloleucef vs Chemotherapy for Treatment of B-Cell Lymphoma. *JAMA Netw Open*.

potentially confounded. ESC questioned whether a lifetime time horizon was appropriate, given that study data only extended to 2–3 years and that long-term extrapolation preserves the benefit of the intervention. Further, in MSAC Application 1519.1 for tisagenlecleucel, the modelled time horizon was 50 years and survival curves converged around 20 years, whereas there is no convergence of survival models for the economic model of brexu-cel. ESC further queried whether assuming no convergence and a very long duration was reasonable, noting it was highly favourable to brexu-cel. However, ESC considered that if brexu-cel is able to offer a potential cure for young patients (although this remains uncertain), then a lifetime horizon of 52 years may be reasonable.

ESC noted that at the 5 year cure point, the resubmission model assumed cured patients would revert to the general population mortality and therefore applied a standardised mortality ratio (SMR) of 2.0 to the cured cohort after the cure point. ESC questioned this assumption and considered that the quality of life in the treated group would not be the same as the general population because of how treatment affects the immune system. ESC noted that in contrast, an SMR of 3.0 was applied in the appraisal of brexu-cel for treating patients (≥ 26 years) with R/R B-ALL by the National Institute of Health and Care Excellence (NICE)¹⁷.

ESC noted that the resubmission ADAR reported the updated incremental cost-effective ratio (ICER) was **\$redacted** per quality-adjusted life year (QALY). ESC noted the ICER was also highly sensitive to the extrapolation function and parametric adjustment to align the parametric curve to the OS and EFS KM data (ranging from **\$redacted** to **\$redacted**; see Table 15) and the price of brexu-cel (a 20% increase in the price resulted in an ICER of **\$redacted**, Table 13). Additional analyses by ESC indicated that reducing the time horizon to 20 years, increasing the SMR to 3.0 and using the progressed disease health state utility from Aristides et al. 2015 resulted in an ICER of more than **\$redacted** per QALY. ESC noted that in comparison, the ICERs in the range of those accepted by PBAC in R/R B-ALL were approximately \$45,000-75,000 per QALY/gained ([blinatumomab November 2016 PSD](#)), while the cost for a complete course of blinatumomab or inotuzumab ozogamicin was around **\$redacted**.

ESC noted the resubmission ADAR had updated the financial analysis to reflect the change the patient eligibility age, the price of brexu-cel and updated some of the hospital costs. However, ESC noted the resubmission ADAR did not revise some assumptions that had previously been noted to create uncertainty in the estimates. For example, the resubmission ADAR applied the same uptake rate assumptions as the original ADAR. The commentary also identified an inconsistent growth rate in the number of predicted services, which was revised in applicant's pre-ESC response and resulted in an increase in the number of services per year. The revised net financial impact to the Australian Government in the applicant's pre-ESC response was estimated to be **\$redacted** in Year 1 increasing to **\$redacted** in Year 6. ESC noted this was more than the estimate in the resubmission ADAR but less than in the original ADAR. ESC considered that the uptake rate remained uncertain, noting small changes in uptake significantly affect the financial estimate. Overall, ESC considered the financial estimates remained uncertain.

ESC noted that the original ADAR proposed a brexu-cel price of **\$redacted** (paid upon infusion), while the resubmission ADAR proposed a reduced price of **\$redacted** (**redacted**% price reduction) and that the subsequent pricing proposal presented a proposed PfP arrangement with an average net price of **\$redacted**. However, ESC noted that the applicant had not justified any of the proposed prices.

¹⁷ National Institute of Health and Care Excellence (NICE) (2023) Technology appraisal guidance TA893: Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over. www.nice.org.uk/guidance/ta893

ESC considered there to be uncertainties and risks that require mitigation through a risk-sharing arrangement. ESC noted applicant's proposed PfP arrangement for brexu-cel included:

- redacted
- redacted

ESC noted that clinical response was defined as the patient being leukaemia-free or the disappearance of cells with morphologic characteristics of leukaemia including the absence of circulating blasts (bone marrow of <5% blasts) and absence of extramedullary disease, which are accepted responses in the National Comprehensive Cancer Network (NCCN) guidelines (version 1.2022) and in the ZUMA-3 criteria. However, ESC noted that MRD thresholds are used to specify eligibility for access to blinatumomab under the Pharmaceutical Benefits Scheme (PBS)¹⁸ redacted. As noted, earlier MRD negativity is accepted to correlate with prognosis and patient quality of life. ESC noted that MRD is more sensitive, so fewer patients will have negative disease (meaning that fewer patients will be eligible for the second payment). MRD was a secondary outcome in the ZUMA-3 study, but the resubmission ADAR did not present data on MRD for the proposed target population. The 33-month follow-up of ZUMA-3 reported that among those with OCR, the MRD negative rate was 98% (95% CI: 91%, 100%) in the combined Phase I and Phase II mITT population (n = 78).

ESC noted the applicant's proposed PfP arrangement assumed redacted. This is based on redacted ZUMA-3 study and that redacted. As noted earlier, ESC considered it likely that the rate of allo-SCT post-brexu-cel treatment is likely to be higher in the Australian clinical setting. ESC also noted that the extent of confounding of these additional therapies on the response rate at 12 months had not been addressed. Redacted, ESC considered that where patients received subsequent allo-SCT after CAR-T therapy then in this situation the second payment should not be payable because confounding meant that clinical response could not be determined at 12 months. Since some patients will subsequently receive allo-SCT, ESC queried whether in this patient population, the PfP arrangement should be structured such that brexu-cel is cost-minimised to blinatumomab and inotuzumab ozogamicin. ESC also considered that, noting the uncertainty in the CR rate and DoR, that following payment schedule suggested in the state and territory submissions may be appropriate:

- Payment 1 upon successful infusion: 10% of the total payment
- Payment 2 based on 12-month response: 40% of total payment
- Payment 3 based on 2 year response: 50% of total payment.

ESC noted that the applicant has also proposed annual patient caps, from redacted patients in Year 1 to redacted patients in Year 3 (a cap of redacted patients in total). The payable amount upon successful infusion in excess of the annual cap was \$redacted. ESC agreed that there should be annual patient caps in place but considered that the proposed caps may underestimate patient numbers, as the applicant assumed decreasing annual age-related incidence.

ESC noted that the applicant's proposed risk sharing arrangement (PfP arrangement and annual patient caps) may not mitigate all of the uncertainties noted by ESC. ESC considered that a future review (after 2-3 years) supported by registry data collection could mitigate some of the uncertainties. ESC considered it was important for the registry to accurately capture survival and relapse outcomes long term. ESC considered that data collection should help address uncertainties

¹⁸ For example, the clinical criteria for the PBS listing for Blinatumomab (11850Q) includes (amongst other things) 'Patient must have achieved a complete remission, AND Patient must be minimal residual disease negative, defined as either undetectable using the same method used to determine original eligibility or less than 10⁻⁴ (0.01%) blasts based on measurement in bone marrow'.

regarding the positioning of the treatment in the clinical management algorithm, the role of allo-SCT and any other potential confounders (for example, co-treatment and responder status).

17. Applicant comments on MSAC's Public Summary Document

Gilead Sciences welcomes the MSAC decision to support public funding of brexucabtagene autoleucl for certain adult patients (aged 26 years old and above) with relapsed or refractory acute lymphoblastic leukaemia, a severe condition affecting a small number of patients with high clinical need. Gilead Sciences is looking forward to collaborating with the Commonwealth and State and Territory governments to provide access to this CAR T-cell therapy in the timeliest manner.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)