

# Medical Services Advisory Committee (MSAC) Public Summary Document

## ***Application No. 1723 – Brexucabtagene autoleucel for adult relapsed or refractory B-precursor acute lymphoblastic leukaemia***

**Applicant:** Gilead Sciences Pty Ltd

**Date of MSAC consideration:** 24-25 November 2022

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

### **1. Purpose of application**

An application requesting public funding through the National Health Reform Agreement (NHRA) of TECARTUS (brexucabtagene autoleucel, also identified as KTE-X19, *anti-CD19 autologous CAR-CD28 T cells KTE-X19, autologous anti-CD19 CAR-CD28 T cells KTE-X19* and abbreviated from here-on-in as brexu-cel) for adult patients ( $\geq 18$  years of age) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (R/R B-ALL) was received from the Gilead Sciences Pty Limited (Gilead) by the Department of Health.

### **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 did not support public funding of brexucabtagene autoleucel (brexu-cel) for adult 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 noted the price of brexu-cel had not been adequately justified and no payment for performance or risk sharing criteria were proposed for consideration by MSAC. 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.

## Consumer summary

This is an application from Gilead Sciences Limited requesting public funding of brexucabtagene autoleucel (brexu-cel) to treat adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia (shortened to R/R B-ALL).

Leukaemia is a type of blood cancer. B-ALL is a fast-growing type of leukemia in which too many B-cell lymphoblasts (immature white blood cells) are found in the bone marrow and blood. These B-cell lymphoblasts are abnormal and also interfere with the production of normal blood cells, therefore causing anaemia, recurrent infections, bruising and bleeding.

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

T cells are part of a person's immune system that attack foreign bodies. CAR-T cell therapy involves taking some of the patient's own blood, and sending it to a laboratory where the T cells are extracted and genetically altered so that they can attack cancer cells. The patient's altered T cells are infused back into them to target and kill the cancer cells in the patient's body.

Brexu-cel is a CAR T-cell therapy that has been trialled in patients with R/R B-ALL. The altered T-cells in brexu-cel bind to a protein called CD19, which is found on some lymphoma cells and leukemia cells, and then kills these cancer cells.

MSAC considered that the evidence on the effectiveness of brexu-cel in R/R B-ALL is uncertain, that there was significant uncertainty around the place of brexu-cel in clinical practice given the range of alternative treatments are available and that it had more severe side effects than other treatments. MSAC also noted that the cost of brexu-cel was very high and the cost effectiveness was very high and uncertain (because the benefit compared to other treatment options is unclear).

MSAC 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.

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

MSAC did not support funding brexu-cel through the National Health Reform Agreement. MSAC considered that the effectiveness of brexu-cel was uncertain, compared with other available therapies, and it resulted in more severe side effects. The cost was also very high, and MSAC was not confident that brexu-cel provided value for money.

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

MSAC noted that this is an application from Gilead Sciences Pty Limited (Gilead) requesting public funding through the NHRA of brexu-cel in R/R B-ALL.

MSAC noted that there is no ratified PICO confirmation as this application bypassed PASC.

MSAC noted that brexu-cel has been recently approved by the Therapeutic Goods Administration for listing on the Australian Register of Therapeutic Goods. MSAC noted that the wording of the marketing authorisation permitted the use of brexu-cel in four possible places within the clinical management algorithm for brexu-cel in R/R B-ALL (i.e. primary refractory; first relapse within 12 months; relapsed or refractory after two or more lines of systemic therapy; relapsed or refractory after allogeneic stem-cell transplant). MSAC also noted the proposed population was based on the ZUMA-3 trial.

MSAC noted the ADAR proposed clinical criteria for usage that were not well-defined, but that additional clinical criteria were included in the applicant's pre-MSAC response. In addition, MSAC noted that the ADAR proposed that the funding of brexu-cel be limited to once per lifetime but then stated that, if clinically appropriate, a second infusion is allowed, as this is what occurred in the ZUMA-3 trial. However, MSAC agreed with ESC's suggestion that 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 absence of evidence for re-treatment. In its pre-MSAC response, the applicant accepted that the proposed restriction would include a limit of one brexu-cel infusion per lifetime for each indication.

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 allogeneic stem cell transplantation (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). MSAC also noted that ESC questioned why tisagenlecleucel (tisa-cel) was not included as a comparator for patients aged 18 to 25 years old as these patients would be eligible for both tisa-cel and brexu-cel (i.e. the overlapped subpopulation in Application 1519 [tisa-cel] with the proposed brexu-cel population). However, MSAC noted in the pre-MSAC response that the applicant withdrew the request for funding brexu-cel in the 18–25 age group, so MSAC noted that tisa-cel was no longer a relevant comparator.

MSAC considered that there are multiple treatment options available within the clinical algorithm for this patient cohort. MSAC noted that this was not the case for tisa-cel, which was recommended for subsidy for the treatment of children and young adults (those aged  $\leq 25$  years) with R/R B-ALL with a high unmet clinical need and very limited treatment options.

MSAC noted that the brexu-cel trial was ZUMA-3<sup>1</sup>, a phase 1 and 2, open-label, single-arm multicentre study in 99 adult patients (78 of whom received an infusion of brexu-cel) with R/R B-ALL. MSAC noted that data on the comparators came from single-arms of other studies and that naïve comparisons between brexu-cel and the comparators were conducted to estimate relative effectiveness; an indirect matched comparison of ZUMA-3 versus SCHOLAR-3<sup>2</sup> (retrospective matched cohort) was also included. MSAC considered that the indirect, naïve comparisons across different cohorts of patients was associated with a high risk of bias to draw inference on relative effectiveness. In particular, MSAC noted that the baseline characteristics of participants across the studies were quite different, the use of cointerventions also differed across studies (e.g. consolidation allo-SCT), the outcomes were variably defined, the sample sizes were small, and follow-up was short. Thus, MSAC considered that the nature of the naïve indirect comparisons and transitivity issues meant there is low certainty regarding the relative effectiveness of brexu-cel compared with all comparators.

MSAC noted that, in terms of comparative safety, brexu-cel is most likely inferior with respect to adverse events known to be associated with brexu-cel, including cytokine release syndrome (CRS), neurological events and cytopenia.

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<sup>1</sup> Shah BD et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *The Lancet*. 2021;398(10299):491-502.

<sup>2</sup> SCHOLAR-3 CSR (Version 1.0). Kite Pharma, Inc. A retrospective cohort study of adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia sampled from historical clinical trials (SCHOLAR-3). 2021

MSAC noted that in terms of effectiveness, that the overall complete remission (OCR) appeared higher for brexu-cel (74%) compared to blinatumomab (36–69%) and ponatinib (41%), but was similar to inotuzumab (68–80%). MSAC noted that the duration of response appeared longer with brexu-cel (and independent of allo-SCT). In terms of survival outcomes, median OS (25 months) and RFS (11.6 months) appeared longer with brexu-cel compared with the comparators (7–9 months and 3.9–7.6 months, respectively). However, MSAC noted that the use of a modified intention-to-treat (mITT) analysis for brexu-cel (where only patients who received an infusion were analysed) likely overestimated the survival benefits of brexu-cel compared with the comparator studies which used ITT analyses.

Overall, MSAC considered it is uncertain whether brexu-cel confers improved durable survival outcomes compared to comparators used in contemporary Australian practice because the certainty of the evidence is low. MSAC considered that the strength of evidence presented was insufficient to determine if brexu-cel was superior to the comparators. In addition, MSAC considered that there was significant uncertainty around the place of brexu-cel in clinical practice given the range of alternative treatments available and that brexu-cel had an inferior safety profile. Based on these factors, MSAC considered that the incremental clinical value of brexu-cel had not been sufficiently demonstrated in a context where other treatment options are available.

MSAC noted that the economic model was developed using a hybrid model approach that included a decision tree and partitioned survival model component. The decision tree differentiates patients between those who receive brexu-cel infusion and those who discontinue prior to infusion (i.e. were not successfully infused). A partition survival approach comprises three mutually exclusive health states: event-free progression, progressed disease and death. MSAC noted that the model used a lifetime time horizon of 57 years and considered that this was not appropriate given there was less than three years of observed clinical data and the long-term effects of brexu-cel were highly uncertain. MSAC noted that the economic evaluation is highly sensitive to the cure assumption that was applied. The ADAR assumed that all patients who were alive at two years after receiving brexu-cel would be cured with a life expectancy similar to the general population after this point. This was adjusted in the pre-ESC response with a weighted analysis (where ‘cure’ was assumed at two years only for those who are relapse free). MSAC noted that ESC considered that this approach still deviated from standard practice of using parametric extrapolations fitted to the observed clinical data. The cure assumption in the model was further amended in the pre-MSAC response where the weighted analysis approach (i.e. cure assumption only applied to those who are relapse free) was implemented five years after brexu-cel (instead of two years). MSAC 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 noted that in its pre-MSAC response, the applicant proposed a revised brexu-cel price of \$■■■■, a ■■■■ reduction from the price proposed in the ADAR (\$■■■■). Incorporating this price with the weighted five-year cure assumption (as described above) resulted in an ICER of \$■■■■ per QALY gained. However, MSAC considered that this estimate was highly uncertain, due to the issues identified in the clinical evidence and the modelling assumptions used (particularly the time horizon and the cure assumptions). Further, MSAC considered that there was uncertainty in the costs included in the model, and that these costs needed to be better informed. MSAC noted the advice from the states and territories and MSAC reinforced a review of the reimbursed CAR-T therapies is needed, in particular to assess the observed data on utilisation, cost and effects (e.g. overall survival data), noting it has previously recommended reviews are carried out 2-3 years following implementation for the reimbursed CAR-T applications.

MSAC noted that the ADAR 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 net financial impact of brexu-cel to the NHRA was estimated to be \$ [REDACTED] in Year 1 to \$ [REDACTED] in Year 6 and this was reduced to \$ [REDACTED] in Year 1 and \$ [REDACTED] in Year 6 in the pre-MSAC response. MSAC considered that these costs were still significant given that the patient population eligible for brexu-cel is small.

MSAC noted that the applicant had not proposed a risk-sharing or pay-for-performance arrangement. MSAC noted that while the applicant was willing to discuss the negotiation of such an arrangement, that this would need to be submitted to MSAC so that it could be given due consideration in light of the clinical and economic evidence presented.

MSAC noted that state and territory submissions shared the same concerns as MSAC, and are also unsupportive of funding brexu-cel because of the uncertainty relating to the effectiveness, costs of delivering the treatment, the severe side effects and high and uncertain cost effectiveness.

## 4. Background

Brexu-cel has not been previously considered by MSAC for the adult R/R B-ALL population. MSAC have previously considered other CAR-T therapies for other conditions, including brexu-cel for mantle cell lymphoma (see Table 1). A further CAR-T therapy has since been considered by MSAC, ciltacabtagene autoleucl to treat refractory or relapsed multiple myeloma (MSAC 1690), which has been added to the table below.

**Table 1 Overview of CAR-Ts considered by MSAC**

MSAC ID	Application title	MSAC meeting(s)
1519	Tisagenlecleucel (CTL019) for treatment of refractory CD19-positive leukaemia and lymphoma	9 April 2019, 28-29 March 2019, 22-23 November 2018
1519.1	Tisagenlecleucel (CTL019) for treatment of relapsed or refractory diffuse large B-cell lymphoma	28-29 November 2019, 1-2 August 2019
1587	YESCARTA™ (axicabtagene ciloleucel [KTE-C19]) for the treatment of refractory or relapsed CD19-positive lymphoma	16 January 2020, 28-29 November 2019
1647	Brexucabtagene autoleucl for relapsed or refractory mantle cell lymphoma	29-30 July 2021
1690	Ciltacabtagene autoleucl, a B-cell maturation antigen-directed chimeric antigen receptor T cell to treat refractory or relapsed multiple myeloma	28-29 July 2022

Source: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/>

## 5. Prerequisites to implementation of any funding advice

Brexu-cel is in the process of being considered by the TGA (application number: BIO-2021-BA-00255-1). The registration dossier for brexu-cel was submitted to the TGA on the 29 October 2021. It is requesting to register brexu-cel on the Australian Register of Therapeutic Goods (ARTG) as a Class 2/3 biological.

The proposed TGA indication is as follows (Attachment 1.1 – TECARTUS Product Information v1.1 – (25 October 2021)):

“TECARTUS is a genetically modified autologous immunocellular therapy for the treatment of adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia.”

Relapsed or refractory disease 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

Brexu-cel is currently TGA-approved for patients with relapsed or refractory mantle cell lymphoma (MCL), who have received two or more lines of therapy, including a BTK inhibitor (unless ineligible or intolerant to treatment with a BTK inhibitor).

## 6. Proposal for public funding

Brexu-cel for adult R/R B-ALL funding is being requested through the NHRA, as has been the case for brexu-cel for the treatment of MCL. Tisagenlecleucel (tisa-cel herein), another CAR-T cell therapy, is currently being jointly funded under the NHRA for R/R B-ALL for paediatric and young adult patients up to the age of 25 years.

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 proposed criteria presented in the ADAR include:

- Patient must be treated in a tertiary public hospital with appropriate credentials
- Patient must be treated by a haematologist working in a multi-disciplinary team specialising in the provision of CAR-T cell therapy.
- The response criteria is OCR which is complete remission (CR) with incomplete haematological recovery (CR+CRi).

Very little detail regarding patient characteristics have been specified in the proposal for public funding in the ADAR; consideration of whether this may best be informed by the inclusion/exclusion criteria of the ZUMA-3 study is required.

The ADAR proposed that the funding of brexu-cel will be limited to once per lifetime. However, if clinically appropriate, a second infusion is allowed, as occurred in the ZUMA-3 trial.

Although specifying that brexu-cel should be limited to 'once per lifetime', consideration of whether the criteria should also specify whether use of any CAR-T therapy should be once per lifetime is required. Tisa-cel (MSAC application 1519) is currently available for the treatment of R/R B-ALL among those aged  $\leq 25$  years. There is therefore the possibility that patients could be treated with tisa-cel as a child (aged  $< 18$  years) and could be treated with brexu-cel when aged  $\geq 18$  years. There is also the possibility of treatment with tisa-cel and brexu-cel while aged 18-25 years, or vice versa. There is no evidence presented to inform the efficacy and safety of tisa-cel or brexu-cel after brexu-cel or tisa-cel, respectively.

The ADAR provides no further detail regarding the possibility of second treatment with brexu-cel or how that would be funded. Consideration of whether this is reasonable is required as there is insufficient clinical evidence for re-treatment. Based on ZUMA-3 Primary Analysis CSR, paragraph 9.4.2, two subjects in Phase 2 and three subjects in Phase 1 were retreated with brexu-cel. Four out five had no response and only one subject had complete response (CR) after the second dose.

## 7. Population

The proposed population is for brexu-cel for the treatment of adult patients ( $\geq 18$  years of age) with R/R B-ALL Relapsed or refractory (R/R) disease 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.

Thus, the ADAR stated 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.

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 mixed-lineage leukaemia (MLL)-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 this submission is B-cell ALL, specifically B-precursor ALL (as opposed to mature B-cell ALL also known as Burkitt leukaemia).

## 8. Comparator

Blinatumomab and inotuzumab ozogamicin are both nominated as the primary clinical and cost-effectiveness comparators in the 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 NCCN in R/R B-ALL. The place in therapy of brexu-cel is similar to that of blinatumomab and inotuzumab ozogamicin. The ADAR states both blinatumomab and inotuzumab ozogamicin are the medicines most likely to be replaced by brexu-cel in clinical practice.

However the ADAR also stated that:

**Reinduction chemotherapy followed by Allo-SCT:** Patients with ALL who experience a relapse following chemotherapy and maintenance therapy are unlikely to be cured by further chemotherapy alone. These patients should be considered for reinduction chemotherapy followed by allo-SCT.

Inclusion of allo-SCT in addition to blinatumomab and inotuzumab ozogamicin as the comparator treatment was also confirmed by clinical experts.

Therefore, the comparators of blinatumomab and inotuzumab ozogamicin could be considered as one component of the comparator treatment pathway, but not the full intended comparator treatment that includes allo-SCT. Whether allo-SCT is included in the comparator treatment arm pathway is not explicit in the ADAR, and if excluded then this could favour brexu-cel as the full treatment effect of the comparator has not been included.

The 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 only 20-25% of ALL patients).

The ADAR also nominated salvage therapy as a secondary comparator. Insufficient information was provided in the ADAR regarding what treatments salvage therapy may include.

The nominated comparators are reasonable, particularly for those aged >25 years.

The ADAR excluded tisa-cel as a comparator based on the following:

- Low percentage of 18–25-year-old patients in the tisa-cel trials
- Lower incidence and new cases in the 18-25 years age group vs. older age group
- No outcome data specific to the 18–25 age group (i.e. the overlapped population with brexu-cel) have been identified.
- Clinician feedback on low patient numbers

The exclusion of tisa-cel as a comparator requires consideration. For patients aged 18-25 years, tisa-cel is arguably the most relevant comparator for brexu-cel, as it would be a clinical decision of which CAR-T therapy to use. Although, as suggested by the ADAR, few patients were aged 18-25 years in the tisa-cel studies, the Kymriah European Public Assessment Report states (p20) that “[n]o differences in efficacy or safety were observed between different age subgroups”. Moreover, although reported as a conference abstract, John et al (2021)<sup>3</sup> reported on outcomes from a prospective study using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry that included 451 patients aged ≤25 years with R/R ALL. Eligible patients received tisa-cel after August 30, 2017, in the USA or Canada. Age-specific analyses were conducted in patients aged <18 and ≥18 [to 25] years at the time of infusion. Thus, there is outcome data specific to the 18–25 age group for tisa-cel. John et al 2021 concluded that “[t]he overall efficacy and safety profiles of commercial tisagenlecleucel reflected those observed in the clinical trial setting and were broadly consistent across age groups. Some important differences between the <18y and ≥18y groups were identified, which may point to challenges in timely identification and/or referral of older patients for CAR-T cell therapy.”

## 9. Summary of public consultation input

Two responses to a targeted consultation request were received from clinicians. These responses stated that brexu-cel appears to be a preferable treatment option compared with blinatumomab and inotuzumab. The likely strategy when using brexu-cel would be using it to treat refractory (after two previous lines of therapy) or later line disease (with inotuzumab or blinatumomab followed by an alloSCT being used first). In addition, bridging therapy (in particular inotuzumab) is a standard option for disease control while patients wait for CAR-T therapy.

Regarding the comparators; the comments stated that tisa-cel is an appropriate comparator for patients aged 18 to 25 years; logistics and turnaround time may impact clinician choice in this age group. It was noted however that there is no data to support the use of tisa-cel and brexu-cel in the

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<sup>3</sup> John S, et al. (2021). Real-World Outcomes for Pediatric and Young Adult Patients with Relapsed or Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (ALL) Treated with Tisagenlecleucel: Update from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry. *Blood* 138 (Supp 1):428.



same patient, and would likely restrict the number of CAR-T therapies in a lifetime to one CAR-T therapy (with other therapeutic modalities or investigational therapies tried if a patient relapses after a CAR-T therapy). The use of alloSCT following inotuzumab and blinatumomab was noted as being part of current standard practice.

In addition, consultation feedback was received from two consumer organisations:

- Leukaemia Foundation (LF)
- Rare Cancers Australia (RCA).

The feedback was strongly supportive of the application and both responses highlighted the poor outcomes and unmet clinical need in adult patients with relapsed or refractory B-ALL. The LF noted that the adverse event profile was considerable but felt that this was manageable and comparable to standard of care with demonstrated survival benefits after brexu-cel treatment. RCA highlighted that there are existing programs to address financial and geographical barriers that may exist for consumers seeking to access the proposed intervention in regional and rural areas in Australia, and that this burden was much less than patients having to relocate to receive treatment overseas.

## **10. Characteristics of the evidence base**

The ADAR was based on naïve, indirect comparisons of single arms from the studies described in Table 2.

Though the ADAR made a reasonable assessment of the risk of bias of the individual studies included in the ADAR, the ADAR has not discussed the risk of bias associated with the indirect, naïve comparisons across single arms of the studies/trials. The indirect, naïve comparisons are likely associated with a high risk of bias.

**Table 2: 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	
<b>Study design</b>	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	
<b>Patients (n)</b>	ITT	Phase I (54)	InO arm (164)	Phase I (37)	Blin arm (271)	Phase I (5)	36	64	45	32
		Phase II (71)	SoC arm (162)	Phase II (35)	SoC arm (134)	Phase II (21)				
	mITT	Phase I (23/45)*	InO arm (164)	n/a	n/a	n/a	n/a	n/a	n/a	n/a
		Phase II (55)	SoC arm (143)							
<b>Intervention</b>	Brexu-cel	InO	InO	Blinatumomab	Blinatumomab	Blinatumomab	Blinatumomab	Blinatumomab	Ponatinib	
<b>Comparator</b>	n/a	SoC	n/a	SoC	n/a	n/a	n/a	n/a	n/a	
<b>Follow-up (months) median (range) [95% CI]</b>	Phase I 22.1 (7.1-36.1)	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 II 16.4 (13.8-19.6)			SoC arm 11.8 (n/s)						
<b>Primary outcomes</b>	Phase I (DLTs)	CR/CRi *** OS	Phase I (DLTs)	OS	Phase I (DLTs)	CR, CRh	CR, CRh	CR, CRh	MaHR	
	Phase II (OCR, CRi, CR) **		Phase II (CR/CRi)		Phase II (CR/CRh)					
<b>Secondary outcomes</b>	Phase I (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 II (DOR, RFS, OS, MRD, allo-SCT rate, OCR & CRi) ***		Phase II (DOR, RFS, OS, MRD)		Phase II (RFS, OS, MRD)					
<b>Population description</b>	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	
<b>Risk of bias</b>	Low to moderate	High	Moderate	High	Moderate	Moderate	Moderate	Moderate	Low to moderate	

Source: Constructed during the evaluation 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, minimal 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  $1 \times 10^6$  CAR T cells per kg bodyweight, \*\* per central assessment, \*\*\* per investigator assessment

Although an extensive list of patient characteristics at baseline in the included studies was presented, only a limited number of these are available for comparison across all studies. In general, the comparator studies are similar with respect to median age (except for Topp et al 2014 where patients were younger) and gender but different to some degree in proportion of patients with Ph+ disease, ECOG status, bone marrow blasts  $\geq 50\%$ , post allogeneic SCT, and prior therapy including salvage therapy. All comparator studies included patients with ECOG score of  $\leq 2$  compared with  $\leq 1$  in ZUMA-3.

With respect to Ph-/+ status, there is some discrepancy in baseline characteristics between studies. For example, studies conducted by Martinelli et al 2017 and Cortes et al 2018 included populations limited only to patients with Philadelphia-positive R/R B cell precursor ALL. By contrast, Kiyoi et al 2020, Stein et al 2019 and the TOWER trial focused on a population restricted to adults with only Philadelphia-negative R/R B cell precursor ALL following allogeneic hematopoietic stem cell transplantation (allo HSCT).

MLL translocation in baseline characteristics was considered by three studies, Kantarjian et al 2019 (INO-VATE), DeAngelo et al 2017 and Topp et al 2014. With respect to MLL translocation, ZUMA-3 was comparable to INO-VATE and DeAngelo et al 2017 (4%, 3.7% and 3%, respectively) compared with 11% in Topp et al 2014. The proportion of patients with Ph+ was also different in these three studies and varied from 6% (Topp et al 2014) to 22% (DeAngelo et al 2017) compared with 27% in ZUMA-3.

As noted by the ADAR, Ph-/+ status and MLL translocation are poor outcomes markers. Overall, differences in the baseline characteristics of patients enrolled in these studies with respect to these known poor prognostic markers were noted, thus estimates of the effectiveness and safety of brexu-cel compared to inotuzumab ozogamicin, blinatumomab, and ponatinib, based on these studies, may be biased. Additionally, given that this is a naïve comparison and a limited number of patient characteristics are available for comparison across all studies, the direction of bias is uncertain.

## 11. Comparative safety

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 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 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, 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 trial.

In summary, brexu-cel is associated with different adverse events compared with current 2<sup>nd</sup> line+ B-ALL therapies (including inotuzumab ozogamicin, blinatumomab, salvage chemotherapy and ponatinib) 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 2<sup>nd</sup> line or later B-ALL therapies.

Table 3 presents the comparative analysis of the number of deaths based on the mITT population and only from Phase 2 of ZUMA-3, whereas all other safety analyses from ZUMA-3 are based on the mITT from both Phase 1 (includes all doses) and Phase 2. This approach produces a selection bias favouring brexu-cel. When including both phases of ZUMA-3 (n=100), the death rate was 54%. Overall, the deaths in ZUMA-3 remained lower compared to comparator studies except for Kiyoi et al 2020 and PACE, 9.5% and 16%, respectively. These differences may be explained by differences in median follow-up (see Table 2).

**Table 3 Deaths: ZUMA-3 vs comparator studies**

	Deaths, n(%)
ZUMA-3 (N=55)	25 (45.0)
INO-VATE (inotuzumab ozogamicin, N= 164; salvage chemotherapy <sup>a</sup> , 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 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

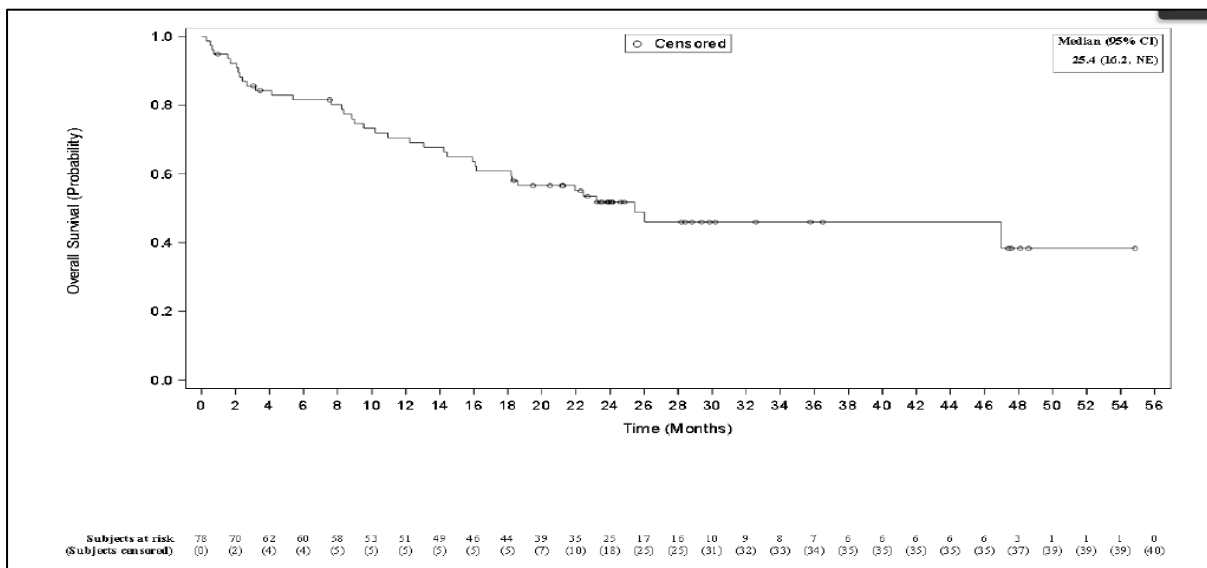
**Source:** ADAR 1723 - TECARTUS R-R Adult B-ALL ADAR with Exec Summ-Final, 2A.3.3.1.6 Deaths, Deaths: ZUMA-3 vs comparator studies, table 51)

## 12. Comparative effectiveness

The application stated that brexu-cel is superior to the submission 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.

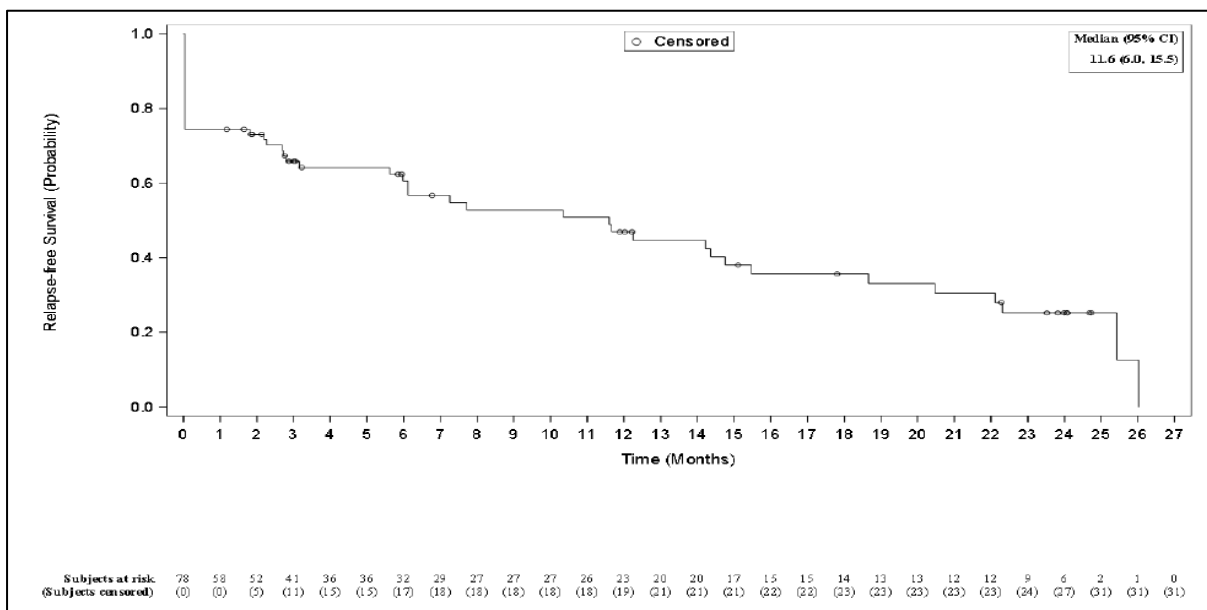
Figure 1 and Figure 2 shows the Kaplan-Meier (KM) curve for overall survival (OS) and relapse-free survival (RFS in the combined Phase 1 and 2 mITT population of ZUMA-3, respectively.

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



Source: Figure 14, p62 of the ZUMA-3 CSR

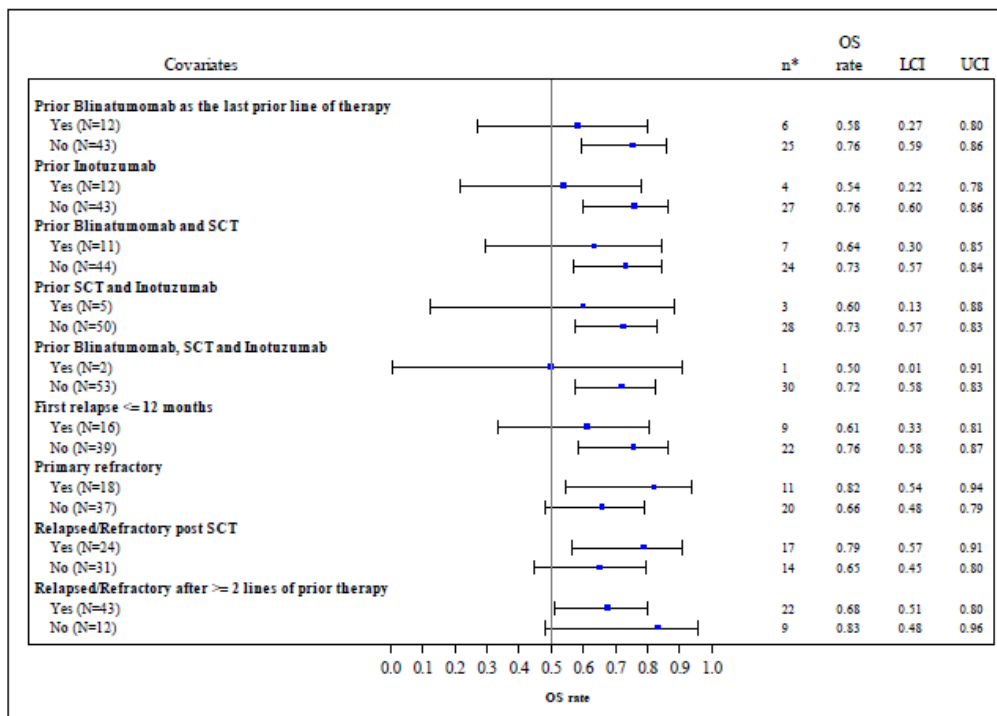
**Figure 2 Kaplan–Meier plot of relapse-free survival (Phase I and II, mITT population): ZUMA-3**



Source: Figure 15, p64 of the ZUMA-3 CSR

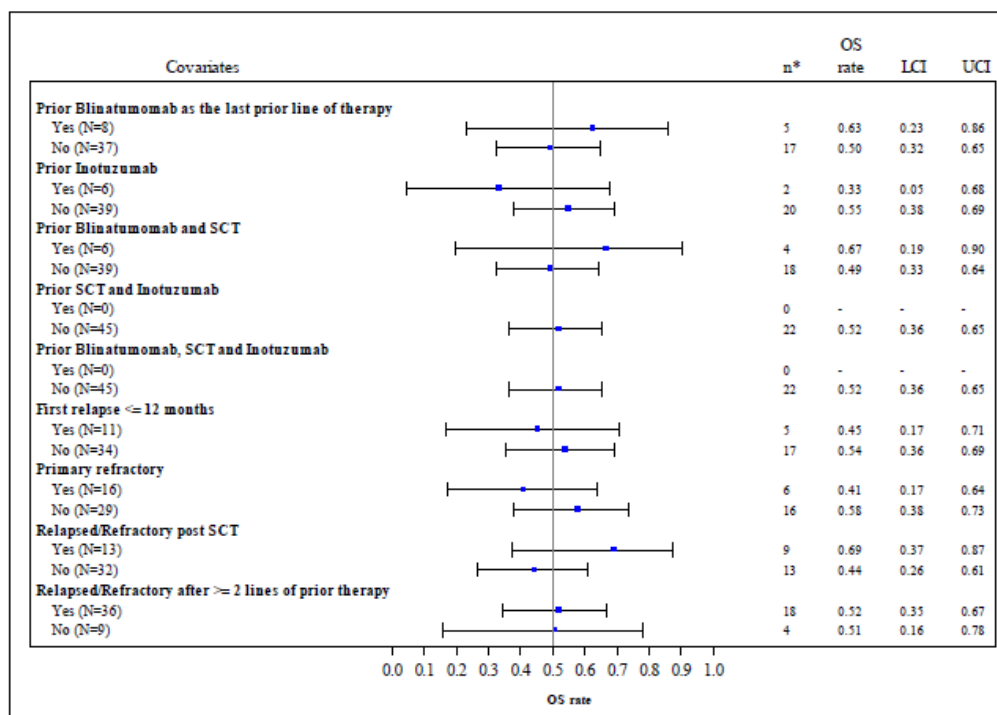
Sub-group analyses for the four populations specified as meeting the definition of R/R B-ALL indicated similar efficacy in terms of OCR, RFS at 6 months and OS at 12 months among those who were (i) primary refractory; (ii) having their first relapse within 12 months; (iii) relapsed/refractory after two or more lines of therapy and (iv) relapsed/refractory after allogeneic stem cell transplant, see Figure 3 and Figure 4 for OS in the Phase 2 and Phase 1 mITT populations, respectively.

Figure 3 Overall survival at 12 months in the four sub-populations (Phase 2, mITT)



Source: Figure 14.2.6.1, p885 of the ZUMA-3 CSR

Figure 4 Overall survival at 12 months in the four sub-populations (Phase 1, mITT)



Source: Figure 14.2.6.2, p888 of the ZUMA-3 CSR

The KM curve for OS and RFS for blinatumomab (the comparator assumed in the base case of the economic evaluation) is presented in Figure 5 and Figure 6, respectively.

**Figure 5 Kaplan–Meier plots of overall survival for blinatumomab (a) TOWER, (b) Stein et al 2019, (c) Martinelli et al 2017 and (d) Topp et al 2014<sup>4</sup>**

Redacted

**Figure 6 Kaplan–Meier plots of relapse-free survival for blinatumomab (a) TOWER, (b) Stein et al 2019, (c) Martinelli et al 2017 and (d) Topp et al 2014<sup>4</sup>**

Redacted

The ADAR reported results from Phase 1 1e6 dose level and Phase 2, combined based on mITT population (only subjects infused with brexu-cel) versus the ITT population from the comparator studies, this approach is favourable to brexu-cel. It has been noted that out of 99 enrolled subjects only 78 were infused. Table 4 shows the difference in endpoint results between mITT and ITT analysis in ZUMA-3, in addition to the results from the comparator studies.

It is apparent from Table 4 that the overall complete response (OCR) rate based on the ITT population in ZUMA-3 is lower by approximately 16% compared to OCR rate based on mITT and becomes more similar to inotuzumab ozogamicin, 58.6% in ZUMA-3 versus 68% in DeAngelo et al 2017, and less than the 80.7% reported in INO-VATE.

No change in the median duration of remission (DOR) was observed. In contrast, median relapse free survival (RFS) decreased significantly by 60%, from 11.6 months (mITT, ZUMA-3) to 7.0 months in the ITT population. There was also a slight decrease in the median overall survival (OS) from 25.4 months (mITT, ZUMA-3) to 23.1 months (ITT, ZUMA-3).

Overall, the comparative analysis based on the mITT population from ZUMA-3, produced overestimated results favouring brexu-cel and, consequently, biased the results of the economic evaluation.

Additionally, endpoints results for combined Phase 1 1e6 dose level and Phase 2 is based on investigator assessment. Central assessment of endpoint results was performed only for Phase 2, including mITT and ITT and showed slightly lower values for OCR of 70.9% versus 72.7% (mITT, n=55) and 54.9% (ITT, n=71).

Also, the total number of subjects with OCR for Phase 1 1e6 dose level and Phase 2, combined was 57 instead of 58 that will reduce the OCR by a further 1% in both populations, mITT and ITT (Study KTE-C19-103 Clinical Study Report Addendum, 21-Month Follow-up, table 8, p.24 and table 22, p.70).

As opposed to the comparator studies, ZUMA-3 reported the highest RFS and OS. Given the apparent difference in baseline characteristics between ZUMA-3 and comparator studies, ZUMA-3 results for OS and RFS should be interpreted with caution. The direction of bias is uncertain.

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<sup>4</sup> Figures 5 and 6 can be accessed through these sources:

(a) Kantarjian H, Stein A, Gökbuğet N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med.* 2017;376(9):836-47.

(b) Stein AS, Kantarjian H, Gökbuğet N, Bargou R, Litzow MR, Rambaldi A, et al. Blinatumomab for Acute Lymphoblastic Leukemia Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant.* 2019;25(8):1498-504.

(c) Martinelli G, Boissel N, Chevallier P, Ottmann O, Gökbuğet N, Topp MS, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. *J Clin Oncol.* 2017;35(16):1795-802.

(d) Topp MS, Gökbuğet N, Zugmaier G, Klappers P, Stelljes M, Neumann S, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol.* 2014;32(36):4134-40.

**Table 4 Comparison of mITT and ITT from ZUMA-3, Phase 1 1e6 dose level and Phase 2, combined with comparator studies**

<b>Outcomes</b>	<b>mITT (n=78) per investigator</b>	<b>ITT (n=99) per investigator</b>	<b>Inotuzumab, range (n=72-164)</b>	<b>Blinatumomab, range (n=21 -271)</b>	<b>Ponatinib PACE, Cortes et al 2018 (n=32)</b>
OCR (CR+CRi/CRh) %, n	74.4% (58/78)	58.6% (58/99)	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)	NR	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)	25.4 (16.2, NE)	23.1 (14.4, 47.7)	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)	7.0 (3.0, 13.2)	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

Source: Attachment 2.3 - ZUMA-3 Addendum CSR.pdf; INO-VATE, Kantarjian et al 2016; 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; Cortes et al, 2018, PACE.

During the evaluation it was observed 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 +CRh into 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 correctly stated that the incidence rate of allo-SCT is relatively low across all comparators. However, it appears that the patients treated with brexu-cel have the lowest incidence rate of allo-SCT. Additionally, some comparator studies reported the incidence rate of allo-SCT among all patients (Kantarjian et al 2017 (TOWER), DeAngelo et al 2017 and Kiyoi et al 2020) whereas others among patients only with remission response (Martinelli et al 2017, Topp et al 2014 and Kantarjian et al 2019 (INO-VATE)).

For example, 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, 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 ZUMA-3.

Moreover, there is a difference in DOR in 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.

HRQoL outcomes were reported only for 51 patients out of 55 for mITT population (71 for ITT population) phase 2 that produce a selection bias and overestimated HRQoL outcomes favouring brexu-cel (ADAR 1723 - TECARTUS R-R Adult B-ALL ADAR with Exec Summ-Final, table 31 and 32). A mean score of EQ-5D-5l is not presented.

There was a significant decrease in number of assessed subjects for EQ-5D-5l and EQ-5D-VAS evaluation from 51 at screening time to 14 at 12 months with a dramatic drop at 24 months with 4 subjects. This decrease in number of subjects could produce biased estimates of EQ-5D-5l and EQ-5D-VAS assessment. Also, a selection of subjects with ECOG score of only  $\leq 1$  will produce a selection bias.

During evaluation for illustration purposes, a comparison of HRQoL outcomes between ZUMA-3 (phase 2, mITT), INO-VATE and TOWER was undertaken. ZUMA-3 presented HRQoL outcomes only based on EQ-5D-5L and EQ-5D VAS whereas INO-VATE reported EORTC QLQ-C30 scores in addition to EQ-5D-5L and EQ-5D VAS. INO-VATE presented mean EQ-5D VAS score at baseline and on the 28 days after treatment. Sample size was significantly bigger in INO-VATE compared to ZUMA-3, n=164 vs 51.

The mean change in EQ-5D VAS score was higher in INO-VATE compared to ZUMA-3, 7.3 and 6.5, respectively. TOWER only reported EORTC QLQ-C30 scores that cannot be compared with EQ-5D-5L and EQ-5D VAS scores from ZUMA-3.

Overall, 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) trials.

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).

The applicant stated that brexu-cel is superior in efficacy and associated with different adverse events and safety profile compared with blinatumomab, inotuzumab ozogamicin, ponatinib or salvage chemotherapy in adult R/R B-ALL patients.

In terms of safety, as stated correctly 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.

Overall, the magnitude of benefits 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, MLL-rearrangement, ECOG status, bone marrow blasts  $\geq 50\%$ , R/R post allogeneic SCT, and prior therapy including salvage therapy,

- lack of direct comparison with blinatumomab, or of a control group in the ZUMA-3 trial,
- dissimilarity in OCR definition between ZUMA-3 and comparator studies,
- use of mITT instead of ITT for comparative analysis. The same issue was identified in the previous application for other CAR-T therapies such as 1519/1519.1 (tisa-cel),
- the presence of bridging therapy that may contribute to the clinical outcomes to some degree,
- the comparative analysis of minimal residual disease between ZUMA-3 and comparator studies was not presented.

### Pre-ESC response

The positioning of brexu-cel can be described as either post blinatumomab/inotuzumab ozogamicin (positions 3 and 4) or prior to blinatumomab/ inotuzumab ozogamicin (positions 1, 2 and 4). The proportion of patients from ZUMA-3 in each position of the treatment pathway is also presented together with estimates derived from local expert opinion (four clinicians) in Table 5.

**Table 5 - Use of brexu-cel in ZUMA-3 with Australian comparison**

ZUMA-3 four sub-groups of R/R Adult ALL (Not mutually exclusive)	ZUMA-3 % (n/N)	AUSTRALIA %, Expert Opinion
1. Primary Refractory	33% (18/55)	20%
2. First relapse if remission was 12months or less	29% (16/55)	25%
3. Relapsed or refractory after two or more line of systemic therapy	78% (43/55)	75%
4. Relapsed or refractory after allogenic stem cell transplant	44% (24/55)	30-35%

Source: Table 2, p2 of Pre-ESC response

## 13. Economic evaluation

The ADAR presented a cost-utility analysis based on a clinical claim of superiority to blinatumomab, with comparisons to inotuzumab ozogamicin, salvage chemotherapy, and ponatinib in scenario analyses.

It has been noted that there is expected to be overlap between brexu-cel and tisa-cel patients. Consequently, while a cost-utility analysis is the most appropriate analysis for the majority of patients in the population, if superiority is accepted, some patients may have access to tisa-cel, in which case, a cost-utility analysis may not be appropriate for those patients.

The economic evaluation 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 discontinue prior to infusion. The approach reasonably captured costs in those who were not infused, with survival estimates for the non-infused group assumed to be equal to the patients receiving comparator treatment. It was considered that the use of an initial decision tree was consistent with the ESC's advice for tisa-cel in MSAC 1519 (p22).

Table 6 presents a summary of the economic evaluation.

**Table 6 Summary of the economic evaluation**

<b>Component</b>	<b>Description</b>
Perspective	Health care system perspective
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
Comparator	Blinatumomab in the base-case analysis Inotuzumab ozogamicin, Salvage chemotherapy, and Ponatinib in scenario analysis
Type(s) of analysis	Cost-utility analysis
Outcomes	<ul style="list-style-type: none"> <li>• Quality-adjusted life-years (QALYs)</li> <li>• Life-years (LYs)</li> </ul>
Time horizon	Lifetime horizon (defined as 57 years) in the model base case compared to a median of 20.5 months (for patients who received brexu-cel) in ZUMA-3 and a median follow-up of 11.7-11.8 months in TOWER
Computational method	Hybrid model including an initial Decision tree to account for ITT set brexu-cel patients who never received treatment and a partitioned survival model.
Generation of the base case	Modelled: Step 1: 1 year time horizon, 0% discount rate, included CAR-T cost, drug cost, administration cost EFS resource use and AE costs Step 2: 2 year time horizon, incorporated the additional costs associated with disease progression, i.e., subsequent treatments, allo-SCT, post-progression resource use, and terminal care costs Step 3: 57 year time horizon, discount rate 5% Step 4: translate LY's to QALY's
Health states	Partition survival model has following health states: <ul style="list-style-type: none"> <li>• Event-free survival</li> <li>• Progressed disease</li> <li>• Death</li> </ul>
Cycle length	1 week
Transition probabilities	Primary data source: <ul style="list-style-type: none"> <li>• ZUMA-3</li> </ul> Other data source for base-case comparator arm: <ul style="list-style-type: none"> <li>• TOWER</li> </ul>
Discount rate	5% for both costs and outcomes
Software	Excel

Source: Table 53, p128 of the ADAR. ITT = intention to treat; r/r- be-ALL = relapsed or refractory B-precursor acute lymphoblastic lymphoma

It was 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, whereas survival was not assumed to converge at all in the ADAR's model. Given the limited ZUMA-3 follow-up, this approach was not reasonable.

The ADAR explicitly modelled a cure fraction. Specifically, the model assumed that after two years all patients still alive would be cured and would revert to background population mortality (with a standard mortality ratio of 2 applied) and would revert to overall population age-adjusted utility values based on Clemens (2014)<sup>5</sup>.

<sup>5</sup> Clemens S, Begum N, Harper C, Whitty JA, Scuffham PA. A comparison of EQ-5D-3L population norms in Queensland, Australia, estimated using utility value sets from Australia, the UK and USA. Qual Life Res. 2014;23(8):2375-81.

The ADAR based this cure assumption at two years on a study conducted in Australia and New Zealand (Kliman 2020)<sup>6</sup>, which included observational data for survival after allogeneic hematopoietic cell transplant (allo-HCT), including ALL patients. The ADAR claimed that this data reflected the impact of sustained remission on survival risk and is informative for the model.

The ADAR cited Kliman (2020) in stating “most deaths after allogeneic HCT occur in the first 2 years because of disease relapse or treatment-related effects, including infection, graft failure, and graft-versus-host disease (GVHD)”. From this, the ADAR considered that survival after 2 years in remission post-transplant is appropriate to estimate long-term survival risk and to be used as a proxy for sustained remission.

It was considered that the ADAR did not justify why a study detailing long term survival in SCT patients would be applicable to brexu-cel patients and blinatumomab patients. It was considered that, overall, the clinical data had generally short follow-up and neither ZUMA-3 nor TOWER 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 trial, the magnitude of benefit was highly uncertain. The ADAR’s approach amplified a possibly overestimated clinical benefit.

Review of MSAC 1519 and 1519.1 during the evaluation indicated that an explicit cure assumption was not modelled in that case. The ADAR’s approach is substantially more favourable to the intervention arm of the model than these previous models for CAR-T therapy.

The ADAR noted that the model structure did not allow for only applying a cure rate to the EFS patients, but this assumption also had to be applied to progressive disease (PD) patients, and the ADAR acknowledged that this is not compatible with the disease pathology. The ADAR claimed this modelling issue was mitigated in three ways:

- This assumption is applied for both brexu-cel and the comparators. It was considered that applying the assumption to both brexu-cel and the comparator is not a mitigation but rather standard modelling practice to apply an assumption about a health state to both arms, when there is no treatment-specific effect.
- This assumption is partially adjusted by applying the utility of those in remission (i.e., Australian general population) only to EFS patients in the economic model. It was considered that this was not a mitigation. Assuming Australian population utility values for any of the included patients was not supported by the evidence; it would be expected that patients in the population will have lasting quality of life effects from the disease and its treatments.
- The SMR used in base-case analysis = 2.0, to reflect a higher mortality rate than indicated from the Kliman study (SMR~1). The ADAR misinterpreted the results of the Kliman study, which indicated an HR for older patients to be closer to 2 (1.63 [CI: 1.30,1.90]). The alternative study used in a sensitivity analysis (Martin 2010) estimated an SMR of 4.0. But more importantly, it was noted that a small SMR adjustment does not mitigate against a substantial modelled benefit that is not adequately justified.

Table 7 presents the results of the stepped economic analysis.

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<sup>6</sup> 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.

**Table 7 Results of the stepped economic analysis**

Step	Brexu-cel	Blinatumomab	Increment	ICER
Step 1 – Incremental cost/EFLY gained, over 1 year time horizon				
Costs	\$█	\$█	\$█	\$█/EFLY gained
EFLYs	0.57	:0.32	0.25	
Step 2 – Incremental cost/LY gained, over 2 years' time horizon				
Costs	\$█	\$█	\$█	█/LY gained
LYs	0.81	0.59	0.21	
Step 3 – Incremental cost/LY gained, over a lifetime horizon of 57 years				
Costs	\$█	\$█	\$█	\$█/LY gained
LYs	8.10	3.85	4.25	
Step 4 – (Base-case): Incremental cost/QALY gained, over a lifetime horizon of 57 years				
Costs	\$█	\$█	\$█	\$█/QALY gained
Life years gained	6.30	2.80	3.50	

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: Table 117, p208 of the ADAR.

Table 8 presents the overall results of the economic evaluation.

**Table 8 Results of the economic evaluation**

Parameter	Brexu-Cel	Blinatumomab	Increment
Costs	\$█	\$█	\$█
Life years	8.10	3.85	4.25
QALYS	6.30	2.80	3.50
<b>Incremental cost per life year gained</b>			\$█/LY gained
<b>Incremental cost per QALY gained</b>			\$█/QALY gained

LY = life year; QALY = quality-adjusted life year.

Source: Table 117, p208 of the ADAR.

Overall, the ICER was high but most likely substantially underestimated due to incremental QALYs being likely overestimated. Incremental costs were primarily driven by brexu-cel acquisition costs.

The key drivers of the model are presented in Table 9.

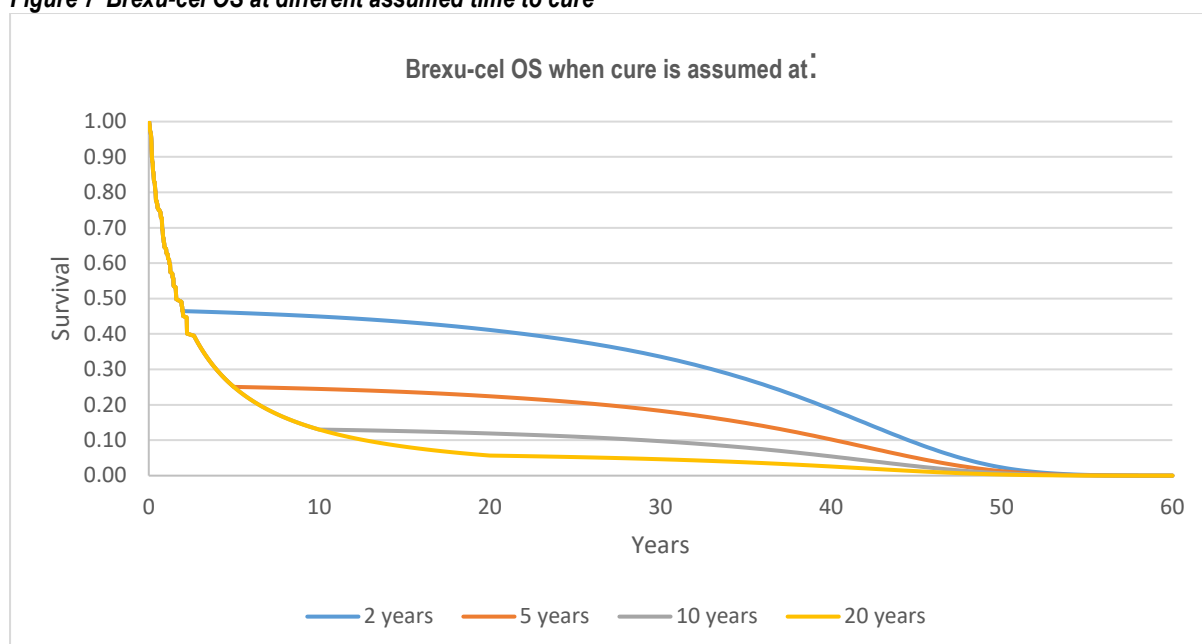
**Table 9 Key drivers of the model**

Description	Method/Value	Impact Base case: \$90,636/QALY gained
Cure assumption	The ADAR assumes that after 2 years, all patients still alive are assumed to be cured and revert to general population utility and general population mortality with a standard mortality ratio applied.	High, favours brexu-cel. Use of 5-year cure point increased the ICER to \$█ gained. Use of a 20 year cure point increased the ICER to \$█
Time horizon	Lifetime horizon (57 years in the base case)	High favours brexu-cel. Use of a 20-year time horizon increased the ICER to \$█
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 \$█/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 \$█/QALY gained

Source: compiled during the evaluation. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

A key driver of the model was the assumption of a two-year cure point. Additional analyses of overall survival by assumed cure point were conducted during the evaluation. As shown in Figure 7 and Figure 8, the assumed two year cure point forces the modelled survival to deviate from standard parametric extrapolations that are fitted to the clinical data. In the brexu-cel arm, the two-year cure assumption was applied before the end of available extrapolation data.

**Figure 7 Brexu-cel OS at different assumed time to cure**

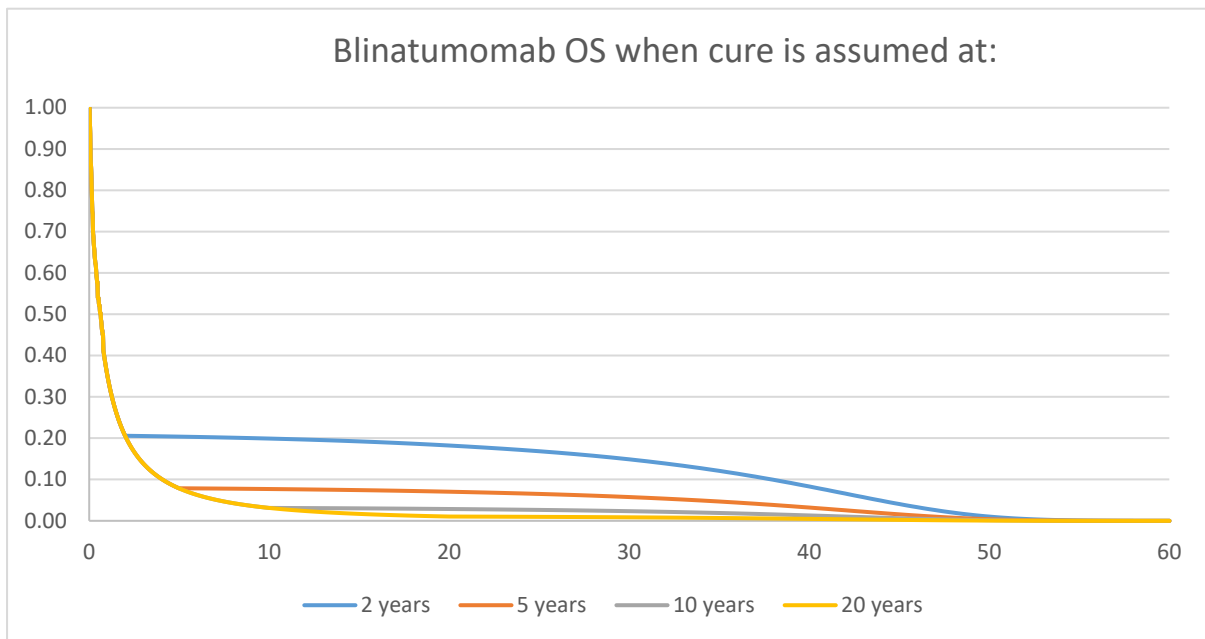


Source: Constructed during the evaluation.

OS = overall survival.

There was a sharp inflection point at 2 years, reflective of the assumption of cure after two years. Given the steep decline in survival preceding this point and the survival plateau after it, the ADAR's assumption of a two-year cure point was substantially different (and favourable) compared with the survival estimates of the ZUMA-3 study.

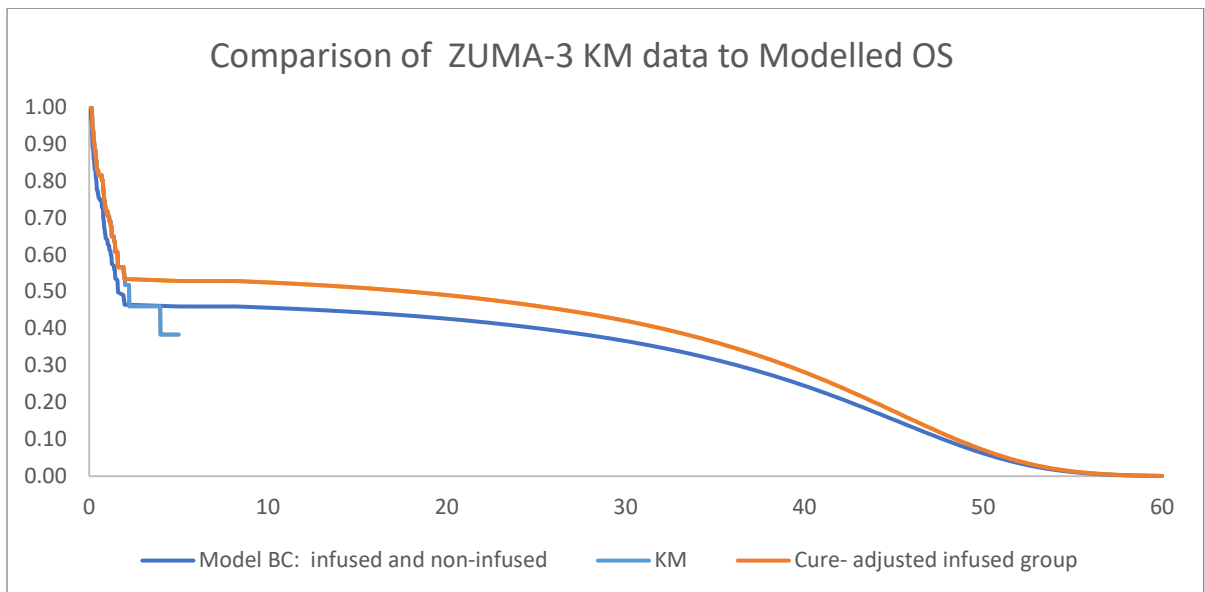
**Figure 8 Blinatumomab OS at different assumed time to cure**



Source: Constructed during the evaluation.  
OS = overall survival.

Figure 9 presents a comparison of long term ZUMA-3 KM estimates to modelled OS.

**Figure 9: Comparison of long-term ZUMA-3 KM to modelled OS**



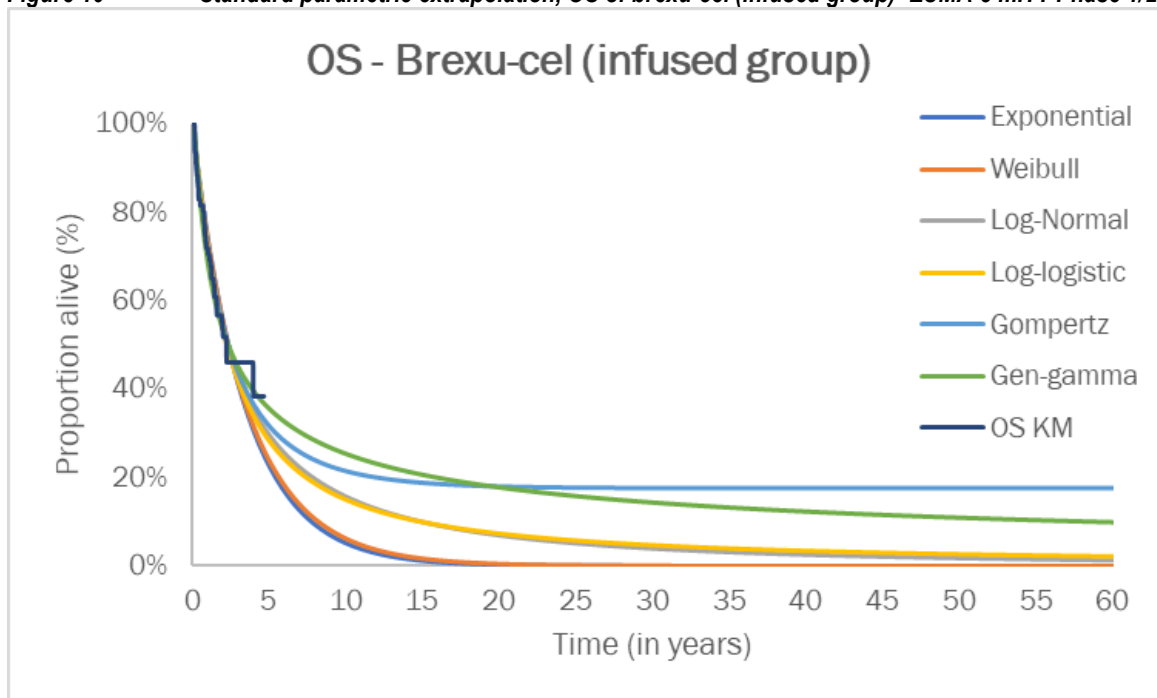
Source: Constructed during the evaluation from data in attached economic evaluation.

Overall, it was considered that the model estimated substantial benefits over a long-time horizon based on a naïve comparison with relatively short follow-up. There is a high degree of uncertainty in these estimates, and they likely overestimate the clinical benefit of brexu-cel compared to ZUMA-3 KM estimates. The modelled economic data plateaued survival before the end of the KM data. This plateau was higher than tail of the KM data.

Even without an explicit cure assumption modelled, it was considered that extrapolations model survival plateaus, which may also implicitly assume that some patients will be cured. This is illustrated in Figure 10 detailing the standard parametric extrapolation for OS in brexu-cel (infused)

patients. Several of the extrapolations model survival plateaus, which may implicitly assume that some patients will be cured. For the OS brexu-cel infused group, the log normal extrapolation, which was applied in the base case, had the best fit.

**Figure 10** Standard parametric extrapolation, OS of brexu-cel (infused group)- ZUMA-3 mITT Phase 1/2



Source: Figure 44, p146 of the ADAR. OS = overall survival.

The results of key univariate and multivariate sensitivity analyses are summarised in Table 10.



**Table 10 Sensitivity analyses**

Analyses	Incremental cost	Incremental QALY	ICER
<b>Base case</b>	\$█	3.50	\$█
Time horizon (base case 57 years)			
Time horizon: 20 years	\$█	2.70	\$█
Time horizon: 30 years	\$█	3.22	\$█
Time horizon: 40 years		3.45	\$█
Cure point (2 years in base case)			
Cure point: 5 years	\$█	2.54	\$█
Utility values (base case PD health state utility source: ZUMA-3)			
PD health state utility source: Aristides (2015)	\$█	3.19	\$█
Standard Mortality Ratio (base Case: 2.0 from Kliman et al., 2020)			
Standard mortality ratio = 4 (Martin et al., 2010)	\$█	3.20	\$█
<b>Assessment group sensitivity analyses</b>			
Cure point: 10 years	\$█	1.93	\$█
Cure point: 20 years	\$█	1.64	\$█
Cure point 57 years (cure assumption removed)	\$█	1.60	\$█
Cure point 20 years & Gen Gamma OS extrapolations for both arms	\$█	2.19	\$█
Cure point 20 years & log logistic OS extrapolations for both arms	\$█	1.54	\$█
Cure point 20 years & exponential OS extrapolations for both arms	\$█	1.30	\$█
Cure point 20 years & Weibull OS extrapolations for both arms	\$█	1.30	\$█
Cure point 20 years & Gompertz OS extrapolations for both arms	\$█	1.28	\$█
Cure point 20 years & PD health state utility from Astrides 2015	\$█	1.58	\$█
Cure point 20 years & SMR of 4	\$█	1.61	\$█

ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressive disease; QALY = quality adjusted life year

Source: Constructed during the evaluation from Table 124, pp208-209 of the ADAR

The ADAR’s sensitivity analyses showed that the model was most sensitive to discount rate, time horizon, and cure point. It was noted that the impact of discount rate and time horizon would be expected in a lifetime horizon with long term modelled benefits, and a treatment with frontloaded costs.

It was considered that the model was highly sensitive to the cure point assumption, assuming a longer time to cure increased the ICER substantially. In addition to the impact of the cure assumption itself, the base case assumption of a cure point at 2 years led to minimal use of the fitted extrapolated curves, and consequently, little impact of the selected extrapolation curve.

There was little difference in ICER’s between selecting a cure point at 20 years and 57 years (removing the cure assumption from the model. Given, that the arguments presented by the model suggest that some cure assumption may be reasonable, a 20 year time horizon was selected for multivariate sensitivity analyses during the evaluation. Multivariate sensitivity analyses conducted during the evaluation to test the effect of extrapolation when extrapolated curves were relied on for 20 years of the model time. The model was also sensitive to extrapolations in this case.

It was considered that the model was also sensitive to an increase in the standardised mortality ratio applied to cured patients, as well as the selected source of utility for patients in the progressive disease state, both of which favoured brexu-cel.

## Pre-ESC response

A 'weighted analysis' to determine the numbers of patients in each arm who are either in PD or EFS was undertaken. The analysis was performed by weighting using the model outcomes for the cure population (i.e., cure point of 2 year being applied to all alive patients) and non-cure population (i.e., using only trial data and parametric extrapolations and not using cure assumption):

- There are 28.76% and 7.89% of patients in EFS in brexu-cel and blinatumomab arm at 2 years, respectively
- There are 46.46% and 20.59% patients alive in brexu-cel and blinatumomab arm at 2 years, respectively
- The percentage of patients in EFS (to OS) is 61.9% and 38.3% in brexu-cel and blinatumomab arm, respectively
- A weighted analysis was performed by assuming that 61.9% and 38.3% in brexu-cel and blinatumomab arm, respectively, would achieve cured cohort outcomes and the remaining would have non-cured cohort outcomes

This then forms the basis of a revised-base case as presented in Table 11.

**Table 11 - Updated economic estimates using a weighted approach**

Parameters	Brexu-cel	Blinatumomab	Incremental	ICER
<b>Results (Cure point assumption not applied - no patients will be considered cured)</b>				
Total cost	\$	\$	\$	
Lys	3.48	1.48	2.00	\$
QALYs	2.60	1.00	1.60	\$
<b>Weighted analysis using weights from the text above</b>				
Total cost	\$	\$	\$	
Lys	6.34	2.39	3.95	\$
QALYs	4.89	1.69	3.20	\$

Source: Compiled from Table 5, p6 of the Pre-ESC response

The ICER in this scenario is ■■■■ higher than the base case ICER. Thus, applying cure assumption to EFS only had a moderate impact on the base case ICER.

## Pre-MSAC response

The pre-MSAC response presented a revised base case which incorporated a 5-year cure point (as opposed to 2 years in the original ADAR); a revised brexu-cel price of \$ ■■■■ and a weighted cured/non-cured approach (as proposed in the pre-ESC response).

The revised base-case is presented in Table 12.

**Table 12 - Updated economic estimates using a 5-year cure point, reduced price of brexu-cel and a weighted approach**

Parameters	Brexu-cel	Blinatumomab	Incremental	ICER
<b>A. Results (Cure point = 5 years applied to all alive patients)</b>				
Total cost	\$	\$	\$	
Lys	5.24	2.13	3.11	\$
QALYs	4.09	1.55	2.54	\$
<b>B. Results (Cure point assumption not applied - no patients will be considered cured)</b>				
Total cost	\$	\$	\$	
Lys	3.48	1.48	2.00	\$
QALYs	2.60	1.00	1.60	\$
<b>C. Weighted results of Analysis 'A' and Analysis 'B'</b>				
Total cost	\$	\$	\$	
Lys	4.96	2.08	2.88	\$
QALYs	3.85	1.51	2.34	\$

Source: Table 3, page 5 of the pre-MSAC response

## 14. Financial/budgetary impacts

It is proposed that brexu-cel will be administered in an inpatient tertiary public hospital setting. A block funding under the National Health Reform Agreement is requested, consistent with the mechanism agreed for funding of other CAR-T therapies. Particularly relevant is tisa-cel which has been approved for the 18 to ≤ 25 year age group within the population (adult patients ≥18 years of age with relapsed or refractory B-precursor acute lymphoblastic leukaemia (B-ALL), that brexu-cel is seeking recommendation for.

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 brexucabtagene autoleucel for adult (≥18-year-old) relapsed or refractory B-ALL are summarised in Table 12.

The financial implications are presented over 6 years (Table 12).

**Table 13 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
<b>Estimated use and cost of the proposed health technology</b>						
Number of people eligible for brexu-cel infusion						
Number of people who receive brexu-cel infusion						
Number of services of brexu-cel per lifetime*						
Cost to the National Health Reform Agreement	\$■	\$■	\$■	\$■	\$■	\$■
<b>Change in use and cost of other health technologies</b>						
Change in use of comparators (PBS/RPBS)	\$■	\$■	\$■	\$■	\$■	\$■
Increase in use of other affected health technologies**	\$■	\$■	\$■	\$■	\$■	\$■
Decrease in use of other affected health technologies***	\$■	\$■	\$■	\$■	\$■	\$■
<b>Net financial impact to the National Health Reform Agreement</b>	\$■	\$■	\$■	\$■	\$■	\$■

Source: constructed during evaluation from Table ES-5, pvii of the ADAR Executive Summary and Table 132, p216 of the ADAR

\*The ADAR acknowledged that small number patients in the clinical trials received more than one transfusion but has requested that the indication is for one transfusion per lifetime and intends to discuss with the department the arrangements if there is a clinical need for a patient to receive an additional transfusion.

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

\*\*\*Refers to the administration, monitoring and adverse events management costs associated with blinatumomab or inotuzumab chemotherapy

The ADAR assumed no change in tisa-cel utilisation as a result of brexu-cel funding. The implications of this are that the ADAR does not assume any market substitution of brexu-cel for tisa-cel in the 18 - ≤25 year old age group, and no additional costs for the NHRA for this patient group. There may be costs incurred from utilisation of brexu-cel in the age group if it is assumed that patients in this age group can receive a tisa-cel transfusion and if clinically required a brexu-cel infusion at a later date but this was not raised in the ADAR. Given the assumption of no change in this age group by the ADAR, it would have been appropriate to have separated out this age group from the rest of the adult population when estimating use of brexu-cel. Using the incidence data from the AIHW study, the 18-≤ 25 year age group represents around 9% of the eligible population (AIHW, 2022, Table S1a.1 & Table 125 of ADAR). Re-estimates of the cost of brexu-cel transfusion alone, if this age group are excluded, for each of the six years, are included below:

<b>Total cost of brexu-cel</b>	\$■	\$■	\$■	\$■	\$■	\$■
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In estimating the change in use of comparators the ADAR assumes substitution of brexu-cel for all other currently used chemotherapy in these patients. This is a patient group for which chemotherapy agents are better described as complements not substitutes, in that they have been used in many patients prior to brexu-cel and the indication does not exclude their use after a brexu-cel transfusion, if required. The assumption of the proportion of chemotherapy substituted by brexu-cel transfusion has not been adjusted for relapse or death as reported in the clinical trials. Similarly, the assumption that all patients in the comparator arm would have received all possible

chemotherapy in a 12-month period, rather than over the course of the disease and allowing for remission and death to occur in the eligible cohort, seems unrealistic.

The AR-DRG used to estimate hospital costs for patients receiving brexu-cel inadequately reflects the complexity of these patients and the ward and medical resources required to administer the transfusion, and monitor and treat adverse events with the exception of CRS.

- The average cost of the proposed technology per patient is \$ \$█/per course in Year 1 (the average decreases slightly over the six years to \$█/course).
- 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.

### Pre-ESC response

The applicant adjusted the estimated of patients that may be eligible as follows:

- Use of 5-year age grouping for age-specific incidence rates per 100,000 updated for 2022
- Estimating the number of patients 18-24 years of age diagnosed with R/R B-ALL separately
- Adjusting the total number of eligible patients 18-24 years of age diagnosed with R/R B-ALL to account for a proportion of patients that would receive brexu-cel or tisa-cel transfusion
- Adjusting proportion of PBS medicines affected to account for the reduction in the number of patients that would receive brexu-cel transfusion
- Updated hospital costs as per the economic model as done in pre-ESC response.

**Table 14 - Updated financial estimates- pre-ESC response**

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated use and cost of the proposed health technology</b>						
Number of people eligible for brexucabtagene autoleucl						
Number of people who receive brexucabtagene autoleucl						
Number of services of brexucabtagene autoleucl						
Cost to the Government	\$█	\$█	\$█	\$█	\$█	\$█
<b>Change in use and cost of other health technologies</b>						
Change in use of comparators	\$█	\$█	\$█	\$█	\$█	\$█
Increase in use of other affected health technologies	\$█	\$█	\$█	\$█	\$█	\$█
Decrease in use of other affected health technologies	\$█	\$█	\$█	\$█	\$█	\$█
<b>Net financial impact to the Government</b>	\$█	\$█	\$█	\$█	\$█	\$█

Source: Table 8, p8 of Pre-ESC response

## Pre-MSAC response

The applicant made the following adjustments to the financial estimates:

- The total number of patients aged between 18 – 25 years old were removed
- The new proposed effective price of brexu-cel was used

As shown in Table 15, the cost to the government for brexu-cel would be \$ [redacted] million in Year 1 (decreased from \$ [redacted] million in the ADAR) up to \$ [redacted] million in Year 6 (decreased from \$ [redacted] million in the ADAR), with the net financial impact to the Government \$ [redacted] million in Year 1 (decreased from \$ [redacted] million in the ADAR) up to \$ [redacted] million in Year 6 (decreased from \$ [redacted] million in the ADAR).

**Table 15 - Updated financial estimates in pre-MSAC response**

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated use and cost of the proposed health technology</b>						
Number of people eligible for brexucabtagene autoleucl						
Number of people who receive brexucabtagene autoleucl						
Number of services of brexucabtagene autoleucl						
Cost to the Government	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>Change in use and cost of other health technologies</b>						
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]
<b>Net financial impact to the Government</b>	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

Source: Table 5, p5 in pre-MSAC response

## 15. Other relevant information

Nil.

## 16. Key issues from ESC to MSAC

### Main issues for MSAC consideration

#### Clinical issues:

- Clinical evidence – The evidence is based on naïve indirect comparisons that have a high risk of bias. ESC also noted that the evidence was non-randomised, immature with short follow-up, contained differences in baseline characteristics and outcome definitions (e.g. definition of OCR varies across studies) and with small patient numbers. ESC considered that this resulted in uncertainty on longer-term outcomes that the clinical benefit of brexu-cel is uncertain and possibly overestimated. Caution should be exercised when interpreting the evidence base.
- Allo-SCT – The impact of consolidation allo-SCT being excluded as a comparator, and on health outcomes when used with brexu-cel and the comparators is uncertain. The evidence showed that 24% of patients received consolidation allo-SCT following brexu-cel, compared to 24–67% in the comparator studies.
- Tisa-cel should be included as a comparator– The applicant should also provide more detailed comparative data on the efficacy and safety of tisa-cel and brexu-cel for the 18–25 year age group. If data are not available on efficacy, a review on general safety of tisa-cel versus brexu-cel should be provided.
- Target population and place in clinical algorithm could be refined – The algorithm is complex; the applicant has placed brexu-cel quite broadly in four possible positions and the groups are not mutually exclusive. Although subgroup analysis demonstrated no difference in survival outcomes, the data are very limited with small patient numbers in each possible place in the clinical algorithm. If clinically appropriate, MSAC may wish to consider whether the population should be more targeted to patients who have relapsed after two or more lines of systemic therapy; this usage may reflect the likely predominant use in clinical practice (as per targeted consultation responses and the applicant’s pre-ESC response) and represents the subgroups with the largest numbers (n>30) in the ZUMA-3 trial.
- 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. If clinically appropriate, the applicant and Department should append treatment criteria and clinical criteria, similar to other reimbursed CAR-T therapy (e.g. clinical criteria used for tisa cel in R/R pALL which the 18-25 year old age group overlaps with the brexu-cel proposed population).

#### Economic issues:

- The price for brexu-cel has not been justified – Additionally, risk sharing or PfP arrangements have not been proposed.
- The base case ICER is highly uncertain given the lack of robust comparative evidence and limitations with extrapolated survival benefits.
- 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 key clinical evidence is too immature to support an assumption of long-term survivorship. It also does not appear to be consistent with the Kaplan–Meier data and parametric estimates of the ZUMA-3 trial data (albeit less than 20% of patients at risk beyond 28 months for OS). The ICER is likely underestimated, largely due to long term survival plateaus modelled through the use of highly optimistic cure assumptions, which was not supported by relevant external evidence.

**Financial issues:**

- The financial estimates were acknowledged to be an overestimate and revised in the pre-ESC response; however, there is some uncertainty in these estimates due to the assumed uptake rate (40–70% from Year 1 to 6).

**Other relevant information:**

- A review of reimbursed CAR-T therapies is needed, in particular the real world efficacy, safety and cost-effectiveness results from the review of tisa cel in R/R pALL (application 1519) would be relevant for this application due to the overlapping population in the 18-25 year old age group with the proposed brexu-cel population of R/R B-ALL.
- Jurisdictions are unsupportive of the application – All of the submissions expressed strong concerns regarding the validity of the clinical evidence, lack of PfP measures, the proposed price and cost of the intervention and underestimated delivery costs borne by the public hospitals.

**ESC discussion**

ESC noted that this application is for the chimeric antigen receptor-T (CAR-T) cell therapy, brexucabtagene autoleucal (brexu-cel) for treatment of adults (people aged 18 years and older) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (R/R B-ALL). The application seeks joint funding by the Commonwealth and states and territories through the High Cost, Highly Specialised Therapy arrangements included in the National Health Reform Agreement (NHRA) Addendum 2020-25. Brexu-cel is also currently being assessed by the Therapeutic Goods Administration (TGA) for the same indication.

ESC noted that patients with R/R B-ALL have a poor prognosis with a limited ability to tolerate adverse events, and that there are currently limited treatment options for these patients – in particular in those aged above 25 years of age due to the availability of reimbursed tisa-cel in those with R/R pALL aged 18-25 years (i.e. the overlapped subpopulation in Application 1519 (tisa-cel) with the proposed brexu-cel population).

ESC noted the targeted consultation feedback received from two clinicians. ESC also noted a key issue for consumers includes the serious side effect profile associated with treatment with brexu-cel.

ESC noted that the applicant-developed assessment report (ADAR) proposed some criteria for treatment, namely that the patient must be treated in a tertiary public hospital with appropriate credentials and treated by a haematologist working in a multidisciplinary team specialising in the provision of CAR-T cell therapy. However, ESC noted that the proposal provided little specific detail on the clinical criteria. ESC considered that further specification of the clinical criteria, modified from previous CAR-T cell applications would be useful.

ESC noted that the ADAR proposed that funding of brexu-cel will be limited to once per lifetime, but also included text that stated “if clinically appropriate, a second infusion is allowed”, as per the pivotal ZUMA-3 trial<sup>7</sup>. ESC considered that a second infusion would be unreasonable, as there is insufficient clinical evidence to support retreatment. For example, in the ZUMA-3 trial, four out of five participants (80%) had no response to a second infusion.

ESC recalled that MSAC recommended funding for tisagenlecleucel (tisa-cel) in May 2019 for the treatment of refractory CD19-positive leukaemia and lymphoma ([Public Summary Document 1519](#)) for patients up to 25 years old. ESC noted therefore that, if this application is supported,

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<sup>7</sup> Shah BD et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *The Lancet*. 2021;398(10299):491-502.



there will be two CAR-T therapy options for this disease. ESC considered that a once per lifetime limit on CAR-T cell therapies for this indication could be appropriate, rather than a limit on the usage of brexu-cel.

ESC noted that there was no ratified PICO as the application bypassed PASC. ESC noted the comparators in the ADAR are blinatumomab, inotuzumab and ponatinib, which are all listed on the Pharmaceutical Benefits Scheme (PBS) for second-line therapy, and salvage chemotherapy. Tisa-cel and allo-SCT were not included as comparators in the ADAR.

ESC noted that the population in Application 1519 (tisa-cel) overlaps with the proposed brexu-cel population in the 18–25-year age range. ESC noted from the ADAR that tisa-cel was excluded as a comparator because of low numbers of 18–25-year-old patients in the tisa-cel and brexu-cel pivotal trials. However, ESC noted the Commentary identified two additional studies (the Kymriah European Public Assessment Report<sup>8</sup> and John et al. 2021<sup>9</sup>) that reported no difference in safety or efficacy for tisa-cel across age groups. ESC noted that the applicant's pre-ESC response reaffirmed that there was a lower incidence of R/R B-ALL in the 18–25-year-old age group, citing three studies (ELIANA<sup>10</sup>, ENSIGN<sup>11</sup>, B2102J<sup>12</sup>). The applicant also provided a limited comparison of the overall complete remission (OCR) rate in the 18–25-year-old age group using the ZUMA-3 trial and the ELIANA trial. ESC suggested that a more detailed comparison in the 18–25-year-old age group of tisa-cel versus brexu-cel, using the additional evidence identified in the Commentary, would be informative. ESC considered that if data are not available on efficacy, that a review on general safety of tisa-cel versus brexu-cel in this age group would be informative.

ESC noted that allo-SCT is recommended as consolidation therapy in high-risk patients, following treatment with the comparator therapy. ESC noted from the ADAR that 24% of patients in the ZUMA-3 trial received consolidation allo-SCT following brexu-cel, and the Commentary questioned if the intervention should be described as brexu-cel ± allo-SCT. The pre-ESC response stated that the ZUMA-3 trial demonstrated that overall survival (OS) is independent of whether patients received consolidation allo-SCT ( $n = 13$ ) or not ( $n = 45$ ). However, ESC considered that due to the nature of the indirect, naïve comparisons across single arms of studies with notable differences in patient baseline characteristics, the contribution of allo-SCT to outcomes when used with brexu-cel and the comparators is uncertain.

Regarding comparative safety, ESC noted the clinical claim that brexu-cel is associated with different adverse events and has a different safety profile to the comparators. ESC noted that the main evidence provided for brexu-cel was the ZUMA-3 trial. ESC noted that brexu-cel had higher rates of serious adverse events (SAEs) compared to inotuzumab and blinatumomab, but similar fatal toxicity and adverse events. Brexu-cel also had more serious treatment-emergent adverse

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<sup>8</sup> European Medicines Agency EPAR. Kymriah : EPAR - Medicine overview (updated). 2022. Available from: [https://www.ema.europa.eu/en/documents/overview/kymriah-epar-medicine-overview\\_en.pdf](https://www.ema.europa.eu/en/documents/overview/kymriah-epar-medicine-overview_en.pdf). Last accessed: 03 June 2022

<sup>9</sup> John S, et al. (2021). Real-World Outcomes for Pediatric and Young Adult Patients with Relapsed or Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (ALL) Treated with Tisagenlecleucel: Update from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry. *Blood* 138 (Supp 1):428

<sup>10</sup> European Medicines Agency SmPC. Kymriah : EPAR - Product Information. 2022. Available from: [https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf). Last accessed: 03 June 2022.

<sup>11</sup> ClinicalTrials.gov. Study of Efficacy and Safety of CTL019 in Pediatric ALL Patients (ENSIGN). 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT02228096>. Last accessed: 03 June 2022.

<sup>12</sup> ClinicalTrials.gov. Phase I/IIA Study of CART19 Cells for Patients With Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma (Pedi CART19). 2020. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01626495>. Last accessed: 03 June 2022.

events (TEAEs) and adverse events (AEs) compared to salvage chemotherapy, and higher toxicities compared to ponatinib. ESC considered that brexu-cel is likely to have inferior safety based on the naïve comparison with respect to AEs of special interest, particularly cytokine release syndrome and neurological events.

Regarding comparative effectiveness, ESC noted that the clinical claim of superior effectiveness was based on naïve indirect comparisons of ZUMA-3 versus the single arm of nine clinical trials (11 treatment arms in total), and an indirect matched comparison of ZUMA-3 versus SCHOLAR-3<sup>13</sup> (retrospective matched cohort). ESC considered that the naïve indirect comparisons have a high risk of bias. ESC also noted that the evidence was non-randomised, immature with short follow-up and with small patient numbers. ESC considered that this resulted in uncertainty on longer-term outcomes and as such the durability of clinical benefit of brexu-cel is uncertain and possibly overestimated.

ESC noted that the populations across the studies all differed in baseline characteristics. Although the median age was similar, there were differences in the proportion of patients with Philadelphia-positive ALL, mixed lineage leukaemia (MLL) translocation, Eastern Cooperative Oncology Group (ECOG) status, percent of bone marrow involvement, and prior allo-SCT and salvage therapy. ESC considered that conclusions from the comparisons should also be interpreted with caution due to the difference in baseline characteristics.

ESC noted the clinical claim of superiority for all endpoints. ESC noted that the OCR for the modified intention-to-treat group was higher for brexu-cel (74%) compared to blinatumomab (36–69%) and ponatinib (41%), but similar compared to inotuzumab (68–80%). ESC considered that because the definition of OCR varies across studies, a naïve comparison of OCR rates between ZUMA-3 and the comparator studies could produce biased overestimates of the clinical superiority of brexu-cel.

ESC noted that the duration of response was longer with brexu-cel. Median OS (25 months) and RFS (11.6 months) were longer with brexu-cel compared to the comparators (7–9 months and 3.9–7.6 months, respectively). ESC noted similar results when comparing to the SCHOLAR-3 trial; brexu-cel was superior for OCR compared to blinatumomab and inotuzumab, 62% of patients were less likely to die when treated with brexu-cel, and 61% were less likely to have an RFS event.

ESC noted that proposed wording of the TGA approval for brexu-cel would allow it to be used in four possible places in the clinical management algorithm as follows:

- primary refractory
- first relapse if remission was 12 months or less
- R/R after two or more lines of systemic therapy
- R/R after allogeneic stem cell transplant (allo-SCT).

ESC noted that a subgroup analysis was performed in the ADAR that demonstrated no difference in OS and relapse-free survival (RFS) when brexu-cel was given in any of the four possible places within the clinical management algorithm. However, ESC considered that, given the very small patient numbers in each subgroup and that the groups were not mutually exclusive meant that there was insufficient data available from the ZUMA-3 trial to inform the efficacy of brexu-cel at each possible position. If clinically appropriate, MSAC may wish to consider whether it would be appropriate to limit the use of brexu-cel to a later line therapy (i.e. patients who have relapsed

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<sup>13</sup> SCHOLAR-3 CSR (Version 1.0). Kite Pharma, Inc. A retrospective cohort study of adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia sampled from historical clinical trials (SCHOLAR-3). 2021

after two or more lines of systemic therapy), as this positioning represents the likely usage in practice (as per the targeted consultation responses and as noted in the applicant's pre-ESC response) and are the subgroups with the largest numbers (only subgroup with  $n > 30$ , noting that the patient numbers in these subgroups were still relatively small).

ESC noted that a comparison of health-related QoL (HRQoL) was difficult. ESC noted that there was a significant decrease in patients completing QoL measures at 24 months in the ZUMA-3 trial ( $n = 55$  at baseline versus  $n = 4$  at 24 months). Additionally, a comparison of QoL outcomes was difficult across studies because different tools were used and different timepoints were assessed. ESC considered that this remained an area of uncertainty.

ESC noted that there were several concerns with the proposed cost of treatment of \$ [REDACTED] (to be paid upon successful infusion). ESC noted that the applicant did not justify the price ([REDACTED] [REDACTED] [REDACTED]), nor did the applicant propose any risk sharing or PfP arrangements (which have been included with other reimbursed CAR-T therapies). However, ESC noted that, in the pre-ESC response, the applicant agreed that a risk sharing and PfP arrangement would need to be negotiated. ESC noted that alternate funding mechanisms, specifically the Medical Treatment Overseas Program (MTO), as highlighted in the state and territory submissions would not be an appropriate funding mechanism for brexu-cel as it is delivered in Australia.

ESC noted that the economic evaluation was a model-based cost-utility analysis (CUA) nominating blinatumomab as main comparator. The economic evaluation used a three-state partitioned survival model (PSM), consisting of event-free survival (EFS), progressed disease (PD) and death. ESC considered PSM to be a practical modelling approach in oncology. However, ESC considered the PSM approach has known limitations due to the lack of structural link between health states and the use of independent modelling to estimate health states occupancy, which impacted the results of the economic evaluation.

ESC considered the biggest sources of uncertainty in the economic model to be the clinical effectiveness inputs; specifically around the cure rate and extrapolation used in the model. ESC considered that this was in addition to the issues and limitations identified with the evidence base, including indirect naïve comparisons, differences in baseline characteristics between cohorts, small sample sizes and short follow-up. ESC noted that standard parametric models were fitted to the observed OS and progression-free survival (PFS) data to project survival endpoints for patients in the ZUMA-3 and TOWER trials, which ESC considered to be appropriate. However, ESC considered the structural assumption, a base case cure point of 2 years, to be highly favourable to brexu-cel. ESC noted the model assumption that, irrespective of treatment or disease status, patients alive at 2 years will experience long-term survivorship close to general population utility values and survival (adjusted with a standardised mortality ratio of 2 in the base case, applied to both arms). The evidence used to justify this assumption was based on 10-year survival outcomes of cancer survivors after allo-SCT.<sup>14</sup>

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. ESC noted the pre-ESC response claimed that brexu-cel can lead to sustained remission that would be similar to maintaining remission after transplant. However, ESC was not convinced by this rationale, and questioned whether the data on long-term survival in allo-SCT patients were applicable, and noted that there was no clinical data to support this assumption, with the assumption forcing the modelled survival to deviate from the parametric extrapolations with a significant inflection point observed in the modelled

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<sup>14</sup> Kliman D, Nivison-Smith I, Gottlieb D, Hamad N, Kerridge I, Purtill D et al. (2020). [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* 26(9):1711–1718.

survival estimates (albeit less than 20% of patients at risk beyond 28 months for OS in ZUMA-3). ESC considered that this would not be clinically plausible. ESC considered the ICER is likely underestimated, largely due to long term survival plateaus modelled through the use of highly optimistic cure assumptions, which was not supported by relevant external evidence.

ESC also questioned the plausibility of applying this cure point assumption to all patients (i.e. those with progressed disease and those without events at 2 years). ESC noted the additional analysis provided in the pre-ESC response that found that applying the cure assumption to patients in the EFS only had a moderate impact on the base case incremental cost-effectiveness ratio (ICER; 10% increase). ESC considered that this additional analysis is informative but for MSAC to accept the revised ICERs in the applicant's pre-ESC response still relied on accepting the cure point assumption of cure at 2 years. ESC noted changing the utility values and costs (such as pre-infusion costs, cost of treatment and subsequent therapies, and adverse event management costs) in the sensitivity analysis did not have a significant impact on the model.

ESC noted that key drivers of the economic model were costs related to brexu-cel, and modelled incremental health outcomes including a large number of patients in the EFS state, and an assumed cure point of 2 years. ESC noted that, based on the 2-year cure assumption, the ICER is \$ [REDACTED] per quality-adjusted life-year (QALY). ESC noted sensitivity analyses showed using a cure point of 5 or 10 years increased the ICER to \$ [REDACTED] (change of 39% from base case) or \$ [REDACTED] (change of 83%), respectively. Due to the uncertainty in the clinical evidence and that the proposed price of brexu-cel has not been adequately justified, ESC noted that across a range of cure point assumptions:

- No cure point: a [REDACTED] price reduction (~\$ [REDACTED]) in the price of brexu-cel would be required to achieve an arbitrary ICER in the range of \$70,000 to 75,000 per QALY gained
- Cure point (10 years): a [REDACTED] price reduction (~\$ [REDACTED]) in the price of brexu-cel would be required to achieve an arbitrary ICER in the range of \$70,000 to 75,000 per QALY gained.

ESC noted that the financial and budgetary impacts used a mixed-model approach with multiple data sources. ESC noted that the estimated use and net financial impact that were included in the ADAR were likely an overestimate, as they assumed no change in the use of tisa-cel in the 18–25-year age range, underestimated hospital costs, and use outdated age-specific incidence rates and proportion of PBS medicines affected. ESC noted the pre-ESC response acknowledged this and provided updated financial estimates, resulting in the number of patients who received brexu-cel decreasing to [REDACTED] patients in pre-ESC response (from [REDACTED] patients in ADAR) in Year 1 to [REDACTED] patients (from [REDACTED] patients) in Year 6 (see Table 11). However, ESC considered there was still some uncertainty in the assumed uptake rate (40–70% from Year 1 to 6) based on the applicant's market research and clinical feedback.

ESC noted that submissions from state and territory governments were not supportive of this application. There were strong concerns about the validity of the clinical evidence, lack of pay for performance (PfP) measures, and the proposed price and cost of the intervention and incorrect delivery costs borne by the public hospitals.

## **17. Applicant comments on MSAC's Public Summary Document**

Gilead Sciences continues to explore ways to bring brexucabtagene autoleucel (brexu-cel) for inclusion into the publicly funded CAR-T program. Brexu-cel is an innovative treatment that is claimed to fulfill the high unmet clinical need for a targeted, small number of adults (25 years and above) with relapsed or refractory B-precursor acute lymphoblastic leukaemia (r/r B-ALL). Compared to younger patients, adults living with r/r B-ALL respond poorly to conventional treatments, have worse prognoses and very limited treatment options available.

## **18. Further information on MSAC**

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