

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1748 - Review of tisagenlecleucel (Kymriah®) for treatment of acute lymphoblastic leukaemia in paediatric and young adult patients (pALL)

Applicant: Novartis Pharmaceuticals Australia (Novartis)

Date of MSAC consideration: 27 July 2023

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

1. Purpose of application

Public subsidy for tisagenlecleucel (TIS) to treat paediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (pALL) that is refractory, in relapse post-transplant, or in second or later relapse, through the National Health Reform Agreements (NHRA) commenced on 31 July 2019. The Department of Health and Aged Care wrote to Novartis Pharmaceuticals (Novartis) in September 2022, providing notice that the review of TIS in pALL had been scheduled for consideration at the July 2023 Medical Services Advisory Committee (MSAC) meeting. Novartis was therefore requested to lodge a submission for MSAC consideration by the 8 February 2023 Applicant Developed Assessment Report (ADAR) lodgement deadline. This is in line with MSAC's recommendation that a review of the clinical and cost effectiveness and budget impact of TIS be conducted at least three years after the commencement of public subsidy.

2. MSAC's advice to the Minister

MSAC reviewed matters related to the public funding of the chimeric antigen receptor T cell therapy (CAR-T) tisagenlecleucel (TIS) for acute lymphoblastic leukaemia in paediatric and young adult patients (pALL). MSAC requested this review in April 2019 when it initially supported funding of TIS, through the National Health Reform Agreement. After reviewing updated evidence from clinical studies, Australian data from the Australian Bone Marrow Transplant Recipient Registry (ABMTRR) and utilisation data supplied by the States and Territories, MSAC considered that the available evidence did not fully address the clinical, economic and financial uncertainties which existed when it initially supported public funding. The review did not adequately address MSAC's previous concerns regarding the uncertainty of clinical outcomes beyond 12 months for TIS for pALL. Australian patient data showed that more patients received other anti-cancer treatments such as allogeneic haematopoietic stem cell transplantation (aHSCT) after using TIS compared to what was expected. MSAC considered that for most patients, TIS is likely used as a bridging therapy to aHSCT or aHSCT is being used to treat relapse post-TIS. MSAC considered that some of the long-term outcomes from observational data were likely influenced by the use of other treatments subsequent to the use of TIS, particularly aHSCT. MSAC considered the economic model likely overestimated the benefit of TIS and underestimated the benefits of the comparator blinatumomab. Data from the States and Territories showed the true total cost of providing treatment with TIS was substantially higher than expected and that although

significantly fewer patients than expected used TIS, the estimated budget impact was similar to that presented in the initial application for this reason. Therefore, MSAC advised a further review should be conducted in 3 years with the need for ongoing data collection. MSAC requested the Department negotiate [REDACTED] based on TIS being a bridging treatment rather than a curative treatment. MSAC advised the [REDACTED] [REDACTED] MSAC noted that the data recorded in the ABMTRR (supported by funding from Novartis) was not complete and lacked robustness when compared to the data the states and territories submitted to the review. MSAC considered that the data collection objectives of MSAC were not being adequately met by the registry and advised the Department should explore how to most effectively and efficiently capture complete data for TIS but also for other CAR-T therapies into the future. MSAC advised that the Department work with all stakeholders to develop a robust, efficient and transparent registry system, including with the states and territories who already capture this data and who facilitate data collection through their hospitals. Given the highly specialised therapy and high costs, MSAC considered that a nationally coordinated process for patient selection and allocation should be adopted for CAR-T therapies (similar to the process for organ transplants).

Consumer summary

Novartis Pharmaceuticals submitted updated information to MSAC about tisagenlecleucel (TIS; brand name Kymriah®). In 2019, MSAC approved government funding for TIS treatment for a type of blood cancer called CD19-positive acute lymphoblastic leukaemia in children and young adults up to 25 years of age (pALL). TIS treatment is for people who had used other treatments before and the leukaemia had come back (relapsed) or if their disease had not responded to other treatment (refractory).

TIS was a new type of treatment called CAR T-cell (chimeric antigen receptor) therapy. TIS and other CAR-T therapies are a type of immunotherapy. It uses a patient's own immune cells (T cells) that are genetically modified in a laboratory to first identify and then attack cancer cells. The initial data presented to MSAC in 2019 was promising but not enough for MSAC to be confident about how well it would work long term. MSAC supported public funding for this treatment on the condition that Novartis needed to show updated data in three years' time. In July 2023, MSAC considered this updated data. TIS treatment is provided by state public hospitals in Sydney, Melbourne, Brisbane and Perth. The state governments of New South Wales, Victoria and Queensland provided data about patients treated in public hospitals. This included patients from other states who travel for treatment. Data about Australian patients is also recorded in the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR).

MSAC considered the new data from the clinical studies, and from the Australian patient registry that was intended to record details of all TIS patients in Australia. MSAC considered that it was still not clear how well TIS worked after 12 months. Many patients in the clinical studies and Australian patients (from the registry) had other treatments including stem cell (bone marrow) transplants. This made it difficult to tell whether the benefits seen were from TIS or whether patients were benefitting from the other treatments they received later. MSAC considered that TIS was not curing most patients as patients were receiving other treatments after they used TIS. Some patients' cancer was returning more than a year after they used TIS. The Australian patient data in the registry was also missing a lot of data.

MSAC considered that the economic evaluation had overestimated the benefits of TIS and underestimated the benefits of blinatumomab. MSAC also noted that TIS treatment had been used less often than expected. There are several possible reasons for this, including the COVID-19 pandemic and the specialised training needed to give the treatment. The states reported that actual costs to deliver the program were much higher than expected.

MSAC considered that a nationally coordinated process for patient selection and allocation should be adopted for CAR-T therapies (similar to the process for organ transplants).

Consumer summary

MSAC considered that future CAR-T reviews should update data on safety, effectiveness, usage, and costs for both the intervention and the comparator.

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

MSAC considered the new data was not enough to improve understanding of how well treatment with TIS works long term. Many patients in the clinical studies and Australian patients had other treatments including stem cell (bone marrow) transplants. MSAC considered that TIS was not curing most patients. Cost data from state and territory governments showed the true cost of providing TIS was substantially higher than expected. MSAC considered another review was needed in 3 years.

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

MSAC recalled that in April 2019, it supported public funding for TIS for the treatment of acute lymphoblastic leukaemia (ALL) in children and young adults up to 25 years old (referred to as paediatric ALL (pALL)) via the National Health Reform Agreement (NHRA). MSAC recalled that when it considered the application in March 2019, it had recognised that there was large unmet clinical need for a small group of patients and the preliminary supportive evidence of a clinically important treatment effect. MSAC had considered that TIS would be acceptably cost-effective in the pALL population with additional risk share measures in place to those proposed in the application to manage and mitigate the remaining areas of clinical, economic and financial uncertainty that existed in the funding proposal. After deferring its advice in March 2019 to allow for the details of a Risk Sharing Arrangement (RSA) to be proposed, MSAC supported public funding in April 2019 after considering the subsequent RSA provided by Novartis ([MSAC application 1519](#)). MSAC also requested the public funding of TIS for pALL to be reviewed at least 24 months after the first patient received treatment (later varied to at least 36 months). The details of the RSA and the requirement for a subsequent review of the public funding were negotiated through a Deed of Agreement (Deed) between the Commonwealth and Novartis following the MSAC's advice.

MSAC noted that in accordance with this review requirement, Novartis lodged an updated applicant-developed assessment report (ADAR) in February 2023. As per the Deed, the purpose of this application is to review all matters relevant to the provision of the treatment, including but not limited to:

- the clinical and cost-effectiveness of the treatment
- usage of the treatment
- financial costs of the treatment
- any other matter relevant to the effectiveness, supply or funding of the treatment.

MSAC noted the review was informed by updated results from the ELIANA and ENSIGN trials, along with data from the B2001X trial, other published studies, and observational Australian data from the Australian Bone Marrow Transplant Recipient Registry (ABMTRR). Given TIS is jointly funded by the Commonwealth and states and territories in line with the High-Cost, Highly Specialised Therapy (HST) arrangements outlined in the 2020-25 Addendum to the NHRA, the states and territories also provided data to inform the review. MSAC noted the applicant's pre-MSAC response claimed the updated ELIANA report "provides an additional 3 years of data since the time tisagenlecleucel was first considered by MSAC for pALL and supports the survival extrapolations in the original economic model" and "suggests that tisagenlecleucel is curative for some patients". MSAC noted that while longer duration follow-up data was provided for overall

survival, the clinical study data was still mostly from single-arm studies. These reported substantial loss to follow up. MSAC also noted that the additional follow-up time had not yielded any additional information for some endpoints.

MSAC recalled that it had previously identified uncertainty regarding the proportion of patients experiencing, and durability of, responses in clinical practice; and uncertainty regarding the number of patients going on to stem cell transplantation after TIS (MSAC 1519 PSD, pg 3). In deliberating on whether previous clinical uncertainty had been addressed, MSAC noted that Kaplan Meier (KM) plots for duration of response and overall survival data (see Figure 1 and Figure 3 in Section 12) indicated that relapse and death outcomes continue to accrue. Therefore, MSAC considered that these data indicate that most patients are not cured or placed into a stable disease state after treatment with TIS but continue to experience disease progression. MSAC noted the New South Wales (NSW) submission stating that some patients experience late relapse greater than 12 months after TIS infusion.

MSAC also noted the health system utilisation data from the states and territories reported the rate of aHSCT after TIS treatment (31%) was higher than originally expected (19%). MSAC considered that this indicated that clinicians do not consider TIS to be a curative treatment and the treatment is likely being used either as a bridging therapy to aHSCT or aHSCT is being used to treat relapse post-TIS. MSAC considered that the clinical evidence did not address whether the longer-term outcomes observed were due to the effect of TIS alone or from subsequent therapies including aHSCT. MSAC noted median overall survival had not been reached in most studies (see Table 6 in Section 12). In the ELIANA study, 42% of patients had died by September 2021. In the ENSIGN study, 47% of patients had died at study termination (median 15-month follow up for OS).

MSAC recalled that it had previously identified uncertainty about the duration of immunoglobulin (intravenous, IVIg, or subcutaneous, SCIg) treatment post TIS (MSAC 1519 PSD, pg 3). Registry data reported the use of IVIg is substantial with 59% of patients with at least 1 year follow-up still receiving IVIg. Approximately 30% of patients received tocilizumab within the first 30 days post-TIS. MSAC considered that there were no new safety signals but considered the occurrence of death due to haemophagocytic lymphohistiocytosis in a non-sponsor study (Ravich et al 2022) ¹ should be formally referred to the TGA by MSAC.

MSAC considered the data being collected in the ABMTRR was incomplete for the purpose of the TIS review. MSAC highlighted the following limitations in the ABMTRR data:

- There were substantial missing data (only █% of patients had follow-up data at 12 months).
- Safety data were only recorded for 100 days.
- Efficacy data were confounded because █% of patients were in remission at the time of infusion, and many patients had multiple therapies (including aHSCT) within the follow-up timeframe.
- Quality of life data were inadequate (only █% recorded at 12 months).
- Comparison of state and ABMTRR data indicated that not all treatments were recorded on the ABMTRR (e.g. the rate of aHSCT was █% based on data reported by the ABMTRR versus 31% based on data from the states and territories).

Overall, MSAC considered that the available evidence did not address MSAC's previous concerns regarding the uncertainty of clinical outcomes of TIS treatment for pALL beyond 12 months. As such, uncertainty regarding the incremental effectiveness of TIS versus blinatumomab (BLN)

¹ Ravich JW, Huang S, Zhou Y, Brown P, Pui CH, Inaba H, Cheng C, Gottschalk S, Triplett BM, Bonifant CL, Talleur AC. Impact of High Disease Burden on Survival in Pediatric Patients with B-ALL Treated with Tisagenlecleucel. *Transplant Cell Ther.* 2022 Feb;28(2):73.e1-73.e9. doi: 10.1016/j.jtct.2021.11.019. Epub 2021 Dec 4. PMID: 34875402; PMCID: PMC8816862.

remained, and new uncertainty had been introduced due to the confounding of survival outcomes due to patients receiving subsequent anti-cancer therapies post-TIS treatment (including additional doses of TIS and aHSCT). MSAC noted that it had previously raised the potential for TIS to be used as a bridge to transplant and considered this had been borne out by the data provided by the states and territories, noting that 31% of patients treated with TIS went on to receive aHSCT.

Regarding the cost-effectiveness of TIS treatment, MSAC noted the updates that had been made to the model to include updated trial and registry data. Both MSAC and the applicant accepted the commentary's corrections to the 'cure' assumptions in the applicant's model. MSAC noted that although costs to deliver TIS had been updated, the costs applied to later health states (progression-free survival and progressive disease) had not been updated from the 2019 model. MSAC considered that it was unclear whether these costs accurately reflect current costs for salvage or support therapy. The comparator remained BLN +/- aHSCT. MSAC noted that although an applicant-funded matched-adjusted indirect comparison²⁵ has been published, the evidence used for the comparator in the model was from a phase I/II trial and was not updated. This made it difficult to compare the outcomes from TIS to BLN. Recent evidence^{16,17} indicates that BLN may provide better outcomes and be associated with higher aHSCT rates than were used in the economic model. MSAC considered that the economic model had overestimated the benefits of TIS and underestimated the benefits of BLN.

A comparison of the costs estimated in the 2019 ADAR with the actual costs incurred by the states showed that real-world costs to deliver the program (excluding the TIS product cost) are higher on average than expected. The costs per TIS treatment were estimated as \$ [redacted] per patient, but NSW reported an average of around \$ [redacted] (range of \$ [redacted] to \$ [redacted]). This includes costs such as infusion admission, inpatient and outpatient costs, and program costs.

MSAC noted that the updated cost per quality-adjusted life year (QALY) with technical corrections applied was calculated as \$ [redacted] but increased to over \$ [redacted] per QALY when the real-world costs of providing TIS (provided by public hospitals) were included. MSAC recalled that its previous support for funding TIS for pALL was based on an ICER of \$ [redacted] per QALY and to maintain this using the commentary respecified model, the price of TIS would need to be reduced to \$ [redacted]. MSAC considered the respecified ICERs were still uncertain due to an implausible extrapolation of overall survival (OS) for TIS, incomplete cost data, and no updated cost or effectiveness data for BLN. MSAC noted that the ICER is sensitive to non-TIS costs and the percentage of patients receiving aHSCT, which underscores the importance of continuing to collect data on these parameters.

Regarding the financial costs of the treatment, MSAC noted that the total financial impact was close to the level expected, but this was due to fewer patients being treated at a higher cost per patient. MSAC recalled that it had previously raised uncertainty in the number of patients who would be selected for treatment, and the number of patients who would ultimately receive treatment (MSAC 1519 PSD, pg 3). MSAC noted that the actual utilisation had been lower than originally predicted. That is, in Year 1, <100 patients had undergone TIS treatment compared with an expected [redacted]; in Year 2, the numbers were <100 versus [redacted]; and in Year 3, the numbers were <100 versus [redacted]. Possible reasons may include:

- the COVID-19 pandemic and its impact on health care delivery, border closures and supply chain disruptions

²⁵ Verneris MR et al. Indirect comparison of tisagenlecleucel and blinatumomab in pediatric relapsed/refractory acute lymphoblastic leukemia. *Blood Adv.* 2021;5(23):5387-95.

¹⁶ Sutton R et al. Outcomes for Australian children with relapsed/refractory acute lymphoblastic leukaemia treated with blinatumomab. *Pediatr Blood Cancer.* 2021;68(5):e28922.

¹⁷ Locatelli F et al. Blinatumomab in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia: RIALTO expanded access study final analysis. *Blood Adv.* 2022;6(3):1004-14.

- implementation issues including:
 - limited clinician confidence in the therapy as it was first in class
 - significant effort required to establish models of care and train the workforce
 - lack of provider awareness for eligibility and toxicity management.

MSAC considered that it was unclear whether utilisation will increase in future. While it is plausible that utilisation may increase, it is also possible that clinicians may move away from TIS treatment and use other immunotherapies as bridging therapy to aHSCT.

MSAC noted submissions from the states and territories raised several key issues. These included challenges with access to and transparency of the ABMTRR data to inform clinician decision making regarding treatment, additional information that should be collected by the registry (e.g. measurable residual disease, B-cell aplasia), higher resource requirements than anticipated, and issues around service delivery and organisation.

MSAC noted the findings from the NSW patient and carer experience evaluation of recent CAR-T therapy. MSAC noted that patients and carers may be incurring substantial out-of-pocket costs for travel where this is not funded through other mechanisms. MSAC noted that some travel costs for patients were being funded by the applicant. MSAC noted that access to social workers was cited as an important, unmet need by the families of patients with ALL. MSAC appreciated feedback provided by patients and carers regarding their lived experience of TIS treatment.

██████ MBS funding for testing for MRD in patients with ALL is being implemented³ and may represent more contemporary clinical care noting that MRD thresholds are also used to specify eligibility for access to BLN under the Pharmaceutical Benefits Scheme (PBS)⁴. ██████

MSAC considered further evidence and review was required before it could advise on an appropriate single payment price for TIS for pALL. MSAC considered that additional data to support a single payment should demonstrate that the treatment response is attributable to a single treatment with TIS (without confounding by repeat infusions or subsequent therapies including aHSCT), and that residual disease-free survival is a surrogate outcome for overall survival. This further evidence should be based on reliable collection of outcomes and full cost data for TIS and BLN in the Australian health system.

MSAC noted that while the actual utilisation of TIS for pALL had been lower than predicted, ██████. This is because MSAC considered there is a risk of TIS being used in earlier lines of therapy, or multiple times in the intended population, ██████. MSAC considered that the limit of one treatment per lifetime remains appropriate, as there is insufficient evidence regarding the incremental safety or effectiveness of second or third treatment with TIS. ██████

MSAC recalled that the intention of the RSA and Deed specifying registry data collection via the ABMTRR was to facilitate comprehensive accessible real-world Australian data collection (both health outcome and healthcare resource use) following TIS treatment for pALL to help address the uncertainties raised by MSAC. However, MSAC had noted significant issues with the ABMTRR data in terms of both quality (incomplete and missing data) and accessibility. MSAC considered the ABMTRR data was incomplete and inadequate to inform whether the expected longer-term effectiveness and safety outcomes from TIS are occurring in practice. MSAC noted that

³ MSAC considered and supported creating new MBS items for the detection of MRD in patients with ALL, using flow cytometry and next-generation sequencing (NGS) methods in November 2022 ([MSAC application 1707](#)) and quantitative molecular assays in March 2023 ([MSAC application 1703](#)).

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

confidentiality clauses in the contractual arrangement between CAR-T sponsors (who fund data collection) and the ABMTRR had restricted the sharing and use of the data. MSAC considered that the objectives of its requested data collection were not being adequately met by the registry and advised the Department should explore how to most effectively and efficiently capture complete data for TIS but also for other CAR-T therapies into the future. MSAC advised that the Department work with all stakeholders, including the states and territories that already capture this data, to develop a robust, efficient and transparent registry system. Data collection should include the reason for subsequent treatment and longer-term outcomes post 12 months. Patient-reported outcome measures and quality of life measures should also be included. MSAC considered greater patient and carer involvement may help capture more quality-of-life data as this could be directly reported by patients.

MSAC considered the findings of this review should be provided to the Pharmaceutical Benefits Advisory Committee (PBAC) and the HTA Review Reference Committee. MSAC considered the findings highlight the challenges associated with collecting real-world evidence to inform 'coverage with evidence development' approaches to funding health technologies.

MSAC considered that a nationally coordinated process for patient selection and allocation should be adopted for CAR-T (similar to the solid organ transplantation process). This may offer a way to improve access (availability and affordability) to TIS for patients living at a distance from a treating centre. Centralised governance would require interjurisdictional support to be successful.

MSAC advised that future CAR-T reviews should update real-world safety, effectiveness, usage and cost data for both the intervention and the comparator. Future CAR-T reviews may need to add in analysis of the sequential use of therapies over time. MSAC considered that the next TIS review for this population should occur in another 3 years.

4. Background

In November 2018, MSAC first considered an application from Novartis requesting a new national funding mechanism for access to TIS for patients with relapsed or refractory pALL or diffuse large B-cell lymphoma (DLBCL; [MSAC application 1519](#)). At the November 2018 meeting, MSAC deferred the decision in relation to the pALL indication and did not support public funding for DLBCL.

In March 2019, MSAC considered a revised application for TIS in pALL (MSAC application 1519) but again deferred its advice on public funding. While recognising the large unmet clinical need for a small group of patients and the preliminary supportive evidence of a clinically important treatment effect, MSAC considered that TIS would be acceptably cost-effective only with additional risk share measures to those proposed in the application to manage the remaining areas of clinical, economic and financial uncertainty that existed in the funding proposal (see March 2019 consideration in [MSAC 1519 Public Summary Document](#) [PSD]).

In April 2019, MSAC recommended public funding for TIS in pALL based on an incremental cost-effectiveness ratio (ICER) of \$■■■■ per quality adjusted life year (QALY) for TIS versus blinatumomab (BLN). The recommendation required a risk sharing arrangement (RSA) to manage any remaining uncertainties in the funding proposal for TIS in pALL that comprised several elements, ■■■■, ■■■■, limitation to a single course of treatment per patient, and the requirement for review of the clinical and cost effectiveness and budget impact of TIS at least three years after the commencement of public subsidy. These recommendations were subsequently outlined in the Deed of Agreement executed between the applicant and the Commonwealth. The purpose

of the ADAR is to meet MSAC’s recommendation that a review of the clinical and cost effectiveness and budget impact of TIS is conducted at least three years after the commencement of public subsidy. As reflected in the Deed of Agreement, this review was to include all matters relevant to the provision of the treatment, including but not limited to the clinical and cost-effectiveness of the treatment, usage of the treatment, financial costs of the treatment or any other matter relevant to the effectiveness, supply or funding of the treatment.

Table 1 Summary of information provided by the applicant for the review requirements as specified in the Deed

Component	Information provided in the ADAR review	How the current assessment report addresses it
To meet the requirements as specified in the Deed		
Clinical effectiveness	Updates for all company-sponsored clinical trials, and results for all protocol specified primary and secondary outcomes be provided.	This was addressed in in Section 2.2. However, the information was not presented in a logical order.
	Reports or publications located by the Company on studies of the treatment not sponsored by the company be included in the review.	This was addressed in Section 2.3. However, this was inadequately addressed. The ADAR excluded retrospective studies from the literature review. As most real-world experience studies are retrospective analyses of registries or hospital databases, most of the real-world data on the safety and effectiveness of TIS were not presented. Seven studies that were excluded due to a retrospective design, were identified in the commentary as relevant to the ADAR. One additional study (Bader et al. 2023) that was published after the literature search date was also identified in the commentary. These have been included in the commentary.
	An updated combined analysis of the ELIANA and ENSIGN studies using latest available data cut from each was provided	This was provided in Section 2.2.5. However, it is not clear why the results presented from the B2001X study were not also included in the combined analysis. An additional study (Levine 2021) reported a pooled safety analysis of ELIANA and ENSIGN of key adverse events (e.g. CRS, neutropenia, neurologic events). It is unclear why this study was discussed in the Pharmacovigilance section and not in Section 2.2.4 where the pooled analysis of the two sponsored studies was undertaken by the applicant.
Clinical safety	Copies of any pharmacovigilance or safety reports available	This was provided in Section 2.6. Pharmacovigilance was presented from FDA only. No data were presented from the TGA.
Cost-effectiveness	Update to the economic model presented to MSAC in March 2019 A) to include results of updated combined analysis of the ELIANA and ENSIGN studies and without other changes. B) to include data from ABMTRR	This was provided in Section 3.2.2. This was provided in Section 3.2.3.
Financial cost	Updated utilisation and financial estimates with reasoning for any changes	This was provided in Section 4.1 and 4.2.
	Overseas subsidy status	This was provided in Section 5.

Component	Information provided in the ADAR review	How the current assessment report addresses it
To address uncertainties highlighted by MSAC in the March 2019 PSD		
Clinical safety and effectiveness	An assessment of any new clinical data available and whether the clinical outcomes from the original submission are supported by the updated clinical study data as well as Australian patient outcomes as captured in the relevant registry	<p>The applicant included a superficial combined analysis of the safety and effectiveness data from the three sponsored and two non-sponsored studies included in the ADAR. Seven additional studies that it is assumed were excluded for a retrospective design, were identified in the commentary, as well as another study published after the literature search date.</p> <p>The commentary has provided a more comprehensive comparison of the data presented in the sponsored and non-sponsored studies, and the Australian registry for both safety and effectiveness in Section 2.5.</p>
Registry safety and effectiveness data	<p>The Australian Bone Marrow Transplant Recipient Registry must include the following data:</p> <ol style="list-style-type: none"> 1. patient-reported outcomes; 2. leukaemia-free survival (morphological complete remission and complete molecular remission); 3. complications, use of high cost medicines, late-onset adverse events and adverse events requiring hospitalisation admission and adverse events including those requiring ICU admission; 4. use and duration of immunoglobulin; 5. rate of reinfusion with any CAR-T therapy; 6. indication for use of CAR-T – for example bridge to stem cell transplant, following transplant; and 7. results for patients infused with non-optimal cell numbers. 	<p>Data have been provided, however there is minimal discussion presented.</p> <ol style="list-style-type: none"> 1. Patient reported outcomes are presented for only 17% of registry cohort at 12 months follow up. 2. Remission is reported. It is unclear how this was measured (e.g., morphological or molecular). 3. Complications and adverse events requiring hospitalisation/ICU admission have only been provided up to 100 days of follow-up. Late-onset events have not been described. 4. Use of immunoglobulin has only been provided up to 12-months of follow-up. Duration is not reported. 5. Presented. No reasons provided for reinfusion. 6. Indication for use of CAR-T not provided. 7. Presented with best response of patients recorded.
Registry TIS, aHSCT and Ig usage data	<p>Information required from registry data to answer uncertainties highlighted by MSAC:</p> <ol style="list-style-type: none"> 1. The number of patients who will be selected for treatment, and the number of patients who will ultimately receive treatment. 2. The number of patients going on to stem cell transplantation 3. The duration of immunoglobulin (intravenous, IVIg, or subcutaneous, SCIg) treatment 	<p>ABMTRR data provided the following information:</p> <ol style="list-style-type: none"> 1. All patients who were eligible for TIS were infused. 2. ■■■. 3. Immunoglobulin usage was only reported as a proportion of patients who received therapy in within first 12 months. Duration was not reported.

Component	Information provided in the ADAR review	How the current assessment report addresses it
Cost-effectiveness	An assessment of whether the costings provided in the initial submission are consistent with the actual costs of treating patients in Australia;	Resource use and cost associated with TIS infusion (excluding cost of TIS) and disease management are substantially lower in the modelled evaluation compared with those provided by the State hospitals. Use of subsequent therapies (including Ig, subsequent dose of TIS, aHSCT and other therapies) was much higher than modelled.
	Where there are changes to clinical outcomes or costs, whether the cost effectiveness as estimated in the original application is still supported.	Based on the higher program costs than estimated by the modelled evaluation, the incremental cost effectiveness ratio is likely much higher than estimated in the original application.
Utilisation	An assessment of utilisation and whether these are as expected and justified	The utilisation of TIS for pALL has been lower than estimated by Novartis and accepted by MSAC under the Deed. This may have been due to many possible reasons, including the COVID-19 pandemic, implementation issues, low clinician confidence in the therapy being first in the class and lack of provider awareness for eligibility and toxicity management.
Financial cost	Whether the updated information supports any changes to the arrangements for payment in the Deed	■ the other program costs realised in the clinical practice are much higher than modelled in the ADAR. Sponsor estimated net cost of TIS program to be approximately \$■ for the first three years of Deed. However, based on the data provided by states, the actual estimates are probably as high as \$■ in the first three years.

ABMTRR = Australian Bone Marrow Transplant Recipient Registry; ADAR = Applicant-Developed Assessment Report; aHSCT = allogeneic haematopoietic stem cell transplantation; CAR-T = Chimeric antigen receptor T-cell; CRS = Cytokine Release Syndrome; FDA = Federal Drug Administration; ICU = intensive care unit; Ig = immunoglobulin; MSAC = Medical Services Advisory Committee; pALL = paediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia; ■ = Public Summary Document; SCT = stem cell transplant; TGA = Therapeutics Goods Administration; TIS = tisagenlecleucel

5. Prerequisites to implementation of any funding advice

Not applicable.

6. Proposal for public funding

In April 2019, MSAC recommended public funding for TIS in pALL based on an incremental cost-effectiveness ratio (ICER) of \$■ per quality adjusted life year (QALY). The recommendation required a risk sharing arrangement (RSA) to manage any remaining uncertainties in the funding proposal for TIS in pALL. That agreement comprised several elements, including ■, limitation to a single course of treatment per patient, and the requirement for MSAC to undertake a review of the clinical and cost effectiveness and budget impact of TIS in pALL, two years after the commencement of public subsidy, which was extended to 3 years in November 2021. Public subsidy for TIS in pALL, through National Health Reform Agreement (NHRA) commenced on 31 July 2019.

- [redacted]
- [redacted]
 - [redacted]
 - [redacted]
- [redacted]
 - A. [redacted]
 - B. [redacted]
 - 1. [redacted]
 - 2. [redacted]
 - 3. [redacted]

- [redacted]
- No amount is payable for a Treatment that does not result in a successful infusion for the patient;
- [redacted]
- [redacted]

- [redacted]
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7. Population

The population to be treated by TIS was defined as paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse.

This has not changed from that described in ADAR 1519.

8. Comparator

The comparator has not changed from that described in ADAR 1519. Blinatumomab is still a valid comparator for relapse/refractory ALL according to both the EviQ⁵ and the NCCN Clinical Practice Guidelines in Oncology for both paediatric ALL⁶ and ALL in adolescents and young adults⁷.

9. Summary of public consultation input

Consultation feedback was received from one (1) professional organisation and targeted consultation feedback from one (1) consumer organisation. The organisations that submitted input were:

- Transplant and Cellular Therapy in Children (TACTIC) group, part of the Australian & New Zealand Childrens Haematology/Oncology Group (ANZCHOG)
- Canteen

TACTIC and Canteen were both strongly supportive of the application. Canteen provided a young patients story of his treatment with CAR-T therapy for ALL to demonstrate the benefits of this treatment for young cancer patients.

The benefits of the proposed medical service for young cancer patients were considered to be:

- that TIS is an effective cellular based treatment for eligible patients with relapsed/refractory acute lymphoblastic leukaemia (ALL)
- that this treatment is less burdensome to the patient with reduced side effects compared to traditional cancer treatments
- improved quality of life for patients, having enough health and energy to engage in meaningful activities, have precious moments with loved ones and maintain their independence
- important for young people to be 'normal' throughout treatment, which includes working or studying, maintaining friendships, pursuing hobbies and passions, and making meaningful contributions such as through fundraising, volunteering and advocacy.

There were no disadvantages raised in the consultation feedback, however TACTIC did raise some concerns regarding refinement of the eligibility criteria to ensure that patients who would benefit most from this therapy, but are currently ineligible, have timely access to it. For example in patients that have experienced extreme toxicity from therapy, or those that may be at increased risk of morbidity and mortality from other therapy (including HSCT), or in the setting of Central Nervous System (CNS) disease. TACTIC also raised that the role of re-infusion and optimal dosing strategies need to be further elucidated.

⁵ EviQ: Acute Lymphoblastic Leukaemia. Blinatumomab. URL: <https://www.eviq.org.au/haematology-and-bmt/leukaemias/acute-lymphoblastic-leukaemia/3404-acute-lymphoblastic-leukaemia-blinatumomab>. Accessed 2 May 2023, last updated 30 June 2022

⁶ Brown, P., Inaba, H., Annesley, C., Beck, J., Colace, S., Dallas, M., DeSantes, K., Kelly, K., Kitko, C., Lacayo, N. and Larrier, N., 2020. Pediatric acute lymphoblastic leukemia, version 2.2020, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, 18(1), pp.81-112.

⁷ Brown, P.A., Shah, B., Advani, A., Aoun, P., Boyer, M.W., Burke, P.W., DeAngelo, D.J., Dinner, S., Fathi, A.T., Gauthier, J. and Jain, N., 2021. Acute lymphoblastic leukemia, version 2.2021, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, 19(9), pp.1079-1109.

State and territory feedback

Reports from state and territory data have included experiences from different stakeholders of the TIS treatment program in Australia. These have been summarised in this section.

Patients and Caregivers

The NSW Review commissioned a patient and carer experience evaluation of recent CAR-T therapy (it is unclear if feedback was specific to TIS or included other types of CAR-T) in the latter part of 2022.

State Health departments and healthcare providers

Stakeholder feedback from state health departments and hospitals was provided by New South Wales, Queensland, Victoria, and Western Australia. Across all reviews, three major themes were apparent:

- Evidence for decision-making
- Resource requirements
- Service delivery and organisation.

Evidence for decision-making

The future of TIS therapy should be guided by a body of evidence that is relevant to the Australian clinical context. This evidence largely comes from the TIS sub-cohort from the Australian Bone Marrow Transplant Recipient Registry.

Feedback from the states identified significant issues around data access and transparency. States expressed a desire for access to real-time registry data to assist with accurate costing, and future development of CAR-T programs through evaluation.

States also expressed concern around lack of resources for the registry itself due to “limited departmental resources.” Specifically, there are concerns around receipt of complete data in a timely fashion.

Outcomes collected by the registry were also raised. Queensland recommended that inclusion of loss of B-Cell Aplasia (BCA) be collected, particularly in patients who have had a complete remission, as it can indicate that relapse is imminent. These data may be useful to inform which patients may derive benefit in consolidative aHSCT. Consequently, there is a desire to review definitions of “complete remission” or “complete remission with incomplete blood count recovery”, as outlined in the Kymriah Deed of Agreement. These composite endpoints may be redefined to include other outcomes such as loss of BCA and Minimal Residual Disease (MRD) which are indicative of imminent relapse. The commentary agrees with this as it was found that recent studies of TIS in ALL are also monitoring duration of BCA. Schultz 2022 reported that BCA was observed in 57% of ALL patients treated with TIS. Additionally, Dourthe 2021 identified that loss of BCA was associated with CD19-positive relapse (SHR 21.7, 95% CI [2.65–177.70], $p = 0.004$). The median time to loss of BCA was 7.7 months, with the vast majority occurring within the first 12 months of follow-up.

Given this, it may also be useful to gather genomics data, if available to identify patients with genetic relapse factors to assist with additional consolidatory therapies.

Resource requirements

The most-common theme, raised by all responding states, was that the TIS program requires a substantial number of resources regarding staffing, time, and consumables, compared to other

treatment programs. This increases the burden on other departments leading to inequity of good health outcomes to other patients.

Limited staffing is a particular concern as the infusion/reinfusion of cells requires specialised training as does laboratory processing and management. In addition, the side effects of CAR-T therapy can be acute and potentially fatal. Therefore, healthcare professionals require additional training to diagnose and treat these events quickly and appropriately.

Across states, it was noted that the cost of treating patients was greater than modelled by the sponsor. While infusion costs were consistent with the model, on-going costs have not been captured appropriately, notably, aHSCT which is costly in of itself.

Additional costs may also be borne from patients who require a second infusion. While the treatment itself is not charged, health systems still bear external costs for the therapy (e.g., cell collection, adverse events etc.).

Service delivery and organisation

Across states, healthcare provider-sponsor relationships were positive. However, one hospital noted that this benefit was predicated on a substantial number of resources to collaborate with the sponsor. These included educational opportunities and review meetings to address service improvement.

Issues with production times were also noted, which has serious implications for the treatment of patients. During the first quarter of 2020, there were shortages in the supply chain that resulted in a median turnaround time of 51 days. By the same time in 2021, turnaround time was reduced to 31 days.

To compound issues, Cell Therapies terminated their manufacturing contract with the sponsor in mid- 2021. To date, this has not adversely affected service delivery yet but may restrict the program's potential for growth.

Recommendations

Patients and carers

- Due to the small number of hospitals offering TIS, up to 40% of patients require interstate travel. Additionally, that TIS treatment and its management of complications can be lengthy for patients (up to 3 months). Therefore, additional support for patients and carers with regard to travel and accommodation needs.

TIS registry

- Realtime access to the ABMTRR for ongoing monitoring and quality control with other administrative datasets.
- Data collection and reporting to include additional information such as genomic risk factors, MRD, loss of BCA.
- Refinement of endpoint definition of "complete remission" to include predictors of relapse (e.g., MRD, presence of BCA).
- Continued support for surveillance on long-term safety and efficacy.

10. Characteristics of the evidence base

The ADAR presented an updated systematic literature review of the Cochrane, Embase and Medline databases, undertaken in November 2022, to identify all relevant studies of TIS in pALL. The Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov and World Health Organisation clinical trial registries were also searched. The search excluded retrospective studies.

The screening process was performed by a single reviewer, which substantially increases the likelihood of a study being missed compared to double screening.

The ADAR included three sponsored trials (ELIANA, ENSIGN and B2001X) and two non-sponsored studies (Pasquini et al 2020; Dourthe et al 2021), as well as a report from the Australian Bone Marrow Transplant Recipient Registry (ABMTRR) relating to the use of TIS to treat pALL in patients aged <26 years.

Three states submitted reports for the ADAR and provided data available on the use of TIS for ALL:

- Victoria (February 2023). Data timeframe: May 2019 to January 2023
- Queensland (8th February 2023). Data timeframe: 1st April 2019 to 28th September 2022
- New South Wales (8th February 2023) Data timeframe: 2020 – 30th June 2022

A report was also provided from Western Australia; however, no quantitative data were provided. There were different data cut-off points across state reports. ■■■ The data from these reports are included as an adjunct to data from the ABMTRR.

One of the exclusion criteria for the literature search was retrospective study design. As most studies reporting on the real-world experience with TIS would be retrospective analyses of registry or treatment centre databases, these studies are relevant. They were not included in the ADAR; it is assumed they were excluded during the literature search, but a list of excluded studies was not included in the ADAR. These studies were considered in the commentary.

The trials and studies that formed the evidence base for the ADAR and the commentary are listed in Table 2.

Table 2 Trials/studies and associated reports presented in the ADAR or identified in the commentary

Trial/study ID	Protocol title/ Publication title	Publication citation
Trials studies presented in the ADAR		
ELIANA NCT02435849	“A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia” Laetsch et al (2022). "Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial."	CSR July 2019 <i>Journal of Clinical Oncology</i> , Jco2200642.
ENSIGN NCT02228096	“A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric subjects with relapsed and refractory B-cell acute lymphoblastic leukemia (ENSIGN)”	CSR May 2019
B2001X NCT03123939	“Phase IIIb study for relapsed/refractory pediatric/young adult acute lymphoblastic leukemia patients to be treated with CTL019”	CSR October 2020
ABMTRR	“Australian registry to assess the long term efficacy and safety outcomes of patients with B lymphocyte malignancies treated with tisagenlecleucel”	Report 4, September 2022
Pasquini et al (2020)	"Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma."	<i>Blood Advances</i> 4(21): 5414-5424.
Dourthe et al (2021)	"Determinants of CD19-positive vs CD19-negative relapse after tisagenlecleucel for B-cell acute lymphoblastic leukemia."	<i>Leukemia</i> 35(12): 3383-3393.
Studies included by the commentary		
PRSZT/DRST Bader et al. (2023)	“CD19-CAR-T cells are an effective therapy of post-transplant relapse in B-ALL patients: Real-World Data from Germany.”	<i>Blood Advances</i> , pp. bloodadvances-2022008981.
Ghorashian et al (2022)	“Tisagenlecleucel therapy for relapsed or refractory B-cell acute lymphoblastic leukaemia in infants and children younger than 3 years of age at screening: an international, multicentre, retrospective cohort study.”	<i>The Lancet Haematology</i> , 9(10), pp.e766-e775.
PRWCC	Fabrizio et al. (2022) “Tisagenlecleucel outcomes in relapsed/refractory extramedullary ALL: a Pediatric Real World CAR Consortium Report.” Schultz et al. (2022) “Disease burden affects outcomes in pediatric and young adult B-cell lymphoblastic leukemia after commercial tisagenlecleucel: a pediatric real-world chimeric antigen receptor consortium report.” Rossoff et al. (2021) “Out-of-specification tisagenlecleucel does not compromise safety or efficacy in pediatric acute lymphoblastic leukemia.”	<i>Blood Advances</i> , 6(2), pp.600-610. <i>Journal of Clinical Oncology</i> , 40(9), pp.945-955. <i>Blood</i> , 138(21), pp.2138-2142.
PRWCC Moskop et al. (2022)	“Real-world use of tisagenlecleucel in infant acute lymphoblastic leukemia.”	<i>Blood Advances</i> , 6(14), pp.4251-4255.
Ravich et al (2022)	“Impact of high disease burden on survival in pediatric patients with B-ALL treated with tisagenlecleucel.”	<i>Transplantation and Cellular Therapy</i> , 28(2), pp.73-e1.

ABMTRR = Australian Bone Marrow Transplant Recipient Registry; DRST = German Registry for Stem Cell Transplantation; PRSZT = Pediatric Registry for Stem Cell Transplantation and Cell Therapy; PRSZT/DRST = Pediatric Registry for Stem Cell Transplantation and Cell Therapy/German Registry for Stem Cell Transplantation; PRWCC = Pediatric Real-World CAR Consortium
Source: Compiled for the commentary based on Section 2 of the ADAR.

Table 3 Key features of the included evidence

References	N	Design/ duration	Risk of bias	Patient population	Outcomes
ELIANA	79	Phase II, SA, MC trial Median follow-up: 28.3 months (range 0.4–49)	Moderate ¹	Paediatric and young adult patients with r/r B-cell ALL aged 3–25 years. Median age at infusion: 11 years (range 3–24)	CR, BOR, MRD, DOR, RFS, EFS, OS, AEs, SAEs, AESIs, Deaths
ENSIGN	64	Phase II, SA, MC trial Median follow-up: 31.74 months (range 18–56).	Moderate ¹	Paediatric and young adult patients with r/r B-cell ALL aged 3–25 years. Median age at infusion: 12.5 years (range 3–25)	CR, MRD, DOR, RFS, EFS, OS, AEs, SAEs, AESIs, Deaths
B2001X	69	Phase IIIb, SA, MC study Median follow-up: 8.9 months (range 1.7–14.4).	Low ²	Paediatric and young adult patients with r/r B-cell ALL aged <26 years Median age at infusion: 10 years (range 0–33)	CR, BOR, MRD, DOR, RFS, EFS, OS, AEs, SAEs, AESIs, Deaths
ABMTRR	55	Registry study Median follow-up: 365 days (range 36–785)	NA	Paediatric and young adult patients with r/r B-cell ALL aged <26 years Median age at infusion: 13 years (range 1–26)	CR, BOR, MRD, DOR, EFS, OS, QoL, AESIs
CIMBTR Pasquini et al (2020)	255	Prospective, SA, MC, observational study Median follow-up: 13.4 months (range 3.5–27.9)	Low ²	Paediatric /young adult r/r ALL Median age at infusion: 13.2 years (range 0.4–26)	CR, BOR, MRD, DOR, EFS, OS, AESIs
AP-HP Hospitals. Dourthe et al (2021)	51	Prospective SA, MC, cohort study Median follow-up: 11.6 months	Low ²	Paediatric /young adult r/r ALL Median age at infusion: 17 years (range 1–29)	AESIs
PRSZT/DRST Bader et al. (2023)	81	Retrospective registry study Median follow-up: 20.8 months (range: 0.6–45)	High ²	Paediatric / young adult patients (age ≤25 years) with B-ALL Median age at infusion: 11.5 years (range 1–25)	CR, DBA, EFS, RFS, OS
15 European centres Ghorashian et al (2022)	35	Retrospective, SA, MC, cohort study Median follow-up: 14 months (IQR 9–21)	Moderate ²	Children with r/r pB-ALL aged <3 years at screening Median age at infusion: 17 months (range 15–25)	CR, DBA, EFS, OS, AESIs
PRWCC Fabrizio, and Shultz (2022)	184	Retrospective registry study Median follow-up: 335 days (range 6–863)	Moderate ²	Paediatric / young adult patients (age ≤25 years) with r/r B-ALL Median age at infusion: 12 years (range 0–26)	DOR, DBA, EFS, OS, AESIs
PRWCC Moskop et al. (2022)	14	Retrospective registry study Median follow-up: 231 days (range 44–856)	High ²	Children aged <3 years who had been diagnosed with infant B-ALL prior to 12 months of age. Median age at infusion: 0 years (range 0–9)	CR, MRD, AESIs

References	N	Design/ duration	Risk of bias	Patient population	Outcomes
JH & SJ Hospitals Ravich et al (2022)	31	Retrospective, SA, MC, cohort study Median follow up: 2.8 months (range 0.7–31)	Moderate ²	Paediatric / young adult patients (age ≤25 years) with r/r B-ALL Median age at infusion: 7.9 years (range 0.8–24)	CR, MRD, DOR, AESIs

AEs = adverse events; AESI = adverse events of special interest; BOR = best overall response; CIR = cumulative incidence of relapse; CR = complete remission; DBA = duration of B-cell aplasia; DOR = duration of remission; EFS = event-free survival; MC = multicentre; MRD = measurable residual disease; OS = overall survival; PFS = progression-free survival; PRSZT/DRST = Pediatric Registry for Stem Cell Transplantation and Cell Therapy/German Registry for Stem Cell Transplantation; QoL = quality of life; RFS = relapse-free survival; SA = single arm; SAEs = serious adverse events

1. Risk of bias assessment undertaken by the sponsor. 2. Risk of bias assessment undertaken in the commentary

Source: Compiled for the commentary based on Section 2 of the ADAR.

In comparison to other real-world studies, patients in the ABMTRR were more likely to receive bridging therapy prior to infusion. Consequently, almost █████% (n=████) of Australian patients were in remission at the point of infusion whereas most study populations were refractory/relapsed ALL at the point of infusion. The only exception to this was Pasquini et al (2020) (CIMBTR) who reported that 37% of patients were in remission at time of infusion. For patients currently in remission, the magnitude of benefit of TIS-infusion is unclear.

As of January 2023, the ABMTRR reported that █████% patients (n=████) were planned to have consolidative allogeneic haematopoietic stem cell transplantation (aHSCT) whilst in remission. █████Data from other real-world registries estimate that aHSCT therapy during remission occurs in 25-30% of the population who achieved remission. This discrepancy has implications for TIS therapy as consolidative aHSCT represents a significant add-on cost to ensure longevity and efficacy of therapy⁸. The comparative effectiveness and cost-effectiveness of TIS therapy (compared to BLN) as a bridging therapy to aHSCT (rather than as a destination therapy) has not been evaluated in the ADAR or commentary.

11. Comparative safety

The commentary compared the combined data for the three sponsored trials with the Australian registry data, and nine publications reporting on safety outcomes from four different registries and from three hospital databases. A summary of the outcomes reported for each study is provided in Table 4. It should be noted that some of the patients enrolled in the sponsored trials are also likely to be enrolled in at least one registry. Thus, the patient cohorts are likely to be overlapping.

The mean follow-up period for the B2001X trial was 8 months, compared with a median follow-up period of 28 and 32 months for the ELIANA and ENSIGN trials, respectively. The follow-up periods for the registry trials varied from 7.6 months to 20.8 months (median 12.7 months). Safety data from the Australian registry only covered the first 100 days of follow up and did not cover the entire follow-up period. Therefore, late-onset events are not captured.

None of the registry studies provided a comprehensive report of adverse events (AEs) and serious adverse events (SAEs) experienced by the included patients.

⁸ Xu, X., Chen, S., Zhao, Z., Xiao, X., Huang, S., Huo, Z., Li, Y. and Tu, S., 2021. Consolidative hematopoietic stem cell transplantation after CD19 CAR-T cell therapy for acute lymphoblastic leukemia: a systematic review and meta-analysis. *Frontiers in oncology*, 11, p.651944.

Table 4 Summary of the safety data for TIS from clinical trials and from real-world experiences

		Combined sponsored trials (2019–2021)	ABMTRR (Sept 2022)	CIBMTR Pasquini et al (2020)	PRSZT/ DRST Bader et al (2023)	PRWCC Fabrizio et al (2022) and Shultz et al (2022)	PRWCC Moskop et al (2022)	AP-HP Hosp. Dourthe et al (2021)	JH & SJ Hosp Ravich et al (2022)	15 European centres Ghorashian et al (2022)
N infused		212		255	81	184	14 (<3 years)	51	31	35 (<3 years)
Infusion reaction:	Any grade Grade 3/4	1.9% 0		NR	NR	4 (2.2%)	NR	NR	NR	NR
Hypogammaglobulinemia	Any grade Grade 3/4	40.1% (30–50) 6.1% (2.9–7.8)		134 (52.5%)	NR	NR	NR	NR	NR	27/31 (87%)
Haemophagocytic lymphohistiocytosis	Any grade Grade 3/4	4.2% (1.6–6.3) 2.4% (0–3.8)		NR	NR	NR	NR	NR	2 (6.5%) NR	NR
AESI:	Any grade Grade 3/4	93.0% (92–94) 65.0% (61–68)		NR	NR	NR	NR	NR	NR	NR
CRS:	Any grade Grade 3/4	73.6% (65–78) 37.3% (30–48)		140 (54.9%) 41 (16.1%)	55 (67.9%) 4 (6.2%)	116 (63.4%) 37 (20.2%)	11 (78.6%) 3 (21.4%)	30 (58.8%) 9 (17.6%)	19 (61.3%) 6 (31.6%)	21 (60%) 5 (15%)
Median days (range):	Time to onset Duration	4.5 (1–22) 7 (1–36)		6 (1–27) 7 (1–76)	NR	5 (1–14) 4 (0–42)	NR	4 (1–12)	4 (0–9)	NR 1.5 (0–4)
Serious neurological:	Any grade Grade 3/4	35.0% (30–39) 9.8% (6.4–13)		69 (27.1%) 23 (9.0%)	6 (7.2%) 4 (6.2%)	39 (21.3%) 12 (6.6%)	0	12 (23.5%) 2 (3.9%)	9 (21.0%) 3 (9.7%)	9 (26%) 0
Median days (range):	Time to onset Duration	8 (2–489) 7 (NR)		7 (1–80) 7 (1–94)	NR	6 (3–25) 5 (1–203)	NR	7 (4–65)	6 (1–15)	NR
Infections:	Any grade Grade 3/4	42.0% (41–43) 18.2% (11–24)		118 (46.3%)	NR	73 (40.3%)	NR	NR	NR	10/34 (29%) 8/34 (24%)
Secondary malignancies		2.5% (1.3–3.6)		6 (2.4%)	NR	1 (1.2%)	NR	NR	NR	NR
Haematopoietic cytopenias (for >28 days)	Any grade Grade 3/4	42.0% (42–42) 35.0% (34–35)		71 (27.8%)	NR	NR	NR	NR	NR	15/23 (65%) 12/23 (52%)
Agammaglobulinemia	Any grade Grade 3/4	43.4% (42–44) 9.8% (6.4–13)		NR	NR	NR	NR	NR	NR	NR
Tumour lysis syndrome:	Any grade	2.8% (1.4–5.1)		NR	NR	13 (7.4%)	NR	NR	NR	NR

	Combined sponsored trials (2019–2021)	ABMTRR (Sept 2022)	CIBMTR Pasquini et al (2020)	PRSZT/DRST Bader et al (2023)	PRWCC Fabrizio et al (2022) and Shultz et al (2022)	PRWCC Moskop et al (2022)	AP-HP Hosp. Dourthe et al (2021)	JH & SJ Hosp Ravich et al (2022)	15 European centres Ghorashian et al (2022)
N infused	212		255	81	184	14 (<3 years)	51	31	35 (<3 years)
Grade 3/4	2.8% (1.4–5.1)								
Deaths	34.0% (13–42)		47 (18.4%)	29 (35.8%)	51 (27.7%)	4 (28.6%)	13 (26%)	3 (9.7%)	NR
Disease progression	26.4% (7.3–39)		NR	25 (30.9%)	38 (20.7%)	3 (21.5%)	NR	2 (6.5%)	
Non-ALL mortality	7.5% (5.8–8.9)			4 (4.9%)	13 (7.1%)	1 (7.1%)		1 (3.2%)	
Transplantation Complication	1.4% (1.3–1.6)			-	5 (2.7%)	1 (7.1%)			
Infection	2.8% (2.5–3.1)				5 (2.7%)	-		-	
Cardiovascular complications	1.4% (1.4–1.6)			-	1 (0.5%)	-		-	
CRS	1.4%			2 (2.5%)	2 (1.1%)*	-	1 (2.0%)*	-	
Neurotoxicity	-			-	1 (0.5%)*	-	2 (3.9%)*	-	
Hemophagocytic lymphohistiocytosis	-				-			1 (3.2%)	
Other	1.9% (1.4–2.5)			2 (2.5%)	-	-		-	

*Both patients who died a neurotoxicity event also had grade 5 CRS

AESI = adverse event of special interest; ALL = acute lymphoblastic leukaemia; CRS = cytokine release syndrome; NR = not reported; PRSZT/DRST = Pediatric Registry for Stem Cell Transplantation and Cell Therapy/German Registry for Stem Cell Transplantation

Source: Commentary Table 17, pg 148 of MSAC 1748 ADAR+inline commentary

Most studies reported on the incidence of the two adverse events of special interest (AEIs), cytokine release syndrome (CRS) and neurotoxicity. The rates of CRS of any grade were similar in the sponsored trials compared with the real-world registries (range 65–78% compared with 59–79%, respectively). Grade 5 CRS events causing death were infrequent. Only one of 212 patients (0.5%) treated with TIS in the three sponsored trials, and 3 of 589 patients (0.5%) who were treated with TIS in the real-world studies had fatal CRS.

Serious neurological disorders of any grade were reported less frequently among patients enrolled in the registries (7–27%) than among patients enrolled in the sponsored trials (30–39%). There have been two deaths attributed to neurotoxicity and both were associated with CRS; one patient enrolled in the PRWCC registry died from cerebral haemorrhage in context of coagulopathy, CRS, and pre-TIS stroke and one patient from the study by Dourthe et al (2021) died from encephalopathy and grade 5 CRS.

Additional malignancies were only reported in two of the sponsored trials and two of the registry studies. Of the 10 patients recorded as being diagnosed with other malignancies, 5 developed myelodysplastic syndrome, 4 had acute myeloid leukaemia and 1 had glioblastoma multiforme. Only two cases of myelodysplastic syndrome and the case of glioblastoma multiforme were determined to have no causal relationship with TIS. The cause of disease in the remaining seven patients was not discussed in the relevant studies. It should be noted that as the follow-up period did not exceed 3 years in any study, the incidence of secondary malignancies requires longer-term studies.

Only one AE was identified as a cause of death in the real-world studies but not in the sponsored trials: hemophagocytic lymphohistiocytosis (Ravich et al 2022)⁹. It was considered to be a contributing factor in the death of several patients who died in the sponsored trials.

In summary, the registries did not identify any serious or fatal complications associated with TIS therapy that were not identified in the sponsored trials. However, the commentary considered that due to the death of one patient treated with TIS in the real-world setting from haemophagocytic lymphohistiocytosis, which was only identified in the sponsored trials as a contributing factor, should be monitored by registries to ensure it is not a cause for concern.

The commentary considered that the long-term safety (i.e. post 3 years) for adverse events such as secondary malignancies has not yet been established. Safety data captured in the Australian registry was incomplete and only covered the first 100 days of follow up, which does not meet the terms set out in the Deed of Agreement. The deed states that the collection and provision of data to the Registry must include late-onset adverse events. The commentary considered the lack of data for late-onset events in the Australian registry to be an issue that should be addressed.

12. Comparative effectiveness

Data from the ABMTRR (September 2022) reported that of the <100 patients who received TIS, <100 (████%) had data available. Of these, █████ (████%) had achieved complete remission (ADAR 1748, Table 2.4-4).

The updated pooled estimates presented by the ADAR only included results from ELIANA and ENSIGN and did not include those from B2001X as it was stated that this study was mainly

⁹ Ravich JW, Huang S, Zhou Y, Brown P, Pui CH, Inaba H, Cheng C, Gottschalk S, Triplett BM, Bonifant CL, Talleur AC. Impact of High Disease Burden on Survival in Pediatric Patients with B-ALL Treated with Tisagenlecleucel. *Transplant Cell Ther.* 2022 Feb;28(2):73.e1-73.e9. doi: 10.1016/j.jtct.2021.11.019. Epub 2021 Dec 4. PMID: 34875402; PMCID: PMC8816862.

conducted for safety data and has not been peer reviewed (Table 5). ESC noted the updated estimates were similar to the estimates previously provided in MSAC 1519 ADAR due to patient loss to follow up and/or study close. Estimates remained relatively stable with an increase in events around the 9-month mark for event-free survival (EFS) and 18-months for overall survival (OS) in the full analysis set (FAS) – treated population. Similar results were observed in the intention-to-treat (ITT) population.

Table 5 Summary of pooled estimates of EFS and OS (ELIANA and ENSIGN)

Month	FAS - Treated			ITT - Enrolled			
	ADAR 1519 (November 2018)	ADAR 1519 (March 2019)	ADAR 1748 (June 2023)	ADAR 1519 (November 2018)	ADAR 1519 (March 2019)	ADAR 1748 (June 2023)	
EFS							
1	86.86%	86.86%	86.81%	Not provided	72.35%	72.25%	
3	77.83%	77.88%	78.86%		70.41%	70.48%	
6	67.75%	66.97%	69.62%		62.07%	62.55%	
9	57.31%	56.50%	60.58%		52.51%	55.24%	
12	51.28%	51.88%	56.35%		44.39%	48.35%	
18	49.45%	51.88%	53.41%		43.38%	45.23%	
24	49.45%	49.62%	49.95%		41.10%	42.51%	
30	49.45%	49.62%	48.48%		41.10%	41.36%	
36	Not available	Not available	46.97%		Not available	38.89%	
42			46.97%				38.89%
48			41.47%				37.39%
54			41.47%				34.14%
60			41.47%				34.14%
OS							
1	97.03%	97.03%	97.22%	Not provided	97.02%	97.07%	
3	91.51%	91.58%	92.36%		87.35%	88.07%	
6	84.91%	85.08%	86.81%		77.09%	77.82%	
9	77.84%	78.04%	77.01%		71.06%	71.78%	
12	71.03%	71.43%	72.06%		66.31%	65.67%	
18	63.43%	64.57%	66.62%		56.59%	59.21%	
24	58.54%	59.70%	62.89%		54.02%	56.97%	
30	58.54%	55.11%	59.64%		50.84%	53.55%	
36	Not available	Not available	57.25%		Not available	49.52%	
42			56.06%				48.49%
48			51.15%				44.27%
54			49.69%				44.27%
60			47.98%				41.49%

EFS = Event Free Survival; FAS = Full Analysis Set; ITT = Intention to treat; OS = Overall Survival

Estimates are pooled from ELIANA and ENSIGN trials. The Median follow-up for the studies were 45.9 and 15.1 months, respectively. EFS was defined in trials as: The time from date of TIS infusion to the earliest of death, relapse or treatment failure

Shaded cells represent data that have been considered previously in ADAR 1519 (November 2018 and March 2019).

Source: Table 2.2-22 of MSAC 1748 ADAR+inline commentary.

The commentary compared the combined data for the three sponsored trials with the Australian registry data (ABMTRR), and six publications reporting on efficacy outcomes from four different registries and from three hospital databases. A summary of the outcomes reported for each study is provided in Table 6.

Dourthe et al (2021) was excluded from this analysis as the article had not reported the outcomes. The sponsor had provided estimates from a Kaplan Meier graph without stating how those estimates were made.

The ABMTRR data provided are from the January 2023 cut-off, as requested for the commentary. The ADAR provided ABMTRR data from the September 2022 cut-off. The 2023 estimates are censored for aHSCT or other subsequent therapy during remission, as opposed to the 2022 estimates which were not. In comparison to the earlier cut-off point, efficacy estimates decreased marginally. It is unclear whether this was due to greater precision or due to a change in the censoring conditions. The Sponsor is requested to present a pooled survival analysis for all Sponsored trials as well as the ABMTRR data.

Overall Response Rate (ORR)

Overall Response Rate (ORR) was determined from the best response observed in patients and could include complete remission (CR) or complete remission with incomplete cell count (CRi). The ABMTRR cohort reported an ORR of █% (timeframe not specified), which was █ than the reported range of █ to █% in sponsored studies, and █% to █% from real-world studies. The █ response rate from the ABMTRR may be biased because █ patients (█%) were in remission at the point of infusion of TIS¹⁰. Of these, █ patients had received bridging therapy.¹¹ It is unclear what extra clinical benefit TIS provides to these patients who are in remission (due to bridging therapy). Further, the comparison of ORR reported by the ABMTRR, sponsor studies and real-world studies is highly uncertain as the follow up period for ORR is highly-variable across studies. ELIANA reported ORR within 3 months, ENSIGN reported ORR at 6 months, whereas the ABMTRR did not specify a time period (Table 6).



Duration of Remission

Duration of Remission (DOR)¹² was not reported in the ABMTRR cohort. ELIANA reported a median duration of 46.8 months. This was longer than the duration reported in the CIBMTR of 12.3 months. Ravich et al 2022 reported 5.2 months (Table 6).

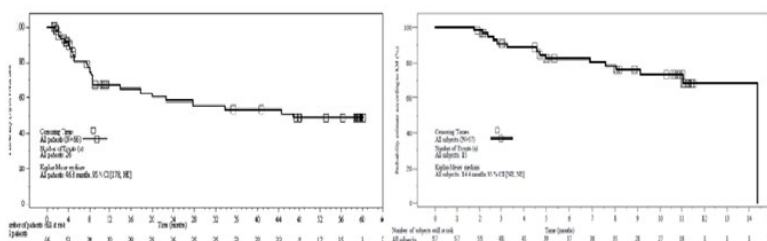


Figure 1 Kaplan Meier plots for DOR for ABMTRR (redacted) and Sponsored trials

ALL = Acute Lymphoblastic Leukemia; ABMTRR = Australian Bone Marrow Transplant Recipient Registry; DOR = Duration of Response

¹⁰ Commentary Table 13, ADAR 1748

¹¹ Additional data from Sponsor

¹² DOR is defined as: duration from the date when the response criteria of CR or CRi is first met to the date of relapse or death due to underlying cancer.

Sources, Left to right: ABMTRR (January 2023); ELIANA CSR Figure 14.2-6.1; B2001X CSR Figure 14.2-1.1;

The proportion of patients in remission at 12 months was estimated to be around [redacted] % from the ABMTRR (Jan 2023, estimated from Table 6), 67.4% in ELIANA, and 70.5% in ENSIGN. Remission rates were reported in two real-world studies: Pasquini et al (2020) reported that 60.9% of patients were in remission at 12 months, and data from PRWCC reported 12-month remission rate of 62%. The proportion of patients in remission at 24 months was [redacted] % for ABMTRR, (estimated from Table 6) and 58.4% for ELIANA. No patients in the B2001X trial were at risk at 24 months. Longer-term data from ELIANA reported that 48.9% of patients were in remission at 5 years of follow-up. However, this was determined from a small sample of patients and should be interpreted with caution. At four years of follow-up, 18 patients were at risk whereas only one patient was at risk at 60 months¹³.

Event Free Survival

Median EFS was not reached in the ABMTRR cohort, and widely varied across the published evidence. Sponsored trials reported median EFS ranging from 15.1 to 23.7 months. Real-world studies reported a range of 4.3 to 20.3 months (see Table 6).

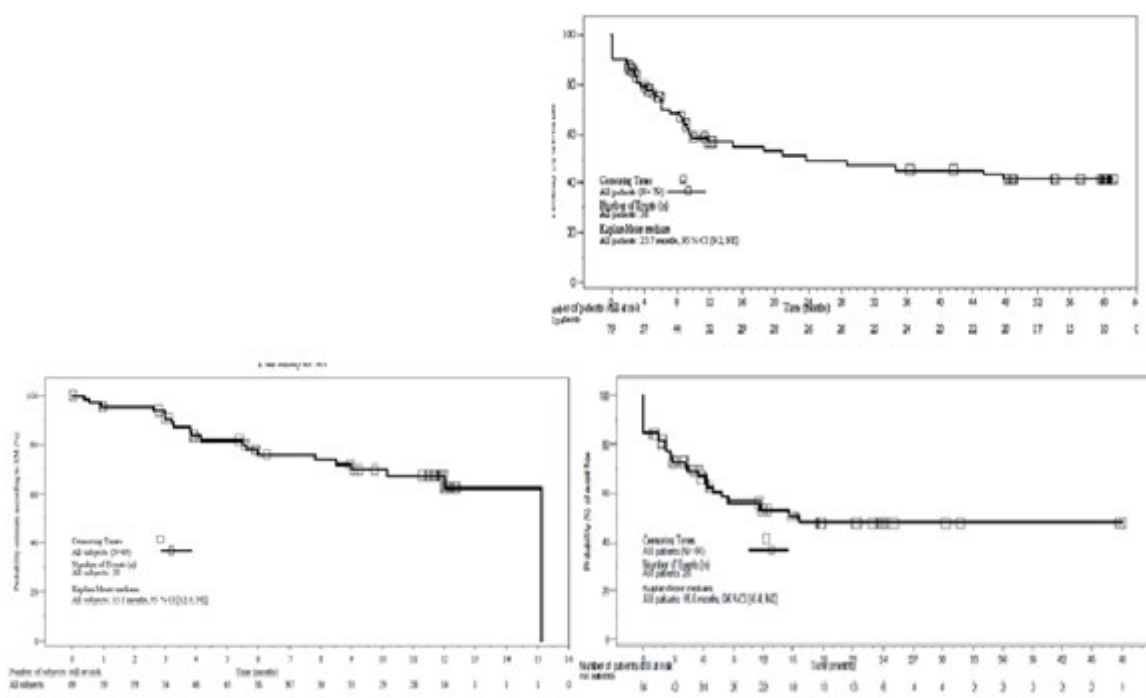


Figure 2 Kaplan Meier analysis of EFS for ABMTRR (redacted) and Sponsored trials

ALL = Acute Lymphoblastic Leukemia; ABMTRR = Australian Bone Marrow Transplant Recipient Registry; EFS = Event Free Survival; Sources top-to-bottom, left-to-right: ABMTRR (January 2023); ELIANA CSR Figure 14.2-8.1; B2001X CSR Figure: 14.2-3.1; ENSIGN CSR Figure 14.2-8.1

EFS at 12-months was estimated to be [redacted] % from the ABMTRR, 67.3% for B2001X, 57.2% for ELIANA, and 53.6% for ENSIGN. These EFS results are higher than reported for other registries such as PRWCC (50%) and CIBMTR (52.4%). EFS at 24-months was [redacted] % from the ABMTRR (estimated from Figure 2); 49.6% from ELIANA; and 47.8% from ENSIGN (Table 6). The

¹³ Figure 14.-2-6.1 document in submission

commentary noted that the method of determining EFS was variable across studies because of what constituted a “treatment failure event”.¹⁴

Overall Survival (OS)

Median OS was not reached in the ABMTRR cohort, or in any of the real-world studies. Only two clinical studies: ENSIGN and B2001X reported median OS of 29.9 and 15.1 months, respectively (Table 6).

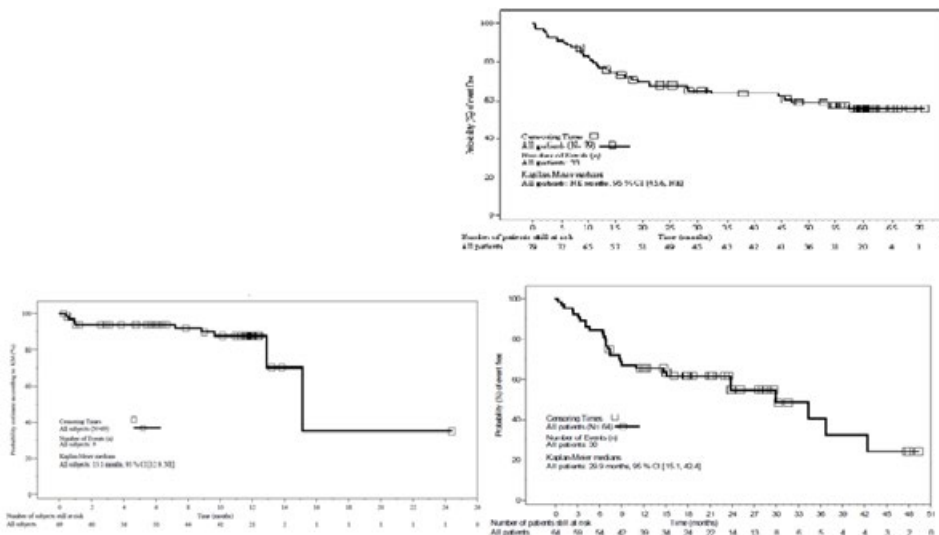


Figure 3 Kaplan Meier analysis of OS for ABMTRR and Sponsored trials

ALL = Acute Lymphoblastic Leukemia; ABMTRR = Australian Bone Marrow Transplant Recipient Registry; OS = Overall Survival
Sources top-to-bottom, left-to-right: ABMTRR (January 2023); ELIANA CSR Figure 14.2-9.1; B2001X CSR Figure: 14.2-4.2; ENSIGN CSR Figure 14.2-9.1

Overall survival (OS) at 12 months was █% from the ABMTRR, 77.1% for ELIANA, 88% for B2001X, and 65.4% for ENSIGN. This was similar to OS reported across real-world studies (Range: 72 to 84%). The notable exception to this is Ravich et al (2022) which reported a 12-month survival of 51.5%. This is likely because the study by Ravich et al (2002) was small (with low precision), and almost half of the patients had high disease burden. Overall survival at 24 months was █% from the ABMTRR (estimated from Figure 3), 67.8% from ELIANA, and 54.7% from ENSIGN. OS at 24 months in B2001X could not be estimated as there was only one person at risk. One real world study (Bader 2023) reported OS at 24 months: 53.2%, which was similar to that reported for the sponsored trials. The commentary noted that the OS analyses off the sponsored trials did not censor for aHSCT or additional treatments.

Duration of B-cell Aplasia

Duration of B-cell aplasia (DBA) was not an outcome reported in the ADAR. However, it is an outcome associated with persistence of TIS in the patient and its loss can signify imminent relapse for the patient, at which point consolidative aHSCT may be recommended. DBA was not reported across clinical trials or in the Australian Registry. However, Ghorashian et al (2022) reported a median DBA of 24.4 months and a 12 month estimate of 70%. This was similar to data from the PRWCC registry estimate of 57%.

¹⁴ Commentary Table 12 the ADAR

Table 6 Summary of the efficacy data for TIS from clinical trials and from real-world experiences

	ELIANA	ENSIGN	B2001X	ABMTRR (Sept 2022)	ABMTRR (Jan 2023)	CIBMTR Pasquini et al (2020)	PRSZT/ DRST Bader et al (2023)	PRWCC Fabrizio et al (2022), Shultz et al (2022) and Rossoff et al (2021)	JH & SJ Hosp Ravich et al (2022)	15 European Centres Ghorashian et al (2022)
<i>N</i> infused	79	64	69			255	81	185	31	35
ORR	82.3%	70.3%	82.6%			85.5%*	51.9%* (42/81)	84.3%* (156/185)	67.7%* (21/31)	88.6%* (31/35)
DOR										
Median DOR	46.8 months	Not reached	Not reached			12.3 months	NR	Not reached	5.2 months	NR
-1 year	67.4% (53.2–78.1)	70.5% (52.8–82.6)	NA			60.9% (49.4–70.5)	NR	62.0%	NR	NR
-2 year	58.4% (43.7–70.5)	62.8% (43.9–76.9)	NR			NR	NR	NR	NR	NR
-3 year	53.9% (39.2–66.5)	NR	NR			NR	NR	NR	NR	NR
-4 year	48.9% (34.1–62.1)	NR	NR			NR	NR	NR	NR	NR
-5 year	48.9% (34.1–62.1)	NR	NR			NR	NR	NR	NR	NR
EFS										
Median EFS	23.7 months	23.7 months	15.1 months			12.24 months	NR	Not reached	4.3 months	20.3 months
-1 year	57.2% (44.5–68.0)	53.6% (39.3–66.0)	67.3% (52.8–78.2)			52.4% (43.4–60.7)	NR	50.0%	35.2%	69% (47–83)
-2 year	49.6% (36.7–61.2)	47.8% (33.0–61.1)	NR			NR	45.3%	NR	NR	NR
OS										
Median OS	Not reached	29.9 months	15.1 months			Not reached	Not reached	Not reached	Not reached	Not reached
-1 year	77.1% (66.1–84.9)	65.4% (52.4–75.7)	88% (76.2–94.1)			77.2% (69.8–83.1)	NR	72.0%	51.5%	84% (64–93)

	ELIANA	ENSIGN	B2001X	ABMTRR (Sept 2022)	ABMTRR (Jan 2023)	CIBMTR Pasquini et al (2020)	PRSZT/ DRST Bader et al (2023)	PRWCC Fabrizio et al (2022), Shultz et al (2022) and Rossoff et al (2021)	JH & SJ Hosp Ravich et al (2022)	15 European Centres Ghorashian et al (2022)
<i>N infused</i>	79	64	69			255	81	185	31	35
<i>-2 year</i>	67.8% (56.1–77.0)	54.7% (39.8–67.4)	NR			NR	53.2%	NR	NR	NR
DBA										
<i>Median DBA</i>	NR	NR	NR			NR	NR	NR	NR	24.4%
<i>-1 year</i>	NR	NR	NR			NR	NR	57%	NR	70% (46–84)
<i>-2 year</i>	NR	NR	NR			NR	50.5%	NR	NR	NR

DOR, EFS, OS and DBA are presented as Kaplan Meier estimate (95% Confidence Interval). DOR and EFS were censored for SCT in ELIANA, B2001X, and ENSIGN

ORR are presented as proportion of best overall response. Values marked with * were calculated by the commentary

ABMTRR = Australian Bone Marrow Transplant Recipient Registry; aHSCT = Allogenic haematopoietic stem cell transplant; DBA = duration of B-cell aplasia; DOR = duration of response; EFS = event-free survival; NA = not applicable; NR = not reported; ORR = Overall Response Rate; OS = overall survival; PRSZT/DRST = Pediatric Registry for Stem Cell Transplantation and Cell Therapy/German Registry for Stem Cell Transplantation; PRWCC = Pediatric Real World CAR Consortium (Fabrizio et al 2022; Schultz et al 2022; Rossoff et al 2021; Moskop et al 2022 for patients under 3 years)

Source: Commentary Table 15, pg 142 of MSAC 1748 ADAR+inline commentary

Multiple TIS infusions

TIS for ALL is indicated for one infusion only. However, there are instances where patients are receiving more than one dose. Additional infusions result in increased costs to the healthcare system and patient/carer, even if the cost of additional dose is covered by the Sponsor. This is because the process of apheresis and patient care, has additional costs in resources and personnel which are not covered by the Sponsor.

Data from the ABMTRR reported that by the end of September 2022, [REDACTED] received 2 infusions and [REDACTED] received three (Table 7).

Table 7 Patients who received multiple TIS infusions

	ABMTRR	QLD	NSW	VIC
Reporting period	Up to September 2022	1st April 2019 to 28th September 2022	2020 to 30th June 2022	May 2019 to January 2023
2 infusions	[REDACTED]	<5	<5	[REDACTED]
3 infusions	[REDACTED]	<5	<5	[REDACTED]

ABMTRR = Australasian Bone Marrow Transplant Recipient Registry; NSW = New South Wales QLD = Queensland; VIC = Victoria; Source: ABMTRR report version 4, and the reviews submitted by state and territories Departments of Health (provided by Department of Health and Aged Care during the evaluation).

In the sponsored trial ENSIGN, two patients (3.1% of infused cohort) were reinfused with TIS. No further details are provided in the ADAR. Reinfusion was reported in two real-world studies. Dourthe et al (2021) reported 3.9% of the cohort was reinfused, due to loss of BCA. Patient response to second infusion was not reported. Ravich et al (2022) reported reinfusions in 12.9% of the cohort due to CD19-positive leukemia or loss of BCA (Table 11).

Across the literature, there were no safety concerns reported. However, Ravich et al (2022) reports that patients responded poorer to the second infusion than the first.

Overall, the key uncertainty across the body of evidence is whether patients underwent additional apheresis to generate the TIS product, or whether they were reinfused with cells from previously manufactured cells as the former may be associated with substantial cost.

OOS infusion

[REDACTED] (Table 8).

This was a lower proportion of OOS infusion in sponsored trials (18.8% to 11.6%). PRWCC reported similar proportion of patients receiving OOS (13% of cohort) (Table 11). Rossoff et al (2021)¹⁵ reported that no difference in efficacy was observed in patients receiving OOS product.

¹⁵ Rossoff J, Baggott C, Prabhu S, Pacenta H, Phillips CL, Stefanski H, Talano JA, Moskop A, Margossian SP, Verneris MR, Myers GD, Karras N, Brown PA, Qayed M, Hermiston M, Satwani P, Krupski C, Keating AK, Wilcox R, Rabik CA, Fabrizio VA, Kunicki M, Chinnabhandar V, Goksenin AY, Curran KJ, Mackall CL, Laetsch TW, Schultz LM. Out-of-specification tisagenlecleucel does not compromise safety or efficacy in pediatric acute lymphoblastic leukemia. *Blood*. 2021 Nov 25;138(21):2138-2142. doi: 10.1182/blood.2021012392. PMID: 34499715; PMCID: PMC8617436.

Table 8 Out of specification infusion with best observed response

	ABMTRR	VIC
Reporting period	Up to September 2022	May 2019 to January 2023
Number of patients infused with OOS tisagenlecleucel product		
Best response (n, %)		
Complete remission achieved		
Continued complete remission		
No complete remission		
Not reported		

ABMTRR = Australasian Bone Marrow Transplant Recipient Registry; OOS = out of specification; VIC = Victoria; Source: Australian Bone Marrow Transplant Recipient Registry (ABMTRR) report version 4, and the reviews submitted by state and territories Departments of Health (provided by Department of Health and Aged Care during the evaluation).

High-cost medicines

Two additional medicines are often required as part of treatment of side effects from TIS therapy: Tocilizumab and Immunoglobulin (Ig),

Tocilizumab is used for treatment and management of CRS¹⁶. Tocilizumab usage decreased from █% at up to 30 days of follow-up to █% at 30-100 days of follow-up. Duration of therapy was not provided in the ADAR (Table 9).

B cell aplasia (BCA) is an on-target, off-tumour toxicity associated with CAR-T treatment. While this outcome is a signal that CAR-T remains in the patient’s body, it can result in hypergammaglobulinemia and leaves the body at an increased risk of infection.¹⁷ █ The updated registry data supplied with the ADAR reported that as of December 2022, █% of patients with follow-up of at least a year were still receiving Ig. Duration of therapy was not reported in the ADAR. █.

¹⁶ Hill JA, Giral S, Torgerson TR, Lazarus HM. CAR-T - and a side order of IgG, to go? - Immunoglobulin replacement in patients receiving CAR-T cell therapy. Blood Rev. 2019 Nov;38:100596. doi: 10.1016/j.blre.2019.100596. Epub 2019 Aug 7. PMID: 31416717; PMCID: PMC6810871.

¹⁷ Hill JA, Giral S, Torgerson TR, Lazarus HM. CAR-T - and a side order of IgG, to go? - Immunoglobulin replacement in patients receiving CAR-T cell therapy. Blood Rev. 2019 Nov;38:100596. doi: 10.1016/j.blre.2019.100596. Epub 2019 Aug 7. PMID: 31416717; PMCID: PMC6810871.

Table 9 High-cost medicine usage up to 12 months follow-up (ABMTRR)

	September 2022	January 2023
Tocilizumab first 30 days		
Yes		
No		
Tocilizumab days 30-100		
Yes		
No		
Not reported		
Immunoglobulin first 30 days		
Yes		
No		
Not reported		
Immunoglobulin days 30-100		
Yes		
No		
Not reported		
Immunoglobulin days -1 year		
Yes		
No		
Not reported		

Results reported as n/N, %

ABMTRR = Australasian Bone Marrow Transplant Recipient Registry; n = number of patients experiencing the event; N= total number of patients; NR = Not reported

Australian Bone Marrow Transplant Recipient Registry (ABMTRR) report version 4, and additional ABMTRR data request supplied by the Sponsor.

Subsequent Stem Cell Transplant (aHSCT)

Subsequent aHSCT, post-TIS may be used in different clinical contexts. It may be used if the patient is relapsed or refractory to TIS (treatment failure). Additionally, aHSCT may be conducted during remission to increase the efficacy of TIS leading to increase relapse free survival and overall survival (consolidative aHSCT)¹⁸. However, in some cases, TIS therapy may be used as bridging treatment for aHSCT¹⁹. At this point, it is not possible to disaggregate the benefit of aHSCT from those provided by TIS.

Recent data from ABMTRR report that [redacted] ([redacted]%) patients underwent aHSCT post TIS infusion. Of those, [redacted] ([redacted]%) were planned and [redacted] ([redacted]%) were due to treatment failure. These data

¹⁸ Xu, X., Chen, S., Zhao, Z., Xiao, X., Huang, S., Huo, Z., Li, Y. and Tu, S., 2021. Consolidative hematopoietic stem cell transplantation after CD19 CAR-T cell therapy for acute lymphoblastic leukemia: a systematic review and meta-analysis. *Frontiers in oncology*, 11, p.651944.

¹⁹ Aamir S, Anwar MY, Khalid F, Khan SI, Ali MA, Khattak ZE. Systematic Review and Meta-analysis of CD19-Specific CAR-T Cell Therapy in Relapsed/Refractory Acute Lymphoblastic Leukemia in the Pediatric and Young Adult Population: Safety and Efficacy Outcomes. *Clin Lymphoma Myeloma Leuk*. 2021 Apr;21(4):e334-e347. doi: 10.1016/j.clml.2020.12.010. Epub 2020 Dec 17. PMID: 33573914.

appear substantially different in comparison to the state data provided for the commentary (Table 10).



Fewer than 5 patients treated in NSW received a transplant, however it is unclear if patients were in remission at this timepoint.²⁰

Fewer than 5 patients treated in Queensland received aHSCT. Reasons for aHSCT include relapse and early loss of BCA.²⁰

In real world studies, the proportion of patients who received aHSCT varied widely: from 2.4% to 26.3%. The larger studies (Pasquini 2020 and PRWCC) reported higher rates of 29.3% and 26.3%, respectively (Table 11).

Other Post-infusion treatments

No other post-infusion treatments were reported from the ABMTRR. Other treatments from state reports are reported in Table 10.



Patients in Queensland (<5) received immunotherapy, additional TIS infusions and salvage chemotherapy.²⁰

Table 10 Post-infusion treatments

	ABMTRR	Victoria	NSW	Queensland
	January 2023	May 2019 to January 2023	2020 – 30th June 2022	1st April 2019 to 28th September 2022
aHSCT		1 ²	<5	<5
Chemotherapy			NR	<5
Immunotherapy			NR	<5
Monoclonal antibodies (not stated)			NR	<5
Radiation ¹			NR	NR

ABMTRR = Australasian Bone Marrow Transplant Recipient Registry; aHSCT = allogenic haemopoietic stem cell transplantation; NR = not reported; NSW = New South Wales



Source: Australian Bone Marrow Transplant Recipient Registry (ABMTRR) report version 4, an additional ABMTRR data request supplied by the Sponsor, and the reviews submitted by state and territories Departments of Health (provided by Department of Health and Aged Care during the evaluation).

²⁰ This sentence has been modified to protect patient privacy.

Table 11 Treatments received by patients included in the sponsored and non-sponsored studies

	ELIANA	ENSIGN	B2001X	ABMTRR (Sept 2022)	CIBMTR Pasquini et al (2020)	AP-HP Hosp. Dourthe et al (2021)	PRSZT/ DRST Bader et al (2023)	15 European centres Ghorashian et al (2022)	PRWCC Fabrizio et al (2022) Shultz et al (2022), and Rossoff (2021)	PRWCC Moskop et al (2022)	JH & SJ Hosp Ravich et al (2022)
N infused	79	64	69		255	51	81	35	185	14	31
TIS-infusion											
Number of ALL patients infused with TIS	81.4%	85.3%	93.2%		100.0%	100.0%	100%	92.1%	92.5%	87.5%	93.9%
Dose infused- total cells x10 ⁸ (median, range)	4.5 (0.2–20.0)	Not identified	3 (0.0–10.0)		NR	NR	NR	2.3x10 ⁶ cells/kg (IQR 2.0–4.4)	1.7 10 ⁶ cells/kg (0.134–7.49)	NR	NR
Out of specification product infused (n, %)	Not identified	18.8%	11.6%		NR	NR	NR	NR	13.0%	NR	NR
Reinfusion with TIS (n, %)	Not identified	3.1%	Not identified		NR	3.9% (2/51)	NR	NR	NR	NR	12.9%
Subsequent aHSCt post-infusion for all patients who reached CR											
During remission	11.4% (8/70)	7.9% (5/45)	1.8% (1/69)		29.3% (34/116)	4.1% (2/49)	2.4% (1/42)	12.9% (4/31)	26.3% (41/156)	11.1% (1/9)	19% (4/21)

	ELIANA	ENSIGN	B2001X	ABMTRR (Sept 2022)	CIBMTR Pasquini et al (2020)	AP-HP Hosp. Dourthe et al (2021)	PRSZT/ DRST Bader et al (2023)	15 European centres Ghorashian et al (2022)	PRWCC Fabrizio et al (2022) Shultz et al (2022), and Rossoff (2021)	PRWCC Moskop et al (2022)	JH & SJ Hosp Ravich et al (2022)
N infused	79	64	69		255	51	81	35	185	14	31
During relapse	Could not be located	Could not be located	1.8% (1/69)		18.1% (21/116)	Not reported	Not reported	6.5% (2/31)	12.2% (19/156)	11.1% (1/9)	42.9% (9/21)

ABMTRR = Australasian Bone Marrow Transplant Recipient Registry; aHSCT = allogenic haematopoietic stem cell transplantation; NR = not reported; PRWCC = Pediatric Real World CAR Consortium (Fabrizio et al (2022), Schultz et al (2022), and Rossoff et al (2021); PRSZT/DRST = Pediatric Registry for Stem Cell Transplantation and Cell Therapy/German Registry for Stem Cell Transplantation

Source: Commentary Table 16, MSAC 1748 ADAR + inline commentary

TIS compared with BLN. The ADAR identified two studies that update the indirect comparison of the effectiveness of TIS and blinatumomab in paediatric r/r ALL previously presented to MSAC. The updated data were not presented in the ADAR review.

Review by the commentary found that Verneris et al. (2021) presented the results of a matched adjusted indirect comparison (MAIC) of TIS (ELIANA) and BLN (NCT01471782). The MAIC analysis found that the both the ELIANA TIS-infused and ITT cohorts exhibited a higher likelihood of CR within 3 months and a lower hazard of death over 18 months than the BLN cohort in both univariate and multivariate analyses (Table 12).

The Kaplan-Meier curves comparing the OS of the ELIANA TIS-treated cohort and the ELIANA ITT cohort with the BLN cohort are shown in Figure 4.

Table 12 MAIC results for CR and OS

Outcome	Univariate		Multivariate*	
	TIS-infused (n=79)	ITT (n=97)	TIS-infused (n=79)	ITT (n=97)
CR	OR = 8.09 (95% CI 3.76, 17.38)	OR = 3.39 (95% CI 1.78, 6.45)	OR = 9.76 (95% CI 4.09, 23.28)	OR = 3.83 (95% CI 1.88, 7.79)
OS	HR = 0.26 (95% CI 0.16, 0.43)	HR = 0.39 (95% CI 0.26, 0.60)	HR = 0.26 (95% CI 0.16, 0.45)	HR = 0.40 (95% CI 0.26, 0.63)

CR = complete remission; HR = hazard ratio; OR = odds ratio; OS = overall survival

* Adjusted for prognostic factors (differences in patient characteristics)

Source: Commentary Table 3 in the MSAC 1748 ADAR + inline commentary

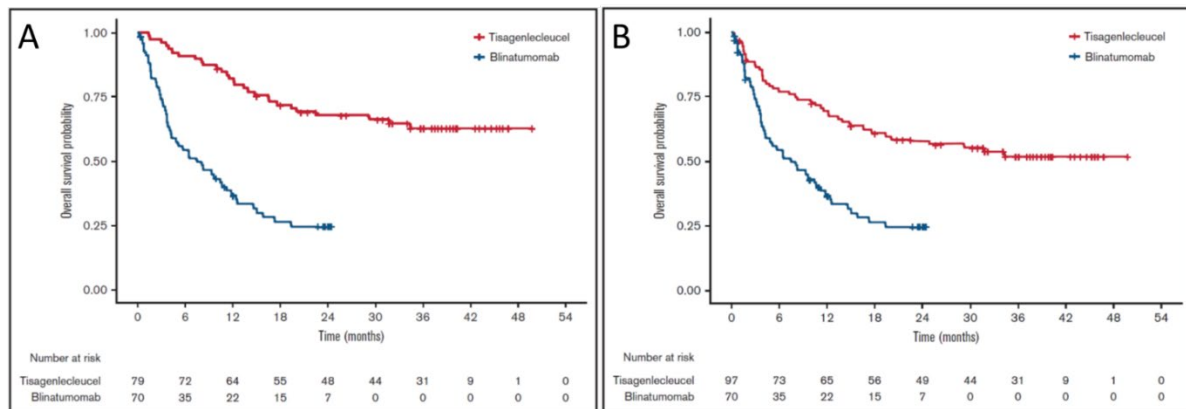


Figure 4 Kaplan-Meier curves of OS after treatment with TIS compared with BLN

The Kaplan-Meier curves showing the observed OS for the ELIANA TIS-infused cohort (A) and the ELIANA ITT cohort (B) compared with the BLN NCT01471782 cohort.

Source: Commentary Figure 1 in the MSAC 1748 ADAR + inline commentary

Clinical conclusion

The ADAR concluded that TIS continues to provide substantial clinical benefit to children and young adults with ALL, where alternative treatments may only extend survival outcomes for weeks to months. They also concluded that there were no new safety signals with longer-term follow-up.

The commentary agreed that the evidence indicates TIS provides a clinical benefit to paediatric and young adult patients with ALL. However, this conclusion should be interpreted with caution.

The ADAR did not provide an updated analysis of TIS and the comparator. The commentary noted that Blinatumomab (BLN) remains an appropriate comparator. A matched indirect comparison of

the ELIANA trial showed that patients were more likely to have a Complete response at 3 months and a lower risk of death at 18 months of follow up. It is uncertain how representative this comparison is of the bodies of evidence for TIS and BLN.

The commentary noted that there were conditions where the magnitude of clinical benefit of TIS could not be disaggregated. The first is in patients who are in remission at the point of TIS-infusion. In these cases, remission was achieved by bridging therapy. Approximately [REDACTED] % of patients from the ABMTRR were in remission at TIS-infusion, however clinical outcomes of this subgroup was not provided. It is unclear what extra benefit TIS provided these patients over their bridging therapy.

The second is in patients who are in remission when they receive aHSCT. This may be done to increase the efficacy of TIS leading to increase relapse free survival and overall survival (consolidative aHSCT). Overall, it is unclear how many patients in the ABMTRR went onto receive consolidative aHSCT. Patients who experience loss of B-cell aplasia (BCA) or changes in MRD are more likely to be recommended for consolidative aHSCT, however uptake of the procedure is dependent on patient preference. Additionally, there is a growing body of evidence of the use of TIS as a bridging treatment to aHSCT.

The commentary agreed with the ADAR that no new safety signals were identified in either the longer-term follow-up of the sponsored trials or from the available registry data. However, the commentary considered that due to the death of one patient treated with TIS in the real-world setting from haemophagocytic lymphohistiocytosis, which was only identified in the sponsored trials as a contributing factor, this should be monitored by registries to ensure it is not a cause for concern. Additionally, the long-term safety (i.e. post 3 years) for adverse events such as secondary malignancies has not yet been established and should also continue to be monitored, along with other adverse events of special interest.

13. Economic evaluation

The ADAR presented a cost-utility model in a stepwise manner, building on the original model that was the basis of MSAC's recommendation in April 2019. Prior to MSAC supporting public funding in April 2019, the economic model had been through several iterations of critiques and revisions, with significant changes made at each stage in response to the concerns raised by the MSAC.

- Step 1 (Base case): Base case model recommended by MSAC in April 2019, [REDACTED] and a single relevant comparator (BLN)
- Step 2 (Trial update): Update to Step 1, incorporating the most recent pooled results of ELIANA and ENSIGN studies, as specified in the Deed
- Step 3 (Comprehensive update): Update to Step 2, using data from the ABMTRR to estimate healthcare resource utilisation and inform the actual costs of TIS in practice. All costs were also updated to reflect 2022 list prices for services and medical products.

A lifetime horizon (88 years) is applied, with future costs and benefits discounted at a uniform annual rate of 5% per year. The computational method was unchanged from the MSAC ADAR 1519. Briefly, the ADAR 1748 model was implemented in Excel and used a cohort analysis of state partitioned survival, where the total time spent in each health state of the model was calculated from the area under/between event free survival (EFS); and/or overall (OS) curves with health states including EFS, Progressive disease (PD) and Dead.

The model employs time varying transition probabilities (derived from a series of observed and parametric survival functions and external mortality data), reflective of data from the clinical trials of and blinatumomab (BLN) and established characteristics of the respective diseases and treatments considered. Kaplan-Meier estimates of EFS and OS by month, from the update of ELIANA and ENSIGN were obtained and used as observed survival times in the economic model. Parametric survival models (lognormal used for both TIS and BLN) were then fitted to the observed data to extrapolate EFS and OS beyond the trial period.

To represent a cure the submission base case stopped the parametric extrapolation in the overall survival curve of both intervention and comparator arms at 5 years, and thereafter applied only all-cause mortality, based on age and gender specific mortality rates reported in Australian Life Tables with application of a standardised mortality rate (SMR) of 9.05 (sourced from published literature) to account for the elsewhere observed increase in all-cause mortality associated with survivors of childhood and adolescent cancer.

The application of the cure to the overall survival curve is problematic because it does not stop the ongoing transitions of patients from EFS to progressive disease over the next few decades in the model, which by definition, does not represent cure and results in (1) an over estimation of patient time in the progressive disease health state, and (2) an underestimation of patient time in the EFS health state as shown in Figure 5.

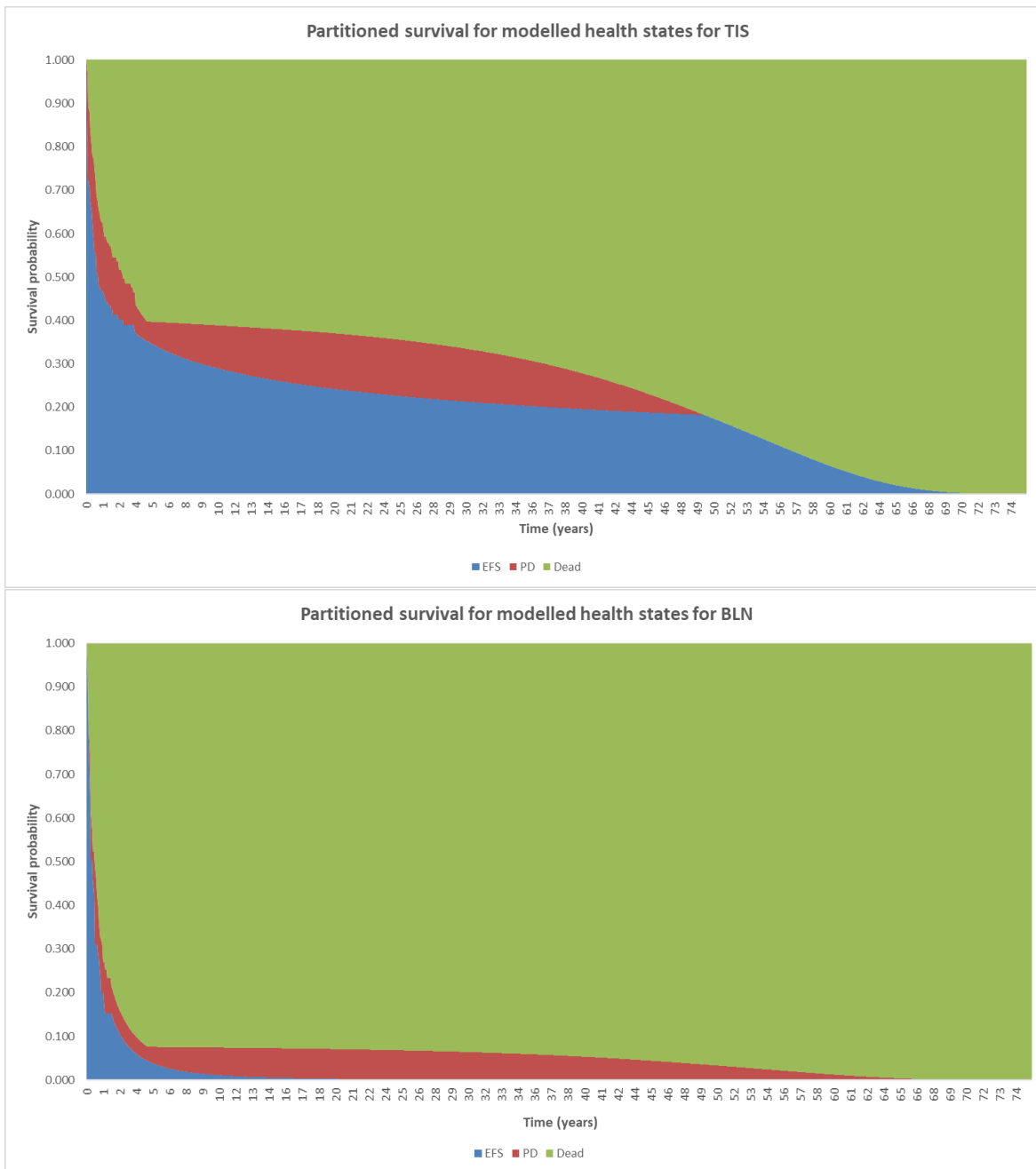


Figure 5 Modelled health states (step 3) in the economic evaluation with the cure function applied to the OS health state after 5 years (as per ADAR).

BLN = blinatumomab; TIS = tisagenlecleucel

Source: Area graphs generated using modelled traces for three health states in the partitioned survival model provided in "TIS pALL CEA (Step 3).xlsx"

Where a 'cure' assumption is reasonable, a more structurally sound approach is to apply it to the EFS curve, because it is only these patients that will be cured. This rectifies the problems identified above and improves the operational validity of the model.

The evaluation performed a number of revisions to the Step 3 model to enact the aforementioned adjustment and address some other minor issues in the model. These revisions include:

- Correcting formulas in the cost calculations for proportion of patients infused;
- Adjustment to the EFS and OS estimates to reflect reassignment of the cure function to the EFS health state; requiring conversion of the 'hard-entered' EFS estimates to be informed by live calculations reflecting;
 - stopped transitions to progression at five years; then
 - once OS drops below EFS, ensuring both curves are effectively replaced by an OS curve informed by adjusted background mortality rates (i.e. all-cause death being the appropriate and only exit from the EFS state).

If the cure function were applied to both the EFS and OS curves, the curves would run parallel and result in an implausible proportion of patients in the progressive disease state until all patients had died.

These adjustments result in operationally valid survival curves and patterns of health state membership (Figure 6). Whether the timing of the cure function at five years is the most clinically plausible approach is uncertain (alternatives are presented in the sensitivity analyses). This revised Model with Step 3 inputs was used as a respecified base case for commentary evaluations.

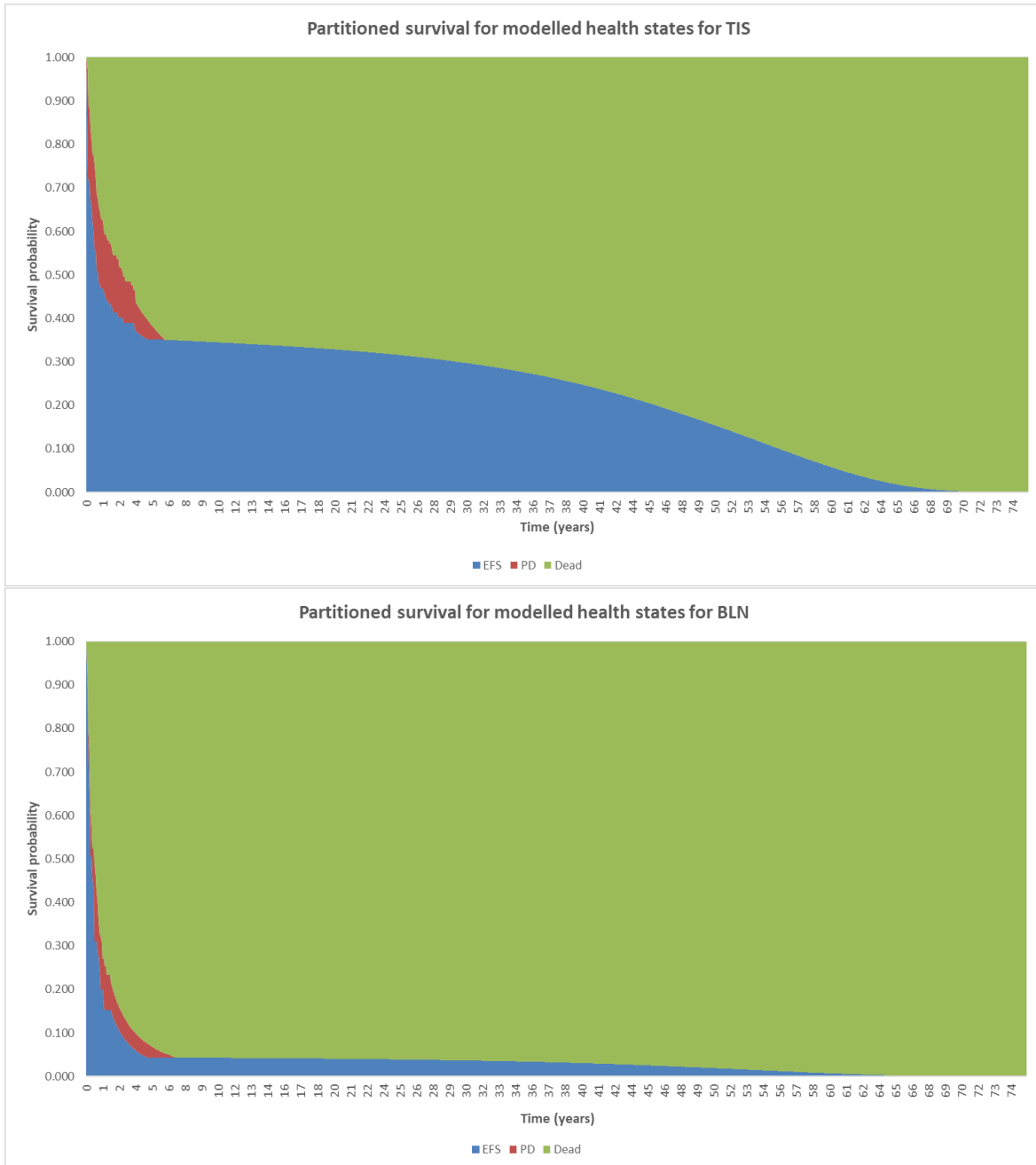


Figure 6 Modelled health states (step 3) in the economic evaluation with the cure function applied to the EFS health state after 5 years (as revised during the evaluation)

BLN = blinatumomab; EFS = event free survival; TIS = tisagenlecleucel

Source: Area graphs generated using modelled traces for three health states in the partitioned survival model provided in "TIS pALL CEA (Step 3)- Critique May 2023 -ADAR base case with Technical corrections.xlsx"

The key elements of the economic evaluation are summarised in Table 13.

Table 13 Summary of the economic evaluation

Component	Description	Commentary
Intervention	Single episode of TIS treatment with curative intent	According to ABMTRR report, █% of the patients had more than one infusion for TIS. It is unclear whether the effectiveness data for these patients were excluded from the analysis or not.
Comparator	BLN +/- SCT;	This was accepted as a valid comparator in the MSAC ADAR 1519 and remains a relevant comparator in the current context.
Perspective	Australian healthcare system	As per the guidelines
Type of evaluation	Cost utility analysis	Appropriate
Sources of evidence	Naïve indirect comparison from single arm trials	The base case (step 1) continues to be informed by a naïve indirect comparison of results from the pooled ELIANA and ENSIGN trials with those of the von Stackelberg (2016) ²¹ study of BLN. Step 2 incorporates the most recent pooled results of ELIANA (September 2021) and ENSIGN (May 2019) studies. Step 3 substitutes some of the inputs with ABMTRR data.
Methods used	Three-state partitioned survival analysis	Unchanged from the MSAC ADAR 1519
Health states	Event Free Survival; Progressive Disease; Dead	Unchanged from the MSAC ADAR 1519 Primary analyses of EFS were censored for aHSCT or new treatment, however it is unclear whether the subsequent dose of TIS (TIS reinfusion) was considered as an event or censoring point or not. OS was not censored for aHSCT or new treatment. The submission applied a cure assumption to the OS curve (effectively distributing the cure between EFS and PD health states) which is not appropriate, therefore the revisions conducted during evaluation adjust the model to apply cure at 5 years to the EFS health state only. Further detail described in 'Transition probabilities'.
Time horizon	Lifetime: 88 years	Although theoretically the lifetime time horizon is reasonable, the actual duration of the lifetime depends on the extrapolation methods. Due to immaturity of survival data from the TIS trials and ABMTRR report, there is considerable uncertainty around whether the extrapolation is accurate and the uncertainty and implications of this increase as the modelled time horizon is increased.
Cycle length	One month (30.44 days)	Unchanged from the MSAC ADAR 1519 and reasonable
Discount rate	5% annual for costs and outcomes	(Appropriate as per the guidelines)
Transition probabilities	Implicit based on analyses of EFS and OS	Step 2 and Step 3 use updated pooled results from ELIANA and ENSIGN. Step 3 did not

²¹ von Stackelberg, A, Locatelli, F, Zugmaier, G, Handgretinger, R, Trippett, TM, Rizzari, C, Bader, P, O'Brien, MM, Brethon, B, Bhojwani, D, Schlegel, PG, Borkhardt, A, Rheingold, SR, Cooper, TM, Zwaan, CM, Barnette, P, Messina, C, Michel, G, DuBois, SG, Hu, K, Zhu, M, Whitlock, JA & Gore, L 2016, 'Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia', J Clin Oncol, vol. 34, no. 36, Dec 20, pp. 4381-4389.

Component	Description	Commentary
		<p>update EFS and OS as observed in ABMTRR may be due to small number of patients and limited follow-up compared with trial results.</p> <p>Estimated EFS and OS are slightly higher with the updated pooled results of ELIANA and ENSIGN compared with the previous model in MSAC ADAR 1519.</p> <p>The ADAR extrapolates ongoing transitions from EFS to PD throughout the model, despite the intention to invoke an assumption of 'cure' at five years. The ADAR applies the 'cure' to the OS transitions – reverting them to an adjusted background mortality rather than an extrapolated curve at five years. The commentary revisions include stopping the EFS to PD transitions at 5 years to reflect the cure assumption, and then from where the EFS and OS curves intersect applying a single OS curve with transitions based on adjusted background mortality.</p>
Resource use and Cost	<p>Step 1 and Step 2 model informed by resource usage in trial and costs sourced from Australian public hospital reports and literature.</p> <p>Step 3 model updates some resource use as interpreted from ABMTRR data and costs are updated to 2022 AUD</p>	<p>Resource used is considerably lower than ABMTRR data reports in Step 3, due to incomplete reporting of clinical management, related hospital admissions and other downstream treatments.</p> <p>Total resource use or costs following TIS infusion (excluding cost of TIS) are substantially lower in the model than costs realised in the Australian clinical practice.</p>
Software	Microsoft Excel	Unchanged

ABMTRR = Australian Bone Marrow Transplant Recipient Registry; ADAR = Applicant Developed Assessment Report; AUD = Australian dollar; BLN = blinatumomab; EFS = event free survival; MSAC = Medical Services Advisory Committee; NHCCDC = National Health Cost Data Collection; OS = overall survival; TIS = tisagenlecleucel

Source: Table 3.1-1, pg 165 of MSAC 1748 ADAR+inline commentary

EFS analyses were censored in ELIANA and ENSIGN studies at the time that another anticancer therapy commenced, usually aHSCT. It is unclear how EFS analysis incorporated subsequent TIS re-infusion, whether it was considered as an event or censoring point or not analysed. The ABMTRR report (September 2022) did not specify how patients were censored for the estimation of EFS and OS. Step 2 and Step 3 of the economic model use updated pooled results from ELIANA and ENSIGN. Step 3 did not update EFS and OS as observed in ABMTRR may be due to small number of patients and limited follow-up compared with trial results. Estimated EFS and OS are slightly higher with the updated pooled results of ELIANA and ENSIGN compared with the previous model in MSAC ADAR 1519.

The “Health states” costs for both arms are assumed to be “ongoing”, \$773 and \$5,784 per cycle (month) for PFS and PD health states respectively and were based on a UK study²² which may not

²² Muszbek, N., A. Kadambi, T. Lanitis, A. J. Hatswell, D. Patel, L. Wang, J. W. Singer and R. Pettengell (2016). "The Cost-effectiveness of Pixantrone for Third/Fourth-line Treatment of Aggressive Non-Hodgkin's Lymphoma." Clin Ther 38(3): 503-515.

be applicable to the Australian settings. This issue was raised in the commentary to the revisions made to ADAR 1519 (March 2019)²³.

■■■■, therefore, the average cost applied in Step 3 appears appropriate.

A summary of the key parameters applied to each step of the economic valuation is presented in Table 14.

Table 14 Key parameter summary for each step of the economic evaluation

	Step 1		Step 2		Step 3	
	(Base case)		(Trial update)		(Comprehensive update)	
Cohort characteristics						
Cohort age (years)	12		12		13	
Proportion female	43.0%		43.0%		40.0%	
Average BSA (m ²)	1.20		1.20		1.20 ¹	
Average weight (kg)	41.90		41.90		41.90 ¹	
Survival data and extrapolation approach						
OS/EFS Data source	ELIANA (April 2018) & ENSIGN (Oct 2017)		ELIANA (Sept 2021) & ENSIGN (May 2019)		ELIANA (Sept 2021) & ENSIGN (May 2019) SMR applied to ABS mortality rates from year 5	
Extrapolation point	24 months		48 months		48 months (SMR applied to ABS mortality rates from year 5)	
Extrapolation models (OS / EFS)	Lognormal / Lognormal		Lognormal / Lognormal		Lognormal / Lognormal	
Healthcare costs						
TIS infused average						
Infused, %	80.6%		81.44%		81.44% ¹	
TIS administration	Utilisation		Utilisation		Utilisation	
	Item cost		Item cost		Item cost	
Leukapheresis	100.0%		100.0%			
	\$5,635		\$5,635		\$6,296	

²³ Source: "13. 1519 – Assessment group critique of additional data_Final.docx"

	Step 1 (Base case)		Step 2 (Trial update)		Step 3 (Comprehensive update)	
Bridging chemotherapy	86.7%	\$1,165	86.7%	\$1,165		\$1,213
Bridging therapy admin.	86.7%	\$468	86.7%	\$468		\$430
Lymphodepleting chemotherapy (LDC)	96.0%	\$660	96.0%	\$660		\$671
LDC Inpatient admin.	65.3%	\$2,040	65.3%	\$2,040		\$1,901
LDC outpatient admin.	34.7%	\$468	34.7%	\$468		\$430
TIS Inpatient admin.	94.7%	\$2,040	94.7%	\$2,040		\$1,901
TIS Outpatient admin.	5.3%	\$468	5.3%	\$468		\$430
ICU for CRS	48.1%	\$4,800	48.1%	\$4,800		\$5,057
Tocilizumab for CRS	39.2%	\$448	39.2%	\$448		\$340
Subsequent SCT	19.0%	\$227,286	19.0%	\$227,286		\$290,695
Other serious AEs	89.9%	\$2,040	89.9%	\$2,040		\$1,901
Average per infused	\$171,787		\$171,787			
Average per enrolled	\$171,123		\$171,123			
BLN	Utilisation	Item cost	Utilisation	Item cost	Utilisation	Item cost
Blinatumomab	100%	\$73,666	100%	\$73,666	100%	\$65,480
Inpatient admin.	100%	\$2,040	100%	\$2,040	100%	\$1,901
Outpatient admin.	100%	\$468	100%	\$468	100%	\$430
ICU for CRS	5.7%	\$4,800	5.7%	\$4,800	5.7%	\$5,057
Tocilizumab for CRS	5.7%	\$448	5.7%	\$448	5.7%	\$340
Subsequent SCT	34.3%	\$227,286	34.3%	\$227,286	34.3%	\$290,695
Other serious AEs	87.1%	\$2,040	87.1%	\$2,040	87.1%	\$1,901
Average per patient	\$186,096		\$186,096		\$197,670	
IVIG	TIS	BLN	TIS	BLN	TIS	BLN
Proportion of use	88%	30%	88%	30%	88%	30%
Acquisition cost	\$943	\$943	\$943	\$943	\$1,152	\$1,152
Administration cost	\$468	\$468	\$468	\$468	\$430	\$430
Average monthly cost	\$1,242	\$423	\$1,242	\$423	\$917.71	\$474.68

	Step 1 (Base case)		Step 2 (Trial update)		Step 3 (Comprehensive update)	
	Mean duration, months	36.00	36.00	36.00	36.00	36.00 ¹

ABMTRR = Australian Bone Marrow Transplant Recipient Registry; ABS = Australian Bureau of Statistics; ADAR = Applicant Developed Assessment Report; AE = adverse event; AUD = Australian dollar; BLN = blinatumomab; CRS = cytokine release syndrome; EFS = event free survival; ICU = intensive care unit; IVlg = intravenous immunoglobulin; LCD = Lymphodepleting chemotherapy; MSAC = Medical Services Advisory Committee; NHCDC = National Health Cost Data Collection; OS = overall survival; SCT = stem cell transplant; TIS = tisagenlecleucel

Source: Table 3.21, MSAC ADAR 1748+inline commentary

Note: Other inputs (Health state costs, utility weights, long term SMR): Unchanged from resubmission base case

¹Sourced from ELIANA as ABMTRR data were unavailable.

²As a percentage of CRS patients

Shaded cells represent model inputs updated in Step 3 based on interpretation of ABMTRR data and costs updated to 2022.

Specific inputs of uncertainty identified in the updated revised base case (Step 3) during the evaluation are discussed below:

- The economic model did not explicitly model the costs of salvage therapy or supportive therapy after TIS failure. However, the EFS and PD health state costs include treatment costs after progression on treatment (\$773 and \$5,784 respectively). While this implicitly includes some costs after treatment failure, whether this accuracy captures salvage or support therapy after failure is uncertain. This is an insufficiently transparent approach to modelling post-TIS costs resulting in concern regarding the accuracy of the modelled cost inputs and outputs associated with EFS and PFS.
- ICU for CRS: Step 3 reduced the estimated ICU admission rate from 48.1% observed in the studies to █%, based on the ABMTRR report that identified █/█ patients as using ICU between days 1-30. However, this is likely to be an underestimate; data on Day 1-30 ICU use is only reported for on █ patients, equating to a █% admission rate (█/█) with additional data for 31-100 days. This is likely to increase over an observation period equivalent to the clinical study. Until more data are available, the Step 1 and 2 estimates may be more appropriate.
- Tocilizumab for CRS: Step 3 uses an estimate of 29%, however during the evaluation ABMTRR data indicated that █/█ (i.e. █%) of TIS patients received tocilizumab.
- The proportion of patients undergoing subsequent aHSCT were estimated based on ELIANA (April 2017) to be 19% in step 1 and step 2 of the model. The ABMTRR data reported only █% (█ patients) had pre-planned aHSCT; this was interpreted by the ADAR to represent the total number of patients who had subsequent aHSCT and applied as an updated model input (replacing the study estimate of 19%) in Step 3. However, clarification received during the Evaluation and data from State hospitals indicated the actual aHSCT rates following TIS were probably closer to 31% (█)²⁴.
- Ig usage: Duration of treatment with Ig post TIS is assumed to be 36 months in the model (Step 3 is unchanged). █ Over an extended time horizon, the modelled estimate of an average duration of 36 months Ig therapy may be an underestimate. The costs for IVlg were described as being administered every 4 weeks, however the model applies these 4-weekly costs to monthly cycles. This approach will slightly underestimate the costs associated with IVlg.

²⁴ ABMTRR has data on ### (█%) patients reported as having subsequent SCT, however this appears likely to rise with longer follow-up. █ NSW reported <5/13 (8%) patients treated at NSW had a subsequent aHSCT. Queensland reported █/█ (50%) patients treated in Queensland had a subsequent aHSCT. This indicates approximately 31-35% (16-18 out of 52) of patients had, or are planned to have, aHSCT, in the available follow-up period.

- All patients in the model are assumed to receive one infusion of TIS. ABMTRR data indicated that around █% of the patients had more than one TIS infusion. Although, █ other adjunctive hospital costs would still be incurred by the patients and state health.
- A simplified approach has been taken with respect to costing adverse events (AE), which assumes all patients experiencing at least one Grade 3/4 AE were admitted to hospital for an average of one week. This simplified approach takes no account of different time-courses of adverse events and the possibility of multiple admissions per patient for different adverse events, or the increased management required for concurrent adverse events.

There remain some uncertainties regarding the true cost of providing CAR-T therapy in Australia, with large variations in costs observed between patients. Table 15 provides comparison of estimates used in the Step 3 -comprehensive update of the economic evaluation and data provided by states Departments of Health. Costs have been provided as averages and ranges to account for the significant variation between patients. Of note, there may be inconsistencies in how the activity-based cost is captured and coded for these patients. NSW Health advised that the Diagnosis Related Group (DRG) changes for this therapy depend on how the coding is initially approached (e.g., by location of tumour). This inconsistency will likely impact the quality of the data for these high-cost therapy reviews. Additionally, the focus of treatment and monitoring has been on the first-year post-transplant in line with the contract arrangements. Complications beyond 1 year are yet to be understood. CAR T-cell therapies are genetically modified cells and patients are required to be followed up for 15 years as part of post market pharmacovigilance. Travel and accommodation arrangements for patients coming from other regions requires significant ongoing resourcing. There are long-term issues supporting access to subcutaneous immunoglobulin (SCIg) replacement, and the necessary equipment and materials (NSW Health submission).

Table 15 Comparison of estimates used in the model Step 3 -comprehensive update with data provided by states Departments of Health

	Previous ADAR (1519) (N= 74)	Current ADAR (1748) (N= 55 for ABMTRR)	Victoria (N= 35)	NSW (N=15)	Queensland (N=<5)
Reporting period	ENSIGN and ELIANA (data cut-off April 2017)	ABMTRR report up to September 2022	May 2019 to January 2023	2020 – 30th June 2022	1st April 2019 to 28th September 2022
Infusion admission cost	\$58,624	\$53,679		NR	
Average total inpatient and outpatient costs	-	-		NR	
Average program cost (excluding TIS product cost)	\$171,123	\$132,791		\$371,000 and the range is \$215,000 – \$1,730,000	\$458,584
Average program cost (including TIS product cost)	\$█ for the enrolled and \$█ for the infused	\$█ for the enrolled and \$█ for the infused	\$█ (range \$█ to \$█)	\$█ and the range is \$█ - \$█.	NR* *equates to \$█ if average TIS cost added.
<i>(average program cost used in Commentary: \$)</i>					
Additional treatment post CAR-T infusion (CAR-T reinfusion, BLN, aHSCT, inotuzumab, chemotherapy)	Blinatumomab (BLN) in the non-infused. Fixed ongoing cost per moth applied to the health states, EFS: \$773 and PD: \$5,784	Blinatumomab (BLN) in the non-infused. Fixed ongoing cost per moth applied to the health states, EFS: \$773 and PD: \$5,784		Other immunotherapies (BLN, inotuzumab) may be used to achieve remission. Usage not provided.	<5 TIS re-infusion and <5 SCTs, details for use of other immunotherapies not provided
Subsequent TIS doses	Not modelled	Not modelled		<5 patients have had a subsequent CAR-T infusion, <5 patients had 2 subsequent infusions	<5 patient had a subsequent reinfusion
Subsequent SCT	19% (based on ELIANA April 2017 data cut-off)			<5 (time period not reported)	<5 (time period not reported) <5 was performed for relapse and <5 was performed pre-emptively for early loss of B cell aplasia
Average cost of SCT	\$227,286	\$290,695		NR	Cost of this treatment is highly variable depends on patient's length of stay, observed range \$175,000 to \$421,000
Tocilizumab	5.7%	█%		47% received tocilizumab	NR

	Previous ADAR (1519) (N= 74)	Current ADAR (1748) (N= 55 for ABMTRR)	Victoria (N= 35)	NSW (N=15)	Queensland (N=<5)
	Average cost per patient \$43	Average cost per patient \$█		Cost not reported.	
Immunoglobulin (Ig) usage and treatment duration	88% receive Ig for 36 months	█% receive Ig for 36 months		9 out of 13 patients receiving Ig post infusion.	25% of patients receiving Ig post infusion. No comments provided on duration of treatment
Reported Immunoglobulin costs (product and/or administration)	\$█ (annual cost of Ig predicted in the first year of the costs traces in the model). Assumed duration of treatment: █ months			Estimated cost varied (dependent on the other procedures) with a range between \$3,000-\$10,000. <i>These data are not reflective of the total Ig cost for each patient. This data is only inclusive of costs at the NSW Health TIS treatment sites; and not ongoing Ig administered by the local hospital/referral centre in NSW and/or interstate</i>	The average cost of SCIg treatments, including product cost, same-day admission, and associated outpatient appointment is around \$6,500 <i>Duration of treatment captured in this cost is unknown</i>

ADAR = Applicant Developed Assessment Report; BLN = Blinatumomab; Immunoglobulin = Ig; EFS = event free survival; NR = not reported; PD = progressive disease; SCT = stem cell transplant; TIS = tisagenlecleucel

Source: Table constructed during the evaluation using data from "TIS pALL CEA (Step 3).xlsx", Australian Bone Marrow Transplant Recipient Registry (ABMTRR) report version 4, and the reviews submitted by state and territories Departments of Health (provided by Department of Health and Aged Care during the evaluation).

Shaded cells represent data previously seen by MSAC (ADAR 1519)

As shown in the Table 15, healthcare resource utilisation and costs are substantially underestimated in the updated model. ABMTRR data reported that █ patients had a planned aHSCT which was interpreted incorrectly as number of patients who had subsequent aHSCT in the model update. Actual number of patients having subsequent aHSCT is much higher and is observed to be rising with longer follow-up. █. NSW Health reported <5/13 patients treated at NSW had a subsequent aHSCT. Queensland Health reported approximately half of patients treated in Queensland had a subsequent aHSCT. This indicates approximately 31-35% (16-18 out of 52) patients had/planned to have aHSCT so far in the follow-up period.

There is considerable uncertainty around the cost estimates based on the Australian data for TIS patients as (i) the data are aggregated and it is unclear exactly what resources are captured or the duration of the data collection, (ii) the patient numbers are still relatively small and there is large variability in resource use and (iii) there is no comparative equivalent source of data to inform the comparator arm of the model.

Average cost per patient (including cost of TIS) was approximately \$ [REDACTED] for patients treated at NSW (N=13) and [REDACTED]. Average cost per patient (excluding cost of TIS) was around \$459,000 for <5 patients treated at Queensland Children Hospital, which would be closer to the average cost reported by NSW and [REDACTED] when average cost of TIS (\$ [REDACTED]) is added to this (~\$ [REDACTED]).

Data provided by the three states clearly indicate that the costs adjunctive to TIS program are significantly underestimated in the updated model. These high costs may be attributed to the various treatment steps and associated inpatient and outpatient episodes involved for TIS infusion, complex adverse event profile and management of these patients, and subsequent re-infusion of TIS or other treatment and/or aHSCt. The possibility of late onset, severe and expensive adverse effects also could not be excluded given the preliminary nature of the clinical evidence provided and small number of patients enrolled in the program.

IVIg usage: Duration of treatment with Ig post receiving TIS is assumed to be 36 months in the model (unchanged from the previous version of the model). [REDACTED]

Results

A summary of discounted results of the three steps of the revised models as estimated in ADAR is provided in Table 16.

Table 16 Summary of discounted results of the stepped evaluation

Results presented in ADAR 1748									
	STEP 1 - Base case			STEP 2 - Trial update			STEP 3 – Comp. update		
	TIS	BLN	INCR.	TIS	BLN	INCR.	TIS	BLN	INCR.
Cost	[REDACTED]	\$283,812	\$ [REDACTED]	[REDACTED]	\$283,795	[REDACTED]	[REDACTED]	\$283,795	[REDACTED]
LYs	7.450	2.250	5.200	8.042	2.250	5.792	7.990	2.240	5.750
QALYs	4.972	1.269	3.703	5.335	1.269	4.066	5.395	1.264	4.131
Cost/ QALY	[REDACTED]								
Results obtained with revised application of cure and calculation corrections applied during the evaluation ^{1, 2}									
	STEP 1 - Base case			STEP 2 - Trial update			STEP 3 – Comp. update		
	TIS	BLN	INCR.	TIS	BLN	INCR.	TIS	BLN	INCR.
Cost	[REDACTED]	\$283,812	[REDACTED]	[REDACTED]	\$283,795	[REDACTED]	[REDACTED]	\$239,072	[REDACTED]
LYs	7.450	2.250	5.200	8.042	2.250	5.792	7.409	1.829	5.580
QALYs	4.972	1.269	3.703	5.335	1.269	4.066	5.241	1.130	4.110
Cost/ QALY	[REDACTED]								

BLN = blinatumomab; INCR = increment; Life year = life year; QALY = quality adjusted life year; TIS = tisagenlecleucel

Source: Table 3.3-1 of the MSAC 1748 ADAR+inline commentary and "TIS pALL CEA (Step 3)- Critique May 2023 -ADAR base case with Technical corrections.xlsx"

¹ Fixing incorrect formulas in the cost calculations for proportion of patients infused (Step 1–3),

² Revisions were made to the Step 3 model to apply the cure function to the EFS health state rather than the OS curve, by stopping further transitions to progression at five years. These include: hard-entered EFS estimates were converted to live calculations to prevent the proportion of patients in the EFS state to be higher than the proportion of OS.

Step 1 of the analysis was the basis of MSAC’s recommendation in April 2019 and the results of this analysis remain unchanged. Step 2 used the latest pooled data for ELIANA and ENSIGN, extending the duration of observed EFS and OS from 24 months to 48 months. There was a small reduction in the ICER to \$ [REDACTED] per QALY due to slight increase in QALYs associated with TIS.

In Step 3, updates to healthcare resource utilisation using ABMTRR data and updated 2022 PBS, MBS and hospital costs were used. These changes resulted in a reduction in the lifetime treatment costs primarily driven by lower percentage of subsequent aHSCTs interpreted by the ADAR from ABMTRR data. Step 3 also included [REDACTED]. These changes indicated a reduction in the discounted ICER from the original \$ [REDACTED] per QALY (Step 1) to \$ [REDACTED] per QALY (Step 3).

Estimated revised ICER in Step 3 (updated using ABMTRR data) of the economic evaluation are lower than previously estimated, however this is due to multiple underestimations of resource use and costs in the intervention arm. Although a higher-than-expected EFS and OS benefits for TIS were observed in the Australian data, this is likely confounded, since several patients had additional subsequent treatments, and it is likely that the remission [REDACTED] was due to subsequent treatment in these patients. Also, as discussed earlier, the implementation of cure in the ADAR model was problematic and revisions were made to the Step 3 model to rectify this issue, and the Commentary-revised model was used for the sensitivity analyses presented below.

Univariate and multivariate sensitivity analyses are presented in Table 17 to highlight some of the uncertainties associated with the model inputs. The alternative input values presented in the table below are all plausible, and shaded inputs represent preferred estimates of input values identified during the Commentary. The ICER is sensitive to the program costs and proportion of patients receiving aHSCT.

Table 17 Sensitivity analysis using Step 3- comprehensive update model as base case¹

	Increment in cost	Increment in QALYs	Cost/QALY	%change
ADAR base case (Step 3)		4.131		
Commentary base case (Step 3 after structural and technical corrections in the model)¹		4.110		
Proportion of enrolled patients who had successful infusion (base case: [REDACTED]%)				
Weighted data based on MSAC quarterly report: [REDACTED]%		4.110		+9%
Collated State hospital data: 100% ⁵		4.110		+17%
Subsequent aHSCT (ADAR estimate: [REDACTED]%)				
ABMTRR clarification: [REDACTED]%		4.019		+14%
Collated State Hospital data: 31%		3.957		+24%
Program costs, excluding TIS product cost and IVIg cost (base case: \$132,865)				
Infused ([REDACTED] %): cost \$457,656 ⁴ , non-infused ([REDACTED] %): cost \$ [REDACTED] ²		4.110		+98%
Infused ([REDACTED] %): cost \$457,656 ⁴ , non-infused ([REDACTED] %): cost \$207,027 ²		4.110		+108%
Infused (100%): \$457,656 ⁴		4.110		+119%
Multivariate analysis³				
Infused: [REDACTED]%, subsequent aHSCT: [REDACTED]%, non-infused costs: \$ [REDACTED], infused program cost: \$457,656		4.019		+113%
Infused: [REDACTED]%, subsequent aHSCT: 31%, non-infused costs: \$ [REDACTED], infused program cost: \$457,656		3.957		+116%

	Increment in cost	Increment in QALYs	Cost/QALY	%change
ADAR base case (Step 3)		4.131		
Commentary base case (Step 3 after structural and technical corrections in the model)¹		4.110		
Infused: █%, subsequent SCT: 31%, non-infused costs: \$█, infused program cost: \$457,656, TIS cost: \$█		3.957		+108%
Infused: █%, subsequent SCT: 31%, non-infused costs: \$█, infused program cost: \$457,656, TIS cost: \$█		3.957		+26%
Infused: █%, subsequent aHSCT: 20%, infused program cost: \$457,656		4.019		+124%
Infused: █%, subsequent aHSCT: 31%, infused program cost: \$457,656		3.957		+128%
Infused: █%, subsequent aHSCT: 31%, infused program cost: \$457,656; TIS cost: \$█		3.957		+119%

aHSCT = allogenic haemopoietic stem cell transplant; QALY = quality adjusted life year; TIS = tisagenlecleucel

¹ Revisions were made to the Step 3 model to apply the cure function to the EFS health state rather than the OS curve, by stopping further transitions to progression at five years. These include; hard-entered EFS estimates were converted to live calculations to prevent the proportion of patients in the EFS state to be higher than the proportion of OS.

² According to MSAC Quarterly report █ patients who were registered did not receive TIS infusion. Of these █ patients had unsuccessful infusion. For these patients (█%) costs included are for apheresis + bridging therapy + lymphodepleting chemotherapy+ salvage chemotherapy regimen. █ had the order cancelled. Therefore, cost for █% non-infused include apheresis + SCR.

³ costs of aHSCT in these multivariate analyses are overridden by blanket program costs. Only utility calculations differ here.

⁴ Average cost per patient (including cost of TIS) was approximately \$█ for patients treated at NSW (N=13) and Victoria for (N= 35). It is assumed that this cost includes the inpatient/outpatient admissions related to IVIg. Average cost of TIS in the updated Step 3 was \$█. The modelled cost for first 12 months of IVIg treatment is \$█. The average adjunctive cost (excluding cost of TIS and IVIg) is estimated by subtracting IVIg and TIS costs from the average cost per patient reported by state hospitals (\$█- \$█- \$█= \$457,656).

⁵ ABMTRR and States data indicated that the infusion rate in Australian cohort was 100%, however the analysis of MSAC Quarterly Report indicated that █ patients who were registered did not receive TIS infusion.

⁶ The cost of TIS would be \$█ if the MSAC wanted to retain the same ICER as when previously recommended (ADAR 1519 April 2019) i.e. \$█cost/QALY using modelling corrections and respecifications.

Shaded rows represent preferred inputs for a respecified case.

Compiled for commentary using "TIS pALL CEA (Step 3).xlsx" and data provided by Department of Health and Aged Care (MSAC Quarterly report, ABMTRR report, and state and territories Health review reports). The corrected model is provided as an attachment to the commentary (TIS pALL CEA (Step 3)- Critique May 2023 -ADAR base case with Technical corrections.xlsx)

The sensitivity analyses do not explore the full range (i.e upper and lower bounds) of plausible values for the various uncertain inputs, therefore the sensitivity analysis presented above does not capture the full extent of the uncertainty around the ICER.

Additional sensitivity analyses were performed to assess the impact of changing TIS price in the respecified model on ICERs. The cost of TIS would need to be \$█ if the MSAC wanted to retain the same ICER as when previously recommended (ADAR 1519 April 2019) i.e. █cost/QALY.

Figure 7 Impact of TIS price on incremental cost per QALY gained (ICER) in the commentary respecified model (figure redacted)

Source: Constructed during the evaluation using "TIS pALL CEA (Step 3)- Commentary base case with technical corrections and respecified inputs.xlsx"

Conclusion

The model provided in the current ADAR was previously accepted by MSAC in April 2019. Model validation checks and the assessment of the extrapolated curves were not provided in ADAR 1748. Further investigations into the modelled curves and model traces during this commentary identified inconsistencies and clinical implausibility associated with the application of the cure assumption in the modelled survival estimates. Model (Step 3) was revised during the evaluation to fix some of these technical and structural issues.

The ADAR estimated revised ICER in Step 3 (updated using ABMTRR data) of the economic evaluation are lower than previously estimated. The commentary considered the ICER to likely be significantly underestimated since the economic evaluation appeared to substantially underestimate the costs of other health resources used alongside TIS therapy. Cost data provided by states (NSW, [REDACTED], QLD) indicated that the cost associated with TIS program are much higher (approximately \$[REDACTED] per patient treated). These high costs may be attributed to the various treatment steps and associated inpatient and outpatient episodes involved for TIS infusion, complex adverse event profile and management of these patients, and subsequent re-infusion of TIS ([REDACTED]% as per ABMTRR data) or other treatment and/or aHSCT (31% according to data provided by states vs [REDACTED]% used in the model update) to consolidate remission.

There is also considerable uncertainty around the estimates based on the Australian data for TIS patients as (i) the data are aggregated and it is unclear exactly what resources are captured or the duration of the data collection, (ii) the patient numbers are still relatively small and there is large variability in resource use and (iii) there is no comparative equivalent source of data to inform the comparator arm of the model.

Although a higher-than-expected EFS and OS benefits for TIS were observed in the ABMTRR data, a number of patients had additional treatments either to consolidate remission (where the clinical symptoms were indicative of future relapse) or after relapse. It is likely that some patients in remission [REDACTED] was due to the effect of subsequent treatment and not TIS in these patients. Therefore, it is uncertain how much of the increase in EFS and OS observed in Australian cohort is due to TIS alone and longer duration of response with TIS infusion should be interpreted with caution. Modelled EFS and OS estimates are based on updated trial data, however the price of TIS, some resource use and response rate were informed by ABMTRR data.

Approximately [REDACTED]% ([REDACTED]/[REDACTED]) of the patients who registered in the program did not receive the successful infusion ([REDACTED] patients) or cancelled the order ([REDACTED]) prior to infusion. This suggests that around [REDACTED]% of the enrolled patients received successful infusion. [REDACTED]% of the patients had re-infusions and some had out of specification product. Although for these subgroup of patients [REDACTED], part of the other program costs would have still incurred. It is uncertain how much of these cost-activities are captured in the data provided by state and territories.

14. Financial/budgetary impacts

The submission presented an updated estimate of the financial impact to the Australian Government of funding TIS through the NHRA over the first three (Deed) years of the program. Actual uptake of TIS for pALL through the NHRA has been lower than estimated in the MSAC

resubmission (ADAR 1519, April 2019) [REDACTED]. The patient numbers estimated in the resubmission, applied in the Deed, and actual numbers are summarised in Table 18.

Table 18 Expected vs. actual number of patients infused with TIS in pALL

	Year 1	Year 2	Year 3	Year 4*	Year 5	Year 6
Resubmission (ADAR 1519, April 2019)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Actual	<100	<100	<100	<100	n/a	n/a

ADAR = applicant developed assessment report; pALL = paediatric acute lymphoblastic leukaemia

Source: Table 4.1-1, p164 of the ADAR 1748+inline commentary

Shaded cells represent data previously accepted by MSAC

TIS was available initially in 2019 –2020 in Victoria and from June 2020 onwards in NSW and Queensland. The commentary considered strict state and territories border rules during the COVID pandemic would have substantially affected the uptake of TIS.

The utilisation of TIS in Australia was likely lower in Australia due to many possible reasons, including the COVID-19 pandemic, implementation issues, low clinician confidence in the therapy being first in the class and lack of provider awareness for eligibility and toxicity management. Also, as TIS treatment availability is limited to only a few centres in Australia, there are patient accessibility and equity concerns. The clinical expert opinion suggested that the uptake of TIS will likely increase in future, in contrast to ADAR’s claim of low utilisation.

The ADAR presented updated financial analysis substituting data from ABMTRR and cost updates as discussed in Section 11, Economic Analysis. The ADAR presented a comparison of the expected versus estimated actual financial cost of TIS to the Australian Government and claimed that the financial cost of TIS was much lower than was estimated in the MSAC ADAR 1519 (April 2019) and Deed.

The actual financial cost of TIS to the Australian Government is significantly underestimated in the submission (see estimated actual in Table 19). [REDACTED] [REDACTED], the adjunctive and ancillary costs realised in clinical practice are consistently much higher than estimated in the submission (as reported in states and territories’ review reports).

This was discussed above in detail in Section 11. In summary, these high costs may be attributed to the various treatment steps and associated inpatient and outpatient episodes involved for TIS infusion, complex adverse event profile and management of these patients, and subsequent re-infusion of TIS or any other treatment and/or aH SCT. Average cost per patient (including cost of TIS) was approximately \$[REDACTED] for patients treated at NSW (N=13) and [REDACTED]. Average cost per patient (excluding cost of TIS) was around \$459,000 for three patients treated at Queensland Children Hospital, which would be closer to the average cost reported by NSW and [REDACTED] when average cost of TIS (\$[REDACTED]) is added to this (~\$[REDACTED]).

Table 19 Expected versus actual financial impact of TIS program

	Year 1	Year 2	Year 3	Year 4*
MSAC ADAR 1519 (April 2019)				
Number of patients				
Direct TIS costs				
Other program costs				
Cost offsets				
Net cost				
Deed				
Number of patients				
Direct TIS costs				
Other program costs				
Cost offsets				
Net cost				
Actual				
Number of patients	18	22	9	3
Direct TIS costs				
Other program costs				
Cost offsets				
Net cost				
Revised estimate of Actual costs, based on data provided by States during evaluation				
Number of patients ¹	18	22	9	3
Direct TIS costs ¹				
Other program costs ²	\$8,399,191	\$10,265,678	\$4,199,595	\$1,399,865
Cost offsets ¹				
Net cost				

TIS = tisagenlecleucel

* Actual data for Year 4 up to 31 Jan 2023

Source: Table 4.2-1, p166 of the MSAC ADAR 1748+inline commentary.

Grey shaded cells represent estimates previously seen by MSAC in ADAR 1519. Blue shaded cells represent estimates based on data provided by States and were calculated during the evaluation.

¹ Estimated cost were sourced from Step 3 of the economic evaluation which provided an updated modelled estimate by substituting some data from ABMTRR. Number of patients with successful infusion and average TIS cost per patient (\$■) used in these calculations were based on the MSAC quarterly report.

² Average cost per patient for TIS infusion program was reported around \$■ (TIS product cost + other program cost) by ■ and NSW Health. Queensland Health estimate was closer to this as well. Average other program cost per patient, \$466,622 were then estimated by subtracting average TIS cost (\$■) from this estimate.

The total financial impact of introducing TIS program in Australia has been substantially higher than what the sponsor initially presented. The sponsor estimated a net cost of the TIS program to be approximately ■ for the first three years of Deed. However, based on the data provided by states, the actual costs (including costs to public hospitals) may be as high as ■ in the first three years despite lower utilisation of TIS than expected. This is largely attributed to the significant underestimation of ancillary program and disease management costs associated with patients treated with TIS. However, the revised costing data needs to be interpreted with caution, given it is non-comparative.

There is also an outstanding concern regarding the costs incurred with out-of-specification product infusions, manufacturing or infusion failures and re-infusions. It is uncertain how much of these cost-activities are captured in the data provided by state and territories.

Given the sponsor is requesting changes in the cost of TIS and removal of patient cap numbers, a sensitivity analysis is provided in Table 20 to assess impact of change in average TIS cost and patient numbers.

Table 20 Sensitivity analysis assessing impact of change in patient numbers and average TIS cost on annual health budget

Average cost for TIS						
Total infused patients	20	28	40	20	28	40
Average other program cost per patient ³	\$466,622					
Total cost for TIS (including program cost)						
BLN (average cost offsets per patient)						
Total cost offsets						
Net cost						

BLN = blinatumomab; TIS = tisagenlecleucel

Compiled for the commentary based on "TIS pALL BIM.xlsx" and data provided by states and territories.

¹ Average TIS cost based on MSAC Quarterly report ending in January 2023.

² Standardised TIS product cost after successful infusion as part of proposed new funding arrangements.

³ Average other program cost per patient, \$466,622 was derived using state and territory data excluding cost of TIS product cost.

Financial Management – Risk Sharing Arrangements

■.

Table 21 ■

[Redacted]	
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■

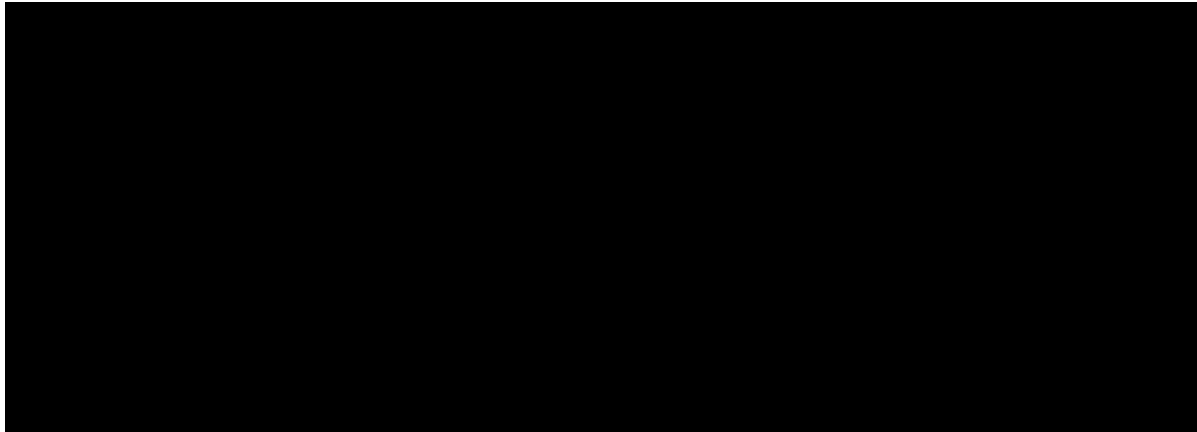
Table 22 ■

[Redacted]	
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■.

■

Table 23 [REDACTED]



[REDACTED]

Based on additional evidence for TIS, including longer-term trial evidence and ABMTRR data, the sponsor claimed that the incremental cost per QALY for TIS is below the threshold previously accepted by MSAC. However, while the sponsor's estimate of the ICER in ADAR 1748 is reduced (\$ [REDACTED] vs \$ [REDACTED] in the previous ADAR 1519 (April 2019)), after the Commentary applied corrections to the model and respecified some of the resource use input values, the ICER was estimated to be \$ [REDACTED]. [REDACTED] Additionally, the utilisation of TIS for pALL has been substantially lower than was estimated by Novartis and accepted by MSAC.

[REDACTED]:

- [REDACTED]
- [REDACTED]

[REDACTED]

A number of patients received out of specification product or re-infusions of TIS. [REDACTED] patients received infusion but it was unsuccessful. Although, sponsor was not reimbursed for these patients, other costs associated with the treatment program were still incurred. Overall, the other program costs associated with TIS infusion are significant and much higher than estimated by the modelled evaluation.

The utilisation of TIS was likely lower in Australia due to many possible reasons, including the COVID-19 pandemic, implementation issues, low clinician confidence in the therapy being first in the class and lack of provider awareness for eligibility and toxicity management. Also, as TIS treatment availability is limited to only few centres in Australia, there are patient accessibility and equity concerns. Therefore, the uptake of TIS will likely increase in future, in contrast to ADAR's claim of low utilisation.

A number of Australian patients ([REDACTED]%) received TIS during complete remission, which was achieved during bridging chemotherapy. It is unclear whether this indicates that Australian patients were in better health at time of TIS-infusion. This is partially supported by the fact that the ABMTRR reported healthier patients according to the Karnofsky/Lansky performance status. There remain concerns of leakage of TIS utilisation in earlier lines of therapy.

15. Other relevant information

Australian data

Across Australia, only three states provide CAR-T infusion services (Table 24). Presently, there is one TGA approved commercial manufacturing site for CAR-T therapies in Australia, Cell Therapies Pty Ltd, (in the Peter MacCallum Cancer Centre in Victoria), in addition to locations in the US and France.

Table 24 Service availability in states and territories across Australia, by indicated age group

Age group	WA/SA/NT/ACT	NSW	VIC	QLD
Paediatrics	Interstate travel required	Sydney Children's Hospital Randwick The Children's Hospital	Royal Children's Hospital	Queensland Children's Hospital
Adolescents		Royal Prince Alfred		
Young adults			Peter MacCallum Cancer Centre	Royal Brisbane and Women's Hospital

ACT = Australian Capital Territory; NSW = New South Wales; NT = Northern Territory; QLD = Queensland; SA = South Australia; Vic = Victoria; WA = Western Australia

Source: Australian Bone Marrow Transplant Recipient Registry (ABMTRR) report version 4, and the reviews submitted by state and territories Departments of Health (provided by Department of Health and Aged Care during the evaluation).

Data from the sponsor show that most patients requiring treatment were from Victoria (█%), and New South Wales (█%). A total of █% of patients required interstate travel for treatment (Table 25).

Table 25 Disposition of patients who required interstate travel

State/Territory	Total patients treated, n	Patients who required interstate travel ¹
ACT		
NSW		
NT		
QLD		
SA		
TAS		
VIC		
WA		
Total		

ACT = Australian Capital Territory; NSW = New South Wales; NT = Northern Territory; QLD = Queensland; SA = South Australia; Vic = Victoria; WA = Western Australia

¹Reported as %, (n/N)

Source: Australian Bone Marrow Transplant Recipient Registry (ABMTRR) report version 4, and the reviews submitted by state and territories Departments of Health (provided by Department of Health and Aged Care during the evaluation).

17. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The updated clinical evidence did not adequately address the uncertainty in clinical outcomes beyond 12 months. The updated studies were single arm only and provided limited data to inform long-term event-free survival (EFS) as the studies had median follow-up of less than 12 months, substantial loss to follow up and for some endpoints, no additional information than was provided in the original ADAR. The applicant claimed that registry data show that response outcomes are better than expected in clinical practice compared with clinical trials. However, registry data were incomplete and confounded by other therapies. The available data on mortality suggests tisagenlecleucel (TIS) is not a curative treatment for most patients.
- Updated data suggests a higher than expected rate of allogeneic haematopoietic stem cell transplantation (aHSCT) after TIS in clinical practice, with the role of TIS changed to a conditioning therapy prior to transplant. This suggests that for most patients, TIS is not a stand-alone, curative therapy as it was positioned and evaluated in the original assessment. There is currently insufficient evidence to fully understand the optimal clinical role of TIS.

Economic issues:

- The economic model likely overestimated the benefits of TIS and potentially underestimated the benefits of blinatumomab in the comparator arm. ESC considered the revised economic model that corrected for the application of the cure function was more reliable than the ADAR's economic model.
- Costs per TIS treatment were estimated as \$█ per patient in the submission, but New South Wales reported an average cost of \$█ (range \$█ to \$█, including the cost of TIS) per patient. Using the higher costs increased the ICER substantially (over \$█ per QALY). However, the costs for the comparator arm were not updated and may also be higher.
- The ICER is uncertain. While the commentary applied a corrected model, the ICER is sensitive to the estimates used for program costs and the proportion of patients receiving aHSCT. Sensitivity analyses show a range of ICERs, from \$█ to \$█.
- The economic evidence remains unclear. There was no update to the comparator and there is no clear evidence to support a change in price. █.

Financial issues:

- Utilisation was lower than predicted in the original submission in terms of patient numbers. Year-to-year variation is expected for this condition as TIS is intended to be used in a very small group of patients meeting certain criteria.
- The total financial impact of providing TIS, including ancillary and adjunct costs is likely close to what was expected in the original application (intended to treat a larger number of patients than were actually treated). This was due to higher ancillary and adjunct costs of providing TIS than presented in the original application.

Other relevant information:

- Substantial uncertainty remains regarding the longer-term outcomes (beyond 1 year) and utilisation of TIS █
- The registry has not been capturing all the data requested by MSAC. State and registry data do not align (the applicant did not have access to the state data). Registry data capture has been incomplete, delayed or absent. Registry arrangements need review to improve data capture and access.

- Future reviews for other CAR T products and indications should update evidence and real-world cost data for both the intervention and the comparator. Information could be elicited using a logically ordered information request template with data tables.

ESC discussion

ESC noted that in 2019, MSAC supported public funding for tisagenlecleucel (TIS) for the treatment of confirmed relapsed/refractory CD19-positive acute lymphoblastic leukaemia (pALL) in children and young adults up to 25 years of age ([MSAC application 1519](#)). Further, ESC noted that, due to considerable clinical, economic and financial uncertainty, MSAC's recommendation required a risk sharing arrangement (RSA). The subsequent Deed of Agreement for funding of TIS under the National Health Reform Agreement outlines the RSA supported by MSAC which included [REDACTED], [REDACTED], a single course of treatment per patient, and the requirement for review of all matters relevant to the provision of the treatment with a new agreement to be renegotiated based upon the review outcomes. The Deed also required the collection and provision of data on the provision of TIS in the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR).

ESC noted that the applicant, Novartis, had lodged an updated Applicant Developed Assessment Report (ADAR) to satisfy the review requirements in the Deed. As per the Deed, the purpose is to review all matters relevant to the provision of the treatment, including but not limited to the clinical and cost-effectiveness of the treatment, usage of the treatment, financial costs of the treatment or any other matter relevant to the effectiveness, supply or funding of the treatment. ESC noted that input from states and territories was also received to inform the review.

ESC noted that there are only eight hospitals in Australia that can deliver TIS therapy, meaning many patients need to travel to metropolitan areas and stay there for months. This may be a significant financial barrier if subsidised travel and accommodation is not available. ESC noted feedback from a patient/carer survey commissioned by NSW Health. The survey highlighted the importance of support from the medical team delivering TIS treatment. Medical staff require time to answer questions from patients and their families. Access to social workers is helpful for patients and their families. The decision to proceed with CAR-T treatment can be traumatic, and mental health support would benefit patients and their carers. ESC noted that patient/carer feedback related more to the experience of going through CAR-T therapy rather than the results achieved. It was perceived as gentler than bone marrow transplant, but patients/carers often reported feeling that there were no other options at their stage of treatment.

ESC reviewed whether the updated clinical evidence supported the clinical outcomes from the original application. ESC noted the updated evidence included updated clinical trial data from the ELIANA (n=79), ENSIGN (n=64) and B2001X (n=69) studies which were all single-arm studies with small numbers of participants. ESC noted that B2001X was primarily focussed on safety but also reported effectiveness outcomes. ESC noted that outcomes in B2001X were not assessed by an independent committee and considered this may be a potential source of bias in outcome assessment. ESC considered patients in B2001X may be in a different phase of disease as it enrolled some patients who had already used blinatumomab.

The ADAR presented pooled data from ELIANA and ENSIGN to provide updated data on event free survival (EFS) and overall survival (OS). No randomised controlled trial data were available. Data from two observational studies and from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) was also reviewed but not included in economic models. ESC noted the commentary also included analysis from observational studies that were excluded in the ADAR. ESC noted the applicant's pre-ESC response, which stated that it did not believe the retrospective studies materially changed its clinical conclusion or reliably informed the subsequent economic and financial analyses. However, ESC considered that these data are useful and provide evidence of real-world experience of TIS treatment.

Regarding safety, ESC noted that updated data were consistent with the previously known safety profile of TIS. Some rare side effects were noted that should be added to the registry capture (human herpesvirus 6 encephalitis, haemophagocytic lymphohistiocytosis). ESC noted that the registry was incomplete as it often did not capture data on whether or not patients experienced common adverse events, with event rates of up to [REDACTED] ([REDACTED]%), following infusion with TIS. [REDACTED] following common adverse events were not completely reported (with rate of non-reporting shown): intensive care unit admission ([REDACTED]%), cytokine release syndrome ([REDACTED]%), immune effector cell-associated neurotoxicity syndrome ([REDACTED]%), hypogammaglobinaemia ([REDACTED]%), organ toxicity ([REDACTED]%), infection ([REDACTED]%), and prolonged cytopenia ([REDACTED]). ESC noted that safety data were only captured to 100 days in the ABMTRR. ESC noted that the registry data on intravenous immunoglobulin G (IVIg) use (used to treat hypogammaglobulinaemia) was insufficient and so uncertainty remains regarding the use and duration of IVIg treatment [REDACTED]. The key long-term safety concern is secondary malignancies. ESC considered this should be explicitly captured in the ABMTRR, with a 15-year funded registry timeframe to ensure any events are captured.

Regarding effectiveness, ESC noted that the applicant claimed the updated data from the ENSIGN and ELIANA trials supported the longer-term efficacy for TIS in pALL, demonstrated by sustained duration of response, EFS and OS with a median follow up of up to 46 months. However, ESC noted that the median follow-up for EFS was less than 12 months for the ELIANA, ENSIGN trials, and B2001X studies. ESC considered the estimates of EFS after 9 months (median follow-up) in the ELIANA trial were unreliable as they were informed by small patient numbers due to significant loss to follow up. In the ENSIGN study, only 4/64 patients completed 12 months as per protocol, and the sponsor terminated the study in 2019. The estimated EFS from the pooled ELIANA and ENSIGN studies was 48% at 12 months compared with 44% in the original ADAR (for the intention-to-treat population).

In the ELIANA study, 42% of patients had died by September 2021. In the ENSIGN study, 47% of patients had died at study termination (median 15-month follow up for OS). Previously, 12-month overall survival was estimated to be 71.0% (95%CI: 61.8, 78.4) pooled analysis of results from the ELIANA/ENSIGN studies. ESC noted that MSAC had supported funding for a single treatment of TIS on the basis that there was a large unmet clinical need for a small group of patients and the preliminary supportive evidence of a clinically important treatment effect. ESC noted that although TIS has been considered a potentially curative treatment, ESC considered that these outcomes were not consistent with a treatment that is curative for many patients. Overall, based on the available updated clinical evidence, ESC considered that EFS data remain short-term and there is little new clinical trial evidence to increase MSAC's confidence that TIS offers a durable long-term response. Overall, ESC considered that substantial uncertainty remains regarding the longer-term outcomes (beyond 1 year) from TIS [REDACTED].

ESC noted that in the models for EFS and OS based on the ELIANA and ENSIGN studies, patients were censored if they had an aHSCT and there is no information for this group of patients. ESC considered this was problematic as there is no data available to inform whether treatment with TIS contributes to patients achieving better outcomes after receiving aHSCT. ESC considered that the decision to undergo aHSCT after TIS may be informed by clinical and patient preference and may not only be offered to patients who have relapsed following infusion with TIS. It appears that TIS is being used as consolidating treatment in practice, facilitating patients to subsequently undergo aHSCT. ESC considered that registry data on the number of aHSCT performed following infusion with TIS are incomplete – [REDACTED] patients subsequently underwent aHSCT [REDACTED]. Data provided by the states suggest that approximately 31% of patients will have aHSCT after TIS treatment (compared with 19% as previously modelled in the 1519 ADAR). ESC considered that there is an increasing recognition that there are sub-groups of patients, most notably those with early loss of B cell aplasia who may benefit from a consolidative aHSCT if eligible. ESC considered that it is unclear whether TIS should be reimbursed at the same price when used as a bridge to aHSCT (by achieving higher rates of MRD-negative remission) as the treatment effect is derived from both TIS and aHSCT.

ESC considered the cost-effectiveness as estimated in the original application to be uncertain. ESC noted the ADAR had updated the previous economic model to incorporate updated clinical evidence for TIS. ESC noted that EFS and OS data were extrapolated and that estimates on the tails of the Kaplan-Meier curves are highly uncertain due to small numbers and censoring. There is limited observed (as opposed to extrapolated) data for TIS after 12 months. ESC noted the commentary had revised the cure assumption (applied at 5 years) in the economic model so it does not assume patients with progressive disease have been cured. ESC accepted the revisions which were also accepted by the applicant in the pre-ESC response. However, the pre-ESC response considered the previous model was acceptable as it did not assume a complete cure.

ESC noted the clinical evidence for blinatumomab was unchanged, however additional evidence has since been published^{25,26}, including observational data from Australian patients. ESC considered the lack of updated data for the comparator is major limitation as the data for the comparator is no longer informed by contemporaneous evidence. ESC considered the lack of updated data for the blinatumomab to also be a major limitation in the economic model. ESC noted the proportion of patients alive in the comparator arm decreased rapidly. ESC considered that this may underestimate the effectiveness of blinatumomab as it was informed by older trials with sicker patients.

ESC noted that MSAC's recommendation was based on an incremental cost-effectiveness ratio (ICER) of \$■■■■. A model using updated cost data and applying technical corrections found the updated ICER to be \$■■■■. ESC considered that the economic model likely overestimated the benefits of TIS and underestimated the benefits from the comparator.

ESC agreed with the commentary revision to increase the proportion of patients undergoing aHSCT (to 31%) as this better reflected Australian clinical practice. ESC noted the updated economic model decreased the proportion of IVIg use to ■■■■% for 3 years (previous submission assumed 88% for 3 years) and considered the duration of use may be underestimated. ESC noted the updated economic model increased tocilizumab use to ■■■■% (previously 5.7%) and decreased intensive care unit (ICU) admission for cytokine release syndrome to ■■■■% (previously 48.1%).

ESC noted that data from the states and territories show that the actual costs associated with providing TIS treatment for patients in Australia (called ancillary and adjunctive costs) are substantially higher than both the estimates in the initial submission and the updated model used in the review. Submissions from the states and territories identified high staff and resource requirements for apheresis, TIS infusion, adverse event monitoring and treatment, additional hospital admission, subsequent aHSCT and/or additional cancer treatments, and outpatient care for ongoing management. The original estimate was that costs per TIS treatment would be \$■■■■ per patient. The average cost of providing TIS in New South Wales and ■■■■ was approximately \$■■■■ (range \$■■■■ to \$■■■■, including TIS) per patient. Data from Queensland also supported this figure. The ICER increased substantially (>\$■■■■/QALY) when the higher costs provided by the states and territories were applied (\$457,656 per infused patient excluding TIS cost). ESC considered that although these represent real-world costs, the costs are non-comparative and the costs associated with the comparator may also be higher as raised by the applicant in the pre-ESC response. ESC considered that comparator costs should be updated in reviews of this kind. States and territories also reflected the requirement for real-time access to the data captured by the ABMTRR to assist with costing and resource allocation and were

²⁵ Locatelli F *et al.* Blinatumomab in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia: RIALTO expanded access study final analysis. *Blood Adv.* 2022;6(3):1004-1014.

²⁶ Sutton R *al.* Outcomes for Australian children with relapsed/refractory acute lymphoblastic leukaemia treated with blinatumomab. *Pediatr Blood Cancer.* 2021;68(5):e28922.

supportive of continuing to collect data for surveillance of long-term safety and efficacy to 15 years.

ESC noted the applicant's claim that observational data from the Centre for International Blood and Marrow Transplant Research and ABMTRR supported the efficacy and safety of TIS in clinical practice. ESC considered this claim was not adequately supported by the data captured in the ABMTRR. ABMTRR data varied from the data in reports received from the states and territories, indicating the extent of the incomplete registry data. ESC considered the ABMTRR data capture to be incomplete, delayed or missing in many instances. In its current state, ESC did not consider the data currently captured by the ABMTRR was adequately reporting the minimum data requested by MSAC (MSAC 1519 Public Summary Document, pg 6). ESC noted that only 62% of patients had efficacy data reported at 12 months which was confounded given 35% of patients were in remission at the time of infusion with TIS and multiple therapies including aHSCT were performed in the same time frame; safety data was only recorded to 100 days; and quality of life data was inadequate with █% available at baseline and only █% Patient Reported Outcome Measures (PROM) at 12 months were recorded. ESC considered the registry data are insufficient to understand true clinical outcomes of CAR-T (TIS) alone, costs, or the quality of life outcomes of patients.

ESC noted that the applicant is responsible for collecting and reporting the data specified in the Deed. ESC considered that the requirement for data reporting to the registry needed to be strengthened to ensure the registry accurately captures all of the data requested by MSAC, including long-term side effects, for each patient. ESC considered that outcome data should be collected at specific timepoints, █. ESC considered that other outcomes such as genomic risk factors and loss of B-cell aplasia could also be captured in the registry. ESC noted that these variables help guide future treatment decisions, such as stem cell transplant.

ESC noted that there had been issues with registry data access. ESC noted the feedback from the ABMTRR that sponsors have placed commercial confidentiality provisions in the contracts that limit the ABMTRR's ability to easily share data with other stakeholders or compare across different products. ESC noted that the Department intends to implement measures to improve access and consistency in reporting across different CAR-T therapies. ESC considered that how the registry is funded and how data can be accessed should be reviewed. The administrative load of managing multiple contracts with, and reports to, sponsors was also a concern for the ABMTRR. ESC considered that future contracts should require data access for all relevant stakeholders for research and reporting purposes. In particular, data should be available to clinicians to assist with 'real time' decision-making. █

ESC considered that there were no data to support the safety or effectiveness of multiple doses of TIS. Therefore, ESC considered a limit of one treatment per lifetime remains appropriate. However ESC noted that █% of patients had more than one TIS infusion which is associated with significant ancillary costs, despite the second treatment itself being made available free of charge, as per the Deed of Agreement. ESC noted the applicant indicated it will no longer provide more than one infusion per patient

█ █. ESC considered that relapse after TIS may be common. ESC considered the response rates may be confounded due to the use of subsequent treatment and that 35% of patients were in remission prior to treatment with TIS.

█ There is increased uncertainty regarding curative benefit, and higher use of other therapies after CAR-T than originally estimated. █

█ █ █.

ESC noted that the number of patients using TIS has been lower than expected. █ have ranged from █ to █ patients, but the numbers treated were <10 in 2020, <100 in 2021, <100 in

2022, and <100 to date in 2023. ESC noted the commentary's statement that uptake is likely to increase in the future. ESC noted the applicant had requested [REDACTED]. [REDACTED]. ESC considered that year-to-year variation in the small number of patients using TIS was reasonable given that TIS is intended to be used in a very small group of patients meeting certain criteria. ESC considered that there is a risk of leakage into earlier lines of therapy. For these reasons ESC advised that it would be reasonable [REDACTED]. ESC considered future utilisation would be affected by future evidence and clinical experience and may increase if longer term clinical outcomes are positive.

ESC noted that the costs associated with providing TIS therapy in public hospitals (adjunctive and ancillary costs) were substantially higher per patient than those previously considered in MSAC Application 1519. ESC noted that including these costs resulted in the estimated net cost of TIS provision to be almost double the estimated costs in the submission. ESC considered that relapse was common following TIS and considered the costs of subsequent therapies should be included in financial implications. ESC further noted that states reported concern that many costs are not captured in the state-based reconciliation, and the states recommended a national cost reconciliation initiative.

ESC noted that further CAR-T reviews will be scheduled in the future for other funded products and indications. ESC advised that the future CAR-T reviews should update evidence and real-world cost data for both the intervention and the comparator. ESC considered that information for the reviews could be elicited from the relevant applicant(s) using a logically ordered information request template with data tables for the applicant to fill in. ESC noted that Department will develop a template to guide future reviews. ESC noted that the Health Technology and Genomics Collaboration is planning to produce an evaluation framework for highly specialised therapies, and ESC could contribute suggestions on what this framework should include.

18. Applicant comments on MSAC's Public Summary Document

Tisagenlecleucel provides an important treatment option for children and young adults with relapsed or refractory acute lymphoblastic leukaemia who have limited treatment options. Longer-term data (up to 5 years) from clinical trials demonstrate tisagenlecleucel continues to provide a major improvement in the treatment of these patients with high unmet medical need. Novartis will continue to work with MSAC and the Department to ensure tisagenlecleucel remains an accessible treatment option in Australia.

19. Further information on MSAC

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