Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1722.1 – Axicabtagene ciloleucel (Yescarta®) for relapsed or refractory large B-cell lymphoma

Applicant: Gilead Sciences Pty Limited

Date of MSAC consideration: 4-5 April 2024

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A re-application requesting public funding through the National Health Reform Agreement (NHRA) of axicabtagene ciloleucel (YESCARTA®), henceforth referred to as AXI, for the treatment of relapsed or refractory (R/R) large B-cell lymphoma (LBCL) in the second-line (2L) setting was received from Gilead Sciences Pty Limited by the Department of Health and Aged Care. AXI is currently funded in the third-line (3L) setting under NHRA Commonwealth and State shared funding arrangements.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the public funding of axicabtagene ciloleucel (AXI) through the NHRA for the treatment of R/R LBCL in the 2L setting. MSAC recognised the clinical need for the proposed treatment in this population. MSAC noted that the updated clinical data demonstrated a statistically significant overall survival (OS) benefit of AXI relative to the standard of care over a longer follow up period, which MSAC considered supported the clinical claim of superior effectiveness. MSAC considered that there remained some uncertainty regarding the comparative safety and as such the non-inferior safety claim was not substantiated but acknowledged that all treatments in this population carry a safety burden.

MSAC recognised that the revised economic evaluation and financial analysis addressed most issues previously raised by MSAC. MSAC considered that the additional clinical data and revisions had improved the robustness of the economic evaluation. However, MSAC noted that there remained some concerns that the adjunct hospital costs continue to be underestimated. MSAC noted the proposed price for treatment with AXI in the 2L setting was higher than the average price previously supported by MSAC for AXI in the 3L setting. MSAC also noted that the application proposed increasing the annual patient cap for AXI but that the current utilisation of AXI is below the current annual patient cap for the 3L setting. Therefore, MSAC support for public funding of AXI in 2L setting was contingent on a risk sharing arrangement that includes the following requirements:

- a single payment of up to $▮▮▮ that corresponds to an incremental cost effectiveness ratio of $ ▮▮▮ per quality adjusted life year; or
- a pay for performance arrangement constructed to achieve an average price of $▮▮▮ per successfully infused patient based on a ▮▮▮% response rate; and

- limit of one successful CAR-T infusion per lifetime; and
- annual patient caps to remain as per current deed for AXI in 3L that has annual caps of █ patients in the first year and ████ in the second year; and
- review of the data to be conducted by MSAC no later than 3 years post the commencement of public subsidy of AXI (for treatment of R/R LBCL in the 2L) for the purposes of understanding the clinical place, utilisation, equity of access and budget impact of AXI for R/R LBCL in Australian clinical practice. Subsequent to an initial review, MSAC may advise whether further review of the clinical effectiveness and cost-effectiveness is warranted.

Consumer summary

This application from Gilead Science Pty Ltd requested public funding of the cell therapy axicabtagene ciloleucel (Yescarta®) for relapsed or refractory large B-cell lymphoma as second-line therapy (second course of treatment, used if the first course of treatment is not effective in treating the disease).

Large B-cell lymphoma is a type of blood cancer that arises from lymphocytes (a type of white blood cell), which are part of the body's immune system. Large B-cell lymphoma is a form of non-Hodgkin's lymphoma, and patients typically present with swelling of the lymph nodes or disease in other parts of the body such as the stomach, bowel, skin and lungs, which can cause swelling and discomfort. In addition, patients can have fever, night sweats and unexplained weight loss.

CAR T-cell therapies are a type of treatment that are used when patients with some types of cancers (currently blood cancers such as large B-cell lymphoma) don't respond to (refractory), or relapse (come back) after other types of treatment, such as chemotherapy. Second-line therapy means that axicabtagene ciloleucel would be a treatment choice for those patients in whom initial therapy, likely chemoimmunotherapy, has not kept the lymphoma under control.

Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell therapy that is produced using a patient's own T-cells (another form of immune cell), making the product unique to each patient. For CAR T-cell therapy, a patient's T-cells are collected and genetically modified in a laboratory to express an anti-CD19 CAR that helps T cells to target the lymphoma B-cells. The modified T-cells are multiplied and then infused back into the patient where they target and kill the cancerous lymphoma B-cells, thereby treating the lymphoma.

MSAC considered that the new data from the key clinical trial showed that axicabtagene ciloleucel is an effective treatment for patients with confirmed large B-cell lymphoma refractory to or relapsed no more than 12 months after completion of first-line treatment with chemoimmunotherapy. MSAC noted that this is a small patient population with a high risk of disease progression and mortality, and who have a high clinical need for an effective treatment need due to poor prognosis.

However, MSAC noted that the price for axicabtagene ciloleucel suggested by the applicant was too high for the treatment to be considered cost-effective. MSAC supported public funding on the condition that the treatment be provided at a lower cost than what was proposed by the applicant.

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

MSAC supported public funding through the National Health Reform Agreement for axicabtagene ciloleucel (Yescarta®) for relapsed or refractory large B-cell lymphoma as second-line therapy, on the condition that the applicant reduced the price. MSAC considered axicabtagene ciloleucel would address a clinical need for a small number of very sick patients and, assuming that the cost is reduced, treatment would provide good value for money. MSAC

Consumer summary
recommended that a review of axicabtagene ciloleucel be undertaken after 3 years to assess its use and costs.

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

MSAC noted that this re-application requested public funding through the NHRA of AXI for the treatment of R/R LBCL in the 2L setting. AXI is currently funded in the third-line (3L) setting under Commonwealth and state-shared funding arrangements for the treatment of R/R diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL).

MSAC recalled that in March 2023, MSAC considered but did not support public funding of AXI (application 1722[1]). MSAC recalled that it had recognised the clinical need for the proposed treatment in this population but considered that from the evidence presented for evaluation, it was uncertain whether AXI demonstrated durable survival outcomes relative to standard of care (SoC), and that AXI had an inferior safety profile. MSAC had acknowledged the additional evidence presented as part of pre-MSAC response for application 1722 but due to the limited time available for evaluation MSAC was unable to thoroughly consider it at that time. MSAC recalled its advice that the economic evaluation required revisions, including incorporation and evaluation of new evidence submitted in the pre-MSAC response and use of progression-free survival (PFS) as the outcome measure along with other revisions. MSAC had considered that the budget impact was high and uncertain, the estimate of patient numbers eligible for treatment and the price of AXI were not adequately justified, and no payment for performance (PfP) or risk sharing agreement (RSA) were proposed for consideration by MSAC in March 2023.

MSAC noted that the resubmission applicant-developed assessment report (ADAR) provided clearer eligibility criteria for AXI treatment in the 2L setting to ensure improved patient selection to achieve optimal outcomes of treatment. MSAC noted the issue raised by the department policy area where the proposed population in the resubmission was broader than the target population in ZUMA-7. However, MSAC noted that aligning patient eligibility criteria for 2L patients with ZUMA-7 trial would mean patients who would be excluded for 2L AXI treatment would end up receiving AXI in the 3L setting.

MSAC noted the clinical management algorithm where currently patients diagnosed with LBCL undergo treatment with the standard first-line therapy of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) and approximately 40% of patients with refractory or relapsed disease go on to receive salvage chemotherapy. Patients who did not respond well to salvage chemotherapy then went on to receive AXI in the 3L setting. MSAC noted the comparator to be SoC, which typically consisted of salvage chemoimmunotherapy followed by collection of peripheral stem cells (for use in autologous stem cell transplant [auto-SCT]). Patients who responded well to salvage chemotherapy then received myeloablative high-dose therapy (HDT) and rescue by means of auto-SCT. MSAC noted the proposed algorithm elevated AXI to 2L setting where LBCL patients relapsed or refractory to RCHOP therapy would become eligible to receive AXI treatment under the proposed listing.

MSAC noted the public consultation feedback were supportive of the application. MSAC noted that from a consumer perspective, there needs to be a role for the patients in governance about

[1] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1722-public

how their data are collected and entered into registries. For example, an electronic method could be used that allows patients to see when their clinical data has been entered into the registry by clinicians. This could be via automated notification, similar to those that can be toggled on in MyHealth Record (to receive an SMS or email when data arrives in the record), or it could be that there is a patient portal where patients would be able to login to see all or some information about their data.

MSAC noted the feedback from the state and territory health authorities. The jurisdictions acknowledged the importance of the therapy but considered that a review of AXI use in the 3L setting should be completed first. MSAC noted that the jurisdictions considered the CAR-T procedure costs assumed in the model were underestimated.

MSAC noted that the clinical evidence presented in the ADAR was based on direct comparative evidence from the ZUMA-7 trial. MSAC noted that ZUMA-7 was a high-quality randomised controlled trial (RCT) directly comparing AXI to SoC for 359 adult patients with LBCL who were refractory to or who had relapsed no more than 12 months after completion of 1L chemoimmunotherapy. MSAC noted in the ZUMA-7 trial the patient group was highly selected because it excluded patients with a history of cardiovascular disease to ensure patients were fit enough to be able to tolerate CAR-T therapy. MSAC noted the resubmission ADAR presented; updated data with a median follow-up of 47.2 months (previous data had a median follow-up of 24.9 months).

MSAC noted the proposed clinical claim was superior effectiveness and non-inferior safety for treatment with AXI in the 2L setting compared to current SoC. MSAC noted the ongoing treatment related toxicities including cytokine release syndromes (CRS) and the costs associated with the need for Intravenous immunoglobulin (IVIG) infusions, the consequences of neurotoxicity including immune effector cell-associated neurotoxicity syndrome (ICANS). MSAC noted that the ADAR claimed that in ZUMA-7 patients who dropped out in the SoC arm after a relapse were no longer followed and this favoured the SoC arm for comparative safety. MSAC noted the safety data from the ZUMA-7 trial, where both arms of the trial had substantial toxicities with mildly greater risk of ≥Grade 3 adverse events (AEs) in the AXI arm especially for people >65 years of age. MSAC considered the safety concern in older people (>65 years of age) was likely relevant as potential eligible Australian population would tend to be in the older age group. MSAC also noted that ESC had highlighted the recent reports on the emergence of T-cell malignancies following BCMA-directed or CD19-directed CAR-T cell immunotherapies. However, MSAC noted these were individual reports with no definitive data available at the time. Overall, MSAC considered that there remained some uncertainty regarding the comparative safety and as such the non-inferior safety claim was not substantiated but acknowledged that all treatments in this population carry a safety burden.

Regarding comparative effectiveness, MSAC noted the updated trial results with the longer median follow-up of 47.2 months provided evidence for an overall survival (OS) benefit favouring AXI over SoC albeit with a wide confidence interval and potential multiple biases. MSAC noted ESC's concerns that the risk of bias of the ZUMA-7 RCT related to the lack of blinding of the investigators and that these biases were likely to favour AXI. ESC had also raised issues as censoring beyond 18 months was high and the curves began to merge at 29 months follow up, but MSAC noted a substantial number of patients were not followed up beyond 12 months in the trial. At 2 years, approximately 50% patients remained in the trial. However, MSAC also noted that the aforementioned issues to be unavoidable, given how the trial was conducted and acknowledged that the OS data mitigated some of the concerns regarding biases.

MSAC noted that the results suggested superiority of AXI compared to SoC, demonstrated primarily by a statistically significant OS benefit in the ZUMA-7 RCT (hazards ratio [HR] = 0.73;

95% CI: 0.54–0.98). This was also supported by PFS (HR = 0.51; 95% CI, 0.38–0.67) and event free survival (EFS) (HR=0.42; 95% CI, 0.33–0.55) results. Overall, MSAC concluded that the updated evidence provided in the resubmission ADAR demonstrated that a clinical claim of superior effectiveness was likely to be appropriate; however, the magnitude of the incremental treatment effect was likely to be lower for response and progression outcomes based on study design limitations.

MSAC noted that resubmission ADAR had again presented an economic evaluation that used a mixture cure model (MCM) as the base case analysis but had also provided alternative analyses using a partitioned survival model (PSM) approach for comparison as previously requested by MSAC. MSAC considered the resubmission ADAR had adequately justified the use of an MCM, as when compared to standard parametric modelling approaches MCM produced similar estimates of cost-effectiveness. However, although MSAC accepted that the use of an MCM had been appropriately justified for this application, MSAC clarified that the uncertainty in the overall survival of patients beyond the available trial follow up timepoint remained and that accepting a MCM approach did not mean that MSAC had concluded that treatment with AXI for R/R LBCL in 2L setting provided a 'functional cure' for any proportion of patients. The resubmission economic evaluation had also addressed the other issues previously raised by MSAC, such as concerns related to the risk of bias with the EFS outcome, the prior exclusion of PFS in the modelled approach and the underestimated overall cost of AXI, while increasing the discount rate (5%) and reducing the time horizon (30 years). MSAC noted the base case incremental cost-effectiveness ratio (ICER) of AXI compared to SoC ($███/ quality-adjusted life year (QALY) gained) in the resubmission ADAR was lower than the base case ICER in the original ADAR ($███/QALY). The outcomes were driven primarily by an incremental gain in QALYs (1.33 QALYs per patient) due to increased survival and a better patient QoL due to longer periods of being progression free, and large cost offsets due to reduced use of subsequent cellular therapy use in the SoC arm.

MSAC noted the modelling was sensitive to the cost of CAR-T therapy and the distribution used for extrapolation beyond reliable trial follow-up data. The economic model was robust to the multiple parameters tested in the sensitivity analyses with small or moderate changes to the ICER) from the base case. Notably, the results were robust with regard to scenarios using the best fitting standard parametric models, utility values from the literature and when a broader set of subsequent therapies from ZUMA-7 trial were used.

MSAC noted the uncertainty in the overall estimated financial impact, with the cost of AXI as the main driver of the high financial impact. MSAC noted that the resubmission ADAR presented two scenarios for the budget impact ("current" and "future"). MSAC noted that in the 1) 'Current Scenario' – AXI is funded only in the 3L setting (i.e. prior to AXI being funded in 2L), and 2) 'Future Scenario' – AXI is funded in the 2L and 3L setting (i.e. proposed"). MSAC considered the model should take into account the fact that there would be decreased usage of AXI in the 3L setting if AXI is funded earlier (i.e. in the 2L setting).

MSAC noted the resubmission ADAR had addressed the majority of the issues previously raised by MSAC, including revised estimation of the proportion of patients who were refractory or relapsed after completion of 1L chemoimmunotherapy, sensitivity analyses testing the proportion of patients with non-Hodgkin's lymphoma, out-of-pocket costs for patients which the resubmission ADAR claimed was covered by a patient support program via Rare Cancers Australia. MSAC noted that the resubmission ADAR had much more comprehensively included the costs of AEs, bridging treatments and post-progression related costs. However, MSAC noted that there remained some concerns that the adjunct hospital costs continue to be underestimated. MSAC noted the resubmission ADAR estimated that if AXI is funded in the 2L setting the net budget impact to the states and commonwealth under the NHRA would be $███ in year 1 increasing to $███ in year 6.

MSAC noted that the resubmission ADAR estimated that ███ patients in the 2L setting and ███ patients in the 3L setting (███ in total) would receive AXI in year 1. MSAC noted the estimated ███ total patients represented a ███% increase in patients over the agreed cap in the current deed for AXI in 3L, which had annual caps of ███ patients in the first year and ███ in the second year. However, MSAC noted that current patient caps for AXI had not been realised in practice, with utilisation in the 3L setting expected to have reached a steady-state. Therefore, MSAC considered the proposed utilisations to be an overestimate and advised that the annual patient caps to remain as per the current deed for AXI in 3L.

MSAC noted that the resubmission ADAR stated that the proposed price for treatment with AXI in the 2L setting (i.e, $███) was identical to pricing in the 3L setting. MSAC noted the price previously supported by MSAC in the 3L setting was $███. MSAC noted that applicant's pre-MSAC response stated the ███ for AXI in the 3L setting is resulting in an average net price of $██████, whereas the $███ price supported by MSAC was based on ██████. MSAC noted the merits of a 2-payment PfP arrangement but also the potential risk that a 2-payment PfP arrangement can result in a higher-than-expected average price paid if the complete response rate is higher in Australian clinical practice than the response rate assumed for the 2-payment PfP arrangement. MSAC noted that the 12-month complete response rate in the ZUMA-7 trial was approximately 65% in a study population with a median age of 59 years. In comparison, the median age is higher (~70-79 years) for the Australian non-Hodgkin Lymphoma population (AIHW, 2017). MSAC agreed with ESC that a 2-payment PfP may not have the same risk of a higher average price paid in the 2L setting due to a higher response rate being observed in this population. MSAC noted that ESC highlighted that if the price of AXI was reduced by ███% ($███), this would achieve a similar (although slightly lower) price to that previously supported by MSAC and that such a reduction would reduce the ICER to $███ per quality-adjusted life-year (QALY) gained. Therefore, MSAC considered that the risk sharing arrangement should include either a 2-payment PfP arrangement that achieves the price previously supported by MSAC in the 3L setting (i.e. $███ per successfully infused patient), or a single payment of up to $███ per successfully infused patient.

MSAC considered that acceptable plans to ensure accurate and complete registry data for expensive therapies such as CAR-T are essential and should be a pre-requisite for funding of AXI in 2L setting. MSAC advised that Australian data be collected and reviewed by MSAC no later than 3 years post the commencement of public subsidy of AXI for treatment of R/R LBCL in the 2L setting for the purposes of understanding the clinical place, utilisation, equity of access and budget impact of AXI for R/R LBCL in Australian clinical practice.

Overall, MSAC supported public funding through the NHRA of AXI in 2L setting for R/R LBCL contingent on a risk sharing arrangement that included the following requirements:

- a single payment of up to $███ that corresponds to an incremental cost effectiveness ratio of $█ per quality adjusted life year; or
- a pay for performance arrangement constructed to achieve an average price of $███ per successfully infused patient based on a ███% response rate; and
- limit of one successful CAR-T infusion per lifetime; and annual patient caps to remain as per current deed for AXI in 3L that has annual caps of █ patients in the first year and ███ in the second year; and
- review of the data to be conducted by MSAC no later than 3 years post the commencement of public subsidy of AXI (for treatment of R/R LBCL in the 2L) for the purposes of understanding the clinical place, utilisation, equity of access and budget impact of AXI for R/R LBCL in Australian clinical practice. Subsequent to an initial review, MSAC may advise whether further review of the clinical effectiveness and cost-effectiveness is warranted.

4. Background

Chimeric antigen receptor (CAR) T-cell products (including AXI in the 3L setting) are funded as Highly Specialised Therapies under the Addendum to the National Health Reform Agreement 2020-2025 (NHRA).

In January 2020, MSAC supported the public funding for AXI for patients with CD19-positive Diffuse Large B Cell Lymphoma (DLBCL), Primary Mediastinal B Cell Lymphoma (PMBCL) and Transformed Follicular Lymphoma (TFL) in the 3L setting (MSAC 1587). Additionally, MSAC has supported tisagenlecleucel (Kymriah®) in certain patients with CD19-positive DLBCL, PMBCL and TFL in this 3L setting (MSAC 1519.1, MSAC 1653 and MSAC 1676). Both are currently being jointly funded by the Commonwealth and the States under the NHRA.

In March 2023, MSAC considered and did not support public funding for AXI as a treatment for R/R LBCL in the 2L setting. From the evidence provided in the MSAC 1722 ADAR, MSAC considered that it was uncertain whether AXI demonstrated durable survival outcomes relative to standard of care, and that AXI had an inferior safety profile. MSAC also considered that the incremental cost-effectiveness ratio (ICER) was highly uncertain and was underestimated due to the optimistic extrapolation of survival favouring AXI. This was driven by the use of event-free survival (EFS) as a primary endpoint was likely to be biased in favour of the AXI arm. Table 1 summarises the key matters of concern that were raised when MSAC previously considered MSAC application 1722, and the commentary's assessment of how the issues were addressed.

Table 1   Summary of key matters of concern from MSAC regarding MSAC application 1722

Component	Matter of concern	Commentary assessment of how the resubmission ADAR has addressed matter of concern
Clinical effectiveness and use of primary effectiveness outcomes in economic analysis	MSAC considered that from the evidence presented, it was uncertain whether AXI demonstrated durable survival outcomes relative to SoC.	Commentary considered addressed. The inclusion of OS as primary effectiveness outcome helps mitigate concerns previously raised by MSAC in MSAC 1722 PSD surrounding reliance on EFS. Updated OS data indicated that AXI was associated with a statistically significant long-term survival benefit over SoC.
Appropriateness of primary clinical effectiveness outcome	MSAC was concerned with the use of EFS as a primary endpoint, which was likely to be biased in favour of AXI.	Commentary considered addressed. The use of OS as the primary outcome and PFS in the economic model helped mitigate concerns previously raised by MSAC in MSAC 1722 PSD surrounding reliance on EFS. However, the commentary considered that the methods to estimate PFS had some issues, specifically: • Patients who had new lymphoma therapy were censored without documented evidence of disease progression. • Bias may be introduced from the timing of assessments post-randomisation, which may overestimate the PFS benefit (i.e., those progressed at Day 50-60 may not be picked up until Day 100, adding an extra 40-day survival). • Patients were censored earlier/progressed more quickly in the SoC arm than the AXI arm, which is a known issue with unblinded trials. • Censoring beyond 18 months was high and the curves began to merge at 29 months follow up.
Economic model specification	MSAC considered the validity of a mixed mixture cure fraction and its use to extrapolate OS based on too short trial follow-up	Commentary considered addressed. The inclusion of OS as primary effectiveness outcome and use of PFS (instead of EFS) in the economic model helped mitigate concerns previously raised by MSAC in MSAC 1722 PSD surrounding reliance on EFS. The resubmission ADAR continued to use a mixture cure

	problematic, along with the use of EFS.	modelling approach for the economic evaluation of AXI in the base case (which was more strongly supported by the addition of the extended follow up evidence) but provided an alternate base case using a partitioned survival model also.
Input variables in economic model	MSAC considered that the modelled frequency of use of 3L+ CAR T-cell therapies in the SoC arm, the costs and disutilities of adverse events, and intensive care unit stays and IVIG usage were not adequately incorporated into the model. This approach favoured AXI.	Commentary considered partially addressed. The revised model included the costs of grade 3+ CRS, neurotoxicity, IVIG therapy and neutropenia. The ADAR argued that applying AE disutilities separately, would be double counting the effects of AEs on the time on treatment utilities as the utilities were based on the ZUMA-7 trial. This would be appropriate; however, the timing of collection of QoL was done when AXI would have very little toxic effects (day one of administration) SoC QoL data was collected at any point beyond 5 days after initiation of salvage chemotherapy and the end of the cycle (day 21) during which the nadir of toxic effects would be experienced at some point. This favoured AXI and was not addressed in the model.
Eligibility criteria for use in practice	MSAC considered that clear eligibility criteria for treatment were not provided. This is required to better define the proportion of patients who would be expected to be treated with AXI in the 2L setting.	Commentary considered addressed. Proposed clinical and treatment criteria for AXI in the 2L setting were provided in the resubmission ADAR (Table 1-7 in ADAR; Table 2 below). The ADAR presented that these criteria will help to ensure suitable patients who can tolerate CAR T-cell therapy were identified for treatment (i.e., improved patient selection to ensure optimal outcomes of treatment are achieved).
Cost-effective price of treatment	MSAC advised that a price for AXI should be ascertained at which it is acceptably cost-effective.	Commentary considered partially addressed. The value of AXI treatment relative to current SoC treatment, as measured by a cost effectiveness ratio, was $██/QALY gained. The ADAR Proposed RSA and PfP criteria for AXI in the 2L
Pricing of the intervention	MSAC noted that the price of AXI had not been adequately justified, and no payment for performance or risk sharing criteria were proposed.	Commentary considered addressed. Proposed RSA and PfP criteria for AXI in the 2L setting were provided in the resubmission ADAR (Table 1-7 in ADAR;). ██████████████
Usage inputs and impact on financial estimates	MSAC noted that the estimate of patients R/R no more than 12 months after completion of 1L treatment and who would be candidates for treatment with AXI (80%) was not justified, nor any reference provided.	Commentary considered addressed. The ADAR used a midpoint of 67%, which is between the Gilead Advisory Board's advice (60%) and the Maurer et al. (2014) study (specifying most relapse occur within the first few years after completing 1L treatment, and 75% appeared to be a proxy for "most"). The commentary considered that this 67% estimate seemed an appropriate representation – though noting the potential variability in the estimate, and that Maurer et al., 2014 "shows that 70% of DLBCL relapses occur within the first year from diagnosis".
High and uncertain budget impact	Due to the lack of clearly defined eligibility criteria for AXI and lack of clarity around the costs of administration and treatment of AE, and the extent of use of 3L CAR T-cell therapies in Australian clinical practice, MSAC considered that the actual budget impact could be higher (i.e. underestimated).	Commentary considered partially addressed. The resubmission ADAR's financial estimates included the costs of Grade 3+ adverse events. The commentary considered that the updated financial projections offered a more robust method for estimating the utilisation of 3L CAR T-cell therapy in Australian clinical settings and how funding for AXI in 2L impacts the utilisation of 3L+ CAR T-cell therapies. However, the way the comparisons were employed in the ADAR underestimates the budget impact of funding AXI in 2L.

High and uncertain budget impact	MSAC noted that the estimated net budget impact to the NHRA was uncertain, in particular due to the lack of clearly defined eligibility criteria for AXI and lack of clarity around costs of administration and treatment of AEs.	Commentary considered partially addressed. The resubmission ADAR provided updated eligibility criteria for treatment of patients who would be expected to be treated with AXI in the 2L setting. The resubmission ADAR also provided additional sensitivity analyses regarding costs of administration and treatment of AEs. However, the commentary considered that the way the comparisons were employed in the ADAR's calculations underestimates the budget impact of funding AXI in 2L.

Source: Table ES-1 in MSAC ADAR 1722.1; MSAC 1722 PSD.
Abbreviations: 2L=second-line; 3L=third-line; ADAR=Applicant-Developed Assessment Report; AE=adverse event; ALL=acute lymphoblastic leukaemia; AXI=axicabtagene ciloleucel; CAR-T=Chimeric Antigen Receptor T-Cell; CRS=Cytokine Release Syndrome; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; IVIG=Intravenous Immunoglobulin; MSAC=Medical Services Advisory Committee; NHRA=National Health Reform Agreement; PMBCL=primary mediastinal large B-cell lymphoma; PSD=Public Summary Document; PfP=Pay for Performance; OS=overall survival; QoL=quality of life; RSA=Risk Share Agreement; SoC=standard of care; TFL=transformed follicular lymphoma.

5. Prerequisites to implementation of any funding advice

Axicabtagene ciloleucel is included on the Australian Register of Therapeutic Goods (ARTG 400895) for the following indications:

YESCARTA® is a genetically modified autologous immunocellular therapy for the treatment of:

- Large B-cell Lymphoma - Patients with relapsed or refractory large B-cell lymphoma (LBCL).
- YESCARTA® is not indicated for the treatment of patients with primary central nervous system lymphoma.
- Follicular Lymphoma - Patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

6. Proposal for public funding

Public funding for AXI for the treatment of R/R LBCL in the 2L setting was sought through the NHRA, as was the case for AXI for treatment of DLBCL in the 3L setting. That is, funding AXI using the same funding mechanisms for certain patients at an earlier stage in the treatment algorithm (i.e., in 2L rather than 3L setting).

The proposed technology would be delivered in select tertiary hospital treatment centres who specialise in delivery of CAR T-cell therapy.

A summary of the proposed request for public funding is provided in Table 2 showing the indication requested, and the proposed clinical and treatment criteria. Table 2 encompasses the eligibility criteria for treatment to better define the patients who would be expected to be treated with AXI in the 2L setting (as suggested by MSAC in the MSAC 1722 PSD).

The ADAR proposed that a pay for performance (PfP) and risk sharing arrangement (RSA) include:
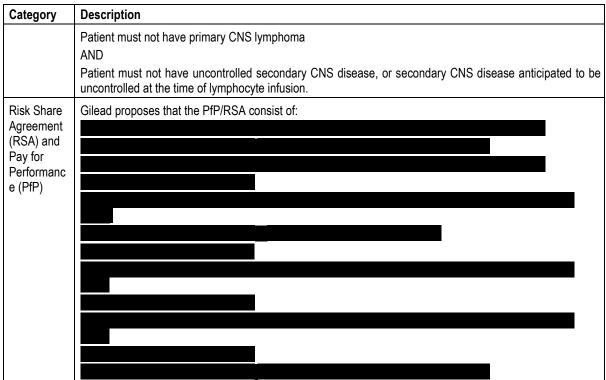
a)
b)

c)

d)
e)

The ADAR stated that the PfP and RSA details based on the principles above will ensure that payment made for each patient who is successfully infused with AXI and who achieved an agreed clinical response reflects a cost-effective price for AXI in the resubmission. However, no details on the RSA or PfP have been provided by the ADAR.

The proposed average price paid per successfully infused patient for AXI is $███, which was used in the economic modelling and the financial estimates was the same as the cost in the 3L setting. The ADAR did not provide the payment amounts and response rates that will be used in the PfP to achieve an average price of $███.

Table 2   Proposed clinical, treatment and public funding criteria

Category	Description

Indication	Adult patients with CD 19 positive LBCL who are relapsed or refractory no more than 12 months after first-line chemoimmunotherapy
	 • LBCL includes the following types defined by the WHO in 2016:
	    o DLBCL, NOS (including ABC or GCB)
	    o DLBCL arising from FL
	    o DLBCL associated with chronic inflammation
	    o DLBCL + EBV
	    o HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement
	    o T-cell/histiocyte-rich LBCL
	    o Primary cutaneous DLBCL, leg type
	    o PMBCL*
	 • First-line therapy must include (at a minimum):
	    o An anti-CD20 monoclonal antibody unless the investigator determined that the tumour was CD20 negative, and
	    o An anthracycline-containing chemotherapy regimen

Clinical criteria	**FOR TFL:** The condition must have relapsed after, or be refractory to, at least one prior chemoimmunotherapy administered after disease transformation. **FOR ALL OTHER LBCL:** The condition must have relapsed after, or be refractory to, at least one prior chemoimmunotherapy **FOR ALL INDICATIONS:** Patient must have a WHO performance status of 0 or 1 AND Patient must have sufficient organ function, including: • Renal function: Creatinine clearance >40mL/min, serum ALT/AST <5 x ULN and total bilirubin <2 x ULN • Cardiac function: absence of symptomatic heart failure (i.e. NYHA grade <2), cardiac left ventricular ejection fraction >/= 40%, or supplementary functional tests and cardiology assessment demonstrating adequate cardiopulmonary reserve. • Pulmonary function: Baseline peripheral oxygen saturation >91% on room air, in the absence of anaemia AND The treatment team must consider the patient's condition can be effectively managed during lymphocyte collection and manufacturing, to allow for the absence of rapidly progressive disease at the time of lymphocyte infusion.
Treatment criteria	Patient must be treated in a tertiary hospital with appropriate credentials AND Patient must be treated by a haematologist working in a multi-disciplinary team specialising in the provision of CAR-T cell therapy AND Patient must not have uncontrolled infection, including uncontrolled HIV or active hepatitis B or C infection AND

Category	Description
	Patient must not have primary CNS lymphoma AND Patient must not have uncontrolled secondary CNS disease, or secondary CNS disease anticipated to be uncontrolled at the time of lymphocyte infusion.
Risk Share Agreement (RSA) and Pay for Performance (PfP)	Gilead proposes that the PfP/RSA consist of: ███████████████████████████████ ████████████████████████████ ███████████████████████████████ ████████████ █████████████████████████████████████ ████████████████████████████ ██████████████ █████████████████████████████████████ ██████████████ ████████████████████████████████████ ████████████ ████████████████████

Source: Table 1-7 in MSAC ADAR 1722.1.

Abbreviations: 2L=second-line; AXI=axicabtagene ciloleucel; ABC=activated B-cell; ALT=alanine transaminase; AST=aspartate transaminase; CAR-T=Chimeric Antigen Receptor T-Cell; CNS= central nervous system; DLBCL=diffuse large B-cell lymphoma; EBV=Epstein-Barr Virus; FL= follicular lymphoma; GCB= germinal center B-cell; HGBL=High-grade B-cell lymphomas; LBCL=large B-cell lymphoma; NOS=not otherwise specified; NYHA= New York Heart Association; PMBCL=primary mediastinal large B-cell lymphoma; PfP=Pay for Performance; RSA=Risk Share Agreement; TFL=transformed lymphoma; ULN=upper limit of normal

*PMBCL (primary mediastinal B-cell lymphoma) histology was excluded in ZUMA-7 because therapy in the 2L setting often utilizes radiation therapy, which is an EFS event and would have confounded the primary endpoint. Clinical advice (Gilead Advisory Board, 4th September 2023) is that patients with PBMCL would show potential difference in outcomes), and that transformed FL can transform from other low grade histologies and patients would benefit from axicabtagene ciloleucel in 2L setting.

7. Population

The ADAR's proposed population was adult patients with LBCL who are refractory or have relapsed no more than 12 months after the completion of first-line therapy.

The proposed intervention would be available in the 2L setting, meaning the following key changes to the clinical management pathway and use of downstream services would occur compared to existing practice:

1) Reduced use of the comparator (SoC) in the 2L setting (see Section 6 below). AXI would substitute for salvage chemotherapy and, in a proportion of patients who respond to chemoimmunotherapy, would also substitute high-dose chemotherapy (HDT) + autologous stem cell transplant (auto-SCT). However, of note AXI will not fully replace SoC in the 2L setting for several reasons (e.g., failure of leukapheresis, preference, access). Because of this, and due to relapse after 12 months of treatment, use of CAR-T cell therapy is still relevant in the 3L setting.

2) Reduced use of CAR T-cell therapy in the 3L setting (both AXI and tisagenlecleucel). MSAC have previously recommended to limit to one successful CAR-T infusion per lifetime for R/R DLBCL (MSAC 1587). Also, there is currently no clinical evidence for the use of a second line of CAR T-cell therapy should an individual progress. This would lead to very limited use of tisagenlecleucel in Australia, though noting that tisagenlecleucel is still the only CAR T-cell therapy option for paediatric acute lymphoblastic leukaemia in Australia.

3) Patients would be eligible to receive SoC post CAR T-cell therapy in the 2L setting, and this would include salvage chemotherapy with or without stem cell therapy. In ZUMA-7, ~10% of patients received stem cell therapy in the 3L setting.

8. Comparator

The ADAR's proposed comparator was standard of care (SoC), which typically consisted of:

1) Salvage chemoimmunotherapy (typical regimens are funded under PBS for the population of interest) followed by collection of peripheral stem cells. For patients who respond well to this step (in practice only 35% to 40%), then received

2) Myeloablative HDT and rescue by means of auto-SCT (HDT + auto-SCT).

The commentary noted that at the time of initiating salvage chemoimmunotherapy (i.e., step 1 of SoC), there were no clear indicators for which patients would respond well and therefore become candidates for HDT + auto-SCT (i.e., step 2 of SoC). The prognosis of patients who do not respond to salvage chemoimmunotherapy (and who, therefore, cannot undergo SCT), and some patients who do not achieve long-term remission after SCT, is poor.

The clinical, economic, and financial evidence presented by the ADAR included 3L CAR T-cell therapy in the comparator arm as part of current SoC. This was an issue raised during ESC's previous consideration of MSAC 1722 ADAR. The ADAR's rate of use of CAR T-cell therapies in 3L (based on the use in the ZUMA-7 trial) did not match what is seen in Australian clinical practice; therefore, the commentary noted that utilisation in 3L for the comparator an important consideration.

The commentary considered that the comparator outlined by the ADAR was appropriate.

9. Summary of public consultation input

A summary of previous consultation feedback received for MSAC Application 1722 is available in the Public Summary Document:
http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1722-public

Further consultation input for this resubmission was received from four (4) professional organisations, two (2) consumer organisations and nine (9) individuals (8 medical specialists and one consumer). The six (6) organisations that submitted input were:
- Australia and New Zealand Transplant and Cellular Therapies (ANZTCT)[i]
- Australasian Leukaemia and Lymphoma Group (ALLG)
- Australasian Lymphoma Alliance (ALA)
- Barwon Health
- Lymphoma Australia
- Rare Cancers Australia

The feedback was supportive of the application.

The applicant's pre-MSAC response also provided a letter of support from the chair of the National Cellular Immunotherapy Patient Prioritisation Committee (NCIPPC) on behalf of participating clinicians.

Benefits:
The feedback indicated the main benefits include:
- The treatment would benefit patients unable to tolerate autologous stem-cell transplant and receiving palliative chemotherapy. Patients whose disease relapses have a very poor

prognosis, and many are not considered suitable or sufficiently fit for high-dose chemotherapy and autologous stem-cell transplant. Bringing AXI into second line of treatment will increase physician familiarity with CAR-T therapy and frequency of use, potentially resulting in treatment for patients closer to home.
- Being able to access the treatment would reduce the exposure of patients to ineffective second line chemotherapy. Also considering that a significant number of patients fail to access CAR-T therapy in the third line setting due to disease progression or the accumulation of toxicities from conventional therapy.
- Clinical evidence has demonstrated that a substantial and clinically meaningful proportion of patients have a complete response after this treatment.
- With CAR-T therapy, patients spend less time in hospital and experience less severe side effects.
- CAR-T therapy is a one-time treatment.
- Less demand for transplant services.
- Increase access to CAR-T for those patients unable to access next-generation CAR-T therapy in clinical trials.

Disadvantages:
The feedback noted the following disadvantages:
- AXI has a documented adverse event profile, although the feedback considered this to be at manageable levels with better preventative and management strategies, informed by the centres delivering the treatment.
- There is substantial resource demand associated with the proposed treatment. The feedback suggested that since CAR-T takes time to manufacture, planning patients for CAR-T at first relapse is important to enable more patients to be treated.

Other Feedback
The toxicity of the treatment along with the initial inpatient and outpatient care requirements needs to be understood by the patient and family/carer.

Lymphoma Australia noted that patients are not receiving access to CAR-T despite a positive recommendation and the lack of a centralised and robust data is leading to an incomplete and potentially misleading capture of patient outcomes in Australia. Lymphoma Australia also noted issues impacting the efficiency in delivery of CAR-T (e.g. bridging therapies, time access/manufacture) and expressed concern that the therapy will be deemed not cost-effective due to an ineffective process and framework to deliver and measure CAR-T in Australia. Several respondents stated that Australia is well behind in the use of CAR-T as a global standard of care across several indications.

A greater number of hospitals both in metropolitan and some regional centres need to be approved as new CAR-T centres rather than it being streamlined to a handful of hospitals. For patients in rural and regional areas, they could be away from home for up to 30 days for post care monitoring. In regard to additional services and support required for patients who may access this treatment the feedback identified the following: psychology, pathology before the treatment, dietitian, physiotherapy/rehabilitation and after nurse care coordinator, along with travel support.

10. Characteristics of the evidence base

The clinical analysis presented in the ADAR was based on direct evidence from the ZUMA-7 trial. The comparative evidence base for AXI for treating LBCL in the 2L setting has not changed since previously considered by MSAC (MSAC 1722 ADAR). However, updated data from the ZUMA-7 randomised controlled trial (RCT) is provided. The original ADAR (MSAC 1722) presented median follow-up of 24.9 months; the resubmission presented median follow-up of 47.2 months.

The ADAR reported that the ZUMA-7 trial was a high quality RCT directly comparing AXI to SoC for 359 adult patients with LBCL who were refractory to or who had relapsed no more than 12 months after completion of 1L chemoimmunotherapy. Key features of the trial are detailed in Table 3.

As raised in the MSAC 1722 ADAR commentary, and agreed by MSAC in the 1722 PSD, there remained "some concerns" associated with the risk of bias of the ZUMA-7 trial (as assessed by the commentary with the Cochrane risk of bias tool [RoB 2]), and that these biases were likely to favour AXI. Key areas where the commentary was concerned that bias may have been introduced were:

- Inability to blind clinicians and investigators to the treatment arms (potentially introducing performance bias).

- Measurement error (ascertainment error); there was flexibility in the timing of assessment and given that clinicians knew which arm their patients were in they may also have been inclined to see their SoC patients earlier (earlier ascertainment of progression) (PET-CT had a -7 +14-day window for first assessment) so that they could move their patients to the new ("better") treatment faster. It is unclear how this would affect the results of the trial but could likely overestimate the PFS/EFS benefit (i.e., those who progressed on day 50–60 may not be picked up until day 100, adding an extra 40-day survival).

- It was unclear as to the reasons why patients were transferred to a "new lymphoma therapy" (considered an event) in the absence of a disease progression event, this could also be influenced by clinicians being unblinded. There were more such incidents in the SoC arm and hence this favoured the AXI arm.

The analysis presented in the ADAR and utilised in the economic model was based on the full analysis set (FAS), defined as all randomised patients when all patients had the opportunity to be followed for the Month 9 disease assessment (i.e., the Month 9 timepoint had passed for all patients).

Table 3   Key features of the included evidence

Reference	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
AXI versus SoC in the 2L setting						
ZUMA-7 trial	N=359 Interventio n: N=180 SoC: N=179	Open label multi-centre RCT; 47.2-month median follow-up	*Some concerns*	LBCL refractory to or relapsed no more than 12 months after completion of 1L treatment with chemoimmun otherapy	• OS • EFS; PFS • Proportion of patients administered definitive therapy • ORR; CRR • Duration of response • TTNT • HRQoL • Quality-adjusted survival • Percentage of patients having AXI infused of those who underwent leukapheresis • Time from leukapheresis to infusion of AXI • Incidence of AEs and SAEs • Incidence of special interest events (CRS, infection and febrile neutropenia, neurologic events, cytopenia (neutropenia, thrombocytopenia, anaemia)) • Healthcare resource use and associated costs • Incremental cost per LYG • Incremental cost per QALY • Number of patients suitable for treatment • Number of patients who receive treatment and associated financial implications	Yes, PFS, OS, Disposition of Yescarta® and SoC patients, TTNT, QALYs.

Source: ZUMA-7 CSR
Abbreviations: 1L=first-line; 2L= second-line; AE=adverse events; AXI=axicabtagene ciloleucel; CRR=complete response rate; CRS=Cytokine Release Syndrome; EFS=event-free survival; HRQoL=health-related quality of life; LBCL=large B-cell lymphoma; LYG=life year gained; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; RCT=randomised control trial; SAE=serious adverse event; SoC=standard of care; TTNT=time to next treatment.

11.   Comparative safety

The evidence base for safety of AXI for treating LBCL in the 2L setting was the same as previously considered by MSAC (MSAC 1722 ADAR) and derived from the ZUMA-7 trial. The resubmission ADAR provided updated data from the ZUMA-7 trial with extended follow up.

The commentary considered that the adverse event (AE) profile of AXI in the ZUMA-7 trial was consistent with the profile observed in other studies of CAR T-Cell therapy in patients with relapsed or refractory LBCL. The frequency of AEs, including those of grade 3 or higher and of serious AEs, was high in both the AXI and SoC arms of the trial (all patients experienced at least one treatment-emergent AE); however, it was higher in the AXI arm. The commentary calculated a significantly higher risk for participants in the AXI arm of any ≥Grade 3 AE (RR=1.09, 95%CI 1.01, 1.19).

The AE profile differed between the two arms in the ZUMA-7 trial, with the incidence of cytokine release syndrome and neurologic events being higher in the AXI group, and the incidence of febrile neutropenia being higher in the SoC group. A summary of the treatment-emergent AEs

from the ZUMA-7 trial are presented in Table 4; the right hand column presents differences in ≥Grade 3 AEs calculated as part of the commentary.

Fatal adverse events considered by trial investigators to be treatment-related occurred in 1 patient (hepatitis B virus reactivation) in the AXI arm, and two patients in the SoC arm (cardiac arrest and acute respiratory distress syndrome).

Table 4   Most common treatment-emergent adverse events, cytokine release syndrome, and neurologic events observed in ZUMA-7

	AXI (n=170)		SoC (n=168)		Difference in Grade ≥3*
	Any grade	Grade ≥3	Any grade	Grade ≥3	RR (95% CI)
Any adverse event — no. (%)	170 (100)	155 (91)	168 (100)	140 (83)	**1.09 (1.01, 1.19)**
Pyrexia	158 (93)	15 (9)	43 (26)	1 (1)	**14.82 (1.98, 110.97)**
Neutropenia†	121 (71)	118 (69)	70 (42)	69 (41)	**1.69 (1.37, 2.08)**
Hypotension	75 (44)	19 (11)	25 (15)	5 (3)	**3.76 (1.44, 9.83)**
Fatigue	71 (42)	11 (6)	87 (52)	4 (2)	2.72 (0.88, 8.37)
Anaemia	71 (42)	51 (30)	91 (54)	65 (39)	0.78 (0.58, 1.04)
Diarrhea	71 (42)	4 (2)	66 (39)	7 (4)	0.56 (0.17, 1.89)
Headache	70 (41)	5 (3)	43 (26)	3 (2)	1.65 (0.4, 6.78)
Nausea	69 (41)	3 (2)	116 (69)	9 (5)	0.33 (0.09, 1.2)
Sinus tachycardia	58 (34)	3 (2)	17 (10)	1 (1)	2.96 (0.31, 28.22)
Leukopenia‡	55 (32)	50 (29)	43 (26)	37 (22)	1.34 (0.92, 1.93)
Thrombocytopenia§	50 (29)	25 (15)	101 (60)	95 (57)	**0.26 (0.18, 0.38)**
Chills	47 (28)	1 (1)	14 (8)	0	-
Hypokalaemia	44 (26)	10 (6)	49 (29)	11 (7)	0.9 (0.39, 2.06)
Hypophosphatemia	45 (26)	31 (18)	29 (17)	21 (13)	1.46 (0.87, 2.43)
Tremor	44 (26)	2 (1)	1 (1)	0	-
Cough	42 (25)	1 (1)	18 (11)	0	-
Decreased appetite	42 (25)	7 (4)	42 (25)	6 (4)	1.15 (0.4, 3.36)
Confusional state	40 (24)	9 (5)	4 (2)	0	-
Hypoxia	37 (22)	16 (9)	13 (8)	7 (4)	2.26 (0.95, 5.35)
Aphasia	36 (21)	12 (7)	0	0	-
Dizziness	36 (21)	2 (1)	21 (13)	1 (1)	1.98 (0.18, 21.59)
Constipation	34 (20)	0	58 (35)	0	-
Vomiting	33 (19)	0	55 (33)	1 (1)	-
Hypomagnesemia	20 (12)	1 (1)	34 (20)	4 (2)	0.25 (0.03, 2.19)
Febrile neutropenia	6 (4)	6 (4)	46 (27)	46 (27)	**0.09 (0.03, 0.23)**
Infection	76 (44.7)	28 (16.5)	53 (31.5)	20 (11.9)	1.38 (0.81, 2.36)
CRS* — no. (%)	157 (92)	11 (6)	—	—	
Pyrexia — no./total no. (%)	155/157 (99)	14/157 (9)	—	—	
Hypotension — no./total no. (%)	68/157 (43)	18/157 (11)	—	—	
Sinus tachycardia — no./total no. (%)	49/157 (31)	3/157 (2)	—	—	
Chills — no./total no. (%)	38/157 (24)	0/157	—	—	
Hypoxia — no./total no. (%)	31/157 (20)	13/157 (8)	—	—	
Headache — no./total no. (%)	32/157 (20)	2/157 (1)	—	—	
Neurologic event* — no. (%)	103 (61)	36 (21)	33 (20)¶	1 (1)	**35.58 (4.93, 256.53)**

	AXI (n=170)		SoC (n=168)		Difference in Grade ≥3*
	Any grade	Grade ≥3	Any grade	Grade ≥3	RR (95% CI)
Tremor	44 (26)	2 (1)	1(1)	0	-
Confusional state	40 (24)	9 (5)	4 (2)	0	-
Aphasia	36 (21)	12 (7)	0	0	-
Encephalopathy	29 (17)	20 (12)	2 (1)	0	-
Paraesthesia	8 (5)	1 (1)	14 (8)	0	-
Delirium	3 (2)	3 (2)	5 (3)	1 (1)	2.96 (0.31, 28.22)

Source: Table 2-14 of the ADAR; Table S6, Westin 2023

Abbreviations: AXI=axicabtagene ciloleucel; CI=confidence interval; CRS=Cytokine Release Syndrome; SoC=standard of care; RR=relative risk

*Statistically significant differences between arms are displayed in bold.

†Neutropenia refers to the combined preferred terms of neutropenia and neutrophil count decreased; ‡ Leukopenia refers to the combined preferred terms of leukopenia and white-cell count decreased; § Thrombocytopenia refers to the combined preferred terms of thrombocytopenia and platelet count decreased; ¶ Other preferred terms that were reported in 1 or 2 patients in the standard-care arm included agitation, cognitive disorder, depressed level of consciousness, hallucination, lethargy, somnolence, taste disorder, anisocoria, bradyphrenia, visual hallucination, head discomfort, hypoesthesia, memory impairment, neuralgia, and nystagmus; * any-grade events of cytokine release syndrome that occurred in at least 15% of the patients in the AXI arm, and any-grade neurologic events that occurred in at least 15% of patients in the AXI or at least 3% of those in the SoC arm.

The ADAR stated that in ZUMA-7, toxicities in the SoC arm were only reported up until the time of an event (after which patient follow-up ceased). Therefore, in relative terms, the number of patients followed for toxicity in the AXI arm was double that of SoC. The commentary acknowledged that the difference in follow-up for toxicity makes differences in safety unclear; however, it does not provide direct support for the claim of noninferior safety of AXI and it should be noted that toxicities tend to occur in the early follow-up period.

The ADAR stated that as clinicians gain experience in the use of AXI, AE rates observed in practice have been falling and are anticipated to fall further. Evidence of this was provided as naïve comparisons across the ZUMA-1 trial and data from real-world practice (Table 1-4 and 1-5 of ADAR). However, the commentary considered further detail on the clinical link between experience and rates of AEs had not been explored. As well, the role of training and workforce in supporting the reduction and management of AEs for AXI needed to be considered.

Clinical claim

MSAC previously concluded that the evidence provided in the initial MSAC 1722 ADAR did not support the clinical claim that the use of AXI in patients with LBCL refractory to, or relapsed no more than 12 months after, completion of 1L treatment with chemoimmunotherapy results in noninferior safety compared with SoC.

Although the resubmission ADAR had again claimed that AXI treatment for R/R LBCL in the 2L setting has noninferior safety compared with SoC, the commentary considered that the updated evidence provided in the resubmission ADAR did not demonstrate sufficient rationale to change MSAC's original conclusion.

12. Comparative effectiveness

The initial MSAC 1722 ADAR presented evidence from ZUMA-7 based on a follow-up of 24.9 months (data cut-off 18 March 2021), whereby both EFS and PFS endpoints favouring AXI were met with a trend of OS benefit. The resubmission ADAR presented ZUMA-7 results based on follow-up of 47.2 months (latest data cut off 25 January 2023). With a longer median follow-up, evidence included primary OS analysis favouring AXI over SoC (HR=0.73; 95% CI: 0.54-0.98). In

addition, other key outcomes such as EFS and PFS remained statistically significantly superior to AXI over SoC. Key clinical effectiveness results are presented in Table 5.

Blinded central assessment for other outcomes was due to cease after primary PFS assessment (first data cut-off; March 2021). In addition to these results presented in MSAC 1722 ADAR, the resubmission ADAR presented results from non-blinded investigator assessment) aligning with the time of primary OS analysis (data cut off 25 January 2023). The commentary considered that though investigator assessment provided more recent data, there is potential for bias in favour of AXI as it was not blinded and therefore investigators may be more likely to assess SoC outcomes more critically and progress participants faster in the SoC arm.

Table 5   Key clinical effectiveness results from the ZUMA-7 trial

Outcome*	MSAC 1722 ADAR Median follow-up 24.9m		MSAC 1722.1 ADAR Median follow-up 47.2m	
	AXI	*SoC*	*AXI*	*SoC*
Proportion of patients administered definitive therapy, n (%)	170 (94.4)	62 (34.6)	No change/additional information reported in the resubmission ADAR	
TTNT (median duration), months (95% CI)	14.7 (6.5, NE)	3.4 (3.1, 4.4)		
Difference (95% CI)	**HR: 0.43 (0.33, 0.56)**			
Deaths (all cause), n (%)	72 (40)	85 (47)	82 (46)	95 (53)
Median OS, months (95% CI)	NR (28.3, NE)	35.1m (18.5, NE)^	NR (28.6m, NE)	31.1m (17.1m, NE)
Difference (95% CI)	HR: 0.73 (0.53, 1.01)		**HR: 0.73 (0.54, 0.98)**	
Median EFS, months (95% CI)	8.3m (4.5, 15.8)	2.0m (1.6, 2.8)	10.8m (5.0, 25.5)	2.3m (1.7, 3.1)
Difference (95% CI)	**HR: 0.40 (0.31, 0.51)**		**HR: 0.42 (0.33, 0.55)**	
Median PFS, months	14.7m (5.4, NE)+	3.7m (2.9, 5.3)+	14.7m (5.4, 43.5)	3.7m (2.9, 5.3)
Difference (95% CI)	**HR: 0.49 (0.37, 0.65)**		**HR: 0.51 (0.38, 0.67)**	
Median duration of response, months (95% CI)	26.9m (13.6, NE)	8.9m (5.7, NE)	41.7m (13.6, NE)	7.8m (5.0, NE)
Difference (95% CI)	HR: 0.74 (0.49, 1.11)		Not reported	
ORR, %	83%	50%	83%	45%
Difference (95% CI)	**33.1% (23.2, 42.1)**		Not reported	
CRR, %	65%	32%	61%	34%

Source: Table ES-2 from MSAC 1722.1 ADAR; Locke et al. 2022; Westin et al. 2023
Abbreviations: ADAR= applicant developed assessment report; AXI=axicabtagene ciloleucel; CI=confidence interval; CR=complete response; EFS=event free survival; HR=hazard ratio; NE=not estimable; NR=not reached; ORR=overall response rate; OS=overall survival; PFS=progression free survival; SoC=standard of care; TTNT=time to next treatment.
Statistically significant differences between arms are displayed in bold.
^Presented results are from an interim analysis from a Clinical Study Report addendum, not included in the original MSAC 1722 ADAR submission but previously considered by ESC and MSAC in MSAC 1722 PSD.
+Presented results were not reported in MSAC 1722 ADAR or PSD (instead median PFS duration was reported in the ADAR). Median PFS analysis results were reported in Locke 2022 which included the OS interim analysis. These have been included in this summary to provide comparison to results presented in the resubmission ADAR.

Overall survival

The primary OS analysis was conducted at a median follow-up of 47.2 months (range, 39.8 to 60.0). It showed a statistically significant improvement in OS with AXI over SoC (HR for death, 0.73; 95% confidence interval [CI], 0.54 to 0.98; p = 0.03 by stratified two-sided log-rank test). At the time of the primary analysis of the updated data, 82 deaths (any cause) had been reported in the AXI arm and 95 deaths in the SoC arm. The median OS had not been reached (95% CI: 28.6

months to not estimable) in the AXI arm and was 31.1 months (95% CI: 17.1 to not estimable) in the SoC arm. The KM estimates of OS at 5-years after randomisation were 53.1% (95% CI: 45.2%, 60.5%) in the AXI arm and was not estimable in the SoC arm. There was considerable censoring of patients beyond 40 months of follow-up, and it is important that outcomes beyond this time were interpreted with caution.
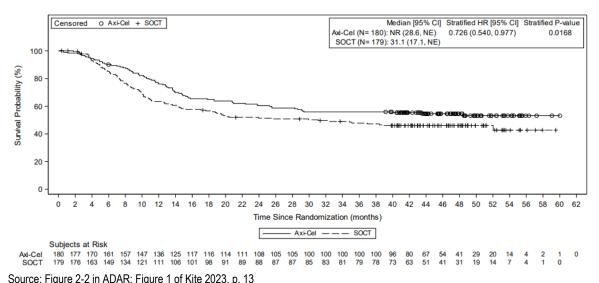
Figure 1   KM Plot of OS by treatment in ZUMA-7 (updated analysis for FAS; data cut-off: 25 Jan 2023)

Source: Figure 2-2 in ADAR; Figure 1 of Kite 2023, p. 13
Abbreviations: Axi-cel=axicabtagene ciloleucel; CI=confidence interval; FAS=full analysis set; HR=hazard ratio; NE=not estimable; NR=not reached; SOCT=standard of care therapy

Event-free survival (EFS) and progression-free survival (PFS)[2]

The ADAR reported that in blinded central assessment, at the time of the data cut-off, 252 EFS events had occurred for 108 patients (60%) in the AXI arm and 144 patients (80%) in the SoC arm. AXI treatment was superior to SoC, with a stratified HR of 0.40 (95% CI: 0.31, 0.51; stratified log-rank p<0.0001). The results of the investigator assessment (data cut off 25 January 2023) were in concordance with the blinded assessment, with a stratified HR of 0.42 (95% CI: 0.33, 0.55).

In blinded central assessment, median PFS was 14.7 months (95% CI: 5.4 months, not estimable) in the AXI arm and 3.7 months (95% CI: 2.9, 5.3 months;) in the SoC arm, with a stratified HR of 0.49 (95% CI: 0.37, 0.65). The results of the investigator assessment (data cut off 25 January 2023) were in concordance with the blinded assessment, with a stratified HR of 0.51 (95% CI: 0.38, 0.67).

In addition to risk of bias concerns associated with non-blinded investigator assessment, the commentary also noted concerns in how censoring and progression of patients impacted EFS and PFS results which had previously been raised in MSAC 1722 PSD. Patients who had new lymphoma therapy were censored without documented evidence of disease progression (detailed on page p.66 and p.70 of ZUMA-7 CSR). Censoring reasons are presented in Table 6 below.

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[2]   EFS was defined as the time from randomization to the earliest date of disease progression per the Lugano Classification, commencement of new lymphoma therapy, or death from any cause. PFS was defined as the time from randomization to disease progression per the Lugano Classification as determined by investigator assessment or death from any cause (ZUMA-7 CSR).

Table 6 Censoring reasons per central and investigator assessment

Censoring reason	Blinded central assessment (data cut-off 18 March 2021)		Non-blinded investigator assessment (data cut-off 25 January 2023)	
	AXI	*SoC*	*AXI*	*SoC*
PFS				
Response ongoing, n (%)	76 (42)	28 (16)	71 (39)	29 (16)
New lymphoma therapy, n (%)	9 (5)	61 (34)	6 (3)	37 (21)
No post-baseline disease assessment, n (%)	0 (0)	1 (1)	0 (0)	1 (1)
Full withdrawal of consent, n (%)	0 (0)	1 (1)	0 (0)	2 (1)
Lost to follow up, n (%)	0 (0)	2 (1)	2 (1)	4 (2)
Subsequent stem cell transplant, n (%)	0 (0)	2 (1)	-	-
Axicabtagene ciloleucel retreatment, n (%)	2 (1)	0 (0)	-	-
Response assessed but no disease at baseline and post- baseline, n (%)	0 (0)	3 (2)	-	-
EFS				
Response ongoing, n (%)	72 (40)	28 (16)	NR	NR
Response assessed but no disease at baseline and post- baseline, n (%)	0 (0)	3 (2)	NR	NR
No post-baseline disease assessment, n (%)	0 (0)	1 (1)	NR	NR
Full withdrawal of consent, n (%)	0 (0)	1 (1)	NR	NR
Lost to follow up, n (%)	0 (0)	2 (1)	NR	NR

Abbreviations: AXI=axicabtagene ciloleucel; EFS=event-free survival; PFS=progression-free survival; NR=not reported;
Source: Table 5 ZUMA-7 CSR Flash Memo 2023; Table 13, Table 20 ZUMA-7 CSR 2021.

Duration of response

In blinded central assessment, direction of response for the AXI arm was 26.9 months (95% CI: 13.6 months, not estimable; range: 0 [+] to 29 [+] months) compared with 8.9 months (95% CI: 5.7 months, not estimable; range: 0 [+] to 32 [+] months) for the SoC arm. There was no significant difference between AXI and SoC in terms of duration of response (stratified HR: 0.736; 95% CI: 0.488, 1.108), though there was crossover of the survival arms near the end of follow up.

Non-blinded investigator assessed median duration of response (data cut off 25 January 2023) was 41.7 months (95% CI, 13.6 to not estimable) and 7.8 months (95% CI, 5.0 to not estimable), in the AXI and SoC arms, respectively.

Response rates

The overall response rate (ORR) for patients in the AXI arm was 83%, compared with 50% for patients in the SoC arm, with a difference between treatment arms of 33.1% (95% CI: 23.2, 42.1); and an odds ratio comparing the AXI arm with the SoC arm of 5.31 (95% CI: 3.08, 8.90) at data cut-off of 18 March 2021 using blinded central assessment. The difference in ORR was driven by differences in complete response (CR) rates. CR rates in the AXI arm and the SoC arm were 65% and 32%, respectively, with a difference between treatment arms of 32.6% (95%CI: 22.8%, 42.4%). The likelihood of achieving CR with AXI (65%) was double that observed for SoC (32%) of ZUMA-7.

At the time of the primary OS analysis (data cut-off: 25 January 2023), the investigator assessed ORR was 83% (61% CR) in the AXI arm and 45% (34% CR) in the SoC arm. At time of data cut-off, 71/180 (39%) and 29/179 patients (16%) in the AXI arm and SoC, respectively, had an ongoing response.

Proportion of patients administered definitive therapy

Of the 179 patients who were randomised to the SoC arm of ZUMA-7, 168 of the 179 (94%) randomised patients received ≥ 1 cycle of salvage chemoimmunotherapy; however, only 34.6% of patients in the SoC arm received the target potentially curative treatment (AXI or HDT + auto-SCT). In the AXI arm, 94% of patients were successfully infused with AXI.

Quality-adjusted overall survival

Quality-adjusted OS was conducted using Q-TWiST analysis, which was not presented in initial MSAC 1722 ADAR. Results suggested that AXI was associated with statistically significant (and the ADAR argued a clearly clinically important) (≥15%) gains in quality-adjusted OS compared to SoC, regardless of the relative decline in QoL associated with treatment toxicity, disease progression, or additional cancer treatment. Additionally, in threshold analysis, results suggested that regardless of a patient's relative preferences for avoiding AEs and EFS events, AXI would give a greater Q-TWiST time and would be preferred. However, the commentary identified some limitations which should be considered in interpretation, namely that analysis considered only AEs of grade ≥3, although less severe AEs also may affect QoL, and a fixed utility value for all AEs of interest was used, regardless of the grade or type of the AE which is unlikely to reflect true utility preferences.

Evidence to support long-term outcomes of AXI (evidence from ZUMA-1 and international CAR T-cell registries)

The ADAR presented evidence from the ZUMA-1 trial to demonstrate long term outcomes of AXI in patients with R/R LBCL. Overall survival is presented in Figure 2, showing a plateau after approximately 18-24 months. The OS curve of ZUMA-1 shows 43% of patients treated with AXI in the 3L+ setting were alive at 5 years, with a median overall survival of 25.8 months.

The ADAR proposed that this similar plateau in mortality risk in ZUMA-1 and ZUMA-7 was evidence of long-term durability of survival benefits of AXI treatment, and therefore applicable to this application. The ADAR also presented real-world data from large international CAR-T therapy registries which showed consistency in clinical effectiveness outcomes across five countries.

While these findings appear to support long term treatment effect of AXI, the commentary considered ZUMA-1 was a single arm study in a later line of therapy and offered limited information for comparison with SoC for longer-term outcomes in the 2L setting.
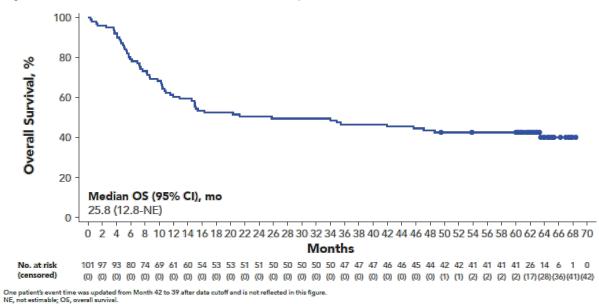
Figure 2   Overall survival in ZUMA-1 at median follow-up of 63.1 months

One patient's event time was updated from Month 42 to 39 after data cutoff and is not reflected in this figure.
NE, not estimable; OS, overall survival.

Source: Figure ES-5 of MSAC 1722.1 ADAR; Report on long term outcomes with axicabtagene ciloleucel in 3L+ setting from the ZUMA-1 trial provided to MSAC Secretariat from Gilead Sciences in February 2023.
Abbreviations: CI=confidence interval; OS=overall survival

Clinical claim

MSAC previously concluded that, from the evidence presented for evaluation in the initial MSAC 1722 ADAR, it was uncertain whether AXI demonstrated durable survival outcomes relative to SoC for the treatment of R/R LBCL in the 2L setting. The resubmission ADAR provided longer term evidence which added durability to the survival outcomes relative to the SoC.

The commentary considered that the updated evidence provided in the resubmission ADAR demonstrated that a clinical claim of superior effectiveness is likely to be appropriate; however, the magnitude of effect was likely to be lower for response, and progression outcomes based on study design limitations.

13.   Economic evaluation

Overview and rationale of the economic evaluation

Based on the ADAR's clinical claim of superiority in clinical effectiveness and noninferior safety, the ADAR presented the results of a cost-utility analysis examining the cost-effectiveness of AXI substituting SoC for the treatment of patients with LBCL refractory to or relapsed no more than 12 months after completion of 1L treatment with chemoimmunotherapy. The analysis was based on extrapolation of the outcomes from the ZUMA-7 trial using data from the most recent data cut point (25 January 2023). The commentary considered a cost-utility analysis, based on a clinical claim of superior effectiveness and non-inferior safety, was appropriate.

The ADAR used a mixture cure modelling (MCM) approach to extrapolate OS and PFS (in place of EFS) as the base case with the addition of a more standard approach to parametric extrapolations of OS and PFS presented in sensitivity analysis. Specifically, the ADAR used an 'uninformed' MCM model in which the cure faction was a parameter of the model and estimated alongside other parameters directly from ZUMA-7 trial data.

Mixture cure models are increasingly used where treatment potentially leads to a cure after a certain period. In contrast to traditional survival analysis, where the assumption is that all

patients are at risk of disease-related death, the cure model allowed for characterisation of the heterogeneity in the plateau areas of survival plots by splitting patients into those who are cured (i.e., those with the approximately the same mortality hazard as the general population) and those who are not (i.e., those with higher mortality hazard than the general population).

The initial MSAC 1722 ADAR used MCM based on 24 months follow up, which MSAC previously had considered to be problematic due to the limited period of follow up. The marked immaturity of the data in MSAC 1722 ADAR produced highly variable estimates of cure fractions ranging from 24% to 54% in the AXI arm and 35 to 49% in the SoC arm. This resulted in modelled cost-effectiveness estimates that were highly uncertain and overly optimistic. In comparison, cure fractions in this resubmission ADAR as estimated for each of the functional forms for the mixture cure model cure showed significantly less variability with cure fractions in the AXI and SoC arms of 50% to 54% and 41% to 45%, respectively. In addition, EFS was a primary outcome measure in MSAC 1722 ADAR, and its extrapolation lacked clinical plausibility since in both arms the proportion of patients experiencing events dropped below the cure fraction by 6 months follow up. While some patients may later experience a cure due to third line treatment it is unlikely that it is at the level that the ADAR had proposed.

Robust estimates of MCMs require two key elements: (1) data from studies with follow-up times that are longer than the anticipated point of cure time, and (2) enough patients at risk at the end of follow-up in order to robustly estimate a cure fraction. The commentary had concerns about both issues. Although the OS KM plot for the AXI arm in ZUMA-7 in MSAC 1722.1 ADAR approximated a plateau towards the end of follow up indicating the likelihood that the remaining population consisted of both 'cured' and 'uncured' patients, the data were heavily right censored and there were small numbers at risk at the tail of follow which introduced uncertainty around cure fraction estimates.
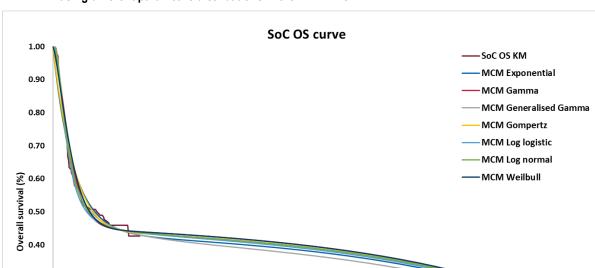
Based on the totality of evidence presented in the updated submission, the commentary considered the use of a mixture cure model was a reasonable choice of modelling approach and produced reliable estimates of cost-effectiveness when compared to appropriately specified standard parametric modelling (PSMs).

Key evidence which the commentary considered when coming to this conclusion included:

- Recent literature regarding modelling approaches to survival data in the presence of a cure fraction indicated MCMs generally produced more accurate and reliable extrapolations of OS and PFS compared to standard parametric distributions. They also allowed for the changes in the hazards of death overtime observed in ZUMA-7.

- Results of long-term follow-up of ZUMA 1 demonstrated an approximate plateau at the end of 5 years of follow up which supported the assumption that a proportion of patients treated with AXI in a 2L setting can be considered cured'. Although AXI was used in a different line in ZUMA-1 (3L) compared to 2L in ZUMA-7, the mechanism of action of AXI was the same in each case and a cure in a proportion of patients in ZUMA-7 was likely based on biological plausibility.

- Studies of other chimeric antigen receptor (CAR) T cell such as tisagenlecleucel and lisocabtagene had demonstrated survival trajectories that also plateaued during follow up supporting a cure fraction for AXI due to the commonality of action of this class of drugs.

- With significantly increased follow up OS KM curves showed evidence of a sustained plateau in AXI arm of ZUMA-7 suggestive of a cure in a proportion of patients. However, the ZUMA-7 data was heavily right censored and there were small numbers at risk at the tail of follow up which introduced uncertainty in estimates of cure fractions.

- Close concordance of projections of PFS and OS estimates produced by the MCM's using data from interim cut points with observed data at the final cut point suggested that the trial data was sufficiently mature that uncertainty surrounding the extrapolation of cost-effectiveness estimates was significantly reduced compared to the previous MSAC 1722 ADAR.

- Convergence and stabilisation of the cure fractions estimated via the MCM across all distributions used for extrapolations of OS and PFS.

Although the survival extrapolations for AXI and SoC using a MCM were different, within in each arm all parametric distributions used for extrapolation produce very similar trajectories for OS. See Figure 3 and Figure 4.

Figure 3   Kaplan-Meier OS curve of observed trial data for the SoC arm with extrapolations of OS over 30 years using different parametric distributions in the ADAR MCM

Abbreviations: KM=Kaplan-Meier; MCM=mixture cure model; OS=overall survival; SoC=standard of care;
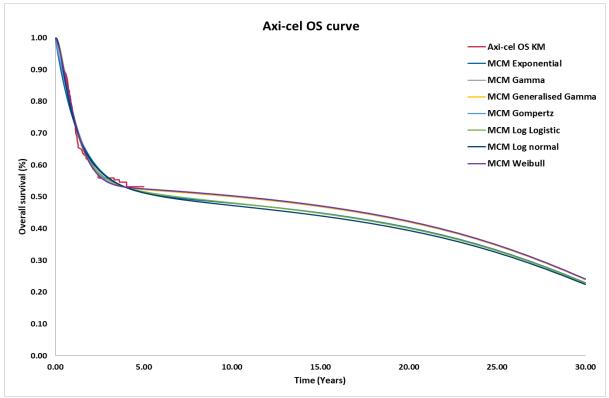Source: Figure 3.3, p 118 of MSAC 1722.1 ADAR

Figure 4   KM OS curve of observed trial data for the AXI arm with extrapolations of OS over 30 years using different parametric distributions in the ADAR MCM

Source: Figure 3.4, p 118 of the ADAR

Consistent with MSAC advice, the revised economic model used a 5% discount rate for costs and health outcomes (compared to 3.5% in the previous submission) and the time horizon was 30 years (reduced from 40 years). The use of a 30-year time horizon was determined appropriate by the commentary given differences in PFS and OS demonstrated in the data from the most recent data cut point of the ZUMA-7 trial, and that the benefits of lower incidence of progression and death will accrue over the fullness of time. The use of PFS in the economic model mitigated concerns about the reliance on EFS in the initial MSAC 1722 ADAR.

Table 7 summarises the key characteristics of the economic evaluation presented in the resubmission ADAR.

Table 7   Summary of the economic evaluation

Component	Description
Perspective	Personal health of person receiving intervention for outcomes Health care system perspective for costs (i.e., costs associated with provision of health care resources regardless of who bears the actual cost)
Population	Patients with confirmed LBCL refractory to or relapsed no more than 12 months after completion of 1L treatment with chemoimmunotherapy
Comparator	Standard of care consisting of salvage chemotherapy ideally followed by myeloablative high-dose chemotherapy and stem cell rescue by means of an autologous stem cell transplant. However, only patients who demonstrate adequate disease response after salvage chemotherapy and for whom a sufficient number of stem cells have been collected are able to receive HDT and an auto-SCT
Type(s) of analysis	Cost-effectiveness (cost per additional life-year) and cost-utility analyses (cost per additional quality-adjusted life-year)
Outcomes	Healthcare resource use and associated costs (including pre- and post-infusion), presented in disaggregated and aggregated format. Incremental cost per life year gained (LYG) Incremental cost per quality adjusted life year (QALY)
Time horizon	30 years in the base case (vs median follow-up of 47.2 months for the key trial)
Computational method	Mixed cured model with a partitioned survival analysis model for comparison
Generation of the base case	Modelling (ZUMA-7 trial did not follow all patients through to death therefore modelling was required)
Health states	Event free, progressed and death (a treatment phase health state was also employed in the model)
Cycle length	1 months
Transition probabilities	Transition probabilities were driven by data from the ZUMA-7 trial and a mixed cure model with survival extrapolation beyond the follow up of the trial. A partitioned survival model without the assumption of a cure fraction has been included for comparison.
Discount rate	5% for both costs and outcomes
Software	Excel

Source: Table 3-2, p 100-101 of the ADAR
Abbreviations: 1L=first line; LBCL=large B-cell lymphoma; HDT=high-dose chemotherapy; SCT=stem cell transplant; LYG=life-year gained; QALY=quality-adjusted life-year

Results

The results of the ADAR base case using a mixture cure model are presented in Table 8. For extrapolation of OS a gamma distribution was used for the AXI arm and generalised gamma distribution was used for the SoC arm. For PFS a loglogistic distribution was used for the AXI arm and a generalised gamma for the SoC arm. The choice of distributions by ADAR was based on the how well the extrapolation fitted the observed data, the statistical fit using AIC and BIC values, and expert opinion.

Table 8   Results of the ADAR base case using a mixture cure model.

Treatment	Total			ICER
	Costs	LYs	QALYs	
AXI	$█████	7.95	6.82	-
SoC	$285,765	6.52	5.49	-
Incremental	**$█████**	**1.43**	**1.33**	**$███ /LYG** **$███ /QALY**

Source: Table 3-35 of ADAR. Abbreviations: 2L=second line; AXI=axicabtagene ciloleucel; ICER=incremental cost-effectiveness ratio; LYG=life-year gained; QALY=quality-adjusted life year; SoC=standard of care

Over a 30-year time-horizon and using a 5% discount rate, the total per patient cost of AXI treatment was $████, and the cost of SoC was $285,765, respectively, leading to an incremental cost of $████. Over the same time horizon, AXI patients accrued 6.82 QALYs compared to 5.49 QALYs for patients in the SoC arm – an increase of 1.33 QALYs. Patients in the AXI arm survived for an additional 1.43 LYs compared to the SoC (Total Lys AXI arm – 7.95; SoC arm – 6.52) demonstrating that the QALY gain was the result of both survival gain and improvement in HRQoL. The ICERs for AXI compared to SoC were $████/LYG and $████/QALY.

One-way sensitivity analyses

The key results of univariate sensitivity analyses presented in the ADAR and calculated by the commentary are presented in Table 9.

Table 9 Results of key sensitivity analyses showing the effect of parameter uncertainty on the ADAR base case economic model

Base case setting	Scenario setting	Incremental		ICER	% change in ICER from base case
		Costs	QALYs		
Base case		**$██**	**1.33**	████	████
Discount rate: 5% per annum	No discounting	$██	2.45	████	████
	3.5% discounting	$██	1.57	████	████
Progression free health state utility source: Zuma-7 EQ-5D-5L based on Australian Tariffs **Post progression health state utility source**: Zuma-1 EQ-5D-5L UK inflated tariffs	**Progression free health state utility source**: Zuma-7 EQ-5D-5L based on UK Tariffs **Post progression health state utility source**: Zuma-1 EQ-5D-5L UK tariffs as observed	$██	1.35	████	████
	Progression free health state utility source: Published literature (Roth et al., 2018[61]) **Post progression health state utility source**: Published literature (tisagenlecleucel 3L DLBCL NICE submission[62])	$██	1.41	████	████
Age related utility adjustment: **Yes**	Age related utility adjustment: **No**	████	1.31	████	████
Base Case: SMR = 1.09 (Maurer et al., 20214)	Alternative SMR = 1 (Assumed same as general population)	████	1.34	████	████
	Alternative SMR = 1.18 (Maurer et al., 20214)	████	1.31	████	████
Subsequent Treatment: Base	**Subsequent Treatment**: Scenario analysis includes all subsequent	████	1.33	████	████

Base case setting	Scenario setting	Incremental		ICER	% change in ICER from base case
		Costs	QALYs		
Base case		$■	**1.33**		
case analysis based on subsequent treatments used in the previous ADAR	therapies administered in the ZUMA-7 trial				
Additional sensitivity analyses conducted by the commentary					
Time horizon (base case = 30 years)	20 years		1.13		
	40 years		1.37		
Cost of auto SCT (base case = $49,950)	10% increase		1.33		
	10% decrease		1.33		
Proportion receiving auto-SCT (base case = 34.6%)	10% increase		1.24		
	10% decrease		1.24		
Proportion of patients receiving subsequent therapies in the AXI arm (base case = 48.9%)	10% increase		1.33		
	10% decrease		1.24		
Proportion of patients receiving subsequent therapies in the SoC arm (base case = 71.5%)	10% increase		1.33		
	10% decrease		1.33		
Proportion of patients receiving 3L AXI in the SoC arm (base case = 70%)	10% increase		1.33		
	10% decrease		1.33		
AXI on-treatment utility (base case 0.883)	0.879 (same as SoC on-treatment utility)		1.33		
Off treatment pre-event utility (base case = 0.891)	10% decrease		1.25		
	10% increase		1.41		
Post progression utility (base case = 0.818)	10% decrease		1.41		
	10% increase		1.24		
Time point at which utility reverts to population norms (base case – 5 years)	10 years		1.33		
	20 years		1.32		
	Never		1.34		
Baseline age (base case = 57.2 years (based on ZUMA-7 trial population	55 years		1.37		
	60 years		1.26		

Source: Table 4.34 ADAR and calculated during commentary

Abbreviations: AIC=Akaike information criterion, ADAR=applicant-developed assessment report; BIC=Bayesian information criterion; MCM=Mixture cure model; OS=Overall Survival; PFS=Progression-Free Survival; SMR=Standard Mortality Ratio; SoC=Standard of Care; UK=United Kingdom

The impact on the base case ICER using different published utility values for patients in remission in 3L DLBCL receiving CAR-T therapies was provided in applicant's pre-ESC response and is presented in the table below.

Table 10. Comparison of ICER with different post progression utility values.

	On trt – Axi-cel	On trt -SoC	Progression free "Off" treatment	Post progression	ICER ($/QALY)	% change in ICER from base case
Base case	0.883	0.879	0.891	0.818	███████	
TIS Irish submission[3]				0.83	███████	
Axi-cel MSAC (Zuma 1)[4]				0.844	███████	
Axi-cel – USA*[5]				0.782	███████	
Axi-cel – USA#[6]				0.823	███████	
CAR-T - USA[7]				0.820	███████	

Source: Table 2 of applicant Pre-ESC response
Abbreviations: Axi-cel = AXI/axicabtagene ciloleucel; ICER= incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; MSAC=Medical Services Advisory Committee; SoC= standard of care; trt= treatment;
*in remission with <6 months of follow-up; #: in remission with >=6 months of follow-up

Structural uncertainty of modelling approach

Mixture cure model

The ADAR presented scenario analysis to determine the sensitivity of the base case MCM to changes in the distribution used for extrapolation of OS. In these scenarios, the distribution for OS was changed in the AXI or SoC arm with all other functional forms remaining unchanged from the base case. The plausibility of the distributions was determined by the ADAR using visual inspection of the KM curves, statistical fit as determined by AIC and BIC values and expert opinion. Additional scenario analyses were conducted during the commentary of other clinically plausible OS extrapolations.

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[3] Carey, N., et al., (2023) Cost-utility and value of information analysis of tisagenlecleucel for relapsed/refractory diffuse large B-cell lymphoma in the Irish healthcare setting. *J Mark Access Health Policy*, 11(1): p. 2166375.
[4] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1587-public
[5] Roth, J.A., et al., (2018) Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. *J Med Econ*, 21(12): p. 1238-1245
[6] ibid
[7] Oluwole, O.O., et al., (2022) Cost-effectiveness of axicabtagene ciloleucel versus lisocabtagene maraleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in the US. *J Med Econ*,. 25(1): p. 541-551.

Table 11 Scenario analyses of the base case MCM economic model demonstrating the sensitivity of the MCM to changes in the OS distributions for extrapolation in the AXI and SoC arms whilst all other functional forms remained unchanged

Base case setting	Scenario setting	Incremental		ICER	% change in ICER from base case
		Costs	QALYs		
Base case		▉	1.33	▉	▉
Axicabtagene ciloleucel OS extrapolation: MCM Gamma (lowest AIC/BIC combined value)(Cure fraction=53.64%) This presents a comparison of variation in the ADAR MCM base compared to scenarios using the MCM where the distribution used for extrapolation of the AXI was changed whilst all other PFS and OS distributions remained unchanged from the base case. That is, the distribution for OS for SoC in the base case MCM is the gamma distribution. For PFS, loglogistic was used in the AXI arm and PFS in the SoC arm was generalised gamma. Note: the loglogistic distribution had an identical combined AIC/BIC value indicating similar statistical fit.	**Axicabtagene ciloleucel OS extrapolation: MCM Loglogistic** (lowest AIC and second lowest BIC value)(Cure fraction=51.05%)	▉	1.18	▉	▉
	Axicabtagene ciloleucel OS extrapolation: MCM Weibull (=second lowest combined AIC/BIC)(Cure fraction=53.90%	▉	1.35	▉	▉
	Axicabtagene ciloleucel OS extrapolation: MCM Generalised gamma (=second lowest combined AIC/BIC)(Cure fraction=53.69%)*	▉	*1.33*	▉	▉
	Axicabtagene ciloleucel OS extrapolation: MCM lognormal (fourth lowest combined (second lowest combined AIC/BIC)(Cure fraction=51.24%)*	▉	*1.12*	▉	▉
SoC OS extrapolation: MCM Generalized gamma (Best statistical fit based on lowest combine AIC/BIC value)(Cure fraction=41.36%) This presents a comparison of variation in the ADAR MCM base compared to scenarios using the MCM where the distribution used for extrapolation of the SoC was changed whilst all other PFS and OS distributions remained unchanged from the base case That is, the distribution for OS for the AXI arm in the base case MCM is the gamma distribution. For PFS, loglogistic was used for the AXI arm and generalised gamma in the SoC arm	**SoC OS extrapolation**: MCM Log-normal (second lowest combined AIC/BIC value)(Cure fraction=44.47%)	▉	1.17	▉	▉
	SoC OS extrapolation: MCM Log-logistic (third best curve based on AIC/BIC value)(Cure fraction=44.05%)	▉	1.20	▉	▉
	SoC OS extrapolation: Gamma (forth best curve based on AIC/BIC value)(Cure fraction=45.20%)*	▉	*1.10*	▉	▉
	SoC OS extrapolation: Weibull (fifth best curve based on AIC/BIC value)(Cure fraction=45.16%)*	▉	*1.10*	▉	▉

Source: Table 4.34 p161 ADAR and *calculated during commentary

The results showed the MCM was sensitive to changes in the distribution used for extrapolation of OS with ICERs varying between $▉ (▉%) to $▉ (▉%). The commentary judged that of the scenarios presented, those presented by the ADAR to be the more clinically plausible. The significantly reduced variability of ICER values generated by the ADAR MCM compared to the previous model presented in MSAC 1722 ADAR demonstrated a significant increase in the robustness of the model.

Partitioned survival model using standard parametric distributions for extrapolation

The ADAR presented ICER estimates for two scenarios using a standard parametric PSM. The plausibility of the distributions was determined by the ADAR using visual inspection of the KM curves, statistical fit as determined by AIC and BIC values and expert opinion. Those distribution that had OS in the SoC care less than AXI arm in ZUMA-7 at 5 years follow up were considered implausible. The commentary judged the two scenarios were the most likely extrapolations based on clinical plausibility. The results are summarised below in Table 12.

Table 12 Results of scenario analyses using a standard partitioned survival model

Distribution used for extrapolation	AXI		SoC		Costs	QALYs	ICER	% change from base case
	PFS	OS	PFS	OS				
Scenario 1	Gompertz	Log-normal	Generalised gamma	Log-normal		1.43		
Scenario 2	Gompertz	Gompertz	Generalised gamma	Gompertz		1.23		

Source: Table 4-34 MSAC 1722.1 ADAR
Abbreviations: AXI=axicabtagene ciloleucel; OS=overall survival; ICER=incremental cost-effectiveness ratio; PFS=progression free survival; QALY=quality-adjusted life-year; SoC=standard of care.

For ease of comparison the commentary included the survival curves of the base case MCM (Figure 4) alongside the survival curves for each scenario generated by the standard PSM (Figure 5 and Figure 6).
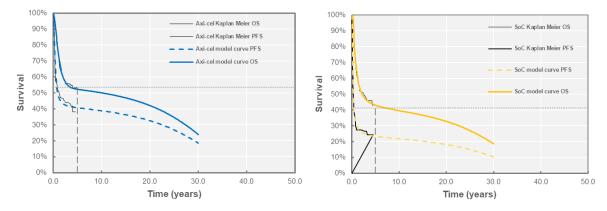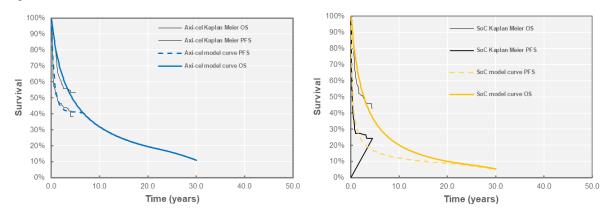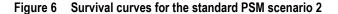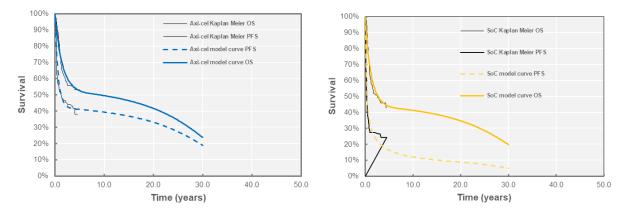
Figure 4   Survival curves for the base case mixture cure model

Figure 5 Survival curves for the standard PSM scenario 1

Figure 6 Survival curves for the standard PSM scenario 2

Whilst both scenarios were clinically plausible, the trajectories of the survival curves in scenario two from a standard PSM followed those of the base case MCM more closely than scenario one. In addition, the ICERs for the MCM and the standard PSM had comparable ICERs ($████ for the PSM and $████ for the MCM), further supporting the use of a MCM as a reasonable modelling approach. The commentary also noted that in scenario one the modelled PFS after 5 years was higher than OS curve, though the economic model was structured to ensure that if this was the case, participants entered the death state.

Table 13   Key drivers of the model

Description	Method/Value	Impact Base case: $ ▮ /QALY gained
Parametric function applied to extrapolate OS	Compared to all other standard parametric functions, the base case distribution (gamma) favours AXI.	High, favours AXI
The proportion of patients receiving CAR T-cell therapy in 3L.	The ADAR assumes that a large proportion of patients that received standard care in 2L would then go on to receive a CAR T-cell therapy in 3L	High, favours AXI
Post-progression utility	The post-event utility in the SoC is likely to be better that that demonstrated in ZUMA-1 (from which the base case utility is derived) since treatment post-event in ZUMA-7 consists not only of BSC but also 3L CAR-T therapy. The way the utilities are applied in the model, means that QALYs are overestimated in favour of axicabtagene.	Moderate, favours AXI
Off treatment pre-event utility	It is unlikely that HRQoL data captures the profiles of change around health states accurately or reliably. Thus, there is significant uncertainty estimates of health state utilities derived from ZUMA-7 trial data. Their application in the model favours axicabtagene	Uncertain, likely favours AXI

Abbreviations: 2L=second line; 3L=third line; AXI=axicabtagene ciloleucel; BSC=best supportive care; CAR-T=chimeric antigen receptor T-cell; HRQoL=health-related quality of life; OS=overall survival; QALY=quality-adjusted life-years; SoC=standard of care.

The commentary acknowledged that the more mature OS data added to the robustness of the MCM approach to the economic evaluation.

The commentary considered the possible biases resulting from the conduct of the ZUMA-7 trial driving the model, and assumptions about the derivation and application of health state utilities, meant that there remained uncertainty in the economic evaluation unrelated to the statistical approach to modelling. The unblinded, open-label nature of the ZUMA-7 trial was considered to be at significant risk of ascertainment bias for a number of outcomes, and there were significant concerns regarding the impact of censoring.

Ascertainment bias

PFS using investigator-assessed data was used, and likely favoured the AXI arm. Clinicians, whose primary consideration is the benefit of their patients, may report progression sooner in the SoC arm to enable earlier access to AXI treatment. Also contributing to the risk of ascertainment bias was the flexibility in the date of assessment of progression (concerns further detailed in Section 8). Heavy censoring early in the KM curve for PFS in the SoC arm compared to the AXI arm supported the presence of ascertainment bias.

Censoring

The trial protocol stipulated those patients who had new lymphoma therapy (except for HDT, TBI for HDT, and auto-SCT while in a protocol therapy-induced response) were censored at their last evaluable disease assessment date before commencement of the subsequent therapy even if they were without documented evidence of disease progression when the new therapy was commenced. The commentary considered this a violation of the assumption of independence of censoring times resulting in PFS estimates that were likely biased and unreliable. There was also significant censoring of participants in the OS analysis post-40 months which may reflect lack of maturity of the data; median survival in the AXI arm has not been met.

Health state utilities

The differential timing at which health state utilities were recorded was likely to favour AXI. On-treatment utility for AXI was likely to be overestimated since utility data were collected outside of the period when treatment side effects and major AEs were likely to be experienced. Conversely, on-treatment utilities in the SoC arm were likely to be underestimated, as these were collected at least 5 days after the intuition of salvage chemotherapy, which was sufficiently long enough for side effect and AEs associated with treatment to have arisen.

There was considerable variation in the time at which utilities in the SoC arm were collected. Salvage chemotherapy cycles are typically 21 days in length with all chemoimmunotherapeutic drugs delivered on day 1, accompanied with prednisolone for days 1-5. Hence, data on HRQoL may have been collected at any point between 5 and 21 days after the initiation of salvage chemotherapy. The commentary considered it was unlikely that the time of collection of HRQoL data captured the profiles of change around health states accurately or reliability.

The commentary considered there was insufficient evidence to support the assumption that the proportion of the cohort event free after 5 years would incur general population age and sex-adjusted utilities beyond 5 years in line with the 'cure' assumption.

CAR T-cell therapy is a novel treatment with an entirely different mechanism of action and toxicity profile compared to SoC. Given that the inflammatory and other toxicities that may arise in the short-term following treatment remain poorly understood, the commentary believed that it was not appropriate to conclude that CAR T-cell therapy was free from long term effects among patients considered "cured". There was insufficient follow-up to determine whether patients treated with CAR T-cell therapy would suffer long term effects (such as development of secondary malignancies) that impact their QoL or the incidence of any such effects. Thus, the commentary considered there was significant uncertainty surrounding estimates for utility values beyond 5 years.

Issues with the justification of modelling approach

The commentary noted that whilst the AIC (Akaike information criteria) and BIC (Bayesian information criteria) were used to guide the selection of models that best fit the data within the length of follow-up, they provided little information about how well the model extrapolated to longer time points. A 'good statistical fit' based on AIC/BIC values with the range of data may nevertheless lead to implausible extrapolations. The ADAR acknowledged the best statistical fit was largely similar across model functions and suggested that clinical plausibility would be an important determinant of the most appropriate models. However, other than stating 'long-term survival estimates (were) based on feedback from clinical experts', the ADAR had provided limited justification for the choice of functional form used for extrapolation. The commentary further noted that eliciting unbiased and meaningful judgements from clinical experts was challenging and highlighted that there were no standard elicitation methods used to capture uncertainty in experts' beliefs.

Key drivers are presented for the MCM model in Table 13, and were the parametric function applied to extrapolate OS and the proportion of patients receiving CAR T-cell therapies in 3L+ setting in SoC arm, followed by post-progression and progression-free 'off-treatment' health state utilities.

Summary

Traditional extrapolation methods such a partitioned survival models do not easily accommodate the complex hazards associated with treatments such as CAR-T where a proportion will never experience the event of interest i.e., they are patients considered cured. However, they continue to be applied in this context and represent the baseline against which to compare more flexible methods.

The commentary acknowledged the significant increase in the robustness of the MCM in this resubmission due to the use of trial data with significantly longer follow. In addition, the commentary noted the close concordance of ICER estimates produced by the MCM base case and an appropriately specified PSM support the reliability of the results of the ADAR economic evaluation. However, extrapolation beyond observed trial data using standard PSMs or more flexible approaches such as MCMs were unavoidably uncertain.

Whilst the standard parametric PSM produced similar estimates compared to the base case MCM, they were significantly dependent of model specification i.e., the distribution used for extrapolation.

14. Financial/budgetary impacts

Justification of the approach and data sources

The ADAR used an epidemiological approach to budget impact analysis to estimate the uptake of the proposed technology.

The ADAR provided a tabulated summary of the issues raised by MSAC and how they were addressed in the resubmission; these are summarised in Table 14.

Table 14   Summary of key financial issues identified in the MSAC 1722 ADAR and approach taken in the current resubmission

The key issue in MSAC 1722 ADAR	Approach taken in the current MSAC 1722.1 ADAR
The estimate of 40% for the proportion of patients who are refractory or who relapse after completion of 1L chemoimmunotherapy is derived from Maurer 2014. This appears to be the upper-end estimate of the 20-40% provided.	The ADAR base case estimate used 30% (the mid-point from Maurer 2014). The commentary considered this was appropriate and sensitivity analyses were conducted given the variability in the estimates.
The estimate of 42% for the proportion of NHL that is LBCL is derived from incidence calculations based on 2021 of 2,500-2,670 cases of LBCL per year. 42% (2670/6400=41.7%) appears to be the upper-end estimate provided.	The ADAR included sensitivity analyses to assess the sensitivity and robustness of these estimates. However, the base case estimate is likely overestimated, as Sehn & Salles, 2021 stated that LBCL represents 30% of all NHL.
MSAC raised the issue of out-of-pocket costs not being included in the model, particularly around hotel costs for those patients who have to stay near to a treatment centre.	The ADAR stated that a patient support program via Rare Cancers Australia which covers transport and accommodation costs for patients is funded by the applicant. The ADAR stated that over half the patients who have received Yescarta® have had their expenses covered by this program. There are no data to support this claim.
The ADAR did not provide a budgetary analysis breakdown for different jurisdictions (i.e., Commonwealth versus state or MBS versus PBS). The assessment team attempted to calculate this, but some cost assumptions	The ADAR stated that due to the overlapping funding responsibilities between the Commonwealth and the States, robust data to inform further cost breakdowns between jurisdictions and between different funding programs are not available. This is only applicable to the cost of CAR-T not the

The key issue in MSAC 1722 ADAR	Approach taken in the current MSAC 1722.1 ADAR
aggregated administration and pharmacy costs, which precluded breakdown.	other costs associated with its administration and should have been considered in the ADAR,
High and uncertain budget impact –Due to the lack of clearly defined eligibility criteria for axicabtagene ciloleucel and lack of clarity around the costs of administration and treatment of AE and the extent of use of 3L+ CAR T in Australian clinical practice, the actual budget impact could therefore be higher (i.e. underestimated)	The updated financial projections include additional costs (grade 3+ adverse events, including CRS, neurotoxicity, IVIG therapy and neutropenia administration costs of axicabtagene ciloleucel).
MSAC noted the high and uncertain budget impact, that the price of axicabtagene ciloleucel had not been adequately justified, and no payment for performance or risk sharing criteria were proposed for consideration by MSAC.	The ADAR recognised the need for a PfP and RSA to be negotiated as a part of the public funding for axicabtagene ciloleucel 2L+ and suggested some criteria to address these (Presented in Section 4 above), but have not included these in the budget impact. i.e. the average price per patient infused with AXI as used in the economic model was used in the budget impact. It is not clear if this is the maximum price or the expected average price once a PfP is achieved. This could overestimate the budget impact if complete response at 12 months is not achieved to the level outlined in a PfP.
MSAC noted that the figure in the ADAR of 80% of patients being refractory or who relapse no more than 12 months after completion of 1L treatment and who would be candidates for treatment with AXI has not been justified nor has any reference been provided.	1722.1 ADAR updated the base case to 67% based a mix of sources ranging from 60 to 75%.

Source: Table 4-2, pg 162 to 164 in MSAC 1722.1 ADAR+in-line commentary
Abbreviations: 1L=first-line; 2L=second-line; 3L=third-line; ADAR= applicant developed assessment report; AXI=axicabtagene ciloleucel; AE=adverse event; CAR-T=Chimeric Antigen Receptor T-Cell; CRS=Cytokine Release Syndrome; IVIG=Intravenous Immunoglobulin; LBCL=Large B-cell Lymphoma; MBS=Medicare Benefits Scheme; MSAC=Medical Services Advisory Committee; NHL=Non-Hodgkin Lymphoma; PBS=Pharmaceutical Benefits Scheme; PfP=Pay for Performance; QoL=quality of life; RSA=Risk Share Agreement

The resubmission ADAR presented two scenarios as analysis of the budget impact: 1) prior to funding ('Current Scenario'), and 2) if funding is approved ('Future Scenario'). In both scenarios, the ADAR presented the 3L+ usage of AXI for patients who relapsed more than 12 months after completion of 1L chemoimmunotherapy (and would therefore not be eligible for AXI in the 2L setting), received SoC in 2L and then relapsed making them eligible for 3L+ usage of AXI. As these do not influence the budget impact of listing AXI in the 2L setting, for simplicity, they were removed from the below estimates, but included later to inform total numbers.

The ADAR's financial estimates only included AXI as the 3L CAR T-cell therapy. This was changed during the commentary's evaluation to include the costs of all CAR T-cell therapies in the budget impact (the price for AXI was used as the proxy price for other CAR T-cell therapies).

In the 'Current Scenario', the ADAR based the population receiving CAR T-cell therapy in 3L on the total projected incidence of refractory or relapsed LBCL no more than 12 months after completion of 1L chemoimmunotherapy who are fit for potentially curative therapy (483 in Year 1), instead of the number of patients that would be likely to be administered AXI if funded in 2L (228 in Year 1). This overestimated the cost offsets of funding AXI in the 2L setting and was corrected during the commentary's evaluation.

In the 'Future Scenario', the ADAR assumed that a proportion of patients that did not receive AXI in the 2L setting (but were eligible), would go on to receive AXI in the 3L setting. While this may be the case, it would not be affected by the funding of AXI in 2L, and therefore this was corrected during the commentary's analysis.

During the commentary's evaluation, only costs associated with the displacement of the comparator were included, and only costs associated with the addition of 2L AXI were included.

Key cost assumptions

The following key cost assumptions and drivers were used for the budgetary impact analysis:

- The average cost of the proposed technology per patient is: $▮
- The average frequency of use of the proposed technology is: 1 per lifetime.

Results

The financial implications to the state and commonwealth health budgets resulting from the proposed funding (under the NHRA) of AXI in the 2L setting are presented over 6 years as summarised in Table 15. The ADAR estimated that ▮ patients in the 2L setting and ▮ patients in the 3L setting (▮ in total) would receive AXI in 2024 (Year 1). The commentary considered the estimated ▮ total patients represented a ▮% increase in patients over the agreed cap in the current deed for AXI in 3L, which had annual caps of ▮ patients in the first year and ▮ in the second year. However, this seemed to be an overestimate of what was happening in practice. These volumes had not been realised in practice with a total of ▮ publicly funded patients infused with AXI between 6/9/2021 to 30/06/2023 according to ABMTRR data (September 2023). The commentary considered that the ADAR's estimated 'current scenario' utilisations (predicting ▮ patients in 2024/Year 1 increasing to ▮ patients in 2029/Year 6) may have been overestimated, and questioned whether a total of ▮ patients receiving AXI in 2024 under a 2L and 3L setting was a reliable estimate.

Table 15   Net financial implications of AXI in the 2L setting to state and commonwealth health budgets.

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Estimated use and cost of the proposed health technology						
Number of patients likely to be administered AXI						
Costs of AXI						
Number of patients likely to be administered ancillary services						
Costs of ancillary services associated with AXI						
Total costs for 2L treatment with AXI						
Post- progression costs after 2L AXI						
Total costs associated with funding of AXI						
Change in use and cost of other health technologies						
Change in use of SoC						
Change in use of CAR-T (3L) *						
Net change in costs to SoC						
Net change in costs to CAR-T (3L) *						

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Total cost offsets associated with funding of AXI*						
Net budget impact to NHRA, State, and Commonwealth health departments on making AXI available for patients with LBCL who are refractory to or have relapsed no more than 12 months after completion of 1L chemoimmunotherapy*						

Source: Section 4 and Attachment 4.1 of the ADAR and compiled during evaluation, *corrected during evaluation*.

* *The ADAR overestimated the number of patients that would receive 3L CAR-T after failure of 2L SoC that would be affected by the funding of AXI, this and values calculated based on this were corrected during evaluation.*

Abbreviations: 1L=first-line; 2L=second-line; 3L=third-line; AXI=axicabtagene ciloleucel; CAR-T=chimeric antigen receptor T-cell; LBCL=large B-cell lymphoma; NHRA= National Health Research Authority; SoC=standard of care,

The ADAR's approach to providing two scenarios introduced some calculations that tended to overestimate the impact of funding AXI in 3L. Mainly, the ADAR based the population receiving 3L AXI in the "current scenario" (i.e. after failure of 2L SoC) on all those who were fit for potentially curative therapy (███ in year 1) not based on the number of patients treated with 2L SoC (███ in year 1). This overestimated the cost offsets of funding AXI in 2L as it overestimated the cost of AXI in 3L. This was corrected during evaluation and a more standard approach of presenting the budget impact; costs associated with funding and change in costs due to funding rather than two scenarios was presented in the commentary.

In the ADAR calculations only the AXI market share was included in the costs as the 3L CAR-T (in both scenarios).

Corrections to the analysis during evaluation by the commentary changed the budget impact from $███ to $███ in Year 1 of listing, and from $███ to $███ in total over the first six years of listing.

The ADAR provided sensitivity analysis, however, given the corrections to the base case during evaluation, an updated sensitivity analysis was conducted (presented in Table 16 below). Detailed justification for the variables and values chosen is provided in Table 4-18 of the ADAR. Sensitivity analysis demonstrated that the budget impact was most sensitive to uptake of 3L CAR T-cell therapy post-SoC progression, and the proportion of refractory or relapsed LBCL who were refractory or relapsed no more than 12 months after completion of 1L chemoimmunotherapy.

Table 16 **Results of sensitivity analysis for net budget impact of making AXI available for patients with LBCL who are refractory to or have relapsed no more than 12 months after completion of 1L chemoimmunotherapy (conducted during evaluation)**

	2024 (Year 1)	2025 (Year 2)	2026 (Year 3)	2027 (Year 4)	2028 (Year 5)	2029 (Year 6)
Base case						
Using AIHW projections (base case = 6,791 in 2024 rising to 7,305 in 2029)						
6,638 in 2024, increasing to 7,494 in 2029						
Proportion of NHL that is LBCL (base case = 42%)						
30%						
Proportion of patients who are refractory or who relapse after completion of 1L chemoimmunotherapy (base case = 30%)						
20%						
40%						
Proportion of refractory or relapsed LBCL who are refractory or relapse no more than 12 months after completion of 1L chemoimmunotherapy (base case = ▮)						
50%						
100%						
Proportion of patients who have adequate physical reserves for potentially curative therapy (base case = ▮)						
76.5%						
93.5%						
Projected uptake of AXI for LBCL in the 2L setting (base case = ▮ in Year 1, increasing ▮ per year to ▮ in Year 6)						
45% in Year 1, increasing to 67.5% in Year 6						
55% in Year 1, increasing to 82.5% in Year 6						
100% all years						
Uptake Rate of CAR-T cell therapies in 3L post SoC treatment in 2L (who relapsed no more than 12 months after completion of 1L chemoimmunotherapy) (base case = ▮ in Year 1, increasing to ▮ in Year 6)						
30% in all years						

Source: Section 4 and Attachment 4.1 of the ADAR and compiled during evaluation.
Abbreviations: AIHW=Australian Institute of Health and Welfare; 1L=first-line; 2L=second-line; AXI=axicabtagene ciloleucel; LBCL=Large B-cell Lymphoma; NHL=Non-Hodgkin Lymphoma; SoC=standard of care

Additional information relating to total numbers of AXI use

Given an RSA may include a patient cap arrangement to mitigate some of the uncertainty regarding utilisation and risk for greater than expected expenditure, the changes to estimated total numbers of AXI in the sensitivity analyses is provided in Table 17.

Table 17   Results of sensitivity analysis for uptake of AXI if funded in 2L for patients with LBCL who are refractory to or have relapsed no more than 12 months after completion of 1L chemoimmunotherapy (conducted during evaluation)

	2024 (Year 1)	2025 (Year 2)	2026 (Year 3)	2027 (Year 4)	2028 (Year 5)	2029 (Year 6)
Base case						
Proportion of NHL that is LBCL (base case = 42%)						
30%						
Proportion of patients who are refractory or who relapse after completion of 1L chemoimmunotherapy (base case = 30%)						
20%						
40%						
Proportion of refractory or relapsed LBCL who are refractory or relapse no more than 12 months after completion of 1L chemoimmunotherapy (base case = ▮)						
50%						
100%						
Proportion of patients who have adequate physical reserves for potentially curative therapy (base case = ▮)						
76.5%						
93.5%						
Projected uptake of AXI for LBCL in the 2L setting (base case = ▮ in Year 1, increasing ▮ per year to ▮ in Year 6)						
45% in Year 1, increasing to 67.5% in Year 6						
55% in Year 1, increasing to 82.5% in Year 6						

Source: Section 4 and Attachment 4.1 of the ADAR and compiled during evaluation.
Abbreviations: 1L=first line; 2L=second line; AXI=axicabtagene ciloleucel; CAR-T=chimeric antigen receptor T-cell; NHL=Non-Hodgkin Lymphoma; QALY=quality-adjusted life-years

15.   Other relevant information

There were pressing policy and implementation considerations that had been raised by MSAC but not discussed in this application related to the use of AXI as well as CAR T-cell therapies.

Demand considerations

The impact of demand on workforce, training and infrastructure capabilities and requirements was not considered. The applicant suggested that – under the current funding scenario – the number of people receiving AXI will increase from ▮▮▮ patients in over 2 years to ▮ in 2024 (in 3L), reaching ▮ by 2029 (Table 4-1 in ADAR). Additionally, if AXI was funded in the 2L setting, the ADAR estimated that ▮ patients will receive AXI in 2024 (across both 2L and 3L), reaching ▮ by 2029 (Table 4-1 in ADAR). The commentary considered given there are only six qualified treatment facilities in Australia, this drastic increase in demand in Year 1 (2024) even under the current 3L-only scenario may not be possible with current capacity, let alone with the additional ▮ in 2024 if funded in the 2L setting. The ADAR did not discuss the capabilities of existing treatment facilities to meet demand, nor any plans for scale-up of other facilities.

Use of AXI in the 2L setting may also have demand and implementation implications for other CAR T-cell therapies, which were not discussed in the ADAR. MSAC had supported the public funding of AXI for patients in the 3L setting (MSAC 1587) and tisagenlecleucel (Kymriah®) in

certain patients with CD19-positive DLBCL, PMBCL and TFL in this 3L setting (MSAC 1519.1, MSAC 1653 and MSAC 1676).

In addition to infrastructure requirements, the applicant stated that AXI is required to be prescribed by physicians who are "experienced in the treatment of patients with haematological malignancies", and administration must be supervised by a haematologist or haematologist-oncologist. The commentary considered with the specialist nature of administration of CAR-T cell therapies, training and workforce requirements needed to be carefully considered. This was especially important given the ADAR's assertion that clinician experience will have important impacts on reducing AEs.

Access and equity

Given that CAR T-cell therapies can only be administered in a handful of specialised facilities (AXI is only available in 6 centres in Australia) in certain metro areas (4 capital cities), the commentary considered there were concerns around accessibility and equity for all eligible populations, especially with the initial demand surge. MSAC 1587 PSD (AXI in the 3L setting) advised the Minister to limit the number of designated treatment centres to balance the need to provide access to patients from all parts of Australia, whilst also ensuring availability of sufficient expertise and efficient use of hospital resources. This is an important consideration but needed to be balanced with the significant demand requirements if AXI is funded in the 2L setting.

Concerns around financial and access burden for patients and support networks were raised in the commentary of MSAC 1722 ADAR. In this ADAR, the applicant described options to support patients' out-of-pocket costs related to transport and accommodation while receiving AXI treatment. These included:

- Gilead funds a patient support program via Rare Cancers Australia which patients and their carer can access for apheresis and then again for the time post-infusion when they are required to be within 2 hours of their treating centre. The ADAR described that more than half the patients who have received AXI to date have had their expenses covered by this program.

- Various state jurisdictions have patient travel assistance schemes in place to reduce the financial burden to patients.

Another issue not discussed in the ADAR, but previously raised by ESC in relation to other CAR T-cell therapy (MSAC 1748 PSD) was the support requirements for patients and families. This included staff time related to consultation with the medical team, access to social workers and mental health support.

Price

The MSAC 1587 PSD advised the Minister to consider rapidly putting in place risk mitigation for equity given the high price of CAR T-cell therapies. It was suggested to utilise the competition between different CAR-T cell therapies to achieve the most efficient price for this service.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- Longer follow-up has been provided for the key trial (ZUMA-7) (median follow-up of 47.2 months, compared to 24.9 months in the initial submission). A statistically and clinically significant overall survival benefit is shown relative to standard of care, with 82 deaths in the AXI arm and 95 deaths in the Standard of Care arm (for AXI HR 0.73, 95% CI 0.54-0.98),

- Multiple sources of bias have been identified in ZUMA-7, including lack of blinding and flexibility of timepoints to assess status (favouring AXI).

- It is unknown whether treatment with AXI for R/R LBCL in the 2L setting is curative or not as data cutoff was 47 months only. There may be a potential for this treatment to evolve into a bridge to transplant however the cost effectiveness of this strategy is unknown.

- The clinical claim of non-inferior safety was not justified due to ongoing novel toxicities along with new reports of increase in T-cell malignancies that were not included in the ADAR.

- The key trial excluded patients ineligible for transplant. The proposed eligibility criteria do not explicitly exclude these patients, although some proposed criteria (such as minimum levels of organ function) may overlap with eligibility criteria for transplant.

Economic issues:

- Overall, the economic model presented is acceptably robust. While the uncertainty is reduced compared to the original submission, some uncertainty remains due to biases identified in ZUMA-7.

- If AXI does become a bridge to transplant in a proportion of patients, this will reduce cost-effectiveness.

Financial issues:

- The proposed price of $███ is claimed to be the same price for AXI for R/R LBCL in the 3L setting. However, this price has not been justified and does not align with the 3L price supported by MSAC (~$█) in MSAC 1587 Public Summary Document). It is also unclear whether the proposed price of $█ represents cost-effectiveness, given the lack of detail for the proposed RSA to achieve the proposed price and the risk of higher prices being paid.

- Real world costs are much higher; the estimated cost of $███ per infusion should be incorporated into the model and recalculated.

Other issues:

- ██ ████.

ESC discussion

ESC noted that this re-application from Gilead Sciences Pty Limited requested public funding through the National Health Reform Agreement (NHRA) of axicabtagene ciloleucel (YESCARTA®), also known as AXI, for the treatment of relapsed or refractory (R/R) large B-cell lymphoma (LBCL) in the second-line (2L) setting. Chimeric antigen receptor T-cell (CAR-T) therapies are funded jointly by the Commonwealth and States and Territories as Highly Specialised Therapies under the NHRA Addendum 2020–2025. ESC noted that AXI is currently funded in the third-line (3L) setting through the NHRA for the treatment of R/R diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL).

ESC noted that in March 2023, MSAC did not support public funding of AXI for treatment of R/R LBCL in the 2L setting. Based on the evidence presented at that time, MSAC considered that it was uncertain whether AXI demonstrated durable survival outcomes relative to standard of care (SoC), and that AXI had an inferior safety profile. MSAC was concerned with the use of event free survival (EFS) as a primary endpoint, which was likely to be biased in favour of the AXI arm. MSAC also considered that the incremental cost-effectiveness ratio (ICER) was highly uncertain and was underestimated due to the optimistic extrapolation of survival favouring AXI.

ESC noted and welcomed consultation inputs from three (3) individuals, all of whom were medical specialists and were supportive of the application. ESC noted the input considered the current SoC to be poor and believed that making AXI a 2L treatment would save patients from undergoing futile treatments. It was also noted that for equitable access, treatment centres for CAR-T therapies are needed for rural/regional areas. ESC noted that any MSAC review would benefit from consumer and carer inputs.

██████████████████████████ The jurisdictions considered that a review of AXI use in the 3L setting should be completed first. The jurisdictions acknowledged the importance of the therapy but suggested that MSAC address the sustainability of CAR-T funding, given the increasing numbers of therapies being developed (for example, ESC noted that an additional application (MSAC 1771) for AXI for R/R follicular lymphoma has been submitted for consideration at the June 2024 ESC meeting). ESC noted that one jurisdiction considered the CAR-T procedure costs assumed in the model to be understated. The jurisdiction's real-world experience with approved CAR-T treatments is that the infusion cost alone is significantly higher, at around $███ per patient, than proposed $███ (for pre-infusion, infusion related stay and post-infusion management).

ESC noted MSAC previously raised concerns, when it considered the previous application (MSAC 1722), regarding the lack of clearly defined eligibility criteria for AXI treatment. ESC noted that the resubmission applicant developed assessment report (ADAR) proposed clearer eligibility criteria for treatment of patients who would be expected to be treated with AXI in the 2L setting. ESC noted the ZUMA-7 key trial excluded patients ineligible for transplant, but the proposed eligibility criteria do not explicitly exclude these patients. ESC queried whether the eligibility criteria should be restricted to transplant eligible population only, in line with ZUMA-7.

ESC noted that currently patients diagnosed with LBCL undergo treatment with the standard first-line therapy of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) and ~40% of patients have refractory or relapsed disease and go on to receive salvage chemotherapy. The ADAR's proposed comparator is SoC, which typically consists of salvage chemoimmunotherapy followed by collection of peripheral stem cells (for use in autologous stem cell transplant [auto-SCT]). Patients who respond well to salvage chemotherapy (in practice, only 35–40%) then receive myeloablative high-dose therapy (HDT) and rescue by means of auto-SCT. ESC noted that the commentary considered the comparator outlined by the ADAR to be appropriate. ESC noted that if AXI is supported for funding in the 2L setting, downstream use of AXI in the 3L setting would be reduced.

ESC noted that the comparative evidence bases for AXI for treating LBCL in the 2L setting, the ZUMA-7 randomised control trial (RCT), had not changed since the previous application was considered by MSAC. However, ESC noted that updated data was provided for some endpoints such as overall survival, however other endpoints such as complete remission were unchanged. The original ADAR presented a median follow-up for survival of 24.9 months; in the resubmission the median follow-up was 47.2 months.

ESC noted that, as previously raised in MSAC 1722 PSD[8], there remain some concerns associated with the risk of bias of the ZUMA-7 trial, likely to favour AXI because:

- The clinicians and investigators were not blinded to the treatment arms (potentially introducing performance bias).

- There was flexibility in the timing of assessment which favoured those in the AXI arm., As clinicians knew which arm their patients were in, they may have been inclined to see their SoC patients earlier leading to meeting an endpoint of progression and becoming censored. This contrasted with the standard 100 day assessment of those in the AXI arm where decisions on progression were made. This methodological approach could likely overestimate the progression-free survival (PFS) benefit in the AXI arm (i.e. those who progressed on day 50–60 would not be picked up until day 100, adding an extra 40-day survival).

- It was unclear why patients were transferred to a "new lymphoma therapy" (considered an event) in the absence of a disease progression event, and this could also be influenced by clinicians being unblinded. There were more such incidents in the SoC arm and hence this favoured the AXI arm. The applicant's pre-ESC response claimed that this had no bearing on the OS benefit, that initiation of a new lymphoma therapy without objective measures of disease progression is regarded as lack of response/treatment failure of 2L therapy and that it is clinical practice to switch a patient who does not respond to salvage chemotherapy to a new lymphoma therapy without waiting for disease progression.

Regarding comparative safety, ESC noted that toxicities in both AXI and SoC arms were substantial. ESC noted that the participants in the AXI arm had significantly higher risk of ≥Grade 3 AEs (relative risk = 1.09, 95%CI 1.01, 1.19). ESC noted that Grade 3 or higher AEs were more common in people >65 years of age in AXI arm vs SoC (94% vs 82%)[9]. ESC noted that the AE profile differed between the two arms in the ZUMA-7 trial, with the incidence of cytokine release syndrome and neurologic events being higher in the AXI group, and the incidence of febrile neutropenia being higher in the SoC group. ESC noted that the only safety data provided was from the ZUMA-7 trial and that data from other sources would have been informative. In addition, the ZUMA-7 trial population had a median age of 59 years compared with the expected median age in the potentially eligible Australian population of 70-79 years.

ESC noted emerging safety concerns related to CAR-T therapies including myelitis, quadriparesis, leucoencephalomyelopathy.[10] ESC noted that the United States Food and Drug Administration is investigating a serious risk of T-cell malignancy following BCMA-directed or CD19-directed CAR-T cell immunotherapies and has updated its product information.[11] ESC noted that this information was not presented in the ADAR or applicant's pre-ESC response.

ESC noted the substantial number of deaths in both AXI and SoC arms. ESC noted that by the end of 4 years follow-up, ~44% of patients had died in the AXI arm while ~54% patients died in the SoC arm. ESC noted that the ADAR claimed that in ZUMA-7 patients who dropped out in the

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[8] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1722-public

[9] Westin, J. R. et al. (2023). Safety and Efficacy of Axicabtagene Ciloleucel versus Standard of Care in Patients 65 Years of Age or Older with Relapsed/Refractory Large B-Cell Lymphoma. *Clin Cancer Res 29*, 1894-1905.

[10] Santomasso BD, et al (2023). How I treat unique and difficult-to-manage cases of CAR T-cell therapy-associated neurotoxicity. *Blood.* 141(20):2443-2451. doi: 10.1182/blood.2022017604. PMID: 36877916; PMCID: PMC10329188.

[11] FDA investigating serious risk of T-cell malignancy following BCMA-directed or CD19-directed autologous chimeric antigen receptor (CAR) T cell immunotherapies

SoC arm after a relapse were no longer followed and this favoured the SoC arm for comparative safety. ESC noted and agreed with the commentary that the difference in follow-up for toxicity made differences in safety unclear; however, it did not provide justification for the claim of noninferior safety of AXI and it should be noted that toxicities tend to occur in the early follow-up period. ESC noted that the role of training and workforce in supporting the reduction and management of AEs for AXI needs to be considered.

Regarding comparative effectiveness, ESC compared the effectiveness outcomes from the previous MSAC 1722 ADAR (24.9 months follow-up) with the updated outcomes reported in the resubmission (47.2 months follow-up) and noted that with a longer median follow-up, the evidence now indicated a statistically significant survival benefit favouring AXI over SoC (Overall Survival [OS] hazard ratio = 0.73; 95% CI: 0.54–0.98). The updated data also indicated that EFS and PFS outcomes for AXI remained statistically significantly superior compared to SoC. ESC noted the complete response (CR) rate (65%) remained unchanged from the previous submission. ESC noted this was because CR was measured at 12 months post successful infusion. ESC queried whether CR should be measured at a later date instead to see whether AXI treatment offers durability of response. ESC noted the CR rate is an important factor in pay-for-performance (PfP) model. However, ESC noted that there was significant censoring of participants in the OS analysis post-40 months and was concerned that it is unclear how this censoring impacts (biases) the results. ESC noted that the ADAR stated a plateau in survival is evident at approximately 2 years indicative of 'functional cure' but did not provide further information on the subgroups that responded vs not responded to AXI treatment in the 2L setting. ESC noted that the subgroup of non-responders went on to have a 3L therapy consisting of either another CAR-T therapy treatment or 3L chemotherapy. ESC noted that some of the patients (n=16) received a subsequent SCT post 3L treatment progression raising potential concerns whether AXI may become a bridge to transplant as seen in the recent Kymriah CAR-T (for paediatric acute lymphoblastic leukaemia [ALL]) review in July 2023.

ESC noted that although the data show significant difference in PFS between the treatment arms in favour of AXI (median PFS of 14.7 months for AXI versus 3.7 months in SoC arm, HR of 0.562; 95% CI: 0.414, 0.762), there is potential for bias in favour of AXI as the study's treatment allocation was not blinded and therefore investigators may have been more likely to assess SoC outcomes earlier and progress participants faster in the SoC arm.

ESC noted that MSAC previously concluded that it was uncertain whether AXI demonstrated durable survival outcomes relative to SoC for the treatment of R/R LBCL in the 2L setting. The resubmission ADAR provided longer-term evidence, which added durability to the survival outcomes relative to the SoC. ESC noted that the updated evidence provided in the resubmission ADAR supported a clinical claim of superior effectiveness however, the magnitude of effect is likely to be lower for response and progression outcomes based on study design limitations.

ESC noted that the ADAR presented a revised cost-utility analysis (CUA) that applied the same overall structure as the previous ADAR but with revisions that addressed most of the issues previously raised by MSAC, such as:

- Length of patient follow-up addressed by using most recent data from ZUMA-7 trial however, the risk of bias from the trial remains.
- Reduced the time horizon to 30 years (from 40 years).
- Proportion of patients in event free state estimated from area under PFS (previously estimated from EFS which likely favoured AXI).
- Costs of grade 3+ cytokine release syndrome (CRS), neurotoxicity and Intravenous immunoglobulin (IVIG) therapy and neutropenia are costed separately.
- Utility decrement captured with 'on treatment' quality of life (QoL) score, which ESC considered reasonable.

- QoL Quality of Life Questionnaire (QLQ) from trial mapped to AUS Euro-QOL, 5 dimensions (EQ-5D), this resulted in higher QoL which introduces some uncertainty.
- More comprehensive costing of AE profile, bridging treatment and post-progression pathway but may require further consideration based on jurisdiction feedback.

ESC noted that the ADAR used a mixture cure modelling approach to extrapolate OS and PFS (in place of EFS) for the base case. Specifically, the ADAR used an "uninformed" mixture cure model in which the cure fraction is a parameter of the model and estimated alongside other parameters directly from ZUMA-7 trial data. However, as requested by MSAC, the ADAR also presented scenario analyses using a more standard approach to parametric extrapolations of OS and PFS. ESC noted that the inclusion of OS as primary effectiveness outcome and use of PFS (instead of EFS) in the economic model helped mitigate the concerns surrounding reliance on EFS in the initial ADAR 1722.

ESC noted that although the survival extrapolations for AXI and SoC using a mixture cure model are different, within each arm all parametric distributions used for extrapolation produce very similar trajectories for OS. ESC also noted the comparative model specifications for the mixture cure model extrapolations versus standard parametric extrapolations were not too dissimilar. ESC agreed with the commentary that it was reasonable to conclude that the mixture cure model presented was acceptably robust and the uncertainty had been reduced. However, some uncertainly remained due to the bias associated with the conduct of ZUMA-7 trial.

ESC noted the revised base case results where the ADAR had much more comprehensively included the costs of AEs, bridging treatments and post-progression related costs. ESC noted that in the revised results, over a 30-year time-horizon and using a 5% discount rate, the ICERs for AXI compared to SoC were reduced from $███ to $███ per life-year gained (LYG) and from $███ to $███ per quality-adjusted life year (QALY) gained. ESC noted the key scenario/sensitivity analyses (i.e., standard parametric extrapolations, use of UK QoL tariffs and the applicant's pre-ESC sensitivity analysis using alternative post progression utility values) did not significantly alter the ICER ($███ to $███ per QALY gained – see Table 8,Table 9 and Table 10 in section 13).

ESC noted that for the financial impact analysis, the resubmission ADAR presented two scenarios: 1) 'Current Scenario' – AXI is funded only in the 3L setting (i.e. prior to funding), and 2) 'Future Scenario' – AXI is funded in the 2L and 3L setting (i.e. proposed). The incremental difference being 'Future' minus 'Current' equalling the total net cost.

ESC noted the uncertainties and issues identified by the commentary. ESC noted the commentary highlighted that the ADAR included 3L for an out-of-scope population, which ESC noted did not impact the analysis and the applicant's pre-ESC response clarified this was included for completeness. The commentary stated that the proportion of non-Hodgkin lymphoma (NHL; 42%) that were LBCL was overestimated compared to the literature (30%). However, ESC accepted the applicant's pre-ESC response, which clarified that the literature suggested ~30% of NHL were DLBCL and as DLBCL represents ~80% of LBCL cases, it was then estimated that 42% of NHL were LBCL (i.e. 33%/80% = 42%). ESC also noted the applicant's pre-ESC response acknowledged and accepted the commentary's correction of the error identified in the ADAR's estimated 3L population who will be receiving CAR T-cell therapy. ESC noted that Australian real-world data for utilisation of CAR-T therapies already supported by MSAC show that actual utilisation has been much lower than anticipated, meaning the estimated utilisation of AXI in this resubmission may be optimistic. Although ESC also noted that utilisation data for some of the supported CAR-T therapies were not available at the time of consideration of this application.

ESC noted that corrections to the analysis during evaluation changed the budget impact from $███ ███ to $███ ███ in year 1 of listing, and from $███ ███ to $███ ███ in total over the first six years of listing.

ESC noted that a risk sharing arrangement (RSA) ▮▮▮ ▮▮▮ ▮▮▮ ▮▮▮ was currently in place to manage risks with the public funding for AXI for R/R LBCL in the 3L setting and an RSA was also proposed for funding AXI for R/R LBCL in the 2L setting. ESC noted discrepancy in CR rates in the trial and real-word experience suggesting trial estimates were not robust for CR rates. ESC considered that a registry to capture data related to complications, use of high-cost medicines, late-onset AEs and AEs requiring hospitalisation would be beneficial. ESC also considered an MSAC review to address issues such as estimates of patient numbers, financial caps, durability of response and complete response rates would be beneficial.

ESC noted that the resubmission ADAR proposed that the price for AXI in the 2L setting be the same as the price for AXI in the 3L setting, which the ADAR stated was $▮▮▮. This price remained unchanged from what was proposed in the previous application of AXI in the 2L setting (i.e. MSAC 1722 ADAR). However, ESC noted that how the applicant had derived this price had not been detailed in the ADAR. Further, ESC noted that the $▮▮▮ price did not align with the price supported by MSAC for AXI for treatment of R/R LBCL in the 3L. That is, ESC noted that in November 2019, MSAC advised that the price it supported for funding in 3L (MSAC application 1587[12]) was "40–45% lower than the price proposed by the applicant". The price proposed for AXI in the 3L in the applicant's pre-ESC response for MSAC 1587 was $▮▮▮, which resulted in the average price per patient recommended by the MSAC being $▮▮▮.

In regard to whether it is appropriate to request the exact same price in the 2L setting as that supported by MSAC in the 3L setting, ESC considered that other factors could be considered in addition to effectiveness, such as total patient numbers, relative efficacy and total budget impact. ESC noted it could be reasonable for MSAC, that if the magnitude of incremental benefit is lower in the 2L setting compared to the 3L setting, to expect a price reduction. ESC noted that the Canadian Agency for Drugs and Technologies in Health (CADTH) had recommended the price of AXI would have to be reduced by 45% to achieve an ICER of $50,000 per QALY gain[13]. Unlike CADTH, health technology assessment committees in Australia (such as MSAC) do not have an explicit threshold above which the estimated ICER would be considered too high and therefore, not cost-effective. However, ESC noted that if the price of AXI was reduced by ▮▮% ($▮▮▮), this would achieve a similar (although slightly lower) price to that previously supported by MSAC and that such a reduction would reduce the ICER to $▮▮▮ per QALY gained.

ESC noted the resubmission ADAR provided criteria for a 2-payment PfP arrangement but did not provide details regarding the payment amounts and complete response rate that would achieve the proposed price. ESC noted that if the complete response rate used to establish the 2-payment PfP arrangement was lower than the actual complete response rate achieved in Australian clinical practice, that this would increase the average price paid and the total financial impact. ESC also noted that actual utilisation data available for currently funded CAR-T in Australia has demonstrated that the actual price paid for other CAR-T therapies is higher than predicted, which is a result of higher response rates in the Australian setting than that estimated from trial data. ESC noted that this issue was highlighted when MSAC reviewed the public funding of tisagenlecleucel (tisa-cel) for treatment of paediatric and young adult patients with R/R acute lymphoblastic leukaemia (MSAC application 1748[14]).

ESC also noted that MSAC had again considered this issue at the November 2023 meeting when MSAC considered and supported public funding for brexucabtagene autoleucel (brexu-cel) for

[12] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1587-public

[13] CADTH Reimbursement Recommendation Axicabtagene Ciloleucel (Yescarta) https://www.cadth.ca/sites/default/files/DRR/2023/PG0293REC-Yescarta-meta.pdf

[14] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1748-public

adult R/R B-precursor acute lymphoblastic leukaemia (B-ALL; MSAC application 1723.1[15]). At that time, MSAC noted the merits for a 2-payment PfP arrangement but considered that there was a high risk that a 2-payment PfP arrangement for brexu-cel for R/R B-ALL would result in a higher than expected average price paid. Because of this risk, MSAC considered that a fixed payment for a successful infusion of brexu-cel may be more appropriate than a 2-payment PfP arrangement. However, ESC noted that the trial data for AXI for treatment of R/R LBCL in 2L indicated a complete response rate of ~65% in a trial population with an average age of 59 years of age. In comparison the average patient age in Australia is higher ~70-79 years of age. Therefore, ESC was unsure if the higher response rate seen in the tisa-cel review would occur for AXI for R/R LBCL in the 2L setting and therefore, 2-payment PfP may not have the same risk for resulting in a higher average price paid due to higher response rate in the Australian clinical setting compared to the trial data.

As raised for other CAR-T, ESC also noted the response rate for AXI would be confounded by the use of other treatments and considered that extending the second payment out to 2 or 3 years would not reduce this uncertainty. If MSAC wished to pursue a 2-payment PfP for AXI for treatment of R/R LBCL in the 2L setting, ESC noted that there are 2, 3 & 4 years data available for AXI and that these data could be used to explore a better informed a 2-payment PfP, along with considering using a lower price (▓▓% reduction discussed above), upper threshold of response rate and outcomes from the future review of AXI in the 3L.

ESC noted that the current RSA for AXI for treatment of R/R LBCL in the 3L setting includes annual patient caps of ▓▓ patients in the first year and ▓▓ in the second year. ESC noted that in the resubmission ADAR, the financial impact analysis estimated that ▓▓ patients would receive AXI in the 2L setting and ▓▓ patients would receive AXI in the 3L setting, totalling ▓▓ patients receiving AXI in year 1. However, these volumes have not been realised in practice with a total of ▓▓ publicly funded patients infused with AXI since supported by MSAC in July 2021 (i.e. since 1st patient infused 6 September 2021 through to the October 2023 quarterly report submitted by the applicant). ESC also noted that since the first CAR-T was supported by MSAC in 2019, a total of ▓▓ patients have been treated with a CAR-T funded under the NHRA. ESC noted the reason for the lower than expected utilisation is not clear and considered that at this time, based on the information available, MSAC may wish to consider not increasing the annual patient caps if MSAC supports AXI for treatment of R/R LBCL in the 2L setting.

ESC also noted policy and implementation issues that were raised by MSAC but not discussed in this application related to the use of AXI as well as CAR T-cell therapies:

- Given there are only six qualified treatment facilities in Australia, the estimated increase in the number of people receiving AXI may not be possible with current capacity. The ADAR did not discuss the capabilities of existing treatment facilities to meet demand, nor any plans for scale-up of other facilities.

- The specialist nature of administration of CAR-T cell therapies, training and workforce requirements, especially given the ADAR's assertion that clinician experience will have important impacts on reducing AEs.

- Given that CAR T-cell therapies can only be administered in six centres in four cities in Australia, there are concerns around accessibility and equity for all eligible populations, especially with the initial demand surge.

- The MSAC 1587 PSD advised the Minister to consider rapidly putting in place risk mitigation for equity given the high price of CAR T-cell therapies. It was suggested to utilise the

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[15] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1723.1-public

competition between different CAR-T cell therapies to achieve the most efficient price for this service.

17. Applicant comments on MSAC's Public Summary Document

Gilead Sciences is pleased that MSAC have supported the public funding of axicabtagene ciloleucel (AXI) through the NHRA for the treatment of R/R LBCL in the 2L setting. We wish to express our sincere gratitude to the professional organisations, patient organisations, clinicians, and patients who took the time to provide consumer comments in support of the application. We will work with the Commonwealth and State and Territories governments with the aim of making access to reimbursed Yescarta for 2L R/R LBCL patients as quickly as possible.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website