Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1722 – Axicabtagene ciloleucel (YESCARTA®) for relapsed or refractory large B-cell lymphoma

Applicant: **Gilead Sciences Pty Limited**

Date of MSAC consideration: **30-31 March 2023**

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

1. Purpose of application

An application requesting public funding 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 for the treatment of LBCL in the third-line (3L) setting under the National Health Reform Agreement.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of axicabtagene ciloleucel (AXI) for the treatment of relapsed or refractory large B-cell lymphoma (LBCL) in the second-line (2L) setting. MSAC recognised the clinical need for the proposed treatment in this population. MSAC considered that from the evidence presented for evaluation, it was uncertain whether AXI demonstrated durable survival outcomes relative to standard of care, and that AXI had an inferior safety profile. MSAC was also 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, and that the trial did not adequately capture the difference between AXI in the 2L vs 3L setting, which had flow on effects to the economic model. 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. MSAC noted that additional evidence to support the application had been provided in the pre-MSAC response, but it did not allow sufficient time for it to be evaluated and therefore it was not able to be fully considered by MSAC.

MSAC advised that the economic evaluation needed revisions, including incorporation and evaluation of new evidence submitted in the pre-MSAC response, use of progression-free survival (PFS) as the outcome measure, use of more standard modelling techniques, along with other revisions. MSAC also advised that a price for AXI should be ascertained at which it is acceptably cost-effective. MSAC noted the high and uncertain budget impact, that the price of AXI had not been adequately justified, and no payment for performance or risk sharing criteria were proposed for consideration by MSAC. MSAC also noted four submissions from the States and Territories were not supportive of the application as joint funders of this highly specialised therapy via the National Health Reform Agreement.

Consumer summary

This is an application from Gilead Science Pty Ltd requesting 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 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.

Axicabtagene ciloleucel is a 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 therapy, a patient's T-cells are collected and genetically modified in a lab to express an anti-CD19 chimeric antigen receptor (CAR) that targets 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.

CAR-T cell therapies are a relatively new 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 second choice after another therapy, likely chemoimmunotherapy.

MSAC considered that, from the evidence presented for evaluation, it was uncertain whether axicabtagene ciloleucel demonstrated durable health benefits compared to current second-line treatments (standard of care), and that it was not as safe as standard of care. MSAC advised that based on this evidence, the application did not demonstrate good value for money. MSAC advised that the application could be improved with revisions, including incorporation and evaluation of new evidence that was submitted late in the process, as well as changes in how the health benefit is measured and analysed. MSAC noted the high and uncertain cost of the treatment, and that no measures to mitigate the high cost or uncertainty were proposed for consideration by MSAC.

MSAC also noted the four submissions from States and Territories were not supportive of the application as joint funders of this highly specialised therapy via the National Health Reform Agreement.

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

MSAC did not support public funding of axicabtagene ciloleucel for the treatment of relapsed or refractory large B-cell lymphoma as second-line therapy. MSAC considered that from the evidence presented, the benefit of treatment is uncertain and there are safety issues compared to current treatments. MSAC advised that further evaluation is needed of new data that is now available as well as adjustments to the analysis to better inform its consideration.

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

MSAC noted that this application is from Gilead Sciences Pty Limited for the chimeric antigen receptor-T (CAR-T) cell therapy, axicabtagene ciloleucel (YESCARTA®), referred to as AXI, for the treatment of relapsed or refractory (r/r) LBCL in the 2L setting. The application seeks joint funding by the Commonwealth and states and territories through the High Cost, Highly

Specialised Therapy arrangements included in the National Health Reform Agreement (NHRA) Addendum 2020–25.

MSAC noted that AXI has recently been approved for usage in this 2L setting by the Therapeutic Goods Administration (TGA). MSAC noted that AXI is also 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).

MSAC noted that it is due to consider a review of the first CAR-T therapy (tisagenlecleucel for paediatric acute lymphocytic leukemia) at its July 2023 meeting; this will be the first review of any CAR-T therapy that has been recommended for public subsidy in Australia. MSAC considered that, despite being for a different patient population, there may be merit to this review being completed prior to any recommendations for AXI being made, as key information pertaining to the real world cost of CAR-T therapies would be expected to be informative.

MSAC noted that there is no ratified PICO confirmation as this application bypassed PASC. The applicant-developed assessment report (ADAR) appropriately addressed the population requirements of the proposed PICO but did not propose clear eligibility criteria for treatment to better define the proportion of patients who would be expected to be treated with AXI in the 2L setting.

MSAC recognised the clinical need for the proposed treatment in this population. The application stated that 6,400 people were diagnosed with non-Hodgkin's lymphoma in 2021 and it is estimated that approximately 2,500 cases of LBCL are diagnosed each year. Of those, approximately 1,000 patients per year will not achieve long-term remission, and [redacted] will be refractory or have relapse no more than 12 months after completion of 1L chemoimmunotherapy. However, MSAC noted that the figure in the ADAR of [redacted] 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.

MSAC noted that the ADAR was based on direct evidence from the randomised-controlled ZUMA-7 trial. This trial compared standard of care (SoC; n = 180 involving salvage chemotherapy and, in responders, high-dose therapy [HDT] with autologous stem cell transplantation [ASCT]) with AXI, (n = 179), in the 2L setting. Patients were permitted to receive a 3L CAR-T (AXI) upon disease progression in the SoC arm; a total of 100 participants (56%) received 3rd line CAR-T therapy after SoC.

MSAC noted that the evidence does 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 (involving salvage chemotherapy and, in responders, HDT + auto-SCT). The adverse event (AE) profile of AXI in the ZUMA-7 trials 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 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. Also, the AE profile differed between the two groups, with the incidence of cytokine release syndrome (CRS) and neurologic events being higher in the AXI group, and the incidence of febrile neutropenia being higher in the SoC group.

MSAC noted the pre-MSAC response from the applicant, which stated that although AEs such as neurologic events and CRS were observed more commonly in the AXI arm, febrile neutropenia was more prevalent in the SoC arm, and that overall, there was no statistically significant difference in the proportion of patients experiencing Grade ≥ 3 serious AEs across both arms. The applicant also stated that improvement in management of AEs is evidenced in the updating of the Special Warnings section of approved Product Information for AXI, which now includes

findings from cohorts 4 and 6 of the ZUMA-1 study that have resulted in revisions to the guidance on managing CRS and neurologic toxicity to reduce the severity of these events. The applicant also stated that the dossier for 3L+ AXI provided to the MSAC Secretariat showed that the rates of CRS and neurologic events in worldwide registries were similar or lower than the rates reported in the ZUMA-1 study. However, MSAC noted that the dossier was not included as part of the submitted ADAR for consideration at its March 2023 meeting.

MSAC noted that EFS was defined as the time from randomisation to the earliest date of disease progression per the Lugano Classification, commencement of new lymphoma therapy, or death from any cause. More than twice as many patients in the AXI arm compared with the SoC arm of the ZUMA-7 trial were still free of events at 24 months (40.5% vs 16.3%, respectively). Median EFS was 8.3 months for patients treated with AXI compared to only 2.0 months for patients treated with SoC. The difference in EFS across the two arms was statistically significant (HR: 0.398; 95% confidence interval [CI]: 0.308, 0.514). However, there were some early events in the SoC arm due to patients who commenced a new lymphoma therapy in the absence of any evaluable disease assessment being assessed as having an event at the randomisation date. Therefore, MSAC considered that the endpoint of EFS is driven by "lymphoma treatment" and is heavily biased to favour the intervention.

MSAC noted that the long-term incremental benefit is highly uncertain as the ADAR did not include data on survival beyond 2 years. MSAC noted that the updated OS data (median duration of follow-up: 45.8 months) provided by the applicant in the pre-MSAC response compared with the updated interim analysis (median duration of follow-up: 20 months) reported in the ADAR which showed a difference in favour of AXI (HR = 0.726 [95% CI: 0.540, 0.977 vs. 0.708 [95% CI: 0.515, 0.972, respectively]. However, MSAC considered there was insufficient time for this to be evaluated or incorporated into the analysis.

MSAC noted that the model compared AXI at 2L with chemotherapy and stem cell transplant rather than the real-world scenario where 3L CAR-T therapy may follow unsuccessful 2L treatment. In other words, there is interest in 2L versus current 3L (AXI or Kymriah®). In its pre-MSAC response, the applicant noted that as there were patients receiving 3L+ CAR-T therapies in the SoC group, the updated significant overall survival (OS) results in ZUMA-7 reflect the real-world treatment pathway and demonstrate the benefit of treating this population earlier with 2L AXI compared to delaying until patients are in 3L or later (3L+). However MSAC noted that the real world data regarding 3L treatment in the Australian setting needs to be incorporated into the model so that it can be evaluated.

MSAC noted that the economic analysis used a mixed-cure fraction model to extrapolate the OS for patients with LBCL in the model. Based on the ZUMA-7 trial data, MSAC considered that the cure rate used in the model may be too optimistic, noting that the Kaplan Meier estimates of OS at 24 months after randomisation in the AXI arm was 60.7% (95% CI: 52.8, 67.7%) compared with 51.3% (95% CI: 43.4%, 58.7%) in the SOC arm. Further, the distribution chosen (generalised gamma) resulted in the most optimistic scenario favouring AXI. The model approach also does not allow for participants experiencing a relapse once they are in the "cured" state. MSAC noted that mixed-cure models are generally used where there are long periods of disease stabilisation, and in this case the evidence in the ADAR did not yet demonstrate this. Therefore MSAC considered a more standard partitioned survival model should also be used as in addition to the mixed-cure model.

MSAC noted ESC's concern that the model was primarily driven by the EFS endpoint, which is an unvalidated endpoint and likely favours AXI. MSAC also noted that the EFS endpoint was available to 15 months and after this point the data were extrapolated.

MSAC noted the respecified base case in the commentary, using a discount rate of 5% and a 30-year time-horizon, which it considered is more appropriate given the average age of patients at presentation. While MSAC considered that the respecified base-case should still be regarded as

exploratory due to the issues noted with the use of EFS and model structure, the resultant ICER of $[redacted] per quality-adjusted life year (QALY) gained was noted.

MSAC noted the ESC additional concerns with the model and that these were investigated in additional exploratory sensitivity analyses (see Table 10). Firstly, it assumes one-off cost of $36,000 for both the administration of a CAR-T therapy and treatment of associated AEs. MSAC agreed that it is clear from the literature that this is likely a significant underestimate of costs, due to factors such as treatment of AEs, intensive care unit stays and intravenous immunoglobulin (IVIG) usage, with $46,575 per month cited[1]. MSAC also noted that the model only assumed a one month utility decrement associated with CAR-T administration. MSAC considered that based on the evidence presented and the literature highlighting the seriousness of the AE profile and significant burden to patients[1], that this would also be a significant underestimate and would favour AXI.

MSAC noted that incorporating increased hospitalisation costs for the first 3.3 months of $46,575 per month and a utility decrement to account for the 25% of patients who required a stay in the intensive care unit resulted in an ICER of $[redacted]/QALY. MSAC noted the pre-MSAC response considered that the ESC sensitivity analyses that applied additional disutilities double count these disutilities and should be corrected. MSAC noted this concern, but considered that specific utility weights for AEs should be used rather than using average utility weights observed from the trial. MSAC noted there is also uncertainty in the uptake of 3L CAR-T in Australia, with lower uptake than was predicted. MSAC noted that the model assumes an uptake of [redacted] however, the pre-ESC response indicated it is approximately [redacted] in the Australian setting and that the ICER was sensitive to this estimate. MSAC noted the pre-MSAC response which stated the sensitivity analysis that applies costs of 3L CAR T-cell therapy for [redacted] of patients (Australian setting) instead of [redacted] of patients (ZUMA-7) in the SoC arm was incorrect because it does not make corresponding changes to outcomes. MSAC acknowledged this issue, but considered that any resubmission should further investigate this model driver, given the local data indicated the use of 3L CAR-T therapy was much lower than the trial.

MSAC noted that no justification for the proposed pricing had been presented. Overall, the net effective average price currently paid for AXI in the 3L setting and sought for AXI in the 2L setting is $[redacted] per patient infused. MSAC noted that the payment schedule based on upon infusion and on outcomes was not included in the ADAR, and although the applicant noted that this could be discussed at a later date, MSAC considered that details of any arrangements would be essential for future applications. MSAC also advised that the economic evaluation needed to be revised and a price for AXI needed to be ascertained at which it is acceptably cost-effective.

MSAC noted that the ADAR presented a financial impact of $[redacted] in Year 1 to $[redacted] in Year 6, with an assumption of one CAR T treatment per lifetime. However, when considering increased hospital costs and a [redacted] uptake rate for 3L CAR-T in multivariate sensitivity analyses, MSAC noted this financial impact increased significantly to $[redacted] in Year 1 to $[redacted] in Year 6.

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. MSAC considered that the actual budget impact could therefore be higher than the $[redacted] in Year 1 and $[redacted] in Year 6 that was stated in the ADAR.

MSAC also noted the four submissions from State and Territory governments, as joint funders of this highly specialised therapy via the National Health Reform Agreement, were not supportive of the application.

Implementation issues were also noted by MSAC including data accessibility issues from the CAR T-cell therapy registry for currently approved products, and potential supply limitations related to limited treatment sites and trained workforce. MSAC considered that should the application be supported in the future, outcomes including OS, Progression Free Survival (PFS), Health-related

Quality of Life (HRQoL), hospitalisations, AEs and costs should be included in a registry, with no commercial confidentiality requirements and with data accessible to all stakeholders.

Overall, MSAC noted that additional evidence to support the application had been provided in the pre-MSAC response, but the new data were not incorporated into the model nor evaluated and therefore it was not able to be fully considered by MSAC.

Therefore, considering the strength of the evidence presented for evaluation with uncertain durability of health outcomes, inferior safety, and a high and uncertain ICER and budget impact, MSAC did not support public funding of AXI for the treatment of r/r LBCL in the 2L setting.

MSAC advised that for any resubmission, the economic evaluation would require revisions, including: incorporation and evaluation of new evidence submitted in the pre-MSAC response (including updated OS data) and any relevant information from the dossier on 3L AXI; incorporation of the respecified base case made in the commentary (including use of 5% discount rate and 30 year time horizon); explicit comparison of AXI as 2L treatment with current 3L CAR T usage; use of PFS as the outcome measure; and use of more standard extrapolation and modelling techniques (partitioned survival model in addition to mixed cure). MSAC also advised that any resubmission should provide information on median timing of endpoint measurements to provide evidence that timing is similar across both study arms; tightened AXI eligibility criteria; reconsideration of price; and include specific proposals for risk sharing arrangements and pay for performance measures.

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).

This is the first ADAR to be considered by the Medical Services Advisory Committee for AXI as a treatment for LBCL in the 2L setting. 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) and is currently being jointly funded by the Commonwealth and the States under the National Health Reform Arrangement (NHRA). Additionally, MSAC has supported tisagenlecleucel (Kymriah®) in certain patients with CD19-positive Diffuse Large B Cell Lymphoma (DLBCL), Primary Mediastinal B Cell Lymphoma (PMBCL) and Transformed Follicular Lymphoma (TFL) in this 3L setting (MSAC 1519.1) and is currently being jointly funded by the Commonwealth and the States under the National Health Reform Arrangement (NHRA).

Table 1 CAR-T cell therapy in B-cell lymphoma related applications to MSAC relevant to this application.

MSAC meeting	Application number	Topic	Outcome	Link
Tisagenlecleucel				
Nov 2018; March 2019; April 2019	1519	For acute lymphoblastic leukaemia (ALL); initial application covered ALL and DLBCL (DLBCL component was later addressed in 1519.1).	MSAC recommended public funding of TIS for treatment of ALL in children and young adults up to 25 years	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519-public
August 2019; November 2019	1519.1	DLBCL amended (post 3 lines of therapy)	MSAC recommended public funding of TIS for certain patients with DLBCL, PMBCL and TFL.	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519.1-public
November 2020 *(bypassed PASC, ESC)*	1653 (minor)	Amendment to eligibility criteria in DLBCL – removal of requirement for CD19-positivity	MSAC did not support removing the requirement for CD19 positivity.	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1653-public
July 2021 *(bypassed PASC, ESC)*	1676 (minor)	Amendment to eligibility criteria to allow (a) TFL, without the requirement for additional systemic therapy post-ASCT; and (b) Grade 3B FL patients, access to treatment	MSAC recommended public funding	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1676-public
Axicabtagene ciloleucel				
July 2021 *(bypassed PASC)*	1587	the treatment of refractory or relapsed CD19-positive DLBCL (post 3 lines of therapy)	MSAC recommended public funding	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1587-public
July 2022 *(bypassed PASC)*	1722	the treatment of refractory or relapsed CD19-positive DLBCL (post 2 lines of therapy)	Current application	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1722-public

Source: MSAC 1587 PSD, 2020; MSAC 1676 PSD, 2021; MSAC 1653 PSD, 2020; MSAC 1519 PSD, 2019
Abbreviations: ALL=acute lymphoblastic leukaemia; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; PMBCL=primary mediastinal large B-cell lymphoma; TFL=transformed follicular lymphoma

5. Prerequisites to implementation of any funding advice

A regulatory submission requesting expansion of the marketing approval for AXI to include patients with LBCL in the 2L setting was submitted to the Therapeutic Goods Administration (TGA) on 2 December 2021 and a final TGA decision was released in December 2022. The indication according to the TGA PI is "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".

The intervention would be delivered in select tertiary hospital treatment centres who specialise in delivery of CAR-T cell therapy. Treatment centres require site qualification from Gilead, and there are currently five locations qualified to deliver AXI (1 in Melbourne, Brisbane, and Perth; 2 in Sydney). Prescription must be completed by physicians who are experienced in the treatment of patients with haematological malignancies. Patients are monitored for adverse events at the centre following treatment for at least 7 days. Patients are then required to remain no more than 2 hours from the treatment centre for 4 weeks following infusion.

6. Proposal for public funding

There is no ratified PICO confirmation as this application bypassed the PASC.

The proposed technology is not new; the applicant is seeking public funding for use of AXI under the same delivery and funding mechanism as is currently available, but at an earlier stage (i.e., in the 2L, rather than 3L setting). Thus, this application is essentially proposing to move AXI forward in certain patients in the treatment algorithm. Funding is sought under a block funding arrangement via Commonwealth and state shared funding for Highly Specialised Therapies under the Addendum to the National Health Reform Agreement 2020-2025 (NHRA).

The ADAR appropriately addressed the population requirements of the proposed PICO but did not propose clear eligibility criteria for treatment to better define the proportion of patients who would be expected to be treated with AXI in the 2L setting. MSAC's advice is requested for the possible eligibility criteria suggested during evaluation (see Table 2 below).

Table 2 Eligibility criteria for AXI

Indication:	Adult patients with CD 19 positive LBCL who are relapsed or refractory no more than 12 months after first-line chemoimmunotherapy. 1. LBCL includes the following types defined by the WHO in 2016: a) DLBCL, NOS (including ABC or GCB) b) HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement c) DLBCL arising from FL d) T-cell/histiocyte-rich LBCL e) DLBCL associated with chronic inflammation f) Primary cutaneous DLBCL, leg type g) EBV+ DLBCL 2. First-line therapy must include (at a minimum): a) An anti-CD20 monoclonal antibody unless the investigator determined that the tumour was CD20 negative, and b) An anthracycline-containing chemotherapy regimen
Treatment criteria:	Patient must be treated in a tertiary public hospital with appropriate credentials AND Patient must be treated by a haematologist working in a multi-disciplinary team specialising in the provision of CAR-T cell therapy AND Patient must not have uncontrolled infection, including uncontrolled HIV or active hepatitis B or C infection AND 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.
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: i. Renal function: Creatinine clearance >40mL/min, serum ALT/AST <5 x ULN and total bilirubin <2 x ULN ii. 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. iii. 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.

The proposed net effective average price for AXI is $[redacted] per patient infused which is the same as the price currently paid for AXI in 3L setting.

7. Population

There is only one PICO set for consideration: adult patients with LBCL who are refractory or have relapsed no more than 12 months after the completion of first-line (1L) therapy. The proposed technology would be used in the 2L, rather than 3L setting, meaning the following key changes to the clinical management pathway and use of downstream services would occur compared to existing practice:

1) No 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) + auto-stem cell transplant (SCT).
2) The ADAR assumed that CAR T-cell therapies will only be able to be used once in a lifetime, and so there will also be some substitution of 3L CAR T-cell therapies. It was noted that MSAC advised to limit to one successful CAR-T infusion per lifetime for r/r DLBCL (MSAC 1587, MSAC 1519.1). In addition, there is currently no clinical evidence for the use of a second line of CAR-T therapy should an individual progress post 2L CAR-T therapy. This could lead to very limited use of tisagenlecleucel (currently used for 3L treatment) in Australia.
3) Patients are eligible to receive SoC post CAR-T in 2L therapy, and this would include salvage chemotherapy with or without stem cell therapy. In Zuma-7 ~10% of patients receive stem cell therapy.

The ADAR appropriately addressed the population requirements of the proposed PICO.

8. Comparator

The applicant's proposed comparator is the standard of care (SoC), which typically consists 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 receive
2) Myeloablative HDT and rescue by means of auto-SCT (HDT + auto-SCT).

It is noted that at the time of initiating salvage chemoimmunotherapy (i.e., step 1 of SoC), it is not possible to identify the patients who will 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 also some patients who do not achieve long-term remission after SCT, is poor in the absence of access to CAR T-cell therapy in the 3L setting.

The comparator outlined by the ADAR appears to be appropriate. However, CAR-T therapy is available in 3L in Australia, therefore MSAC's advice on whether an explicit comparison of the potential treatment sequences would provide additional information and be meaningful (i.e. 2L chemotherapy followed by 3L CAR T compared with 2L CAR T followed by 3L salvage), given the assumption that CAR T usage will be restricted to one successful infusion per lifetime.

9. Summary of public consultation input

Consultation input was received from three organisations and three individuals, two of whom were individual specialist with experience with treating patients with blood cancers and one consumer. The three organisations that submitted input were consumer organisations:

- Lymphoma Australia (LA)
- Leukaemia Foundation (LF)
- Rare Cancers Australia (RCA)

All organisations and individuals were strongly supportive of making this therapy available to patients at an earlier line in therapy, highlighting the poor prognosis of patients with relapsed or refractory LBCL and the significant benefits the therapy may offer patients. Both LA and LF noted the burden of toxicity and adverse events associated with therapy, but that this was variable and, in some cases, well tolerated compared with current standard of care. LA and LF also noted the ZUMA-7 trial in support of patients being eligible for the therapy prior to undergoing a bone marrow transplant which is not without its own long term side effects.

One specialist considered that these patients should receive this intervention at an earlier line of treatment since some patients may be too unwell to receive treatment at the 3rd line stage.

All consultation input noted the curative intent of the therapy as the main benefit to patients. The consultation input also considered that making this available at an earlier line in therapy is of benefit to the patient as they would not have to endure more treatments that may not benefit them prior to being eligible for the therapy, which may also reduce the cost to the health system. One specialist considered other benefits related to more efficient use of hospital resources with potential avoidance of autologous transplantation, which is a medically demanding intervention and destined to fail in the vast majority of patients.

Both specialists noted the disadvantages are costs, limitation of the care to specialised centres only, and some patients requiring to relocate to a treatment centre for administration of the therapy. There are also risks of infection and low blood counts if treatment is successful

LF also noted disadvantages of the proposed medical service related to the limited access for patients to receive the therapy, with some eligible patients potentially needing to travel long distances and stay away from home for a number of weeks; LF and RCA did not express any disadvantages of the proposed medical service.

10. Characteristics of the evidence base

The clinical analysis presented in the application was based on direct evidence from the ZUMA-7 trial, which published 15 reports. The ADAR considered that the ZUMA-7 trial was a high quality randomised controlled trial (RCT) directly comparing AXI to SoC for patients with LBCL who were refractory to or who had relapsed no more than 12 months after completion of 1L chemoimmunotherapy. The ZUMA-7 trial was deemed to have some concerns associated with the risk of bias (as assessed with the Cochrane risk of bias tool [RoB 2]), and that these biases were likely to favour AXI.

The applicant also provided evidence from near-market comparators (lisocabtagene maraleucel and tisagenlecleucel) retrieved from supplementary evidence searches.

Tisagenlecleucel is not registered on the TGA for use in the 2L setting and therefore it may not be considered an appropriate near-market comparator for this application (tisagenlecleucel is only registered in the 3L setting). Lisocabtagene maraleucel is currently not registered for use in Australia and there is no evidence provided for its use in clinical practice (given the market for CAR T-cell therapies in the 3L setting is shared between tisagenlecleucel and axicabtagene ciloleucel). Therefore, lisocabtagene maraleucel is not an appropriate near-market comparator for this application.

ZUMA-7 trial

The ZUMA-7 trial was a single head-to-head RCT comparing AXI to SoC in in 359 adult patients with LBCL (based on the WHO 2016 lymphoma categorisation) who were refractory to or relapsed no more than 12 months after completion of 1L treatment with a chemoimmunotherapy regimen.

Table 3 Key features of the included evidence.

References	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 Intervention: N=180 SoC: N=179	OL, MC, RCT; 25 month median follow-up	*Some concerns*	LBCL refractory to or relapsed no more than 12 months after completion of 1L treatment with chemoimmuno therapy	• Proportion of patients administered definitive therapy • ORR and CRR • Duration of response • EFS and PFS • TTNT • HRQoL • Overall survival • 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 events of special interest (cytokine release syndrome (CRS), infection and febrile neutropenia, cytopenia (neutropenia, thrombocytopenia, anaemia), neurologic events) • 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, for all clinical efficacy outcomes used in the model: EFS, Overall survival, Disposition of Yescarta and SoC patients, QALYs.

Source: ZUMA-7 CSR, 2021.
Abbreviations: 1L=first-line; AE=adverse events; CRR=complete response rate; EFS=event-free survival; HRQoL=health-related quality of life; LBCL=large B-cell lymphoma; LYG=life year gained; MC=Multi centre; ORR=objective response rate; OL=open label; PFS=progression-free survival; QALY=quality adjusted life year; RCT=randomised control trial; SAE=serious adverse events; TTNT=time to next treatment.

The ZUMA-7 trial was judged to be associated with some concerns of bias. The key area where some concerns of bias were introduced was around the inability to blind clinicians and investigators to the treatment arms (potentially introducing performance bias), and there were some concerns of bias regarding measurement error (ascertainment error); There was flexibility in the timing of assessment and given that clinicians knew what arm their patients were in they may also be 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 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). In addition to that 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 incidents of this in the SoC arm and hence this favoured the AXI arm.

Therefore, the overall risk of bias was determined to have "some concerns".

11. Comparative safety

The adverse event (AE) profile of AXI in the ZUMA-7 trials 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. Also, the AE profile differed between the two groups, 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.

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

The evidence does 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 (involving salvage chemotherapy and, in responders, HDT + auto-SCT).

The applicant stated that as clinicians gain experience in the use of AXI, rates of adverse events observed in practice have been falling and are anticipated to fall further. However, further detail of the role of clinician experience in prevention of rates of AEs has not been explored in the ADAR. As well, the role of training and workforce in supporting the reduction of AEs for AXI needs to be considered.

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)*
Anemia	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)	2 (1)	*2.47 (0.49, 12.56)*
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	-
Hypokalemia	44 (26)	10 (6)	49 (29)	11 (7)	*0.9 (0.39, 2.06)*
Hypophosphatemia	45 (26)	31 (18)	29 (17)	21 (12)	*1.46 (0.87, 2.43)*
Cough	42 (25)	1 (1)	18 (11)	0	-
Decreased appetite	42 (25)	7 (4)	42 (25)	6 (4)	*1.15 (0.4, 3.36)*
Hypoxia	37 (22)	16 (9)	13 (8)	7 (4)	*1.22 (0.6, 2.45)*
Dizziness	36 (21)	2 (1)	21 (12)	1 (1)	*1.98 (0.18, 21.59)*
Constipation	34 (20)	0	58 (35)	0	-
Vomiting	33 (19)	0	55 (33)	1 (1)	-
Febrile neutropenia	4 (2)	4 (2)	46 (27)	46 (27)	***0.09 (0.03, 0.23)***
Cytokine release syndrome — 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. (%)	102 (60)	36 (21)	33 (20)	1 (1)	***35.58 (4.93, 256.53)***
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	-
Paresthesia	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, Locke 2021.
Abbreviations: CI=confidence interval; SoC=standard of care; RR=relative risk

12. Comparative effectiveness

The evidence supports 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 superior effectiveness compared with SoC (involving salvage chemotherapy and, in responders, HDT + auto-SCT). However, the magnitude of effect may not be as great as in the trial, due to the biases outlined further below. Key results are summarised in Table 5. Time-to-event results are presented in Figures 1 and 2.

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

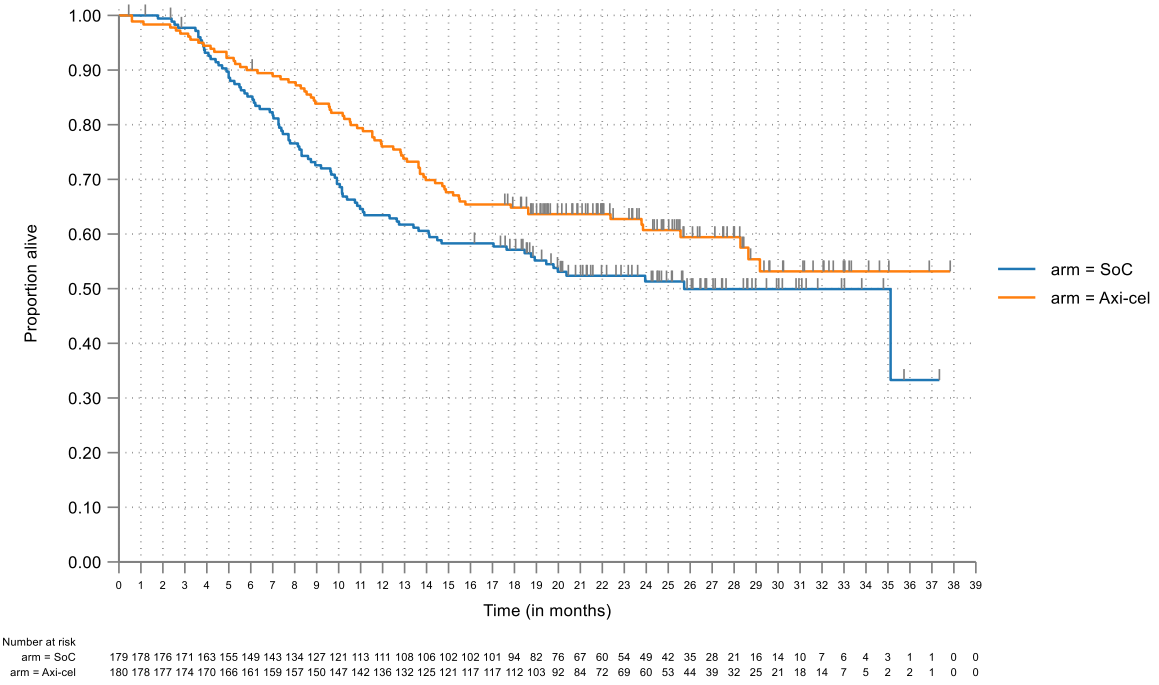
Outcome	AXI N = 180	Standard of care N = 179	Difference (95% CI)
Proportion of patients administered definitive therapy, n (%)	170 (94.4)	62 (34.6)	
ORR, n (%)	150 (83)	90 (50)	33.1% (23.2, 42.1)*
CRR, n (%)	117 (65)	58 (32)	
PRR, n (%)	33 (18)	32 (18)	
Median follow up (EFS), months (95% CI)	23.0 (20.9, 24.0)	21.2 (20.4, 23.7)	
Duration of response: Median, months (95% CI)	26.9 (13.6, not estimable)	8.9 (5.7, not estimable)	HR: 0.74 (0.49, 1.11)
EFS			
Median, months (95% CI)	8.3 (4.5, 15.8)	2.0 (1.6, 2.8)	**HR: 0.40 (0.31, 0.51)**
EFS at 24 months, % (95% CI)	40.5% (33.2%, 47.7%)	16.3% (11.1%, 22.2%)	
PFS (median duration), months (95% CI)	14.9 (7.2, not estimable)	5.0 (3.4, 8.5)	**HR: 0.56 (0.41, 0.76)**
TTNT, (median duration) months (95% CI)	14.7 (6.5, not estimable)	3.4 (3.1, 4.4)	**HR: 0.43 (0.33, 0.56)**
Overall survival			
Deaths (all cause), n (%)	72 (40)	85 (47)	**HR: 0.71 (0.52, 0.97)**
Median OS, months (95% CI)	Had not been reached	25.7 (17.6, not estimable)	
Alive at 24 months, % (95% CI)	60.7% (95% CI: 52.8%, 67.7%)	51.3% (43.4%, 58.7%)	

Source: ZUMA-7 CSR, 2021
* Result in percentage difference; **Bold** = statistically significant difference
Abbreviations: CI=confidence interval; CRR=Complete Response Rate; EFS=Event free survival; ORR=Objective Response Rate; OS=Overall survival; PRR=partial (metabolic) response rate

Overall survival

KM analysis of OS is conducted based on the FAS. Stratified Cox regression models were used to generate the estimated OS hazard ratio and 2-sided 95% confidence intervals for AXI relative to SoC. Despite high rates of switching to 3L CAR T-cell therapy in the SoC arm of the ZUMA-7 trial, superior EFS translated to superior overall survival (OS) in the AXI-treated cohort versus the SoC cohort over a median follow-up of over 24 months. The hazard ratio for OS was 0.708 (95% CI: 0.515, 0.972). Median survival had not been reached in the AXI arm of the trial and was 25.7 months in the SoC arm. At 2 years, 60.7% and 51.3% of patients were alive in the AXI and SoC arms, respectively (see Figure 1). The KM curves start to come together at around 30 months, which suggests that the ongoing effect for overall survival may not be realised; however, there is considerable censoring of patients beyond 18 months of follow-up and it is important that outcomes beyond this time are interpreted with caution.

Figure 1 Overall survival in ZUMA-7 by treatment.



Abbreviations: Axi-cel=axicabtagene ciloleucel; SoC=standard of care
Source: Figure 3-7, p76 of the ADAR

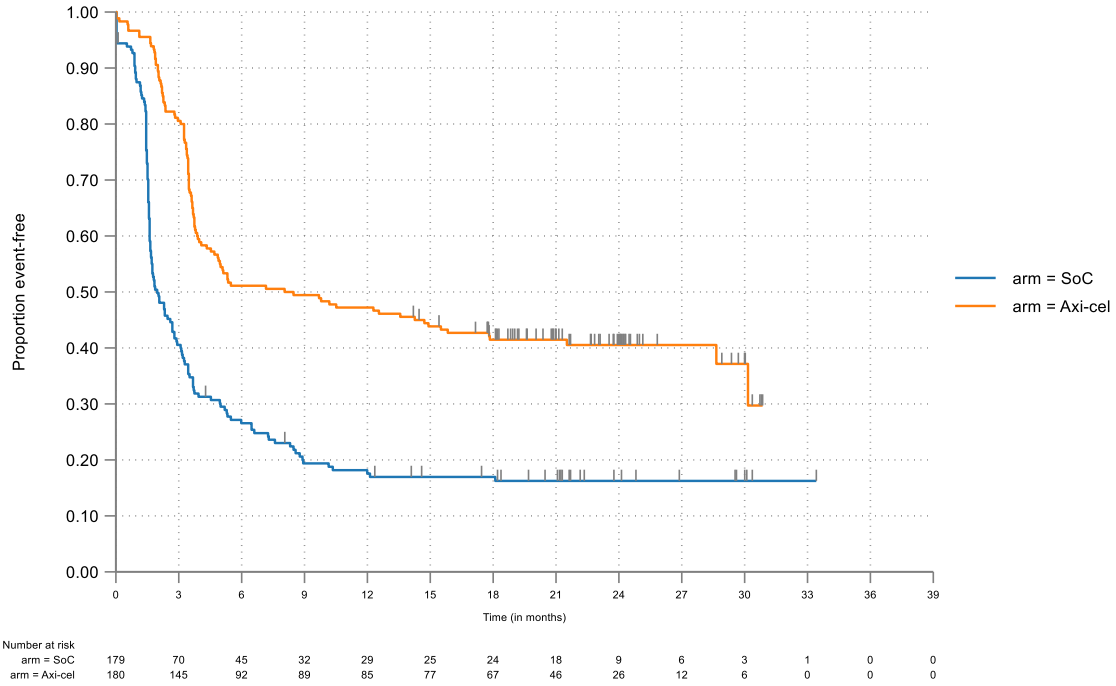
The assessment team has independently judged the overall risk of bias as some concern. The key area of concern is the timing of assessments (50, 100, and 150 after randomisation). It is unclear how this would affect the results of the trial, but could overestimate the PFS benefit (i.e., those who progressed on day 50–60 may not be picked up until day 100, adding an extra 40-day survival). Given that the clinicians were not blinded, they may also be inclined to see their patients earlier in the standard of care arm (PET-CT had a -7 +14-day window for first assessment) so that they could move their patients to the new treatment faster.

The claim of superior efficacy is likely to be appropriate; however, the magnitude of effect is likely to be lower for response, progression and event free survival based on how the study was conducted.

Event-free survival (EFS)

EFS was defined as the time from randomisation to the earliest date of disease progression per the Lugano Classification, commencement of new lymphoma therapy, or death from any cause. More than twice as many patients in the AXI arm compared with the SoC arm of the ZUMA-7 trial were still free of events at 24 months (40.5% vs 16.3%, respectively; see Figure 2). Median EFS was 8.3 months for patients treated with AXI compared to only 2.0 months for patients treated with SoC. The difference in EFS across the two arms was statistically significant (HR: 0.398; 95% CI: 0.308, 0.514). However, there were some early events in the SoC arm due to patients who commenced a new lymphoma therapy in the absence of any evaluable disease assessment been assessed as having an event at the randomization date.

Figure 2 Event-free survival in ZUMA-7 by treatment.



Patients who did not meet the criteria for an event had their data censored (tick marks). In the axi-cel group, 108 patients had an event; 82 (76%) had progression, 11 (10%) had a change in therapy, 11 (10%) died, and 4 (4%) had a best response of stable disease up to and including the day 150 assessment after randomization. In the standard-care group, 144 patients had an event; 75 (52%) had progression, 63 (44%) had a change in therapy, and 6 (4%) died.
Abbreviations: Axi-cel=axicabtagene ciloleucel; SoC=standard of care
Source: Figure 3-12, p80 of the ADAR

Complete response rate (CRR) and ORR

The proportion of patients achieving complete response (CR) in the AXI arm of the ZUMA-7 trial was double the rate observed in the SoC arm (65% vs 32%, respectively), and the difference was statistically significant. The difference in CR rates translated to a difference in ORR (83% vs 50% for AXI and SoC, respectively; difference: 33.1%; 95% CI: 23.2%, 42.1%).

Proportion of patients administered definitive therapy

Of the 179 subjects who were randomised to the SoC arm of ZUMA-7, 168 of the 179 (93.9%) randomised subjects 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 94.4% of patients received the full AXI treatment regimen.

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

Supplementary information – comparison of ZUMA-7 trial with near-market comparators

Neither lisocabtagene maraleucel or tisagenlecleucel were considered near-market comparators during evaluation. However, supplementary trial evidence for their use in 2L was provided in the ADAR. Only naïve comparisons were made with no attempt to adjust for indirect treatment comparison, therefore any interpretation of the evidence should be taken with caution.

The BELINDA trial found that tisagenlecleucel was not superior to standard salvage therapy in the 2L setting. The results from BELINDA demonstrate that CAR T-cell therapy trials can be associated with substantially different outcomes despite targeting the same antigen. The TRANSFORM trial found that lisocabtagene maraleucel was superior to SoC in terms of ORR, CR and EFS, but not different in OS.

There were some differences in trial design and definition of EFS which may have important impacts on interpretation of clinical effectiveness. The most stringent definition of EFS was applied in ZUMA-7, where patients were required to still have stable disease at Day 150 (approximately Week 21) to be considered as having an event, in BELINDA the timepoint was Week 12 (Day 84), and in TRANSFORM the timepoint was Week 9 (Day 63). This may have contributed to slightly lower event rates being observed in both arms of the ZUMA-7 trial compared to the TRANSFORM trial.

13. Economic evaluation

Overview and rationale of the economic evaluation

Based on the clinical claim of superiority in clinical effectiveness and noninferior safety, a cost-effectiveness analysis and cost-utility analysis were deemed appropriate.

The ADAR presented the results of a cost-utility analysis examining the cost-effectiveness of substituting AXI for SoC for the treatment of patients with LBCL refractory to or relapsed no more than 12 months after completion of 1L treatment with chemoimmunotherapy. A cost-effectiveness approach is justified given that AXI is demonstrated to be therapeutically superior to SoC in the population of interest. The analysis is based on extrapolation of the outcomes from the ZUMA-7 trial.

A summary of the key characteristics of the economic evaluation is detailed in Table 6.

Table 6 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 LBCL who are confirmed refractory to or have relapsed no more than 12 months after 1L 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	40 years in the model base case (vs 2 years in the key trial)
Computational method	Partitioned survival analysis
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 driving by data from the ZUMA-7 trial and a mixed cure model with survival extrapolation beyond the follow up of the trial.
Discount rate	3.5% for both costs and outcomes 5% used in commentary's respecified base case ICER (consistent with MSAC guidelines)
Software	Excel

Abbreviations: 1L=first-line; ICER=incremental cost-effectiveness ratio; LBCL=large B-cell lymphoma; LYG=life year gained; QALY=quality adjusted life year

During evaluation the base case was respecified to address a number of issues including to correct an error in the event free survival calculation. A base case discounting of 3.5% is inappropriate as 5% discount rate is the preferred and standard approach as per the MSAC Guidelines and has been incorporated into the respecified base case.

Given the mean age of patients in the ZUMA-7 study was 57 years, the model examines costs and outcomes over 40 years. This is an appropriate approach in a disease scenario where treatments lead to differences in EFS and OS that leads to lower relapse and death that can accrue over the fullness of time. However, in this situation a 40 year time horizon is considerably long for this population and given the clinical evidence; the average age in the Australian patient population is likely older (with the median population being in the 70-79 age category based on 2017 data from AIHW (non-Hodgkin Lymphoma)) (AIHW, 2017) and the clinical data supporting the evidence has a median follow-up of just over 2 years (with immature overall survival data). The model also incorporates a cure rate survival which is based on highly optimistic values. Overall, the long-time horizon favours AXI. A 30-year time horizon has been included in the respecified base case.

The type of economic analysis presented is a partitioned survival analysis comparing mean EFS and OS of AXI to SoC in patients with LBCL. Partitioned survival analysis model is appropriate for this setting. However, the partitioned survival analysis model structure limits the extent to which

sensitivity analyses can be used to explore clinical uncertainties especially in the extrapolation period as there is no link between event free survival and overall survival. Given the uncertainty around the indirect clinical evidence the use of a state transition model would allow assessment of clinical uncertainties in the extrapolation period.

Extrapolation of overall survival

The ADAR use a mixed cure fraction model to extrapolate the overall survival for patients with LBCL in the model (Figure and Figure).

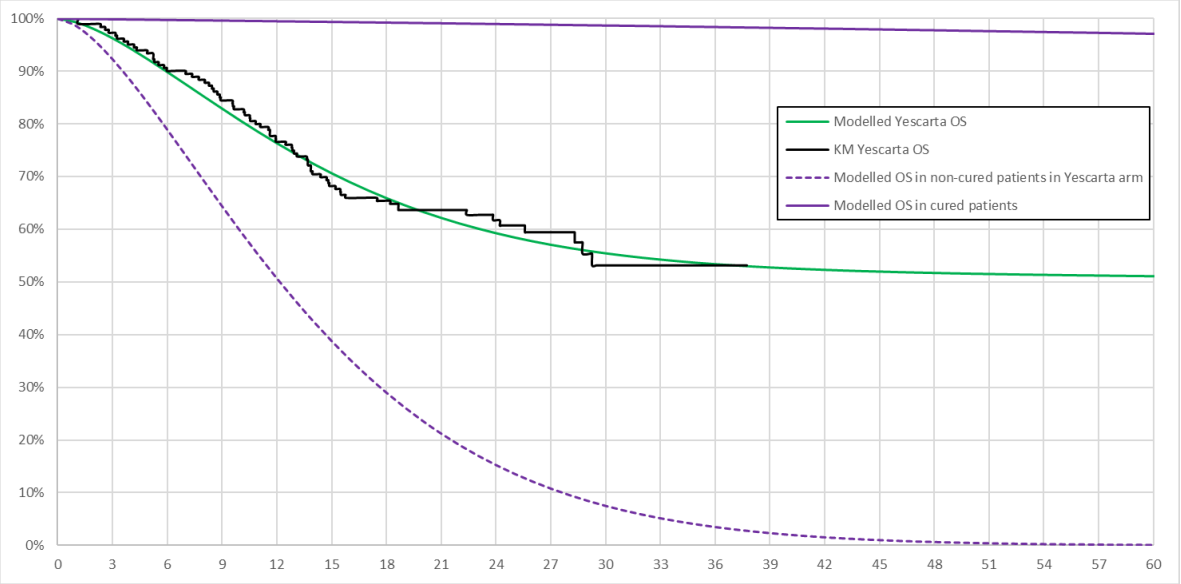


Figure 3: OS assumed in cured, non-cured and resultant modelled axicabtagene ciloleucel arm compared to the KM function from ZUMA-7

Source: Figure ES-6, p10 of the ADAR

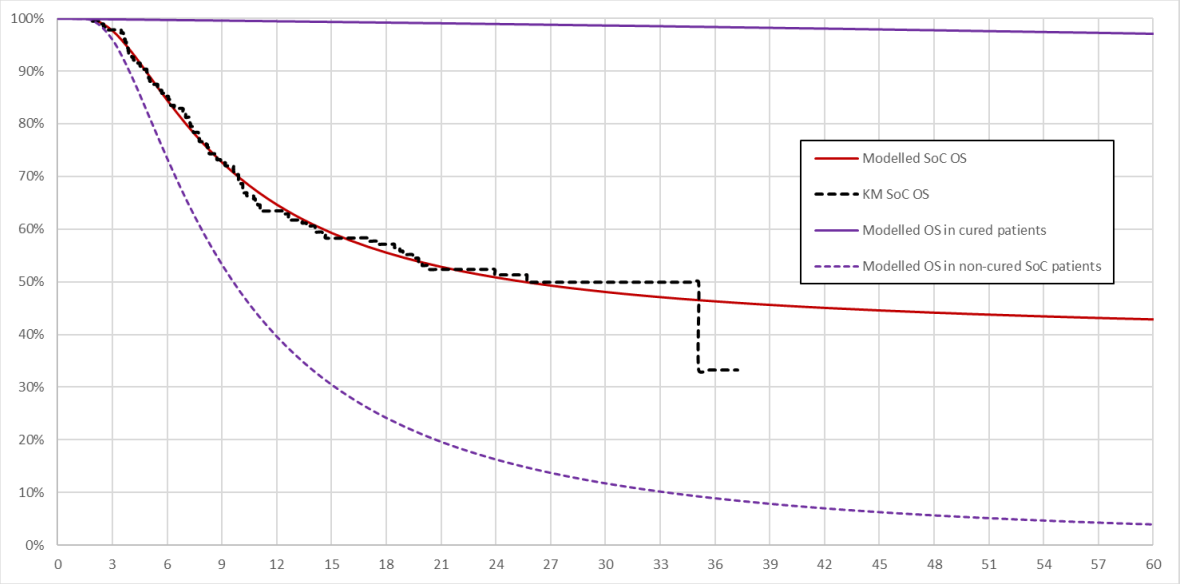


Figure 4: OS assumed in cured, non-cured and resultant modelled SoC arm compared to the KM function from ZUMA-7

Source: Figure ES-7, p11 of the ADAR

Using this cure fraction approach on two years follow up data would be inappropriate. As stated in the ADAR "The cure fractions should be interpreted with caution since cure fractions represent the proportion of patients that experience adjusted general population mortality as determined by a logistic model which uses data on the pattern of death observed in the ZUMA-7 trial only." The data from ZUMA-7 is limited by size (180 in each arm) and length – only 24 month follow up so the results of the cure fraction analysis is limited in value. While the ADAR makes an argument that this is statistical cure rates of the population rather than the individual it still needs to be grounded in clinical practice. The cure fractions range from 24-54% in the AXI arm and 35 – 49% in the SoC arm, the extrapolation chosen by the ADAR is the most favourable for the AXI arm (53% vs 42% in the SoC arm). The ADAR considered that the generalised gamma functional form was most appropriate as it had the lowest average AIC/BIC and its application in the base case of the modelled economic evaluation produced clinically plausible survival functions. However, according to the attached economic evaluation spreadsheet, the lowest AIC and BIC for SoC was log normal and the lowest AIC and BIC for AXI was logistic.

Cure mixture models also need to be grounded in sound clinical practice, in both arms the proportion of patients experiencing events drops below the cure fraction by 6 months follow up, while some of these patients may later experience a "cure" due to third line treatment it is unlikely that it is at the level that the ADAR has proposed. Unfortunately, it was not possible to determine normal extrapolations from the data, as only cure fraction extrapolations were provided.

Also of note, using this approach led to the survival curves separating from cycle 38 to 109, where the difference between survival expands rather than coming together as would be expected in a survival model, it is not until cycle 153 that the survival curves begin their tapering journey. Therefore, the survival gains in the model increases (the survival curves separate more - rather than just maintained) after the clinical trial data has stopped. This seems improbable and inappropriate.

Extrapolation of event free survival

The ADAR used independent standard parametric functions to extrapolate the EFS for patients with LBCL in the model; for both arms, the Gompertz function provided the best fit to the data and was used for extrapolation (Figure 5)

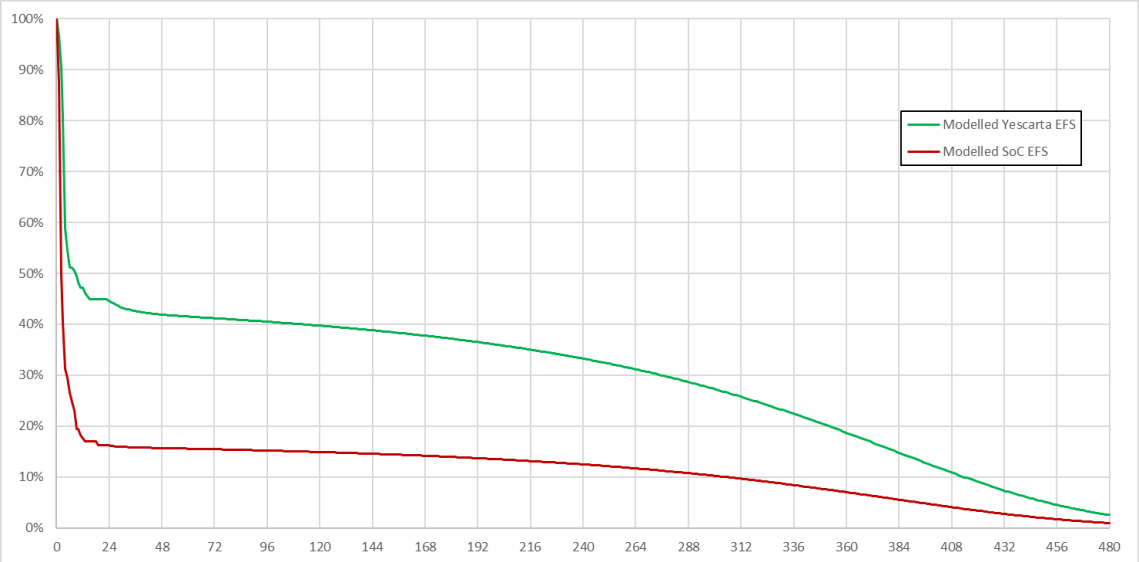


Figure 5: Extrapolated event-free survival by treatment as projected by the modelled economic analysis

Source: Figure 3-14, p82 of the ADAR

The chosen extrapolations seem appropriate; however, how the extrapolations are applied in the model was not appropriate. The model states it is using the KM curves up to 24 months and extrapolation after this; however, this is not the case; there is an error in the model and AXI curves only follow KM curves up to 15 months. This was corrected in the respecified base case and led to an increase in the ICER.

Utility weights

Quality of life was assessed through the ZUMA-7 trial and the utilities derived from the administration of the Euro-QOL, 5 dimensions, 5 levels (EQ-5D-5L) instrument were used to value life-years in the event-free and post-event health states in the model. This would have been an appropriate approach; however, there were some concerns with regards to the validity of the values from the trial and other approaches could have been taken. There were considerable missing HRQoL data points, the assessment team was unable to independently verify the utility weights applied in the economic analysis and based on the data in the CSR it would be inappropriate to apply the reduced utility for 3 full cycles in the model. Also, it is unclear whether the Australian value sets were used in the derivation of the EQ-5D-5L.

Given the adverse event profile it would seem unlikely that the standard of care arm would have a lower utility than the AXI arm, as adverse event disutility was not applied in the model (due to using trial HRQoL data) this adverse event profile was not accounted for in the analysis.

Costs

Overall, the resource items and unit costs have been retrieved from appropriate sources. However, some unit costs which could not be simply derived from publicly available administration and pharmacy costs were derived from existing literature and may underestimate the cost of CAR-T therapy. Also, some of these references were not provided, so the assessment team could not independently examine the method. No jurisdictional data was used to supplement the costs.

There is some uncertainty around the cost data provided by the ADAR. A substantial number of sources are from old studies >10 years old and the costs may not be relevant due to changes in practice. For example, a recent review of Autologous SCT costs in Tasmania (Reeve et al, 2018) put the mean cost of the most expensive approach at $45,213 (with Conditioning regimens included in the price); costed in the model at $79,536 based on a 2009 study. Also, the only 2L SoC included in the model is R-ICE; however, this is likely to have limited overall impact in the economic evaluation. The costs associated with end-of-life care are likely to be higher with the mean costs associated with the last 6months of life in cancer patients being $28,091 in Australia. There is also considerable uncertainty around how the 3L setting is applied in the model. The model is based on the subsequent lines of therapy for patients in ZUMA-7. Approximately 56% of the population in ZUMA-7 on standard of care received a CAR T-cell therapy, this is applied in the model. However, the ADAR argues that only about [redacted] of 3L patients in Australia receive CAR-T therapy in 3L. The costs associated with standard of care is heavily weighted by this subsequent therapy.

Given the increase in infrastructure and workforce required to increase the surge in demand for CAR-T therapy in 2L it could be appropriate to include upfront costs associated with these in the model and the financial impact.

Subsequent therapies are not completely covered for AXI arm, with only treatment with SCT (both autologous and allogeneic) accounted for in the model; this only accounts for 10% of the patients and whereas the CSR reports that an additional 41% received subsequent therapies. The economic model assumed all other subsequent therapy are salvage chemotherapy, and other

therapies were not included which could be more expensive than salvage, for example. brentuximab, nivolumab, obinutuzumab, pembrolizumab, or polatuzumab. This favours AXI.

Costs of adverse events have not been incorporated into the model. This was based on the ADARs assumption that there was noninferior safety between the two treatments. While the ADAR did include length of stay and per day hospital costs, the per day costs were based on the "weighted average per diem cost for admissions related to lymphoma and non-acute leukaemia". This cost is based on the average cost regardless of treatment regimen. Therefore, the cost of differential treatment (between AXI and SoC) required to deal with adverse events was not included in the economic model. This was not appropriate and favours AXI.

Adverse events

As the ADAR considered that AXI was non inferior in terms of adverse events compared to SoC they did not include disutilities or costs associated with adverse events. As demonstrated above, AXI is inferior in terms of safety to SoC and these disutilities and costs should be incorporated into the model.

Results of the economic evaluation

The ADAR results are presented in Table 7.

During evaluation the base case was respecified to rectify an error in the event free survival calculation; correct the discount rate from 3.5% to 5%; reduce the time horizon to 30 years (Table 8).

Table 7 Results of the economic evaluation base case presented in the ADAR (i.e., discount rate of 3.5%, time horizon of 40 years and an error identified in the EFS modelling)

Step	AXI in 2L setting	SoC	Increment	ICER
ADAR Base case				
Costs	$[redacted]	$[redacted]	$[redacted]	
QALY	7.494	6.201	1.294	$[redacted]

Abbreviations: 2L=second-line; ICER incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SoC=standard of care

Table 8 Results of the economic evaluation using the respecified base case presented in the commentary (discount rate 5%, time horizon of 30 years and correction to the EFS modelling error)

	AXI in 2L setting arm	SoC arm	Increment
Discounted costs over 30 years			
Costs of second-line treatment	$[redacted]	$[redacted]	$[redacted]
Cost of post-event treatment	$[redacted]	$[redacted]	$[redacted]
Costs of palliation	$[redacted]	$[redacted]	$[redacted]
Costs over a 30-year time horizon (discounted)	$[redacted]	$[redacted]	$[redacted]
Discounted outcomes over 30 years			
Mean EFS (in years)	5.757	2.479	3.278
Life-years over a 30-year time horizon (discounted)	8.003	6.683	1.320
QALYs over a 30-year time horizon (discounted)	6.269	5.219	1.050
Incremental cost per life-year gained over a lifetime (30-year) time horizon			**$[redacted]**
Incremental cost per QALY gained over a lifetime (30-year) time horizon			**$[redacted]**

Abbreviations: 2L=second-line; EFS=event-free survival; QALY=quality-adjusted life year; SoC=standard of care

The key drivers of the model identified during evaluation were extrapolation of long-term outcomes for OS and EFS, the proportion of patients receiving CAR T-cell therapy in 3L and time horizon (Table 9).

Table 9 Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Treatment effect continued beyond 25-month trial period for up to 40 years. The model use a cure fraction model to extrapolate the data	*High, favours AXI*
Time horizon	The way the model was developed, means that the treatment effect is continued for the time horizon without the support of clinical evidence	*High, favours AXI*
Discount Rate	3.5% used in the model, versus 5% required by MSAC	*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*

Abbreviations: 2L=second-line; 3L=third-line; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year.

Uncertainty analysis: model inputs and assumptions

The results of key univariate and multivariate sensitivity analyses conducted during evaluation are summarised below.

Sensitivity analysis was conducted for discount rate, time horizon, baseline age, cost of auto-SCT, cost of hospitalization for AXI, parametric function applied to extrapolate OS, SMR and utility weights. The sensitivity analyses indicate that the results of the economic analysis are most sensitive to the discount rate (with higher discount rates favouring SoC) and to the functional form used to extrapolate OS. Results are presented in Table 10.

Table 10 Respecified base case[a] and sensitivity analysis (commentary); *Updated to include ESC additional sensitivity analyses for exploratory purposes*

Variables altered in sensitivity analysis	Incremental costs	Incremental QALYs	ICER
Respecified base case results (by AG)	**$**	**1.050**	**$**
Discount rate (respecified base case = 5%)			
• 3.5%	$	1.231	$
Time horizon (respecified base case = 30 years)			
• 40 years	$	1.086	$
Baseline age (base case = 57.2)			
• 55 years	$	1.077	$
• 70 years	$	0.769	$
Cost of auto-SCT (base case = $79,536)			
• 20% lower than estimated	$	1.050	$
• 20% higher than estimated	$	1.050	$
Cost of hospitalisation for AXI (base case = $36,621.99)			
• 20% lower than estimated	$	1.050	$
• 20% higher than estimated	$	1.050	$
Utilities			
• in first cycles the same (0.780)	$	1.048	$
• disutility in first cycle AXI (0.672)	$	1.041	$
Parametric function applied to extrapolate OS (base case = generalised gamma)			
• Exponential*	$	-0.397	
• Weibull	$	0.565	$
• Gompertz	$	0.805	$
• Lognormal*	$	-1.098	
• Loglogistic*	$	0.041	$
ESC additional exploratory sensitivity analyses (SA)			
ESC SA1: Subsequent 3L CAR-T = [redacted] (BC: 56%)	*$*	*1.050*	*$*
ESC SA2: Trial-based ICER	*$*	*0.126*	*$*
ESC SA3: Time horizon = 15 years (Respecified BC=30 years)	*$*	*0.738*	*$*
ESC SA4: EFS assume same in each arm in absence of PFS[a]	*$*	*1.031*	*$*
ESC SA5: Hospitalisation cost (3.3 months$46,575[b])*	*$*	*1.050*	*$*
ESC SA6: Utility of AXI first 3 months to consider 25% ICU for AEs	*$*	*1.031*	*$*
ESC SA7: SA5+SA6	*$*	*1.031*	*$*
ESC SA8: SA1+ SA5+SA6	*$*	*1.031*	*$*

[a] During evaluation the base case was corrected to rectify an error in the event free survival calculation; change the discount rate from 3.5% to 5% and reduce the time horizon to 30 years; these parameters are applied throughout the table unless they have been specifically varied.

Abbreviations: AE= adverse event; BC = base case ICER=incremental cost-effectiveness ratio; QALY=quality adjusted life year; OS=overall survival; SCT= stem cell transplant

[a] Modelled EFS values assumed to be the same in each arm

[b] 1 Australian dollar (AUD) = 1 United States dollar (USD); 3.3 months of $46,575 taken from Maziarz et al 2022

Scenario analysis conducted during the evaluation is presented in Table 11.

Table 11 Results of scenario analysis around the modelled economic evaluation using the respecified base case[a]

Variables altered in scenario analysis	Incremental costs	Incremental QALYs	ICER
Base case results	**$**	**1.050**	**$**
• Discount rate 5% • Time horizon 10 years	$	0.535	$
• Discount rate 5% • Time horizon 10 years • Tasmania Auto SCT	$	0.535	$
• Discount rate 5% • Time horizon 10 years • Tasmania Auto SCT - $45,213 • end-of-life care - $28,091	$	0.535	$
• Discount rate 5% • Time horizon 40 years • Tasmania Auto SCT - $45,213 • end-of-life care - $28,091 • 36% of patients in SOC receiving AXI	$	1.086	$
• Discount rate 5% • Time horizon 40 years • Tasmania Auto SCT - $45,213 • end-of-life care - $28,091 • 36% of patients in SOC receiving AXI • Tapering overall survival and EFS between 10 and 20 years	$	0.637	$

Source: Compiled during evaluation

[a] During evaluation the base case was corrected to rectify an error in the event free survival calculation; change the discount rate from 3.5% to 5% and reduce the time horizon to 30 years.

14. Financial/budgetary impacts

Justification of the approach and data sources

An epidemiological approach to budget impact analysis was used to estimate the uptake of the proposed technology. A validation of the estimates generated by the epidemiological approach was conducted using a market share approach.

The ADAR did not tabulate the data sources used in the financial model but provided these as a listed summary. It would be beneficial to tabulate and justify all data sources used in the financial model. From scoping of the literature by the assessment team, it appears that the sources used are the best available evidence for the analysis and are therefore appropriate.

Key cost assumptions

The following key cost assumptions/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.
- Per MSAC advice for 1587 (AXI in the 3L setting), it is proposed that a payment is made in two instalments: (1) upon infusion of the manufactured product, and (2) at an agreed time in the future dependent on the outcomes observed in patients. However, this was not included in the financial estimates.

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 ("Although the majority of patients treated with immunochemotherapy respond to treatment, 20% to 40% of patients will either fail to achieve remission or they will relapse").

The estimate of 42% for the proportion on NHL that is LBCL is derived from incidence calculations based on Sehn 2021 of 2500-2670 cases of LBCL per year. 42% (2670/6400=41.7%) appears to be the upper end estimate provided. It may therefore be appropriate to conduct sensitivity analysis or provide an explanation for assuming the maximum.

Given the increase in infrastructure and workforce required to increase the surge in demand for CAR-T therapy in 2L it may be appropriate to include upfront costs associated with these in the financial impact. The payment schedule of upon infusion and on outcomes was not included in the financial estimates.

Financial impacts – evaluation results

The financial implications to the Highly Specialised Therapies resulting from the proposed listing of AXI in the 2L setting are summarised below.

There were some errors noted in the calculations around the ABS population and incidence data and using ≥ 16 years when the trial was limited to ≥ 18 years. These have been corrected during evaluation as described in footnote below Table 12.

Table 12 Net financial costs of AXI in the 2L setting to the state and commonwealth health departments.

	2023 (Year 1)	2024 (Year 2)	2025 (Year 3)	2026 (Year 4)	2027 (Year 5)	2028 (Year 6)
Number of patients likely to be administered AXI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of AXI	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Costs of ancillary services associated with AXI	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total costs for 2L treatment with AXI	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Post- progression costs after 2L AXI	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total costs associated with funding of AXI	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: 1L=first-line; 2L=second-line; SoC=standard of care

Note the estimated Australian population aged ≥ 16 years during evaluation was corrected during evaluation using ABS input data from >18 y, as the trial. This resulted in Australian population data of 21,139,340 in Year 1; 21,474,344 in Year 2; 21,809,267 in Year 3; 22,148,287 in Year 4; 22,487,778 in Year 5 and 22,828,373 in Year 6 (from 21,734,626 in Year 1; 22,082,338 in Year 2; 22,422,054 in Year 3; 22,759,127 in Year 4; 23,086,141 in Year 5; and 23,411,238 in Year 6 in the ADAR). Using this ABS input data, resulted in the number of patients treated with AXI of [redacted] in Year 1; [redacted] in Year 2; [redacted] in Year 3; [redacted] in Year 4; [redacted] in Year 5; [redacted] in Year 6 (compared with [redacted] in Year 1; [redacted] in Year 2; [redacted] in Year 3; [redacted] in Year 4; [redacted] in Year 5 and [redacted] in Year 6 in the ADAR)

Table 13 Net financial offsets of AXI in the 2L setting to the state and commonwealth health departments

	2023 (Year 1)	2024 (Year 2)	2025 (Year 3)	2026 (Year 4)	2027 (Year 5)	2028 (Year 6)
Costs of 2L SoC avoided	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Post-progression costs after 2L SoC avoided	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total costs avoided with funding of AXI	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: 1L=first-line; 2L=second-line; SoC=standard of care

Table 14 Net financial implications of AXI in the 2L setting to the state and commonwealth health departments.

	2023 (Year 1)	2024 (Year 2)	2025 (Year 3)	2026 (Year 4)	2027 (Year 5)	2028 (Year 6)
Total costs associated with funding of AXI	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total costs avoided with funding of AXI	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net budget impact AXI to NHRA	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

The ADAR's assumptions of eligibility and uptake at each stage of the clinical management process require sensitivity analysis given they are primarily "best guesses" and sometimes not justified or referenced (Table 15). Therefore, the assessment team has undertaken a sensitivity analysis with key variables (see Table 16).

Table 15 Variables chosen for sensitivity analysis and justification of values.

Variable	Base case	Sensitivity values	Justification
Proportion on NHL that is LBCL	42%	39%	42% (2670/6400=41.7%) is the upper estimate derived from incidence calculations based on Sehn 2021 of 2500-2670 cases of LBCL per year. Conduct sensitivity testing for lower limit of 39% (2500/6400=39.06%).
Proportion of patients who are r/r after completion of 1L chemoimmunotherapy.	40%	20%, 30%	Maurer 2014 cites 20-40%
Proportion of r/r LBCL who are refractory or relapse no more than 12 months after completion of 1L chemoimmunotherapy	[redacted]	50%, 100%	75% appears to be a proxy for "most", testing upper and lower limits
Proportion of patients who have adequate physical reserves for potentially curative therapy		70%, 90%	75% appears to be a proxy for "most", testing upper and lower limits
Projected uptake of AXI for LBCL in the 2L setting	[redacted] in Year 1, increasing [redacted] per year to [redacted] in Year 6	100% all years 50% in Year 1, increasing 10% per year to 100% in Year 6	Other potential uptake rates explored. 100% uptake across all years does not represent what the rates would be in real practice but provides an indication of the maximum financial outlay in absence of any further information.

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 by the assessment team).

	2023 (Year 1)	2024 (Year 2)	2025 (Year 3)	2026 (Year 4)	2027 (Year 5)	2028 (Year 6)
Base case	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Proportion on NHL that is LBCL (base case = 42%)						
39%	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Proportion of patients who are refractory or who relapse after completion of 1L chemoimmunotherapy (base case = [redacted])						
20%	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
30%	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Proportion of refractory or relapsed LBCL who are refractory or relapse no more than 12 months after completion of 1L chemoimmunotherapy (base case = [redacted])						
50%	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
100%	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Proportion of patients who have adequate physical reserves for potentially curative therapy (base case = [redacted])						
70%	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
90%	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Projected uptake of axicabtagene autoleucel for LBCL in the 2L setting (base case = [redacted] in Year 1, increasing [redacted] per year to [redacted] in Year 6) (equivalent reduction in 3L)						
50% in Year 1, increasing 10% per year to 100% in Year 6	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
100% all years	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: 1L=first-line; 2L=second-line; LBCL= large B-cell lymphoma; NHL=non-Hodgkin lymphoma; SoC=standard of care

Market share

In addition, the ADAR states that the CAR T-cell therapies market is shared evenly between AXI and tisagenlecleucel. As tisagenlecleucel is not yet approved for use in the 2L setting, this may not be an initial consideration for demand, but should be noted for the future.

Across jurisdictions

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 aggregated administration and pharmacy costs which precluded breakdown. Given the current funding mechanism for the intervention in 3L setting (cost sharing across Commonwealth and state as Highly Specialised Therapies under the National Health Reform Agreement) is proposed for the 2L setting, it can be assumed that this proposed funding mechanism remains appropriate, therefore the granular budget impacts on a jurisdiction level are not critical for an MSAC decision.

15. Other relevant information

There are pressing policy and implementation considerations that have not been discussed in this application.

Demand considerations

The impact of demand on workforce, training and infrastructure capabilities and requirements have not been considered. The applicant suggests that the number of people receiving AXI will increase from [redacted] per year in the 3L setting (as of year ending 31 July 2022) to an additional [redacted] in 2023, reaching [redacted] by 2025, in the 2L setting. Given there are only five qualified treatment facilities in Australia, a [redacted] increase in demand in Year 1 (2023) may not be possible given current positioning. The ADAR did not discuss the current capabilities of existing treatment facilities to meet demand, nor any plans for scale-up of other facilities.

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. With the specialist nature of administration of CAR-T cell therapies, training and workforce requirements need to be carefully considered. This is especially important given the applicant's assertion that clinician experience will have important impacts on reducing AEs.

Clinical management and eligibility

The proposed clinical management framework is currently underdeveloped. The assessment team believes the management algorithm will be more complex than is presented in this ADAR. As an example, Figure 1-4 showed patients who are refractory or relapsed after 1L treatment will then either undergo CAR T-cell therapy OR salvage chemotherapy (and follow the existing clinical management pathway). The figure is not completely accurate, as the aim is for CAR T-cell therapy to replace salvage chemotherapy; therefore, salvage chemotherapy would not be an option in the 2L setting. While this is impractical given current service limitations and capacity issues, it would be a more accurate representation of intended practice for this submission.

Appropriate decision criteria for the clinical management pathway is also required. This was not presented by the applicant in the ADAR, but the assessment team suggests eligibility criteria for admission for AXI in 2L (suggested criteria provided in Table C1).

The applicant did not indicate how long the manufacturing process for CAR-T cell therapies takes. Given clinical treatment decisions for 2L and 3L treatment may be time-dependent, this is an important consideration. In addition, the increase in demand may have impacts on manufacturing time and order backlog which need to be considered.

The patient eligibility for subsidy for AXI should be aligned with the Therapeutic Goods Administration (TGA) and the ZUMA-7 trial. The TGA eligibility is "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" whereas the ZUMA 7 trial patients had to be adult subjects with LBCL (based on the WHO 2016 lymphoma categorisation) who were refractory to or relapsed no more than 12 months after completion of 1L treatment with a chemoimmunotherapy including a CD20 monoclonal antibody and an anthracycline-containing regimen.

Access and equity

Given that AXI can only be administered in a handful of specialised facilities (5 centres in Australia) in certain metro areas (4 capital cities), there are 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 needs to be balanced with the significant demand requirements if AXI is funded in the 2L setting.

The ADAR mentions that patients are required to remain no more than 2 hours from the treatment centre for 4 weeks following infusion (after the initial 7-day hospitalisation). There are potentially substantial out of pocket costs associated with this for those who do not have such accommodation or additional income available to meet these post-treatment requirements, but this was not discussed.

The proposed intervention should be implemented with a registry of participants and their outcomes, and would require an expert advisory panel, including consumer representation, to continue to oversee the appropriate use of AXI in 2L patients.

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. This should be considered, especially given the only current competitor in Australia for AXI (tisagenlecleucel) is not funded in the 2L setting and so AXI would have sole place in the market at this line of treatment.

In addition, no pay for performance or risk share proposals were included in the application.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- Clinical effectiveness is less clear than as presented in the ZUMA-7 trial data – Flexible timing on survival endpoints is likely to favour AXI. Thus, there is high uncertainty related to the observed incremental magnitude of effect of AXI, due to the unblinded trial (in particular EFS and PFS) and the extent of treatment switching in the trial (which broke randomisation)
- Long term incremental benefit of AXI is highly uncertain –There are no survival data beyond 2 years where the hazard curves are observed to approximate and there are comparable death rates in both arms. Data presented in the ADAR are now two years old and an updated analysis of overall survival (OS) according to the treatments received would be informative, including to inform or validate the modelled OS
- EFS as the primary endpoint in the ZUMA-7 trial – The observed difference in EFS is primarily driven by the time to 'new lymphoma therapy' and this endpoint is likely to be heavily biased in favour of the AXI arm, due to the unblinded nature of the trial and potential performance and measurement bias. Disease progression (as measured by

progression-free survival [PFS]) would likely be a more reliable endpoint, however, would likely still be biased due to the trial design.

- Comparative safety – Safety is likely inferior and AEs unique to AXI including cytokine release and neurological AEs are not captured in the model. This favours AXI.
- Comparator– The nominated comparator does not include reimbursed 3L CAR-T therapy (although it is included as a subsequent therapy in the algorithm), which could be replaced with the introduction of AXI in 2L. This suggests that the application has only compared AXI at the second line stage, in comparison to chemotherapy and stem cell transplant, rather than a real-world scenario where 3rd line CAR-T therapy may follow unsuccessful 2nd line treatment. This suggests the model has not captured the difference between AXI in the 2nd vs 3rd line setting.

Economic issues:

- Model specification – The validity of the modelling approach results is queried, as a mixed cure fraction model is used to extrapolate OS based on too short trial follow-up, and use of EFS (rather than PFS). In addition, although the commentary's respecified base-case is more appropriate than the ADAR's base case, it should be regarded as exploratory due to these issues noted with the use of EFS and model structure.
- Additional concerns with model –The modelled frequency of use of 3L CAR-T in the SoC arm, the costs and disutilities of adverse events, and intensive care unit stays and IVIG usage have not been adequately incorporated into the model. This approach favours AXI.

Financial issues:

- High and uncertain budget impact –Due to the lack of clearly defined eligibility criteria for AXI and lack of clarity around 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)

Other relevant information:

- State and Territory government submissions are not supportive of the application
- No pay for performance or risk share measures were proposed by the sponsor.
- Registry data should be made available to stakeholders, however this was not addressed.

ESC discussion

ESC noted that this application is from Gilead Sciences Pty Limited for the chimeric antigen receptor-T (CAR-T) cell therapy, axicabtagene ciloleucel (YESCARTA®), referred to as AXI, for the treatment of relapsed or refractory (r/r) large B-cell lymphoma (LBCL) in the second-line (2L) setting. The application seeks joint funding by the Commonwealth and States and T3erritories through the High Cost, Highly Specialised Therapy arrangements included in the National Health Reform Agreement (NHRA) Addendum 2020-25.

AXI has recently been approved for usage in this 2L setting by the Therapeutic Goods Administration (TGA). ESC noted that AXI is also 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 the applicant has bypassed PASC and that the PICO has been provided as part of the Applicant Developed Assessment Report (ADAR). ESC noted that tisagenlecleucel (Kymriah) is another CAR-T therapy currently funded under the NHRA for the 3L treatment of r/r DLBCL. Both CAR-T therapies used in the 3L setting are restricted to one CAR-T infusion per patient per lifetime; ESC therefore considered that the key question is the comparative safety, effectiveness and cost effectiveness of AXI given in the 2L setting compared with giving AXI (or Kymriah) in the

3L setting (i.e. 2L AXI followed by 3L salvage chemotherapy +/- stem cell transplantation compared with 2L chemotherapy +/- stem cell transplantation followed by 3L CAR-T). ESC noted that in the pre-ESC response, the applicant contends that the trial does in fact represent this comparison of treatment sequences (inclusive of 2L and 3L therapy options in each arm), given that many in the standard of care (SoC) arm did receive AXI and patients in the AXI arm who met the criteria for new anti-lymphoma therapy could receive further therapy (the majority of those who proceeded to 3L received salvage chemotherapy which, in some cases, was followed by SCT). ESC however considered that it was not clear how reflective this usage was of Australian practice and that this did not fully answer the clinical question of interest.

ESC noted that consultation input was received from one individual specialist with experience in treating patients with blood cancers, who supported the service being publicly funded.

ESC noted that the ADAR was based on direct evidence from the randomised controlled ZUMA-7 trial. This trial compared SoC, n=180 (involving salvage chemotherapy and, in responders, high-dose therapy [HDT] with autologous stem cell transplantation [ASCT]) with AXI, n=179, in the 2L setting. Patients were permitted to receive a 3L CAR-T (AXI) upon disease progression in the SoC arm; a total of 100 participants (56%) received 3rd line CAR-T therapy after SoC. ESC noted that treatment switching was not planned and broke randomisation, and it was unclear if this can confound the outcomes. ESC noted that the ZUMA-7 trial had extensive exclusion criteria and considered that this would have implications for the eligibility criteria of AXI in practice, which were not clearly defined in the ADAR.

Regarding comparative safety. ESC noted that there was significant drop-out in the SoC arm and only 60 participants were assessed in safety outcomes (as 100 participants subsequently received 3L CAR-T therapy). ESC noted that of the participants analysed, the adverse event (AE) profile of AXI in the ZUMA-7 trial was consistent with the profile observed in other studies of CAR-T therapy in patients with r/r 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. Also, the AE profile differed between the two groups, with the incidence of cytokine release syndrome and neurologic events being significantly higher in the AXI group, although the incidence of febrile neutropenia was higher in the SoC group. ESC noted that 25% of participants in the AXI arm required a stay in the intensive care unit for a median of 5 days and that only 5% of participants in the SoC arm required an intensive care unit stay for a median of 3 days and this was not captured in the model. ESC noted that the applicant stated that as clinicians gain experience in the use of AXI, rates of AEs observed have been falling and are anticipated to fall further. However, evidence to support this was lacking. In addition, the role of training and workforce in supporting the reduction of AEs for AXI needs to be considered. ESC also noted that some of the AE treatments given in the trial (e.g.,65% of participants received tocilizumab) are not currently reimbursed for such usage in Australia and the cost not included in modelling. Overall, ESC considered that the claim of noninferior safety of AXI compared with SoC was not supported by the evidence presented.

Regarding comparative effectiveness, ESC noted that although the primary evidence came from a randomised, controlled trial, there was potential for bias. For example, clinicians and investigators were not blinded to the treatment arms (potentially introducing performance bias) and 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, which could also be influenced by clinicians being unblinded. There were more incidents of this in the SoC arm and hence this favoured the AXI arm. ESC also noted that the flexibility in the timing of assessments for patients in the ZUMA-7 trial likely introduced measurement bias. Patients had a –7 to +14 day window in which to have PET-CT assessment performed, which could result in bias in reporting of events in favour of AXI. ESC noted that in the pre-ESC response, the applicant stated that potential flexible timing of endpoints is unavoidable and may also be similar in both arms.

However, ESC noted that the applicant did not provide information on the median timing, which could provide further clarity around this issue.

ESC noted that a primary outcome presented in the ADAR was event-free survival (EFS), and this was a composite outcome defined as 1) the time from randomisation to the earliest date of disease progression (per the Lugano Classification); 2) commencement of new lymphoma therapy; or 3) death from any cause. According to this definition, more than twice as many patients in the AXI arm compared with the SoC arm of the ZUMA-7 trial were still free of events at 24 months (40.5% vs 16.3%, respectively). Median EFS was 8.3 months for patients treated with AXI compared to only 2.0 months for patients treated with SoC. The difference in EFS across the two arms was statistically significant (HR: 0.398; 95% CI: 0.308, 0.514). However, ESC noted that this difference was primarily driven by the time to 'new lymphoma therapy' with significant numbers in the SoC arm documented to meet this criterion each time new treatment was commenced, with negligible numbers in the AXI arm at specified timepoints. This endpoint is likely to be heavily biased in favour of the AXI arm, due to the unblinded nature of the trial and the possible performance and measurement bias that could be present. EFS also noted that EFS is not a validated endpoint in lymphoma trials in existing FDA regulatory approvals[1] and ESC considered harder endpoints should carry more weight.

ESC noted that disease progression (as measured by progression-free survival [PFS]) would likely be a more reliable endpoint as it does not include changing to a new lymphoma therapy. However, ESC noted that PFS would likely still be biased due to the trial design with patients in the SoC arm assessed at a potentially earlier time point than those in the AXI arm, however considered that PFS, along with overall survival, are more appropriate endpoints for MSAC consideration.

ESC noted that when considering the difference in overall survival (a more objective endpoint), at the median follow-up of 24.9 months, 64 out of 180 participants in the AXI arm had died and 75 out of 179 participants in the SoC arm had died due to various causes. A total of 52 participants (29%) patients in the AXI arm and 65 (36%) in the SoC arm had died due to disease progression. The Clinical Study Report addendum reported an update to the interim OS analysis, which was reported in the ADAR. ESC further noted that whether the differences in overall survival were statistically significant or not were heavily influenced by the timepoint at which the analysis occurred and whether the results were adjusted for treatment switching:

- The median overall survival evaluated as an interim analysis in the ZUMA-7 trial publication reported no statistically significant difference in OS (HR = 0.73 [95% CI: 0.52, 1.01) compared with the updated interim analysis reported in the ADAR which showed a difference in favour of AXI (HR = 0.708 [95% CI: 0.515, 0.972])
- Results of a prespecified sensitivity analysis which was conducted to address the confounding effects of treatment switching showed a difference in favour of AXI using the rank-preserving structural failure time model (RPSFT) but no difference was observed using the inverse probability of censoring weights model (IPCW) [HR = 0.58 [95% CI: 0.42, 0.81) vs. HR = 0.70 [95% CI: 0.46, 1.05, respectively).

ESC considered that the long-term incremental benefit is highly uncertain as there was no data on survival beyond 2 years where the hazard curves are observed to approximate and there appears to be comparable death rates in both arms at ~24 months to 28 months (N at risk in SoC arm: 27% to 12%, respectively). ESC noted that the data cutoff for data used in the ADAR was 2021 (ie. 2 years ago) and considered that an updated analysis of overall survival would be informative, including to inform or validate the modelled OS.

[1] FDA (2022) listed EFS for LBCL as the following: The agency anticipates that this surrogate endpoint could be appropriate for use as a primary efficacy clinical trial endpoint for drug or biologic approval, although it has not yet been used to support an approved new drug application (NDA) or biologics licence applications (BLA)

ESC noted that the ADAR presented a cost-utility analysis. The economic analysis used a mixed cure fraction model to extrapolate the overall survival (OS) for patients with LBCL in the model. ESC noted that this model type is typically used when a long period of disease stabilisation has been observed; and that this was not the case with the evidence presented for AXI. ESC considered that based on the ZUMA-7 trial data, the cure rate may be too optimistic, noting that the Kaplan Meier estimates of OS at 24 months after randomisation in the AXI arm were 60.7% (95% CI: 52.8, 67.7%) compared with in the SOC 51.3% (43.4%, 58.7%) reported in the ADAR (see Figure 1) Further, ESC noted that the distribution chosen (generalised gamma) resulted in the most optimistic scenario favouring AXI. The model approach also does not allow for participants experiencing a relapse once they are in the 'cured' state.

ESC noted that the model was primarily driven by the EFS endpoint, which is an unvalidated endpoint and likely favours AXI. ESC also noted that the EFS endpoint was available to 15 months and after this point distributions were applied. As previously noted, ESC advised that PFS would be more appropriate for MSAC consideration and that the model should be re-specified using PFS rather than EFS. ESC noted the base case results presented in the ADAR used a discount rate of 3.5% and ESC considered that there was no justification for this and that the base case should apply a discount rate of 5% as per the guidelines. ESC noted that the ADAR base case used a long time-horizon (40 years), and that this is considerably long for this population and favours AXI. ESC noted that a 30-year time horizon was included in the respecified base case and ESC considered this would be more appropriate given the average age of patients at presentation. ESC noted that the revised discount rate and time horizon (30 years) had been incorporated into a revised base case presented in the commentary. While ESC considered that the respecified base-case should be regarded as exploratory due to the issues noted with the use of EFS and model structure, the resultant incremental cost effectiveness ratio (ICER) of $[redacted] per quality adjusted life year (QALY) gained was noted.

ESC noted additional key concerns with the model and investigated these in additional sensitivity analyses (see Table 10). Firstly, it assumes one-off cost of $36,000 for both the administration of a CAR-T therapy and treatment of associated AEs. However, ESC noted that it is clear from the literature that this is likely a significant underestimate of costs, due to factors such as treatment of AEs, intensive care unit stays and IVIG usage, with $46,575 per month cited[2]. ESC also noted that the model only assumed a one month utility decrement associated with CAR-T administration. ESC considered that based on the evidence presented and the literature highlighting the seriousness of the AE profile and significant burden to patients[3], that this would also be a significant underestimate and would favour AXI.

ESC noted that incorporating increased hospitalisation costs for the first 3.3 months of $46,575 per month and a utility decrement to account for the 25% of patients who required a stay in the intensive care unit resulted in an ICER of $[redacted] per QALY gained.

ESC noted that there is uncertainty in the uptake of 3L CAR-T in Australia with lower uptake than was predicted. ESC noted that the model assumes an uptake of [redacted] however, the pre-ESC response indicated it is approximately [redacted] in the Australian setting. ESC noted that the ICER was sensitive to this estimate, increasing to $[redacted] per QALY gained when [redacted] instead of [redacted] of patients receive a 3L CAR-T therapy.

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2 Richard T. Maziarz, Hongbo Yang, Qing Liu, Travis Wang, Jing Zhao, Stephen Lim, Soyon Lee, Anand Dalal & Vamsi Bollu (2022) Real-world healthcare resource utilization and costs associated with tisagenlecleucel and axicabtagene ciloleucel among patients with diffuse large B-cell lymphoma: an analysis of hospital data in the United States, Leukemia & Lymphoma, 63:9, 2052-2062, DOI: 10.1080/10428194.2022.2060503

3 Howell, T.A., Matza, L.S., Jun, M.P. *et al.* Health State Utilities for Adverse Events Associated with Chimeric Antigen Receptor T-Cell Therapy in Large B-Cell Lymphoma.*PharmacoEconomics Open* **6**, 367–376 (2022). https://doi.org/10.1007/s41669-021-00316-0

Regarding the estimates of financial impact, ESC noted that the ADAR presented a financial impact of $[redacted] in Year 1 to $[redacted] in Year 6. However, ESC noted that many of the concerns identified in the clinical and economic analyses flowed into the financial estimates. When considering increased hospital costs and a [redacted] uptake rate for 3L CAR-T in multivariate sensitivity analyses, ESC noted this financial impact increased significantly to $[redacted] in Year 1 to $[redacted] in Year 6. These estimates resulted in a net budget impact to the National Health Reform Agreement of $[redacted] in Year 1 and up to $[redacted] in Year 6. However, ESC noted these additional costs appeared to be driven by the increased hospital costs (first 3.3 months of $46,575 per month), rather than changing the uptake of 3L CAR-T to [redacted]

ESC noted that while the estimated net budget impact to the NHRA was high, it was also 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. ESC considered that the actual budget impact could therefore be higher (i.e. underestimated).

ESC noted that MSAC is due to consider a review of the first CAR-T therapy, (tisagenlecleucel for paediatric acute lymphocytic leukemia), at its July 2023 meeting; this will be the first review of any CAR-T therapy that has been recommended for public subsidy in Australia. ESC considered that, despite being for a different patient population, there may be merit to this review being completed prior to any recommendations for AXI being made, as key information pertaining to the financial implications of CAR-T therapies would be expected to be informative.

ESC noted that the applicant has proposed that the price for treatment with AXI in the 2L setting is identical to pricing in the 3L setting, where a payment is made upon infusion of the manufactured product and a second payment is payable at an agreed time in the future dependent on the outcomes observed in patients. ESC noted that no justification for this pricing had been presented. Overall, the net effective average price currently paid for AXI in the 3L setting and sought for AXI in the 2L setting is $[redacted] per patient infused. ESC noted that the payment schedule of upon infusion and on outcomes was not included in the ADAR, and although the applicant noted that this could be discussed at a later date, details of any arrangements would be essential for MSAC to consider.

ESC noted that the State and Territory government submissions are not supportive of the application. These submissions include concerns around lack of long-term evidence regarding efficacy and safety of AXI, proposed costs not being reflective of the current real cost of service provision of AXI in a public hospital setting, assumptions in the economic analysis not being supported by the clinical evidence, continued uncertainty about the real-world benefits of CAR-T therapy due to the short time since the completion of the initial trials and limited real world experience with lower uptake of currently supported CAR-T therapies than predicted.

ESC considered that a registry of outcomes is essential. Such a registry could provide data on overall survival, progression-free survival, hospitalisations, AEs, quality of life and costs of delivery. Appropriate arrangements with the applicant need to be made to ensure data access for all stakeholders.

17. Applicant comments on MSAC's Public Summary Document

Gilead is pleased to note that the MSAC recognised the clinical need for axicabtagene ciloleucel in this patient population. All organisations and the patient community were strongly supportive of this application and making this therapy available to patients at an earlier line in therapy due to the unmet need. They highlighted the poor prognosis of patients with relapsed or refractory LBCL after first line treatment, and the significant benefits this therapy offers to patients.

Given the different patient population, indication and treatment delivery centres, it is unclear how informative or relevant the outcome of the review of tisagenlecleucel would be for this application.

The primary OS outcomes from ZUMA-7 strongly support the significant benefits of axicabtagene ciloleucel when used as an earlier line of therapy in this patient population. Gilead will continue to work with MSAC and the Department to secure public funding for axicabtagene ciloleucel.

18. Further information on MSAC

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