Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1771 – Axicabtagene ciloleucel (Yescarta®) for patients with relapsed or refractory follicular lymphoma

Applicant: **Gilead Sciences Pty Ltd**

Date of MSAC consideration: **1-2 August 2024**

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

1. Purpose of application

An application requesting public funding through the National Health Reform Agreement (NHRA) of axicabtagene ciloleucel (Yescarta®), henceforth referred to as AXI, for the treatment of patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy was received from Gilead Sciences Pty Limited by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of axicabtagene ciloleucel (AXI) through the National Health Reform Agreement (NHRA) for the treatment of relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy. MSAC acknowledged the clinical need for new therapies for this patient population, and considered that AXI appeared to offer clinical benefit, particularly in progression free survival. However, MSAC noted that due to the low certainty of evidence, the magnitude of benefit was highly uncertain. MSAC considered that AXI had an inferior safety profile compared to the current standard of care.

MSAC considered the cost-effectiveness of AXI was highly uncertain, due to low certainty in comparative evidence, uncertain real-world costs and the unsubstantiated cure assumption used in the economic model. Given the slowly progressing, indolent nature of the disease, MSAC considered the duration of follow-up in the clinical study was insufficient to justify the modelled cure assumption. MSAC considered longer term data were required, or in the absence of longer term data the economic evaluation should be revised to remove the cure assumption.

MSAC considered the financial impact was highly uncertain due to uncertainty in the estimated utilisation, adjunctive hospital costs being underestimated and potential cost-savings being overestimated. MSAC noted the proposed price of AXI had not been adequately justified and considered a price reduction along with a risk sharing arrangement would be required for any future re-application. MSAC noted the states and territories (joint funders of this highly specialised therapy via the National Health Reform Agreement (NHRA)) considered that more real-world data was needed to inform the costs associated with the use of AXI and the price of AXI.

Consumer summary

This application from Gilead Sciences Pty Ltd requested public funding under the National Health Reform Agreement (NHRA) of the cell-therapy axicabtagene ciloleucel (Yescarta®) for patients with relapsed or refractory follicular lymphoma as third-line therapy (that is, if two or more previous courses of treatment have not been effective).

Follicular lymphoma is a type of blood cancer that arises from a type of white blood cell (specifically B cells), which form part of the body's immune system to fight infections. Follicular lymphoma is a slow-growing cancer and patients may go through stages where they don't have any symptoms and don't need treatment (called an indolent stage). When symptoms appear, patients may present with painless swelling of lymph nodes, fatigue, shortness of breath, night sweats, fever and weight loss.

Axicabtagene ciloleucel is a chimeric antigen receptor T-cell (CAR-T) 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 laboratory to attack the cancer-causing 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 lymphoma) don't respond to treatment (refractory), or their cancer comes back (relapses) after treatment. Other types of treatment include chemotherapy or other immunotherapy.

MSAC recognised the clinical need for new treatments for follicular lymphoma patients and considered that the clinical data for axicabtagene ciloleucel appeared to show that it was more effective than the current standard of care treatment, but limitations with the clinical study made it uncertain as to the size of the benefit (e.g. the axicabtagene ciloleucel study did not include a control arm). MSAC also noted there appeared to be a high rate of adverse events associated with the treatment. MSAC noted that while feedback suggested patients may be willing to take these risks due to the perceived benefit of treatment, the cost associated with these adverse events for state and federal governments, as well as for patients, are uncertain because of the lack of Australian data. Because follicular lymphoma is a disease that progresses slowly, MSAC considered it was important to have data that followed patients for a longer time than was presented in the application. MSAC considered longer-term evidence may reduce uncertainty about adverse events and improve understanding of the longer-term success of the treatment. Clinical data over a longer time would also help to reduce the uncertainty in the economic and financial estimates for axicabtagene ciloleucel. MSAC also noted the three submissions from states and territories (joint funders of this highly specialised therapy via the NHRA) considered more data from real-world experience was required to better inform the consideration.

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 patients with relapsed or refractory follicular lymphoma as third-line therapy. MSAC acknowledged the clinical need for new treatments for these patients. Due to the slow-growing nature of the disease and the limitations with the evidence presented, MSAC considered that the magnitude and duration of clinical benefits following axicabtagene ciloleucel treatment of follicular lymphoma were uncertain. In addition, MSAC considered the high and uncertain costs of the treatment meant that it was not good value for money.

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

MSAC noted that this application from Gilead Sciences sought public funding under the NHRA for axicabtagene ciloleucel (AXI, also known as YESCARTA®, a chimeric antigen receptor T-cell [CAR-T] therapy) in the third-line (3L) or later setting for patients with r/r FL.

MSAC noted that this indication had not been previously considered by MSAC, but that AXI is currently funded for a number of other lymphomas, namely r/r CD19-positive diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL). Funding for AXI for the treatment of r/r large B cell lymphoma (LBCL) in the second-line (2L) setting was also supported by MSAC in April 2024. MSAC further noted that AXI has been approved by the Therapeutic Goods Administration (TGA) for use in FL after two or more lines of systemic therapy[1].

MSAC noted the feedback from states and territories that outlined concerns regarding the costs associated with providing AXI treatment (both financial costs, including those associated with the high rate of adverse events, and personal costs to patients who experience these adverse events) and the uncertainty of the clinical evidence presented in the applicant developed assessment report (ADAR). MSAC also noted that state and territory feedback considered it was important to complete a full review of the clinical benefits and cost-effectiveness of AXI for the treatment of r/r DLBCL in the 3L setting prior to supporting further public funding of AXI.

MSAC also noted the consultation input received, including from individual experts along with Australia and New Zealand Transplant & Cellular Therapies Ltd, Australasian Leukaemia & Lymphoma Group, Leukaemia Foundation, Lymphoma Australia and Rare Cancers Australia. MSAC noted that the feedback received was supportive of the application, with responses highlighting the anticipated improvement in survival and quality of life with AXI, and the need for new therapies to treat FL. Respondents agreed that extended follow up was required before patients with r/r FL could be considered cured, with suggestions from specialists ranging from at least 5 years to at least 10 years without relapse. Respondents also noted that there are barriers to accessing AXI for rural and regional patients, and that multidisciplinary post-treatment services would be required for all patients for immediate complications, as well as longer term follow up.

MSAC noted the proposed clinical, treatment and public funding criteria for AXI, including the changes recommended by ESC. For the proposed indication, ESC had suggested that anti-CD20 monotherapy (such as rituximab) should not be considered a prior line of therapy, to maintain consistency with the eligibility criteria in the ZUMA-5 study (the pivotal study in the application). In the pre-MSAC response, the applicant stated that single-agent anti-CD20 therapy is recommended as a first-line or second-line treatment option for patients with r/r FL in clinical management guidelines[2,3], and there may be clinical grounds for not combining anti-CD20 therapy with an alkylating agent, for example for patients with contraindications. The applicant argued that it would not be equitable to prevent these patients from being eligible for AXI. MSAC noted that ZUMA-22 (a phase 3, open-label, multicentre, randomised controlled trial), to evaluate the efficacy and safety of AXI compared with standard of care (SOC) therapy in patients with r/r

[1] TGA summary https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=400895&agid=%28PrintDetailsPublic%29&actionid=1

[2] Dreyling, M, et al. (2021). "Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†☆." *Ann Oncol* 32(3): 298-308.

[3] Zelenetz AD et al. (2021) NCCN Guidelines® Insights: B-Cell Lymphomas, Version 5.2021. *J Natl Compr Canc Netw.* Nov;19(11):1218-1230. doi: 10.6004/jnccn.2021.0054. PMID: 34781267.

FL (NCT05371093[4]) was underway and primary study completion was expected in 2030. MSAC noted that the SOC arm in the ZUMA-22 trial included therapies that did not involve alkylating agents. MSAC considered that it may be reasonable to specify in the indication that alkylating agents must be included along with anti-CD20 as prior therapy, unless contraindicated. MSAC noted ESC's concern that the eligible population would increase if anti-CD20 monotherapy was counted as a prior therapy. However, MSAC considered that the extent to which the number of eligible patients would increase was uncertain but likely low, and that it would be inequitable to deny AXI treatment to patients for whom alkylating agents were contraindicated.

MSAC noted the applicant's proposed changes to the treatment criteria regarding renal, cardiac and respiratory function parameters, and considered that these were reasonable to ensure consistency with organ function criteria established for AXI for the treatment of patients with LBCL in Australia. MSAC noted ESC's proposed change to the treatment criteria to specify that the patient must not have a history or suspicion of central nervous system (CNS) involvement by lymphoma. In the pre-MSAC response, the applicant stated that feedback from clinicians indicated that CNS involvement in FL was a very rare occurrence, and that it would not be clinically justified or fair to exclude those patients. However, MSAC noted that the study criteria for ZUMA-5 specified "Individual has no known presence or history of central nervous system (CNS) involvement by lymphoma". MSAC further noted that the Australian Register of Therapeutic Goods (ARTG) indication for AXI for LBCL states that it is not indicated for patients with primary central nervous system lymphoma. Therefore, MSAC agreed with ESC's proposed change to ensure alignment between the study and funding eligibility criteria as well as the ARTG indication. MSAC noted as per current practice, the proposed technology would be delivered in selected tertiary hospital treatment centres that specialised in delivery of CAR T-cell therapy, and therefore required jurisdictional support.

MSAC advised that payment should be made on successful infusion, in line with other CAR-T therapies. MSAC considered whether AXI should be restricted to once per lifetime per patient, or once per lifetime for treatment of FL, noting that FL can transform to other lymphomas and AXI is currently funded for DLBCL. MSAC queried how the states and territories managed the restrictions in current clinical practice, but considered this was an area of uncertainty that could be in scope for the planned review of AXI for DLBCL.

MSAC noted the clinical management algorithms. In the current management algorithm, patients diagnosed with FL who were asymptomatic or had low tumour burden were often not treated and kept under observation. If disease progressed and patients were able to tolerate active treatment, a range of SOC options were available. MSAC considered that the proposed comparator (SOC, represented by a basket of PBS-funded therapies) was appropriate. MSAC noted AXI was to be used as a 3L therapy in the proposed clinical algorithm, and that it was unlikely that AXI would completely replace SOC due to factors including failure of leukapheresis, patient preference and access to therapy. Additionally, MSAC noted ESC's advice that bispecific antibody therapy was on the horizon for the treatment of FL, and that the choice and position of CAR-T versus bispecific antibodies in the clinical management of patients was unclear. MSAC also noted that the role of stem cell transplant (SCT) in post CAR-T FL treatment remained uncertain.

MSAC noted the pivotal clinical study (ZUMA-5) was a single-arm, multicentre, phase 2 study involving 127 patients with indolent FL who had r/r disease after two or more lines of therapy. Clinical endpoints were measured at 12 months and 48 months, and efficacy was compared to the SCHOLAR-5 study (a retrospective cohort study using SOC) at 18 months and 48 months. For

[4] https://clinicaltrials.gov/study/NCT05371093

the primary analysis (18-month follow-up), the overall response rate was 94% in patients who received AXI, compared with 50% in patients who received SOC. For the updated analysis (48--month follow-up), the overall response rate was 94% (AXI arm) compared with 54% (SOC arm). Kaplan–Meier curves also showed substantial differences in progression-free survival (PFS) and overall survival (OS).

MSAC acknowledged the improvement in PFS following treatment with AXI compared to SOC, as shown by the early and sustained separation of data points in the Kaplan–Meier curve over 60 months. However, given that FL is a condition that progresses slowly, MSAC concluded that longer-term follow-up data were required to be able to adequately assess any survival benefit. MSAC acknowledged that other CAR-T therapies had been recommended for public funding without longer-term follow-up data, but that these were for indications that progress more rapidly than r/r FL. Overall, MSAC concluded that the clinical claim that AXI had superior effectiveness compared to SOC for the treatment of r/r FL in the 3L setting was reasonable but the magnitude of benefit was highly uncertain due to low-certainty evidence, indirect comparisons with transitivity, methodological and transparency issues, high risk of bias in both the ZUMA-5 and SCHOLAR-5 studies, and the use of a historical and retrospective comparator.

Regarding comparative safety, MSAC noted that the ZUMA-5 study data (48-month follow-up) indicated that adverse events were similar to those seen following AXI treatment for other indications, and similar to other CAR-T therapies. MSAC noted that in the ZUMA-5 study, 99% of patients experienced treatment emergent adverse events (TEAE) and out of those 86% of patients experienced a Grade 3 or higher TEAE, and 52% of patients experienced at least one serious TEAE. Furthermore, significant side effects such as cytokine release syndrome (78%), any neurological event (56%), cytopenia (73%), infection (56%), and hypogammaglobulinaemia (20%) were seen in patients treated with AXI. MSAC concluded that the claim that AXI had inferior safety compared with SOC was likely reasonable, but noted that comparative safety of AXI versus SOC was based on naive comparisons of various clinical studies with a high risk of bias, and the limited and low-certainty data resulted in overall uncertainty.

For the economic evaluation, MSAC noted that the ADAR presented a cost-utility analysis examining the cost-effectiveness of AXI versus SOC for the treatment of patients with r/r FL after two or more lines of systemic therapy. The analysis was based on extrapolation of outcomes from ZUMA-5 and data from the propensity weighted SCHOLAR-5 analysis. The ADAR model applied a cure assumption to the AXI arm at 5 years, at which point the survival of 'cured' patients was assumed to match general population mortality, with a standardised mortality ratio (1.09) applied to model excess mortality. MSAC noted the base case incremental cost-effectiveness ratio (ICER) of AXI compared to SOC **$Redacted**/quality-adjusted life year (QALY) gained). MSAC noted the sensitivity analysis that changed the cure point from 5 years to 10 years increased the base case ICER to **$Redacted** per QALY gained.

MSAC agreed with ESC that the 40% cure rate after 5 years of PFS in patients treated with AXI was not well supported by the evidence presented in the ADAR. MSAC reiterated that, given that r/r FL is an indolent disease, the duration of follow-up in the clinical study was insufficient to justify the modelled cure assumption. MSAC agreed with ESC that there was a need to consider a longer period of remission for FL (at least 10 years, given that some patients relapse at 10 years) before assuming that a patient with r/r FL may be cured. MSAC recalled that in previous recommendations for other CAR-T therapies, MSAC had consistently expressed concern regarding the uncertainty of modelling cure and had not explicitly accepted the ICERs as cost-effective. MSAC agreed with ESC that the cure assumption should be removed from the base case model, and the model should take a new approach, for example, with a focus on PFS gains instead.

MSAC agreed with ESC that the proposed price of $Redacted for AXI was not justified based on the ICER and the uncertainty in the economic model. In addition, MSAC did not consider that the uncertainties regarding OS and cure assumption could be mitigated by a price reduction alone.

MSAC considered the financial impact was highly uncertain due to uncertainty in the estimated utilisation, adjunctive hospital costs being underestimated and potential cost-savings being overestimated.

Overall, MSAC did not support public funding for AXI for patients with r/r FL due to the high level of clinical, economic and financial uncertainty. MSAC considered any future re-application would require longer-term follow-up data or, in the absence of longer-term data, an economic model that does not assume cure, and includes a reduced price for AXI. MSAC further advised that any re-application would require reconsideration by ESC.

MSAC reiterated the need for improved data from real-world experience with CAR-T therapies in the Australian health system. MSAC considered that data were required to be collected and available to inform costs and longer-term outcomes (including survival, cure and adverse events), as well as program implementation. MSAC considered the planned review of AXI could also explore any challenges associated with the integration of care across clinical services. MSAC noted equity issues due to access to CAR-T therapies being primarily limited to large hospitals located in the Modified Monash Model 1 (MMM1) areas for clinical reasons and considered whether telehealth could facilitate post-discharge activities to improve access.

MSAC noted the recommendations for and against AXI reimbursement in international jurisdictions.

4. Background

MSAC has not previously considered AXI for the treatment of r/r FL after two or more lines of systemic therapy (i.e. in the third-line (3L) setting or later).

AXI is currently funded for the treatment of patients with r/r CD19-positive Diffuse Large B Cell Lymphoma (DLBCL), Primary Mediastinal B Cell Lymphoma (PMBCL) and Transformed Follicular Lymphoma (TFL) in the 3L setting under NHRA Commonwealth and State and Territory shared funding arrangements (MSAC application 1587[5]).

A re-application requesting public funding of AXI for the treatment of r/r large B-cell lymphoma (LBCL) in the second-line (2L) setting was considered and supported by MSAC at the April 2024 meeting (MSAC application 1722.1[6]).

5. Prerequisites to implementation of any funding advice

AXI was first included on the Australian Register of Therapeutic Goods (ARTG) on 11 February 2020 for r/r LBCL (ARTG ID 329770). The indication was extended to include patients with r/r FL after two or more lines of systemic therapy on 12 December 2022 (ARTG ID 400895).

The approved therapeutic indication for AXI is as follows:

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

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

[6] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1722.1-public

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

6. Proposal for public funding

Public funding for AXI for the treatment of r/r FL in the 3L setting (or later) is sought through the NHRA.

Consistent with current practice, the proposed technology would be delivered in select tertiary hospital treatment centres that specialise in delivery of Chimeric Antigen Receptor (CAR) T-cell therapy.

The ADAR proposed an average net effective price for AXI for r/r FL of $Redacted per patient infused. The ADAR claimed this price was identical to the current price for AXI for r/r DLBCL in the 3L setting. However, per the Public Summary Document (PSD) for MSAC 1587[7], the average price previously supported by MSAC for AXI for r/r DLBCL in the 3L setting was $Redacted. Further, details on the proposed risk share arrangement including the proposed PfP arrangement (e.g. payment amounts, the estimated response rate, the definition of response and timepoint, etc.) were not provided by the ADAR (i.e. ADAR simply states the applicant is open to discuss this).

The Commentary further noted that in the ZUMA-5 study (pivotal evidence in the ADAR), patients who achieved a partial response (PR) or better at the 3-month disease assessment and subsequently experienced disease progression had the option to be retreated with AXI, and there may be potential for growth in the market without a restriction in place. The Commentary considered it important to address whether AXI in this setting should be limited to a single treatment per lifetime, consistent with MSAC advice for other supported CAR-T therapies.

A summary of the proposed request for public funding is provided in Table 1 showing the indication requested, and the proposed treatment and clinical criteria. Potential additions to align with ZUMA-5 include defining 'adults' as those aged 18 years or older and specifying the WHO 2016 classification.

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

Table 1 Proposed clinical, treatment and public funding criteria for AXI

Category	Description
Indication	Adults with Grade 1, Grade 2 or Grade 3a follicular lymphoma (based on the WHO classification) who are relapsed or refractory after two or more lines of systemic therapy *and have symptomatic disease and/or high tumour burden following relapse. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent*[a]
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 multidisciplinary 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~~ *Patient must not have a history or suspicion of CNS involvement by lymphoma*
Clinical criteria	Patient must have a ECOG performance status of 0 or 1 AND Patient must have sufficient organ function, including: • Renal function: Creatinine clearance ≥60mL/min, serum ALT/AST ≤2.5 x ULN and total bilirubin ≤1.5mg/dL • Cardiac function: left ventricular ejection fraction (LVEF) ≥50%, or supplementary functional tests and cardiology assessment demonstrating adequate cardiopulmonary reserve • Pulmonary function: Baseline peripheral oxygen saturation >92% on room air 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
Pay for performance and risk share arrangement	Consistent with the current funding for AXI in DLBCL, Gilead is open to discuss the specific details of the PfP and RSA for AXI in the treatment of relapsed or refractory follicular lymphoma

Abbreviations: AXI=axicabtagene ciloleucel; CNS=central nervous system; DLBCL= diffuse large B-cell lymphoma; ECOG= Eastern Cooperative Oncology Group; PfP=pay for performance; RSA=risk sharing arrangement
Source: Table 9 of MSAC 1771 ADAR+in-line commentary
ESC recommendations included using italics and strikethrough
a –Single-agent anti-CD20 antibody (e.g. rituximab) would not count as a prior line of therapy for eligibility.

The Commentary noted that the requested restriction (Table 1) was not fully consistent/aligned with the eligibility criteria of the pivotal ZUMA-5 study. The following eligibility criteria for the ZUMA-5 study are not stipulated for the requested population for public funding:

- Prior therapy with an anti-CD20 monoclonal antibody combined with an alkylating agent (single-agent anti-CD20 antibody did not count as line of therapy for eligibility);
- At least one measurable lesion according to the Lugano Response Criteria for Malignant Lymphoma;

- No known history or suspicion of central nervous system (CNS) involvement by lymphoma;
- At least 2 weeks or 5 half-lives, whichever was shorter, must have elapsed since any prior systemic therapy and enrolment, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy and enrolment;
- Absolute neutrophil count ≥ 1000/μL; platelet count ≥ 75,000/μL; absolute lymphocyte count ≥ 100/μL; and
- No clinically significant pleural effusion.

Patients with history of allogeneic stem cell transplant or autologous transplant within 6 weeks of planned leukapheresis, prior CD19 targeted therapy, prior CAR therapy or other genetically modified T-cell therapy were also excluded from ZUMA-5 but not the requested population.

Two recent publications (Neelapu et al. 2024[8] and Iacoboni et al. 2024[9]) have reported that recent prior bendamustine use before AXI/ CD19-targeted CAR T-cell therapy may negatively impact treatment response.

7. Population

The ADAR's proposed population was adult patients with Grade 1, Grade 2, or Grade 3a FL and r/r disease after two or more lines of therapy. However, as per the applicant's clinical algorithm, there is a subset of patients who may be asymptomatic and/or low tumour burden and therefore not require active therapy (see Figure 2 & 3, MSAC 1771 PICO Set Document).

ESC considered that additional eligibility criteria should be included within the patient population definition, to align with the clinical study criteria and international guidelines, and to reflect the subpopulation intended for active treatment and therefore those most likely to benefit from AXI. Specifically, ESC considered that the proposed population should exclude patients who have history or suspicion of central nervous system involvement by lymphoma, and that anti-CD20 monotherapy should not be counted as a prior line of therapy, which are included in Table 1, above.

The proposed intervention would be available in the 3L setting and would be used in place of current technology. Compared to existing practice, this would result in reduced use of the comparator (SOC) in the 3L setting. AXI would substitute SOC in Australia, consisting of (as nominated by the ADAR) anti CD20 monotherapy, anti CD20 therapy in combination with chemotherapy, chemotherapy, and phosphoinositide-3-kinase δ (PI3Kδ) inhibitors. However, of note, AXI is not expected to fully replace SOC for several reasons (e.g., failure of leukapheresis, preference, access).

[8] Neelapu SS, et al. (2024) Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). *Blood*. 143(6):496-506

[9] Iacoboni G, et al. (2024) Recent Bendamustine Treatment Before Apheresis Has a Negative Impact on Outcomes in Patients With Large B-Cell Lymphoma Receiving Chimeric Antigen Receptor T-Cell Therapy. *J Clin Oncol*. 42(2):202-217

8. Comparator

The ADAR described that there is no uniformly recommended systemic treatment for patients with FL who are r/r after two or more lines of systemic therapy. Instead, treatments are chosen based on individual patient circumstances such as the mechanism of action and duration of response to prior treatments.

The ADAR's proposed comparator was SOC, represented by a 'basket' of the following regimens, all currently funded on the PBS:

- anti CD20 monotherapy
- anti CD20 therapy in combination with chemotherapy
- chemotherapy
- PI3Kδ inhibitor.

The ADAR's proposed comparator was based on an applicant-commissioned analysis of the LaRDR, an Australian registry capturing patient demographics, disease characteristics, treatment details and outcomes. However, the Commentary noted that within the LaRDR report, only 13 patients (representing 1.3% of the total cohort (N=971)) had commenced 3L therapy, and as such, the results of this analysis may not be a reliable representation of 3L treatment in Australia. Moreover, of these 13 patients, eight had an ECOG of 0 or 1 and would be eligible for AXI treatment.

As ZUMA-5 was a single-arm study, results from ZUMA-5 were compared with a retrospective external cohort of patients (SCHOLAR-5; Ghione et al. 2022), which was used by the ADAR to represent real world data for the effectiveness of SOC in patients with r/r FL after two or more lines of systemic therapy. The Commentary noted that in the SCHOLAR-5 cohort:

- Older SOC therapies may have been used as patients initiated a third or higher line of therapy between July 2014 – December 2020 (while patients enrolled in ZUMA-5 received AXI between June 2017 – July 2020). For example, it appears a number of patients were treated with a phosphatidylinositol 3-kinase inhibitor, a class of drugs that is now infrequently used in the treatment of FL[10].
- Patients were based in the US and Europe, and therefore treatment received may not be reflective of clinical practice in Australia.
- The index treatment (i.e. ≥3L treatments) received by the cohort included, for example, allogenic stem cell transplant (SCT); autologous SCT; and experimental therapy representing 27% (39/143) and 32% (26.8/85) of the unweighted and propensity score weighted SCHOLAR-5 cohort respectively – which were not part of the ADAR's nominated SOC basket of regimens. As such, 'SOC' (i.e. 3L treatment as represented by the SCHOLAR-5 cohort) may not be consistent with the SOC nominated by the ADAR, and it was unclear what impact this may have on the magnitude of benefit. The ADAR did not comment on how the nominated comparator 'SOC' was comparable to the treatments used by the SCHOLAR-5 cohort.

ESC considered that the proposed comparator, i.e. the SOC therapies in the SCHOLAR-5 cohort, was appropriate, and compares well to the current SOC in the Australian setting. The

[10] Tonino SH & Kersten MJ. (2024) The quest for a cure in follicular lymphoma. *Blood*. 142(6):475-476

Commentary considered it important to note that patients in the SCHOLAR-5 could be considered to be more frail compared to the patients in the ZUMA-5 study.

9. Summary of public consultation input

Consultation input was welcomed from two (2) professional organisation, three (3) consumer organisations, three (3) individuals who were medical specialists, and one (1) from a medical specialist who had included input from specialist colleagues in the feedback provided.

The organisations that submitted input were:

- Australia and New Zealand Transplant & Cellular Therapies Ltd (ANZTCT)
- Australasian Leukaemia & Lymphoma Group (ALLG)
- Leukaemia Foundation
- Lymphoma Australia
- Rare Cancers Australia.

The consultation feedback received was supportive of the application.

Benefits

- Axicabtagene ciloleucel (AXI, also known as YESCARTA® or axi-cel) appears to be a highly effective therapy and can overcome chemotherapy resistance to induce deep and durable remissions.
- There are limited treatments for relapsed or refractory (r/r) follicular lymphoma and more options are needed to treat this disease. Availability of AXI would increase treatment options for the patients.
- Longer life expectancy and quality of life, with improved ability of patients to function day to day. It could spare young people the substantial morbidity of allogeneic stem cell transplantation and improve outcomes for patients who are transplant ineligible.
- Less toxicity and fewer side effects than current alternate treatments (e.g. stem cell transplant [SCT]).
- Improved overall survival with AXI would reduce the number of patients who require further intervention (4L or more therapy) and lessen the burden and costs on the healthcare system.
- Equity of access to an effective agent that can induce meaningful duration of remission, independent of the availability of clinical trials, including at tertiary hospitals that normally cover rural centres.

Disadvantages

- Patients needing to have completed numerous lines of treatment before commencing AXI therapy was considered a disadvantage (i.e. that the application is only for AXI in the third line or later).
- The treatment is time consuming and requires hospitalisation.
- The adverse event profile includes cytokine release syndrome, neurotoxicity, infection and cytopenias, however current preventative and management strategies are bringing the adverse events to manageable levels.

Additional Comments

The ALLG noted patients will require specific medical and logistical services before treatment including a multidisciplinary meeting to discuss optimum treatment choice and support to facilitate local accommodation for patients from rural areas. Required post treatment services would include clinical services to manage any immediate complications, such as cytokine release syndrome (CRS) and immune effector cell associated neurological toxicity (ICANS). These would include 24-hour access to an emergency department with CRS/ICANS management procedures,

24-hour pharmacy dispensing, an experienced haematology service, intensive care unit (ICU), neurology, infectious disease, and radiology. An allied health team and staff to coordinate discharge planning and follow up procedures would also be required.

Rare Cancers Australia suggested that providing earlier access to AXI, rather than requiring numerous treatments before treatment with AXI can be commenced, would require fewer visits/hospitalisation which would lessen the burden on the hospital system.

The feedback noted the need to address the barriers in accessing treatment for rural/regional patients. There is a need for an education process for clinicians from sites that have little knowledge of CAR-T and the referral process to ensure patient equity and centricity.

The need for a consistent national approach was raised, with Lymphoma Australia suggesting the establishment of a national roundtable to understand issues and opportunities to deliver a national structure that would enable improved education and access for patients and clinicians.

Medical specialists from whom input was received generally agreed that the patient population was well defined, and that further limiting to exclude patients with central nervous system disease who have been treated and are stable is not necessary. The responses also agreed that, for the purposes of determining eligibility of access to AXI for patients with r/r FL at the third line or later, single agent rituximab should not be considered a line of therapy.

The respondents agreed that extended follow up would be required before a patient with r/r FL could be considered cured and that current study follow up for AXI was too short (48 months) to determine cure. However, there was no consensus among the medical specialists regarding the timeframe or other parameters required for patients with r/r FL to be considered cured. The suggested appropriate follow up time without relapse to conclude a patient was cured ranged from at least 5 years to at least 10 years.

The medical specialists also noted AXI was not suitable for some patients with r/r FL, including those with severe comorbidities where tolerability and toxicity may be an issue, and patients who prefer a palliative approach. One specialist noted that there appears to be some evidence that efficacy of AXI is drastically reduced in patients with recent bendamustine treatment, and therefore that they may consider excluding such patients from treatment with AXI.

Respondents considered that AXI would likely replace SCT, or delay SCT in cases of CAR-T cell therapy failure. This is particularly with reference to allogenic SCT, where specialists noted that autologous SCT is already rarely used in this setting.

10. Characteristics of the evidence base

The pivotal clinical evidence presented by the ADAR was based on ZUMA-5, a phase 2 single-arm multicentre, open-label study assessing the safety and efficacy of AXI. As ZUMA-5 was a single-arm study, clinical evidence presented by the ADAR on the comparative efficacy of AXI vs SOC was based on a comparison of patients enrolled in ZUMA-5 with an external control group of patients enrolled in an international, multicentre, retrospective cohort study, SCHOLAR-5. The ADAR was based on a published comparison of ZUMA-5 and SCHOLAR-5 at 18 months (Ghione 2022) and further analyses presented in the ADAR at 48 months.

In the comparative analysis, select patient baseline characteristics (variables from the data that were prespecified to be of ‘high’ or ‘medium’ importance) were balanced between the ZUMA-5 and SCHOLAR-5 cohorts to account for the potential imbalance of confounders through the application of propensity score methods (via standardised mortality ratio (SMR) weighting). The Commentary noted that variables ranked as ‘low’ importance were unadjusted for as “the need to modify the propensity score from the initial implementation precluded the addition of low

priority variables, as pre-specified in the statistical analysis plan" (p8 of the Appendix to Ghione 2022). For example, patients in ZUMA-5 tended to have better ECOG performance status compared to patients in the SCHOLAR-5 cohort, which was unadjusted for (ECOG 0: primary analysis: 59% vs 33%; secondary analysis: 62% vs 33%); such differences may not be adequately accounted for in the analysis and may result in the comparison being biased in favour of AXI. Ultimately, this analysis was an unanchored comparison which, the Commentary considered, did not necessarily account for all observed (and unobserved) differences in the compared patient cohorts.

The Commentary considered that while the use of propensity weighting via SMRs improved the comparability between the ZUMA-5 and the SCHOLAR-5 cohorts, the use of SMRs was not justified by the ADAR and it was unclear how this was applied. It was also unclear whether the same propensity scoring methods that were applied in the primary (18 month) comparative analysis (Ghione 2022) were also used in the updated 48-month analysis. The ADAR also presented supplementary evidence from a comparison of outcomes reported for a real-world cohort of patients treated with AXI at the Center for International Blood and Marrow Transplant Research (CIBMTR) with a group of patients from the SCHOLAR-5 cohort. Key features of the studies presented by the ADAR are detailed in Table 2. The Commentary considered these studies were prone to a high risk of bias:

- ZUMA-5: The risk of bias was high due to the single-arm, open-label study design, and a primary outcome (overall response rate (ORR) as assessed by an independent radiology review committee per Lugano classification) which the Commentary considered was subjective in nature.
- ZUMA-5 vs SCHOLAR-5 (Ghione 2022): The risk of bias was high given the context of how these two separate studies were used in their clinical evaluation; these studies were conducted at different time periods on different patients, and were not powered nor designed for this purpose. As such, the results of this analysis should be considered highly uncertain.
- AXI real-world evidence (RWE) vs SCHOLAR-5 (Kambhampati 2023): Given the context of how the two separate studies were used in this analysis (similar to the comparative analysis undertaken for ZUMA-5 vs SCHOLAR-5 described above), the risk of bias was likely high, and the results of this study should be interpreted with caution.

It should be noted that the ADAR did not report on the comparative safety of AXI vs SOC based on ZUMA-5 vs SCHOLAR-5, which was used as pivotal evidence for comparative efficacy. The studies used by the ADAR for their analysis of comparative safety are not included in Table 2.

For comparative safety, the ADAR compared an overview of adverse events reported in ZUMA-5 with adverse events reported in SOC clinical studies (detailed in Table 5). The ADAR acknowledged that there was heterogeneity regarding the study populations, dates of enrolment and baseline characteristics of enrolled patients, but considered it reasonable to include in an exploratory assessment of comparative safety as these studies reported safety outcomes associated with a wide range of treatment regimens recommended to be used in patients with r/r FL. However, the Commentary noted that the ADAR did not provide information on the search strategy employed (if any) in the identification of these studies, and it was unclear whether all relevant studies/trials were captured. Therefore, the Commentary considered the comparative safety evidence presented by the ADAR had a high risk of evidence selection bias. Moreover, the studies used by the ADAR in their safety comparison appeared to be older and it was unclear whether these would be representative of SOC in Australia; the risk of bias of these studies was not reported by the ADAR; the patient populations were not fully aligned; and patient demographic and clinical characteristics did not appear to be appropriately assessed by the

ADAR. As such, the naïve comparison presented by the ADAR may be of limited value for MSAC decision making.

Table 2 Key features of the included evidence

References	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Pivotal evidence						
ZUMA-5	FL=127 Primary analysis (IAS)=84 [a] Updated analysis (FAS)=127 [a]	Single arm, multicentre, Phase 2 study; primary (12 month) analysis [b] and 48-month follow-up analysis [c]	High	Adult patients with indolent non-Hodgkin lymphoma (FL or MZL) and relapsed or refractory disease after two or more lines of therapy	Primary: ORR Key secondary: CRR, PFS, OS, TTNT, safety	Yes (via post hoc comparison)
ZUMA-5 vs SCHOLAR-5 (Ghione 2022)	Primary analysis (IAS): 171 ZUMA-5=86 SCHOLAR-5=85 Updated analysis (FAS): 255 ZUMA-5=127 SCHOLAR-5=128	Patients enrolled in ZUMA-5 were compared with an external control group of patients enrolled in a multicentre, retrospective cohort study (SCHOLAR-5); primary (minimum 18-month follow-up) analysis [d] and 48-month follow-up analysis [c]	High	Adult patients with follicular lymphoma and relapsed or refractory disease after two or more lines of therapy	ORR, CRR, PFS, OS, TTNT	Yes
Supportive evidence						
AXI RWE vs SCHOLAR-5 (Kambhampati 2023) [e]	433 AXI RWE=256 SCHOLAR-5=177	Patients who received commercial AXI from the CIBMTR were compared with SCHOLAR-5 data (described above); survival outcomes reported at month 6 [f]	High	Adult patients with follicular lymphoma and relapsed or refractory disease after two or more lines of therapy	ORR, CRR, PFS, OS	No
Comparator safety evidence						
LYM-3001 (Coiffier 2011)	676 Ritux=340 Ritux+bort=336	R, OL 205 days (safety assessed through 5*35 day cycles + 30 days)	NA	Adult patients with relapsed Grade 1 or 2 follicular lymphoma	Safety	No
GADOLIN (Sehn 2016)	396 Obin+benda=194 Benda=202	R, OL Up to 24 months (safety assessed through 6*28 cycles + 28 days in obin+benda or 24 months for benda)	NA	Adult patients with relapsed iNHL refractory to rituximab	Safety	No

References	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
DELTA (Gopal 2014)	125 Idelalisib	SA, OL Safety assessed to 30 days after the last dose	NA	Adult patients with iNHL who had no response to rituximab+alkylating agent or relapsed ≤6 months of these therapies	Safety	No

Abbreviations: AXI= axicabtagene ciloleucel; Benda=bendamustine; CIBMTR = Center for International Blood and Marrow Transplant Research; CRR=complete response rate; FAS= full analysis set; FL=follicular lymphoma; IAS=inferential analysis set; iNHL=indolent non-Hodgkin lymphoma; MZL=marginal zone lymphoma; NA=not assessed; Obin+benda=obinitizumab+bendamustine; OL=open-label; ORR=overall response rate; OS=overall survival; PFS=progression free survival; R=randomised; Ritux=rituximab; Ritux+bort=rituximab+bortezomib; RWE=real-world evidence; TTNT=time to next treatment

a Note that safety outcomes from the primary analysis of ZUMA-5 was based on the Safety Analysis Set of all FL and MZL patients (N=146) treated with any dose of AXI with a median actual follow-up time of 14.0 months. At the updated 48-month analysis, safety outcomes are reported for the Safety Analysis Set (N=124) comprised of all patients with FL treated with any dose of AXI.

b The primary analysis was performed when at least 80 patients with FL in the IAS have had the opportunity to be followed for 12 months after the first disease response assessment

c The 48-month analysis was conducted when median potential follow-up time after AXI infusion for all dosed FL patients had reached at least 48 months.

d Median follow-up 25.4 months and 23.3 months for ZUMA-5 and SCHOLAR-5 respectively.

e A conference abstract only was provided with the ADAR and therefore the results of this should be interpreted with caution.

f Due to varying follow-up lengths by treatment (median 7 months for AXI and 37 months for standard of care).

Source: Table 15 of MSAC 1771 ADAR+in-line commentary

11. Comparative safety

Safety outcomes are presented from two analyses of the ZUMA-5 study:

- The primary analysis of ZUMA-5 (median actual follow-up time of 14.0 months; data cutoff date 12 March 2020), based on the safety analysis set (N=146) comprised of all patients with FL or marginal zone lymphoma treated with any dose of AXI.
- An updated analysis of ZUMA-5 (median follow-up of 48 months; data cutoff date 31 March 2023) based on the safety analysis set (N=124) comprised of all patients with FL treated with any dose of AXI.

A summary of adverse events reported in the ZUMA-5 study is provided in Table 3, with adverse events Grade ≥3 (severe or medically significant) and Grade 5 (death related to adverse events) outlined for additional context. Among FL patients in the updated analysis, 123 patients (99%) had at least 1 adverse event; 107 patients (86%) had worst Grade 3 or higher adverse events, and 65 patients (52%) had serious adverse events.

Table 3 Summary of adverse events: safety analysis set

	Primary (12 month) analysis of ZUMA-5			Updated 48 month analysis of ZUMA-5
	FL (N=124), n (%)	MZL (N=22), n (%)	iNHL (N=146), n (%)	FL (N=124), n (%)
Any TEAE	123 (99%)	22 (100%)	145 (99%)	123 (99%)
Worst Grade 5	3 (2%)	1 (5%)	4 (3%) [a]	10 (8%)
Worst Grade ≥ 3	105 (85%)	21 (95%)	126 (86%)	107 (86%)
Any Serious TEAE	54 (44%)	16 (73%)	70 (48%)	65 (52%)
Worst Grade 5	3 (2%)	1 (5%)	4 (3%)	10 (8%)
Worst Grade ≥ 3	40 (32%)	14 (64%)	54 (37%)	52 (42%)
Any AXI related TEAE	118 (95%)	22 (100%)	140 (96%)	118 (95%)
Worst Grade 5	1 (1%)	0 (0%)	1 (1%)	2 (2%)
Worst Grade ≥ 3	70 (56%)	16 (73%)	86 (59%)	72 (58%)
Any serious AXI related TEAE	37 (30%)	12 (55%)	49 (34%)	41 (33%)
Worst Grade 5	1 (1%)	0 (0%)	1 (1%)	2 (2%)
Worst Grade ≥ 3	25 (20%)	9 (41%)	34 (23%)	29 (23%)

Abbreviations: TEAE=treatment emergent adverse event; iNHL=indolent non-Hodgkin lymphoma; MZL=marginal zone lymphoma
a One patient died due to progressive disease that was listed as an adverse event in the database.
Source: Table 26 of MSAC 1771 ADAR+in-line commentary

In the updated 48-month analysis, for patients with FL treated with AXI:

- The most frequently reported adverse events were pyrexia (83%), hypotension (48%), headache (45%), fatigue (41%) and neutropenia (38%).
- The most frequently reported adverse events assessed as being related to AXI were pyrexia (80%), hypotension (38%), headache (33%), tremor (27%) and neutropenia (27%).

Identified risks related to the use of AXI were presented by the ADAR; these include cytokine release syndrome, neurological events, cytopenias, infections, hypogammaglobulinemia and secondary malignancies. A summary of the rate and grade of these adverse events of special interest is provided in Table 4.

The applicant's pre-ESC response stated that despite being TEAEs of special interest, neither persistent hypogammaglobulinemia nor persistent cytopenia were considered of particular concern for patients treated with AXI for r/r FL. The pre-ESC response highlighted that at the updated 48-month analysis of ZUMA-5, of the 91 cytopenia events reported, 79 were reported as resolved at the data cutoff date, with just 12/91 (13%) remaining ongoing. Similarly, at the 48-month follow-up analysis data cutoff date of the 25 patients reporting hypogammaglobulinaemia in ZUMA-5, 9/25 (36%) were ongoing and the majority of events were Grade 2 severity, with none reported as serious adverse events.

Table 4 Adverse events of special interest: safety analysis set

	Primary (12 month) analysis of ZUMA-5			Updated 48 month analysis of ZUMA-5
	FL (N=124), n (%)	MZL (N=22), n (%)	iNHL (N=146), n (%)	FL (N=124), n (%)
Any TE CRS [a]	97 (78%)	22 (100%)	119 (82%)	97 (78%)
Grade 5	1 (1%)	0 (0%)	1 (1%)	1 (1%)
Grade ≥3	8 (6%)	2 (9%)	10 (7%)	8 (6%)
Any TE neurological event	70 (56%)	17 (77%)	87 (60%)	70 (56%)
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade ≥3	19 (15%)	9 (41%)	28 (19%)	19 (15%)
Any TE cytopenia	91 (73%)	18 (82%)	109 (75%)	91 (73%)
Grade 5	NR	NR	NR	NR
Grade ≥3	86 (69%)	16 (73%)	102 (70%)	86 (69%)
Any TE infection	65 (52%)	13 (59%)	78 (53%)	69 (56%)
Grade 5	0 (0%)	1 (5%)	1 (1%)	3 (2%)
Grade ≥3	18 (15%)	5 (23%)	23 (16%)	24 (19%)
Any TE hypogammaglobulinemia	22 (18%)	4 (18%)	26 (18%)	25 (20%)
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade ≥3	1 (1%)	0 (0%)	1(1%)	1 (1%)
Any TE secondary malignancies	NR	NR	8 (5%)	NR

Abbreviations: CRS=cytokine release syndrome; TE=treatment emergent; iNHL=indolent non-Hodgkin lymphoma; MZL=marginal zone lymphoma
a CRS events are graded according to a modification of the criteria of Lee and colleagues.
Source: Table 29 of MSAC 1771 ADAR+in-line commentary

As ZUMA-5 was a single-arm study, for comparative safety, the adverse events reported in ZUMA-5 were compared with adverse events reported in clinical studies of anti CD20 (rituximab) monotherapy, anti CD20 therapy in combination with chemotherapy (obinutuzumab plus bendamustine and rituximab plus bortezomib), chemotherapy (bendamustine or bortezomib) and PI3Kδ inhibitor (idelalisib) regimens.

A summary of the populations and adverse events reported in the included studies are provided in Table 5. A higher proportion of patients treated with AXI (86%) were assessed as having adverse events Grade ≥3 compared with patients treated with SOC regimens (21% – 62%).

Table 5 Summary of populations and adverse events of the included clinical studies

	Updated 48 month analysis of ZUMA-5	LYM-3001: (Coiffier et al. 2011)		GADOLIN: (Sehn et al. 2016)		DELTA: (Gopal et al. 2014)
	AXI (N=124)	Rituximab (N=339)	Rituximab+ bortezomib (N=334)	Obinutuzumab +bendamustine (N=194)	Bendamustine (N=202)	Idelalisib (N=125)
Population	Adult patients with iNHL and relapsed or refractory disease after two or more lines of therapy	Adult patients with relapsed Grade 1 or 2 FL		Adult patients with relapsed iNHL refractory to rituximab		Adult patients with iNHL who had no response to rituximab+alkylating agent or relapsed ≤6 months of these therapies
FL population	100%	100% (inclusion criteria)		155 (80%)	166 (82%)	72 (58%)
Any adverse event, n (%)	123 (99%)	265 (78%)	316 (95%)	191 (98%)	194 (98%)	103 (82%)
Any treatment related adverse event, n (%)	118 (95%)	156 (46%)	Related to rituximab: 206 (62%) Related to bortezomib: 276 (83%)	NR	NR	NR
Any adverse event Grade ≥ 3, n (%)	107 (86%)	70 (21%)	152 (46%)	132 (68%)	123 (62%)	68 (54%)
Any serious adverse event, n (%)	41 (33%)	37 (11%)	59 (18%)	74 (38%)	65 (33%)	NR

Abbreviation: FL=follicular lymphoma; iNHL=indolent non-Hodgkin lymphoma; NR=not reported
Source: Prepared during evaluation using Table 31 of MSAC 1771 ADAR.

Frequently reported adverse events (any Grade) reported in the included studies are outlined in Table 6. The ADAR noted that the adverse event profile of AXI differs to the adverse event profile of SOC treatment regimens included by the ADAR. Notably, hypotension was the second most frequently reported adverse event for patients treated with AXI (48%) but was not frequently reported in patients treated with SOC. Further, the proportion of patients experiencing pyrexia was high for AXI treatment (83%) compared with SOC (10% – 28%).

The ADAR described that the exploratory assessment of comparative safety suggested that, overall, AXI has an inferior safety profile compared with SOC regimens based on the higher proportion of patients experiencing adverse events Grade ≥3. The Commentary considered that the ADAR's claim that AXI was inferior in terms of safety compared with SOC may be reasonable, though it was difficult to determine with certainty (including the extent of this inferiority) given the limited data presented.

Table 6 Frequently reported summary of adverse events of the included clinical studies

Rank (%)	Updated 48 month analysis of ZUMA-5	LYM-3001: (Coiffier et al. 2011)		GADOLIN: (Sehn et al. 2016)		DELTA: (Gopal et al. 2014)
	AXI (N=124)	Rituximab (N=339)	Rituximab+ bortezomib (N=334)	Obinutuzumab +bendamustine (N=194)	Bendamustine (N=198)	Idelalisib (N=125)
1	Pyrexia (83%)	Infection (27%)	Infection (53%)	Infusion-related reaction (69%)	Infusion-related reaction (64%)	Diarrhoea (43%)
2	Hypotension (48%)	Nausea or vomiting (11%)	Diarrhoea (52%)	Nausea (54%)	Nausea (61%)	Nausea (30%) Fatigue (30%)
3	Headache (45%)	Pyrexia (10%)	Nausea or vomiting (36%)	Fatigue (40%)	Fatigue (34%)	Cough (29%)
4	Fatigue (41%)	Cough (9%)	Pyrexia (25%)	Neutropenia (35%)	Diarrhoea (31%)	Pyrexia (28%)
5	Neutropenia (38%)	Diarrhoea (8%)	Fatigue (22%)	Cough (28%) Pyrexia (28%)	Neutropenia (29%)	Decreased appetite (18%) Dyspnoea (18%)

Source: Table 32 of MSAC 1771 ADAR+in-line commentary

12. Comparative effectiveness

The ADAR presented effectiveness outcomes of the ZUMA-5 study from the:

- Primary analysis (minimum follow-up of 12 months; data cutoff date 12 March 2020) based on the inferential analysis set (N=84) (first 84 patients with FL enrolled, treated with any dose of AXI, and had the opportunity to be followed for 12 months from the first disease assessment date).
- 48-month follow-up analysis (median follow-up of 48 months; data cutoff date 31 March 2023), based on the full analysis set (N=127) (of all patients with FL enrolled in ZUMA-5).

For the comparative analysis of ZUMA-5 vs SCHOLAR-5, effectiveness outcomes were presented for the:

- Primary comparative analysis (minimum follow-up of 18 months) based on the inferential analysis set from ZUMA-5 (N=86) (first 86 subjects with FL enrolled, treated with any dose of AXI, and had the opportunity to be followed for 18 months (updated 18-month analysis of ZUMA-5)); and
- Updated 48-month comparative analysis (median follow-up of 48 months) based on the full analysis set from ZUMA-5 (N=127). The Commentary noted that the results for the updated 48-month comparative analysis was provided by the submission in free text (no formulas) in an excel workbook and therefore could not be independently verified during the evaluation.

The comparative analysis presented by the ADAR incorporated a propensity score weighted population from the SCHOLAR-5 cohort.

Overall[11] response rate

The primary effectiveness outcome of the ZUMA-5 study was ORR, defined as the incidence of complete response (CR) or PR as determined by independent central assessment per Lugano classification (Cheson 2014). In ZUMA-5, assessments of response were performed using fluorodeoxyglucose positron emission tomography with contrast-enhanced CT (PET-CT). The Commentary noted that comparatively, SCHOLAR-5 included some CT-based response assessment and some PET-alone-based response assessments, which may have introduced measurement bias.

The ORR for the primary and updated analysis are presented in Table 7. In the primary analysis of ZUMA-5, 94% of patients were assessed as having a CR (79%) or PR to treatment with AXI. The ORR of 94% was significantly (p<0.0001) greater than the historical control rates of 40%, thus ZUMA-5 met it primary objective[12]. In the updated analysis of ZUMA-5, there was no change in the ORR of 94% or CR of 79% that was reported at the primary analysis of ZUMA-5.

Table 7 Overall response rate reported in ZUMA-5

	Primary (12 month) analysis of ZUMA-5 (N=84): IAS	Updated 48 month analysis of ZUMA-5 (N=127): FAS
Number of overall responders* (CR+PR), n (%)	79 (94%) (95% CI 87%, 98%), p<0.0001	119 (94%) (95% CI 88%, 97%)

Abbreviations: IAS=inferential analysis set; CR=complete response; FAS=full analysis set; PR=partial response
* Based on central assessment for primary analysis and investigator assessment for updated analysis. For comparison, the number of overall responders (investigator assessed) in the primary analysis (IAS) was 80 (95%) (95% CI 88%, 99%) (Table 17, p92 of the ZUMA-5 primary analysis CSR).
Source: Table 34 of MSAC 1771 ADAR+in-line commentary

The comparative effectiveness of AXI vs SOC for the outcome of ORR reported in the assessment of ZUMA-5 vs SCHOLAR-5 is outlined in Table 8. In the updated analysis, the ADAR reported a 40% difference in ORR for patients treated with AXI (ORR 94%) compared with SOC (ORR 54%) (p-value <0.0001). The Commentary noted that while results suggested the superiority of AXI over SOC, the 95% confidence intervals for the reported odds ratios were very wide, which adds additional uncertainty in the estimates (in addition to the uncertainty that stems from the indirect comparison).

[11] Overall response rate and objective response rate were used interchangeably in the applicant developed assessment report.

[12] The assessment of the primary efficacy endpoint of ORR in ZUMA-5 in the inferential analysis set had 93% power to test the null hypothesis that the ORR was 40% versus the alternative hypothesis that the ORR was 60%, with a 1-sided alpha level of 0.0237.

Table 8 Overall response rate reported for ZUMA-5 vs weighted SCHOLAR-5

	ZUMA-5 vs SCHOLAR-5: Primary (18 month) comparative analysis				ZUMA-5 vs SCHOLAR-5: Updated 48 month comparative analysis			
	ZUMA-5 (N=86)	SCHOLAR-5 (N=85)	Absolute diff (95% CI)[a]	Odds ratio (95% CI)	ZUMA-5 (N=127)	SCHOLAR-5 (N=128)	Absolute diff (95% CI)[a]	Odds ratio (95% CI)
No. of overall responders, n (%)	81 (94%)	42 (50%)	44% (31%, 55%), p <0.0001	16.2 (5.6, 46.9)	119 (94%)	69 (54%)	40% (30%, 49%), p <0.0001	12.7 (5.2, 30.6)

Abbreviations: CI=confidence interval; CR=complete response; diff=difference; PR=partial response; diff=difference
a: Calculated during preparation of ADAR
Source: Table 35 of MSAC 1771 ADAR+in-line commentary

Progression-free survival

Progression free survival (PFS) was a secondary effectiveness outcome of ZUMA-5, defined as the time from the AXI infusion date (analysis based on the inferential analysis set) or the enrolment/leukapheresis date (analysis based on the full analysis set) to the date of disease progression or death due to any cause. The primary analysis of PFS was determined by independent central assessment per Lugano classification (Cheson 2014). Sensitivity analysis was conducted in ZUMA-5 for the analysis of PFS in the inferential analysis set, based on the investigator's assessment of response.

PFS for subjects who received any subsequent anti-cancer therapy (including SCT or retreatment with AXI) in the absence of prior documented progression was censored at the date of the last evaluable disease assessment prior to subsequent anti-cancer therapy or the last evaluable disease assessment prior to SCT. The Commentary noted that this may be biased in favour of AXI, noting that four (5%) patients who started new anticancer therapy or received retreatment with AXI were censored in the primary analysis (see Table 9).

The assessment of PFS for patients enrolled in ZUMA-5 and censoring reasons are summarised in Table 9. At the primary analysis of ZUMA-5, PFS data was relatively immature with only 27% (23/84) of patients assessed as having a PFS event. The Commentary noted that compared to the PFS (in the inferential analysis set) based on central assessment, the proportion of patients assessed as having a PFS event (in the inferential analysis set) based on investigator assessment was higher in the sensitivity analysis (27% central assessment vs 35% investigator assessment, respectively). However, upon examining the censoring reason, there were more patients with an on-going response in the base case (54 patients vs 52 patients). It is also not clear why there are differences in outcomes such as death and retreatment between central and investigator assessment. At the updated 48-month analysis of ZUMA-5, 45% (57/127) of patients were assessed as having a PFS event (investigator assessment). Median PFS was reported as being 57.3 months (4.8 years), with 53% of patients remaining progression free 48 months (4 years) after enrolment in ZUMA-5 according to investigator assessment.

Table 9 Progression free survival reported in ZUMA-5

	Primary (12 month) analysis* of ZUMA-5 (N=84): IAS	Sensitivity analysis^ of ZUMA-5 (N=84): IAS	Updated 48 month analysis^ of ZUMA-5 (N=127): FAS
Events, n (%)	23 (27%)	29 (35%)	57 (45%)
Censored, n (%)	61 (73%)	55 (65%)	70 (55%)
Kaplan-Meier median, months (95% CI)	NE (23.5, NE)	NE (23.5, NE)	57.3 (30.9, NE)
Event			
Disease progression, n (%)	18 (21%)	25 (30%)	39 (31%)
Death from any cause, n (%)	5 (6%)	4 (5%)	18 (14%)
Censoring reason			
Response ongoing, n	54	52	61
Lost to follow-up, n (%)	1 (1%)	1 (1%)	2 (2%)
Withdrawal of consent, n (%)	0 (0%)	0 (0%)	3 (2%)
Investigator decision, n (%)	1 (1%)	1 (1%)	1 (1%)
Started new anticancer therapy, n (%)	2 (2%)	1 (1%)	1 (1%)
Retreatment with AXI, n (%)	2 (2%)	0 (0%)	1 (1%)
Response assessed but no disease, n (%)	1 (1%)	0 (0%)	0 (0%)
Response not yet assessed, n (%)	0 (0%)	0 (0%)	1 (1%)
Progression free rate, % (95% CI)			
12 months	78% (67%, 85%)	76% (65%, 84%)	80% (72%, 86%)
24 months	62% (41%, 77%)	55% (36%, 70%)	66% (57%, 74%)
36 months	Not reached	Not reached	57% (48%, 65%)
48 months	Not reached	Not reached	53% (43%, 62%)

Abbreviations: IAS=inferential analysis set; FAS=full analysis set; NE=not evaluable
Note: The median follow-up time for PFS in the primary analysis was 15.2 months (95% CI: 14.7, 17.8) and.17.1 months (95%CI: 14.9, 18.0 months) for the base case and sensitivity analysis, respectively.
The median follow-up time was 48.7 months (95% CI: 38.4, 49.2 months) in the 48 month follow-up.
* Central assessment
^ Investigator assessed
Source: Table 42 of MSAC 1771 ADAR+in-line commentary

The comparative effectiveness of AXI vs SOC for the outcome of PFS reported in the assessment of ZUMA-5 vs SCHOLAR-5 is outlined in Table 10. At the updated analysis of ZUMA-5 vs SCHOLAR-5, results suggested that AXI was associated with a significant improvement in PFS (hazard ratio (HR)= 0.27, 95% CI: 0.18, 0.40), and patients treated with AXI reported an improvement in median PFS of 44.3 months (3.7 years) vs patients treated with standard care.

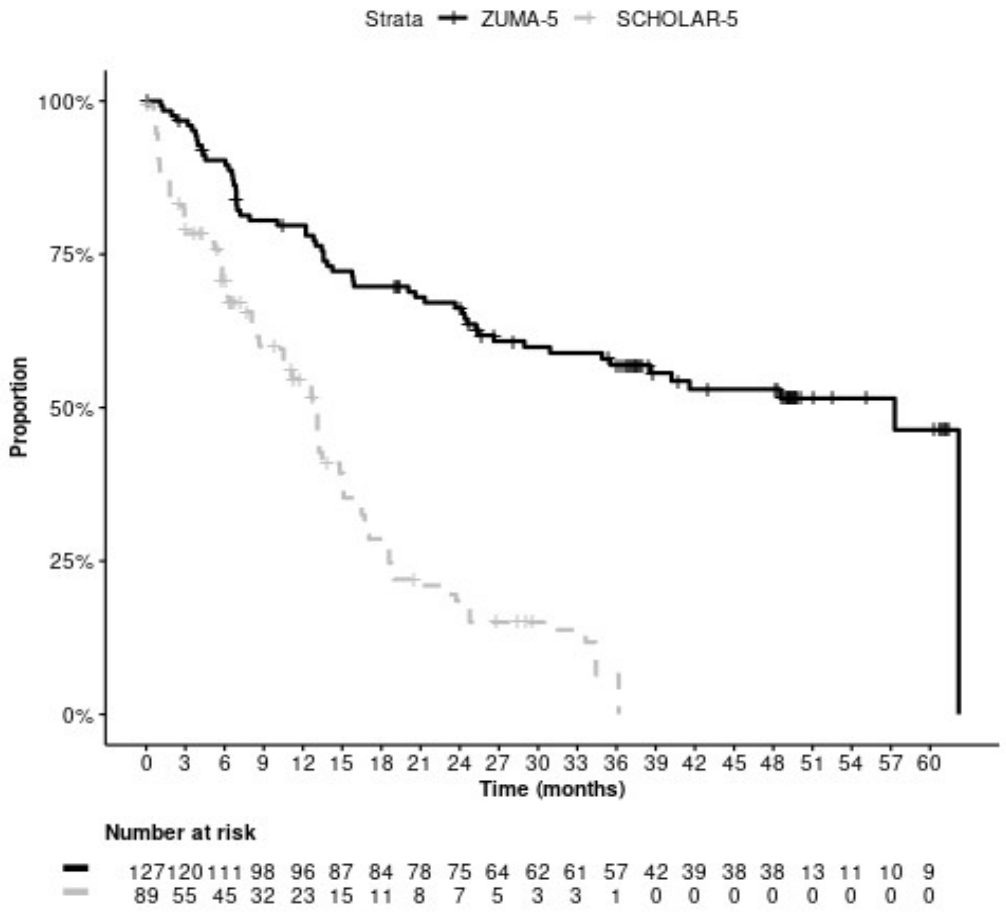
Table 10 Progression free survival reported for ZUMA-5 vs weighted SCHOLAR-5

	ZUMA-5 vs SCHOLAR-5: Primary (18 month) comparative analysis				ZUMA-5 vs SCHOLAR-5: Updated 48 month comparative analysis			
	ZUMA-5 (N=86)	SCHOLAR-5 (N=56)*	Absolute diff	Hazard ratio (95% CI)	ZUMA-5 (N=127)	SCHOLAR-5 (N=89)^	Absolute diff	Hazard ratio (95% CI)
Kaplan-Meier median, months (95% CI)	NR (23.5, NE)	12.7 (6.2, 14.7)	NE	0.30 (0.18, 0.49)	57.3 (30.9, NE)	13.0 (7.8, 15.5)	44.3	0.27 (0.18, 0.40)

Abbreviations: diff=difference; NE=not evaluable; NR=not reached
* SCHOLAR-5 sample size for PFS was 56. The progression dates were not collected for the subsequent line of therapy in the DELTA trial; therefore, subcohort B was not included in the PFS analysis (p853, Ghione et al. 2022).
^ The reduced SCHOLAR-5 sample size for PFS was not explained by the submission.
Source: Table 43 of MSAC 1771 ADAR+in-line commentary

The Kaplan-Meier plot of PFS based on the updated 48-month comparative analysis of ZUMA-5 vs SCHOLAR-5 is provided in Figure 1. Early and sustained separation of the AXI PFS curve from the SOC PFS curve was observed.

Figure 1 Kaplan-Meier plot of progression free survival ZUMA-5 vs SCHOLAR-5: Updated comparative analysis



Source: Figure 8 of MSAC 1771 ADAR+in-line commentary.
Note: This could not be located and therefore could not be verified during the evaluation.

Results presented by the ADAR suggested superiority of AXI over SOC in terms of ORR and PFS. However, the Commentary considers that the following points regarding the comparative efficacy of ZUMA-5 vs SCHOLAR-5 populations should be noted:

- Potential transitivity issues may exist between the cohorts used in the ADAR's comparative analysis, despite the application of propensity scoring.
- Even though the index date of treatment after July 2014 in SCHOLAR-5 cohort was chosen to reduce time-period bias due to the introduction of PI3Kδ inhibitors and because the Lugano criteria for disease assessment was formalised in 2014, Ghione 2022; p854) acknowledged that "response assessment in subcohorts A and B included CT scans using older criteria". Therefore, this introduced measurement bias (unclear in what direction) given the ZUMA-5 cohort was assessed per the Lugano classification. It was unclear how many patients may have been affected.
- PFS censoring applied in ZUMA-5 (where patients who received any subsequent anti-cancer therapy (including SCT or retreatment with AXI) in the absence of prior documented progression were censored) may be biased in favour of ZUMA-5, while censoring rules for SCHOLAR-5 cohort were not provided by the ADAR and could not be located during the evaluation. Therefore, it was unclear how patients who 'progressed' were determined in SCHOLAR-5.
- Patients could be assessed as 'progressed' more quickly whilst receiving SOC in SCHOLAR-5 than compared to ZUMA-5, as clinicians may be more likely to push SOC patients to progress quicker in order to switch treatments when SOC was perceived as not working, particularly in a real-world setting.
- Bias may be introduced from the misalignment of the timing of assessments between the two studies, potentially overestimating time to progression in the study with less frequent disease assessments. Patients enrolled in ZUMA-5 were assessed at Week 4, then 3 monthly, and if a patient's disease had not progressed by Month 24, disease assessments were to continue to be performed per SOC, whereas the frequency of assessments in SCHOLAR-5 was not reported, though Ghione et al. (2022) expected this to be less frequent in real-world practice.

Therefore, the results of this analysis should be considered highly uncertain.

Overall survival

Overall survival (OS) was a secondary effectiveness outcome of ZUMA-5, defined as the time from the AXI infusion date (analysis based on the inferential analysis set) or the enrolment/leukapheresis date (analysis based on the full analysis set) to the date of death due to any cause.

The assessment of OS for patients treated with AXI in ZUMA-5 is summarised in Table 11. At the primary analysis of ZUMA-5, OS data was relatively immature with only 15% (13/84) of patients having died from any cause. At the updated analysis of ZUMA-5, death from any cause was reported in 30% (38/127) of patients. Median OS was still not evaluable, however the ADAR claimed that based on the lower-bound of the 95% CI for median OS being 62.2 months, it can be deduced that there is a <5% chance that the median duration of OS will be below 62.2 months (5.1 years). Patients in ZUMA-5 had a 72% chance of remaining alive 48 months (4 years) after enrolment.

Table 11 Overall survival reported in ZUMA-5

	Primary (12 month) analysis of ZUMA-5 (N=84): IAS	Updated 48 month analysis of ZUMA-5 (N=127): FAS
Death from any cause, n (%)	13 (15%)	38 (30%)
Alive	71 (85%)	89 (70%)
Kaplan-Meier median, months (95% CI)	NE (NE, NE)	NE (62.2, NE)
Overall survival rate, % (95% CI)		
12 months	93% (85%, 97%)	97% (92%, 99%)
24 months	72% (52%, 85%)	88% (81%, 93%)
36 months	Not reached	76% (67%, 83%)
48 months	Not reached	72% (64%, 79%)

Abbreviations: IAS=inferential analysis set; FAS=full analysis set; NE=not evaluable
Note: The median follow-up time for OS in the primary analysis was 18.0 months (95%CI: 16.6, 18.2 months).
The median follow-up time for OS in the 48 month follow-up was 53.4 months (95%CI: 50.7, 55.7 months).
Source: Table 45 of MSAC 1771 ADAR+in-line commentary

The comparative effectiveness of AXI for the outcome of OS reported in the assessment of ZUMA-5 vs SCHOLAR-5 is outlined in Table 12. At both the primary and updated analysis of OS, patients treated with AXI were observed as having a reduced risk of death compared to patients treated with standard care (HR=0.42, 95% CI: 0.21, 083 and HR=0.58, 95% CI: 0.35, 0.96, respectively). The Commentary noted that the 95% CI for the reported HR in the updated analysis was wide (0.35, 0.96).

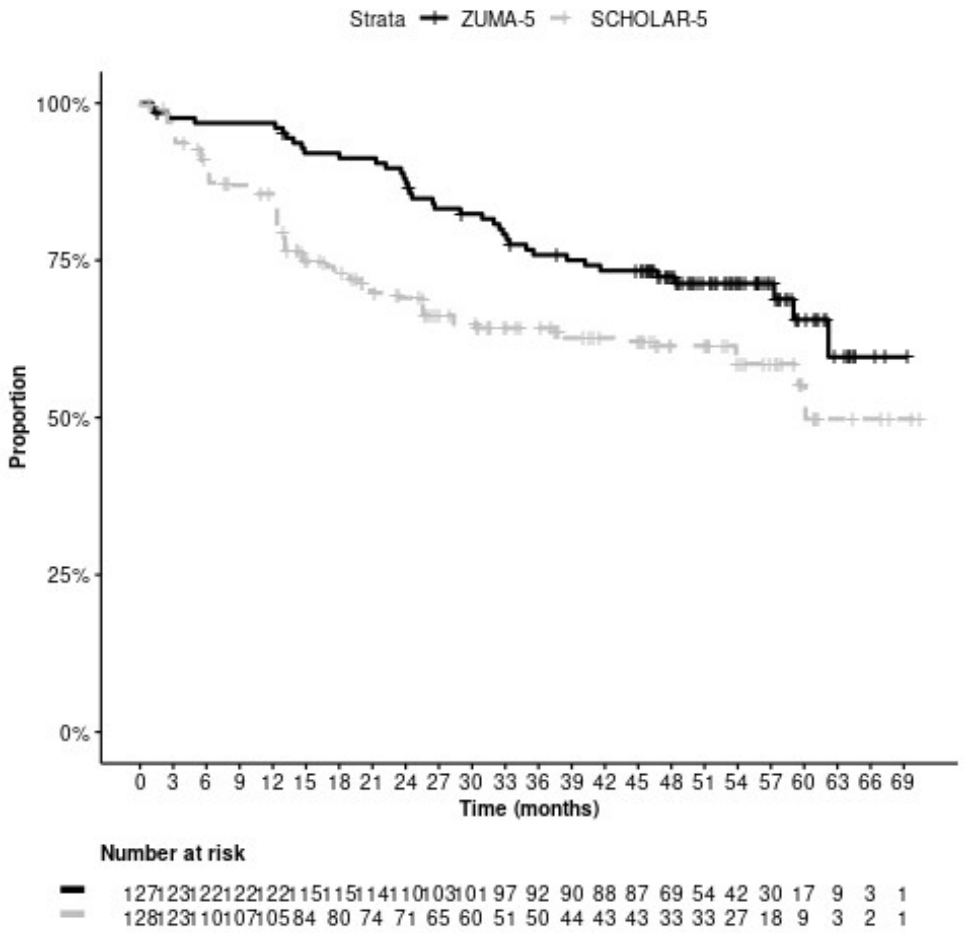
Table 12 Overall survival reported for ZUMA-5 vs weighted SCHOLAR-5

	ZUMA-5 vs SCHOLAR-5: Primary (18 month) comparative analysis				ZUMA-5 vs SCHOLAR-5: Updated 48 month comparative analysis			
	ZUMA-5 (N=86)	SCHOLAR-5 (N=85)	Absolute diff (95% CI)	Hazard ratio (95% CI)	ZUMA-5 (N=127)	SCHOLAR-5 (N=128)	Absolute diff (95% CI)	Hazard ratio (95% CI)
Kaplan-Meier median, months (95% CI)	NR (31.6, NE)	59.8 (21.9, NE)	NE	0.42 (0.21, 0.83)	NE (62.2, NE)	NE (38.4, NE)	NE	0.58 (0.35, 0.96)

Abbreviations: diff=difference; NE=not evaluable
Source: Table 46 of MSAC 1771 ADAR+in-line commentary

The Kaplan-Meier plot of OS based on the updated comparative analysis of ZUMA-5 vs SCHOLAR-5 is provided in Figure 2. Early and sustained separation of the AXI OS curve from the SOC OS curve was observed.

Figure 2 Kaplan-Meier plot of overall survival ZUMA-5 vs SCHOLAR-5: Updated comparative analysis



Source: Figure 10 of MSAC 1771 ADAR+in-line commentary
Note: This could not be located and therefore could not be verified during the evaluation.

The results presented by the ADAR suggested superiority of AXI compared to SOC (ZUMA-5 vs SCHOLAR-5) in terms of OS benefit. However, the Commentary had concerns regarding the transitivity between the compared populations and bias. Overall, the Commentary considered that the magnitude of benefit was highly uncertain.

Supportive evidence (Kambhampati et al. 2023)

Supplementary evidence was presented by the ADAR from a study (Kambhampati 2023) comparing outcomes reported for a real-world cohort of patients treated with AXI as 3L treatment at the CIBMTR with a group of patients from the SCHOLAR-5 cohort. It is unknown whether any of these patients were enrolled in ZUMA-5. The Commentary noted that while the SCHOLAR-5 cohort was used, it was unclear how these patients were derived, as the cohort numbers (N=120) differed from those presented in the comparative analysis against ZUMA-5 (SCHOLAR-5 N=143, later reduced to 85 after the application of propensity scoring; Ghione 2022), and it was also unclear what SOC treatments were received by this cohort as this was not reported. The Commentary further noted that a full publication of this analysis was not available at the time of the evaluation, and only an abstract was provided by the ADAR. As such, the results of this analysis should be interpreted with caution.

A summary of efficacy outcomes from ZUMA-5 and the Kambhampati (2023) analysis is provided in Table 13.

Table 13 Summary of efficacy outcomes from ZUMA-5 and AXI RWE vs SOC

	ZUMA-5	AXI RWE vs SOC			
	Updated 48 month analysis of ZUMA-5 (N=127): FAS	AXI RWE	SOC (weighted SCHOLAR-5)	Absolute difference (95% CI)[a]	Odds (ORR)/Hazard (PFS and OS) ratio (95% CI)
Overall response rate					
Number of overall responders (CR+PR), % (95% CI)	94% (88%, 97%)	92% (88%, 95%)	67% (60%, 74%)	25% (17%, 33%), p <0.0001	4.9 (2.4, 10.3)
Progression free survival					
Progression free at 6 months, % (95% CI)	90% (84%, 94%)	88% (83%, 91%)	64% (46%, 77%)	24% (16%, 32%), p<0.0001	0.41 (0.220, 0.77)
Overall survival					
Overall survival at 6 months, % (95% CI)	97% (92%, 99%)	97% (94%, 99%)	85% (73%, 92%)	12% (6%, 18%), p=0.0006	0.15 (0.06, 0.34)

Abbreviations: CR=complete response; FAS=full analysis set; ORR=overall response rate; OS=overall survival; PFS=progression free survival; PR=partial response; RWE=real world evidence; SOC=standard of care
a: Calculated during the evaluation
Note: The absolute difference calculated by the submission could not be replicated during the evaluation. The values calculated during the evaluation were: PFS: 24% (95% CI: 8%, 40%), p=0.0033; and OS: 12% (95% CI: 2%, 22%), p=0.0167
Source: Table 51 in MSAC 1771 ADAR+in-line commentary

The Commentary noted that while the results of the AXI RWE vs SCHOLAR-5 (Kambhampati 2023) suggested superiority of AXI over SOC in terms of ORR, PFS, and OS, the following points regarding the comparative efficacy of the two populations should be noted:

- Potential transitivity issues may exist between the cohorts used in the ADAR's comparative analysis, despite the application of propensity scoring.
- Results were based on immature data (where survival outcomes were reported at month 6) and may not be informative for decision making.
- Analysis was based on patients who received commercial AXI between March 2021 – May 2023 compared to patients (SCHOLAR-5) who initiated historical SOC between July 2014 – December 2020, and may be biased in favour of AXI given older SOC therapies may have been used. It was also unclear what SOC treatments were received by the SCHOLAR-5 cohort as this was not reported.
- It was unclear how response to treatment was assessed, or how censoring was applied in both cohorts as this was not reported by the ADAR or Kambhampati (2023).
- Patients could be assessed as 'progressed' more quickly while receiving SOC in SCHOLAR-5 compared to AXI, as clinicians may be more likely to push SOC patients to progress quicker in order to switch treatments when SOC was perceived as not working, particularly in a real-world setting.
- Bias may be introduced from the misalignment of the timing of assessments between the two studies, potentially overestimating time to progression in the study with less frequent disease assessments. The timing of assessments was not known as this was not reported for both cohorts.

Therefore, the results of this analysis should be interpreted with caution and considered highly uncertain.

Clinical claim

The ADAR described AXI as superior compared with SOC in terms of effectiveness. While the results suggested superiority of AXI compared to SOC (reported for ZUMA-5 vs SCHOLAR-5 (Ghione 2022); and AXI RWE vs SCHOLAR-5 (Kambhampati 2023)), key issues identified in the Commentary included:

- Potential transitivity issues may exist between the cohorts used in the ADAR's comparative analysis, despite the application of propensity scoring.
- Lack of consistency (and information) on how response to treatment was assessed between different cohorts.
- Censoring methodology may favour AXI in ZUMA-5, while censoring rules were not reported for the SCHOLAR-5 cohort or in the analysis by Kambhampati (2023).

Overall, the Commentary considered that while the claim of superior efficacy may be reasonable, the magnitude of benefit was highly uncertain.

The ADAR described that AXI was inferior in terms of safety compared with SOC. While a clinical claim of inferior safety vs SOC was made, the ADAR claimed that the adverse event profile of AXI is manageable in clinical practice. The Commentary considered that the claim of inferiority safety of AXI may be reasonable, though it was difficult to determine with certainty (including the extent of this inferiority) given the limited data presented.

13. Economic evaluation

Based on the ADAR's claim of superior efficacy and inferior safety, the ADAR presented a cost-utility analysis examining the cost-effectiveness of AXI versus SOC for the treatment of patients with r/r FL after two or more lines of systemic therapy. The analysis is based on extrapolation of outcomes from ZUMA-5 and data from the propensity weighted SCHOLAR-5 analysis.

Though the curves incorporated into the model appeared consistent with the Kaplan Meier curves presented in Figure 1 and Figure 2, the Commentary could not fully verify these curves due to the non-transparent nature of the analysis.

The ADAR modelled cure using a piecewise approach, assuming a cure point at 5 years, at which overall survival (OS) in 40% of patients in the AXI arm was assumed to match general population mortality with a standardised mortality ratio applied to model excess mortality (with the remainder of the population following the parametric extrapolation of survival).

This extrapolation was based on an unanchored propensity weighted comparison of ZUMA 5, (48-month median potential follow-up) and SCHOLAR-5.

Table 14 presents an overview of the model structure and key model parameters.

Table 14 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy
Prior testing	Not applicable
Comparator	SOC (including cyclophosphamide, fludarabine, bendamustine, obinutuzumab, rituximab, doxorubicin, vincristine, bortezomib, idelalisib, prednisolone)
Type(s) of analysis	Cost-utility analysis
Outcomes	Life years gained, quality-adjusted life years
Time horizon	30 years in the model base case vs 4 years in the ZUMA-5 study
Computational method	Partitioned survival analysis
Generation of the base case	Modelled. The economic model applies outcomes from the modelled comparison of ZUMA-5 vs SCHOLAR-5 presented in Figure 1 and Figure 2 . (Based on the propensity weighting of SCHOLAR-5 and updated ZUMA-5 results).
Health states	Progression free survival Progressed disease Dead
Cycle length	1 month - Half cycle correction was applied for costs (except for those assumed to occur at the start of the model) and outcomes.
Transition probabilities	Extrapolated survival data (PFS and OS) for AXI and SOC derived from the comparison of ZUMA-5 vs SCHOLAR-5 and background (all-cause) mortality used to transition patients between health states. (In addition to extrapolation, cure was assumed for all progression free AXI patients at 5 years, after which point a SMR of 1.09 was applied).
Discount rate	5% for both costs and outcomes
Software	Microsoft Excel

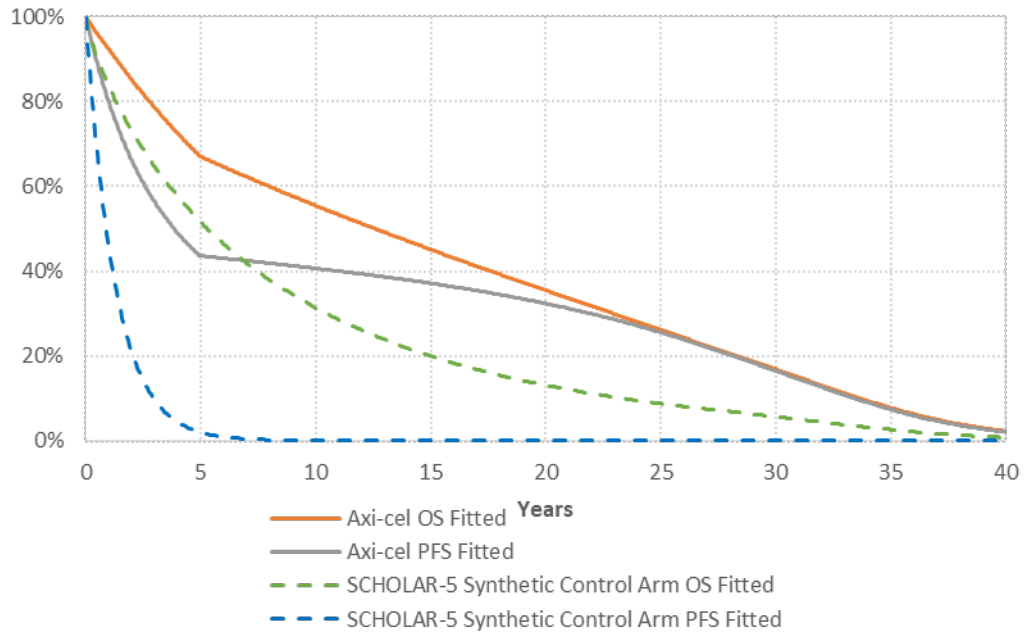
Source: Table 52 of MSAC 1771 ADAR+in-line commentary.
AXI = axicabtagene ciloleucel; OS = overall survival; PFS = progression free survival; SMR = standardised mortality ratio; SOC = standard of care

From the Kaplan Meier data of ZUMA-5, OS for AXI was modelled up to 5 years using an exponential extrapolation and PFS was extrapolated using a log-logistic extrapolation. After 5 years, cure was assumed for all progression free AXI patients, after which point a survival matched general population mortality and a standardised mortality ratio of 1.09 was applied (based on Maurer 2014).

From the propensity weighted SCHOLAR-5 curve, OS for SOC was modelled up to the end of the time horizon (30 years) using a Weibull curve and PFS was modelled by an exponential curve. No cure was assumed for SOC.

Figure 3 presents the survival curves in the economic evaluation.

Figure 3 Survival curves applied in the base case analysis



Source: Figure 21 of MSAC 1771 ADAR+in-line commentary
Axi-cel = axicabtagene ciloleucel; OS = overall survival; PFS = progression free survival.

The ADAR considered that the choice of a 5-year cure was supported by:

- The observed OS for patients treated with AXI at the updated 48 month analysis.
- The clinical plausibility of some patients with follicular lymphoma achieving an effective cure based on the broader evidence from other clinical trials of AXI.
- Precedent MSAC decision-making for alternate CAR T therapies.

The ADAR noted that at a median follow-up of 48 months, only 38/127 (30%) of patients had died and that the slope of the Kaplan Meier curve was flat from approximately 32 months. The ADAR considered that while survival probability does gradually decrease over time after this time point, this would partially be a result of all-cause (non-follicular lymphoma) death.

The ADAR also noted that from the 32-month time point approximately 99 patients remained at risk of death. Thus, the plateauing effect observed is unlikely to be driven by prolonged OS reported in a small number of 'good performing' patients beyond 32 months.

The Commentary noted that ZUMA-5 Kaplan Meier data presented in the economic model indicate that the OS at 32 months was 0.791, at 48 months was 0.713 and at 65 months was 0.596. Acknowledging this reflects the tail of the Kaplan Meier data, the Commentary noted that this constitutes an 8% decrease in 16 months and a decrease of 20% in less than three years. Such a trend does not reflect all-cause mortality for that age group and does not indicate a survival plateau that would support an assumption of cure. The Commentary also noted that the ADAR did not discuss observed PFS even though the cure assumption also applied to PFS, which may have also been overestimated with a cure assumption.

The ADAR also considered that the clinical plausibility of cure for some patients was supported by results in refractory B-cell lymphoma (ZUMA-1, 3L; ZUMA-7, 2L) and real world evidence from a 5-year case series of tisagenlecleucel treated patients at the hospital of University of Pennsylvania (Chong 2021). The Commentary observed that none of the cited references are directly relevant

to AXI treatment of r/r FL and that the observed follow-up of all of the references is substantially shorter than the 30-year time horizon during which benefit is accrued in the ADAR's model. The Commentary also considered that FL can have long periods between relapses compared to other haematological malignancies, although the duration of remission shortens substantially in the multiple refractory settings. It was unclear to what extent follow-up data from other cancers would be appropriate to the r/r setting.

The ADAR also considered that a modelling approach incorporating a cure rate in some patients was adopted in previous economic evaluations of CAR T therapies assessed by MSAC (MSAC 1519.1, MSAC 1587). Specifically, the ADAR considered that the evidence supporting the current ADAR was more mature (longer study follow-up) and considered to be more robust (more patients remaining alive) compared with precedent MSAC submissions where the incorporation of a cure rate has supported MSAC recommending CAR-T therapies in other indications.

However, review of the cited PSDs during the Commentary indicated consistent concerns by MSAC regarding uncertainty of modelling cure and did not explicitly accept the ICERS as cost-effective. Table 15 presents the relevant MSAC consideration, the type of cure modelling, and relevant comments by MSAC or MSAC ESC. Overall, MSAC previous consideration and basis of support for CAR T therapy for other indications does not create a precedent and does not support the modelling approach used in this ADAR.

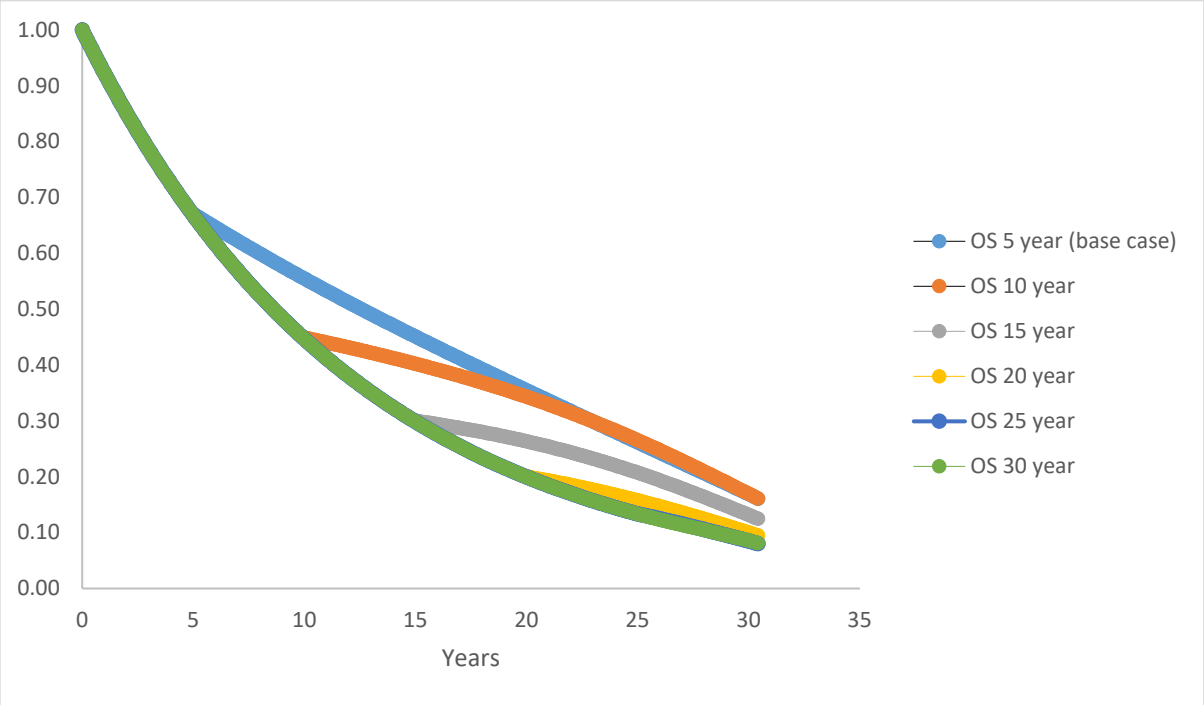
Table 15 Previous MSAC or ESC comment regarding model and / or cure assumptions

MSAC item	Cure modelling approach	Comment
1519.1	No explicit cure described, but spline approach used.	ESC noted a number of issues remained with the economic model that meant that the incremental cost (ICER) per quality adjusted life year (QALY) was likely underestimated
1587	Mixed cure model	MSAC considered that the application itself did not provide a suitable basis for making a funding recommendation (because a reliable ICER could not be calculated). Recommendation based on non-inferiority to tisagenlecleucel
1723.1	5 year cure point and 2.0 SMR	ESC questioned the assumption of 5 year cure point and 2.0 SMR as well as utility reverting back to progression free in cured patients.

Source: Compiled during evaluation from MSAC 1519.1 PSD, MSAC 1587 PSD, MSAC 1723.1 PSD

Figure 4 presents an analysis conducted by the Commentary showing modelled OS by selected cure point times from 5 years (base case) to 30 years (equivalent to no explicit cure assumed).

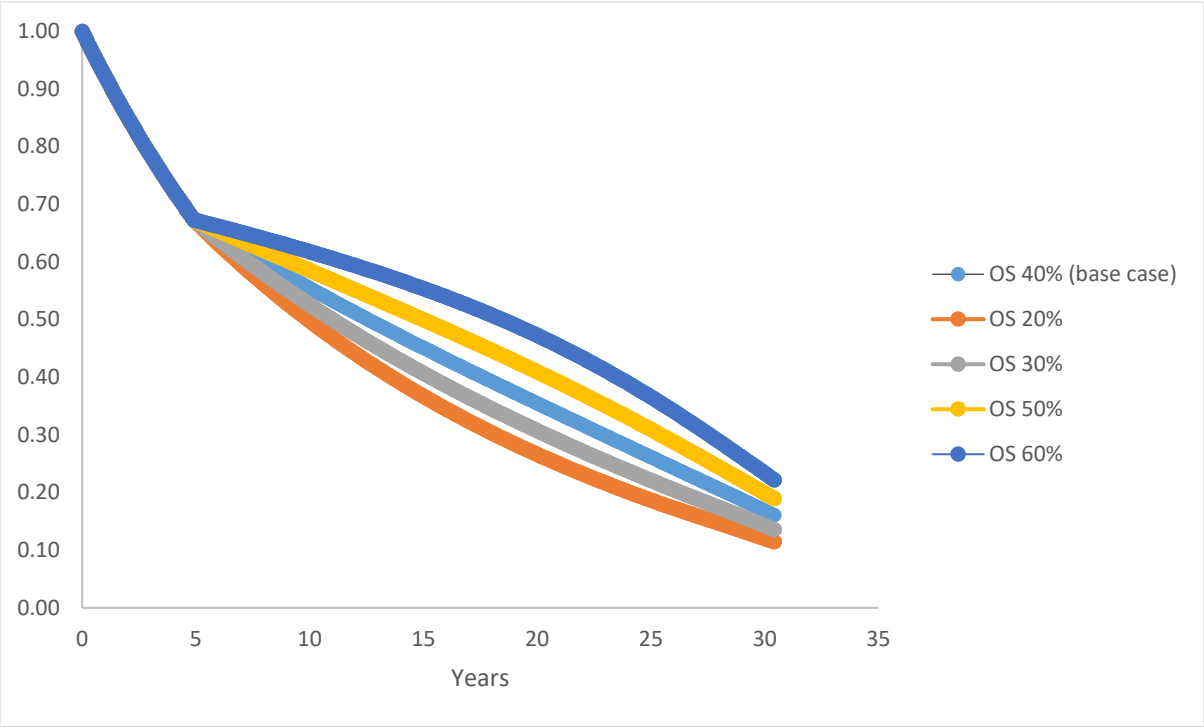
Figure 4 Overall survival by cure point from 5 years to 30 years



Source: conducted during the evaluation.
OS = overall survival

One other key cure assumption was that at 5 years, 40% of the patients would be cured. This cure fraction could also be changed in the economic model. Figure 5 shows an analysis conducted by the Commentary to show the impact of cure fraction on modelled overall survival.

Figure 5 Overall survival by cure fraction



Source: conducted during the evaluation.
OS = overall survival

The Commentary noted that the model was highly sensitive to differing assumptions of cure point and cure fraction. Follicular lymphoma is currently considered incurable (Tonino & Kersten 2024).[13] Consequently, assumptions of long-term cure based on 5-year median survival results may have been optimistic, and would favour AXI.

The ADAR applied a standardised mortality ratio (SMR) of 1.09 based on Maurer 2014 to patients who were cured, to account for excess mortality in these patients. The Commentary noted that Maurer 2014 included newly diagnosed DLBCL patients who received rituximab and anthracycline-based chemotherapy as initial therapy. It was unclear how relevant the SMR calculated from this population would be to a 3L or later line of treatment in FL patients.

A review of the scientific literature and health technology assessments for evidence for event-free survival (EFS)-OS surrogacy (Assouline 2022)[14] identified in the Commentary reported that there were no patient-specific or cohort level analyses regarding the validity of surrogacy of OS for EFS in r/r follicular lymphoma.

The Commentary supposed that in the absence of a clear SMR value for follicular lymphoma, it may be reasonable to expect that the SMR for a later line treatment would be higher than that of newly diagnosed DLBCL patients. For example, the Commentary identified a retrospective study of consecutively collected patient data from the Japanese nationwide transplant registry Fujimoto 2021, which concluded that SMRs of patients with follicular lymphoma after auto-HSCT were significantly higher than that of the general population (EFS 24: 2.7 EFS 60: 3.7). The model did not include SMR as a user modifiable input. However, during the evaluation, the SMR of 1.09 was changed to 2.7 and 3.7, which led to an increase in the ICER of 19% and 31%, respectively.

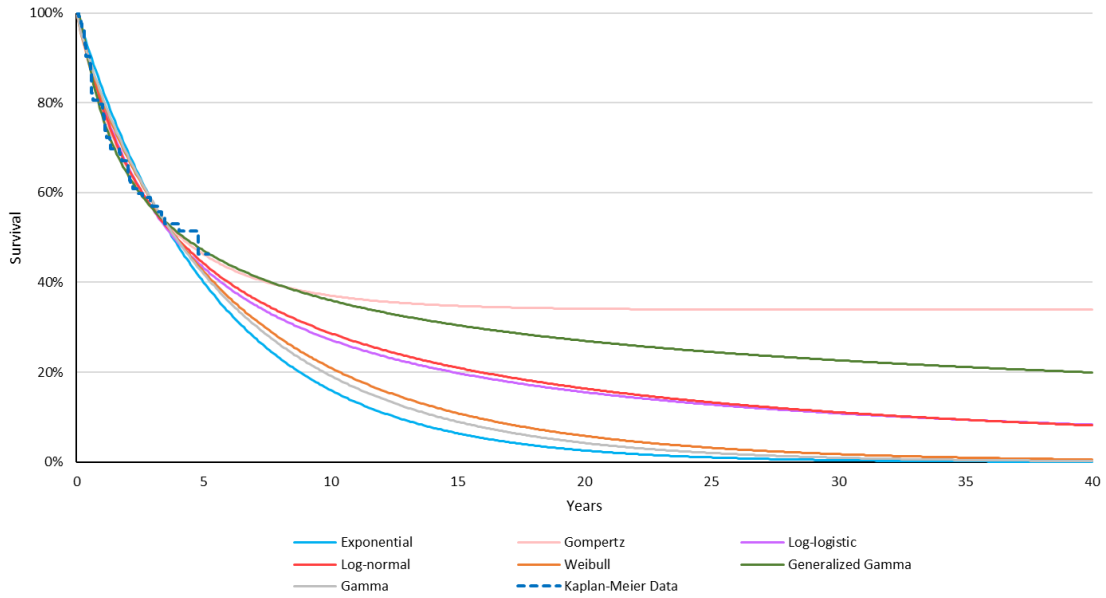
The Commentary noted that the ADAR's extrapolation sensitivity analyses did not indicate substantial impact to the ICER. However, the extrapolation method used in the economic evaluation is inclusive of 40% of patients being assumed to be cured at 5 years. During the evaluation, sensitivity analyses for AXI OS extrapolations assuming no cure were conducted to see the impact on the ICER, which was substantial.

The figures below show the extrapolations for AXI without a cure assumption, and those for SOC. It was noted during the Commentary that some of the extrapolations overestimated overall survival compared to general population mortality after approximately Year 25 of the time horizon. However, the ADAR adjusted the extrapolated curves for both general population mortality and applied a SMR to account for mortality in cured patients. Consequently, the Commentary considered this reasonable.

[13] Tonino SH & Kersten MJ (2024) The quest for a cure in follicular lymphoma. *Blood*. 143(6):475–476. doi: https://doi.org/10.1182/blood.2023022796

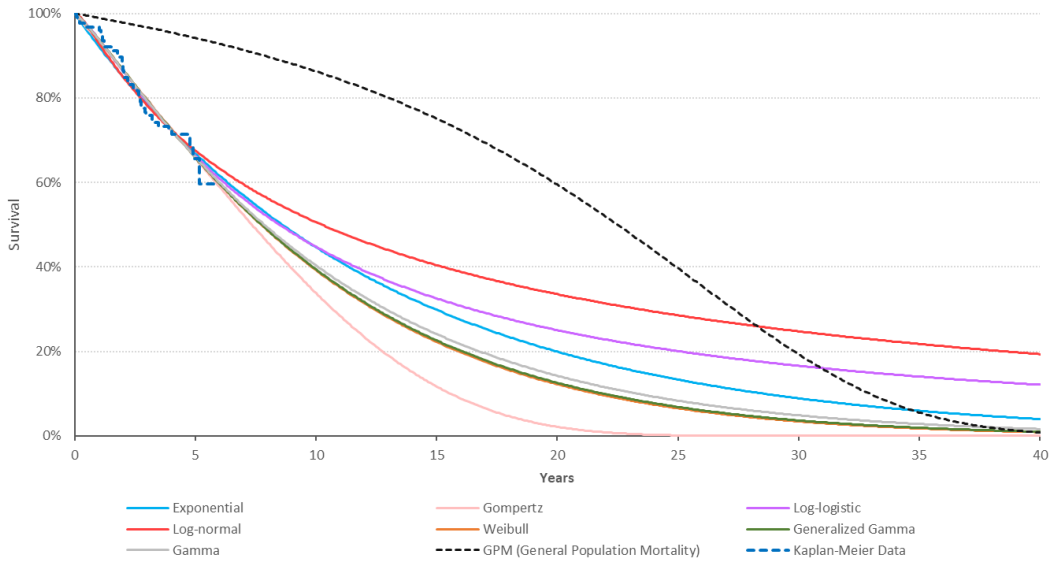
[14] Assouline S, et al. (2022) Validity of event-free survival as a surrogate endpoint in haematological malignancy: Review of the literature and health technology assessments. *Crit Rev Oncol Hematol*. 175:103711. doi: 10.1016/j.critrevonc.2022.103711.

Figure 6 Parametric extrapolations of PFS for AXI



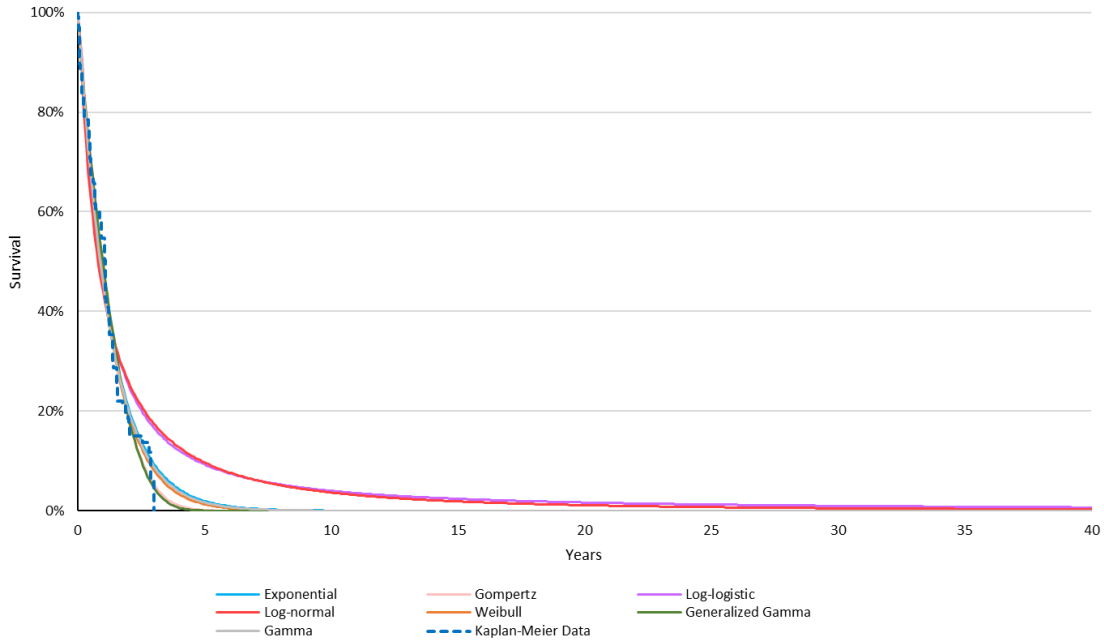
Source: Figure 13of MSAC 1771 ADAR + in-line commentary
Note: extrapolations presented reflect extrapolated survival from study data and are prior to the adjustment for general population mortality and standardised mortality ratio.

Figure 7 Parametric extrapolations of OS for AXI



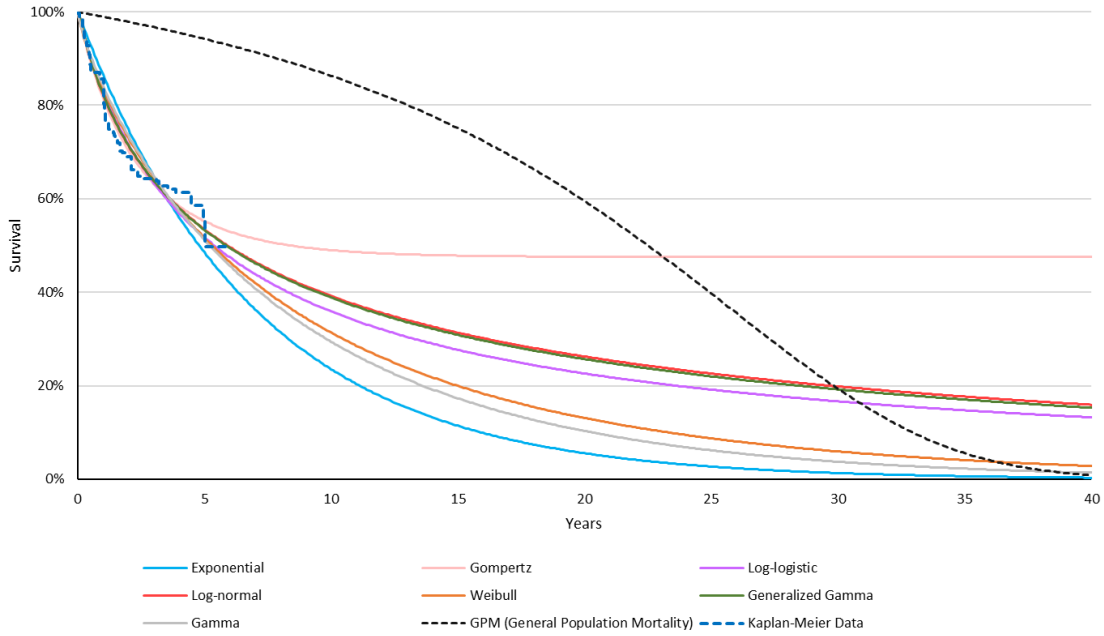
Source: Figure 14 of MSAC 1771 ADAR + in-line commentary
Note: extrapolations presented reflect extrapolated survival from study data and are prior to the adjustment for general population mortality and standardised mortality ratio.

Figure 8 Parametric extrapolations of PFS for SOC



Source: Figure 15 of MSAC 1771 ADAR + in-line commentary
Note: extrapolations presented reflect extrapolated survival from study data and are prior to the adjustment for general population mortality and standardised mortality ratio.

Figure 9 Parametric extrapolations of OS for SOC



Source: Figure 16 of MSAC 1771 ADAR + in-line commentary
Note: extrapolations presented reflect extrapolated survival from study data and are prior to the adjustment for general population mortality and standardised mortality ratio.

The base case of the economic evaluation applied the log-logistic and exponential curves for AXI PFS and OS respectively, and the exponential and Weibull curves for SOC PFS and OS, respectively.

The Commentary concluded that the model was not sensitive to extrapolation choice for PFS in the SOC arm.

With regard to extrapolation of OS in the SOC arm, the ADAR considered that the long-term survival plateau modelled by the Gompertz extrapolation was likely overly optimistic, which the Commentary considered likely reasonable. However, the Commentary considered that that there was little basis to conclude that the Weibull extrapolation was a more accurate modelling of long-term survival than the log-logistic, log-normal and generalised gamma models. Selecting any of these would increase the ICER by 18 to 30%.

The ADAR relied on utilities sourced from Papaioannou 2012 which relied on utilities from an unpublished report of the "Oxford Outcomes Study" (also referred to as Wild 2005[15] and Wild 2006[16]).

The Commentary noted that these utilities reflected newly diagnosed FL patients and not necessarily those who are refractory or relapsed after 2 or more lines of therapy. During the evaluation, more appropriate utilities could not be identified. However, for indicative purposes utility values from Cher 2020[17] in r/r DLBCL were used as they may better approximate utility for a refractory setting in haematological malignancy. Overall, however, the model was not substantially sensitive to choice of utility.

The ADAR included costs associated with AXI cell treatment and administration, SOC treatment and administration, subsequent treatment costs, adverse events, medical services, hospital services and end of life care. The Commentary noted that the hospitalisation costs ($1,995.62 per day based on AR_DRG v11 code 61A minus pharmacy and critical care costs) may have been underestimated.

The ADAR assumed no additional costs for AXI retreatment. Additionally, the ADAR assumed that 100% of patients in the AXI arm would receive lymphodepleting chemotherapy and AXI. The Commentary considered this was inconsistent with ZUMA-5 which indicated that 2% of the full analysis set did not receive lymphodepleting chemotherapy or AXI. However, it was unclear if these patients were followed up to the point of an event. Consequently, the Commentary considered that the ADAR's approach was more conservative and likely more reasonable.

Other costs had minimal impact on the ICER.

The ADAR included costs of autologous and allogenic SCT in the SOC arm, but not in the AXI arm. The ZUMA-5 (48-month follow-up analysis) CSR indicated that in the safety set of ZUMA-5, 1/119 patients received autologous stem cell transplant and 6/119 patients received allogenic stem cell transplant. The Commentary noted that there does not appear to be a strong consensus on the role of CAR T in FL, specifically regarding the extent to which it is a replacement for, rather than a bridge to, stem cell transplant. Consequently, assuming no subsequent stem cell transplant may underestimate the ICER.

End of life costs were estimated from Langton 2016. The cohort of patients in Langton 2016 included Australian Government Department of Veterans' Affairs (DVA) clients with a notifiable

[15] Lewis G. Utility elicitation in patients with follicular lymphoma. Unpublished report by Oxford Outcomes prepared for Roche UK 2005.

[16] Wild D, et al. Utility elicitation in patients with follicular lymphoma. 2006. International Society for Pharmaeconomics and Outcomes Research (ISPOR), 9th Annual European Congress, Copenhagen, Denmark, 28–31 October 2006.

[17] Cher BP, et al. (2020) Cost utility analysis of tisagenlecleucel vs salvage chemotherapy in the treatment of relapsed/refractory diffuse large B-cell lymphoma from Singapore's healthcare system perspective. J Med Econ. 23(11):1321-1329, DOI: 10.1080/13696998.2020.1808981

cancer diagnosis recorded in the New South Wales Central Cancer Registry (NSW CCR) between 1994 and 2009 and were at least 65 years at death. The Commentary considered that given the broad timeframe and range of cancer types, it was unclear to what extent these costs would be relevant to the present day FL setting. The Commentary also noted that these costs included clinical visits and procedures as well as prescription medicines, which are already included separately in the model. Consequently, the application of costs calculated from Langton 2016 likely double-counts costs. Overall, however, removing end of life costs had minimal impact on the ICER.

Table 16 presents the results of the economic evaluation.

Table 16 Results of the economic evaluation

	AXI	SOC	Increment	ICER
Costs	**$Redacted**	$82,227	**$Redacted**	
Life-years	8.92	5.98	2.94	**$Redacted**/life year
QALYs	6.80	4.07	2.72	**$Redacted/QALY**

Source: Table 70 of MSAC 1771 ADAR+in-line commentary
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SOC = standard of care.

Key drivers of the model are presented in Table 17.

Table 17 Key drivers of the model

Description	Method/Value	Impact Base case: $Redacted/QALY gained
Cure point	5 years	*High, favours AXI* *Increasing the cure point to 10 years increased the ICER to **$Redacted**/ QALY gained* *Removing the cure assumption increased the ICER to **$Redacted**/QALY gained.*
SOC OS extrapolation	Weibull	*High, uncertain* *Selecting an exponential extrapolation decreased the ICER to **$Redacted**/ QALY gained* *Selecting a lognormal extrapolation increased the ICER to **$Redacted**/ QALY gained*
Cure fraction	40% of AXI patients in PFS state at 5 years will be cured, remainder will continue to follow parametrically extrapolated OS and PFS	*High, favours AXI* Decreasing the cure fraction to 20% increases the ICER to **$Redacted**/ QALY gained Removing the cure assumption increases the ICER to ***$Redacted**/QALY gained*
SMR	1.09	*Moderate, favours AXI,* Increasing the SMR to 2.7 increases the ICER to **$Redacted**/QALY gained Increasing the SMR to 3.7 increases the ICER to **$Redacted**/ QALY gained

Source: constructed during the evaluation.
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year. OS = overall survival; PFS = progression free survival; QALY = quality adjusted life-year; SOC = standard of care; SMR = standardised mortality ratio;

The results of key sensitivity analyses are in Table 18.

Table 18 Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change
Base case (BC)	**$Redacted**	**2.72**	**$Redacted**	
Discounting: 3.5% (5% in base case)	**$Redacted**	3.25	**$Redacted**	-14%
Time horizon 20 years (30 years in the base case)	**$Redacted**	*2.27*	**$Redacted**	*20%*
Utilities from Cher 2020 (BC =Papaioannou 2012)	**$Redacted**	*2.48*	**$Redacted**	*10%*
Cure point (5 years in BC)				
10 years (120 months)	**$Redacted**	*2.26*	**$Redacted**	*22%*
15 years (180 months)	**$Redacted**	*1.87*	**$Redacted**	*48%*
20 years (240 months	**$Redacted**	*1.72*	**$Redacted**	*62%*
25 years (300 months)	**$Redacted**	*1.68*	**$Redacted**	*65%*
No cure (30 years)	**$Redacted**	*1.68*	**$Redacted**	*65%*
Cure fraction (40% in BC)				
20%	**$Redacted**	*2.14*	**$Redacted**	*28%*
30%	**$Redacted**	*2.42*	**$Redacted**	*13%*
50%	**$Redacted**	*3.01*	**$Redacted**	*-10%*
SMR (1.09 in BC)[a]				
2.7	**$Redacted**	*2.29*	**$Redacted**	*19%*
3.7	**$Redacted**	*2.08*	**$Redacted**	*31%*
SOC OS extrapolation (BC = Weibull)				
Exponential	**$Redacted**	*3.21*	**$Redacted**	*-15%*
Loglogistic	**$Redacted**	*2.29*	**$Redacted**	*18%*
Lognormal	**$Redacted**	*2.07*	**$Redacted**	*30%*
Generalised gamma	**$Redacted**	*2.10*	**$Redacted**	*29%*
Gamma	**$Redacted**	*2.87*	**$Redacted**	*-5%*

Source: Constructed during the evaluation.
AXI = axicabtagene ciloleucel; BC = base case; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year OS = overall survival; PFS = progression free survival. SMR = standardised mortality ratio; SOC = standard of care
[a] by replacing 1.09 to 2.7 and 3.7 in the formulas in cells K31:1014 and X31:1014 in the 'calcs_survselections' worksheet

The Commentary considered that, overall, the model was highly sensitive to the assumptions made regarding long term survival for either treatment. This included the cure fraction assumption, cure point assumption, OS parametric extrapolation choice for SOC, and SMR for cured patients. The impact of varying any of these assumptions on the ICER suggests how uncertain the long-term benefit of AXI would be over a 30-year time horizon. Given the lack of consensus on the possibility of cure in r/r FL, it appears that the ADAR's cure assumptions favour AXI and likely underestimate the ICER.

Additionally, the benefit is estimated based on the clinical comparison of ZUMA-5 and the propensity weighted SCHOLAR-5 results. As discussed above, this analysis was an unanchored comparison which, the Commentary considered, did not necessarily account for all observed (and unobserved) differences in the compared patient cohorts. This was highly uncertain, and the model did not include functionality to test this uncertainty.

The ADAR argued that a 5% discount rate distorts results against interventions where costs are largely accrued upfront and health outcomes are accrued over a prolonged period of time. As such, the base case ICER of **$Redacted**/QALY is not considered by the applicant to be a fair and

reasonable estimation of the true cost-effectiveness of AXI as LYs and QALYs are disproportionately impacted by discounting.

As acknowledged by the ADAR, this is the standard methodology for MSAC, which ensures all health technologies are evaluated based on the same guidelines. Additionally, it was noted during the Commentary that reducing or removing discounting, in addition to unreasonably favouring AXI, would increase the relative importance of the highly uncertain long-term survival extrapolations.

14. Financial/budgetary impacts

The data sources used to estimate the financial implications in the ADAR are presented below.

Data	Source / value	Justification/ Comment
Epidemiological data inputs		
Australian population	Australian Bureau of Statistics, Population Projections, Australia 2017	Reasonable.
Age-standardised incidence rate of follicular lymphoma	5.44/100,000: Australian Institute of Health and Welfare, Cancer data in Australia	An average of the incidence rate reported in the previous 5 years with data available (2015-2019) was applied
% incident cases of staged as Grade 3b	7.5%: Barraclough 2023	Applied value of 7.5% represents the midpoint of estimate of 5%-10% outlined in the article This value was applied to calculate the proportion of follicular lymphoma cases with Grade 1-3a (i.e. the complement to the proportion with Grade 3b)
% incident cases commencing 2L treatment within 36 months	13%: Commissioned analysis of the Lymphoma and Related Diseases Registry. (LaRDR)	Applied based on the funding request for AXI being restricted to patient relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. The basis for limiting this estimate to those that commenced 2L treatment within 36 months was not explained.
% patients relapsed or refractory after 2+ lines of therapy expected to receive 3L therapy	61%: Survey of 4 Australian clinicians experienced in the management of follicular lymphoma	Applied value of 61% represents the average of the responses (range 50%-90%). This indicates a wide range of responses to the survey, which suggest large financial uncertainty.
% patients currently treated in 3L treated with AXI instead	70%: Survey of 4 Australian clinicians experienced in the management of follicular lymphoma	Applied value of 70% represents the average of the responses (range 60%-80%)
% patients not currently treated in 3L treated with AXI	36%: Survey of 4 Australian clinicians experienced in the management of follicular lymphoma	Applied value of 36% represents the average of the responses (range 20%-50%) The Commentary noted that except for stating that only patients fit enough for treatment would be treated with AXI, the ADAR did not discuss why these patients are not currently treated with 3L treatment. It is unclear if they are assumed to be unfit for any treatment or 'Watching/waiting.' Given the range of estimates from the survey, it is possible that there was lack of clarity in the survey respondents as well.
Health resource cost inputs		
NHRA costs: AXI acquisition	**$Redacted**	-
Hospital costs (Public)	NHCDC Cost weights for AR-DRG Version 11.0, 2021-21, Public Sector	The Commentary considered this was consistent with economic evaluation. Hospitalisation costs may be

Data	Source / value	Justification/ Comment
PBS costs	PBS, January 2024	underestimated given assumption of no subsequent stem cell transplant for CAR-T. PBS cost savings may be overestimated given the more costly PBS therapies (idelalisib and obinutuzuamb) may be over-represented compared to the Australian setting.
MBS costs	$118.90: Item 13950, MBS January 2024	The ADAR did not include other monitoring and management MBS that had been included in the economic evaluation. Though this was inappropriate, it would have minimal impact on costs to Government.

Source: Table 74 of MSAC 1771 ADAR+in-line commentary
2L = second line; 3L = third line; AR-DRG = Australian refined diagnosis-related groups; AXI = axicabtagene ciloleucel; MBS = Medicare Benefits Schedule; NHCDC = National Hospital Cost Data Collection; NHRA = National Health Reform Agreement; PBS = Pharmaceutical Benefits Scheme

The ADAR estimated the eligible population through the following steps:

1. Estimating prevalent pool (based on incident cases from 2021-2023) and incident cases in Year 1 (2024) based on ABS statistics and from Age-standardised incidence rate (5.44/100,000) of follicular lymphoma from the Australian Institute for Health and Welfare (AIHW).
2. Excluding stage 3b patients by adjusting for 7.5% of 3b follicular lymphoma patients based on Barraclough 2023.
3. Applying the percentage of incident cases commencing second line treatment within 36 months of diagnosis (13%) based on a commissioned analysis from the Lymphoma and Related Diseases Registry (LaRDR).
4. Applying the percentage of patients who relapse or are refractory to second line treatment based on a survey of 4 Australian clinicians (61%).
5. Applying the percentage of patients currently being treated in third line who would receive AXI instead based on a survey of 4 Australian clinicians (70%).
6. Applying the percentage of patients not receiving third line treatment who would be healthy enough to receive AXI based on a survey of 4 Australian clinicians (36%).

The financial implications resulting from the proposed listing of AXI are summarised in Table 19 and sensitivity analyses testing the uncertainty in the assumptions informed by expert opinion are summarised in Table 20.

Table 19 Net financial implications of AXI to the government

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Estimated use and cost of the proposed health technology						
Number of people who receive AXI	**Redacted**	**Redacted**	**Redacted**	**Redacted**	**Redacted**	**Redacted**
Total NHRA costs[a]	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
Change in use and cost of other health technologies						
Change in Hospital costs	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
Change in costs to the PBS	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
Net change in costs to the MBS	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
Net financial impact to Government	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**

Source: Tables 80-84, pp124-127 of the ADAR.
AXI = axicabtagene ciloleucel; MBS = Medicare Benefits Schedule; NHRA = National Health Reform Agreement; PBS = Pharmaceutical Benefits Scheme
[a] Based on requested AXI price of **$Redacted** and number of patients treated with AXI

The ADAR estimated a total cost to the NHRA of **$Redacted** in Year 1, increasing to **$Redacted** in Year 6, and a net cost to Government of **$Redacted** in Year 1, increasing to **$Redacted** in Year 6.

Overall, the Commentary considered that that key source of uncertainty included the proportion of patients relapsed or refractory to two or more lines of therapy and expected to receive third line therapy (Table 20). These estimates were based on a survey of 4 Australian clinicians and ranged from 50% to 90%.

Additionally, the Commentary considered that it was likely that the savings to PBS were overestimated due to the SOC over- weighting more costly components of obinutuzumab and idelalisib. Similarly, the role of SCT in post-CAR T follicular lymphoma remains uncertain, and the ADAR's assumption that AXI would have no subsequent SCT use likely underestimated net hospitalisation costs. Overall, however, neither PBS nor hospitalisation costs would be expected to be key drivers of the financial impact.

Table 20 Results of sensitivity analysis: overall net cost to government

Parameter	2024	2025	2026	2027	2028	2029
Base case						
Overall net cost to government	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
Third line treatment uptake						
Proportion patients relapsed or refractory after two prior lines of therapy expected to receive third line therapy						
Lower bound response: 30%	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
Upper bound response: 90%	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
Axi-cel uptake						
What proportion of patients that currently receive a third line treatment do you anticipate would be treated with AXI instead?						
Lower bound response: 60%	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
Upper bound response: 80%	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
What proportion of patients that are currently untreated would you expect to be treated with AXI?						
Lower bound response: 20%	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**
Upper bound response: 50%	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**	**$Redacted**

Source: Table 87 of MSAC 1771 ADAR+in line commentary

15. Other relevant information

AXI was considered by the National Institute for Health Care Excellence (NICE) for treatment of relapsed or refractory follicular lymphoma after 3 or more systemic treatments in adults in 2023 but was not recommended (TA894). The NICE considered that the clinical evidence was "from a small study [ZUMA-5: Full Analysis Set N=80 follicular lymphoma patients with three/more lines of prior therapy; 18-month follow-up data] that suggests that axicabtagene ciloleucel increases the amount of time people have before their condition gets worse and how long they live, but it is uncertain by how much". [18]

AXI was considered and recommended by The Canadian Agency for Drugs and Technologies in Health (CADTH) pCODR Expert Review Committee (pERC) for reimbursement for the treatment of adult patients with relapsed or refractory (r/r) grade 1, 2, or 3a follicular lymphoma (FL) after 2 or more lines of systemic therapy (which must have included an anti-CD20 monoclonal antibody combined with an alkylating agent). CADTH considered that the phase II, multi-centre, single-arm, open-label study (ZUMA-5; N = 127) demonstrated that axicabtagene ciloleucel resulted in benefits in the primary endpoint of response rates for adult patients with r/r FL after 2 or more lines of systemic therapy. This recommendation was contingent on conditions listed in Table 1 of CADTH's Reimbursement Recommendation for AXI, including a reduction in price. The submitted price was $485,021 per 1-time infusion. CADTH noted a price reduction of 82% to 95% would be required for axicabtagene ciloleucel to be cost-effective at a willingness -to-pay (WTP) threshold of $50,000 per QALY gained, relative to current standards of care. CADTH also noted that the magnitude of survival benefit is uncertain given the limitations with the comparative evidence, and given the degree of remaining uncertainty, noted that greater price reductions may be required.[19]

[18] https://www.nice.org.uk/guidance/ta894/chapter/1-Recommendations
[19] https://www.cadth.ca/sites/default/files/DRR/2023/

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The comparative evidence was informed by an indirect comparison of axicabtagene ciloleucel (AXI) (informed by the ZUMA-5 study, a single-arm, open label study) and the nominated comparator, standard of care represented by a 'basket' of treatments that are funded via the Pharmaceutical Benefits Scheme (informed by the SCHOLAR-5 study, an international retrospective cohort study).
- The clinical evidence is of low quality due to the high risk of bias in both the ZUMA-5 and SCHOLAR-5 studies, along with the indirect nature of the comparison with transitivity, methodological and transparency issues, plus the use of a historical and retrospective comparator.
- Although the indirect comparison suggested that AXI is likely to have superior effectiveness and inferior safety compared to the comparator, the magnitude of benefit is highly uncertain,

Economic issues:

- The low overall quality of evidence and the approaches to estimating the comparative benefit created uncertainty in the economic analysis. While the claim of superior effectiveness may be reasonable in light of the available data, the magnitude of the incremental benefit is uncertain which translates into the uncertainty of the incremental cost-effectiveness ratio (ICER).
- A wide range of incremental benefits can be generated from pairing AXI and SOC arm extrapolations that are inherently uncertain.
- The cure assumption remains speculative as no compelling case was made based on data or evidence. The specific parameters for the model implementation of cure benefit (cure point and proportion affected) and the subsequent survival benefit (standardised mortality ratio, SMR) are uncertain. Clinical data are not mature enough to determine whether a proportion of the patients are cured. ESC considered that, in order to better align with the available evidence, the model could remove the cure assumption from the base case and focus on the gains in progression free survival (PFS). This would also effectively remove the uncertainty from the SMR adjustment, which ESC considered to be optimistic in the base case.
- Other assumptions that form the basis for modelling (no stem cell transplant [SCT] or further treatment in the intervention arm, no retreatment) are uncertain and may favour AXI.

Financial issues:

- The financial impact is uncertain, although there is limited variation across the input parameters tested in one-way sensitivity analyses.

ESC discussion

ESC noted that this application from Gilead Sciences sought public funding under the National Health Reform Agreement (NHRA) for axicabtagene ciloleucel (AXI, also known as YESCARTA®, a chimeric antigen receptor T-cell [CAR-T] therapy) in the third-line (3L) setting for patients with relapsed or refractory (r/r) follicular lymphoma (FL).

ESC noted that AXI was first included on the Australian Register of Therapeutic Goods (ARTG) on 11 February 2020 for r/r large B-cell lymphoma (LBCL; ARTG ID 329770). The indication was extended to include patients with r/r FL after two or more lines of systemic therapy on 12 December 2022 (ARTG ID 400895).

ESC noted that AXI is currently funded for the treatment of patients with r/r CD19-positive diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL) in the 3L setting under NHRA Commonwealth and state shared funding arrangements (MSAC application 1587). A re-application requesting public funding under the NHRA of AXI for the treatment of r/r large B-cell lymphoma (LBCL) in the second-line (2L) setting was considered and supported by MSAC at the April 2024 meeting (MSAC application 1722.1). ESC noted that the applicant was willing to discuss details of a pay-for-performance (PfP) and risk share arrangement (RSA) for AXI for the treatment of r/r FL in the 3L setting, consistent with the current funding for AXI in DLBCL.

ESC noted and welcomed consultation input from 2 consumer organisations and 3 individuals (all of whom were medical specialists). ESC noted that all feedback received was supportive of the application. ESC noted that Rare Cancers Australia supported publicly funding AXI for treating patients with FL, and that these patients considered it important to have access to this treatment. Patients believed that the benefits of AXI outweigh the risks, and they expected the treatment to improve quality of life and the ability to function. The patients considered that AXI compares favourably with other treatments with associated toxicities and side effects. ESC noted that one patient was given months to live but a year later is currently working and enjoying family life, and the patient attributed this to AXI treatment. Rare Cancers Australia also noted that while hospitalisation is required to receive AXI, which is time consuming, patients are willing to undergo the treatment for the benefit of time and quality of life achieved afterwards. Rare Cancers Australia therefore supported expediting the drug for earlier access, which would allow more patients to experience these benefits, leading to improved overall survival rates and reducing the burden and costs to the healthcare system. ESC noted that the not-for-profit Australasian Leukaemia and Lymphoma Group (ALLG) for clinicians stated that FL is currently incurable, but noted that AXI has a high response rate and a safety profile at least comparable to other similar treatments. The ALLG also noted the substantial demand on resources associated with AXI. ESC noted that ALLG stated that allogenic stem cell transplant (SCT) does not induce remissions, and is associated with significant risks. In contrast, it considered that CAR-T cell therapy can induce durable remissions in FL patients and improve quality of life, relieving the burden on families and carers. The ALLG considered that currently there is sufficient capacity in treatment centres across the states to deliver this therapy. ESC noted the feedback did not provide a clear consensus on the timeframe for when a patient would be considered to be 'cured', with suggestions ranging from 5 to 10 years without relapse, given the slow course of disease.

ESC also noted the input from the states and territories acknowledged the importance of therapies in this setting, but outlined concerns regarding the costs associated with providing AXI and the uncertainty of the clinical evidence. ESC also noted that state and territory feedback considered it important to complete a full review of the clinical benefits and cost effectiveness of AXI use in the 3L setting for r/r DLBCL prior to further public funding of AXI.

ESC noted the nominated comparator, standard of care (SOC), was represented by a basket of therapies that are funded under the Pharmaceutical Benefits Scheme (PBS) including anti-CD20 monotherapy (usually rituximab), anti-CD20 therapy in combination with chemotherapy, chemotherapy alone and PI3Kδ inhibitor. ESC noted there are no clear clinical guidelines or uniformly recommended 3L treatments for patients with r/r FL and considered that the proposed comparator was appropriate. ESC also noted that the applicant had commissioned an analysis of relevant data from the Lymphoma and Related Disease Registry (LaRDR); however, only 13 patients had commenced 3L therapy and data were incomplete. Due to these limitations, ESC did not consider this analysis to be a reliable or informative representation of FL disease in Australia.

ESC noted that, consistent with current practice, the proposed technology would be delivered in select tertiary hospital treatment centres that specialise in the delivery of CAR T-cell therapy. ESC noted that the proposed clinical criteria are in line with other CAR-T cell therapies and international guidelines. However, ESC noted that the proposed clinical criteria were not fully consistent with the eligibility criteria in the ZUMA-5 study and advised that the following criteria should be added to the proposed restriction:

- Prior therapy with an anti-CD20 monoclonal antibody combined with an alkylating agent
- No known history or suspicion of central nervous system (CNS) involvement by lymphoma

ESC considered that the remaining clinical criteria used in the key study were relevant for trial purposes but did not need to be included in the proposed clinical criteria (that is, at least one measurable lesion according to the Lugano Response Criteria for Malignant Lymphoma; elapsed time between any prior systemic therapy (except for systemic inhibitory/stimulatory immune checkpoint therapy) and enrolment; absolute neutrophil count ≥ 1000/μL; platelet count ≥ 75,000/μL; absolute lymphocyte count ≥ 100/μL; and no clinically significant pleural effusion).

ESC noted the proposed clinical management algorithm and considered it was consistent with Australian clinical practice. ESC noted FL is an indolent form of lymphoma and as such patients may not undergo immediate treatment if relapse occurs, rather patients are only treated if treatment criteria are met for symptomatic disease and/or high tumour burden. ESC considered the population proposed for AXI should be restricted to patients who meet the requirement for treatment (i.e. symptomatic disease and/or high tumour burden following relapse). ESC advised that the proposed population should exclude patients who have central nervous system involvement (consistent with the ZUMA-5 study), and that anti-CD20 monotherapy should not be counted as a prior line of therapy. ESC advised that if anti-CD20 monotherapy was counted as a prior therapy this would substantially increase the eligible population.

ESC noted the pivotal clinical study (ZUMA-5) was a single-arm, multicentre, phase 2 study involving 127 patients with indolent FL who had relapsed or refractory disease after two or more lines of therapy. Clinical endpoints were measured at 12 months and 48 months, and efficacy was compared to the SCHOLAR-5 study (a retrospective cohort study using SOC) at 18 months and 48 months. ESC noted that the primary end point of overall response rate, defined as complete response and partial response according to Lugano Response Criteria and measured using a positron emission tomography (PET) scan was standard. However, ESC noted that in SCHOLAR- 5, response was sometimes measured using computed tomography (CT) scans only and considered that CT scans were less sensitive in detecting relapsed or refractory disease. For the primary analysis (18-month follow-up), the overall response rate was 94% in patients who received AXI, compared with 50% in patients who received SOC. For the updated analysis (48-month follow-up), the overall response rate was 94% (AXI arm) compared with 54% (SOC arm). Kaplan–Meier curves also showed substantial differences in progression-free survival (PFS) and overall survival (OS). However, ESC noted that the natural course of r/r FL is slow, so survival is expected to be longer than in other conditions for which AXI is indicated.

ESC also noted that results from a real-world cohort of patients treated with AXI at the Centre for International Blood and Marrow Transplant Research (and compared with a subgroup of patients from the SCHOLAR-5 study) was provided as supportive evidence. The results of this indirect analysis also suggested that AXI was superior to SOC. However, ESC noted that it was unclear which patients from SCHOLAR-5 were included or which SOC treatments they received. ESC also noted that other issues with the comparison included: use of a historical control cohort, data immaturity, unclear censoring and transitivity concerns.

Overall, ESC agreed with the Commentary that the clinical claim that AXI had superior effectiveness compared to SOC for the treatment of r/r FL in the 3L setting was reasonable but

highly uncertain due to low-quality evidence from the single-arm open label study, indirect comparisons, and the historical and retrospective comparator.

Regarding the safety of AXI, ESC noted the ZUMA-5 study data (48-month follow-up) indicated adverse events were similar to those seen following AXI treatment for other indications, and similar to other CAR-T therapies. ESC noted that in the ZUMA-5 study, 99% of patients had a treatment emergent adverse event (TEAE), where 86% of patients had a worst grade TEAE of Grade 3 or higher, and 52% had at least one serious TEAE. ESC noted that the most frequently reported adverse events in patients treated with AXI were pyrexia (80% of patients), hypotension (38%), headache (33%), tremor (27%), and neutropenia (27%). ESC noted that the following adverse events attributable to AXI use were also reported: cytokine release syndrome (78% of patients), any neurological event (56%), cytopenia (73%), infection (56%), and hypogammaglobulinaemia (20%). ESC noted that comparative safety of AXI versus SOC was based on naive comparisons of various clinical studies with a high risk of bias, and the limited and low-quality data resulted in uncertainty. Overall, ESC agreed with the Commentary that the claim of inferior safety of AXI compared with SOC was likely reasonable.

ESC noted the economic model used a cost-utility analysis with three health states (progression free survival, progressed disease with on and off treatment components, and death) and a 30-year time horizon. ESC noted that the survival curves applied in the base case analysis used the 48-month data from ZUMA-5, extrapolated this to 5 years, and then applied a cure assumption of 40% to the intervention arm, with no cure assumption in the comparator arm. ESC also noted the wide range of values considered for health-related quality of life, which may have been overestimated particularly regarding the progression-free state; however, sensitivity analyses performed by the Commentary showed this had a moderate effect (+10%) on the incremental cost-effectiveness ratio (ICER). Regarding the costs, ESC noted the concerns raised in the Commentary (including that a second infusion was not included, that SCT was included for SOC but not for AXI, and other minor issues), but ESC considered that the costs in the model were generally appropriate, and these issues did not appear to have a major impact on the ICER as the main driver was the cost of AXI treatment.

ESC noted the substantial implications of the cure assumption on incremental benefits in the model. ESC noted the ADAR stated the cure assumption was based on OS and PFS at 48 months, clinical plausibility based on data from other AXI indications, and previous MSAC considerations of CAR-T therapies. ESC considered that a 40% cure rate after 5 years of PFS was not well supported by the evidence in the ADAR, particularly given the slow natural course of the disease. ESC considered that there needs to be a long period of remission for FL, at least 10 years given some patients relapse at 10 years, before considering a patient with r/r FL may be cured. As such, ESC considered the 48-month follow-up data from the ZUMA-5 study was too immature to support a curative assumption of 40% at 5 years. ESC also noted the applicant's assertion that MSAC had previously accepted a cure rate in other CAR-T applications that had data with fewer patients and shorter follow-up. However, ESC noted that MSAC had in fact consistently expressed concern regarding the uncertainty of modelling cure and had not explicitly accepted the ICERs as cost-effective. Further, regarding the mixture cure model presented for MSAC application 1722.1, MSAC expressly stated that MSAC had not concluded that treatment with AXI for R/R LBCL in 2L setting provided a 'functional cure' for any proportion of patients. Further, ESC considered that the approach to ESC and MSAC deliberations in relation to these therapies should evolve as the data evolve. ESC considered the assumption that cured patients would revert to the general population mortality with a standardised mortality ratio (SMR) of 1.09 applied was highly optimistic. ESC noted that the alternative SMR values (2.7 and 3.7 from a retrospective study in FL after auto-HSCT using patient data from national transplant registry in Japan) tested by the Commentary had a considerable impact on the ICER. ESC considered the sensitivity analyses with these alternative SMR were informative but also may be overly conservative. ESC considered

the appropriate SMR value was somewhere between the ADAR's base case and the Commentary sensitivity analyses.

Given that the uncertainty regarding the cure assumption and SMR, which created significant uncertainty in the model, ESC considered that cure assumption should be removed from the base case model and instead focus on the PFS gains. This would also remove the uncertainty regarding the SMR applied in the base case.

ESC noted the base case ICER of **$Redacted** per quality-adjusted life year (QALY) gained, using the proposed price of AXI of **$Redacted**. However, ESC noted that if a single payment of **$Redacted** (which corresponded to an ICER of **$Redacted** in application 1722.1) for AXI was used as supported by MSAC for r/r LBCL, the ICER would be **$Redacted**/QALY. If a price for AXI of **$Redacted** (which corresponded to the PfP and RSA for application 1722.1), the ICER would be **$Redacted**/QALY.

ESC noted the sensitivity analyses, which showed that the ICER was sensitive to the time horizon, cure point, cure fraction, SMR and extrapolation method. ESC queried whether a more conservative base case could be established by choosing values that lie between the ADAR's base case and the Commentary sensitivity analyses, but concluded that this would still involve a high degree of uncertainty, so would likely not be helpful for MSAC decision-making. ESC agreed with the Commentary that a discounting rate of 5% was appropriate to use.

ESC noted the ADAR used an epidemiological approach for the financial analysis. ESC noted the net financial impact to government was estimated at above **$Redacted** per year. ESC considered that the cost savings may have been overestimated. ESC noted a number of parameters that informed the utilisation estimates were assumptions based on a survey of four clinicians that displayed a high variation in responses. ESC noted that the assumptions informed by expert opinion were tested in sensitivity analyses, showing that these assumptions created uncertainty in the expected number of treated patients but did not have a large effect on the estimated financial impact. Overall ESC considered that the estimated financial impact to government was uncertain.

ESC noted MSAC's recent advice regarding a PfP and RSA for AXI for treatment of r/r LBCL in the 2L setting and considered that a PfP and RSA to mitigate uncertainties (in the clinical evidence, cost-effectiveness, utilisation and financial impact) would be also appropriate for this application. However, ESC considered that for each application, the unique evidence and acceptable revised base case ICER should be taken into account when establishing the PfP and RSA. For AXI as a treatment for r/r FL in the 3L setting, ESC considered that the proposed price was not justified based on the ICER and the uncertainty in the economic model, but that it might be difficult to address this uncertainty using a price reduction alone, given the long-term and curative claims. ESC considered that a 12-month complete response outcome might be sufficient to address the uncertainty relating to successful infusion, but that a longer-term mechanism may be required to address the uncertainty of OS and claimed curative benefits. ESC considered that an annual financial cap based on patient numbers would be reasonable to manage the uncertainty in the utilisation and potential financial impact.

ESC noted that AXI for FL has been registered by the United States Food and Drug Administration (FDA) for treatment after two or more lines of systemic therapy[20]. AXI has also been authorised for use by the European Medicines Agency in patients with r/r FL after three or more lines of

[20] FDA Resources for Information: Approved Drugs (2021) FDA grants accelerated approval to axicabtagene ciloleucel for relapsed or refractory follicular lymphoma - https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-axicabtagene-ciloleucel-relapsed-or-refractory-follicular-lymphoma

systemic therapy[21]. Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health [CADTH]) recommended reimbursement for AXI for the treatment of r/r FL after two or more lines of systemic therapy but that a price reduction of 82% to 95% would be required AXI for to be cost-effective at a WTP threshold of $50,000 per QALY gained[22]. However, the National Institute for Health and Care Excellence (NICE) did not recommend funding AXI for treatment of r/r FL after 3 or more systemic treatments[23].

ESC considered that, if AXI is supported, a review should be required as part of the RSA. A systematic approach to devising new, fit-for-purpose payment mechanisms may be necessary for therapies that have a high cost and curative claim. This should define the minimum viable data required to support performance payments, as well as for other purposes (such as clinical and health services research, and surveillance of the condition). ESC considered that registry data collected from patients should also specify prior therapies (such as prior bendamustine use) to allow future analysis.

ESC noted that bispecific antibody therapy was on the horizon for the treatment of FL. Bispecific antibody therapy is available in other countries (but not yet in Australia) and real-world results appeared to be comparable to CAR-T therapy, with similar adverse events. However, ESC noted that the choice and position of CAR-T versus bispecific antibodies in the clinical management of patients was unclear.

17. Applicant comments on MSAC's Public Summary Document

While Gilead Sciences is disappointed with the outcome, we are pleased that MSAC acknowledged that axi-cel is likely superior to SOC in terms of effectiveness, that there is a clinical need for new therapies for this patient population, and that all public consultation feedback received from both the clinical and patient community was supportive of the application, noting the anticipated improvement in survival and quality of life for patients.

Gilead Sciences would like to sincerely thank the clinicians, professional organisations and patient organisations who took the time to provide input and comment on this application; we will continue to work with MSAC to achieve public funding for axi-cel for r/r FL and bring this important treatment to patients in a timely manner.

18. Further information on MSAC

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

[21] EMA Medicines (2024) Yescarta - https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta

[22] CADTH Reimbursement Recommendation: Axicabtagene ciloleucel (Yerscarta). Canadian Journal of Health Technologies. November 2023, 3(11) - https://www.cadth.ca/axicabtagene-ciloleucel-0

[23] NICE Technical appraisal guidance TA894 (2023) Axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma - https://www.nice.org.uk/guidance/ta894