



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1587 – Axicabtagene ciloleucel (CAR-T therapy) for the treatment of refractory or relapsed CD19-positive lymphoma

Applicant: Gilead Sciences Pty Ltd

Date of MSAC consideration: MSAC out-of-session, 16 January 2020
MSAC 77th Meeting, 28-29 November 2019

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

1. Purpose of application

An application requesting public funding of axicabtagene ciloleucel, henceforth referred to as AXI, for the treatment of relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL) including DLBCL not otherwise specified (NOS) and transformed follicular lymphoma (TFL), primary mediastinal B-cell lymphoma (PMBCL) and high grade B-cell lymphoma (HGBCL) was received from Gilead Sciences Pty Ltd.

AXI, and the broader health technology (CAR T-cell therapy), are not eligible for funding through the MBS or PBS.

Tisagenlecleucel (TIS), another CAR-T cell therapy, is currently being jointly funded by the Commonwealth and the States under the National Health Reform Arrangement (NHRA) for acute lymphoblastic leukaemia in children and young adults.

2. MSAC's advice to the Minister

January 2020 MSAC consideration

Following the MSAC's November 2019 decision to defer providing advice to the Minister for Health on the public funding of AXI for DLBCL, TFL and PMBCL, the Therapeutics Goods Administration (TGA) Clinical Evaluation Report and Delegate's Summary became available. The TGA delegate has indicated (s)he is minded to approve AXI for registration for the same indications for which public funding has been sought.

On receipt of this advice from the TGA, the MSAC confirmed its support for the public funding of AXI out-of-session on 16 January 2020, without making any changes to the other parts of its advice to the Minister from November 2019.

Consumer summary

In November 2019 and January 2020, MSAC considered an application from Gilead Sciences Pty Ltd for public funding of axicabtagene ciloleucel (AXI, Yescarta®) – a type of CAR-T cell therapy (chimeric antigen receptor T-cell therapy). The application requested public funding of AXI for adult patients with ‘confirmed relapsed or refractory diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL)’.

CAR-T cell therapies such as AXI, are used when patients with some types of cancer, such as lymphoma or leukaemia, don’t respond to (refractory), or relapse after, other types of treatment, such as chemotherapy. CAR-T cell therapy involves taking some of the patient’s own blood, and sending it to a laboratory where the T cells are extracted and altered so that they can attack cancer cells. The patient’s changed T cells are infused back into them to target and kill the cancer cells in the patient’s body.

MSAC held a stakeholder consultation meeting on CAR-T cell therapy for B-cell lymphoma (12 November 2019; minutes for this meeting are at <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1587-public>

MSAC’s advice to the Commonwealth Minister for Health

In January 2020, MSAC advised the Minister it supported the public funding for AXI for patients with CD19-positive Diffuse Large B Cell Lymphoma (DLBCL), Primary Mediastinal B Cell Lymphoma (PMBCL) and Transformed Follicular Lymphoma (TFL) as described in the eligibility criteria in Table 1 (page 5). MSAC agreed that current evidence demonstrates that AXI gives some patients, who have exhausted all other treatments, a new chance at possibly achieving remission.

MSAC agreed that AXI should only be offered to patients who are considered fit enough, as the therapy can have very severe side effects in some people. MSAC took advice from clinicians who treat patients with lymphoma and who have used AXI in deciding what the eligibility criteria for treatment with AXI should be.

MSAC advised that AXI is a very expensive therapy. MSAC considered a number of measures need to be put in place to manage the use of public funds for AXI. Many of these measures need to be agreed between the applicant, and the Commonwealth and/or the States.

MSAC had deferred its advice in November 2019 to allow the Therapeutic Goods Administration (TGA) to complete its assessment of whether AXI is suitable for marketing in Australia. The TGA regulates therapeutic goods including prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products. Almost any product for which therapeutic claims are made must be entered in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia (tga.gov.au). As the TGA has now completed its assessment, MSAC could consider this matter again in January 2020.

November 2019 MSAC consideration

MSAC deferred making a recommendation on the public funding of AXI for DLBCL, TFL and PMBCL pending a regulatory decision by the Therapeutic Goods Administration (TGA).

However, MSAC advised the Minister that, subject to the TGA making a decision in favour of approving AXI for inclusion on the Australian Register of Therapeutic Goods, MSAC was minded to support the public funding of AXI at an average price per patient that is 40-45% lower than the price proposed by the applicant **redacted**, and if the following measures were implemented to contain the risks associated with public funding:

- treatment must be delivered by a haematologist working in a multi-disciplinary team specialising in the provision of CAR-T cell therapy;
- treatment must be delivered in a tertiary public hospital with appropriate credentials;
- governance and prescribing rules to ensure treatment is directed to patients most likely to benefit;
- **Redacted**;
- **Redacted**;
- **Redacted**;
- **Redacted**;
- no payment for AXI for an unsuccessful infusion (i.e. an infusion of product that does not meet the TGA agreed specification for minimum cell numbers);
- no payment for AXI if a patient is apheresed but does not receive the infusion of engineered lymphocytes;
- **Redacted**;
- a limit to one successful CAR-T infusion per lifetime for r/r DLBCL, including DLBCL NOS and TFL, PMBCL and HGBCL;
- **Redacted**;
- **Redacted**;
- data on the use of AXI for B cell lymphoma's in Australia to be recorded by the Australian Bone Marrow Transplant Recipient Registry (ABMTRR), with the cost of data collection met by the applicant; and
- An initial progress review at Year 1 to assess appropriateness of patient eligibility criteria and patient numbers, with a full review of clinical effectiveness, cost-effectiveness and budget impact, based on all data and information available at the time, to be conducted by the MSAC no later than 2 years post the commencement of public subsidy of CAR-T cell therapy for DLBCL (note: Gilead will provide a submission to initiate this review). **Redacted** will be renegotiated as part of this review.

MSAC also advised the Minister consider rapidly putting in place further risk mitigation strategies, including, but not limited to utilising the competition between different CAR-T cell therapies to achieve the most efficient price for this service; and limiting the number of designated treatment centres to balance the need to provide access to patients from all parts of Australia whilst also ensuring availability of sufficient expertise and efficient use of hospital resources.

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

On consideration of the issues raised in the Evaluation Sub-Committee (ESC) advice regarding the applicant's economic model, particularly the use of different structures in the two model arms, and the inflexibility of the model to reasonable sensitivity analyses, the MSAC considered it was difficult to use the model as a basis for a subsidy decision.

MSAC noted the advice provided at the stakeholder meeting by clinicians with experience in treating lymphoma and CAR-T cell therapy was supportive of eligibility criteria that are consistent with those used in the ZUMA-1 clinical trial of AXI, albeit with some

modification. Based on that advice in the context of the available evidence and the treatment algorithm presented by the applicant, MSAC advised that treatment with AXI is suitable for funding in patients meeting the following criteria:

Table 1: Eligibility criteria for AXI

Indication:	Relapsed or refractory CD19-positive: <ul style="list-style-type: none"> • diffuse large B-cell lymphoma (DLBCL); • primary mediastinal large B-cell lymphoma (PMBCL); • transformed follicular lymphoma (TFL)
Treatment criteria:	Patient must be treated in a tertiary public hospital with appropriate credentials AND Patient must be treated by a haematologist working in a multi-disciplinary team specialising in the provision of CAR-T cell therapy AND Patient must not have uncontrolled infection, including uncontrolled HIV or active hepatitis B or C infection AND Patient must not have primary CNS lymphoma AND Patient must not have uncontrolled secondary CNS disease, or secondary CNS disease anticipated to be uncontrolled at the time of lymphocyte infusion.
Clinical criteria:	<p>FOR DLBCL and PMBCL: The condition must have</p> <ul style="list-style-type: none"> (i) relapsed after autologous stem cell transplantation; or (ii) have relapsed after, or be refractory to, at least two prior systemic therapies <p>FOR TFL: The condition must have relapsed after, or be refractory to, at least two prior systemic therapies administered after disease transformation.</p> <p>FOR ALL INDICATIONS: Patient must have a WHO performance status of 0 or 1 AND Patient must have sufficient organ function, including:</p> <ul style="list-style-type: none"> i. Renal function: Creatinine clearance >40mL/min, serum ALT/AST <5 x ULN and total bilirubin <2 x ULN ii. Cardiac function: absence of symptomatic heart failure (i.e. NYHA grade <2), cardiac left ventricular ejection fraction >= 40%, or supplementary functional tests and cardiology assessment demonstrating adequate cardiopulmonary reserve. iii. Pulmonary function: Baseline peripheral oxygen saturation >91% on room air, in the absence of anaemia <p>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.</p>

MSAC further advised that appropriate governance measures be put in place to ensure that these treatment criteria are adhered to. Such measures could comprise of compliance checks using the data reported to the registry, and random auditing of primary records at the treatment site.

MSAC noted the data available on the safety and effectiveness of AXI in the indications requested for subsidy were primarily derived from the ZUMA-1 clinical trial. This was a single arm open label study in 101 patients (modified intent to treat data set (mITT)) with refractory DLBCL, TFL or PMBCL or relapsed after autologous stem cell transplant.

MSAC noted the applicant sourced data on the safety and effectiveness of a salvage chemotherapy regimen (SCR), which is the current standard of care, from the SCHOLAR-1 study. This was a retrospective, patient-level pooled analysis funded by the applicant to evaluate survival and response rates in (r/r) DLBCL, TFL and PMBCL. Data were included for 636 patients.

MSAC noted the applicant also provided data on the near market comparator, TIS, from the JULIET study.

MSAC considered that, although the ZUMA-1 trial had a high risk of bias and the propensity matched comparison between ZUMA-1 (phase 2 mITT population, n = 101) and SCHOLAR-1 (n = 412) does not completely overcome that issue, it was satisfied that treatment with AXI is superior to SCR in terms of effectiveness and likely inferior in terms of safety. However, MSAC remained concerned that the nature of the comparison meant the extent of benefit of AXI over SCR cannot be accurately quantified. Furthermore, although MSAC was reassured by the headline 3-year data from the ZUMA-1 trial included in the pre-MSAC response (overall survival at 1 year, 2 years and 3 years: 60%, 51% and 47% respectively), MSAC continued to have some concerns about the durability of benefit of AXI.

MSAC noted the applicant claimed the ZUMA-1 and JULIET clinical trials were sufficiently similar to support a comparison between the two CAR-T cell therapies AXI and TIS. MSAC considered it is difficult to assess whether AXI is non-inferior in terms of effectiveness compared to TIS because a formal direct or in-direct comparison of the two CAR-T cell therapies is not possible, as both therapies have only been studied in single arm trials. Additionally, there is no clear basis to determine a minimal clinically important difference in this setting. Overall, although numerically the results for AXI appear slightly better than those for TIS to date, having regard to the issues described above, MSAC concluded that, on balance, AXI is at least clinically non-inferior to TIS.

MSAC noted a difference between the JULIET and ZUMA-1 trials was that the former allowed bridging chemotherapy between cell collection and cell infusion and the latter did not. The MSAC noted the advice it had received from clinicians was that the use of bridging therapy was a clinical practice decision and should not be part of the descriptor.

MSAC agreed with its ESC that the economic model presented by the applicant was not informative for decision-making. MSAC considered the structure of the model of primary concern, noting that a three-state partition survival model was applied to the SCR arm and a four-state Markov model was applied to the AXI arm, without adequate justification for the different approaches. The use of the four state structure for AXI appeared to drive the much larger QALY gain estimated for AXI in the applicant's economic model than was seen in the TIS economic model presented to MSAC in August 2019 (see MSAC PSD 1519.1 August 2019). In contrast, the estimated QALY gains from the SCR arms of both models are similar (1.45 in AXI model versus 1.77 in TIS model), and both models used the same study data to populate the SCR arm.

MSAC was also very concerned that the incremental cost-effectiveness ratio (ICER) was not flexible to a range of sensitivity analysis suggesting a lack of model plausibility. For instance, of the 48 sensitivity analyses presented in the critique of the application, only 13 led to a change in the ICER of greater than \$redacted, or circa 10% of the base case ICER (upwards or downwards). In this context, MSAC noted the applicant had attempted to address the ESC's concerns that the model underestimated costs by not including any further costs for the "cured" population (e.g. monitoring, relapse associated costs, other health care costs related to their DLBCL treatment) by doubling the cost inputs applied to the cured population from

\$redacted to **\$redacted** per month. However, this change in inputs only led to a 2% change in the ICER.

The MSAC noted the ESC could not advise on an acceptable alternative base-case ICER.

Overall, MSAC considered that although the application itself did not provide a suitable basis for making a funding recommendation (because a reliable ICER could not be calculated), as described above, the Committee had sufficient information before it to be satisfied that AXI was at least clinically non-inferior to TIS. Additionally, having considered the totality of information available to it, MSAC agreed the estimated incremental QALY gain of 1.225 for TIS (PSD 1519.1 August 2019 MSAC) provided an alternative and more plausible estimate of the extent of benefit of treatment with CAR-T cell therapy for the specified B cell lymphomas.

MSAC noted that, applying this estimate of QALY gain, a reduction in the price of AXI of 40-45% would be required to achieve an ICER similar to that estimated in the applicant's pre-ESC economic model. MSAC agreed that at this reduced price, treatment with AXI would be acceptably cost effective if the **redacted** was enhanced by:

- **Redacted;**
- **Redacted;**
- **Redacted;**
- **Redacted;**
- having no payment for AXI for an unsuccessful infusion (i.e. an infusion of product that does not meet TGA agreed specification for minimum T-cell count);
- having no payment for AXI if a patient is apheresed but does not receive the infusion of engineered lymphocytes;
- **Redacted;** and
- a limit to one successful CAR-T infusion per lifetime for r/r DLBCL, including DLBCL NOS and TFL, PMBCL and HGBCL.

MSAC further advised the **redacted** should not exceed the **redacted** that is currently paid for TIS for the paediatric acute lymphoblastic leukaemia (pALL) indication, and should preferably be somewhat lower. The B cell lymphoma patient cohort is considerably older than the pALL population and therefore cannot achieve the same lifetime gains from treatment as the pALL cohort.

MSAC noted the applicant estimated the total number of patients who will be treated with AXI, including patients with PMBCL, ranged from **redacted** in year 1 to **redacted** in year 6, with the 6-year total being **redacted** patients (see also Table 16). MSAC noted the number of patients the applicant estimated would be treated over the first 6 years of public funding was around **redacted**% higher than estimated by MSAC in August 2019 (see table 17). However, the MSAC August 2019 estimates did not account for patients with PMBCL who comprise 3- 4% of the Non Hodgkin lymphoma population.

MSAC also noted the applicant's financial estimates do not take account of patients who are prepared for infusion but are not successfully infused, noting that 91% of patients enrolled in the ZUMA-1 trial were successfully infused (100% of enrolled patients were apheresed).

MSAC considered the applicant has modestly overestimated the number of patients who will be eligible for treatment with AXI. MSAC considered its August estimates in its consideration of TIS for DLBCL, increased by 4% to account for patients with PMBCL, the most suitable estimates for progressing public funding.

MSAC was concerned the applicant's financial estimates inappropriately claimed an offset equivalent to the estimated cost of a salvage chemotherapy regimen +/- autologous stem cell transplant (total \$**redacted**) for every patient treated with AXI. MSAC considered this approach did not account for patients whose disease progresses soon after receiving AXI and who then go on to receive salvage chemotherapy. MSAC noted approximately 40% of patients had progressed 6 months after receiving AXI, increasing to approximately 55% by 12 months, and on this basis considered it appropriate for an offset equivalent to the cost of salvage chemotherapy to be applied to half of patients successfully infused with AXI.

MSAC noted there is a risk that CAR-T cell therapy will be used for patients in whom treatment has not been demonstrated to be effective or cost-effective, including patients who are not eligible for treatment under the recommended prescribing rules and patients with other cancers.

MSAC recommended that any risk sharing arrangements put in place for AXI should include financial caps. MSAC considered it appropriate that the **redacted**.

MSAC further considered it appropriate for the Commonwealth to **redacted**.

MSAC requested it be provided with an update on the number of patients referred, screened, prepared and infused with AXI one year after the commencement of public funding of CAR-T cell therapy for the above-specified B cell lymphomas. MSAC considered it may be appropriate to revise the patient number estimates and financial caps for the second year if there is a large divergence from the estimated numbers, upwards or downwards, in year 1.

MSAC indicated it wished to conduct a full review of clinical effectiveness, cost-effectiveness and budget impact of AXI no later than 2 years post the commencement of public subsidy of CAR-T cell therapy for the above-specified B cell lymphomas (note: Gilead will provide a submission to initiate this review). MSAC indicated its intention to re-examine **redacted** as part of this review.

MSAC considered that, as with TIS for pALL, data on the use of AXI for B cell lymphomas in Australia should be recorded by the Australian Bone Marrow Transplant Recipient Registry, with the cost of data collection met by the applicant. This would ensure a single Australia source of data for all CAR-T therapies in all indications and from all treatment centres. The data collected in the registry should align with international data collections to ensure comparability and access and thus contribute to global knowledge. The registry should include the following minimum data:

- the date of first referral, postcode of patient and referring physician;
- date of apheresis and infusion for treated patients;
- number of patients referred but not accepted, for treatment with CAR-T cell therapy, including the reason;
- patient-reported outcomes;
- lymphoma-free survival (complete and partial metabolic response);
- complications, use of high cost medicines, late-onset adverse events and adverse events requiring hospitalisation and adverse events including those requiring ICU admission;
- use and duration of immunoglobulin;
- rate of reinfusion with any CAR-T therapy (noting the cost of reinfusion of such therapy will not be funded under the proposed arrangement);
- indication for use of CAR-T – for example bridge to stem cell transplant, following transplant; and

- results for patients infused with non-optimal cell numbers (noting that for the purposes of subsidy, this is considered an unsuccessful infusion).

Finally, MSAC noted the considerable number of clinical trials being conducted with CAR-T cell therapies across a range of indications and the very high associated funding implications. MSAC advised the Minister consider rapidly putting in place further risk mitigation strategies, including, but not limited to utilising the competition between different CAR-T cell therapies to achieve the most efficient price for this service across all indications; and limiting the number of designated treatment centres to balance the need to provide access to patients from all parts of Australia whilst also ensuring availability of sufficient expertise and efficient use of hospital resources.

4. Background

This is the first application for AXI for r/r DLBCL, including DLBCL NOS and TFL, PMBCL and HGBCL. MSAC has not previously considered AXI for any use.

MSAC has considered another CAR-T therapy, tisagenlecleucel (TIS) for adult patients with confirmed r/r DLBCL, most recently at the August 2019 meeting. TIS is also being considered at the November 2019 MSAC meeting.

In brief, in August 2019, MSAC did not support public funding for TIS for the treatment of adults with confirmed r/r DLBCL. MSAC recognised the unmet clinical need and accepted that TIS had been shown to be clinically effective in some patients. However, MSAC considered more work is needed to identify the patients most likely to benefit from treatment and, based on the outcomes of that work, to refine the estimates of number of patients and financial impact of subsidy. MSAC continued to have some concerns regarding the effectiveness and cost-effectiveness of TIS (Public Summary Document [PSD] Application 1519.1, p1).

In April 2019, MSAC provided advice that it supported the public funding of TIS for treatment of relapsed or refractory acute lymphoblastic leukaemia (ALL) in children and young adults up to 25 years old, noting the proposed risk share arrangement appropriately managed the clinical, economic and financial uncertainty existing in the funding proposal. (PSD Application 1519, p2).

5. Prerequisites to implementation of any funding advice

A regulatory submission for AXI was submitted to the Therapeutic Goods Administration (TGA) on 17 December 2018. The Applicant anticipates a final TGA decision in December 2019 - January 2020. It is proposed that AXI will be supplied as a trademarked class 4 biological product, pending TGA approval.

The submission stated that treatment with AXI will only be available in a limited number of highly specialised tertiary hospitals. Each hospital will be required to undergo a rigorous qualification process undertaken by the Applicant to ensure that all quality and safety requirements can be satisfied. Training will be provided to healthcare professionals by the Applicant onsite as part of the qualification process. **Redacted.**

6. Proposal for public funding

Requested price

The submission's **redacted** proposed price (list and effective) for AXI is \$**redacted**, which encompasses the procurement of AXI, inclusive of transportation and manufacturing costs.

Redacted.

The applicant indicated a willingness to negotiate on price based on HTA principles.

In addition, the Applicant considered that the best approach for any potential **redacted** arrangement would be based on **redacted**.

Gilead also indicated its awareness of the MSAC recommendation that the Australian Bone Marrow Transplant Recipient Registry (ABMTRR) be used as a single registry for all CAR-T cell therapy in Australia. Gilead indicates a willingness to work with the Department on agreeing a registry approach that can be used to meet the MSAC recommendation and the requirements of the TGA AXI Risk Management Plan.

7. Summary of public consultation feedback/consumer Issues

Nil.

8. Proposed intervention's place in clinical management

The current and proposed clinical management algorithm for AXI is presented in Figure 1.

The submission noted the clinical management pathway for the nominated population is complex and may include chemotherapy, systemic therapy, radiotherapy, high-dose therapy, salvage chemotherapy and SCT.

AXI is expected to substitute the current clinical practice of salvage chemotherapy for patients with r/r DLBCL, including DLBCL NOS and TFL, PMBCL and HGBCL after two lines of systemic therapy and relapse after, or ineligibility for SCT.

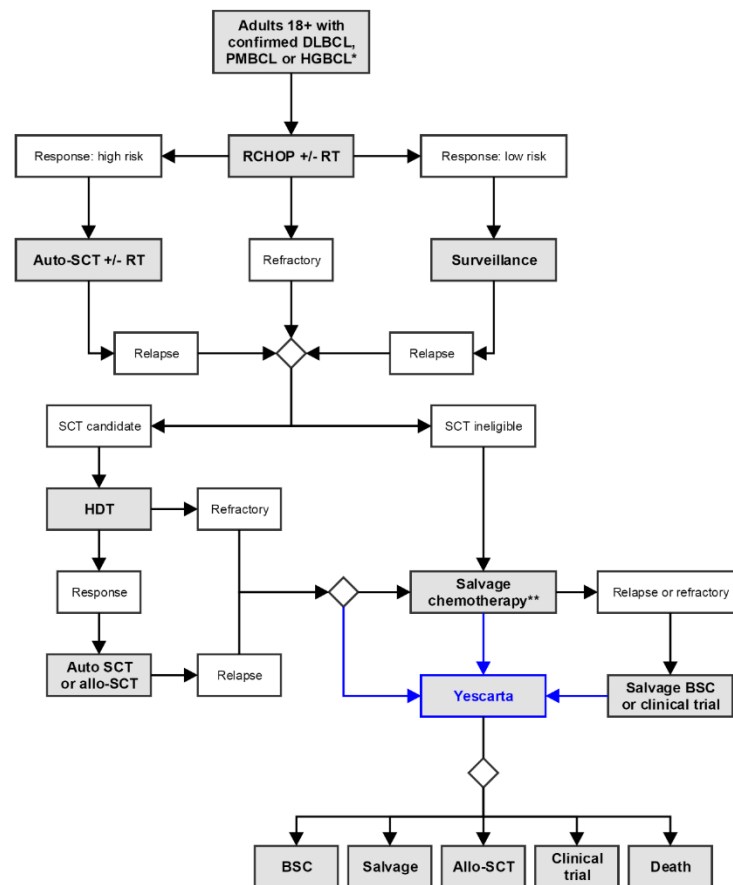


Figure 1: Current and proposed clinical management algorithm

Abbreviations: DLBCL = diffuse large B-cell lymphoma, also called DLBL; HDBL = high grade B cell lymphoma; BPMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma; RCHOP= Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RT= radiotherapy; SCT = Stem Cell Transplant; HDT = high-dose therapy; BSC = best supportive care
 Notes: Proposed changes to the current clinical management algorithm are depicted by blue lines

* Adult patients with large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

** Salvage chemotherapy is composed predominantly of rituximab-based chemotherapy regimens.

9. Comparator

The submission nominated rituximab-based salvage chemotherapy (SCR) as the main comparator.

The submission acknowledged TIS (plus bridging therapy) as a near market comparator.

The submission noted that TIS is not indicated for TFL and PMBCL, and considered that, in these patients salvage chemotherapy would remain the appropriate comparator.

The Critique noted that should TIS be recommended for public subsidy, this would be the more appropriate comparator for all patients in whom both TIS and AXI are indicated. In addition, the JULIET study of TIS included patients with TFL (19%).

10. Comparative safety

The clinical evidence presented in the submission was primarily based on three studies:

- ZUMA-1 (N=111): was a single-arm, open label study of AXI in patients with r/r DLBCL, TFL and PMBCL. ZUMA-1 consisted of two phases with the primary

analysis set (modified intention-to-treat [mITT]) only including infused patients (n=101);

- SCHOLAR (N=636): was a retrospective, patient-level pooled analysis to evaluate responses and survival rates of SCR in patients with r/r NHL, including DLBCL, TFL and PMBCL; and
- JULIET (N=165): was a single-arm, open-label, multicentre, international phase 2 study of TIS in adults with r/r DLBCL.

The Critique stated that in the JULIET trial, a lower proportion of enrolled patients received an infusion (n=115/165).

The JULIET and ZUMA-1 trials differed in whether or not enrolled patients could access bridging chemotherapy, with patients enrolled in JULIET permitted to have bridging chemotherapy, and patients enrolled in ZUMA-1 not being permitted to have bridging chemotherapy. However, ESC considered it was unclear if the different approaches to bridging chemotherapy in JULIET and ZUMA-1 meant there were differences in the populations enrolled in the two trials.

The patient dispositions from the ZUMA-1 and JULIET trials are summarised in Table 2 below.

Table 2 Summary of patient disposition ZUMA-1 and JULIET

	ZUMA-1	JULIET
Screened	124	238
Enrolled	111	165
Infused	101	111

ZUMA-1

The key safety results for AXI from the ZUMA-1 trial are summarised in Tables 3 and 4.

Three of 101 patients had fatal AE's (excluding progression); nearly all patients (93%) had CRS events, and 11 % had grade 3/ 4 CRS events.

Table 5 presents a safety comparison of AXI and SRC.

The Critique noted the lack of direct comparative evidence or even anchored indirect evidence made accurately assessing relative differences in safety between AXI vs. SCR difficult. For the few adverse events (AEs) where there was side by side comparative evidence (refer Table 4), point estimates of AEs were substantially higher for AXI than SCR.

Table 3 Key safety results for AXI Phase 2 Cohorts 1 and 2 by analysis – ZUMA-1

	Primary Analysis N = 101 n (%)	12-month Analysis N = 101 n (%)	24-month Analysis N = 101 n (%)
Any TEAE	101 (100)	101 (100)	101 (100)
SAE	52 (51)	54 (53)	55 (54)
Grade 3 or higher TEAEs	96 (95)	98 (97)	99 (98)
Fatal AE excluding disease progression	3 (3)	3 (3)	3 (3)
Grade 3 or higher CRS	13 (13)	12 (12)	11 (11)
Grade 3 or higher neurologic events	28 (28)	29 (29)	31 (31) ^a

Source: Table 13, p30 of SBA

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; SAE = serious adverse event; TEAE = treatment-emergent adverse event

a. Since the 12 month analysis, no new or ongoing axicabtagene ciloleucel-related neurologic events occurred.

Source: ZUMA-1 24-month analysis addendum (ZUMA-1 CSR 24-Month Analysis Addendum, 2018), Table 30, Page 60.

Table 4 Summary of safety results in ZUMA-1 (2-year analysis, data cut-off 11 August 2018, median follow-up of 27.1 months for phase 2 mITT patients)

	Phase 1 &2 N=108; n (%)	Phase 2 MITT N=101; n (%)
Patients with an AE	108 (100)	101 (100)
Patients with Grade \geq 3 AE	106 (98)	99 (98)
Patients with an SAE	60 (56)	55 (54)
Death due to AE, excluding PD	4 (4)	3 (3)
Deaths due to AXI related AEs	2 (2)	2 (2)
Patients with neurologic events	72 (67)	66 (65)
Patients with grade \geq 3 neurologic events	35 (32)	31 (31)
Patients with CRS	100 (93)	94 (93)
Patients with Grade \geq 3 CRS	12 (11)	11 (11)
Patients with infection	45 (42)	41 (41)
Patients with grade \geq 3 infection	30 (28)	26 (26)
Patients with thrombocytopenia	67 (62)	63 (62)
Patients with grade \geq 3 thrombocytopenia	43 (40)	39 (39)
Patients with neutropenia	93 (86)	87 (86)
Patients with Grade \geq 3 neutropenia	86 (80)	80 (79)
Patients with anaemia	73 (68)	69 (68)
Patients with Grade \geq 3 Anaemia	49 (45)	45 (45)

Source: Table B.37, p154 of the SBA (Table 25 of the Critique).

AE= adverse event; CRS = cytokine release syndrome; mITT = modified intention to treat; PD = progressive disease; SAE = serious adverse events.

Table 5 Safety comparison of AXI and SCR

	AXI	Salvage chemotherapy (rituximab-based)	
	ZUMA-1 N=108	CORAL N=197, R-ICE N=191, R-DHAP	NCIC-CTG LY.12 N=306, GDP N=304, DHAP Approx. 70% received rituximab
Type of Adverse Event, n (%)			
Median follow-up treatment start	27.1 months	27 months	53 months
Any adverse event, n (%)	108 (100)	NA	NA
Adverse event suspected to be related to study drug, n (%)	107 (99)	NA	NA
Serious adverse event, %	60 (56)	NA	NA
Serious adverse event suspected to be related to study drug	39 (36)	NA	NA
Grade 3 or 4 adverse event	97 (90)	NA	GDP, 47% DHAP, 61%
Grade 3 or 4 adverse event suspected to be related to study drug	NA	NA	NA
Any grade	100 (93)	NA	NA
Grade 3	7 (6)	NA	NA
Grade 4	4 (4)	NA	
Any grade	45 (42)	G3 or 4, R-ICE 11 (6%) DHAP 15(8%)	G3 or 4, GDP 13% DHAP 16%
Grade 3	≥G3, 30 (28)	-	-
Grade 4		-	-
Any grade	Thrombo, 67 (62) Neutro, 93 (86) Anaemia, 73 (68)	Plasma levels provided	NA
Grade 3	≥G3 Thrombo, 43 (40) ≥G3 Neutro, 86 (80) ≥G3 Anaemia, 49 (45)	NA	NA
Grade 4	NA	NA	NA
Any grade	72 (67)	NA	NA
Grade 3	32 (30)	NA	NA
Grade 4	3 (3)	NA	NA
Any grade	39 (36)	G3 or 4, R-ICE 33 (17%) DHAP 31 (16%)	G3 or 4, GDP 9% DHAP 23%
Grade 3	33 (31)	-	-
Grade 4	2 (2)	-	-NA
Any grade	2 (2)	NA	NA
Grade 3	NA	NA	NA
Grade 4	NA	NA	NA

Source: Modified from Table B.64, p 190-191 of the SBA (Table 26 of the Critique).

DHAP = dexamethasone, cytarabine, cisplatin; G = grade; GDP = Gemcitabine, dexamethasone, and cisplatin ; NA= not applicable; . R-ICE = rituximab, ifosfamide, carboplatin, and etoposide;

† Events are those with two or more reported cases, regardless of their relationship to the study drug.

‡ Cytokine release syndrome was graded with the use of the University of Pennsylvania grading scale and managed by a protocol-specific algorithm.19

JULIET

The key safety results for TIS in JULIET study are summarised in Table 6.

Table 6 Safety of TIS – JULIET

Type of Adverse Event	Number of patients (%)		
	Patients with Any Event N = 111	Patients with Events Starting ≤8 Wk Infusion N = 111	Patients with Events Starting >8 Wk Infusion N = 96
Any adverse event	111 (100)	111 (100)	69 (72)
Adverse event suspected to be related to study drug	99 (89)	96 (86)	30 (31)
Serious adverse event	72 (65)	55 (50)	30 (31)
Serious adverse event suspected to be related to study drug	52 (47)	46 (41)	9 (9)
Grade 3 or 4 adverse event	99 (89)	94 (85)	47 (49)
Grade 3 or 4 adverse event suspected to be related to study drug	70 (63)	64 (58)	21 (22)

Source: Table 14, p30 of SBA ; (Schuster SJ, 2019), Table 2, page 54.

The PSD for the August 2019 MSAC consideration of TIS notes no substantial changes in the proportion of patients with adverse events were observed in the updated JULIET data (May 2018 cut-off (<http://msac.gov.au/internet/msac/publishing.nsf/Content/1519.1-public>, page 9).

11. Comparative effectiveness

ZUMA-1

After a median follow-up of 27.1 months, median OS in the phase 2 mITT population (n=101) was not reached (95% CI 12.8 months – not estimable), with an estimated 2-year survival rate of 50.5% (95% CI: 40.2–59.7%). Notably, few deaths occurred from approximately 17 months post AXI infusion and the Kaplan-Meier curve appeared to reach a plateau at approximately 22 months. Estimated OS rates for the mITT analysis set at 6, 12, 18, and 24 months were 79.2%, 60.4%, 52.5%, and 50.5%, respectively, for Cohorts 1 and 2 combined. The key efficacy data for AXI is summarised in Table 7 and Figure 2.

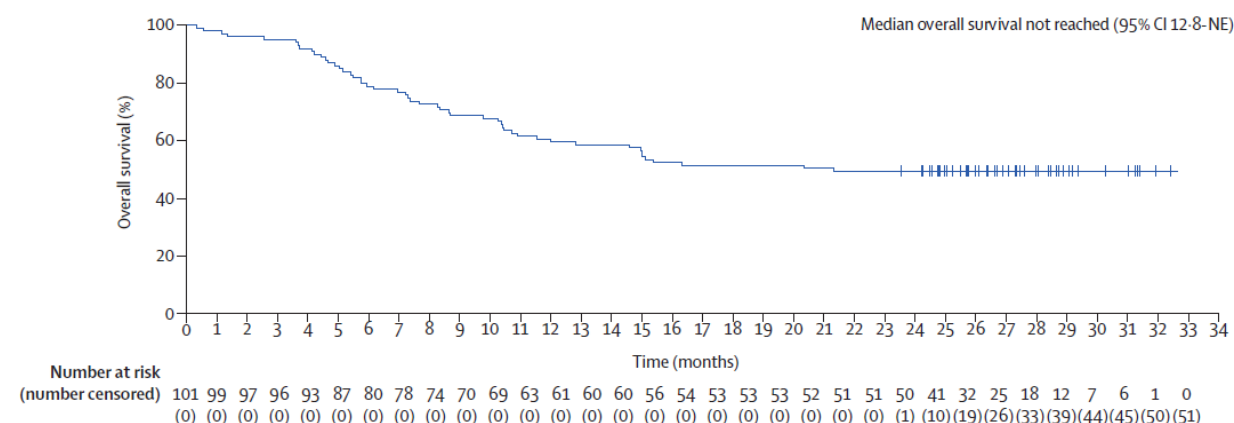
Table 7 ZUMA-1 key efficacy data from primary, 12-month and 24-month analyses (investigator assessed mITT population)

	Primary Analysis N = 101 n (%)	12-month Analysis N = 101 n (%)	24-month Analysis N = 101 n (%)
Median Follow-up (Months)	8.7	15.1	27.1
ORR	83 (82)	84 (83)	84 (83)
CR	55 (54)	59 (58)	59 (58)
Median DOR (Months)	8.1	11.1	11.1
Median PFS (Months)	5.9	5.9	5.9
Median OS (Months)	Not reached	Not reached	Not reached

Abbreviations: CR = complete response; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Source: ZUMA-1 24-month analysis addendum (ZUMA-1 CSR 24-Month Analysis Addendum, 2018), Table 26, page 51.

Figure 2 OS in the ZUMA-1 phase 2 mITT population after a median follow-up of 27.1 months



Source: (Locke F, 2019)

The OS rates for the full analysis set at 6, 12, 18, and 24 months were 81.1%, 59.5%, 49.5%, and 47.7%, respectively, for Cohorts 1 and 2 combined (Table 8).

Table 8 OS in ZUMA-1 Full analysis set

	Cohort 1 (N = 81)	Cohort 2 (N = 30)	Phase 2 Overall (N = 111)
OS			
No. of subjects	81	30	111
Censored (%)	35 (43)	18 (60)	53 (48)
KM Median (95% CI) OS time (in month)	15.4 (11.1, NE)	NE (11.6, NE)	17.4 (11.6, NE)
OS (95% CI) at			
3 Month	95.1 (87.4, 98.1)	80.0 (60.8, 90.5)	91.0 (83.9, 95.0)
6 Month	81.5 (71.2, 88.4)	80.0 (60.8, 90.5)	81.1 (72.5, 87.2)
9 Month	66.7 (55.3, 75.8)	76.7 (57.2, 88.1)	69.4 (59.9, 77.0)
12 Month	56.8 (45.3, 66.7)	66.7 (46.9, 80.5)	59.5 (49.7, 67.9)
15 Month	51.9 (40.5, 62.1)	66.7 (46.9, 80.5)	55.9 (46.1, 64.5)
18 Month	45.7 (34.6, 56.1)	60.0 (40.5, 75.0)	49.5 (40.0, 58.4)
24 Month	43.2 (32.3, 53.6)	60.0 (40.5, 75.0)	47.7 (38.2, 56.7)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; OS, overall survival.

Notes: Percentages are based on all enrolled subjects.

OS is defined as the time from the leukapheresis date to death from any cause.

Disease status used is investigator assessment of disease status per (Cheson et al, 2007).

Source:

24-month follow-up analysis of Zuma-1 cohorts 1 and 2, Addendum to Module 5.3.5.1 Zuma-1 Clinical Study Report: SCHOLAR-1 Results for OS (Table 9), and response and complete response rates (Table 10) are presented below [Note, results for ZUMA-1 are included for comparison].

Table 9 Overall Survival estimates; Scholar-1

		ZUMA-1 N = 101	CORAL N = 170	LY12 N = 219	MAYO N = 82	MDACC N = 165	Overall N = 636
Survival Status at Last Follow-up	N	101	170	196	72	165	603
	Alive (Censored)	71 (70.0)	34 (20.0)	39 (19.9)	6 (8.3)	19 (11.5)	98 (16.3)
	Dead	30 (30.0)	136 (80.0)	157 (80.1)	66 (91.7)	145 (88.5)	505 (83.7)
Median (months) (95% CI)		NE (10.4, NE)	6.5 (5.8, 8.7)	6.6 (5.7, 8.1)	5.0 (4.1, 6.0)	6.6 (5.7, 7.8)	6.3 (5.9, 7.0)
Kaplan-Meier Estimates	6-Month OS (95% CI)	80 (71, 87)	55 (47, 62)	55 (48, 62)	39 (28, 50)	54 (46, 62)	53 (49, 57)
	1-year OS (95% CI)	55 (36, 70)	30 (23, 37)	31 (24, 37)	18 (10, 27)	28 (21, 35)	28 (25, 32)
	2-year OS (95% CI)	NE	22 (16, 28)	23 (17, 29)	10 (05, 19)	17 (12, 24)	20 (16, 23)
	Median OS (mos) (95% CI)	NE	6.5 (5.8, 8.7)	6.6 (5.7, 8.1)	5.0 (4.1, 6.0)	6.6 (5.7, 7.8)	6.3 (5.9, 7.0)

Abbreviations: CI = confidence intervals; mos = months; NE = not estimable; OS = overall survival

Source: Table 11, p29 of SBA

Table 10 SCHOLAR Response and Complete Response rates

	ZUMA-1 N = 101	CORAL N = 170	LY12 N = 219	MAYO N = 82	MDACC N = 165	Overall N = 636
Response rate to subsequent therapy						
N	101	170	106	82	165	523
Responders, n (%)	83 (82)	53 (31.2)	28 (26.4)	21 (25.6)	33 (20.0)	135 (25.8)
95% Exact CI	(73, 89)	(24.3, 38.7)	(18.3, 35.9)	(16.6, 36.4)	(14.2, 26.9)	(22.1, 29.8)
DerSimonian-Laird Estimator	NA	NA	NA	NA	NA	25.7 (20.9, 31.3)
Complete response rate to subsequent therapy						
N	101	170	106	82	165	523
Responders, n (%)	55 (54)	26 (15.3)	2 (1.9)	6 (7.3)	11 (6.7)	135 (25.8)
95% Exact CI	(44, 64)	(10.2, 21.6)	(0.2, 6.6)	(2.7, 15.2)	(3.4, 11.6)	(6.3, 11.3)
DerSimonian-Laird Estimator	NA	NA	NA	NA	NA	7.0 (20.9, 31.3)
Partial response rate to subsequent therapy						
N	101	170	106	82	165	523
Responders, n (%)	28 (28)	27 (15.9)	26 (24.5)	15 (18.3)	22 (13.3)	90 (17.2)
95% Exact CI	(19, 38)	(10.7, 22.3)	(16.7, 33.8)	(10.6, 28.4)	(8.5, 19.5)	(14.1, 20.7)
DerSimonian-Laird Estimator	NA	NA	NA	NA	NA	17.5 (13.3, 22.7)

Abbreviations: CI = confidence interval; CRR = complete response rate; NA = not applicable

Source:: Table 10, p29 of SBA

JULIET

The key efficacy data for TIS is summarised in Table 11.

Table 11 JULIET Study ORR and DoR in ITT population

	Infused patients	Enrolled patients
Primary endpoint	EAS main cohort N = 93	N = 165
Overall response rate (ORR) (CR+PR) n (%) (95% CI)	48 (51.6) (41.0, 62.1)	56 (33.9) (26.8, 41.7)
CR, n (%)	37 (39.8)	40 (24.2)
PR, n (%)	11 (11.8)	16 (9.7)
Response at month 3		N = 165
ORR, n (%)	35 (37.6)	39 (23.6)
CR, n (%)	30 (32.3)	33 (20.0)
Response at month 6	N = 92	N = 165
ORR, n (%)	30 (32.6)	34 (20.6)
CR, n (%)	27 (29.3)	30 (18.2)
Duration of response (DOR)	N = 48	N = 56
Median (months) (95% CI)	Not reached (10.0, NE)	Not reached (10.0, NE)
% relapse free probability at 6 months	68.2	66.7
% relapse free probability at 12 months	65.1	63.7
Other secondary endpoints	FAS N = 111	N = 165
Overall survival (OS)		
% survival probability at 6 months	62.1	56.2
% survival probability at 12 months	49.0	40.2
Median (months) (95% CI)	11.7 (6.6, NE)	8.2 (11.7)

DCO: 8-Dec-2017, Source: Table 12, p29 of SBA

The Critique presented a side by side comparison of AXI and TIS OS in the ZUMA-1 and JULIET trials (Table 12, updated to include latest TIS results as reported in MSAC PSD for Application 1519.1).

The Critique noted the differences in OS:

- in the infused analyses sets may be attributed to differences in population and disease characteristics, though a difference in treatment effect cannot necessarily be ruled out; and

- in the enrolled sets appear to be primarily driven by the differences in the proportion of patients infused (91% in ZUMA-1; 67% in JULIET – see also comments in section 10 regarding the differences in study design).

Table 12 Overall survival in infused and enrolled populations in JULIET and ZUMA-1

Endpoint	Infused patients		Enrolled patients	
	JULIET	ZUMA-1	JULIET	ZUMA-1
	N=111	N=101	N=165	N=111
Median OS (months) (95% CI)	11.1 (6.6, NE)	NE (12.8, NE)	8.2 (5.8, 11.7)	17.4, (11.6, NE)

Source: Table B.51, p168 of the SBA; Table 21, pp46-47 and Table 155d (no page number indicated, p214 of Adobe Reader) of ZUMA-1 24 Month Analysis Addendum document, updated to incorporate results from Table 3 of PSD for TIS (1519.1).

NE = not estimable; OS = overall survival; PFS = progression free survival.

The Critique noted that a side by side comparison was insufficient to establish superiority of one CAR-T treatment over the other.

Clinical claim

The applicant claimed, based on the evidence available:

- AXI has superior efficacy compared to SCR (main comparator) in patients with DLBCL including TFL, DLBCL NOS, HGBCL and PMBCL, with a consistent and well-characterised safety profile.
- AXI has similar efficacy and safety compared to TIS + bridging chemotherapy (near-future comparator), in patients with DLBCL, including DLBCL NOS and TFL and HGBCL.

The Critique stated that the quality of evidence presented for all three described interventions had a high risk of bias. Regarding the main comparator, SCR, even in spite of the general poor quality of evidence, the presented treatment effect in terms of both response and survival between AXI and SCR indicated that AXI was most likely superior to SCR.

The Critique considered that estimating the strength of this effect is challenging given the nature of the evidence. The economic evaluation (see below) relies on the assumption that AXI is curative in approximately **redacted**% of patients: this assumption is not consistent with the clinical claim.

The Critique considered the claim AXI has a consistent and well-characterised safety profile may be misleading, given that nearly all patients (93%) suffer CRS events and that there is little long term safety information on a treatment that, biologically speaking, may be active for life. Comparative safety evidence against SCR is generally lacking, but the little existing evidence indicates substantially higher rates of Grade 3 or 4 adverse events, febrile neutropenia, and infection are experienced by patients treated with AXI.

12. Economic evaluation

The submission provided a cost-utility analysis based on a clinical claim of superior efficacy compared with SCR (Table 13). Though the submission did not claim inferior safety, it incorporated adverse events into the economic evaluation, but did not include utility decrements associated with AXI treatment.

Table 13 Summary of the economic evaluation

Component	Description
Comparator	Salvage chemotherapy
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Clinical studies, published scientific literature and national statistics for health outcomes and effectiveness data; recommended sources for unit costs
Time horizon	Lifetime (44 years)
Outcomes	QALYs
Methods used to generate results	Markov model
Health states	In the AXI arm: <ul style="list-style-type: none"> • Pre-progression ('uncured') • Pre-progression ('cured') • Post-progression • Death In the salvage chemotherapy arm: <ul style="list-style-type: none"> • Pre-progression ('uncured') • Post-progression • Death
Cycle length	Monthly
Discount rate	5% per annum, applied to costs and outcomes
Software packages used	Microsoft® Excel®

Source: Table D.2, p253of the SBA.

AXI = axicabtagene ciloleucel; QALY = quality adjusted life year

The Critique noted a key driver of the model is the selection of a four state model in the AXI arm that assumes a long term cure for nearly **redacted**% of patients and perfect health (utility=1.0, adjusted to 0.844 in the pre-ESC response) associated with this cured state.

The Critique also noted the submission did not adequately address the issue that model clinical estimates and to a certain degree costs (see below) were based on an infused rather than enrolled or intention to treat (ITT) population.

The pre-ESC response updated the economic model to use ITT data.

Overall, the Critique stated that the current model, as structured, may not be informative for decision making. Specifically, there are two major, interdependent structural issues that could not be modified during the assessment:

1. The submission created a four state model assuming that a large proportion of AXI patients would be cured (survival is set to equal age and gender adjusted Australian population average). No scenario analyses were provided based on three state survival models (where alternative assumptions could be made regarding cure after a certain amount of time in model has lapsed). This made the four state model, and all of the sensitivity analyses with various survival curves presented for it, highly favourable to AXI, and given that this survival extrapolation is likely to be the most uncertain and important driver of the model, it renders the model insensitive to changes in most other inputs.
2. Central to the four state model is the π (*submission's base case value: 0.388, range 0.380-0.392*) parameter, or estimated cure proportion, which is estimated parametrically and hence varies slightly by chosen extrapolation, but appears to be based on the proportion of PFS patients at the ZUMA-1 cut-off (*submission's base case AXI arm PFS = Weibull extrapolation*). Though this value could be altered in the model document, the applicant communicated via email that "this would not be

appropriate, since this is an outcome of the estimated survival curve” the applicant’s point is reasonable from a technical point of view. It is for this reason that the model is uninformative, because the model has inflexibly assumed a cure rate based on highly optimistic values of a small n single arm trial with two years of follow-up. Additionally, the model as included explicitly models a high cure proportion over a life time horizon based on two year follow-up, with no flexibility for altering cure assumptions.

In the pre-ESC response, the Applicant defended its use of the mixed cure model (a partitioned survival approach in which progression-free (PFS) and overall survival (OS) estimates are modelled independently). Gilead also indicated its appreciation that long-term certainty of curative intent/duration of cure is fundamental to the cost effectiveness of AXI and requested that the re-presented results of the economic model provided with the pre-ESC response be considered alongside the applicant’s willingness to **redacted** arrangement (see also Pre-ESC response section below).

The results of the submission’s economic evaluation are presented in Table 14.

Table 14 Results of the stepped economic evaluation (submission)

Analysis	AXI arm	SCR	Incremental
Step 1: Incremental cost per additional month of PFS, over a one-year time horizon			
Expected cost per patient	\$redacted	\$redacted	\$redacted
Mean PFS (months)	0.59	0.28	0.31
Incremental cost per additional month of PFS, over a one-year time horizon			\$redacted
Step 2: Incremental cost per additional month of OS, over a one-year time horizon			
Expected cost per patient	\$redacted	\$redacted	\$redacted
Mean OS (months)	0.83	0.48	0.35
Incremental cost per additional month of OS, over a one-year time horizon			\$redacted
Step 3: Incremental cost per life year gained, over a lifetime horizon			
Expected cost per patient	\$redacted	\$redacted	\$redacted
Life years gained	6.744	2.211	4.533
Incremental cost per life year gained, over a lifetime horizon			\$redacted
Step 4 (base case analysis): Incremental cost per QALY, over a lifetime horizon			
Expected cost per patient	\$redacted	\$redacted	\$redacted
QALYs gained	6.146	1.453	4.693
Incremental cost per quality adjusted life year gained, over a lifetime horizon			\$redacted

Source: Table D.26, p 285 of the SBA.

AXI = axicabtagene ciloleucel; OS, overall survival, PFS, progression free survival; SCR = salvage chemotherapy

The Critique stated that the results likely underestimate the incremental cost-effectiveness ratio (ICER), primarily due to the specification of the four state model, which likely substantially overestimated the survival benefits associated with AXI.

The Critique noted the model was not very sensitive to OS post-progression extrapolation in the AXI arm: largely due to the four state model, which assumes that **redacted**% of the entire AXI cohort remains progression free for the entirety of the model.

Applicant pre-ESC response

The Applicant advised that the approach taken in the MSAC submission is not fundamentally different to that taken in other jurisdictions, including in the submission to National Institute of Clinical Excellence (NICE) in England. For context, the Applicant stated that the NICE

accepted the concept of curative intent/duration of cure of AXI based on 1-year clinical data, whereas the MSAC submission was based on 2-year data. Thus the model assumption regarding the proportion of patients who will be cured based on the two-year data (39%) remain unchanged. The Applicant did revise the:

- **Redacted**
- Utility for cured patients to Australian population norms mean of 0.844 (from 1.0), using the Assessment of Quality of Life- six dimension [AQoL-6D] tool from Maxwell et al. 2016 (Table 10).
- The clinical estimates and costings to reflect an ITT population. The Applicant stated it sourced ITT data which indicated the log-logistic distribution was now applied for AXI PFS (from Weibull [the Applicant noted life years gained fell from **redacted** to **redacted** in pre-ESC response]) . In addition, the multipliers applied previously to leukapheresis (**redacted**) and conditioning chemo/acquisition (**redacted**) costs were set to **redacted** - to reflect the change in the population.

Table 15 Additional sensitivity analyses provided by the applicant in the pre-ESC response (abridged version)

Scenario	Incremental cost	Incremental QALY	ICER (\$/QALY)	Comments
Submitted base case	\$redacted	redacted	\$redacted	
Analyses to establish effective price				
Application of age-based population utility norms for remission/cure from 1.0 to as per Maxwell et al (2016)	\$redacted	3.968	\$redacted	
<i>Critique's values</i>		3.924	\$redacted	
Utility in remission/cure set to age-based population utility norms to remission/cure (as per Maxwell et al (2016)) AND 11.51% price cut (\$redacted)	\$redacted	3.968	\$redacted	redacted
<i>Critique's values</i>		3.924	\$redacted	

Source: Table 2, pp8-9 of Applicant pre-ESC response
 The Assessment Group who performed the Critique checked the Applicant's pre-ESC response model values (included above)

The Applicant also confirmed a willingness to **redacted** (see section 5).

13. Financial/budgetary impacts

The submission used an epidemiological approach to estimate the financial implications of using AXI to the healthcare system (Table 16).

The submission estimated a total net budget impact of **\$redacted** in Year 1 increasing to **\$redacted** in Year 6 of funding for a total of **\$redacted** at the initial requested list price for AXI of **\$redacted**.

Table 16 Total costs to the healthcare system associated with AXI

Budget Impact	Per patient	Year 1 2020	Year 2 2021	Year 3 2022	Year 4 2023	Year 5 2024	Year 6 2025
Number of patients to receive AXI	-	redacted	redacted	redacted	redacted	redacted	redacted
Cost of AXI treatment	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost offset from displacement of salvage chemotherapy	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net Budget impact (total costs - cost offsets)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Source: Table E.22, p321 of the SBA.
 AXI = axicabtagene ciloleucel

The Critique highlighted the key issues affecting the submission’s financial estimates:

- If the financial estimates excluded unfit patients from the population, such as patients over the age of 80 or with European Cooperative Oncology Group performance scale (ECOG) performance of greater than two, for example, it would be likely that the expected use and financial impact of listing AXI would be decreased.
- The financial model was based on a list price. Reductions in effective prices would likely have a substantial effect on financial estimates.
- The model did not clearly specify its assumptions regarding the adjustment of ‘% AXI candidates’ - presumably the **redacted**% value is inclusive of uptake, access, and potential market share considerations - but it was unclear how this value was derived.
- The submission did not factor in patients intended to be infused who were not infused.

Table 17 provides the MSAC estimated number of TIS patients with DLBCL (including TFL) treated over the first 6 years (PSD 1519.1, August 2019, page 6). MSAC recognised these estimates could require further review based on the final agreed TIS eligibility criteria.

Table 17 Estimated number of infused DLBCL patients for TIS.

DLBCL	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Total infused patients	132	199	194	186	186	188	1084

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Eligible Patient Population	MSAC may wish to define the eligible population for public funding more tightly than the requested by the application. Note: the outcomes of the stakeholder meeting to be held on 12 November 2019 may help inform this discussion. MSAC may wish to consider limiting CAR-T cell therapy to a single treatment per lifetime.
Survival data are immature. Claims of superior effectiveness and non-inferior safety are unsubstantiated	Overall survival data in phase 2 mITT population of the ZUMA-1 trial remain immature with median OS not reached (median follow up 27.1 months). Considerable uncertainty remains around the size and the durability of the benefit of treatment with AXI versus rituximab based salvage chemotherapy (SCR) given no randomized control trial and limited follow-up Treatment with AXI is associated with significant risk of adverse events. MSAC may wish to consider whether proposed pay-for-performance arrangement (based on survival at 12 months) is adequate to address these uncertainties.
Effectiveness and safety of AXI versus TIS	The MSAC may wish to consider whether there is sufficient information available to support a conclusion that AXI is likely non-inferior to TIS in terms of effectiveness and safety in patients with DLBCL and TFL. The MSAC may also wish to consider whether it is appropriate to extrapolate any conclusion of non-inferiority to PMBCL (6 - 12% of all DLBCL), as patients with this condition were not included in the TIS JULIET clinical trial.
Naïve comparison basis for the modelling of incremental benefit	The weakness of clinical evidence translates into model uncertainty with respect to incremental benefit. The Critique and the pre-ESC Applicant response argue the incremental benefit may be over- or under-estimated.
Model may not be informative for determining cost effective price.	The key modelling issue is the inclusion of a 'cured' health state. Approximately 40% of the AXI treated population enter this health state, with limited clinical data available to support this assumption. As a consequence, the model is not sensitive to changes in inputs that are key drivers in similar models, including choice of parametric functions for OS extrapolation and overall cost of treatment. The Pre-ESC Applicant response made a number of adjustments to the model based on the information provided in the Critique but these may be insufficient to address the overall model uncertainty.
Other model issues	Other issues with the model include Whether it underestimates costs by not including any further costs for the "cured" population (eg monitoring, relapse associated costs, other health care costs related to their DLBCL treatment), The extrapolation methods may overestimate the benefit of AXI or underestimate the benefit of SCR The starting age in the model compared to patients who will be treated in Australia
Financials issues	The estimated number of patients is higher than the number MSAC considered reasonable for TIS in August 2019, even accounting for the need to increase the estimates by 6 – 12% to account for the PMBCL population.

ESC discussion

The ESC noted DLBCL consists of multiple diseases, some of which have poor prognosis depending on the genetic profile. The refractory and relapsed population also differ clinically. In Australia, all DLBCL patients receive rituximab as part of first line combination chemotherapy. Relapsed disease is treated with second line chemotherapy regimen or autologous stem cell transplant (ASCT). Refractory disease is treated with multiple lines of therapy and many patients are never candidates for ASCT.

The ESC further noted the planned stakeholder meeting to help inform the MSAC on eligibility for treatment of DLBCL with CAR-T cell therapy as well as the appropriate

criteria for measuring response. Clinicians and representatives of consumer organisations, Gilead, Novartis, and the state and territory health departments will be invited to the meeting.

ESC advised MSAC may wish to consider whether CAR-T cell therapy should be limited to a single use per life time.

The ESC noted the application had strong support from the relevant consumer representative groups. The ESC also noted the consumer feedback indicating that equity of access could be an issue as the therapy will only be given in selected tertiary hospitals. In addition, there could be significant out-of-pocket costs if patients are required to travel to these centres to receive treatment. The ESC acknowledged there are state and commonwealth programs available that provide some support to patients in these situations.

ESC noted that clinical data provided in support of the application are limited, with only single arm studies, one each for AXI [prospective], TIS [prospective] and Salvage Chemotherapy (SCR) [retrospective], and with small patient numbers informing the naive comparisons. The pivotal study for AXI (ZUMA-1) has a high risk of bias due to its single arm, open label design.

In terms of safety, ESC noted that the applicant presented a comparison of the safety data for AXI from the ZUMA-1 trial with rituximab-based SCR from the SCHOLAR-1 trial. ESC considered the results of this comparison should be interpreted with caution because of the lack of direct comparative safety data or even anchored indirect evidence. ESC also agreed the applicant's claim that AXI has a consistent and well-characterised safety profile may not be reasonable, due to a lack of long-term safety data and due to 95% of all patients suffering cytokine release syndrome (CRS).

In terms of effectiveness, ESC considered the claim AXI is superior to SCR to be reasonably supported, however, the magnitude and durability of the benefit was difficult to estimate reliably given the quality of the evidence, and noting the ZUMA-1 population was different to the SCHOLAR-1 population. ESC noted the submission attempted to address this issue using standardised and propensity score matching. However, the Critique noted the application did not adequately account for European Cooperative Oncology Group performance scale (ECOG) status differences in ZUMA-1 vs. SCHOLAR-1, which likely overestimated the incremental benefit of AXI relative to SCR.

ESC considered the submission's claim that AXI has similar efficacy and safety compared to TIS (near-future comparator) in patients with DLBCL, including DLBCL NOS and TFL and HGBCL, may be reasonable, although noted it is only supported by a side-by-side comparison of the outcomes of two single arm trials.

ESC agreed with the concerns raised in the Critique regarding the economic model. In particular, the highly optimistic and inflexible assumption in the model that almost 40% of patients are cured by treatment is not well supported by the clinical evidence.

ESC also noted that the incremental cost-effectiveness ratios (ICERs) are stable in most of the sensitivity analyses, probably because of the inclusion of the cured health state. This lack of change in the outputs of the model when inputs are varied is concerning.

ESC had a number of other concerns with the model including: whether it underestimates costs by not including any further costs for the "cured" population (eg monitoring, relapse associated costs, other health care costs related to their DLBCL treatment); whether the extrapolation methods potentially overestimate the benefit of AXI or underestimate the

benefit of SCR; and whether the starting age in the model is reflective of the age of the patient group who will be treated in Australia.

ESC noted the Applicant's pre-ESC response maintained the same mixed -cure model structure, but revised certain model inputs: reduced the effective price of AXI; adjusted the costings to reflect the intention-to treat population (rather than per-protocol population); and adjusted the utility value in the curative health state to a more reasonable estimate. However, ESC did not consider these adjustments adequately addressed its concerns with the economic model.

ESC noted that the estimated quality-adjusted life year (QALY) gain for AXI in its economic model was 4.7 compared to an estimate of 1.2 for TIS in its economic model.

Overall, ESC agreed with the Critique that the model is not informative for decision making.

ESC also noted the Applicant pre-ESC response proposed a **redacted**. ESC considered this proposition requires further consideration by the MSAC as it relies on acceptance of the approach taken in the economic model.

ESC noted the estimated number of patients is higher than the number MSAC considered reasonable for TIS in August 2019, even accounting for the need to increase the estimates by 6 – 12% to account for the PMBCL population.

ESC considered that if the financial estimates were revised to exclude potentially unfit patients from the eligible patient population, the expected use and financial impact of listing AXI would be decreased. In addition, ESC noted the Applicant pre-ESC response did not update the financial estimates for **redacted**.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

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