Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1519.1 – Tisagenlecleucel (CTL019) for treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

Applicant: **Novartis Pharmaceuticals Australia Pty Ltd**

Date of MSAC consideration: **MSAC 77th Meeting, 28-29 November 2019**
MSAC 76th Meeting, 1-2 August 2019

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

1. Purpose of application

November 2019 MSAC consideration

MSAC reconsidered the public funding of tisagenlecleucel (TIS) for adult patients with confirmed relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL) in the context of the advice it received at the CAR-T stakeholder meeting held on 12 November 2019. MSAC also considered new information provided by the sponsor, Novartis Pharmaceuticals Pty Limited (Novartis), subsequent to the stakeholder meeting.

August 2019 MSAC consideration

A revised application (resubmission) was received from Novartis by the Department of Health for tisagenlecleucel (TIS) for adult patients with confirmed relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL).

TIS is an individualised single-delivery immunocellular therapy using autologous T cells which are genetically reprogrammed with a chimeric antigen receptor (CAR) that identifies and destroys CD19-expressing (malignant and non-malignant) B-cells. TIS is a chimeric antigen receptor T-cell (CAR-T) therapy and a Class 4 Biological Product. CAR-T therapy cannot be easily defined as a service or a medicine; it is a process to genetically modify a patient's T-cells. It is therefore not suitable for reimbursement through the Medicare Benefits Schedule (MBS) or the Pharmaceutical Benefits Scheme (PBS).

TIS is currently being jointly funded by the Commonwealth and the States under the National Health Reform Arrangements (NHRA) for use in relapsed and refractory acute lymphoblastic leukaemia in children and young adults up to age 25 years.

2. MSAC's advice to the Minister – November 2019

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the public funding of tisagenlecleucel (TIS) for certain patients with CD19-positive Diffuse Large B Cell Lymphoma (DLBCL), Primary Mediastinal B Cell Lymphoma (PMBCL) and Transformed Follicular Lymphoma (TFL). The MSAC recommendation for public funding was based on, among other matters, its assessment that the cost-effectiveness of TIS, although high, would be acceptable if the **redacted** price is no higher than that proposed in the submission, 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**;
- **Redacted**;
- **Redacted**;
- no payment for TIS for an unsuccessful infusion;
- no payment for TIS if a patient is apheresed but does not receive the infusion of engineered lymphocytes;
- a limit to one successful CAR-T infusion per lifetime;
- **Redacted**;
- **Redacted**;
- data on the use of TIS for B cell lymphoma's in Australia should be recorded by the Australian Bone Marrow Transplant Recipient Registry, with the cost of data collection met by the applicant; and
- An initial progress review at Year 1 to assess appropriateneness of patient eligibility criteria and patient numbers, with a full review of clinical effectiveness, cost-effectiveness and budget impact to be conducted by the MSAC no later than 2 years post the commencement of public subsidy (note: Novartis 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.

Consumer summary
At its November 2019 meeting, MSAC considered an application from Novartis Pharmaceuticals Australia Pty Ltd for public funding of tisagenlecleucel (TIS) – a type of CAR-T cell therapy (chimeric antigen receptor T-cell therapy). The application requested public funding of TIS for adult patients with 'confirmed relapsed or refractory diffuse large B-cell lymphoma (DLBCL)'.

Consumer summary

CAR-T cell therapies such as TIS, 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 has considered this request previously (November 2018 and August 2019) and held a stakeholder consultation meeting (12 November 2019; minutes for this meeting are at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519.1-public

MSAC's November 2019 advice to the Commonwealth Minister for Health

MSAC supported public funding for tisagenlecleucel (Kymriah®, TIS) 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 4). MSAC agreed that current evidence demonstrates that TIS gives some patients, who have exhausted all other treatments, a new chance at possibly achieving remission. MSAC also noted that the current evidence shows that TIS therapy works better for children and young adults with blood cancers than with adults.

MSAC agreed that TIS should only be offered to patients who are considered fit enough as as determined by their treatment team according to the eligibility criteria in Table 1, 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 TIS in deciding what the eligibility criteria for treatment with TIS should be.

MSAC advised that TIS 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 TIS. Many of these measures need to be agreed between the applicant, and the Commonwealth and/or the States.

Summary of consideration and rationale for MSAC's advice – November 2019

November 2019

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 JULIET clinical trial of TIS, albeit with some modification. On the basis of that advice in the context of the available evidence and the treatment algorithm presented by the applicant, MSAC advised that treatment with TIS be made available to the following patients in Table 1.

Table 1: Eligibility criteria for TIS

Indication:	Relapsed or refractory CD19-positive: • 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:	**FOR DLBCL and PMBCL:** The condition must have (i) relapsed after autologous stem cell transplantation; or (ii) have relapsed after, or be refractory to, at least two prior systemic therapies **FOR TFL:** The condition must have relapsed after, or be refractory to, at least two prior systemic therapies administered after disease transformation. **FOR ALL INDICATIONS:** Patient must have a WHO performance status of 0 or 1 AND Patient must have sufficient organ function, including: i. Renal function: Creatinine clearance >40mL/min, serum ALT/AST <5 x ULN and total bilirubin <2 x ULN ii. Cardiac function: absence of symptomatic heart failure (i.e. NYHA grade <2), cardiac left ventricular ejection fraction >/= 40%, or supplementary functional tests and cardiology assessment demonstrating adequate cardiopulmonary reserve. iii. Pulmonary function: Baseline peripheral oxygen saturation >91% on room air, in the absence of anaemia AND The treatment team must consider the patient's condition can be effectively managed during lymphocyte collection and manufacturing, to allow for the absence of rapidly progressive disease at the time of lymphocyte infusion.

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 site.

MSAC acknowledged, as previously, that TIS has been shown to be clinically effective in some patients. MSAC was reassured by the high level updated results from the single arm JULIET clinical trial (cut-off 1 July 2019), noting these data are consistent with the data seen by the MSAC from earlier JULIET trial cut-offs (December 2017, May 2018 and December 2018), but acknowledging the small patient numbers for whom longer term data is available (see Table 2 and Figures 1 and 2).

Table 2: Summary of clinical effectiveness outcomes JULIET

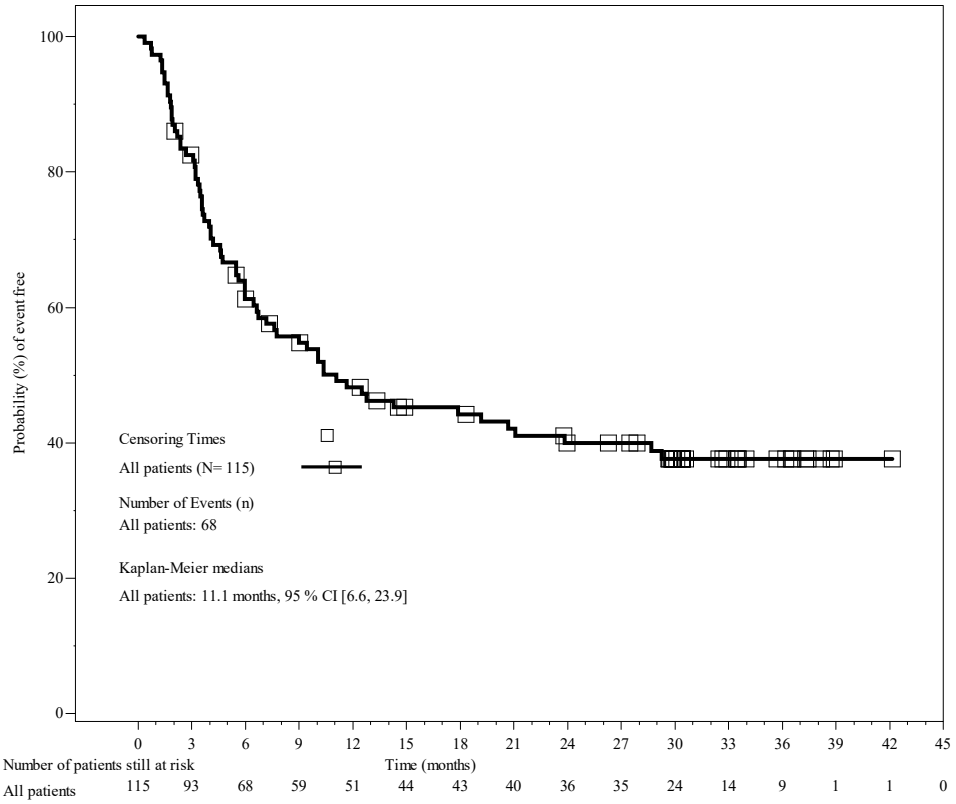
	May 2018 (n = 115)*	December 2018 (n = 115)	July 2019 (n = 115)
ORR n/N% [95% CI]	53/99 (53.5) [43.2;63.6]	60 (52.2) (42.7,61.6)	60 (52.2) (42.7; 61.6)
Median PFS [95% CI]	2.9 [2.3;4.2]	2.9 [2.3; 5.2]	Redacted
Median OS [95% CI]	11.1 [6.6; NE]	10.3 [6.6; 21.1]	11.1 [6.6; 23.9}

ORR: overall response rate = CR (complete response) + PR (partial response; PFS: progression free survival (relative to onset of response); OS: overall survival (relative to first TIS infusion).
Source: May 2018 1519.1 PSD, Table 3; December 2018 & July 2019: Novartis submission November 2019

Figure 1: Kaplan-Meier plot of progression free survival (PFS) censoring HSCT by independent review committee (IRC) assessment (FAS); 1 July 2019 data cut-off

Redacted

Figure 2: Kaplan-Meier plot of overall survival (OS) (FAS); 1 July 2019 data cut-off



Time is relative to first CTL019 infusion date, 1 month=30.4375 days
Source: November 2019, page 11

MSAC was further reassured by the early data from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy (CT) Registry provided by the applicant.

MSAC noted the applicant continues to request **redacted** price of $**redacted** for TIS, regardless the MSAC's previous concerns around the cost-effectiveness of TIS at this price.

MSAC recalled the base case incremental cost per quality adjusted life year (QALY) at this price is $**redacted** and likely to be underestimated. MSAC further recalled the outcomes of the economic model are most sensitive to the price of TIS, the method of extrapolation and the starting age of the model and any reasonable variations of these give rise to unacceptably high cost effectiveness ratios. MSAC noted the modelled time horizon is 50 years, although the survival curves converge at around 20 years.

MSAC noted that if the starting age in the model is set at 65 (rather than 56 years in the base case), the incremental cost per QALY increases to $**redacted**, requiring a reduction in the price of TIS to $**redacted** to achieve $**redacted**/QALY. Similarly, if the starting age in the model is set at 75 years, the incremental cost per QALY increases to $**redacted**. Under these circumstances, the price for TIS would require lowering to $**redacted** to achieve $**redacted**/QALY.

MSAC considered there was potential for the cost-effectiveness ratio to increase to an unacceptable level if the proportion of patients aged ≥ 65 years in clinical practice is greater than in the JULIET clinical trial. Thus, although MSAC agreed with the stakeholder meeting consensus that access to treatment with TIS should be based on fitness for therapy rather than on chronological age, MSAC considered it appropriate for any funding arrangement to manage the risk that the cost-effectiveness of treatment would reduce if the proportion of patients aged ≥ 65 years is higher in practice than it was in the JULIET clinical trial (25%).

MSAC noted the applicant proposed **redacted** arrangement to address ongoing uncertainty regarding the clinical effectiveness and durability of benefit. MSAC noted the key elements of the applicant's **redacted** were:

- **Redacted**
- **Redacted**.

MSAC agreed the **redacted** proposed by the applicant went some way towards addressing its concerns around cost-effectiveness. However MSAC was concerned that, amongst other matters:

- **Redacted**.
- **Redacted**.

Overall, MSAC considered TIS to be acceptably cost-effective in the context of a high, unmet clinical need for effective treatment options for this patient group, however considered the **redacted** should be enhanced by:

- **Redacted**;
- **Redacted**;
- **Redacted**; and
- **Redacted**.

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

The MSAC also did not accept the sponsor's proposal that a patient could be offered a second TIS infusion if there are sufficient excess leukapheresis material available to manufacture a second infusion of TIS, as the cost-effectiveness of second or subsequent doses of CAR-T cell therapy has not been demonstrated. Additionally, **redacted**, substantial ancillary costs would continue to be accrued. MSAC considered it appropriate for there to be a limit of one successful CAR-T infusion per lifetime until further evidence is available.

MSAC noted that an application for public funding of an alternative CAR-T cell therapy, axicabtagene ciloleucel (AXI, Yescarta®), for use in the same B-cell lymphomas is being considered at the same MSAC meeting. MSAC noted the application for TIS does not include a comparison with AXI. The MSAC considered it is difficult to conclude whether TIS is non-inferior in terms of effectiveness compared to AXI 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 the single arm trials (JULIET and ZUMA-1), and there is no clear basis to determine a minimal clinically important difference. Having regard to these issues, MSAC concluded that, on balance, the two CAR-T cell therapies, TIS and AXI are clinically non-inferior to each other.

MSAC noted the applicant had revised its estimate of the numbers of patients treated with TIS. The applicant's revised estimates took as their starting point the estimates derived by MSAC at its August meeting (see Table 5), and made the following revisions

- The number of patients projected to be diagnosed with Non-Hodgkin Lymphoma have been updated so year 1 is 2020;
- PMBCL (3%) and TFL (0.6%) patients have been included in the eligible patient population
- The proportion of patients assumed to be unfit for treatment with TIS has been estimated at **redacted**%; and
- Uptake in year 1 has been increased from **redacted**% to **redacted**% to reflect the availabilty of a second Australian treatment site and the ongoing work to establish further treatment sites.

The applicant's revised financial estimates are presented in Table 3.

Table 3: Applicant's Revised Financial Estimates

DLBCL + PMBCL + TFL	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Patient Numbers infused	redacted	redacted	redacted	redacted	redacted	redacted	redacted
Patient numbers non-infusion	redacted	redacted	redacted	redacted	redacted	redacted	redacted
Redacted CAR-T cost per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	
Anciliary cost per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	
Anciliary cost per non infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	
Average cost offset per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	
Total CAR-T COST	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total Ancillary Cost	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Cost offsets	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Net Program Cost	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

MSAC noted that, after taking into account the small number of additional patients with PMBCL or TFL, 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.

MSAC noted the principal reasons for the higher patient numbers were the assumptions that a larger number of patients would be treated in the first year of funding and that **redacted**% of patients with relapsed or refractory disease will not be eligible for treatment with CAR-T cell therapy because of ECOG status, organ function or co-morbidities. MSAC recalled that in August 2019 it had assumed 36% of patients would not be eligible for treatment, whereas in the JULIET study 31% of screened patients were not eligible for enrolment.

Overall, MSAC considered the proportion of patients ineligible for treatment with CAR-T cell therapy remains a major source of uncertainty for the financial estimates with the total program cost, before offsets ranging from approximately $**redacted** over 6 years if 36% of patients are assumed ineligible, to $**redacted** over 6 years if **redacted**% are considered ineligible.

MSAC considered it probable the applicant has overestimated the number of patients who will be eligible for treatment with TIS. MSAC considered the true proportion of patients ineligible for treatment is likely to be closer to that proposed by MSAC in August 2019.

MSAC was also concerned the applicants financial estimates inappropriately claimed an offset equivalent to the estimated cost of a salvage chemotherapy regimen ($54,297) for every patient successfully infused with TIS. MSAC considered this approach did not account for patients who do not respond to TIS and then go on to receive salvage chemotherapy soon after. MSAC noted the objective response rate in the JULIET clinical trial was 52.2%, 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 TIS.

MSAC noted the applicant provides a patient support program (MY CAR-T) which, the applicant claims is aimed at reducing patients' out-of-pocket expenses for travel and accommodation. **Redacted**, but noted that, notwithstanding, it should be accounted for when the Independent Hospital Pricing Authority calculates the cost of delivering this service.

MSAC noted the adjusted financial estimates presented in Tables 4 (**redacted**% patients ineligible, offsets claimed for 50% of all infused patients and 5 (36% patients ineligible, offsets claimed for 50% of all infused patients).

MSAC's overall conclusion, taking into account the factors above, the epidemiology of this condition and the number of available services providers, is that it is unlikely the patient numbers in Table 5 will be achieved in either of the first 2 years of subsidy.

Table 4: Applicant's Financial Estimates with adjusted offset

DLBCL + PMBCL + TFL	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Patient Numbers infused	redacted	redacted	redacted	redacted	redacted	redacted	redacted
Patient numbers non-infusion	redacted	redacted	redacted	redacted	redacted	redacted	redacted
Redacted CAR-T cost per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	
Anciliary cost per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	
Anciliary cost per non infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	
Average cost offset per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	
Total CAR-T COST	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total Ancillary Cost	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Cost offsets	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Net Program Cost	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

Table 5: MSAC Financial Estimates

DLBCL + PMBCL + TFL	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Patient Numbers infused	182	211	213	206	207	210	1229
Patient numbers non-infusion	redacted	redacted	redacted	redacted	redacted	redacted	redacted
Redacted CAR-T cost per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Anciliary cost per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Anciliary cost per non infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Average cost offset per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total CAR-T COST	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total Ancillary Cost	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Cost offsets	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Net Program Cost	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

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 noted the applicant's statement it has "*provided its best and final price offer,* **redacted**.

MSAC further noted the applicant's proposal that the financial risk to Government of subsidy outside the eligible patient population be managed **redacted**. MSAC rejected this proposal **redacted**, noting it has the potential to exclude otherwise eligible patients from treatment **redacted**.

MSAC reaffirmed its advice to the Minister from August 2019 that any risk sharing arrangements put in place for TIS should include **redacted**. MSAC considered it appropriate that the **redacted**.

MSAC considered the **redacted** arrangement put in place between the Commonwealth and the applicant for TIS for pALL **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 TIS one year after the commencement of public funding. MSAC considered it may be appropriate to revise the patient number estimates **redacted** 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 TIS no later than 2 years post the commencement of public subsidy (note: Novartis will provide a submission to initiate this review). As part of this review MSAC requested the applicant update the current economic model to include the latest available JULIET trial data on PFS, OS, rates of transplant post TIS and immunoglobulin usage. MSAC indicated its intention to again examine patient numbers **redacted** as part of this review.

The MSAC considered that, as with pALL, data on the use of TIS for B cell lymphoma's 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 admission 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.

3. MSAC's advice to the Minister – August 2019

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for tisagenlecleucel for the treatment of adults with confirmed relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). MSAC recognised the unmet clinical need and accepted that tisagenlecleucel 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 tisagenlecleucel.

Consumer summary

Tisagenlecleucel (TIS) is a type of chimeric antigen receptor T cell (CAR-T) therapy. CAR-T therapy is used when patients with some types of cancer, such as lymphoma or leukaemia, don't respond to (otherwise known as refractory), or relapse after, other types of treatment, such as chemotherapy. CAR-T 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 cell are infused back into them to target and kill the cancer cells in the patient's body.

This application requested public funding for TIS for patients with relapsed or refractory diffuse large B-cell lymphoma, or DLBCL.

MSAC's August 2019 advice to the Commonwealth Minister for Health

MSAC did not support public funding for TIS for DLBCL at this time because, based on the information in the application, it is not sure how well TIS works for people with DLBCL and the sponsor has asked for a very high price for TIS. TIS can be a very toxic therapy and it can't be used in all patients with DLBCL. MSAC felt that more work needs to be done to help doctors and patients choose whether to use TIS.

MSAC did not accept parts of the sponsor's economic evaluation of TIS treatment. MSAC also could not calculate how many people might need TIS each year, so it could not estimate the financial impact of funding. MSAC has asked the sponsor to do more work to address these issues.

Summary of consideration and rationale for MSAC's advice – August 2019

This application was a resubmission for tisagenlecleucel (TIS) for treatment of relapsed or refractory DLBCL.

Applicant hearing

The applicant was granted a hearing, which included a slide presentation.

MSAC first heard from an Australia clinician who has treated a number of r/r DLBCL patients with TIS. The clinician described their experience using this therapy and presented

clinical vignettes for two patients. Overall, the clinician considered TIS provides an important new therapeutic option for patients with r/r DLBCL who have limited other treatment options.

The applicant focussed on the use of the spline versus lognormal extrapolation methods in the modelled economic evaluation, and argued that a spline extrapolation method was better suited to the data than a lognormal extrapolation method. The applicant considered that the lognormal extrapolation was overly conservative and inconsistent with the observed data to date, and expressed the view that a lognormal extrapolation underestimates the effect of TIS.

MSAC asked the applicant about the proportion of r/r DLBCL patients who might be treated with TIS in Australia if the conditions of subsidy were aligned with the Therapeutic Goods Administration (TGA) approved indication. The clinician noted that in practice patient suitability for TIS will be based on considerations including the patient's performance status and renal function. Older patients are more likely to have comorbidities that would render them unsuitable for TIS. However, the clinician considered it likely that in Australian clinical practice slightly more patients would be found suitable for therapy than in the JULIET clinical trial, where less than half of all screened patients went on to receive TIS (see also Figure 1 below). In their experience, more patients who begin manufacturing turn out to receive treatment. This was due to improvements in manufacturing turnaround and capacity in the commercial setting, as compared to the trial setting.

MSAC asked why the modelled ICERs were similar for the DLBCL and paediatric acute lymphoblastic leukemia (pALL) populations despite the large differences in modelled life-years (LYs) gained. MSAC noted that the economic model for the pALL population (for which funding was considered and accepted by MSAC in April 2019) estimated 6.8 life-years gained and an incremental cost-effectiveness ratio (ICER) of about $**redacted** per QALY. By contrast the economic model for the DLBCL population estimated an increment of 1.4 LYs and an ICER of $**redacted** per QALY. The applicant was unable to provide an explanation for this at the hearing which satisfied the MSAC. This point is discussed further below.

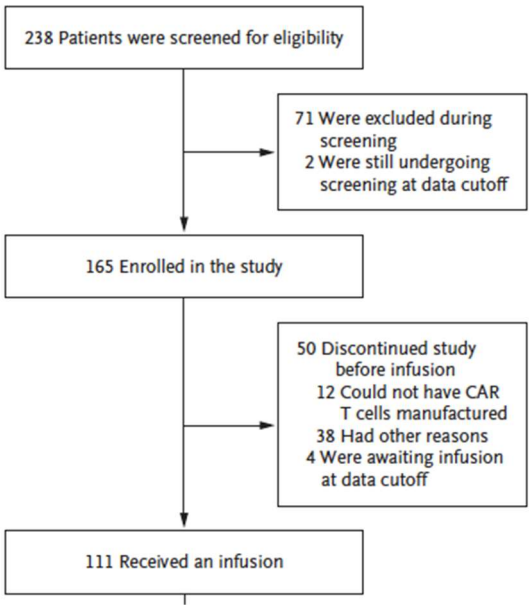
In response to being asked whether there are any randomised controlled studies being conducted in this patient population, the applicant indicated there are three international multicentre randomised controlled trials currently looking at CAR-T therapy compared with autologous stem cell transplant in DLBCL patients who relapse within 12 months of diagnosis. However, these trials are still in the recruitment stage. The applicant stated it was not aware of any ongoing randomised controlled studies in patients whose disease has relapsed after autologous stem cell transplant, ie the majority of the population in whom subsidy is currently proposed.

MSAC discussion

The MSAC noted that the population treated in the key clinical study, JULIET (C2201) was narrower than the population for whom subsidy is proposed, as a significant proportion of the screened patient population did not meet the eligibility criteria (see Figure 3). The MSAC further noted the JULIET eligibility criteria considered the fitness of the patient to receive treatment with TIS, and consequently are highly relevant to establishing the conditions of use of TIS in Australia.

In addition, even amongst those patients eligible to enrol in the JULIET study, around one-third did not go on to receive treatment with TIS; including 16/165 patients who died, between enrolment and infusion, and a further 16/165 who had their treating physician decide against further participation between enrolment and infusion.

Figure 3: Patient disposition, JULIET study

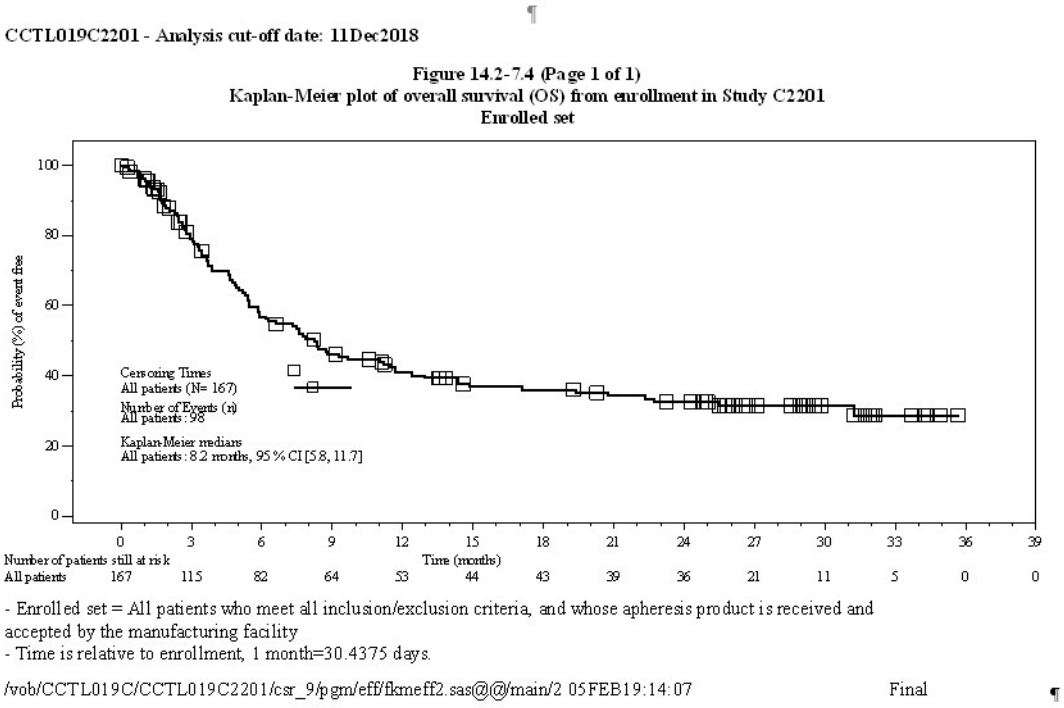


MSAC acknowledged the comments made by the clinician in the sponsor hearing that it was likely that Australian clinicians would want to treat a broader population than in the JULIET trial. However, MSAC noted evidence is currently only available for the trial population and the effectiveness and toxicity of TIS has not been established in a broader population, which will include patients who were considered too unwell for treatment in JULIET. MSAC considered it critically important that treatment with TIS is used only in patients likely to be fit enough to tolerate the treatment. MSAC recommended the Department convene a discussion with relevant stakeholders including treating clinicians, consumers, and representatives of the sponsor, Commonwealth and State/Territory governments to consider the criteria for eligibility for CAR-T therapy. MSAC considered the outcomes of that discussion should inform any future subsidy proposal made by the sponsor.

MSAC noted the inclusion of the December 2018 data cut from the JULIET trial in the resubmission had minimal effects on the observed overall survival (OS) and progression-free survival (PFS). In the December 2018 data cut, median PFS was 4.6 months (95% CI: 3.7, 5.2) which was the same as the May 2018 data cut (4.6 months [3.68, 5.19]). The median overall survival in the December 2018 data cut was 8.2 (5.8, 11.7 months) compared to 8.25 months (5.82, 11.7 months) in the May 2018 results presented at the November 2018 meeting.

MSAC agreed TIS shows an overall benefit compared with salvage chemotherapy regimen (SCR); however noted that the evidence of benefit is derived from a single arm trial in which the overall duration of follow-up remains short and the number of patients small (see Figure 4). Overall the results for TIS in treating DLBCL are not as promising as those seen for the pALL population (proportion alive at 12 months post-infusion 40% versus 71% for the pALL population).

Figure 4: Kaplan Meier plot of Overall Survival (enrolled set) for December 2018 Data cut



Source: Figure F142_7_04.rtf file in the update DLBCL_20 Feb folder

MSAC noted the calculated differences seen in the LYs and ICERs for the pALL and DLBCL populations. In the absence of an explanation from the sponsor during the hearing which satisfied the MSAC, an analysis was undertaken to clarify this issue:

> Assuming that different extrapolations are appropriate for the two populations (lognormal for the pALL population and spline for the DLBCL population), then the higher number of LYs in the pALL population (6.8) relative to the DLBCL population (1.4) are consistent with the higher observed response rate and younger age of the pALL population. Thus, the extrapolation methods, and the inclusion of different treatment-related costs must explain the similar ICER for the two diseases. At a TIS price of $**redacted** the additional costs for treating DLBCL would be $**redacted** vs around $**redacted** for pALL. Thus MSAC considered the explanation for these differences must lie in a significant difference in treatment costs for DLBCL. However, it was not clear to MSAC whether the cost differences in the TIS arms of the models are an accurate reflection of differences in disease management for DLBCL relative to pALL.

MSAC noted the revised economic analysis provided by the applicant with this application resulted in a base case incremental cost per quality adjusted life year of $**redacted** which is somewhat higher than is usually acceptable and likely, for the reasons set out by the ESC, to be underestimated.

MSAC further noted the outcomes of the economic model are most sensitive to the price of TIS, the method of extrapolation and the starting age of the model and any reasonable variations of these give rise to unacceptably high cost effectiveness ratios.

MSAC was concerned that if treatment in Australia is given to a much wider population than included in the JULIET trial thereby including less fit patients, this would also have an unfavourable impact on the cost-effectiveness of treatment.

MSAC considered the number of patients likely to be infused in Australia is a key issue that has not been resolved by the resubmission. MSAC considered the sponsor's revised estimates of patient numbers and financial impact of subsidy presented with the pre-MSAC response remain implausibly high, although acknowledged that the NHS England patient number estimates referred in Addendum 2 to the critique are an underestimate.

MSAC considered the patient numbers and financial impacts of subsidising TIS for r/r DLBCL would be more accurate if they were amended so:

- AIHW Australian Cancer Database figures are used to project the population diagnosed with NHL. This includes registry data for new diagnosed cases from all states and territories to 2015.
- Patients unfit for TIS are excluded. MSAC considered that the proportion of patients over age 80 in the Victorian Cancer Registry (Wong Doo et al. (2019), Table 1, p4) could be used as a proxy for estimating the proportion of patients of all ages unfit for TIS; with the addition of the proportion having an ECOG more than 2 in Crump 2017 (Table 1 p1803).

Incorporating these changes into the sponsor's estimates results in a total number of TIS treated patients over 6 years of 1084 at a total cost of $**redacted** million (TIS component of therapy only (see Table 6).

Table 6 Estimated costs for infused patients

DLBCL	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Total infused patients	132	199	194	186	186	188	1084
TIS cost per infused patient	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	
Total cost - infused patients	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

MSAC recognised these estimates could require further review based on the final agreed TIS eligibility criteria.

MSAC considered that, for this application to be successful, a risk-sharing agreement similar to the one put in place for the pALL population needs to developed. MSAC considered the risk-sharing arrangement should include **redacted**, data collection requirements and arrangements for further review(s) by MSAC. **Redacted**.

MSAC noted the final JULIET data would be available in 2023, and considered this might be an appropriate trigger for an MSAC review, although it may also be necessary to schedule an earlier review around 2 years after the commencement of subsidy.

MSAC considered that any resubmission could bypass ESC.

4. Background

This is the first resubmission for TIS for r/r diffuse DLBCL. At the November 2018 meeting, MSAC previously did not support public funding for TIS for adults with confirmed r/r DLBCL. Specifically, MSAC requested the definition of the appropriate eligible population needed to be redefined, as well as amendments made to the economic evaluation and a

reduced price for TIS ascertained at which it is acceptably cost-effective [Final Public Summary Document (PSD) Application No. 1519, 2018, 2019, p6].

5. Prerequisites to implementation of any funding advice

This was unchanged, refer to Application 1519 Final PSD 2018, 2019, p9.

6. Proposal for public funding

The previous submission requested creation of a new national funding mechanism, suitable for providing equitable and affordable patient access to this highly specialised and individualised hybrid genetic therapeutic process, across both approved indications.

However, MSAC considered that the funding model for the proposed pALL population should reflect the current Commonwealth–state agreements for funding through public hospitals and that in the future, a Nationally Funded Centres Program model could be considered. For the r/r DLBCL population, it was suggested that a centre would subsequently be required in every state due to the larger patient numbers [PSD Application No. 1519, 2018, 2019, p8].

The resubmission stated that issues around the appropriate funding model for CAR-T therapies lie beyond the expertise of the applicant or scope of the resubmission. However, as noted previously, Novartis is willing to work closely with MSAC, the Department of Health and broader Australian Government to develop a suitable program that addresses these general principles and ensures timely and affordable access to this important new therapeutic process.

Requested price
The resubmission proposed a reduced effective price for the r/r DLBCL indication of **redacted**.

Table 7: Redacted

Redacted.

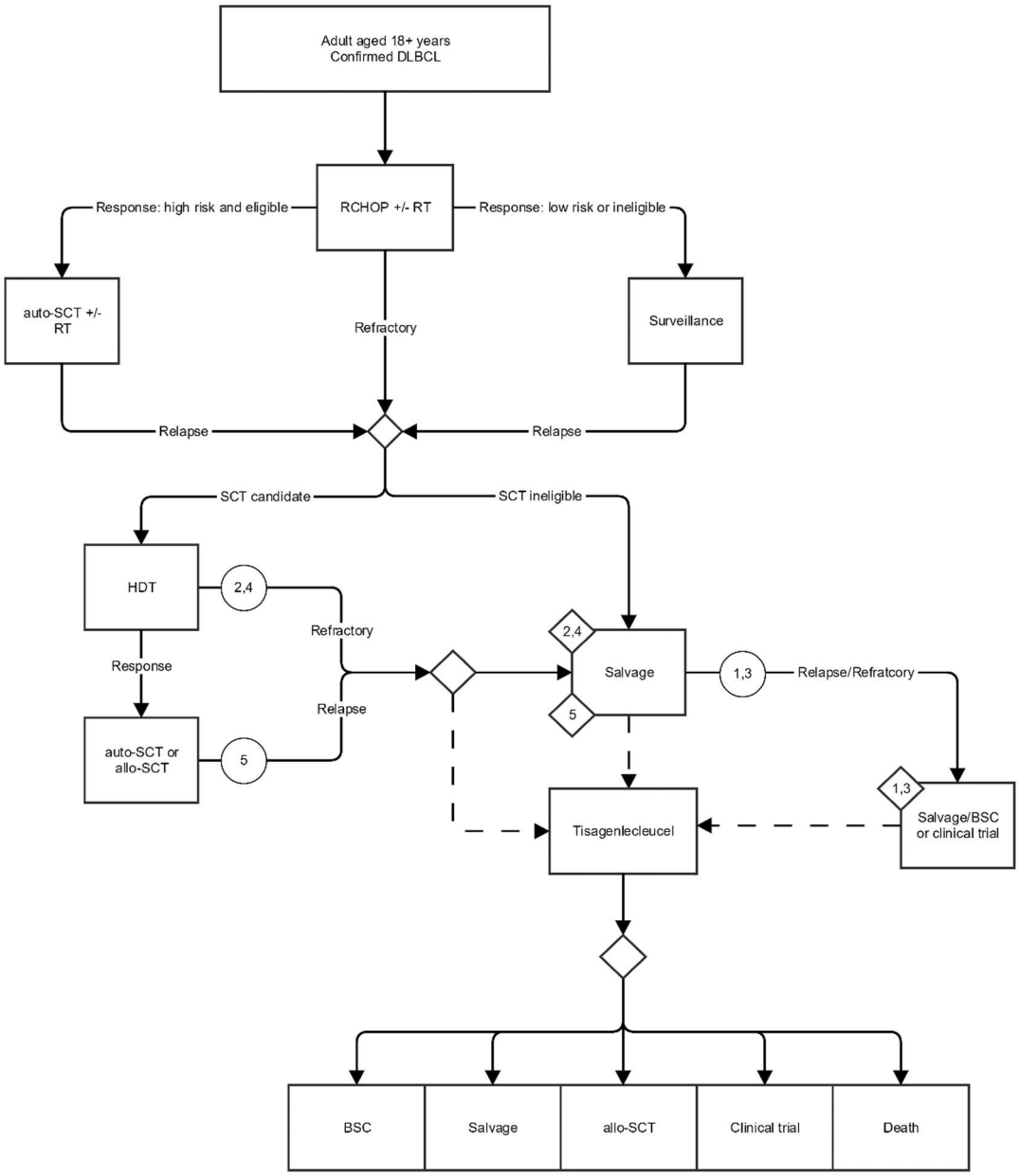
7. Summary of Public Consultation Feedback/Consumer Issues

This was unchanged, refer to Application 1519 Final PSD 2018, 2019, p10.

8. Proposed intervention's place in clinical management

This was unchanged; refer to Application 1519 Final PSD 2018, 2019, p10.

Figure 5: Current and proposed management algorithm for DLBCL



The solid lines represent current pathways, and dotted lines the proposed changes with the addition of tisagenlecleucel;

The circles indicate the patient subgroups suggested in the PICO Confirmation and the diamonds the potential comparators for each of these

Options following tisagenlecleucel treatment are also shown, noting that patients would not be eligible to return for a second infusion.

9. Other options for MSAC consideration

Nil.

10. Comparator to the proposed intervention

Consistent with the previous submission, the main comparator was SCR. MSAC previously accepted the proposed comparators Application 1519 Final PSD 2018, 2019, p10.

However, MSAC also considered that the r/r DLBCL population has other treatment options available to them, and the comparative effectiveness of TIS against these options had not been adequately explored [Final PSD, p9]. The resubmission stated there are no other therapeutic options commercially available in Australia for r/r DLBCL for which clinical

effectiveness, safety or cost is significantly different to those regimens canvassed in the submission; hence the resubmission proposed the same comparator previously assessed by MSAC [Resubmission 1519.1 2019, p28].

11. Comparative safety

The resubmission relied on results from the data cut date of 21 May 2018 from the JULIET trial (intention-to-treat (ITT) N=167; Infused N=115). Specifically, the resubmission presented 'non-CSR' safety analyses, which the Critique highlighted the non-CSR analyses did not defined adverse events (AE)s in same terms (relative to CSR-based AEs in previous submission). However, the Critique stated that it was unlikely this difference in definition made a large difference.

The Critique stated overall, no substantial changes in the proportion of patients with adverse events was presented in the updated JULIET data (note Table 7 summarises safety outcomes).

12. Comparative effectiveness

The resubmission relied on results from the data cut date of 21 May 2018 from the JULIET trial (Table 8).

Table 8 Comparative summary results from the DLBCL trials

Outcome	JULIET (May 2018)		U-PEN	SCHOLAR	CORAL_E1	CORAL_E2
Efficacy outcomes	Enrolled: N=167	Infused: N=115	N=14 (DLBCL)	N=523	N=203	N=75
ORR, n/N (%) [95% CI]	53/147 (36.1) [28.3; 44.4]	53/99 (53.5) [43.2;63.6]	7 (50) NR	134 (26.0) [21.9,29.6]	79 (38.9) [32.2, 46.0]	33 (44.0) [32.5, 55.9]
Median PFS (months) [95% CI]	4.6 [3.7;5.2]	2.9 [2.3;4.2]	3.2 [0.9, NE]	NR	NR	NR
Median OS (months) [95% CI]	8.25 [5.8;11.7]	11.1 [6.6; NE]	22.2 [NR]	6.3 [5.9,7.0]	4.4 [NR]	10.0 [NR]
Safety outcomes	Infused: N = 115			Corazelli 2009: Patients = 62; Courses = 291		
Patients with AEs, n(%)	115 (100)		NR	Total AEs n (n per course)		1,629 (5.6)
Grade ¾	104 (90.4)		NR	Grade ¾		368 (1.3)
Drug-related	102 (88.7)		NR	NR		
Serious AEs	79 (68.7)		NR			
Deaths	3 (2.6) *		NR	Deaths n(%)		1 (1.7)
CRS (any grade)	66 (57.4)		16 (57.0)	NR		

Abbreviations: ORR = overall response rate; PFS = Progression Free Survival; OS = Overall Survival; AE = Adverse Event; CRS = Cytokine release syndrome; NE = Not evaluable; NR = not reported; CI = Confidence Interval; * Deaths within 30 days post TIS infusion

The Critique provided a comparison of results from 11 December 2018 data cut-off with resubmission's May 2018 data cut, noting the updated results indicated similar estimates of effect size for progression free survival (PFS) and overall survival (OS). Specifically, the main new OS evidence presented is approximately 6 months more of follow-up, indicating a similar survival trend.

13. Economic evaluation

The resubmission presented a cost-utility analysis, using a similar model structure as previous submission. A summary of the key issues and how they were addressed in resubmission's revised base case is provided in Table 9.

Table 9 Summary of issues raised and how they have been addressed

Issue	Response
Naïve indirect comparisons of single arm trials	No change, with the revised base case continuing to be informed by a naïve indirect comparison of results from the TIS trials with those of the SCHOLAR meta-analysis. No direct or indirect randomised trials have (or are likely to) become available which would facilitate a more formal comparison. Results of an updated MAIC analysis are presented in Section B of the resubmission, however this is considered an experimental approach and would require a likely-invalid assumption of proportional hazards in order to be incorporated in the economic evaluation.
Maturity of evidence from TIS trials	The revised base case is informed by updated results from most recent available analysis of the JULIET trial (May 2018) in which the median time from infusion to the data cut-off was 19.3 months.
Intention to treat analysis	Whilst Novartis maintains the infused population is most appropriate, acknowledging the strong views expressed by the evaluators, the resubmission adopts the ITT population in the base case analysis. The revised base case is informed by PFS and OS outcomes for the total enrolled population from the above analysis of JULIET, under an extremely conservative assumption that observed rates of non-infusion in that trial will be replicated in the real-world commercial setting. Estimated costs for this proxy ITT cohort are adjusted for the proportion of patients who do not receive TIS, under the reasonable assumption that such patients would likely receive an alternative standard chemotherapy regimen.
Unclear/uncertain extrapolation of survival curves	The revised base case is informed by data from JULIET only, as opposed to the POOLED dataset including pseudo individual patient level data from U-PEN. Furthermore, model selection is based on the best fitting parametric model for each PFS/OS dataset for TIS and SCR, as opposed to the probability weighted approach presented in the original submission. Based on these criteria, flexible cubic spline models with either 1 or 2 knots have been used to extrapolate outcomes from the observed trial period of approximately 20 months until the assumed application of a common long term mortality rate as discussed below.
Long term mortality	The common long-term survival model in the revised base case uses general age based Australian mortality rates with a standardised mortality ratio for DLBCL survivors. The model is applied from 36 months reflecting available literature suggesting that DLBCL patients achieve an effective cure after around 24 months of PFS (Maurer, Ghesquieres et al. 2014). The observed OS curve for SCR in the SCHOLAR study also flattens out after approximately 3 years, suggesting that this is where SMR adjusted mortality rates should begin to apply.
Consideration of SCT following TIS	Costs and potential quality of life effects of subsequent SCT following either TIS or SCR were included in the original model and have been retained here. Comparative rates of SCT have been obtained from the respective clinical trials. Survival outcomes drawn from the same trials are inclusive of any additional effects from these downstream procedures. However, there are insufficient data with which to separately model the effects of alternative rates of subsequent SCT post TIS or SCR.
Average age of patients in the trials vs. Australian population	The starting age of patients remains estimated based on the mean age of patients in the relevant TIS dataset; 56 years as per the enrolled population in the May 2018 analysis of JULIET. Subgroup analyses key outcomes by age presented in Section B of the resubmission did not suggest that this was an important short-term treatment effect modifier. While the potential longer term survival benefits obtained as a result of TIS treatment would theoretically be less in an older population, it is uncertain that Australian patients will be materially older or have worse life expectancy than those in JULIET. Furthermore, an redacted is being proposed which will substantively address this uncertainty.
Oversimplified costing of adverse events	A more comprehensive trial-based approach to the costing of adverse events has been implemented, which separately and discretely considers all reported Grade 3/4 events occurring at a frequency <4% in either group. This is considered an extremely conservative approach, as many of these events would be reported and managed concurrently, often within the context of the initial treatment episode. However, this is balanced by the absence of any reliable information on longer term adverse outcomes of TIS.
Underestimation of IVIg use	The assumed mean duration of IVIg use has been increased from redacted to 15 months in line with evolving clinical opinion and experience. Additional sensitivity analyses are also presented.

Issue	Response
Constant health state utility weights	A time-based reduction in health state utilities has been added into the evaluation, as previously described in the AGCR. For the revised base case, this has been set at 0.0005 per cycle, or approximately 0.06 over 10 years.

The results of discounted total and incremental costs, outcomes and incremental cost-effectiveness ratios (ICER)s for the revised evaluation are provided in Table 10.

Table 10: Summary of discounted incremental results

Outcome	TIS	SCR	Incremental
Median PFS (months)	4.000	4.000	0.000
Median OS (months)	8.000	6.000	2.000
Discounted Costs	$redacted	$redacted	$redacted
Discounted Life Years	4.007	2.538	1.469
Discounted QALYs	3.046	1.768	1.278
Discounted Cost/LY			$redacted
Discounted Cost/QALY			$redacted

The Critique's one-way sensitivity analyses indicated:

- for varying the method for parametric extrapolation the ICER ranged from SCR dominant (exponential for all survival curves) to $**redacted** (lognormal for TIS; Gamma for SCR);
- for varying the start age in model the ICER ranged from $**redacted** (model age: 60 years) to $**redacted** (model age: 70 years).

Using the lognormal curves for all parametric extrapolation, the Critique's multivariate sensitivity analyses indicated the ICER ranged from $**redacted** (TIS price: $**redacted**) to $**redacted** (start age: 65 years).

In summary, the Critique stated that the resubmission's economic evaluation based on a naïve comparison has substantial evidentiary problems that lead to high economic uncertainty and at times illogical results. Acknowledging the strong limitations of the clinical evidence, it appears likely that the ICER is extremely underestimated in the resubmission.

In the Pre-ESC response, the applicant provided an updated economic model for TIS, with the following changes applied to the re-application base case:

- The results from the December 2018 data-cut of JULIET were applied to the model (compared to May 2018 in the re-application).
- The PFS and OS extrapolation is forced from cycle 24 instead of cycle 20, reflecting the additional observed data available.
- The TIS PFS and OS extrapolation models changed from Spline 2 to Spline 1 and Spline 3, as these were the best fitting models to the updated data cut.
- The price of TIS was reduced from $**redacted** to $**redacted**.
- No changes were made to the SCR arm, other than forcing PFS and OS extrapolation from cycle 24 instead of cycle 20.

The revised base case ICER per QALY is presented in Table 11.

Table 11 Results of the revised economic evaluation

Outcome	TIS	SCR	Increment
Base case (Spline 1/3 for TIS OS/PFS and Spline 1 for SCR OS/PFS)			
Discounted Costs	$redacted	$redacted	$redacted
Discounted Life Years	3.962	2.538	1.425
Discounted QALYs	2.992	1.768	1.225
		Discounted Cost/LY	$redacted
		Discounted Cost/QALY	**$redacted**

14. Financial/budgetary impacts

The resubmission's financial estimates (Table 12) included the following changes:

- The resubmission considers the financial impact of the proposed program across all government healthcare budgets;
- Estimates of the eligible population in the first two years of the analysis have been increased to account for current prevalent relapsed / refractory DLBCL cases;
- Additional disaggregated uptake assumptions have been applied, incorporating updated expectations around geographical access and likely utilisation of CAR-T therapy;
- The previous market share approach has been discarded and revised estimates account for the total expected uptake of CAR-T therapies within the target r/r DLBCL indication;
- Cost estimates have been refined to separately consider infused and non-infused patients, explicitly assuming that the applicant will not receive any funding for the latter group;
- Increased costs related to Grade 3/4 adverse events and prolonged IVIg administration have been incorporated, consistent with the revised economic evaluation; and
- The launch price of TIS has been reduced, **redacted**, in line with the new pricing proposal.

Table 12: Estimated financial impact

Total Patients	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Eligible population	redacted	redacted	redacted	redacted	redacted	redacted	redacted
TIS patients (infused)	redacted	redacted	redacted	redacted	redacted	redacted	redacted
TIS patients (non-infused)	redacted	redacted	redacted	redacted	redacted	redacted	redacted
TIS costs (infused)	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Other costs (infused)	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Other costs (non-infused)	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Cost offsets (SCR)	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Net budget impact	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

Source: Section E Workbook, Inputs worksheet

The Critique stated the most important change in financial estimates was the near tripling of total infused patients over the first six years of listing. Other important changes included the TIS price reduction, and the more conservative costing of AEs.

The Pre-ESC response offer of a lower price has not been incorporated into these estimates.

15. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
The definition of the eligible population remains broad	Based on TGA approved indication, MSAC may wish to define the eligible population for public funding more tightly than the TGA-approved indication.
Survival data are immature. Claims of superior effectiveness and non-inferior safety are unsubstantiated	The applicant presented the same data-cut from the JULIET study (May 2018) as the pre-ESC updates for the previous application. Results from a more recent data-cut (December 2018) are relied on in the pre-ESC Response to the current application but have not been independently evaluated. Considerable uncertainty remains around the size and the durability of the benefit. Treatment with TIS is associated with significant risk of adverse events.
Comparative effectiveness of TIS against other treatment options	The applicant has not addressed this; the applicant states that it was unclear as to what was required. Although not explicitly stated in the MSAC Advice for the previous application, ESC was of the view that it was not unreasonable to expect there to be a consideration of the effectiveness of emerging immunotherapies for the proposed population.
Issues with the economic modelling	The base case may be overly optimistic, as the following assumptions substantially affect the ICER: • extrapolation method; and • starting age.
Uncertainty in the budget impact	Likely that utilisation and cost estimates for TIS are significantly overestimated.
Risk mitigation proposals	The final price offer and the proposed risk-sharing arrangement may not be sufficient to offset the clinical, economic and budget uncertainties with this subsidy proposal.

ESC Discussion

Application 1519.1 is a re-application that seeks MSAC support for the public subsidy of tisagenlecleucel (TIS) for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

The ESC noted the re-application included:

- an updated price;
- **redacted**;
- updated clinical data (the economic analysis was only updated with the new clinical data as part of the pre-ESC response);
- an updated economic analysis and
- updated financial estimates.

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 chemotherapy, and then a second-line

chemotherapy regimen or autologous stem cell transplantation (ASCT). Refractory disease is treated with multiple lines of therapy and many patients are never candidates for ASCT.

The ESC noted the change to the proposed eligibility for subsidy to reflect the wording of the TGA approval:

- previous application: adult patients with relapsed or refractory DLBCL who are ineligible for or relapse after autologous stem cell transplant (ASCT)
- current application: adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy.

The resubmission argued that the eligible population would effectively remain the same as in the previous application. However, ESC considered that the revised eligibility criteria may not adequately describe the patients most likely to benefit from therapy and advised that the MSAC may wish to include additional criteria, for example: performance status; whether or not ASCT is counted as a line of systemic therapy; and whether or not treatment with CAR-T therapy should be limited to once per lifetime. ESC further noted that the characteristics that might render patients ineligible for ASCT (e.g. older age/frailty, multiple co-morbidities) might also render them unsuitable for CAR-T therapy, and that the JULIET clinical trial protocol included a number of eligibility criteria directed at ensuring that patients are fit enough for treatment with TIS.

The ESC noted the re-application included updated clinical data from the single arm JULIET study, with headline results for the 11 December 2018 data cut-off provided post application and incorporated into the economic analysis provided with the pre-ESC response.

The ESC noted the median Progression Free Survival (PFS) based on the December 2018 cut-off of the JULIET data was 4.6 months (95% CI: 3.7, 5.2) which was the same as at the May 2018 data cut (4.6 months [3.68, 5.19]). However, ESC also noted the short median duration of follow up and very low numbers of at risk patients at later time points in the PFS and Overall Survival (OS) Kaplan Meier curves. Although the ESC was somewhat reassured by the additional clinical results, it was of the view that there continues to be considerable uncertainty around the long term outcomes of treatment.

The ESC acknowledged the sponsor proposes **redacted** for the DLBCL indication, and that this may be the most feasible/practical approach to addressing the concerns raised in the evaluation while providing timely access to this therapy. The ESC considered the **redacted** in the context of this disease. The ESC also noted the proposed **redacted**.

ESC noted the updated JULIET safety data, and that there were no changes to the proportion of patients with adverse events (AEs).

The ESC noted the applicant had included an extra study (Corazzelli 2009) to inform the modelling of AEs in the SCR arm of the economic model. However, the Critique noted that the Corazzelli study followed patients with B-cell non-Hodgkin lymphoma after treatment with gemcitabine and oxaliplatin (with or without rituximab). ESC agreed with the Critique that it is unclear if these AE data would be applicable to the DLBCL population treated with R-DHAP – the salvage chemotherapy most likely to be used in Australia and the one assumed for the economic evaluation. The Critique also noted that Corazzelli did not look at AEs as a proportion of events over patients treated, but rather the proportion of cycles with individual adverse events over number of courses of treatment. The ESC considered that this did not form a reasonable basis for comparison of AEs in the economic model.

The ESC noted the re-application included changes to the economic evaluation (re-application model), and that the latest version of the economic model provided with the pre-ESC response (pre-ESC model) had the following changes applied to the re-application base case:

- The results from the December 2018 data-cut of JULIET were applied to the model (compared to May 2018 in the re-application);
- The PFS and OS extrapolation was forced from cycle 24 instead of cycle 20, reflecting the additional observed data available;
- The TIS PFS and OS extrapolation models were changed from Spline 2 to Spline 1 and Spline 3, as these were the best fitting models to the updated data cut; and
- The price of TIS was reduced from $**redacted** to $**redacted**.

The ESC noted that the updated economic model is based on the intention-to-treat (ITT) population, consistent with the MSAC advice from its November 2018 consideration. However, the ESC noted a number of issues remain with the economic model that mean that the incremental cost (ICER) per quality adjusted life year (QALY) is likely underestimated:

- The extrapolation of survival in the TIS arm may be overly optimistic. The base case (Spline 1/3 for TIS OS/PFS and Spline 1 for SCR OS/PFS) discounted cost/QALY is $**redacted**. Alternative extrapolation methods result in higher discounted costs/QALY (eg using lognormal for all survival curves, the discounted cost/QALY is $**redacted**; using loglogistic for all survival curves, the discounted cost/QALY is $**redacted**) (See also Table 3 in the addendum to the Critique)
- The starting age in the model (56 years) is lower than the age of diagnosis in Australia (60 – 70 years). In the model provided in the re-application, the base care discounted cost was $**redacted** /QALY, which increased to $**redacted** /QALY if the starting age in the model was 60 years and to $**redacted** /QALY at age 70 years.

The Critique considered it counter intuitive that the modelled ICER in the ITT population in the pre-ESC model was lower than in the infused population ($**redacted** versus $**redacted**). The same outcome was also observed in the model provided with the previous application. The applicant explained this is a mathematical artefact as a result of the extrapolation. The ESC considered the applicant's explanation may be reasonable, with this outcome being possible in some scenarios.

The ESC noted the applicant had updated the financial estimates as follows:

- to consider the financial impact of the proposed program across all government healthcare budgets;
- the eligible population in the first two years of the analysis has been increased to account for current prevalent r/r DLBCL cases;
- additional disaggregated uptake assumptions have been applied, incorporating updated expectations around geographical access and likely utilisation of CAR-T therapy;
- the previous market share approach has been discarded and revised estimates account for the total expected uptake of CAR-T therapies within the target r/r DLBCL indication;
- cost estimates have been refined to separately consider infused and non-infused patients, explicitly assuming that the applicant will not receive any funding for the latter group;
- increased costs related to Grade 3/4 adverse events and prolonged IVIg administration have been incorporated, consistent with the revised economic evaluation; and
- the price of TIS has been reduced.

The ESC considered it likely that the utilisation and cost estimates for TIS in DLBCL are significantly over-estimated, noting:

- in an overseas program, one-third of the patients recommended for CAR-T therapy did not receive the transfusion because of disease progression or death. However the submission assumes higher uptake rates will occur in Australia;
- many patients in this DLBCL population who are unsuitable for ASCT as a second-line treatment due to comorbidities and/or age would also be unsuitable for TIS therapy, given the safety profile of TIS.
- the submission's estimates for the total infused population in Australia greatly exceed the NHS England patient number estimates for tisagenlecleucel and for axicabtagene ciloleucal (Yescarta®), noting the UK estimates do not account for market share (ie the two populations overlap), and also the estimated UK patient population eligible for axicabtagene ciloleucal is higher to account for its wider indication[1]. This is in spite the total population covered by NHS England being around 56 million compared to the Australian population of 26 million.

The ESC requested the Department undertake a second independent review of the utilisation and financial estimates presented in the submission and provide these to the MSAC as an annex to the critique.

Finally, the ESC noted there continue to be media reports suggesting Novartis may be experiencing difficulties in manufacturing product to regulatory standards, in particular for DLBCL patients. The ESC requested the applicant provide an update on the current manufacturing failure rate with its pre-MSAC response.

Overall, with the exception of the adoption of ITT analyses in the economic model, the ESC was of the view that none of the areas of clinical, economic or budget uncertainty previously identified by the MSAC have been substantively addressed in the re-application. The ESC considered that the **redacted** may not adequately address these issues and requires further development and refinement.

16. Other significant factors

Nil.

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

Novartis welcomes the MSAC recommendation of tisagenlecluecel for patients with DLBCL. After considerable efforts from the MSAC, the Department of Health and Novartis, we look forward to reimbursed access for eligible Australian patients to this innovative, personalised therapy.

18. Further information on MSAC

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

[1] https://www.england.nhs.uk/wp-content/uploads/2018/12/Tisagenlecleucel-Chimeric-Antigen-Receptor-T-Cell-CAR-T-Therapy-for-ALL-and-DLBCL.pdf
https://www.england.nhs.uk/wp-content/uploads/2018/12/Axicabtagene-Ciloleucel-Chimeric-Antigen-Receptor-T-Cell-CAR-T-Therapy-for-the-treatment-of-adult-patients-wit.pdf