



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1653 – Amendment to eligibility criteria for Tisagenlecleucel (CTL019) for treatment of relapsed or refractory diffuse large B-cell lymphoma – removal of the requirement for patients to be “CD19-positive”

Applicant: Novartis Pharmaceuticals Australia Pty Ltd

Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020

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 removal of the requirement for patients to be CD-19 positive to access publicly funded treatment with tisagenlecleucel (TIS) (Kymriah[®]) for diffuse large B-cell lymphoma (DLBCL) was received from Novartis Pharmaceuticals Australia Pty Ltd by the Department of Health.

2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support amending the eligibility criteria for tisagenlecleucel (TIS) (Kymriah[®]) for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) by removing the requirement for patients to test positive for CD-19 expression on their B-cells.

MSAC considered that since tisagenlecleucel is a cell-based therapy specifically targeting CD-19 expression, and since there is no minimum threshold set for CD-19 positivity, the argument for removing the requirement was not adequately supported.

Consumer summary
<p>Novartis Pharmaceuticals Australia Pty Ltd submitted an application to remove the requirement for being CD-19 positive to access tisagenlecleucel for people with relapsed or refractory diffuse large B-cell lymphoma.</p> <p>Tisagenlecleucel is a CAR-T cell therapy (CAR stands for chimeric antigen receptor and a T or thymus cell is a white blood cell that has a key role in our immune system). CAR-T cell therapy is used when patients with some types of cancer, such as lymphoma or leukaemia, don’t respond to (are refractory), or relapse after, other types of treatment, such</p>

Consumer summary

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 their body to target and kill the cancer cells.

Tisagenlecleucel is a cell-based therapy that targets CD-19. The Medical Services Advisory Committee (MSAC) therefore considered it important for the patients receiving this therapy to be CD-19 positive. MSAC considered there was not enough evidence to support removing the requirement to be CD-19 positive.

MSAC's advice to the Commonwealth Minister for Health

MSAC recommended that the requirement for being CD-19 positive should not be removed. This is because there was not enough evidence to suggest that patients who are not CD-19 positive would still benefit from the therapy.

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

MSAC noted that Application 1653 is a minor submission requesting removal of the requirement to be CD-19 positive for publicly funded treatment with tisagenlecleucel (TIS) for refractory/relapsed DLBCL in adults, primary mediastinal large B-cell lymphoma and transformed follicular lymphoma.

MSAC noted the applicant's assertion in its pre-MSAC response that a retrospective analysis of the JULIET study revealed that there is no clear relationship between high and low CD-19 expression and response to TIS. MSAC agreed, but considered this to be of limited relevance, as the funding eligibility criteria do not include a threshold for CD-19 positivity. MSAC further noted that all patients in the JULIET study for whom CD-19 levels were done had some level of CD-19 expression. The applicant also asserted that CD-19 testing is not routine practice, but MSAC noted advice from the state jurisdictions that immunohistochemistry (IHC) testing for CD-19 is routine in Australia.

MSAC noted that TIS is a chimeric antigen receptor T-cell (CAR-T) therapy – also known as CTL019 – it comprises autologous T-cells genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor. MSAC thus considered it appropriate for patients who receive TIS to be CD-19 positive in absence of any evidence that it is effective in patients who are not CD-19 positive.

MSAC noted the state responses were, in general, not supportive of the change, noting among other things that CD-19 testing is routine clinical care, and that removing the criteria for CD-19 positivity may affect the payment agreement.

MSAC noted that removing the criteria for CD-19 positivity would have potential implications for axicabtagene (Gilead) and childhood acute lymphoblastic leukaemia.

MSAC noted that the CAR-T program requires ongoing evaluation.

MSAC noted that emerging data on pre-treatment with other CD19 treatments (such as blinatumumab) may influence response to CAR-T therapy.

MSAC considered that if TIS is to be used in a wider population or if the requirement for CD19 positivity is to be removed, that the applicant must come back with a new submission with additional evidence to support the change.

4. Background

TIS was recommended for public funding for the treatment of diffuse large B-cell lymphoma (DLBCL); primary mediastinal large B-cell lymphoma (PMBCL) or transformed follicular lymphoma (TFL) at the November 2019 MSAC meeting (MSAC 1519.1).

5. Prerequisites to implementation of any funding advice

TIS is TGA registered for (1) the treatment of paediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse and (2) the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. TIS is not indicated for patients with primary central nervous system lymphoma.

6. Proposal for public funding

The application proposed that the removal of the requirement for a patient to test positive for CD19 expression should be made for two reasons:

1. CD19 positivity was not part of the eligibility criteria in the pivotal JULIET trial which was considered at the November 2019 MSAC meeting; and
2. CD19 testing is not standard clinical practice in treating DLBCL.

The applicant considered that the change to the listing would not affect the financial implications of public funding for these indications since the financial estimates considered at the November 2019 MSAC meeting did not exclude CD19 low/negative patients. The applicant also considered that there may be potential delay and/or restricted access to treatment of TIS due to the requirements of CD19 testing to be conducted.

The application provided evidence from three sources:

- Summary of evidence of CD19 expression in DLBCL
- Patient eligibility criteria for the pivotal JULIET trial (C2201)
- Exploratory analysis of CD19 expression and overall response from the JULIET study, including individual patient data for CD19 “low/negative” patients.

7. Summary of public consultation feedback/consumer Issues

There was no public consultation feedback received for this minor application.

8. Proposed intervention’s place in clinical management

Description of Proposed Intervention

The current eligibility criteria for treatment with TIS is detailed in the below table with suggested amendment to the criteria marked in strikethrough.

Table 1: MSAC recommended eligibility criteria for TIS

Indication:	<p>Relapsed or refractory CD19 positive:</p> <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:	<p>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.</p>
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>

Source: MSAC PSD 1519.1

The application asserted that testing for CD19 is not standard in clinical practice for DLBCL. However, advice provided by one of the representing state jurisdictions for the National Health Reform Agreement (NHRA), provided information that the test to confirm patients as CD19 positive is simple and can be done as part of usual clinical work-up of a patient.

9. Comparative evidence

The application asserted that most B cell lymphomas express high levels of CD19 and that CD19 is present to some extent in all B cell lymphomas, and there is no agreed standard threshold for defining CD19 positivity.

The application noted the JULIET clinical trial that provided the basis for the MSAC subsidy recommendation at the November 2019 MSAC Meeting, did not include confirmation of CD19 expression as an eligibility criterion.

The application presented results from a retrospective analysis of CD19 expression in available tumour tissues of patients conducted in a central laboratory by an exploratory quantitative fluorescent IHC assay.

The application noted the analysis had the following limitations:

- The analysis was based on a single “baseline” biopsy of a subset of the patients who received a TIS infusion in the study (82 of 111).
- Many of the samples were taken months before infusion of tisagenlecleucel (1 month to 1 year in 60 of 82 patients and more than 1 year in 22 of 82 patients).
- Heterogeneity in CD19 expression from different lesions or different parts of the lymph nodes could exist.
- The score used to divide patients into CD19 positive and CD19 negative/low has not been validated.

The results of the retrospective analysis are provided in Table 2.

Table 2: Best overall response by CD19 expression levels (full analysis set)

	Dec 2017 data cut-off		Feb 2020 data cut-off	
	CD19 high expression (N=redacted)	CD19 low expression (N=redacted)	CD19 high expression (N=redacted)	CD19 low expression (N=redacted)
Best overall response	n (%)	n (%)	n (%)	n (%)
CR	redacted (redacted)	redacted (redacted)	redacted (redacted)	redacted (redacted)
PR	redacted (redacted)	redacted (redacted)	redacted (redacted)	redacted (redacted)
SD	redacted (redacted)	redacted (redacted)	redacted (redacted)	redacted (redacted)
PD	redacted (redacted)	redacted (redacted)	redacted (redacted)	redacted (redacted)
Unknown	redacted (redacted)	redacted (redacted)	redacted (redacted)	redacted (redacted)
ORR (CR + PR)	redacted (redacted)	redacted (redacted)	redacted (redacted)	redacted (redacted)
ORR 95% CI	redacted, redacted	redacted, redacted	redacted, redacted	redacted, redacted

The 95% CIs are exact Clopper-Pearson CIs

Abbreviations: CI, confidence interval; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

Patients were classified as CD19 high expression if they had an AQUA score $\geq 10,000$, and low/negative expression if they had an AQUA score $< 10,000$. No patient had negative CD19 expression, as all patients tested had some level of CD19 expression

All patients in the low CD19 group had some level of CD19, ranging from **redacted** to **redacted**. Some patients with a documented low level of CD19 recorded a complete response, and conversely some patients with a documented high level of CD19 experienced disease progression.

Overall, the application claimed there is no clear relationship between CD19 status, as measured in this analysis and outcomes in terms of complete response (CR) and partial response (PR). However, the limitations in the study also meant that it is difficult to exclude the possibility that there is a relationship between CD19 level measured just prior to treatment and outcome.

10. Economic evaluation

There was no economic evaluation presented for this application as it was a minor application.

11. Financial/budgetary impacts

The application expected there to be no change to the patient numbers and financial estimates that were submitted as part of the November 2019 MSAC resubmission (1519.1), as the

estimated number of eligible patients were not adjusted for the proportion of patients who would test as CD19 'positive'. The costings submitted for this application were therefore the same with patient estimates up to January 2020, as was provided for Application 1519.1.

The application did not request any changes to the current risk share arrangements for TIS in DLBCL.

12. Other significant factors

Nil

13. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

14. Further information on MSAC

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