



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1676 – Amendments to eligibility criteria for tisagenlecleucel for treatment of relapsed or refractory diffuse large B-cell lymphoma – amend clinical criteria for patients with Transformed Follicular Lymphoma (TFL) and propose inclusion of patients with grade 3B follicular lymphoma (3B FL)

Applicant: Novartis Pharmaceuticals Australia Pty Ltd

Date of MSAC consideration: 82nd MSAC Meeting, 29-30 July 2021

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

1. Purpose of application from Novartis

An application was received from Novartis Pharmaceuticals Australia Pty Ltd, concerning tisagenlecleucel (Kymriah) to:

- (a) allow transformed follicular lymphoma (TFL) patients who have undergone prior autologous stem cell transplant (ASCT) to access tisagenlecleucel, without the requirement for additional systemic therapy post-ASCT; and
- (b) treat Grade 3B FL patients as diffuse large B-cell lymphoma (DLBCL) patients in eligibility criteria, due to the similarity of grade 3B FL to DLBCL in terms of presentation, behaviours and outcomes.

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 supported the minor changes to the eligibility criteria for tisagenlecleucel (as proposed in the Pre-MSAC response) regarding certain patients with transformed follicular lymphoma (TFL) and certain patients with grade 3B follicular lymphoma (FL). MSAC considered there would be a very small number of additional patients that would be eligible and there was support for these changes from the National CAR-T Patient Prioritisation Committee and from the States and Territories.

Redacted.

Consumer summary
Tisagenlecleucel (TIS) is a CAR-T cell therapy (CAR stands for chimeric antigen receptor, and a T 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,

Consumer summary

don't respond to (are 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 their body (i.e. flowed back into the body via a cannula in a large vein) to target and kill the cancer cells.

MSAC has already supported public funding for TIS (Kymriah®), including for patients with CD19-positive diffuse large B-cell lymphoma (DLBCL) and transformed follicular lymphoma (i.e when follicular lymphoma changes into a more aggressive lymphoma type). MSAC agreed that TIS gives some patients who have exhausted all other treatments a new chance at possibly achieving remission. At that time, 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.

In this application, Novartis Pharmaceuticals Australia Pty Ltd, the manufacturer of TIS, had two requests, each involving slight changes to eligibility criteria.

- The first request was that people who have transformed follicular lymphoma who have undergone autologous stem cell transplant (ASCT) be able to access TIS, without needing to have additional therapy that treats the whole body, such as chemotherapy, after ASCT. (ASCT uses healthy blood stem cells from the patient's body to replace diseased or damaged bone marrow cells.)

- The second request was that people who have grade 3B follicular lymphoma are treated the same as those people with DLBCL because grade 3B follicular lymphoma is similar to DLBCL in the fact that it is fast growing (compared to grades 1, 2 and 3A, which are slow growing).

MSAC considered there would be a very small number of additional people who would be eligible, and noted there was support for these changes from the National CAR-T Patient Prioritisation Committee, and from the States and Territories.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported the request for minor changes to the eligibility criteria for tisagenlecleucel regarding certain people (as specified in the application) with transformed follicular lymphoma and certain people (as specified in the application) with grade 3B follicular lymphoma.

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

MSAC noted that an application was received from Novartis Pharmaceuticals Australia Pty Ltd in April 2021, concerning the funding under the National Health Reform Agreement of tisagenlecleucel (Kymriah®).

The first request from the applicant was to allow TFL patients who have undergone prior autologous stem cell transplant (ASCT) to access tisagenlecleucel, without the requirement for additional systemic therapy post-ASCT. MSAC noted that JULIET, the pivotal study in this setting, included 21 patients with TFL (of 111 patients in the full analysis set). However, the subgroup reporting in JULIET is not sufficiently precise to inform efficacy and safety for this small group (TFL patients relapsing after one line of therapy, including ASCT, after transformation). Despite this, efficacy and safety outcomes reported for JULIET's overall

population are assumed to apply, as is MSAC’s view of comparative safety, clinical effectiveness and cost-effectiveness from the original application 1519.1.

The second request from the application was to treat grade 3B FL patients as diffuse large B-cell lymphoma (DLBCL) patients in eligibility criteria, due to the similarity of grade 3B FL to DLBCL in terms of presentations, behaviours and outcomes. MSAC noted that it is broadly accepted that grade 3B FL is managed as DLBCL and that this proposal will help ensure consistency of use across treatment centres. MSAC noted that there is a very low risk of leakage to grade 3A FL.

MSAC also noted that the applicant asserted that there is age-based inequity of access at the state/territory-level. However, MSAC noted that no evidence was submitted regarding age-based inequity of access.

4. Background

Tisagenlecleucel (Kymriah) is a Class 4 biological with the following TGA indication:

KYMRIAH is a genetically modified autologous immunocellular therapy indicated for 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. KYMRIAH is also indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Kymriah is not indicated for patients with primary central nervous system lymphoma.

Tisagenlecleucel is a CD19-directed chimeric antigen receptor (CAR) – T cell therapy that is treated as a high cost, highly specialised therapy (HST) as per the National Health Reform Agreement (Schedule J, i.e. Addendum to NHRA, 2020-2025)¹.

Health technology assessments of Kymriah have been conducted as follows:

Table 1: Kymriah applications

MSAC meeting/s	Applic'n number	Topic	Outcome	Link
Nov 2018; March 2019; April 2019	1519	Acute lymphoblastic leukaemia (ALL). Initial application covered ALL and DLBCL. (DLBCL component was later addressed in 1519.1.)	MSAC recommended public funding of TIS for treatment of ALL in children and young adults up to 25 years	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519-public
August 2019; November 2019	1519.1	DLBCL. Initial application covered DLBCL.	MSAC recommended public funding of TIS for certain patients with DLBCL, PMBCL and TFL.	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519.1-public
November 2020 (bypassed PASC, ESC)	1653 (minor)	Amendment to eligibility criteria in DLBCL - removal of requirement for CD19-positivity	MSAC did not support removing the requirement for CD19 positivity.	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1653-public
July 2021 (bypassed PASC, ESC)	1676 (minor)	(Current application)		

¹ https://www.federalfinancialrelations.gov.au/content/npa/health/other/NHRA_2020-25_Addendum_consolidated.pdf (see C11, C12, Appendix A, and Appendix B)

MSAC in November 2019 recommended eligibility criteria² for tisagenlecleucel in DLBCL informed by, amongst other things, a November 2019 stakeholder meeting that sought advice about appropriate eligibility criteria.

Axicabtagene ciloleucel (Yescarta; Gilead Sciences) has been recommended by MSAC³ for use in DLBCL and related lymphomas. The application requested public subsidy to treat relapsed / refractory DLBCL, including DLBCL not otherwise specified, TFL, primary mediastinal B-cell lymphoma and high grade B-cell lymphoma (HGBCL). In the Public Summary Document (PSD), the indication was described as:

Relapsed or refractory CD19-positive:

- Diffuse large B-cell lymphoma (DLBCL)
- Primary mediastinal large B-cell lymphoma (PMBCL)
- Transformed follicular lymphoma (TFL)

The Yescarta PSD implied MSAC accepted use in HGBCL, as follows:

treatment with AXI would be acceptably cost effective if the **redacted** was enhanced by: ... a limit to one successful CAR-T infusion per lifetime for r/r DLBCL, including DLBCL NOS and TFL, PMBCL and HGBCL

Regarding the relationship of HGBCL to DLBCL, clinicians may be regarding HGBCL as a type of DLBCL; this seems appropriate, though possibly some HGBCL may resemble forms of B-cell lymphoma other than DLBCL.

Yescarta has the following TGA indication:

YESCARTA is a genetically modified autologous immunocellular therapy for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, 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. YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

(A paper by Neelapu et al (2019)⁴ indicates that ZUMA-1, the pivotal study for Yescarta in this use, enrolled many patients with HGBCL.)

5. Proposal for public funding

The proposed modifications to the current MSAC-recommended and publicly funded use of Kymriah in DLBCL is summarised below, with *blue, and italicised text*:

² Table 1 (Eligibility criteria for TIS) at

[http://www.msac.gov.au/internet/msac/publishing.nsf/Content/A2B10F9A03293BC8CA2583CF001C7A4D/\\$File/1519.1%20Final%20updated%20PSD%20Nov%2019_redacted.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/A2B10F9A03293BC8CA2583CF001C7A4D/$File/1519.1%20Final%20updated%20PSD%20Nov%2019_redacted.pdf)

³[http://www.msac.gov.au/internet/msac/publishing.nsf/Content/B5B780278B3A4B48CA2583C9001B80BB/\\$File/1587%20Final%20PSD%20Nov%2019_redacted.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/B5B780278B3A4B48CA2583C9001B80BB/$File/1587%20Final%20PSD%20Nov%2019_redacted.pdf)

⁴ <https://www.sciencedirect.com/science/article/pii/S1083879118309704>

Table 2: Eligibility criteria for tisagenlecleucel

Indication:	Relapsed or refractory CD19-positive: <ul style="list-style-type: none"> • diffuse large B-cell lymphoma (DLBCL) • <i>Grade 3B follicular lymphoma (3BFL)</i> • 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, 3BFL and PMBCL: The condition must have <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 FOR TFL: <i>After disease transformation</i> , the condition must have <ul style="list-style-type: none"> (i) relapsed after <i>autologous stem cell transplantation</i>, or (ii) <i>have relapsed after, or be refractory to, at least two prior systemic therapies administered after disease transformation</i> FOR ALL INDICATIONS: Patient must have a WHO performance status of 0 or 1 AND Patient must have sufficient organ function, including: <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 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.

Summary of Application – Key issues for MSAC

The application by Novartis was on behalf of the National CAR-T Patient Prioritisation Committee (NCPPC), and included a letter dated 31st March 2021, from the Chair of the NCPPC, Professor Simon Harrison.

Concerning the request to change eligibility for TFL patients with prior autoSCT, the key clinical issues are that:

- Although JULIET [1], the pivotal study in this setting, included 21 patients with TFL (of 111 patients in the full analysis set), the sub-group reporting in JULIET is not sufficiently granular to inform efficacy and safety for this small group (TFL patients relapsing after 1 line of therapy, including autoSCT, after transformation). Efficacy and safety outcomes reported for JULIET's overall population are assumed to apply, as is MSAC's view of comparative safety, clinical effectiveness and cost-effectiveness from Application 1519.1.

- Most TFL patients transform to DLBCL, and so may be eligible after autoSCT (used to treat the DLBCL) without the need for additional systemic therapies, ‘anyway’.
- Where autoSCT has been used in treatment of the antecedent FL, some patients may not be captured by the proposed wording (but they would become eligible on failure of two lines of therapy for transformed disease).

Concerning the request to specifically include patients with grade 3B FL, it is broadly accepted that 3B FL is managed as DLBCL. This proposal will help ensure consistency of use across treatment centres. There is a very low risk of leakage to 3A FL.

Despite the minor changes to eligibility criteria noted above, Novartis has proposed no changes to current patient and financial estimates, arguing that:

- Patient and financial estimates from the November 2019 resubmission considered by MSAC included patients with TFL, irrespective of the number of lines of therapy post-transformation; and
- Grade 3B FL patients are very uncommon and consequently no changes to the patient and financial estimates are proposed for these patients, particularly as biologically grade 3B FL is considered equivalent to DLBCL.

The NCPPC writes that the changes would result in “only a very minor, if any, increase in patient numbers”.

Across both proposed changes, it appears the impact on utilisation is very modest, but because Kymriah is expensive, there could still be a moderate budget impact even with a single ‘additional’ patient. The Western Australia Department of Health submission sought clarity about impact on patient / financial numbers, “as the number of patients in the new eligibility criteria will be greater than zero”. While there seems **redacted**, any actual increase in use needs to be funded (therefore budgeted for in advance) in part by the States and Territories.

An estimated 3-15 extra patients will be infused per year, if the eligibility changes are accepted. This assumes no impact on patient numbers due to the TFL change, and 3-10 new patients in Year 1 based on the 3B FL change, rising to 7-15 new patients in Year 6. The 3B FL estimates assume that 10% of FL is grade 3B, but the actual proportion may be less than 10%, and as low as ~5%. The other source of major uncertainty is uptake.

MSAC’s attention is drawn to the issue raised by Novartis concerning equity of access, however no specific evidence was submitted to inform the concern raised, and feedback from States and Territories (other than Western Australia) did not touch on this issue.

6. Summary of public consultation feedback/consumer Issues

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

7. Proposed intervention’s place in clinical management

TFL in patients with prior autoSCT

Proposal and rationale

Eligibility for tisagenlecleucel using the TFL criteria now requires that the patient has relapsed after, or been refractory to, at least two systemic therapies given after disease transformation.

An alternative criterion is being proposed, such that a patient who has relapsed after autoSCT, given after disease transformation, would be eligible (without requiring any extra line of systemic therapy after disease transformation):

After disease transformation, 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 administered after disease transformation*

In the submission's letter from the NCPCC, a rationale for the change is given:

...patients with a prior history of indolent lymphoma which then transforms may do so relatively late in their natural history, exhausting standard therapies for DLBCL along the way, including stem cell transplantation. Offering stem cell transplant to a patient more than once is never done, due to the toxicity of the procedure and lack of evidence.

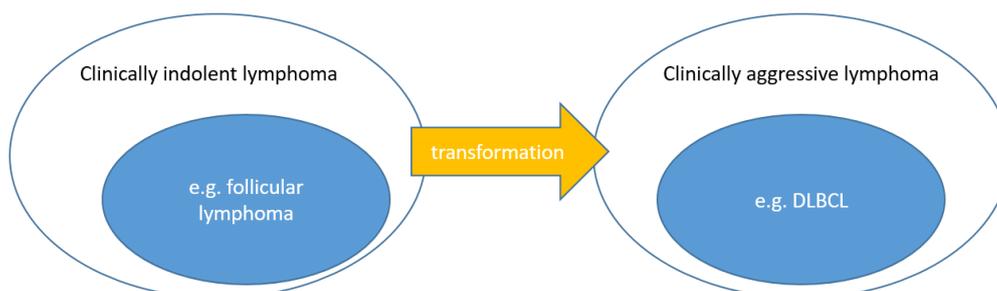
The NCPCC have reviewed several cases of patients who have exhausted curative treatment options for their transformed lymphoma (DLBCL) because they have had autologous transplantation as a treatment for their first transformation event⁵. Clinicians have made the case that the requirement for an additional line of treatment places the patient at risk of receiving ineffective therapy that does not have curative potential, and also ultimately of reducing the potential for CAR-T to provide benefit in the instance that the patient develops toxicity for such therapy.

Further information about TFL

Histological transformation refers to evolution from clinically indolent lymphoma (such as FL) to clinically aggressive lymphoma (DLBCL being commonest)⁶.

Patients here are eligible in two broad circumstances (as long as other criteria are met):

- (i) Transformation *from* any indolent lymphoma *to* DLBCL (i.e. "DLBCL") (or *to* PMBCL, if that ever occurs)
- (ii) Transformation *from* FL *to* any aggressive lymphoma (i.e. "TFL")



Transformation *from* any indolent lymphoma *to* DLBCL (i.e. "DLBCL")

Histologic transformation to DLBCL, may occur from FL but also from clinically indolent B cell lymphoproliferative disorders other than FL, e.g. SLL/CLL.

⁵ This is taken to mean, autoSCT to treat FL (FL being the 'first transformation event')

⁶ <https://www.uptodate.com/contents/histologic-transformation-of-follicular-lymphoma> Freedman and Friedberg. Histologic transformation of follicular lymphoma. Topic 4724 Version 32.0 Last updated Oct 02, 2020.

Clinicians have previously requested confirmation that patients with transformation to DLBCL from CLL, who meet all eligibility criteria (including requirements about lines of therapy used to treat transformed disease), are eligible for NHRA HST-funded Kymriah.

The Department's advice has been that such patients would be eligible, i.e. earlier CLL is not an exclusion. Eligibility is on the basis of the new diagnosis of DLBCL, not on the basis of histological transformation (since, for eligibility on the basis of transformation, the antecedent condition must be FL, not other indolent conditions). Advice was that:

Patients ... with Diffuse Large B Cell Lymphoma (DLBL) who have previously transformed from Chronic Lymphocytic Leukemia (CLL) and otherwise fully satisfy the criteria - of having DLBL and have relapsed after the appropriate number of lines of prior therapy (ie 'relapse after autoSCT' or 'relapse after /refractoriness to at least 2 prior systemic therapies') following the diagnosis of DLBL, are eligible.

Transformation from FL to any aggressive lymphoma (i.e. "TFL")

This situation is the subject of the Novartis proposal to modify clinical criteria.

In most cases of transformation, pathology is consistent with DLBCL; less commonly, FL evolves into other aggressive lymphomas. The criteria allow eligibility in the case of transformation **from FL to any** aggressive lymphoma (assuming all relevant criteria are met). UpToDate³ considers that this list of aggressive lymphomas includes grade 3B FL; that is, FL that evolves to grade 3B FL (but not to a 'lower' grade) would be seen as TFL.

AutoSCT in management of FL and TFL

According to Freedman and Friedberg in UpToDate^{7,8}, transplant is used in selected patients who have early treatment failure (i.e. refractory FL or early relapse of FL), or in patients with histologic transformation.

There is no standard treatment for histologic transformation, but the goal of therapy for most patients is to eliminate the aggressive component of disease (i.e. the histologically transformed cells) while minimising toxicity. Cure of the aggressive disease component does not necessarily equate to cure of the indolent component.

A treatment algorithm from UpToDate shows that autoSCT may be offered, in the treatment of TFL, in various settings. For example, in patients who (for treatment of FL) had received chemo-immunotherapy, the suggestion is to treat TFL with chemo-immunotherapy with plans to proceed to autoSCT if there is at least a partial response. This is essentially one line of therapy (in the sense that disease has not relapsed prior to autoSCT, and autoSCT is being used to consolidate response obtained by chemo-immunotherapy, to sustain remission).

So, in this algorithm, autoSCT is being used to consolidate the first line or second line of treatment for transformed disease. It is not clear how closely this algorithm would be followed in Australia. Lossos and Gascoyne (2011) [2] offer a broadly similar algorithm (their Figure 3).

Whether the evidence considered in App'n 1519.1 included patients in this category is relevant. Freedman and Friedberg note "the ZUMA-1 study of axi-cel and the JULIET study

⁷ https://www.uptodate.com/contents/treatment-of-relapsed-or-refractory-follicular-lymphoma?topicRef=83847&source=see_link#H31594622 Freedman and Friedberg. Treatment of relapsed or refractory follicular lymphoma. Topic 4755 Version 72.0 Last updated Mar 12, 2021

⁸ https://www.uptodate.com/contents/autologous-hematopoietic-cell-transplantation-in-follicular-lymphoma?sectionName=Relapsed%20disease&topicRef=4755&anchor=H179016836&source=see_link#H179016822 Freedman and Friedberg. Autologous hematopoietic cell transplantation in follicular lymphoma. Topic 4709 Version 18.0 Last updated Mar 18, 2020

of tisagenlecleucel in relapsed or refractory DLBCL included patients with HT of FL [histological transformation of follicular lymphoma], but subgroup specific data are limited”.

Clinical issues for MSAC consideration

1. The number of patients diagnosed with TFL may depend on approach to re-biopsy on relapse (disease progression). In the PRIMA study in previously untreated FL, of 194 patients with histologic confirmation of relapse (after median 6 years), 40/194 (21%) showed histologic transformation.
2. Although TFL might imply ‘histological’ transformation, MSAC eligibility criteria do not stipulate biopsy-proven transformation. UpToDate refers to studies estimating biopsy-proven HT and ‘clinical HT’. TFL numbers may also depend on the extent of clinical identification of ‘transformed’ disease, even though the ‘gold standard’ TFL definition requires histological evidence [2].
3. Upon transformation, patients may have a concurrent diagnosis of FL and DLBCL, i.e. indolent and aggressive components.
4. In terms of evidence of efficacy and safety in this group, there is no reason to think outcomes are any different than for the broader group studied in JULIET. In JULIET, sub-group analysis showed no difference in overall response rate between patients who had previously had HSCT (54% ORR) and patients who had not (50% ORR).
5. Some “TFL” patients are likely to be eligible even using the current criteria, i.e. based on refractoriness / relapse after two lines of therapy.
6. Most transformation is *to* DLBCL. Such patients may be eligible with existing DLBCL criteria. However, some transformation from FL is to aggressive lymphomas other than DLBCL; it is necessary to address eligibility for these patients.
7. The change brings TFL into line with DLBCL / PMBCL, where the eligibility criterion concerning autoSCT already exists (noting that line of therapy in TFL is identified as line of therapy *after* transformation). TFL is by definition an aggressive lymphoma, e.g. most transformation is to DLBCL.
8. To have proceeded to autoSCT in this setting, it is a requirement that a patient must be in response to chemoimmunotherapy. So, to have failed autoSCT is to have failed after ‘chemoimmunotherapy induction and autoSCT consolidation’.
9. The wording of the criteria cannot be simplified (i.e. TFL bracketed with DLBCL and PMBCL) because it is important to emphasise that the lines of treatment that must have been failed (before eligibility for Kymriah) concern treatment of transformed disease – not treatment of the preceding indolent lymphoma.
10. The proposed amendment does not necessarily address the situation where patients may have had autoSCT for treatment of FL – then transformed. In this circumstance, if the message from NCPCC still holds that patients would not receive a second ASCT, then for eligibility, there would need to be failure of at least two lines of systemic therapy against the transformed disease. The NCPCC’s letter suggests this can occur: “*patients with a prior history of indolent lymphoma which then transforms may do so relatively late in their natural history, exhausting standard therapies for DLBCL along the way, including stem cell transplantation*”. However, the proposed eligibility criteria are fairly clear in this regard, that *after disease transformation*, the condition must have relapsed after autoSCT, or must have relapsed after, or be refractory to, at least two prior systemic therapies.

Grade 3B follicular lymphoma

Proposal and rationale

The proposal is to list Grade 3B FL as an eligible lymphoma subtype. The rationale centres on similarity of grade 3B FL to DLBCL in terms of presentation, behaviours and outcomes. The letter from NCPCC states:

...this condition is treated as DLBCL in all other clinical settings and thus our recommendation is that this patient group should be eligible under the DLBCL wording as is standard in most clinical trials in DLBCL, and routine clinical practice.

The mention of 3B FL as an eligible subtype is framed as ensuring no confusion about the eligibility of such patients, and ensuring consistency across different centres.

Further information about 3B FL

Grading of follicular lymphoma

Centrocytes (small B cells) predominate in FL; centroblasts (large B cells) are usually in the minority but by definition are always present. Grading using the WHO Classification is by counting the number of centroblasts (large cells) per high power field⁹:

Grade 1: 0-5 centroblasts / high power field (hpf)

Grade 2: 6-15 centroblasts / hpf

(These grades 1-2 are often lumped together because clinical outcomes do not differ and the classification has been deemed unreliable.¹⁰)

Grade 3: more than 15 centroblasts / hpf.

Grade 3a: centrocytes are present

Grade 3b: solid sheets of centroblasts

Prognosis varies with, amongst other things, grade. UpToDate notes:

The minor differences in clinical behavior and response to treatment have not supported a different treatment approach toward grade 1 versus grade 2 FL. Thus, although the grading system remains in place, for clinical decision making, grade 1 and 2 FL should be approached similarly and considered to be clinically indolent lymphomas. Although controversial, molecular genetics as well as clinical behavior suggest that FL grade 3a is an indolent disease.

By contrast, FL grade 3b is synonymous with what is often referred to as follicular large cell lymphoma. Unlike lower grade FLs, this histologic variant has a lesser tendency to involve the bone marrow or peripheral blood and often presents with larger lymphoid masses. Although follicular architecture is preserved, the clinical presentation, behavior, and outcome with treatment more closely approximates that of diffuse large B cell lymphoma (DLBCL). In contrast to DLBCL, the relapse rate of FL grade 3b is higher following combination chemotherapy, but the survival is longer.

References to relapse and survival in grade 3b FL are from papers published in 2003.

⁹ <https://www.uptodate.com/contents/clinical-manifestations-pathologic-features-diagnosis-and-prognosis-of-follicular-lymphoma#H11>

¹⁰ https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf page MS-24

Treatment guidelines

ESMO's recommendations about FL place 3B FL as an aggressive B-NHL (Dreyling et al, 2016 [3]; <https://www.sciencedirect.com/science/article/pii/S0923753419316606>):

FL grade 3B (with sheets of blasts) is considered an aggressive lymphoma and treated as such, whereas grade 1, 2 and 3A should be treated as indolent disease

...If there is evidence (histological grade 3B or clinical signs of transformation) of more aggressive lymphoma, an anthracycline-based regimen [rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)] should be applied.

NCCN guidelines for B-NHL (https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf) distinguish FL (grade 1-2) from FL (grade 3) – specifically, page BCEL-1 notes that FL grade 3 is considered a subtype of DLBCL, with the following footnote:

FL, grade 3b is commonly treated as DLBCL. The management of FL, grade 3a is controversial and treatment should be individualised.

NCCN guidelines expand on this (page MS-24), but the above quote summarises NCCN's position sufficiently.

Clinical issues for MSAC consideration

Classification as grade 3A or grade 3B FL is based on histology. Listing 3B FL may risk leakage into 3A FL, a commoner entity. This seems unlikely: prognosis is better for 3A FL than 3B, and treatment options exist even in multiply relapsed 3A FL.

Barracough et al (2021) [4] have published an Australian perspective on the diagnostic and therapeutic challenges of grade 3B FL. These authors note that about half of cases of 3B FL are composite forms, with concurrent presence of either lower-grade FL or DLBCL in diagnostic specimens. Thus, even histological diagnosis of the condition is not necessarily clear-cut.

Kymriah has demonstrated efficacy in DLBCL (Juliet) and recently, FL (Elara). Top-level outcomes from Elara have been publicised¹¹, suggesting good outcomes in heavily pre-treated FL patients; similarly, Yescarta showed activity in FL in ZUMA-5.

The TGA indication for Kymriah in B-NHL references DLBCL and excludes primary CNS lymphoma. In the sense that MSAC has already recommended use in B-NHL subsets akin to DLBCL (but as per the 2016 WHO classification, not DLBCL), such as PMBCL and TFL (where there may be transformation to lymphomas other than DLBCL), inclusion of G3B FL in the eligibility criteria raises no concern.

8. Financial/budgetary impacts

TFL in patients with prior autoSCT

The submission asserted that:

No changes to the current patient and financial estimates are proposed due to the requested changes to the MSAC eligibility criteria for tisagenlecleucel in DLBCL.

¹¹ <https://www.prnewswire.com/news-releases/novartis-kymriah-pivotal-trial-demonstrates-strong-response-rates-and-a-remarkable-safety-profile-in-relapsed-or-refractory-follicular-lymphoma-301304063.html>

Patient and financial estimates from the November 2019 resubmission considered by MSAC included patients with TFL, irrespective of the number of lines of therapy post transformation.

...

The current estimates already account for a proportion of patients (0.6%) with TFL, based on 20% of all NHL cases and approximately 3% of these transform to DLBCL per year, irrespective of the number of lines of therapy post transformation.

It seems reasonable to suppose this change is unlikely to affect Kymriah's utilisation, on the basis that many TFL patients may be considered eligible if they transform to DLBCL. Also, of those few patients who, technically, might be considered to be 'newly eligible' because of the proposed change (e.g. patients transforming to other aggressive B-cell lymphomas), many will become eligible for Kymriah after failure of an additional line of systemic therapy, within the existing criteria.

In relation to estimates used earlier for TFL, the proportion of patients with TFL (0.6%) is based on applying the 3% rate of transformation (from FL to TFL per year) to the number of incident cases of FL (n~1500 per year). Evidently given long-term survival in FL, there is a much larger prevalent pool, and the risk of transformation may apply to all such patients.

To take a fairly recent, large study of the incidence of TFL (Al-Tourah et al, 2008) [5], an annual risk of 3% was identified for patients. However, this annual risk applied not to incident patients, but to the pool of patients that had received a diagnosis over about 15 years (1986-2001); indeed, a finding of the study was that risk did not plateau:

The risk of transformation is a continuous 3% per year from the time of diagnosis of indolent lymphoma for at least 15 years of follow-up, with a 10-year risk of 30%.

One financial issue to draw to MSAC's attention now, therefore, is whether the expected number of patients with TFL eligible for Kymriah needs revision. Calculation to date only considers risk of transformation in incident patients. Also, as per discussion above of biopsy on disease progression and histological vs clinical diagnosis of transformation, estimation of TFL patient numbers appears uncertain. Given that TFL patients will likely be a small minority of Kymriah users, and given **redacted** of Kymriah, this does not appear to be a major concern.

Grade 3B follicular lymphoma

The submission asserted that:

No changes to the current patient and financial estimates are proposed due to the requested changes to the MSAC eligibility criteria for tisagenlecleucel in DLBCL.

...grade 3B FL patients are very uncommon and consequently no changes to the patient and financial estimates are proposed for these patients, particularly as biologically grade 3B FL is considered equivalent to DLBCL.

Grade 3B FL is not very uncommon amongst B-NHL ("in large series, G3B FL represents 5-10% of FL cases" [4]). However, it is plausible that patients with grade 3B FL are *already* being treated based on DLBCL guidelines, and might even be considered eligible for Kymriah under existing criteria by some clinicians.

According to Lymphoma Australia¹², FL makes up 20-25% of NHL. Assuming 5836 NHL cases in Year 1, if 25% of these are FL, this equates to 1459 FL cases. If 10% of these are grade 3B, this equates to 146 grade 3B FL cases. **Redacted.**

9. Other significant factors

Equity of access

In the application, Novartis also draws to MSAC's attention an issue concerning equity of access, as follows:

Novartis would also like to raise the potential for States to apply narrower eligibility criteria to that specified by MSAC, potentially resulting in inequitable access. Anecdotally, older patients above a certain age are being excluded from treatment in some States. Novartis requests that MSAC consider how the issue of inequitable access may be addressed, such as through the Deed of Agreement, to specify that access to publicly funded treatment will not be further restricted by the State or Territory, beyond the criteria recommended by MSAC.

The Commonwealth negotiates a Deed of Agreement with Novartis that, aligning with relevant MSAC recommendations, defines circumstances when funding under the NHRA Addendum (i.e. HST framework) applies. However, the States and Territories can decide the circumstances when Kymriah will be used in their public hospital systems.

Feedback from Western Australia's Department of Health notes that:

Age should not be a sole discriminator when considering suitability for CAR T therapy, however older patients often have lower life expectancies with many chronic and end-stage comorbidities. Therefore, subsequent life-expectancy, if CAR T therapy was necessary should be taken into account.

No other feedback was received from State and Territory submissions on this issue, and there is only the sponsor's reference to an anecdotal report that age is being used in this way to exclude patients. In the ABMTRR report, the highest age for a DLBCL patient was 77 years (of n=28 in the dataset). The age range in JULIET was 22-76 years; the JULIET protocol did not have any upper limit on age, but did have typical exclusions such as 0-1 ECOG performance status and adequate organ function.

10. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

11. Further information on MSAC

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

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1. Schuster, S.J., et al., *Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma*. N Engl J Med, 2019. **380**(1): p. 45-56.
2. Lossos, I.S. and R.D. Gascoyne, *Transformation of follicular lymphoma*. Best Pract Res Clin Haematol, 2011. **24**(2): p. 147-63.

¹² [Follicular Lymphoma - Lymphoma Australia](#)

3. Dreyling, M., et al., *Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Ann Oncol, 2016. **27**(suppl 5): p. v83-v90.
4. Barraclough, A., et al., *The diagnostic and therapeutic challenges of Grade 3B follicular lymphoma*. Br J Haematol, 2021.
5. Al-Tourah, A.J., et al., *Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma*. J Clin Oncol, 2008. **26**(32): p. 5165-9.