National Institute for Health and Care Excellence

Single Technology Aprpaisal

Tisagenlecleucel for treating follicular lymphoma after 2 or more therapies [ID3950]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Anthony Nolan	Tisagenlecleucel is a CD19-directed genetically modified autologous T-cell immunotherapy that has previously demonstrated positive outcomes for patients with relapsed or refractory B-cell lymphomas, such as DLBCL. Results and follow-up of patient participants recruited by March 2021 within the phase 2 ELARA trial (NCT03568461) has demonstrated a Complete Response Rate (CRR) of 69.1% with all identifiable signs of malignancy having disappeared, with an Overall Response Rate (ORR) of 86.2% indicating significant response from across the cohort. This study and its cohort reports point to tisagenlecleucel being safe and effective in extensively pretreated r/r follicular lymphoma (FL), including in high-risk patients. It is appropriate that this technology be evaluated for this patient population.	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
	Novartis	Novartis considers this topic appropriate to be referred to NICE, given the high unmet need faced by patients with 3L follicular lymphoma.	Thank you for your comment. No action needed.
	NCRI-ACP-RCP-RCR	Yes. CAR-T therapy is a novel, targeted technology for treatment of B-cell lymphomas that has the potential of delivering long term remissions. It is therefore appropriate for this technology to be evaluated by NICE in the setting of relapsed/refractory follicular lymphoma (FL), which is essentially an incurable condition.	Thank you for your comment. No action needed.
Wording	Anthony Nolan	The remit references treating FL patients who have received 2 or more therapies, and this is in line with those experiencing refractory or relapsed disease. The wording could be clarified to specify this is solely in relation to adult patients.	Thank you for your comment. The population specifies that this scope is for adults with refractory or relapsed follicular lymphoma in the section of the technology. We do not normally put this information in the remit. No action needed.
	Novartis	Yes, the wording of the remit is appropriate	Thank you for your comment. No action needed.
	NCRI-ACP-RCP-RCR	Yes [the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider]	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
Timing issues	Anthony Nolan	Most FL patients will experience disease relapse, though usually after a prolonged progression-free survival (PFS) with initial therapy. It has been suggested that approximately 20% of patients with follicular lymphoma will relapse within 2 years of diagnosis. The strongest predictor of a poor outcome is the progression of the disease within 2 years after diagnosis following treatment with chemoimmunotherapy which predicts a 5-year OS of approximately only 50%[1]. Novel and newly established technologies are well suited for indications with relatively high prevalence and no established cure such as r/r FL. Authorised introduction of such technologies should not be delayed for benefit of today's patients, and tomorrows. [1] - Maurer MJ, Bachy E, Ghesquieres H, et al. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. Am J Hematol 2016; 91: 1096–1101.	Thank you for your comment. No action needed.
	Novartis	Current treatment options for relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies are limited. Patients typically cycle through anti-CD20 immuno-chemotherapy regimens with worsening prognosis at each relapse, particularly those in high-risk subgroups. As stated in the draft scope "*duration of response to chemoimmunotherapy and survival decreases with each subsequent relapse of follicular lymphoma*" There is a high unmet need for non-cytotoxic therapy offering high rates of durable complete response and with a manageable safety profile. Thus, the evaluation of this technology, which has the potential to meet this high unmet need is relatively urgent.	Thank you for your comment. No action needed.

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	NCRI-ACP-RCP-RCR	This evaluation is timely as there are no current licensed therapies for FL outside of immunochemotherapy and Lenalidomide + Rituximab. Moreover, response duration and progression free survival progressively shorten with each line of treatment. As mentioned, CAR-T therapy can potentially lead to long term remissions and so if appropriate the benefits of this technology should be transferred to patients sooner rather than later.	Thank you for your comment. No action needed.
Additional comments on the draft remit	Anthony Nolan	-	No action needed.
	Novartis	No comments	No action needed.
	NCRI-ACP-RCP-RCR	-	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Anthony Nolan	The background does not adequately describe the histologic transformation that can be experienced in a small number of indolent non-Hodgkin lymphomas such as FL. These diseases can transform into more aggressive fast-growing lymphomas such as DLBCL or potentially certain leukaemia's. Patients with multiple clinical high-risk factors are at elevated risk of transformation.	Thank you for your comment. The background section of the scope has been amended accordingly.

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		Tackling FL to achieve complete remission at earlier stages before transformation can occur, can add to improved patient outcomes and overall quality of life.	
	Novartis	No comments	No action needed.
	NCRI-ACP-RCP-RCR	Yes. It is adding that follicular lymphoma is the commonest type of indolent lymphoma, and that like healthy B-cells, FL expresses the CD19 protein.	Thank you for your comment. No action needed
The technology/ intervention	Anthony Nolan	The description included is limited in scope, it would benefit from a more detailed explanation of tisagenlecleucel being a single infusion therapy. It should also be noted that recipients must first have a session of leukapheresis to collect their stem cells for product manufacturing. Given the nature of the technology, the description would also benefit from including the safety profile, not least the risk, and management, of Cytokine release syndrome (CRS) which itself can be life threatening. Neurological, renal and cardiac injuries have also been recorded post-infusion.	Thank you for your comment. Only limited descriptions of technologies are included within scopes. Additional considerations including the nature of the technology and its safety profile will be considered during the appraisal process and evaluated by the evaluation committee. No action needed.
	Novartis	No comments	No action needed.

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	NCRI-ACP-RCP-RCR	Our experts believe it would be useful to have a bit more detail here for e.g. - this is a chimeric antigen receptor T-cell (CAR-T) therapy directed against CD19.	Thank you for your comment. Only limited descriptions of technologies are included within scopes. No action needed.
Population	Anthony Nolan	The defined population appears to be appropriate. In defining the impact of age on treatment outcome in patients with follicular lymphoma (FL) is challenging. Age >60 years is used as a risk factor in commonly applied risk scores. There have been a small number of FL cases cited in paediatrics, and if felt clinically appropriate, tisagenlecleucel should be considered off-label in these very limited circumstances.	Thank you for your comment. No action needed.
	Novartis	The population is defined appropriately in the broadest sense. If the evidence allows, Novartis would like to consider high risk or later line subgroups.	Thank you for your comment. These subgroups have been added into the scope for consideration.
	NCRI-ACP-RCP-RCR	Yes, the population is defined appropriately. The groups below need to be considered. There will be a group of patients that have received or will receive front line treatment for FL on the current UK front line trial (PETREA) with immunochemotherapy followed by Lenalidomide+Rituximab maintenance. These patients should not be excluded from accessing CAR-T therapy as	Thank you for your comment. The evaluation committee will consider these issues during the course of the appraisal.

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		next line treatment, as technically they would have received 2 combination therapies within a single line of treatment. It is increasingly recognised that exposure to bendamustine close to the time of apheresis for CAR-T therapy can adversely affect the manufacturing process and T-cell function. As Bendamustine is a relatively common chemotherapy treatment in relapsed FL, this scenario should ideally be factored in considering CAR-T therapy is a one-off treatment with significant resource implications.	
Comparators	Anthony Nolan	In describing comparator third-line regimens, Linton et al[2] note the most common regimen as rituximab plus bendamustine (R-benda) followed by rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and rituximab used as a single agent (R-mono). Preferred regimens have altered over time; however, all have delivered overall unfavourable outcomes, representing a continued unmet medical need. It should be noted that the comparators carry significant toxicity profiles, making patient tolerance a particular management issue for clinical teams. [2]- Kim Linton, Cristina Julian, Adam Gibb, Ellie White, Emma-Frances Armstrong, Yun Li, Yutong Liu, Ashwini Shewade, John Radford, Treatment Patterns and Outcomes in Patients with Relapsed/Refractory Follicular Lymphoma Who Received Third Line Therapy at the Christie NHS Foundation Trust in the UK, Blood, Volume 138, Supplement 1, 2021, Page 5011.	Thank you for your comment. No action needed.
	Novartis	On 29th April 2022, the European Commission (EC) approved Tisagenlecleucel (Kymriah) for the treatment of adult patients with relapsed or	Thank you for your comment.

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		refractory follicular lymphoma (FL) after **two or more lines** of systemic therapy. Two of the comparators listed in the draft scope are typically used earlier in the treatment pathway and therefore would not be comparators in the 3rd Line + setting: • Obinutuzumab with bendamustine followed by obinutuzumab maintenance is typically used 1L or 2L • Rituximab in combination with chemotherapy is also typically used 1L or 2L Axicabtagene ciloleucel (Yescarta) is currently being appraised by NICE and the expected publication date is stated as TBC on the NICE web page https://www.nice.org.uk/guidance/indevelopment/gid-ta10578 Axicabtagene ciloleucel also recently (22nd April 2022) received CHMP positive opinion for "*the treatment of adult patients with relapsed or refractory follicular lymphoma (FL)* ***after three or more lines*** *of systemic therapy"* https://www.ema.europa.eu/en/medicines/human/summaries-opinion/yescarta Of note is that the respective axicabtagene ciloleucel and tisagenlecleucel anticipated marketing authorisation wordings do not align, with tisagenlecleucel being indicated for 3L FL and axicabtagene ciloleucel for 4L FL Novartis acknowledges that axicabtagene ciloleucel could potentially be a comparator if it is reimbursed and adopted by the NHS prior to a submission	NICE guidance for obinutuzumab (TA629) and for rituximab (TA137) does not restrict either of these therapies to earlier parts of the treatment pathway. Because of this, both therapies have been kept within the scope as potential comparators. Comparators within scope documents are kept broad and comprehensive. If the company do not consider any of these relevant comparators, rationale for this can be included within the submission. No action needed.

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		being made for the tisagenlecleucel appraisal, and if tisagenlecleucel is restricted to a 4L FL subgroup. Mosunetuzumab is also currently being appraised by NICE and the expected publication date is stated as January 2023 on the NICE web page https://www.nice.org.uk/guidance/indevelopment/gid-ta10816 Given the high unmet need in the 3L FL population and the relative urgency of the tisagenlecleucel NICE appraisal as explained above, a NICE submission before January 2023 is anticipated ([redacted]) and therefore mosunetuzumab is not expected to be a comparator or standard of care.	
	NCRI-ACP-RCP-RCR	The evidence for Obinutuzumab with Bendamustine followed by Obinutuzumab maintenance is in the second line setting following relapse within 6 months of a rituximab containing regimen and so this is not an appropriate comparator. Both Lenalidomide with Rituximab and Rituximab in combination with chemotherapy are appropriate comparators. Axicabtagene ciloleucel and Mosunetuzumab are also appropriate comparators if NICE approved.	Comparators within scope documents are kept broad and comprehensive. NICE guidance for obinutuzumab (TA629) does not restrict use to the second line and so this has been included as a potential comparator. No action needed.

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Outcomes	Anthony Nolan	Overall Survival (OS) and Progression-Free Survival (PFS) are particularly important to monitor for future relapse as a result of sanctuary sites, or disease transformation. Ongoing follow-up and long-term data capture will be critical in assessing complete remission and PFS rates over time.	Thank you for your comment. No action needed.
	Novartis	No comments	No action needed.
	NCRI-ACP-RCP-RCR	The outcome measures listed in the scope are appropriate for this technology.	Thank you for your comment. No action needed.
Economic analysis	Anthony Nolan	-	No action needed.
	Novartis	The economic analysis will align with reference case stipulations as noted in the draft scope, however, non-reference case discounting of 1.5% will also be considered. As noted in the case for change consultation document for the NICE methods of health technology evaluation, "*NICE understands there is broad interest in potentially curative technologies including ATMPs, and a policy-level drive to support them"*. The report explored the use of a non-reference case discount of 1.5% for these technologies that have high upfront costs and long-term health benefits such as ATMPs and other one-off treatments.	Thanks for your comment. Non-reference case analyses and discounting will need further justifying within the company submission.

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		Furthermore, section 4.5.3 of the NICE health technology evaluations manual (2022), states that the "*committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects*" if certain criteria are met. Given, the innovative potential of Tisagenlecleucel, an ATMP and a one-off treatment, consideration of a non-reference case discount of 1.5% is justified.	
	NCRI-ACP-RCP-RCR	The economic analysis and time horizon considerations mentioned in the scope are appropriate.	Thank you for your comment. No action needed.
Equality	Anthony Nolan	The median age for FL is >60-65 years, with tisagenlecleucel carrying the potential for significant toxicity profiles, such as difficulty breathing, fever (38°C or higher), chills/shaking chills, confusion, severe nausea, vomiting, diarrhoea, severe muscle or joint pain, very low blood pressure, dizziness/light headedness and headaches. Older aged patients and those with co-morbidities can be particularly affected by high intensity regimens. The product requires extensive clinical oversight and follow-up care, meaning patient and their carers have to attend hospital on a regular basis. This can be difficult if the unit is located at a distance from their home. This can be compounded yet still of the cost of travelling is prohibitive for families. Patient information for novel technologies such as CAR-T is very important. Patients receiving a third-line therapy are in a vulnerable state and should be provided with accessible information that achieves significant comprehension of the benefits, risks and long-term impact of the product.	Thank you for your comment. No action needed.

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	Novartis	No comments	No action needed
	NCRI-ACP-RCP-RCR	No problems with discrimination are foreseen based on the proposed remit and scope.	Thank you for your comment. No action needed.
Other considerations	Anthony Nolan	-	No action needed
	Novartis	No comments	No action needed
	NCRI-ACP-RCP-RCR	While considering NHS costs it is useful to consider intravenous/subcutaneous immunoglobulin usage costs in the post CAR-T setting as most patients develop B-cell aplasia.	Thank you for your comment. Appropriate usage costs for inclusion will be considered during the appraisal process. No action needed.
Innovation	Anthony Nolan	The current standard of care, and the comparators cited in the draft scope all carry significant toxicity profiles which can be difficult to manage. There exists a credible unmet need for patients with multiple relapsed/refractory follicular lymphoma. Toxicities aside, most agents particularly PI3-kinase inhibitors, are associated with a fairly limited progression-free survival, working for about a year. After that, options are even more limited. Tisagenlecleucel offers the potential not only for greater levels of efficacy but	Thank you for your comment. The evaluation committee will consider the innovation of the product during the appraisal process. No action needed.

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		for reduced or alternative toxicity profiles that may be better tolerated by patients, and managed by their clinical teams.	
	Novartis	Tisagenlecleucel is an innovative, **one-time**, potentially **definitive treatment** that offers high rates of **durable complete responses** and **prolonged PFS** in **heavily pretreated** patients with R/R FL, including those with **high-risk disease characteristics**, while providing a well-characterised and **manageable safety profile**. The one-time treatment and prolonged disease control with tisagenlecleucel translates into a reduction of the need for subsequent therapies and long-term healthcare utilisation. Furthermore, tisagenlecleucel has the flexibility of being administered in the **outpatient** or inpatient setting due to the manageable safety profile, which may reduce healthcare resource utilisation. Tisagenlecleucel thus represents a step-change in the management of patients with R/R FL after two or more lines of systemic treatment. Whilst the QALY calculation is expected to capture the main health-related benefits, it may not fully capture the significant impact to patients' and carers' lives of having a one-time treatment with curative potential. The main clinical trial evidence comes from an ongoing Phase II (ELARA) trial (NCT03568461). This is supported by evidence from a pilot Phase IIa study (NCT02030834) with longer follow-up	Thank you for your comment. The evaluation committee will consider the innovation of the product during the appraisal process. No action needed.

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	NCRI-ACP-RCP-RCR	CAR-T therapy is an important, novel, targeted technology for treatment of B-cell lymphomas. It offers the potential for long term remissions in follicular lymphoma and is therefore a step-change from currently available therapies. From the experience already gained on the NHS with using these therapies in other B-cell malignancies, the toxicities are manageable, and procedure related mortality is low.	Thank you for your comment. The evaluation committee will consider the innovation of the product during the appraisal process. No action needed
Questions for consultation	Anthony Nolan	No comments-	No action needed.
	Novartis	*Where do you consider tisagenlecleucel will fit into the existing care pathway for refractory or relapsed follicular lymphoma?* If reimbursed, tisagenlecleucel is expected to be used in the NHS in line with its marketing authorisation: i.e. for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. *Would tisagenlecleucel be a candidate for managed access?* Given the high unmet need, Novartis will explore all viable options with NICE and NHS England to enable access to this innovative technology	Thank you for your comment. No action needed.
	NCRI-ACP-RCP-RCR	Tisagen would fit in well as a treatment option beyond second line in the management of FL and would be a candidate for managed access.	Thank you for your comment. No action needed.
	Anthony Nolan	-	No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Novartis	No comments	No action needed.
	NCRI-ACP-RCP-RCR	-	No action needed

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Lymphoma Research Trust