National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lisocabtagene maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B after first-line chemotherapy [ID3887]

Response to consultee and commentator 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

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Anthony Nolan	The topic and evaluation route are appropriate.	Thank you for your comment. No action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	It is appropriate for NICE to evaluate this topic and the single technology appraisal (STA) route is also considered appropriate.	Thank you for your comment. No action required.
Wording	Anthony Nolan	The wording is reflective of the issues of clinical and cost-effectiveness.	Thank you for your comment. No action required.

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	Bristol-Myers Squibb Pharmaceuticals Ltd.	The wording of the remit is appropriate.	Thank you for your comment. No action required.
Timing Issues	Anthony Nolan	There is some urgency around the need for an additional CAR-T therapy option for patients given Kymriah (tisagenlecleucel) has not been submitted for evaluation by NICE for this indication after exiting the Cancer Drugs Fund (CDF).	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	No comments.	Thank you for your comment. No action required.
Additional comments on the draft remit	Anthony Nolan	No comments	Thank you for your comment. No action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	No additional comments.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Anthony Nolan	We would suggest that the prognosis for patients who have refractory or relapsed disease is added to the background information. We also suggest noting that the use of CAR-T as a first-line treatment for refractory or relapsed DLBCL is increasingly considered standard of care.	Thank you for your comment. The scope has been updated to reflect prognosis of relapsed refractory disease. Thank you for your comment. Treatments recommended in Cancer Drugs Fund are not considered as the standard care. No action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	BMS request the following updates are made to the background information to more accurately reflect the population being considered in this appraisal: • The use of terms such as large B-cell lymphoma (LBCL) and aggressive B-cell lymphoma should be avoided because these are broad, encompassing terms that capture lymphoma subtypes not considered in this appraisal. The World Health Organisation (WHO) Classification of Haematolymphoid Tumours 5th edition defines 18 different LBCL subtypes.[1] Of these, four are being considered in this appraisal: diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B). BMS therefore request the title of this appraisal is updated to "Lisocabtagene	Thank you for your comment. The scope has been updated to reflect the suggested changes.

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		maraleucel for treating relapsed or refractory diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma or follicular lymphoma grade 3B after first-line chemoimmunotherapy''. • In addition, the background information in the draft scope currently refers to DLBCL only throughout, which does not reflect the population being considered in this appraisal. BMS therefore request the draft scope is updated to use LBCL throughout where appropriate, and clearly state that the LBCL subtypes of relevance to this appraisal are DLBCL, HGBCL, PMBCL and FL3B. Where information specific to DLBCL is used (e.g. epidemiology data), BMS request the draft scope notes that this is due to a lack of alternative data sources available for LBCL. • Similarly, BMS also request the sentence 'Lisocabtagene maraleucel (Breyanzi, Bristol-Myers Squibb) does not currently have a marketing authorisation in the UK for treating relapsed or refractory DLBCL' is updated to 'Lisocabtagene maraleucel (Breyanzi, Bristol-Myers Squibb) does not currently have a marketing authorisation in the UK for treating relapsed or refractory LBCL after one prior therapy' to more accurately reflect the population being considered in this appraisal (i.e. patients with the four specific subtypes of LBCL, and not just diffuse large B-cell lymphoma [DLBCL]) and the current marketing authorisation for liso-cel in the UK. ○ [redacted], ○ Liso-cel is already licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B after two or more lines of systemic therapy	Thank you for your comment. The scope has been updated to reflect the suggested changes. Thank you for your comment. The scope has been updated to reflect the suggested changes.

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		Finally, BMS request the sentence 'Lisocabtagene maraleucel is being studied in a single arm phase 3 clinical trial in people with DLBCL or with other aggressive B-cell malignancies' is updated to 'Lisocabtagene maraleucel is being studied in a randomised controlled phase 3 clinical trial in patients with DLBCL, HGBCL, PMBCL or FL3B, who were eligible for stem cell transplantation (SCT)'. This is to accurately reflect the trial design and study population of the TRANSFORM (NCT03575351) trial, which forms the primary evidence base for this submission.[2]	Thank you for your comment. The scope has been updated to reflect the suggested changes.
Population	Anthony Nolan	Yes.	Thank you for your comment. No action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	In line with the comments in the Background Information section above, BMS request the population is updated to 'People with relapsed or refractory DLBCL, HGBCL, PMBCL or FL3B after 1 prior therapy', to more accurately reflect the population being considered in this appraisal. This population is in line with the [redacted], and the population included in the pivotal TRANSFORM trial, which forms the primary evidence base for this submission. In addition, BMS would like to highlight the population addressed in this submission will be restricted to patients who are eligible for SCT. This represents a subpopulation of the licensed indication in order to align with the population included in the pivotal TRANSFORM trial, where only patients who are eligible for SCT were enrolled. Liso-cel for the treatment of relapsed or refractory (r/r) LBCL patients who are ineligible for high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) is currently being	Thank you for your comment. Population description has been amended as suggested in line the expected licence indication.

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		evaluated in the Phase II trial TRANSCEND-PILOT (NCT03483103), which is not considered in this submission and would be appraised separately.	
Subgroups	Anthony Nolan	NA	Thank you for your comment. No action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	No comment.	Thank you for your comment. No action required.
Comparators	Anthony Nolan	Autologous stem cell transplant may be an additional comparator.	Thank you for your comment The scope has been updated to reflect the suggested changes.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	BMS request the current comparator of “Established clinical management without lisocabtagene maraleucel but not limited to chemotherapy, with or without rituximab” is replaced with “immunochemotherapy, with HDCT plus ASCT in responders”. As detailed in the NICE pathway for treating DLBCL, patients who are fit enough to tolerate intensive therapy should be offered multi-agent immunochemotherapy at relapse, primarily to obtain sufficient response to allow consolidation with ASCT.[4] This is not clear from the current wording around chemotherapy in the draft scope, which omits the primary intent of immunochemotherapy management (to prepare for ASCT).	Thank you for your comment. The scope has been updated to reflect the suggested changes. The list of comparators is kept inclusive at this stage. Polatuzumab vedotin with rituximab and bendamustine may be used by some people

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		In addition, according to UK clinical experts, the preferred re-induction regimens prior to HDCT and ASCT include R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin), R-ICE (rituximab, ifosfamide, carboplatin, etoposide) and R-DHAX (rituximab, dexamethasone, cytarabine, and oxaliplatin) with R-GDP being the most commonly used and R-ICE being the least commonly used. The other regimens included in the NICE draft scope (R-ESHAP, R-GEMOX and R-IVE) are not used in UK clinical practice and therefore not considered relevant comparators in this appraisal, in line with the feedback received from UK clinical experts.	and is considered a relevant comparator.
Outcomes	Anthony Nolan	NA	Thank you for your comment. No action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	Event-free survival (EFS) is the primary endpoint from the TRANSFORM trial.2 For r/r LBCL, this endpoint is more clinically relevant than progression-free survival (PFS) given the curative intent of treatment. In this indication, 'stable disease' is not considered a successful treatment outcome, and therefore, patients who remain progression-free but with stable disease are moved onto receive a subsequent treatment line. In TRANSFORM, these patients could crossover into the liso-cel arm and as a result, any comparison of progression-free survival between liso-cel and standard of care is likely to be biased. In line with the approach taken in TA895, EFS will therefore be used alongside overall survival (OS) and health-related quality of life (HRQoL) data	Thank you for your comment. The scope has been updated to reflect the suggested changes.

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		to capture the most important health related benefits of liso-cel in the cost-effectiveness modelling.	
Equality	Anthony Nolan	CIinical teams have to consider the fitness of patients to recieve more intensive cancer treatments, and to this end the age of patients can be used as a proxy for levels of fitness, which then impacts whether they are treated for “curative intent” . R/R DLBCL patients across all ages who are fit enough should be able to access CAR-T, and specifically liso-cel, if it is considered more tolerable and less toxic than other comparators by clinical teams.	Thank you for your comment. Comment noted. No action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	No comment	Thank you for your comment. No action required.
Other considerations	Anthony Nolan	**NA**	Thank you for your comment. No action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd.	No comment	Thank you for your comment. No action required.
Questions for consultation	Anthony Nolan	Anthony Nolan would consider lisocabtagene maraleucel to be a first-line option for people with relapsed or refractory aggressive non-Hodgkin lymphoma.	Thank you for your comment. Comments noted. No action required.

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		We do believe this would be a candidate for managed access. We believe the use of lisocabtagene maraleucel may result in substantial benefits in comparison to the negative long term effects of HDT and stem cell transplant, such as on bone health, risk of secondary malignancies, infertility and others.	
	Bristol-Myers Squibb Pharmaceuticals Ltd.	**Do you consider that the use of lisocabtagene maraleucel can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** As noted above, the TRANSFORM trial will be the primary evidence source for this submission and will provide the data for inclusion in the economic model. However, as the TRANSFORM trial began in [redacted],, with the last patient randomised in [redacted],, the trial will not capture the improved efficacy of newly recommended third-line (3L) treatments glofitamab (TA927), loncastuximab tesirine (TA947) and epcoritamab (GID-TA10931). The differences in subsequent treatments between the trial and UK clinical practice would likely underestimate the benefit of liso-cel. This is because patients who progressed after receiving liso-cel in the TRANSFORM trial received less effective 3L therapies compared to what would now be received in UK clinical practice. The overall efficacy of the liso-cel arm from the trial may therefore be underestimated. Furthermore, given the majority ([redacted]%) of patients receiving standard of care (SoC) at second-line (2L) in the trial who experienced an event-free survival (EFS) event received 3L CAR-T therapy, which is available in UK clinical practice, the overall efficacy of the SoC arm from TRANSFORM trial is considered generalisable to UK clinical practice.[7] As such, the comparison between liso-cel versus SoC from the trial	Thank you for your comment. Comments noted. No action required.

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		is likely to be a conservative estimate compared to UK clinical practice, as patients receiving 2L liso-cel will receive more effective 3L therapies in clinical practice than were received in the trial. Though it is challenging to quantitatively model this difference, it is therefore likely there are further QALY gains not reflected in the trial data. Finally, providing routine access to CAR-T therapy at 2L would increase the number of patients eligible to receive this definitive, curative therapy in the 2L setting and ensure the UK is at the forefront of medical advances.	
	Anthony Nolan	NA	No action required
Additional comments on the draft scope	Bristol-Myers Squibb Pharmaceuticals Ltd.	No further comments	Thank you for your comment. Comments noted. No action required

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

Lymphoma Action