National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma

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			
Wording	Incyte	The draft remit contains the following wording regarding the indication for tafasitamab with lenalidomide (LEN): for treating adults with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). Please correct this statement to reflect the current proposed indication statement: for treating adults with R/R DLBCL, including DLBCL arising from low grade lymphoma, who are not eligible for, or refuse, autologous stem cell transplant (ASCT).	The remit uses 'within it's MA' to capture the full indication in line with MA wording. No action required.
Timing Issues	Incyte	Currently there are limited treatment options that provide benefit and are well-tolerated for patients with R/R DLBCL who are not eligible for, or refuse ASCT representing a high unmet need. Tafasitamab is considered an innovative medicine [redacted]	Comment noted. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit	Incyte	No comments	No action required

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Incyte	None	No action required
The technology/ intervention	Incyte	None	No action required
Population	Incyte	The draft scope includes the wording 'high dose chemotherapy'. Please correct the statement to reflect the current proposed indication for tafasitamab: Adults with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), including DLBCL arising from low grade lymphoma, who are not eligible for, or refuse, autologous stem cell transplant (ASCT). There is no evidence that any sub-groups in this population should be considered separately as the treatment effect of tafasitamab with LEN in the L-MIND study was consistent with the overall R/R DLBCL population for all sub-groups investigated e.g. by prior lines of therapy or refractory status (Salles)	Thank you for your comments. The population has been updated to remove 'high dose chemotherapy'.
Comparators	Incyte	There are no established therapies for patients with R/R DLBCL who are ineligible for transplant. Before the recent entry to the market of polatuzumab, the most commonly used regimens were gemcitabine and/or	Thank you for your comment. The scope states that there is no

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		platinum-based therapies in combination with rituximab. At this stage of the treatment pathway clinicians may also offer enrolment in a clinical trial. Expert feedback confirmed that current clinical practice for this population is variable across the country depending on expertise of the treatment centre. Clinical decisions on treatment are also impacted by individual opinion and patient choice. The rituximab-containing regimens mentioned in this draft scope [R-GemOx(rituximab, gemcitabine oxaliplatin), R-Gem(rituximab gemcitabine), R-P-MitCEBO(rituximab, prednisolone, mitoxantrone cyclophosphamide, etoposide bleomycin, vincristine), (R-)DECC(rituximab, dexamethasone, etoposide, chlorambucil, lomustine), BR (bendamustine, rituximab)] are used as salvage treatments prior to transplant and DHAP, ICE or IVE would not be appropriate for this transplant ineligible patient population. Therefore these regimens would not be considered as appropriate comparators. Additionally, a limited number of randomised control studies exist comparing the outcomes of salvage regimens in the R/R setting and these have provided no evidence of superiority of one over the other. (Van Den Neste, Crump, Mounier) Pixantrone is rarely used clinically and for this reason was also not considered a comparator - in line with TA559, TA567 and TA649. Best supportive care was not be a suitable comparator as chemotherapy would normally be offered for this group of patients. However, guidelines also recommend considering enrolment in clinical trials for some patients (Tilly, Chaganti). Upon consultation UK experts suggest that once available through routine commissioning, there would be rapid uptake of the polatuzumab/bendamustine/rituximab (pola+BR) regimen [TA649].	established clinical management at this stage in the pathway so the comparators are kept broad. Recruitment in a clinical trial is not standard clinical practice and would not be considered a comparator. Some patients are expected to receive chemotherapy. The scope has been amended to reflect that comparators 'may include' those listed. Pixantrone is used for some patients so it is considered a relevant comparator. The appraisal committee will discuss the most appropriate comparator during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical

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		Incyte proposes that based on the timelines for this appraisal the most suitable comparator would be pola+BR.	and cost-effectiveness evidence and current clinical practice.
Outcomes	Incyte	Include the following outcome: • Duration of response This outcome in combination with response rates, has particularly relevant as it represents durability of subsequent treatment response in these R/R patients.	No action required. 'Response rates' captures different response measures (including duration of response). The list of outcomes measures in the scope is not intended to be exhaustive.
Economic analysis	Incyte	None	No action required
Equality and Diversity	Incyte	No equality issues were identified	No action required
Other considerations	Incyte	None identified	No action required
Innovation	Incyte	Tafasitamab is an Fc-engineered, humanized, monoclonal antibody that binds to CD19. The mechanism of action of tafasitamab entails enhanced antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and direct cytotoxicity (apoptosis/inhibition of proliferation).	Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the

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		Tafasitamab in combination with LEN shows increased anti-leukemic and anti-lymphoma activity in preclinical in vitro and in vivo models. Both drugs induce direct cytotoxicity leading to the killing of lymphoma cells. Both drugs activate and stimulate immune effector cells, particularly NK cells that attack the lymphoma cells. Tafasitamab strongly activates the NK cells via the enhanced Fc-portion and LEN also activates and stimulates NK cells (Awan) demonstrated that the modulation of immune effector cells by LEN enhances the NK-mediated ADCC exerted by tafasitamab, resulting in increased cancer cell killing compared to single- agent treatment. In a human lymphoma xenograft model, combination of tafasitamab with LEN demonstrated that the median survival in severe combined immunodeficiency mice was superior compared to either monotherapy. This immunotherapeutic combination of tafasitamab and LEN offers an effective and well tolerated treatment option for patients with R/R DLBCL who progressed after one or more rituximab plus chemotherapy-based therapies and represents a step change in the management of R/R DLBCL Tafasitamab is considered an innovative medicine [redacted]	technology. No change to scope.
NICE Pathways	Incyte	Tafasitamab with LEN is expected to replace current rituximab-chemo regimens for patients with R/R DLBCL who are ineligible or refuse ASCT.	Thank you for your comment.
Questions for consultation	Incyte	Questions on comparators, outcomes, subgroups and innovation have already been addressed in the above sections. Responses to additional questions are provided below: How do you define people for whom ASCT is not suitable? During expert consultation clinicians reported that patients were assessed to be ineligible for ASCT if they were not ‘fit’ enough to tolerate very high dose	Thank you for your comments. No change to scope.

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		chemotherapy (i.e. based on age, co-morbidities, or inadequate response to salvage chemotherapy). Would you expect ASCT to be feasible after treatment with tafasitamab in this population? Expert feedback suggests that this rationale isn't plausible based on the low likelihood of patients being 'chemosensitive' post treatment with a tafasitamab LEN regimen. The L-MIND study was not designed to investigate tafasitamab+LEN as a salvage regimen for patients suitable for ASCT as the study did not include this patient population. Where do you consider tafasitamab in combination with lenalidomide will fit into the existing NICE pathway, Blood and bone marrow cancers? Tafasitamab with LEN is expected to replace current rituximab-chemo regimens for patients with R/R DLBCL who are ineligible or refuse ASCT.	
Additional comments on the draft scope	Incyte	No additional comments	No action required.

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

- Lymphoma Action