National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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	Gilead	As noted in the timing issues section of this form, earlier use of axicabtagene ciloleucel (axi-cel; Yescarta®) in the diffuse large B-cell lymphoma (DLBCL) pathway could offer more patients the opportunity of cure, which would help improve the health of the population.	Comment noted. No action needed.
	Incyte	No comment.	No action needed.
	NCRI-ACP-RCP-RCR	Yes [it would be appropriate to refer this topic to NICE for appraisal].	No action needed.
Wording	Gilead	The wording of the remit reflects our current understanding.	No action needed.
	Incyte	No 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 that NICE should consider].	No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	Gilead	DLBCL is a curative disease but sadly not all patients achieve cure within the current management pathway. Potentially curative treatment options include high dose therapy (HDT) plus autologous stem cell transplant (ASCT), and chimeric antigen receptor T-cell (CAR T-cell) therapy, but the latter is only available at third or later line in current practice. At first relapse, the only potentially curative treatment option currently is therefore HDT plus ASCT, which can only follow a sufficient response to immunochemotherapy. For patients who have early relapse (within 12 months of response to first line therapy) or primary refractory DLBCL, there is a lower expectation of response to further immunochemotherapy than in patients who had a good response to immunochemotherapy at first line (due to reduced or absent chemosensitivity among other factors). The cure rate with second line treatment of early relapse or primary refractory DLBCL in current practice is estimated at ≤[redacted]% with between [redacted]% of early relapse or primary refractory DLBCL patients not receiving potentially curative treatment at second line (data on file). Reasons for patients not receiving ASCT can include a lack of sufficient response to immunochemotherapy, intolerance to immunochemotherapy, intolerance to HDT, progressive disease post immunochemotherapy response, and stem cell mobilisation failure. The availability of axi-cel at second line for early relapse or primary refractory DLBCL would facilitate earlier use of this potentially curative treatment in replacement of further immunochemotherapy in patients for whom there is a lower expectation of response to facilitate HDT plus ASCT. Opening up access to axi-cel at this stage in the management pathway, when patients have only been through one treatment line to date (compared to the two treatment lines patients need to have been through to be eligible for axi-cel in the current pathway), offers more DLBCL patients the opportunity of cure.	Comment noted. No action needed.

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	Incyte	No comment.	No action needed.
	NCRI-ACP-RCP-RCR	Need for urgency as currently there is a significant unmet need in 2nd line therapy for refractory and early relapsed DLBCL after R-CHOP. ZUMA-7 trial included patients who were refractory to R-CHOP or relapsed 'early' (within 1 year) of R-CHOP. This group of patients have a dismal outcome. Although patients can potentially access CAR-T cell therapy 3rd line disease progression may result in poor performance score (ie not 0-1) and hence be ineligible for this treatment modality.	No action needed.
Additional comments on the draft remit	Gilead	-	No action needed.
	Incyte	-	No action needed.
	NCRI-ACP-RCP-RCR	No [additional comments].	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Gilead	No comment.	No action needed.
	Incyte	No comment.	No action needed.
	NCRI-ACP-RCP-RCR	Yes, this is accurate.	No action needed.
	Gilead	No comment.	No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
The technology/ intervention	Incyte	No comment.	No action needed.
	NCRI-ACP-RCP-RCR	Yes [the description of technology is accurate].	No action needed.
Population	Gilead	[redacted]	Comment noted. The population within the scope has been kept broad. The company can narrow the population for consideration within its submission.
	Incyte	The population defined in the draft scope may reflect a broader population than that investigated in the clinical study supporting this indication. The pivotal study in this assessment - ZUMA-7 (NCT03391466) (1) compared axicabtagene ciloleucel with standard of care (SOC). SOC was described as a protocol-defined, platinum-based salvage combination chemotherapy regimen followed by high-dose therapy and autologous stem cell transplant (ASCT) in those who respond to salvage chemotherapy. This implies that all patients in the study were eligible for an ASCT at enrolment. This represents a subset of the population detailed in the draft scope, as not all patients who have relapsed or refractory diffuse large B-cell lymphoma (DLCBL) after 1 systemic therapy, are eligible for an ASCT.	Comment noted. The population within the scope has been kept broad. The company can narrow the population for consideration within its submission.
	NCRI-ACP-RCP-RCR	Yes. Broadly, patients are considered to either transplant eligible or transplant ineligible. ZUMA-7 trial included patients who were potential transplant eligible and were refractory to R-CHOP or relapsed 'early' (within 1 year).	Comment noted. The population within the scope has been kept broad. The company can narrow the population for

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			consideration within its submission.
Comparators	Gilead	"Salvage chemotherapy with or without rituximab" should be replaced with "immunochemotherapy, with high dose therapy (HDT) plus autologous stem cell transplant (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. This is not clear from the current wording around salvage chemotherapy in the draft scope, which omits the primary intent of immunochemotherapy management i.e. to prepare for ASCT. Of the salvage chemotherapy options currently listed, GEMOX is generally reserved for less fit patients. We also ask for the use of 'salvage' to be removed, aligning to the movement away from such terminology in the clinical community (due to its potentially negative connotations and arguable inaccuracy in a market where novel treatments are available at later lines). Polatuzumab vedotin with rituximab and bendamustine is only a treatment option for patients who have been determined as non-candidates for transplant. Tafasitamab with lenalidomide is also being assessed for use in this patient population. As we are planning to submit for reimbursement in patients intended for transplant, these are not relevant comparators to the decision problem we will address.	Comment noted. Salvage chemotherapy with multi-agent immunochemotherapy is used primarily to obtain sufficient response to allow consolidation with autologous or allogeneic stem cell transplantation, but is also beneficial even if not followed by transplantation. Use of the terminology "salvage chemotherapy" within future NICE appraisals is being investigated by the NICE editorial team. Comparators have been kept broad. The company can justify its choice of comparators within the submission.

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	Incyte	Based on the limitations outlined above in defining the population for draft scope, both treatment regimens: polatuzumab vedotin in combination with bendamustine and rituximab and tafasitamab in combination with lenalidomide, would be inappropriate comparators as these two regimens are indicated for relapsed or refractory DLBCL patients who are non-transplant eligible (2,3).	Comment noted. Comparators have been kept broad. The company can justify its choice of comparators within the submission. No action needed.
	NCRI-ACP-RCP-RCR	Yes. Most common relevant comparator regimens used in the UK are GDP, ICE, ESHAP or IVE +/- rituximab followed by ASCT in chemosensitive patients. GDP+/- R is commonly used. A comparator for the ZUMA-7 data is not these agents at 2nd line: • bendamustine (only for people not suitable for transplant) • tafasitamab with lenalidomide (subject to NICE appraisal)	Comment noted. Comparators have been kept broad. The company can justify its choice of comparators within the submission. No action needed.
Outcomes	Gilead	DLBCL is a curative disease and therefore the intent of treatment is to cure. DLBCL patients who do not respond to second line immunochemotherapy and therefore are non-candidates for HDT plus ASCT will be moved on to a new therapy for potential cure at the earliest opportunity. Event-free survival (EFS) is an endpoint that classes a best 'response' of stable disease and new therapy commencement prior to radiographic disease progression as an event alongside radiographic disease progression and death. This is the most clinically relevant endpoint for DLBCL given the curative intent of treatment. Reflecting its relevance to this setting, EFS is an established endpoint in DLBCL trials and is the primary endpoint in the ZUMA-7 trial. EFS will	Comment noted. The outcomes included within the scope are kept broad. Additional disease-relevant endpoints can be included within the submission for consideration by the committee. No action needed.

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		therefore be used alongside OS and HRQL data to capture the most important health related benefits of axi-cel in the cost-effectiveness modelling.	
	Incyte	No comment	No action needed.
	NCRI-ACP-RCP-RCR	Yes. The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life. We agree these capture the most important health related benefits (and harms) of the technology It would be sensible to also include event free survival (EFS) as this was a primary endpoint of the ZUMA-7 trial.	Comment noted. The outcomes included within the scope are kept broad. Additional disease-relevant endpoints can be included within the submission for consideration by the committee. No action needed.
Economic analysis	Gilead	The economic analysis will align with the NICE reference case.	Comment noted. No action needed.
	Incyte	No comment	No action needed.

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	NCRI-ACP-RCP-RCR	2 year PFS and OS is a reasonable timeframe.	Comment noted. No action needed.
Equality and Diversity	Gilead	We do not foresee any equality concerns.	Comment noted. No action needed.
	Incyte	No comment	No action needed.
	NCRI-ACP-RCP-RCR	Zuma 7 trial only included patients who had primary refractory disease or those who relapsed within 12 months of 1st line therapy. Patients relapsing >12 months after 1st line therapy were not included. Current SOC of intensive 2nd line chemotherapy +/- ASCT is delivered in BCSH level 3 units. CAR T therapy on the other hand will only be delivered in commissioned CAR T centres. This may mean longer travelling distance for some patients receiving 2nd line therapy. As the number of CAR-T centres increase this should be less of an issue. Another patient group to consider are 16-17 year olds who were not enrolled in this trial but who are treated similarly to 18 years old in UK centres.	Comment noted. NICE is required by law to look at any protected characteristics and whether any recommendation could cause unlawful discrimination. Where similar issues have been raised in previous appraisals (e.g. TA559 and TA567), the commissioning expert from NHS England confirmed that national multidisciplinary teams would be established to ensure equality of referral and treatment access.

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			The committee will not make recommendations based on age but will be restricted by the marketing authorisation for axicabtagene autoleucel. The appraisal committee will consider any equality issues.
Other considerations	Gilead	No comment	No action needed.
	Incyte	No comment	No action needed.
	NCRI-ACP-RCP-RCR	If data available, the following measures may provide useful information: Proportion of patients receiving CAR T therapy in 3rd line setting after failing SOC 2nd line therapy and outcome of patients failing 2nd line CAR T therapy.	Comment noted. The company can choose to submit data for relevant subgroups if the evidence allows.
Innovation	Gilead	Axi-cel was the first of the breakthrough class of CAR T-cell therapies to enter the market and represented a step-change in the treatment of R/R DLBCL when approved for use within the cancer drugs fund (CDF) for third or later line use in 2019 (TA559). Earlier use of axi-cel could offer more patients the opportunity of cure and thus further revolutionise the R/R DLBCL pathway.	Comment noted. No action needed.
	Incyte	No comment	No action needed.

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	NCRI-ACP-RCP-RCR	Yes [the technology is considered to be innovative in its potential to make a significant and substantial impact on health-related benefits]. Salvage chemotherapy and plan for consolidation ASCT has been the 'standard of care' since 1996 for suitably fit patients. CAR T therapy is a form of advanced cellular immunotherapy which has revolutionised treatment of relapsed/ refractory DLBCL. Outcomes for patients failing 1st line therapy are sub-optimal in the rituximab era. CAR T therapy in this setting would represent a step change in treatment. Access to this treatment modality earlier in treatment course: 2nd line rather than 3rd line could result in improved access, with improvement in the outcomes measured.	Comment noted. No action needed.
Questions for consultation	Gilead	-	No action needed.
	Incyte	No comment	No action needed.
	NCRI-ACP-RCP-RCR	No additional comments	No action needed.
Additional comments on the draft scope	Gilead	-	No action needed.
	Incyte	No comment	No action needed.
	NCRI-ACP-RCP-RCR	No additional comments on the draft scope Scope as described seems appropriate for the technology and applicability to the UK practice.	Comment noted. No action needed.

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

Lymphoma Action