National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin 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	Kite a Gilead Company	As outlined in the timing issues section below, there is an urgency of this appraisal borne from the current unmet medical need of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) after three lines of systemic therapy. An innovative treatment option in this setting is a priority issue that could help improve the health of the population. This is therefore an appropriate topic for imminent NICE appraisal.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. No action required.
Wording	Kite a Gilead Company	Gilead anticipate that the marketing authorisation will be for the treatment of [redacted], and therefore propose a change to the wording to reflect this.	Comment noted. The remit has been kept broad to capture any potential changes to the marketing authorisation.
Timing Issues	Kite a Gilead Company	Adult patients with R/R FL after three lines of therapy have poor outcomes. It is therefore important that patients have access to axicabtagene ciloleucel (henceforth Yescarta®) at the earliest possible opportunity as Yescarta would be the first CAR-T therapy available for these patients.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the

Section	Consultee/ Commentator	Comments [sic]	Action
			date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information please see https://www.nice.org.uk/guidance/indevelopment/gid-ta10578.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Kite a Gilead Company	Marginal zone lymphoma content can be removed in line with the update to the anticipated marketing authorisation that focuses the target population to follicular lymphoma. Please add the reference for the following statement “most people (80%) present with advanced disease (stage III to IV)”	Comment noted. The scope aims to provide a broad background of the topic. Therefore, the information about marginal zone lymphoma has been left in. The reference has been added for the noted statement.
	Janssen-Cilag Ltd	N/A	No action required.
The technology/ intervention	Kite a Gilead Company	No Comment	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Janssen-Cilag Ltd	N/A	No action required.
Population	Kite a Gilead Company	Gilead anticipate that the marketing authorisation will be for the treatment of [redacted], and therefore propose a change to the wording to reflect this.	Comment noted. The population has been kept broad to include the types of non-Hodgkin lymphoma studied in the clinical trial (ZUMA-5). This is to ensure the scope is appropriate if the marketing authorisation changes. The committee can consider a population that is narrower than the scope, if this is where the company chooses to position it or the marketing authorisation is narrower.
	Janssen-Cilag Ltd	N/A	No action required.
	Roche Ltd.	CAR-Ts work well for patients with certain patient characteristics. Restricting the label to a subgroup might be more cost-effective for the NHS.	Comment noted. No action required.
Comparators	Kite a Gilead Company	There is no established standard of care for adult patients with relapsed or refractory FL after three or more lines of systemic therapy (the population to which the anticipated marketing authorisation will be based); at this stage in the pathway, treatment decisions are made on a case-by-case basis taking into account factors such as patient fitness, treatment goals and response/durability of response to prior therapy. The	Comment noted. Chemotherapy alone has been added as part of clinical management. The remaining comparators have been kept in because

Section	Consultee/ Commentator	Comments [sic]	Action
		terminology of 'established clinical management without axicabtagene ciloleucel' is therefore misleading and we request this be replaced with chemotherapy which is the only potential treatment option not already listed as an independent comparator. Of the independent comparators that are already listed, we would expect obinutuzumab with bendamustine and lenalidomide with rituximab to be used earlier in the treatment pathway than the fourth-line or later settings. In addition, rituximab monotherapy and best supportive care would be reserved for patients not fit enough to receive intensive active treatment and therefore would not be relevant comparators for patients being considered for CAR T-cell therapy.	they may be used as third line treatment which is consistent with the line of treatment in the ZUMA-5 trial. The scope aims to be inclusive so comparators are included even if only applicable to a small number of people. The committee can discuss the most appropriate comparators during the appraisal.
	Janssen-Cilag Ltd	The list of comparators is adequate – but Janssen feels additional clarification is needed for two of the comparators below: • Established clinical management without axicabtagene ciloleucel for MZL • Best supportive care for MZL/FL	Comment noted. Established clinical management has been updated to 'Clinical management without axicabtagene ciloleucel including chemotherapy (such as cyclophosphamide, fludarabine, bendamustine or chlorambucil)'. Best supportive care has been included because some people may have supportive treatments other than those listed as comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
	Roche Ltd.	Revaluate how often Rituximab monotherapy is used as a treatment.	Comment noted. The scope aims to be inclusive, so comparators are included even if only applicable to a small number of people. The committee can discuss the most appropriate comparators during the appraisal.
Outcomes	Kite a Gilead Company	Yes [the outcome measures capture the most important health related benefits (and harms) of the technology]	Comment noted. No action required.
	Janssen-Cilag Ltd	N/A	No action required.
Economic analysis	Kite a Gilead Company	The economic analysis will align with reference case stipulations, as worded in the draft scope.	Comment noted. No action required.
	Janssen-Cilag Ltd	N/A	No action required.
Equality and Diversity	Kite a Gilead Company	We do not envisage any equality issues arising from the proposed remit and scope	Comment noted. No action required.
	Janssen-Cilag Ltd	N/A	No action required.
	Roche Ltd.	There are only a number of CAR-T centres available across the UK so equal access to patients might be something to evaluate.	Comments noted. The committee will consider whether its

Section	Consultee/ Commentator	Comments [sic]	Action
			recommendations could have a different impact on people protected by the equality legislation than on the wider population.
Other considerations	Kite a Gilead Company	No Comment	No action required.
	Janssen-Cilag Ltd	N/A	No action required.
	Roche Ltd.	It takes some time to manufacture CAR-Ts. Evaluate how this will be modelled in the submission?	Comment noted. The committee will consider evidence presented to it. No action required.
Innovation	Kite a Gilead Company	Yescarta would be the first CAR-T introduced to the clinical pathway of care and is a breakthrough therapy offering a potentially curative treatment option to adult patients with R/R FL after three lines of systemic therapy; a patient group for who there is no established standard of care in current practice and who have poor outcomes with salvage treatment options. We believe Yescarta will be associated with significant and substantial health-related benefits and will represent a step-change in the management of R/R FL. Although the main health-related benefits will be captured in the QALY calculation, it is difficult to quantify the true difference a single infusion treatment with curative potential could make to the lives of patients and their carers. Data relating to the main health-related benefits of Yescarta are provided by the ZUMA-5 trial (NCT03105336).	Comment noted. The innovative nature of the technology will be considered by the committee based on evidence presented to it. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Janssen-Cilag Ltd	Janssen recognises that CAR-T is a novel mechanism of action	Comment noted. The innovative nature of the technology will be considered by the committee based on evidence presented to it. No action required.
Questions for consultation	Kite a Gilead Company	• *Do you consider that there will be any barriers to adoption of this technology into practice?* NHS England have established a framework of delivery centres spread across the UK to provide commercially available CAR-T treatment. Due to the rare nature of R/R FL, the addition of Yescarta is not expected to exceed the capacity of these centres or require any additional infrastructure, or otherwise present barriers to adoption of the technology into practice. • *Would it be appropriate to use the cost comparison methodology for this topic?* Cost-effectiveness analysis will be included in this submission. Yescarta is expected to provide improved clinical outcomes at likely greater cost than current treatment, making cost-comparison an inappropriate choice. • *Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?* Yescarta is a single infusion treatment with curative potential and is therefore uniquely different in its clinical efficacy and resource use implications compared to any of the listed comparators.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		• *Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?* The primary and secondary endpoints from the ZUMA-5 trial are ORR, PFS and OS, which are clinically relevant endpoints in oncology clinical trials. • *Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?* Comparator data will be provided by the [redacted], which will be reporting prior to submission. [redacted] and therefore is the most robust data set available to inform comparative effectiveness estimates, in the absence of a head-to-head study.	
	Janssen-Cilag Ltd	*"Have all relevant comparators for axicabtagene ciloleucel been included in the scope?"* Yes – see clarification below for two of the comparators: • Established clinical management without axicabtagene ciloleucel *for MZL* • Best supportive care *for MZL/FL* *"Are the outcomes listed appropriate?"* Yes	Comment noted. The comparators have been updated (see responses to comparator comments). The committee may consider potential health related benefits that are not captured by QALY calculations.

Section	Consultee/ Commentator	Comments [sic]	Action
		"Are there any subgroups of people in whom axicabtagene ciloleucel is expected to be more clinically effective and cost effective or other groups that should be examined separately?" No *"Where do you consider axicabtagene ciloleucel will fit into the existing NICE pathway, Non-Hodgkin's lymphoma?"* R/R MZL/FL, as per trial *"NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:* • *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which axicabtagene ciloleucel will be licensed;* • *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;* • *could have any adverse impact on people with a particular disability or disabilities.* *Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts."* No	

Section	Consultee/ Commentator	Comments [sic]	Action
		"Do you consider axicabtagene ciloleucel to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?" Janssen recognises that CAR-T is a novel mechanism of action *"Do you consider that the use of axicabtagene ciloleucel can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?"* The prolonged treatment-free interval during remission is likely to increase the sensitivity of the disease to subsequent salvage therapies – which may not be captured via usual utility extraction methods *"To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly."* CAR-T are not just drugs but procedures and involve significant set-up periods, certifications for genetically modified Advanced therapy medicinal products (ATMPs) etc. Currently there is a lack of industry standards. The approval for patients eligible for CARTs is going to be centralised, hence the assumption is that this in itself will increase waiting times. Additionally, there are limited centres who can provide CARTs, e.g. only 7 centres in the UK for B cell Lymphoma *"NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness*	

Section	Consultee/ Commentator	Comments [sic]	Action
		of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). *NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.* • *Would it be appropriate to use the cost comparison methodology for this topic?* No Comment • *Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?* *No Comment* • *Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?* The primary outcome, being objective response rate (ORR) – including complete response (CR) and partial response (PR) is clinically relevant as it is a valid surrogate for progressed disease and overall survival.	

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

Lymphoma Action