Single Technology Appraisal (STA)
Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma

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
Wording	Kite pharma	The wording in the MAA is as follows: [redacted]	Comment noted.
	Janssen	Yes, the wording of the remit does reflect the issues.	Comment noted. The remit has been updated to reflect the population in the trial.
Timing Issues	Kite pharma	[redacted]	Comment noted.
	Royal College of Pathologists (RCP)	For patients who fail second line therapy, this is an area of very high unmet need so I would assess as urgent.	Comment noted. NICE aims, where possible, to produce timely guidance in line with

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			health technologies receiving their marketing authorisations.
Additional comments on the draft remit	Kite pharma	[redacted]	Comment noted.

Comment 2: the draft scope

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Background Information	RCP	In the draft scope the description of the comparators needs revision; BEAM and autologous stem cell transplantation is only used in patients who remain chemo sensitive to salvage therapies such as R- DHAP, R-ESHAP or R-ICE and as these are only achieve a good response in less than 20% of R CHOP failures (eg as published in the ORCHARRD trial Van Imhoff G I et al JCO 2017) there remains a clear majority of relapse and refractory patients with high unmet need for whom BEAM and stem cell transplantation is not an option. For patients 'for whom a stem cell transplant is not an option' rituximab monotherapy is of no value in relapsed DLBCL and is never used, the other options are purely palliative and the most common option for these patients will be to be offered entry into a clinical trial.	Comments noted. BEAM chemotherapy and rituximab monotherapy have been removed as comparators in the scope. For comparators please see the response below.

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		For patients ‘who have had 2 of more prior therapies’ , pixantrone is widely regarded by Specialists as of very little value and is little used. UK Audit data eg Eyre and Collins from Oxford supports this view. The evidence base submitted to the NICE appraisal was very poor (I was an invited expert) and the trial required by the Committee has not been completed in the timetable promised at the time of the initial assessment. My personal view is that it is unlikely to be renewed when it is reassessed.	
The technology/ intervention	Kite pharma	[redacted]	Comments noted.

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		[redacted]	
	RCP	More detail at this point would be useful especially regarding risks of the therapy	Comment noted. The background section is only intended to provide a brief description of the technology.
Population	Kite pharma	[redacted]	Comment noted.
	Janssen	Yes, the population seems appropriately defined.	Comment noted. No further action required
	RCP	'***Is the population defined appropriately? Are there groups within this population that should be considered separately?'*** Yes	Comment noted. No further action required
Comparators	Kite pharma	Based on ESMO guidelines and interviews with clinicians we believe there are several treatment regimens, with no universal standard of care. The treatments used in the setting are as follows:	Comments noted. The clinical expert at the scoping workshop

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		RVP: rituximab + vinblastine + prednisolone GEMP-P: gemcitabine + cisplatin + methylprednisolone (where gemcitabine has not been used as a salvage therapy Etoposide + rituximab + prednisolone In addition, patients may be eligible for allogeneic transplantation or participation in Phase 1/2 clinical trials with novel and experimental agents, or may be offered palliation with radiotherapy radioimmunoconjugates or rituximab monotherapy. The treatment options for relapsed/refractory PMBCL and TFL appear to be similar to those for DLBCL and as listed above We believe that Pixantrone should not be included as a comparator in this technology appraisal for the following reasons: 1. [redacted] We would argue that this is a different patient population to the label (conditional) granted to Pixantrone which is, multiply relapsed or refractory aggressive non-Hodgkin's B‑cell lymphoma In addition recent results of a multicentre UK-wide retrospective study evaluating the efficacy of Pixantrone in relapsed, refractory diffuse large B cell lymphoma (Post NICE guidance), showed limited utility and benefit in the	explained that salvage chemotherapy of DHAP, GDP, ICE, and IVE (with or without rituximab) were used in clinical practice after both R-CHOP and after second line salvage therapy. It was therefore agreed that DHAP, GDP, ICE, and IVE (with or without rituximab) would be included as comparators in the scope. Comment noted. Consultees were also in agreement that pixantrone monotherapy (although only used as treatment options for a small minority of patients) should remain as a comparator in the scope as it was recommended

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		management relapsed and refractory aNHL patients. (British Journal of Haematology. March, 2016, Toby A. Eyre) 2. NICE guidance only recommends Pixantrone as an option for treating adults with multiply relapsed or refractory aggressive non-Hodgkin's B‑cell lymphoma only if: • the person has previously been treated with rituximab and • the person is receiving third- or fourth-line treatment and	by NICE as a treatment option in TA306.
	Janssen	Yes, these seem to represent standard treatments currently used in the NHS.	Comment noted. No further action required
	RCP	R CHOP is only used for front line therapy in DLBCL and all patients suitable for this intervention (Axicabtagene ciloleucel – AC) will have failed R-CHOP so it cannot be a comparator For BEAM and stem cell transplant - not a comparator, as chemosenstive patients who respond to second line therapy will not need therapy with A-C. Rituximab monotherapy – no value in this patient group Pixantrone –see previous paragraph- very unlikely to be of therapeutic use to these patients Most of these patients will be offered a clinical trial	Comments noted. Consultees were in agreement during the scoping workshop that R-CHOP and rituximab monotherapy were not appropriate comparators and therefore have been removed from the scope. The clinical expert at the scoping workshop explained that therefore the appropriate comparators for

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			axicabtagene ciloleucel would be 3rd line salvage chemotherapy, DHAP, GDP, ICE or IVE (with or without rituximab. Therefore BEAM has been removed as a comparator in the scope. Consultees were also in agreement that pixantrone monotherapy (although only used as treatment options for a small minority of patients) should remain as a comparator in the scope as it was recommended by NICE as a treatment option in TA306

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Outcomes	Kite pharma	While median PFS and OS remain important clinical endpoints, these data take some time to mature and become available. Complete Response (CR) means all detectable tumour has disappeared. CR is a standard clinical outcome measure used in many in clinical trials in DLBCL. Clinicaltrials.gov[44] currently lists 281 interventional studies in DLBCL with Complete Response as a measure. A CR, if durable, represents a potential cure. If someone has advanced cancer, a CR is also the best result you can actually see from treatment. Therefore CR represents an important clinical endpoint in its own right.	Comment noted. Complete response would be captured in the outcome 'response rate' so no change required.
	Janssen	Yes, these outcome measures capture the most important health related benefits and harms of the technology.	Comment noted. No further action required.
	RCP	Overall survival is currently very short so this will be the most important parameter Adverse effects also important	Comment noted. No further action required.
Economic analysis	Kite pharma	The time horizon will be the life time of patients	Comment noted. No further action required
	Janssen	A lifetime horizon would seem appropriate.	Comment noted. No further action required
	RCP	Extremely important due to the very high costs involved	Comment noted. No further action required
Innovation	Kite pharma	We believe Axicabtagene ciloleucel is a ***step change*** in the management of patients with relapsed or refractory DLBCL who are ineligible for ASCT. Axicabtagene ciloleucel is a new and innovative personalised cellular cancer immunotherapy.	Comment noted. The company is encouraged to describe the innovative nature of axicabtagene ciloleucel

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		T cells are collected from the patient and engineered *ex vivo* to express a chimeric antigen receptor (CAR) which programmes them to target and kill the cancer cells when they are returned to the patient in a single infusion. It will potentially be the first in a new class of CAR-T therapies to be approved in Europe. In the treatment of relapsed/refractory DLBCL, Axicabtagene ciloleucel will address an area of high unmet need in which patients have very poor prognosis, with median OS of ~6.6 months with salvage chemotherapy which represents the current Standard of Care. SCHOLAR – 1 Because of the innovative nature of CAR-T therapy, and the challenges of comparative clinical trials in this therapy area, there is a need to address the uncertainty around the actual levels of benefit that would be delivered that will be extrapolated from small single-arm trials to long-term patient outcomes. The SCHOLAR-1 study represents a potential comparison to help address some of that uncertainty. SCHOLAR-1 combines multiple sources of evidence (2 RCTs, 2 observational sources). Overall survival was estimated from pooled subject record level data in the Survival analysis set using the Kaplan-Meier (KM) method. Kaplan-Meier plots, the median survival time (95% confidence interval), and the survival rates at 1- and 2-years were estimated. Prior to pooling the data from SCHOLAR-1, we assessed heterogeneity between the data sources, found it to be non-significant, and hence proceeded with pooling. Standardised and propensity score analyses were conducted to match the patient population close to the ZUMA-1 trial population. We believe that SCHOLAR-1 adds valuable evidence supporting the efficacy of axicabtagene ciloleucel. We believe that pooling the studies offers the greatest statistical power to the analysis but recognise that additional analyses such as comparisons using individual studies may offer reassurance regarding the conclusions.	in its submission to NICE. No action required.

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		Second question; Health benefits can be captured by the QALY	
	Janssen	Yes, we consider the technology to be innovative. No, we do not believe that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation.	Comment noted. The innovative nature of axicabtagene ciloleucel will be taken into account in the committee's discussion. No action required.
	RCP	Yes, this therapy is highly innovative and potentially a 'step change ' ***Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?*** Yes Data presented in Abstract form to high quality conferences such as the American Society of Haematology (ASH) , European Haematology association (EHA) and the International Congress on Malignant Lymphoma (ICML). Peer reviewed publications are rare at present.	Comment noted. The innovative nature of axicabtagene ciloleucel will be taken into account in the committee's discussion. No action required.
Equality	RCP	Therapy, at least initially, is likely to be carried out in a limited number of centres so equality of access for patients across the country will be important	Comments noted. During the scoping workshop the clinical expert stated that axicabtagene ciloleucel

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			would be given to patients at transplant centres, which are well distributed across England. It was therefore agreed that this could not be considered to be an equalities issue in this appraisal.
Questions for consultation	Pfizer	**Which regimen(s) is/are the most appropriate comparator for axicabtagene ciloleucel** According to UK clinical practice the following regimens can be considered to be the key comparators for axicabtagene ciloleuce: • Pixantrone • R-ICE, rituximab, ifosfamide, carboplatin and etoposide • R-IVAC, rituximab + ifosfamide + cytarabine + etoposide **Is best supportive care a relevant comparator and how is it be defined** • Best supportive care is a relevant comparator, as a standard NHS package of care it includes steroids, radiotherapy and blood product support. **Are the outcomes listed appropriate?** • Duration of remission is a key consideration in chimeric antigen receptor and T cell receptor (CAR-T) therapy and should also be included.	Comments noted. See above responses to comments on the comparators. Comments noted. This will be captured in the outcome 'progression free survival'. No change required.

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		Equity concerns • CAR-T therapies will likely only be available in level 4 tertiary centres with the sufficient clinical skills and resources to manage procedures such as leukapheresis and potential side effects like cytokine release syndrome. **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts on equality.** **Evidence should be collected on the following** • Availability of manufacturing pathways for CAR-Ts, turnaround time for access to leukapheresis machines, and the impact on current care pathways to accommodate the increase in numbers of patients requiring leukaephereis	Comment noted. During consultation on the draft scope, a consultees stated 'that Therapy, at least initially, is likely to be carried out in a limited number of centres so equality of access for patients across the country will be important' During the scoping workshop the clinical expert stated that axicabtagene ciloleucel would be given to patients at transplant centres, which are well distributed across England.

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		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 • Yes, access to leukapheresis machines is at a premium and is limited to certain centres only – if this was a widely adopted therapy then this pathway would require modification and support. The side effects of CAR-Ts may require specialist input and specialist therapies (such as with tocilizumab) which are likely only to be found in tertiatry centres and therefore the model of care for advanced haematological malignancies throughout the country would need to be standardised into level 4 centres with relevant expertise and facilities.	See equality impact assessment form for scoping. Comment noted. No change required to scope.
	RCP	This is a novel technology , assessment of adverse reactions and long term follow up data will be crucial. In my opinion even if this assessment is positive further, ongoing assessment of outcomes will be vital.	Comment noted. No change required.

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

Department of Health
Eisai