National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ciltacabtagene autoleucel for treating relapsed or refractory multiple myeloma

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
Wording	UK Myeloma Forum	This is a timely appraisal. CAR T cells are at the forefront of new immunotherapies that specifically target myeloma. It is a significant move forward in the management of this incurable cancer, particularly for patients that have exhausted conventional chemotherapeutic options.	Thank you for your comment. No action needed.
	Janssen	No comments.	No action needed
	Zentiva UK	No comments	No action needed
	Myeloma UK	Myeloma UK considers the remit to reflect the issues of clinical and cost effectiveness.	Thank you for your comment. No action needed
Timing Issues	UK Myeloma Forum	There is an urgent need to identify and implement novel effective therapies that target myeloma cells using new mechanisms of action, that lead to longer periods of disease control and overall survival	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6

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			months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Janssen	The appropriate population for this scope is patients with relapsed or refractory multiple myeloma (RRMM) previously treated with a proteasome inhibitor (PI) and immunomodulatory agent (IMiD) and an anti-CD38 monoclonal antibody (MoAB; please see below the additional comments on the draft remit). In this population, there is a substantial unmet need. Treatment options are limited and suboptimal, often consisting of repeat treatment with previously trialled regimens.[1] Moreover, prognosis and quality of life are poor, with very short overall and progression-free survival,[2] highlighting the significant burden of illness and poor survival prospect associated with this late stage in therapy. Ciltacabtagene autoleucel (cilta-cel) is an advanced therapeutic medicinal product that has shown unprecedented results in a heavily pre-treated and refractory population.[3] Taken together, the urgency of this appraisal to the NHS is considerably high. References 1Mikhael J. Treatment Options for Triple-class Refractory Multiple Myeloma. Clin Lymphoma Myeloma Leuk. 2020;20(1):1-7.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.

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		2Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33(9):2266-75. 3Madduri D, Berdeja JG, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. CARTITUDE-1: phase 1b/2 study of ciltacabtagene autoleucel, a B-cell maturation antigen–directed chimeric antigen receptor T cell therapy, in relapsed/refractory multiple myeloma. 62nd ASH Annual Meeting and Exposition: American Society of Hematology; 2020.	
	Zentiva UK	No comments	No action needed
Additional comments on the draft remit	Janssen	The scope is based on the incorrect clinical trial for cilta-cel. CARTITUDE is cilta-cel's clinical development programme. It consists of several clinical trials. One of these is the phase 1b/2, single-arm CARTITUDE-1 trial, which will support the first indication for cilta-cel in patients with RRMM who have received 3 or more prior lines of therapy, including a PI, an IMiD and an anti-CD38 MoAB. The scope should be based on this trial. Results from CARTITUDE-1 reflecting a median follow-up of ~9 months were presented at the 2020 American Society of Hematology congress.[1] The current draft scope is based on CARTITUDE-4, which will support a later indication of cilta-cel at an earlier position in the treatment pathway. CARTITUDE-4 is currently ongoing with no data read-outs expected soon, and so it will not be contributing evidence to this appraisal. Therefore, this scope should be based on CARTITUDE-1, rather than CARTITUDE-4. References 1Madduri D, Berdeja JG, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. CARTITUDE-1: phase 1b/2 study of ciltacabtagene autoleucel, a B-cell maturation antigen–directed chimeric antigen receptor T cell therapy, in	Thank you for your comment. The scope will be based on the CARTITUDE-1 trial as requested.

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		relapsed/refractory multiple myeloma. 62nd ASH Annual Meeting and Exposition: American Society of Hematology; 2020.	
	Zentiva UK	No comments	No action needed

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	UK Myeloma Forum	The description of therapies that are NICE approved are correct. Lenalidomide maintenance is approved by NICE after autologous stem cell transplantation. The phase 1/2 CARTITUDE-1 trial (Madduri et al, ASH 2020), required patients to have received at least 3 prior lines that include a PI, IMID and anti-CD38 therapy, or at least 1 prior line and to be PI and IMID double refractory as well as an anti-CD38 antibody exposed. The phase 3 CARTITUDE-4 trial on which this appraisal is based requires prior treatment with Lenalidomide and to be refractory to this drug. The trial population is important as this will influence what the appropriate comparators are.	Thank you for your comment. The background section has been changed to better reflect the CARTITUDE-1 trial.
	Janssen	Only NICE guidance in the fourth- and subsequent-line settings is relevant to this appraisal.	Thank you for your comment. The background section has been updated accordingly. Treatment options for 2nd and 3rd line have been removed.

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	Zentiva UK	NICE also recommends technology appraisal guidance [TA658]: Isatuximab, plus pomalidomide and dexamethasone for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment only if they have had 3 previous lines of treatment.	Thank you for your comment. The background section has been updated accordingly and TA658 has been added.
	Myeloma UK	We consider this information to be complete and accurate.	Thank you for your comment. Not action needed
The technology/ intervention	UK Myeloma Forum	The technology description is accurate. It should be noted this will be the first CAR T-cell to be available for patients with myeloma. The target of the treatment, BCMA, is highly expressed on myeloma cells. However Ciltacatagene autoleucel predominantly induces direct plasma cell cytotoxicity by T cell mediated lysis and engagement of the wider immune system through cytokine secretion rather than signalling through BCMA as described. It is the target for a wave of new therapy developments in myeloma.	Thank you for your comment. This section has been changed to reflect the CARTITUDE-1 trial. It also indicates that the technology is a one-off treatment. No further action needed.
	Janssen	The text should clarify that the technology is administered as a single intravenous infusion. Per previous comments, this section describes the CARTITUDE-4 trial. The relevant trial for this indication is CARTITUDE-1	Thank you for your comment. This section has been updated accordingly.
	Zentiva UK	No comments	No action needed
	Myeloma UK	Yes	No action needed

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Population	UK Myeloma Forum	As mentioned above the phase 3 CARTITUDE-4 trial is assessing this technology in a population that is Lenalidomide refractory and 1-3 prior lines. In the current pathway transplant eligible patients can receive Lenalidomide maintenance after induction treatment (first line). Most patients would receive Lenalidomide as third line in combination the Ixazomib (via CDF), or as second line. Non-transplant eligible patients can receive Lenalidomide upfront as well. This is important as this will influence what the appropriate comparators are.	Thank you for your comment. The population has been updated in line with comments received by the company.
	Janssen	In line with the inclusion criteria of the CARTITUDE-1 trial, this should be "Adults with relapsed/refractory multiple myeloma who have had at least 3 previous therapies".	Thank you for your comment. The population has been updated accordingly.
	Zentiva UK	No comments	No action needed
	Myeloma UK	We have been informed by the submitting company that this HTA will be based on the results of the clinical trial CARTITUDE-1 which included adult patients with multiple myeloma who had received three or more prior regimens or were double-refractory to an immunomodulatory drug and proteasome inhibitor. This would mean that the population outlined in the scoping would be incorrect. Multiply relapsed patients who have 3 or more prior lines of therapy need greater options for disease control. A new CAR-T therapy at this stage in the	Thank you for your comment. The population has been updated in line with comments received by the company.

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		treatment pathway would address a significant unmet need for this patient population.	
Comparators	UK Myeloma Forum	Most patients currently receive Lenalidomide as 3rd line in combination with Ixazomib via CDF. An appropriate comparator is therefore Pomalidomide Dexamethasone (4th line). Panobinostat Bortezomib Dexamethasone is rarely used at 4th line and therefore is not an appropriate comparator. Currently a group of patients could receive Lenalidomide in the frontline setting, either following the newly approved transplant eligible (maintenance) or on the non-transplant eligible pathway. We would expect these patients to receive a proteosome inhibitor (PI) based regimen at this stage (Bortezomib Daratumumab Dexamethasone via CDF, or Carfilzomib Dexamethasone) at first relapse. These would be appropriate comparators earlier in the pathway. As patients need to be Lenalidomide refractory to receive this technology (entry requirement for the CARTITUDE-4 trial) lenalidomide is not an appropriate comparator.	Thank you for your comment. The comparator list has been changed to better reflect possible comparators in the 4th and subsequent line setting since the scope has been amended to be based on the CARTITUDE-1 trial as requested by the company. The appraisal committee will discuss the most appropriate comparators during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice. Only technologies that are

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			routinely commissioned by the NHS can be considered as comparators by the appraisal committee. Therefore, technologies that are currently funded through the Cancer Drugs Fund will not be considered.
	Janssen	As CARTITUDE-1 does not provide evidence for using cilta-cel after 1 or 2 previous therapies, the relevant comparators in this scope should be limited to those that reflect current NHS treatment after 3 previous therapies. Per NICE TA658 (published in Nov 2020), the NICE appraisal committee concluded that "after 3 previous lines of treatment, pomalidomide plus dexamethasone is the only relevant comparator" (section 3.5). Other comparators currently listed in the draft scope for people who have had 3 previous therapies are: • Panobinostat plus bortezomib and dexamethasone: this is used to a much lesser extent than pomalidomide-based therapy as a fourth-line treatment given its high toxicity. • Lenalidomide plus dexamethasone: this is not a relevant comparator after 3 previous therapies because patients would have received it earlier in therapy as first- (TA587) or second- (TA586) line treatment.	Thank you for your comment. The comparator list has been updated and comparators in 2nd and 3rd line treatments have been removed. The appraisal committee will discuss the most appropriate comparators during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness

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			evidence and current clinical practice.
	Zentiva UK	No comments	No action needed
	Myeloma UK	As discussed above this HTA is based on the clinical trial CARTITUDE-1 which is positioned for multiple myeloma patients who have had three or more prior regimens. This would indicate that the comparators in the treatment pathway are: Pomalidomide, in combination with low-dose dexamethasone (TA427) Panobinostat in combination with bortezomib and dexamethasone (TA380) Further to theses CDF Funded treatments would include: Daratumumab Monotherapy (TA510) Isatuximab, plus pomalidomide and dexamethasone (TA658)	Please see response to comments on comparators by UK Myeloma Forum.
Outcomes	UK Myeloma Forum	Yes. Response rates including MRD status.	No action needed
	Janssen	No comments.	No action needed
	Zentiva UK	No comments	No action needed

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	Myeloma UK	Yes	No action needed
Economic analysis	UK Myeloma Forum	Appropriate time horizon for survival following1 prior lines of treatment for relapsed myeloma patient would be likely be more than 10 years.	Thank you for your comment. No action needed.
	Janssen	No comments.	No action needed
	Zentiva UK	No comments	No action needed
	Myeloma UK	No comment	No action needed
Equality and Diversity	UK Myeloma Forum	The main equality issue will be ease of access. Previous CAR T-cell approvals have led to administration in a limited number of CAR-T designated treatment centres reducing potential access if patients are not geographically linked or able to access these centres. This may be a particular issue for patients that may not be able to afford the travel costs of attending the CAR-T centre. There are no other equality issues	Thank you for your comment. 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

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			ensure equality of referral and treatment access. The appraisal committee will consider any equality issues.
	Janssen	No comments.	No action needed
	Zentiva UK	No comments	No action needed
	Myeloma UK	No comment	No action needed
Other considerations	Janssen	Subgroup analyses based on previous lines of therapy should be removed as patients who have had 1 or 2 previous therapies should be excluded from the scope.	Thank you for your comment. The committee might want to assess subgroups if the evidence allows. Type and line of previous treatments might still be relevant subgroups. No action needed.
	Zentiva UK	No comments	No action needed
	Myeloma UK	No additional suggestions	No action needed
Innovation	UK Myeloma Forum	CAR T cell therapy is an extremely innovative modality of treatment for cancer. This would be the first cellular immunotherapy available for myeloma patients and targets the malignant plasma cell in a novel way achieving very	Thank you for your comment. Innovation will be considered in

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		deep responses in patients with multiple prior lines of treatment. It also provides patients with a treatment-free-interval following CAR-T infusion which is unlike other approved myeloma treatments. It addresses an unmet need for patients who have no / or limited treatment options.	more detail by the appraisal committee as part of the full appraisal. No action needed.
	Janssen	Cilta-cel is an advanced therapeutic medicinal product that has shown unprecedented results in a heavily pre-treated and refractory population[1] with limited treatment options[2] and an extremely poor prognosis in UK clinical practice.[3] As such, cilta-cel represents a significant "step-change" in therapy. Moreover, cilta-cel being a one-time infusion allows patients prolonged treatment-free periods before further treatment is needed, which is associated with improved quality of life.[4] This benefit of treatment may not be adequately captured in the QALY calculation. References 1Madduri D, Berdeja JG, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. CARTITUDE-1: phase 1b/2 study of ciltacabtagene autoleucel, a B-cell maturation antigen–directed chimeric antigen receptor T cell therapy, in relapsed/refractory multiple myeloma. 62nd ASH Annual Meeting and Exposition: American Society of Hematology; 2020. 2Mikhael J. Treatment Options for Triple-class Refractory Multiple Myeloma. Clin Lymphoma Myeloma Leuk. 2020;20(1):1-7. 3Holt M, Taube J, Carmichael J, Feyler S, Cheesman S, Lee L, et al. Real-world, multi-centre review of the effectiveness of dara monotherapy and patients' response to subsequent therapies. 25th EHA Annual Congress: European Hematology Association; 2020. 4Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple	Thank you for your comment. Innovation will be considered in more detail by the appraisal committee as part of the full appraisal. No action needed.

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		myeloma: a UK cross-sectional survey. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2013;21(2):599-607.	
	Zentiva UK	No comments	No action needed
	Myeloma UK	Cilta-Cel is a B-cell maturation antigen (BCMA) genetically modified autologous chimeric antigen receptor (CAR) T cell immunotherapy. This would be the first of its kind in the treatment of multiple myeloma and as such we would consider this a step change in innovation. Whilst data for this treatment is immature, results from the Phase 1/2 CARTITUDE-1 study which evaluated the efficacy and safety of cilta-cel in heavily pre-treated patients with relapsed and refractory multiple myeloma have been promising. The study has demonstrated a very high overall response rate with two thirds of patients reaching a stringent complete response. As the myeloma pathway expands and patients are treated with different systemic anti-cancer treatments there is a need for a novel/innovative treatment for multiply relapsed patients who are refractory to immunomodulatory agents, proteasome inhibitors, and CD38 monoclonal antibodies.	Thank you for your comment. Innovation will be considered in more detail by the appraisal committee as part of the full appraisal. No action needed.
	Janssen	Please see above comments on comparators and established clinical practice in the NHS for RRMM. Cilta-cel will fit into the existing NICE pathway after 3 previous therapies, as a fourth- or subsequent-line treatment.	Thank you for your comment. No further action needed.

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	Zentiva UK	No comments	No action needed
	Myeloma UK	No further comments	No action needed
	Janssen	None	No action needed
	Zentiva UK	No comments	No action needed

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

Amgen Ltd
Novartis Pharmaceuticals UK
Royal College of Pathologists – endorse the UK Myeloma Forum