National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Idecabtagene vicleucel for treating relapsed and refractory multiple myeloma in people who have received at least 3 prior therapies

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	Celgene, a Bristol Myers Squibb (BMS) company	The population should be defined as per the anticipated license. Please modify to "…within its marketing authorisation for treating multiple myeloma in people who have received at least 3 prior therapies, **including an IMiD, a PI, and an anti-CD38 antibody**." This change should be applied throughout the scope.	Thank you for your comments. The remit of the scope has been updated to ensure it is broad enough to cover any potential marketing authorisation. Idecabtagene vicleucel will be appraised for treating multiple myeloma within its marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
	Janssen-Cilag	The remit should specify pre-treatment with a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody (i.e., 'triple-class exposure') – a key inclusion criterion in the clinical trial for this technology.	Thank you for your comment. The remit of the scope has been updated to ensure it is broad enough to cover any potential marketing authorisation. Idecabtagene vicleucel will be appraised for treating multiple myeloma within its marketing authorisation.
	UK Myeloma Forum	Yes. The wording in the remit reflects the issues.	Thank you for your comment. The remit of the scope has been updated to ensure it is broad enough to cover any potential marketing authorisation.
	Myeloma UK	Myeloma UK considers the remit to reflect the issues of clinical and cost effectiveness.	Thank you for your comment. The remit of the scope has been updated to ensure it is broad enough to cover any potential marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	Celgene, a BMS company	Despite advancements in treatment options, relapsed and refractory multiple myeloma remains incurable and there is a significant unmet need for patients who have failed the three most commonly used treatment classes (IMiD, PI and anti-CD38 antibody). At this stage, outcomes are poor and life expectancy is very short.	Thank you for your comments. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation.
	Janssen-Cilag	No comments.	No action required.
	UK Myeloma Forum	There is an urgent need for novel therapies in myeloma. It is incurable with patients experiencing a cycle of responses and relapses with eventful development of drug resistant disease and then death due to myeloma. 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 comments. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation.
	Myeloma UK	None.	No action required.
Additional comments on the draft remit	Celgene, a BMS company	None.	No action required.
	Janssen-Cilag	None.	No action required.
	UK Myeloma Forum	None.	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Myeloma UK	None.	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Celgene, a BMS company	Minor comment that NICE technology appraisal guidance TA311 is not referred to for untreated multiple myeloma eligible for stem cell transplant.	Thank you for your comment. The background section has been amended to only refer to NICE guidance for people with relapsed or refractory multiple myeloma after 2 prior therapies, to better align with the population of interest for this appraisal.
	Janssen-Cilag	In the context of relapse assessment, may be beneficial to describe patients with the highest unmet need such as those with worse survival outcomes seen in patients with a high-risk cytogenetic profile or treatment-refractory disease.	Thank you for your comments. This section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	UK Myeloma Forum	The background is accurate and complete.	Thank you for your comment. No action required.
	Myeloma UK	We consider this information to be complete and accurate.	Thank you for your comment. No action required.
The technology/ intervention	Celgene, a BMS company	No comments.	No action required.
	Janssen-Cilag	It may be worth noting that the technology is a second-generation CAR construct derived from autologous T-cell with anti-BCMA fragment (extracellular), 4-1BB co-stimulatory domain and a CD3-zeta signalling intracellular domain. The final drug product may also be characterised by the proportion of CAR+ CD4 and CD8 T-cells. Before receiving the medicinal product, patient may receive bridging therapy and will require conditioning therapy with fludarabine and cyclophosphamide.	Thank you for your comments. This section of the scope is intended to provide a brief summary of the technology and is not designed to be exhaustive. No action required.
	UK Myeloma Forum	The technology description is accurate. It should be noted this will be the first CAR T-Cell to gain marketing authorisation in myeloma. Preliminary data is unprecedented in this setting. The target of the treatment (BCMA) is highly expressed on myeloma cells making it a specific target. As such it is the target for a wave of new therapy developments in myeloma. Idacabtagene is at the forefront of these new developments.	Thank you for your comments. This section of the scope is intended to provide a brief summary of the technology and is not designed to be

Section	Consultee/ Commentator	Comments [sic]	Action
			exhaustive. No action required.
	Myeloma UK	Yes.	Thank you for your comment. No action required.
Population	Celgene, a BMS company	The population should be defined as per the anticipated license: adult patients with multiple myeloma who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody. There are no relevant subgroups that should be considered separately.	Thank you for your comments. The population has been left broader than suggested, to ensure idecabtagene vicleucel can be appraised within its eventual marketing authorisation. The population therefore states “at least 3 prior therapies” only. No action required.
	Janssen-Cilag	Per above comment, this population is importantly characterised by prior exposure to a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.	Thank you for your comment. The population has been left broader than suggested, to ensure idecabtagene vicleucel can be appraised within its eventual marketing authorisation. The

Section	Consultee/ Commentator	Comments [sic]	Action
			population therefore states “at least 3 prior therapies” only. No action required.
	UK Myeloma Forum	This is described accurately. It is most likely suitable for patients who would be considered medically fit enough to undergo stem cell transplant.	Thank you for your comment.
	Myeloma UK	We consider the population to be appropriately defined.	Thank you for your comment.
Comparators	Celgene, a BMS company	Anti-CD38 antibodies including daratumumab are a recent addition to the treatment pathway and currently only available via the CDF. Therefore, there is a substantial lack of evidence in the relevant patient population (those who have received a prior IMID, PI, and an anti-CD38) and no established standard of care exists for these patients. Panobinostat in combination with bortezomib and dexamethasone was not considered a relevant comparator in the recent isatuximab + pomalidomide + dexamethasone appraisal [ID1477] as it is only given to a few patients in clinical practice, due to the toxic adverse events. It may be used in patients who have received at least four prior therapies, however the number of patients who progress to this line of treatment is low and they may not be able to tolerate the adverse events. Therefore, panobinostat in combination with bortezomib and dexamethasone should be removed from the list of comparators. Conventional chemotherapy regimens are rarely given in clinical practice to treat patients who have received at least 3 prior treatments. Clinicians use pomalidomide in combination with dexamethasone in preference as the toxicity of the conventional chemotherapy tends to be unacceptably high, and	Thank you for your comments. This section has been updated to remove conventional chemotherapy regimens and best supportive care from the list of relevant comparators. The scope is intended to be broad, so as not to exclude potentially relevant comparators. Panobinostat in combination with bortezomib and dexamethasone is recommended in NICE technology appraisal

Section	Consultee/ Commentator	Comments [sic]	Action
		there are no real efficacy data at fourth and fifth line. Patients may receive conventional chemotherapy at as a final treatment option, but these patients would not be fit enough to receive ide-cel. Therefore, conventional chemotherapy regimens should be removed from the list of comparators. Best supportive care is considered to be palliative treatment and these patients would not be fit enough to receive ide-cel. Therefore, BSC should be removed from the list of comparators.	380 for use after 2 prior therapies. At the time of writing, final guidance (and therefore final committee considerations) has not been published for ID1477. Therefore, this combination has been retained as a comparator in the scope.
	Janssen-Cilag	Conventional chemotherapy regimens do not reflect standard-of-care treatment for these patients. After 3 or 4 previous therapies, there are effective and NICE-recommended treatment options such as pomalidomide plus dexamethasone, which is the standard of care in the UK after 3 prior therapies (in patients previously treated with an anti-CD38 antibody i.e. the population of interest in this appraisal). This echoes the statement in the ACD for ID1477 that 'The committee concluded that after 3 previous treatments, pomalidomide plus dexamethasone is the only relevant comparator' (section 3.3). Panobinostat in combination with bortezomib and dexamethasone is used to a lesser extent in this setting. Likewise, best supportive care is not a relevant comparator as CAR-T therapy is an intensive and elaborate process involving multiple hospital stays, travel to/from specialist centres which may require lodging away from home due to distances travelled, chemotherapy pre-treatment and potentially a stay in temporary accommodation post treatment for a few weeks with a carer, in addition to the treatment itself and associated toxicity which may require ICU	Thank you for your comments. This section has been updated to remove conventional chemotherapy regimens and best supportive care from the list of relevant comparators. The scope is intended to be broad, so as not to exclude potentially relevant comparators. Panobinostat in combination with bortezomib and dexamethasone is

Section	Consultee/ Commentator	Comments [sic]	Action
		admission. In clinical practice, patients receive active treatment if they are fit enough to receive it. Those who are not fit enough to receive active treatment, and receive best support care instead, are highly unlikely to be those who will receive CAR-T therapy.	recommended in NICE technology appraisal 380 for use after 2 prior therapies. At the time of writing, final guidance (and therefore final committee considerations) has not been published for ID1477. Therefore, this combination has been retained as a comparator in the scope.
	UK Myeloma Forum	The main comparator is pomalidomide / dexamethasone. Neither conventional chemotherapy or best supportive care would be appropriate comparators. They would be considerations after 5 or 6 lines of treatment. They are also generally considered to be more short term palliative options rather than active treatment options due to their poor efficacy. There is extremely limited data to support their use and should not be comparators. Panobinostat / bortezomib / dexamethasone is a less frequently used combination for patients with more than 3 prior lines of therapy due to a relatively poor clinical experience when administered to heavily pre-treated patients.	Thank you for your comments. This section has been updated to remove conventional chemotherapy regimens and best supportive care from the list of relevant comparators. The scope is intended to be broad, so as not to exclude potentially relevant comparators. Panobinostat in combination with

Section	Consultee/ Commentator	Comments [sic]	Action
			bortezomib and dexamethasone is recommended in NICE technology appraisal 380 for use after 2 prior therapies. At the time of writing, final guidance (and therefore final committee considerations) has not been published for ID1477. Therefore, this combination has been retained as a comparator in the scope.
	Myeloma UK	Yes.	Thank you for your comment. However, this section has been updated in line with other comments on the comparators. Please see earlier responses to comments in this section.
Outcomes	Celgene, a BMS company	The following outcomes are also relevant in addition to those listed: • Overall response rate	Thank you for your comment. The scope

Section	Consultee/ Commentator	Comments [sic]	Action
		• Complete response rate	has been updated to mention these outcomes under response rates, which is already included as an outcome measure.
	Janssen-Cilag	Adverse effects of treatment should include specific class effects namely, cytokine release syndrome and neurotoxicity, which are serious and potentially life-threatening adverse effect associated with CAR-T therapy.	Thank you for your comment. The scope includes adverse effects of treatment as a broad outcome measure, which will encompass specific treatment-emergent adverse events.
	UK Myeloma Forum	We would additionally suggest including measurable residual disease (MRD) as an outcome measure.	Thank you for your comment. The list of outcomes is not exhaustive, therefore information on measurable residual disease can be submitted in the appraisal. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Myeloma UK	Yes.	Thank you for your comment. No action required.
Economic analysis	Celgene, a BMS company	A lifetime horizon is appropriate for this technology.	Thank you for your comment. As multiple myeloma is an incurable disease, a lifetime horizon is appropriate. No action required.
	Janssen-Cilag	Information assessing the intent-to-treat population vs. those who receive the CAR-T infusion may help provide indicative numbers of patients who may be eligible in the real-world setting i.e., account for manufacturing challenges, out-of-specification product and factors associated with the timely delivery of the innovative treatment.	Thank you for your comments. No action required.
	UK Myeloma Forum	Appropriate time horizon for survival following 3 prior lines of treatment for relapsed myeloma patient would no more than 10 years.	Thank you for your comment. The NICE reference case stipulates that the time horizon should be “sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared”. As multiple

Section	Consultee/ Commentator	Comments [sic]	Action
			myeloma is an incurable disease, a lifetime horizon is appropriate. No action required.
	Myeloma UK	No comments.	No action required.
Equality and Diversity	Celgene, a BMS company	No comments.	No action required.
	Janssen-Cilag	No comments.	No action required.
	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 treatment centres reducing potential access if patients are not geographically linked or able to access these centres. There are no other equality issues.	Thank you for your comments. Access to treatment based on geography is an implementation issue and cannot be addressed in technology appraisal guidance. No action required.
	Myeloma UK	No comments.	No action required.
Other considerations	Celgene, a BMS company	No comments.	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Janssen-Cilag	Analysis of subgroups of patients who may derive more benefit in the real-world setting such as those grouped by level of prior tumour burden (e.g., number of prior therapies), cytogenetic risk, bridging therapy and exploratory biomarkers of cytokine release syndrome (e.g., age, baseline BCMA level/expression).	Thank you for your comments. If evidence allows the clinical and cost effectiveness of idecabtagene vicleucel in subgroups will be considered by the committee.
	UK Myeloma Forum	Nil.	No action required.
	Myeloma UK	No Additional Suggestions.	Thank you for your comment. No action required.
Innovation	Celgene, a BMS company	Idecabtagene vicleucel (ide-cel) is the first chimeric antigen receptor T cell therapy for Multiple Myeloma (MM). If approved, it will also be the first licensed treatment to target B-cell maturation antigen (BCMA), a cell surface protein universally expressed on malignant plasma cells that is associated with promoting MM cell survival.[1] The ide-cel construct includes an anti-BCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain.[2] Antigen-specific activation of Ide-cel results in CAR-positive T cell proliferation, cytokine secretion and subsequent cytolytic killing of BCMA-expressing cells. Ide-cel is a unique treatment that requires a one-time administration rather than requiring continuous therapy like comparator treatments, reducing burden of care.	Thank you for your comments. Any innovative aspects of the technology will be considered by the appraisal committee based on evidence presented to it. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Outcomes remain poor in triple-class exposed RRMM patients who progress on immunomodulatory agent (IMiD) agents, proteasome inhibitors (PIs), and anti-CD38 antibodies (the population of interest).[2,3] Ide-cel presents a step change versus comparator treatments by dramatically improving prognosis in the relevant patient population (prior IMID, a PI, and an anti-CD38), which has a high unmet medical need, no curative options, no standard of care, and short expected survival (OS of 9.2 months for triple-refractory and 5.6 months for penta-refractory patients[1]). In the pivotal KarMMa study (NCT03361748), 84% were triple- and 26% were penta-refractory. Despite this, in the most recent analysis (data cut-off: 14 Jan 2020), the overall response rate was 73%, and median OS was 19.4 months across all dose levels and 78% of patients were alive at 12 months.[2] In addition, ide-cel was tolerable and grade ≥3 cytokine release syndrome and neurotoxicity occurred in 5% & 3% of patients, respectively.[2] As ide-cel is intended for patients who would otherwise be considered for end-of-life treatment, improving prognosis and HRQL will not only significantly benefit them but also their family and friends; emotionally as well as physically. Although some aspects of the above health-related benefits will be captured in the QALY calculation, the true value of this innovative treatment is likely to be underestimated. **References** 1. Tai & Anderson; Targeting B-cell maturation antigen in multiple myelomaImmunotherapy 2015; 7(11), 1187-1199. 2. Bristol Myers Squibb. Bristol Myers Squibb and bluebird bio to Present Updated Positive Results from Pivotal KarMMa Study of Ide-cel in Relapsed and Refractory Multiple Myeloma Patients at ASCO20.	

Section	Consultee/ Commentator	Comments [sic]	Action
		2020. (Updated: 13 May 2020) Available at: https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-and-bluebird-bio-present-updated-positive. Accessed: 20 May 2020. 3. Gandhi U et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019; 33(9):2266-2275	
	Janssen-Cilag	No comments.	No action required.
	UK Myeloma Forum	This is an extremely innovative therapy. It is a first in class treatment within myeloma that is both a novel technology but also has a novel target which is relatively myeloma specific 9BCMA). Toxicities are manageable on the basis of initial studies and the accumulated experience with CAR T-cells used in other diseases. The reported responses and durations of response are unprecedented in such a heavily pre-treated myeloma patient population. The introduction of anti-BCMA CAR T-cells for myeloma represents a step change in therapy for the disease in the relapsed / refractory setting.	Thank you for your comments. Any innovative aspects of the technology will be considered by the appraisal committee based on evidence presented to it. No action required.
	Myeloma UK	Idecel 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 2 KarMMa study, which evaluated the efficacy and safety of idecel in heavily pre-treated patients with relapsed and refractory multiple myeloma have been promising. The study met its primary endpoint of overall response rate and key secondary endpoint of complete response rate with responses in nearly three-quarters of patients with relapsed/refractory multiple myeloma.	Thank you for your comments. Any innovative aspects of the technology will be considered by the appraisal committee based on evidence presented to it. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		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.	
Questions for consultation	Celgene, a BMS company	No comments.	No action required.
	Janssen-Cilag	No comments.	No action required.
	UK Myeloma Forum	We would expect the technology to fit in the existing NICE pathway for patients of suitable medical fitness who have relapsed / refractory myeloma and have previously received proteosome inhibitor (bortezomib), immunomodulatory therapy (lenalidomide) and anti-CD38 monoclonal antibody (daratumumab). According to the current NICE pathway it will most likely fit as a 4th line therapy.	Thank you for your comments. No action required.
	Myeloma UK	None.	No action required.
Additional comments on the draft scope	Celgene, a BMS company	None.	No action required.
	Janssen-Cilag	None.	No action required.
	UK Myeloma Forum	None.	No action required.
	Myeloma UK	None.	No action required.

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

Leukaemia Care

Novartis