National Institute for Health and Care Excellence

Health Technology Evaluation

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable [ID6249]
Response to stakeholder organisation 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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Johnson & Johnson	Johnson & Johnson consider it important that NICE evaluate daratumumab in combination with bortezomib, lenalidomide and dexamethasone (DBLd) for patients suitable for transplant as there remains an unmet need for enduring response leading to improved outcomes and delaying the need for subsequent therapies. Patients suitable for transplant currently predominantly receive daratumumab in combination with bortezomib, thalidomide and dexamethasone (DBTd) induction and consolidation (as per TA763) followed by lenalidomide maintenance (as per TA680). DBLd provides patients the opportunity to receive induction and consolidation with DBLd followed by daratumumab with lenalidomide (DL) maintenance as per daratumumab's marketing authorisation and summary of product characteristics (SmPC). DBLd is expected to deliver improved clinical outcomes compared to current standard of care and, as such, is most suitable for evaluation following the single technology appraisal route.	Thank you for your comments. The route for this evaluation has been changed to Single Technology Appraisal.

Section	Stakeholder	Comments [sic]	Action
		Johnson & Johnson intend to submit evidence for the full marketing authorisation, including DL maintenance. Johnson & Johnson acknowledge, however, that a cost comparison approach is most relevant to the induction and consolidation component of the regimen.	
	Myeloma UK	Yes, this topic is appropriate for a NICE appraisal.	Thank you for your comment. No change to scope required.
	The UK Myeloma Society	This is an appropriate evaluation for NICE to undertake as UK patients with multiple myeloma require access to new treatments that can prolong survival and improve quality of life. Dara-VRD with DR maintenance has shown impressive progression free survival and depth of response in the PERSEUS Trial, with a manageable safety profile.	Thank you for your comments. No change to scope required.
Wording	Johnson & Johnson	The wording of the remit is appropriate.	Thank you for your comment. No change to scope required.
	Myeloma UK	The wording of the scope reflects the issues of clinical and cost effectiveness.	Thank you for your comment. No change to scope required.
	The UK Myeloma Society	The wording is appropriate and the suggested comparators for this technology are suitable such as Dara-VTD, VTD, VCD etc. However, the wording is not clear whether this appraisal will include just Dara-VRD induction, or induction + consolidation or induction consolidation + maintenance which is crucially important to patients. This may be because the treatment is not licensed yet. The health economic considerations are sound as it is likely that the deliverability of Dara-VRD will be like the existing option of Dara-VTD given	Thank you for your comments. The wording of the remit is intended to match the anticipated marketing authorisation wording. No change to scope required.

Section	Stakeholder	Comments [sic]	Action
		that both regimens include two oral drugs and two subcutaeneous injections. There may be additional benefit for patients receiving Dara-VRD with improved toxicity profile following substitution of lenalidomide for thalidomide.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Johnson & Johnson	The intervention should be updated to specify daratumumab in combination with bortezomib, lenalidomide and dexamethasone (DBLd) as induction and consolidation therapy along with daratumumab plus lenalidomide (DL) maintenance treatment.	Thank you for your comment. The intervention wording in the scope has been updated to clarify this.
	Myeloma UK	We consider this information to be sufficient. However, the description of the technology is confusing because it refers to the indication for non- stem cell transplant eligible myeloma patients.	Thank you for your comment. The technology section refers to the appraisal for untreated multiple myeloma when a stem cell transplant is unsuitable because this is a closely related technology appraisal in development.
	The UK Myeloma Society	The background is fine, could place more emphasis on the impact of myeloma plasma cells on normal immunity and the immunosuppressive nature of the disease, which can be improved with effective treatment. Dara-	Thank you for your comment. The background section of the scope is intended to

Section	Consultee/ Commentator	Comments [sic]	Action
		VRD has shown improved duration of remission and depth of response in trials.	be very brief. No change to scope required.
Population	Johnson & Johnson	Yes, the population is defined appropriately	Thank you for your comment. No change to scope required.
	Myeloma UK	We consider the population to be appropriately defined.	Thank you for your comment. No change to scope required.
	The UK Myeloma Society	The incidence of myeloma is a bit low – CRUK figures quotes 6240 cases of myeloma per year from 2017-2019 and this is rising due to ageing population.	Thank you for your comment. NICE prefers to use the more recent statistics from 2021, with recognition that these are for England only rather than the UK as a whole. No change to scope required.
Subgroups	Johnson & Johnson	No subgroups have been identified for which DBLd followed by DL maintenance is expected to be more clinically or cost effective. Therefore, Johnson & Johnson do not consider any subgroups that should be considered separately.	Thank you for your comment. No change to scope required.
	Myeloma UK	We are not aware of any patient subgroups where daratumumab with bortezomib, lenalidomide and dexamethasone would be more clinically of cost effective.	Thank you for your comment. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		The published data for this treatment regimen does contain some preplanned subgroup analyses however, the comparator used in the trial is not the standard of care in England.	
	The UK Myeloma Society	Patients with high risk cytogenetic disease have an unmet need for better treatment at present as they have inferior survival outcomes. The regimen Dara-VRD is more like the effective treatment regimens that have been used in clinical trials for patients with high risk disease such as the UK MUK 9 trial (Dara-VCRD induction and extended consolidation and maintenance) and the GMMG Concept trial (Isatuximab-KRD with Isatuximab-Lenalidomide maintenance) and approval of Dara-VRD in the UK will provide additional benefit for high risk patients, particularly if Dara-Len maintenance is also approved post-transplant.	Thank you for your comment. No change to scope required.
Comparators	Johnson & Johnson	Induction and consolidation Johnson & Johnson considers DBTd as the most relevant comparator to DBLd as induction and consolidation treatment with estimated current market share of [redacted]. In addition, Johnson & Johnson understands that a small minority of patients may still receive bortezomib with thalidomide and dexamethasone (BTd) or bortezomib with cyclophosphamide and dexamethasone (BCd, off-label) as induction and consolidation treatment. Johnson & Johnson does not consider the following treatments included in the NICE draft scope as relevant comparators: • **Bortezomib with dexamethasone** (TA311) is not a relevant comparator as clinical feedback confirmed the doublet therapy is rarely offered to patients for whom a stem cell transplant would be suitable and was not deemed a relevant comparator to DBTd in TA763	Thank you for your comments. The comparators section of the NICE scope is intended to be broad and inclusive. The company should justify any exclusions in its evidence submission. In response to aligned comments from stakeholders that the off label cyclophosphamide with thalidomide and dexamethasone is rarely used, this combination has been removed from the

Section	Consultee/ Commentator	Comments [sic]	Action
		• **Cyclophosphamide with thalidomide and dexamethasone** (off-label) is not a relevant comparator as clinical feedback confirmed CTd is rarely used and was not deemed a relevant comparator to DBTd in TA763 <u>Maintenance</u> Lenalidomide monotherapy is the only NICE recommended maintenance treatment after an autologous stem cell transplant (TA680). Johnson & Johnson understand that it represents current SoC, used by the majority of newly diagnosed transplant-eligible multiple myeloma patients.	scope. The scope has been updated to note that lenalidomide monotherapy is the comparator in the maintenance phase of treatment.
	Myeloma UK	We agree that the treatments listed are approved/available for use as an initial treatment for myeloma patients when a stem cell transplant is suitable. However, this list does not reflect the treatments patients receive in clinical practice. The standard of care for stem cell transplant eligible myeloma patients in England is daratumumab with bortezomib, thalidomide and dexamethasone induction (NICE technology appraisal 763) followed by lenalidomide maintenance (NICE technology appraisal 680). The other comparators are no longer widely used, if at all, and are not relevant comparators.	Thank you for your comments. The comparators in the scope have been kept broad. However cyclophosphamide with thalidomide and dexamethasone has been removed following agreement across stakeholders submitting consultation responses that this is not used
	The UK Myeloma Society	Most of the regimens quoted are good comparators apart from CTD which is unlicensed and very rarely used. The most logical comparator is Dara-VTD as since the approval of this regimen the other options such as VTD and VCD are very rarely used for transplant eligible patients.	Thank you for your comments. The comparators in the scope have been kept broad. However cyclophosphamide with

Section	Consultee/ Commentator	Comments [sic]	Action
			thalidomide and dexamethasone has been removed following agreement across stakeholders submitting consultation responses that this is not used
Outcomes	Johnson & Johnson	Yes, the outcomes listed are appropriate. Johnson & Johnson propose to add sustained minimal residual disease (MRD)-negativity (defined as the absence of malignant cells at a sensitivity threshold of 10−5 or lower) for at least 12 months) as an additional response-based outcome measure.	Thank you for your comment. The NICE scope intends to provide broad relevant outcomes for consideration in the evaluation, but does not recommend specific measures. The scope already lists minimal residual disease-negative status as an outcome the relevant definition of this outcome can be considered in the evaluation . No change to scope required.
	Myeloma UK	Yes [the outcomes listed are appropriate].	Thank you for your comment. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
	The UK Myeloma Society	The outcomes listed are appropriate.	Thank you for your comment. No change to scope required.
Equality	Johnson & Johnson	No equality issues have been identified.	Thank you for your comment. No change to scope required.
	Myeloma UK	We don't anticipate that a positive recommendation would impact people within the patient population for which the treatment is licensed, who are protected by the equality legislation differently to the wider population. As with all treatments the costs incurred by hospital visits and time off work will have a more significant impact on people with lower incomes	Thank you for your comment. No change to scope required.
	The UK Myeloma Society	People with protected characteristics have much lower rates of participation in clinical trials due to factors such as inability to access treatment in larger centres, language barriers and in some cases mistrust. These groups are much more likely to follow standard NICE approved treatment pathways which means that it is especially important to them that NICE approved treatments are at the cutting edge of development. The current best option in the UK (Dara-VTD-transplant-lenalidomide) is inferior to treatment available in clinical trials such as Myeloma XV/RADAR where combined CD38 antibody and lenalidomide consolidation and maintenance is available for genetic and clinically high-risk groups. If Dara-VRD with Dara-lenalidomide maintenance is approved in the UK this uplift in induction and maintenance would bring the treatment of those patients outside of trials almost to the level of quality of those within trials and benefit those from backgrounds who do not often take part in research or don't want to for other reasons.	Thank you for your comments. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	Johnson & Johnson	The registrational clinical study for DBLd in newly diagnosed transplant-eligible multiple myeloma (PERSEUS) included a stopping rule based on minimal residual disease (MRD) negativity. After at least 24 months of maintenance therapy, daratumumab therapy was discontinued in patients who had a complete response or better and had sustained MRD–negative status for at least 12 months. MRD testing will therefore be needed to adhere to the SmPC.	Thank you for your comment. Please include the costs of MRD testing associated with the stopping rule in the company submission for this appraisal No change to scope required.
Questions for consultation	Johnson & Johnson	**Where do you consider daratumumab in combination will fit into the existing care pathway for multiple myeloma?** Johnson & Johnson considers that DBLd will be positioned as an induction and consolidation therapy, followed by DL maintenance therapy, as an alternative to DBTd followed by lenalidomide maintenance in transplant-eligible newly diagnosed MM patients. **Please select from the following, will insert the technology be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):**	Thank you for your comments. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		C **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** Comparators and subsequent treatments are prescribed in secondary care with routine follow-up in secondary care. **Would daratumumab in combination be a candidate for managed access?** <u>Induction and consolidation</u> Johnson & Johnson does not consider DBLd a candidate for managed access on the basis that the suggested change is to exchange thalidomide with lenalidomide in the NICE recommended DBTd induction and consolidation regimen. As fixed duration therapy of 4 plus 2 cycles (approximately 6-months, with transplant performed between induction and consolidation phases), and the more tolerable safety profile associated with lenalidomide compared with thalidomide, Johnson & Johnson expect DBLd to deliver similar efficacy with improved tolerability at [redacted] cost compared to existing standard of care. <u>Maintenance</u> With regard to maintenance therapy, Johnson & Johnson does not consider DL maintenance a candidate for managed access on the basis that the inherent uncertainty in modelling long-term outcomes associated with a front-line therapy with curative potential are unlikely to be resolved within the typical 2–3-year period of managed access.	

Section	Consultee/ Commentator	Comments [sic]	Action

		Do you consider that the use of daratumumab in combination can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?
		The use of daratumumab in combination can result in potential substantial health-related benefits that are unlikely to be included in the QALY calculation. Such health-related benefits include:
		• The curative potential as a result of prolonged remission associated with DBLd followed by DL maintenance can result in:
		  ○ Reduced demand for informal care, i.e., reduced carer burden
		  ○ Positive social and economic impact associated with patients being able to get back to work, helping to reduce financial stress and anxiety
		• The sense of hope associated with long-term disease control and the prospect of a functional cure is also expected to positively impact the emotional and psychological well-being of patients with multiple myeloma.
		• The value of innovation in the frontline treatments as it marks a significant advancement in the treatment landscape. It aligns with the priorities of NICE and NHS, which focus on treatments that are effective, patient-friendly, and resource-efficient.
		
		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.
		In addition to feedback from clinicians and patients, supporting evidence for uncaptured health benefits may include:
		• Result from literature searches	

Section	Consultee/ Commentator	Comments [sic]	Action
		• Patient preference market research **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 daratumumab in combination 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 issues have been identified in relation to the exclusion of any people protected by the equality legislation who fall within the patient population or recommendations that have a different impact or adverse impact on people with particular disabilities. **NICE is considering evaluating this technology through its cost comparison evaluation process.**	

Section	Consultee/ Commentator	Comments [sic]	Action
		Please provide comments on the appropriateness of appraising this topic through this process. **(Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).** **Technologies can be evaluated through the cost-comparison process if they are expected to provide similar or greater health benefits, at a similar or lower cost, compared with technologies that have been previously recommended (as an option) in published NICE guidance for the same indication. Companies can propose cost-comparison topics to NICE at any stage during topic selection and scoping. NICE will route technologies for evaluation through the cost-comparison process if it is agreed during scoping that the process is an appropriate route to establish the clinical and cost effectiveness of the technology.** A cost comparison route is not appropriate for this appraisal when considering the full front-line treatment sequence including maintenance as the technology is expected to offer improved health benefits versus current standard of care. As such, a full cost-utility analysis is required. **NICE's health technology evaluations: the manual states the methods to be used where a cost comparison case is made.** - **Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators?**	

Section	Consultee/ Commentator	Comments [sic]	Action
		The technology is likely to offer improved clinical effectiveness and potential functional cure than the comparator, and downstream cost savings due to a shorter period of time cycling through subsequent treatments for those relapsing following treatment. - **Will the intervention be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe.** Yes, the technology will be used in the same place in the treatment pathway as the comparator. No recent major changes to the treatment pathway. - **Will the intervention be used to treat the same population as the comparator(s)?** Yes - **Overall is the technology likely to offer similar or improved health benefits compared with the comparators?** The technology is likely to offer improved health benefits compared with the relevant comparator. - **Would it be appropriate to use the cost-comparison methodology for this topic?** No, the cost-comparison methodology is not appropriate for this topic when considering the full front-line treatment sequence including maintenance.	
	Myeloma UK	**Would daratumumab in combination be a candidate for managed access?** *Yes – the trial is still ongoing.*	Thank you for your comments. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of daratumumab in combination can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? *A key advantage of the regimen being assessed in this appraisal is that it doesn't contain thalidomide. Whilst thalidomide is effective, it is known to have significant side effects and to be hard to tolerate. It is associated with a higher risk of peripheral neuropathy than lenalidomide. Peripheral neuropathy has a significant impact on the lives of myeloma patients and carers. It affects the dexterity of hands and feet and causes chronic pain and tingling which can make some daily tasks more challenging.* *There are several clinical studies comparing thalidomide to lenalidomide containing regimens that will support this.* *We have patient testimony and survey data which highlights the impact of peripheral neuropathy.* *Improving remission times and life expectancy will positively impact carers and family members.* *It is a treatment for newly diagnosed patients. The first remission is often the deepest, longest remission and the period when a patient's quality of life is highest. It is widely held as the best opportunity to gain the best response with the longest time until disease progression. It is also the point in their disease where many patients will have the best quality of life post-diagnosis because their burden of treatment and illness is less than patients who are multiply relapsed.* *We have patient testimony which highlights the impact of long remission times and deep responses.*	