National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Daratumumab 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
Appropriateness	*It is important that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would this topic be appropriate for a NICE appraisal?*		
	Janssen-Cilag	Janssen believes this is an appropriate topic to refer to NICE for appraisal	Comments noted. An appraisal of daratumumab has been scheduled into NICE's technology appraisal work programme.
	Celgene Ltd	No Comments	Thank you.
	Myeloma UK	Myeloma UK considers it appropriate to refer daratumumab for appraisal by NICE.	Comments noted. An appraisal of daratumumab has been scheduled into NICE's technology appraisal work programme.
	The Royal College of Pathologists	Yes, this is appropriate as this technology has recently received marketing authorization by the FDA and is a first-in-class monoclonal antibody for the treatment of myeloma, that has shown unprecedented results in the relapsed	Comments noted. An appraisal of daratumumab has been

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		setting.	scheduled into NICE's technology appraisal work programme.
	UK Myeloma Forum	Yes, this is appropriate as this technology has recently received marketing authorization by the FDA and is a first-in-class monoclonal antibody for the treatment of myeloma, that has shown unprecedented results in the relapsed setting.	Comments noted. An appraisal of daratumumab has been scheduled into NICE's technology appraisal work programme.
Wording	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*		
	Janssen-Cilag	Janssen considers the wording of the remit to be appropriate	Comment noted. No action required.
	Celgene Ltd	No Comments	Thank you.
	Myeloma UK	Yes.	Comment noted. No action required.
	The Royal College of Pathologists	Yes	Comment noted. No action required.
	UK Myeloma Forum	Yes	Comment noted. No action required.
Timing Issues	*What is the relative urgency of this appraisal to the NHS?*		
	Janssen-Cilag	No comment	Thank you.
	Celgene Ltd	How does this align with the ongoing appraisal of Daratumumab monotherapy (ID933)?	An appraisal of daratumumab monotherapy has been scheduled earlier in NICE's work programme to ensure that timely guidance is produced

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			(daratumumab monotherapy already has a marketing authorisation).
	Myeloma UK	Extremely urgent. Needs of patients are not being fully met at this stage of myeloma and more effective treatment combinations are urgently needed to delay relapse and maintain quality of life. The data from available trials clearly demonstrate the ability of daratumamab to significantly increase progression free and overall survival in this group of patients.	Comments noted. An appraisal of daratumumab has been scheduled into NICE's technology appraisal work programme.
	The Royal College of Pathologists	Myeloma remains an incurable cancer. The drug Daratumumab represents a significant advance in the ability to treat and control myeloma and should be made available to the NHS as soon as possible	Comments noted. An appraisal of daratumumab has been scheduled into NICE's technology appraisal work programme.
	UK Myeloma Forum	Myeloma remains an incurable cancer. The drug Daratumumab represents a significant advance in the ability to treat and control myeloma and should be made available to the NHS as soon as possible	Comments noted. An appraisal of daratumumab has been scheduled into NICE's technology appraisal work programme.
Additional comments on the draft remit	Janssen-Cilag	No comment	Thank you.
	Celgene Ltd	No Additional Comments	Thank you.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	*Consider the accuracy and completeness of this information.*		
	Janssen-Cilag	No comment	Thank you.

Section	Consultee/ Commentator	Comments [sic]	Action
	Celgene Ltd	No Comments	Thank you.
	Myeloma UK	Please note in this section, that by the time daratumumab is being appraised, NICE may have started to consider/reached final decisions on the following appraisals/drug combinations: • Carfilzomib in combination with lenalidomide and dexamethasone for relapsed myeloma • Carfilzomib in combination with dexamethasone for relapsed myeloma • Lenalidomide in combination with dexamethasone at first relapse • Ixazomib in combination with lenalidomide and dexamethasone for relapsed myeloma • Imnovid in combination with dexamethasone for relapsed myeloma • Daratumumab monotherapy in relapsed myeloma The background information should include the above information.	Comments noted. The technology appraisals in development that relate to this appraisal are listed in the scope (please see 'Related NICE recommendations and NICE pathways').
	The Royal College of Pathologists	This is mostly accurate High dose chemotherapy and stem cell transplant is not used as a treatment option in isolation but is used as consolidation following successful salvage therapy typically at 2nd or 3rd line for highly selected patients. Thalidomide may be used for relapsed disease but there is limited comparative evidence following the use of bortezomib and lenalidomide.Typically it would be used in combination with corticosteroids and/or alkylating agents (most commonly cyclophosphamide). Chemotherapy with alkylating agents as monotherapy is now infrequently used and only when there are no other options for treatment. In the era of so called novel therapies (e.g. bortezomib, lenalidomide, thalidomide, panobinostat) there is extremely limited evidence for efficacy and they are more often considered a palliative treatment. Anthracycline based treatment is only very rarely used for relapsed myeloma and usually only as part of a combination treatment.	Comments noted. The background section is designed to give a brief overview of current NICE guidance and practice, for a general audience. No changes to the scope are required.

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	UK Myeloma Forum	This is mostly accurate High dose chemotherapy and stem cell transplant is not used as a treatment option in isolation but is used as consolidation following successful salvage therapy typically at 2nd or 3rd line for highly selected patients. Thalidomide may be used for relapsed disease but there is limited comparative evidence following the use of bortezomib and lenalidomide.Typically it would be used in combination with corticosteroids and/or alkylating agents (most commonly cyclophosphamide). Chemotherapy with alkylating agents as monotherapy is now infrequently used and only when there are no other options for treatment. In the era of so called novel therapies (e.g. bortezomib, lenalidomide, thalidomide, panobinostat) there is extremely limited evidence for efficacy and they are more often considered a palliative treatment. Anthracycline based treatment is only very rarely used for relapsed myeloma and usually only as part of a combination treatment.	Comments noted. The background section is designed to give a brief overview of current NICE guidance and practice, for a general audience. No changes to the scope are required.
The technology/ intervention	*Is the description of the technology or technologies accurate?*		
	Janssen-Cilag	No comment	Thank you.
	Celgene Ltd	No Comments	Thank you.
	Myeloma UK	Yes.	Comment noted. No action required.
	The Royal College of Pathologists	Yes	Comment noted. No action required.
	UK Myeloma Forum	Yes	Comment noted. No action required.
Population	*Is the population defined appropriately? Are there groups within this population that should be considered separately?*		
	Janssen-Cilag	To avoid any ambiguity, the population should be defined as: Adults with multiple myeloma who have received at least 1 prior therapy.	Comment noted. The population wording is consistent with the appraisal remit, and the

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			'comparator' section further specifies the number of prior therapies. No action required.
	Celgene Ltd	No Comments	Thank you.
	Myeloma UK	Yes. No, unless there is a need to do retrospective analysis to identify patients who may benefit more than others from the new treatment.	Comments noted. No action required.
	The Royal College of Pathologists	Yes	Comments noted. No action required.
	UK Myeloma Forum	Yes	Comments noted. No action required.
Comparators	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*		
	Janssen-Cilag	Janssen considers the list of comparators to be complete but would suggest altering 'Bortezomib' to 'Bortezomib (with or without dexamethasone)' to better reflect the evidence base and way in which bortezomib is used in clinical practice	Comment noted. The scope has been amended.
	Celgene Ltd	At second line post bortezomib, conventional chemotherapy should be a comparator as in TA171 part review. At 3rd line plus Daratumumab monotherapy should be a comparator depending on timing and outcome of ID933.	Comments noted. The scope has been amended. The timing of the daratumumab monotherapy appraisal means that it will not be established practice in time for this appraisal and therefore cannot be included as a comparator.

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	Myeloma UK	Our comments on the comparators are as follows: - Please note that bortezomib is no longer available as a treatment at first relapse in England if patients have already had bortezomib in the front line setting (TA 228). Its use as a retreatment is restricted by NHS England - Depending on whether ixazomib is granted a positive CHMP decision, there is the potential for ixazomib to be a comparator at first and second relapse. This appraisal has been paused by NICE but may restart accordingly.	Comments noted. No changes to the scope are needed.
	The Royal College of Pathologists	2nd line therapy: Bortezomib based treatment is suggested by NICE. A proportion of patients will have received 1st line bortezomib and will not be suitable for bortezomib at 2nd line (ongoing drug toxicity, poor response). Currently there are not suitable options for these patients at 2nd line. The appropriate comparator for daratumumab + bortezomib + dex is bortezomib + dex. If carfilzomib + dexamethasone is approved by NICE then this would be an appropriate comparator for Daratumumab+ bortezomib+dexamethasone. 3rd line therapy: Lenalidomide + dexamethasone based therapy or panobinostat + bortezomib + dexamethasone is approved by NICE at 3rd line. In practice Lenalidomide + dexamethasone is by far the commonest combination used at 3rd line. This is the most appropriate comparator for Daratumumab + lenalidomide + dexamethasone. Panobinostat + bortezomib + dex is a possible comparator but is not currently frequently used. Pomalidomide + dex is not a suitable comparator as the marketing authorisation mandates prior exposure to and refractoriness to lenalidomide. In practice it is not helpful or appropriate to consider these combinations at a single specific timepoint in the patient journey as there are a number of potential treatment options at first line and heterogenous responses to that first line which need to be taken into account. It would be more appropriate to	Comments noted. No changes to the scope are needed. When selecting the most appropriate comparator(s), the committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to

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		consider the 3 drug combination (daratumumab + bortz/dex or len/dex) in comparison with bortezomib or len/dex when these are used.	the methods of technology appraisal (2013).
	UK Myeloma Forum	2nd line therapy: Bortezomib based treatment is suggested by NICE. A proportion of patients will have received 1st line bortezomib and will not be suitable for bortezomib at 2nd line (ongoing drug toxicity, poor response). Currently there are not suitable options for these patients at 2nd line. The appropriate comparator for daratumumab + bortezomib + dex is bortezomib + dex. If carfilzomib + dexamethasone is approved by NICE then this would be an appropriate comparator for Daratumumab+ bortezomib+dexamethasone. 3rd line therapy: Lenalidomide + dexamethasone based therapy or panobinostat + bortezomib + dexamethasone is approved by NICE at 3rd line. In practice Lenalidomide + dexamethasone is by far the commonest combination used at 3rd line. This is the most appropriate comparator for Daratumumab + lenalidomide + dexamethasone. Panobinostat + bortezomib + dex is a possible comparator but is not currently frequently used. Pomalidomide + dex is not a suitable comparator as the marketing authorisation mandates prior exposure to and refractoriness to lenalidomide. In practice it is not helpful or appropriate to consider these combinations at a single specific timepoint in the patient journey as there are a number of potential treatment options at first line and heterogenous responses to that first line which need to be taken into account. It would be more appropriate to consider the 3 drug combination (daratumumab + bortz/dex or len/dex) in comparison with bortezomib or len/dex when these are used.	Comments noted. No changes to the scope are needed. When selecting the most appropriate comparator(s), the committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to the methods of technology appraisal (2013).

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Outcomes	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?*		
	Janssen-Cilag	Janssen considers this to be an appropriate set of outcomes	Comments noted. No action required.
	Celgene Ltd	PFS2 is an important endpoint which should be included if captured.	Comment noted. It was considered that as overall survival and progression-free survival are already included outcomes, PFS2 would not be a key outcome that would affect decision-making. No action required.
	Myeloma UK	Yes.	Comments noted. No action required.
	The Royal College of Pathologists	In addition we would suggest that complete response is also used as an outcome measure as this is an indication of quality of response and is associated with progression free and overall survival. We would also highlight that progression free survival is a widely accepted surrogate for overall survival in myeloma	Comments noted. It was considered that as overall survival, progression-free survival and response rates are already included outcomes, complete response would not be a key outcome that would affect decision-making. No action required.
	UK Myeloma Forum	In addition we would suggest that complete response is also used as an outcome measure as this is an indication of quality of response and is associated with progression free and overall survival. We would also highlight that progression free survival is a widely accepted	Comments noted. It was considered that as overall survival, progression-free

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		surrogate for overall survival in myeloma	survival and response rates are already included outcomes, complete response would not be a key outcome that would affect decision-making. No action required.
Economic analysis	*Comments on aspects such as the appropriate time horizon.*		
	Janssen-Cilag	No comment	Thank you.
	Celgene Ltd	No Comments	Thank you.
	Myeloma UK	No comments to add.	Thank you.
	The Royal College of Pathologists	No comment	Thank you.
	UK Myeloma Forum	No comment	Thank you.
Equality and diversity	*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 remit and scope may need changing in order to meet these aims. In particular, please tell us if the remit and scope:* • *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/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*		
	Janssen-Cilag	No comment	Thank you.
	Celgene Ltd	No Comments	Thank you.
	Myeloma UK	No comments to add.	Thank you.
	The Royal College of Pathologists	No equality issues	Comment noted. No action required.

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	UK Myeloma Forum	No equality issues	Comment noted. No action required.
Innovation	*Do you consider the technology 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)?* *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?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*		
	Janssen-Cilag	Janssen considers daratumumab, as the first in class fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb), is highly innovative and offers patients with a rare and incurable disease the opportunity for deep and durable response and significant extension of life. Daratumumab was granted the Orphan Drug Designation (ODD) for the treatment of MM/plasma cell myeloma by the United States (US) Food and Drug Administration (FDA) on May 8, 2013 and by the European Commission (EC) on July 17, 2013. In addition, daratumumab was granted Fast Track and Breakthrough Therapy Designation by the FDA The innovative mechanism of action is the underlying reason for the increased efficacy compared to current therapies used in r/r MM. Daratumumab has demonstrated efficacy as a single-agent and when used in combination with current therapies offers highly significant improvements in clinical outcomes. Furthermore, as a targeted agent daratumumab does not add to the treatment toxicity burden.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.
	Celgene Ltd	No Comments	Thank you.
	Myeloma UK	Daratumumab is an innovative technology and is the first drug in a decade or more with the ability to have a significant and substantial impact and the potential to bring about a step change in the treatment of myeloma. Daratumamab would very likely score highly from a patient preferences perspective in the context of benefit risk analysis i.e. it brings with it the potential of very impressive responses with a very modest investment of risk	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.

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		of adverse events. These data are rarely collected as part of CDP's and there is currently no validated way in which the QALY accurately captures this type of data even if they were available. The Pollux Phase III trial, which looked at daratumumab in combination with lenalidomide and dexamethasone in 569 myeloma patients, highlights extremely compelling data on its positive impact on the number of responses to treatment (when compared to lenalidomide and dexamethasone alone). It also points to a strong impact on progression free survival and ultimately on overall survival. The positive effect of daratumumab is seen across all stages of relapse. The Castor Phase III trial, a trial involving 498 patients, also demonstrated an excellent improvement in the response rates to treatment when daratumumab is used in combination with bortezomib and dexamethasone. This was compared to bortezomib and dexamethasone alone. Structured interviews with patients and feedback to our patient services, such as the Myeloma Infoline, provide Myeloma UK with evidence about what patients value in new treatments. This information shows that for patients, the benefit of adding daratumumab to the current standard of care significantly outweighs the inconvenience of attending hospital for the initial required duration. In addition, data from the CASTOR and POLLUX trials show that the adverse events associated with daratumumab significantly decline after the first few cycles. Patients report that daratumumab is tolerable and has an acceptable side-effect profile.	
	The Royal College of Pathologists	This is an exceptionally innovative technology and is considered to be a "gamechanger" amongst myeloma specialists. It is the first therapy that is able to specifically target myeloma cells, and is extremely well tolerated apart from manageable infusion related reactions during the first or second infusions (<10% grade 3-4) with very few discontinuations. Moreover it is associated with unprecedented outcomes for relapsed myeloma patients whether in combination with bortezomib or lenalidomide in the published	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.

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		Phase 3 trials (clinical benefit over control arms seen with hazard ratios of 0.39 and 0.37 respectively). Responses are deep, and even when only partial responses are achieved, significant prolongation of time to relapse is seen.	
	UK Myeloma Forum	This is an exceptionally innovative technology and is considered to be a "gamechanger" amongst myeloma specialists. It is the first therapy that is able to specifically target myeloma cells, and is extremely well tolerated apart from manageable infusion related reactions during the first or second infusions (<10% grade 3-4) with very few discontinuations. Moreover it is associated with unprecedented outcomes for relapsed myeloma patients whether in combination with bortezomib or lenalidomide in the published Phase 3 trials (clinical benefit over control arms seen with hazard ratios of 0.39 and 0.37 respectively). Responses are deep, and even when only partial responses are achieved, significant prolongation of time to relapse is seen.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.
Other considerations	Janssen-Cilag	The combination of daratumumab with lenalidomide and dexamethasone is unlikely to be cost-effective, even at **zero price** as a result of the borderline cost-effectiveness of lenalidomide and dexamethasone. Janssen would like to highlight that as we are not the manufacturer of lenalidomide, we have no influence on the pricing of lenalidomide and would like to discuss this further with NICE as a matter of urgency. This situation only serves to highlight the limitations of the cost per QALY framework.	Comments noted. For more details about potential alternative approaches to appraising treatments which are not cost-effective at zero price, please see NICE's Decision Support Unit report on Assessing technologies that are not cost-effective at a zero price (July 2014).
	Celgene Ltd	No Comments	Thank you.
	Myeloma UK	none	Thank you.
	The Royal College of	Nil	Thank you.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pathologists		
	UK Myeloma Forum	Nil	Thank you.
Questions for consultation			
	Janssen-Cilag	It is proposed that daratumumab will fit into the existing NICE pathway for blood and bone marrow cancers in the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.	Comments noted. No action required.
	The Royal College of Pathologists	These are answered above	Comments noted. No action required.
	UK Myeloma Forum	These are answered above	Comments noted. No action required.
	Celgene Ltd	At second line post bortezomib, conventional chemotherapy should be a comparator as in TA171 part review. At 3rd line plus Daratumumab monotherapy should be a comparator depending on timing and outcome of ID933.	Comments noted. The scope has been amended. The timing of the daratumumab monotherapy appraisal means that it will not be established practice in time for this appraisal and therefore cannot be included as a comparator.
	Myeloma UK	1. At this point in time, given the stage of licensing we are at, we consider it appropriate to appraise both daratumumab treatment combinations together. 2. We are not currently aware of any subgroups that daratumumab is more effective in. This may change as the data matures from the two Phase III trials and following the licensing process. 3. Given the effectiveness of daratumumab in the majority of treatment stages, daratumumab combinations are likely to be used in myeloma patients at all stages of relapse, depending on their previous treatment	Comments noted. No changes to the scope are needed.

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		history/response rate and the judgement of their clinician. It is most likely to be approved at both first and second relapse.	
Additional comments on the draft scope	Janssen-Cilag	No additional comments	Thank you.
	Celgene Ltd	No Additional Comments	Thank you.
	The Royal College of Pathologists	Nil	Thank you.

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

Department of Health