National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Selinexor with low-dose dexamethasone for treating relapsed refractory multiple myeloma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Celgene	n/a	
	Karyopharm Therapeutics	Because myeloma can be refractory at every stage of the disease, we would suggest that the remit includes the word 'relapsed'. This will also ensure that the wording of the remit is closer to the likely MA wording. To that end, we suggest: *To appraise the clinical and cost effectiveness of Selinexor with low-dose dexamethasone within its marketing authorisation for the treatment of patients with relapsed refractory multiple myeloma (RRMM).*	Thank you for your comment. The remit of the scope has been updated to include **relapsed** refractory multiple myeloma.
	Myeloma UK	Yes. It is noted that final marketing authorisation has not yet been granted and close attention must be paid to the final wording, given the complexity of the trial population.	Thank you for your comment.

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	UK Myeloma Forum	This is a timely appraisal. Selinexor is a first in class oral selective exportin-1 (XPO-1) inhibitor. 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.
Timing Issues	Celgene	n/a	
	Karyopharm Therapeutics	Fairly urgent due to potential unmet need for treatment.	Thank you for your comment.
	Myeloma UK	No comment	Thank you for your response.
	UK Myeloma Forum	This is urgent – there is a need to rapidly introduce effective therapies to help prolong disease control and overall survival. Importantly this is an oral therapy that is well tolerated.	Thank you for your comment.
Additional comments on the draft remit	Celgene	n/a	
	Karyopharm Therapeutics	n/a	
	Myeloma UK	n/a	
	UK Myeloma Forum	n/a	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action

Background information	Celgene	The tabular summary of possible treatment sequences omits the following ongoing appraisals:
		• First line
		  • Lenalidomide (ID474 – suspended)
		• Second line
		  • Lenalidomide (ID667 – suspended)
		  • Daratumumab with bortezomib (ID974)
			Thank you for your comment. The background section has been amended.

	Karyopharm Therapeutics	The background information is accurate, and we have no comments to make.	Thank you for your comment.
	Myeloma UK	No comment.	Thank you for your response.
	UK Myeloma Forum	The description of therapies available either via NICE approval or via CDF is correct. It is important to clarify what therapies are routinely used for patients at 4th line and beyond. In current practice patients would receive: Daratumumab monotherapy (TA510) Pomalidomide plus dexamethasone (TA427) Panobinostat plus bortezomib and dexamethasone (TA380). In clinical practice it is only given to those patients who are **not** refractory to bortezomib.	Thank you for your comment. • **Daratumumab, bendamustine and ixazomib in combination with lenalidomide**: these comparators have been removed from the scope in line with NICE's position

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		It is **not** appropriate to include Ixazomib in combination with lenalidomide and dexamethasone for use within the CDF (TA505) as patients receive this as 3rd line therapy. Best supportive care is not defined but may include single agent thalidomide, or cyclophosphamide or dexamethasone alone. Some patients would receive palliative care alone.	statement on the 'consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product'. • **Panobinostat plus bortezomib and dexamethoasone**: TA380 recommends panobinostat in combination with bortezomib and dexamethasone for adults with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an

Section	Consultee/ Commentator	Comments [sic]	Action
			immunomodulatory agent. This includes a wider population than people who are not refractory to bortezomib. Therefore, no changes have been made to this comparator in the scope. A potential subgroup analysis based on prior lines of therapy has been added, please see the 'other considerations' section.
The technology/ intervention	Celgene	n/a	
	Karyopharm Therapeutics	Yes	Thank you for your comment.
	Myeloma UK	No comment.	Thank you for your response.

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	UK Myeloma Forum	TA is appropriately described.	Thank you for your comment.
Population	Celgene	n/a	
	Karyopharm Therapeutics	We would suggest the following wording to better reflect the population: Relapsed refractory multiple myeloma. NICE might also want to specify the sub-population of penta-refractory patients who must be refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and one anti-CD38 monoclonal antibody (mAb), as this will impact where Selinexor and low-dose dexamethasone fits into the current pathway and what its comparators will be.	Thank you for your comment. The scope population has been updated to include **relapsed** refractory multiple myeloma. The subgroup of people refractory to at least one proteasome inhibitor, one immunomodulatory agent and one anti-CD38 monoclonal antibody has been added to the scope, please see the 'other considerations' section.
	Myeloma UK	We note the "penta-refractory" subgroup within the clinical study. Without prejudice to any forthcoming appraisal we record the complexity and access anomalies which are in danger of arising in the myeloma pathway with increasing use of sub-groups within treatment "lines".	Thank you for your comment. The subgroup of people refractory to at least one proteasome inhibitor, one

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			immunomodulatory agent and one anti-CD38 monoclonal antibody has been added to the scope, please see the 'other considerations' section.
	UK Myeloma Forum	This should include myeloma patients who have received at least 3 prior lines, and are refractory to both an Imid (lenalidomide or pomalidomide), Proteosome (bortezomib or carfilzomib), and have received an alkylating agent. There are no specific subgroups that should be considered separately.	Thank you for your comment. The subgroup of people refractory to at least one proteasome inhibitor, one immunomodulatory agent and one anti-CD38 monoclonal antibody has been added to the scope, please see the 'other considerations' section.
Comparators	Celgene	Conventional chemotherapy is not listed as a comparator, however was considered relevant in ID667 (second line) and TA427 (fourth line, plus)	Thank you for your comment. The comparators in the scope have been updated to include conventional chemotherapy.

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	Karyopharm Therapeutics	The list of comparators is comprehensive. The most likely best alternative care are those treatments that are approved in fourth and/or fifth line in the current treatment pathway.	Thank you for your comment.
	Myeloma UK	We agree that these are the standard treatments available for this patient population. It does become more difficult to define standard of care at fifth line and beyond.	Thank you for your comment.
	UK Myeloma Forum	The comparators are not correct as they are listed. It is not appropriate to include: 1. Panobinostat plus bortezomib and dexamethasone (TA380). In clinical practice it is only given to those patients who are not refractory to bortezomib. The evidence for selinexor in combination with dexamethasone is for patients who are refractory to proteasome inhibitors (Vogl et al, JCO 2017, https://doi.org/10.1200/JCO.2017.75.5207) 2. Ixazomib in combination with lenalidomide and dexamethasone for use within the CDF (TA505). The evidence for selinexor in combination with dexamethasone is for patients who are refractory to Imids, such as Lenalidomide (Vogl et al, JCO 2017, https://doi.org/10.1200/JCO.2017.75.5207). In addition it would be inappropriate to include Ixazomib as this is a proteasome inhibitor. 3. Bendamustine, as this is rarely used in this patient population. Pomalidomide maybe an appropriate comparator. However published data supports the use of selinexor in combination with dexamethasone is for patients who are quad refractory (ie refractory to Lenalidomide and Dexamethasone (Vogl et al, JCO 2017,	Thank you for your comment. • **Panobinostat plus bortezomib and dexamethasone**: The evidence base for selinexor includes people who are refractory to a proteasome inhibitor, but not all proteasome inhibitors. Therefore panobinostat plus bortezomib and dexamethasone is considered a relevant comparator. • **Daratumumab, bendamustine and ixazomib in**

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		https://doi.org/10.1200/JCO.2017.75.5207). This will depend on what the license states are appropriate prior treatments. Daratumumab is an appropriate comparator. Best supportive care may be an appropriate comparator (but needs to be clearly defined). Increasingly due to very limited efficacy treatments in this category are considered palliative.	**combination with lenalidomide**: these comparators have been removed from the scope in line with NICE's position statement on the 'consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product'.
Outcomes	Celgene	n/a	
	Karyopharm Therapeutics	The outcomes listed capture many of the most important health-related benefits, but they won't capture patient preferences for treatment expressed in the context of benefit-risk trade-offs. This is an extremely important concept in relapsed refractory myeloma and underscores the need for patient involvement in such appraisals.	Thank you for your comment. The appraisal committee will consider the views of the patient/carer representatives alongside the evidence on clinical and cost effectiveness.

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	Myeloma UK	Yes	Thank you for your comment.
	UK Myeloma Forum	Yes. Response rates including MRD status.	Thank you for your comment.
Economic analysis	Celgene	n/a	
	Karyopharm Therapeutics	All of this seems fine. The company would be willing to discuss commercial arrangements at the appropriate time in the appraisal process.	Thank you for your comment.
	Myeloma UK	No comment	Thank you for your response.
	UK Myeloma Forum	Yes	Thank you for your comment.
Equality and Diversity	Celgene	n/a	
	Karyopharm Therapeutics	We are not aware of any equality issues that would have a significant or material impact in this appraisal.	Thank you for your comment.
	Myeloma UK	No comment	Thank you for your response.
	UK Myeloma Forum	No equality issues	Thank you for your comment
	Celgene	n/a	

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Other considerations	Karyopharm Therapeutics	We have nothing to add.	Thank you for your response.
	Myeloma UK	n/a	
	UK Myeloma Forum	n/a	
Innovation	Celgene	n/a	
	Karyopharm Therapeutics	We do not consider Selinexor to be innovative in the context of the questions you stipulate opposite i.e. it does not represent a step-change in treatment management. That said, it does bring a new mechanism of action to the treatment of myeloma and this is an important step forward in the treatment of patients with relapsed refractory myeloma who have had several prior lines of treatment. This is a difficult to treat group, and therefore we consider the magnitude of response to Selinexor and low-dose dexamethasone in this disease setting to be impressive. We believe the QALY will adequately capture all of these benefits alongside taking account of the patient perspective.	Thank you for your comment.
	Myeloma UK	While the treatment has a different mechanism of action to the “backbone” treatments available in the current myeloma pathway and this is welcome, the data from the single arm trial of Selinexor with dexamethasone does not demonstrate delivery of a step-change in the treatment of myeloma.	Thank you for your comment.

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	UK Myeloma Forum	Selinexor is extremely innovative – it is the first in class oral selective exportin1 (XPO1) inhibitor. It has a novel mechanism of action. It addresses an unmet for patients who have no / or limited treatment options. Importantly it is an oral medication that is very well tolerated. This has a particular advantage in a patient with added co-morbidities of their disease and side effect of prior therapies.	Thank you for your comment.
Questions for consultation	Celgene	n/a	
	Karyopharm Therapeutics	We believe that the majority of the questions for consultation set out on pages 6 and 7 of the scoping documents have been addressed above. We do not see any barriers to the adoption of this technology into practice. However, we are aware of NHS-E plans to introduce a treatment commissioning algorithm for myeloma in the near future to which all NHS-E trusts must sign-up to. It would be good to explore the potential risks to adoption of this being in place ahead of a potential approval from NICE. We agree with the appropriateness of a STA process.	Thank you for your comment.
	Myeloma UK	No comment beyond the points answered above.	Thank you for your response.
	UK Myeloma Forum	Certain subgroups may have added benefit. Those patients with poor risk cytogenetic features may have a higher response rate, based on the limited published data. Established UK clinical practice after 3 lines of therapy is as outlined above. Daratumumab is most commonly utilised at 4th line due to the limited scope for its use via TA510. Pomalidomide / dex and Panobinostat / bortezomib /	Thank you for your comment. Subgroup analysis based on cytogenic risk factors has been added to the scope, please see the

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		dex used at 5th and 6th line respectively depending on IMId and/or bortezomib refractoriness. Best supportive care – whilst the use of thalidomide, weekly cyclophosphamide, high dose dexamethasone or melphalan (oral or intermediate dose) could all be considered to be best supportive care there is extremely limited data regarding their efficacy in the recent era following introduction of agents such as pomalidomide, daratumumab, carfilzomib, ixazomib. This approach is increasingly considered to be a palliative rather than active measure. It is likely that Selinexor would fit at 4th line or beyond in the myeloma treatment pathway. We would suggest daratumumab monotherapy and pomalidomide / dexamethasone as appropriate comparators.	'other considerations' section. The comparators in the scope have been updated to include conventional chemotherapy.
Additional comments on the draft scope	Celgene	n/a	
	Karyopharm Therapeutics	None. We have requested an OMA meeting which we believe will be extremely helpful in preparing to take part in this appraisal. We are committed to working in partnership with NICE and NHS-E, and to take an open, transparent and solution-orientated approach. We are aware of the important role that NICE has in recommending to NHS-E on how best to allocate scarce resources for the best health outcomes for patients. We have a confident, but balanced and fair view of the potential benefits and risks of Selinexor and are firmly focused on ensuring access for patients.	Thank you for your comment.
	Myeloma UK	No comment.	Thank you for your response.

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	UK Myeloma Forum	n/a	

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

The Department of Health and Social Care