Single Technology Appraisal

Selinexor with bortezomib and low-dose dexamethasone for treating relapsed refractory multiple myeloma [ID3797]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Selinexor with bortezomib and low-dose dexamethasone for treating relapsed refractory multiple myeloma [ID3797]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Menarini Stemline**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Myeloma UK

3. **Comments on the Draft Guidance from experts:**
   a. Neil Rabin and Karthik Ramasamy – clinical experts, nominated by UK Myeloma Society

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 10:00am on Friday 23 February 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Menarini Stemline

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1. Factual inaccuracy	On page 3, the second line indication is described as multiple myeloma that is refractory (has not responded) to both lenalidomide and daratumumab. 'Has not responded' is not an accurate description of refractory in this setting and should be removed. Daratumumab and lenalidomide are used until progression. Therefore, patients who respond remain on treatment until they progress i.e. have become refractory. Therefore, it is incorrect to state that refractory means a patient has not responded.
2. Correction	In section 2.3 page 5, the price of the 32 pack is included. This pack is not available in the UK and should be removed. The company submission will be updated to remove this pack size

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3. Factual inaccuracy	On page 10, the inclusion criteria for the BOSTON trial are described as relapsed or remitting multiple myeloma, this should be relapsed or refractory multiple myeloma.
4. Factual inaccuracy	On page 10 of the draft guidance, the median ages for the BOSTON trial population are incorrect; they were 68 years for the second line population, and 66 years for the third line population.
5 Factual inaccuracy	On page 13, the way the hazard ratios are presented is misleading. The direction of the hazard ratios is for comparators *versus* selinexor + bortezomib + dexamethasone, **not** for selinexor + bortezomib + dexamethasone *versus* the comparators. The bullets should read: The indirect treatment comparisons (see Section 3.7) showed: • In the second line setting, no statistically significant differences in progression-free survival (hazard ratio=0.73, 95% credible interval: 0.31 to 1.67]) or overall survival (hazard ratio=0.89, 95% credible interval: 0.32 to 2.45) when carfilzomib plus dexamethasone was compared to the selinexor combination. • In the third line setting, third line, no statistically significant differences in progression-free survival (hazard ratio=0.66, 95% confidence interval: 0.34 to 1.28) or overall survival (hazard ratio=1.29, 95% confidence interval: 0.63 to 2.64) when the ixazomib combination was compared to the selinexor combination. • In the third line setting, no statistically significant differences in progression-free survival (hazard ratio=0.80, 95% credible interval: 0.26 to 2.28) or overall survival (hazard ratio=1.24, 95% credible interval: 0.45 to 3.46) when the panobinostat combination was compared to the selinexor combination.
6.Overall survival benefit	On page 16 (section 3.12), it is stated that, in principle, the Committee considered that overall survival differences should be modelled, but because of a lack of evidence, it preferred the EAG's base case of assuming overall survival to be equal between treatments. The EAG states that the assumption of overall survival being equal was based on the following considerations: • After first line overall survival is likely to be similar regardless of treatments at different lines; • No statistically significant differences in survival were seen for any of the comparisons; • Overall survival is immature and uncertain. There are important issues with the EAG considerations, in particular with the first two, which means the simplistic assumption of overall survival being equal should be reconsidered: **It is incorrect to assume overall survival is the same after first line:** On page 16 of the draft guidance (section 3.12), it is stated that "clinical advisers to the EAG suggested that after first line, overall survival is likely to be similar regardless of treatments at different lines".

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	In-depth clinical and patient expert feedback we have obtained is that it is categorically incorrect to assume overall survival is the same after first line despite the treatment received at different lines. Disease control and survival rates in myeloma patients decrease rapidly from their first line of treatment and continue to decrease over subsequent lines, with 61% receiving second line, 38% receiving third line, and only 1% reaching fifth line treatment.(1) It is implausible for overall survival to be similar for all patients across the treatment lines. **It is clinically plausible for selinexor + bortezomib + dexamethasone to provide an overall survival benefit** In-depth clinical and patient expert feedback that we obtained supports that an overall survival benefit with selinexor + bortezomib + dexamethasone is clinically plausible. This is related to selinexor providing a new mode of action, as part of a triplet regimen, to be included in the treatment pathway. On page 8 of the draft guidance (section 3.2), the clinical experts highlighted the need for a range of treatment options with different mechanisms of action. Adding treatments with new mechanisms of action into the treatment pathway will likely improve overall survival outcomes. **Selinexor + bortezomib + dexamethasone has a statistically significant improvement in overall survival compared to bortezomib + dexamethasone in patients who are refractory to lenalidomide.** The Committee noted on page 22 (section 3.19) of the draft guidance that there is an increasing unmet need for new treatment options at third line for people whose condition is refractory to lenalidomide. Clinical feedback we have obtained strongly suggests that there is an increasing lenalidomide refractory population at third line, given the current treatment pathway frequently utilises lenalidomide in the front-line setting (or second line setting if patients are still lenalidomide naïve) in both transplant eligible and transplant ineligible populations given that lenalidomide, in all such settings, is given continuously until progression In this lenalidomide refractory population in the BOSTON study, selinexor + bortezomib + dexamethasone has been shown to statistically significantly improve overall survival compared to bortezomib + dexamethasone. (26.68 months *versus* 18.65 months; hazard ratio=0.531; 95% confidence interval: 0.297, 0.949; *P*=0.030). These overall survival data are key to consider given that the current treatment pathway means that an increasing number of patients are relapsing with lenalidomide-refractory disease. We acknowledge that given the absence of lenalidomide refractory data for panobinostat + bortezomib + dexamethasone, it is not possible to include a formal comparison in this population *versus* selinexor + bortezomib + dexamethasone. Therefore, the network meta-analysis results being considered are in the overall populations in the third line setting. **There were no statistically significant differences for both overall survival and progression-free survival *versus* comparators** This is shown on page 13 of the draft guidance (section 3.8), where the results of the network meta-analysis are reported as follows: • At second line no statistically significant differences in progression-free survival or overall survival compared with carfilzomib + dexamethasone.

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	• At third line no statistically significant differences in progression-free survival or overall survival compared with the ixazomib combination. • At third line no statistically significant differences in progression-free survival or overall survival compared with the panobinostat combination. **Given there is uncertainty across both progression-free survival and overall survival results from the network meta-analysis/ matching-adjusted indirect comparison, the EAG has taken a pessimistic approach when considering the network meta-analysis/ matching-adjusted indirect comparison results** Although in both the second line and third line settings, there was no statistical difference for progression-free survival and overall survival in the network meta-analysis, for an endpoint showing a numerical disadvantage of selinexor + bortezomib + dexamethasone *versus* the comparator (progression-free survival second line & third line, overall survival second line), the EAG has used the hazard ratio from the network meta-analysis/ matching-adjusted indirect comparison. However, contrastingly, in the third line setting with a numerical advantage in overall survival, the EAG has not used this hazard ratio but assumed equal efficacy across interventions. This seems counter-intuitive and overly pessimistic, given the similar uncertainty in the comparative estimates for the endpoints. **The Company, therefore, maintains that the hazard ratio from the network meta-analysis should be used for the comparators in third line, as was done for the second line, with progression-free survival being numerically inferior and overall survival being numerically superior in third line.** The updated 3L+ network meta-analysis and the unanchored matching-adjusted indirect comparison of selinexor + bortezomib + dexamethasone *versus* ixazomib + lenalidomide + dexamethasone demonstrate that the selinexor combination is numerically inferior to panobinostat + bortezomib + dexamethasone, and ixazomib + lenalidomide + dexamethasone in terms of progression-free survival whilst numerically superior in overall survival. The clinical rationale for why progression-free survival could be inferior, whilst overall survival is superior, is that the prior treatments of patients entering the ixazomib + lenalidomide + dexamethasone and panobinostat + bortezomib + dexamethasone studies were very different to those participating in BOSTON, with one consideration being that these patients would be lenalidomide-sensitive compared to those in the BOSTON study, where 32% were lenalidomide-refractory on entering the study. This difference in the biology of patients entering the study, supports why progression-free survival may be inferior, with lenalidomide refractory patients having worse outcomes. The rationale for why overall survival can be considered superior has been provided above. **Our contention is that good practice means the results from the network meta-analysis/ matching-adjusted indirect comparison should be treated consistently across both endpoints. So, if the numerical results from the network meta-analysis/ matching-adjusted indirect comparison are not directly used, then given neither progression-free survival nor overall survival showed statistically significant differences in third line, as a minimum, then assuming equal efficacy for <u>both</u> progression-free survival and overall survival would be appropriate.**

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7. Updated cost-effectiveness results	In light of comments addressed in the first ACM and ongoing discussions with NHS England, the company has revised the simple PAS discount applicable to selinexor to - *commercial in confidence information removed* With the revised PAS discount applied and using the EAG's model assumptions with the exception of its approach to overall survival (estimated using comparator hazard ratios relative to bortezomib + dexamethasone as outlined in comment 6 above), the company notes the following incremental results relative to panobinostat + bortezomib + dexamethasone: Incremental costs: -£-1,124 Incremental QALYs: 0.373 Incremental cost-effectiveness ratio: -£3,018

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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References

1. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. 2016;175(2):252-64.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Myeloma UK

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..

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1	**We believe the Committee decision is unreasonable and should re-consider routine commissioning of the selinexor combination at 3rd line.** The significant unmet need among the patient population relevant to this appraisal and the innovative nature of selinexor should be grounds for a more flexible approach to considering this treatment as a choice for clinicians and patients. Myeloma UK is extremely disappointed that NICE did not recommend the selinexor combination at third line, particularly for patients who are refractory to the ixazomib combination or intolerant to the panobinostat combination.
2	**We are concerned that the Committee did not fully consider the rapidly evolving myeloma treatment pathway. We believe the committee should give further weight to the innovative nature of this treatment.** Evidence presented included randomised clinical trial data and adjusted indirect comparisons to NHSE standard of care. The cost-effectiveness comparison of the selinexor combination compared to the panobinostat combination and the ixazomib combination at 3rd line does not reflect the current and evolving treatment pathway and the resulting lack of options for patients requiring urgent treatment at third line. Selinexor is a first in class selective inhibitor of nuclear transport (SINE) therapeutic. This is important for optimal clinical management of disease progression for patients whose myeloma is refractory to existing myeloma treatments. Our patient community rely heavily on the availability of drugs with new mechanisms of action to be able to keep their myeloma under control. The approval of this novel therapy at 3rd line would be a welcome step towards building a clinically optimal treatment pathway. Treatments are urgently needed which have novel mechanism of action to meet the needs of multiply relapsed myeloma patients.
3	**We are concerned that the Committee did not acknowledge that the comparator combinations are not appropriate for all patients**. Our patient experts and clinicians highlighted that patients with prior exposure to lenalidomide can not be treated with the ixazomib combination and may not be suitable due for the panobinostat combination due to toxicity treatment-limiting side effects. The recommendation to deny access for these patients is inequitable.
4	**We are concerned that the Committee did not fully consider the critical importance of clinician and patients having options at third line to provide immediate treatment and enable future treatment.** Commissioning of selinexor would offer patients an option for treating current disease progression and allow patients to benefit from forthcoming innovative treatments scheduled for NICE appraisals.

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	Knowing that their current and future myeloma treatment needs are being met has a significant impact on a patient's health and psychological well-being.
5	**We are concerned that the Committee has placed variable emphasis on the progression-free survival (PFS) data for patients at 3rd line and believe their recommendation is unreasonable**. The draft recommendation made by the committee noted that there are no statistically significant differences in PFS between the selinexor combination and ixazomib or panobinostat combinations. The Committee recommended the selinexor combination at 2nd line in comparison to carfilzomib taking into consideration that there was no statistically significant difference in OS (Overall Survival) or PFS. The Committee's decision to highlight a numerically inferior PFS difference arising from the indirect treatment comparisons for the selinexor combination at 3rd line against the comparator combinations is unreasonable.
6	**We are concerned that the Committee did not fully consider the PFS benefit of selinexor**. The selinexor combination data demonstrates a clinically effective and a safe option for patients who cannot be treated with ixazomib or panobinostat combinations. Further, evidence submitted (Jagannath et al 2023) showed that progression free survival improves with dose reduction in clinical practise should be given additional weighting.
7	**We are concerned that the Committee did not fully consider the expert evidence submitted by patients and clinicians. Myeloma UK is concerned that patient and clinician experts will not be invited to the second committee meeting.** The proposed commissioning of the selinexor combination at 2nd line and 3rd line was supported by expert patients and clinicians. The committee agreed that the selinexor regimen has good implementation factors including oral dosing and effective toxicity management. Patient and clinician expert knowledge of the myeloma pathway is critical to ensuring that NICE considers real-world requirements and outcomes.
8	**We are concerned that the Committee did not fully consider the psychological well-being of patients denied access to a drug combination with proven safety and efficacy.** The patient population under consideration for this appraisal face a severe burden of disease including psychological well-being impacted by living with a relapse-remitting incurable disease. Further, there is a significant deleterious health impact for this population if they are denied access to an effective treatment combination when they are clinically progressing and have limited options. Myeloma patients at 3rd line have already experienced disease progression through two lines of treatment. As noted by the committee, at each stage of progression the disease burden, quality of life and psychological well-being are increasingly impacted.
9	**We are concerned that the Committees recommendation may be viewed as discriminatory based on the average age of the patient community.** The average age of myeloma patients at 3rd line and beyond needs to be considered to avoid unlawful discrimination. Our patient community expects access to the best treatments, based on their health status, including the refractory nature of their myeloma and drug toxicity contraindications.

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	By limiting the use of the selinexor combination to 2nd line treatment, and restricting 3rd line patients to existing combinations that they may be refractory or not tolerate will result in older patients not having access to an effective treatment that can provide progression free survival and increased quality of life.

Insert extra rows as needed

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE
Name of commentator person completing form:	NEIL RABIN AND KARTHIK RAMASAMY

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that …….. We are pleased that this has been recommended for second line. However we are concerned about some of the assumptions that have been used to consider third line treatment.
1	Section 3.8. Clinical effectiveness results. •'at third line, no statistically significant differences in progression-free

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	survival (HR 0.66, 95% CI 0.34 to 1.28) or overall survival (HR 1.29, 95% CI 0.63 to 2.64) compared with Ixazomib combination •at third line, no statistically significant differences in progression-free survival (HR 0.80, 95% CrI 0.26 to 2.28) or overall survival (HR 1.24, 95% CrI 0.45 to 3.46) compared with panobinostat combination.' We think there is good clinical data that would support a potential survival benefit of Selinexor Bortezomib Dexamethasone in Lenalidomide relapsed / refractory patients based on recently published data. This should be considered by the committee. European Haematology Association 2023 Abstract: P886 Title: EFFICACY, SURVIVAL AND SAFETY OF SELINEXOR, BORTEZOMIB AND DEXAMETHASONE (SVD) IN PATIENTS WITH LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA: SUBGROUP DATA FROM THE BOSTON TRIAL. In addition, If patients are Lenalidomide non refractory, a combination of Ixazomib Lenalidomide and dexamethasone is preferred evidenced by SACT NHSE data
2	Section 3.12. Overall survival benefit. 'The EAG noted that an overall survival benefit likely includes varying impacts of subsequent treatments on overall survival after disease progression. In addition, clinical advisers to the EAG suggested that after first line, overall survival is likely to be similar regardless of treatments at different lines.' We dispute the suggestion that OS is similar regardless of different lines of treatment. There are several studies which have shown a difference in OS between interventions beyond first line (Overall Survival With Daratumumab, Lenalidomide, and Dexamethasone in Previously Treated Multiple Myeloma (POLLUX): A Randomized, Open-Label, Phase III Trial, Dimopoulos et al, JCO 2023 or Overall Survival With Daratumumab, Bortezomib, and Dexamethasone in Previously Treated Multiple Myeloma (CASTOR): A Randomized, Open-Label, Phase III Trial, Sonneveld et al, JCO 2022). Although this did not reached statistical significance, the OS favoured Selinexor Bortezomib Dex compared to comparators in the network meta-analysis.
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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

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NICE National Institute for Health and Care Excellence

Selinexor with bortezomib and low-dose dexamethasone for treating relapsed refractory multiple myeloma [ID3797]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 10:00am on Friday 23 February 2024. Please submit via NICE Docs.

- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Single Technology Appraisal

Selinexor with bortezomib and dexamethasone for previously treated multiple myeloma [ID3797]

Comments on the DG received from the public through the NICE Website

Name	Redacted
Comments on the DG:	

Has all of the relevant evidence been taken into account?
Relapsed / refractory disease vs refractory?

https://clinicaltrials.gov/study/NCT03110562

https://ashpublications.org/ashclinicalnews/news/5496/BOSTON-Selinexor-Improves-Progression-Free

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
not reviewed.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No.
Presumably the indication is relapsed / refractory myeloma? i.e. either never responded or progressed after initial response.
Primary refractory myeloma is rare with dara-len treatment.
Some patients (or clinicians on basis if clinical risk) may choose to not receive dara at first line, they should not be disadvantaged from possible SVd treatment.
The third line treatments are very limited and therefore are a major issue in clinical practice; therefore SVd should be available there. It is dissembling to state in "why the committee made these recommendations" that ixazomib - lenalidomide- dex is available at third line. That is not the case for the situation assessed of prior lenalidomide refractory disease (e.g. see Blueteq high cost drugs forms). The committee recognised there is only one treatment option at third line - bortezomib with panabinostat, so SVd is reasonable appropriate alternative at third line.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
none identified

Selinexor with bortezomib and low-dose dexamethasone for treating relapsed or refractory multiple myeloma [ID3797]

EAG critique of the company response to the Draft Guidance

March 2024

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136081.

1 Introduction

This document provides the External Assessment Group's (EAG's) critique of the company's response to the draft guidance (DG) document produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of selinexor with bortezomib and low-dose dexamethasone (SVd) for treating relapsed or refractory multiple myeloma.

In the DG, the committee considered that the EAG's base case assumptions reflected its preferred assumptions. The assumptions informing the EAG's base case for the third-line (3L) subgroup is as follows:

- EAG scenario 1 – combined scenario implementing the EAG's preferred assumptions for treatment effectiveness in the model.
- EAG scenario 2 – overall survival (OS) for comparators equal to bortezomib with dexamethasone (Vd) (no OS benefit).
- Company scenario B11 – health state utility values (HSUVs) based on line of therapy and progression status.
- EAG scenario 4 – combined scenario implementing the EAG's preferred assumptions for subsequent treatments.
- EAG scenario 6 – inclusion of administration cost for oral chemotherapy.
- EAG scenario 7 - combined scenario implementing the EAG's preferred assumptions for adverse events (AEs).
- Company scenario B16 – EAG clinical experts resource use assumptions.
- EAG scenario 8 – End of life care cost from the PSSRU.[1]

Details of the individual scenarios can be found in the EAG report.

The company has provided its preferred base case for the comparison with panobinostat with bortezomib and dexamethasone (PanoVd) for the third-line (3L) subgroup. The company accepted all of the committee's preferred assumptions with the exception of the assumption of overall survival (OS) equal to Vd for all treatments (no OS benefit). However, the company did not provide any additional evidence to support the inclusion of an OS benefit SVd in its DG comments. Additionally, the committee considered that ixazomib with lenalidomide and dexamethasone was a relevant

comparator and so the EAG has provided the results with the company's preferred assumptions for OS applied.

The company provided a revised patient access scheme discount of [redacted] for selinexor. All results presented in this document include the revised PAS for selinexor. However, confidential PAS discounts are available for comparators and subsequent treatments. As such, the EAG has produced a confidential appendix to this document. Analyses included in the confidential appendix include the committee preferred base case results, the company preferred base case results and scenario analyses conducted by the EAG.

Table 1 and Table 2 presents the committee and company preferred base case results, respectively, for the 3L subgroup. Table 3 presents the fully incremental results based on the company preferred analysis. The EAG has not presented fully incremental analysis for the committee base case as treatment effectiveness estimates for ixazomib with lenalidomide and dexamethasone (IxaRd) and panobinostat with bortezomib and dexamethasone (PanoVd) are from two different indirect treatment comparison (ITC) methods and so are not directly comparable to one another. As such, for the 3L subgroup, the EAG considers pairwise incremental cost-effectiveness ratios (ICERs) for SVd against the comparators to be more appropriate.

Table 1. Committee preferred base case results – SVd versus 3L comparators

Interventions	Total Costs (£)	Total LY	Total QALYs	Δ costs (£)	Δ Lys	Δ QALYs	Pairwise ICER (£/QALY)
Deterministic results							
SVd	[redacted]	2.75	[redacted]				
IxaRd	284,753	2.75	[redacted]	-113,539	0.00	-0.04	2,719,558 (SW)
PanoVd	171,299	2.75	[redacted]	-85	0.00	-0.02	3,555 (SW)
Probabilistic results							
SVd	[redacted]	-	[redacted]	-	-	-	-
IxaRd	275,008	-	[redacted]	-114,477	-	-0.04	2,789,635 (SW)
PanoVd	155,080	-	[redacted]	5,450	-	-0.02	Dominated

Abbreviations: 2L, second-line; ICER, incremental cost-effectiveness ratio; IxaRd, ixazomib plus lenalidomide and dexamethasone; LY, life year; NHB, net health benefit; PanoVd, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life-year; SVd, selinexor plus bortezomib and dexamethasone; SW, south-west.

Table 2. Company's preferred base case (post-ACM1) – SVd versus 3L comparators

Interventions	Total Costs (£)	Total LY	Total QALYs	Δ costs (£)	Δ LYs	Δ QALYs	Pairwise ICER (£/QALY)
Deterministic results							

SVd	[redacted]	3.45	[redacted]	-	-	-	-
IxaRd	372,869	4.83	[redacted]	-196,160	-1.38	-0.94	208,260 (SW)
PanoVd	177,833	2.83	[redacted]	-1,124	0.62	0.37	Dominant
Probabilistic results							
SVd	[redacted]	-	[redacted]	-	-	-	-
IxaRd	363,592	-	[redacted]	-189,608	-	-1.05	181,039 (SW)
PanoVd	156,599	-	[redacted]	17,385	-	0.25	68,208

Abbreviations: 2L, second-line; ICER, incremental cost-effectiveness ratio; IxaRd, ixazomib plus lenalidomide and dexamethasone; LY, life year; PanoVd, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life-year; SVd, selinexor plus bortezomib and dexamethasone.

Table 3. Fully incremental analysis for 3L subgroup based on the company's preferred assumptions

Interventions	Total Costs (£)	Total QALYs	Δ costs versus baseline (£)	Δ QALYs versus baseline	ICER (£/QALY) versus baseline	Fully incremental ICER (£/QALY)
Deterministic results						
SVd	[redacted]	[redacted]	-	-	-	-
PanoVd	177,833	[redacted]	1,124	-0.37	Dominated	Dominated
IxaRd	372,869	[redacted]	196,160	1.38	208,260	208,260
Probabilistic results						
PanoVd	[redacted]	[redacted]	-	-	-	-
SVd	173,985	[redacted]	17,385	0.25	68,208	68,208
IxaRd	363,592	[redacted]	206,993	1.30	158,954	181,039

Abbreviations: Δ, incremental; 3L, third-line; ICER, incremental cost-effectiveness ratio; IxaRd, ixazomib plus lenalidomide and dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life-year; SVd, selinexor in combination bortezomib and dexamethasone.

The EAG highlights that the company's preferred base case for the 3L subgroup can be considered as a scenario around the committee's preferred base case which explores the inclusion of an OS benefit for SVd.

2 EAG critique of company draft guidance comments

The company's comments on the draft guidance focussed mainly on the issue of the overall survival (OS) benefit in the model (comment 6 of the company's response to the draft guidance [DG]). The EAG notes that no new evidence or additional analyses for OS have been provided by the company. Furthermore, in the DG, the committee considered that, "*in principle, that overall survival differences should be modelled. But, because of the lack of evidence, it preferred the EAG's base case in which no differences in overall survival between treatments were modelled, and overall survival relative to bortezomib plus dexamethasone was applied for all treatments*".

As such, given nothing additional has been provided by the company to substantiate inclusion of an OS benefit in the model, the EAG's base case (which is the committee's preferred base case) remains unchanged. Nonetheless, the EAG has addressed key points raised by the company in comment 6 of their response to the DG in Table 4 below.

Table 4. EAG response to the company's comment 6 on the draft guidance

Company draft guidance comment	EAG response
It is incorrect to assume overall survival is the same after first line: On page 16 of the draft guidance (section 3.12), it is stated that "clinical advisers to the EAG suggested that after first line, overall survival is likely to be similar regardless of treatments at different lines". In-depth clinical and patient expert feedback we have obtained is that it is categorically incorrect to assume overall survival is the same after first line despite the treatment received at different lines. Disease control and survival rates in myeloma patients decrease rapidly from their first line of treatment and continue to decrease over subsequent lines, with 61% receiving second line, 38% receiving third line, and only 1% reaching fifth line treatment.(1) It is implausible for overall survival to be similar for all patients across the treatment lines.	The EAG agrees with the company that overall survival is different for patients at different lines of treatment. The EAG's initial comments, that *"[…] patients' OS is likely to be similar irrespective of the treatments they receive at different lines",* relates to an expected similarity in OS between patients receiving different treatments at a certain line, e.g. at 3L, and not an expected similarity in OS between different lines.
It is clinically plausible for selinexor + bortezomib + dexamethasone to provide an overall survival benefit. In-depth clinical and patient expert feedback that we obtained supports that an overall survival benefit with selinexor + bortezomib + dexamethasone is clinically plausible. This is related to selinexor providing a new mode of action, as part of a triplet regimen, to be included in the treatment pathway. On page 8 of the draft guidance (section 3.2), the clinical experts highlighted the need for a range of treatment options with different mechanisms of action. Adding treatments with new mechanisms of action into the treatment pathway will likely improve overall survival outcomes.	The EAG agrees with the company that it is theoretically possible for different treatments to provide different OS outcomes for patients with relapsed/refractory multiple myeloma but that this theoretical benefit needs to be proven with the appropriate evidence. The EAG does not consider the evidence presented by the company prior to ACM1 to be robust enough to justify an OS benefit for SVd relative to IxaRd or PanoVd in the 3L setting. Additionally, no further evidence from BOSTON has been provided, nor any real-world data to support the company's view that SVd improves OS compared with current treatments available in the NHS.
Selinexor + bortezomib + dexamethasone has a statistically significant improvement in overall survival compared to bortezomib + dexamethasone in patients who are refractory to lenalidomide. The Committee noted on page 22 (section 3.19) of the draft guidance that there is an increasing unmet need for new treatment options at third line for people whose condition is refractory to lenalidomide. Clinical feedback we have obtained strongly suggests that there is an increasing lenalidomide refractory population at third line, given the current treatment pathway frequently utilises lenalidomide in the front-line	The EAG recognises the overall survival subgroup analysis in lenalidomide refractory patients, which was presented in Section 3.3.3 of the original EAG report. In the lenalidomide-refractory subgroup of BOSTON, SVd had a larger associated OS than Vd alone:

setting (or second line setting if patients are still lenalidomide naïve) in both transplant eligible and transplant ineligible populations given that lenalidomide, in all such settings, is given continuously until progression In this lenalidomide refractory population in the BOSTON study, selinexor + bortezomib + dexamethasone has been shown to statistically significantly improve overall survival compared to bortezomib + dexamethasone. (26.68 months *versus* 18.65 months; hazard ratio=0.531; 95% confidence interval: 0.297, 0.949; *P*=0.030). These overall survival data are key to consider given that the current treatment pathway means that an increasing number of patients are relapsing with lenalidomide-refractory disease. We acknowledge that given the absence of lenalidomide refractory data for panobinostat + bortezomib + dexamethasone, it is not possible to include a formal comparison in this population *versus* selinexor + bortezomib + dexamethasone. Therefore, the network meta-analysis results being considered are in the overall populations in the third line setting.	- BOSTON lenalidomide refractory subgroup: SVd OS: 26.68 months; Vd OS: 18.65 months; hazard ratio=0.531; 95% confidence interval: 0.297 to 0.949; *p*=0.030). The EAG notes this represents a larger OS difference than reported in the BOSTON ITT population: - BOSTON ITT population, updated analysis: SVd OS: 36.67 months; Vd OS: 32.76 months; hazard ratio=0.838; 95% confidence interval: 0.603 to 1.166; *p*=0.147. However, the EAG notes that: - The lenalidomide-refractory subgroup analysis was not pre-specified, and not reported in the CSR, although a lenalidomide exposed subgroup was presented. - The lenalidomide-refractory subgroup analysis has been presented for all BOSTON patients (2L, 3L and 4L combined, n=106), rather than at 3L (n=41) or 3L+ (n=76) for comparison with PanoVd or IxaRd; - As noted by the company, no comparative data are available for PanoVd within a lenalidomide refractory subgroup. It is therefore unclear if a similar increase in OS would be observed for patients who are refractory to lenalidomide when treated with PanoVd compared to Vd. As such, indirect treatment comparisons could not be performed against relevant comparators within a lenalidomide refractory subgroup.

There were no statistically significant differences for both overall survival and progression-free survival *versus* comparators. This is shown on page 13 of the draft guidance (section 3.8), where the results of the network meta-analysis are reported as follows: At second line no statistically significant differences in progression-free survival or overall survival compared with carfilzomib + dexamethasone. At third line no statistically significant differences in progression-free survival or overall survival compared with the ixazomib combination. At third line no statistically significant differences in progression-free survival or overall survival compared with the panobinostat combination. **Given there is uncertainty across both progression-free survival and overall survival results from the network meta-analysis/ matching-adjusted indirect comparison, the EAG has taken a pessimistic approach when considering the network meta-analysis/ matching-adjusted indirect comparison results.** Although in both the second line and third line settings, there was no statistical difference for progression-free survival and overall survival in the network meta-analysis, for an endpoint showing a numerical disadvantage of selinexor + bortezomib + dexamethasone *versus* the comparator (progression-free survival second line & third line, overall survival second line), the EAG has used the hazard ratio from the network meta-analysis/ matching-adjusted indirect comparison. However, contrastingly, in the third line setting with a numerical advantage in overall survival, the EAG has not used this hazard ratio but assumed equal efficacy across interventions. This seems counter-intuitive and overly pessimistic, given the similar uncertainty in the comparative estimates for the endpoints. **The Company, therefore, maintains that the hazard ratio from the network meta-analysis should be used for the comparators in third line, as was done for the second line, with progression-free survival being numerically inferior and overall survival being numerically superior in third line.**	The EAG recognises that there were no statistically significant differences for both overall survival and progression-free survival versus comparators. However, the EAG disagrees with the company that there is similar uncertainty in the comparative estimates for PFS and OS between SVd and key comparators for the following reasons: - PFS was the primary outcome of BOSTON and the key comparator trials; - The PFS data from BOSTON are more mature than the OS data; - Comparisons within and between trials for OS are confounded by different subsequent treatment use, with there being imbalances in subsequent therapy use for patients in BOSTON following SVd or Vd (Table 38 of EAG report), and similar imbalances within PANORMAMA-1 (Table 38 of EAG report). The EAG considers these differences in subsequent treatment use to increase the uncertainty and potential bias in comparative OS estimates relative to comparative PFS estimates; - The BOSTON OS results are sensitive to the choice of OS adjustment performed by the company. In the EAG report, the EAG noted that slightly more optimistic HRs, calculated with re-censoring, were used in the company ITC analyses, compared to the HRs presented in the CS that were calculated without re-censoring (EAG report page 80); - While neither PFS or OS comparisons were statistically significant, this does not necessarily reflect a similar amount of uncertainty or risk of bias in each analysis. Overall, the EAG highlights substantial uncertainty in both the estimates of PFS and OS resulting from the company's indirect treatment analyses. This is reflected in the wide credible and confidence intervals, reflecting significant uncertainty in the magnitude and direction of any differences.

The updated 3L+ network meta-analysis and the unanchored matching-adjusted indirect comparison of selinexor + bortezomib + dexamethasone versus ixazomib + lenalidomide + dexamethasone demonstrate that the selinexor combination is numerically inferior to panobinostat + bortezomib + dexamethasone, and ixazomib + lenalidomide + dexamethasone in terms of progression-free survival whilst numerically superior in overall survival. The clinical rationale for why progression-free survival could be inferior, whilst overall survival is superior, is that the prior treatments of patients entering the ixazomib + lenalidomide + dexamethasone and panobinostat + bortezomib + dexamethasone studies were very different to those participating in BOSTON, with one consideration being that these patients would be lenalidomide-sensitive compared to those in the BOSTON study, where 32% were lenalidomide-refractory on entering the study. This difference in the biology of patients entering the study, supports why progression-free survival may be inferior, with lenalidomide refractory patients having worse outcomes. The rationale for why overall survival can be considered superior has been provided above. **Our contention is that good practice means the results from the network meta-analysis/ matching-adjusted indirect comparison should be treated consistently across both endpoints. So, if the numerical results from the network meta-analysis/ matching-adjusted indirect comparison are not directly used, then given neither progression-free survival nor overall survival showed statistically significant differences in third line, as a minimum, then assuming equal efficacy for both progression-free survival and overall survival would be appropriate.**	However, the EAG considers the uncertainty and risk of bias to be more substantial in the OS analyses. The EAG considers longer term data on OS outcomes for each treatment in the pathway, and consideration of differences in subsequent treatment use within and between comparator trials, is needed to substantiate inclusion of an OS benefit in the model for any treatment.

The EAG would like to highlight a factual inaccuracy in the company's response: "*Although in both the second line and third line settings, there was no statistical difference for progression-free survival and overall survival in the network meta-analysis, for an endpoint showing a numerical disadvantage of selinexor + bortezomib + dexamethasone versus the comparator (progression-free survival second line & third line, overall survival second line), the EAG has used the hazard ratio from the network meta-analysis/ matching-adjusted indirect comparison. However, contrastingly, in the third line setting with a numerical advantage in overall survival, the EAG has not used this hazard ratio but assumed equal efficacy across interventions*."	In the EAG base case, the assumption of equal OS using Vd as the baseline was assumed for both the 2L and 3L subgroups, and not only in the 3L subgroup. Progression-free survival for both the 2L and 3L subgroups was estimated by applying comparator HRs from the ITCs to the baseline Vd PFS curve. As such, the EAG has taken a consistent approach for its preferred base case analysis in using the ITC estimates for PFS but not for OS in both the 2L and 3L subgroups.

Abbreviations: CI, confidence interval; CSR, clinical study report; CrI, credible interval; EAG, external assessment group; IxaRd, ixazomib + lenalidomide + dexamethasone; HR, hazard ratio; ITC, indirect treatment comparison; NMA, network meta-analysis; OS, overall survival; PanoVd, panobinostat + bortezomib + dexamethasone; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone; 2L, second line; 3L, third line; 3L+, third line plus.

3 NICE requested scenarios for subsequent treatments

The National Institute of Health and Care Excellence (NICE) has requested the EAG to explore alternative assumptions for subsequent treatment costs, based on feedback from clinical experts (Section 3.13 of the draft guidance [DG]). In the DG, the committee heard from clinical experts that:

- The proportion of people having subsequent treatment based on BOSTON (80%) was unlikely representative and considered it to be around 20%.
- After third line, there would be no significant differences in subsequent treatments based on whether people had selinexor combination or panobinostat combination treatment.
- After third line, multiple myeloma is likely to be refractory to lenalidomide and people are more likely to have pomalidomide plus dexamethasone (Pd) as a next line of treatment.

As such, the EAG ran a combined scenario (scenario 1) which assumed the following:

- The proportion of 3L patients that go on to subsequent treatment is assumed to be 20%.
- No differences in subsequent treatments received irrespective of treatment received at 3L.
- At fourth-line (4L) subsequent treatments are split between Pd (80%) and chemotherapy (20%) and that at fifth-line (5L), the split is 20% Pd and 80% chemotherapy.

Additionally, NICE requested to see a scenario where there is no difference in the cost of subsequent treatments for SVd and comparators. The EAG notes that in the model, the cost of subsequent treatments is linked to the length of time patients spend in the progressed disease health state, informed by progression-free survival (PFS) and overall survival (OS). As such, in combination with scenario 1, a one-off cost of subsequent treatment was estimated based on the weighted weekly cost of subsequent treatment multiplied by the duration of subsequent treatment, which was assumed by the company to be nine months. Please refer to Section 4.2.6.3 of the EAG report for further details of the subsequent treatment cost parameters. The one-off cost of subsequent treatments was estimated to be £15,366.

Since a single subsequent treatment cost is assumed for all treatments, the incremental cost is always zero. Therefore, for the scenario different approaches to modelling subsequent treatment costs, such that they are equal for all treatment arms, or even excluding this cost from the model only affects the total costs and does not impact on the scenario's ICER (incremental cost-effectiveness ratio). However, the EAG notes that the scenario assuming no difference in subsequent

treatment costs favours patients on SVd as PFS is estimated to be shorter compared to patients on PanoVd and IxaRd, and so spend longer in the progressed disease health state.

Table 5 presents the deterministic results of the EAG's scenario analyses for subsequent treatment costs applied to the committee preferred based case for 3L subgroup and Table 6 presents the probabilistic scenario analysis results.

Table 5. NICE requested deterministic scenario analysis for subsequent treatments

	Results per patient	SVd (1)	IxaRd (2)	PanoVd (3)	Incremental value (1-2)	Incremental value (1-3)
0	**Committee preferred base case**					
	Total costs (£)	[redacted]	284,753	171,299	-113,539	-85
	QALYs	[redacted]	[redacted]	[redacted]	-0.04	-0.02
	ICER (£/QALY)	-	-	-	2,719,558 (SW)	3,555 (SW)
1	**Clinical expert feedback assumptions for subsequent treatments presented in draft guidance**					
	Total costs (£)	[redacted]	276,342	118,334	-163,768	-5,761
	QALYs	[redacted]	[redacted]	[redacted]	-0.04	-0.02
	ICER (£/QALY)	-	-	-	3,922,680 (SW)	240,135 (SW)
2	**Equal subsequent treatment costs for all treatment arms**					
	Total costs (£)	[redacted]	289,543	120,363	-176,329	-7,150
	QALYs	[redacted]	[redacted]	[redacted]	-0.04	-0.024
	ICER (£/QALY)	-	-	-	4,223,549 (SW)	298,060 (SW)
3	**Company preferred base case (inclusion of OS benefit) + scenario 1**					
	Total costs (£)	[redacted]	315,660	120,258	-197,524	-2,121
	QALYs	[redacted]	[redacted]	[redacted]	-0.94	0.37
	ICER (£/QALY)	-	-	-	209,708 (SW)	Dominant
4	**Company preferred base case (inclusion of OS benefit) + scenario 2**					
	Total costs (£)	[redacted]	316,301	121,127	-197,507	-2,333
	QALYs	[redacted]	[redacted]	[redacted]	-0.94	0.37
	ICER (£/QALY)	-	-	-	209,690	Dominant

Abbreviations: 3L, third-line; AE, adverse event; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab with pomalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west; Vd, bortezomib with dexamethasone.

Table 6. NICE requested probabilistic scenario analysis for subsequent treatments

	Results per patient	SVd (1)	IxaRd (2)	PanoVd (3)	Incremental value (1-2)	Incremental value (1-3)
0	**Committee preferred base case**					

	Total costs (£)	[redacted]	275,008	155,080	-114,477	5,450
	QALYs	[redacted]	[redacted]	[redacted]	-0.04	-0.02
	ICER (£/QALY)	-	-	-	2,789,635 (SW)	Dominated
1	**Clinical expert feedback assumptions for subsequent treatments presented in draft guidance**					
	Total costs (£)	[redacted]	264,370	113,816	-154,791	-4,237
	QALYs	[redacted]	[redacted]	[redacted]	-0.04	-0.02
	ICER (£/QALY)	-	-	-	3,726,341 (SW)	197,131 (SW)
2	**Equal subsequent treatment costs for all treatment arms**					
	Total costs (£)	[redacted]	274,834	118,492	-163,205	-6,863
	QALYs	[redacted]	[redacted]	[redacted]	-0.04	-0.02
	ICER (£/QALY)	-	-	-	3,972,465 (SW)	319,929 (SW)
3	**Company preferred base case (inclusion of OS benefit) + scenario 1**					
	Total costs (£)	[redacted]	318,901	115,449	-202,875	577
	QALYs	[redacted]	[redacted]	[redacted]	-1.05	0.26
	ICER (£/QALY)	-	-	-	193,256	2,184
4	**Company preferred base case (inclusion of OS benefit) + scenario 2**					
	Total costs (£)	[redacted]	323,707	120,290	-206,488	-3,071
	QALYs	[redacted]	[redacted]	[redacted]	-1.05	0.26
	ICER (£/QALY)	-	-	-	197,122 (SW)	Dominant

Abbreviations: 3L, third-line; AE, adverse event; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab with pomalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west; Vd, bortezomib with dexamethasone.

4 References

1. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care Manual 2022. 2022. Available from: https://www.pssru.ac.uk/unitcostsreport/. Date accessed.