

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

STA Report

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List of Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
3L+	Third-line plus
4L	Fourth line
AE	Adverse event
Af/Am	African American
AFT	Accelerated Failure Time
AIC	Akaike information criterion
BIC	Bayesian inflation criterion
BSA	Body surface area
BTd	Bendamustine + thalidomide + dexamethasone
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHMP	The Committee for Medicinal Products for Human Use
CI	Confidence interval
CMQ	Customised MedDRA query
CR	Complete response
CrI	Credible interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical Study Report
DSU	Decision Support Unit
DRd	Daratumumab plus lenalidomide plus dexamethasone
DVTd	Daratumumab plus bortezomib plus thalidomide plus dexamethasone
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EORTC QLQ-CIPN20	European Organisation for Research and Treatment of Cancer quality of life Chemotherapy-Induced Peripheral Neuropathy questionnaire
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer quality of life multiple myeloma questionnaire
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
ESMO	European Society for Medical Oncology
HRQoL	Health-related quality of life

ICER	Incremental cost-effectiveness ratio
IMWG	International Myeloma Working Group
INV	Investigator
IRC	Independent Review Committee
IMiD	Immunomodulatory drugs
ISS	International Staging System
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IxaRd	Ixazomib in combination with lenalidomide and dexamethasone
Kd	Carfilzomib plus dexamethasone
KM	Kaplan-Meier
KRd	Carfilzomib in combination with lenalidomide and dexamethasone
MA	Marketing authorisation
MAIC	Matching-adjusted indirect comparison
MCMC	Markov Chain Monte Carlo
MedDRA	Medical dictionary for regulatory activities
MGUS	Monoclonal gammopathy of undetermined significance
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple myeloma
MR	Minimal response
MRD	Minimal residual disease
NE	Not evaluable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PanoVd	Panobinostat in combination with bortezomib and dexamethasone
PAS	Patient access scheme
PD	Progressed disease
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazards
PI	Proteasome inhibitors
PR	Partial response
PN	Peripheral neuropathy
PSA	Probabilistic sensitivity analysis

PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QLQ	Quality of life
Rd	Lenalidomide plus dexamethasone
RDI	Relative dose intensity
R-ISS	Revised International Staging System
RPSFT	Rank-preserving structural failure time
RRMM	Relapsed and/or refractory multiple myeloma
SAP	Statistical analysis plan
SC	Subcutaneous
SCT	Stem cell transplant
Sd	Selinexor plus dexamethasone
SD	Standard deviation
SINE	Selective inhibitor of nuclear export
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
SVd	Selinexor plus bortezomib plus dexamethasone
SW	South West
TEAE	Treatment-emergent adverse event
ToT	Time on treatment
TSD	Technical support document
TSE	Two-stage estimation
TTD	Time to discontinuation
TTR	Time to response
VCd	Bortezomib plus cyclophosphamide plus dexamethasone
Vd	Bortezomib plus dexamethasone
VGPR	Very good partial response
VTd	Bortezomib plus thalidomide plus dexamethasone
WTP	Willingness to pay
XPO1	Exportin 1 protein

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

The company has proposed a confidential patient access scheme (PAS) discount of [REDACTED] on the list price, and all results presented in this report are inclusive of the discount. Confidential PAS discounts are available for comparators included in the analyses. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, and sensitivity and scenario analyses, as well as all EAG analyses.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 presents a summary of the EAG's key issues on the evidence submitted on the clinical and cost effectiveness of selinexor, in combination with bortezomib and low-dose dexamethasone (SVd) treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received one or two prior lines of treatment.

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Suitability of the Company NMA comparison for IxaRd vs SVd	3.4, 3.4.3
2	Influence of the assumption of proportional hazards on the approach to treatment effectiveness in the model	4.2.3
3	Overall survival benefit associated with treatments included in the analysis	4.2.3.6
4	Estimation of subsequent treatment costs	4.2.6.4
5	Estimation of the impact on costs and QALYs of adverse events	4.2.4, 4.2.5.4, 4.2.6.8

Abbreviations: EAG, External Assessment Group; IxaRd, ixazomib + lenalidomide + dexamethasone; NMA, network meta-analysis; QALYs, quality-adjusted life-years; SVd, selinexor + bortezomib + dexamethasone.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows:

- Alternative assumptions for long-term progression-free survival (PFS), overall survival (OS) and time on treatment for all treatments included in the cost-effectiveness analysis.
- What next line of treatment a patient receives if their disease progresses, based on the current NHS pathway and what treatment they have previously received.
- How the impact, in terms of costs and quality of life, of adverse events are included in the cost-effectiveness analysis.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, when compared with other available treatments in the NHS pathway, the technology is modelled to affect QALYs by:

- Reducing PFS for patients who have had two prior lines of treatment (hereafter known as the 3L subgroup).
- Increasing OS for the 3L subgroup.
- Reducing PFS and OS for patients who have had one prior line of treatment (hereafter known as the 2L subgroup).

Overall, the technology is modelled to affect costs by:

- Its lower cost per treatment cycle than current treatments.
- Its lower administration costs than current treatments at second-line (2L).
- Its higher administration costs than current treatments at third-line (3L).

The modelling assumptions that have the greatest effect on the ICER are:

- The estimation of PFS, OS and time on treatment.
- Whether or not there is an overall survival benefit associated with treatments for RRMM.
- The costs of subsequent treatments for patients who disease progresses.
- The assumed impact of adverse events for the duration of time patients are on treatment.

1.3 The clinical effectiveness evidence: summary of the EAG's key issues.

Table 2. Issue 1: 3L+ network meta-analysis

Report section	3.4, 3.4.3
Description of issue and why the EAG has identified it as important	NMA comparison for OS and for PFS between SVd/Vd and IxaRd. The EAG considers the Company's 3L+ NMA to be limited by: • The use of an unanchored MAIC to connect the network; • The double use of Vd data from BOSTON; • The use of "by-arm" median PFS data from two trials where HRs were not available; • The potential violation of proportional hazards throughout the networks; • The inclusion of a study including patients with a median of 5 prior lines of anti-MM therapy, likely representing a different disease stage and treatment responsiveness to the other included studies; • Including two trials which started in 2003 for which the relative treatment effectiveness estimates may no longer be valid, especially for OS; • Including several studies for which the OS estimate has not been adjusted for treatment switching. Instead, the EAG prefers an unanchored MAIC approach that avoids the limitations associated with the 3L+ NMA. The Company provided unanchored MAICs for SVd and Vd against IxaRd, and the EAG considered the unanchored MAICs between Vd and IxaRd to be the most appropriate.
What alternative approach has the EAG suggested?	Unanchored MAICs directly comparing Vd with IxaRd for PFS and OS for the 3L+ population. These analyses were provided by the Company at Clarification.
What is the expected effect on the cost-effectiveness estimates?	The EAG made a number of changes to treatment effectiveness in the model, including the unanchored MAICs directly comparing Vd with IxaRd for PFS and OS for the 3L+ population and the impact on the cost-effectiveness results is discussed further in Issue 2.
What additional evidence or analyses might help to resolve this key issue?	The EAG received the requested analyses at Clarification.
Abbreviations: EAG, External Assessment Group; MAIC, matching adjusted indirect comparison, IxaRd, ixazomib + lenalidomide + dexamethasone; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone; 2L, second line; 3L+ third line plus.	

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Table 3. Issue 2: Assumption of proportional hazards

Report section	4.2.3
Description of issue and why the EAG has identified it as important	Based on log-cumulative hazard plots and Schoenfeld residual plots presented in Section B.3.4.1 and B.3.4.2 of the CS, the company concluded that the PH assumption was not violated for OS and TTD for both the 2L and 3L subgroups and for PFS for the 3L subgroup only, and so chose to model these outcomes jointly for SVd and Vd, with comparator HRs applied to the SVd curve as the baseline. The EAG investigated the diagnostic plots supplied in the CS but concluded that the PH assumption was violated for PFS, OS and TTD for both the 2L and 3L subgroups from BOSTON. The EAG considers that as the PH assumption does not hold for outcomes within BOSTON, modelling survival curves jointly and using SVd extrapolations of outcomes as the baseline to apply comparator HRs is not appropriate.
What alternative approach has the EAG suggested?	The EAG considers that it is more robust to use independently fitted models for PFS, OS and TTD as the company has access to patient-level data from BOSTON and it removes the need to assume proportional hazards holds between SVd and Vd. However, because HRs are estimated from the ITC, only independent models which support the PH assumption (such as the exponential, Weibull and Gompertz distributions) are suitable. With regards to the appropriate baseline to apply comparator HRs from the ITC, the EAG considers that as Vd is the common treatment to link into the network for the ITC, the PH assumption should be investigated for the trials informing the network for the 2L and 3L analysis. Based on diagnostic plots provided by the company for trials included in the ITC, the EAG considers that the PH assumption for PFS holds for most of the trials (which may be considered the more clinically important outcome) but there is evidence to suggest there is no significant difference in OS for trials included in the ITC. Thus, it is more appropriate that Vd is used as the baseline to apply comparator HRs from the ITC to for PFS, OS and TTD for both the 2L and 3L subgroups. The EAG considers the following approach is more appropriate for treatment effectiveness in the model: - Independently fitted models for the extrapolation of BOSTON PFS, OS and TTD for SVd and Vd. - Extrapolations of PFS, OS, TTD for Vd from BOSTON as the baseline for applying comparator treatment effects. - The EAG's preferred extrapolations of PFS, OS and TTD for the 2L and 3L subgroups – Sections 4.2.3.4, 4.2.3.6, 4.2.3.8. 2L subgroup: PFS - Weibull; OS - Weibull; TTD - Gompertz with PFS cap. 3L subgroup: PFS - lognormal; OS - Weibull; TTD - generalised gamma with PFS cap. Company's unanchored MAIC estimate for IxaRd used in 3L analysis (Issue 1)

What is the expected effect on the cost-effectiveness estimates?	For the 2L subgroup, the EAG's alternative assumptions for treatment effectiveness changed the ICER from £605,630 (south-west quadrant) to dominant. For the 3L subgroup, the ICER for IxaRd switched from dominant to £171,605 (south-west quadrant) and for PanoVd the ICER changed from dominant to £6,024. The EAG notes that the changes in the ICERs are driven by estimated OS benefits for treatments and this is discussed further in Issue 3.
What additional evidence or analyses might help to resolve this key issue?	The EAG's analysis resolves the issue for the 2L subgroup and for OS in the 3L subgroup. However, for the 3L subgroup, independently fitted PH models for PFS and TTD were not suitable and instead, AFT models were used. As such, the EAG requests the company to derive PFS estimates from the ITC for IxaRd and PanoVd that are suitable for use with AFT models.

Abbreviations: 2L, second-line; 3L, third-line; AFT, accelerated failure time; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; IxaRd, ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; PFS, progression-free survival; PH, proportional hazards; SvD, selinexor with bortezomib and dexamethasone; TTD, time to treatment discontinuation; Vd, bortezomib with dexamethasone.

Table 4. Issue3: Overall survival benefit

Report section	3.4, 4.2.3.5
Description of issue and why the EAG has identified it as important	Overall survival in BOSTON is highly uncertain, even with adjustments made for crossover, as data are immature (median not reached for the 2L subgroup) and crossover adjusted OS HRs for the ITT, 2L and 3L analyses are not statistically significant (95% confidence intervals cross one, see Table 26). Additionally, based on data from the trials for comparators considered in the analysis (Kd, IxaRd and PanoVd), no statistically significant differences in OS were observed, based on the 95% CIs around the OS HRs. Differences in subsequent treatments received upon disease progression are likely to have a significant influence on OS. The EAG's clinical experts considered that after one prior line of treatment, patients' OS is likely to be similar irrespective of the treatments they receive at different lines, as they are unlikely to be off treatment until they get to their sixth line of treatment. As such, improvements in PFS at each line are potentially more clinically relevant. Moreover, the EAG considers that OS from BOSTON includes the survival impact of subsequent treatments for patients who progress to 3L and beyond.
What alternative approach has the EAG suggested?	In addition to the EAG's preferred treatment effectiveness assumptions (Issue 1), the EAG considers that it may be appropriate to assume no OS benefit for any of the treatments and use Vd as the baseline for OS included in the model. The EAG also explored scenarios around its preferred base case using SVd as the baseline for OS as well as inclusion of an OS benefit
What is the expected effect on the cost-effectiveness estimates?	For the 2L subgroup, the magnitude of ICER increased from £605,630 (south-west quadrant) to approximately £10 million (south-west quadrant). For the 3L subgroup, the ICER for IxaRd switched from dominant to approximately £2.5 million (south-west quadrant) and for PanoVd the ICER changed from dominant to dominated.
What additional evidence or analyses might help to resolve this key issue?	The EAG's scenarios resolves this issue in lieu of long-term OS for treatments in the RRMM NHS pathway becoming available within the timeframe for this appraisal.
Abbreviations: 2L, second-line; 3L, third-line; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; IxaRd, ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.	

Table 5. Issue 4: Costs of subsequent treatments

Report section	4.2.6.4
Description of issue and why the EAG has identified it as important	The company included the cost of subsequent therapies given on disease progression after treatment with SVd and comparators. The company calculated a weighted average estimate of treatments provided beyond 2L or 3L for each treatment arm (weighted-basket approach) based on data from BOSTON and excluding treatments not available in the NHS. However, the EAG considers that the base case approach does not fully consider the sequence of treatments a patient may have, contingent on treatment received in their previous line of therapy and thus the proportions of each subsequent treatments assumed may not reflect UK clinical practice. For example, the EAG's clinical experts advised that patients who had previously received IxaRd would not go on to receive further treatment with lenalidomide plus dexamethasone (Rd), while the company assumes 56% of patients treated with IxaRD would go on to receive Rd. Additionally, the EAG's clinical experts stated that at 3L and 4L, treatment with chemotherapy is not used often given the availability of other more effective treatments in the pathway. The EAG's clinical experts also considered that only a small proportion of patients would receive daratumumab monotherapy. Furthermore, bendamustine is no longer available in the NHS and IsaPd is not routinely commissioned as it still in the Cancer Drugs Fund (CDF).
What alternative approach has the EAG suggested?	In response to a request from the EAG, the company provided market share data for 3L and 4L treatments, sourced from existing market research conducted by the company. The EAG used the market share data along with assumptions based on the current NHS treatment pathway to estimate alternative proportions of subsequent treatments. Additionally, the EAG's clinical experts advised that a cyclophosphamide-based chemotherapy regimen should be assumed instead of bendamustine. The EAG's scenario exploring an alternative approach to subsequent treatment costs is combined with its preferred assumptions from treatment effectiveness (Issue 2), as time spent in progression forms part of the cost calculation. However, the scenario is not combined with the scenario removing the OS benefit for treatment (Issue 3), but both scenarios form part of the EAG base case.
What is the expected effect on the cost-effectiveness estimates?	For the 2L subgroup, the ICER changed from £605,630 (south-west quadrant) to dominant. For the 3L subgroup, the ICER for IxaRd switched from dominant to £172,112 (south-west quadrant) and for PanoVd the ICER changed from dominant to £3,384.
What additional evidence or analyses might help to resolve this key issue?	Real world evidence on RRMM treatment usage and duration of time spent on each treatment in the NHS would facilitate more accurate subsequent treatment cost calculations.
Abbreviations: 2L, second-line; 3L, third-line; 4L, fourth-line; DRd, daratumumab with lenalidomide and dexamethasone; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; IxaRd, ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.	

Table 6. Issue 5: Impact of adverse events

Report section	4.2.4, 4.2.5.4, 4.2.6.8
Description of issue and why the EAG has identified it as important	The company included the impact of AEs as weekly event rates for the entire duration patients are on treatment. The EAG considers that the company's approach is inappropriate and results in a bias against treatments which have longer PFS as patients are on treatment for longer. For all comparators, PFS is estimated to be longer than SVd, thus the weekly assumption is biased in favour of SVd. Additionally, AE data from BOSTON are based on incidence, rather than prevalence, thus using a weekly event treats the data as if it were prevalence data, which is inappropriate. Other issues with the estimation of AE costs were identified, including the company's use of inpatient costs only from the NHS reference costs schedule and the assumption that all AEs would be managed between primary and secondary care.
What alternative approach has the EAG suggested?	The EAG considers that it is more appropriate to capture AEs as a one-off impact at the start of the model and remove the link with length of treatment. Furthermore, the applying AEs as a one-off impact is more typically seen for NICE oncology technology appraisals. Additionally, the EAG's clinical experts advised that AEs would be predominantly managed in secondary care during outpatient appointments. As such, the EAG obtained alternative unit costs from the NHS reference cost schedule, as well as assuming all AEs are managed in secondary care.
What is the expected effect on the cost-effectiveness estimates?	For the 2L subgroup, the magnitude of ICER decreased from £605,630 (south-west quadrant) to £595,024 (south-west quadrant). For the 3L subgroup, the ICERs for IxaRd and PanoVd remained dominant. However, the EAG notes that for PanoVd, the incremental costs substantially reduced as a result of the EAG's preferred approach to AEs.
What additional evidence or analyses might help to resolve this key issue?	If the company does have the appropriate AE rate based on prevalence data available to it for all of the treatments under consideration, using that data with their current approach might be reasonable. Otherwise, the EAG's scenario resolves the issue.
Abbreviations: 2L, second-line; 3L, third-line; AE, adverse event; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab with pomalidomide and dexamethasone; IxaRd, ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone.	

1.5 Other key issues: summary of the EAG's view

Secondary issues identified for committee consideration include the following:

- The Company's positioning of SVd at 2L is for a subgroup of patients who are refractory to lenalidomide and daratumumab, which is narrower than the NICE final scope – Section 2.2.1;
- Health state utility values (HSUVs) from BOSTON should be based on line of therapy and progression status – Section 4.2.5.2;

- An administration cost for oral chemotherapy should be included in the cost-effectiveness analysis – Section 4.2.6.2;
- Resource use assumptions that are more reflective of the NHS – Section 4.2.6.6;
- End of life care cost from the PSSRU should be used in the economic model – Section 4.2.6.10.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 7 and Table 9 present the EAG's preferred assumptions as well as the EAG deterministic and probabilistic base case ICERs for the 2L and 3L subgroups. Table 8 and Table 10 present probabilistic scenarios around the EAG base case.

Table 7. EAG preferred assumptions and deterministic base case ICER - SVd versus Kd (2L subgroup)

Scenario	Incremental costs (£)	Incremental QALYs	Cumulative ICER (change from company base case)
Company base case post clarification	■	■	605,630 (SW)
EAG preferred treatment effectiveness assumptions	■	■	Dominant
OS for comparators equal to Vd	■	■	10,017,804 (SW)
Utility values by line of therapy and progression status	■	■	10,036,592 (SW)
EAG preferred subsequent treatments	■	■	8,601,271 (SW)
Administration cost for oral chemotherapy	■	■	8,400,870 (SW)
EAG preferred – AE costs*	■	■	6,612,455 (SW)
EAG clinical expert resource use assumptions*	■	■	6,612,455 (SW)
End of life care cost from the PSSRU*	■	■	6,612,455 (SW)
EAG's preferred deterministic base case - combination of all scenarios	■	■	6,612,455 (SW)
EAG's preferred probabilistic base case - combination of all scenarios	■	■	8,694,817 (SW)

Abbreviations: Abbreviations: 2L, second-line; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; Kd, carfilzomib with dexamethasone; OS, overall survival; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west; Vd, bortezomib with dexamethasone.

* The EAG notes that that while the incremental costs and ICER does not change for the scenario, the total costs are impacted by the change in assumption.

Table 8. Results of the EAG's scenario analyses – 2L subgroup

	Results per patient	SVd	Kd	Incremental value
0	EAG preferred base case			
	PSA total costs (£)	■	431,480	■
	PSA QALYs	■	■	■

	PSA ICER (£/QALY)	-	-	8,694,817 (SW)
	Deterministic ICER (£/QALY)	-	-	6,612,455 (SW)
1	OS for comparators equal to SVd			
	PSA total costs (£)	■	490,202	■
	PSA QALYs	■	■	■
	PSA ICER (£/QALY)	-	-	7,342,967 (SW)
	Deterministic ICER (£/QALY)	-	-	6,841,118 (SW)
2	Inclusion of an OS benefit for treatments			
	PSA total costs (£)	■	475,592	■
	PSA QALYs	■	■	■
	PSA ICER (£/QALY)	-	-	Dominant
	Deterministic ICER (£/QALY)	-	-	Dominant
3	Use of utility values from Hatswell et al. ¹			
	PSA total costs (£)	■	432,400	■
	PSA QALYs	■	■	■
	PSA ICER (£/QALY)	-	-	5,907,004 (SW)
	Deterministic ICER (£/QALY)	-	-	4,323,476 (SW)

Abbreviations: 2L, second-line; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; Kd, carfilzomib with dexamethasone; OS, overall survival; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west.

Table 9. EAG's preferred model assumptions – 3L subgroup

Preferred assumption	vs. IxaRd			vs. PanoVd		
	Cum. Δ costs (£)	Cum. Δ QALYs	Cumulative ICER (£/QALY)	Cum. Δ costs (£)	Cum. Δ QALYs	Cum. ICER (£/QALY)
Company base case post clarification	■	■	Dominant	■	■	Dominant
EAG preferred treatment effectiveness assumptions	■	■	171,605 (SW)	■	■	6,024
OS for comparators equal to Vd	■	■	2,577,373 (SW)	■	■	Dominated
Utility values by line of therapy and progression status	■	■	2,583,364 (SW)	■	■	Dominated
EAG preferred subsequent treatments	■	■	2,324,202 (SW)	■	■	Dominated
Administration cost for oral chemotherapy	■	■	2,569,239 (SW)	■	■	Dominated

EAG preferred – AE costs*	■	■	2,445,681 (SW)	■	■	Dominated
EAG clinical expert resource use assumptions*	■	■	2,445,681 (SW)	■	■	Dominated
End of life care cost from the PSSRU*	■	■	2,445,681 (SW)	■	■	Dominated
EAG's preferred deterministic base case - combination of all scenarios	■	■	2,445,681 (SW)	■	■	Dominated
EAG's preferred probabilistic base case - combination of all scenarios	■	■	2,457,260 (SW)	■	■	Dominated

Abbreviations: 3L, third-line; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; IxaRd, ixazomib with lenalidomide and dexamethasone; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west; Vd, bortezomib with dexamethasone.

* The EAG notes that while the incremental costs and ICER does not change for the scenario, the total costs are impacted by the change in assumption.

Table 10. Results of the EAG's scenario analyses – 3L subgroup

	Results per patient	SVd (1)	IxaRd (2)	PanoVd (3)	Incremental value (1-2)	Incremental value (1-3)
0	EAG preferred base case					
	PSA total costs (£)	■	272,739	154,929	■	■
	PSA QALYs	■	■	■	■	■
	PSA ICER (£/QALY)	-	-	-	2,457,260 (SW)	Dominated
	Deterministic ICER (£/QALY)	-	-	-	2,445,681 (SW)	Dominated
1	OS for comparators equal to SVd					
	PSA total costs (£)	■	315,972	177,410	■	■
	PSA QALYs	■	■	■	■	■
	PSA ICER (£/QALY)	-	-	-	2,602,287 (SW)	Dominated
	Deterministic ICER (£/QALY)	-	-	-	2,694,487 (SW)	Dominated
2	Inclusion of an OS benefit for treatments					
	PSA total costs (£)	■	364,847	156,864	■	■

	PSA QALYs	■	■	■	■	■
	PSA ICER (£/QALY)	-	-	-	171,546 (SW)	108,755
	Deterministic ICER (£/QALY)				196,251 (SW)	27,347
3	Use of utility values from Hatswell et al. ¹					
	PSA total costs (£)	■	275,666	155,321	■	■
	PSA QALYs	■	■	■	■	■
	PSA ICER (£/QALY)	-	-	-	1,534,107 (SW)	Dominated
	Deterministic ICER (£/QALY)	-	-	-	1,506,548 (SW)	Dominated
Abbreviations: 3L, third-line; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; IxaRd, ixazomib with lenalidomide and dexamethasone; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west.						

For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.1 and 6.2.

2 Introduction and background

2.1 Introduction

This report provides the External Assessment Group's (EAG's) critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of selinexor (brand name: Nexpovio®; Menarini-Stemline UK) in combination with bortezomib and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RR-MM) who have received one or two prior lines of treatment.

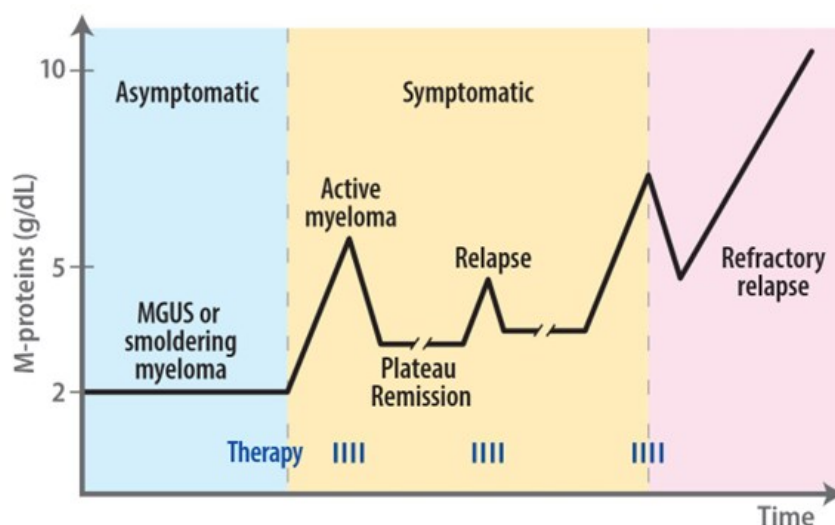
2.2 Background

MM is a progressive blood cancer of the plasma cells inside the bone marrow.² Most often, MM is preceded by a non-cancerous asymptomatic stage called monoclonal gammopathy of undetermined significance (MGUS).³ In some patients an early form of asymptotic MM is identifiable, called smouldering myeloma.⁴ Initially, MM may have few symptoms and may be diagnosed through patients presenting with musculoskeletal pain and/or fatigue or asymptomatic blood testing.^{5, 6} Blood tests for MM detect paraproteins in the blood that are immunoglobulin fragments produced by malignant plasma cells, and such tests are also used in the monitoring of MM.^{7, 8} Eventually, MM will progress to cause symptoms throughout the body, including the bones, kidneys, blood, and immune system.⁹ Section B1.3 of the Company Submission (CS) provides an overview of the aetiology and development of MM, and the National Institute for Health and Care Excellence (NICE) has published guidance on the diagnosis and management of myeloma (NG35, 2018).⁹

Between 2016 and 2018, an average of 5,951 new cases of MM were diagnosed each year in the UK, accounting for 2% of total UK cancer cases.¹⁰ Forty-three percent of people with MM were diagnosed aged 74 years and over, with a peak incidence rate in people aged 85 to 89 years.¹⁰ MM is more common in men than in women,¹⁰ and significantly higher in people with an African, Caribbean or any other black background compared to people in Asian, White or Multiple ethnic groups (95% confidence interval [CI] of the standardised rate ratio of MM incidence between black and white ethnic groups in England, 2013 to 2017: 2.7 to 3.0).¹¹

Treatments for MM aim to kill cancer cells, prevent end-organ damage, provide periods of disease plateau or remission, and prolong survival, but they are non-curative. Patients with MM may progress through several lines of therapy, with periods of remission followed by relapse (Figure 1).⁹ If a patient's disease becomes non-responsive to a therapy after prior minimal response or better, the disease is termed relapsed or refractory.

Figure 1. A typical progression of multiple myeloma. Reproduced from CS Figure 1.



Abbreviations: CS, Company submission; MGUS, monoclonal gammopathy of undetermined significance

Source: Reproduced from CS Figure 1; Durie et al. 2018 (International Myeloma Foundation)¹²

The International Myeloma Workshop Consensus Panel 1 developed the following definition of relapsed and refractoriness in MM:¹³

- Refractory myeloma: “disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease (PD) while on therapy.”
 - Relapsed and refractory myeloma: “disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course”;
 - Primary refractory myeloma: “disease that is nonresponsive in patients who have never achieved a minimal response or better with any therapy”;
- Relapsed myeloma: “previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either ‘primary refractory myeloma’ or ‘relapsed-and-refractory myeloma’ categories”.

2.2.1 Treatment pathway for RR-MM

Pharmacological treatments for MM include proteasome inhibitors (PI), immunomodulatory drugs (IMiD) that target cereblon E3 ligase,¹⁴ and anti-CD38 monoclonal antibodies, which are often used in combination with corticosteroids and/or conventional chemotherapy. Table 11 provides an

overview of the names and common abbreviations of drugs used in UK clinical practice for the treatment of MM.

Table 11. Names and common abbreviations of drugs used in UK clinical practice for the treatment of MM.

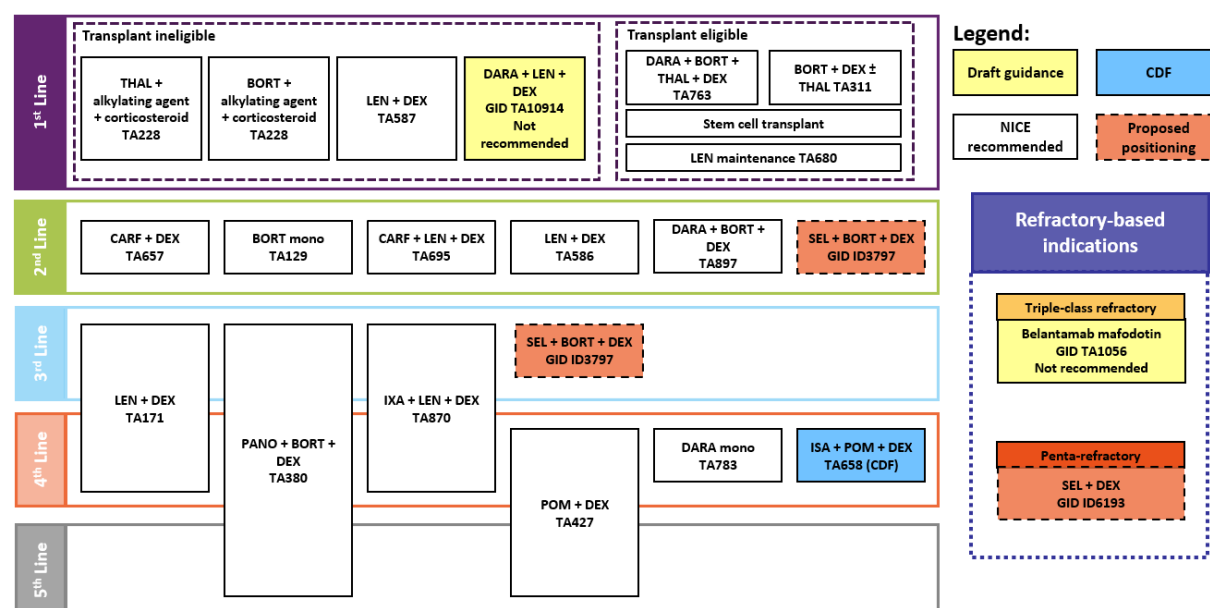
of MM.

Class	Suffix	Examples	Abbreviation
Proteasome inhibitors	—zomib	bortezomib	V
		carfilzomib	K
		ixazomib	Ixa
Immunomodulatory drugs	—lidomide	lenalidomide	R
		thalidomide	T
		pomalidomide	P
Anti-CD38 monoclonal antibodies	—mab	daratumumab	D
		isatuximab	Ixa

Abbreviations: MM, multiple myeloma

Section B1.3.3 of the CS provides the Company’s overview of the current treatment pathway for MM. This is summarised in Figure 2, which includes the proposed positioning for SVd in the current appraisal (ID3797) and the proposed positioning for Sd in ID6193. First line (1L) treatment for MM depends on if a patient is eligible or ineligible for autologous stem cell transplant (SCT) or not. Those eligible for SCT are likely to receive daratumumab + bortezomib + thalidomide + dexamethasone (DVTd) prior to their SCT, which is then followed by lenalidomide maintenance therapy until progression. In contrast, at the time of the Company Submission, those ineligible for SCT at 1L were likely to receive either: i) a fixed duration of bortezomib + an alkylating agent + a corticosteroid, or, ii) lenalidomide + dexamethasone (Rd) until progression. Following the recent recommendation of daratumumab + lenalidomide + dexamethasone (DRd) at 1L, it is now anticipated that most SCT-ineligible patients will receive DRd at 1L (Section 2.2.1.1). SCT-eligibility is determined by a host of factors, including a patients age, renal status, frailty, performance status and comorbidities,⁹ with younger and patients with better performance status and fewer comorbidities being most likely to be eligible. The EAG’s clinical experts stated that, broadly speaking, patients under the age of 65 to 70 years are deemed transplant eligible.

Figure 2. Company outline of the current and future treatment pathway for MM based on existing NICE guidance (Reproduced from CS Figure 2).



Source: Reproduced from CS Figure 2; based on published NICE guidance

The EAG's clinical experts agreed that Figure 2 provides a reasonable overview of the treatment options available for MM, with published NICE guidance. However, they noted the following points (Table 12):

Table 12. EAG's clinical expert comments on the treatment pathway for RR-MM outlined by the Company.

Line of therapy	EAG's clinical expert comments
All	Combination therapies with a greater number of agents are usually preferred over combination therapies with fewer agents.
1L, SCT eligible patients	DVTd is preferred over VTd prior to autologous SCT for most patients.
1L, SCT ineligible patients	- Thalidomide + an alkylating agent + a corticosteroid is rarely used in clinical practice in England and Wales; - Prior to DRd being approved at 1L, most patients would receive a bortezomib or lenalidomide containing regiment at 1L; - Following NICE recommendation at 1L, DRd is likely to become the most used therapy at 1L in clinical practice in England and Wales, despite not currently being used widely.
2L	- The 2L options outlined by the Company are a reasonable reflection of the treatment options available; - However, bortezomib monotherapy is not used in clinical practice, rather bortezomib is used in combination with dexamethasone (Vd). The EAG notes this has been previously recognised by NICE, and that Vd was included as a 2L comparator in the Final Scope of TA457 as "bortezomib (with or without dexamethasone)".¹⁵

3L	• The 3L options outlined by the Company are a reasonable reflection of the treatment options currently available for RRMM; • There are limited treatment options at 3L, especially as most patients will be lenalidomide exposed/refractory and daratumumab exposed. There is a clear unmet need at 3L for safe and effective therapies; • PanoVd may only be used at 3L for a minority of patients due to its toxicity profile, however the same concerns may be applicable for SVd. One of the EAG's clinical experts commented that the use of PanoVd may be very rare at 3L, but others deemed it an appropriate comparator.
Abbreviations: DVTd, daratumumab + bortezomib + thalidomide + dexamethasone; EAG, external assessment group; RRMM, relapsed and/or refractory multiple myeloma; SCT, stem cell transplant; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone; VTd, bortezomib + thalidomide + dexamethasone; 1L, first line; 2L, second line; 3L, third line;	

Overall, the EAG considers that Figure 3 and the CS to provide a reasonable overview of the current MM treatment pathway, caveated by the comments in Table 12. The EAG notes that a patient's eligibility for each treatment at 2L and 3L depends on which previous treatment an individual has been exposed to and/or is refractory to. The EAG's clinical experts outlined how patients are very likely to be refractory to treatments they have previously been exposed to, if the treatment given until progression – such as lenalidomide. As lenalidomide maintenance therapy is given to SCT eligible patients after transplantation, nearly all SCT-eligible patients progressing to 2L will be refractory to lenalidomide, and therefore will not receive a lenalidomide-based regimen at 2L. The EAG's clinical experts highlighted that as bortezomib is given for fixed duration at 1L (bortezomib + alkylating agent + corticosteroid) or 2L (Vd), retreatment with bortezomib is possible at 2L+, providing a patient had an acceptable response to their first bortezomib-containing regimen.

2.2.1.1 Daratumumab + lenalidomide + dexamethasone (DRd) at 1L

In the CS, the Company highlighted how a potential recommendation of DRd at 1L for SCT ineligible patients would change the RR-MM treatment pathway:

“DRd is undergoing continued technology appraisal at first-line, with an expected publication date of the 23rd of August 2023. Should DRd be commissioned at 1L, the UK clinical experts considered SVd to be an option at 2L in transplant ineligible patients who receive DRd upfront.”

Final draft guidance for daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable (TA10914) was published on 22 September 2023 recommending DRd, within its marketing authorisation, as an option for untreated MM in adults, when an autologous stem cell transplant is unsuitable.

The EAG agrees that, following the recommendation of DRd for routine commissioning, the treatment landscape for transplant ineligible MM patients will change. The EAG further notes the Company's clarified its preferred position for SVd at 2L is for patients who are refractory to daratumumab and lenalidomide following first-line treatment:

"The company positioning of SVd is for patients who are refractory to both daratumumab and lenalidomide, as this is where the current unmet need lies." (Company Response to Clarification Question A32)

The Company highlighted that, while the positioning of SVd *"is not related in any way to the prior use of stem cell transplantation"*, the population of patients who will be lenalidomide and daratumumab refractory in the current NICE pathway will almost exclusively consist of SCT-ineligible patients receiving DRd at 1L:

"Clinical feedback was that patients eligible for treatment with daratumumab or lenalidomide at 2L would be treated with a daratumumab or lenalidomide containing regimen and not selinexor. Based on the current NICE MM treatment pathway, patients receiving DRd at 1L (transplant ineligible) are treated to progression with both daratumumab and lenalidomide and would therefore not be eligible to receive either agent at 2nd line. SCT-eligible patients receive daratumumab as induction therapy, i.e prior to the stem cell transplant, and not until progression. Therefore, these patients would remain eligible for daratumumab, and clinical feedback is that clinicians would use a daratumumab containing regimen, in the 2L setting and patients would not be considered for SVd." (Company Response to Clarification Question A32)

The EAG notes the following:

- Even though DRd has been recommended as a 1L therapy for SCT ineligible patients, a proportion of SCT-ineligible patients will likely still not receive DRd at 1L, but these patients would not be eligible for SVd at 2L under the Company's proposed positioning;
- Median progression free survival (PFS) for DRd was 61.9 months in the pivotal Phase 3 trial, after a median follow-up of 64.5 months.¹⁶ As such, it will take time for the incident population DRd-experienced patients to comprise a significant proportion of the 2L population.

2.3 Critique of the company's definition of the decision problem

Table 13 summarises the EAG's critique of the company's definition of the decision problem.

Table 13. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	People with relapsing or refractory multiple myeloma who have had 1 to 3 prior therapies	Adults with relapsed refractory multiple myeloma who have received 1 or 2 prior lines of therapy. - At 2L, the Company clarified they are positioning SVd in patients who have received daratumumab and lenalidomide in the front-line setting; - At 3L the Company positioning of SVd is not contingent on a specific prior treatment combination.	This positioning is narrower than the EMA and MHRA-licensed indications of adult patients with multiple myeloma who have received at least one prior therapy. This positioning is supported by UK myeloma experts, who have highlighted the current significant unmet need in the 3L setting, which they anticipate may expand more to 2L as the treatment landscape evolves, particularly in the 1L.	The EAG considers the Company's positioning of SVd at 2L and 3L to be justified, despite this being narrower than the population outlined in the marketing authorisation. The EAG notes that the proposed positioning at 2L, for patients who are refractory to daratumumab and lenalidomide following first-line treatment, is much narrower than the prevalent and anticipated incident 2L population, and will predominantly consist of SCT-ineligible patients who received DRd at 1L.
Intervention	Selinexor in combination with bortezomib and dexamethasone	Nexpovio® (selinexor) in combination with bortezomib and low-dose dexamethasone	As specified in the final scope.	SVd as described in the CS matches the intervention outlined in the NICE final scope. The administration and dosing of SVd in the BOSTON trial matches that outlined in the SmPC.
Comparator(s)	For people who have had 1 prior therapy: - bortezomib monotherapy - lenalidomide plus dexamethasone	For people who have received 1 prior line of therapy: carfilzomib plus dexamethasone For people who have received 2 previous lines of therapy:	Since this submission addresses a restricted population, comparators were considered for 2L and 3L only. It is anticipated that the rapidly evolving treatment landscape in	At 2L, the Company has restricted the comparators in-line with the Company's narrower positioning of SVd for patients who are refractory to daratumumab and lenalidomide following first-line treatment. The EAG

	• carfilzomib plus lenalidomide and dexamethasone • carfilzomib plus dexamethasone • daratumumab plus bortezomib and dexamethasone For people who have had 2 prior therapies: • lenalidomide plus dexamethasone • ixazomib plus lenalidomide and dexamethasone • panobinostat plus bortezomib and dexamethasone For people who have had 3 or more prior therapies: • pomalidomide plus low-dose dexamethasone • daratumumab monotherapy • ixazomib plus lenalidomide and dexamethasone • lenalidomide plus dexamethasone • panobinostat plus bortezomib and dexamethasone • isatuximab plus bortezomib and dexamethasone (subject to ongoing NICE appraisal)	• ixazomib plus lenalidomide and dexamethasone • panobinostat plus bortezomib and dexamethasone Evidence for SVd versus Vd is from the BOSTON study. Evidence versus other comparators is from a global systematic review and NMA of treatment for RRMM.	RRMM, particularly in 1L, will result in the unmet need expanding to 2L. Myeloma clinical expert opinion was that, should DRd be reimbursed at first-line (GID TA10914, expected publication August 2023), patients receiving this regimen would be daratumumab and lenalidomide-relapsed and/or refractory and would therefore not receive DVd, Rd, or KRd at 2L (which also requires prior treatment with bortezomib that these patients would likely not have received). Furthermore, since bortezomib monotherapy is a singlet therapy, experts stated that it would not be used, and therefore it was their opinion that the only comparator in this scenario would be Kd. In the 3L indication, expert clinical opinion was that Rd would not be used where there are triplet combinations available, including ixazomib, which is given in combination with Rd. Therefore, in this submission, the comparators to SVd at 3L are IxaRd and PanoVd.	agrees it is appropriate to no longer consider the following interventions comparators at 2L, as patients will have previously relapsed on lenalidomide and daratumumab containing regimens: • lenalidomide plus dexamethasone; • carfilzomib plus lenalidomide and dexamethasone; • daratumumab plus bortezomib and dexamethasone. At 3L, the EAG agrees with the Company that Rd would not be used where there are triplet combinations available, and therefore agrees with the Company restricting the comparators to IxaRd and PanoVd at 3L
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	For people who have had any number of prior therapies: • conventional chemotherapy regimens • best supportive care • belantamab mafodotin (subject to ongoing NICE appraisal)			
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	The outcomes considered in this submission include: • overall survival • progression-free survival • response rates • adverse effects of treatment (including time to discontinuation) • health-related quality of life The model considers progression-free survival, overall survival, health-related quality of life, time on treatment and adverse effects of treatment.	As specified in the final scope.	The CS includes all outcomes included in the NICE final scope. The EAG critiques the measurement and assessment of these outcomes in Section 3.2.4 and Section 3.3.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	The cost-effectiveness of the treatments is expressed in terms of incremental cost per quality-adjusted life year, with net monetary benefit and net health benefit also reported. The cost-effectiveness model uses a partitioned survival analysis approach, whereby extrapolated OS, PFS and ToT	Where commercially confidential discounts apply to comparators, list prices are assumed. The cost-effectiveness model accompanying the submission includes fields allowing for comparator PAS assumptions to be applied.	The economic analysis adheres to the reference case and reflects the final scope.

	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account	outcomes are used to estimate the distribution of patients across health states over time. Model health states are progression-free, progressed disease and death, with the progression-free health state subdivided into on and off treatment. A lifetime time horizon of 35 years is considered, with modelled overall survival of less than 0.1% after 35 years. Costs are considered from an NHS and Personal Social Services perspective. Generic prices are applied to comparator therapies available in generic form. List prices are applied for comparators with a confidential commercial discount.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • prior therapies	Data reported for 2L and 3L populations. Data reported for subgroup analyses of the ITT for lenalidomide-refractory participants and PI-naïve participants.	The BOSTON study was a randomised controlled trial of SVd versus Vd in patients who had received one to three prior lines of therapy (i.e., 2L to 4L). Subpopulation data permitted reporting safety and efficacy data for 2L participants and 3L participants in line with the narrower population addressed	Efficacy data are presented separately for following subgroups/analysis sets: • ITT population • 2L subgroup • 3L subgroup • 3L+ subgroup • lenalidomide-refractory subgroup • PI-naïve subgroup

			in this submission. Subgroup data for prior therapies were not available within the line of therapy subpopulations. In the 2L setting, it is anticipated that treatment with SVd would follow relapse after DRd upfront. PI naïve data from the ITT population are therefore reported, as a proxy. Given the current and evolving pathway, patients reaching 2L and 3L are likely to be lenalidomide relapsed and/ or refractory, and therefore data from a post-hoc subgroup analysis of lenalidomide-refractory patients are described.	Cost-effectiveness analyses are presented separately for the 2L and 3L setting, but no cost-effectiveness analysis is provided for the entire population of the NICE scope, or the 2L and 3L setting together. The EAG considers this appropriate given the different comparators at each line.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	There are several risk factors associated with multiple myeloma, including: age, gender, family history, and ethnicity. It is not expected that this evaluation will exclude any people protected by equality legislation, nor lead to recommendations that will have an adverse impact on people with a particular disability or disabilities. The BOSTON trial included adult (≥18) years), male and female	No difference to scope	NA

		patients of different ethnic backgrounds, including patients from the UK.		
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Abbreviations: DVd; daratumumab + lenalidomide + dexamethasone; EAG, external assessment group; IxaRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; KRd, carfilzomib + lenalidomide + dexamethasone; MHRA, Medicines and Healthcare Products Regulatory; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PanoVd, panobinostat + bortezomib + dexamethasone; PAS, patient access scheme; PFS, progression-free survival; PI, proteasome inhibitor; Rd, lenalidomide + dexamethasone; RRMM, relapsed and/ or refractory multiple myeloma; SVd, selinexor + bortezomib + dexamethasone; ToT, time on treatment; UK, United Kingdom; Vd, bortezomib + dexamethasone; 1L, first line; 2L, second line; 3L, third line; 4L, fourth line.

2.3.1 Population

The population considered by the company for this STA is adult patients with RR-MM who have received one or two prior lines of treatment. The population under consideration is a restricted sub-population of the marketing authorisation (MA) for the triplet therapy, SVd, which indicated for patients who have received at least one prior therapy. The restricted population proposed by the company is a deviation from the NICE final scope, which outlines the relevant population to be adult patients with multiple myeloma who have received at least one prior therapy.

The Company further restrict the relevant population at 2L for patients who are refractory to daratumumab and lenalidomide following 1L treatment, i.e., primarily those who are SCT-ineligible and who have received DRd at 1L based on the current NICE pathway.

The population considered in the economic model are adult patients with RR-MM who have received one or two prior lines of treatment. Cost-effectiveness analyses are presented separately by one prior line of treatment and two prior lines of treatment.

Clinical data from BOSTON for SVd and Vd for the 2L and 3L subgroups are used to inform the economic model, along with outputs from the company's network meta-analyses to inform the clinical effectiveness of comparators considered for the cost-effectiveness analysis. Baseline characteristics included in the economic model were obtained from BOSTON (presented in Table 14). Please see Section 3.2 and Table 6 of the CS for further details on baseline characteristics from BOSTON.

Table 14. Modelled population baseline characteristics (taken from the company's post-clarification model)

Baseline characteristic	Value used in the economic model	
	2L subgroup	3L subgroup
Age (baseline)	67.18	65.33
% male	0.55	0.67
ECOG (baseline)	0.68	0.77
EQ-5D-3L (baseline)	0.72	0.72
Patient weight (kg)	76.41	76.77
Patient BSA	1.83	1.85
Abbreviations: 2L, second line; 3L, third line; BSA, body surface area; ECOG; Eastern Cooperative Oncology Group; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level Version; kg, kilogram.		

2.3.2 Intervention

Selinexor is a selective inhibitor of nuclear export (SINE) compound that prevents exportin 1 (XPO-1) mediated protein from cell nuclei.¹⁷ XPO-1 is over expressed in cancer cells and promotes cell proliferation, with SINE compounds such as selinexor inhibiting XPO1-dependent nuclear export and instead promoting apoptosis.^{18, 19} Selinexor is indicated in combination with bortezomib and dexamethasone for the treatment of adult patients with RR-MM who have received at least one prior line of treatment (CS Appendix C).

The dosing regimen for SVd included in the economic model is based on that received in BOSTON, summarised in Table 15, and matches the posology outlined in the summary of product characteristics (SmPC; CS, Appendix C).

Table 15. Treatment dosing regimen for SVd from BOSTON

Treatment	Dose per administration	Dose regimen	Treatment cycle length	Treatment duration
Selinexor	100 mg	Taken orally once weekly on day 1 of each week.	35 days	Treatment until progression of disease or unacceptable toxicity.
Bortezomib	1.3 mg/m ²	Administered subcutaneously once weekly on day 1 of each week for 4 weeks followed by 1 week off.	35 days	Treatment until progression of disease or unacceptable toxicity.
Dexamethasone	20 mg	Taken orally twice weekly on days 1 and 2 of each week	35 days	Treatment until progression of disease or unacceptable toxicity.

Abbreviations: m², metre-squared; mg, milligram; SVd, selinexor in combination with bortezomib and dexamethasone

2.3.3 Comparators

2.3.3.1 Second line

The Company included the following comparator in its cost-effectiveness modelling at 2L:

- Carfilzomib plus dexamethasone (Kd).

The Company did not include the following comparators listed in the NICE final scope:

- bortezomib monotherapy;
- lenalidomide plus dexamethasone;
- carfilzomib plus lenalidomide and dexamethasone; and

- daratumumab plus bortezomib and dexamethasone.

The EAG agrees that, given the Company's positioning of SVd at 2L for patients who are refractory to daratumumab and lenalidomide following 1L, it is unlikely that these patients would be considered for a lenalidomide or daratumumab-containing regimen at 2L. The EAG also agrees with the Company that bortezomib monotherapy is rarely used in UK clinical practice, and instead the EAG notes that bortezomib plus dexamethasone may be an option at 2L, potentially off-label in combination with cyclophosphamide (VCd). This view has been shared by the EAG's clinical experts and NICE, which in the Guidance Executive review of TA129 (Bortezomib monotherapy for relapsed multiple myeloma) stated that:²⁰

"NICE is aware of the widespread use of off label combination therapy [of bortezomib] with dexamethasone. Therefore, the impact of any potential NICE recommendation for [bortezomib plus dexamethasone] combination therapy could only be limited, and therefore NICE guidance could not be considered to add value."

In addition, in the 2020 final appraisal document of TA657, Vd was highlighted as a relevant comparator for the appraisal of Kd at 2L (section. 4.3).²¹ The EAG's clinical experts highlighted that Vd is not used widely in UK clinical practice at 2L for RRMM, but this may change with the approval of DRd at 1L for SCT-ineligible patients. Following DRd at 1L, the effective number of treatment options at 2L will reduce for these patients, and Vd could then be a plausible option as, excluding Kd, the only other bortezomib containing regimen, DVd, would not be appropriate for use in most patients relapsing following daratumumab at 1L. However, the EAG notes that existing clinical trial evidence from the ENDEAVOR trial suggests that Kd has a greater efficacy than Vd for the treatment of RR-MM at 2L (median PFS Kd: 22.2 months, median PFS Vd 10.1 months, HR: 0.45, 95% CI 0.33 to 0.61).²² The EAG further notes that as bortezomib is the same drug class as carfilzomib, a proteasome inhibitor, Kd will be the preferred therapy over Vd for patients eligible to receive a PI at 2L. As carfilzomib containing regimens are not available at 1L, patients will not be refractory to carfilzomib at 2L.

Hence, the EAG agrees with the Company that the relevant comparator at 2L is Kd.

2.3.3.2 Third line

The Company included the following comparators in its cost-effectiveness modelling at 3L:

- Ixazomib plus lenalidomide and dexamethasone (IxaRd); and
- Panobinostat plus bortezomib and dexamethasone (PanoVd).

The Company did not include the following comparators listed in the NICE final scope:

- Lenalidomide plus dexamethasone.

The EAG agrees with the Company's positioning: given the availability of IxaRd at 3L, and that ixazomib is not available earlier in the treatment pathway, it is unlikely that patients would receive Rd over IxaRd at 3L.

The dosing regimen for comparators included is summarised in Table 16, and matches the posology outlined in the summary of product characteristics for each treatment.

Table 16. Comparator dosing regimens included in the model

Treatment		Dose per administration	Dose regimen	Treatment cycle length	Treatment duration
Kd	Carfilzomib	Starting dose of 20 mg/m ² (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 56 mg/m ² (maximum dose 123 mg).	Intravenously as a 30-minute infusion on two consecutive days, each week for three weeks (days 1, 2, 8, 9, 15, and 16) followed by a 12-day rest period (days 17 to 28)	28 days	Treatment until progression of disease or unacceptable toxicity.
	Dexamethasone	20 mg	Administered orally on days 1, 2, 8, 9, 15, 16, 22, and 23.	28 days	Treatment until progression of disease or unacceptable toxicity.
IxaRd	Ixazomib	4 mg	Administered orally once a week on Days 1, 8, and 15.	28 days	Treatment until progression of disease or unacceptable toxicity.
	Lenalidomide	25 mg	Administered daily on Days 1 to 21	28 days	Treatment until progression of disease or unacceptable toxicity.
	Dexamethasone	40 mg	Administered on Days 1, 8, 15, and 22	28 days	Treatment until progression of disease or unacceptable toxicity.
PanoVd	Panobinostat	20 mg	Taken orally once a day, on days 1, 3, 5, 8, 10 and 12 of a 21 day cycle. Patients should be treated initially for eight cycles. It is recommended that patients with clinical benefit continue the treatment for eight additional cycles.	21 days	The total duration of treatment is up to 16 cycles (48 weeks).
	Bortezomib	1.3 mg/m ²	Given as an injection on days 1, 4, 8, 11 of a 21 day cycle for cycles 1-8. Then given on days 1 and 8 of a 21-day cycle for cycles 9-16	21 days	The total duration of treatment is up to 16 cycles (48 weeks).
	Dexamethasone	20 mg	Taken orally on days 1, 2, 4, 5, 8, 9, 11, 12 of a 21 day cycle for cycles 1-8. Then given on days 1, 2, 8 and 9 of a 21 day cycle for cycles 9-16	21 days	The total duration of treatment is up to 16 cycles (48 weeks).

Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; m², metre squared; mg, milligram; PanoVd, panobinostat plus bortezomib and dexamethasone.

2.3.4 Outcomes

The outcomes provided in the CS appropriately reflect the outcomes listed in the final scope issued by NICE:

- overall survival;
- progression-free survival;
- response rates;
- adverse effects of treatment and;
- health-related quality of life.

A critique of the assessment and statistical analyses of these outcomes in BOSTON is provided in Section 3.2.4 and Section 3.3.

3 Clinical effectiveness

3.1 Critique of the methods review

The Company conducted a broad systematic literature review (SLR) aiming to identify evidence of the efficacy, safety, and tolerability of selinexor and comparators for the treatment of relapsed or refractory multiple myeloma (RR-MM). The SLR was broader than necessary to identify all evidence relevant to the final scope issued by the National Institute for Health and Care Excellence (NICE) for this appraisal.²³ It identifies evidence relevant to both the second line and third line (2L to 3L) setting for selinexor + bortezomib + dexamethasone (SVd, current appraisal) and the fifth line and beyond (5L+) pentarefractory setting for selinexor + dexamethasone (Sd, ID6193),²⁴ and also includes a wider range of comparators than outlined in the NICE final scope, including several not used in clinical practice in England and Wales. The protocol for the review was registered prior to the initial screening phase on PROSPERO (CRD42023397589).²⁵

A summary of the Company's SLR is presented in Appendix D of the Company Submission (CS), and further details were provided by request in the SLR report.²⁶ After deduplication, the titles and abstracts of 24,918 records were screened independently by two reviewers, with 2,505 records entering full-text appraisal by two independent reviewers. A total of 948 records were included in the review, including 932 records from database searches, trial registers, conference searches and websites and a further 16 from other hand searches.

Two studies of SVd in a population relevant to the current appraisal were identified, BOSTON and STOMP. BOSTON was a Phase 3 randomised, open-label, clinical trial of SVd vs Vd in adults with RR-MM, who had received 1 to 3 prior lines of treatment.²⁷ BOSTON is the source of efficacy and safety data of SVd in the cost-effectiveness modelling. STOMP is a Phase 1/2 open-label, parallel assignment study of selinexor in combination with a variety of other therapies for RR-MM, across 11 arms. One of these arms is SVd (n=42, n=24 with the recommended dose). The Company does not present outcome data from STOMP,²⁸ and the EAG agrees that the BOSTON trial is the correct focus of the cost-effectiveness modelling.

Of the 18 comparators included in the global SLR, four were deemed relevant by the company to the current appraisal. However, the external assessment group (EAG) notes that the network meta-analyses (NMAs) were run at the global scale, with the relevant contrasts presented in the CS. As

such, data from 19, 13, 22 and 16 studies inform the networks for 2L PFS, 2L OS, 3L+ PFS and 3L+ OS, respectively. These NMAs are critiqued by the EAG in Section 3.4.

The EAG is satisfied that no relevant trials were missed in the SLR, and, while the EAG was concerned some relevant subgroup data may have been missed during data extraction, the Company extracted these data as part of the Clarification stage. The EAG critique of the Company SLR is presented in Table 17.

Table 17. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal.

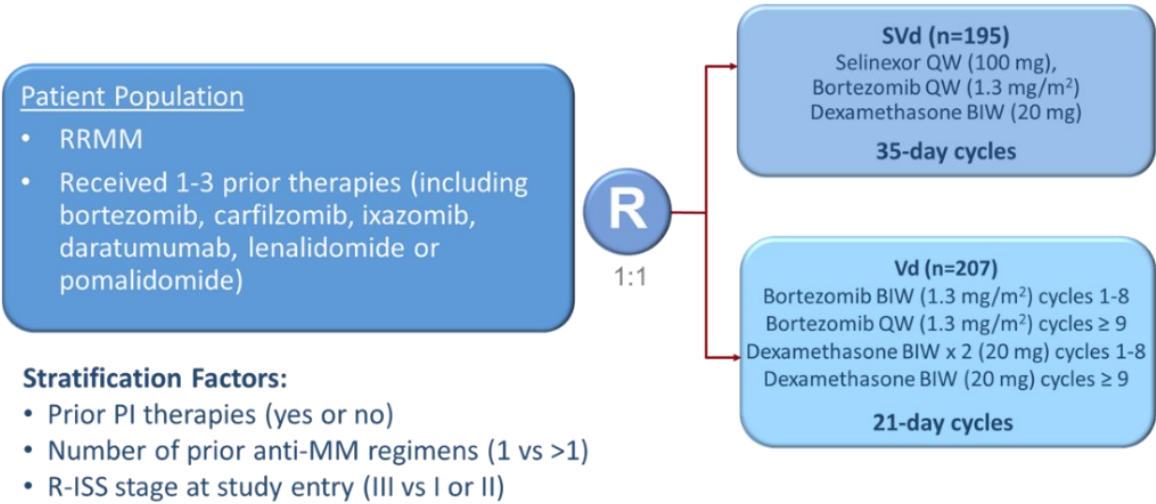
Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D1.1.1	Appropriate The Company searched an appropriate range of databases, trial registers, HTA websites and conferences.
Search strategies	Appendix D1.1.1	Appropriate Search dates: 4 to 11 February 2023 The search terms were broader than necessary for the final scope as issued by NICE, including a wider range of comparators than listed in the NICE scope.
Inclusion criteria	Appendix D1.1.2; Appendix D Table 1.	Appropriate The inclusion criteria of the SLR were broader than the population and interventions listed in NICE Final Scope, and broader than the decision problem addressed by the Company in this submission. The Company identified both RCT and non-RCT evidence relevant to the submission, with non-RCT evidence extracted where no relevant RCT data were identified.
Screening	Appendix D1.1.2	Appropriate Title and abstract appraisal, and full text appraisal, was performed by two independent reviewers.
Data extraction	Appendix D1.1.2	Some concerns (resolved) Data extraction was performed by a single reviewer and validated by another. The EAG was concerned that relevant subgroup data for a key trial (TOURMALINE-MM1) in a key subgroup (3L+) had not been extracted, however following Clarification the Company extracted and used these data in the indirect treatment comparisons.
Tool for quality assessment of included	Appendix D1.1.3 Table 11; Appendix D1.3 Table 12	Appropriate The Company used the NICE checklist for RCTs (adapted from The Centre for Reviews and Dissemination guidance) to assess the risk of bias in BOSTON and other included studies. In response to Clarification Question A26, the Company updated the risk of bias assessment to include an assessment of

study or studies		bias for each line-of-therapy subgroup analysis used in the indirect treatment comparisons, in addition to the overall ITT populations. The EAG considers this to have been conducted appropriately, and free-text justifications for each decision were presented.
Abbreviations: CS, company submission; EAG, External Assessment Group; HTA, health technology assessment; ITT, intention to treat; NICE, National Institute of Health and Care Excellence; RCT, randomised controlled trial; SLR, systematic literature review		

3.2 Critique of trials of the technology of interest

BOSTON was a Phase 3 randomised, open-label, clinical trial of SVd vs Vd in adults with RR-MM, who had received 1 to 3 prior lines of treatment.²⁷ The study design of BOSTON is presented in Figure 3, and a detailed overview of the BOSTON trial is presented in Section B2.3 of the CS.

Figure 3. BOSTON study design (Reproduced from CS Figure 4)



Abbreviations: BIW, twice a week; QW, once per week; mg, milligrams; MM, multiple myeloma; PI, proteasome inhibitor; R-ISS, Revised International Staging System; RRMM, relapsed/refractory multiple myeloma; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib and dexamethasone.
Source: CS Figure 4

In BOSTON, 402 patients were randomised 1:1 to either SVd (n=195) or Vd (n=207). Randomisation was stratified on prior PI therapy (yes or no), the number of prior treatment lines (1 or 2+), and Revised International Staging System (R-ISS) stage (III or I-II). The primary outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC) masked to treatment group, and overall survival (OS) and response rates were secondary outcomes. The EAG’s critique of the design, conduct and analysis of BOSTON is presented in Table 18.

Table 18. EAG's critique of the design, conduct and analysis of BOSTON.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	B2.5, Appendix D	Appropriate Randomisation was implemented using interactive response technology and was stratified based on prior PI therapy (yes or no), the number of prior treatment lines (1 or 2+), and Revised International Staging System (R-ISS) stage (III or I-II).
Concealment of treatment allocation	B2.5, Appendix D	Appropriate Randomisation was implemented using interactive response technology.
Eligibility criteria	B2.3.1	Appropriate The EAG's clinical experts considered the eligibility criteria of BOSTON to be reasonably reflective of patients who would be eligible to receive SVd at 2L or 3L in UK clinical practice, although noted BOSTON contained a low proportion of ECOG status ≥ 2 patients that is typical of oncology clinical trials.
Blinding	B2.3.1	Minor concerns The EAG notes that BOSTON was an open-label trial, however the EAG considers the risk of bias for outcome assessment to be low for OS and to be mitigated for PFS due to the objective definition of progressed disease used, and assessment being performed by a blinded IRC. The EAG notes that the CS did not state whether the IRC was blinded, but in the trial primary publication it is stated that: "efficacy assessments were based solely on laboratory test results and were evaluated by an independent review committee that was masked to the treatment groups". ²⁷
Baseline characteristics	Section B2.3.2, Table 6	Minor concerns Generally, baseline characteristics were well balanced between arms in the ITT population and the 2L and 3L subgroups. However, the number of patients with prior SCT differed between arms in both the ITT population (SVd arm: 39.0%; Vd arm: 30.4) and notably within the 2L subgroup (SVd arm: 39.4%; Vd arm 23.2%), which was a stratum in the randomisation schedule.
Dropouts	Section B2.3.1, Appendix D1.2	Minor concerns The number of patients discontinuing SVd treatment due to withdrawal by patient, adverse event, lost to follow-up or physician decision was higher in the SVd arm than the Vd arm in both the primary and updated analyses. The EAG considered it plausible that these dropouts were related to prognosis, i.e., not at random, but is satisfied that the Company's sensitivity analyses demonstrated the magnitude of any resulting bias was low (discussed further in Section 3.3.1).
Statistical analysis		

Sample size and power	B2.4	Some concerns BOSTON was designed to achieve 80% power to detect a difference of 4.1 months in median PFS, assuming a median PFS for SVd of 13.5 months and 9.4 months for Vd. The power analysis was conducted based on previous studies, rather than considering clinically important differences. The EAG considers 80% to detect a median PFS difference of 4.1 months to be at high risk of missing clinically important differences and is concerned that the power to detect such differences is considerably lower in the prespecified 2L subgroup and 3L subgroup. There was no formal power analysis concerning overall survival in BOSTON.
Handling of missing data	CSR Section 9.7.1.4.	Appropriate The amount of missing baseline data was low. Missing outcome data were not imputed, but the Company conducted sensitivity analyses around missing data resulting from dropouts, which the EAG discusses in Section 3.3.1.
Outcome assessment	B2.3.1	Appropriate Despite being an open-label trial, the EAG considers the risk of bias for outcome assessment to be low for OS and to be mitigated for PFS due to the objective definition of progressed disease used, and assessment being performed by a blinded IRC.
Analysis dates	B2.4	Primary and Updated Analyses Two analyses were presented in the CS and CSR. The primary analysis (18 February 2020) was the pre-specified primary analysis, and the updated analysis (15 February 2021) was conducted at the request of The Committee for Medicinal Products for Human Use (CHMP). The Company use the results from the updated analysis in the cost-effectiveness analyses. The EAG is content with this decision, as the updated analysis provides more mature survival data, and due to it being conducted following an external request, the EAG considers the timing of the analysis to be at low risk of bias.
Abbreviations: 2L, second line; 3L, third line; CHMP, The Committee for Medicinal Products for Human Use; CS, company submission; CSR, clinical study report; EAG, External Assessment Group; IRC, independent review committee; ITT, intention to treat; OS, overall survival; PI, proteasome inhibitor; PFS, progression-free survival; R-ISS, Revised International Staging System		

3.2.1 Population

The baseline characteristics of patients randomised in BOSTON are presented in Table 6 and Table 7 of the CS, for the “all randomised”, 2L and 3L groups. The EAG’s clinical experts considered these characteristics to be reasonably reflective of RR-MM patients at 2L and 3L in UK clinical practice, with the following exceptions:

- The median age of patients (2L: 68 years; 3L: 66 years), is slightly lower than UK clinical practice, reflecting a typical clinical trial population;
- Only 21.7% of patients at 2L and 48.8% of patients at 3L had been exposed to lenalidomide. In UK clinical practice, this proportion would be substantially higher, considering the majority of patients who had prior SCT (31.3% 2L, 43.4% 3L) would have received lenalidomide maintenance therapy at 1L, and around half of SCT-ineligible patients would have received a lenalidomide containing regimen at 1;
- The proportion of black or African American patients randomised in BOSTON (2L: 2.0%; 3L: 3.1%) is substantially lower than would be expected across the UK. A retrospective study from University College Hospital, London, reported that 15% of MM patients' self-reported ethnicity was black,²⁹ although ethnicity varied across the UK.

However, the EAG's clinical experts did not anticipate these differences to likely lead to meaningful treatment effect modification. In contrast, they considered that:

- The proportion of patients with ECOG status 2 (2L: 7.1%, 3L: 10.1%) or status 3+ (ECOG > 2 patients were excluded from BOSTON) was lower than would be expected in clinical practice, where the proportion of ECOG status 2+ would be closer to 20%. Given such patients may be less likely to tolerate the adverse event profile of SVd, this may affect: i) the duration of time patients are able to stay on treatment, and subsequently response; and ii) the severity of the adverse events they might experience.

The EAG also noted that within the 2L subgroup of BOSTON – a subgroup used as a stratification factor in randomisation – the proportion of patients with prior SCT was higher in the SVd arm (39.4%) than Vd arm (23.2%), as was the proportion of patients with R-ISS stage I (SVd arm, 33.3%; Vd arm, 23.2%). The EAG's clinical experts noted this may reflect a fitter group of patients with better prognosis in the SVd arm of the BOSTON 2L subgroup compared to the Vd arm. The EAG requested that the Company's survival analyses be performed with SCT as an additional covariate in Clarification Question A1, but the Company declined, noting that as the Cox proportional hazard models were already stratified based on R-ISS score, it was not appropriate to stratify based on a further proxy of disease severity. The Company also noted that other prognostic factors related to SCT eligibility, such as age, were balanced between arms.

3.2.1.1 *Line of therapy subgroups*

The EAG notes that the cost-effectiveness analysis in this submission is based upon the 2L and 3L subgroups of the BOSTON trial, which recruited patients at 2L (49% of participants), 3L (32% of participants) and 4L (19% of participants). Randomisation was stratified by prior lines of therapy, but this was only dichotomous, 1 prior line or 2 or more prior lines. As such, the 2L subgroup used in these analyses was a subgroup that randomisation was stratified on, whereas the 3L subgroup was only examined as an “exploratory” subgroup in the clinical study report. Despite this, the EAG notes that:

- Given the proposed positioning of SVd as a 3L treatment in this appraisal, focusing on the 3L subgroup is justified;
- Baseline characteristics were reasonably balanced within the 3L subgroup;
- For the indirect treatment comparisons, the 3L+ subgroup was used, for which randomisation was stratified on, due to the available comparator data also being from 3L+ subgroups.

3.2.1.2 *Prior exposure to bortezomib in the 2L subgroup*

The EAG notes that most (65.2%) patients in the 2L subgroup of BOSTON had previous exposure to bortezomib, i.e., likely received a bortezomib containing regimen at 1L. However, the Company is positioning SVd at 2L specifically following treatment with daratumumab and lenalidomide at 1L. Such a population would therefore be bortezomib naïve when receiving SVd at 2L, in contrast to most BOSTON trial participants. While the EAG does not consider there to be strong evidence that prior exposure to bortezomib itself would be a meaningful treatment effect modifier, the EAG notes that to be included in BOSTON, a patient who has previously received bortezomib or another PI must have achieved the following criteria:

Prior treatment with bortezomib or other PI was allowed provided the following criteria were met:

- Best response achieved with prior bortezomib at any time was $\geq$ partial response (PR) and with last PI therapy (alone or in combination) was $\geq$ PR and;
- Participant did not discontinue bortezomib due to Grade $\geq$ 3 related toxicity; and
- Must have had at least 6-month PI-treatment free interval prior to Cycle 1 Day 1 of study treatment.

Hence, patients who did not respond to prior bortezomib therapy were excluded from the trial. Such an exclusion criterion would not be available for the incident population of patients who would be eligible for SVd at 2L in clinical practice, as they would not have received bortezomib previously. The EAG's clinical experts expected the proportion of PI-naïve patients who would not respond to a PI containing regimen at 1L to be less than 15%, although at 2L the proportion may be slightly higher. The EAG notes that this may bias the absolute PFS rates in BOSTON; however, as bortezomib was used in both the SVd and Vd arm of BOSTON, it is not expected to meaningfully affect the relative treatment effect.

3.2.2 Intervention

The dosing regimen of SVd in BOSTON has been outlined in Table 15 and matches that of the SmPC (CS Appendix C). The EAG notes that treatment with SVd “should be continued until disease progression or unacceptable toxicity” (CS Appendix C, page 2).

3.2.3 Comparators

The dosing regimen of Vd in BOSTON was Vd dosing regimen was detailed in Table 5 of the CS:

Cycles 1 through 8; 21-day cycles:

- Bortezomib at a dose of 1.3 mg/m² SC on Days 1, 4, 8, and 11 of each 21-day cycle;
- Dexamethasone as an oral 20 mg dose on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle

Cycles ≥9; 35-day cycles

- Bortezomib at a dose of 1.3 mg/m² SC on Days 1, 8, 15 and 22 of each 35-day cycle;
- Dexamethasone as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29 and 30 of each 35-day cycle

Patients in the Vd arm were treated until progression.

This contrasts with the SmPC for Vd in UK clinical practice,³⁰ where Vd recommended to be administered for a fixed period: specifically, bortezomib 1.3mg/m² is administered twice weekly for two weeks on days 1, 4, 8, and 11 in a 21 day treatment cycle, and dexamethasone is administered orally at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the bortezomib treatment cycle, and “patients

achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles.”³⁰

The EAG consider this difference between the dosing regimen of Vd in BOSTON versus in the SmPC to:

- Potentially underestimate the effectiveness of SVd relative to Vd, as patients in the Vd arm of BOSTON could be treated with Vd for a longer duration in BOSTON than in UK clinical practice.

However, the EAG’s clinical experts also stated that in UK clinical practice, Vd may be given once weekly, rather than twice weekly as in BOSTON and as outlined in the SmPC, and they anticipated this to be more effective than twice weekly dosing, i.e., the dosing regimen in BOSTON likely to underestimate the effectiveness of Vd, if at all. The EAG’s clinical experts stated once weekly dosing would likely lead to a reduction in the incidence of neuropathy, and ultimately lead to longer time on treatment, a higher cumulative dose due to fewer dropouts and fewer dose reductions compared to twice weekly dosing.

3.2.4 Outcomes

The outcomes reported in the BOSTON trial include all of the outcomes listed in the final scope issued by NICE,²³ namely PFS, OS, response rate, health-related quality of life (HRQoL) and the frequency of adverse events (AEs).

PFS and OS are the efficacy outcomes included in the cost-effectiveness modelling. In BOSTON, PFS was defined as the time from randomisation until the first of IRC-confirmed progressed disease, or death, with progressed disease being defined according to the International Myeloma Working Group (IMWG) response criteria.³¹

“Any one or more of the following criteria:

- Increase of 25% from lowest confirmed response value in one or more of the following criteria:
 - Serum M-protein (absolute increase must be ≥ 0.5 g/dL);
 - Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL;
 - Urine M-protein (absolute increase must be ≥ 200 mg/24 h);

- Appearance of a new lesion(s), $\geq 50\%$ increase from nadir in SPD of >1 lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion >1 cm in short axis;
- $\geq 50\%$ increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.”

The EAG notes that, while BOSTON was an open-labelled trial, the objective IMWG response criteria and use of a blinded IRC mitigates the potential for bias during PFS outcome assessment, which the EAG considers to be a low risk of bias.

For OS, the EAG notes the following points should be considered when interpreting the treatment effects of SVd relative to Vd within BOSTON, and relative to other comparators through indirect treatment comparisons:

- Treatment switching from Vd to SVd within BOSTON has the potential to bias OS results against SVd in BOSTON, and should be adjusted for with appropriate methods (discussed in Section 3.3.2.1);
- The choice of which subsequent therapies a patient receives after progression on SVd or Vd could bias OS estimates in favour of or against SVd in BOSTON (discussed in Section 3.3.2.1);
- Treatment switching, adjustment and subsequent therapy use must be considered when considering the transitivity assumption in any indirect treatment comparisons including BOSTON and comparator trials (discussed in Section 3.4).

As such, despite OS being an objective measure on the individual level, the EAG considers there to be the potential for bias in the analysis of OS when comparing SVd to key comparators.

For HRQoL, BOSTON measured the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy (EORTC QLQ-CIPN20) as a secondary endpoint, and the EORTC Quality of Life of Cancer Patients (EORTC QLQ-C30) and EuroQol 5-Dimension 5-Length Questionnaire (EQ-5D-5L) as exploratory endpoints.

3.3 Critique of the clinical effectiveness analysis and interpretation

The Company present results from both the primary analysis and updated analysis of BOSTON, and the efficacy and safety data from the updated analysis are used in the cost-effectiveness modelling. The primary analysis (18 February 2020) was the pre-specified primary analysis, and the updated

analysis (15 February 2021) was conducted at the request of The Committee for Medicinal Products for Human Use (CHMP).

The EAG agrees with the decision to use the updated analysis in the cost-effectiveness modelling as it provides more mature survival data. Due to the analysis being conducted following an external CHMP request, the EAG considers the decision to conduct the analysis, and the timing of the analysis, to be at low risk of bias.

3.3.1 Primary outcome: PFS as assessed by IRC

In the updated analysis, median PFS was greater in the SVd arm in the ITT population (13.24 months, 95% CI: 11.73 to 23.43), 2L subgroup (21.03 months, 95% CI: 13.24 to not estimable [NE]), and 3L subgroup (12.91 months, 95% CI: 9.23 to 25.86), compared to the Vd arm (ITT population: 9.46 months, 95% CI: 8.11 to 10.78; 2L subgroup: 10.68 months, 95% CI: 7.26 to 16.39; 3L subgroup: 9.43 months, 95% CI: 8.11 to 12.55). These data were consistent with the results of the primary analysis, which are reproduced in Table 19.

Table 19. PFS based on IRC assessment by treatment arm (BOSTON ITT population). Reproduced from CS Table 11.

	Primary analysis (18 February 2020)						Updated analysis (15 February 2021)					
	All		2L		3L		All		2L		3L	
	SVd	Vd	SVd	Vd	SVd	Vd	SVd	Vd	SVd	Vd	SVd	Vd
n	195	207	99	99	65	64	195	207	99	99	65	64
Median follow-up time, months (95% CI)	13.17 (10.64 to 15.34)	16.53 (14.39 to 17.71)	NR	NR	NR	NR	13.47 (10.64 to 24.87)	24.48 (21.16 to 29.17)	NR	NR	NR	NR
Median PFS, months (95% CI)	13.93 (11.73 to NE)	9.46 (8.11 to 10.78)	16.62 (13.24 to NE)	10.68 (7.26 to 16.39)	12.91 (9.23 to NE)	9.43 (8.11 to 12.55)	13.24 (11.73 to 23.43)	9.46 (8.11 to 10.78)	21.03 (13.24 to NE)	10.68 (7.26 to 16.39)	12.91 (9.23 to 25.86)	9.43 (8.11 to 12.55)
One-sided P-value ^a	0.007		0.032		0.101		0.006		0.014		0.121	
Hazard ratio ^{a,b,c} (95% CI)	0.702 (0.528 to 0.933)		0.661 (0.426 to 1.025)		0.717 (0.432 to 1.192)		0.710 (0.542 to 0.930)		0.621 (0.407 to 0.950)		0.750 (0.462 to 1.217)	

Abbreviations: CI, confidence interval; INV, investigator; IRC, independent review committee; ITT, intent-to-treat population; n, number of patients; NE, not estimable; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.

^a Calculated by Stratified Log-rank Test

^b Stratified for prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at study entry

^c Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties

Source: CS Table 11.

The EAG notes that:

- Across these analyses, SVd is associated with a PFS benefit over Vd;
- The 95% confidence intervals for the PFS hazard ratios (HRs) were wide in the ITT population (updated analysis HR: 0.71, 95% CI: 0.54 to 0.93), 2L subgroup (updated analysis HR: 0.62, 95% CI: 0.41 to 0.95) and 3L subgroups (updated analysis HR: 0.75, 95% CI: 0.46 to 1.22);
 - In the 3L subgroup, the estimated HR 95% CIs overlapped with 1 in both the primary and updated analyses. The width of the 3L subgroup 95% CI is not unexpected given the trial was only 80% powered to detect a PFS benefit of 4.1 months in the ITT population, but this uncertainty will propagate throughout the indirect treatment comparisons;
- In the updated analysis, the median follow-up time for the Vd arm was noticeably larger (24.5 months) than the median follow-up time for the SVd arm (13.5 months), which was less noticeable in the primary analysis (SVd: 13.2 months; Vd: 16.5 months);
 - Asymmetric follow-up times may be problematic if proportional hazards (PH) do not hold; however, the EAG notes the similarity of the HR estimates between the updated and primary analysis;
- PH did not appear to hold, suggesting that the HR and associated confidence intervals may be challenging to interpret but it is difficult to predict the direction or magnitude of the resulting bias.

The EAG also noted that the number of dropouts for reasons other than progressed disease and/or death were higher in the SVd arm than the Vd arm, with 43% of patients in the SVd arm discontinuing due to “Withdrawal by patient, adverse event, lost to follow-up or physician decision”, compared to 26% of patients in the Vd arm (Table 20).

Table 20. Reasons for discontinuation in BOSTON for the primary and updated analyses

Reason for discontinuation	Primary analysis		Updated analysis	
	SVd arm (N=195)	Vd arm (N=207)	SVd arm (N=195)	Vd arm (N=207)
Any discontinuation	158 (81%)	168 (81%)	174 (89%)	188 (91%)
Progressed disease	67 (34%)	107 (52%)	76 (39%)	118 (57%)
Death	12 (6%)	12 (6%)	14 (7%)	14 (7%)
Non-compliance	0 (0%)	0 (0%)	1 (1%)	2 (1%)

Withdrawal by patient, adverse event, lost to follow-up or physician decision	79 (41%)	49 (24%)	83 (43%)	54 (26%)
Abbreviations: CS, company submission; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone. Source: Figure 2 and Figure 3, CS Appendix D				

The EAG considered it plausible that these dropouts were not at random, and instead are likely related to the toxicity of selinexor, which likely constitute informative censoring in the Company analyses. The EAG notes that the Company performed a range of sensitivity analyses around discontinuations in the CSR. Specifically:

- when the primary analysis was repeated but patients were not censored at discontinuation, a [REDACTED]
[REDACTED]
[REDACTED] (CSR page 87)
and;
- When discontinuation was treated as PFS event then: [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] (CSR page 88).

The EAG considers the first analysis to be the most meaningful sensitivity analysis, and are re-assured that magnitude of the PFS benefit in this sensitivity analysis was similar to the primary analysis. The EAG interpret these data as indicating that: i) SVd offers a PFS benefit over Vd in BOSTON, but that, ii) due to its adverse event profile, patients are more likely to discontinue SVd earlier than Vd.

In the CSR, the Company also noted that: [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] (CSR page 88).

Overall, the EAG considers the analysis of PFS to provide good evidence of a PFS benefit for people with RR-MM for SVd compared Vd at the dosing regimens used in BOSTON, but notes uncertainty in the magnitude of this benefit, especially for the smaller 3L subgroup.

3.3.2 *Secondary outcomes*

3.3.2.1 *OS*

In the CS, the Company presented OS results adjusted for 77 (37%) of patients crossing over from the Vd arm following progressed disease to receive either SVd or Sd. In the updated ITT analysis, median OS (95% confidence interval) was 36.67 months (30.19 months to not estimable) in the SVd arm and 32.76 months (25.11 months to not estimable) in the Vd arm, a difference that was not statistically significant (HR: 0.84, 95% CI: 0.60 to 1.17; $p = 0.15$), although the EAG notes that BOSTON was not powered to detect a pre-specified difference in OS. Adjusted OS estimates by line of therapy are provided in Table 21. The EAG notes that, while OS estimates numerically favoured SVd in each line of therapy analysis, no analysis was statistically significant – although the EAG notes the potential violation of PH makes the p values and HRs of the results inaccurate to an unknown degree.

Table 21. OS by treatment arm (BOSTON ITT population). Reproduced from CS Table 13.

	Primary analysis (18 th February 2020)						Updated analysis (15 th February 2021)					
	All		2L		3L		All		2L		3L	
	SVd	Vd	SVd	Vd	SVd	Vd	SVd	Vd	SVd	Vd	SVd	Vd
n	195	207	99	99	65	64	195	207	99	99	65	64
Median follow-up time, months (95% CI)	13.17 (10.64 to 15.34)	16.53 (14.39 to 17.71)	NR	NR	NR	NR	13.47 (10.64 to 24.87)	24.48 (21.16 to 29.17)	NR	NR	NR	NR
Median OS, months (95% CI)	NE (NE, NE)	24.97 (22.48, NE)	NE (NE, NE)	24.97 (23.49, NE)	NE (21.39, NE)	NE (19.06, NE)	36.67 (30.19, NE)	32.76 (25.11, NE)	NE (26.68, NE)	32.76 (24.97, NE)	36.67 (31.74, NE)	29.01 (21.80 (NE)
One-sided P-value ^a	0.132		0.155		0.142		0.147		0.344		0.066	
Hazard ratio ^{a,b,c} (95% CI)	0.805 (0.549 to 1.179)		0.749 (0.427 to 1.311)		0.676 (0.329 to 1.388)		0.838 (0.603 to 1.166)		0.909 (0.570 to 1.450)		0.612 (0.321 to 1.166)	

Abbreviations: CI, confidence interval; INV, investigator; IRC, independent review committee; ITT, intent-to-treat population; n, number of patients; NE, not estimable; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.

^a OS adjusted for crossover

^b Calculated by Stratified Log-rank Test

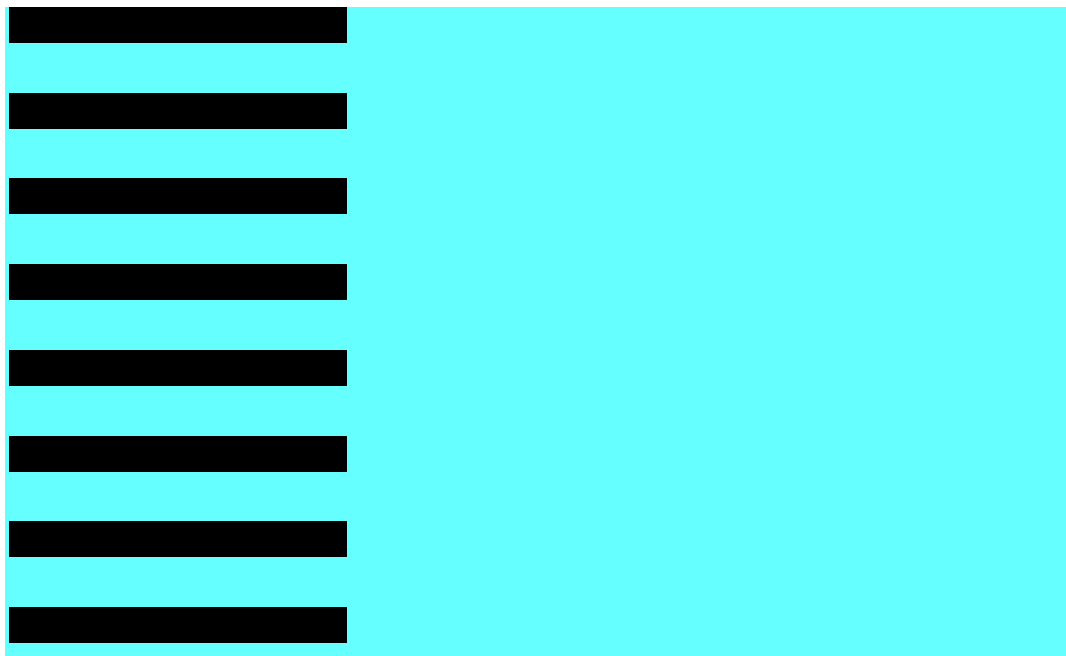
^c Stratified for prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at screening

^d Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties

Source: CS Table 13.

The EAG considers it appropriate to adjust for crossover in the analysis for OS, but asked for further clarification from the Company regarding the selection of the adjustment criteria. The EAG noted that:

- In the CS, the Company presented the adjusted OS results following a two-stage estimation method with re-censoring, which formed the Company's base case OS estimates. Unadjusted OS and adjusted OS without re-censoring were explored as scenario analyses;
- The [REDACTED] model used to generate counterfactual survival times in the two-stage estimation procedure adjusted for the following prognostic characteristics at the time of progression:



The EAG considered this to be a reasonable set of prognostics characteristics to adjust for in order to minimise the likelihood of residual confounding. The EAG notes it has assumed the same prognostic characteristics were adjusted for in the 2L and 3L/3L+ subgroup analyses as were reported for the ITT population in the CSR.;

- In the BOSTON statistical analysis plan (SAP), it was stated that [REDACTED]
[REDACTED]
[REDACTED]
- In the BOSTON CSR, an adjusted HR was also presented [REDACTED]
[REDACTED]

The EAG requested further details of the alternative methods explored for OS adjustment from the Company at Clarification, but the Company only provided adjusted Kaplan-Meier curves using the two-stage estimation procedure with and without re-censoring. The EAG therefore considers the choice of adjustment procedure to be at risk of bias, and the EAG was unable to assess the consistency or quality of the results of each method considered. No details on whether an [REDACTED] [REDACTED] was implemented were provided, and the only results provided using [REDACTED] was a [REDACTED], which, in light of potential non-PH, is difficult to interpret. The EAG notes that OS data using two-stage estimation method was supplied during regulatory approval for the EMA, which concluded that “no evidence of detrimental effect on survival has been observed [for patients treated with SVd]”.³²

While the EAG considers the methods used to adjust for crossover in BOSTON to be appropriate, the EAG considers the relationship between crossover and OS to be complicated, because:

- Patients crossing over from Vd to SVd or Sd have relapsed following Vd treatment, as such, the efficacy of SVd for these patients is likely diminished as they will be Vd exposed or refractory;
 - Accordingly, PFS2 was notably shorter for patients crossing over to SVd or Sd from Vd than those who did not crossover, which is opposite to the direction of adjustment for overall survival;
 - The decision to crossover onto another Vd containing regimen will likely affect future treatment choices and sequencing, which may affect OS.

In response to Clarification Question A4, the Company provided the classes of subsequent therapies patients received and PFS2 by arm in BOSTON. The EAG notes some concerns about the quality of the data provided in Table 2 of the Company Response to Question A4, as the stated sample sizes do not correspond to the number of individuals reported in the cells of the Table. Nevertheless, the EAG notes that while subsequent therapy use appears reasonably balanced in the ITT population, the proportion of patients receiving subsequent PI-based regimens [REDACTED]

3.3.2.2 Response rates

Although not included in the cost-effectiveness modelling, response rates were included in the final scope issued by NICE. The overall response rate was higher in the SVd arm than the Vd arm in the: ITT analysis (Table 12, CS: SVd overall response rate: 76.9%; Vd overall response rate: 63.3%); 2L analysis (SVd overall response rate: 80.8%; Vd overall response rate: 66.7%); and 3L analysis (SVd overall response rate: 76.9%; Vd overall response rate: 60.9%). The EAG consider these data to be in-line with the primary PFS outcome reported in BOSTON.

3.3.2.3 Time to discontinuation

Median time to discontinuation (TTD) was presented in Section B2.6.3.2 of the CS, and was similar between SVd and Vd in the ITT, 2L and 3L analyses of the primary and updated analysis (CS Table 14). The shape of the SVd and Vd Kaplan-Meier curves were closely matched for each analysis (CS Figure 10).

3.3.3 Efficacy Subgroup Analyses

CS Appendix E presents subgroup analyses for two exploratory subgroups of potential interest:

- PI-naïve patients (also presented in the CSR); and
- Lenalidomide-refractory patients (not presented in the CSR).

These subgroup analyses are relevant for both the 2L and 3L positioning of SVd:

- At 2L, the company is positioning SVd for patients who have received lenalidomide and daratumumab at 1L. Therefore, following the current NICE recommended pathway, SCT-ineligible patients will be PI naïve and lenalidomide exposed, and likely refractory, at 2L.
- At 3L, nearly all patients will be both PI-experienced and lenalidomide exposed or refractory.

In the BOSTON ITT population, 53 (27.2%) patients in the SVd arm and 53 (25.6%) patients in the Vd arm were lenalidomide-refractory, and 47 (24.1%) patients in the SVd arm and 48 (24.6%) patients in the Vd arm were PI-naïve. Most PI naïve patients were from the 2L subgroup of BOSTON, whereas lenalidomide-refractory patients were relatively more common in the 4L subgroup of BOSTON, as expected.

Median PFS for both subgroups are reproduced below. Median PFS was greater in the SVd subgroup than Vd subgroup for both analyses:

- Lenalidomide-refractory subgroup median PFS:
 - SVd 10.2 months (95% CI: 5.8 months to not estimable [NE])
 - Vd 7.1 months (95% CI: 3.5 months to 9.8 months)
- PI-naïve subgroup median PFS:
 - SVd 29.5 months (95% CI: 27.5 months to NE)
 - Vd 9.7 months (95% CI: 8.4 months to 23.7 months)

For the lenalidomide-refractory subgroup, median OS was also reported, which again was greater in the SVd subgroup than the Vd subgroup:

- Lenalidomide-refractory subgroup median OS:
 - SVd 26.7 months (95% CI: 16.9 months to NE)
 - Vd 18.6 months (95% CI: 13.9 months to 29.0 months)

It was not reported whether and how the lenalidomide-refractory subgroup OS analysis was adjusted for crossover.

The EAG considers it reassuring that the results of these relevant subgroup analyses are in-line with the overall ITT, 2L and 3L analyses. The EAG notes that the magnitude of the difference in median PFS in the PI-naïve subgroup is around 10 months greater than that observed in the ITT, 2L and 3L analyses. However, the EAG considers the interpretation of these results to be complicated because of:

- The majority of censoring events happening within 8 months of randomisation;
- The small sample size of the subgroups;
- The similarity of the overall response rates (ORR) between the SVd (ORR: 76.6%) and Vs (ORR: 70.8%) arms, although the $\geq$ complete response (CR) response rate was higher in SVd ($\geq$ CR 24.%) than the Vd arm ($\geq$ CR 14.6%);
- The lack of a plausible reason why prior PI-experience would modify the relative treatment effect of SVd compared to Vd, especially considering the Vd regimen provided longer dosing of the PI (bortezomib) than the SVd regimen.

3.3.4 Health-Related Quality of life

The CS reported on three measures of health-related quality of life from BOSTON. The European Organisation for Research and Treatment of Cancer (EORTC) quality of life (QLQ) questionnaire to assess chemotherapy-induced peripheral neuropathy (EORTC QLQ-CIPN20) was a secondary endpoint of the trial. As later outlined in Section 3.3.5, peripheral neuropathy is a very common adverse event of bortezomib therapy,³³ and as bortezomib is given less frequently in SVd than in Vd, a reduction in bortezomib-related side effects may be expected in the SVd arm of BOSTON. In Table 15 of the CS, the Company reported a significant reduction in the rate of worsening in one of three of the EORTC QLQ-CIPN20 scales reported in the ITT population.

In Table 16 and Table 17 of the CS, the Company reported the results of the EORTC QLQ-C30 and EQ-5D-5L, respectively. Both the EORTC QLQ-C30 and EQ-5D-5L were exploratory endpoints in BOSTON with little difference between the SVd and Vd arms: a small improvement was observed in EORTC QLQ-C30 and a small worsening of EQ-5D-5L pre and post treatment for both arms.

3.3.5 Safety

The Company reported adverse events from BOSTON from the full safety population — all patients who had received at least one dose of the study treatment — from the updated analysis only. The EAG considers this reasonable, and considers that, given the greater toxicity profile of SVd relative to Vd, including the full population that also includes a number of patients at 4L will, if anything, lead to less favourable safety results than the separate 2L or 3L subgroups. The Company, in contrast, states that, “there is no reason to believe safety data would differ by prior line of therapy”, but only provides a general reference to the BOSTON CSR to support this.

The frequency of treatment emergent adverse events (TEAEs) in BOSTON is reproduced in Table 22. Nearly all patients had at least one TEAE (SVd arm: 99.5%; Vd arm: 97.1%), however the frequency of Grade 3 or 4, Grade 4 and serious TEAEs was substantially greater in the SVd arm than Vd arm (Grade 3 or 4, SVd: 78.5%, Vd: 56.4%; Grade 4, SVd: 19.0%, Vd: 10.8%; Serious TEAEs, SVd: 54.4%, Vd 38.7%). The Company also highlighted that the, “overall incidence of Grade ≥ 2 peripheral neuropathy events was statistically significantly lower in the SVd arm (21.5%) as compared to the Vd arm (35.8%) ($P=0.0008$)”, and that peripheral neuropathy was the most frequent TEAE that led to treatment discontinuation in both arms. Peripheral neuropathy is reported as a very common adverse event of bortezomib therapy,³³ and as such the lower frequency of peripheral neuropathy in

the SVd arm of BOSTON is likely due to the lower frequency of bortezomib dosing in the SVd arm than the Vd arm.

Table 22. Frequency of treatment emergent adverse events (TEAEs) and peripheral neuropathy in the safety population of BOSTON (Reproduced from CS Table 19).

	All	
	SVd arm	Vd arm
n	195	204
Patients with at least one, n (%)		
TEAE	194 (99.5)	198 (97.1)
Grade 3/ 4 TEAE ^a	153 (78.5)	115 (56.4)
Grade 4 TEAE ^a	37 (19.0)	22 (10.8)
Serious TEAE	106 (54.4)	79 (38.7)
TEAE leading to dose modification ^b	173 (88.7)	156 (76.5)
TEAE leading to dose reduction	141 (72.3)	106 (52.0)
TEAE leading to dose interruption	167 (85.6)	139 (68.1)
TEAE leading to study discontinuation	41 (21.0)	34 (16.7)
TEAE leading to death	14 (7.2)	13 (6.4)
Incidence of Grade ≥ 2 peripheral neuropathy^d, n (%)		
Patients with at least one Grade ≥ 2	42 (21.5)	73 (35.8)
Abbreviations: AE, adverse event; NA, not applicable; NR, not reported; R-ISS, revised international staging system; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone; TEAE, treatment-emergent adverse event; TRAE treatment-related adverse event		
Data cut-off date: 15 th February 2021		
Note: For patients who cross over, adverse events that occurred after the crossover are not included.		
^a Based on maximum severity grade of each patient		
^b The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption as the same patient could fall into more than one of these categories		
^c AEs were considered treatment-related if selinexor-related and/ or bortezomib-related, and/ or dexamethasone-related		
^d Incidence of any Grade ≥ 2 peripheral neuropathy were an AE of interest (key secondary safety endpoint)		
Source: CS Table 19		

The rates of individual adverse events included in the economic model, TEAEs of Grade 3+ are reported in Table 23. In BOSTON, the toxicity profile of SVd was notably more severe than Vd, with over a 5% greater proportion in absolute terms of patients reporting the followed Grade 3+ AEs in the SVd arm than the Vd arm: anaemia; asthenia; cataract; diarrhoea; fatigue; nausea; neutropenia; and thrombocytopenia.

Table 23. Treatment-emergent Grade 3 or higher AEs included in the economic model (BOSTON safety population, reproduced from CS Table 20 and CSR Table 14.3.1.1.2.4)

	SVd arm	Vd arm	Total
n	195	204	399
Patients with at least one treatment emergent Grade 3+ AE^a, n (%)	167 (85.6)	128 (62.7)	295 (73.9)
Anaemia	32 (16.4)	21 (10.3)	53 (13.3)
Asthenia	16 (8.2)	9 (4.4)	25 (6.3)
Cataract	22 (11.3)	4 (2.0)	26 (6.5)
Diarrhoea	13 (6.7)	1 (0.5)	14 (3.5)
Fatigue	26 (13.3)	2 (1.0)	28 (7.0)
Hypophosphataemia	11 (5.6)	3 (1.5)	14 (3.5)
Nausea	15 (7.7)	0 (0.0)	15 (3.8)
Neutropenia	18 (9.2)	7 (3.4)	25 (6.3)
Peripheral neuropathy	9 (4.6)	18 (8.8)	27 (6.8)
Pneumonia	28 (14.4)	25 (12.3)	53 (13.3)
Thrombocytopenia	79 (40.5)	36 (17.6)	115 (28.8)

Abbreviations: AE, adverse event; CMQ, customised MedDRA query; MedDRA, medical dictionary for regulatory activities; SVd, selinexor + bortezomib + dexamethasone; Sd, selinexor + dexamethasone; Vd, bortezomib plus dexamethasone.

Updated data cut-off date: 15th February 2021

^a MedDRA preferred terms

^b Includes multiple preferred terms for pneumonia CMQ

Source: CS Table 20 and CSR Table 14.3.1.1.2.4.³⁴

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 ITC methods

Section 2.9 of the CS outlines the Company's indirect treatment comparisons (ITCs) for SVd versus Kd (2L) and IxaRd and PanoVd (3L) for PFS and OS. The Company performed network meta-analyses (NMAs) from a global perspective with a wide range of comparators. Comparator trials were identified for inclusion in the ITCs based on the global clinical SLR critiqued in Section 3.1. The EAG considered this SLR to capture all trials relevant to the decision problem. The ITC results for the subset of the comparators deemed relevant to the current appraisal were presented in the CS, with the full results reported in an ITC report. Due to limited reporting of 3L data in comparator trials, the Company's NMA for 3L included data from 3L+ populations in clinical trials, including BOSTON, which the EAG deemed appropriate. Following a request by the EAG, the Company also performed an unanchored matching adjusted indirect comparison (MAIC) between IxaRd from TOURMALINE-MM1 and SVd and Vd from BOSTON in the 3L+ setting.

The Company's general NMA method was to perform a Bayesian NMA using Markov chain Monte Carlo (MCMC) simulation in WinBUGS. A burn-in of 50,000 iterations was used and 20,000 further samples were retained for analysis. Results were presented as median HRs and 95% credible intervals. Both fixed and random effects were conducted, but random effects models were preferred due to the *a priori* recognition of significant heterogeneity in the studies entering the network. The EAG reproduced the Company OS NMAs to calculate estimates of statistical fit of both the fixed effect and random effects NMA, which produced similar deviance information criteria. The EAG agrees with the Company that the random effects models are appropriate. Vague priors were used for all parameters than for the between-study standard deviation, for which an informative half-normal distribution, $HN(0, 0.32^2)$, was used.

The Company also performed sensitivity analyses using first-order random intercept model fractional polynomial models, but noted due to the limited number of studies per treatment comparisons that the uncertainty around the resulting HRs was large. The EAG considers the rationale for exploring fractional polynomials – that PH do not hold in many trials – to be appropriate, but accepts the Company's concern regarding the large amount of uncertainty in the results due to only one or two studies being available for each treatment comparison, and that the resulting extrapolated survival estimates were “[REDACTED]”.³⁵ The EAG further notes that the EAG's concerns regarding the suitability of the evidence network for the constant-HR NMAs

(Section 3.4.3) apply equally to the fractional-polynomial models employed. The Company also conducted NMAs for subgroups of patients with no prior exposure to PIs, prior exposure to lenalidomide and lenalidomide-refractory patients. The results of these analyses were not presented in the CS, but were reported in the ITC report.³⁵ In-line with the EAG's comments on the BOSTON trial subgroup analyses in Section 3.3.3, the EAG considers that while these subgroup analyses to be relevant, but that it is appropriate to focus on the overall 2L and 3L+ networks.

The EAG presents ITCs results for each comparator against both Vd and SVd in the following sections. This is because the EAG's preferred economic modelling approach is to use the Vd PFS and OS curves as the baseline throughout the economic analyses using independently fitted curves, as the PH assumption was potentially violated throughout BOSTON analyses.

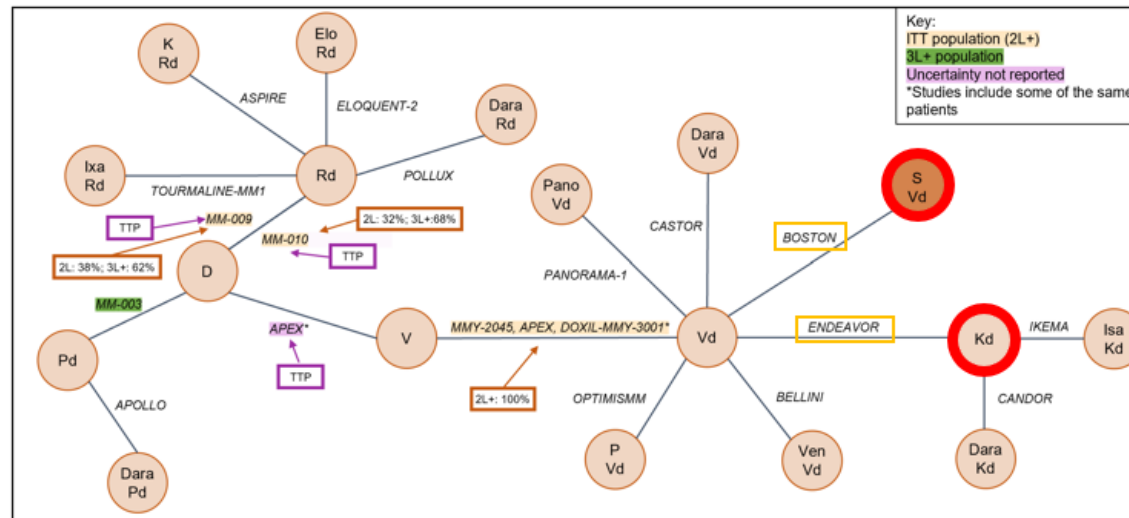
3.4.2 2L NMA

3.4.2.1 *Comparison of included studies*

The network diagram of the Company's 2L NMA is presented in Figure 4. The EAG notes that the network simplifies when considering either the Company's preferred comparator (Kd) or the EAG's preferred comparators (Kd and Vd). The simplified network consists of two trials: BOSTON (SVd) and ENDEAVOR (Vd). The EAG presents this simplified network in Figure 5.

Figure 4. Company's network of evidence for the 2L NMA, conducted with a global perspective (Reproduced from CS Figure 11)

PFS, 2L



Legend:

○ Relevant intervention

Relevant connection

OS, 2L

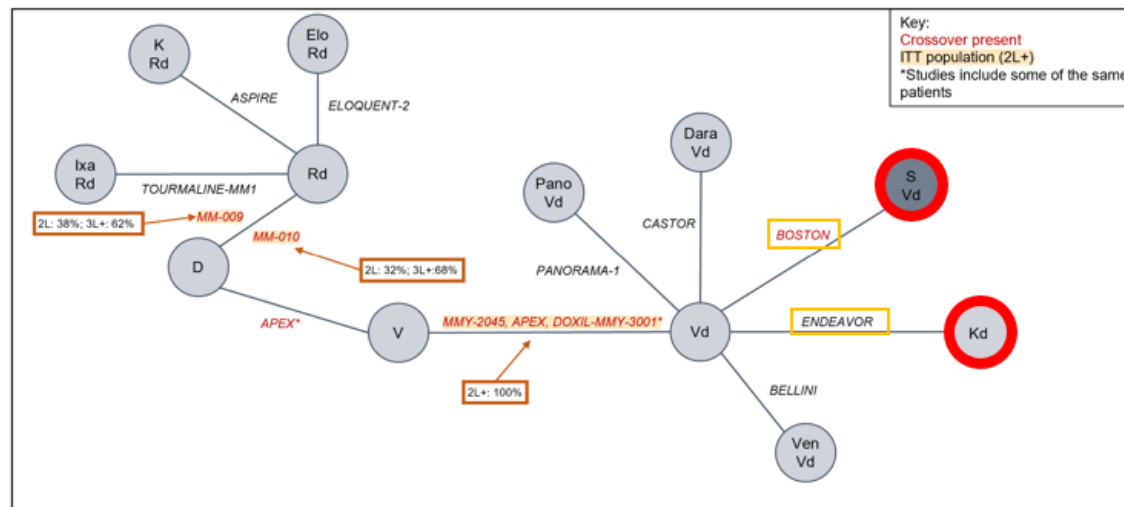
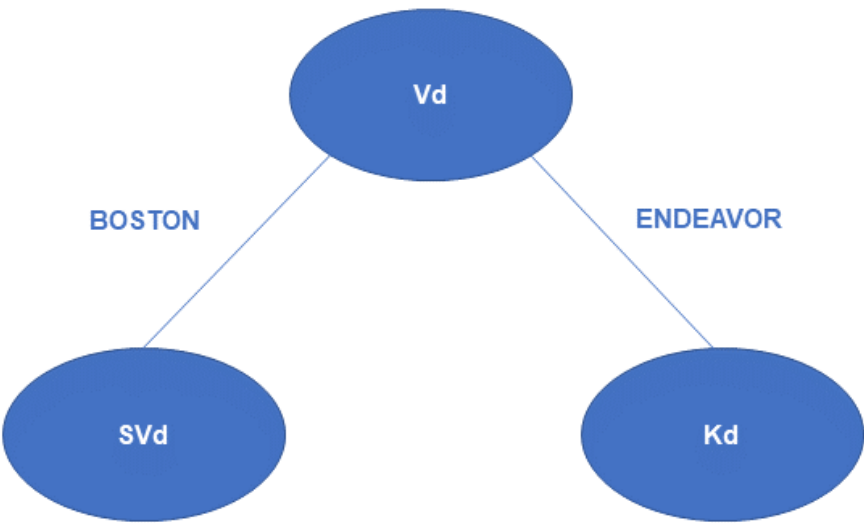


Figure 5. EAG’s simplified network of trials for the 2L population



ENDEAVOR was an international Phase 3 RCT of Kd versus Vd in RR-MM patients who had previously received 1-3 lines of anti-MM therapy. A comparison of the study design of BOSTON and ENDEAVOR is presented in Table 24. The EAG considers BOSTON and ENDEAVOR to have similar designs, but noted three sources of substantial heterogeneity between the trials:

- The study start date of ENDEAVOR (June 2012) was 5 years prior to BOSTON (May 2017);
- Crossover following disease progression was permitted in BOSTON, but not in ENDEAVOR;
- After Cycle 8 (Week 24), bortezomib dosing frequency was reduced in the BOSTON Vd arm from 4 doses every 3 weeks to 4 doses every 5 weeks. In ENDEAVOR, bortezomib dosing was 4 doses every 3 weeks until progression.

Table 24. Comparison of the study design of BOSTON and ENDEAVOR trials in the Company 2L NMA

	BOSTON	ENDEAVOR
Study design	Phase 3 open-label (crossover permitted)	Phase 3 open-label
Study sites	165 sites; 21 countries	241 sites across 27 countries
Study start date	May 2017	June 2012
Identified data cuts	February 2020 February 2021	November 2014 January 2017 July 2017 August 2017

N participants randomised	402; 1 prior = 198	929; 1 prior = 464
Stratification factors	Prior PI therapies (yes vs. no), number of prior lines of treatment (1 vs. 2 or more), and R-ISS stage (III vs. I-II) at study entry	Previous PI therapy (yes vs. no), previous lines of treatment (1 vs. 2/3), ISS stage (I vs II–III), and planned route of bortezomib administration (IV or SC)
Intervention	SVd	Kd
Comparator	Vd	Vd
Vd dosing	Bortezomib - Cycles 1 - 8 (3-week [21-day] cycle) 1.3 mg/m² SC on Days 1, 4, 8, and 11; - Cycles ≥ 9 (5-week [35-day] cycle) 1.3 mg/m² SC on Days 1, 8, 15, and 22. Dexamethasone - Cycles 1 - 8 (3-week [21-day] cycle) 20-mg oral on Days 1, 2, 4, 5, 8, 9, 11, and 12. - Cycles ≥ 9 (5-week [35-day] cycle) oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30.	Bortezomib 21-day cycle bortezomib (1.3 mg/m ² ; 3–5 s IV bolus or SC) on days 1, 4, 8, and 11; Dexamethasone 21-day cycle 20mg oral or IV on days 1, 2, 4, 5, 8, 9, 11, and 12.
Crossover	Permitted at the point of IRC-confirmed objective PD per IMWG criteria, for patients in the Vd arm	Not permitted
Inclusion criteria (prior treatment)	1-3 prior lines	1-3 prior treatments
Inclusion criteria (response to prior PI)	≥ PR to bortezomib and last PI; - At least 6-month PI-treatment free interval prior to Cycle 1 Day 1	≥ PR to bortezomib; - At least 6-month bortezomib-treatment free interval until first study treatment
Primary outcome	PFS by IRC	PFS by IRC
Other endpoints	ORR; VGPR; CR; sCR; MRD-negative; OS; DOR; TTNT; TTR; PFS2; PN; HRQoL; safety	OS; ORR; DOR; PN; safety
PFS assessment criteria	IRC-confirmed, per IMWG response criteria	IRC-confirmed, per IMWG response criteria

Abbreviations: Bort, bortezomib; CR, complete response; Dex, dexamethasone; DOR, duration of response; HRQoL, health-related quality of life; IMWG, International Myeloma Working Group; INV, investigator; IRAC, independent response adjudication committee); IRC, independent response committee; ISS, international staging system; IV, intravenously; IxaRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; MRD, minimal residual disease; NMA, network meta-analysis; NR, not reported; ORR, overall response rate; OS, overall survival; PanoVd, panobinostat + bortezomib + dexamethasone; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PN, peripheral neuropathy; Rd, lenalidomide + dexamethasone; R-ISS, revised international staging system; SC,

subcutaneously; sCR, stringent complete response; SVd, selinexor + bortezomib + dexamethasone; TTNT, time to next treatment; TTP, time to progression; TTR, time to response; VCD, bortezomib + cyclophosphamide + dexamethasone, bortezomib + dexamethasone; VDR, bortezomib + lenalidomide + dexamethasone; VGPR, very good partial response.

A comparison of the baseline characteristics of the 2L subgroups of BOSTON and ENDEAVOR are provided in Table 25. Where data were not reported for the ENDEAVOR 2L subgroup, the EAG has extracted data from the ENDEAVOR ITT population using the primary publication and clinical trial registry record.^{22, 36} The EAG notes that the ENDEAVOR 2L population appears to have less severe disease than the BOSTON 2L population, being on average younger, with a lower baseline ECOG performance status, lower R-ISS staging and fewer high risk cytogenetic abnormalities. In addition, the frequency of SCT was lower in the ENDEAVOR ITT population than the BOSTON 2L population, and patients were less exposed to bortezomib.

Table 25. A comparison of the baseline characteristics of the 2L subgroup from BOSTON and 2L subgroup and ITT population of ENDEAVOR

Baseline characteristic		BOSTON 2L		ENDEAVOR 2L		ENDEAVOR ITT	
		SVd arm	Vd arm	Kd	Vd	Kd	Vd
		99	99	232	232	464	465
Age, years	Median (range)	67 (45 to 87)	69 (44 to 90)	66 (36 to 89)	63.5 (39 to 88)	NA	NA
Gender, n (%)	Male	55 (55.6)	53 (53.5)	NR	NR	240 (51.7)	229 (49.2)
Race, n (%)	White	83 (83.8)	81 (81.8)	NR	NR	34 (87.5)	353 (75.9)
	Black- Af/Am	2 (2.0)	2 (2.0)	NR	NR	8 (1.7)	9 (1.9)
	Asian	10 (10.1)	10 (10.1)	NR	NR	56 (12.1)	57 (12.3)
	Other	0 (0.0)	0 (0.0)	NR	NR	2 (0.4)	1 (0.2)
	Missing	4 (4.0)	6 (6.1)	NR	NR	50 (10.8)	45 (9.7)
Baseline ECOG performance	0	39 (39.4)	38 (38.4)	110 (47.4)	131 (56.5)	NA	NA
	1	52 (52.5)	55 (55.6)	104 (44.8)	92 (39.7)	NA	NA
	2	8 (8.1)	6 (6.1)	18 (7.8)	9 (3.9)	NA	NA
Time since initial diagnosis (years)	Median (range)	2.9 (0.4 to 23.0)	2.8 (0.4 to 18.4)	NR	NR	NR	NR
R-ISS stage at study entry	R-I	33 (33.3)	23 (23.2)	109 (47.0)	115 (49.6)	NA	NA
	R-II	52 (52.5)	62 (62.6)	68 (29.3)	62 (26.7)	NA	NA
	R-III	9 (9.1)	6 (6.1)	55 (23.7)	55 (23.7)	NA	NA
	Missing	5 (5.1)	8 (8.1)	0	0	NA	NA
Baseline creatinine	<30	2 (2.0)	4 (4.0)	14 (6.0)	17 (7.3)	NA	NA
	30-60	27 (27.3)	31 (31.3)	26 (11.2)	27 (11.6)	NA	NA

clearance (mL/ min)	>60	70 (70.7)	64 (64.7)	192 (82.8)	188 (81.0)	NA	NA
Cytogenetic abnormalities, n (%)	del(17p)/p53	12 (12.1)	8 (8.1)	NR	NR	NR	NR
	t(14;16)	4 (4.0)	3 (3.0)	NR	NR	NR	NR
	t(4;14)	10 (10.1)	15 (15.2)	NR	NR	NR	NR
	1q21	41 (41.4)	36 (36.4)	NR	NR	NR	NR
	All high-risk cytogenetic	50 (50.5)	48 (48.5)	44 (19.0)	53 (22.8)	NA	NA
Prior SCT, n (%)		39 (39.4)	23 (23.2)	NR	NR	266 (57.3)	272 (58.6)
Exposure to prior anti-MM drug classes, n (%)	PIs	70 (70.7)	74 (74.8)	NR	NR	NR*	NR*
	IMiDs	51 (51.5)	57 (57.6)	NR	NR	NR*	NR*
Exposure to prior anti-MM drugs, n (%)	Bortezomib	64 (64.7)	65 (65.7)	96 (41.4)	101 (43.5)	NR*	NR*
	Carfilzomib	7 (7.1)	8 (8.1)	NR	NR	NR*	NR*
	Ixazomib	1 (1.0)	1 (1.0)	NR	NR	NR*	NR*
	Daratumumab	3 (3.0)	3 (3.0)	NR	NR	NR*	NR*
	Lenalidomide	23 (23.2)	20 (20.2)	51 (22)	47 (20.3)	NR*	NR*
	Pomalidomide	0 (0.0)	0 (0.0)	NR	NR	NR*	NR*
*Not extracted as ITT population unlikely to reflect 2L subgroup for prior drug exposure. Abbreviations: Af/Am, African American; ECOG, Eastern Cooperative Oncology Group; IxaRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; PanoVd, panobinostat + bortezomib + dexamethasone; Rd, lenalidomide + dexamethasone; R-ISS, revised international staging system; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone							

Outcome data entering the NMA for BOSTON and ENDEAVOR are presented in Table 26. The EAG notes, that, despite HRs calculated based on a two-stage estimation procedure without re-censoring being presented throughout the CS, the Company used the slightly more liberal HRs calculated with re-censoring in the ITC analyses. The EAG does not consider there to be a strong reason to prefer the estimate with or without re-censoring, and so notes this is a liberal assumption from the Company.

Table 26. Outcome data for BOSTON and ENDEAVOR in the 2L NMA.

	BOSTON		ENDEAVOR	
	SVd	Vd	Kd	Vd
Population	2L only		2L only	
n	99	99	232	232
Median follow-up time, months (95% CI) - latest datacut	28.71*	28.65*	44.3*	43.7*
	(27.24 to 29.90)	(27.63 to 29.67)		
Median PFS, months (95% CI)	21.03	10.68	22.2	10.1
	(13.24 to NE)	(7.26 to 16.39)		

Hazard ratio PFS, (95% CI)	0.621 (0.407 to 0.950)		0.447 (0.330 to 0.606)	
Median OS, unadjusted for crossover, months (95% CI)	NE		51.3	43.7
	(26.68 to NE)			
Hazard ratio OS, unadjusted for crossover (95% CI)			0.771 (0.583 to 1.018)	
Median OS, adjusted for crossover, months (95% CI)	NE	32.76	NA	NA
	(26.68 to NE)	(24.97 to NE)		
Hazard ratio OS, adjusted for crossover without re-censoring (95% CI)	0.909 (0.570 to 1.450)		NA	
Hazard ratio OS, adjusted for crossover with re-censoring (95% CI)	0.870 (NR)		NA	
N (%) of participants crossing over	NA	30 (30.3%)	NA	NA
Method of adjustment for crossover	Two-stage method	Two-stage method	NA	NA
*Based on the ITT population				
Abbreviations: CI, confidence interval; Kd, carfilzomib and dexamethasone; NE, not estimable; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone; 2L, second line.				

3.4.2.2 2L NMA Results

In the Company's preferred random effects NMA, Kd was numerically superior to SVd for both PFS (HR=0.73, 95% CrI: 0.31 to 1.67) and OS (HR=0.89, 95% CrI: 0.32 to 2.45). Kd was superior to Vd for both PFS (HR=0.45, 95% CrI: 0.26 to 0.80) and numerically superior for OS (HR=0.77, 95% CrI: 0.39 to 1.53). As expected, the Company random effects NMA values capture the ENDEAVOR trial reported differences between Kd and Vd (Table 26), albeit with wider uncertainty intervals due to the use of a random effects model and uncertainty propagating throughout the network. Using the WinBUGS files provided, the EAG was able to closely replicate the Company's random effects model. In the NMA, all 95% credible intervals were wide, reflecting significant uncertainty in the magnitude and direction of any differences.

3.4.2.3 EAG critique

The EAG considers the Company's NMA to be appropriate to compare Kd with SVd. While the Company's 2L network was complex, the comparison between Kd and SVd approximates a Bucher ITC. The EAG noted that the ENDEAVOR 2L population had less severe baseline characteristics than the BOSTON 2L population. As the Kd versus SVd comparison is anchored through a common control arm, Vd, imbalances in treatment effect modifiers between trials risks introducing bias into the analysis. The EAG notes that two specific baseline characteristics have been raised as potential treatment effect modifiers:^{37, 38}

- Line of therapy:
 - The potential treatment modifying effect of line of therapy is controlled for in the Company analysis by using the 2L subgroup from both trials, which was a factor for stratified randomisation in both trials;
- Prior treatment exposure and refractory-status:
 - Prior exposure to lenalidomide was balanced between BOSTON and ENDEAVOR, and prior exposure to bortezomib was slightly lower in ENDEAVOR than BOSTON. However, as both arms of BOSTON and both arms of ENDEAVOR included a PI, and eligibility criteria included prior response to a PI, prior PI exposure is not expected to meaningfully modify the relative treatment effect in each trial.

The EAG highlights a recent systematic literature review and NMA assessing the evidence for effect modification by refractory status and number of treatment lines for treatments for RR-MM.³⁷ The SLR/NMA found very weak evidence for treatment effect modification, and noted that the magnitude of any effect modification was likely small enough that conclusions of ITCs would be relatively unaffected. Nevertheless, the authors noted, and the EAG agrees, that the studies that were examined for potential effect modification were not powered to detect subgroup interactions.

The EAG further notes that crossover for OS analyses, and differences in bortezomib dosing between trials, are likely treatment effect modifiers. However, as outlined in Section 3.3.2.1, the EAG considers the adjustment for OS in BOSTON to be suitable, and as outlined in Section 3.4.2.1, the EAG considers the likely treatment modifying effect of the small differences in Vd dosing between ENDEAVOR and BOSTON to be small, and likely conservative.

Overall, the EAG considers the results of direct anchored comparison between Kd and SVd to likely be robust to treatment effect modification, and that there is:

- Evidence that SVd is inferior to Kd in terms of PFS at 2L;
- Uncertainty around whether there are OS differences between SVd and Kd.

Finally, the Company stated that:

“participants in the ENDEAVOR trial were likely exposed to less effective drugs in 1L, including chemotherapy, that boosted the impact of Kd in 2L in terms of PFS and OS, compared to the impact of SVd in the BOSTON trial, where patients could have had access to regimens with better efficacy at 1L. Therefore, the nature of the NMA, that does not always correct for the differences in terms of type of prior therapies, is a conservative approach that favours Kd over SVd and might not reflect the real efficacy of these regimens in the current clinical practice, where the standard of care at 1L includes more efficacious drugs that might not have been available at the time of the trials.”

The EAG agrees with the Company that treatment effect modification is a key area for future research in comparative analyses of treatments for RR-MM. However, the EAG does not consider the Company to have provided strong evidence that systematic differences in prior treatment regimens between BOSTON and ENDEAVOR will have meaningfully modified the relative treatment effect within each trial in a manner that would systematically favour Kd. The EAG notes that the Company’s concerns about such treatment effect modification due to differences in study timing between BOSTON (start date: 2017) and ENDEAVOR (start date: 2012) can only be heightened when consider the Company’s NMA for the 3L+ population, which includes MM-009 and MM-010 (start dates: 2003).³⁹

[3.4.2.4 Restricted NMA and Anchored MAIC](#)

At Clarification, the EAG requested the Company perform either an NMA restricted to the 2L studies including a Vd arm, a Bucher ITC between BOSTON and ENDEAVOR or an anchored MAIC between BOSTON and ENDEAVOR. The EAG requested these analyses to test the effects of excluding much of the heterogeneity from the network that was not directly informing the SVd, Vd and Kd comparisons. The results of the restricted NMA (performed at 2L and 3L+) were directly in line with the overall NMAs (Table 17, Company Clarification Response).

The Company also provided an anchored MAIC between BOSTON and ENDEAVOR, which provided results that were considerably more favourable for SVd compared to the NMA results (PFS anchored MAIC HR Kd vs SVd 1.052, 95% CI: 0.583 to 1.898; OS anchored MAIC HR Kd vs SVd 1.385, 95% CI: 0.726 to 2.642). The EAG notes that, while the direction of the adjustment is reassuring, the anchored MAIC adjusted for six factors: age; ECOG PS; R-ISS; cytogenetic risk; receipt of prior bortezomib; and receipt of prior lenalidomide. The justification for including these factors was “to overcome differences in study populations”, yet it is unclear whether any of these variables are treatment effect modifiers, rather than prognostic factors. In an anchored MAIC, only treatment effect modifiers should be adjusted for, and treatment effect modifiers should be identified through an evidenced based procedure.⁴⁰ In sum, the EAG does not consider the results of the anchored MAIC to be more appropriate than the unadjusted NMA-based methods of indirect treatment comparison, and recognises the Company has also retained their original 2L NMA, rather than the anchored MAIC, in its base case.

3.4.3 3L+ NMA and unanchored MAICs

3.4.3.1 Comparison of included studies

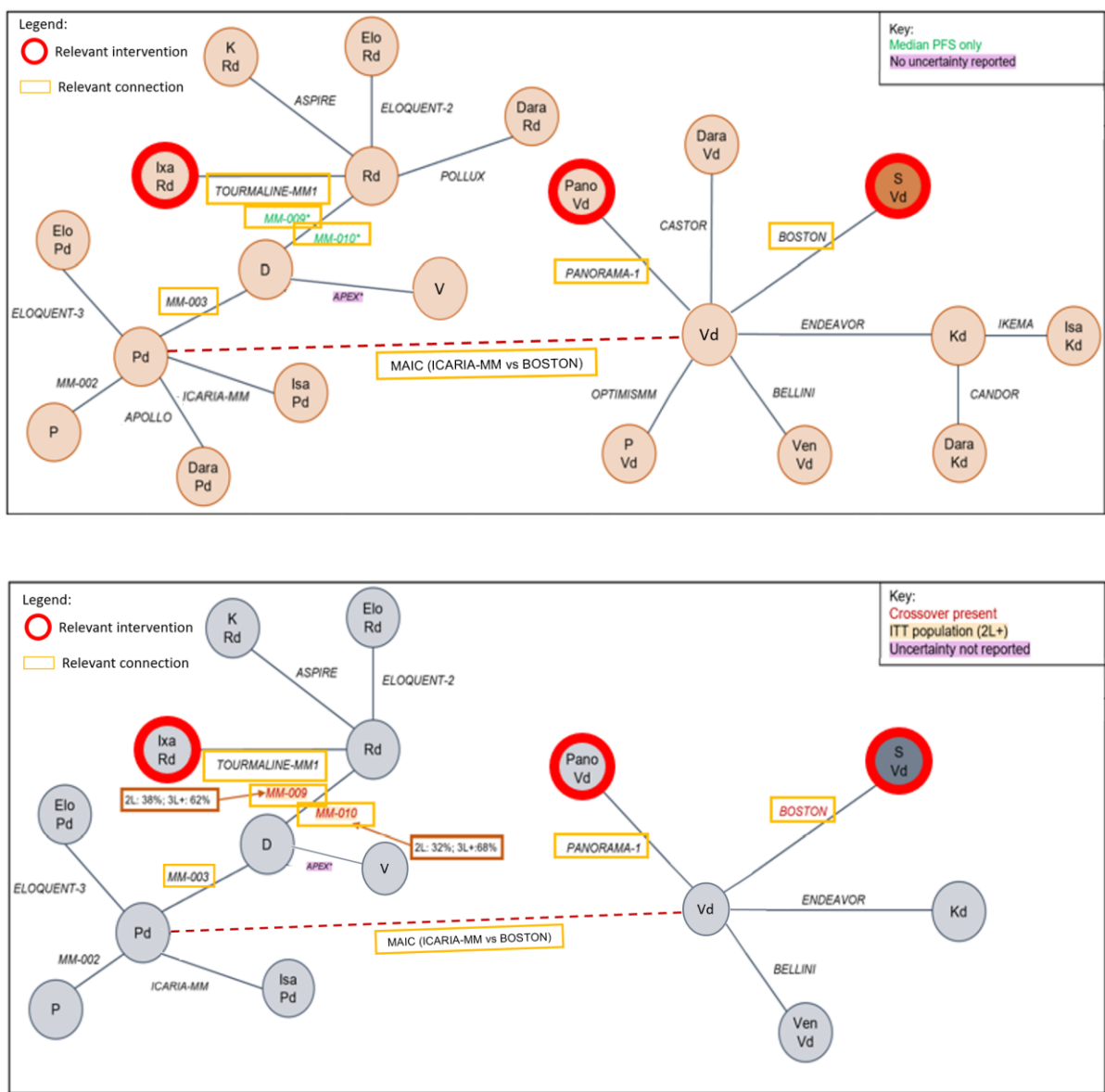
In the initial submission, the Company presented a 3L+ NMA that the EAG critiqued in Clarification Question A19 based on the following points:

- The large amount of between-study heterogeneity in the evidence network connecting SVd and IxaRd;
- The use of a matched-control analysis to connect the network, where RCTs were not available;
- The use of some clinical trials from over 15 years ago, where the treatment landscape for multiple myeloma was markedly different to more recent trials;
- The “double use” of the APEX 2006 clinical trial, both in the D vs V contrast and V vs Vd contrast, meaning that any bias and sampling variance included in APEX will be amplified in the NMAs;
- The use of median PFS and OS rather than HRs for some contrasts, and the use of TTP rather than PFS as an outcome for some studies.
- The NMA producing clinically implausible results for some contrasts (Clarification Question A24)

Many of these concerns were shared by the Company’s own clinical experts, and the EAG commends the transparency of the Company in providing these concerns in Appendix N of the CS.

Following Clarification, the Company provided an updated 3L+ NMA that the Company stated should be taken to supersede the original NMA. The EAG agrees that the updated NMA mitigates some, but not all of the concerns, of the original NMA. The network diagram of the Company’s updated 3L+ NMA is presented in Figure 6.

Figure 6. Company’s network of evidence for the 3L+ NMA, conducted with a global perspective (Reproduced from Company Clarification Response Supplementary Appendix: 3L+ NMA update)



In this NMA, the EAG notes that the risk of bias differs for comparisons with IxaRd and PanoVd:

- For PanoVd, the EAG considers the NMA to be appropriate, and to reflect a Bucher like comparison between SVd from BOSTON and PanoVd from PANORAMA-1;
- For IxaRd, the EAG considered the updated network to still be at high risk of bias because of:
 - The need to perform an unanchored MAIC between Pd (ICARIA-MM) and Vd (BOSTON) to connect the network;
 - The double use of Vd data from BOSTON to estimate the Pd vs Vd HR and Vd vs SVd HR;
 - The use of by-arm median PFS data from MM-009 and MM-010;
 - The potential violation of the PH assumption for numerous contrasts throughout the network for both PFS and OS;
 - The inclusion of MM-03 in which the median number of previous lines of anti-MM was 5 (Table 10 of Company response to Clarification), likely representing a different disease severity and treatment responsiveness to the other included studies; and
 - Substantial heterogeneity in the trials included in the network, including two trials starting in 2003, in which data were only available for a mixed 2L and 3L population (MM-009 and MM-010).³⁹ The EAG considered it plausible that treatment effect modifiers would be imbalanced across the network, especially for OS in terms of subsequent therapies that patients could receive. For example, the EAG considers it plausible that the relative OS treatment effect of Rd vs dexamethasone (MM-009/MM-010) observed in 2003 to 2008 would not be the same as the relative treatment effect that would be observed today, due to the availability of many more effective therapies at later lines available today. The likely instability of relative OS treatment effects over time was noted in the overall survival analysis of the TOURMALINE-MM1 trial, which noted that: *“translation of PFS benefit into OS benefit and interpretation of OS has become increasingly confounded by more extensive use of subsequent therapies with optimized sequencing.”*⁴¹

The EAG considers the risk of bias for estimates of OS between IxaRd and SVd to be further higher due to the presence of unadjusted crossover in MM-009, MM-010 and MM-003, which was noted in the Company ITC report:

[REDACTED]
[REDACTED] (ITC report page 56).³⁵

In MM-009/MM-010, 47.6% of patients randomised to dexamethasone plus placebo crossed over upon disease progression or unblinding to Rd or another lenalidomide-based regimen.³⁹ In an analysis attempting to adjust for crossover in MM-009/MM-010, estimated OS for patients randomised to dexamethasone was substantially reduced:⁴²

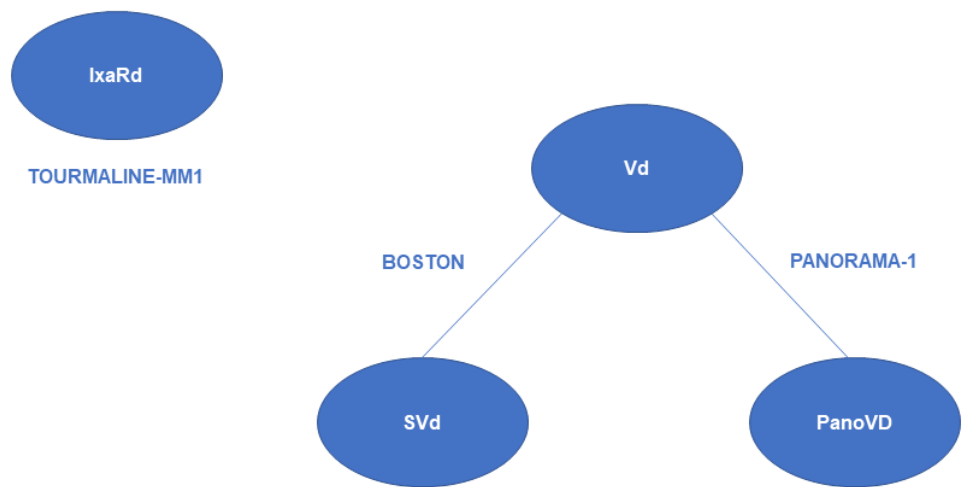
- For patients with one prior line of therapy: from 33.6 months (observed) to 19.5 months (adjusted);
- For patients with two or more prior therapies: estimated OS reduced from 27.3 months (observed) to 11.6 months (adjusted).

HRs were not available for the adjusted estimates, but the EAG notes these HRs would markedly favour Rd over dexamethasone. This would lead to a substantial change in the OS estimate in favour of IxaRd over Vd or SVd in the Company's NMA, if the adjusted HRs were incorporated into the Company's 3L+ NMA. Conversely, the lack of OS adjustment in MM-003 would bias results in the opposite direction, i.e., in favour of SVd.⁴³ The cumulative impact of adjusting for crossover in the OS analyses is unknown, and reflects a major uncertainty and limitation in the OS NMA analyses for IxaRd vs Vd and SVd.

To address these concerns, the EAG requested the Company conduct unanchored MAICs between SVd and Vd from BOSTON directly with IxaRd from TOURMALINE-MM1. The EAG considered the unanchored MAIC would likely: i) provide less uncertain evidence than the NMA methods; and ii) allow a more transparent and straightforward assessment of risk, direction and magnitude of bias compared to the NMA methods. The EAG identified the data necessary to perform these unanchored MAICs, and the Company then provided the requested MAICs.

In the EAG's preferred analyses, the evidence network simplifies from the Company's NMA in Figure 6 to the network depicted in Figure 7. This network involves a Bucher-like comparison between SVd from BOSTON and PanoVd from PANORAMA-1, taken from the Company's 3L+ NMA. Note, due to the evidence for this comparison being informed by the full evidence network, the estimation of between-study heterogeneity is informed by the trials throughout the network. Comparisons between IxaRd (TOURMALINE-MM1) and SVd (BOSTON) or Vd (BOSTON) are made through unanchored MAICs.

Figure 7. EAG’s simplified network of trials for the 3L+ population



A comparison of the study design of BOSTON, PANORAMA-1 and TOURMALINE-MM1 is presented in Table 27.

Table 27. A comparison of the study design of BOSTON, PANORAMA-1 and TOURMALINE-MM1

	BOSTON	PANORAMA-1	TOURMALINE-MM1
Study design	Phase 3 open-label (crossover permitted)	Phase 3 double-blind	Phase 3 double-blind
Study sites	165 sites; 21 countries	215 sites across 34 countries	147 sites across 26 countries
Study start date	May 2017	December 2009	August 2012
Identified data cuts	February 2020 February 2021	September 2013 August 2014 June 2015	October 2014 July 2015 September 2020
N participants randomised	402; 2 prior = 129 3 prior = 75	768; 2 prior = 232 3 prior = 139	722; 2 or 3 prior = 297
Stratification factors	Prior PI therapies (yes vs. no), number of prior lines of treatment (1 vs 2 or more), and R-ISS) stage (III vs I-II) at study entry	Number of previous treatment lines (1 vs 2 to 3) and previous use of bortezomib treatment (yes vs no)	Number of prior therapies (1 vs 2 or 3), previous exposure to PIs (not exposed vs. exposed), and ISS stage (I or II vs III)
Intervention	SVd	PanoVd	IxaRd
Comparator	Vd	Vd	Rd
Vd dosing	Bortezomib	Placebo+Vd	NA

	- Cycles 1 - 8 (3-week [21-day] cycle) 1.3 mg/m² SC on Days 1, 4, 8, and 11; - Cycles ≥ 9 (5-week [35-day] cycle) 1.3 mg/m² SC on Days 1, 8, 15, and 22. Dexamethasone - Cycles 1 - 8 (3-week [21-day] cycle) 20-mg oral on Days 1, 2, 4, 5, 8, 9, 11, and 12. - Cycles ≥ 9 (5-week [35-day] cycle) oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30.	Treatment Phase 1 (eight 3-week cycles): Placebo orally 3 times/ week for the first 2 weeks Bortezomib 1.3mg/m² IV on days 1, 4, 8, and 11 Dexamethasone 20mg orally on the days of and after bortezomib. At the end of treatment phase 1, patients with clinical benefit, defined as at least no change on day 1 of cycle 8 could proceed to treatment phase 2 (four 6-week cycles), in which placebo was given on a similar schedule, but bortezomib was given once per week during weeks 1, 2, 4, and 5 and dexamethasone was given on the same and subsequent days as bortezomib. Treatment was given until relapse or progression	
Crossover	Permitted at the point of IRC-confirmed objective PD per IMWG criteria, for patients in the Vd arm	Not permitted	Not permitted
Inclusion criteria (prior treatment)	1-3 prior lines	1-3 prior treatments	1-3 prior treatments
Inclusion criteria (response to prior PI)	≥ PR to bortezomib and last PI; - At least 6-month PI-treatment free interval prior to Cycle 1 Day 1	Patients refractory to bortezomib were excluded	NA
Primary outcome	PFS by IRC	PFS by INV	PFS by IRC
Other endpoints	ORR; VGPR; CR; sCR; MRD-negative; OS; DOR; TTNT; TTR; PFS2; PN; HRQoL; safety	OS; ORR; CR; DOR; TTR; TTP; HRQoL; safety	OS; ORR; CR; VGPR; DOR; TTP; safety;
PFS assessment criteria	IRC-confirmed, per IMWG response criteria	Investigator assessed by modified EBMT criteria	Double-blinded and assessed by IRC using IMWG Uniform Response Criteria

Abbreviations: Bort, bortezomib; CR, complete response; Dex, dexamethasone; DOR, duration of response; EBMT, European Group for Blood and Marrow Transplantation; HRQoL, health-related quality of life; IMWG, International Myeloma Working Group; INV, investigator; IRAC, independent response adjudication committee; IRC, independent response committee; ISS, international staging system; IV, intravenously; IxaRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; MRD, minimal residual disease; NMA, network meta-analysis; NR, not reported; ORR, overall response rate; OS, overall survival; PanoVd, panobinostat + bortezomib + dexamethasone; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PN, peripheral neuropathy; Rd, lenalidomide + dexamethasone; R-ISS, revised international staging system; SC, subcutaneously; sCR, stringent complete response; SVd, selinexor + bortezomib + dexamethasone; TTNT, time to next treatment; TTP, time to progression; TTR, time to response; VCD, bortezomib + cyclophosphamide + dexamethasone, bortezomib + dexamethasone; VDR, bortezomib + lenalidomide + dexamethasone; VGPR, very good partial response.

The EAG notes the two following key differences between BOSTON, PANORAMA-1 and TOURMALINE-MM1:

- PANORAMA-1 and TOURMALINE-MM1 were double-blind trials, whereas BOSTON was an open label trial. In the EAG's quality assessment of BOSTON, the EAG noted that the potential for bias in the open-label BOSTON was likely mitigated due to the use of a blinded IRC to assess PFS, and OS being an objective endpoint. The EAG notes that crossover from Vd to a selinexor-containing regimen was only permitted following confirmation of progression by the blinded IRC, rather than investigator assessment.
- PFS was measured in PANORAMA-1 by the investigator and used modified EBMT criteria rather than IMWG response criteria. The EAG considered this unlikely to substantially affect the relative treatment effect reported in a double-blind clinical trial, but notes the PANORAMA-1 publication suggested that using modified EBMT rather than IMWG response criteria may underestimate the efficacy of PanoVd relative to Vd.⁴⁴

Table 28. A comparison of the baseline characteristics of the BOSTON, PANORAMA-1, and TOURMALINE MM-1. (Adapted from Table 9, Company response to Clarification)

Baseline characteristic		BOSTON 3L		PANORAMA-1 ITT		TOURMALINE MM-1 3L+	
		SVd	Vd	PanoVd	PBO+Vd	IxaRd	Rd
		65	64	387	381	148	149
Age, years	Median (range)	66 (40 to 80)	67 (38 to 84)	63 (28 to 84)	63 (32 to 83)	65.9 (9.46)*	66.1 (10.09)*
Gender, n (%)	Male	46 (70.8)	41 (64.1)	202 (52)	205 (54)	81 (55)	86 (58)
Race, n (%)	White	55 (84.6)	50 (78.1)	249 (64)	250 (66)	34 (87.5)	353 (75.9)
	Black- Af/Am	1 (1.5)	3 (4.7)	5 (1)	17 (4)	8 (1.7)	9 (1.9)
	Asian	8 (12.3)	8 (12.5)	128 (33)	104 (27)	56 (12.1)	57 (12.3)
	Other	0 (0.0)	0 (0.0)	5 (1)	10 (3)	2 (0.4)	1 (0.2)
	Missing	1 (1.5)	3 (4.7)	NR	NR	50 (10.8)	45 (9.7)
Baseline ECOG performance	0	21 (32.3)	22 (34.4)	175 (45)	162 (43)	59 (40)	58 (39)
	1	35 (53.9)	38 (59.4)	191 (49)	186 (49)	77 (52)	74 (50)
	2	9 (13.9)	4 (6.3)	19 (5)	29 (8)	10 (7)	15 (10)
Time since initial diagnosis (years)	Median (range)	4.3 (1.5 to 16.6)	3.7 (0.8 to 22.0)	NR	NR	NR	NR
R-ISS stage at study entry	R-I	18 (27.7)	22 (34.4)	156 (40)	152 (40)	NR	NR
	R-II	44 (67.7)	37 (57.8)	104 (27)	92 (24)	NR	NR
	R-III	1 (1.5)	5 (7.8)	77 (20)	86 (23)	20 (14)	18 (12)
	Missing	2 (3.1)	0 (0.0)	50 (13)	51 (13)	NA	NA
Baseline creatinine clearance (mL/ min)	<30	0 (0.0)	6 (9.4)	NR	NR	3 (2)	2 (1)
	30-60	18 (27.7)	16 (25.0)	NR	NR	16 (11)	21 (14)

	>60	47 (72.3)	42 (65.6)	NR	NR	129 (87)	125 (84)
Cytogenetic abnormalities, n (%)	del(17p)/p53	4 (6.2)	5 (7.8)	NR	NR	17 (11)	14 (9)
	t(14;16)	1 (1.5)	4 (6.3)	NR	NR	2 (1)	1 (<1)
	t(4;14)	7 (10.8)	6 (9.4)	NR	NR	12 (8)	12 (8)
	1q21	29 (44.6)	19 (29.7)	NR	NR	NR	NR
	All high-risk cytogenetic	33 (50.8)	26 (40.6)	79 (66)	88 (71)	30 (20)	28 (19)
Prior SCT, n (%)		29 (44.6)	27 (42.2)	215 (56)	224 (59)	266 (57.3)	272 (58.6)
Exposure to prior anti-MM drug classes, n (%)	PIs	50 (76.9)	50 (78.1)	NR	NR	113 (76)	114 (77)
	IMiDs	58 (89.2)	50 (78.1)	NR	NR	100 (68)	102 (68)
Exposure to prior anti-MM drugs, n (%)	Bortezomib	45 (69.2)	46 (71.9)	169 (44)	161 (42)	NR	NR
	Carfilzomib	4 (6.2)	6 (9.4)	NR	NR	NR	NR
	Ixazomib	1 (1.5)	2 (3.1)	NR	NR	NR	NR
	Daratumumab	3 (4.6)	0 (0.0)	NR	NR	NR	NR
	Lenalidomide	33 (50.8)	30 (46.9)	72 (19)	85 (22)	NR	NR
	Pomalidomide	2 (3.1)	2 (3.1)	NR	NR	NR	NR

*Mean age

Sources: CS Table 8, Company response to clarification Table 9, NICE committee papers Ixazomib citrate for treating relapsed or refractory multiple myeloma [ID807] response to clarification Table 8

Abbreviations: Af/Am, African American; ECOG, Eastern Cooperative Oncology Group; IxaRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; PanoVd, panobinostat + bortezomib + dexamethasone; Rd, lenalidomide + dexamethasone; R-ISS, revised international staging system; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone

Outcome data entering the NMA for the 3L+ subgroups of BOSTON, PANORAMA-1 and TOURMALINE-MM1 are presented in Table 29. The EAG notes, that, despite HRs calculated based on a two-stage estimation procedure without re-censoring being presented throughout the CS, the Company used the slightly more liberal HRs calculated with re-censoring in the ITC analyses. The EAG does not consider there to be a strong reason to prefer the estimate with or without re-censoring, and so notes this is a liberal assumption from the Company.

Table 29. Outcome data entering the Company NMA for the 3L+ subgroups of BOSTON, PANORAMA-1 and TOURMALINE-MM1

Population	BOSTON		PANORAMA-1		TOURMALINE-MM1	
	SVd	Vd	PanoVd	Vd	IxaRd	Rd
	3L+		3L+		3L+	
n	96	108	188	183	148	149
Median follow-up time, months (95% CI) - latest datacut	28.71* (27.24 to 29.90)	28.65* (27.63 to 29.67)	NR	NR	85.0*	85.1*
Median PFS, months (95% CI)	11.76 (7.39 to 15.38)	9.43 (6.83 to 9.69)	12 (9.5 to 13.7)	7.6 (6.0 to 8.7)	NR	12.9
Hazard ratio PFS, (95% CI)	0.805 (0.559 to 1.159)		0.64 (0.50 to 0.83)		0.580 (0.401 to 0.838)	
Median OS, unadjusted for crossover, months (95% CI)	31.74 (30.19 to NE)	■	34.6 (27.73 to 41.95)	30.0 (24.80 to 39.92)	53	43
Hazard ratio OS, unadjusted for crossover, (95% CI)	■		0.96 (0.74 to 1.26)		0.845 (0.642 to 1.114)	
Median OS, adjusted for crossover, months (95% CI)	31.74 (30.19 to NE)	NE (22.48 to NE)	NA	NA	NA	NA
Hazard ratio OS, adjusted for crossover, without re-censoring (95% CI)	0.829 (0.518 to 1.328)		NA		NA	

Hazard ratio OS, adjusted for crossover, with re-censoring (95% CI)	0.770 (NR)		NA		NA	
N (%) of participants crossing over	NA	47 (43.5%)	NA	NA	NA	NA
Method of adjustment for crossover	Two-stage method	Two-stage method	NA	NA	NA	NA

*Based on the ITT population

Abbreviations: CI, confidence interval; IxaRd, ixazomib + lenalidomide + dexamethasone; NE, not estimable; NMA, network meta-analysis; OS, overall survival; PanoVd, panobinostat + bortezomib + dexamethasone; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; Rd, lenalidomide + dexamethasone; Vd, bortezomib + dexamethasone; 2L, second line.

3.4.3.2 3L+ NMA results

3.4.3.2.1 Comparison with SVd

In the Company's preferred random effects NMA:

- IxaRd was numerically superior to SVd for PFS (HR: 0.69, 95% CrI: 0.12 to 3.29) but numerically inferior to SVd for OS (HR: 1.09, 95% CrI: 0.24 to 5.18); and
- PanoVd was numerically superior to SVd for PFS (HR: 0.80, 95% CrI: 0.26 to 2.28) but numerically inferior to SVd for OS (HR: 1.24, 95% CrI: 0.45 to 3.46).

These data are presented in Table 30, alongside the outcome of the EAG requested unanchored MAIC between IxaRd and SVd. The results of the unanchored MAIC were in line with the updated NMA:

- IxaRd was numerically superior to SVd for PFS (HR: 0.66, 95% CI: 0.34 to 1.28) but numerically inferior to SVd for OS (HR: 1.29, 95% CI: 0.63 to 2.64).

Table 30. Results of the Company 3L+ NMA and unanchored MAIC between SVd and relevant 3L comparators

Comparison	Updated NMA		Unanchored MAIC	
	PFS HR (95% CrI)	OS HR (95% CrI)	PFS HR (95% CI)	OS HR (95% CI)
IxaRd versus SVd	0.692 (0.118 to 3.291)	1.094 (0.236 to 5.181)	0.66 (0.34 to 1.28)	1.29 (0.63 to 2.64)
PanoVd versus SVd	0.797 (0.262 to 2.281)	1.240 (0.454 to 3.462)	NA	NA

Abbreviations: CI, confidence interval; CrI, credible interval; IxaRd, ixazomib + lenalidomide + dexamethasone; NMA, network meta-analysis; OS, overall survival; PanoVd, panobinostat + bortezomib + dexamethasone; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; Rd, lenalidomide + dexamethasone; 3L+, third line plus.

3.4.3.2.2 Comparison with Vd

While the Company did not report the comparisons with Vd in the CS, the EAG extracted the point estimates from the economic model. In the Company's preferred random effects NMA:

- SVd was superior to Vd for PFS (HR: 0.80) and OS (HR: 0.77);
- IxaRd was superior to Vd for PFS (HR: 0.56) and OS (HR: 0.85);
- PanoVd was superior to Vd for PFS (HR: 0.64) and OS (HR: 0.96).

These data are presented in Table 31, alongside the outcome of the EAG requested unanchored MAIC between IxaRd and Vd. The results of the unanchored MAIC were in line with the direction updated NMA, although provided more favourable HRs for IxaRd compared to Vd:

- IxaRd was superior to Vd for PFS 0.37 (0.23 to 0.60) and OS 0.48 (0.29 to 0.79).

Table 31. Results of the Company 3L+ NMA and unanchored MAIC between Vd and relevant 3L comparators

Comparison	Updated NMA		Unanchored MAIC	
	PFS HR (95% CrI)	OS HR (95% CrI)	PFS HR (95% CrI)	OS HR (95% CrI)
SVd versus Vd	0.8023 (NR)	0.7744 (NR)	NA	NA
IxaRd versus Vd	0.5593 (NR)	0.8488 (NR)	0.37 (0.23 to 0.60)	0.48 (0.29 to 0.79)
PanoVd versus Vd	0.6414 (NR)	0.9608 (NR)	NA	NA

Abbreviations: CI, confidence interval; CrI, credible interval; IxaRd, ixazomib + lenalidomide + dexamethasone; NMA, network meta-analysis; OS, overall survival; PanoVd, panobinostat + bortezomib + dexamethasone; PFS, progression-free survival; Rd, lenalidomide + dexamethasone; Vd, bortezomib + dexamethasone; 3L+, third line plus.

3.4.3.3 Unanchored MAIC detailed results

The Company performed unanchored MAICs comparing the IxaRd 3L+ subgroup from TOURMALINE-MM1 to the 3L+ SVd subgroup (Section 3.4.3.3.1) and 3L+ Vd subgroup (Section 3.4.3.2.2) from BOSTON. The EAG requested that the Company perform fully adjusted MAICs, and notes that the Company MAICs used eight factors for the matching process “based on previous clinical validation of prognostic factors in MM and on the availability of these baseline characteristics from the TOURMALINE-MM1 trial”:

- Age;

- Sex;
- ECOG performance status;
- R-ISS and ISS (assumed equivalent as BOSTON reported R-ISS and TOURMALINE-MM1 ISS);
- Cytogenetic risk;
- Prior SCT;
- Prior PI exposure; and
- Prior IMiD exposure.

The EAG notes the following baseline characteristics were available from TOURMALINE-MM1 and BOSTON that could have been matched on:

- Race;
 - The EAG notes that, where reported, race was reasonably balanced between TOURMALINE-MM1 and BOSTON, and the large amount of missing race data in TOURMALINE-MM1 (~10%) may make any matching procedure inaccurate;
- Creatinine clearance;
 - The EAG considers there to be evidence that creatinine clearance is a prognostic factor, however notes that not including creatinine clearance in the matching process is likely conservative, as baseline creatinine clearance was higher in TOURMALINE-MM1 than in BOSTON.

The Company unanchored MAICs were performed in R, and the Company provided example code to the EAG. The EAG considered the technical implementation of the MAICs to be appropriate.

3.4.3.3.1 Comparison with SVd

After matching, the effective sample size of the BOSTON IPD was ■■■, a loss of ■■■ Baseline characteristics of the BOSTON SVd 3L+ subgroup before and after matching are presented in Table 32.

Table 32 Summary of baseline characteristics in TOURMALINE-MM1 (IxaRd) and BOSTON trial (SVd) prior to, and after MAIC weighting (Reproduced from Company Response to Clarification Question A30)

Factor	TOURMALINE-MM1 ⁴⁵	BOSTON IPD ⁴⁶	
		Prior to matching	Post matching
Number of patients	148	96	■■■
Arm	IxaRd	SVd	SVd

Age Mean (SD)	65.9 (9.46)	64.4 (9.72)	65.9
Sex, n (%) Male	54.7%	62.5%	54.7%
ECOG PS, n (%) 0 1 2	40.4%* 52.7%* 6.8%*	31.3% 56.3% 12.5%	40.4% 52.7% 6.8%
R-ISS, n (%) 3	13.5%†	3.3%*	13.5%
Cytogenetic risk, n (%) High	20.3%	20.8%	20.3%
Stem cell transplant, n (%) Yes	58.1%	38.5%	58.1%
Prior PI exposure, n (%) Yes	76.4%	81.3%	76.4%
Prior IMiD exposure, n (%) Yes	67.6%	90.6%	67.6%
Abbreviations: ESS, effective sample size; IMiD, immunomodulatory drug; IPD, individual patient data; ISS, International Staging System; IxaRd, ixazomib plus lenalidomide plus dexamethasone; PI, proteasome inhibitor; R-ISS, Revised International Staging System; SD, standard deviation; SVd, selinexor plus bortezomib plus dexamethasone. Notes: *Missing values were excluded prior to calculating % †Reported as ISS			

The results of the unanchored MAIC for PFS comparing IxaRd and SVd are presented in Table 33. IxaRd was numerically superior to SVd (weighted HR: 0.66, 95% CI: 0.34 to 1.28).

Table 33. Unanchored PFS MAIC results – IxaRd (TOURMALINE-MM1) versus SVd (BOSTON)
(Reproduced from Company Response to Clarification Question A30)

Comparator study	BOSTON SVd sample size	ESS	ESS %	HR naïve [95% CI]	HR weighted [95% CI]
TOURMALINE-MM1	91*	■	■	0.53 (0.35 to 0.81)	0.66 (0.34 to 1.28)
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; IMiD, immunomodulatory drug; PI, proteasome inhibitor; PS, performance status; R-ISS, Revised International Staging System; SCT, stem cell transplant; SVd, selinexor plus bortezomib plus dexamethasone. Notes: *Five patients did not report R-ISS and were therefore excluded from the analyses.					

The unadjusted and adjusted SVd Kaplan-Meier curve and digitised IxaRd curve are presented in .

Figure 8. [REDACTED]

[REDACTED]

[REDACTED] (Reproduced from Company Response to Clarification Question A30)



The results of the unanchored MAIC for OS comparing IxaRd and SVd are presented in Table 34. Weighting had a large influence on the point estimate for OS (naïve HR: 0.66 95% CI: 0.34 to 1.28; weighted HR: 1.29, 95% CI: 0.63 to 2.64). The EAG is concerned about the accuracy of the calculated OS HRs, due to the shape of the Kaplan-Meier curves suggesting PH do not hold, especially for the weighted SVd data compared to the digitised IxaRd data. These curves are presented in Figure 9.

[REDACTED]

[REDACTED]

[REDACTED] (Reproduced from Company Response to Clarification Question A30)

.

Table 34. Unanchored OS MAIC results – IxaRd (TOURMALINE-MM1) *versus* SVd (BOSTON)
(Reproduced from Company Response to Clarification Question A30)

Comparator study	BOSTON SVd sample size	ESS	ESS %	HR naïve [95% CI]	HR weighted [95% CI]
TOURMALINE-MM1	91*	[REDACTED]	[REDACTED]	0.60	1.29

				(0.38 to 0.95)	(0.63 to 2.64)
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; IMiD, immunomodulatory drug; PI, proteasome inhibitor; PS, performance status; R-ISS, Revised International Staging System; SCT, stem cell transplant; SVd, selinexor plus bortezomib plus dexamethasone.					
Notes: *Five patients did not report R-ISS and were therefore excluded from the analyses.					

Figure 9. [REDACTED]

[REDACTED]

[REDACTED] (Reproduced from Company Response to Clarification Question A30)



3.4.3.3.2 Comparison with Vd

After matching, the effective sample size of the BOSTON IPD was [REDACTED], a loss of [REDACTED] Baseline characteristics of the BOSTON SVd 3L+ subgroup before and after matching are presented in Table 35.

Table 35. Summary of baseline characteristics in TOURMALINE-MM1 (IxaRd) and BOSTON trial (Vd) prior to- and after MAIC weighting (Reproduced from Company Response to Clarification Question A30)

Factor	TOURMALINE-MM1 ⁴⁵	BOSTON IPD ⁴⁶	
		Prior to matching	Post matching
Number of patients	148	108	[REDACTED]
Arm	IxaRd	Vd	Vd
Age	65.9 (9.46)	65.0 (9.98)	65.9

Mean (SD)			
Sex, n (%)			
Male	54.7%	57.4%	54.7%
ECOG PS, n (%)			
0	40.4%*	36.1%	40.4%
1	52.7%*	54.6%	52.7%
2	6.8%*	9.3%	6.8%
R-ISS, n (%)			
3	13.5% [†]	9.8%*	13.5%
Cytogenetic risk, n (%)			
High	20.3%	24.1%	20.3%
Stem cell transplant, n (%)			
Yes	58.1%	37.0%	58.1%
Prior PI exposure, n (%)			
Yes	76.4%	78.7%	76.4%
Prior IMiD exposure, n (%)			
Yes	67.6%	83.3%	67.6%
Abbreviations: ESS, effective sample size; IMiD, immunomodulatory drug; IPD, individual patient data; ISS, International Staging System; IxaRd, ixazomib plus lenalidomide plus dexamethasone; PI, proteasome inhibitor; R-ISS, Revised International Staging System; SD, standard deviation; Vd, bortezomib plus dexamethasone.			
Notes: *Missing values were excluded prior to calculating %			
[†] Reported as ISS			

The results of the unanchored MAIC for PFS comparing IxaRd and Vd are presented in Table 36. Weighting had little influence on the estimated HRs OS (naïve HR: 0.37, 95% CI: 0.25 to 0.53; weighted HR: 0.37, 95% CI: 0.23 to 0.60).

Table 36 Unanchored PFS MAIC results – IxaRd (TOURMALINE-MM1) versus Vd (BOSTON)
(Reproduced from Company Response to Clarification Question A30)

Comparator study	BOSTON Vd sample size	ESS	ESS %	HR naïve [95% CI]	HR weighted [95% CI]
TOURMALINE-MM1	102*	■	■	0.37 (0.25 to 0.53)	0.37 (0.23 to 0.60)
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; IMiD, immunomodulatory drug; PI, proteasome inhibitor; PS, performance status; R-ISS, Revised International Staging System; SCT, stem cell transplant; Vd, bortezomib plus dexamethasone.					
Notes: *Six patients did not report R-ISS and were therefore excluded from the analyses.					

The unadjusted and adjusted SVd Kaplan-Meier curve and the digitised IxaRd curve are presented in **Error! Reference source not found..**

Figure 10. [REDACTED]

[REDACTED]

[REDACTED] (Reproduced from Company Response to Clarification Question A30)



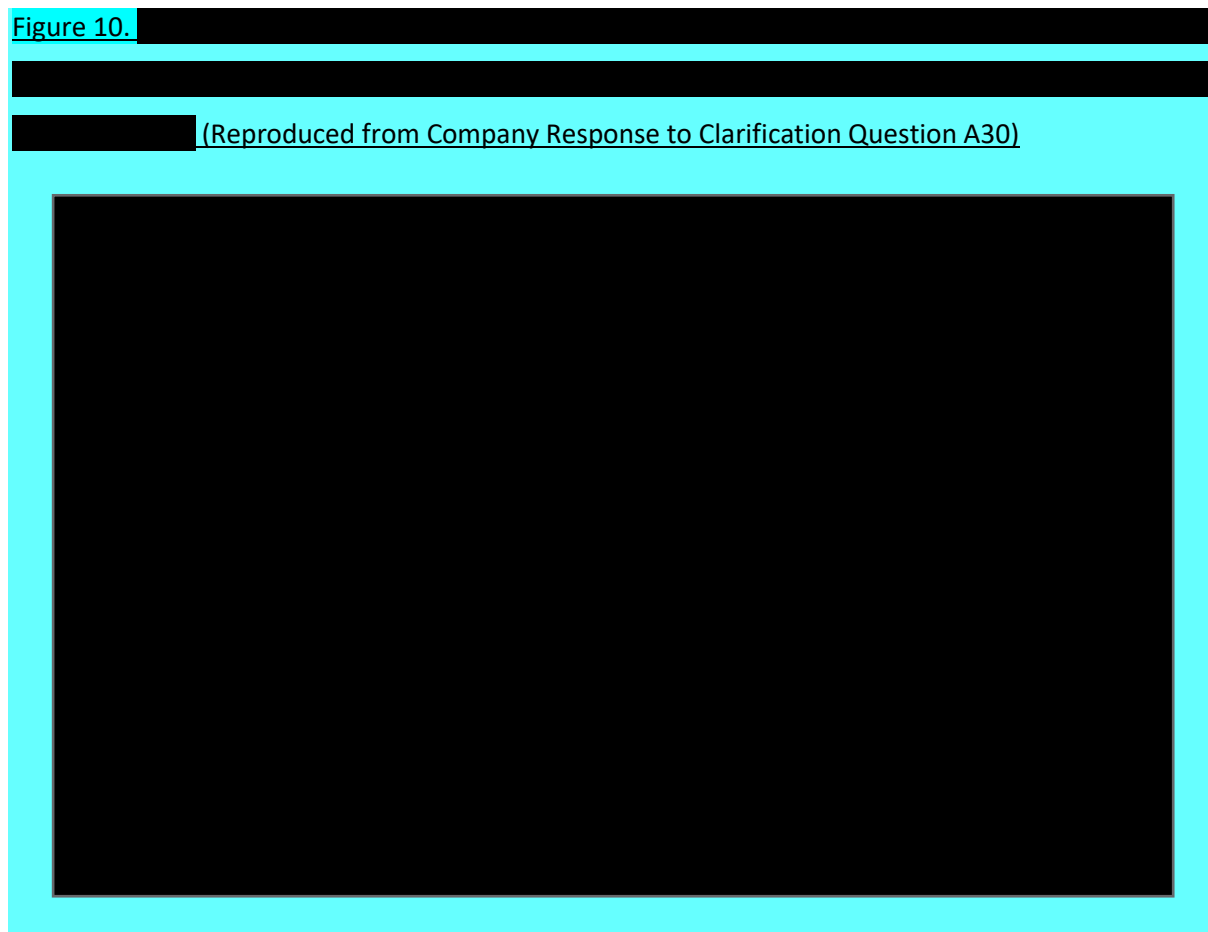
The results of the unanchored MAIC for OS comparing IxaRd and Vd are presented in Table 36. Weighting had little influence on the estimated HRs OS (naïve HR: 0.47, 95% CI: 0.30 to 0.74; weighted HR: 0.48, 95% CI: 0.29 to 0.79).

Table 37. Unanchored OS MAIC results – IxaRd (TOURMALINE-MM1) *versus* Vd (BOSTON)

(Reproduced from Company Response to Clarification Question A30)

Comparator study	BOSTON Vd sample size	ESS	ESS %	HR naïve [95% CI]	HR weighted [95% CI]
TOURMALINE-MM1	102*	[REDACTED]	[REDACTED]	0.47 (0.30 to 0.74)	0.48 (0.29 to 0.79)
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; IMiD, immunomodulatory drug; PI, proteasome inhibitor; PS, performance status; R-ISS, Revised International Staging System; SCT, stem cell transplant; Vd, bortezomib plus dexamethasone.					
Notes: *Six patients did not report R-ISS and were therefore excluded from the analyses.					

The unadjusted and adjusted SVd Kaplan-Meier curve and the digitised IxaRd curve are presented in Figure 10.



3.4.3.4 EAG critique

The EAG considers the Company to have explored an appropriate range of methods for conducting indirect treatment comparisons between SVd, PanoVd and IxaRd:

- For SVd compared to PanoVd, the EAG considers the Company's NMA, which approximates a Bucher ITC, to be appropriate;
- For IxaRd, the Company performed three distinct methods to connect the unconnected evidence network that is typical of RR-MM. Each of these strategies have been used in previous HTA submissions, but rarely are all performed:
 - Connecting the unconnected network using an observational matched-pairs analysis (Original NMA);

- Connecting the unconnected network using an unanchored MAIC between Vd BOSTON and a non-target Pd population (ICARIA-MM) and performing an NMA on the resulting network (Company updated NMA);
- Directly comparing SVd and Vd from BOSTON with IxaRd from TOURMALINE-MM1.

The EAG has outlined its critique of the Company's original and updated NMAs in Section 3.4.1, and prefers the direct unanchored MAIC method. The EAG notes the Company's updated NMA at Clarification also uses an unanchored MAIC, but includes the additional uncertainty of the wider heterogeneous evidence network.

Of the unanchored MAICs performed (IxaRd vs SVd, and IxaRd vs Vd), the EAG considers the unanchored MAICs comparing IxaRd to Vd to be most robust. This is because:

- There was a greater overlap between the IxaRd arm of TOURMALINE-MM1 and the Vd arm of BOSTON than the SVd arm of BOSTON, despite the relative balance of baseline characteristics between the BOSTON SVd and Vd 3L+ groups:
 - This is especially the case for two key prognostic factors: ISS/R-ISS Stage 3, which comprised 13.5% of patients for IxaRd, 9.8% of patients for Vd and 3.3% of patients for SVd; and ECOG performance status (0/1/2), which was 40%/53%/7% for IxaRd, 36%/55%/9% for Vd and 31%/56%/13% for SVd.
- The MAIC-adjusted OS SVd Kaplan-Meier curve crosses the IxaRd curve, suggesting a strong violation of PH, although the EAG notes that formal testing of PH was not available for any MAIC analysis.

3.4.3.4.1 EAG preferred assumptions for PFS

The EAG considers there to be some evidence of the inferiority of SVd to relevant comparators in terms of PFS. The EAG notes that the 95% CrI and CIs around the PFS estimates are wide, but notes that this is typical of network NMAs and unanchored MAICs in which the constituent trials are only powered to detect within-trial effects. The EAG's preferred source of inputs for the economic model for PFS are:

- Kd 2L: Company 2L NMA;
- PanoVd 3L+: Company updated 3L+ NMA;
- IxaRd 3L+: unanchored MAIC comparing IxaRd (TOURMALINE-MM1) and Vd (BOSTON)

While the EAG's preference for PFS data is for it to come from the Company's NMAs, the EAG prefers the comparisons with Vd over the comparisons with SVd, due to uncertainty around the PH assumption in BOSTON. These HRs are then implemented in independently fitted curves, with Vd from BOSTON being used as the baseline for the comparator curves, as described in Section 4.2.3.2.

3.4.3.4.2 EAG preferred assumptions for OS

The EAG notes greater uncertainty regarding the relative treatment effect of SVd and key comparators for OS. At 2L, the point estimated favoured Kd compared to SVd (2L OS HR: 0.89, 95% CrI: 0.32 to 2.45). At 3L+, for both PanoVd compared to SVd (3L+ OS NMA: HR: 1.24, 95% CrI: 0.45 to 3.46), and IxaRd (3L+ OS unanchored MAIC HR: 1.29, 95% CI: 0.63 to 2.64), the 95% uncertainty intervals were very wide and contained estimates that are compatible with large OS benefits for each comparator. The EAG has previously noted concerns about the interpretation of OS results from BOSTON due to potential imbalances in later-line therapies (Section 3.3.2.1). The EAG notes that observed OS differences in clinical trials for RRMM will be influenced both by: i) the effects of the intervention a patient is randomised to; and ii) differences in the subsequent therapies that patients receive after disease progression.

Data on subsequent therapy use is limited from both BOSTON – which the Company provided at Clarification, and the key comparator trials. These data are summarised in Table 38. The EAG considers these data to provide evidence of meaningful differences in subsequent therapy use between arms within each key comparator trial, and [REDACTED] These data suggest that indirect comparisons of future OS are confounded to an unknown, but potentially substantial degree, and that the already wide estimates of uncertainty from the NMA and unanchored MAIC analyses may underestimate the actual uncertainty in the OS estimates.

One abstract attempting to adjust for bias in subsequent therapy use in TOURMALINE-MM1, in which “70.64% of patients received between 1- 12 lines of subsequent therapies” reported that, in the ITT population, methods for adjusting for subsequent therapy use reduced the OS HR from 0.939 in favour of IxaRd to between 0.68 and 0.89, depending on which method was used.⁴⁷ As this was a published abstract, the EAG was unable to critique the methods used, but this highlights that the magnitude of bias associated with future treatment use may be as large or larger than the point estimates of between-treatment differences in OS from the ITCs.

Table 38. Subsequent therapy use reported in BOSTON, ENDEAVOR, PANORAMA-1 and TOURMALINE-MM1 (Adapted from Clarification Response Table 11)

	BOSTON		BOSTON		ENDEAVOR		PANORAMA-1		TOURMALINE-MM1	
	SVd	Vd	SVd	Vd	Kd	Vd	PanoVd	Vd	IxaRd	Rd
Population	2L only		3L+		2L only (data only available for ITT population)		3L+ (data only available for ITT population)		3L+ (data only available for ITT population)	
n	99	99	96	108	232	232	188	183	148	149
Subsequent therapy received										
PI-based regimens	■	■	■	■	118*	57*	42*	48*	122**	141**
IMiD-based regimens	■	■	■	■	258*	332*	78*	111*	NR	NR
anti-CD38-based regimens	■	■	■	■	NR	NR	12*	5*	63*	86*
Chemotherapy	■	■	■	■	NR	NR	NR	NR	NR	NR
Alkylating agents	■	■	■	■	152*	170*	58*	83*	NR	NR
Abbreviations: IMiD, immunomodulatory drug; ITT, intention to treat; NR, not reported; PI, proteasome inhibitor; 2L, second line; 3L+, third line plus.										
* Based on ITT population										
** Receiving PI-based regimens in the next-line therapy										

Given the likelihood of bias and confounds in the estimated OS HRs across BOSTON and key comparator trials, and the presence of a standardised treatment algorithm in UK clinical practice which will allow patients on each therapy to receive a similar pattern of anti-MM therapies for the majority of their treatment, the EAG considers the current evidence that SVd is associated with a non-statistically significant survival benefit over IxaRd or PanoVd to be weak.

The EAG recognises that the point estimates of the OS ITC analyses favour Kd over SVd, and SVd over PanoVd and IxaRd, but notes there is considerable uncertainty around whether these estimates are: i) in the correct direction; and ii) of an appropriate magnitude. Hence, the EAG considers assuming a similar OS benefit for all therapies – noting that patients who survive will be able to receive at least two further lines of other therapies – is a reasonable assumption that is associated with a low decision risk in the 3L setting. This assumption of equal OS for SVd and comparators forms the EAG base case, but a scenario analysis including differences in OS between SVd and comparators is provided. As with PFS, the EAG uses the comparisons with Vd from the Company NMAs and unanchored MAICs when modelling OS differences. Curves are fitted independently for comparators, using Vd from BOSTON as the baseline, and SVd (Section 4.2.3.2).

3.5 Conclusions of the clinical effectiveness section

The Company has presented evidence in support of the clinical effectiveness and safety of selinexor with bortezomib and low-dose dexamethasone for treating relapsed refractory multiple myeloma in two populations:

- Patients at 2L who are refractory to lenalidomide and daratumumab. Based on the current NICE recommended treatment pathway for MM, this population will predominantly comprise of SCT-ineligible patients who have received the recently approved DRd at 1L;
 - The relevant comparator at 2L was Kd;
- Patients at 3L, irrespective of prior treatment exposure;
 - The relevant comparators at 3L were IxaRd and PanoVd.

An open-label Phase 3 RCT comparing SVd and Vd, BOSTON, provided the key clinical effectiveness and safety evidence for SVd in the submission. The EAG considered BOSTON to be at relatively low

risk of bias, and considered the BOSTON population to be reasonably representative of clinical practice in England and Wales.

BOSTON provided evidence of the superiority of SVd compared to Vd in terms of PFS (primary outcome), and weaker evidence of the superiority of SVd compared to Vd in terms of OS (secondary outcome) for the ITT, 2L and 3L populations. In BOSTON, SVd was associated with notable toxicity, including elevated rates of the following Grade 3 AES: anaemia; asthenia; cataract; diarrhoea; fatigue; nausea; neutropenia; and thrombocytopenia.

The Company performed NMAs to obtain estimates of the relative treatment effect of SVd vs comparators at 2L and 3L+. Due to limited reporting of 3L subgroup data in comparator trials, the NMA was performed on 3L+ patient data, which included both 3L and 4L data. At 2L, the EAG considered the Company's NMA to be appropriate, and to approximate a Bucher ITC between ENDEAVOR (Kd vs Vd) and BOSTON (SVd and Vd). At 3L+, the EAG considered the Company's NMA to be appropriate for the comparison of PanoVd and SVd, which again approximated a Bucher ITC between PANORAMA-1 (PanoVd vs Vd) and BOSTON (SVd and Vd). However, the EAG had strong concerns about the Company's original and updated NMA for the comparison between IxaRd and SVd due to the use of large and heterogeneous evidence network, including a non-randomised comparison, median PFS data, studies considerably older than BOSTON for which the relative treatment effects may no longer be valid, and studies where crossover was not adjusted for in the OS analysis. For the IxaRd comparison, the EAG prefers an unanchored MAIC analysis that the Company provided in response to Clarification. The Company provided unanchored MAICs comparing IxaRd with SVd and Vd. The EAG's preferred MAIC was the comparison with Vd, as this benefitted from the best overlap of patient characteristics and retained the largest effective sample size.

The EAG notes that the results of the ITCs were uncertain, but considers there to be evidence of the inferiority of SVd relative to Kd (2L), IxaRd (3L) and PanoVd (3L) in terms of PFS. The EAG considers the OS analyses more difficult to interpret, due to OS being contingent on all future lines of therapy patients received in BOSTON and comparator trials. However, the EAG considers there to be reasonable evidence of a similar effect on OS for all comparators.

4 Cost effectiveness

Table 39 and Table 40 below presents the incremental cost-effectiveness results of the company's updated (i.e., post clarification) base case results. Results presented in this document are inclusive of a [REDACTED] patient access scheme (PAS) discount for selinexor. Results using list price for selinexor are presented in the company's clarification response.

Table 39. Company's base case results post clarification – SVd versus Kd (2L subgroup)

Interventions	Total Costs (£)	Total LY	Total QALYs	Δ costs (£)	Δ LYs	Δ QALYs	ICER (£/QALY)
Deterministic results							
Kd	319,769	4.28	[REDACTED]	-	-	-	-
SVd	[REDACTED]	3.85	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	605,630 (SW quadrant)
Probabilistic results							
Kd	316,740	-	[REDACTED]	-	-	-	-
SVd	[REDACTED]	-	[REDACTED]	[REDACTED]	-	[REDACTED]	334,464 (SW quadrant)
Abbreviations: ICER, incremental cost-effectiveness ratio; Kd, carfilzomib plus dexamethasone; LY, life year; QALY, quality-adjusted life-year; SVd, selinexor in combination with bortezomib and dexamethasone; SW, south-west.							

Table 40. Company's base case results post clarification – SVd versus 3L comparators

Interventions	Total Costs (£)	Total LY	Total QALYs	Δ costs (£)	Δ LYs	Δ QALYs	Pairwise ICER (£/QALY)
Deterministic results							
SVd	[REDACTED]	3.91	[REDACTED]	-	-	-	-
IxaRd	230,087	3.68	[REDACTED]	[REDACTED]	0.23	[REDACTED]	Dominant
PanoVd	138,207	3.38	[REDACTED]	[REDACTED]	0.53	[REDACTED]	Dominant
Probabilistic results							
SVd	[REDACTED]	-	[REDACTED]	-	-	-	-
IxaRd	225,416	-	2.66	[REDACTED]	-	[REDACTED]	1,293,485 (SW quadrant)
PanoVd	125,546	-	2.35	[REDACTED]	-	[REDACTED]	39,743
Abbreviations: Δ, incremental; 3L, third-line subgroup; 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 in combination bortezomib and dexamethasone; SW, south-west.							

Table 41. Fully incremental analysis for 3L subgroup

Interventions	Total Costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	Incremental ICER (£/QALY)
Deterministic results					
SVd	■	■	-	-	-
PanoVd	138,207	■	■	■	Dominated by SVd
IxaRd	230,087	■	■	■	Dominated by SVd
Probabilistic results					
PanoVd	125,546	■	-	-	-
SVd	■	■	■	■	39,743
IxaRd	225,416	■	■	■	1,293,485
Abbreviations: Δ, incremental; 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; SW, south-west.					

4.1 EAG comment on the company's review of cost effectiveness evidence

The company conducted a single systematic literature review (SLR) in February 2023 to identify cost effectiveness, health-related quality of life (HRQoL), healthcare costs and resource evidence that could inform the cost-effectiveness analysis of selinexor compared to comparator interventions in adult patients with relapsed or refractory multiple myeloma (RRMM) who have received two prior lines of therapy.

The SLR included searches of bibliographic databases (MEDLINE, Embase, Econlit) key regulatory and HTA websites, and conference proceedings.

A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant evidence is presented in Table 42. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 42. Summary of company's systematic literature review and EAG critique

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G 1.1	Appendix G 1.1	Appendix G 1.1	Appropriate. Relevant bibliographic databases, key

				regulatory and HTA websites assessed.
Inclusion/ exclusion criteria	Appendix G 1.2	Appendix G 1.2	Appendix G 1.2	Appropriate.
Screening	Appendix G 1.2	Appendix G 1.2	Appendix G 1.2	Appropriate. PICOS study design criteria used for relevance screening.
Data extraction	Appendix G 1.2	Appendix G 1.2	Appendix G 1.2	Appropriate.
Quality assessment of included studies	Appendix G 1.2	Appendix G 1.2	Appendix G 1.2	Appropriate. Drummond checklist used for quality assessment.
Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life; PICOS, population, intervention, comparators, outcomes, study design.				

Overall, the company's SLR identified 358 records which met the inclusion criteria after primary and secondary screening. Of these five provided cost-effectiveness evidence relevant to the decision problem, 45 provided usable HRQoL evidence and two cost and resource use evidence.

The five cost-effectiveness studies identified by the company as relevant to the decision problem were cost-utility analyses of relevant comparators. Three studies were NICE technology appraisals (TA657, TA380 and TA870) of carfilzomib with dexamethasone (Kd), panobinostat in combination with bortezomib and dexamethasone (PanoVd) and ixazomib in combination with lenalidomide and dexamethasone (IxaRd), as well as two SMC reviews of Kd and PanoVd.⁴⁸⁻⁵² Table 21 and Table 23 of the company submission (CS) presents a summary of the cost-effectiveness studies and key features of the economic models.

The cost-effectiveness studies were used by the company to inform the approach to the *de novo* cost-effectiveness model (CEM), while the HRQoL studies were used to validate the health state utilities calculated by the company and cost and resource use studies used to inform the additional health care resource use and costs included in the CEM.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 43 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 43. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Appropriate
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis with fully incremental analysis has been provided by the company.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime (35 years)
Synthesis of evidence on health effects	Based on systematic review	The company performed an appropriate systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs based on EQ-5D-5L data from BOSTON, mapped to EQ-5D-3L, used in the base case analysis.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L data obtained directly from patients in BOSTON, mapped to EQ-5D-3L using the Hernandez-Alava mapping algorithm as recommended by NICE. ^{53, 54}
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Patients in BOSTON are representative of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs included in the analysis have been sourced using NHS reference costs, ⁵⁵ BNF, ⁵⁶ PSSRU, ⁵⁷ and published literature

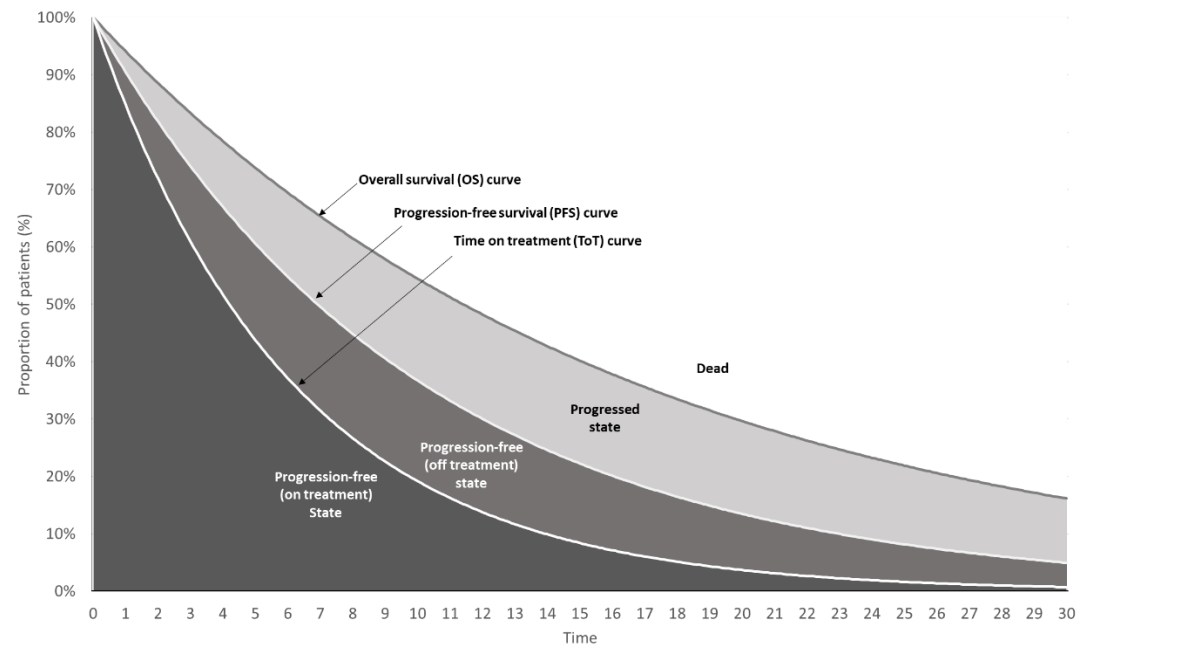
		and are reported in pounds sterling for the price year 2022.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for both costs and health effects.
Abbreviations: EAG, External Assessment Group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year		

4.2.2 Modelling approach and model structure

A single *de novo* economic model was developed in Microsoft® Excel to assess the cost-effectiveness of selinexor in combination with bortezomib and dexamethasone (hereafter referred to as SVd) for the treatment of adult patients with RRMM who have received one or two prior lines of treatment. Cost-effectiveness analyses are presented separately by one prior line of treatment (2L population) and two prior lines of treatment (3L population).

The company adopted a partitioned survival analysis (PartSA) model structure, with three health states: progression-free, progressed and dead. The progression-free health state is further sub-divided into progression-free (on-treatment) and progression-free (off-treatment). Figure 11 presents the company’s PartSA model structure. The company state that the chosen model structure is in line with previous HTA multiple myeloma models.

Figure 11. Partitioned survival model structure (reproduced from Figure 15 of the CS)



All patients enter the model in the progression-free health state and are assumed to start their next line of multiple myeloma (MM) treatment (2L or 3L). During each model cycle, patients in the progression-free health state can be either on-treatment or off-treatment if they are experiencing unacceptable toxicity. From the progression-free health state, patients can transition to either the progressed health state when they experience disease progression or die (thus transitioning to the dead health state). When patients transition to the progressed health state, they remain there until death.

Extrapolations of clinical outcomes data, including progression-free survival (PFS), overall survival (OS) and time to treatment discontinuation (TTD), using standard parametric curves are implemented in the model to estimate the proportion of patients occupying a health state in any given model cycle. PFS is used to estimate the proportion of patients occupying the progression-free health state, OS is used to model the death state and TTD is used to estimate the proportion of patients who are progression-free and on-treatment. The proportion of patients occupying the progressed health state for any given cycle is calculated as the difference between OS and PFS per cycle. A detailed description of how the survival curves were estimated and implemented in the model is provided in Section 4.2.3.

A model cycle length of one week with half-cycle correction applied was implemented in the economic model to facilitate modelling of treatment regimens with varying treatment cycle lengths. The model time horizon was set to 35 years, considered by the company to be sufficiently long enough to capture a lifetime as the median age in BOSTON at baseline was 67 years for the 2L population and 65 years for the 3L population. The perspective of the analysis was based on the UK national health service (NHS), with costs and benefits discounted using a rate of 3.5%, as per the NICE reference case.⁵⁴

4.2.2.1 *ERG Critique*

The EAG considers the structure of the company's economic model is appropriate, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other appraised multiple myeloma models. The one-week length used in the model is suitable for modelling different treatment regimens with varying treatment cycle lengths and adequately captures important changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. Half-cycle correction has been

appropriately applied in the model to prevent over or under-estimation of costs and quality-adjusted life-years (QALYs).

4.2.3 *Treatment effectiveness*

In this section, the EAG first provides a summary of the company's general approach to treatment effectiveness, with the following subsections covering the detail of PFS, OS and TTD included in the economic model.

4.2.3.1 *General approach to treatment effectiveness*

Survival outcomes in the economic model for SVd and Vd are calculated using extrapolations of BOSTON Kaplan Meier (KM) PFS and OS data for the 2L and 3L subgroups. To account for crossover in BOSTON, the company adjusted OS data for Vd from BOSTON using the two-stage estimation approach with re-censoring. The data cut-off point for all analyses was 15 February 2021. Relative treatment effectiveness of comparators was estimated via the company's indirect treatment comparison (ITC), described in Section 3.4. The hazard ratios (HRs) generated from the company's ITC (presented in Table 44) were applied to the baseline SVd extrapolations of PFS and OS.

Time to treatment discontinuation (TTD) estimates in the model for SVd and Vd are based on extrapolations of TTD KM data for 2L and 3L subgroups from BOSTON. For the comparators, trial-level TTD data were not publicly available, therefore the company applied PFS HRs from the ITC to the baseline TTD extrapolation for SVd. The company explored a scenario where TTD was equal to PFS for all treatments in the model.

To select the best survival curve for the extrapolation of BOSTON KM data for PFS, OS and TTD, the company first assessed whether the assumption of proportional hazards (PH) held for each outcome for both the 2L and 3L subgroups from BOSTON, using log-cumulative hazard plots and Schoenfeld residuals plots. The company used the outcomes of the PH assessment to decide to either jointly or independently fit survival distributions. Extrapolations of the KM data were then performed using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma). However, the EAG notes, that of the models explored, only the exponential, Weibull and Gompertz distributions support the proportional hazards assumption.⁵⁸

To select an appropriate distribution for the extrapolation of each outcome, the company assessed the fit of each modelled curve against the observed KM data using statistical goodness of fit

statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the model. Table 45 summarises the company's base case selection of survival curves for PFS, OS and TTD alongside estimated mean life-years by treatment for each outcome. Plots of the survival curves for PFS, OS and TTD are presented in the following subsections.

Table 44. Company base case comparator hazard ratios from the ITC versus SVd

Comparator	PFS hazard ratio vs SVd (95% CrI)	OS hazard ratio vs SVd (95% CrI)
2L subgroup		
Kd	0.727 (0.308 to 1.673)	0.887 (0.321 to 2.452)
3L subgroup		
IxaRd	0.692 (0.118 to 3.291)	1.094 (0.236 to 5.181)
PanoVd	0.797 (0.262 to 2.281)	1.240 (0.454 to 3.462)

Abbreviations: 2L, second-line; 3L, third-line; CrI, credible interval; ITC, indirect treatment comparison; IxaRd, ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; PanoVd, panobinostat with bortezomib and dexamethasone; SE, standard error; SVd, selinexor with bortezomib and dexamethasone; vs, versus.

Table 45. Summary of company's base case selection of survival curves and estimated mean life-years by treatment

Outcome	2L subgroup				3L subgroup				
	Extrapolation	Mean LYs			Extrapolation	Mean LYs			
		SVd	Vd	Kd		SVd	Vd	IxaRd	PanoVd
PFS	Independently fitted Gamma distribution	2.30	1.36	3.15	Jointly fitted lognormal distribution	1.92	1.25	2.68	2.32
OS	Jointly fitted Gamma distribution	3.85	3.24	4.28	Jointly fitted Weibull distribution	3.91	2.50	3.68	3.38
TTD	Jointly fitted Gamma distribution	1.12	1.00	1.50	Jointly fitted log-logistic distribution	1.04	0.95	1.64	1.36

Abbreviations: 2L, second-line; 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; LYs, life years; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; PFS, progression-free survival; SVd, selinexor with bortezomib and dexamethasone; TTD, time to treatment discontinuation; Vd, bortezomib with dexamethasone.

4.2.3.2 EAG critique of the general approach

Overall, the EAG considers the company's general approach to the survival analysis for PFS, OS and TTD to be generally appropriate. However, the EAG has concerns around the interpretation of the PH assumption for PFS, OS and TTD from BOSTON and the selection of curves supporting the PH assumption. Based on log-cumulative hazard plots and Schoenfeld residual plots presented in Section B.3.4.1 and B.3.4.2 of the CS, the company concluded that the PH assumption was not violated for OS and TTD for both the 2L and 3L subgroups and for PFS for the 3L subgroup only, and so chose to model these outcomes jointly for SVd and Vd, with comparator HRs applied to the SVd curve as the baseline. For the 2L subgroup, the company concluded that the PH assumption was violated for PFS and used independently fitted curves for SVd and Vd, with comparator HRs from the ITC applied to the SVd curve as the baseline.

The EAG investigated the diagnostic plots supplied in the CS but based on visual inspection, concluded that the PH assumption was violated for PFS, OS and TTD for both the 2L and 3L subgroups. For the log-cumulative hazards plots, curves which are not straight, crossing, overlapping or non-parallel indicated a violation of the proportional hazards assumption and this was seen for OS, where for the 3L subgroup, curves were not straight (Figure 16 of the CS) and for the 2L subgroup curves were crossing (Figure 22 of the CS). For the 3L subgroup, the PFS log-cumulative hazard plots showed curves which were non-parallel and slightly curved (Figure 18 of the CS). Curves on the log-cumulative hazards plots for TTD for both subgroups were overlapping and crossing (Figure 20 and Figure 26 of the CS). All Schoenfeld residual plots produced lines which were not straight, suggesting visually that the PH assumption did not hold.

Additionally, the EAG recalled guidance provided in the NICE Decision Support Unit technical support document 14 (DSU TSD 14), which states that, *"when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach – the assumption should be tested which will indicate whether it may be preferable to separately fit parametric models to each treatment arm"*.⁵⁸

As such, the EAG considers that it is more robust to use independently fitted models for PFS, OS and TTD as the company has access to patient-level data from BOSTON and it removes the need to assume proportional hazards holds between SVd and Vd.

Additionally, because the EAG considers that the PH assumption does not hold for outcomes within BOSTON, using SVd extrapolations of outcomes as the baseline to apply comparator HRs is not appropriate. As Vd is the common treatment to link into the network for the ITC, the EAG considered that the PH assumption should be investigated for the trials informing the network for the 2L and 3L analysis to determine if it is appropriate to use Vd as the baseline for comparator outcomes in the economic model.

During the clarification stage, the EAG asked the company to explore whether the PH assumption holds for trials informing the 2L and 3L+ networks (clarification question A16). The company provided the requested analyses in response to clarification question A16 and found that for most of the trials informing the 2L and 3L+ networks, the PH assumption held for PFS. However, the company considered that for OS, the PH assumption was violated for some trials included in the 3L+ network but held for 2L network.

The EAG assessed the OS diagnostic plots provided in response to clarification question A16, but considered that for ENDEAVOR in the 2L network, OS curves for Kd and Vd were overlapping (OS HR 0.77, 95% CI: 0.58 to 1.02) and the same was seen for ICARIA-MM (isatuximab with pomalidomide and dexamethasone versus pomalidomide plus dexamethasone, OS HR 0.76, 95% CI: 0.57 to 1.01) in the 3L+ network, indicating that for these trials there is no significant difference in OS. The EAG considers this finding more important than determining if PH holds. Whether there is an OS benefit for treatments early in the RRMM pathway is a key issue for the cost-effectiveness analysis, and the EAG considers that it may be appropriate to assume equal OS for all treatments, but this is explored further in Section 4.2.3.6.

Overall, the EAG considers that as Vd is the common comparator to link into the network for the ITC and the PH assumption for PFS holds for most of the trials (which may be considered the more clinically important outcome), it is more appropriate that Vd is used as the baseline to apply comparator HRs from the ITC to for PFS, OS and TTD for both the 2L and 3L subgroups.

During the clarification stage, the EAG requested, and the company supplied, scenarios exploring the company's preferred independently fitted PFS, OS and TTD curves for SVd and Vd with comparator HRs from the ITC applied to the Vd curve (response to clarification question B4 and B5). As discussed in Section 3.4, the EAG had some concerns with the company's base case ITC results and instead put forward an alternative view for ITC estimates for comparators to inform the EAG's preferred

assumptions. Table 46 presents the EAG's preferred HRs versus Vd from the ITC and Table 47 summarises the company's approach to the scenario using Vd as the baseline in the economic model and results of the scenario are presented in Section 6.2. Plots of the survival curves for PFS, OS and TTD are presented in the following subsections and summarised in Appendix 8.1.

Table 46. EAG preferred Comparator hazard ratios versus Vd

Comparator	PFS hazard ratio vs Vd	OS hazard ratio vs Vd
2L subgroup		
Kd	0.45 [0.26 to 0.80]	0.77 [0.39 to 1.53]
3L subgroup		
IxaRd	0.37 [0.63 to 2.64]	0.48 [0.29 to 0.79]
PanoVd	0.64 [0.27 to 3.00]	0.96 [0.85 to 1.89]

Abbreviations: 2L, second-line; 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; vs, versus.

Table 47. Company's approach to Vd as the baseline for the estimation of comparator treatment effectiveness

Outcome	2L subgroup				3L subgroup				
	Extrapolation	Mean LYs			Extrapolation	Mean LYs			
		SVd	Vd	Kd		SVd	Vd	IxaRd*	PanoVd
PFS	Independently fitted Gamma distribution	2.30	1.36	2.99	Independently fitted lognormal distribution	1.77	1.38	2.68	2.29
OS	Independently fitted Gamma distribution	3.99	3.13	3.91	Independently fitted Gamma distribution	3.81	3.01	3.47	3.12
TTD	Independently fitted Gamma distribution	1.12	0.99	2.08	Independently fitted lognormal distribution	0.98	1.01	2.17	1.81

Abbreviations: 2L, second-line; 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; LYs, life years; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; MAIC, matched-adjusted indirect comparison; PFS, progression-free survival; SVd, selinexor with bortezomib and dexamethasone; TTD, time to treatment discontinuation; Vd, bortezomib with dexamethasone.

*In the company's scenario, the IxaRd vs Vd HR from the ITC is 0.56 for PFS and 0.85 for OS. As mentioned in Section 3.4.3, the EAG prefers HRs for IxaRd vs Vd from the unanchored MAIC.

The Vd baseline scenario, using the company's preferred ITC estimates for the comparators did not change the direction of the ICER for the 3L subgroup, remaining dominant against IxaRd and PanoVd. However, for the 2L subgroup analysis, the deterministic ICER switched from £605,630 (south-west

quadrant) to dominant. The EAG notes, that in the company's base case for the 2L subgroup, OS for SVd was lower than Kd, in line with the results from the ITC but when using Vd as the baseline, OS for SVd is marginally better than Kd, resulting in a QALY gain of 0.1 and switching the deterministic ICER to dominant. As mentioned previously, the estimation of an OS benefit for treatments is a key issue for the cost-effectiveness analysis and this is discussed further in Section 4.2.3.6.

Nonetheless, the EAG considers that independently fitted survival curves for SVd and Vd from BOSTON, along with using Vd as the baseline to apply comparator treatment effects is appropriate and thus is included in the EAG base case presented in Section 6.3. However, the EAG considers the choice of independently fitted survival curves selected by the company do not support the PH assumption, and this is key when applying HRs from the ITC for the comparators to the baseline curve. The EAG recalled guidance from DSU TSD 14, which states that, *"Where one HR is applied to the entire modelled period, the proportional hazards assumption must be made"*.⁵⁸ The only models which support the PH assumption are the exponential, Weibull and Gompertz distributions. This issue is discussed further in the below subsections.

4.2.3.3 Progression-free survival

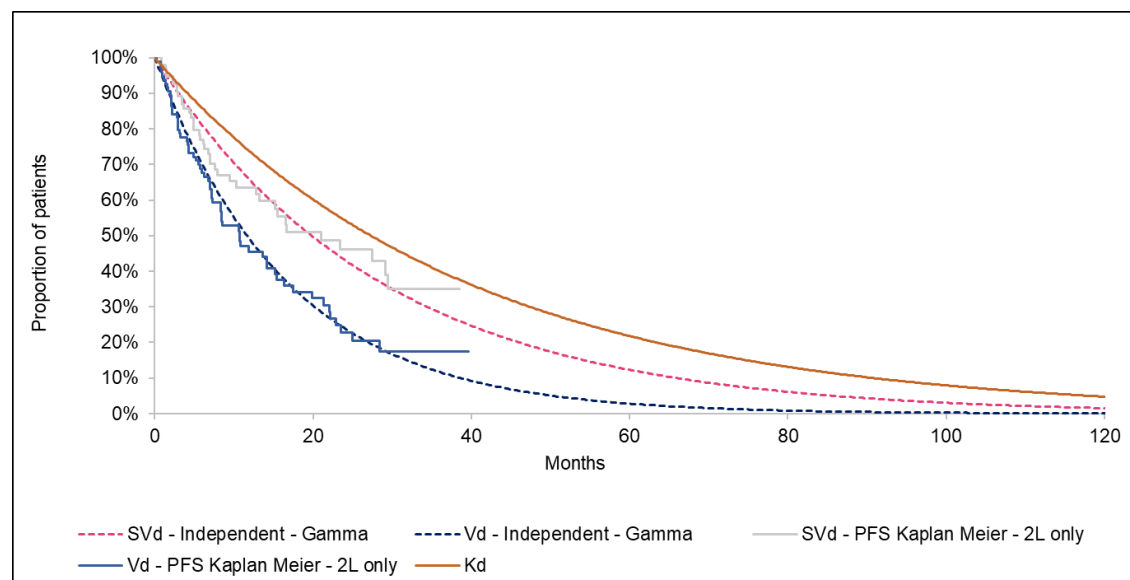
Based on the log-cumulative hazard plots and Schoenfeld residuals (Figure 18 and Figure 24 of the CS for the 3L and 2L subgroups, respectively), the company considered that the PH assumption held for PFS for the 3L subgroup from BOSTON and decided to use jointly fitted survival curves for SVd and Vd for the base case. For the 2L subgroup, the company considered the PH assumption was violated and thus for the base case, chose to use independently fitted survival curves for SVd and Vd.

The company used the extrapolation of SVd PFS as the baseline curve to apply comparator HRs obtained from the ITC described in Section 3.4 and presented earlier in Table 44. For the extrapolation of SVd PFS, the company selected the gamma distribution for the 2L subgroup and the lognormal distribution for the 3L subgroup, based on AIC/BIC statistics, visual fit and advice from the company's clinical experts that PFS exceeding 10% beyond 10 years was unlikely. However, the EAG notes that the company did not consider if the selected distributions support the PH assumption and whether there were any real-world datasets that could have been used to inform the selection of an appropriate survival extrapolation.

In the model, PFS is capped to OS to ensure that the per-cycle probability of being alive and progression-free does not exceed the per-cycle probability of death. Extrapolations of PFS for all

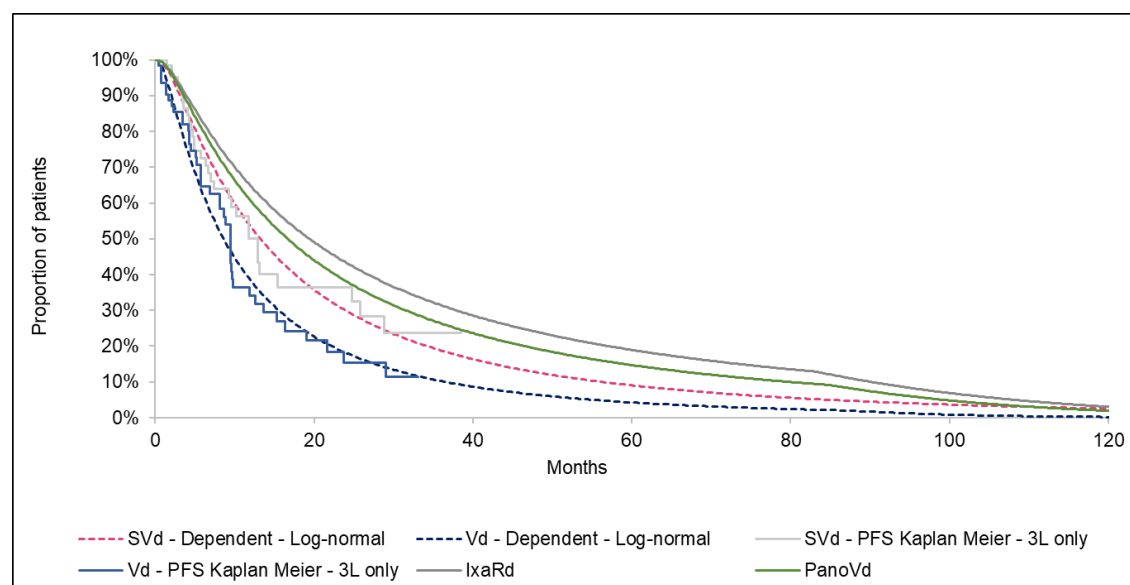
treatments for the 2L and 3L subgroups are presented in Figure 12 and Figure 13 and landmark estimates of PFS for treatments by subgroups are presented in Table 51.

Figure 12. Extrapolation of PFS for SVd, Vd and Kd – 2L subgroup



Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

Figure 13. Extrapolation of PFS for SVd, Vd, IxaRd and PanoVd – 3L subgroup



Abbreviations: 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; KM, Kaplan-Meier; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

Table 48. Landmark estimates of PFS for treatments by subgroup included in the economic model

Treatments	Estimated PFS at 5 years	Estimated PFS at 10 years	Estimated PFS at 20 years	Estimated PFS at 30 years
2L subgroup				
SVd	12.39%	1.53%	0.02%	0.00%
Kd	21.92%	4.79%	0.23%	0.01%
3L subgroup				
SVd	9.08%	2.55%	0.02%	0.00%
IxaRd	19.01%	3.09%	0.01%	0.00%
PanoVd	14.77%	1.95%	0.00%	0.00%
Abbreviations: 2L, second-line; 3L, third-line; IxaRd; ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; PanoVd, panobinostat with bortezomib and dexamethasone; PFS, progression-free survival; SVd, selinexor with bortezomib and dexamethasone.				

Plots of all the assessed distributions compared with the KM data and AIC/BIC statistics can be found in Figure 19 and Table 25 of the CS for the 3L subgroup and Figure 25 and Table 28 of the CS for the 2L subgroup. Additionally, the company explored all jointly and independently fitted standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) in scenario analyses to assess the impact of alternatives curves on the ICER.

4.2.3.4 EAG critique of progression-free survival

The EAG considers that the company's approach to model PFS curves independently for the 2L subgroup is appropriate as the PH assumption did not appear to hold based on the diagnostic plots presented in the CS. However, as HRs from the ITC are used to estimate survival curves for the comparators, the chosen distribution needs to support the PH assumption. As mentioned earlier, the only distributions which support the PH assumption are the exponential, Weibull and Gompertz.⁵⁸

As the company's preferred independently fitted gamma curve does not support the PH assumption, the EAG assessed the fit and clinical plausibility of the independently fitted exponential, Weibull and Gompertz curves. The EAG considered that the Weibull curve had a marginally better visual fit and similar statistical fit to the company's selected gamma curve.

To assess the long-term PFS estimates, beyond the observed data, the EAG performed a targeted search for real-world long-term survival for patients at 2L on Vd and Kd but was unable to find relevant published data. Instead, the EAG relied on advice from its clinical experts to validate the company's estimates of survival in the model. The Weibull curve produced an estimate of mean PFS

of around 2.38 years for SVd, which was considered to be clinically plausible, as the EAG's clinical experts advised that at 2L, in their clinical experience, average remission is around two years.

For the 3L subgroup, the EAG considers that diagnostic plots showed a violation of the PH assumption and thus joint modelling of PFS for SVd and Vd is inappropriate and independent models are preferred. Additionally, the company's selection of the jointly fitted lognormal curve is an accelerated failure time (AFT) model not a PH model and did not provide a good visual fit to the observed KM between 12 to 24 months, with the OS cap being implemented for the comparators at around seven years (Figure 13). The OS cap affects the PanoVd arm more, as in the company's base case, the PFS HR for PanoVd was 0.797, but the 10-year estimate of PFS was 1.95%, compared with 2.55% for the SVd arm.

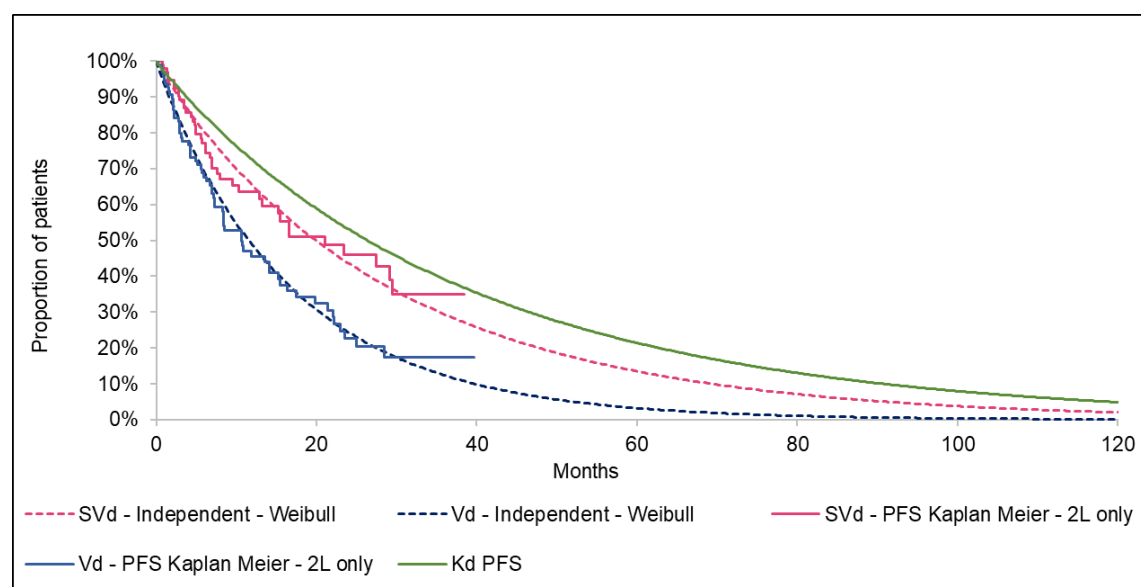
During the clarification stage, the EAG requested the company to present its preferred independent extrapolation of PFS for the 3L subgroup and they selected the lognormal curve for both SVd and Vd, stating that estimated PFS is consistent with OS (i.e. the OS cap is not implemented) and had a good visual fit to the observed data from BOSTON. The EAG highlights, that while the OS cap is not needed for SVd using the independent lognormal curve, it is implemented for IxaRd and PanoVd and all curves converge at around 11 years.

The EAG considers that use of the independently fitted lognormal curve produces results for the comparators that are more consistent with the HRs produced from the ITC, with 10-year PFS estimates of 1.73%, 2.76% and 1.72% for SVd, IxaRd and PanoVd, respectively. However, the EAG again highlights, that the lognormal does not support the PH assumption.

As mentioned earlier, because comparator PFS curves are estimated using a HR from the ITC, the only eligible survival models that can be considered are the exponential, Weibull and Gompertz distributions. The EAG investigated whether one of these was suitable for use in the 3L analysis but found that none provided a good fit to the observed data. As the company's preferred lognormal curve is an AFT model, it is more appropriate to estimate an AFT factor from the ITC. Thus, to resolve this issue, the EAG requests the company to provide analysis for the 3L subgroup to estimate an AFT factor for the comparators to apply to the preferred lognormal curve. In lieu of the AFT analysis, the EAG includes the lognormal curve in its preferred base case, but acknowledges the limitations of estimating comparators curves using an HR applied to an AFT model.

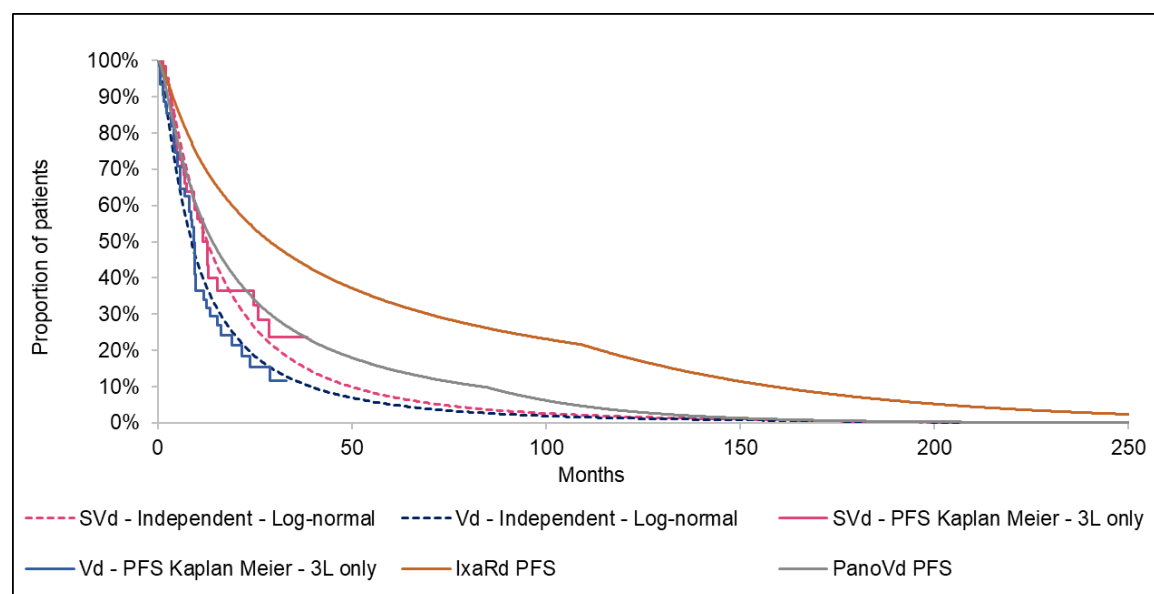
As mentioned in Section 4.2.3.2, the EAG prefers to use the Vd curve as the baseline to apply comparator HRs from the ITC for all outcomes, including PFS (see Table 46 for comparator HRs vs Vd). Therefore, for its preferred assumptions (presented in Section 6.3), the EAG considers that independently fitted models for PFS are preferred along with use of the Vd curve as the baseline for applying comparator treatment effects from the ITC (presented in Table 46). Additionally, the independently fitted Weibull curve for the 2L subgroup and lognormal curve for the 3L subgroup are included in the EAG base case, with the acknowledgement that use of the lognormal curve to estimate comparator curves is a limitation. Figure 14 and Figure 15 presents the independently fitted PFS curves, with Vd used as the baseline to apply the EAG's preferred comparator HRs from the ITC (presented in Table 46) for the 2L and 3L subgroups and these have been used in the EAG's preferred base case, presented in Section 6.3.

Figure 14. Extrapolation of PFS for SVd, Vd and Kd using independently fitted Weibull curves and with Vd used as the baseline to apply comparator HR – 2L subgroup



Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

Figure 15. Extrapolation of PFS for SVd, Vd, IxaRd and PanoVd using independently fitted lognormal curves and with Vd used as the baseline to apply comparator HRs – 3L subgroup



Abbreviations: 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

4.2.3.5 Overall Survival

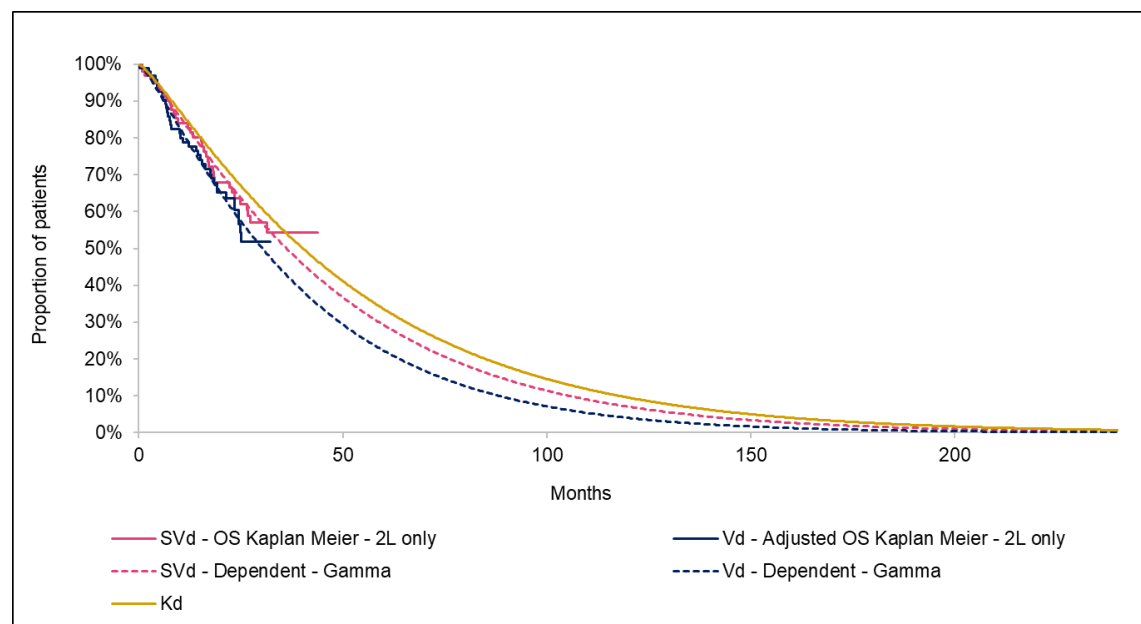
In BOSTON, patients in the Vd arm of the trial could crossover to SVd or selinexor with low-dose dexamethasone (Sd) upon disease progression. In the clinical study report (CSR) for BOSTON, independent review committee (IRC) confirmation of progressed disease for those patients in the Vd arm was required prior to crossover and initiation of SVd or Sd. In the intention-to-treat (ITT) population, 77 (37%) Vd patients crossed over to SVd or Sd upon confirmed disease progression.

The company adjusted Vd OS data for crossover using the two-stage estimation (TSE) method with re-censoring applied, in line with analyses submitted to the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA). Kaplan-Meier curves for SVd and Vd (adjusted for crossover) for both the 2L and 3L subgroup are presented in Figure 8 of the CS and these are used to inform the survival analysis of OS included in the economic model.

Based on the log-cumulative hazard plots and Schoenfeld residuals (Figure 16 and Figure 22 of the CS for the 3L and 2L subgroups, respectively), the company considered that the PH assumption held for OS for both the 2L and 3L subgroups from BOSTON and decided to use jointly fitted survival curves for SVd and Vd for the base case.

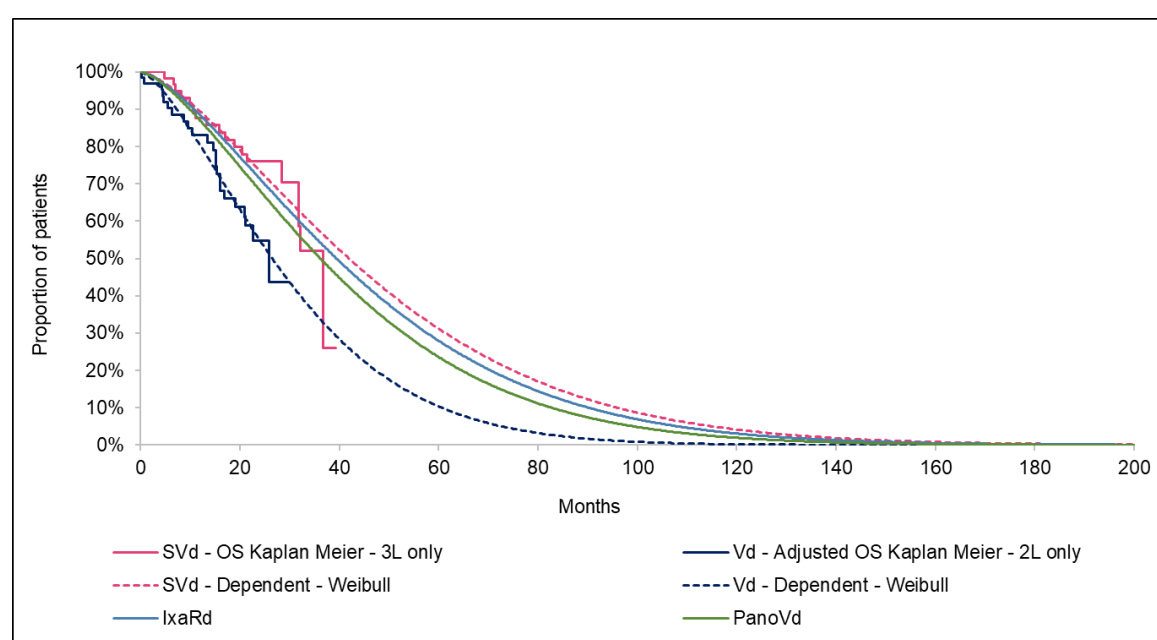
The company used the extrapolation of SVd OS as the baseline curve to apply comparator treatment effects obtained from the indirect treatment comparisons described in Section 3.4 and presented earlier in Table 44. For the extrapolation of SVd OS, the company selected the gamma distribution for the 2L subgroup and the Weibull distribution for the 3L subgroup, based on AIC/BIC statistics, visual fit and advice from the company's clinical experts that OS exceeding 10% beyond 10 years was unlikely and also all extrapolations that predicted 0% survival at 10 years were clinically implausible. Additionally, the company considered consistency in OS extrapolations between the 2L and 3L subgroups, such that the 3L extrapolation of OS could not exceed the 2L extrapolations. However, the EAG notes that gamma distribution does not support the PH assumption. Extrapolations of SVd OS for the 2L and 3L subgroups are presented in Figure 12 and Figure 13, with landmark estimates of OS for treatments by subgroups presented in Table 49.

Figure 16. Extrapolation of OS for SVd, Vd and Kd – 2L subgroup



Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; OS, overall survival; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

Figure 17. Extrapolation of OS for SVd, Vd, IxaRd and PanoVd – 3L subgroup



Abbreviations: 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; KM, Kaplan-Meier; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

Table 49. Landmark estimates of OS for treatments by subgroup included in the economic model

Treatments	Estimated OS at 5 years	Estimated OS at 10 years	Estimated OS at 20 years	Estimated OS at 30 years
2L subgroup				
SVd	29.37%	7.08%	0.37%	0.02%
Kd	33.74%	9.55%	0.70%	0.05%
3L subgroup				
SVd	31.35%	4.17%	0.02%	0.00%
IxaRd	28.11%	3.09%	0.01%	0.00%
PanoVd	23.75%	1.95%	0.00%	0.00%

Abbreviations: 2L, second-line; 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; PanoVd, panobinostat with bortezomib and dexamethasone; OS, overall survival; SVd, selinexor with bortezomib and dexamethasone.

In the model, OS is capped by age- and sex-adjusted general population mortality estimates.⁵⁹ Plots of all the assessed distributions compared with the KM data and AIC/BIC statistics can be found in Figure 1 and Table 24 of the CS for the 3L subgroup and Figure 23 and Table 27 of the CS for the 2L subgroup. As with PFS, the company explored all jointly and independently fitted standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) in scenario analyses to assess the impact of alternatives curves on the ICER.

4.2.3.6 EAG critique of overall survival

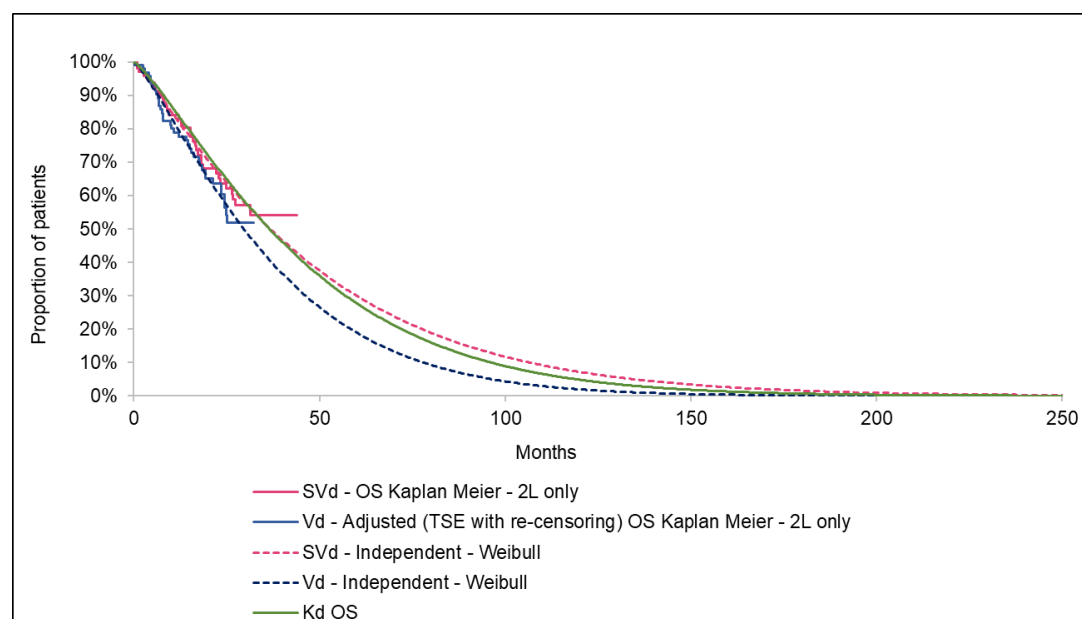
As mentioned in Section 4.2.3.2, the EAG considers that diagnostic plots for OS for both the 2L and 3L subgroups showed a violation of the PH assumption and thus joint modelling of OS for SVd and Vd is inappropriate and independent models are preferred. During the clarification stage, the EAG requested the company to present its preferred independent extrapolation of OS for the 2L and 3L subgroups. The company selected the gamma curve for both SVd and Vd for both subgroups, stating that estimated 10- years OS estimates fall within 1-10% range suggested by its clinical experts. However, the EAG notes that the gamma distribution does not support the assumption of PH to apply HRs from the ITC for the comparators to the selected curve. Furthermore, the company did not investigate whether there were any real-world datasets that could have been used to inform the selection of an appropriate survival extrapolation.

The EAG investigated the independently fitted exponential, Weibull and Gompertz distributions, as these support PH, for the 2L and 3L subgroups. Additionally, the EAG performed a targeted search for real-world long-term survival for RRMM patients at different lines of treatment to validate the estimates produced in the model, but was unable to find relevant published data. Instead, the EAG relied on advice from its clinical experts to validate the company's estimates of survival in the model.

For the 2L subgroup, the EAG considers that the Weibull curve had the best statistical fit out of all the assessed independently fitted curves, was considered to produce clinically plausible estimates of OS and had a similar visual fit to the observed data as the company's preferred gamma distribution. The Weibull curve produced more conservative estimates of OS compared to the gamma curve but had minimal impact on the ICER (see results of scenario in the company's updated results document post clarification). However, as the Weibull curve supports the PH assumption, the EAG considers it to be more appropriate for the analysis and has included it in its preferred assumptions.

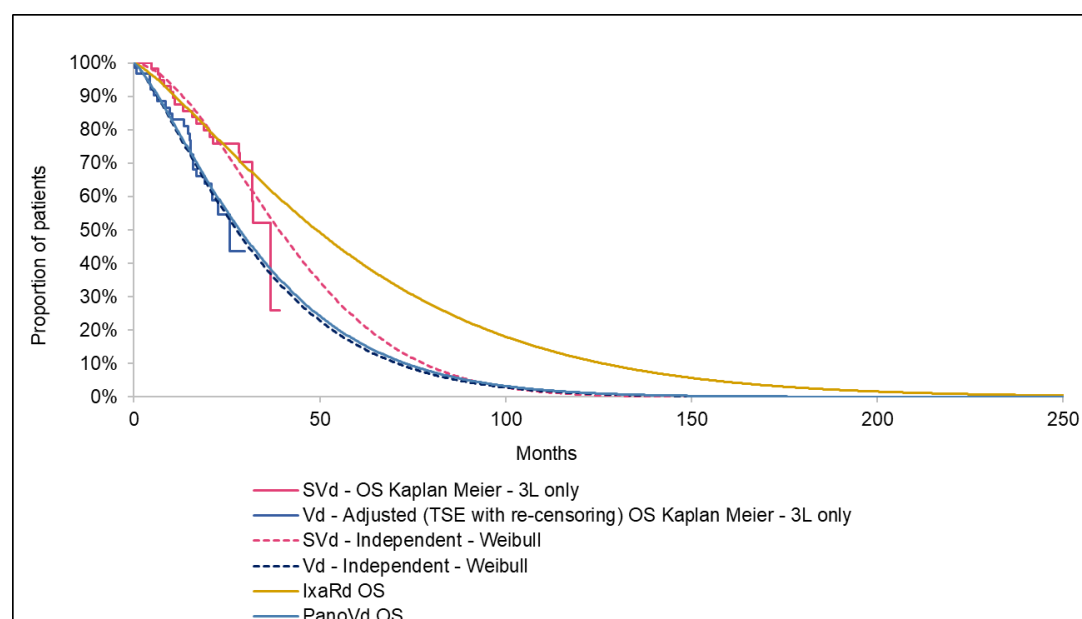
For the 3L subgroup, the EAG considered the Weibull curve provided a good fit to the observed data, with 10-year survival for SVd, lxaRd and PanoVd estimated to be under 1% for all treatments. Figure 18 and Figure 15 presents the independently fitted OS curves for the 2L and 3L subgroups, with Vd used as the baseline to apply the EAG's preferred comparator HRs from the ITC (presented in Table 46).

Figure 18. Extrapolation of OS for SVd, Vd and Kd using independently fitted Weibull curves and with Vd used as the baseline to apply comparator HR – 2L subgroup



Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; OS, overall survival; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone

Figure 19. Extrapolation of OS for SVd, Vd, IxaRd and PanoVd using independently fitted Weibull curves and with Vd used as the baseline to apply comparator HR – 3L subgroup



Abbreviations: 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; KM, Kaplan-Meier; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

The EAG notes that the OS extrapolation of Kd is slightly worse compared with SVd, which is different to ITC OS estimate of Kd vs SVd, but this is a function of using Vd as the baseline curve. However, the assumption of an OS benefit for any of the treatments considered for the 2L and 3L analysis is a key concern for the EAG. Overall survival in BOSTON is highly uncertain, even with adjustments made for crossover, as data are immature (median not reached for the 2L subgroup) and crossover adjusted OS HRs for the ITT, 2L and 3L analyses are not statistically significant (95% confidence intervals cross one, see Table 50). Additionally, based on data from the trials for comparators considered in the analysis (Kd, IxaRd and PanoVd), no statistically significant differences in OS were observed, based on the 95% CIs around the OS HRs presented in Table 50.

Differences in subsequent treatments received upon disease progression are likely to have a significant influence on OS. Even though for BOSTON, Vd OS analysis was adjusted for crossover, the EAG noted other differences in subsequent treatments received in the SVd and Vd groups (Table 38, Section 3.4.3.4.2). Such imbalances were also observed in key comparator trials, and likely introduce substantial bias into the ITC estimates of OS differences between SVd, Vd and key comparators (Section 3.4.3.4.2).

Table 50. Overall survival hazard ratios from key trials informing the cost-effectiveness analysis

Key trials	Overall survival hazard ratio (95% CI)
2L subgroup	
BOSTON: SVd vs Vd	0.909 (0.570 to 1.450)
ENDEAVOR: Kd vs Vd	0.771 (0.583 to 1.018)
3L subgroup	
BOSTON: SVd vs Vd	0.612 (0.321 to 1.166)
TOURMALINE-MM1: IxaRd vs Rd	0.845 (0.642 to 1.114)
PANORAMA-1: PanoVd vs Vd	0.96 (0.74 to 1.26)
Abbreviations: 2L, second-line; 3L, third-line; CI, confidence interval; IxaRd; ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; PanoVd, panobinostat with bortezomib and dexamethasone; OS, overall survival.	

As mentioned earlier, the EAG performed a targeted search for real-world long-term survival for RMM patients at 2L and 3L to validate the estimates produced in the model, but was unable to find relevant published data.

As such, the EAG consulted with its clinical experts around expected OS for RRMM patients at different lines of treatment and their view was aligned with the data from the key trials. The EAG's clinical experts considered that after one prior line of treatment, patients' OS is likely to be similar

irrespective of the treatments they receive at different lines, as they are unlikely to be off treatment until they get to their sixth line of treatment. As such, improvements in PFS at each line are potentially more clinically relevant. Moreover, the EAG considers that OS from BOSTON includes the survival impact of subsequent treatments for patients who progress to 3L and beyond.

In the CS, the company explored scenario analyses which assumed an OS HR of 1 for all comparators (i.e. no OS benefit for any treatments) with SVd as the baseline OS. While the EAG considers assuming no OS benefit for all treatments is relevant for decision-making as it reduces the uncertainty in the economic model, the issue of using SVd as the baseline curve is relevant. As mentioned in Section 4.2.3.2, because the EAG considers that the PH assumption doesn't hold between SVd and Vd in BOSTON, using SVd extrapolations of outcomes as the baseline to apply comparator HRs is not appropriate. Instead, the EAG prefers the use of Vd curve as the baseline to apply comparator treatment effects (which will assume an OS HR of 1).

For consistency with PFS, the EAG has included the use of the Vd OS as the basis of OS for all treatment comparisons and using the independent Weibull OS curve for both 2L and 3L subgroups in its preferred base case (Section 6.3). A scenario around the EAG base case using SVd as the OS curve for all treatments is also presented in Section 6.3. Additionally, even though the EAG considers that OS is highly uncertain, the committee may consider that an OS benefit is plausible, therefore the EAG includes a scenario around its base case that includes an OS benefit, using the Weibull curves for the extrapolation of SVd OS and estimating comparator OS using the EAG preferred ITC HRs (presented in Table 46) applied to the Vd Weibull OS curve for both the 2L and 3L subgroups.

4.2.3.7 Time to treatment discontinuation

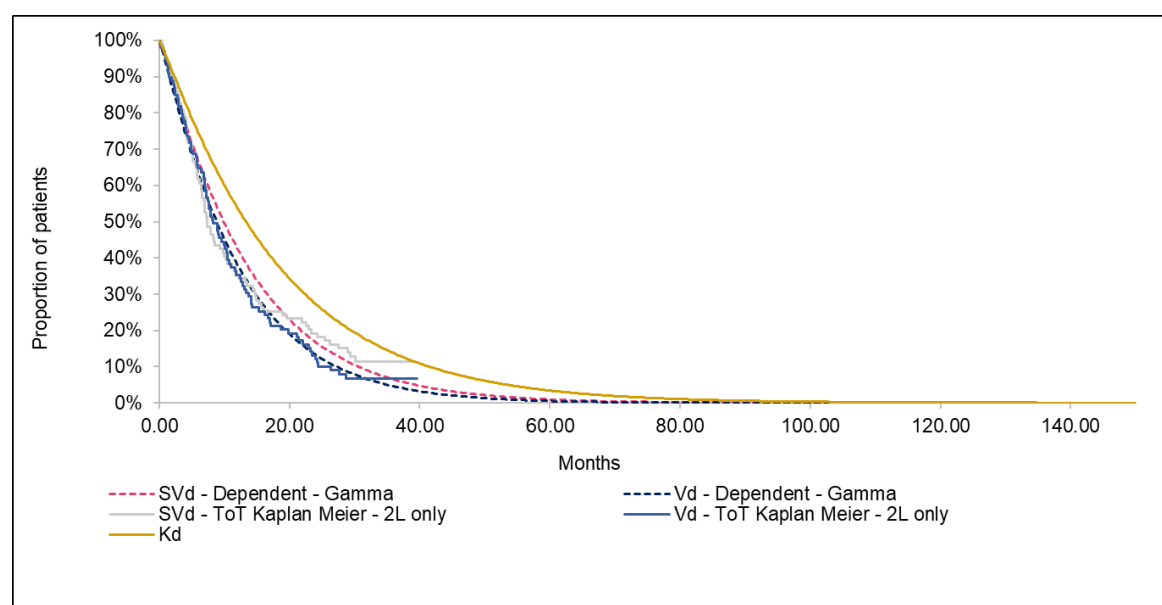
Based on the log-cumulative hazard plots and Schoenfeld residuals (Figure 20 and Figure 26 of the CS for the 3L and 2L subgroups, respectively), the company considered that the PH assumption held for TTD for both the 2L and 3L subgroups from BOSTON and decided to use jointly fitted survival curves for SVd and Vd for the base case. For the extrapolation of SVd TTD, the company selected the gamma distribution for the 2L subgroup and the log-logistic distribution for the 3L subgroup, based on AIC/BIC statistics, visual fit and advice from the company's clinical experts that most patients would discontinue treatment before 10 years. Extrapolations of SVd TTD for the 2L and 3L subgroups are presented in Figure 20 and Figure 21.

Published TTD KM data for comparators considered in the model for each subgroup were not available. As such, for the base case the company applied PFS HRs from the ITC to the baseline TTD extrapolation for SVd (see Table 44). Additionally, the company explored scenarios where TTD was equal to PFS for all treatments in the model.

In the company base case, TTD does not exceed PFS, but a TTD to PFS cap is available in the model to ensure patients are not accruing treatment costs if they have disease progression. Ten-year TTD landmark estimates for treatments by subgroups are presented in Table 51.

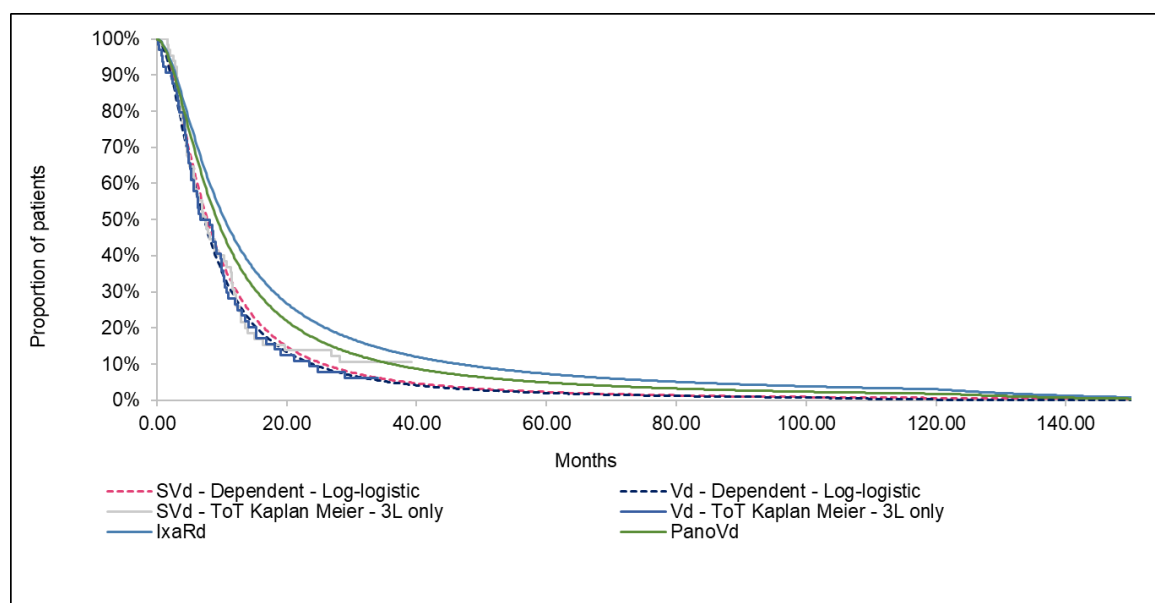
Plots of all the assessed distributions compared with the KM data and AIC/BIC statistics can be found in Figure 21 and Table 26 of the CS for the 3L subgroup and Figure 27 and Table 29 of the CS for the 2L subgroup. In the CS, the company explored all jointly and independently fitted standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) in scenario analyses to assess the impact of alternatives curves on the ICER.

Figure 20. Extrapolation of TTD for SVd, Vd and Kd – 2L subgroup



Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; OS, overall survival; SVd, selinexor with bortezomib and dexamethasone; ToT / TTD, time to treatment discontinuation; Vd, bortezomib with dexamethasone.

Figure 21. Extrapolation of TTD for SVd, Vd, IxaRd and PanoVd – 3L subgroup



Abbreviations: 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; KM, Kaplan-Meier; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; ToT / TTD, time to treatment discontinuation; Vd, bortezomib with dexamethasone.

Table 51. Ten-year landmark estimates of TTD for treatments by subgroup included in the economic model

Treatments	Estimated TTD at 10 years
2L subgroup	
SVd	0.01%
Kd	0.10%
3L subgroup	
SVd	0.65%
IxaRd	3.07%
PanoVd	1.81%

Abbreviations: 2L, second-line; 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; TTD, time to treatment discontinuation

4.2.3.8 EAG critique of time-to-treatment discontinuation

The company chose to model TTD for SVd and Vd jointly based on diagnostic plots demonstrating that the PH assumption holds. Joint models for TTD include a treatment arm coefficient which aims to capture difference between SVd and Vd. However, based on the KM curves and diagnostic plots, the EAG considers that the PH doesn't hold for TTD between SVd and Vd from BOSTON for both

subgroups, primarily because the curves are overlapping indicating no substantial differences. Moreover, TTD data from BOSTON are almost mature for both trial arms and any treatment-related differences in duration of treatment will be present in the KM data. Therefore, independent models are likely to be a more robust to predict TTD outside of the observed data.

During the clarification stage, the EAG requested the company to present its preferred independent extrapolation of TTD for both the 2L and 3L subgroups. For both SVd and Vd, the company selected the gamma curve for the 2L subgroup and the lognormal curve for the 3L subgroup, stating that these curves were consistent with PFS and provided a good visual fit to the observed data, with low impact on cost-effectiveness results. The EAG notes that for 2L subgroup, the gamma curve ranked the lowest in terms of statistical fit amongst the assessed independent distributions and overpredicted TTD between six to 19 months.

Additionally, both the gamma and lognormal distribution do not support the PH assumption. Therefore, the EAG investigated the independently fitted exponential, Weibull and Gompertz distributions, as these support PH, for the 2L and 3L subgroups.

The EAG considers that Gompertz curve provided a better visual fit to both the SVd and Vd observed TTD data for the 2L subgroup and had a better statistical fit compared to the company preferred gamma distribution. Use of the Gompertz curve for the 2L subgroup requires TTD to be capped to PFS, as at the tail of the TTD extrapolation exceeds PFS (after around 10 years).

For the 3L subgroup, KM curves for SVd and Vd overlap and cross in several places, resulting in extrapolations that cross. In the company's scenario exploring the preferred independently fitted lognormal extrapolation of TTD, curves for SVd and Vd crossed, but in the long-term estimates of SVd were higher than Vd.

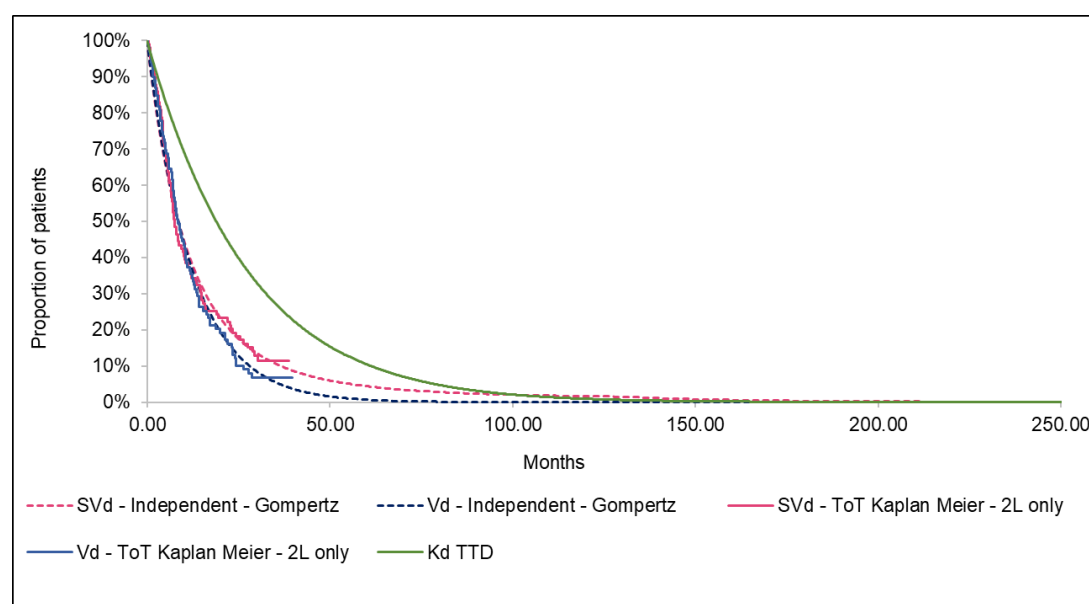
The EAG investigated the exponential, Weibull and Gompertz models to see if they provided a good fit to the observed 3L data but found that none were suitable. The EAG considers that the generalised gamma curve had a better visual to the observed data and ranked second best in terms of statistical fit amongst the assessed independent distributions

For the 3L analysis of TTD in the model, the parameters of the generalised gamma distribution did not indicate this was the same as the Weibull distribution, but instead was more similar to the lognormal distribution. In Section 4.2.3.4, the EAG recommended that the company provide analysis

for the 3L subgroup to estimate a PFS AFT factor for the comparators to apply to the preferred PFS lognormal curve. Given that the company use PFS treatment effects from the ITC to estimate TTD curves for the comparators, the PFS AFT factor could be applied to the generalised gamma curve, which would resolve the issue.

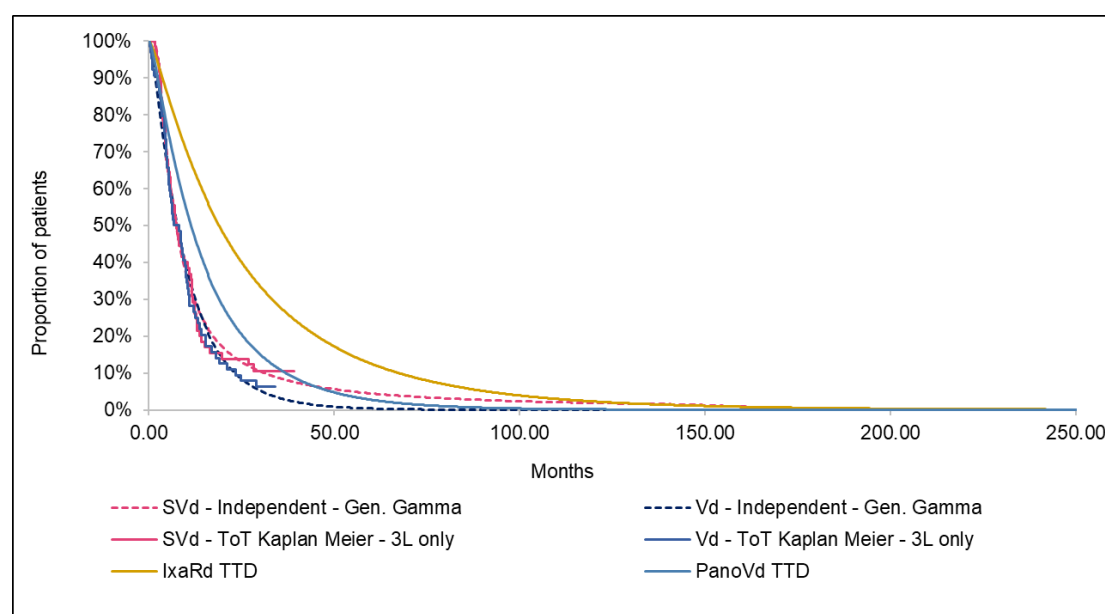
The EAG has included the independently fitted Gompertz curve for the 2L subgroup and the generalised gamma curve for the 3L subgroup (with the acknowledgement of the limitations of estimating comparators curves using an HR applied to an AFT model) along with TTD capped to PFS (Figure 22 and Figure 23) in its preferred base case. Additionally, as discussed in Section 4.2.3.2, it is more appropriate that Vd is used as the baseline to apply comparator HRs to TTD for both the 2L and 3L subgroups (see Table 46 for PFS HRs versus Vd) and this is also included in the EAG preferred base case, presented in Section 6.3. The EAG notes that for the 3L subgroup, TTD for SVD exceeds IxaRd and PanoVd, but this is a function of using Vd as the baseline for comparators and data from BOSTON for SVd.

Figure 22. EAG Gompertz preferred extrapolation of TTD for SVd, Vd and Kd – 2L subgroup



Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; SVd, selinexor with bortezomib and dexamethasone; TTD, time to treatment discontinuation; Vd, bortezomib with dexamethasone

Figure 23. EAG preferred generalised gamma extrapolation of TTD for SVd, Vd, IxaRd and PanoVd – 3L subgroup



4.2.4 Adverse events

For the base case analysis, the company included grade 3 and above treatment-emergent AEs (TEAEs) in 5% or more of patients in the SVd arm of BOSTON. The company included the impact of AEs as weekly event rates to control for between study differences in length of follow up. As a scenario, the company explored included AEs as a one-off impact in the first cycle of the model. The impact of AEs is accounted for the entire duration patients are on treatment.

Adverse events by treatment arm and weekly event rates included in the model are presented in Table 52. Please refer to Section 4.2.4 and 4.2.6 for further details of the health-related quality of life (HRQoL) and cost impact of AEs in the model.

Table 52. Adverse events by treatment arm included in the model (adapted from Table 32 of the CS)

Adverse event	2L/ 3L		2L				3L			
	SVd n = 195		Vd n = 204		Kd n = 463		IxaRd n = 361		PanoVd n = 381	
	N	Weekly rate	N	Weekly rate	N	Weekly rate	N	Weekly rate	N	Weekly rate
Anaemia	32	0.0013	21	0.0008	80	0.0009	41	0.0003	NR	-
Asthenia	16	0.0007	9	0.0004	NR	-	NR	-	NR	-
Cataract	22	0.0009	4	0.0002	NR	-	19	0.0001	NR	-
Diarrhoea	13	0.0005	1	0.0000	19	0.0002	36	0.0003	97	0.0090

Fatigue	26	0.0011	2	0.0001	32	0.0004	13	0.0001	91	0.0085
Febrile neutropenia	1	0.0000	1	0.0000	NR	-	NR	-	NR	-
Hypertension	8	0.0003	6	0.0002	69	0.0008	11	0.0001	11	0.0010
Hypophosphataemia	11	0.0005	3	0.0001	NR	-	NR	-	33	0.0031
Leukopenia	1	0.0000	1	0.0000	1	0.0000	NR	-	1	0.0001
Lymphopenia	7	0.0003	3	0.0001	1	0.0000	NR	-	1	0.0000
Lower respiratory tract infection	4	0.0002	5	0.0002	NR	-	NR	-	NR	-
Nausea	15	0.0006	0	0.0000	NR	-	6	0.0000	21	0.0020
Neutropenia	18	0.0007	7	0.0003	12	0.0001	94	0.0007	NR	-
Hyperglycaemia	4	0.0002	4	0.0002	NR	-	NR	-	NR	-
Peripheral neuropathy	9	0.0004	18	0.0007	11	0.0001	9	0.0001	68	0.0063
Pneumonia	28	0.0011	25	0.0010	0.07	0.0000	52	0.0004	48	0.0045
Thrombocytopenia	79	0.0032	36	0.0014	58	0.0007	77	0.0006	NR	-
Source	BOSTON ²⁷		BOSTON ²⁷		TOURMALINE-MM1 ⁴¹		ENDEAVOUR ²²		PANORAMA ⁴	
Abbreviations: 2L, second-line; 3L, third-line; CS, company submission; IxaRd, ixazomib in combination with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; NR, not reported; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.										

4.2.4.1 EAG critique

The EAG considers that the company's approach to including the impact of AEs as a weekly event rate for the entire duration patients are on treatment is inappropriate and results in a bias against treatments which have longer PFS as patients are on treatment for longer. For all comparators, PFS is estimated to be longer than SVd, thus the weekly assumption is biased in favour of SVd.

The underlying assumption when AEs are accounted for while on treatment is that the AEs are not managed well in clinical practice. However, the EAG considers that once a treatment-emergent AE is identified and appropriate treatment given to manage it, then the severity of the AE should be reduced, along with the associated costs and HRQoL.

In their clarification response, the company agreed that AEs will have a fixed duration rather than persisting across the period of treatment, but acknowledged that there is a lack of data of the timing of events. The EAG considers that it is more appropriate to capture AEs as a one-off impact at the start of the model and remove the link with length of treatment. Furthermore, the applying AEs as a one-off impact is more typically seen for NICE oncology technology appraisals. Table 53 presents the

rate of AEs when applied as a one-off impact in the first cycle of the model. The EAG has included the one-off impact of AEs in its preferred assumptions, presented in Section 6.3.

Table 53. One-off adverse events by treatment arm

Adverse event	2L/ 3L		2L				3L			
	SVd n = 195		Vd n = 204		Kd n = 463		IxaRd n = 361		PanoVd n = 381	
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Anaemia	32	0.164	21	0.103	80	0.173	41	0.114	NR	-
Asthenia	16	0.082	9	0.044	NR	-	NR	-	NR	-
Cataract	22	0.113	4	0.020	NR	-	19	0.053	NR	-
Diarrhoea	13	0.067	1	0.005	19	0.041	36	0.100	97	0.255
Fatigue	26	0.133	2	0.010	32	0.069	13	0.036	91	0.239
Febrile neutropenia	1	0.005	1	0.005	NR	-	NR	-	NR	-
Hypertension	8	0.041	6	0.029	69	0.149	11	0.030	11	0.029
Hypophosphataemia	11	0.056	3	0.015	NR	-	NR	-	33	0.087
Leukopenia	1	0.005	1	0.005	1	0.000	NR	-	1	0.002
Lymphopenia	7	0.036	3	0.015	1	0.000	NR	-	1	0.001
Lower respiratory tract infection	4	0.021	5	0.025	NR	-	NR	-	NR	-
Nausea	15	0.077	0	0.000	NR	-	6	0.017	21	0.055
Neutropenia	18	0.092	7	0.034	12	0.026	94	0.260	NR	-
Hyperglycaemia	4	0.021	4	0.020	NR	-	NR	-	NR	-
Peripheral neuropathy	9	0.046	18	0.088	11	0.024	9	0.025	68	0.178
Pneumonia	28	0.144	25	0.123	0.07	0.000	52	0.144	48	0.126
Thrombocytopenia	79	0.405	36	0.176	58	0.125	77	0.213	NR	-
Source	BOSTON ²⁷		BOSTON ²⁷		TOURMALINE-MM1 ⁴¹		ENDEAVOUR ²²		PANORAMA ⁴⁴	

Abbreviations: 2L, second-line; 3L, third-line; CS, company submission; IxaRd, ixazomib in combination with lenalidomide and dexamethasone; Kd, carfilzomib with dexamethasone; NR, not reported; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

4.2.5 Health-related quality of life

4.2.5.1 Calculation of health state utility values

The health state utility values (HSUVs) included in the model for both 2L and 3L analyses are informed by EQ-5D-5L data collected in the BOSTON clinical trial. All patients in the ITT population completed the EQ-5D-5L questionnaire at baseline, day 1 of each treatment cycle and at the end of treatment. EQ-5D-5L data from baseline to end of treatment were recorded for 388 participants of

the 402 trial participants (96.5%). As the NICE methods guide recommends the use of EQ-5D-3L utility data for the reference case, the company mapped the EQ-5D-5L patient level responses from BOSTON to EQ-5D-3L using the Hernandez-Alava mapping algorithm as recommended by NICE.^{53, 54}

The company pooled utility estimates across the BOSTON study arms to maximise the number of observations as it was assumed that patient HRQoL was not dependent on treatment received, and differences in treatment-related AE profiles which were considered separately.

The company used a mixed effects model to estimate HSUVs from the mapped EQ-5D-3L data from BOSTON. Patient-level characteristics explored as covariates by the company included sex, age, race, years since diagnosis, baseline ECOG score, baseline EQ-5D-3L value, treatment arm and progression status. A backwards stepwise regression approach using statistical goodness-of-fit according to AIC and BIC statistics and log-likelihood statistics was used to determine the final regression model. The final list of covariates considered in the regression model included treatment arm (Vd), age, baseline ECOG, baseline EQ-5D-3L and progression status. Of these covariates, treatment arm was found to have a non-significant p value ($\text{Pr}[>F]$) but was retained in all models regardless.

Table 54. Mixed effects model coefficients. Reproduced from Table 33 in the CS).

	Coefficient	Standard Error	F-value	P-value
Intercept	0.3885	0.0554	-	-
Arm (Vd)	-0.0061	0.0137	0.1967	0.6577
Age	-0.0019	0.0007	6.3708	0.0120
Baseline ECOG	-0.0356	0.0120	8.8269	0.0032
Baseline EQ-5D-3L	0.5913	0.0315	351.6078	<0.0001
Progression status (PFS)	0.0377	0.0061	38.4348	<0.0001

Abbreviations: ECOG, Eastern Cooperative Oncology Group EQ-5D-3L, EuroQol five dimension – 3 levels; PFS, progression-free survival; Pr, probability; Vd, bortezomib plus dexamethasone.

The final utility regression is outlined below.

$$Utility = 0.3885 - 0.0061\beta_1 - 0.0019\beta_2 - 0.0356\beta_3 + 0.5913\beta_4 + 0.0377\beta_5$$

$$\beta_1 = \text{Arm (Vd)}$$

$$\beta_2 = \text{Age}$$

$$\beta_3 = \text{Baseline ECOG}$$

$$\beta_4 = \text{Baseline EQ} - 5D - 3L$$

$\beta_5 = PFS\ Status\ (Y)$

Based on the company's final regression model, utility values for the progression-free (PF) and progressed (PD) health states for SVd and Vd treatment were estimated, and a mean of these values taken to produce treatment independent utility values which were used in the model (Table 55). As a scenario the company explored using utility estimates specific to each treatment arm by using the BOSTON Vd population as a proxy for all treatments other than SVd.

Table 55. Model health state utility values by treatment. Reproduced from Table 34 in the CS.

Health state	SVd	Vd	Treatment Independent*
Progression-free	0.700	0.694	0.697
Progressed	0.663	0.657	0.660

Abbreviations: SVd, selinexor plus bortezomib plus dexamethasone; Vd, bortezomib plus dexamethasone
 *Mean of the SVd and Vd utility values for the health state.
 Note: 95% confidence intervals around estimates not provided by the company

As the company pooled EQ-5D data across the ITT population, no distinction was made for line of therapy subgroups (for instance between 2L, 3L or 4L treatment groups), with the justification that observations for each individual subgroup were too low to produce unbiased results.

The company noted that utility estimates applied in previous NICE TAs for RRMM captured in the SLR were examined and compared to those calculated from BOSTON as a means of validating the base case model utilities.

In addition to the NICE TAs, a meta-analysis by Hatswell *et al.* (2019) was similarly used.¹ The Hatswell *et al.* study consisted of an SLR to identify utility values across all lines of MM, while also including EQ-5D-3L utility estimates from the APEX study (phase III clinical trial comparing bortezomib against dexamethasone), the EMMOS (Europe, Middle East and Africa Multiple Myeloma Observational Study) registry (2358 MM patients), and a network meta-analysis using all values identified in the study.^{1, 60} The company explored the utility values from Model 4 of the Hatswell *et al.* study (Table 56) in a scenario. Based on Hatswell *et al.*, for the 2L subgroup the company assumed that the progression free health state utility was equal to 2L patients (0.62) and the mean utility of 3L+ patients (3L, 4L and 5L+) were used (0.55) for the progressed health state and for the 3L subgroup, the progression free utility was equal to 3L patients (0.59) and the mean utility of 4L and 5L+ patients (0.52) was used for the progressed health state.¹ The utilities used in the company's scenario using the Hatswell *et al.* utilities are outlined in Table 57.

Table 56. Model 4 EQ-5D utility analysis from Hatswell *et al.* 2019 ¹

Line of treatment	Utility value (95%CI)
Second	0.62 (0.46 to 0.79)
Third	0.59 (0.57 to 0.61)
Fourth	0.578 (0.28 to 0.88)
Five plus	0.469 (0.02 to 0.92)

Abbreviations: CI, confidence interval; EQ-5D, EuroQol five dimension

Table 57. Adaptation of the Hatswell *et al.*¹ utilities to the company model health states.

Health state	2L subgroup	3L subgroup
Progression-free	0.62	0.59
Progressed	0.55	0.52

Abbreviations: 2L, second-line; 3L, third-line.

4.2.5.2 ERG Critique

As the company has not included line of therapy as a covariate in the utility regression model, no HRQoL distinction is made between patients treated at 2L and 3L in the economic model. The EAG noted that the meta-analysis presented by Hatswell *et al.* demonstrated a utility difference between subsequent lines of therapy (not a significant difference between 2L and 3L but significant between 3L and 4L) and this was also supported by the EAG's clinical experts who considered that given the length of time on treatment and the toxicity of treatments, HRQoL is likely to be reduced for each subsequent line of treatment. Therefore, the EAG considers that not accounting for line of therapy may bias the calculated HSUVs given there is likely to be a utility differences between subsequent lines of therapies. As a scenario the company was asked to provide a regression model where the treatment arm covariate was excluded and line of therapy included. The company provided the requested the regression model and health state utility values as described in the regression model and Table 58 below.

$$Utility = 0.4126 - 0.002\beta_1 - 0.034\beta_2 + 0.59139\beta_3 + 0.0276 - 0.0103\beta_5$$

 $\beta_1 = \text{Age}$
 $\beta_2 = \text{Baseline ECOG}$
 $\beta_3 = \text{Baseline EQ} - 5D - 3L$
 $\beta_4 = \text{PFS Status (Y)}$

β_5 = Prior line of therapy

Table 58. Model health state utility values by line of therapy. Reproduced from Table 31 in the CS.

Health state	2L	3L
Progression-free (95% CI)	0.706 (0.687 to 0.725)	0.694 (0.681 to 0.712)
Progressed (95% CI)	0.668 (0.648 to 0.689)	0.659 (0.641 to 0.676)
Abbreviations: SVd, selinexor plus bortezomib plus dexamethasone; Vd, bortezomib plus dexamethasone		

The EAG considers that the BOSTON utilities by line of therapy and progression status aligned with those of other relevant NICE TAs as described in Table 36 of the CS. The scenario using utilities by line of treatment and progression status had minimal impact on the ICERs, with the direction remaining the same against all comparators. Nonetheless, even though the impact on the ICER was minimal, the EAG considers that it is more methodologically robust to consider utilities by line of therapy and progression status and thus has included it in its preferred assumptions, presented in Section 6.3.

The EAG considered that upon disease progression, patients are moved to their next line of therapy and therefore it may be appropriate to assume that the utility value for the progressed health state should be equivalent to the utility value of the next line of therapy. Given the lack of evidence in the CS detailing the time between patient progression/discontinuation and starting a subsequent line of treatment, the EAG consulted its clinical experts who suggested that in clinical practice patients would be moved on to the next line of treatment as quickly as possible if safe to do so. As such the EAG conducted a scenario in which the 2L progressed health state utility was made equal to the 3L progression-free utility based on data from BOSTON, which had minimal impact on the ICERs, presented in Section 6.2.

The EAG explored a scenario around the EAG base case using the Hatswell *et al.* utility values (Table 57 and results are presented in Section 6.3.

4.2.5.3 Disutility associated with adverse events

The company applied a utility decrement attributable to AEs in the model to reflect the impact of these events on a patient's HRQoL. Table 59 outlines the disutility and duration associated with each AE included in the model and their source. See Section 4.2.4 for the AE inclusion criteria in the economic model and in-trial AE incidence for the intervention and comparators.

AE disutility was applied in the model as a total utility decrement per weekly cycle for all AEs while patients are on treatment (Table 60). The weekly AE disutility decrement was calculated using the disutilities associated with AEs, the duration of AEs and the weekly probability of patients experiencing AEs derived from the incidence of AE's from clinical trials. As a scenario the company explored applying AEs as a one-off event in the first cycle of the model.

Table 59. Adverse event utility decrements. Reproduced from Table 37 in the CS.

AE description	Utility decrement	Utility decrement source	AE duration (Weeks)	AE duration source
Anaemia	-0.31	NICE TA897 [previously TA573], ⁶¹ NICE GID-TA11060, ⁶² NICE TA695 ⁶³	1.53	NICE TA897 [previously TA573], ⁶¹ NICE GID-TA11060, ⁶² NICE TA695 ⁶³
Asthenia	-0.12	NICE TA658 ⁶⁴	2.09	Assumed equal to fatigue
Cataract	-0.14	NICE TA695 ⁶³	26.09	NICE TA695 ⁶³
Diarrhoea	-0.10	Jakubowiak <i>et al.</i> (2016), ⁶⁵ NICE TA783 ⁶⁶	1.00	Assumption
Fatigue	-0.12	NICE GID-TA11060, ⁶² NICE TA897 [previously TA573], ⁶¹ NICE TA695, ⁶³ Nikolaou <i>et al.</i> 2021 ⁶⁷	2.09	NICE GID-TA11060, ⁶² NICE TA897 [previously TA573], ⁶¹ NICE TA695 ⁶³ Jakubowiak <i>et al.</i> 2016 ⁶⁵
Febrile neutropenia	-0.15	Jakubowiak <i>et al.</i> 2016 ⁶⁵	1.89	Assumed equal to neutropenia
Hyperglycaemia	0.00	Assumption	0.00	Assumption
Hypertension	0.00	NICE TA897, ⁶¹ NICE GID-TA11060, ⁶² NICE TA695 ⁶³	0.00	NICE TA897, ⁶¹ NICE GID-TA11060, ⁶² NICE TA695 ⁶³
Hypophosphatemia	0.00	NICE TA695 ⁶³	0.00	NICE TA695 ⁶³
Leukopenia	0.00	NICE GID-TA10568, ⁶⁸ NICE TA783, ⁶⁶ Nikolaou <i>et al.</i> 2021 ⁶⁷	0.00	Assumption
Lymphopenia	-0.07	NICE GID-TA11060, ⁶² NICE TA695, ⁶³ NICE TA897 [previously TA573] ⁶¹	2.21	NICE GID-TA11060, ⁶² NICE TA695, ⁶³ NICE TA897 [previously TA573], ⁶¹ Jakubowiak <i>et al.</i> 2016 ⁶⁵
Lower respiratory tract infection	-0.19	NICE TA783 [lower respiratory infection] ⁶⁶	1.71	Assumed equal to pneumonia
Nausea	-0.10	Jakubowiak <i>et al.</i> 2016, ⁶⁵ NICE TA658, ⁶⁴ NICE TA783 ⁶⁶	1.00	Assumption
Neutropenia	-0.145	NICE TA897 [previously TA573], ⁶¹ Nikolaou <i>et al.</i> 2021 ⁶⁷	1.89	NICE TA897 [previously TA573] ⁶¹
Peripheral neuropathy	-0.065	NICE TA897 [previously TA573], ⁶¹ NICE GID-TA11060, ⁶² Jakubowiak <i>et al.</i> (2016) ⁶⁵	1.14	NICE TA897 [previously TA573], ⁶¹ NICE GID-TA11060, ⁶² Jakubowiak <i>et al.</i> 2016 ⁶⁵
Pneumonia	-0.19	NICE TA897 [previously TA573], ⁶¹ NICE GID-TA11060 ⁶²	1.71	NICE TA897, ⁶¹ NICE GID-TA11060 ⁶²
Thrombocytopenia	-0.31	NICE TA897 [previously TA573] ⁶¹	2.01	NICE TA897 [previously TA573] ⁶¹

Table 60. Weekly utility decrements

Treatment	Weekly utility decrement
SVd	-0.0078
Vd	-0.0036
IxaRd	-0.0015
Kd	-0.0012
PanoVd	-0.0152

Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; SVd, selinexor plus bortezomib plus dexamethasone; Vd, bortezomib plus dexamethasone.

4.2.5.4 ERG Critique

The EAG considers that the adverse events, their estimated disutilities and durations included by the company in the model are appropriate.

However, as mentioned in Section 4.2.4, the EAG prefers the AEs to be captured as a one-off impact at the start of the model time horizon. The company's weekly AE application approach relies on the calculation of weekly probability of patients experiencing AEs based on the patient years of exposure and the number of patients experiencing specific AE events. The probability therefore does not account for patients experience multiples of the same event and is heavily influence by patient deaths which limit patient years of exposure. Additionally, upon treatment initiation patients are monitored regularly, therefore once an AE has been identified by a clinician, treatment will be given to manage it or patients will discontinue treatment.

Furthermore, as mentioned in Section 4.2.4, the company's approach to including the impact of AEs as a weekly event rate for the entire duration patients are on treatment is inappropriate and results in a bias against treatments which have longer PFS as patients are on treatment for longer. Notably, the company's assumption of a weekly disutility results in a higher value for PanoVd out of the all the interventions for the 3L subgroup, whereas when estimated as a one-off disutility, PanoVd has the lowest disutility impact.

As such, the EAG considers that a one-off disutility associated with AEs applied in the first cycle of the model (Table 61) is more appropriate in contrast to the company's weekly application approach and is included in the EAG's preferred assumptions, presented in Section 6.3.

Table 61. One off utility decrement by treatment.

Treatment	One-off utility decrement
SVd	-0.9717
Vd	-0.4522
IxaRd	-0.5597
Kd	-0.2278
PanoVd	-0.4287

Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; SVd, selinexor plus bortezomib plus dexamethasone; Vd, bortezomib plus dexamethasone.

4.2.5.5 Age-related utility decrements

Utilities in the model were adjusted for age, as per the NICE methods guide.² General population utility values adjusted for age and sex were obtained from the HSE 2014 dataset, as recommended by the DSU.⁶⁹ The EAG considers that the general population utility values used by the company are appropriate.

4.2.6 Resource use and costs

The company included costs relevant to drug acquisition, administration, subsequent treatment, health states, adverse events and terminal care in the economic model. Unit costs reflected 2021/22 prices and where necessary, costs for previous years were inflated using the PSSRU 2022 Hospital and Community Health Services pay and price indices.²¹

The company has proposed a confidential patient access scheme (PAS) discount of [REDACTED] on the list price, and all results presented in this report are inclusive of the discount. Confidential PAS discounts are available for ixazomib, lenalidomide, carfilzomib, daratumumab, isatuximab and pomalidomide. As such, the EAG has produced a confidential appendix to the EAG report. Analyses in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

4.2.6.1 Drug acquisition and administration costs

The intervention considered for the economic analysis is selinexor in combination with bortezomib and dexamethasone (SVd). The proposed list price of selinexor is £9,200 per pack of 20 units of 20mg tablets (or £460 per tablet), resulting in a discounted price of [REDACTED] per pack of 20 units of 20mg

tablets (or ■■■ per tablet) with the proposed PAS discount of ■■■ applied to the list price. As nausea is a common side-effect of selinexor, the company also included the cost of ondansetron, a 5-hydroxytryptamine antagonist, to manage the effects of nausea while on treatment and was assumed in the model to be taken two to three times per day.

As described in Section 2.3.3, the comparator considered in the company base case for the 2L subgroup is carfilzomib with dexamethasone (Kd) and for the 3L subgroup, comparators included ixazomib in combination with lenalidomide and dexamethasone (IxaRd) and panobinostat in combination with bortezomib and dexamethasone (PanoVd).

Dosing regimens according to the Summary of Product Characteristics (SmPCs) for SVd and each comparator are presented in Section 2.3.2 and Section 2.3.3 and are summarised below in Table 63, along with the drug acquisition costs per cycle included in the model. Table 39 in the CS outlines the unit costs of the intervention, comparators and subsequent therapy used to estimate drug acquisition costs per cycle. In the company base case, drug wastage was included.

The company included the relative dose intensity (RDI) for all treatments in the model where data were available (Table 63). Where RDI was not reported in comparator publications, the company assumed RDI was 100%. In the BOSTON trial, the RDI of selinexor, bortezomib and dexamethasone were measured as 78.9%, 88.4% and 100% respectively.

Treatments were administered either orally, subcutaneously (SC) or intravenously (IV) with the dosing of SC and IV treatments being dependent on body surface area (BSA) or patient weight, taken from BOSTON (see Section 2.3.1 for baseline characteristics included in the model by subgroup). Administration costs were applied per administration in the economic model. Unit cost of drug administrations included in the economic model are outlined in Table 62 and drug administration costs per treatment cycle are presented in Table 63.

Table 62. Drug administration costs for non-oral therapies by mode of administration. Reproduced from Table 40 in the CS.

Mode of administration	Cost per administration	Source
Subcutaneous	£119.00	National Schedule of NHS Costs - Year 2021-22 - Community Health Services - Specialist Nursing, Cancer Related, Adult, Face to face - N10AF ⁷⁰
Intravenous (first)	£440.71	National Schedule of NHS Costs - Year 2021-22 - CHEMOTHERAPY - Deliver Complex Chemotherapy, including

		Prolonged Infusional Treatment, at First Attendance OP - SB14Z ⁷⁰
Intravenous (subsequent)	£326.46	National Schedule of NHS Costs - Year 2021-22 - CHEMOTHERAPY - Deliver Subsequent Elements of a Chemotherapy Cycle - SB15Z ⁷⁰
Abbreviations: NHS, National Health Service		

Table 63. Drug acquisition and administration costs per treatment cycle

	Treatment	Dose per admin (mg)	Number of admins per treatment cycle	Cycle (days)	Administration	Dose intensity	Drug cost per treatment cycle	Administration cost per first cycle	Administration cost per subsequent cycle
SVd	Selinexor	100	5.00	35	Oral	78.9%	■	-	-
	Bortezomib	1.30	4.00	35	SC	88.4%	£224	£476	£476
	Dexamethasone	20	10.00	35	Oral	100.0%	£5	-	-
	Ondansetron (concomitant)	8	87.5	35	Oral	100.0%	£6.65	-	-
IxaRd	Ixazomib	4	3.00	28	Oral	97.4%	£6,336	-	-
	Lenalidomide	25	21.00	28	Oral	93.8%	£976	-	-
	Dexamethasone	40	4.00	28	Oral	92.2%	£4	-	-
Kd	Carfilzomib	20	2.00	28	IV	91.0%	£1,408	£881	£653
	Carfilzomib	56	4.00	28	IV	91.0%	£7,040	£1,763	£1,306
	Carfilzomib	56	6.00	28	IV	91.0%	£10,560	£2,644	£1,959
	Dexamethasone	20	8.00	28	Oral	100.0%	£4	-	-
PanoVd	Panobinostat	20	6.00	21	Oral	80.7%	£4,656	-	-
	Bortezomib	1.30	4.00	21	SC	75.7%	£224	£476	£476
	Bortezomib	1.30	2.00	21	SC	75.7%	£112	£238	£238
	Dexamethasone	20	8.00	21	Oral	87.5%	£4	-	-
	Dexamethasone	20	4.00	21	Oral	87.5%	£2	-	-

Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; IV, intravenous; Kd, carfilzomib plus dexamethasone; m², metre squared; mg, milligram; NA, not applicable; PanoVd, panobinostat plus bortezomib and dexamethasone; SC, subcutaneous; SVd, selinexor plus bortezomib and dexamethasone

4.2.6.2 EAG critique

Overall, the EAG considers that the costing approach and calculations in the economic model to estimate drug acquisition and administration costs are appropriate. However, the EAG notes that an administration cost for oral chemotherapy is available within the NHS Reference Costs schedule (HRG code SB11Z, £217), which should be included in the economic model.⁵⁵ During the clarification stage, the EAG requested that the company include the oral chemotherapy administration cost as a scenario, but the company stated that the use of oral chemotherapy is assumed to be comparable across arms and including the administration cost would have minimal impact on the ICERs and therefore did not provide the scenario.

Instead, the EAG ran a scenario which includes the administration cost of oral chemotherapy, presented in Section 6.2, but this had minimal impact on the ICER. Nonetheless, the EAG considers the administration cost for oral chemotherapy should be included in the EAG base case for completeness, presented in Section 6.3.

4.2.6.3 Subsequent treatments

Given that MM is characterised by successive relapses, the company included the cost of subsequent therapies given on disease progression after treatment with SVd and comparators. As the patient treatment pathway is highly dependent on prior line of treatment, the company calculated a weighted average estimate of treatments provided beyond 2L or 3L for each treatment arm (weighted-basket approach). The therapies included as subsequent treatments in the company base case, presented in Table 64, are based on those received in BOSTON.

The company excluded therapies unavailable in the NHS and rescaled the proportion of patients receiving the remaining treatments. This was estimated in the model using the data from BOSTON on the proportion of patients treated with a NHS provided subsequent treatment, the mean number of subsequent therapies received per patient (1.6 treatments) and the total number of patients who received subsequent treatments. Additionally, the weighting of subsequent treatments was dependent on the treatment received at baseline in the model, ensuring that no patient received the same initial treatment as a subsequent treatment.

The proportion of patients assumed to receive subsequent treatments was informed using data from BOSTON. In the trial, 182 of the 229 patients (79%) who progressed received subsequent treatments and this was included in the economic model.

Subsequent treatment costs were applied to patients following disease progression in the company base case. Additionally, the company conducted a scenario analysis to explore the implications of costing subsequent treatments upon treatment discontinuation of primary treatment instead of progression, which had minimal impact on the ICER.

The company stated that the duration of time each subsequent treatment was costed for was nine months, as this was the approach used in the NICE submission for daratumumab with bortezomib and dexamethasone (DvD) (TA897).⁶¹ In TA897, DvD was appraised as a 2L treatment only and the submitting company only assumed one further line of subsequent treatment (3L only) and based the duration of 3L treatment on the median OS of 3L+ patients in CASTOR (nine months).⁶¹

Additionally, the company explained that assuming the duration of time on each subsequent treatment was nine months allowed information on the different dosing regimens and treatment cycle lengths associated with each subsequent treatment to be incorporated and a weekly cost of each subsequent treatment to be calculated and applied in the economic model. A total weighted average of subsequent treatments was then calculated by the company using the weekly cost of each subsequent treatment, the proportion of patients receiving each subsequent treatment, the estimated time spent in the progression health state by model treatment arm and the assumed duration of time over which subsequent treatments were costed (nine months in the company's base case).

Chemotherapy as a subsequent treatment was costed by the company using bendamustine + thalidomide + dexamethasone (BTd) as proxy, based on the dosing schedule from Lau *et al.* 2015.⁷¹

Table 64. Subsequent treatment proportions and costs by treatment arm in the model

Subsequent treatment	Weekly cost	SVd (2L)		SVd (3L)		IxaRd		Kd		PanoVd	
		%	Weighted weekly cost	%	Weighted weekly cost	%	Weighted weekly cost	%	Weighted weekly cost	%	Weighted weekly cost
Chemotherapy	£334	41.01%	£62.37	41.01%	£49.06	42.69%	£102.28	41.01%	£85.19	41.41%	£93.81
Dara monotherapy	£2,299	18.04%	£189.06	18.04%	£148.61	18.78%	£309.85	18.04%	£258.22	18.22%	£284.21
IsaPd	£4,539	2.46%	£50.89	2.46%	£40.00	2.56%	£83.40	2.46%	£69.50	2.48%	£76.50
IxaRd	£1,829	6.56%	£54.68	6.56%	£42.98	0.00%	-	6.56%	£74.68	6.63%	£82.20
PanoVd	£1,988	1.64%	£13.02	1.64%	£10.23	1.71%	£21.33	1.64%	£17.78	0.00%	-
Pd	£2,222	42.65%	£431.83	42.65%	£339.43	44.40%	£707.71	42.65%	£589.77	43.07%	£649.14
Rd	£245	54.13%	£60.43	54.13%	£47.50	56.35%	£99.03	54.13%	£82.53	54.67%	£90.83
Estimated time in Progression (weeks)	-	85.87		109.25		54.55		62.88		57.69	
Total weighted weekly cost of subsequent treatments	-	£685.31		£538.70		£1,051.95		£935.96		£1,014.67	

Abbreviations: IsaPd, isatuximab plus pomalidomide and dexamethasone; IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; Pd, pomalidomide plus dexamethasone; Rd, lenalidomide plus dexamethasone; SVd, selinexor plus bortezomib and dexamethasone

4.2.6.4 EAG critique

The EAG considers there are several issues with the company's base case assumptions related to the estimation of subsequent treatments costs in the model. The EAG acknowledges the company's attempts to reflect the NHS treatment pathway (presented in Section 2.2.1), but considers that the base case approach does not fully consider the sequence of treatments a patient may have, contingent on treatment received in their previous line of therapy and thus the proportions of each subsequent treatments assumed may not reflect UK clinical practice.

For example, the EAG's clinical experts advised that patients who had previously received IxaRD would not go on to receive further treatment with lenalidomide plus dexamethasone (Rd), while the company assumes 56% of patients treated with IxaRD would go on to receive Rd. Additionally, the EAG's clinical experts stated that at 3L and 4L, treatment with chemotherapy is not used often given the availability of other more effective treatments in the pathway. The EAG's clinical experts also considered that only a small proportion of patients would receive daratumumab monotherapy.

Furthermore, bendamustine is no longer available in the NHS and isatuximab in combination with pomalidomide and dexamethasone (IsaPd) is not routinely commissioned as it still in the Cancer Drugs Fund (CDF), therefore the EAG considers these options should not be included in the costs of subsequent treatments. For chemotherapy, the EAG's clinical experts advised that a cyclophosphamide-based chemotherapy regimen would be used.

At clarification, the EAG requested the company to provide an alternative approach to subsequent treatments in the model that more appropriately captures the NHS treatment pathway and clinical practice. In response, the company did not provide an alternative approach and instead explained that due to the considerable heterogeneity in patients journeys in the real world and NHS, it is unlikely that data from BOSTON (which notably is used in the company base case) or other available data sources will provide a suitable basis for estimating such differences accurately. However, the company did provide a scenario removing IsaPd for the costs of subsequent treatments (scenario presented in Section 6.3), but did not correct the chemotherapy cost to remove bendamustine and instead cost a cyclophosphamide-based chemotherapy regimen.

As the company did not provide an alternative approach to overcome the issues with subsequent treatments, the EAG suggested an alternative approach using market share data for treatments in the 3L+ pathway for RRMM, where available, to estimate costs of subsequent treatment that more

closely reflect UK clinical practice. In response to the EAG's additional request, the company provided market share data for 3L and 4L treatments, sourced from existing market research conducted by the company. For 5L treatments, the company based their assumptions on feedback received from their clinical experts that chemotherapy would be used, as well as market share for pomalidomide with dexamethasone (Pd) proposed as part of an ongoing appraisal of selinexor with dexamethasone (Sd) in the penta-refractory setting (ID6193).²⁴

Market share data put forward by the company are presented in Table 65. For the scenario, the company combined the market share data with the relative proportions of patients reaching subsequent lines of treatment as identified in Yong *et al.* 2016 (presented in Table 65). The EAG notes that the proportion of patients reaching each line of therapy from Yong *et al.*, is based on an observational chart review (n=4,997) performed by 435 physicians treating multiple myeloma patients during 2014, in Belgium, France, Germany, Italy, Spain, Switzerland and the UK. Table 66 presents the proportions of each subsequent treatment received following 2L and 3L treatment for the scenario, although the EAG is unclear how these proportions were estimated.

Results of the company's alternative subsequent treatment are presented in Table 15 of the company's response to follow-up clarification questions. For the comparison with Kd and IxaRd, the direction of the deterministic ICER did not change, but the magnitude of the ICER reduced. For the comparison with PanoVd, the deterministic ICER changed from dominant to £177,168 (north-east quadrant).

Table 65. Subsequent treatments by market share. Reproduced from Table 11 and Table 12 in the company's follow up clarification question response.

	3L	4L	5L
IxaRd	■	-	-
PanoVd	■	-	-
Pd	-	■	-
Chemotherapy*	■	■	■
Best supportive care	-	-	■
Estimated proportion of diagnosed patients reaching line of therapy (Yong et al. 2016) ⁷²	38%	15%	1%
Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; Pd, pomalidomide plus dexamethasone; Sd, selinexor plus bortezomib and dexamethasone			
*Cyclophosphamide plus dexamethasone assumed			

Table 66. Weighting estimates used to inform mean weekly treatment cost assumptions in the company market share scenario (Table 13 of the company’s follow up clarification question response)

Relative weighting of subsequent therapies	IxaRd	PanoVd	Pd	Chemotherapy
2L	■	■	■	■
3L	■	■	■	■
Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; Pd, pomalidomide plus dexamethasone.				

The EAG considers that calculating the distribution of subsequent treatments at each treatment line of treatment based on market share data is a more robust approach to estimating costs that would be reflective of UK clinical practice compared to the company’s base case assumptions. However, the EAG highlights that in 4L, patients who have not previously received IxaRd and PanoVd would still be eligible for those treatments, especially if their previously line of treatment was SVd or Kd.

Additionally, while Yong *et al.* provides data on the proportion of patients reaching each line of therapy, these data are based on patient charts from other countries and not only the UK, therefore may not be reflective of a patient’s journey in the NHS.⁷² Instead, the EAG considers that given that efficacy data are based on BOSTON, it is preferable to use the proportion of patients going on to subsequent treatments in the trial (79.5%) to adjust the market share data to estimate the proportion of patients reaching later lines of treatment.

As such, the EAG reweighted the subsequent treatment proportions according to the company’s market share data, assumed patients who had not received specific treatments in a previous line of treatment would receive them as subsequent treatments and assumed that the proportion of patients that would go on to a subsequent line of treatment was equal to that seen in BOSTON (79.5%), presented in Table 67. The EAG acknowledges that assuming a constant proportion of patients receiving next line of therapy is conservative, as it is likely that there will be a decline in patients being eligible for later lines of treatment, as highlighted in Yong *et al.*

Table 67. EAG's preferred assumptions for subsequent treatment proportions

Treatment and line	2L subgroup				3L subgroup					
	SVd		Kd		SVd		IxaRd		PanoVd	
	Market share/ assumption	Proportion based on attrition (79.5%)	Market share/ assumption	Proportion based on attrition (79.5%)	Market share/ assumption	Proportion based on attrition (79.5%)	Market share/ assumption	Proportion based on attrition (79.5%)	Market share/ assumption	Proportion based on attrition (79.5%)
3L										
IxaRd	■	■	■	■	N/A	N/A	N/A	N/A	N/A	N/A
PanoVd	■	■	■	■	N/A	N/A	N/A	N/A	N/A	N/A
Chemotherapy	■	■	■	■	N/A	N/A	N/A	N/A	N/A	N/A
4L										
IxaRd*	■	■	■	■	■	■	■	■	■	■
PanoVd*	■	■	■	■	■	■	■	■	■	■
Pd†	■	■	■	■	■	■	■	■	■	■
Chemotherapy†	■	■	■	■	■	■	■	■	■	■
5L										
PanoVd‡	■	■	■	■	■	■	■	■	■	■
Pd†	■	■	■	■	■	■	■	■	■	■
Chemotherapy‡	■	■	■	■	■	■	■	■	■	■

Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; N/A, not applicable; PanoVd, panobinostat plus bortezomib and dexamethasone; Pd, pomalidomide plus dexamethasone; SVd, selinexor plus bortezomib and dexamethasone.

*For the 2L subgroup at the 4L, market share data for IxaRd and PanoVd are switched to capture patients who did not get those treatments in the previous line.

†Market share data for each treatment multiplied by the remaining proportion not on IxaRd or PanoVd. For example 4L Pd = 1-(% IxaRd+% PanoVd)*4L Pd market share

‡For the 2L subgroup, proportion based on the percentage that did not receive treatment in the previous line. For example, 5L Pd = 1-% 4L Pd. For the 3L subgroup, chemotherapy proportion is based on market share data and remainder is split between PanoVd and Pd.

Using the EAG recalculated proportion of patients receiving each subsequent treatment, the company's weekly cost of each treatment presented in Table 64 (with chemotherapy assumed to be cyclophosphamide plus dexamethasone), and maintaining the company's subsequent treatment duration of nine months for each treatment along with the time spent in progression for each treatment arm, the EAG calculated the weighted weekly costs as described in Table 68 for the 2L and 3L subgroups. The EAG's preferred subsequent treatment costs incorporate the EAG's preferred extrapolation assumptions for PFS and OS (including OS benefit for treatments), as described in Section 4.2.3. For the EAG's scenario, the cost of chemotherapy is assumed to be based on cyclophosphamide plus dexamethasone as presented in Table 14 of the company's response to follow-up clarification questions (£15.73). Results of the EAG's subsequent treatment scenario are presented in Section 6.2 and is also included in the EAG's preferred base case, presented in Section 6.3.

Table 68. EAG preferred weighted weekly subsequent treatment costs at 2L.

Treatment and line	2L subgroup		3L subgroup		
	SVd	Kd	SVd	IxaRd	PanoVd
3L					
IxaRd	■	■	N/A	N/A	N/A
PanoVd	■	■	N/A	N/A	N/A
Chemotherapy	■	■	N/A	N/A	N/A
4L					
IxaRd	■	■	■	■	■
PanoVd	■	■	■	■	■
Pd	■	■	■	■	■
Chemotherapy	■	■	■	■	■
5L					
PanoVd	-	-	■	■	-
Pd	■	■	■	■	■
Chemotherapy	■	■	■	■	■
Total weighted weekly cost	■	■	■	■	■
Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; Pd, pomalidomide plus dexamethasone; SVd, selinexor plus bortezomib and dexamethasone.					

4.2.6.5 Health-state unit costs and resource use

In the company base case, health state resource use was assumed to be the same across both 2L and 3L treated patients, which the company explained was due to the paucity of data to stratify between lines of therapy. The health care resource use assumed in the economic model was based on assumptions included in TA897 and are outlined in Table 69.⁶¹ Health state resource use costs were sourced from NHS Reference Costs 2021/22 and aggregated to calculate an average weekly resource use cost for each health state.⁷⁰ A weekly cost of £63 was calculated for the progression-free and progressed health states for both 2L and 3L patients.

Table 69. Weekly resource use unit costs and frequencies per health state. Reproduced from Table 42 in the CS.

Resource description	Unit cost	NHS reference cost code	Weekly resource use (units): progression-free*	Weekly resource use (units): progressed†
Haematologist clinical visit	£232.78	Consultant led- Multi-professional Non-Admitted Face-to-Face Attendance, Follow-up - WF02A ⁷⁰	0.23	0.23
Full blood count	£2.96	Directly accessed pathology services - Haematology - DAPS05 ⁷⁰	0.21	0.21
Biochemistry	£2.39	Directly accessed pathology services - Integrated blood services - DAPS03 ⁷⁰	0.19	0.19
Protein electrophoresis	£1.55	Directly accessed pathology services - Clinical biochemistry - DAPS05 ⁷⁰	0.13	0.13
Immunoglobulin	£7.61	Directly accessed pathology services - Immunology - DAPS06 ⁷⁰	0.12	0.12
Urinary light chain excretion	£8.53	Directly accessed pathology services - Microbiology - DAPS07 ⁷⁰	0.05	0.05
Red blood cell transfusions	£695	HRG Data Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over - SA44A ⁷⁰	0.01	0.01
Platelet transfusions	£695	HRG Data Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over - SA44A ⁷⁰	0.00	0.00
Total weighted weekly cost	-	-	£63	£63

*resource frequencies sourced from NICE TA897⁶¹

†resource frequency assumed the same as progression-free

4.2.6.6 EAG critique

The EAG's clinical experts agreed with the company's assumption that health care resource use would be the same or similar between progression-free (PF) and progressed disease (PD) patients, as it is likely patients will remain on some kind of treatment until 6L.

The EAG's clinical experts also agreed with the majority of the company's health care resource use assumptions included in the model, with the only exception being that serum light chain reaction was used in routine clinical practice and not urinary light chain excretion. Additionally, the EAG's clinical experts considered that compared to the frequency of health care resource use assumed by the company, many of the resources would be used more frequently by patients, as presented in Table 70 below. During the clarification stage, the EAG requested, and the company provided, a scenario implementing the EAG's clinical expert resource use assumptions and results are presented in Section 6.2. The scenario had an impact on the magnitude of the ICER, but not the direction. However, the EAG includes the EAG's clinical experts' assumption in its preferred base case for completeness.

Table 70. EAG preferred health care resources and use.

Resource description	Annual resource use	Weekly resource use*
Haematologist clinic visit	Monthly	0.23
Complete blood count test	Monthly	0.23
Blood chemistry	Monthly	0.23
Protein electrophoresis	Monthly	0.23
Immunoglobulin	Monthly	0.23
Serum light chain testing excretion	Monthly	0.23
G-CSF injections	6 per year	0.12
Red blood cell transfusions	2 per year	0.04
Platelet transfusion	2 per year	0.04

Abbreviations: G-CSF, granulocyte colony stimulating factor.

4.2.6.7 Adverse event unit costs and resource use

In the company base case, AE costs were stratified by cases managed between primary and secondary care. The proportions assumed for AEs managed in each type of setting were based on assumptions made in TA870, which assessed IxaRd against Rd for RRMM patients at 2L and 3L.⁵⁰ Where proportions from NICE TA870 were not available, an equal distribution was assumed across

primary and secondary care. See Section 4.2.4 for the AE inclusion criteria and incidence of each type of AE included in the economic model for the SVd and comparators.

Secondary care costs were taken from NHS Reference Costs 2021/2022 and primary care costs were obtained from the PSSRU (2022), assuming a standard appointment time with a GP of 9.22 minutes.

^{57, 70} The weighting of AEs by cost and care setting are outlined in Table 71.

Adverse event costs were applied per weekly cycle in the economic model. To calculate a weekly cost, each AE costs was multiplied by the associated weekly probability (presented in Section 4.2.4) and summed, providing a weekly adverse event cost per treatment arm as outlined in Table 72.

Table 71. Cost per adverse event. Reproduced from Table 43 in the CS.

Treatment-Emergent Adverse Events	% of AEs that are secondary care	% of AEs that are primary care	Cost in secondary care	Cost in primary care	Weighted average cost of AEs
Anaemia	94%	6%	£4,315	£42	£4,059
Asthenia	0%	100%	£4,777	£42	£42
Cataract	50%	50%	£8,851	£42	£4,447
Diarrhoea	99%	1%	£4,777	£42	£4,729
Fatigue	0%	100%	£4,777	£42	£42
Febrile neutropenia	98%	2%	£5,398	£42	£5,290
Hypertension	50%	50%	£2,300	£42	£1,171
Hypophosphataemia	50%	50%	£239	£42	£141
Leukopenia	50%	50%	£239	£42	£141
Lymphopenia	50%	50%	£239	£42	£141
Lower respiratory tract infection	50%	50%	£4,439	£42	£2,240
Nausea	0%	100%	£4,777	£42	£42
Neutropenia	98%	2%	£5,398	£42	£5,290
Hyperglycaemia	50%	5%	£239	£42	£141
Peripheral neuropathy	98%	2%	£4,439	£42	£4,351
Pneumonia	100%	0%	£3,657	£42	£3,657
Thrombocytopenia	99%	1%	£3,519	£42	£3,484
Abbreviations: AE, adverse event					

Table 72. Weighted weekly adverse event costs. Reproduced from Table 44.

Treatment arm	Weighted weekly costs
SVd	£33
IxaRd	£11
Kd	£9

PanoVd	£89
Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; SVd, selinexor plus bortezomib and dexamethasone	

4.2.6.8 EAG critique

In the CS, NHS reference costs codes used for the AE costs were not provided. During the clarification stage, the company was requested to provide these codes for validation, which the company supplied. However, the EAG noted that the majority of AEs were assumed to be based on inpatient costs from the NHS reference costs schedule. The EAG's clinical experts advised that AEs would be predominantly managed during outpatient appointments. Additionally, the EAG considers that many of the NHS reference costs used by the company are inappropriate. For example, diarrhoea and fatigue were costed using the HRG code SA17H which corresponds to a malignant disorder of the lymphatic or haematological systems. Therefore, the EAG considers that AE costs used in the company's base case are potentially inflated and instead the EAG compiled a list of more suitable NHS reference costs for AEs to be included in the model and these are presented in Table 70.

As mentioned in Section 4.2.4.1, the EAG considers that the company's approach to including the impact of AEs as a weekly event rate for the entire duration patients are on treatment is inappropriate and results in a bias against treatments which have longer PFS as patients are likely to be on treatment for longer. For all comparators, PFS is estimated to be longer than SVd, thus the weekly assumption is biased in favour of SVd. Instead, the EAG considers that it is more appropriate to capture AEs as a one-off impact at the start of the model and remove the link with length of treatment. Furthermore, applying AEs as a one-off impact at the start of the model time horizon is typically accepted for NICE oncology appraisals. Table 74 presents the one-off cost of AEs by treatment arm based on the EAG's preferred NHS reference costs for AEs.

Furthermore, when validating the assumed proportions of AEs managed between primary and secondary care with the EAG's clinical experts, they explained that the majority, if not all, AEs would be managed by the consultant team in secondary care, with this being especially true for Grade 3+ AEs which are those included in the economic model. Based on the EAG's clinical experts' advice, the EAG requested, and the company provided, a scenario in which all AEs were managed in secondary care and results are presented in Section 6.2.

Overall incorporating the EAG preferred one-off AE costs, with all cases assumed to be managed in secondary care led to a decrease in the magnitude of the ICERs for both the 2L and 3L subgroups, but notably incremental costs in the comparison with PanoVd substantially reduced (presented 6.2). As such, the EAG's preferred AE assumptions are included the EAG preferred base case, presented in Section 6.3.

Table 73. EAG preferred AE costs

Treatment-Emergent Adverse Events	Company preferred AE cost	Company NHS reference Costs source	EAG preferred AE cost	EAG NHS reference Costs source
Anaemia	£4,442	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA03G & SA03H	£866	National Schedule of NHS Costs - Year 2021-22, Total HRGs, SA04G-SA04L
Asthenia	£3,372	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA17H	£2,015	National Schedule of NHS Costs - Year 2021-22, Total HRGs, SA01G-SA01K
Cataract	£7,868	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, BZ33Z-BZ31A, BZ30A	£817	National Schedule of NHS Costs - Year 2021-22, Total HRGs, BZ30A-BZ33Z
Diarrhoea	£3,372	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA17H	£1,422	National Schedule of NHS Costs - Year 2021-22, Total HRGs, FD10J-FD10M
Fatigue	£3,372	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA17H	£2,015	National Schedule of NHS Costs - Year 2021-22, Total HRGs, SA01G-SA01K
Febrile neutropenia	£6,485	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA30E-SA30A	£1,150	National Schedule of NHS Costs - Year 2021-22, Total HRGs, SA30A-SA30E
Hyperglycaemia	£239	National Schedule of NHS Costs - Year 2021-22, Directly Accessed Pathology Services, DAPS03, Outpatient Care, Medical oncology service, WF02A	£1,533	National Schedule of NHS Costs - Year 2021-22, Total HRGs, KB02G-KB02K
Hypertension	£2,300	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, EB04Z	£770	National Schedule of NHS Costs - Year 2021-22, Total HRGs, EB04Z
Hypophosphatemia	£239	National Schedule of NHS Costs - Year 2021-22,	£1,365	National Schedule of NHS Costs - Year 2021-22,

		Directly Accessed Pathology Services, DAPS03, Outpatient Care, Medical oncology service, WF02A		Total HRGs, SA08G-SA08J
Leukopenia	£239	National Schedule of NHS Costs - Year 2021-22, Directly Accessed Pathology Services, DAPS03, Outpatient Care, Medical oncology service, WF02A	£1,365	National Schedule of NHS Costs - Year 2021-22, Total HRGs, SA08G-SA08J
Lower respiratory tract infection	£3,744	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, DZ22Q- DZ22K	£1,635	National Schedule of NHS Costs - Year 2021-22, Total HRGs, DZ22k-DZ22Q
Lymphopenia	£239	National Schedule of NHS Costs - Year 2021-22, Directly Accessed Pathology Services, DAPS03, Outpatient Care, Medical oncology service, WF02A	£1,365	National Schedule of NHS Costs - Year 2021-22, Total HRGs, SA08G-SA08J
Nausea	£3,372	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA17H	£1,844	National Schedule of NHS Costs - Year 2021-22, Total HRGs, FD10A-FD10M
Neutropenia	£6,485	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA30E-SA30A	£1,365	National Schedule of NHS Costs - Year 2021-22, Total HRGs, SA08G - SA08J
Peripheral neuropathy	£3,745	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, DZ22Q- DZ22K	£1,868	National Schedule of NHS Costs - Year 2021-22, Total HRGs, AA26C-AA26H
Pneumonia	£5,080	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, DZ11V-DZ11K	£2,512	National Schedule of NHS Costs - Year 2021-22, Total HRGs, DZ11K-DZ11V
Thrombocytopenia	£4,331	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA12K-SA12G	£993	National Schedule of NHS Costs - Year 2021-22, Total HRGs, SA12G-SA12K
Abbreviations: AE, adverse event				

Table 74. EAG's preferred one-off adverse event costs

Treatment arm	One-off costs of AEs
SVd	£11
IxaRd	£3
Kd	£2

PanoVd	£39
Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; SVd, selinexor plus bortezomib and dexamethasone	

4.2.6.9 Terminal care

The company included a one-off cost of terminal care applied upon death in the economic model. A cost of £4,823 was used in the economic model, informed by a study by Round *et al.* 2015 which assessed the mean healthcare costs across breast, colorectal, lung and prostate cancers in the UK, inflated to the 2021/22 cost year using PSSRU (2022).^{57, 73}

4.2.6.10 EAG critique

Based on relevant RRMM TAs (NICE TA987 and TA870) terminal care costs were sourced from the end-of-life care section of the PSSRU which the EAG considers to be a more appropriate source and maintains consistency with NICE guidance for RRMM. The EAG therefore conducted a scenario using the cancer end of life care cost from the PSSRU (£13,712), presented in Section 6.2 and included in the EAG's preferred assumptions, presented in Section 6.3.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

A proposed confidential patient access scheme (PAS) discount for SVd is applied in the company's base case and is therefore reflected in the results presented in this report. As confidential PAS discounts are available for comparators, the External Assessment Group (EAG) has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

5.1.1 Second-line subgroup

Table 75 presents the cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

In the base case probabilistic analysis, an incremental quality-adjusted life-year (QALY) loss of [REDACTED] over carfilzomib with dexamethasone (Kd) along with [REDACTED] for selinexor in combination with bortezomib and dexamethasone (SVd), generates an incremental cost-effectiveness ratio (ICER) of £334,464 (south-west quadrant). The net health benefit (NHB) based on the deterministic results using the £20,000 and £30,000 threshold is [REDACTED] and [REDACTED], respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 75. Company's base case results post clarification – SVd versus Kd (2L subgroup)

Interventions	Total Costs (£)	Total LY	Total QALYs	Δ costs (£)	Δ LYs	Δ QALYs	ICER (£/QALY)
Deterministic results							
Kd	319,769	4.28	[REDACTED]	-	-	-	-
SVd	[REDACTED]	3.85	[REDACTED]	[REDACTED]	-0.43	[REDACTED]	605,630 (SW quadrant)
Probabilistic results							
Kd	316,740	-	[REDACTED]	-	-	-	-
SVd	[REDACTED]	-	[REDACTED]	[REDACTED]	-	[REDACTED]	334,464 (SW quadrant)
Abbreviations: ICER, incremental cost-effectiveness ratio; Kd, carfilzomib plus dexamethasone; LY, life year; QALY, quality-adjusted life-year; SVd, selinexor plus bortezomib and dexamethasone; SW, south-west.							

A PSA scatterplot is presented in Figure 24 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 25. Based on these analyses, the probability that SVd is cost effective versus lxaRd is 99.2% at a willingness to pay (WTP) threshold of £20,000 and 98.4% at a WTP threshold of £30,000.

Figure 24. Scatterplot of PSA estimates on a cost-effectiveness plane SVd versus Kd at 2L (Figure 6 of the company's additional clarification response document)

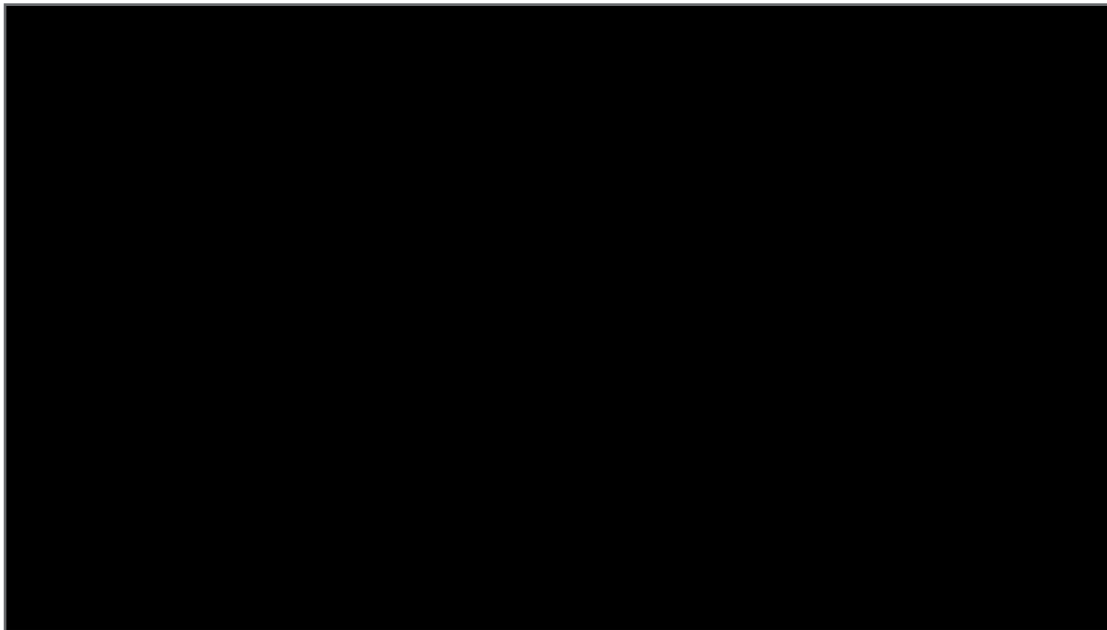
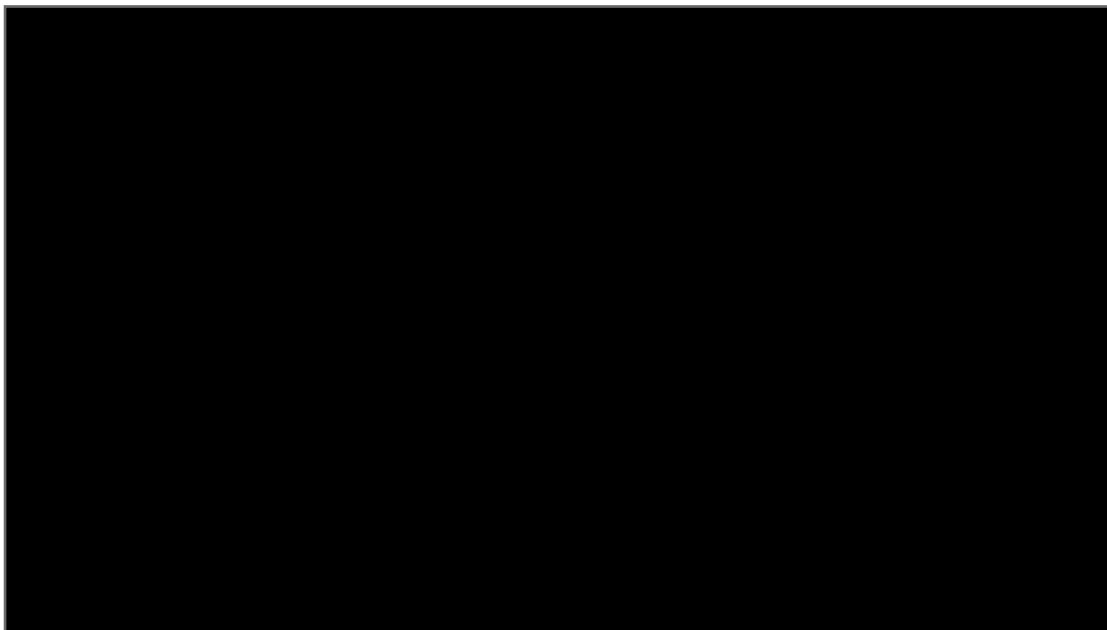


Figure 25. Cost-effectiveness acceptability curve for SVd versus Kd at 2L (Figure 7 of the company's additional clarification response document)



5.1.2 Third-line subgroup

Table 76 presents the cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses. Table 77 presents fully incremental analysis for the third-line subgroup (3L subgroup). The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

For the 3L subgroup, in the base case probabilistic analysis, an incremental quality-adjusted life-year (QALY) [REDACTED] over ixazomib in combination with lenalidomide and dexamethasone (IxaRd) along with [REDACTED] for SVd, generates an ICER of £1,293,485 (south-west quadrant). The NHB based on the deterministic results using the £20,000 and £30,000 threshold is [REDACTED] and [REDACTED], respectively.

For the comparison with panobinostat in combination with bortezomib and dexamethasone (PanoVd), SVd generates an incremental QALY gain of [REDACTED] and incremental costs of [REDACTED] resulting in an ICER of £39,743. The NHB based on the deterministic results using the £20,000 and £30,000 threshold is [REDACTED] and [REDACTED], respectively.

The EAG notes, that compared with the deterministic results for the 3L subgroup, the probabilistic analysis results in a change in the direction of the ICER from dominant for both comparators to south-west quadrant compared with IxaRd and north-east quadrant compared with PanoVd. The EAG considers that is driven by the uncertainty in the indirect treatment comparison estimates for IxaRd and PanoVd included in the analysis. The company did not provide probabilistic results for each scenario explored, therefore the results provided in Section 5.2 for the 3L subgroup may not be reliable for decision-making. However, the EAG considers that the PSA results are robust for decision-making as it captures the overall uncertainty in the analyses.

Table 76. Company's base case results post clarification – SVd versus 3L comparators

Interventions	Total Costs (£)	Total LY	Total QALYs	Δ costs (£)	Δ LYs	Δ QALYs	Pairwise ICER (£/QALY)
Deterministic results							
SVd	[REDACTED]	3.91	[REDACTED]	-	-	-	-
IxaRd	230,087	3.68	[REDACTED]	[REDACTED]	0.23	[REDACTED]	Dominant
PanoVd	138,207	3.38	[REDACTED]	[REDACTED]	0.53	[REDACTED]	Dominant
Probabilistic results							

SVd	■	-	■	-	-	-	-
IxaRd	225,416	-	■	■	-	■	1,293,485 (SW quadrant)
PanoVd	125,546	-	■	■	-	■	39,743

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; SW, south-west.

Table 77. Fully incremental analysis for 3L subgroup

Interventions	Total Costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	Incremental ICER (£/QALY)
Deterministic results					
SVd	■	■	-	-	-
PanoVd	138,207	■	■	■	Dominated by SVd
IxaRd	230,087	■	■	■	Dominated by SVd
Probabilistic results					
PanoVd	125,546	■	-	-	-
SVd	■	■	■	■	39,743
IxaRd	225,416	■	■	■	1,293,485

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; SW, south-west.

A PSA scatterplot of SVd versus IxaRd is presented in Figure 26 and for PanoVd is presented in Figure 27. A CEAC for SVd, IxaRd and PanoVd is presented in Figure 28. Based on these analyses, the probability that SVd is cost effective versus IxaRd and PanoVd is 37% at a WTP threshold of £20,000 and 42% at a WTP threshold of £30,000.

Figure 26. Scatterplot of PSA incremental estimates for SVd versus IxaRd at 3L (Figure 3 of the company's additional clarification response document)

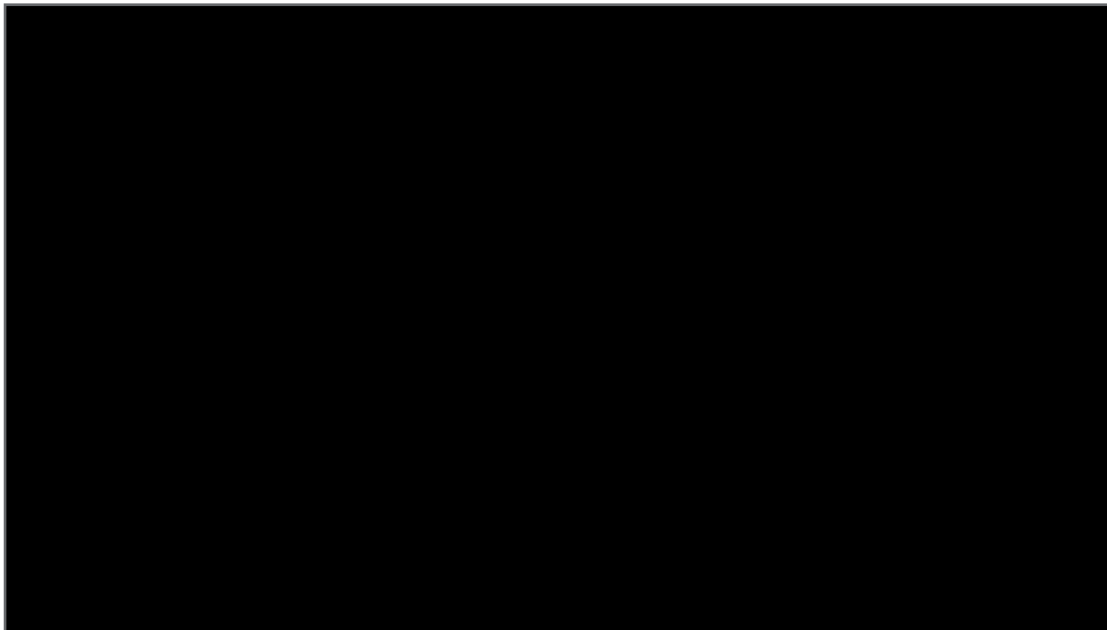


Figure 27. Scatterplot of PSA incremental estimates for SVd versus PanoVd at 3L (Figure 4 of the company's additional clarification response document)

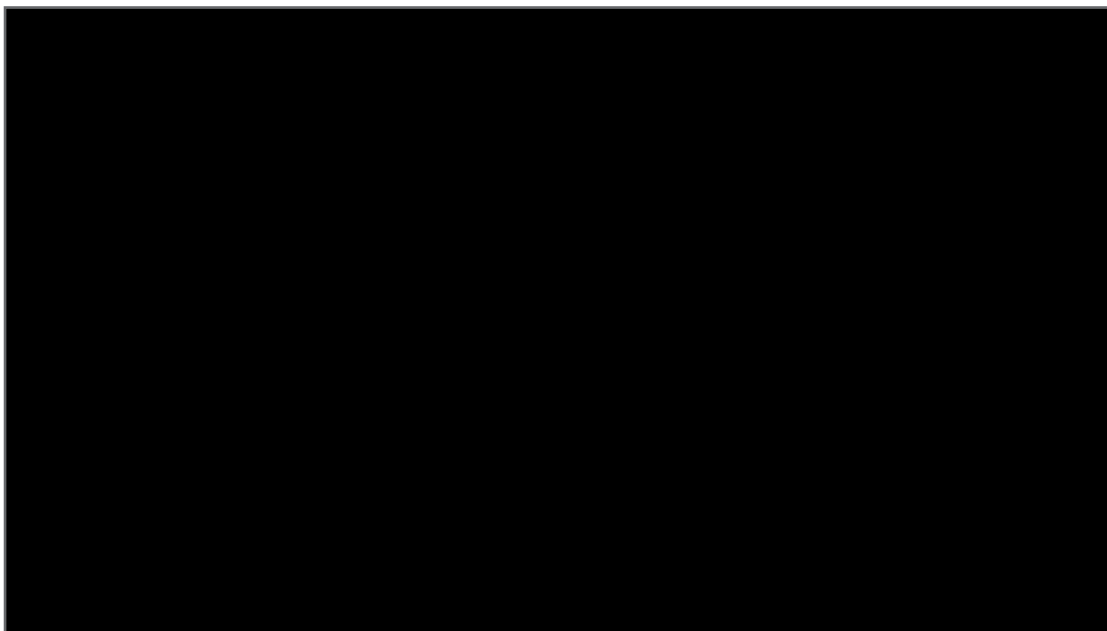
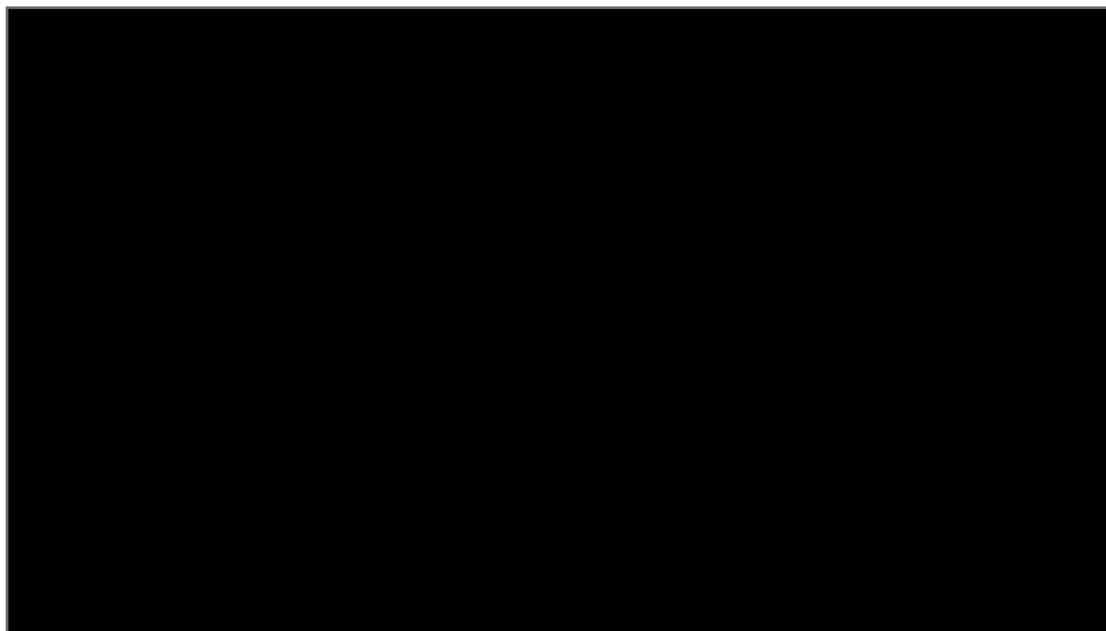


Figure 28. Cost-effectiveness acceptability curves for SVd, IxaRd and PanoVd at 3L (Figure 5 of the company's additional clarification response document)



5.2 Company's sensitivity analyses

5.2.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact, on the ICER, of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated using the tornado diagram in Figure 29 for SVd versus KD, Figure 30 for SVd versus IxaRd and Figure 31 for SVd versus PanoVd. For all analyses, the ICERs were most sensitive to the progression-free survival (PFS) and overall survival (OS) hazard ratios (HRs), and OS and PFS parametric curves.

Figure 29. Tornado plot – SVd vs Kd

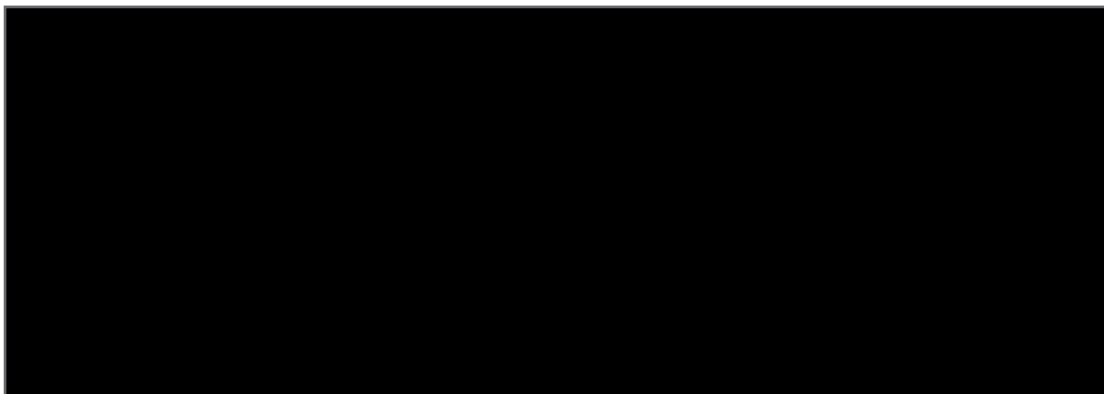


Figure 30. Tornado plot – SVd vs lxaRd

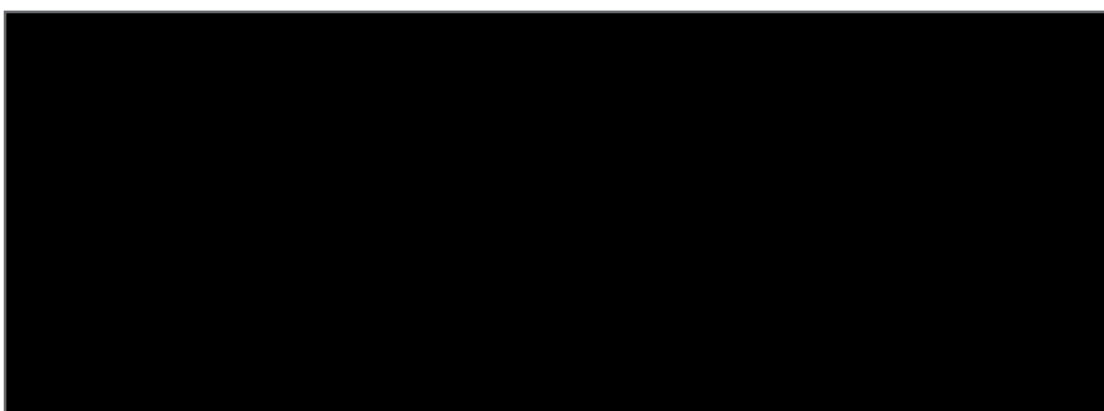
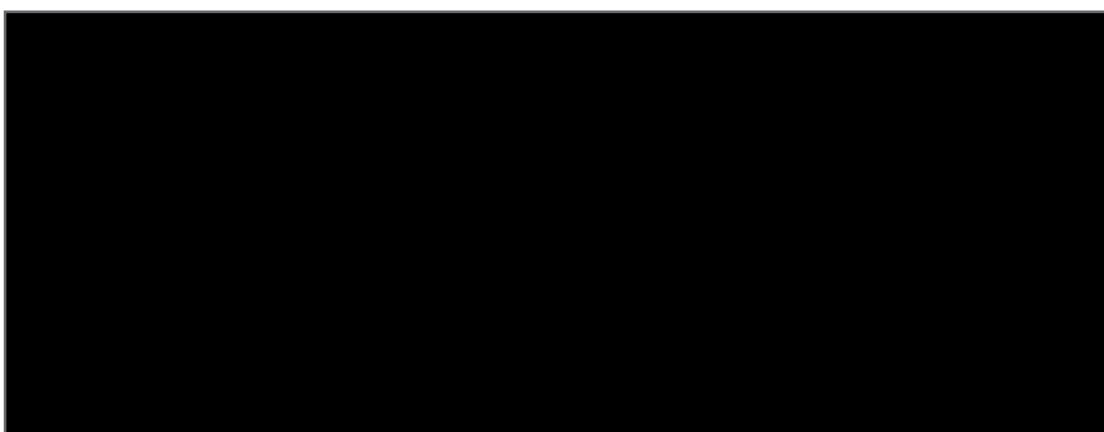


Figure 31. Tornado plot – SVd vs PanoVd



5.2.2 *Scenario analysis*

The company undertook an extensive series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. In addition, the company conducted several additional scenario analyses requested by the EAG. Results of all the company's scenario analyses post clarification can be found in the company's revised base case document as part of their clarification response. In their main clarification response, results of scenarios conducted by the company at the request of the EAG were applied to the company's original base case rather than the updated base case. As such, the EAG ran all the EAG requested scenarios again using the company's updated base case and results are presented in Section 6.2.

5.3 Model validation and face validity check

Section B.3.15.1 in the company submission outlines the company's approach to the validation of the economic model. The EAG is satisfied that the company's approach was thorough and robust. Additionally, the EAG did not identify any errors in the economic model.

6 Additional economic analysis undertaken by the EAG

6.1 Exploratory and sensitivity analyses undertaken by the EAG

As part of the clarification stage, the External Assessment Group (EAG) requested several analyses which were provided by the Company. However, the scenarios, and therefore results, presented in the Company's clarification response were applied to the Company's original base case rather than the Company's revised base case post clarification. As such, the EAG has re-run the scenarios requested in Section B of the clarification letter and results for the second-line (2L) and third-line (3L) subgroup are presented in Table 78 and Table 79, respectively.

In Section 4 of this report, the EAG has described several scenarios that warrant further exploration in addition to the Company's own sensitivity and scenario analyses to ascertain the impact of these changes on the incremental cost-effectiveness ratio (ICER). The scenarios that the EAG has performed are as follows:

1. A combined scenario implementing the EAG's preferred assumption for treatment effectiveness in the model, including:
 - a. Independently fitted models for the extrapolation of BOSTON progression-free survival (PFS), overall survival (OS) and time to treatment discontinuation (TTD) for selinexor in combination with bortezomib and dexamethasone (SVd) and bortezomib with dexamethasone (Vd) (Company scenario B5) – Section 4.2.3.2.
 - b. Extrapolations of PFS, OS and time to TTD Vd from BOSTON as the baseline for applying comparator treatment effects (Company scenario B5) – Section 4.2.3.2.
 - c. The EAG's preferred extrapolations of PFS, OS and TTD for the 2L and 3L subgroups – Sections 4.2.3.4, 4.2.3.6, 4.2.3.8.
 - i. 2L subgroup: PFS – Weibull; OS – Weibull; TTD – Gompertz with PFS cap.
 - ii. 3L subgroup: PFS – lognormal; OS – Weibull; TTD – generalised gamma with PFS cap.
 - iii. Company's unanchored matched adjusted indirect comparison (MAIC) estimate for ixazomib with lenalidomide and dexamethasone (IxaRd) used in 3L analysis – Section 3.4.3.
2. Scenario 1 in combination with no OS benefit (OS for comparators equal to Vd) – Section 4.2.3.6.

3. Scenario 1 in combination with no OS benefit (OS for comparators equal to SVd) – Section 4.2.3.6.
4. Combined scenario of the EAG’s preferred assumptions for the costs of subsequent treatments (Section 4.2.6.4), including:
 - a. EAG’s preferred approach to treatment effectiveness (scenario 1);
 - b. Alternative assumptions for proportions of each subsequent treatment based on the Company’s market share data and the NHS treatment pathway;
 - c. Chemotherapy costs based on cyclophosphamide plus dexamethasone.
5. Company scenario B11, including the 2L progressed health state utility equal to the 3L progression free utility based on data from BOSTON (2L subgroup only) – Section 4.2.5.2.
6. Administration cost of oral chemotherapy - 4.2.6.2.
7. Combined scenario of the EAG’s preferred assumptions for adverse events (AEs), including
 - a. Alternative AE unit costs based on the NHS reference costs schedule 2021/22⁵⁵ - Section 4.2.6.8;
 - b. one off impact of AEs – Section 4.2.4.1;
 - c. All AEs managed in secondary care (Company scenario B18)– Section 4.2.6.8.
8. End of life care cost from the PSSRU⁵⁷ - Section 4.2.6.10.

6.2 EAG scenario analysis

Table 78 and Table 79 presents the results of the EAG exploratory analyses described in Section 6.1. Results reported include the Company’s proposed patient access scheme (PAS) discount on the list price of [REDACTED]. Confidential PAS discounts are available for ixazomib, lenalidomide, carfilzomib, daratumumab, isatuximab and pomalidomide. As such, the EAG has produced a confidential appendix to the EAG report. Analyses in the confidential appendix include the Company base case results, scenario analyses and EAG base case and scenario analyses.

Table 78. Results of the EAG’s deterministic scenario analyses – 2L subgroup

	Results per patient	SVd	Kd	Incremental value
0	Company base case post clarification			
	Total costs (£)	[REDACTED]	319,769	[REDACTED]
	QALYs	[REDACTED]	[REDACTED]	[REDACTED]
	ICER (£/QALY)	-	-	605,630 (SW)
	Company scenarios in response to EAG clarification questions			
B4	Company preferred independent distributions for PFS (gamma), OS (gamma) and TTD (gamma)			
	Total costs (£)	[REDACTED]	322,068	[REDACTED]

	QALYs	■	■	■
	ICER (£/QALY)	-	-	580,050 (SW)
B5	Company preferred independent distributions for PFS (gamma), OS (gamma) and TTD (gamma) + Vd as baseline for comparators (HRs versus Vd)			
	Total costs (£)	■	413,520	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	Dominant
B11	BOSTON Utility values by line of therapy and progression status			
	Total costs (£)	■	319,769	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	599,403 (SW)
B14	Removal of IsaPd from subsequent treatment costs			
	Total costs (£)	■	317,285	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	605,656 (SW)
B16	EAG clinical experts' health state resource use estimates			
	Total costs (£)	■	344,082	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	613,668 (SW)
B18	Adverse events managed only in secondary care			
	Total costs (£)	■	319,993	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	603,273 (SW)
B25	Company's alternative estimation of subsequent treatment costs using market share data			
	Total costs (£)	■	332,280	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	522,939 (SW)
EAG scenarios				
1	Combined scenario implementing the EAG's preferred assumption for treatment effectiveness in the model			
	Total costs (£)	■	415,266	■
	QALYs	■	■	■
	ICER (£/QALY)			Dominant
2	Scenario 1 + OS for comparators equal to Vd			
	Total costs (£)	■	379,426	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	10,017,804 (SW)
3	Scenario 1 + OS for comparators equal to SVd			
	Total costs (£)	■	425,200	■

	QALYs	■	■	■
	ICER (£/QALY)	-	-	8,108,022 (SW)
4	EAG subsequent treatment assumptions + EAG preferred treatment effectiveness assumptions + chemotherapy assumed to be cyclophosphamide plus dexamethasone			
	Total costs (£)	■	460,604	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	Dominant
5	HSUV for the progressed health state equal to HSUV for the 3L progression-free health state (BOSTON data)			
	Total costs (£)	■	319,769	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	621,054 (SW)
6	Administration cost for oral chemotherapy			
	Total costs (£)	■	327,557	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	602,882 (SW)
7	EAG preferred AE unit costs + one-off impact of AEs + all AEs managed in secondary care			
	Total costs (£)	■	319,061	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	595,024 (SW)
8	End of life care cost from the PSSRU ⁵⁷			
	Total costs (£)	■	328,212	■
	QALYs	■	■	■
	ICER (£/QALY)	-	-	605,560 (SW)
Abbreviations: 2L, second-line; 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 79. Results of the EAG's deterministic scenario analyses – 3L subgroup

	Results per patient	SVd (1)	IxaRd (2)	PanoVd (3)	Incremental value (1-2)	Incremental value (1-3)
0	Company updated base case - post clarification					
	Total costs (£)	■	230,087	138,207	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	Dominant
Company scenarios in response to EAG clarification questions						
B4	Company preferred independent distributions for PFS (lognormal), OS (gamma) and TTD (lognormal)					
	Total costs (£)	■	212,469	138,844	■	■
	QALYs	■	■	■	■	■

	ICER (£/QALY)	-	-	-	Dominant	Dominant
B5	Company preferred independent distributions for PFS (lognormal), OS (gamma) and TTD (lognormal) + Vd as baseline for comparators (HRs versus Vd)					
	Total costs (£)	■	280,281	139,810	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B11	BOSTON Utility values by line of therapy and progression status					
	Total costs (£)	■	230,087	138,207	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B14	Removal of IsaPd from subsequent treatment costs					
	Total costs (£)	■	227,427	135,643	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B16	EAG clinical experts' health state resource use estimates					
	Total costs (£)	■	250,995	157,426	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B18	Adverse events managed only in secondary care					
	Total costs (£)	■	230,223	141,892	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B25	Company's alternative estimation of subsequent treatment costs using market share data					
	Total costs (£)	■	246,150	157,268	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	187,293
EAG scenarios						
1	Combined scenario implementing the EAG's preferred assumption for treatment effectiveness					
	Total costs (£)	■	301,409	137,321	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	171,605 (SW)	6,024
2	Scenario 1 + OS for comparators equal to Vd					
	Total costs (£)	■	240,084	132,618	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	2,577,373 (SW)	Dominated
3	Scenario 1 + OS for comparators equal to SVd					
	Total costs (£)	■	272,885	140,363	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	2,621,917 (SW)	169,421 (SW)

4	EAG subsequent treatment assumptions + EAG preferred treatment effectiveness assumptions + chemotherapy assumed to be cyclophosphamide plus dexamethasone					
	Total costs (£)	■	313,936	150,412	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	172,112 (SW)	3,384
6	Administration cost for oral chemotherapy					
	Total costs (£)	■	247,488	146,733	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	Dominant
7	EAG preferred AE unit costs + one-off impact of AEs + all AEs managed in secondary care					
	Total costs (£)	■	229,174	131,964	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	Dominant
8	End of life care cost from the PSSRU ⁵⁷					
	Total costs (£)	■	238,546	146,683	■	■
	QALYs	■	■	■	■	■
	ICER (£/QALY)	-	-	-	Dominant	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.						

6.3 EAG preferred assumptions

In this section, the EAG presents its preferred base case for the cost-effectiveness of SVd for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received one or two prior lines of treatment. The assumptions that form the EAG's preferred base case are listed below.

- EAG scenario 1 – combined scenario implementing the EAG's preferred assumptions for treatment effectiveness in the model.
- EAG scenario 2 – OS for comparators equal to 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 AEs
- Company scenario B16 – EAG clinical experts resource use assumptions.

- EAG scenario 8 – End of life care cost from the PSSRU.⁵⁷

The EAG has explored several scenarios around the preferred base case to assess the impact of alternative assumptions on the ICER and these include:

- OS for comparators equal to SVd (EAG scenario 3);
- Inclusion of an OS benefit for treatments (removal of EAG scenario 2);
- Use of utility values from Hatswell *et al.*¹

The EAG considers that based on the results of its preferred base case results for the 2L and 3L subgroup, the difference in SVd compared with Kd, IxaRd and PanoVd centres around costs, as the incremental QALY differences are very small. However, the EAG does not consider that this means treatments are all as effective as each other. Based on the indirect treatment comparisons (ITCs) all comparators are estimated to have better PFS than SVd, but similar OS. As such, comparator treatments gain a small amount of additional benefit by patients remaining pre-progression longer, despite having the same OS. As mentioned previously, the EAG's clinical experts consider that the main objective of treatment at 2L and 3L is to keep patients progression-free for as long as possible.

6.3.1 Second-line subgroup

Table 80 and Table 81 present the results of the EAG's preferred assumptions and Table 82 present the results of scenarios around the EAG base case.

Table 80. EAG's preferred model assumptions – 2L subgroup

Preferred assumption	Section in EAG report	Cum. incremental costs	Cum. incremental QALYs	Cumulative ICER (£/QALY)
Company base case post clarification	-	■	■	605,630 (SW)
EAG scenario 1 – treatment effectiveness assumptions	4.2.3	■	■	Dominant
EAG scenario 2 – OS for comparators equal to Vd	4.2.3.6	■	■	10,017,804 (SW)
Company scenario B11 – utility values by line of therapy and progression status	4.2.5.2	■	■	10,036,592 (SW)
EAG scenario 4 – subsequent treatments	4.2.6.4	■	■	8,601,271 (SW)
EAG scenario 6 – administration cost for oral chemotherapy	4.2.6.24.2.6.8	■	■	8,400,870 (SW)

EAG scenario 7 – AE costs*	4.2.6.8	■	■	6,612,455 (SW)
Company scenario B16 – EAG clinical expert resource use assumptions*	4.2.6.6	■	■	6,612,455 (SW)
EAG scenario 8 – End of life care cost from the PSSRU*	4.2.6.9	■	■	6,612,455 (SW)
EAG preferred base case	-	■	■	6,612,455 (SW)

Abbreviations: Abbreviations: 2L, second-line; Cum, cumulative; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; Kd, carfilzomib with dexamethasone; OS, overall survival; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west; Vd, bortezomib with dexamethasone.

* The EAG notes that that while the incremental costs and ICER does not change for the scenario, the total costs are impacted by the change in assumption.

Table 81. EAG's preferred base case results – SVd versus Kd (2L subgroup)

Interventions	Total Costs (£)	Total LY	Total QALYs	Δ costs (£)	Δ LYs	Δ QALYs	ICER (£/QALY)	NHB (£30K)
Deterministic results								
Kd	424,323	2.98	■	-	-	-	-	-
SVd	■	2.98	■	■	0.00	■	6,612,455 (SW)	■
Probabilistic results								
Kd	431,480	-	■	-	-	-	-	-
SVd	■	-	■	■	-	■	8,694,817 (SW)	■

Abbreviations: 2L, second-line; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; Kd, carfilzomib with dexamethasone; NHB, net health benefit; OS, overall survival; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west.

Table 82. Results of the EAG's probabilistic scenario analyses – 2L subgroup

	Results per patient	SVd	Kd	Incremental value
0	EAG preferred base case			
	PSA total costs (£)	■	431,480	■
	PSA QALYs	■	■	■
	PSA ICER (£/QALY)	-	-	8,694,817 (SW)
	Deterministic ICER (£/QALY)	-	-	6,612,455 (SW)
1	OS for comparators equal to SVd			
	PSA total costs (£)	■	490,202	■
	PSA QALYs	■	■	■
	PSA ICER (£/QALY)	-	-	7,342,967 (SW)
	Deterministic ICER (£/QALY)	-	-	6,841,118 (SW)
2	Inclusion of an OS benefit for treatments			
	PSA total costs (£)	■	475,592	■

	PSA QALYs	■	■	■
	PSA ICER (£/QALY)	-	-	Dominant
	Deterministic ICER (£/QALY)			Dominant
3	Use of utility values from Hatswell et al. ¹			
	PSA total costs (£)	■	432,400	■
	PSA QALYs	■	■	■
	PSA ICER (£/QALY)	-	-	5,907,004 (SW)
	Deterministic ICER (£/QALY)	-	-	4,323,476 (SW)

Abbreviations: 2L, second-line; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; Kd, carfilzomib with dexamethasone; OS, overall survival; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west.

6.3.2 Third-line subgroup

Table 83 and Table 84 present the results of the EAG's preferred assumptions and Table 85 present the results of scenarios around the EAG base case. The EAG has not presented fully incremental analysis for its preferred cost-effectiveness as treatment effectiveness estimates for IxaRd and PanoVd are from two different ITC methods and so are potentially not directly comparable to one another. As such, for the 3L subgroup, the EAG considers pairwise ICERs for SVd against the comparators to be more appropriate. Additionally, the EAG's base case deterministic and probabilistic results for the 3L subgroup are coherent with one another and the EAG considers that this is driven by the use of the unanchored matched-adjusted indirect comparison PFS hazard ratio for IxaRd as well as the removal of the OS benefit for all treatments.

Table 83. EAG's preferred model assumptions – 3L subgroup

Preferred assumption	Section in EAG report	vs IxaRd			vs PanoVd		
		Cum. Δ costs (£)	Cum. Δ QALYs	Cumulative ICER (£/QALY)	Cum. Δ costs (£)	Cum. Δ QALYs	Cum. ICER (£/QALY)
Corrected Company base case	-	■	■	Dominant	■	■	Dominant
EAG scenario 1 – treatment effectiveness assumptions	4.2.3	■	■	171,605 (SW)	■	■	6,024
EAG scenario 2 – OS for comparators equal to Vd	4.2.3.6	■	■	2,577,373 (SW)	■	■	Dominated
Company scenario B11 – utility values by line of therapy and progression status	4.2.5.2	■	■	2,583,364 (SW)	■	■	Dominated
EAG scenario 4 – subsequent treatments	4.2.6.4	■	■	2,324,202 (SW)	■	■	Dominated

EAG scenario 6 – administration cost for oral chemotherapy	4.2.6.24.2.6.8	■	■	2,569,239 (SW)	■	■	Dominated
EAG scenario 7 – AE costs*	4.2.6.8	■	■	2,445,681 (SW)	■	■	Dominated
Company scenario B16 – EAG clinical expert resource use assumptions*	4.2.6.6	■	■	2,445,681 (SW)	■	■	Dominated
EAG scenario 8 - End of life care cost from the PSSRU*	4.2.6.9	■	■	2,445,681 (SW)	■	■	Dominated
EAG preferred base case	-	■	■	2,445,681 (SW)	■	■	Dominated

Abbreviations: 3L, third-line; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; IxaRd, ixazomib with lenalidomide and dexamethasone; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west; Vd, bortezomib with dexamethasone.

* The EAG notes that while the incremental costs and ICER does not change for the scenario, the total costs are impacted by the change in assumption.

Table 84. EAG's preferred base case results – SVd versus 3L comparators

Interventions	Total Costs (£)	Total LY	Total QALYs	Δ costs (£)	Δ LYs	Δ QALYs	Pairwise ICER (£/QALY)	NHB (£30K)
Deterministic results								
SVd	■	2.75	■	-	-	-	-	-
IxaRd	284,753	2.75	■	■	0.00	■	2,445,681 (SW)	■
PanoVd	171,299	2.75	■	■	0.00	■	Dominated	■
Probabilistic results								
SVd	■	-	■	-	-	-	-	-
IxaRd	272,739	-	■	■	-	■	2,457,260 (SW)	■
PanoVd	154,929	-	■	■	-	■	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 85. Results of the EAG's scenario analyses – 3L subgroup

	Results per patient	SVd (1)	IxaRd (2)	PanoVd (3)	Incremental value (1-2)	Incremental value (1-3)
0	EAG preferred base case					
	PSA total costs (£)	■	272,739	154,929	■	■
	PSA QALYs	■	■	■	■	■
	PSA ICER (£/QALY)	-	-	-	2,457,260 (SW)	Dominated
	Deterministic ICER (£/QALY)	-	-	-	2,445,681 (SW)	Dominated
1	OS for comparators equal to SVd					
	PSA total costs (£)	■	315,972	177,410	■	■
	PSA QALYs	■	■	■	■	■
	PSA ICER (£/QALY)	-	-	-	2,602,287 (SW)	Dominated
	Deterministic ICER (£/QALY)	-	-	-	2,694,487 (SW)	Dominated
2	Inclusion of an OS benefit for treatments					
	PSA total costs (£)	■	364,847	156,864	■	■
	PSA QALYs	■	■	■	■	■
	PSA ICER (£/QALY)	-	-	-	171,546 (SW)	108,755

	Deterministic ICER (£/QALY)				196,251 (SW)	27,347
3	Use of utility values from Hatswell et al. ¹					
	PSA total costs (£)	■	275,666	155,321	■	■
	PSA QALYs	■	■	■	■	■
	PSA ICER (£/QALY)	-	-	-	1,534,107 (SW)	Dominated
	Deterministic ICER (£/QALY)	-	-	-	1,506,548 (SW)	Dominated
Abbreviations: 3L, third-line; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; IxaRd, ixazomib with lenalidomide and dexamethasone; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; QALY, quality-adjusted life-year; SVd, selinexor with bortezomib and dexamethasone; SW, south-west.						

6.4 Conclusions of the cost effectiveness section

Generally, the EAG considers the Company's submitted cost-effectiveness analysis adheres to the decision problem defined in the NICE final scope.²³ However, the EAG considers there is a substantial amount of uncertainty in the cost-effectiveness analysis, driven primarily by the assumed treatment effectiveness of all interventions included in the model and the long-term impacts of these have on overall survival. As mentioned in Section 3, the EAG considers there to be evidence of the inferiority of SVd relative to carfilzomib with dexamethasone (Kd), ixazomib with lenalidomide and dexamethasone (IxaRd) and panobinostat with bortezomib and dexamethasone (PanoVd) in terms of PFS. However, the OS analyses are more difficult to interpret, due to OS being contingent on all future lines of therapy patients received in BOSTON and comparator trials.

There is no robust evidence of a statistically significant difference in OS for treatments and thus the EAG considers that it may be appropriate to assume no OS benefit for any treatments in the cost-effectiveness analysis. The EAG acknowledges that this assumption has a profound impact on the cost-effectiveness analysis and advises that, even though SVd is estimated to be inferior when it comes to PFS, any benefit estimated in the Company's base case analysis hinges on SVd having longer OS than its comparators. As such, the committee needs to consider the plausibility of an OS benefit associated with SVd and more broadly for all treatments considered in the analysis.

Furthermore, the Company's assumption that proportional hazards (PH) holds between SVd and Vd for PFS and OS in BOSTON is not appropriate. Based on diagnostic plots provided by the Company, the EAG considers that the PH assumption is violated and this has downstream consequences in terms of using SVd as the baseline to apply comparator effects, as well as the choice to jointly fit

survival curves. Instead, the EAG considers it is more appropriate to use Vd as the baseline survival in the model, as Vd is the common treatment to link into the network for the ITC the PH assumption for PFS holds for most of the trials included in the network (which may be considered the more clinically important outcome). Additionally, based on the decision support unit (DSU) technical support document (TSD) 14, independently fitted models which support the PH assumption are preferred by the EAG as HRs are estimated from the ITC for comparators included in the cost-effectiveness analysis.

In addition to the uncertainties around long-term outcomes in the economic model, the EAG considers that the Company's underlying assumptions to cost subsequent treatments in the model were not well aligned with the NHS treatment pathway and how subsequent treatments would be given in the clinical practice. The EAG recognises that a patient's journey through the RRMM NHS treatment pathway is highly dependent on previous lines of treatment received, but that the pathway is well defined and has attempted to estimate alternative assumptions around subsequent treatments in the model that would be more reflective of clinical practice.

Moreover, the Company base case assumptions for AEs were also not considered to be reflective of how patients would be managed in the NHS. The main assumption around AEs that had the biggest impact on the cost-effectiveness results was that costs and disutility associated with AEs would be experienced for the entire duration patients were on treatment. Therefore, treatments with longer PFS and thus longer time on treatment (which was all comparators in the analysis) would accumulate the impact of AEs over that time. Additionally, AE data from BOSTON are based on incidence, rather than prevalence, thus using a weekly event treats the data as if it were prevalence data, which is inappropriate. Therefore, the EAG considers that the Company's approach to AEs was biased against comparators in the economic model. Instead, the EAG considers that it is more clinically plausible to capture AEs as a one-off impact at the start of the model and remove the link with length of treatment. Applying AEs as a one-off impact is more typically seen for NICE oncology technology appraisals.

Overall, the EAG believes there is a substantial amount of uncertainty in the cost-effectiveness analysis. The EAG considers that based on the results of its preferred base case results for the 2L and 3L subgroup, the difference in SVd compared with Kd, IxaRd and PanoVd centres around costs, as the incremental QALY differences are very small. However, the EAG does not consider that this means treatments are all as effective as each other. Based on the ITCs all comparators are estimated

to have better PFS than SVd, but similar OS. As such, comparator treatments gain a small amount of additional benefit by patients remaining pre-progression longer, despite having the same OS. As mentioned previously, the EAG's clinical experts consider that the main objective of treatment at 2L and 3L is to keep patients progression-free for as long as possible.

7 References

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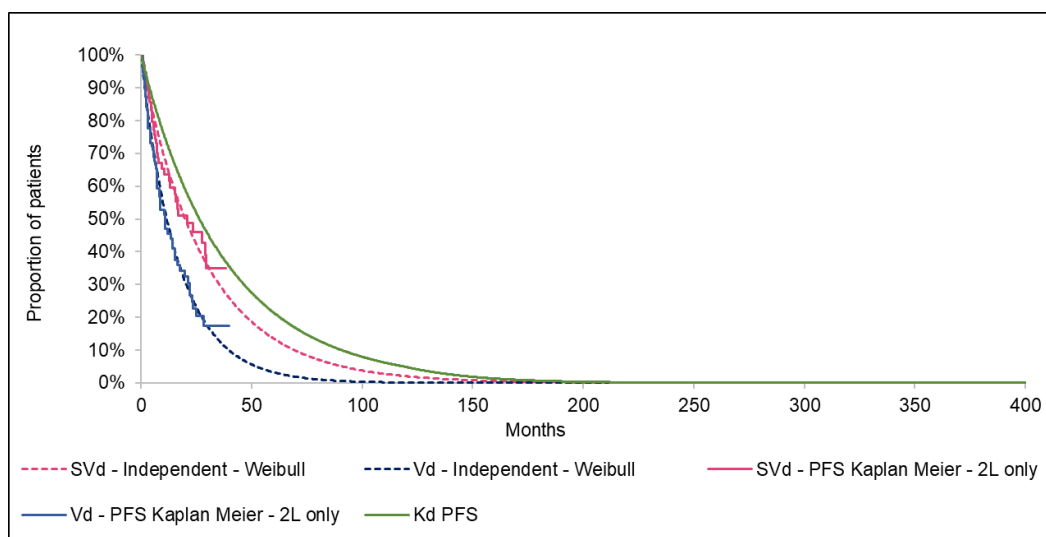
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8 Appendices

8.1 Summary of EAG preferred treatment effectiveness extrapolations

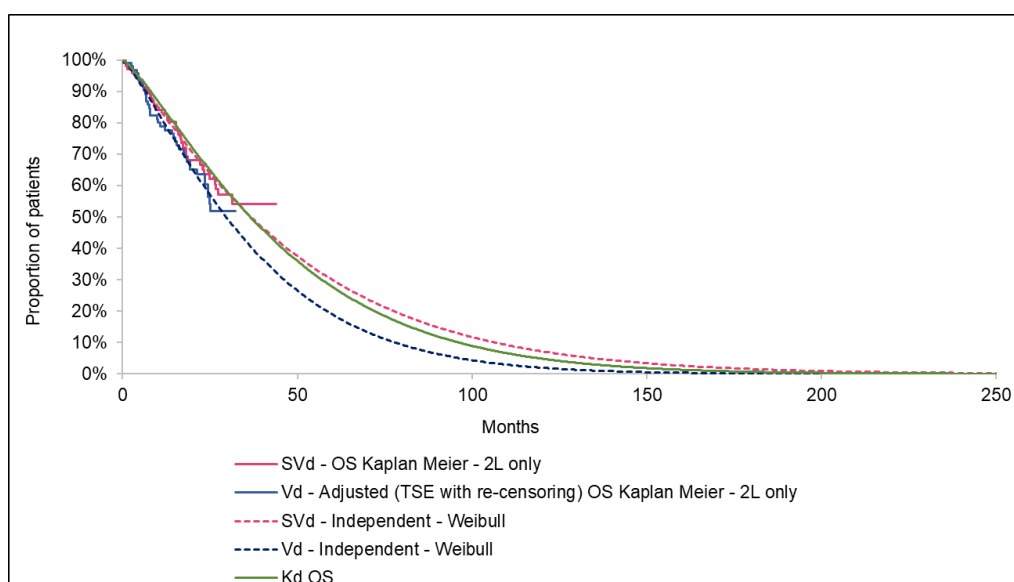
8.1.1 Second-line subgroup

Figure 32. Extrapolation of PFS for SVd, Vd and Kd using independently fitted Weibull curves and with Vd used as the baseline to apply comparator HR – 2L subgroup



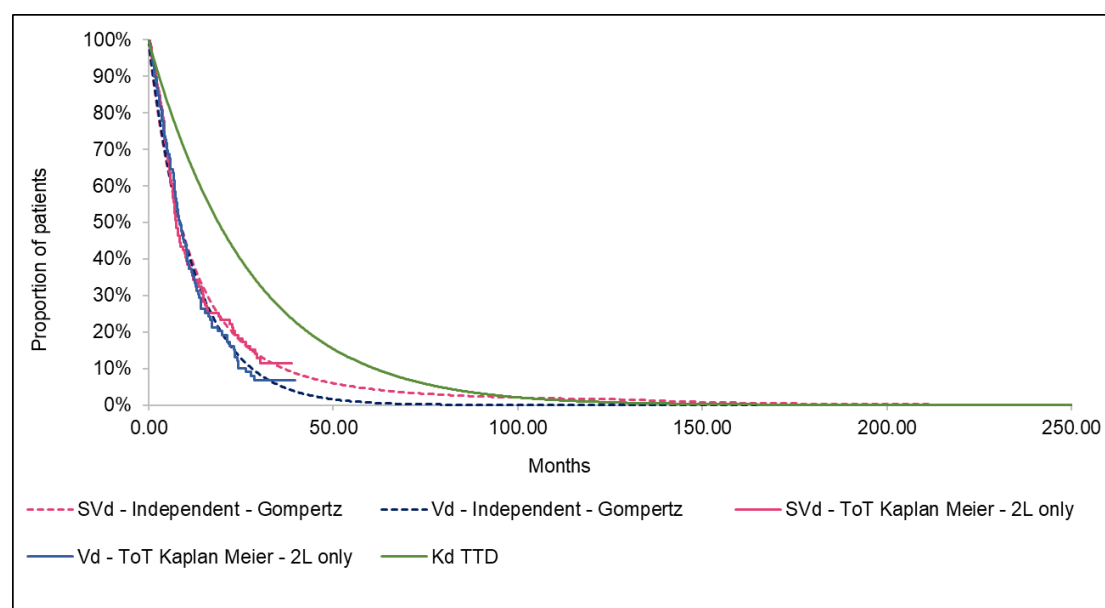
Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone

Figure 33. Extrapolation of OS for SVd, Vd and Kd using independently fitted Weibull curves and with Vd used as the baseline to apply comparator HR – 2L subgroup



Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; OS, overall survival; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone

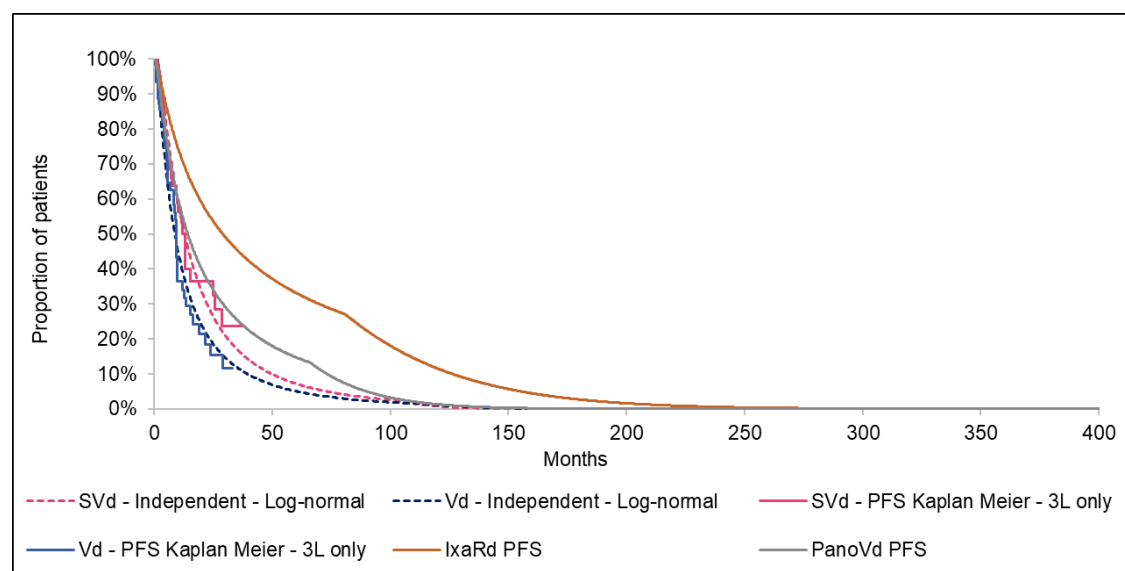
Figure 34. EAG Gompertz preferred extrapolation of TTD for SVd, Vd and Kd – 2L subgroup



Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; SVd, selinexor with bortezomib and dexamethasone; TTD, time to treatment discontinuation; Vd, bortezomib with dexamethasone

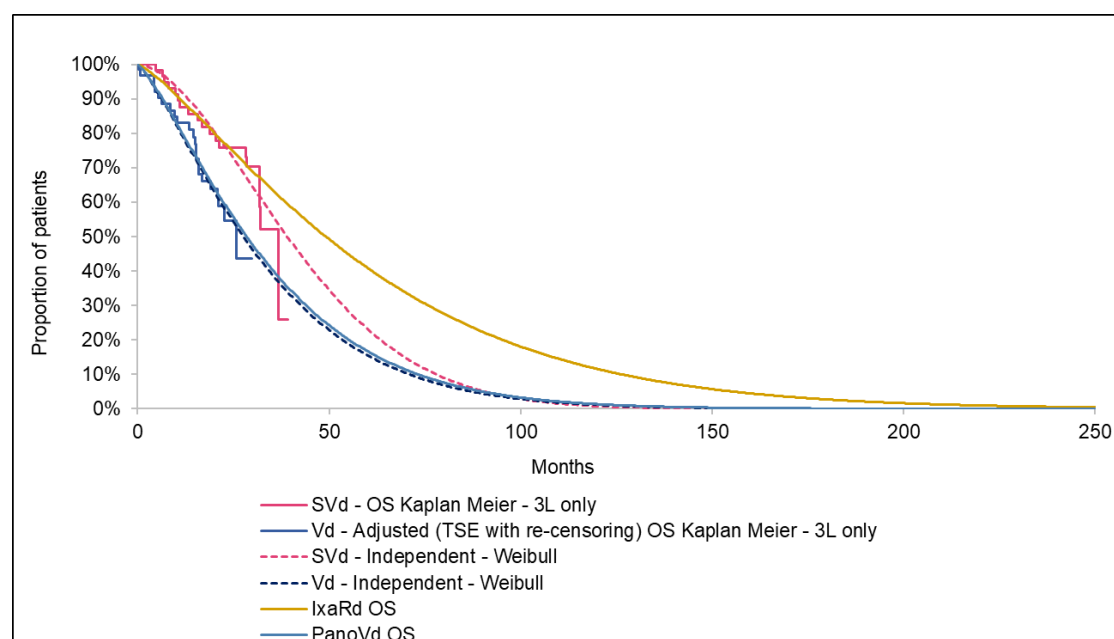
8.1.2 Third-line subgroup

Figure 35. Extrapolation of PFS for SVd, Vd, IxaRd and PanoVd using independently fitted lognormal curves and with Vd used as the baseline to apply comparator HRs – 3L subgroup



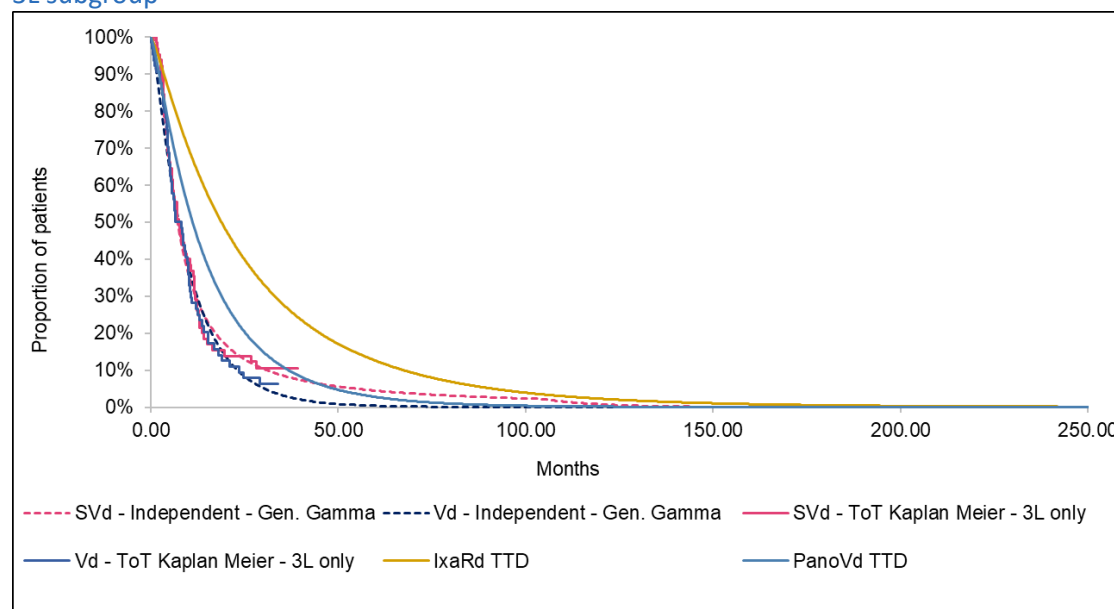
Abbreviations: 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

Figure 36. Extrapolation of OS for SVd, Vd, IxaRd and PanoVd using independently fitted Weibull curves and with Vd used as the baseline to apply comparator HR – 3L subgroup



Abbreviations: 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; KM, Kaplan-Meier; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

Figure 37. EAG preferred generalised gamma extrapolation of TTD for SVd, Vd, IxaRd and PanoVd – 3L subgroup



Abbreviations: 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; KM, Kaplan-Meier; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; TTD, time to treatment discontinuation; Vd, bortezomib with dexamethasone.

Single Technology Appraisal

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

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