Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Menarini Stemline:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Myeloma UK
   b. UK Myeloma Society

4. **External Assessment Report** prepared by BMJ Technology Assessment Group

5. **External Assessment Report – factual accuracy check**

6. **Statements from experts:**
   a. Dr. Neil Rabin, Consultant Haematologist and Chair of UK Myeloma Society – clinical expert, nominated by UK Myeloma Society
   b. Rosemary Dill – patient expert, nominated by Myeloma UK

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

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Document B

Company evidence submission

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Contents

Tables and Figures

Glossary of abbreviations

Term	Definition
1L	First-line
2L	Second-line
3L	Third-line
3L+	Third-line plus
5-HT3	5-hydroxytryptamine
AE	Adverse event
Af/Am	African American
AFT	Accelerated failure time
AIC	Akaike information criterion
AUC	Area under curve
BCLPD	Bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab
BNF	British National Formulary
BIC	Bayesian information criterion
BORT	Bortezomib
BTD	Bendamustine plus thalidomide and dexamethasone
BSA	Body surface area
CARF	Carfilzomib
CAR-T	Chimeric antigen receptors cell therapy
CBR	Clinical benefit rate
CCT	Conventional chemotherapy
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability
CEM	Cost-effectiveness model
CHMP	The Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CODA	Convergence output and diagnosis analysis
CR	Complete response
CRD	Centre for Reviews and Dissemination
CUA	Cost-utility analysis
DARA	Daratumumab
DCE	Discrete choice experiment
DEX	Dexamethasone
DOR	Duration of response
DPd	Daratumumab plus pomalidomide and dexamethasone
DRd	Daratumumab in combination with lenalidomide and dexamethasone

DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DVd	Daratumumab in combination with bortezomib and dexamethasone
ECOG	Eastern Cooperative Oncology Group
EHA	European Haematology Association
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
EORTC QLQ-CIPN20	European Organization for Research and Treatment of Cancer quality of life Chemotherapy-Induced Peripheral Neuropathy questionnaire
EORTC QLQ-MY20	European Organization 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
ESS	Effective sample size
FE	Fixed effects
FP	Fractional polynomial
GID	Guidance in development
HCRU	Healthcare resource use
HDACi	Histone deacetylase inhibitors
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
Ig	Immunoglobulin
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
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
LEN	Lenalidomide

LOT	Line(s) of therapy
LY	Life-year
MA	Marketing authorisation
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
mITT	Modified intent-to-treat
MM	Multiple myeloma
MoA	Mechanism of action
MR	Minimal response
MRD	Minimal residual disease
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NFkB	nuclear factor κB
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
ONS	Office of National Statistics
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PANO	Panobinostat
PanoVd	Panobinostat in combination with bortezomib and dexamethasone
PAR	Public assessment report
PAS	Patient access scheme
PD	Progressive disease
PF	Progression free
PFS	Progression-free survival
PI	Proteosome inhibitor
PN	Peripheral neuropathy
PR	Partial response
PRO	Patient reported outcome

PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
Rd	Lenalidomide plus dexamethasone
RDI	Relative dose intensity
RE	Random effects
R-ISS	Revised International Staging System
RRMM	Relapsed and/ or refractory multiple myeloma
SACT	Systemic Anti-Cancer Therapy (Dataset)
SAE	Serious adverse event
SC	Sub-cutaneous
sCR	Stringent complete response
SCT	Stem cell transplant
Sd	Selinexor plus dexamethasone
SD	Stable disease
SdX	Selinexor plus dexamethasone crossover population (crossed over from Vd to Sd)
SE	Standard error
SEL	Selinexor
SINE	Selective inhibitor of nuclear export
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STC	Simulated treatment comparison
STD	Standard deviation
SVd	Selinexor in combination with bortezomib and dexamethasone
SVdX	Selinexor in combination with bortezomib and dexamethasone crossover population (crossed over from Vd to SVd)
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
THAL	Thalidomide
TOI	Trial Outcome Index
ToT	Time on treatment
TRAE	Treatment-related adverse event
TSD	Technical support document

TSE	Two-stage- estimation
TTD	Time to discontinuation
TTNT	Time to next treatment
TTP	Time to progression
TTR	Time to response
Vd	Bortezomib plus dexamethasone
VGPR	Very good partial response
WTP	Willingness to pay
XPO1	Exportin 1 protein

Condition-specific terminology

Term	Description
Penta-refractory	Refractory to two proteasome inhibitors, two immunomodulatory drugs, and an anti-CD38 monoclonal antibody
Proteosome inhibitors	Including: bortezomib, carfilzomib and ixazomib
Immunomodulatory drugs	Including: lenalidomide, pomalidomide, and thalidomide
Anti-CD38 monoclonal antibodies	Including: daratumumab, and isatuximab

B1 Decision problem, description of the technology and clinical care pathway

B1.1 Decision problem

The pathway of treatments for multiple myeloma (MM) is complex and evolving rapidly. MM is a multi-faceted haematological cancer which is incurable. People with MM often require multiple lines of treatment throughout the course of their disease. Clinicians and patients place a high value on having access to safe and effective treatment combinations at different points in the treatment pathway, which include differing but complementary and synergistic mechanisms of action (MoA), as patients become increasingly refractory to different classes of drug as they progress through treatment lines.

Selinexor is a novel selective inhibitor of nuclear export (SINE) compound that blocks exportin 1 (XPO1) and forces nuclear accumulation and activation of tumour suppressor proteins, inhibits nuclear factor κB (NFkB), and reduces oncoprotein messenger RNA translation.[1] Selinexor is the first SINE inhibitor to be licensed in the treatment of MM, with two licensed combinations of two different indications.[2,3] NICE is appraising both in parallel, as detailed in Table 1.

Table 1 Summary of selinexor indications undergoing concurrent NICE appraisal

NICE ID	Posology[3]	MHRA licensed indication[3]	Pivotal trial evidence[4,5]
ID3797	SVd: 35-day treatment cycle of selinexor 100mg orally once weekly on Day 1, bortezomib 1.3mg/m^2 SC once weekly on Day 1 for 4 weeks followed by 1 week off, plus dexamethasone 20mg orally twice weekly on Days 1 and 2	For the treatment of adult patients with MM who have received at least one prior therapy	BOSTON Phase 3 RCT of SVd *versus* Vd **Relevant efficacy populations:** **2L n=198** **3L n=129**
ID6193	Sd: 28-day treatment cycle of selinexor 80mg orally on Day 1 and Day 3 of each week, plus dexamethasone 20mg orally twice weekly on Day 1 and Day 3 of each week	For the treatment of MM in adult patients who have received at least four prior therapies, and whose disease is refractory to at least two PIs, two IMiDs and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy (penta-refractory)	STORM Phase 2b, 2-part, single arm trial of Sd **Relevant efficacy population penta-refractory participants in Part 2 mITT (BCLPD-refractory) n=83**

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; IMiDs, immunomodulatory imide drugs; PIs, proteasome inhibitors; mAb, monoclonal antibody; MHRA, Medicines and Healthcare products Regulatory Agency; mITT, modified intent-to-treat; MM, multiple myeloma; RCT, randomised controlled trial; Sd, Selinexor + dexamethasone; SVd, Selinexor + bortezomib + dexamethasone; 2L, second-line; 3L, third-line.

Menarini-Stemline UK Ltd request that NICE appraise:

- SVd in the second-line (2L) and third-line (3L) setting of the UK treatment pathway (i.e., for adult patients who have received one or two prior lines of therapy), a positioning 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 the first-line (1L) treatment paradigm.
- Sd in the later line relapsed and/ or refractory MM (RRMM) setting, specifically in patients who have received at least four prior therapies, and who are refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, also known as penta-refractory, and who have demonstrated disease progression on the last treatment, as per the MHRA marketing authorisation (MA).

This pragmatic approach ensures that selinexor, as a SINE compound with a new MoA, can be made available to patients in the key areas of unmet need identified by UK myeloma experts and where the evidence base for the treatment best supports its use.

This submission dossier relates to the decision problem for NICE TA ID3797 selinexor in combination with bortezomib and dexamethasone, for 2L and 3L MM. The decision problem addressed in this submission is summarised in Table 2. A separate submission (ID6193) covers the penta-refractory indication and decision problem.

The MA for SVd is for the treatment of adult patients with MM who have received at least one prior therapy. This submission focuses on part of that technology's marketing authorisation, i.e., the population of adults with RRMM who have received either one prior line of therapy (second-line [2L]) or two prior lines of treatments (third-line [3L]). This positioning is supported by UK myeloma experts, who report a significant unmet need for additional treatment options in the 3L setting and anticipate future unmet need at 2L as the treatment landscape evolves, particularly in the first line. The company submission differs from the final NICE scope in terms of the restricted population and, thereby relevant comparators.

Table 2 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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 Clinical evidence regarding SVd is from the BOSTON study, a phase 3 open label randomised controlled trial of SVd *versus* bortezomib plus dexamethasone (Vd) in patients who had received 1 to 3 prior lines of therapy. The BOSTON study reported data by line of therapy for those at 2L and those at 3L.	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.[3] 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.
Intervention	Selinexor in combination with bortezomib and dexamethasone	Nexpovio® (selinexor) in combination with bortezomib and low-dose dexamethasone	As specified in the final scope.
Comparator(s)	● For people who have had 1 prior therapy: • bortezomib monotherapy • lenalidomide plus dexamethasone • 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	For people who have received 1 prior line of therapy: • carfilzomib plus dexamethasone For people who have received 2 previous lines of therapy: • 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.	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 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

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• lenalidomide plus dexamethasone • panobinostat plus bortezomib and dexamethasone • isatuximab plus bortezomib and dexamethasone (subject to ongoing NICE appraisal) ● For people who have had any number of prior therapies: • conventional chemotherapy regimens • best supportive care • belantamab mafodotin (subject to ongoing NICE appraisal)		ixazomib, which is given in combination with Rd. Therefore, in this submission, the comparators to SVd at 3L are IxaRd and PanoVd.
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.
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 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	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 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	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.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	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 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.
Special considerations including issues	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	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	No difference to scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
related to equity or equality	the evidence that has underpinned the marketing authorisation granted by the regulator.	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 patients of different ethnic backgrounds, including patients from the UK.	

Abbreviations: DVd; daratumumab + lenalidomide + dexamethasone; 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.

B1.2 Description of the technology being appraised

Table 3 provides a summary of the technology being appraised, selinexor (Nexpovio®). The UK MHRA Summary of Product Characteristics and Public Assessment Report are included in Appendix C.[2,3]

Table 3 Technology being appraised

UK approved name and brand name	Selinexor; Nexpovio®
Mechanism of action	Selinexor is a reversible covalent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). XPO1 is the major mediator of the nuclear export of many cargo proteins including tumour suppressor proteins (TSPs), growth regulators and mRNAs of growth promoting (oncogenic) proteins. XPO1 inhibition by selinexor leads to marked accumulation of TSPs in the nucleus, cell cycle arrest, reductions in several oncoproteins such as c-Myc and cyclin D1, and apoptosis of cancer cells. The combination of selinexor, dexamethasone and bortezomib demonstrated synergistic cytotoxic effects in multiple myeloma *in vitro* and increased antitumour activity in murine xenograft multiple myeloma models *in vivo*, including those resistant to proteasome inhibitors.[3]
Marketing authorisation/CE mark status	Selinexor was first licensed for use by the MHRA in May 2021, in combination with dexamethasone (Sd) in penta-refractory disease. In February 2023, the MHRA approved selinexor in combination with bortezomib and dexamethasone (SVd) after 1 prior line of therapy.[3]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	SVd is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. This is the indication addressed by this company submission but with focus on a specific positioning of after one prior therapy (second-line) or after two prior therapies (third-line) only. Sd is indicated for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, (penta-refractory) and who have demonstrated disease progression on the last therapy. This indication is addressed in a separate company submission, submitted to NICE simultaneously (GID-TA11223).[3]
Method of administration and dosage	Selinexor is for oral use. The recommended selinexor, bortezomib and dexamethasone doses based on a 35-day cycle are as follows: ● Selinexor 100mg taken orally once weekly on Day 1 of each week. The dose of selinexor should not exceed 70 mg/m^2 per dose. ● Bortezomib 1.3mg/m^2 administered subcutaneously once weekly on Day 1 of each week for 4 weeks followed by 1 week off. ● Dexamethasone 20mg taken orally twice weekly on Days 1 and 2 of each week. Treatment with selinexor combined with bortezomib and dexamethasone should be continued until disease progression or unacceptable toxicity. The tablet should be swallowed whole with water. It should not be crushed, chewed, broken, or divided in order to prevent risk of skin irritation from the active substance. It can be taken with or without food. Patients should be advised to maintain adequate fluid and caloric intake throughout treatment. Intravenous hydration should be considered for patients at risk of

	dehydration. Prophylactic concomitant treatment with a 5-HT3 antagonist and /or other anti-nausea agents should be provided prior to and during treatment with selinexor. If a selinexor dose is missed or delayed or a patient vomits after a dose of selinexor, the patient should not repeat the dose. Patients should take the next dose on the next regularly scheduled day. Dose modifications for selinexor (from 100mg once weekly) in response to adverse events should be made as follows, when in combination with bortezomib and dexamethasone: ● First reduction 80mg once weekly ● Second reduction 60mg once weekly ● Third reduction 40mg once weekly If symptoms do not resolve, treatment should be discontinued. Required action regarding selinexor dose modifications in response to certain adverse events are detailed in the SmPC.[3] There is an AE risk mitigation educational programme underway to establish strategies for preventing, mitigating, and managing selinexor-associated toxicities and AEs including cytopenia, nausea, anorexia, GI toxicity, and fatigue.[3]
Additional tests or investigations	Patients should have their full blood counts assessed at baseline, during treatment, and as clinically indicated, and should be monitored more frequently during the first two months of treatment. Patients at a high risk for tumour lysis syndrome should be monitored closely.[3]
List price and average cost of a course of treatment	Proposed selinexor list price per pack: £14,720 per 32x20mg £9,200 per 20x20mg £7,360 per 16x20mg £5,520 per 12x20mg £3,680 per 8x20mg
Patient access scheme (if applicable)	A patient access scheme in the form of a simple discount of [redacted] is in the process of being submitted to NHS England.
Abbreviations: AE, adverse event; GI, gastrointestinal; MHRA, Medicines and Healthcare products Regulatory Agency; NHSE, National health Service England; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; SINE, selective inhibitor of nuclear export; SmPC, summary of product characteristics; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone; XPO1, exportin 1.	

B1.3 Health condition and position of the technology in the treatment pathway

B1.3.1 Overview of the health condition

Multiple myeloma (MM) is a rare, clonal B-cell malignant neoplasm, characterised by accumulation of abnormal clonal plasma cells (myeloma cells) in the bone marrow microenvironment.[6] MM can be caused by several genetic plasma cell abnormalities which modify the expression of adhesion molecules on the cell surface, and the cellular response to growth stimuli within the bone marrow, promoting cell growth, survival, and migration.[7] Malignant plasma cell clones make an excess of a specific immunoglobulin

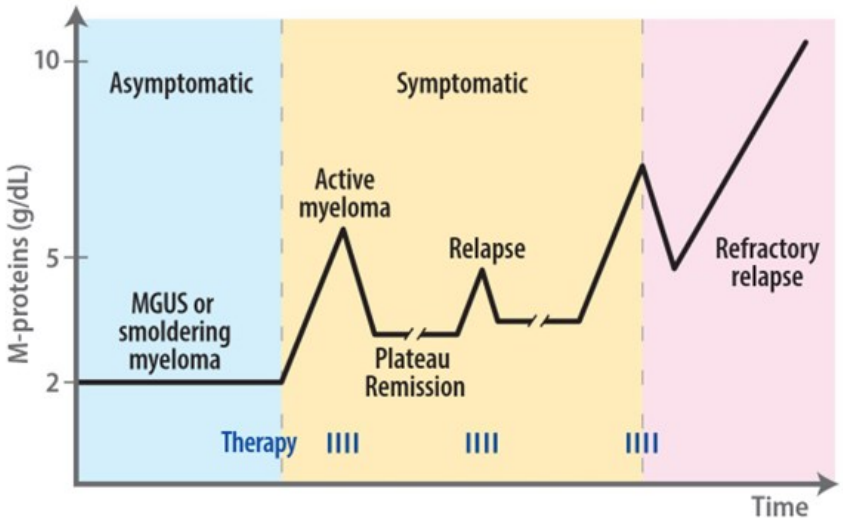
(which comprises two heavy chains and two light chains), and also an excess of additional light chains, paraproteins which are detectable in the blood and useful in both the diagnosis and monitoring of MM.

Symptomatic or active myeloma typically presents with symptoms referred to as CRAB, and differentiates itself from monoclonal gammopathy of unknown significance (MGUS) and smouldering myeloma.[8,9] The acronym CRAB summarises the most typical clinical manifestations of multiple myeloma, these being hypercalcaemia, renal failure, anaemia, and bone disease. As the bone marrow becomes filled with malignant plasma cells, the ability of haematopoietic stem cells to produce new blood cells is diminished, which can lead to anaemia, neutropenia, thrombocytopenia and immune paresis with resulting infection. Cytokines released by tumour cells stimulate osteoclast mediated bone resorption causing hypercalcaemia, bone pain and increased risk of fracture. Renal failure can result from the toxic effects of the paraproteins mentioned above on the renal glomeruli and tubules, as well as direct toxicity from hypercalcaemia. Hypercalcaemia can also lead to gastrointestinal (GI) symptoms such as thirst, nausea and constipation, as well as neurological effects including confusion, drowsiness, and neuropathy.[8-13]

In the plasma cells of MM patients, levels of XPO1, a key nuclear export receptor, are higher than in healthy people.[6,14] When XPO1 is overexpressed, tumour suppressor proteins are exported and lose their anti-neoplasm functionality. This leads to erroneous growth signalling and oncogenic cell expansion. High XPO1 levels are associated with poor disease prognosis and resistance to chemotherapies.[6,14]

Despite advances in treatment, MM remains incurable in the majority of patients; most patients relapse on treatment and require multiple lines of treatment. The typical pattern of disease progression for MM patients is presented in Figure 1.[15] As patients pass through each line of treatment, their fitness and general health decline, and their symptom burden increases. Chance of survival worsens with each progressive line of treatment leading to attrition, with the time to relapse with triplet regimens being longer than doublet regimens.[16-20] Early treatment with a range of combination treatments with different mechanisms of action (MoA) is therefore valuable in prolonging survival.

Figure 1 Graphical representation of MM disease progression phases



Abbreviations: MGUS, monoclonal gammopathy of undetermined significance

Source: Durie et al. 2018 (International Myeloma Foundation)[15]

B1.3.2 Epidemiology

MM accounts for approximately 1% of all cancers and 10% of haematological cancers.[16,21,22] MM is more prevalent in the elderly, with a median age at initial diagnosis of approximately 70 years, as well as in males and people of African descent.[7,18,22-26] Median survival is five to seven years, with a five-year survival prognosis ranging between 40% and 72% in Europe.[22,24] A global ageing population has caused a 136% increase in the global incidence of MM between 1990 and 2019.[22] In 2020 the global incidence of MM was 176,404, of which 28.9% occurred in Europe, and the global mortality was 117,077.[22]

In the UK, approximately 5,800 people are diagnosed with MM every year.[27] In Europe around 95% of those diagnosed with MM receive 1L treatment, of which 61% receive 2L treatment, and around 38% receive 3L.[17] This results in around 3,360 patients in the UK who are eligible for 2L treatment, and 2,090 eligible for 3L treatment.[28,29]

B1.3.3 Clinical pathway of care

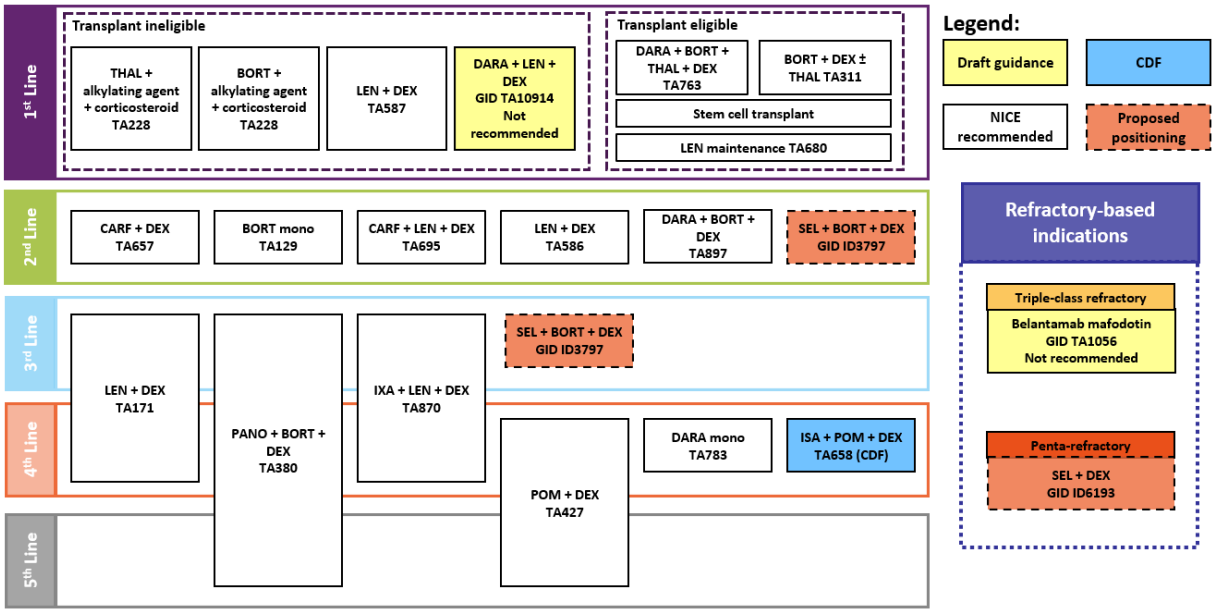
MM treatment aims to prolong time to progression, and to increase depth of response and the duration of survival, while maintaining or improving HRQoL. The treatment landscape for MM is complex, with various interventions and combination regimens recommended across treatment lines. Treatment strategy is personalised to patients,

where possible, considering age, frailty, cytogenetics, and comorbidities, whilst managing the side effects of treatments.[30,31] As patients pass through lines of treatment, previous class/ drug exposure and refractoriness also play a key part in decision-making.

Several UK and European organisations have published guidelines for the management of MM.[9,32-35] The NICE guidelines for myeloma (NG35), published in February 2016 and updated in 2018, cover MM diagnosis and management.[33] However, the MM treatment landscape has evolved dramatically within the last five years, with multiple NICE recommendations from technology appraisals of new treatments being published that are not reflected in the NG35 guidance.

An overview of the current pathway for the treatment of relapsed and/ or refractory MM (RRMM), based on published NICE guidance, is presented in Figure 2, including the proposed positioning of selinexor in combination with bortezomib and dexamethasone (SVd), and the proposed positioning of selinexor in combination with dexamethasone, subject to a separate appraisal (GID-TA11223).

Figure 2 Devised treatment pathway including proposed SVd positioning based on current NICE guidance



Source: based on published NICE guidance
Correct to the 22nd of June 2023

The company conducted two UK Advisory Boards across both selinexor indications.[36,37] In surveys distributed to attendees ahead of the Advisory Boards,

clinical experts were asked to comment on the regimens most commonly used in their clinical practice at 2L and 3L treatment of RRMM. Overall, expert opinion was largely consistent with the pathway laid out in Figure 2, based on NICE guidance.

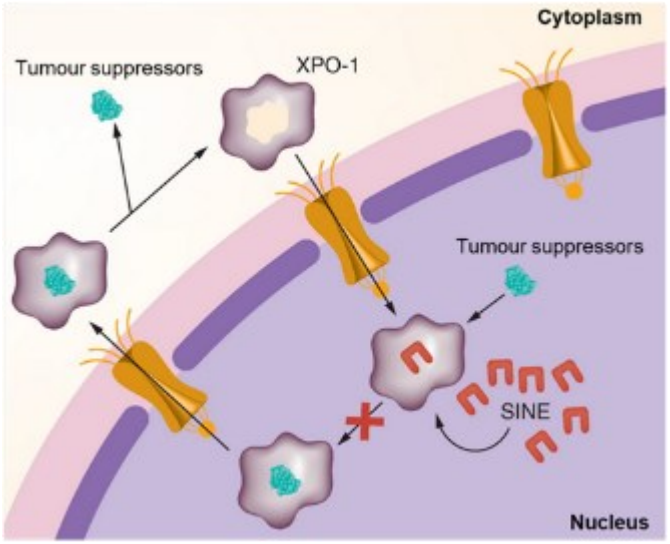
At 2L, in the absence of daratumumab in combination with lenalidomide and dexamethasone (DRd) at 1L, experts reported that the carfilzomib-lenalidomide-dexamethasone (KRd) and daratumumab-bortezomib-dexamethasone (DVd) triplets are currently received most often. However, if DRd is recommended in 1L, practice will evolve over time as patients will enter 2L refractory to daratumumab and lenalidomide, making both of these triplet combinations, (KRd and DVd), unsuitable. This will lead to a future unmet need in the 2L. At 3L, experts agreed that ixazomib in combination with lenalidomide and dexamethasone (IxaRd) is used most frequently.[36]

Based on UK myeloma expert feedback, it is anticipated that SVd will be used following a daratumumab-containing regimen; currently, this would place SVd at 3L following receipt of DVd at 2L. However, 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.

B1.3.4 The introduction of selinexor

Selinexor is an oral, bioavailable, first-in class, selective inhibitor of nuclear export (SINE) compound that specifically blocks activity of exportin 1 (XPO-1) which is involved in cytoplasmic translocation of some tumour suppressor proteins (TSPs) (Figure 3).[1,38] Nuclear export of these TSPs leads to their inactivation which allows malignant cells to evade apoptosis and to proliferate. XPO-1 is often overexpressed in MM cells; binding of selinexor to XPO-1 results in nuclear localisation of TSPs maintaining their proapoptotic function, resulting in apoptosis of myeloma cells.[39,40]

Figure 3 Mechanism of action of selinexor



Abbreviations: SINE, selective inhibitor of nuclear export (selinexor); XPO-1, exportin-1.
Source: Adapted from Talati (2018).[38]

Selinexor has EMA and MHRA marketing authorisation in combination with bortezomib and dexamethasone for adult MM patients who have received at least one prior line of treatment, and in combination with dexamethasone for adult MM patients who have received at least four prior lines of treatment, are refractory to at least two immunomodulatory imide drugs (IMiDs), two proteosome inhibitors (PIs), and one anti-CD38 therapy (penta-refractory), and who experienced disease progression on their last line of treatment.[3,41] The former positioning is addressed in this submission, and the latter in a separate technology appraisal (GID-TA11223).

B1.3.5 Unmet need

Clinicians and patients place high value on having access to a range of safe and effective treatment combinations with different MoAs, because as patients pass through lines of treatment they experience increasing refractoriness to different classes of treatments, depending on what they received in prior lines. The choice of treatment becomes highly personalised, with previous class/ drug exposure and refractoriness playing a key part in decision-making, and therefore access to a range of treatment options is required.[30,31] Furthermore, the burden of intravenous infusion administration can impact on quality of life and therefore there is demand for more orally delivered treatment options.

The use of combination treatment (doublet or triplets) provides deeper responses which correlate with longer overall survival for patients.[25] However since multi-drug resistance is common in MM, class-switching between combinations is preferable.[42] At the UK Market Access Advisory Board, clinicians expressed the need for additional choice of triplet combinations, particularly those offering a new MoA to the treatments currently offered in early-line triplet combinations.[37] The positioning of selinexor at 2L and 3L would address this need by introducing a drug class with a new MoA into the treatment pathway.

Clinicians present at the Advisory Board highlighted a particular current unmet need at 3L, stating that there is a gap in the current MM treatment pathway for a new class of treatment. The myeloma experts affirmed that patients reaching 3L will already be lenalidomide-exposed and/ or refractory and are also likely to have already been exposed, and/ or refractory to the anti-CD38 monoclonal antibody (mAb), daratumumab.[37] Thereby, there is an urgent need for a new combination treatment with a novel mechanism of action to increase treatment options at 3L. This would permit class-switching and limit re-treatment with the same class of drug to overcome early resistance and prolong survival.

The treatment paradigm for MM is complex and rapidly evolving as new treatment regimens become available across the lines of therapy. Importantly, the technology appraisal of DRd is ongoing and although it is currently not recommended by NICE, it may become available in the near future. If this were to happen, the uptake in transplant-ineligible patients would likely be high, resulting in further need for a triplet combination at 2L with a new mechanism of action for a population of patients who would be daratumumab and lenalidomide exposed/ refractory a proteasome inhibitor [PI]-naïve. SVd would permit a double drug class change between 1L and 2L in these patients.

B1.3.6 Impact of the condition on the quality of life of patients, their families, and carers

MM patients are often exposed to various interventions with a range of adverse event (AE) profiles resulting in a high burden for patients, carers, and society. The humanistic burden of RRMM is considerable and stems from multiple causes: MM symptoms, AEs of treatment, family and caregiver stress, fear of recurrence and the time and travel

burden of accessing treatment. The financial burden on the patient and their family can also be substantial and negatively impact health-related quality of life (HRQoL). The humanistic and financial burden of RRMM increases with each subsequent line of therapy; relapse has a devastating impact on the emotional and physical quality of patients' lives, with multiple relapses leading to loss of hope and increased distress about the exhaustion of effective treatment options.[23,43-45]

A multi-centre cross-sectional study into the impact of disease-related symptoms on HRQoL sampled two cohorts of patients with MM across 18 UK centres.[46] Data collection for HRQoL included the EORTC QLQ-C30, EORTC-QLQ-MY20, EQ-5D-3L, as well as the MyPOS for symptom status and palliative care concerns. Overall, the survey reported that patients with MM (N=557, of which n=30 (5.4%) were previously untreated and n=404 (n=72.5%) had received 1 or 2 prior lines of treatment)) experienced the following HRQoL events based on EORTC QLQ-C30 criteria: decreased physical functioning (98.9% of patients), decreased cognitive functioning (80.2%), financial difficulties (78.4%), severely decreased role functioning (46.7%), severe financial difficulties (43.3%). Fatigue (88%), pain (72%), and breathlessness (61%) were reported as the most common symptoms.[46] Furthermore, an SLR and meta-analysis of symptoms in MM found that decreased physical functioning (based on EORTC criteria) occurred in 98.9% of patients, decreased cognitive functioning occurred in 80.2%, and financial difficulties occurred in 78.4%.[11]

Despite the negative impact of adverse events on the humanistic burden, it has been shown that patient HRQoL is generally better when receiving active treatment compared to those receiving palliative care.[43] In the second- and third-line setting, a European (UK, Belgium, France, Germany, Ireland, and Italy) prospective, multicentre, observational, longitudinal study investigated the HRQoL of RRMM patients requiring 2L or 3L treatment with bortezomib (n=96) or lenalidomide (n=162).[47] Three questionnaires were used to measure HRQoL: EORTC QLQ-C30, QLQ-MY20, and the QLQ-CIPN20. For both treatments, a minor decline was observed in the majority of HRQoL domains, but slight improvements were observed for future perspectives, pain, financial difficulties, and disease symptoms. Overall, patients' HRQoL remained stable despite AEs and challenges from treatment. This demonstrates the importance

of the availability of effective treatment options at each line of therapy for maintaining patient outlook and, thereby, their quality of life.[47]

Multiple myeloma often results in the families/ caregivers of patients also committing a large amount of time on managing their condition and accessing treatment.[48] MM impairs caregivers' ability to work and increases caregiver absenteeism,[49] as well as causing caregivers to report difficulties with coping, uncertainty about the future, and feelings of isolation.[50] Some studies have demonstrated greater impacts on the HRQoL and psychological wellbeing of the carers than the patients.[48,50,51] One cross-sectional, multi-site study assessed the impact of MM on caregivers across lines of treatment (n=43 newly diagnosed, n=40 with 2-3 lines of treatment, and n=44 with ≥4 lines of therapy). The CareGiver Oncology QOL questionnaire was used to measure HRQoL, and the Hospital Anxiety and Depression Scale and the Posttraumatic Stress Disorder (PTSD) Checklist were used to measure symptoms of anxiety and depression and PTSD, respectively. Caregiver QoL and psychological distress did not differ between line of treatment, and a high proportion of caregivers experienced clinically significant anxiety (44%), depression (16%), and PTSD symptoms (24%).[48]

B1.4 Equality considerations

There are several risk factors associated with MM, including age, gender, family history, and ethnicity.[7,18,23-26] Stakeholders have raised no potential equality issues. 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 study, the source of efficacy evidence in the model presented in this submission, included adult (≥18) years), male and female patients of different ethnic backgrounds and included UK centres.[4]

B2 Clinical effectiveness

B2.1 Identification and selection of relevant studies

To identify evidence of the clinical efficacy and safety of selinexor and relevant comparator treatments for the treatment of patients with RRMM, a systematic literature review (SLR) was conducted to support this company submission for SVd, but also the simultaneous company submission of Sd in the penta-refractory setting (GID-TA11223).[52] The SLR has two research questions. The one that relates to the scope of this company submission was:

1. What is the relative clinical efficacy and safety of selinexor in combination with bortezomib and dexamethasone versus comparators, for the treatment of adult patients with RRMM who have received one or two prior lines of therapy?

The SLR was undertaken according to the principles of systematic reviewing published in the Cochrane Handbook, and the NICE Methodology Process and Methods guide.[53,54] The SLR search strategy and study selection methods are described in Appendix D.[52]

B2.2 List of relevant clinical effectiveness evidence

Based on SLR output, one randomised clinical trial (RCT) will inform the model presented in this submission, the pivotal phase 3 BOSTON trial of SVd *versus* Vd (Table 4; described in Section B2.3 to B2.6).[4]

One additional trial was identified as providing data relevant to the decision problem. STOMP is a phase 1/2 open-label, parallel assignment study of selinexor in combination with backbone treatments for RRMM and newly diagnosed MM, inclusive of an experimental arm treated with selinexor plus bortezomib and low-dose dexamethasone (experimental arm 2, n=42 participants, of which n=24 had the recommended phase 2 dose).[55] The STOMP trial data are not included in the model due to the low number of eligible patients.

Table 4 Clinical effectiveness evidence

Study	Bortezomib, Selinexor, and Dexamethasone in Patients with Multiple Myeloma (BOSTON)[4,56]
Study design	Phase 3, randomised, controlled, open-label, multicentre study
Population	Adult patients with RRMM who had received 1 to 3 previous lines of therapy
Intervention(s)	Selinexor plus bortezomib and dexamethasone (SVd)
Comparator(s)	Bortezomib plus dexamethasone (Vd)
Indicate if trial supports application for marketing authorisation	Yes
Indicate if trial used in the economic model	Yes
Rationale for use/non-use in the model	BOSTON is the pivotal trial of SVd in the 2L/ 3L/ 4L [a] setting, providing key efficacy and safety outcome data utilised in the economic model.
Reported outcomes specified in the decision problem	• **PFS** • ORR • DOR • **OS** • TTNT • PFS2 [b] • TTR • **Safety and tolerability (including TTD)** • **HRQoL** (EORTC QLQ-CIPN20, EORTC QLQ-C30; EQ-5D-5L)
All other reported outcomes	Incidence of ≥Grade 2 neuropathy events; ORR1[c]; PFS1[d] (all secondary endpoints)

Abbreviations: DOR, duration of response; EQ-5D-5L, EuroQoL 5-dimension 5-level; HRQoL; health-related quality of life; ORR; overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed and/ or refractory multiple myeloma;Sd, selinexor + dexamethasone; SVd, selinexor + bortezomib + dexamethasone; SVdX, selinexor + bortezomib + dexamethasone crossover population (crossed over from Vd to SVd); TTD, time to discontinuation; TTNT, time to next treatment; TTR, time to response; Vd, bortezomib with dexamethasone; 2L, second-line; 3L, third-line; 4L, fourth-line.

[a] Only 2L and 3L patients are relevant to the decision problem in this submission

[b] PFS on first post-SVd/ Vd/ SVdX treatment)

[c] ORR in participants who crossed over from Vd to SVd treatment (SVdX)

[d] PFS in participants who crossed over from Vd to SVd treatment (SVdX)

Source: Clinical study report[56]

B2.3 Summary of methodology of the relevant clinical effectiveness evidence

Section summary

- The phase 3, open label, randomised, controlled BOSTON trial of SVd *versus* Vd provides the only evidence for SVd, relevant to this decision problem.
- Participants in BOSTON had received 1-3 prior lines of therapy (randomised n=402).
- Pre-specified subpopulation analyses of participants who had received one prior line of therapy (2L, n=198) and two prior lines of therapy (3L, n=129) provide the clinical effectiveness data applicable to the decision problem addressed in this submission.

B2.3.1 Trial methodology of relevant trials

The pivotal phase 3 BOSTON trial was a global, open-label, controlled RCT comparing the efficacy, HRQoL, and safety of SVd *versus* Vd in adult patients with RRMM who had received one to three prior lines of therapy (Table 5; Figure 4).[4] Participants were randomly allocated (1:1) to receive SVd or Vd with randomisation stratified based on prior PI therapies (yes *versus* no), number of prior lines of treatment (one *versus* two or more), and Revised International Staging System (R-ISS) stage (III *versus* I-II) at study entry. SVd dosing regimen was selinexor 100mg once per week, plus bortezomib 1.3mg/m^2 once weekly, and dexamethasone 20mg twice per week. Vd dosing regimen was bortezomib 1.3mg/m^2 twice weekly for the first 24 weeks and once per week thereafter, and dexamethasone 20mg four times per week for the first 24 weeks and twice per week thereafter. Prespecified dose modifications for AEs related to selinexor was to reduce to 80mg per week in the first instance, followed by 60mg, then 40mg. Patients received their study regimen until progressive disease was confirmed by the independent review committee (IRC), discontinuation, pregnancy, unacceptable toxicity, withdrawal of consent, death, or study termination.[4,56,57]

Patients in the Vd arm were permitted to cross over to a treatment that included selinexor plus dexamethasone with or without bortezomib (SVdX or SdX, respectively). Crossover was permitted at the point of IRC-confirmed objective progressive disease per the International Myeloma Working Group (IMWG) criteria, for patients in the Vd arm. Patients in the Vd arm who were able to tolerate continued bortezomib treatment

crossed over to SVdX treatment whereas patients in the Vd arm who had significant tolerability issues with bortezomib (patients who were unable to tolerate continue bortezomib treatments due to Grade >2 peripheral neuropathy or Grade ≥2 peripheral neuropathy with pain) crossed over to SdX treatment.[56,57] A summary of the BOSTON trial design is described in Table 5, and depicted in Figure 4.

Table 5 Summary of trial design of the BOSTON RCT

Trial name	BOSTON (NCT03110562)
Location	Global, multicentre study, including the UK
Trial design	Phase 3, randomised, controlled, open-label, multicentre study
Key dates	First patient dosed: 7th June 2017 Data cut-off dates: 18th February 2020 (primary analysis); 15th February 2021 (updated analysis)
Patient disposition & follow-up	Of 457 patients screened for eligibility, 402 were randomly allocated to receive SVd (n=195, 49.0%) or Vd (n=207, 51.0%). 195 (100.0%) patients in the SVd arm received treatment and 204 (98.6%) patients in the Vd arm received treatment. As of 15th February 2021, the median follow-up was 28.71 months in the SVd arm and 28.65 months in the Vd arm. Of the 399 patients who were dosed in the study, 362 (90.7%) patients had discontinued study treatment (174 [89.2%] in the SVd arm and 188 [92.2%] in the Vd arm) with progressive disease (48.6% across both arms), AEs (14.8% across both arms), and withdrawal by patient (14.5% across both arms) being the most common reasons for overall discontinuation. More patients discontinued due to PD in the Vd arm compared to the SVd arm (57.8% *versus* 39.0%). Discontinuations due to deaths on or within 30 days of last dose of treatment were similar in the two arms. 37 (9.3%) patients continued to receive the study treatment (21 [10.8% in the SVd arm and 16 [7.8%] in the Vd arm).
Eligibility criteria and participants	***Disease criteria:*** Histologically confirmed MM with measurable disease per IMWG guidelines as defined by at least one of the following: • Serum M-protein ≥0.5 g/dL (>5 g/L) by serum protein electrophoresis or for Ig A myeloma, by quantitative serum IgA levels; or • Urinary -protein excretion at least 200 mg/24 hours; or • Serum FLC ≥100 mg/L, provided that the serum FLC ratio is abnormal (normal FLC ratio: 0.26 to 1.65). Eastern Cooperative Oncology Group (ECOG) score of ≤2 and adequate hepatic, renal and hematopoietic function. Documented evidence of progressive MM (based on Investigator's determination according to the IMWG response criteria) on or after their most recent regimen. ***Prior anti-MM therapies:*** Have at least 1 prior, and no more than 3 prior lines of therapy. Induction therapy followed by stem cell transplant and consolidation/ maintenance therapy were considered as 1 line of therapy. Prior treatment with bortezomib or other PI was allowed provided the following criteria were met: • Best response achieved with prior bort at any time was ≥PR and with last PI therapy (alone or in combination) was ≥PR and; • Participant did not discontinue bortezomib due to Grade ≥3 related toxicity and; • Must have had at least 6-month PI-treatment free interval prior to Cycle 1 Day 1 of study treatment
Settings and location where data were collected	123 study sites across 21 countries including: Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Greece, Hungary, India, Israel, Italy, Poland, Romania, Russian Federation, Serbia, Spain, Ukraine, United Kingdom, and United States.

Trial drugs **Interventions (n=1)** **Comparators (n=1)**	**Intervention:** Selinexor plus bortezomib plus dexamethasone (35-day cycles): • Selinexor 100mg orally (5 tables of 20mg each) on Days 1, 8, 15, 22 and 29 of each 35-day cycle • Bortezomib 1.3mg/m^2 subcutaneously on Days 1, 8, 15, and 22 of each 35-day cycle • Dexamethasone 20mg orally on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle Prespecified dose modifications for AEs related to selinexor: • Dose level -1: 80mg per week • Dose level -2: 60mg per week • Dose level -3: 40mg per week **Comparator:** Bortezomib plus dexamethasone (Cycles 1 through 8; 21-day cycles): • Bortezomib will be given at a dose of 1.3 mg/m2 SC on Days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles. • Dexamethasone will be given as an oral 20-mg dose on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles. Bortezomib plus dexamethasone (Cycles ≥9; 35-day cycles) • Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35-day cycle. • Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.
Permitted and disallowed concomitant medication	To minimise nausea associated with selinexor treatment, 5-hydroxytryptamine (5-HT3) antagonists (ondansetron 8mg or equivalent) starting on C1D1 before the first dose of selinexor was recommended. Alternative treatment could be provided if the patient did not tolerate 5-HT3 antagonists. Supportive measures for optimal medical care were provided to all patients in both arms during participation in this study. In addition to the required prophylactic therapy with 5-HT3 antagonists, supportive care per NCCN and/ or institutional guidelines was used as clinically indicated at the discretion of the Investigator. Concomitant medications included any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study. Patients received concomitant medications to treat symptoms, AEs, and intercurrent illnesses that were medically necessary as part of standard care. If clinically indicated, palliative radiation therapy to nontarget lesions was permitted but study treatment was held for ≥1 day before the start of palliative radiation therapy and ≥1 day following each dose of palliative radiation therapy. Study treatment was not discontinued solely due to palliative radiation.
Primary outcomes (including scoring methos and timings of assessments)	Progression free survival defined as the time from the date of randomisation until the first date of IRC-confirmed PD, per IMWG response criteria, or death due to any cause, whichever occurred first.
Other outcomes used in the economic model/ specified in the scope	Key secondary: ORR (IRC); ≥VGPR, ≥CR; ≥sCR or MRD-negative (for patients who achieved a CR or sCR); incidence of Grade 2 or higher PN events Non-key secondary: OS; DOR; ORR1;[a] PFS1;[b] TTNT; TTR; PFS2;[c] PN (EORTC QLQ-CIPN20); safety and tolerability Exploratory: PFS and ORR in R-ISS and ISS subgroups; discontinuation rate; HRQoL (EORTC QLQ-C30 AND EQ-5D-5L); correlation of incidence and severity of PN by AE reports and QLQ-CIPN20; response to SdX treatment
Disease response assessment	Patient response was assessed by the procedures described in the following subsections and graded according to the IMWG response criteria (Kumar 2016).[25] Per the IMWG, quantitative Ig levels by nephelometry could be used in place of SPEP for routine M-protein measurement for patients with IgA or IgD myeloma. Also, per the IMWG, response

	could be confirmed if the patient failed to provide a 24-hour urine sample after screening activities occurred. Two consecutive assessments were needed to confirm response. For patients who achieved CR or sCR, confirmatory samples for SPEP with serum protein immunofixation, quantitative Ig, and serum FLC were collected in duplicate at the time of the response and the duplicate samples were provided to the central laboratory. A confirmatory 24-hour urine sample was also collected, and an aliquot was provided to the central laboratory for UPEP with urine protein immunofixation.
Assessment schedule	Patients randomised to the SVd and Vd arms underwent MM evaluations every 3 weeks from baseline MM evaluations on C1D1 (regardless of drug holidays or interruptions) through the first day of Week 37 (i.e., 12 MM evaluations after C1D1) to identify patients who progressed quickly, then every 5 weeks for the remainder of the study regardless of the cycle length. SVdX patients and SdX patients underwent MM evaluations every 5 weeks. If additional MM disease assessments were performed at unscheduled times, those results were documented on the eCRF as unscheduled visits.
Pre-planned subgroups	Age group; sex; race; ethnicity; region; prior PI therapies; patients with one prior *versus* more than one prior anti-MM regimen; baseline R-ISS stage; baseline ISS stage; baseline cytogenetic abnormalities; last PI received

Abbreviations: AE, adverse event; CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC QLQ-CIPN20; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy Module; EORTC QLQ-C30; European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FLC, free light chains; HRQoL, health-related quality of life; Ig, immunoglobulin; IgA, immunoglobulin A; IgD, immunoglobulin D; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; MM, multiple myeloma; MRD, minimal residual disease; MM, multiple myeloma; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PI, proteosome inhibitor; PN, peripheral neuropathy; R-ISS, Revised International Staging System; sCR, stringent complete response; SVd, selinexor + bortezomib + dexamethasone; SVdX, selinexor + bortezomib + dexamethasone crossover population (crossed over from Vd to SVd); TTNT, time to next treatment; TTR, time to response; UPEP, urine protein electrophoresis; Vd, bortezomib and dexamethasone; VGPR, very good partial response;5-HT3, 5-hydroxytryptamine

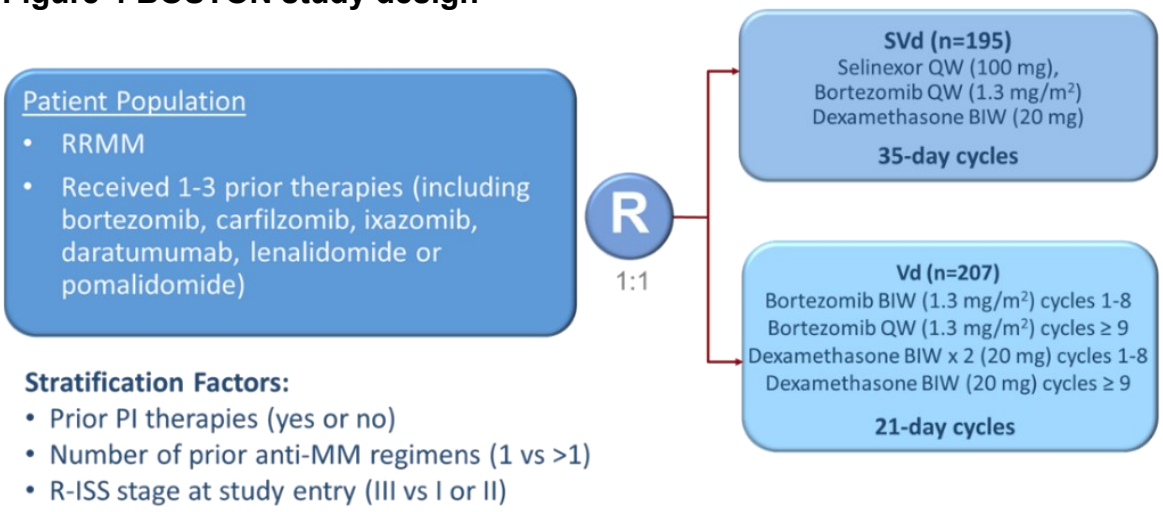
[a] ORR for SVdX patients only

[b] PFS for SVdX patients only

[c] PFS for patients who received treatment after SVd/ Vd/ SVdX

Source: Study protocol, statistical analysis plan, and clinical study report[56-58]

Figure 4 BOSTON study design



Abbreviations: IA, interim analysis; ORR, overall response rate; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; SVdX, selinexor + bortezomib + dexamethasone crossover population (crossed over from Vd to SVd); Vd, bortezomib and dexamethasone.
Source: Data on file.[59]

B2.3.2 Demographics and baseline characteristics of participants of relevant trials

The flow of participants through the BOSTON trial is summarised in a CONSORT diagram in Appendix D. The baseline demographics and characteristics of participants in the BOSTON trial are summarised in Table 6. A summary of prior anti-MM therapies of patients within the BOSTON trial is provided in Table 7.

B2.3.2.1 Baseline demographics

Overall, 402 patients were randomly allocated to receive SVd (n=195) or Vd (n=207). Of these patients, 36 (9%) were from the UK, 19 (9.7) in the SVd arm and 17 (8.2) in the Vd arm.[56,59]

Baseline demographics and treatment history were both well balanced across the two treatment groups. Median age of trial participants was 67.0 years (range: 38-90) overall; 66.0 (40-87) in the SVd arm and 67.0 (38-90) in the Vd arm. More males were enrolled in the study than females (SVd: 59.0%; Vd: 55.6%) and race was predominantly White (SVd: 82.6%; Vd: 79.7%). Most participants had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (SVd: 89.7%, Vd: 92.3%), and a R-ISS score of I or II (87.1% overall; SVd: 88.7%, Vd: 85.5%). Almost half of participants had high-risk chromosomal abnormalities (i.e., del17p/p53, t(14;16), t(4;14) or 1q21; 47.8% overall; SVd: 49.7%, Vd: 45.9%). Of note, 56 (28.7%) patients in the SVd arm and 70 (33.8%) in the Vd arm had moderate to severe renal dysfunction with a creatinine clearance of <60 mL/min at baseline, which is common in myeloma.[56,59]

All 402 randomised participants had received prior anti-MM treatments, as per the trial inclusion criteria. The median number of prior lines of therapy was 1 (range: 1-3) in the SVd arm, and 2 (range: 1-3) in the Vd arm. A total of 148 (75.9%) patients in the SVd arm and 159 (76.8%) in the Vd arm had prior PI therapies. A majority of patients in both arms were previously treated with bortezomib (68.7% in the SVd arm, 70.0% in the Vd arm). Seventy-seven (39.5%) patients in the SVd arm and 77 (37.2%) in the Vd arm had received prior treatment with lenalidomide. Of note, more patients on the SVd arm had received prior pomalidomide and daratumumab (each 5.6%) than on the Vd arm (3.4%, 2.9%). 34.6% of participants had received a prior SCT, 39.0% in the SVd arm and 30.4% in the Vd arm.[56,59]

Baseline characteristics were generally well-balanced between, and within, the 2L and 3L subpopulations, however participants in the 2L population, had lower rates of prior treatment with IMiDs, than those at 3L (54.6% *versus* 83.7%), which is to be expected since they have received an additional line of therapy. Accordingly, the rates of prior treatment with the IMiDs lenalidomide and pomalidomide were also lower in the 2L population compared to the 3L population (lenalidomide: 21.7% *versus* 48.8%; pomalidomide: 0% *versus* 3.1%).[56,59]

Compared to UK clinical practice, the BOSTON patient population had a lower median age (67 years compared to 72 years at initial diagnosis). In the BOSTON population, 17.4% were over 75 years of age, where in the UK this figure is almost double (44% at initial presentation), and over 90% of patients had a good performance status while living with multiple co-morbidities and concomitant non-oncologic medications. These differences between the trial and UK population are often a consequence of the strict inclusion requirements for patients' eligibility to be entered into clinical trials in general. Furthermore, white patients made up 82.6% of the demographic confirming that ethnic minorities were underrepresented in BOSTON. Ethnic minorities are often mis-presented in trials due to socio economic factors that limit their participation.[60]

Table 6 Baseline characteristics of participants in BOSTON trial

		All randomised			2L randomised			3L randomised		
		SVd arm	Vd arm	Total	SVd arm	Vd arm	Total	SVd arm	Vd arm	Total
n		195	207	402	99	99	198	65	64	129
Baseline demographics										
Age, years	Median (range)	66 (40-87)	67 (38-90)	67 (38-90)	67 (45-87)	69 (44-90)	68 (44-90)	66 (40-80)	67 (38-84)	66 (38-84)
Gender, n (%)	Male	115 (59.0)	115 (55.6)	230 (57.2)	55 (55.6)	53 (53.5)	108 (54.6)	46 (70.8)	41 (64.1)	87 (67.4)
Race, n (%)	White	161 (82.6)	165 (79.7)	326 (81.1)	83 (83.8)	81 (81.8)	164 (82.8)	55 (84.6)	50 (78.1)	105 (81.4)
	Black or Af/Am	4 (2.1)	7 (3.4)	11 (2.7)	2 (2.0)	2 (2.0)	4 (2.0)	1 (1.5)	3 (4.7)	4 (3.1)
	Asian	25 (12.8)	25 (12.1)	50 (12.4)	10 (10.1)	10 (10.1)	20 (10.1)	8 (12.3)	8 (12.5)	16 (12.4)
	Other	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	5 (2.6)	9 (4.4)	14 (3.5)	4 (4.0)	6 (6.1)	10 (5.1)	1 (1.5)	3 (4.7)	4 (3.1)
Baseline ECOG performance	0	69 (35.4)	77 (37.2)	146 (36.3)	39 (39.4)	38 (38.4)	77 (38.9)	21 (32.3)	22 (34.4)	43 (33.3)
	1	106 (54.4)	114 (55.1)	220 (54.7)	52 (52.5)	55 (55.6)	107 (54.0)	35 (53.9)	38 (59.4)	73 (56.6)
	2	20 (10.3)	16 (7.7)	36 (9.0)	8 (8.1)	6 (6.1)	14 (7.1)	9 (13.9)	4 (6.3)	13 (10.1)
Time since initial diagnosis (years)	Median (range)	3.81 (0.4-23.0)	3.59 (0.4-22.0)	3.70 (0.4-23.0)	2.9 (0.4-23.0)	2.8 (0.4-18.4)	2.8 (0.4-23.0)	4.3 (1.5-16.6)	3.7 (0.8-22.0)	4.2 (0.8-22.0)
R-ISS stage at study entry	R-I	56 (28.7)	52 (25.1)	108 (26.9)	33 (33.3)	23 (23.2)	56 (28.3)	18 (27.7)	22 (34.4)	40 (31.0)
	R-II	117 (60.0)	125 (60.4)	242 (60.2)	52 (52.5)	62 (62.6)	114 (57.6)	44 (67.7)	37 (57.8)	81 (62.8)
	R-III	12 (6.2)	16 (7.7)	28 (7.0)	9 (9.1)	6 (6.1)	15 (7.6)	1 (1.5)	5 (7.8)	6 (4.7)
	Missing	10 (5.1)	14 (6.8)	24 (6.0)	5 (5.1)	8 (8.1)	13 (6.6)	2 (3.1)	0 (0.0)	2 (1.6)
Baseline creatinine clearance (mL/ min)	<30	3 (1.5)	10 (4.8)	13 (3.2)	2 (2.0)	4 (4.0)	6 (3.0)	0 (0.0)	6 (9.4)	6 (4.7)
	30-60	53 (27.2)	60 (29.0)	113 (28.1)	27 (27.3)	31 (31.3)	58 (29.3)	18 (27.7)	16 (25.0)	34 (26.4)
	>60	139 (71.3)	137 (66.2)	276 (68.7)	70 (70.7)	64 (64.7)	134 (67.7)	47 (72.3)	42 (65.6)	89 (69.0)

		All randomised			2L randomised			3L randomised		
		SVd arm	Vd arm	Total	SVd arm	Vd arm	Total	SVd arm	Vd arm	Total
n		195	207	402	**99**	**99**	**198**	**65**	**64**	**129**
Cytogenetic abnormalities, n (%)	del(17p)/p53	21 (10.8)	16 (7.7)	37 (9.2)	12 (12.1)	8 (8.1)	20 (10.1)	4 (6.2)	5 (7.8)	9 (7.0)
	t(14;16)	7 (3.6)	11 (5.3)	18 (4.5)	4 (4.0)	3 (3.0)	7 (3.5)	1 (1.5)	4 (6.3)	5 (3.9)
	t(4;14)	22 (11.3)	28 (13.5)	50 (12.4)	10 (10.1)	15 (15.2)	25 (12.6)	7 (10.8)	6 (9.4)	13 (10.1)
	1q21	80 (41.0)	71 (34.3)	151 (37.6)	41 (41.4)	36 (36.4)	77 (38.9)	29 (44.6)	19 (29.7)	48 (37.2)
	All high-risk cytogenetic abnormalities[c]	97 (49.7)	95 (45.9)	192 (47.8)	50 (50.5)	48 (48.5)	98 (49.5)	33 (50.8)	26 (40.6)	59 (45.7)

Abbreviations: Af/Am, African American; ECOG, Eastern Cooperative Oncology Group; R-ISS, revised international staging system; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone

[a] Patients in the safety population who crossed over from the Vd arm to the SVdX treatment arm and have received at least one dose of selinexor

[b] Patients in the safety population who crossed over from the Vd arm to the SdX treatment arm and have received at least one dose of selinexor

[c] High-risk cytogenetic abnormalities include: del(17p)/p53, t(14;16), t(4;14), and 1q21

Source: Data on file[59]

Table 7 Anti-MM treatment history of patients within the BOSTON trial

		All randomised			2L randomised			3L randomised		
		SVd arm	Vd arm	Total	SVd arm	Vd arm	Total	SVd arm	Vd arm	Total
n		195	207	402	**99**	**99**	**198**	**65**	**64**	**129**
Prior anti-MM therapies										
Number of prior LOT	Median (range)	1 (1-3)	2 (1-3)	2 (1-3)	1	1	1	2	2	2
	1 prior, n (%)	99 (50.8)	99 (47.8)	198 (49.3)	99 (100)	99 (100)	198 (100)	0 (0.0)	0 (0.0)	0 (0.0)
	2 priors, n (%)	65 (33.3)	64 (30.9)	129 (32.1)	0 (0.0)	0 (0.0)	0 (0.0)	65 (100)	64 (100)	129 (100)
	3 priors, n (%)	31 (15.9)	44 (21.3)	75 (18.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

		All randomised			2L randomised			3L randomised		
		SVd arm	Vd arm	Total	SVd arm	Vd arm	Total	SVd arm	Vd arm	Total
n		**195**	**207**	**402**	**99**	**99**	**198**	**65**	**64**	**129**
Prior SCT, n (%)		76 (39.0)	63 (30.4)	139 (34.6)	39 (39.4)	23 (23.2)	62 (31.3)	29 (44.6)	27 (42.2)	56 (43.4)
Exposure to prior anti-MM drug classes, n (%)	PIs	148 (75.9)	159 (76.8)	307 (76.4)	70 (70.7)	74 (74.8)	144 (72.7)	50 (76.9)	50 (78.1)	100 (77.5)
	IMiDs	138 (70.8)	147 (71.0)	285 (70.9)	51 (51.5)	57 (57.6)	108 (54.6)	58 (89.2)	50 (78.1)	108 (83.7)
Exposure to prior anti-MM drugs, n (%)	Bortezomib	134 (68.7)	145 (70.1)	279 (69.4)	64 (64.7)	65 (65.7)	129 (65.2)	45 (69.2)	46 (71.9)	91 (70.5)
	Carfilzomib	20 (10.3)	21 (10.1)	41 (10.2)	7 (7.1)	8 (8.1)	15 (7.6)	4 (6.2)	6 (9.4)	10 (7.8)
	Ixazomib	6 (3.1)	3 (1.5)	9 (2.2)	1 (1.0)	1 (1.0)	2 (1.0)	1 (1.5)	2 (3.1)	3 (2.3)
	Daratumumab	11 (5.6)	6 (2.9)	17 (4.2)	3 (3.0)	3 (3.0)	6 (3.0)	3 (4.6)	0 (0.0)	3 (2.3)
	Lenalidomide	77 (39.5)	77 (37.2)	154 (38.3)	23 (23.2)	20 (20.2)	43 (21.7)	33 (50.8)	30 (46.9)	63 (48.8)
	Pomalidomide	11 (5.6)	7 (3.4)	18 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.1)	2 (3.1)	4 (3.1)

Abbreviations: IMiD, immunomodulatory imide drug; LOT, line of therapy; mAbs, monoclonal antibodies; MM, multiple myeloma n, number of patients; NR, not reported; PIs, proteasome inhibitors; SCT, stem cell transplant; SdX, selinexor + low-dose dexamethasone (crossover); STD, standard deviation; SVd, selinexor + bortezomib + dexamethasone; SVdX, selinexor + bortezomib + dexamethasone (crossover); Vd, bortezomib plus dexamethasone

[a] Patients in the safety population who crossed over from the Vd arm to the SVdX treatment arm and have received at least one dose of selinexor

[b] Patients in the safety population who crossed over from the Vd arm to the SdX treatment arm and have received at least one dose of selinexor

Source: Data on file[59]

B2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Study populations of BOSTON

The analysis populations in the BOSTON trial are summarised in Table 8. Six patients were excluded from the per-protocol population: three patients (all from the Vd arm) did not receive the study drug, and a further three patients (two from the Vd arm, and one patient from the SVd arm) were excluded from the per-protocol population due to <70% compliance of study drug (two patients) and protocol deviation (one patient).[56]

All efficacy analyses were conducted using the intent-to-treat (ITT) population, unless otherwise specified and all tests (log-rank tests, Cochran-Mantel-Haenszel tests) were one-sided, unless otherwise stated.[56] Patient response was assessed centrally by an IRC according to the IMWG response criteria for MM.[25,56] The response data refer to these assessments by the IRC, unless otherwise specified.[56]

Table 8 Populations for analysis in the BOSTON trial

Analysis set	Population	n (%)
Total randomised patients	402	
Efficacy populations		
Intent-to-treat population: The ITT population consisted of all patients who were randomised to the study treatment, regardless of whether or not they received the study treatment. This population was used for the primary analyses of efficacy. Patients were analysed in the treatment arm to which they were randomised and strata assignment at the time of randomisation.	Total	402 (100.0)
	SVd arm	195 (48.5)
	Vd arm	207 (51.5)
Per-protocol population: The per-protocol population consisted of all ITT patients who had study treatment compliance ≥70% and who had no major protocol violations that affect assessment of efficacy. Patients who progressed or died were included regardless of the duration of time on the study treatment. This population was used for the supportive analyses of efficacy. Patients were analysed in the treatment arm to which they were randomised.	Total	396 (98.5)
	SVd arm	194 (48.3)
	Vd arm	202 (50.2)
Safety populations		
Total safety population:	Total	399 (99.3)
	SVd arm	195 (48.5)

Analysis set	Population	n (%)
Total randomised patients	402	
The safety population consisted of all patients who had received at least one dose of the study treatment. Patients were analysed according to the treatment they received.	Vd arm	204 (50.7)
Additional analysis population		
The SVdX population consisted of a subset of patients in the Vd arm of the safety population who crossed over from the Vd arm to SVdX treatment after IRC confirmation of PD on Vd and had received at least one dose of selinexor.	SVdX arm	64 (15.9)
The SdX population consisted of a subset of patients in the Vd arm of the safety population who crossed over from the Vd arm to SdX treatment after IRC confirmation of PD on Vd and had received at least one dose of selinexor.	SdX arm	13 (3.2)

Abbreviations: IRC, independent review committee; ITT, intent-to-treat; n, number of patients; PD, progressive disease; SdX, selinexor + dexamethasone (crossover); SVd, selinexor + bortezomib + dexamethasone; SVdX, selinexor + bortezomib + dexamethasone crossover population (crossed over from Vd to SVd); Vd, bortezomib + dexamethasone.

Source: clinical study report[56]

Statistical analyses

A summary of the statistical analyses in the BOSTON trial is provided in Table 9.

All summary statistics were reported among the corresponding analysis population and by each scheduled assessment time point whenever applicable. Summary statistics for continuous variables included the n, median, mean, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages were presented with the denominators for the percentages determined based on the analysis population used, unless otherwise specified. For time-to-event variables, the Kaplan-Meier (KM) method was used for descriptive summaries.[56]

In general, missing baselines were not imputed. The following approaches were default methods for missing data handling in summary tables:

- Categorical data at baseline are summarised using counts (n) and percentages (%). The denominator was the total number of patients in a corresponding treatment arm, based on the population specified for the summary, unless otherwise specified. Missing data are presented as a separate category.
- Continuous data are summarised based on observed data only.

The updated analysis based on the data cut-off date of 15th of February 2021 was conducted per The Committee for Medicinal Products for Human Use (CHMP) request. The updated analysis is non-inferential, and the *P*-values were therefore nominal.[56]

Table 9 Summary of statistics analyses in the BOSTON trial

Hypothesis objective	The primary objective of the BOSTON trial was to compare PFS based on the IRC's disease outcome assessments in patients randomised to the SVd arm *versus* the Vd arm.
Statistical analysis	*Primary endpoint:* The number and percentage of patients who had a PFS event will be reported. Median PFS with 95% confidence interval (CI) will be summarised using the Kaplan-Meier (KM) method for each treatment arm. The KM curve for PFS will be provided by treatment arm. A stratified log-rank test will be used to compare the PFS between treatment arms (SVd *versus* Vd) for the primary efficacy assessment. The strata will include prior PI therapies, number of prior lines of therapy, and R-ISS stage at study entry. Hazard ratios and its 95% CI will be estimated by a stratified Cox proportional hazards model, with Efron's method of tie handling, with treatment as the factor. A non-stratified log-rank test and a Cox proportional hazards model will be used as sensitivity analyses. *Secondary endpoints:* The key secondary endpoints will be tested using the hierarchical testing procedure to maintain the overall type I error at a 1-sided 0.025 level of significance. Comparison of the ORR between the 2 treatment arms (SVd arm *versus* Vd arm) was performed using the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors including prior PI therapies, the number of prior anti-MM regimens, and the R-ISS stage at study entry. The CMH estimate of odds ratio and its 95% CI and *P*-value for testing the treatment difference is reported. The Breslow-Day test was used to evaluate the homogeneity of the odds ratios across the strata associated with this endpoint. Patients missing MM disease assessments after C1D1 were treated as non-responders. The forest plot of estimated odds ratio is provided for each stratification factor. The analysis of the response rate for responses ≥VGPR based on the IRC's assessment was performed in a similar manner to the primary efficacy endpoint of ORR using the CMH test. For OS, DOR, TTNT, TTR, analyses were performed by treatment arm (SVd arm *versus* Vd arm) based on the stratified log-rank test. The strata included prior PI therapies, the number of prior lines of therapy, and the R-ISS stage at study entry. A switch-adjusted HR was calculated for OS to account for crossover, using a two-stage estimation method.[61,62] For ORR1, the percentage of patients achieving a confirmed PR or better (i.e., PR, VGPR, CR, or sCR) was tested assuming a null hypothesis fixed threshold value of 10% against a 1-sided alternative hypothesis of >10% using exact methods for a 1-sample binomial without stratification. For all the non-key secondary survival endpoints, the median with 95% CI values were estimated based on the KM method for each treatment arm and the KM curves are provided.

Sample size, power calculation	The sample size was designed to have 80% power to detect a median time to PFS for patients treated with SVd of 13.5 months *versus* patients treated with Vd of 9.4 months, using a 1-sided alpha of 0.025, 15 months accrual, 18 months follow-up, 1:1 allocation of treatment to SVd:Vd, and allowing for an IA of PFS (second IA) for futility or superiority, with the treatment difference assessed by a log-rank test. Based on these statistical assumptions, a total of 267 PFS events were required for the final analysis. To achieve these events, a total of approximately 364 patients (~182 patients per arm) were required for enrolment. The justification of a median time to PFS of 9.4 months in the Vd arm was based on recent clinical studies (ENDEAVOR and CASTOR), both of which had similar eligibility criteria to this BOSTON study where PFS was 9.4 months (Dimopoulos *et al.* 2016)[63] and 7.2 months, respectively (Palumbo *et al.* 2016)[64]. Median time to PFS in the SVd arm was based on preliminary results from Karyopharm's ongoing STOMP study (Study KCP-330-017). An exponential dropout rate of 0.65% per month (equivalently approximately 10% dropout after 18 months) was assumed.
Data management, patients withdrawals	The ITT population was used for all primary analyses of efficacy, defined as all patients who were randomised to each intervention. Patients who crossed over from the Vd arm to receive selinexor (SVdX or SdX) did so following confirmed IRC progressive disease and were therefore included in primary efficacy ITT analyses.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; DOR, duration of response; IA, interim analysis; IRC, independent review committee; ITT, intention-to-treat; KM, Kaplan-Meier; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R-ISS, revised – international staging system; sCR, stringent complete response; Sd, selinexor + dexamethasone; SdX, selinexor + dexamethasone (crossover); SVd, selinexor + bortezomib + dexamethasone; SVdX, selinexor + bortezomib + dexamethasone crossover population (crossed over from Vd to SVd); TTNT, time to next treatment; TTR, time to response; Vd, bortezomib plus dexamethasone; VGPR, very good partial response.
Source: Clinical study protocol, Statistical analysis plan, and Clinical study report[56-58]

B2.5 Critical appraisal of relevant clinical effectiveness evidence

Critical appraisal of the BOSTON trial was conducted using the NICE checklist for RCTs (adapted from The Centre for Reviews and Dissemination (CRD) guidance) and is summarised in Table 10.[54,65,66] The full assessment is included in Appendix D.

Since BOSTON was an RCT, the methods employed to reduce the risk of bias were largely effective. Randomisation was carried out appropriately, with the use of interactive response technology, and was stratified. The baseline characteristics of participants were well-balanced across the treatment groups and treatment discontinuation rates were similar between arms (primary analysis: SVd 81.0%, Vd 82.4%; updated analysis: SVd 89.2%, Vd 92.2%). Efficacy analyses were performed

in the ITT population which consisted of participants randomised to each arm, regardless of whether they received treatment and all pre-defined outcomes were reported.[4,56,57]

As an open-label trial, there were some concerns surrounding the risk of bias arising from the lack of blinding of the patients, caregivers and outcome assessors to the allocated treatment.[57]

Table 10 Quality assessment of RCTs summary

	BOSTON[4,56] (yes/ no/ not clear/ N/A)
Was randomisation carried out appropriately?	**YES**
Was the concealment of treatment allocation adequate?	**YES**
Were the groups similar at the outset of the study in terms of prognostic factors?	**YES**
Were the care providers, participants and outcome assessors blind to treatment allocation?	**NO**
Were there any unexpected imbalances in drop-outs between groups?	**NO**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**NO**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**YES**
Did the authors of the study publication declare any conflicts of interest?	**YES**
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[65,66]	

B2.6 Clinical effectiveness results of the relevant trials

Section summary

- BOSTON provides pivotal evidence of clinical effectiveness for SVd.
- Clinical effectiveness data applicable to the decision problem is the BOSTON 2L and 3L data. The overall BOSTON ITT data are also reported for context.
- At the primary data cut, the primary endpoint of BOSTON, IRC-assessed PFS was improved in the SVd arm compared to the Vd arm in both the 2L and 3L subpopulations, representing a 34% and 28% reduction in the risk of PD or death at 2L and 3L, respectively, with the difference at 2L being statistically significant

(2L: HR=0.66, 95% CI: 0.43, 1.03; *P*=0.032; 3L: HR=0.72, 95% CI: 0.43, 1.19; *P*=0.101). This PFS benefit was maintained in the updated analysis (2L: 21.03 months *versus* 10.68 months; HR=0.62, 95% CI 0.41, 0.95; *P*=0.014; 3L: 12.91 months *versus* 9.43 months; HR=0.75, 95% CI 0.46, 1.22; *P*=0.121).

- ORR was also significantly improved in the SVd arm compared to the Vd arm in both the 2L (80.8% *versus* 65.7%; OR: 2.20; 95% CI: 1.15, 4.22; *P*=0.0082) and 3L participants (76.9% *versus* 60.9%; OR: 2.14; 95% CI: 0.99, 4.59; *P*=0.0253).
- Median OS was not reached for SVd at the time of primary analysis in either the 2L or 3L participants. At the updated analysis, 3L participants receiving SVd had an OS of 36.67 months, a gain of approximately 7 months compared to those receiving Vd. OS was not reached in 2L participants receiving SVd.
- SVd provides an efficacious, oral treatment option with a novel MoA for patients requiring triplet therapy with a class-switch at 2L and 3L.

The following sections describe the primary efficacy endpoint, key secondary endpoint, and other secondary endpoints from the BOSTON trial for the ITT population as well as the 2L and 3L subpopulations, the populations relevant to this decision problem.

B2.6.1 BOSTON primary efficacy endpoint – progression-free suvival

B2.6.1.1 Primary analysis (18th February 2020)

At the primary analysis, the primary efficacy endpoint of BOSTON, IRC-assessed progression-free survival (PFS), was met (HR=0.70, 95% CI:0.53, 0.93; *P*=0.007) (Table 11; Figure 5). Median PFS was significantly improved in the SVd arm compared to the Vd arm at 2L (16.62 months *versus* 10.68 months; HR=0.66, 95% CI: 0.43, 1.03; *P*=0.032) representing a 34% reduction in risk of progressive disease (PD) or death. At 3L, participants receiving SVd demonstrated a numerically longer PFS than those receiving Vd (12.91 months *versus* 9.43 months; HR=0.72, 95% CI: 0.43, 1.19; *P*=0.101) (Table 11; Figure 5).[59]

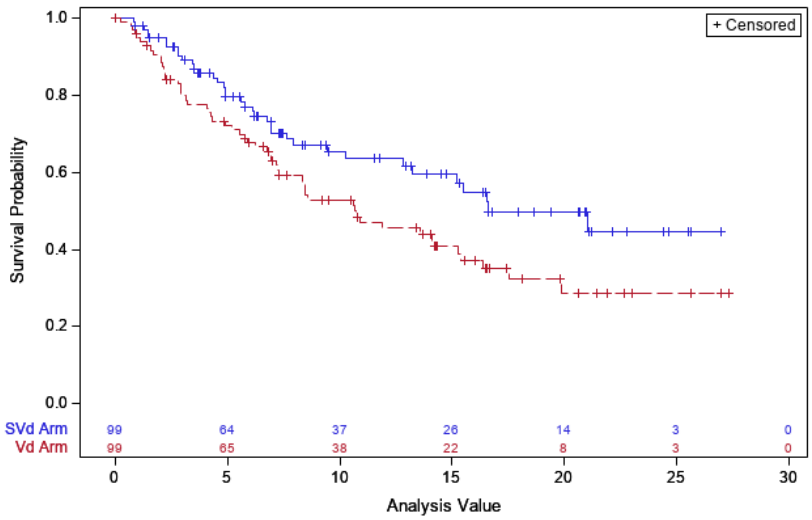
B2.6.1.2 Updated analysis (15th February 2021)

The updated analysis demonstrated that the SVd arm continued to show a statistically significant, and clinically meaningful, improvement for the primary efficacy endpoint of PFS, compared to the Vd arm. (HR=0.71; *P*=0.006). At 2L participants receiving SVd

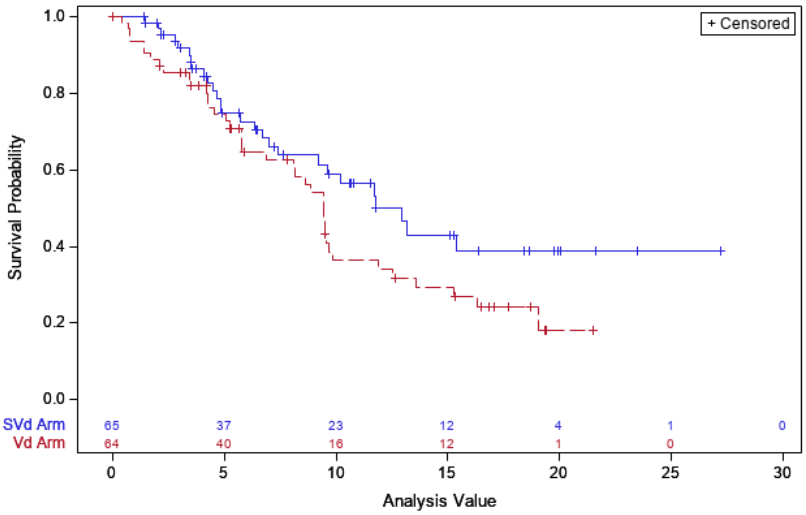
demonstrated a significantly longer PFS than those receiving Vd (21.03 months *versus* 10.68 months; HR=0.62, 95% CI: 0.41, 0.95; *P*=0.014), representing a 38% reduction in risk of PD or death. At 3L, participants receiving SVd had a numerically longer PFS than those receiving Vd (12.91 months *versus* 9.43 months; HR=0.75, 95% CI: 0.46, 1.22; *P*=0.121) (Table 11; Figure 6).[59]

Figure 5 Kaplain-Meier curve of IRC-assessed PFS in the ITT population of BOSTON from the primary analysis

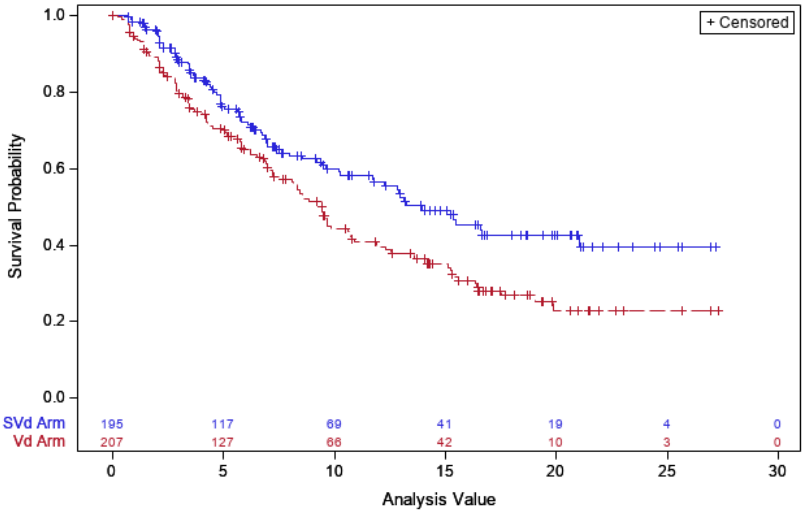
2L



3L



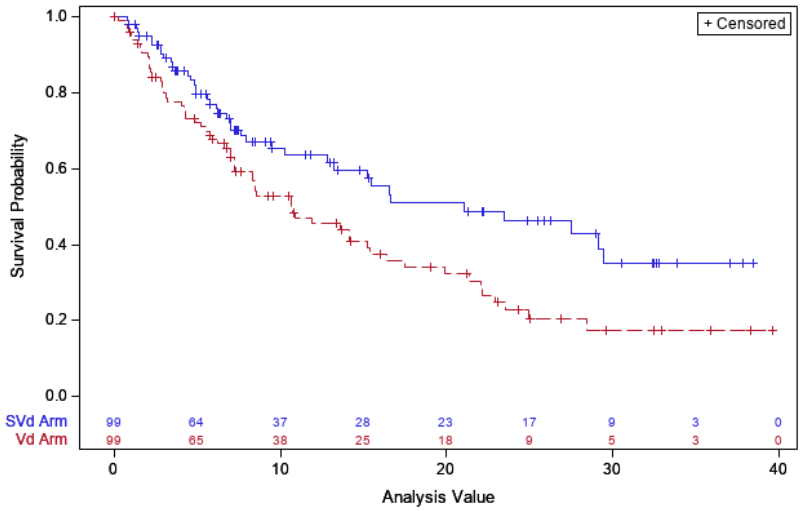
ITT



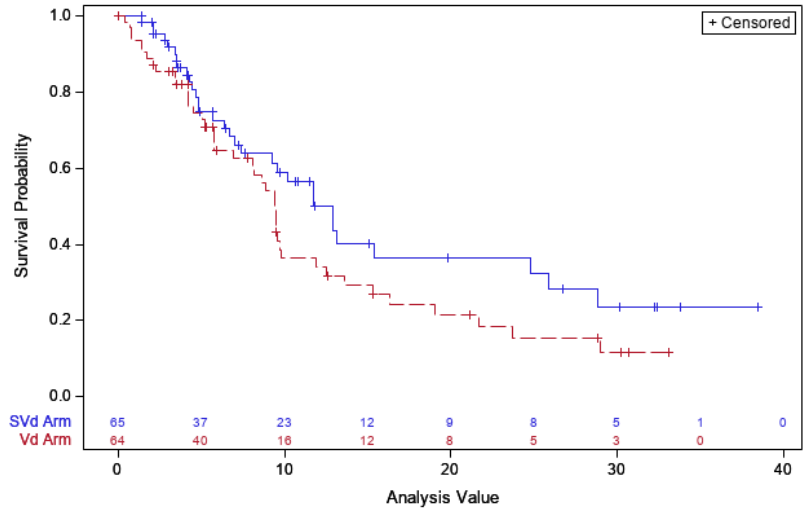
Abbreviations: HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.
Source: Data on file for February 2020 data cut.[59]

Figure 6 Kaplain-Meier curve of IRC-assessed PFS in the ITT population of BOSTON from the updated analysis

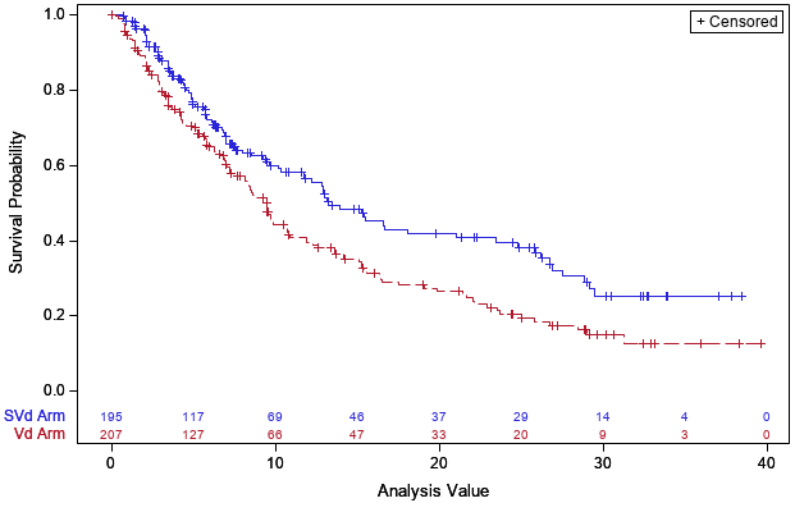
2L



3L



ITT



Abbreviations: HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; PFS, progression-free survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.
Source: Data on file for February 2021 data cut.[59]

Table 11 PFS based on IRC assessment by treatment arm (BOSTON ITT population)

	Primary analysis (18th February 2020)						Updated analysis (15th 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, 15.34)	16.53 (14.39, 17.71)	NR	NR	NR	NR	13.47 (10.64, 24.87)	24.48 (21.16, 29.17)	NR	NR	NR	NR
Median PFS, months (95% CI)	13.93 (11.73, NE)	9.46 (8.11, 10.78)	16.62 (13.24, NE)	10.68 (7.26, 16.39)	12.91 (9.23, NE)	9.43 (8.11, 12.55)	13.24 (11.73, 23.43)	9.46 (8.11, 10.78)	21.03 (13.24, NE)	10.68 (7.26, 16.39)	12.91 (9.23, 25.86)	9.43 (8.11, 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, 0.933)		0.661 (0.426, 1.025)		0.717 (0.432, 1.192)		0.710 (0.542, 0.930)		0.621 (0.407, 0.950)		0.750 (0.462, 1.217)	
Patients with events, n (%)	80 (41.0)	124 (59.9)	36 (36.4)	55 (55.6)	27 (41.5)	39 (60.9)	92 (47.2)	137 (66.2)	40 (40.4)	62 (62.6)	31 (47.7)	42 (65.6)
Patients censored, n (%)	115 (59.0)	83 (40.1)	63 (63.6)	44 (44.4)	38 (58.5)	25 (39.1)	103 (52.8)	70 (33.8)	59 (59.6)	37 (37.4)	34 (52.3)	22 (34.4)

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: data on file[59]

B2.6.2 BOSTON key secondary endpoint – response rate

Overall response rate data from the primary and updated analyses are summarised in Table 12.

In the primary analysis, the IRC-assessed overall response rate (ORR) (the proportion of patients who achieved a partial response or better before IRC confirmed PD or initiated a new MM treatment or crossover) was significantly higher in the SVd arm than in the Vd (76.4% *versus* 62.3%; odds ratio [OR]: 1.96; 95% CI; 1.26, 3.05; *P*=0.0012). ORR was significantly improved in the SVd arm compared to the Vd arm in both the 2L participants (80.8% *versus* 65.7%; OR: 2.20; 95% CI: 1.15, 4.22; *P*=0.008) and the 3L participants (76.9% *versus* 60.9%; OR: 2.14; 95% CI: 0.99, 4.59; *P*=0.025) (Table 12). Duration of response (DOR) was numerically longer in the SVd arm compared to the Vd arm in 2L (NE *versus* 14.72 months) and 3L participants (14.00 months *versus* 11.86 months).[59]

In the updated analysis (datacut: 15th of February 2021), the IRC-determined ORR remained significantly higher in the SVd arm than in the Vd arm 76.9% *versus* 63.3%; odds ratio: 1.9441; 95% CI=1.2468, 3.0314; *P*=0.002). ORR remained numerically higher in the SVd arm compared to the Vd arm in both the 2L participants (80.8% *versus* 66.7%) and 3L participants (76.9% *versus* 60.9%), as did DOR (2L: 26.25 *versus* 14.72 months; 3L: 12.22 months *versus* 11.86 months).[59]

Table 12 ORR based on IRC assessment by treatment arm (BOSTON ITT)

	Primary analysis (18th February 2020)						Updated analysis (15th 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**
Overall response rate[a], n (%)	149 (76.4)	129 (62.3)	80 (80.8)	65 (65.7)	50 (76.9)	39 (60.9)	150 (76.9)	131 (63.3)	80 (80.8)	66 (66.7)	50 (76.9)	39 (60.9)
Exact 95% CI	69.8, 82.2	55.3, 68.9	71.7, 88.0	55.4, 74.9	64.8, 86.5	47.9, 72.9	70.4, 82.6	56.3, 69.9	71.7, 88.0	56.5, 75.8	64.8, 86.5	47.9, 72.9
Odds ratio[b] (95% CI)	1.96 (1.26, 3.05)		2.2024 (1.1500, 4.2181)		2.1368 (0.9944, 4.5914)		1.9441 (1.2468, 3.0314)		NR		NR	
P-value[b]	0.0012		0.0082		0.0253		0.0016		NR		NR	
Duration of response												
Median duration of response, months (95% CI)[d]	20.27 (12.55, NE)	12.88 (9.26, 15.77)	NE (14.75, NE)	14.72 (11.07, NE)	14.0 (8.77, NE)	11.86 (7.39, NE)	17.28 (12.55, 26.25)	12.88 (9.26, 15.77)	26.25 (14.75, NE)	14.72 (11.07, 22.11)	12.22 (8.77, NE)	11.86 (7.39, 22.90)
One-sided P-value[e,f]	0.136		0.203		0.437		0.110		0.099		0.461	
Hazard ratio[e,f,g] (95% CI)	0.813 (0.562, 1.175)		0.791 (0.454, 1.378)		0.946 (0.496, 1.806)		0.810 (0.578, 1.134)		0.711 (0.421, 1.199)		0.972 (0.533, 1.771)	
Patients with events, n (% of responders)	53 (35.6)	66 (51.2)	25 (31.3)	30 (46.2)	19 (38.0)	21 (53.8)	65 (43.3)	79 (60.3)	29 (36.3)	37 (56.1)	23 (46.0)	24 (61.5)
Patients censored, n (% of responders)	96 (64.4)	63 (48.8)	55 (68.8)	35 (53.8)	31 (62.0)	18 (46.2)	85 (56.7)	52 (39.7)	51 (63.8)	29 (43.9)	27 (54.0)	15 (38.5)

	Primary analysis (18th February 2020)						Updated analysis (15th 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

Abbreviations: CI, confidence interval IRC, independent review committee; ITT, intent-to-treat population; n, number of patients; ORR, overall response rate; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone

[a] Overall response rate is the proportion of patients who achieve a partial response or better, before IRC-confirmed progressive disease or initiating a new anti-myeloma treatment

[b] Calculated by Cochran-Mantel-Haenszel Test which was stratified by prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at screening

[c] Includes very good partial response, complete response, and stringent complete response

[d] The number of participants analysed differed for this endpoint All: SVd n=149, Vd n=129; 2L: SVd n=80, Vd n=65; 3L: SVd n=50, Vd n=39

[e] Calculated by Stratified Log-rank test

[f] Stratified for prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at screening

[fg]Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties

Source: Clinical study report and data on file.[56,59]

B2.6.3 BOSTON other endpoints

Non-key secondary and exploratory endpoints in the BOSTON trial included; overall survival (OS), DOR (reported in Section B2.6.2), ORR and PFS for the crossover population, time to next treatment (TTNT), TTR, PFS2, time to discontinuation (TTD), and EORTC QLQ-CIPN20 assessment of peripheral neuropathy;[56] however, not all of these outcomes are directly relevant to the decision problem in this submission. DOR and TTR are reported in Section B2.6.2, and EORTC QLQ-CIPN20 in Section B2.6.3.2. Overall survival data and TTD are described in Sections B2.6.3.1 and B2.6.3.2, respectively.

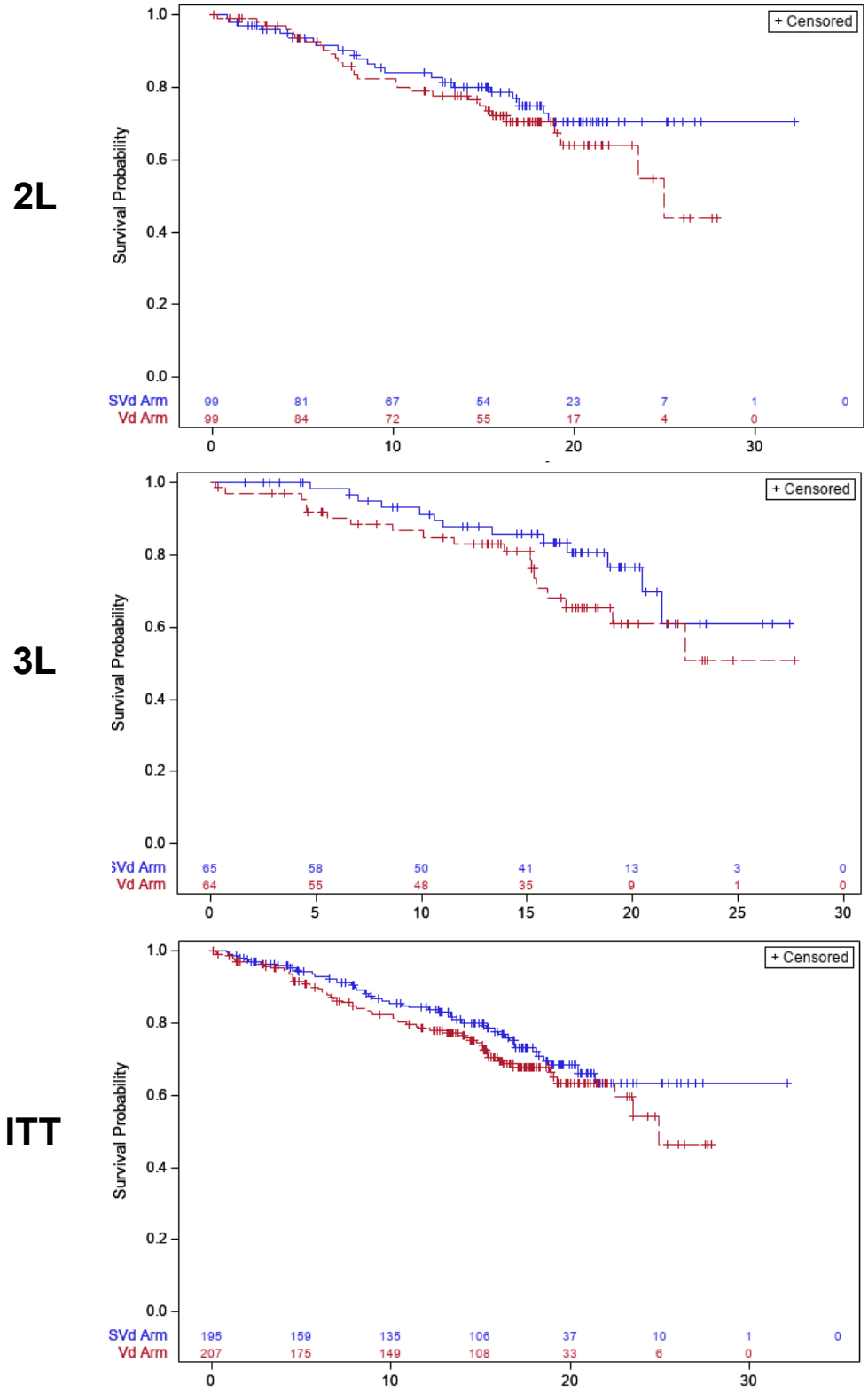
B2.6.3.1 Overall survival

In the ITT population, 77 (37%) patients from the Vd arm crossed over after confirmed PD to receive a regimen that included selinexor (SVdX or SdX), therefore OS data presented are adjusted for crossover (a switch-adjusted HR was calculated for OS to account for crossover, using a two-stage estimation method).[56]

Median OS was not reached for SVd at the time of the primary analysis (18th February 2020), with 24.1% to 30.0% of death events having occurred in the SVd and Vd arms, respectively. Median OS for patients in the Vd arm was 24.97 months (95% CI: 22.48, NE) (Table 13; Figure 7). Median OS was also not reached for SVd at the time of primary analysis in either the 2L or 3L participants. At 2L, 22.2% to 29.3% of death events had occurred in the SVd and Vd arms, respectively. At 3L 20.0% to 29.7% of death events had occurred in the SVd and Vd arms, respectively. The median OS for the Vd arm was 24.97 (95% CI: 23.49, NE) at 2L, and was not reached at 3L.[59]

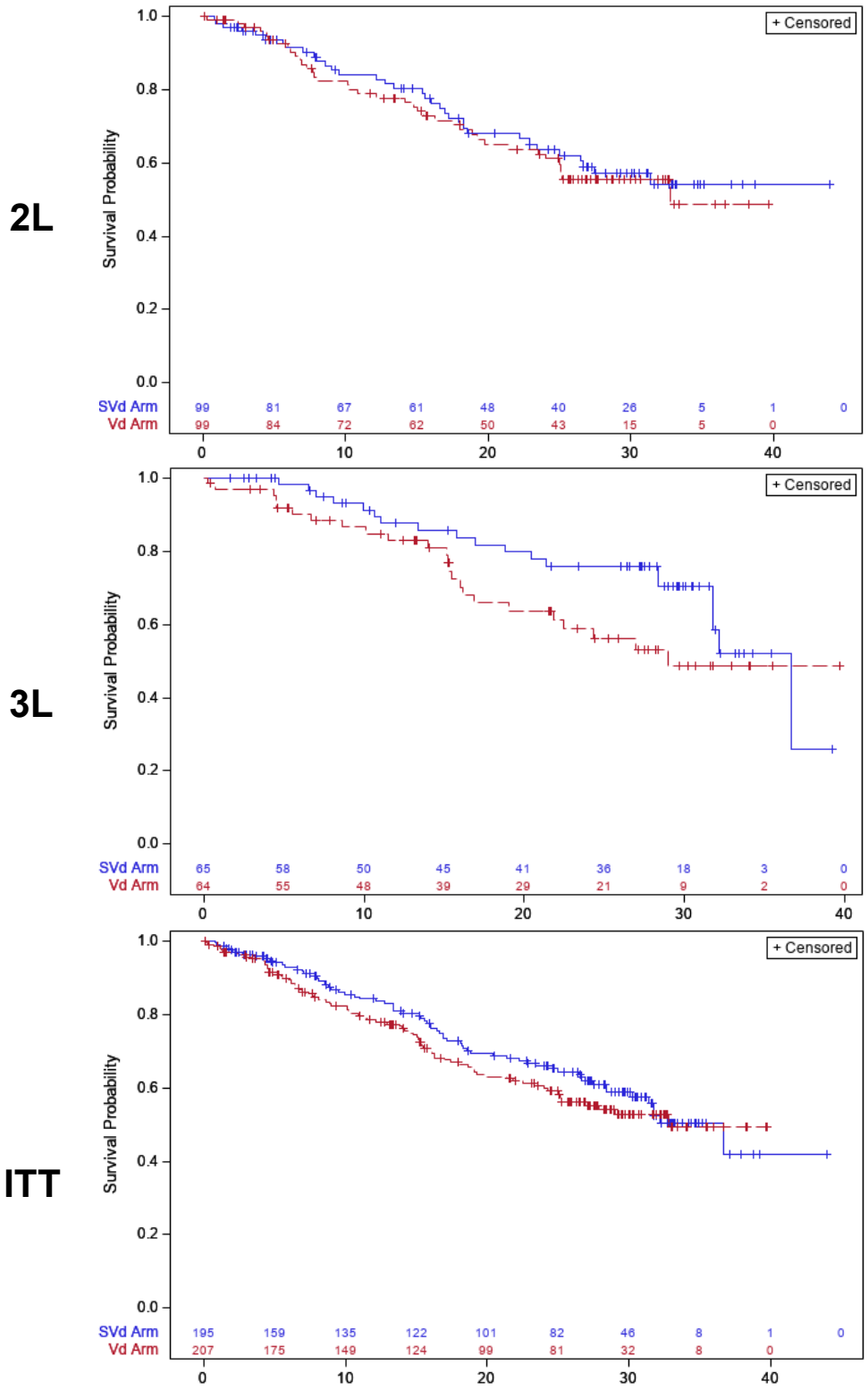
At the time of the updated analysis cut-off date (15th February 2021), the median OS was 36.67 (95% CI: 30.19, NE) months in the SVd arm and 32.76 (95 CI: 25.11, NE) months in the Vd arm, a median improvement of approximately 4 months in patients treated with selinexor (Table 13; Figure 8). At 3L there was a median improvement of approximately 7 months in the patients treated with SVd compared to those receiving Vd (36.67 months [95% CI: 31.74, NE] *versus* 29.01 months [95% CI: 21.8, NE]). Median OS in 2L patients receiving SVd had not been reached at the time of the updated analysis, and was 32.76 months (95% CI: 24.97, NE) in those receiving Vd. These data continue to support the therapeutic value of selinexor.[59]

Figure 7 Kaplain-Meier curve of OS in the ITT population of BOSTON from the primary analysis



Abbreviations: ITT, intention-to-treat; OS, overall survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.
OS adjusted for crossover.
Source: Data on file for 18th February 2020 data cut.[59]

Figure 8 Kaplain-Meier curve of OS in the ITT population of BOSTON from the updated analysis



Abbreviations: ITT, intention-to-treat; OS, overall survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.
OS adjusted for crossover
Source: Data on file for 15th February 2021 datacut.[59]

Table 13 OS by treatment arm (BOSTON ITT population)

	Primary analysis (18th February 2020)						Updated analysis (15th 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 OS[a], 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[b,c]	0.132		0.155		0.142		0.147		0.344		0.066	
Hazard ratio[b,c,d] (95% CI)	0.805 (0.549, 1.179)		0.749 (0.427, 1.311)		0.676 (0.329, 1.388)		0.838 (0.603, 1.166)		0.909 (0.570, 1.450)		0.612 (0.321, 1.166)	
Death, n (%)	47 (24.1)	62 (30.0)	22 (22.2)	29 (29.3)	13 (20.0)	19 (29.7)	68 (34.9)	80 (38.6)	34 (34.3)	38 (38.4)	19 (29.2)	24 (37.5)
Patients censored, n (%)	148 (75.9)	145 (70.0)	77 (77.8)	70 (70.7)	52 (80.0)	45 (70.3)	127 (65.1)	127 (61.4)	65 (65.7)	61 (61.6)	46 (70.8)	40 (62.5)

Abbreviations: CI, confidence interval; IRC, independent review committee; ITT, intent-to-treat population; n, number of patients; OS, overall 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: Data on file.[59]

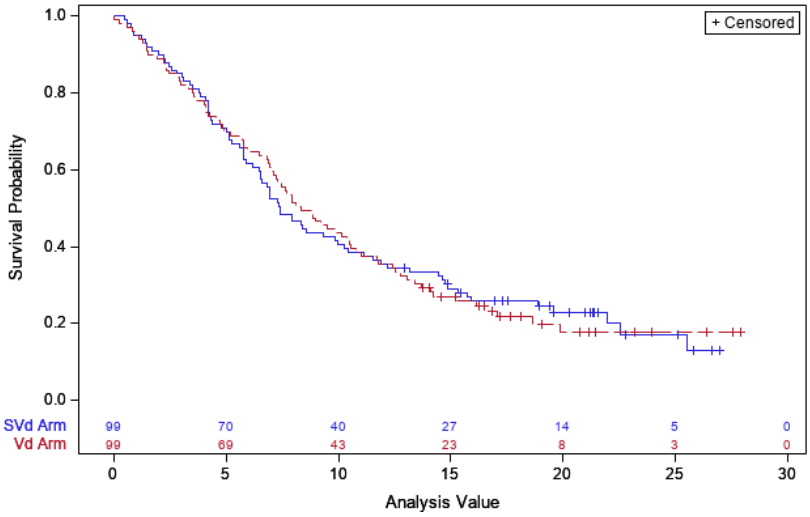
B2.6.3.2 Time to discontinuation

Median time to discontinuation (TTD) had been reached at the primary analysis (18th of February 2020) (Figure 9; Table 14). Median TTD was similar in patients receiving SVd compared to those receiving Vd in the ITT population (7.1 months *versus* 7.95 months; HR=0.99; 95% CI: 0.79, 1.23; *P*=0.460), 2L population (7.39 months *versus* 8.34 months; HR=1.01; 95% CI: 0.72, 1.40; *P*=0.489), and the 3L population (7.46 months *versus* 7.41 months; HR=0.96; 95% CI: 0.65, 1.41; *P*=0.412).[59]

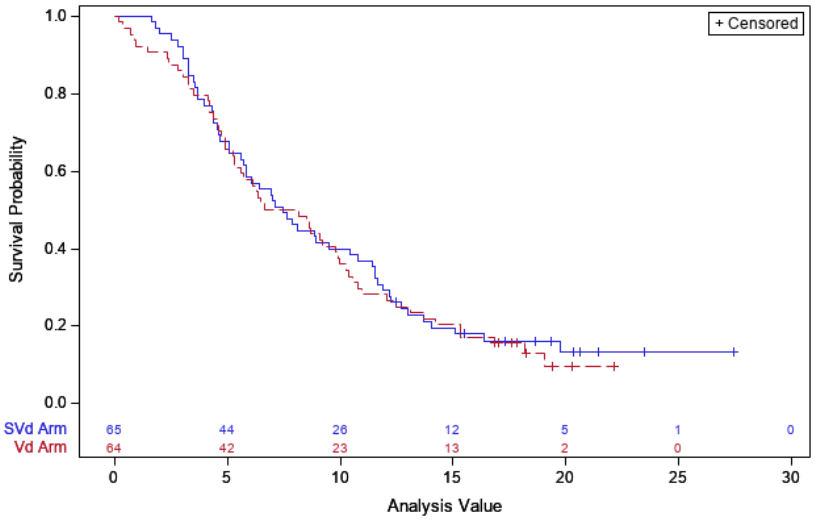
Updated analysis (15th of February 2021) TTD KM curves are included in Figure 10.

Figure 9 Kaplain-Meier curves of TTD in the ITT population of BOSTON from the primary analysis

2L



3L



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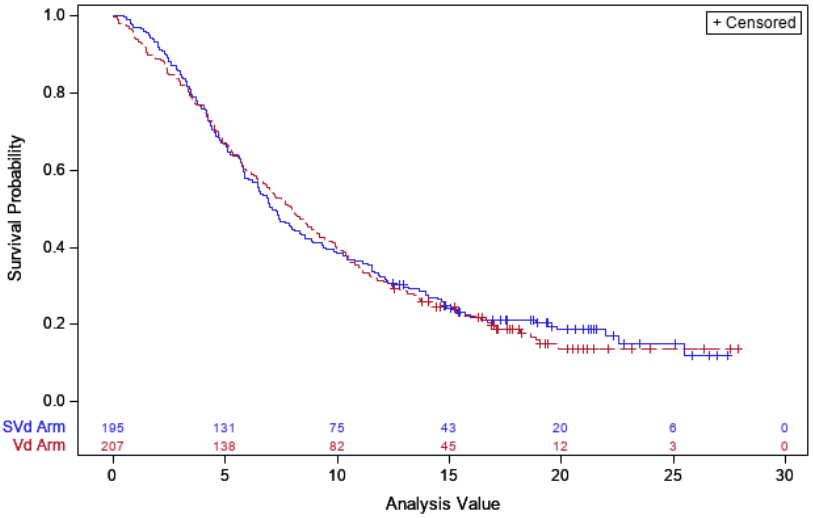
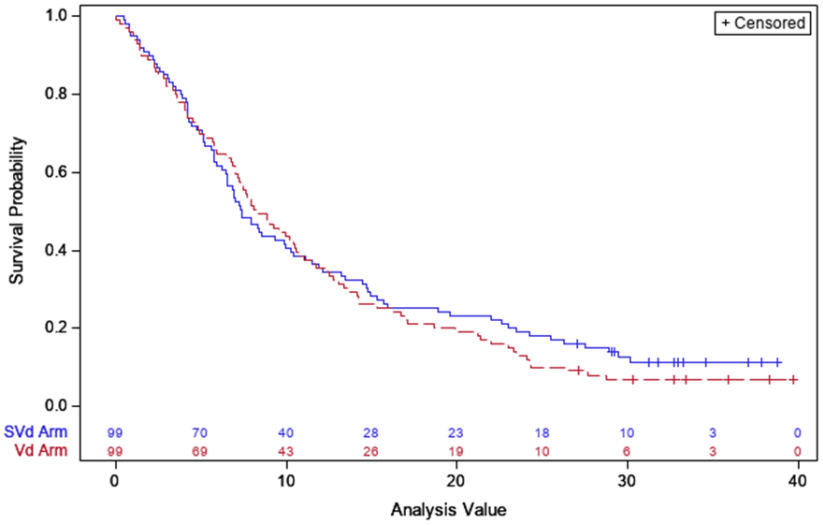


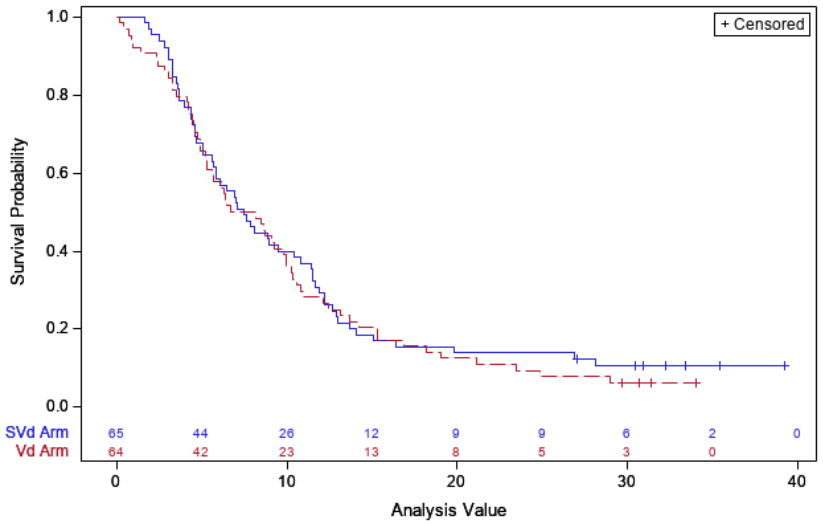
Abbreviations: ITT, intention-to-treat; OS, overall survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.
Source: Data on file.[59]

Figure 10 Kaplain-Meier curves of TTD in the ITT population of BOSTON from the updated analysis

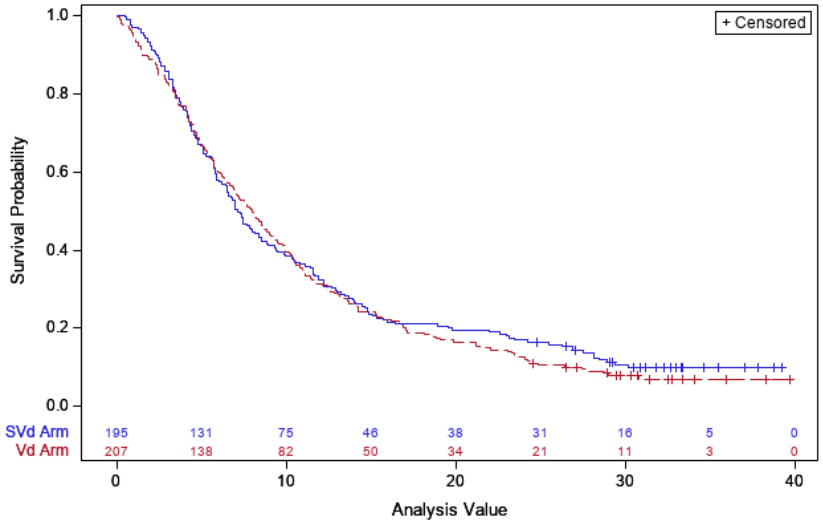
2L



3L



ITT



Abbreviations: ITT, intention-to-treat; OS, overall survival; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.
Source: Data on file.[59]

Table 14 Time to discontinuation by treatment arm (BOSTON ITT)

	Primary analysis (18th February 2020)						Updated analysis (15th 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 TTD, months (95% CI)	7.10 (6.44, 8.54)	7.95 (6.80, 9.23)	7.39 (6.51, 10.45)	8.34 (7.13, 10.81)	7.46 (5.85, 11.40)	7.41 (5.62, 9.95)	7.10 (6.44, 8.54)	7.95 (6.8, 9.23)	7.39 (6.51, 10.45)	8.34 (7.13, 10.81)	7.46 (5.85, 11.40)	7.41 (5.62, 9.95)
One-sided P-value[a]	0.460		0.489		0.412		0.356		0.255		0.401	
Hazard ratio[a] (95% CI)	0.989 (0.794, 1.233)		1.005 (0.724, 1.395)		0.958 (0.652, 1.409)		0.962 (0.780, 1.187)		0.901 (0.660, 1.231)		0.954 (0.656, 1.388)	
Events, n (%)	158 (81.0)	171 (82.6)	78 (78.8)	78 (78.8)	55 (84.6)	56 (87.5)	174 (89.2)	191 (92.3)	87 (87.9)	92 (92.9)	58 (89.2)	60 (93.8)
Patients censored, n (%)	37 (19.0)	36 (17.4)	21 (21.2)	21 (21.2)	10 (15.4)	8 (12.5)	21 (10.8)	16 (7.7)	12 (12.1)	7 (7.1)	7 (10.8)	4 (6.3)

Abbreviations: CI, confidence interval; IRC, independent review committee; ITT, intent-to-treat population; n, number of patients; SVd, selinexor + bortezomib + dexamethasone; TTD, time to discontinuation; Vd, bortezomib + dexamethasone
[a] Calculated by Stratified Log-rank Test
Source: Data on file.[59]

B2.6.4 Health-related quality of life

HRQoL was measured in BOSTON using the EORTC QLQ-CIPN20 measure (secondary endpoint), EORTC QLQ-C30 measure, and EQ-5D-5L (exploratory endpoints).[56,59]

B2.6.4.1 EORTC QLQ-CIPN20

Patient-reported peripheral neuropathy (PN) was assessed using the EORTC QLQ-CIPN20 questionnaire. By the updated analysis (datacut: 15th of February 2021), a significantly lower mean change from baseline score was observed in the SVd arm compared to the Vd arm, in the 2L and ITT populations, for the sensory scale, indicating reduced worsening in sensory symptom burden in patients receiving selinexor (2L: *P*=0.003; ITT: *P*=0.0003). Change from baseline was similar in both arms for the sensory scale in the 3L population, and in motor symptoms and on the autonomic scale for all populations (Table 15).[59]

B2.6.4.2 EORTC QLQ-C30

The EORTC QLQ-C30 was an exploratory endpoint only in the BOSTON trial. The change from baseline to end of treatment data at the time of the primary analysis (datacut: 18th February 2020) and the updated analysis (datacut: 15th February 2021) for global health status are summarised in Table 16. Both treatment arms showed a similar reduction in the EORTC QLQ-C30 global health status score at end of treatment, reflecting improved quality of life in all populations.[59]

B2.6.4.3 EQ-5D-5L

The EQ-5D-5L was an exploratory endpoint only in the BOSTON trial. The change from baseline to end of treatment data at the time of the primary and updated analyses (datacuts: 18th February 2020 and 15th February 2021, respectively) are summarised in Table 17. SVd and Vd treatment arms demonstrated a similar, small reduction in the EQ-5D-5L index at end of treatment, in both the 2L and 3L populations.[59]

Table 15 Linear mixed effect model for change from baseline in EORTC QLQ-CIPN20 scores in the ITT population of BOSTON

	Primary analysis (18th February 2020)						Updated analysis (15th 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
EORTC QLQ-CIPN20 sensory systems												
Rate of change (weekly mean change)												
Estimated rate of change	0.0586	0.1763	0.0554	0.2261	0.0745	0.1859	0.0378	0.1660	0.0467	0.2182	0.0485	0.1641
Estimated mean treatment difference (SE)	-0.1177 (0.0394)		-0.1707 (0.0584)		-0.1114 (0.0703)		-0.1282 (0.0335)		-0.1715 (0.0508)		-0.1156 (0.065)	
95% CI of mean treatment difference	-0.1962, -0.0392		-0.2908, -0.0505		-0.2532, 0.0304		-0.1952, -0.0613		-0.2766, -0.0665		-0.2477, 0.0165	
P-value	0.0038		0.0072		0.1205		0.0003		0.0026		0.0843	
EORTC QLQ-CIPN20 motor systems												
Rate of change (weekly mean change)												
Estimated rate of change	0.0996	0.1597	0.0802	0.1154	0.1361	0.2079	0.0938	0.1559	0.0726	0.1169	0.1327	0.1965
Estimated mean treatment difference (SE)	-0.0602 (0.0415)		-0.0352 (0.0428)		-0.0717 (0.0854)		-0.0621 (0.0381)		-0.0443 (0.0387)		-0.0638 (0.0822)	
95% CI of mean treatment difference	-0.1423, 0.0220		-0.1216, 0.0513		-0.2431, 0.0996		-0.1375, 0.0134		-0.1229, 0.0343		-0.229, 0.1015	
P-value	0.1497		0.416		0.405		0.1058		0.2600		0.4417	
EORTC QLQ-CIPN20 autonomic systems												
Rate of change (weekly mean change)												
Estimated rate of change	0.1393	0.0521	0.1172	0.0739	0.0360	0.0302	0.1056	0.0688	0.0947	0.0922	0.0194	0.0317
Estimated mean treatment difference (SE)	0.0872 (0.0560)		0.0433 (0.0615)		0.0058 (0.1255)		0.0368 (0.0501)		0.0025 (0.0561)		-0.0123 (0.1218)	
95% CI of mean treatment difference	-0.0240, 0.1984		-0.0797, 0.1663		-0.2500, 0.2616		-0.0631, 0.1366		-0.1098, 0.1148		-0.2622, 0.2376	
P-value	0.1228		0.4842		0.9634		0.4654		0.9645		0.9204	

Abbreviations: CI, confidence interval; SE, standard error; Sd, selinexor + dexamethasone; SVd, selinexor + bortezomib + dexamethasone
Source: Data on file.[59]

Table 16 Change from baseline in EORTC QLQ-C30 Global Health Status in BOSTON

	Primary analysis (18th February 2020)						Updated analysis (15th 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
Rate of change (weekly mean change)												
Estimated rate of change	-0.0549	-0.0091	-0.0552	-0.0051	-0.0555	-0.0584	-0.0482	-0.0159	-0.0591	-0.0311	-0.0636	-0.0341
Estimated mean treatment difference (SE)	-0.0458 (0.0417)		-0.0501 (0.0540)		0.0029 (0.0875)		-0.0323 (0.0339)		-0.028 (0.0436)		-0.0295 (0.069)	
95% CI of mean treatment difference	-0.1286, 0.0369		-0.1586, 0.0585		-0.176, 0.1819		-0.0998, 0.0352		-0.1163, 0.0604		-0.1719, 0.1128	
P-value	0.2746		0.3584		0.9734		0.3442		0.5249		0.6724	

Abbreviations: CI, confidence interval; SE, standard error; Sd, selinexor + dexamethasone; SVd, selinexor + bortezomib + dexamethasone
Source: Data on file.[59]

Table 17 Change from baseline in EQ-5D-5L Global Health Status in BOSTON

	Primary analysis (18th February 2020)						Updated analysis (15th 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
Rate of change (weekly mean change)												
Estimated rate of change	-0.0008	-0.0008	-0.0005	-0.0004	-0.0013	-0.0021	-0.0008	-0.0008	-0.0006	-0.0006	-0.0014	-0.0021
Estimated mean treatment difference (SE)	0 (0.0004)		-0.0001 (0.0004)		0.0008 (0.0009)		0.0001 (0.0003)		0 (0.0004)		0.0007 (0.0008)	
95% CI of mean treatment difference	-0.0007, 0.0007		-0.0009, 0.0007		-0.0009, 0.0026		-0.0006, 0.0007		-0.0008, 0.0008		-0.0010, 0.0024	
P-value	0.9586		0.8488		0.3500		0.8654		0.9840		0.3883	

Abbreviations: CI, confidence interval; SE, standard error; Sd, selinexor + dexamethasone; SVd, selinexor + bortezomib + dexamethasone
Source: Data on file.[59]

B2.7 Subgroup analysis

Analyses of PFS, ORR and DOR were predefined for the following subgroups of the ITT in BOSTON:

- Age group;
- Sex (male *versus* female);
- Race (white *versus* others);
- Ethnicity (Hispanic or Latino *versus* Not Hispanic or Latino);
- Region (region 1, region 2, region 3 and region 4 [as defined in randomisation]);
- Prior PI therapies (yes or no);
- Patients with 1 prior anti-MM regimen *versus* >1 prior anti-MM regimen;
- Baseline R-ISS stage (Stage III *versus* Stage I or II);
- Baseline ISS stage (Stage III *versus* Stage I or II);
- Baseline cytogenetic alterations (del[17p]; translocation t[4;14]; translocation t[14;16]; 1q21 amplification) for high risk population and separately for each cytogenetic alteration;
- Last PI received prior to the 6-month PI treatment-free interval for those patients who received prior PI (bortezomib, carfilzomib, ixazomib, other).[57,58]

Subpopulation data permitted reporting of efficacy data for 2L participants and 3L participants in line with the narrower population addressed in this submission. However, further subgroup data were not available within the line of therapy subpopulations.[56]

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 described in Appendix E, 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 a post-hoc subgroup analysis of lenalidomide-refractory patients was performed. Data for these analyses are included in Appendix E.

B2.8 Meta-analysis

Based on SLR output,[52] one trial will inform the model presented in this submission, the pivotal phase 3 BOSTON trial of SVd *versus* Vd.[4] Therefore, a meta-analysis was not performed. A network meta-analysis (NMA) performed with data for relevant comparators is presented in Section B2.9.

B2.9 Indirect and mixed treatment comparisons

Based on a clinical SLR, a feasibility assessment and subsequent global NMA was conducted of eighteen interventions for 2L and 3L+ treatments for RRMM.[67] Networks were constructed for 3L+, rather than 3L only, and therefore data from the 3L+ networks will be utilised for the 3L population in this decision problem, in the absence of specific 3L data. Expert validation of the NMA was performed, where the experts in attendance validated this approach (Appendix N). Of eighteen globally relevant interventions, four are relevant to this decision problem, connected by seven clinical trials and a matched-pairs analysis formed from three additional trials.[67] A summary of the trials included in the NMA, and the methods of analysis used are included in Appendix D.

As per the decision problem (Table 2), the comparators relevant to this submission are Kd in the 2L setting, and PanoVd and IxaRd in the 3L setting. The full networks for 2L and 3L+ are included in Figure 11 and Figure 12 respectively, with the relevant interventions and connections highlighted.

At 2L, Kd was numerically superior to SVd in OS (random effects [RE] model HR=0.89, 95% CI: 0.32, 2.45) and PFS (RE model HR=0.73, 95% CI: 0.31, 1.67). The HR estimates were consistent across the RE and fixed effects (FE) models (Figure 13 and Figure 14).[67] Although these results showed that SVd had a slightly lower efficacy than Kd in the subgroup of patients with only one prior LOT, it is key to highlight that most of these results are likely driven by the type of prior therapies received by participants in each trial. The ENDEAVOR trial was run between 2012 and 2018,[63] and the 1L regimens available at that time might have been different than the 1L treatment options received by patients in the BOSTON trial (conducted instead between 2016 and 2021),[4] which could have affected the relative overall efficacy of SVd compared to Kd. More specifically, 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.

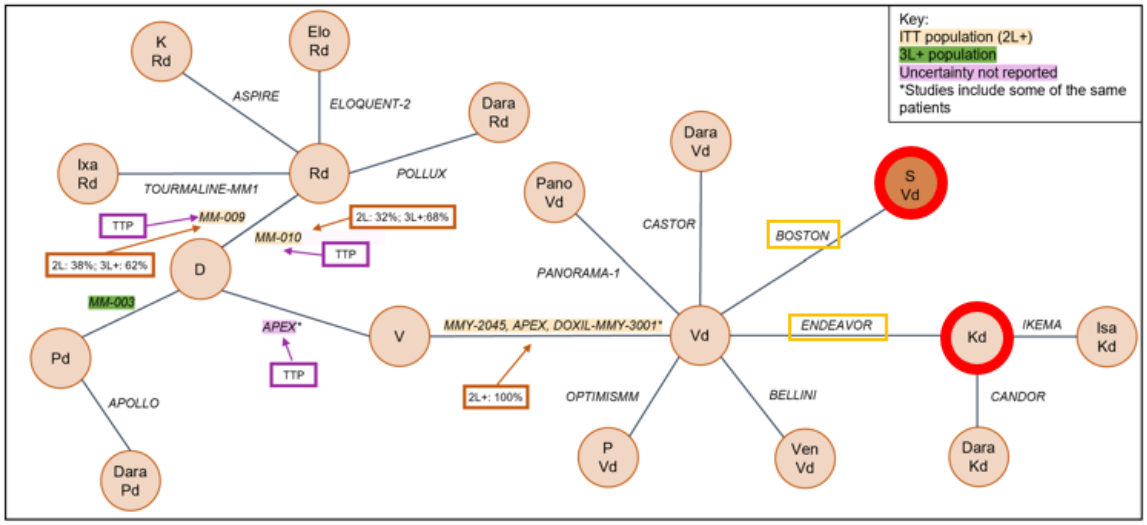
At 3L, SVd was numerically superior in OS (RE models; IxaRd HR=1.06, CI: 0.21, 5.25; PanoVd HR=1.25, CI: 0.45, 3.44) whilst IxaRd and PanoVd were slightly numerically superior to SVd in PFS (RE models; IxaRd HR=0.95, CI: 0.18, 4.58; PanoVd HR=0.80, CI: 0.27, 2.36). The direction of HR estimates was consistent across the RE and FE models (Figure 13 and Figure 14).[67] To interpret these results, it is again necessary to highlight some differences between the BOSTON trial, where few initial patients were enrolled at the end of 2016,[4] and the PANORAMA-1 and TOURMALINE-MM1 trials, which started enrolling patients in 2009 and 2012, respectively.[68,69] As before, the different timelines impact the type of prior therapies available at 1L and 2L, thereby affecting the efficacy of treatments used in 3L+. More specifically, fewer participants were exposed to lenalidomide in the PANORAMA-1 and TOURMALINE-MM1 trials (19% and 12% respectively),[68,69] compared to the patients in the BOSTON trial (39%).[4] Moreover, while in the BOSTON trial 27% patients were refractory to lenalidomide (i.e., difficult-to-treat patients),[4,56] it is unknown how many patients were refractory to lenalidomide in the other two trials, which raised the concern that PanoVd and IxaRd patient response might have been overestimated, due to the lower number of patients who already relapsed on lenalidomide. Therefore, as with the 2L network, the NMA results appear to be conservative for SVd compared to what might be expected in the current clinical practice. These data and associated interpretation are supported by PI-naïve and lenalidomide-refractory network analyses performed as part of the NMA, where across the 2L+ population, SVd was more efficacious than Kd, PanoVd, and IxaRd.[67]

None of the HRs from the two networks were significant in the 2L or 3L+ setting (95% CIs crossed a value of 1.0).[67] During the NMA validation (Appendix N), the experts

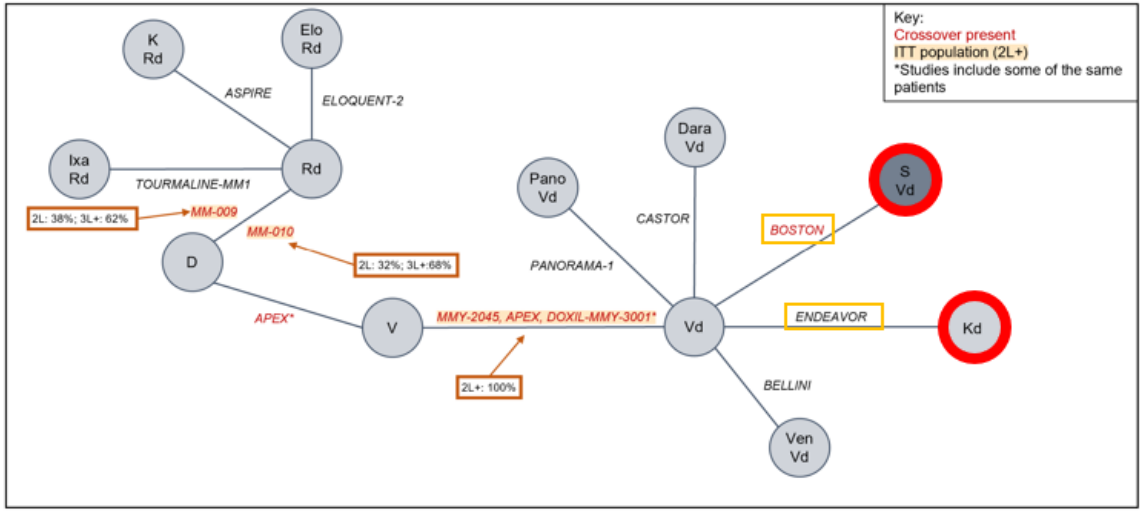
highlighted that wide confidence intervals are common in this type of analysis, due to the large number of comparators, and confirmed that the point estimates are still clinically relevant.

Figure 11 Network of evidence from the 2L NMA

PFS, 2L



OS, 2L



Legend:

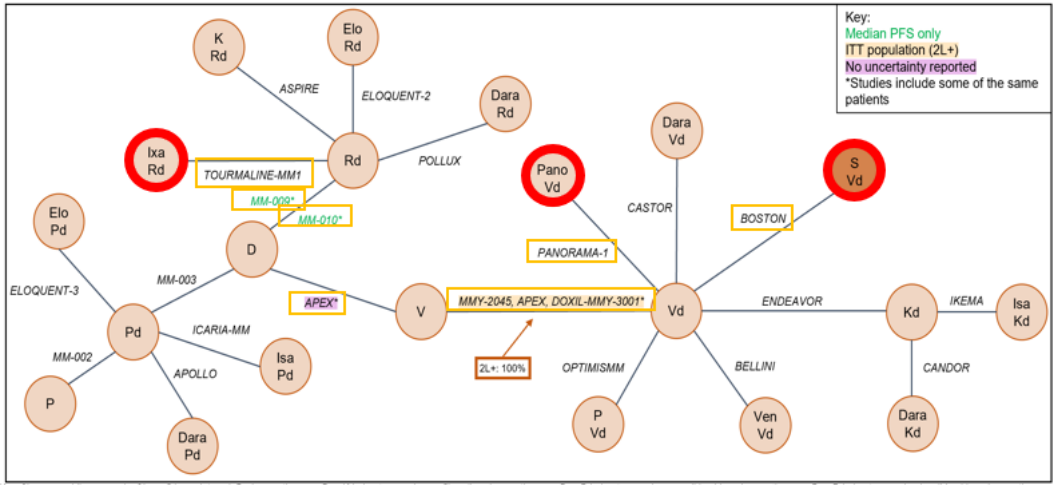
Relevant intervention

Relevant connection

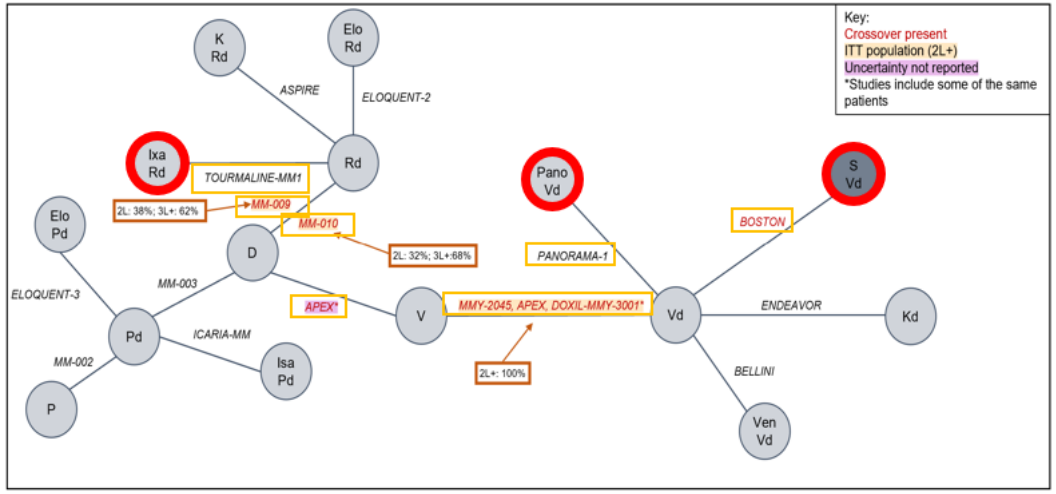
Source: Selinexor for the treatment of relapsed and refractory multiple myeloma: network meta-analysis.[67]

Figure 12 Network of evidence from the 3L+ NMA

PFS, 3L+



OS, 3L+



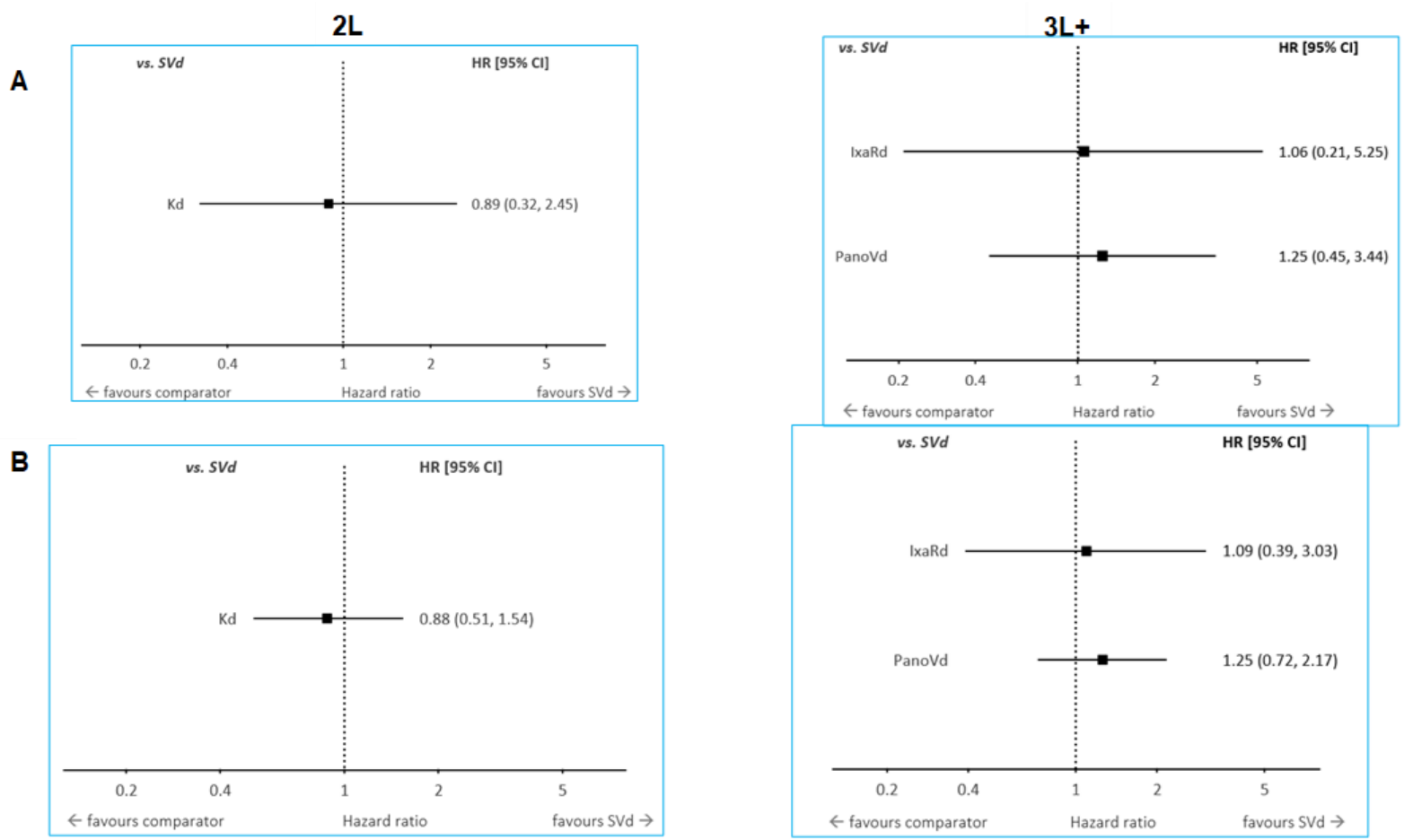
Legend:

Relevant intervention

Relevant connection

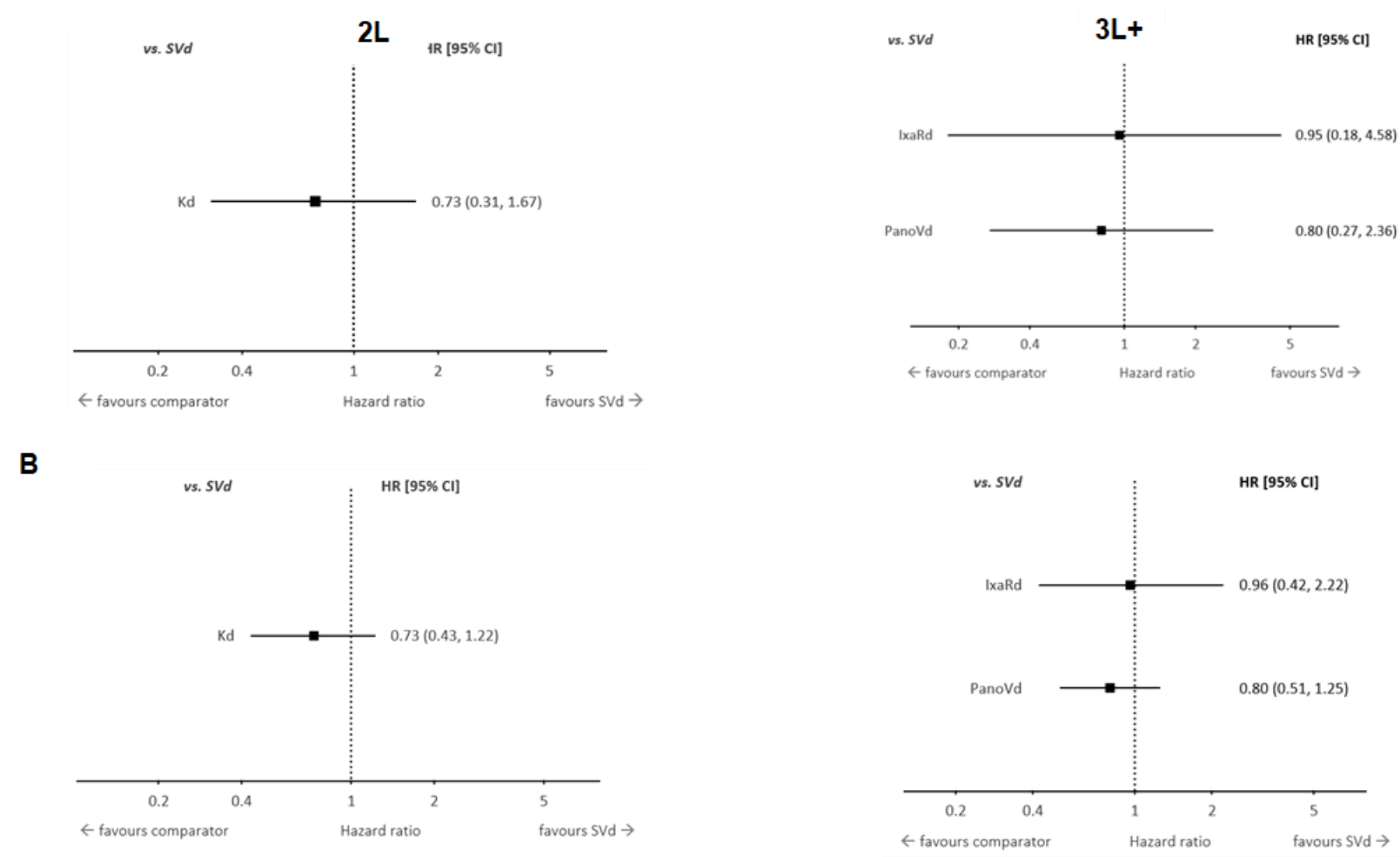
Source: Selinexor for the treatment of relapsed and refractory multiple myeloma: network meta-analysis.[67]

Figure 13 OS results from the NMA



OS results from an NMA with random effects (A) and fixed effects (B)
Abbreviations: HR, hazard ratio; IxaRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; PanoVd, Panobinostat + bortezomib + dexamethasone; SVd, selinexor + bortezomib + dexamethasone; 2L, second-line; 3L+, third-line plus.
Source: Selinexor for the treatment of relapsed and refractory multiple myeloma: network meta-analysis.[67]

Figure 14 PFS results from NMA



PFS results from an NMA with random effects (A) and fixed effects (B)
Abbreviations: CI, confidence interval; HR, hazard ratio; IxaRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; PanoVd, Panobinostat + bortezomib and dexamethasone; SVd, selinexor + bortezomib and dexamethasone; 2L, second-line; 3L+, third-line plus.
Source: Selinexor for the treatment of relapsed and refractory multiple myeloma: network meta-analysis.[67]

Uncertainties in the indirect and mixed treatment comparisons

The NMA approach was adopted to allow comparative efficacy to be estimated between SVd and a large number of relevant comparators within one analysis. Across all of the analyses, a large amount of uncertainty was present; very few comparisons (and none of those included in the CEA) were statistically significant (95% CI included a HR estimate of 1.0), with both the FE and RE point estimates demonstrating this same level of variance.[67] This variance is common in such analyses, compounded by the large number of comparators within the network. Sensitivity to this uncertainty is explored in the CEA through the use of alternative scenarios, as outlined in Section B3.12.3.

Due to a limited evidence base, a matched-pairs analysis was used to permit a connection between bortezomib monotherapy and dexamethasone, exclusion of which would have substantially reduced the size of the network.[67] An alternative strategy would be to assume equivalence between Rd and Vd, however it was deemed more robust to utilise the data from the matched-pairs analysis. Furthermore, in terms of the reduced network analysed as part of this submission, this connection was only required to provide a link between IxaRd and the rest of the 3L+ network; PanoVd and Kd both had direct connections via the PANORAMA-1 and ENDEAVOR studies, respectively. Additionally, within the 3L+ network, the inclusion of MM-009 and MM-010 was required to provide vital connections to the rest of the network, despite these studies only reporting OS data for a 2L+ population.[67]

The 3L+ network was used as a proxy for the 3L patients relevant to this submission, in the absence of more appropriate comparisons,[67] however this was considered an appropriate strategy by the experts who partook in the NMA validation.

B2.10 Adverse reactions

The safety population included all patients who had received at least one dose of the study treatment and patients were analysed according to the treatment they received (SVd, n=195; Vd, n=204). Safety data is reported for the most recent data cut only (i.e., the longest follow-up; updated data cut: 15th February 2021) and for the whole safety population since there is no reason to be believe safety data would differ by prior line of therapy.[56]

The average treatment duration and exposure to each study drug are summarised in Table 18. The mean duration of study treatment was 47.8 (STD: 43.90) weeks in the SVd arm, and 44.1 (STD: 39.25) weeks in the Vd arm. The median selinexor dose received per week in the SVd arm was 80.0mg (range: 29.7-136.7). The median bortezomib dose per body surface area received per week was 0.93mg/m^2 (range: 0.3, 2.6) in the SVd arm and 1.32mg/m^2 (range: 0.5, 2.6) in the Vd arm.[56]

Table 18 Summary of treatment exposure during BOSTON

	SVd	Vd
Duration of study treatment [weeks]		
Mean (STD)	47.8 (43.9)	44.1 (39.3)
Median (range)	30.0 (1, 171)	32.0 (1, 173)
Selinexor exposure		
Duration of exposure [weeks], mean (STD)	47.2 (44.0)	N/A
Dose [mg]/ week, median (range)	80.0 (29.7, 136.7)	N/A
Bortezomib exposure		
Duration of exposure [weeks], mean (STD)	45.4 (42.7)	43.4 (39.2)
Dose [mg/m^2]/ week, median (range)	0.9 (0.3, 2.6)	1.3 (0.5, 2.6)
Dexamethasone exposure		
Duration of exposure [weeks], mean (STD)	47.5 (43.84)	43.1 (38.52)
Dose [mg]/ week, median (range)	36.2 (11.9, 41.7)	43.6 (8.4, 80.0)

Abbreviations: STD, standard deviation; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.
Data cut: 15th of February 2021
Source: Clinical study report.[56]

An overview of treatment-emergent adverse events (TEAEs) is provided in Table 19.

The incidence of Grade 3/4 TEAEs, serious adverse events (SAEs), treatment discontinuation due to TEAEs, and dose modifications due to TEAEs were higher in the SVd arm, compared with the Vd arm as expected due to a 3-drug combination in the SVd arm *versus* the 2-drug combination in the Vd arm (Grade 3/4 TEAE [78.5% *versus* 56.4%], SAE [54.4% *versus* 38.7%], TEAE leading to study treatment discontinuation [21.0% *versus* 16.7%], and TEAE leading to dose modification [88.7% *versus* 76.5%]). Notably, despite the higher incidence of Grade 3/4 AEs and SAEs in

the SVd arm, the proportion of patients experiencing a TEAE leading to death was similar between arms (7.2% *versus* 6.4%). The overall incidence of Grade ≥2 PN events was statistically significantly lower in the SVd arm (21.5%) as compared to the Vd arm (35.8%) (*P*=0.0008). The number of patients who experienced severe (Grade 3/4) PN in the BOSTON study was nearly twice as high in the Vd arm than in the SVd arm (8.8% *versus* 4.6%, respectively).[56]

PN was the most frequent TEAE leading to discontinuation of treatment in both arms however the incidence of treatment discontinuations (4.6% in SVd *versus* 7.8% in Vd) and dose modifications (21.5% in SVd versus 32.8% in Vd) due to PN was lower in the SVd arm compared with the Vd arm. Overall, SVd was associated with significantly lower rates of Grade ≥2 PN compared to the Vd arm.[56]

In conclusion, the safety profile of SVd was consistent with the known safety profiles of selinexor and Vd; there were no new toxicities. The AEs that occurred more frequently in the SVd *versus* Vd (thrombocytopenia, fatigue, nausea, anaemia, decreased appetite, weight decreased, cataract, asthenia, and vomiting [≥10% higher]) were expected events, and were typically reversible, and generally manageable, with supportive care and/ or dose modification. The BOSTON study also confirms that selinexor is not associated with major organ (cardiac, pulmonary, renal, or liver) toxicities and that clinically significant cumulative toxicities, including PN, are minimal. Additionally, the infection risk was similar between arms. In the SVd arm, there was ~30% lower frequency of any-grade PN and ~50% lower frequency of Grade 3/4 PN compared to the Vd arm. Although PN was the most common cause of treatment discontinuation in both arms, the frequency of discontinuation due to PN was 38% lower in the SVd compared to the Vd arm. This is consistent with the lower dose of bortezomib used in the SVd arm.[56]

Table 19 Summary of TEAEs and TRAEs in the BOSTON safety analysis population

	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)
Patients with at least one, n (%)		
Treatment- related TEAE[c]	187 (95.9)	167 (81.9)
Grade 3/ 4 TRAE[a]	137 (70.3)	84 (41.2)
Grade 4 TRAE[a]	28 (14.4)	17 (8.3)
Serious TRAE	58 (29.7)	24 (11.8)
TRAE leading to dose modification[b]	158 (81.0)	131 (64.2)
TRAE leading to dose reduction	139 (71.3)	102 (50.0)
TRAE leading to dose interruption	145 (74.4)	97 (47.5)
TRAE leading to study discontinuation	32 (16.4)	27 (13.2)
TRAE leading to death	4 (2.1)	1 (0.5)
Incidence of Grade ≥2 peripheral neuropathy[d], n (%)		
Patients with at least one Grade ≥2	42 (21.5)	73 (35.8)
Grade 2	33 (16.9)	55 (27.0)
Grade 3	8 (4.1)	18 (8.8)
Grade 4	1 (0.5)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)
Cochran-Mantel-Haenszel Test (SVd *versus* Vd)[e]		
Odds ratio (95% CI)	0.4878 (0.3124, 0.7617)	
One-sided *P*-value	0.0008	

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: 15th 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)
[e] Stratified by prior proteasome inhibitor therapies (yes or no), number of prior anti-myeloma regimens (1 or >1), and R-ISS state at study entry (R-ISS stage III versus stage I or II)
Source: Clinical study report[56]

Table 20 Treatment-emergent Grade 3 or higher AEs occurring in ≥5% of patients (BOSTON safety population)

	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)
Thrombocytopenia	79 (40.5)	36 (17.6)	115 (28.8)
Pneumonia[b]	28 (14.4)	25 (12.3)	53 (13.3)
Anaemia	32 (16.4)	21 (10.3)	53 (13.3)
Fatigue	26 (13.3)	2 (1.0)	28 (7.0)
Peripheral neuropathy	9 (4.6)	18 (8.8)	27 (6.8)
Cataract	22 (11.3)	4 (2.0)	26 (6.5)
Asthenia	16 (8.2)	9 (4.4)	25 (6.3)
Neutropenia	18 (9.2)	7 (3.4)	25 (6.3)
Nausea	15 (7.7)	0 (0.0)	15 (3.8)
Diarrhoea	13 (6.7)	1 (0.5)	14 (3.5)
Hypophosphataemia	11 (5.6)	3 (1.5)	14 (3.5)

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: Clinical study report[56]

B2.11 Ongoing studies

There are no ongoing studies of SVd that will provide evidence relevant to this submission.

B2.12 Interpretation of clinical effectiveness and safety evidence

Section summary

- At the primary data cut, the primary endpoint of BOSTON, IRC-assessed PFS was improved in the SVd arm compared to the Vd arm in both the 2L and 3L populations, representing a 34% and 28% reduction in the risk of PD or death at 2L and 3L, respectively, with the difference at 2L being statistically significant (2L: HR=0.66, 95% CI: 0.43, 1.03; *P*=0.032; 3L: HR=0.72, 95% CI: 0.43, 1.19; *P*=0.101). This PFS benefit was maintained in the updated analysis (2L: 21.03 months *versus* 10.68 months; HR=0.62, 95% CI 0.41, 0.95; *P*=0.014; 3L: 12.91 months *versus* 9.43 months; HR=0.75, 95% CI 0.46, 1.22; *P*=0.121).
- ORR was also significantly improved in the SVd arm compared to the Vd arm in both the 2L (80.8% *versus* 65.7%; OR: 2.20; 95% CI: 1.15, 4.22; *P*=0.0082) and 3L participants (76.9% *versus* 60.9%; OR: 2.14; 95% CI: 0.99, 4.59; *P*=0.0253).
- Median OS was not reached for SVd at the time of primary analysis in either the 2L or 3L participants. At the updated analysis, 3L participants receiving SVd had an OS of 36.67 months, a gain of approximately 7 months compared to those receiving Vd. OS was not reached in 2L participants receiving SVd.
- Selinexor is an oral treatment with a novel MoA, which provides an efficacious treatment option as SVd to patients requiring triplet therapy with a class-switch, at both 2L and 3L.

There remains significant unmet need in the early treatment lines of RRMM, with UK myeloma experts reporting the need for additional choice of triplet regimens, particularly those offering a new MoA. Triplet regimens are preferred since they typically improve the depth of response, PFS, and OS;[25] those containing a new MoA would permit class-switching between regimens and limit re-treatment with the same class of drug, overcoming the issue of refractoriness to treatment.

It has been identified that there is currently a particular unmet need at 3L, where patients will likely already be exposed and/ or refractory to both lenalidomide and daratumumab. In these patients, SVd would provide the only triplet regimen option permitting class-switching to a therapy with a novel mechanism of action. However, with the treatment pathway for MM rapidly evolving, and the potential for DRd (expected publication date 23rd of August 2023) to be commissioned at 1L, the upfront use of daratumumab and lenalidomide for transplant ineligible patients, would lead to a future unmet need in 2L, with current recommended triplet regimens becoming unsuitable due to being either a daratumumab or lenalidomide-containing combination.

Selinexor is a novel, oral SINE compound which induces apoptosis in myeloma cells, inferring anti-tumour activity;[1,38-40] a new MoA compared to current MM treatment regimens. The BOSTON study forms the evidence base for this submission and was an international, Phase 3, RCT of SVd *versus* Vd, at 123 sites across 21 countries, including the UK.[4] The ITT population of BOSTON included participants with one to three prior lines of therapy (LOT), with data available specifically for those who had received one prior LOT (i.e., 2L) and those who had received two prior LOT (i.e., 3L).[4,56,59] Data are therefore available for the place in therapy where UK myeloma experts expressed the areas of greatest unmet need, which form the populations addressed in this submission. With the high unmet need, the UK represented one of the highest enrolments in the BOSTON trial.[56]

The primary efficacy endpoint of BOSTON was IRC-assessed PFS. PFS, OS, HRQoL, and safety and tolerability data (including TTD) from the BOSTON study are included in the cost-effectiveness model for this submission. Participants receiving SVd at 2L demonstrated a 38% statistically significant reduction in IRC-assessed PFS compared to those receiving Vd (updated analysis [15th of February 2021]: 21.03 months *versus* 10.68 months; HR=0.62, 95% CI: 0.41, 0.95; *P*=0.014); statistically significant higher ORR (primary data cut [18th of February 2020]: 80.8% *versus* 65.7%, *P*=0.0062); and a numerically longer OS (updated data cut: 32.76 months in the Vd arm, SVd not estimable). At 3L, there was a 25% reduction in IRC-assessed PFS (updated data cut: 12.91 months *versus* 9.43 months; HR=0.75, 95% CI: 0.46, 1.22; *P*=0.121); statistically significant higher ORR (primary data cut: 76.9% *versus* 60.9%, *P*=0.0253); and a

numerically longer overall survival (updated data cut: 36.67 months *versus* 29.01 months).[4,56,59]

Additional sub-group data are available, although not by line of therapy, for both the PI-naïve and lenalidomide-refractory populations in the BOSTON study, which further demonstrate the value of switching MOA when considering the next line of therapy (Appendix E).[56,59] Furthermore, these subgroup data are representative of the population who would receive SVd in clinical practice following a daratumumab-containing regimen.

Although the data for BOSTON does not provide head-to-head data for a relevant comparator in this decision problem, the randomised, controlled design with a comparator of Vd, allowed pivotal connections against other trials of Kd at 2L, and IxaRd and PanoVd at 3L, permitting a network meta-analysis as described in Section B2.9).[67] At 2L, Kd was numerically superior to SVd in OS (RE model HR=0.89, 95% CI: 0.32, 2.45) and PFS (RE model HR=0.73, 95% CI: 0.31, 1.67). At 3L, SVd was numerically superior in OS (RE models; IxaRd HR=1.06, CI: 0.21, 5.25; PanoVd HR=1.25, CI: 0.45, 3.44) whilst IxaRd and PanoVd were slightly numerically superior to Svd in PFS (RE models; IxaRd HR=0.95, CI: 0.18, 4.58; PanoVd HR=0.80, CI: 0.27, 2.36).[67] However, the comparator trials were all carried out much earlier than BOSTON,[4,63,68,69] and therefore treatment options available at earlier lines (participant prior therapies) will have varied substantially. Many patients in the earlier trials will likely have received chemotherapy in earlier lines, rather than the more effective alternatives that are now available, which would have the potential to bolster the effect of 2L and 3L treatments. In particular, there were differences between trials in the proportion of participants exposed/ refractory to lenalidomide, a typically difficult-to-treat population, with the BOSTON population typically containing a higher proportion.[4,68,69] Therefore, the point estimates attained through the 2L and 3L+ NMA are likely conservative estimates, supported by the PI-naïve and lenalidomide-refractory analyses of the 2L+ network, where SVd demonstrated superior efficacy against Kd, IxaRd, and PanoVd.

The addition of selinexor to Vd (SVd) led to no new toxicities, the safety profile was consistent with the known safety profiles of selinexor and Vd. Adverse reactions that occurred more frequently in the SVd *versus* the Vd arm were expected events and

were typically reversible and manageable with supportive care and dose modification. The frequency of Grade ≥3 TEAEs and dose discontinuations due to TEAEs were higher in the SVd arm compared with the Vd arm, however this is to be expected with a three-drug combination (SVd) *versus* a two-drug combination (Vd). The BOSTON trial demonstrated that selinexor is not associated with major organ toxicities, and that clinically significant cumulative toxicities, such as peripheral neuropathy, are minimal.[56]

The dosing for selinexor can be modified to manage adverse events if required. It is recommended to reduce the dose of selinexor from 100mg once-weekly to 80mg once-weekly in the first instance, followed by 60mg once-weekly if required, and then 40mg once-weekly.[56,57] In the BOSTON trial, the median dose for selinexor after dose reductions was 80mg. In those patients that required appropriate dose reductions, the incidence of clinically relevant AEs significantly reduced compared to those patients that required no dose adjustments. Furthermore, the dose reduction was indicative of patients staying on treatment for a longer period of time and therefore extending their PFS benefit.[56,59]

With the use of triplet therapies earlier in the treatment of RRMM, there is a need to be able to offer patients the choice of an effective triplet therapy in those patients that have received daratumumab and lenalidomide containing regimens, that provides the opportunity to use a new MoA. Currently this need is seen at 3L but with the potential earlier introduction of daratumumab and lenalidomide with DRd in 1L, this need in the future would move to the 2L. Overall, the SVd regimen offers an effective triplet treatment option, with selinexor providing an oral treatment option, with a manageable safety profile, giving clinicians the option to not need to re-treat patients with the same classes of drugs they have received in earlier lines.

B3 Cost-effectiveness

B3.1 Considerations around positioning in current and prospective patient cohorts

As outlined in section B1.3.3, UK myeloma experts consulted during the development of the company submission have identified a particular role for SVd as a treatment option for RRMM following daratumumab-containing regimens.[36,37]

In the current treatment pathway, in which DVd has recently been recommended for routine commissioning as a second-line (2L) therapy, the immediate priority positioning for SVd identified by clinical experts is as a third-line (3L) treatment option. Anticipating that DRd may enter routine commissioning as a first-line (1L) treatment for transplant-ineligible patients (subject to final guidance from NICE, pending at the time of the current submission), clinical experts expect that clinical demand for SVd will extend to 2L, providing the option of a double class switch to patients with prior exposure to daratumumab and lenalidomide from first-line treatment with DRd (and hence ineligible for treatment with DVd at 2L, as well as ineligible for KRd and Rd given refractoriness to lenalidomide).

To ensure that the cost-effectiveness analysis (CEA) remains relevant in an evolving treatment landscape, the cost-effectiveness of SVd in 3L and 2L patient populations is considered as two separate base case analyses. The 3L results consider the cost-effectiveness of SVd *versus* the comparators and positioning most relevant to the current treatment pathway, while 2L results reflect the MM pathways expected to apply in the near future.

Importantly, while analyses are presented in the context of two distinct ‘visions’ of the MM treatment pathway, the expectation is that both will apply concurrently, albeit to different cohorts of patients. This approach is not intended to suggest a separation of the decision problem but rather to consider cost-effectiveness relevant both to patients that have been treated according to the current pathway or to a future pathway, using the evidence most directly relevant to either line.

B3.2 Published cost-effectiveness studies

B3.2.1 Identification of studies

To identify evidence of the cost-effectiveness, healthcare costs and resource use, and HRQoL/ utility evidence in RRMM, an economic systematic literature review (SLR) was conducted to support this company submission for SVd, but also the simultaneous company submission of Sd in penta-refractory MM (NICE ID6193).[70] The SLR research question related to the scope of this submission is:

What is the cost-effectiveness of selinexor compared to comparator interventions in adult patients with relapsed or refractory multiple myeloma (RRMM), who have received one or two prior lines of therapy?

The SLR was undertaken according to the principles of systematic reviewing published in the Cochrane Handbook, the Centre for Reviews and Dissemination (CRD), and the NICE Methodology Process and Methods guide.[53,54,65,66] The SLR search strategy and study selection methods are described in Appendix G.[70]

B3.2.2 Description of identified studies

The SLR identified a number of published cost-effectiveness studies and technology appraisals in RRMM, of which five are directly relevant to the decision problem addressed by this submission. All were cost-utility analyses of SVd comparators in an indication relevant to the decision problem. Three were NICE TAs of Kd, PanoVd, and Ixa Rd,[28,71,72] and two were SMC appraisals of Kd and PanoVd.[73,74] The CEA from these five UK HTA appraisals are summarised in Table 21.

The majority of relevant cost-effectiveness studies reported a three-state partitioned survival model (PSM) of progression-free, progressed disease and death, with one presenting a four-state model defining progression-free by on-treatment and off-treatment. Where reported, model time horizon ranges from 18.7 years to 40 years, with the majority reporting the use of a lifetime horizon. Cycle length varied between 1 week and 3 weeks for the PSMs and discount rates were reported as 3.5% for costs and outcomes, where reported.

Additional information on the methods of identification and a more detailed description of relevant studies is reported in Appendix G.

Table 21 Summary list of published cost-effectiveness studies

Study/ Year (Intervention)	Patient population	Summary of modelling approach	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost per QALY gained)
NICE TA380 (2016)[71] (PanoVd)[a]	Patients with multiple myeloma who have received at least one prior therapy (2L+) Modelled population: 3L+ DCE [to bortezomib and an IMiD] RRMM with subgroups of 2-3 prior lines (3L-4L) and 2+ prior lines (3L+)[c]	CUA from a NHS England perspective [England & Wales, UK] PanoVd *vs.* Rd (2-3 prior lines), Vd (2+ prior lines) Semi-Markov model; 3 health states (PF, PD, Death) Source of efficacy data: PANORAMA-1	Base case; (2-3 prior lines) PanoVd: 1.52 QALYs, Rd: 1.41 QALYs (2+ prior lines) PanoVd: 1.652 QALYs Vd: 1.480 QALYs Final OS data analysis; PanoVd: 1.59 QALYs Rd: 1.47 QALYs PanoVd: 1.712 QALYs Vd: 1.646 QALYs	Base case; (2-3 prior lines) PanoVd: £146,310 Rd: £143,048 (2+ prior lines) PanoVd: £137,447 Vd: £131,555 Final OS data analysis; PanoVd: £141,707 Rd: £140,281 PanoVd: £140,388 Vd: £149,297	Base case; (2-3 prior lines) PanoVd vs. Rd: £17,833 /QALY, £30,701/L Y (discounted, with PAS) (2+ prior lines) PanoVd vs. Vd: £24,095/ QALY, £34,333/ LY (discounted, with PAS) Final OS data analysis; PanoVd vs. Rd: £11,527/ QALY, £6,783/ LY (discounted, with PAS) PanoVd vs. Vd: PVd dominant (PanoVd more effective and less expensive than Vd)
NICE TA657 (2020)[72] (Kd)[b] [previously TA457 (2017)]	Adults with multiple myeloma who have received at least one prior therapy (2L+) Modelled population: 2L RRMM and 3L RRMM	CUA from an NHS and PSS perspective [England & Wales, UK] Kd *vs.* Vd PSM; 3 health states (PF, PD, Death) Source of efficacy data: ENDEAVOR, ASPIRE	**2L:** Company's revised base case, Kd *vs.* Vd; Kd: 3.88 QALYs; 5.74 LYs Vd: 2.79 QALYs; 4.23 LYs ERG preferred base case; Kd: 2.70 QALYs Vd: 2.13 QALYs **3L:** Company's revised base case, KRd *vs.* Rd; KRd: 3.67 QALYs Rd: 2.88 QALYs	**2L:** Company's revised base case, Kd *vs.* Vd; Kd: £117,660 Vd: £93,769 ERG preferred base case; Kd: £108,436 Vd: £71,512 **3L:** Company's revised base case, KRd *vs.* Rd; KRd: £127,140	**2L:** Company's revised base case, Kd *vs.* Vd; £22,009/ QALY ERG preferred base case; £64,325/ QALY **3L:** Company's revised base case, KRd *vs.* Rd; £41,429/ QALY ERG preferred base case; £52,439/ QALY

Study/ Year (Intervention)	Patient population	Summary of modelling approach	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost per QALY gained)
			ERG preferred base case; KRd: 3.15 QALYs Rd: 2.56 QALYs	Rd: £94,528 ERG preferred base case; KRd: £122,944 Rd: £92,263	
NICE TA870 (2023)[28] (IxaRd)[a] [previously NICE TA505 (2018)]	Adult patients with multiple myeloma who have received ≥1 previous therapy (2L+). Modelled population: 2L/ 3L RRMM	CUA from a NHS and PSS perspective [England & Wales, UK] Rd (2+ prior lines), Vd (1 prior line) PSM; 3 health states (PF, PD, Death) Source of efficacy data: TOURMALINE-MM1	Original NICE submission (TA505): IxaRd: 3.68 QALYs, Rd: 2.70 QALYs New company base case (TA870): IxaRd: 3.18 QALYs Rd: 2.47 QALYs 1 prior therapy; Vd: 1.596 QALYs IxaRd: 3.932 QALYs 2 prior therapies; Rd: 2.2041 QALYs IxaRd: 3.1736 QALYs Corrected base case results following correction during clarification question phase; 1 prior therapy; IxaRd: 3.93 QALYs Vd: 1.74 QALYs	Company base case; 1 prior therapy; Vd: £38,770 IxaRd: £201,274 2+ prior therapies; Rd: £91,428 IxaRd: £222,532 Corrected base case results following correction during clarification question phase; 1 prior therapy; IxaRd: £201,274 (with PAS) Vd: £40,612	Original NICE submission (TA505): £31,691/QALY ERG's base case; IxaRd vs. Rd: £70,975 Original company base case (Covariate adjusted base case, with PAS), with PAS; 1 prior therapy; IxaRd vs. Vd: £69,565/ QALY 2 prior therapies; IxaRd vs. Rd: £135,237/ QALY Corrected company base case; 1 prior therapy; IxaRd vs. Vd: £73,333/QALY Updated base case, removing lenalidomide PAS, with Ixazomib PAS; 1 prior therapy; IxaRd vs. Vd: £85,557/ QALY Updated base case, removing lenalidomide PAS,

Study/ Year (Intervention)	Patient population	Summary of modelling approach	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (cost per QALY gained)
					and applying ERG NMA OS HR, with Ixazomib PAS; 1 prior therapy; IxaRd vs. Vd: IxaRd dominated (lower QALYs)
SMC 1242/17 (2017)[74] (Kd)[b]	Adult patients with multiple myeloma who have received at least one prior therapy (2L+). Modelled population: 2L/ 2L+ RRMM	CUA [Scotland, UK]. Perspective NR. Kd *vs.* Vd PSM; 3 health states (PF, PD, Death) Source of efficacy data: ENDEAVOR	NR	NR	Kd vs. Vd: £33,522/QALY (with carfilzomib PAS) Kd vs. Vd, only 1 prior therapy: £24,820/QALY (with carfilzomib PAS)
SMC 1122/16 (2016)[73] (PanoVd)[a]	Adult patients with multiple myeloma who have received at least two prior regimens including bortezomib and an IMiD (DCE) (3L+)	CUA [Scotland, UK]. Perspective NR. PanoVd *vs.* Rd PSM; 4 states (PF on-tx, PF off-tx, PD, Death) Source of efficacy data: PANORAMA-1, MM-009, MM-010	NR	NR	PanoVd vs. Rd: £11,527/ QALY (with PAS)

Abbreviations: CUA, cost-utility analysis; DCE, double-class refractory; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IMiD, immunomodulatory imide drug; IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; KRd, carfilzomib plus lenaidomide and dexamethasone; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; NR, not reported; OS, overall survival; PanoVd, panobinostat plus bortezomib and dexamethasone; PAS, patient access scheme; PD, progressive disease; PSM, partitioned survival model; PSS, Personal Social Services; QALY, quality-adjusted life year; Rd, lenalidomide plus dexamethasone; RRMM, relapsed and/ or refractory multiple myeloma; SMC, Scottish Medicines Consortium; TA, technology appraisal; tx, treatment; UK, United Kingdom; Vd, bortezomib plus dexamethasone; 2L, second-line; 3L, third-line

B3.3 Economic analysis

- **Summary of economic analysis**
- The economic analysis presents base case results to demonstrate cost-effectiveness in two contexts: the current pathway (reflecting an expectation that SVd would be used primarily as a 3L treatment) and the expected future pathway assuming that DRd becomes a 1L treatment for transplant-ineligible patients (with SVd used as a 2L therapy).
- A *de novo* partitioned survival model was developed in Microsoft Excel to estimate the incremental lifetime costs and QALYs associated with SVd relative to IxaRd and PanoVd at 3L, and *versus* Kd at 2L.
- Progression and survival for SVd were estimated using parametric curves fitted to Kaplan-Meier curves calculated from the SVd arm of the BOSTON trial. Myeloma clinical expert opinion was sought to validate appropriate curve selection alongside evaluations of statistical/ visual fit.
- Estimates of comparative efficacy among patients receiving relevant comparator treatments were based on 2L and 3L+ NMAs *versus* comparator studies. Base case results reflect point estimate hazard ratios from NMA random-effects models, with alternative assumptions around relative efficacy explored in scenario analyses.
- Health state utility estimates were derived from BOSTON trial data (mapped from the EQ-5D-5L to EQ-5D-3L), with utility decrements associated with adverse events sourced from literature.
- Resource use and cost estimates were derived from published literature.
- Base and scenario cost-effectiveness results are reported as pairwise ICERs (costs per incremental QALY) and net health benefit (NHB) for SVd *versus* IxaRd and PanoVd at 3L, and Kd at 2L. Output of the CEM is reported as incremental cost-effectiveness ratios (ICERs) and estimates of net health benefit and net monetary benefit at willingness-to-pay (WTP) thresholds of £20,000 and £30,000. Deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analysis (PSA) test the impact of key uncertainties on cost-effectiveness results.
- Severity modifiers were explored but not found to be applicable to 3L or 2L analyses using base case settings.

- Results show SVd to be cost-effective *versus* all 3L comparators (IxaRd, PanoVd) and 2L comparators (Kd) explored when applying a PAS discount of [redacted] to the price for selinexor and applying list price costs for comparator therapies.
- SVd remains a cost-effective treatment option at 3L and 2L when tested in sensitivity analysis

B3.3.1 Patient population

The economic evaluation considers the cost-effectiveness of selinexor in combination with bortezomib and dexamethasone (SVd) for multiple myeloma (MM) patients that have received one or two prior lines of therapy. As outlined in Section B1.1, this corresponds to a narrower population than the MHRA marketing authorisation (MA) for SVd, which covers patients that have received one to three prior lines.[3] The focus on 2L and 3L use targets key areas of unmet need for a new RRMM therapy in current and prospective pathways identified through engagement with UK myeloma experts.

As outlined in Section B1.3.3, myeloma experts have identified a significant unmet need in the 3L setting, as well as anticipating an increasing move to 2L as the treatment landscape (particularly at 1L) evolves, with the potential introduction of DRd into clinical practice.[37] To provide analyses and cost-effectiveness results that are clinically relevant in a dynamic RRMM treatment pathway landscape, base case estimates are considered based on two separate analyses:

- **Base case 3L results** (based on current treatment pathway) explores the cost-effectiveness of SVd *versus* 3L comparators (IxaRd, PanoVd), in the expectation that a primary use case for SVd would be following treatment with a daratumumab-therapy (DVd) at 2L.
- **Base case 2L results** (based on expectations around the near-future treatment pathway) explores the cost-effectiveness of SVd versus 2L comparators (Kd), as a double-class switch having received DRd as a 1L therapy, for patients not eligible for stem-cell transplant.

The analyses use treatment effect data specific to the 3L and 2L subgroups of BOSTON (129 patients across both arms at 3L and 198 patients at 2L, from an ITT population of 402 patients across all lines (2L+) of the trial). The baseline

characteristics of each subgroup compared against the ITT population are summarised in Table 22.

Table 22 Patient characteristics used in the economic analysis

	BOSTON ITT	BOSTON 2L only	BOSTON 3L only
N:	402	198	129
Age: mean (SD)	65.98 (9.47)	67.18 (8.90)	65.33 (9.47)
Male: n (%)	230 (57%)	108 (55%)	87 (67%)
ECOG: mean, SD	0.73 (0.62)	0.68 (0.60)	0.77 (0.62)
1 prior therapy: n (%)	198, (49%)	198 (100%)	0 (0%)
2 prior therapies: n (%)	129, (32%)	0 (0%)	129 (100%)
3 prior therapies: n (%)	75, (19%)	0 (0%)	0 (0%)
Weight (kg): mean (SD)	76.20 (15.11)	76.41 (14.87)	76.77 (15.20)
BSA (m^2): mean (SD)	1.83 (0.21)	1.83 (0.21)	1.85 (0.21)

Abbreviations: BSA, body surface area; ITT, intention to treat; kg, kilogram; m^2, metre-squared; n, number; SD, standard deviation; 2L, second-line; 3L, third-line.
Source: clinical study report and data on file[56,59]

B3.3.2 Model structure

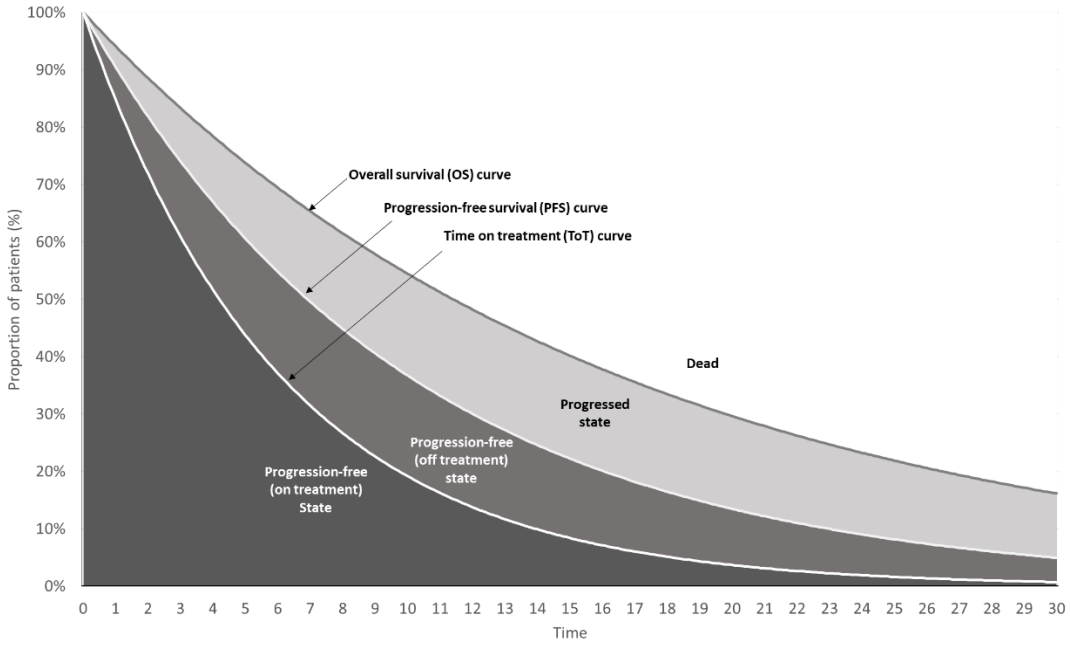
No existing economic model was identified via the SLR (Appendix G) for the evaluation of the cost-effectiveness of SVd in RRMM in the UK. Consequently, appropriate model structures were explored based on the features and limitations of evidence available for SVd and comparators and with consideration of NICE Decision Support Unit (DSU) guidance (specifically NICE TSDs 14, 15, 16 and 19)[75-78] and recommendations provided by EAGs and the NICE committee in relation to the approaches of previous appraisals.

A standard partitioned survival model (PSM) structure was identified as being most suitable for this evaluation, aligned with previous NICE appraisals in this disease area (Table 21). The PSM structure, illustrated in Figure 15, is a well-established modelling approach for the cost-effectiveness analysis of oncology therapies. In common with state transition approaches (the most frequently used alternative), the PSMs typically categorise patients into three main health states: progression-free, progressed, and dead. In common with several of the examples identified from previous NICE

submissions, PFS was subdivided in the CEA according to whether patients are on or off treatment, to incorporate assumptions that not all patients will be treated until disease progression.

Whereas Markov methods estimate the distribution of patients across health states by estimating transitions between each state at specific time intervals, the PSM does so directly from the area between overall survival (OS) and progression-free survival (PFS) curves, as illustrated in Figure 15. As discussed in NICE TSD 19,[78] this is a particular advantage for analyses of the type considered for SVd where indirect comparisons are required against comparator treatments for which patient data are not available. Kaplan-Meier curves for OS and PFS, both common and widely-reported endpoints in published literature, alongside summary patient data are sufficient for informing relative estimates without the need for transition probabilities to be estimated.

Figure 15 Illustration of partitioned survival model structure



The model applies a cycle length of one week to facilitate the modelling of dosing regimens that may not be coterminous with larger timeframes. A half-cycle correction has been applied in the base case analysis.

A lifetime horizon is used with costs and QALYs estimated over 35 years from model baseline (fewer than 1% of patients in either arm remain alive at the end of the

modelled period in each of the main scenarios). This model length was chosen in keeping with previous RRMM NICE appraisals (Table 23) where most previous appraisals adopt a model period of between 30 and 40 years as a proxy lifetime horizon. The economic analysis perspective is that of the National health service (NHS) and personal social services research unit (PSSRU), as per the NICE reference case.

The cost-effectiveness analysis of SVd *versus* 3L and 2L comparators is assessed as two separate scenarios, with base case and sensitivity/ scenario analyses reported separately for each. Unless specified otherwise, the model structure, inputs (including unit costs and resource use levels) and assumptions listed in the sections below apply to both 3L and 2L analyses. Where possible, however, the CEA draws on subpopulation data specific to patients at the relevant line of treatment. Line-specific estimates include progression and survival rates, indirect treatment comparisons, treatment durations, and subsequent treatment options. As randomisation in the BOSTON study was stratified by prior lines of therapy (one *versus* two or more), the distribution of patients across arms (see Section B2.3.2) remains well-balanced with this approach applied.

A summary of the features of economic models used in previous NICE technology appraisals used to inform the design and assumptions of the *de novo* analysis is provided in Table 23.

Table 23 Features of the economic analysis

	Previous evaluations								Current evaluation	
Factor	**TA657[72]**	**TA129[79]**	**TA695[80]**	**TA586[81]**	**TA897 [previously TA573][29]**	**TA171[82]**	**TA380[71]**	**TA870[28]**	**Chosen values**	**Justification**
Model structure	Partitioned survival model	Semi-Markov state transition model	Partitioned survival model	Discrete event simulation	Partitioned survival model	Discrete event simulation	Direct comparison survival analysis with data from clinical trials	Partitioned survival model	Partitioned survival model	Suitability for the trial endpoints and in keeping with precedence
Time horizon	40 years	15 years	40 years	30 years	30 years	30 years	25 years	Lifetime (99% patients died)	35 years	Lifetime (<1% alive)
Perspective	NHS and PSS	NHS	NHS and PSS	NHS and PSS	NHS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NICE reference case
Cycle length	3 weeks	3 weeks	28 days	Continuous time	1 week	Continuous time	3 weeks	1 week	1 week	Flexible, coterminous with dosing schedules
Half-cycle correction	Applied	Not applied	Applied	Not applicable	Applied	Not applicable	Applied	Applied	Applied	Limited impact with 1-week cycle length
Discount rate for costs and outcomes	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	NICE reference case
Health effects measure	QALYs, LYs	LYs	QALYs	QALYs	QALYs	QALYs	QALYs	QALYs, LYs	QALYs	NICE reference case
Treatment waning effect?	Not applied	Not applied	Not applied. While the committee thought that	Not applied: model driven by	Not applied	Not applied	Not applied	Not applied. Committee thought that treatment	Not applied	Consistent with previous evaluations

	Previous evaluations								Current evaluation	
			treatment effect waning was likely, the ICERs were in an acceptable range.	response rates				waning would be largely captured in the trial.		
Source of utilities	EORTC QLQ-C30 from the ENDEAVOR trial mapped to EQ-5D	Utility values from van Agthoven *et al.* 2004	EORTC QLQ-C30 from the ASPIRE trial mapped to EQ-5D	Utility values from van Agthoven *et al.* (2004)	EQ-5D-5L from the CASTOR trial mapped to EQ-5D-3L	Utility values from van Agthoven *et al.* (2004)	Mapped utility values from the PANORAMA-1 trial, Acaster *et al.* study	EQ-5D from the TMM1 trial	EQ-5D-5L from the BOSTON trial	NICE reference case
Source of treatment costs	BNF	APEX trial	MIMS UK Drug Database, eMIT	BNF, eMIT	MIMS UK Drug Database,	BNF	BNF	BNF, eMIT	BNF (branded), eMIT (generic)	Consistent with previous evaluations and relevant to the NHS and PSS
Source of other costs	NHS reference costs	NHS Outpatient Mandatory Tariff 2005/06, Bruce *et al.* 1999, expert interviews	NHS reference costs, PSSRU unit costs	NHS reference costs	NHS reference costs	NHS reference costs	NHS reference costs	NHS reference costs, PSSRU unit costs	NHS reference costs, PSSRU unit costs	Consistent with previous evaluations and relevant to the NHS and PSS

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire – Core 30; EQ-5D-3L/5L, EuroQol five dimension – 3 levels/ 5 levels; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; TA, technology appraisal; UK, United Kingdom

B3.3.3 Intervention technology and comparators

B3.3.3.1 Intervention

Analyses for the 3L and 2L positionings assess the cost-effectiveness of selinexor in combination with bortezomib and dexamethasone (SVd) for the treatment of MM. Evidence and assumptions around the clinical effectiveness of SVd for all analyses are derived from aggregated and patient-level data from the BOSTON clinical trial, in which the SVd combination was delivered over 35-day cycles until disease progression or discontinuation due to toxicity.

For the purposes of the CEA, the scheduling of doses described in the trial protocol was adopted, but dose adjustments were also applied to reflect observed practices assumed to be generalisable to real-world practice (described in more detail in Section B3.5.4). Patients are assumed to remain on treatment until disease progression or earlier discontinuation, as informed by time to discontinuation in the BOSTON trial.

B3.3.3.2 Comparators

The CEA compares SVd against the 3L and 2L comparators identified by clinicians as being viable treatment options in either setting based on the current treatment landscape (3L analyses) and possible future landscape assuming reimbursement of DRd as a first-line therapy (2L analyses). As outlined in Section B1.1, the relevant comparators considered are:

For patients that have received two previous therapies (3L):

- Panobinostat plus bortezomib plus dexamethasone (PanoVd)
- Ixazomib plus lenalidomide plus dexamethasone (IxaRd)

For patients that have received one previous therapy (2L):

- Carfilzomib plus dexamethasone (Kd)

B3.4 Clinical parameters and variables

The following sections cover the methods for handling extrapolation of the clinical data and relative effectiveness (indirect comparisons) in the analyses of the 3L current and 2L expected near future treatment pathway positionings for SVd.

B3.4.1 Third line (3L) analysis of BOSTON time-to-event data: OS, PFS and time on treatment (ToT)

PFS, OS and ToT endpoints corresponding to patients treated with SVd were derived from patient-level data from the 15th February 2021 data cut of the BOSTON trial.

For each endpoint, parametric curves were fitted both independently (i.e., only to the SVd arm of the trial), and jointly (dependent curves fitted to both SVd and Vd arms, with the calculation of a treatment arm coefficient to capture differences between the two). Each approach has its advantages: the jointly-fitted estimates draw on a greater pool of evidence, informed by approximately twice the number of observations, but assumes proportionality between the two arms. Independent curve fitting avoids the undue influence of the comparator arm on estimates, and requires fewer assumptions, but incurs greater uncertainty associated with sample size.

Proportional hazards assessments were conducted for each set of analyses, and results from both jointly- and independently-fitted models are presented in scenario analyses. Given the role of Vd as a 'bridging' arm between SVd and NMA comparators, jointly-fitted curves were prioritized in the base case to preserve estimated relativities between SVd and Vd unless clear violations of proportional hazards were violated. In cases where Schoenfeld residual tests suggested a potential violation, a visual assessment was made of log-log and Schoenfeld residual plots, the results of proportional assessments in larger BOSTON populations were considered (to determine whether sample size was a likely factor) and the consistency of extrapolations using both approaches was compared against with landmark estimates from clinical experts to assess face validity.

For the joint estimation of overall survival, it was necessary to adjust for the crossover of patients from the Vd to SVd arm in the BOSTON trial prior to curve fitting. This was carried out using a two-stage-estimation (TSE) approach, aligned with the company submission to EMA. According to this approach, disease progression (as a precursor to treatment switching) is used as a secondary baseline timepoint, to differentiate between pre- and post-progression survival rates. This allowed for the influence of treatment switching to be accounted for, controlling for prognostic factors at baseline and at progression. Adjusted OS estimates with re-censoring (to avoid bias from informative censoring introduced by the methodology) are implemented in the base

case, with results using unadjusted OS and adjusted OS with re-censoring explored as model scenarios.

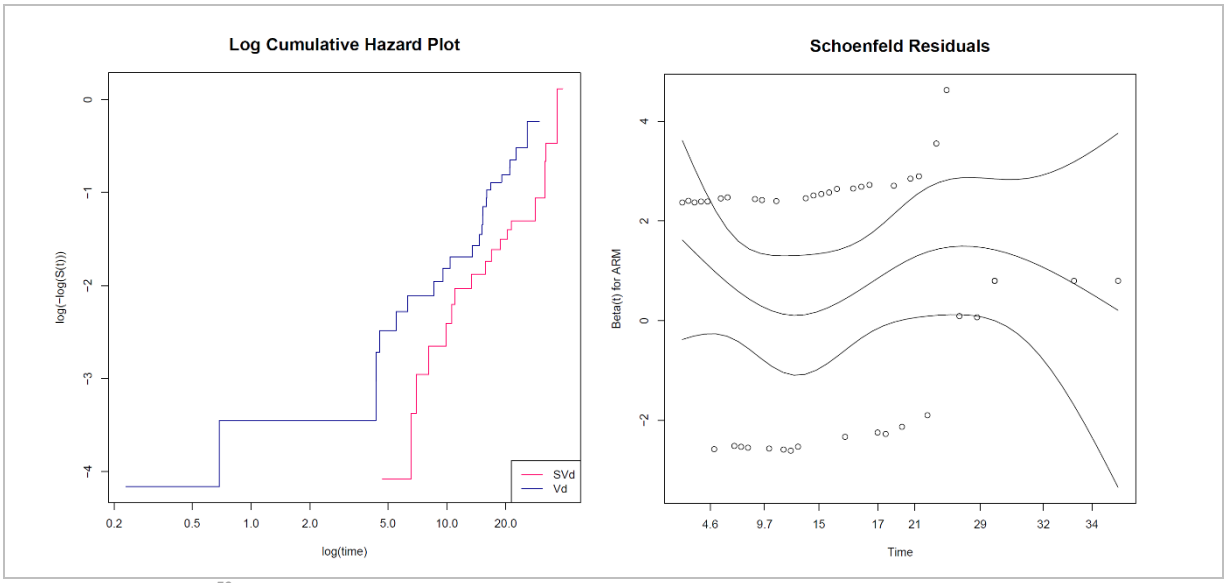
Seven parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) were fitted to data for each endpoint. Appropriate curve selection was determined according to statistical and visual goodness of fit and the clinical plausibility of extrapolations as determined by myeloma experts during an expert Advisory Board held in May 2023.[36] Expert clinical and health economic input was sought at the same time regarding the need for more flexible (spline or piecewise) extrapolation approaches.

Overall survival is capped in the model to ensure that age-specific survival rates do not exceed general population levels based on ONS mid-year mortality estimates for 2018-2020.

B3.4.1.1 ***Overall survival (OS)*** *– 3L*

TSE to remove the effect of crossover from the Vd arm to selinexor in 24/64 patients in the 3L population improved the OS hazard ratio for SVd *vs.* Vd in favour of SVd, from 0.63 to 0.55 (95% CI: 0.28 – 1.08); median OS of 36.7 months and 25.8 for SVd and Vd arms, respectively. Using the adjusted OS curve for Vd, the Schoenfeld residuals test highlighted a potential violation of proportional hazards assumptions (*P*=0.02); however, visual inspection of log-log plots for either arm (Figure 16) did not show clear signs of non-parallelism between the curves. As Schoenfeld residual tests for broader and more populated samples of the BOSTON population did not suggest a proportional hazards violation (*P*=0.20 in the 2L+ (ITT) population; *P*=0.16 in the 3L+ population,[83] jointly-fitted distributions were considered appropriate to use in the base case.

Figure 16 Log-log and Schoenfeld residual plots: overall survival (BOSTON 3L)



Source: Data on file[59]

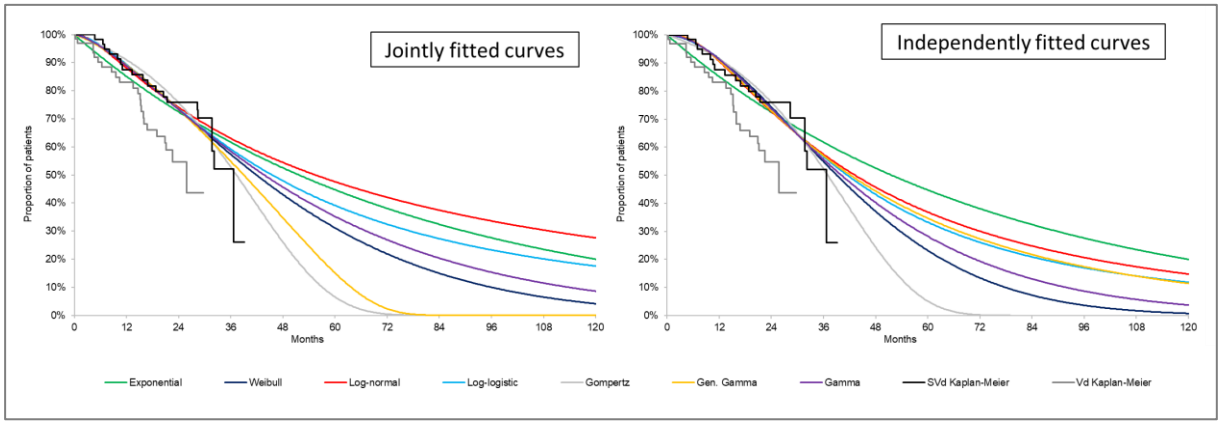
Parametric curves fitted to patients in the SVd arm are shown over the first 10-years of extrapolation in Figure 17. Landmark survival estimates corresponding to each curve and the underlying Kaplan-Meier curve are provided data in Table 24**Error! Reference source not found.** alongside Akaike Information Criterion (AIC) and Bayesian Information Critierion (BIC) measures of statistical fit. Of the parametric curves explored, the Weibull distribution provided the closest statistical fit to OS data based on AIC and BIC, although the small range of values for each measure (AIC ranging from 216.9 to 218.7 across curves; BIC from 220.2 to 224.6) suggests little informative difference. In terms of visual fit, all curves appear reasonably well aligned to the Kaplan-Meier curve over the first 24 months from baseline, beyond which numbers of observed data are heavily impacted by right censoring and greater separation across curves is evident.

Without a clear ranking in terms of statistical fit, curve selection for the base case focuses largely on clinical interpretation: in particular, how well each extrapolation corresponds to clinicians' expectations around landmark survival rates beyond the trial period. Presented with OS curves fitted to the 2L/ 3L BOSTON population at an Advisory Board meeting for SVd held in May 2022, the two myeloma experts present (both UK based Consultant Haematologists) suggested that while it was difficult for a single survival estimate to be identified as most the plausible, reasonable assessments could be made as to which could be ruled out based on implausible OS extrapolations.

For a 2L or 3L population, myeloma expert opinion was that extrapolations exceeding 10% survival at 10 years were unlikely to be credible based on current evidence, as were those suggesting 0% survival at the same time point. Applying an expected 1-10% OS range to 3L curve selections narrowed the range of curves to the Weibull (4% alive at 10 years) or gamma (9% alive). Of these, the Weibull had the better statistical fit based on AIC and BIC and was selected for the 2L base case.

Curve selection was also validated in terms of the consistency between extrapolation assumptions in the 3L and 2L analyses: specifically, to ensure that OS assumed in the 3L should not exceed that assumed in the earlier line (2L) analysis. Clinical feedback sought at the Advisory Board related to a combined 2L/ 3L population (at the time the distinction between 2L and 3L positionings for SVd to reflect current and future treatment pathway expectations was not being made). As that the 10-year survival estimate of 1-10% of patients corresponded to the overall 2/3L population, the gamma extrapolation (9% survival at 10 years) is a likely over-estimate in the context of 3L patients only, and difficult to reconcile with the levels assumed in the 2L analysis (Section B3.4.2.1).

Figure 17 Parametric curves: overall survival (BOSTON 3L)



Source: Data on file[59]

Table 24 Summary landmark and goodness of fit information: parameterised SVd overall survival curves (BOSTON 3L)

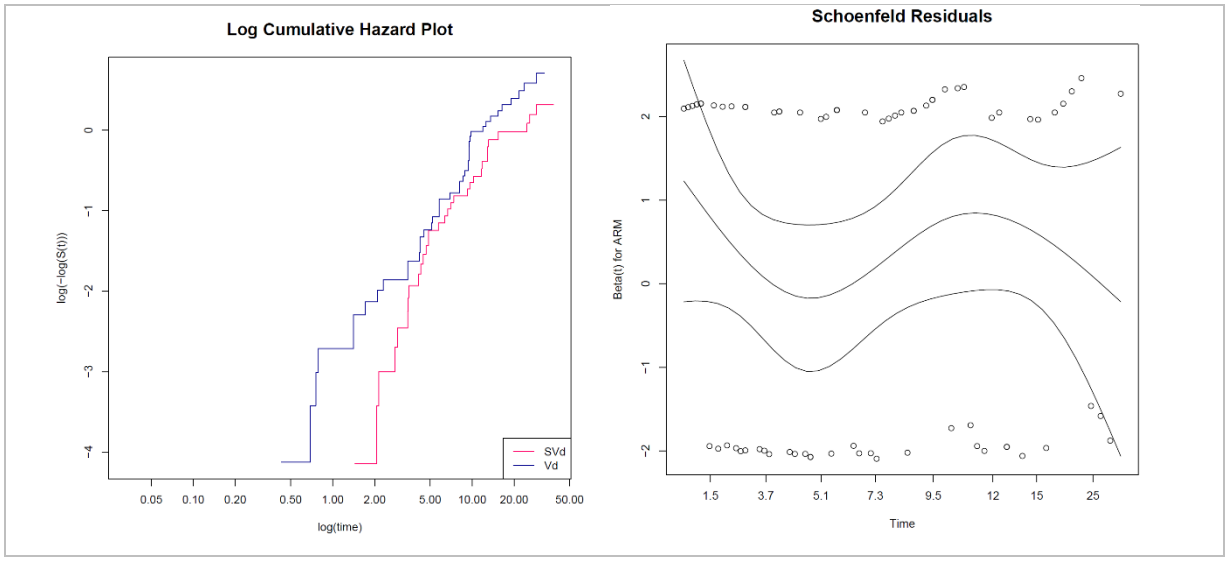
	Statistical fit				Summary survival				
	AIC	BIC	Sum	Rank	Medianmonths	1Y	2Y	5Y	10Y
Kaplan-Meier	-	-	-	-	36.7	88%	76%	-	-
Jointly fitted curves									

	Statistical fit				Summary survival				
	AIC	BIC	Sum	Rank	Medianmonths	1Y	2Y	5Y	10Y
Exponential	426.1	431.8	857.8	6	51.7	85%	72%	45%	20%
Weibull	421.7	430.3	852.0	2	42.1	89%	73%	31%	4%
Lognormal	429.4	438.0	867.3	7	55.7	88%	74%	48%	28%
Loglogistic	423.4	432.0	855.4	4	45.5	89%	73%	39%	18%
Gompertz	419.4	428.0	847.4	1	37.5	91%	76%	7%	0%
Generalised Gamma	422.4	433.9	856.3	5	39.1	89%	73%	15%	0%
Gamma	422.5	431.1	853.6	3	43.9	89%	73%	35%	9%
Independently fitted curves									
Exponential	218.3	220.2	438.5	4	51.5	85%	73%	45%	20%
Weibull	216.9	220.8	437.7	1	38.9	92%	74%	23%	1%
Lognormal	219.9	223.8	443.7	7	43.2	91%	73%	37%	15%
Loglogistic	217.7	221.7	439.4	5	41.4	91%	74%	33%	12%
Gompertz	217.0	220.9	437.9	2	36.8	91%	76%	5%	0%
Generalised Gamma	218.7	224.6	443.4	6	42.1	91%	73%	35%	11%
Gamma	217.2	221.1	438.3	3	40.0	91%	74%	28%	4%
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Y, year; 3L, third-line									

B3.4.1.2 ***Progression-free survival – 3L***

At 3L, participants receiving SVd had a numerically longer PFS (median 12.9 months) than those receiving Vd (median 9.4 months, HR=0.75, P=0.121). Proportional hazards were assumed to hold based on the Schoenfeld residuals test (p=0.10) and log-log / Schoenfeld residual plots (Figure 18), and jointly-fitted curves were therefore applied in the base case analysis.

Figure 18 Log-log and Schoenfeld residual plots: progression-free survival (BOSTON 3L)

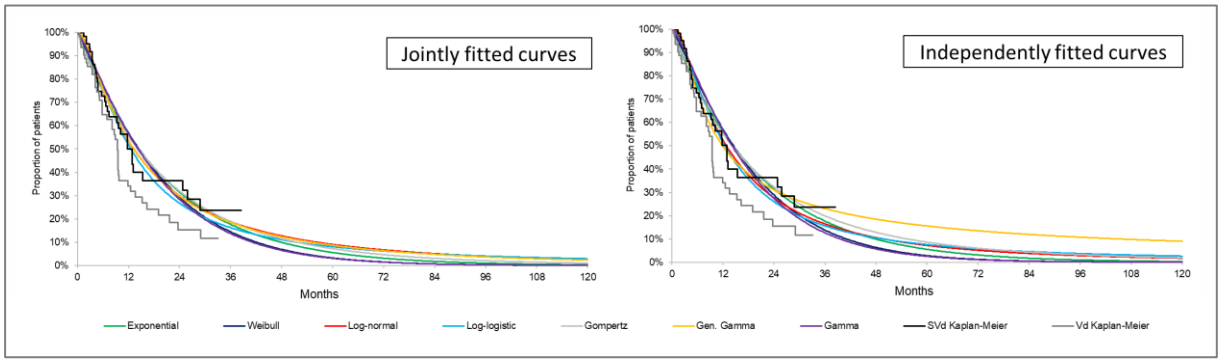


Source: Data on file

Parametric curves fitted to patients in the SVd arm and extrapolated over a 10-year time horizon are shown in Figure 19, with AIC and BIC measures and landmark extrapolation estimates shown in Table 25.

Relative to the parametric curves fitted to OS, all the PFS extrapolations were more closely aligned, with implied 10-year PFS ranging from 0.1% (Weibull) to 2.9% (log-logistic). Since all fell within the expected range based on clinical opinion elicited during the May 2023 Advisory Board meeting (suggesting that a 10-year progression-free survival would be uncommon but not implausible), the lognormal curve is applied in the base case analysis as the highest-ranking distribution in terms of both AIC and BIC (AIC 551.7 from a range of 551.7 to 560.0; BIC 560.3 from a range of 560.3 to 568.6).

Figure 19 Parametric curves: progression-free survival (BOSTON 3L)



Source: Data on file

Table 25 Summary landmark and goodness of fit information: parameterised progression-free survival curves (BOSTON 3L)

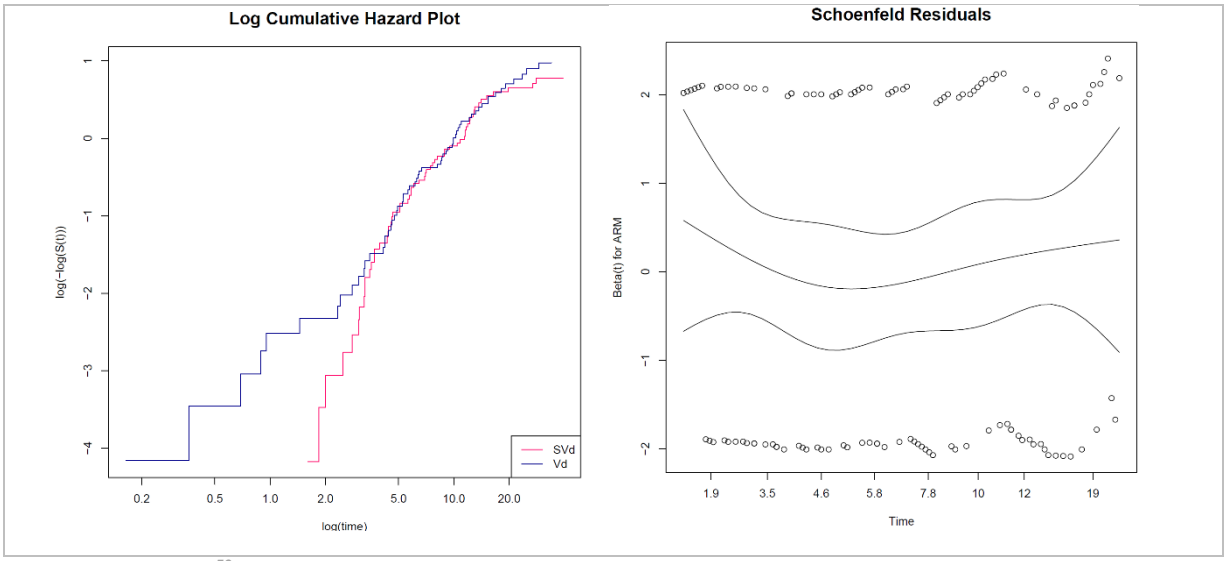
	Statistical fit				Summary survival				
	AIC	BIC	Sum	Rank	Median months	1Y	2Y	5Y	10Y
Kaplan-Meier	-	-	-	-	12.9	50%	36%	-	-
Jointly fitted curves									
Exponential	558.1	563.9	1122.0	4	14.3	56%	32%	6%	0%
Weibull	558.6	567.1	1125.7	6	14.3	57%	29%	3%	0%
Lognormal	551.7	560.3	1112.0	1	13.1	54%	30%	9%	3%
Loglogistic	552.1	560.7	1112.8	2	12.4	52%	27%	8%	3%
Gompertz	560.0	568.6	1128.6	7	14.3	56%	32%	7%	1%
Generalised Gamma	553.7	565.1	1118.8	3	13.1	54%	30%	9%	2%
Gamma	557.3	565.9	1123.2	5	14.0	57%	28%	3%	0%
Independently fitted curves									
Exponential	252.1	254.2	506.3	4	14.3	56%	32%	6%	0%
Weibull	253.1	257.4	510.5	6	14.3	57%	29%	3%	0%
Lognormal	245.9	250.2	496.1	1	12.6	53%	28%	7%	2%
Loglogistic	248.0	252.3	500.3	3	12.4	52%	26%	8%	3%
Gompertz	253.9	258.3	512.2	7	14.0	55%	32%	9%	2%
Generalised Gamma	244.9	251.4	496.4	2	11.7	50%	31%	16%	9%
Gamma	252.0	256.4	508.4	5	14.3	56%	32%	6%	0%

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Y, year; 3L, third-line

B3.4.1.3 Time on treatment – 3L

The Schoenfeld residuals test found that the proportional hazards assumption may hold between the treatment arms (p-value=0.62) and jointly-fitted curves were therefore considered in the base case analysis. Parametric curves fitted to the ToT endpoint are shown for the SVd arm in Figure 21 with summary information in Table 26.

Figure 20 Log-log and Schoenfeld residual plots: time on treatment (BOSTON 3L)

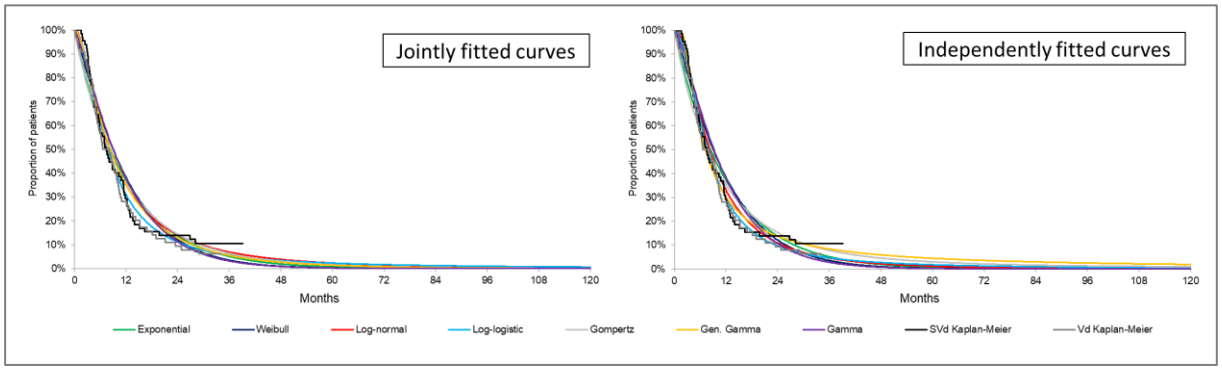


Source: Data on file[59]

In terms of AIC and BIC measures, the log-logistic curve provided the closest statistical fit to observed patient data, ranking highest in both measures (AIC 792.6, range 792.6 to 813.6; BIC 801.2, range 801.2 to 822.1). In terms of visual fit compared to other parametric curves, the log-logistic also provided better alignment with the Kaplan-Meier curve from approximately 12 months post baseline.

Clinical opinion received from the two myeloma experts at the Advisory Board suggested that continued treatment at 10 years was in theory possible provided that patients had not progressed and side-effects of treatment were managed, although numbers would be expected to be extremely low and correspond to only a portion of those progression-free at the same time point. Based on statistical and visual fit and the logical cap of ToT by disease progression, a log-logistic curve is applied in the base case.

Figure 21 Parametric curves: SVd time on treatment (BOSTON 3L)



Source: Data on file[59]

Table 26 Summary landmark and goodness of fit information: parameterised time on treatment curves (BOSTON 3L)

	Statistical fit				Summary survival				
	AIC	BIC	Sum	Rank	Median months	1Y	2Y	5Y	10Y
Kaplan-Meier	-	-	-	-				-	-
Jointly fitted curves									
Exponential	812.2	817.9	1122.0	4	8.3	37%	14%	1%	0%
Weibull	811.2	819.8	1125.7	6	9.0	38%	12%	0%	0%
Lognormal	800.5	809.1	1112.0	1	8.0	35%	14%	2%	0%
Loglogistic	792.6	801.2	1112.8	2	7.6	31%	11%	2%	1%
Gompertz	813.6	822.1	1128.6	7	7.8	36%	15%	2%	0%
Generalised Gamma	801.2	812.7	1118.8	3	8.3	35%	13%	1%	0%
Gamma	807.9	816.5	1123.2	5	9.0	38%	11%	0%	0%
Independently fitted curves									
Exponential	407.2	409.4	506.3	4	8.3	37%	14%	1%	0%
Weibull	407.6	412.0	510.5	6	9.0	38%	12%	0%	0%
Lognormal	390.1	394.4	496.1	1	8.0	33%	11%	1%	0%
Loglogistic	389.9	394.2	500.3	3	7.6	30%	10%	2%	0%
Gompertz	407.9	412.3	512.2	7	7.6	35%	15%	3%	1%
Generalised Gamma	384.7	391.3	496.4	2	7.1	30%	14%	4%	2%
Gamma	404.6	409.0	508.4	5	9.2	38%	11%	0%	0%

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Y, year; 3L, third-line

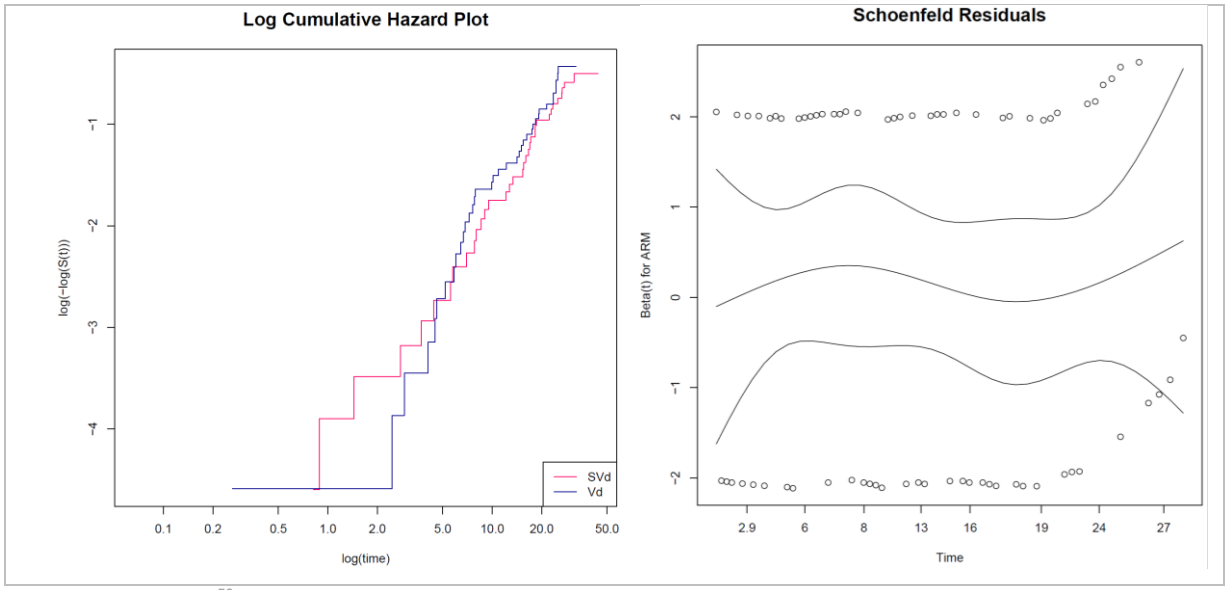
B3.4.2 Second line (2L) analysis of BOSTON time-to-event data: OS, PFS and time on treatment (ToT)

PFS, OS and ToT endpoints corresponding to patients treated with SVd after one prior therapy (i.e., those receiving SVd at 2L) were derived from patient-level data from the 15th February 2021 data cut of the BOSTON trial. As with the 3L analyses, parametric curves (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) were fitted both jointly and independently between SVd and Vd arms to extrapolate outcomes beyond the trial period.

*B3.4.2.1 **Overall survival** – 2L*

In keeping with the 3L analysis, OS data from BOSTON corresponding to the 2L population were adjusted using a two-stage estimation (TSE) approach to remove the effect of crossover from Vd to SVd (affecting 30 out of 99 patients at 2L). Following this adjustment, the Schoenfeld residuals test suggested that proportional hazards may hold between the treatment arms with a p-value of 0.49 (Figure 22). Jointly-fitted curves were therefore used for base case selection.

Figure 22 Log-log and Schoenfeld residual plots: overall survival (BOSTON 2L)



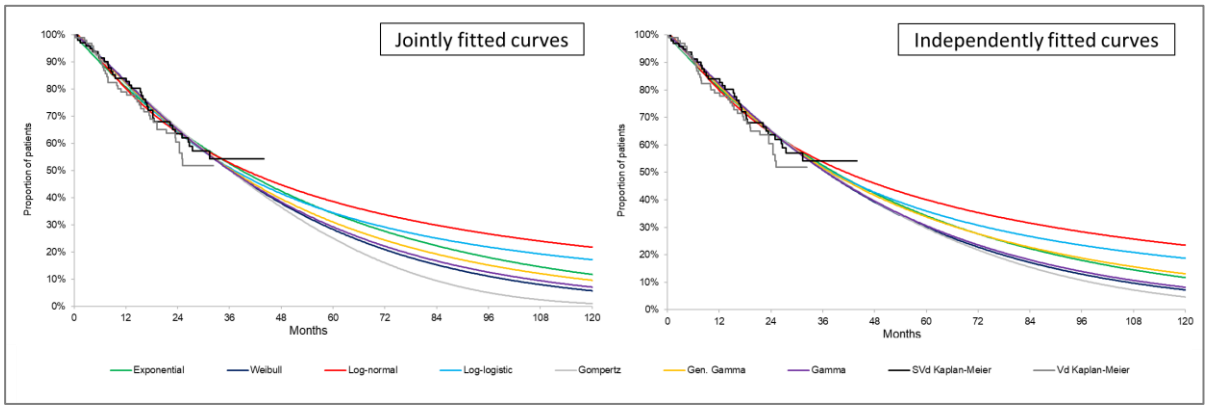
Source: Data on file[59]

Parametric curves for OS fitted to 2L patients in the SVd arm are shown for the first 10 years of extrapolation in Figure 23, with statistical fit data presented in Table 27. From a statistical standpoint, the exponential curve was the best fitting in terms of combined AIC and BIC ranking, followed by the log-logistic. AIC and BIC measures showed little

numerical difference between curves, however, and similarly close approximations of 1- and 2-year survival rates derived from the Kaplan-Meier curve for the SVd arm.

Applying the same set of clinical responses as considered in the 3L setting, exponential, log-normal and log-logistic curves were excluded based on extrapolated 10-year survival rates in excess of 20% of the patient population. Further, the 10-year survival rate of 1% estimated using the Gompertz was considered likely to be a too pessimistic extrapolation for a 2L only setting, given that expected range of 1-10% survival at 10 years elicited from clinical experts was provided in the context of a combined 2L and 3L patient population. Of the remaining curves considered (gamma, generalised gamma and Weibull), the gamma was best fitting and selected in the base case, with an extrapolated estimate of 7% survival at 10 years.

Figure 23 Parametric curves: overall survival (BOSTON 2L)



Source: Data on file[59]

Table 27 Summary landmark and goodness of fit information: parameterised overall survival curves (BOSTON 2L)

	Statistical fit				Summary survival				
	AIC	BIC	Sum	Rank	Medianmonths	1Y	2Y	5Y	10Y
Kaplan-Meier	-	-	-	-	NR	84%	64%	-	-
Jointly fitted curves									
Exponential	703.6	710.2	1413.7	1	38.6	81%	65%	34%	12%
Weibull	703.2	713.1	1416.2	4	36.1	83%	65%	28%	6%
Lognormal	705.9	715.7	1421.6	6	39.6	80%	64%	39%	22%
Loglogistic	702.8	712.7	1415.5	2	37.0	82%	64%	34%	17%
Gompertz	704.6	714.4	1419.0	5	36.1	83%	66%	25%	1%
Generalised Gamma	704.9	718.1	1423.0	7	36.6	82%	65%	31%	10%
Gamma	703.0	712.9	1415.9	3	36.1	83%	65%	29%	7%
Independently fitted curves									

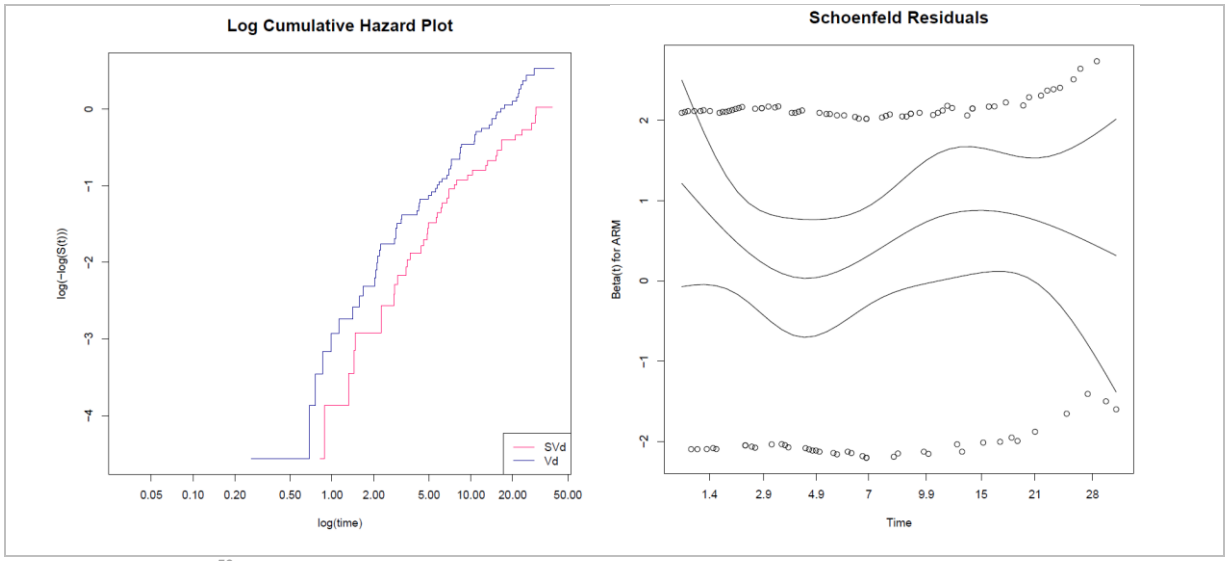
Exponential	343.6	346.2	689.9	1	38.6	81%	65%	34%	12%
Weibull	345.0	350.2	695.2	4	36.6	82%	65%	30%	7%
Lognormal	345.6	350.8	696.5	6	41.4	80%	65%	40%	23%
Loglogistic	344.7	349.9	694.6	2	38.2	82%	65%	36%	19%
Gompertz	345.5	350.7	696.2	5	37.3	82%	65%	30%	5%
Generalised Gamma	346.8	354.6	701.4	7	37.7	82%	65%	34%	13%
Gamma	344.9	350.1	695.1	3	36.8	82%	65%	31%	8%
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; NR, not reported; Y, year; 2L, second-line									

B3.4.2.2 ***Progression-free survival – 2L***

Median PFS in the 2L population, shown as a Kaplan-Meier curve in section B2.6.1.2 was 21.0 months in the SVd arm; significantly longer at the 5% level than the 10.7-month median observed in the Vd arm of BOSTON (HR=0.62, *P=0.01)*.[59]

The Schoenfeld residual test suggested a potential violation of proportional hazards assumption (*P*=0.012). Although this could not be corroborated from the log-log plots (log cumulative hazard curves for either arm, shown in Figure 24, appear reasonably parallel), tests for proportional hazards in the larger 2L+ (ITT) population of BOSTON also suggested possible violations for PFS, to a greater level of significance (*P*=0.003). For the base case, therefore, independently-fitted curves were considered most appropriate.

Figure 24 Log-log and Schoenfeld residual plots: progression-free survival (BOSTON 2L)

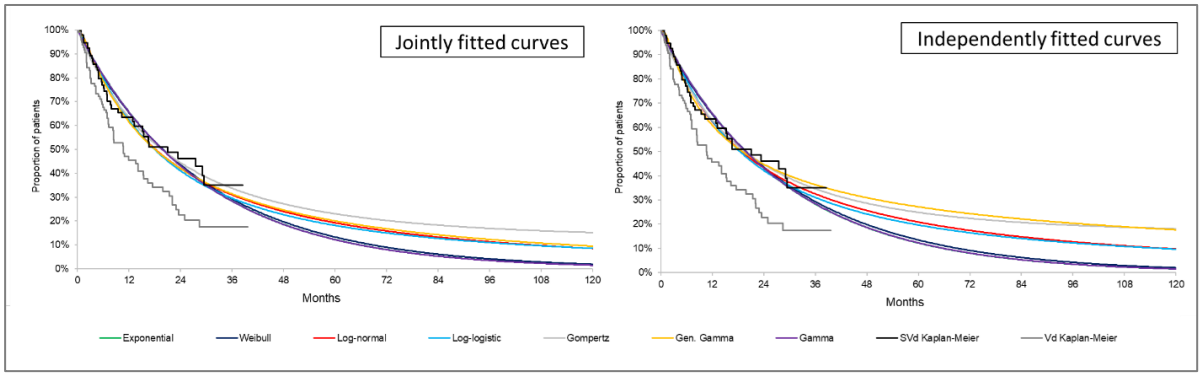


Source: Data on file[59]

Parametric curves fitted to PFS in the SVd arm are shown over the first 10 years of extrapolation in Figure 25. AIC and BIC values are shown in Table 28. As was shown in the 3L analysis, parametric curves performed similarly well in terms of statistical fit and visual correspondence to the Kaplan-Meier curve observed for PFS in the 2L subgroup of the BOSTON SVd population.

Lognormal, log-logistic, Gompertz and generalised gamma curves all yielded 10-year PFS exceeding the extrapolations selected for OS and were therefore excluded from the shortlist of base case curves as likely over-estimates. Despite nominally different AIC and BIC values, the extrapolations for exponential, Weibull and gamma distributions were nearly identical. With little further informative basis for ranking, the gamma distribution was considered based on alignment with the curve selection made for OS.

Figure 25 Parametric curves: progression-free survival (BOSTON 2L)



Source: Data on file[59]

Table 28 Summary landmark and goodness of fit information: parameterised progression-free survival curves (BOSTON 2L)

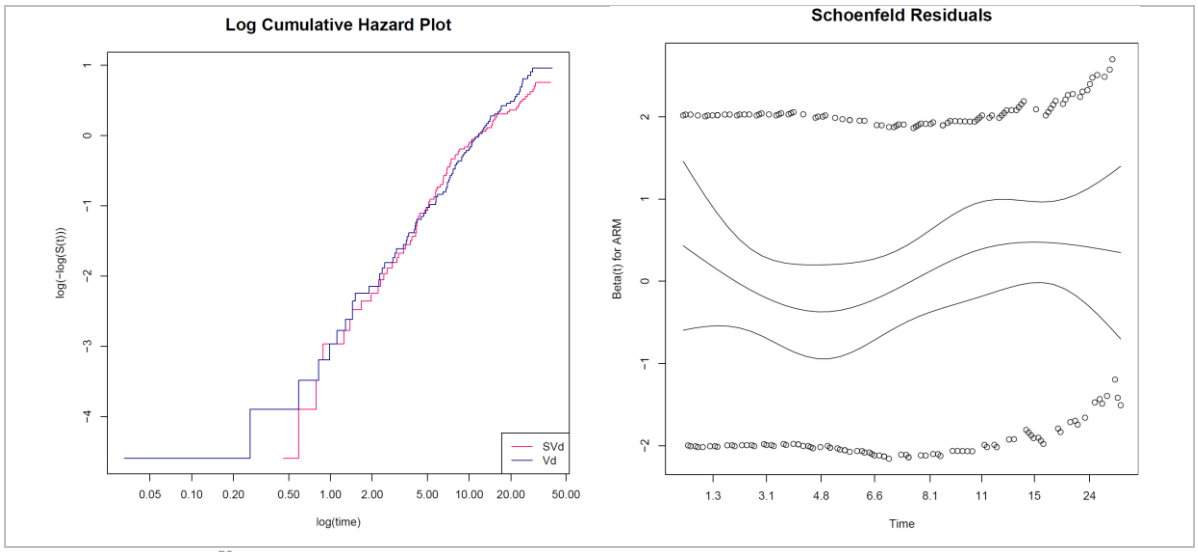
	Statistical fit				Summary survival				
	AIC	BIC	Sum	Rank	Medianmonths	1Y	2Y	5Y	10Y
Kaplan-Meier	-	-	-	-	21.0	64%	46%	-	-
Jointly fitted curves									
Exponential	826.0	832.6	1658.7	4	19.8	66%	43%	12%	1%
Weibull	827.9	837.7	1665.6	6	19.8	65%	44%	13%	2%
Lognormal	819.0	828.8	1647.8	1	18.2	62%	42%	19%	8%
Loglogistic	822.4	832.2	1654.6	2	17.9	62%	41%	18%	9%
Gompertz	825.2	835.0	1660.2	5	19.5	63%	45%	23%	15%
Generalised Gamma	820.9	834.0	1654.9	3	17.9	62%	42%	20%	9%
Gamma	826.0	832.6	1658.7	4	19.5	66%	43%	12%	1%

Independently fitted curves									
Exponential	350.2	352.8	703.0	3	19.8	66%	43%	12%	1%
Weibull	352.1	357.3	709.4	6	19.8	65%	44%	13%	2%
Lognormal	346.6	351.8	698.3	1	18.6	62%	43%	21%	10%
Loglogistic	349.1	354.3	703.3	4	18.4	63%	42%	20%	10%
Gompertz	350.5	355.7	706.2	5	19.5	63%	45%	25%	18%
Generalised Gamma	347.3	355.0	702.3	2	18.9	61%	45%	27%	18%
Gamma	352.1	357.8	709.6	3	19.8	66%	43%	12%	1%
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Y, year; 2L, second-line									

B3.4.2.3 Time on treatment -2L

Median ToT was similar between arms, at 7.39 months in the SVd arm and 8.34 months in the Vd arm (HR=0.90 95% CI:0.81–1.52). Proportional hazards assessments suggested that assumptions may hold (*P*=0.494; Figure 26) and jointly-fitted curves were therefore used for base case selection.

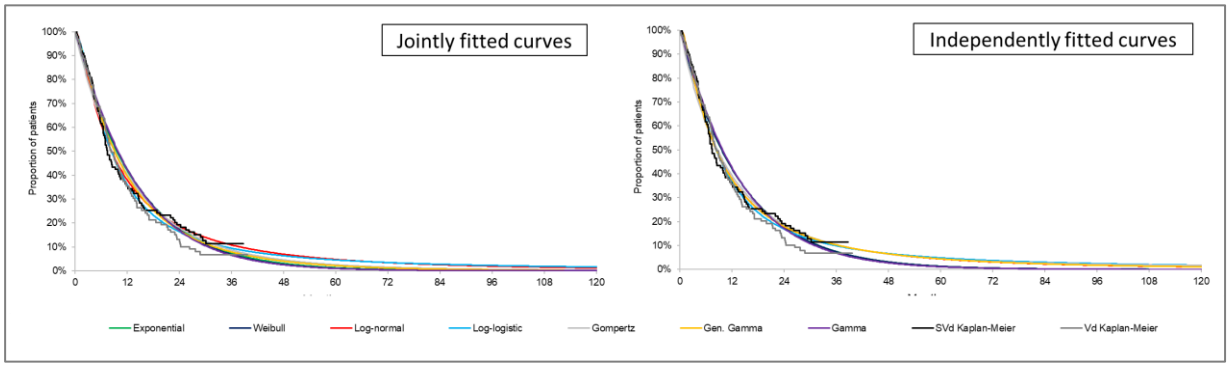
Figure 26 Log-log and Schoenfeld residual plots: time on treatment (BOSTON 2L)



Source: Data on file[59]

Parametric curves fitted to time on treatment KM curves for the 2L population of BOSTON are shown in Figure 27, with summary information in Table 29. In keeping with the 3L analysis, Kaplan-Meier data were mature, and parametric curves showed very little variation in terms of statistical fit or the extrapolated number of patients remaining on treatment at landmark time points. With low sensitivity in terms of the area under the curve corresponding to each, and little further basis for selection, the gamma curve was selected in the base case on the grounds of consistency with OS and PFS selections.

Figure 27 Parametric curves: SVd time on treatment (BOSTON 2L)



Source: Data on file[59]

Table 29 Summary landmark and goodness of fit information: parameterised time on treatment curves (BOSTON 2L)

	Statistical fit				Summary survival				
	AIC	BIC	Sum	Rank	Medianmonths	1Y	2Y	5Y	10Y
Kaplan-Meier	-	-	-	-	7.4	35%	19%	-	-
Jointly fitted curves									
Exponential	1280.5	1287.1	1658.7	4	9.4	42%	18%	1%	0%
Weibull	1282.0	1291.9	1665.6	6	9.7	43%	17%	1%	0%
Lognormal	1285.0	1294.9	1647.8	1	8.3	38%	19%	5%	1%
Loglogistic	1274.1	1284.0	1654.6	2	8.3	36%	16%	5%	2%
Gompertz	1281.5	1291.4	1660.2	5	9.0	41%	18%	3%	0%
Generalised Gamma	1278.1	1291.2	1654.9	3	9.0	40%	17%	2%	0%
Gamma	1281.1	1290.9	1666.0	7	9.9	43%	17%	1%	0%
Independently fitted curves									
Exponential	633.2	635.8	703.0	3	9.4	42%	18%	1%	0%
Weibull	635.2	640.4	709.4	6	9.4	42%	18%	1%	0%
Lognormal	625.8	631.0	698.3	1	8.3	38%	18%	4%	1%
Loglogistic	625.6	630.8	703.3	4	8.3	37%	17%	5%	2%
Gompertz	632.9	638.1	706.2	5	8.5	39%	19%	4%	2%
Generalised Gamma	627.8	635.6	702.3	2	8.3	38%	18%	4%	1%
Gamma	634.8	640.0	709.6	7	9.7	43%	17%	1%	0%

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Y, year; 2L, second-line

B3.4.3 Indirect treatment comparisons

Comparator OS and PFS are estimated by applying HRs, derived from NMAs described in section B2.9, to the parametric curves of the SVd arm. Due to the lack of comparator data for ToT, duration of treatment for comparators is estimated by applying the HR for PFS to the SVd ToT curve from BOSTON, reflecting an assumption that similar relativities across treatments exist with regard to treatment duration as for disease progression.

In the absence of a NMA specific to 3L patients only, the CEA used HRs estimated from an NMA conducted in a 3L+ setting, identified by myeloma experts as a suitable proxy during an ITC validation exercise (Appendix N). Importantly, the NMA considered 3L+ patients from BOSTON as well as from comparator studies. Hence, the potential limitation of this approach is around the generalisability of 3L+ HRs to 3L, rather than any bias resulting from an imbalanced ITC estimate. HRs applied in the 2L analysis were taken from NMA results that were directly equivalent (comparing BOSTON 2L data against the other 2L study population).

NMA results using both fixed effects (FE) and random effects (RE) approaches were considered in the economic analysis, with RE results applied in the base case to control for unobserved differences assumed to exist between trials. From each NMA, HRs *versus* SVd estimated in 20,000 simulations were included in the CEM as convergence output and diagnosis analysis (CODA). Median sampled values were applied in the deterministic base analysis, and 2.5% and 97.5% percentiles from the simulations used for one-way sensitivity analyses (OWSA).

Time-varying hazard ratios were explored for PFS and OS by fitting first-order fractional polynomial (FP) estimates (relaxing proportional hazards assumptions) in the 3L+ analysis. Difficulties in achieving convergence were encountered, potentially due to the limited number of studies to inform each comparison: neither first-order FP estimates in the 2L setting nor second-order estimates in the 3L+ setting are available, therefore the case for non-proportional hazards approaches was explored with health economists and clinical experts at the May 2023 Advisory Board,[36] where it was suggested that time-varying treatment effects would only be expected when comparing between treatments with differing discontinuation rules (treatments administered until disease progression/ toxicity *versus* treatments with a fixed duration).

PFS and OS hazard ratios for SVd *versus* the relevant 3L and 2L comparators are reported in Table 30 and Table 31. Point estimates from the RE models are applied in the base case as the most appropriate estimate of relative efficacy irrespective of confidence interval range, which was found to cross a value of 1.0 in comparisons using either approach. Importantly, this was also the case for pairwise estimates between treatments already in the UK treatment pathway, and the lack of significance was noted by clinicians during the validation of NMA results as common in the context

of MM treatment networks due to the large spread of studies with limited overlapping evidence.

Compared with the population included in the BOSTON trial, those included in several of the comparator studies informing the network (particularly those carried out in less recent years) will have received less effective treatments at 1L/2L. As patients' exposure and refractoriness to prior therapies has a direct influence on response, the limited capacity to control or match populations in an NMA framework mean that this imbalance is likely to lead to an underestimate of the clinical benefit associated with SVd. Subgroup analyses of the BOSTON trial controlling for prior PI treatment / refractoriness to lenalidomide point to likely impact of this potential source of bias: at 2L in particular, NMA focusing on PI-naïve populations (providing a closer alignment between the BOSTON subgroup and comparator studies than in ITT/broader populations) showed superior results *versus* Kd, with PFS hazard ratios of 0.62 and 0.73 favouring SVd.

Table 30 Median, lower, and upper bound HRs (CIs) from the NMA models for PFS and OS in the 3L population

Comparator	PFS HR *vs*. SVd			OS HR *vs*. SVd		
	Median	Lower bound	Upper bound	Median	Lower bound	Upper bound
Random effects model results						
IxaRd	0.95	0.18	4.58	1.06	0.21	5.25
PanoVd	0.80	0.27	2.36	1.25	0.45	3.44
Fixed effects model results						
IxaRd	0.96	0.42	2.22	1.09	0.39	3.03
PanoVd	0.80	0.51	1.25	1.25	0.72	2.17

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; IxaRd, ixazomib plus lenalidomide and dexamethasone; NMA, network meta-analysis; OS, overall survival; PanoVd, panobinostat plus bortezomib and dexamethasone, PFS, progression-free survival; SVd, selinexor plus bortezomib and dexamethasone; 3L, third-line

Table 31 Median, lower, and upper bound HRs (CIs) from the NMA models for PFS and OS in the 2L population

Comparator	PFS HR *vs*. SVd			OS HR *vs*. SVd		
	Median	Lower bound	Upper bound	Median	Lower bound	Upper bound
Random effects model results						
Kd	0.73	0.31	1.67	0.89	0.32	2.45
Fixed effects model results						
Kd	0.73	0.43	1.21	0.88	0.51	1.54

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; Kd, carfilzomib plus dexamethasone; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; SVd, selinexor plus bortezomib and dexamethasone; 2L, second-line

B3.4.4 Adverse events

The model includes estimates of the costs and disutilities associated with Grade 3-4 adverse events that were reported in 5% or more of patients in the BOSTON SVd arm as a conservative approach, AEs in comparator studies were not considered, for example cardiotoxicity had an incidence greater than 5% in the ENDEAVOR but was not considered in the cost effectiveness model, likely underestimating costs associated with Kd and favouring comparators *versus* SVd. To control for between-study differences in the length of follow-up, weekly event rates were estimated assuming a uniform distribution of events over time (Table 32). Base case analysis includes AE-related costs and disutilities applied weekly in the model, a scenario analysis has been performed to explore the impacts of applying all AE effects in the first cycle.

AE rates from BOSTON were based on SVd patients in the safety population (patients at 2L or beyond) and were not estimated separately for 2L and 3L patients.

Table 32 Estimated weekly probabilities of patients experiencing Grade 3+ AEs (≥5%)

	SVd		IxaRd		Kd		PanoVd	
Months follow-up	28.7		85		44.30		6.5	
N	195		361		463		381	
Event	n	Weekly rate	n	Weekly rate	n	Weekly rate	n	Weekly rate
Anaemia	32	0.0013	41	0.0003	80	0.0009	NR	0.0000
Asthenia	16	0.0007	NR	0.0000	NR	0.0000	NR	0.0000

Cataract	22	0.0009	19	0.0001	NR	0.0000	NR	0.0000
Diarrhoea	13	0.0005	36	0.0003	19	0.0002	97	0.0090
Fatigue	26	0.0011	13	0.0001	32	0.0004	91	0.0085
Febrile Neutropenia	1	0.0000	NR	0.0000	NR	0.0000	NR	0.0000
Hypertension	8	0.0003	11	0.0001	69	0.0008	11	0.0010
Hypophosphatenia	11	0.0005	NR	0.0000	NR	0.0000	33	0.0031
Leukopenia	1	0.0000	NR	0.0000	1	0.0000	1	0.0001
Lymphopemia	7	0.0003	NR	0.0000	1	0.0000	1	0.0000
Lower respiratory tract infection	4	0.0002	NR	0.0000	NR	0.0000	NR	0.0000
Nausea	15	0.0006	6	0.0000	NR	0.0000	21	0.0020
Neutropenia	18	0.0007	94	0.0007	12	0.0001	NR	0.0000
Hyperglycaemia	4	0.0002	NR	0.0000	NR	0.0000	NR	0.0000
Peripheral neuropathy	9	0.0004	9	0.0001	11	0.0001	68	0.0063
Pneumonia	28	0.0011	52	0.0004	0.07	0.0000	48	0.0045
Thrombocytopenia	79	0.0032	77	0.0006	58	0.0007	NR	0.0000
Source	BOSTON[56]		TOURMALINE-MM1[69]		ENDEAVOUR[63]		PANORAMA-1[68]	

Abbreviations: AE, adverse event; IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; N, number; NR, not reported; PanoVd, panobinostat plus bortezomib and dexamethasone; SVd, selinexor plus bortezomib and dexamethasone

B3.5 Measurement and valuation of health effects

B3.5.1 Health-related quality of life data from the BOSTON study

EQ-5D data collected in the BOSTON clinical trial is the primary source of HRQoL evidence used to inform health state utility assumptions in the economic analysis for both the 3L and 2L analyses. The EQ-5D-5L instrument was administered at study baseline, at day 1 of each treatment cycle, and at the end of treatment in either arm. To derive estimates of utility, patient-level responses were mapped to the EQ-5D-3L using the algorithm published in Hernandez-Alava *et al*. (2020) as the mapping approach recommended by NICE.[54,84]

Pooled estimates across BOSTON study arms are applied in the base case, to maximise the number of observations informing estimates and reflecting the assumption that HRQoL is independent of treatment regimen, other than through adverse event disutilities (modelled separately to the underlying health state utility values). Utility estimates specific to each treatment arm, with the BOSTON Vd

population as a proxy for HRQoL in treatments other than SVd, are explored as a scenario analysis.

B3.5.1.1 Mapping

To inform the utility regression and align with NICE guidance, EQ-5D-5L measures were mapped to the EQ-5D-3L using the Hernandez-Alava *et al*. (2020) mapping algorithm.[84]

Given that a generic preference-based measure (EQ-5D-5L) was collected in BOSTON, mapping from a disease specific measure (e.g., EORTC-QLQ-C30) to a generic preference-based measure to obtain utility values was not necessary.

B3.5.1.2 Health state utility estimation

Utility values corresponding to model health states were estimated from the mapped EQ-5D-3L values using mixed effects models (described in more detail in Appendix M). Patient-level characteristics including sex, age, race, years since diagnosis, baseline ECOG score, baseline EQ-5D-3L value, treatment arm and progression status were explored as covariates, and backwards stepwise regression methods used to identify the final list of variables. The final model (Table 33), determined on the basis of statistical goodness-of-fit according to AIC, BIC, and log-likelihood score, included treatment arm, age, baseline ECOG, baseline EQ-5D-3L and progression status as variables.

Table 33 Random effects model coefficients

	Coefficient	**Standard Error**	**F-value**	**Pr(>F)**
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.

Notes: Random effects standard deviations: Subject ID 0.1212; Visit number 0.0075. AIC: -3987.15 BIC: -3899.40 Log-likelihood: 2007.57

In the base case for both the 3L and 2L cost effectiveness analyses, utilities are based on observations pooled across both arms of BOSTON and assumed to be generalisable across model comparators. Utility values are assumed to be the same for both 3L and 2L populations; observations for each individual subgroup in the BOSTON trial were too low to produce unbiased results, hence the utility regression equation included data using the whole ITT population. The resulting equation to estimate the utility score is:

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

B_1=Arm (Vd)

β_2=Age

β_3=Baseline ECOG

β_4=Baseline EQ-5D-3L

β_5=PFS Status (Y)

Base case model baseline age and ECOG values yield a predicted utility score of 0.697 for the progression-free health state and 0.660 for progressed disease. The CEM includes an option to apply treatment-specific utilities for SVd *versus* all other comparators (which are assumed equal to Vd in this scenario) or to average these utilities across treatment arms (Table 34).

Table 34 Model heath state utility values by treatment

	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			

Age-related decrements are applied using the coefficient estimated in the RE model with all other parameters held at baseline values. A scenario analysis explored the use of age-related decrements from Ara and Brazier as an alternative source.[85]

B3.5.2 Health-related quality-of-life studies

The economic SLR conducted in RRMM, described in Section B3.2 (and Appendix G), identified published records of utility and/ or disutility values in RRMM populations. The BOSTON trial collected EQ-5D data directly, which has been applied in the economic modelling as described in Section B3.5.1, with additional published records used to add supportive evidence, fill data gaps, and validate assumptions. One such additional study was Hatswell *et al.* (2019),[86] an SLR of utility values across all lines of MM, with an elicitation of EQ-5D-3L utility values from the APEX study and EMMOS registry (as regression-based estimates using a UK tariff), and a network meta-analysis using the utility values identified. Mean utilities were estimated from the meta-regression analysis in all lines of MM, with a variety of models considering alternative valuation approaches presented (including results that considered EQ-5D utility values only). Utility estimates from Model 2 of this study (Table 35) were referenced as a key evidence source in several other records identified in the economic SLR, and provide a useful benchmark for assessing the face validity of utility estimates as well as an alternative source of estimates for the economic model in the absence of line-specific estimates from the BOSTON study. Utility estimates applied in previous NICE TAs in RRMM relevant to the decision problem have been examined as a further source of validation for the model base case utilities (Table 36). These show that BOSTON health state utility values are within the expected range of values previously used in NICE TAs with a marginal difference between utility values applied at 2L and 3L.

Table 35 Hatswell et al. (2019) Model 2 utility analysis

Hatswell *et al.* (2019) study[86]	**Utility values (95% CI)**
Model 2 – EQ-5D only [meta-analysis model parameters]	Second line: 0.620 (0.590, 0.650) Third line: 0.606 (0.561, 0.630) Fourth line: 0.494 (0.403, 0.570) Stem cell transplant: 0.066 (0.056, 0.170)
Abbreviations: CI, confidence interval; EQ-5D, EuroQol five dimension	

Table 36 Utility values identified in NICE TAs relevant to the economic model

PF utility values	**PD utility values**	**Source**
2L		
Cycles 1-2; Range 0.714 – 0.737	Range: 0.638 – 0.698	NICE GID-TA11060/[87] NICE TA897 (2023) [DaraVd];[29] NICE TA695 (2021) [KRd];[80] NICE TA657 (2023) [Kd].[72]

Cycles 3+; Range: 0.714 – 0.761		
2L+		
Range: 0.679 (SD 0.182) – 0.720 (SD 0.200) VGPR+: 0.712 PR: 0.674 Stable disease: 0.653	PD: 0.654	NICE TA380 (2016) [PanoVd];[71] NICE TA870 (2023) [IxaRd].[28]
3L		
Cycles 1-2; Range: 0.690 Cycles 3+; Range: 0.689 – 0.699	Range: 0.637	NICE TA657 (2023) [Kd][72]
3L+		
On-treatment; Range: 0.75 - 0.77 Off-treatment; Range: 0.65 - 0.67 [EQ-5D values only]	Range: 0.61 – 0.63 [EQ-5D values only]	NICE TA427 (2017) [Pd][88]
Abbreviations: AE, adverse event; DaraVd, daratumumab plus bortezomib and dexamethasone; EQ-5D, EuroQol five dimension; GID, guidance in development; IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; KRd, carfilzomib plus lenalidomide and dexamethasone; NICE, National Institute for Health and Care Excellence; PanoVd, panobinostat plus bortezomib and dexamethasone; Pd, pomalidomide plus dexamethasone; PD, progressed disease; PF, progression-free; PR, partial response; SD, standard deviation; TA, technology appraisal; VGPR, very good partial response; 2L, second-line; 3L, third-line		

Appendix H provides further detail on identified sources of both utility values and disutilities that were considered for relevance to this decision problem. Utility values used for base or scenario model estimates are summarised in Section B3.5.3 and the disutilities applied in the economic model reported in Section B3.5.4.

B3.5.3 Health-related quality-of-life data used in the cost-effectiveness analysis

The model base case assumes a pre-progression utility value of 0.697 and a post-progression value of 0.660, corresponding to the treatment-independent estimates from BOSTON described in Section B3.5.1.2. Scenario analyses explore the substitution of BOSTON utilities with line-specific utility estimates from published literature (e.g., Hatswell *et al.* 2019)[86] identified in the economic SLR. The inclusion of general population age related utility decrements are also explored in scenario analysis.

B3.5.4 Adverse reactions

Active treatment of RRMM can result in a variety of adverse events (AEs). Treatment-emergent Grade 3+ AEs occurring in ≥5% of patients in either treatment arm of the BOSTON study were included in the economic analysis. In total 17 adverse events were included in the CEM. The HRQoL impacts of these AEs have been captured in the model as weekly utility decrements for patients in each treatment arm. The associated utility decrements and duration of each AE in weeks have been taken from a variety of published sources and previous NICE appraisals, or by assumption where no values from other sources have been identified (Table 37).

Table 37 Adverse Event Utility Decrements

AE description	Utility decrement	Utility decrement source	AE duration (Weeks)	AE duration source
Anaemia	-0.31	NICE TA897 [previously TA573],[29] NICE GID-TA11060,[87] NICE TA695[80]	1.53	NICE TA897 [previously TA573],[29] NICE GID-TA11060,[87] NICE TA695[80]
Asthenia	-0.12	NICE TA658[89]	2.09	Assumed equal to fatigue
Cataract	-0.14	NICE TA695[80]	26.09	NICE TA695[80]
Diarrhoea	-0.10	Jakubowiak *et al*. (2016),[90] NICE TA783[91]	1.00	Assumption
Fatigue	-0.12	NICE GID-TA11060,[87] NICE TA897 [previously TA573],[29] NICE TA695,[80] Nikolaou *et al.* (2021)[92]	2.09	NICE GID-TA11060,[87] NICE TA897 [previously TA573],[29] NICE TA695[80] Jakubowiak *et al*. (2016)[90]
Febrile neutropenia	-0.15	Jakubowiak *et al.* (2016)[90]	1.89	Assumed equal to neutropenia
Hyperglycaemia	0.00	Assumption	0.00	Assumption
Hypertension	0.00	NICE TA897,[29] NICE GID-TA11060,[87] NICE TA695[80]	0.00	NICE TA897,[29] NICE GID-TA11060,[87] NICE TA695[80]
Hypophosphatemia	0.00	NICE TA695[80]	0.00	NICE TA695[80]
Leukopenia	0.00	NICE GID-TA10568,[93] NICE TA783,[91] Nikolaou *et al.* (2021)[92]	0.00	Assumption
Lymphopenia	-0.07	NICE GID-TA11060,[87] NICE TA695,[80] NICE TA897 [previously TA573][29]	2.21	NICE GID-TA11060,[87] NICE TA695,[80] NICE TA897 [previously TA573],[29] Jakubowiak *et al*. (2016)[90]
Lower respiratory tract infection	-0.19	NICE TA783 [lower respiratory infection][91]	1.71	Assumed equal to pneumonia
Nausea	-0.10	Jakubowiak *et al*. (2016),[90] NICE TA658,[89] NICE TA783[91]	1.00	Assumption
Neutropenia	-0.145	NICE TA897 [previously TA573],[29] Nikolaou *et al.* (2021)[92]	1.89	NICE TA897 [previously TA573][29]
Peripheral neuropathy	-0.065	NICE TA897 [previously TA573],[29] NICE GID-TA11060,[87] Jakubowiak *et al*. (2016)[90]	1.14	NICE TA897 [previously TA573],[29] NICE GID-TA11060,[87] Jakubowiak *et al*. (2016)[90]

Pneumonia	-0.19	NICE TA897 [previously TA573],[29] NICE GID-TA11060[87]	1.71	NICE TA897,[29] NICE GID-TA11060[87]
Thrombocytopenia	-0.31	NICE TA897 [previously TA573][29]	2.01	NICE TA897 [previously TA573][29]
Abbreviations: AE, adverse event; GID, guidance in development; NICE, National Institute for Health and Care Excellence; TA, technology appraisal				

Total utility impact of AEs was calculated as the utility decrement weighted by the time to AE resolution, reflecting assumptions around both severity and duration. A scenario analysis is tested applying no utility decrements for adverse events, under the conservative assumption that AEs would incur no HRQoL impact.

B3.6 Cost and healthcare resource use identification, measurement and valuation

The economic analysis was conducted from an NHS and Personal Social Services (PSS) perspective. Resource use estimates for health state costs were sourced from study data and published literature, or assumptions informed or validated through discussions with UK clinical experts where otherwise unavailable.

Standard unit cost sources were used to identify mean cost estimates applicable to each resource type, including the British National Formulary (BNF)[94] and electronic Market Information Tool (eMIT)[95] websites, used to identify the cost of branded and generic drugs, respectively; and NHS reference cost and PSSRU unit cost publications (for costing discrete events and interactions with healthcare professionals such as routine disease monitoring and the treatment of adverse events).[96,97] Where resource and/ or cost estimates were identified from previous MM appraisals (resource use estimates for transfusion, derived from TA427), updated costs were sought using the same or updated cost codes as those provided in the source document.

Costs considered in the cost effectiveness analysis include drug acquisition, administration costs, subsequent therapies, health-state specific resource use, adverse events, and a one-off cost of terminal care. All costs are stated in 2021/22 prices. Any cost estimates prior to 2022 for which a current unit cost has not been identified are inflated using PSSRU 2022 Hospital and Community Health Services (HCHS) pay and price indices.[96]

As described in Section B3.2.1, an economic SLR was conducted to identify publications reporting cost-effectiveness studies, along with cost and resource use and HRQoL/ utility data, in patients with RRMM.[70] While a number of studies across RRMM populations and different countries were identified, cost and resource use data identified in recent NICE technology appraisals were considered the most relevant to inform the economic model. Appendix I reports further detail on the cost and/ or resource use studies identified.

B3.6.1 Intervention and comparators' costs and resource use

Selinexor was administered in the BOSTON trial as an oral 100mg dose (up to a maximum 70mg per m^2), equating to five tablets of 20mg. Selinexor was taken once per week (five times per 35-day cycle). Bortezomib was administered subcutaneously at a dose of 1.3mg/m^2 once weekly on Day 1 for 4 weeks followed by 1 week off; and dexamethasone was administered as a fixed oral 20mg dose twice weekly (10 days of each 35-day cycle).[3]

The acquisition cost for selinexor is £9,200 per 20 units of 20mg tablets (£460 per 20mg tablet) at list price. The dosing regimen of SVd applied in the CEM reflects the SmPC for selinexor and is aligned with the BOSTON clinical trial, whereby selinexor is costed at a dose of 100mg (five tablets of 20mg) on Days 1, 8, 15, 22 and 29 of each 35-day cycle; bortezomib is costed at a dose of 1.3mg/m^2 on days 1, 8, 15 and 22 of each 35-day cycle and dexamethasone is costed at a dose of 20mg on Days 1, 2, 8, 9, 15, 16, 22, 23, 29 and 30 of each 35-day cycle.[3,56] Nausea is a common side effect of Selinexor, ondansetron is administered to all patients in the cost effectiveness analysis to manage the effects of nausea. Ondansetron is costed at £1.33 per 10-unit pack (8mg), administered 87.5 times per 35-day cycle.

Costs for comparators were sourced from the British National Formulary (BNF) accessed in April 2023 or, where available, from the electronic marketing information tool (eMIT; accessed in April 2023) for therapies that are available in a generic form.[94,95] Dosing regimens for comparators were informed by the relevant SmPC.

Table 39 presents the unit drug costs for each comparator therapy and subsequent treatment considered in the CEM.

For intravenous (IV) or subcutaneous (SC) administration schedules, the dosing depends on the body surface area (BSA) or weight of the patient. The BSA and weight for each population considered in the CEM were obtained from the BOSTON clinical trial data. The base case assumes no vial sharing i.e., wastage between vials is considered. Drug wastage for oral therapies is also included in the base case. The option to assume vial sharing where there is no wastage from partial vial use is available within the CEM.

The relative dose intensity (RDI) reflects the proportion of the actual dose received compared with the planned dose and aims to reflect information in relation to dose reductions and interruptions. Mean dosages observed across all cycles of the BOSTON clinical trial equated to RDI levels of 78.9%, 88.4% and 100% for selinexor, bortezomib and dexamethasone, respectively.[56,59] In the base case, RDI is included in the drug cost calculations. Where RDI was not reported in comparator publications, 100% RDI is assumed.

Administration costs are presented in Table 40. The administration cost for SC therapies is £119.00 based on the NHS Reference Costs 2021/2022 (Community Health Services - Specialist Nursing, Cancer Related, Adult, Face to face - N10AF),[97] for SC therapies this administration cost is applied per administration. The administration cost for IV therapies is £440.71 for the first administration and £326.46 for subsequent administrations based on the NHS Reference Costs 2021/2022 (Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance – outpatient and Deliver Subsequent Elements of a Chemotherapy Cycle – outpatient, respectively), for IV therapies the administration cost is applied per administration.[97]

Table 38 Summary of dosing regimens per treatment

		Dose per admin (mg)	Dosing unit	Number of admins per treatment cycle	Start cycle	Stop cycle	Cycle (days)	Administration	Weighting	Dose intensity
SVd	Selinexor	100.00	mg	5.00	1	To discontinuation	35	Oral	NA	78.9%
	Bortezomib	1.30	mg/m^2	4.00	1	To discontinuation	35	SC	NA	88.4%
	Dexamethasone	20.00	mg	10.00	1	To discontinuation	35	Oral	NA	100.0%
	Ondansetron (concomitant)	8	Mg	87.5	1	To discontinuation	35	Oral	NA	100.0%
IxaRd	Ixazomib	4	mg	3.00	1	To discontinuation	28	Oral	NA	97.4%
	Lenalidomide	25	mg	21.00	1	To discontinuation	28	Oral	NA	93.8%
	Dexamethasone	40	mg	4.00	1	To discontinuation	28	Oral	NA	92.2%
Kd	Carflizomib	20	mg/m2	2.00	1	1	28	IV	NA	91.0%
	Carfilzomib	56	mg/m2	4.00	1	1	28	IV	NA	91.0%
	Carfilzomib	56	mg/m2	6.00	2	To discontinuation	28	IV	NA	91.0%
	Dexamethasone	20	mg	8.00	1	To discontinuation	28	Oral	NA	100.0%
PanoVd	Panobinostat	20.00	mg	6.00	1	16	21	Oral	NA	80.7%
	Bortezomib	1.30	mg/m^2	4.00	1	8	21	IV	NA	75.7%
	Bortezomib	1.30	mg/m^2	2.00	9	16	21	IV	NA	75.7%
	Dexamethasone	20.00	mg	8.00	1	8	21	Oral	NA	87.5%
	Dexamethasone	20.00	mg	4.00	9	16	21	Oral	NA	87.5%

Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; IV, intravenous; Kd, carfilzomib plus dexamethasone; m^2, metre squared; mg, milligram; NA, not applicable; PanoVd, panobinostat plus bortezomib and dexamethasone; SC, subcutaneous; SVd, selinexor plus bortezomib and dexamethasone

Source: Data on file[59]

Table 39 Intervention, comparator and subsequent therapy unit costs

	Vial size/ unit strength (mg)	Cost per pack (£)	Unit per pack	Source
Selinexor	20.00	£9,200	20.00	Data on file[59]
SC Bortezomib	3.50	£56	1.00	eMIT 2022[95]
IV Bortezomib	3.50	£56	1.00	eMIT 2022[95]
Oral Dexamethasone	2.00	£2.46	50	eMIT 2022[95]
IV Dexamethasone	3.30	£3	10.00	eMIT 2022[95]
Ondansetron	8	£1,33	10	BNF 2022[94]
SC Daratumumab	1800.00	£4,320	1.00	BNF 2022[94]
IV Daratumumab	100.00	£360	1.00	BNF 2022[94]
IV Carfilzomib	10.00	£176	1.00	BNF 2022[94]
Pomalidomide	4.00	£8,884	21.00	BNF 2022[94]
Lenalidomide	25.00	£976	21.00	eMIT 2022[95]
Ixazomib	4.00	£6,336	3.00	BNF 2022[94]
Panobinostat	20.00	£4,656	6.00	BNF 2022[94]
Abbreviations: BNF, British National Formulary; eMIT, electronic Market Information Tool; IV, intravenous; mg, milligram; SC, subcutaneous				

Table 40 Administration costs for non-oral therapies by mode of administration

Mode of administration	Cost per administration	Source
Subcutaneous	£119.00	National Schedule of NHS Costs [4] - Year 2021-22 - Community Health Services - Specialist Nursing, Cancer Related, Adult, Face to face - N10AF[97]
Intravenous (first)	£440.71	National Schedule of NHS Costs [4] - Year 2021-22 - CHEMOTHERAPY - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance OP - SB14Z[97]
Intravenous (subsequent)	£326.46	National Schedule of NHS Costs [4] - Year 2021-22 - CHEMOTHERAPY - Deliver Subsequent Elements of a Chemotherapy Cycle - SB15Z[97]
Abbreviations: NHS, National Health Service		

B3.6.2 Subsequent Therapies

MM is a treatable but incurable cancer characterised by successive relapses. Resistance to treatments already received in earlier lines means that many patients will receive multiple lines of therapy over the course of their disease. Subsequent therapies are costed within the CEM to capture the costs of treatment beyond progression on the current (3L or 2L) treatment.

Patient treatment pathways are highly individualised according to factors such as refractoriness to prior therapies and expected tolerance of side-effects. As a simplification, a weighted-basket approach is taken; costs reflect a weighted average estimate of the therapies beyond 3L or 2L that would be used in each treatment arm. The subsequent treatments modelled are relevant for each treatment line, e.g., 3L patients moving onto 4L treatment, and 2L patients moving onto 3L treatment, as per the UK clinical pathway.

The BOSTON clinical trial was used to determine the number of patients receiving subsequent therapies in the model: 182 patients were recorded as receiving subsequent treatment and 229 patients progressed across the trial follow-up. Therefore, 79.5% (182/229) of patients are assumed to receive subsequent treatment in the cost effectiveness analysis. This figure was confirmed to be a reasonable generalisation of expected levels in the UK population by myeloma experts involved in the May 2023 Health Economic Advisory Board.[36] The types of treatments received as subsequent therapies were derived from the distribution of subsequent therapies recorded in BOSTON clinical trial data, with those unavailable in the UK pathway of recommended treatments excluded and the remainder rescaled to achieve an equivalent overall level of receipt. Based on myeloma expert advice, rules were also applied to ensure that treatments received at model baseline would not be received again subsequently. Subsequent therapy costs are applied to patients following progression in the base case, with a scenario analysis to assess the impact of assuming subsequent therapies are used at the point of discontinuation (i.e., prior to progression, if the initial treatment ended earlier due to toxicity).

The duration of each subsequent therapy is assumed to be nine months, aligning with the NICE submission for DVd (TA573, superseded by TA897).[29] This assumption allows for weighted average weekly costs to be estimated for treatments in which dosing schedules and costs varied across cycles. Where chemotherapy is received as a subsequent therapy, costs are based on a bendamustine + thalidomide + dexamethasone (BTD) regimen; the dosing schedule aligns with Lau *et al*. (2015)[98] and the costs for bendamustine and thalidomide are sourced from eMIT. Chemotherapy is associated with a weekly cost of £334 (reflecting the combined acquisition and administration cost of BTD as a proxy estimate).

The cost of daratumumab monotherapy is estimated based on the average weekly acquisition and administration cost of DPd minus the costs of Pd, resulting in a weekly cost of £2,822. Subsequent therapy distributions and weekly costs, for both 2L and 3L populations, are reported in Table 41.

Table 41 Subsequent therapy distribution

	Treatment received as a subsequent therapy						
	Chemotherapy	Dara mono	IsaPd	IxaRd	PanoVd	Pd	Rd
Weekly cost	£334	£2,299	£4,539	£1,829	£1,988	£2,222	£245
Duration of Therapy (weeks)	39.13	39.13	39.13	39.13	39.13	39.13	39.13
SVd	41.01%	18.04%	2.46%	6.56%	1.64%	42.65%	54.13%
IxaRd	42.69%	18.78%	2.56%	0.00%	1.71%	44.40%	56.35%
Kd	41.01%	18.04%	2.46%	6.56%	1.64%	42.65%	54.13%
PanoVd	41.41%	18.22%	2.48%	6.63%	0.00%	43.07%	54.67%

Abbreviations: Dara mono, daratumumab monotherapy; 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

B3.6.3 Health-state unit costs and resource use

As a conservative assumption, given existing limited data to stratify between health states, health state resource use costs are assumed to be equal between health states, across both the 3L and 2L settings. Healthcare resources required by patients are aligned with the estimates for patients that are progression-free / on treatment reported in the NICE submission for DVd (TA573, superseded by TA897).[29] Routine health state costs include Haematologist clinical visits, full blood counts, biochemistry, protein electrophoresis, immunoglobulin, urinary light chain excretion, red blood cell transfusions and platelet transfusions.

The weekly resource usage for both patients in the progression free and progressed health state is multiplied by unit costs sourced from NHS Reference Costs 2021/22,[97] then aggregated to calculate an average weekly resource cost for each health state - £63 in both instances (Table 42).

Table 42 Weekly resource use unit costs and frequencies per health state

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

Abbreviations: NA, not applicable

[a] resource frequencies sourced from NICE TA897,[29] TA427[88]

[b] resource frequency assumed the same as progression-free

B3.6.4 Adverse reaction unit costs and resource use

The CEM costs adverse events assuming a weighting of cases managed in primary *versus* secondary care, assuming the same proportion in each setting (by AE type) as was applied in NICE TA870 (IxaRd).[28]

For AEs not reported in the corresponding source (cataracts, hypophosphataemia, leukopenia, lymphopenia, and hyperglycaemia), an equal distribution was assumed across settings. Secondary care costs were obtained from the NHS Reference Costs

2021/2022 and primary care costs were obtained from the PSSRU (2022) reflecting a standard appointment time (9.22 minutes).[96,97] Table 43 presents the weighted cost of each AE applied in the CEM.

Arm-specific weekly adverse event rates are calculated from the data on overall event rates and follow-up time reported in studies relevant to each treatment (Table 43).

The costs of each AE are multiplied by the weekly probability of each AE to provide weighted estimates for weekly adverse event costs per treatment arm in the model (Table 44).

Table 43 Cost per adverse event

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%	£4,442	£42	£4,178
Asthenia	0%	100%	£3,372	£42	£42
Cataract	50%	50%	£7,868	£42	£3,955
Diarrhoea	99%	1%	£3,372	£42	£3,339
Fatigue	0%	100%	£3,372	£42	£42
Febrile neutropenia	98%	2%	£6,485	£42	£6,357
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%	£3,744	£42	£1,893
Nausea	0%	100%	£3,372	£42	£42
Neutropenia	98%	2%	£6,485	£42	£6,357
Hyperglycaemia	50%	5%	£239	£42	£141
Peripheral neuropathy	98%	2%	£3,745	£42	£3,671
Pneumonia	100%	0%	£5,080	£42	£5,080
Thrombocytopenia	99%	1%	£4,331	£42	£4,288

Abbreviations: AE, adverse event

Table 44 Weighted weekly adverse event costs

	Weighted weekly costs
SVd	£38
IxaRd	£12

Kd	£9
PanoVd	£78
Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; SVd, selinexor plus bortezomib and dexamethasone	

B3.6.5 Miscellaneous unit costs and resource use

To account for the cost of terminal care, a one-off cost per patient of £4,823 is applied in the model upon death. This cost is taken from Round *et al*. (2015) and inflated to 2021/22 costs using PSSRU (2022), which assesses the mean healthcare costs across all cancers, in the absence of data specific to RRMM.[96,99]

B3.7 Severity

Absolute and relative QALY shortfalls were estimated by comparing the estimated quality-adjusted life expectancy (QALE) of patients receiving the most effective comparator (in terms of total lifetime QALY estimates) in each positioning against the expected QALE in an age- and gender-matched general population. QALE in the general population was estimated using the approach and sources recommended by Schneider *et al* (2021):[100]

- Life tables: England, 2018-2020 (pooled)
- Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study
- Health state profiles: EQ-5D-3L from the Health Survey for England 2014
- Model: ALDVMM by Hernandez Alava, *et al.* (2022)[101]

Shortfall calculations for both 3L and 2L settings are shown in Table 45. In a 3L population aged 65.3 years and 67% male (as assumed in the base case), a general population quality-adjusted life expectancy (QALE) of 10.8 was estimated. The QALE in the IxaRd arm using base model settings was 2.5: a shortfall of 8.2 QALYs (76%) relative to the general population.

In the 2L setting, a general population QALE of 10.1 QALYs was estimated using base case age (67.2 years) and gender (55% male). The QALE estimate in the Kd arm of the model for an equivalent population was 2.9 QALYs: a shortfall of 7.2 (71%).

Since the absolute and relative shortfalls in both base analyses were below the shortfall thresholds, no modifier has been applied in either analysis.

Table 45 summary features of QALY shortfall analysis

	3L	2L
Starting age (years)	65.33	67.18
Proportion male (%)	67%	55%
Expected total QALYs for the general population	10.8	10.1
Most effective comparator	IxaRd	Kd
Total QALYs that people living with a condition would be expected to have with current treatment	2.5	2.9
QALY shortfall (absolute)	8.2	7.2
QALY shortfall (relative)	76%	71%
QALY modifier	1.0	1.0

Abbreviations: IxaRd, ixazomib plus lenalidomide and dexamethasone; Kd, carfilzomib plus dexamethasone; QALY, quality-adjusted life year; 2L, second-line; 3L, third-line

B3.8 Uncertainty

Because of the incurable nature of MM and the need for successive treatments to be planned around patients' prior exposure to treatments and tolerance of side effects, pathways are complex and often highly individualised. Furthermore, treatment decisions are determined not only by relative efficacy at the current line of treatment but also how exposure might influence opportunities for effective treatments later in the pathway. Consequently, the specific treatment pathway varies both between patients and is evolving and changing over time. This submission attempts to address potential shifts in the treatment pathway pre-emptively by considering alternative positioning and comparator base cases. To reflect the current treatment pathway, SVd is positioned as a 3L option following a daratumumab-containing regimen at 2L but as the landscape is expected to change if DRd is recommended as a 1L treatment, then SVd also becomes a 2L option in transplant ineligible patients. The uncertainty associated in the evolving MM treatment landscape and pathway is reflected in the two economic analyses base cases that have been presented for the current 3L positioning and the addition of a near future 2L positioning for SVd.

A further complication of the dynamic treatment landscape is that the range of comparator treatments explored in clinical trials tends to vary, limiting the level of overlap available for establishing networks of evidence.

B3.9 Managed access proposal

The company has proposed the submission for consideration for routine commissioning with a simple PAS.

B3.10 Summary of base-case analysis inputs and assumptions

B3.10.1 Summary of base-case analysis inputs

Key base case model inputs, with measurements of uncertainty are described in Table 46.

Table 46 Summary of variables applied in the economic model for 3L and 2L analyses

		3L analysis		2L analysis		
Variable	**Distribution**	**Value**	**Confidence interval range**	**Value**	**Confidence interval range**	**Reference to section in submission**
Model settings						
Time horizon	Fixed	35 years	N/A	35 years	N/A	B3.3.2
Cycle length	Fixed	1 week	N/A	1 week	N/A	B3.3.2
Half cycle correction	Fixed	Applied	N/A	Applied	N/A	B3.3.2
Discount rate (costs)	Fixed	3.5%	N/A	3.5%	N/A	B3.3.2
Discount rate (outcomes)	Fixed	3.5%	N/A	3.5%	N/A	B3.3.2
Patient baseline characteristics						
Age at baseline	Normal	65.33	64.41 to 66.25	67.18	66.25 to 68.10	B2.3.2
Proportion male at baseline	Beta	0.67	0.62 to 0.72	0.55	0.50 to 0.59	B2.3.2
ECOG score at baseline	Normal	0.77	0.71 to 0.83	0.68	0.62 to 0.74	B2.3.2
EQ-5D-3L at baseline	Beta	0.72	0.71 to 0.73	0.72	0.71 to 0.73	B3.5.1
Weight	Normal	76.77	75.30 to 78.25	76.41	74.94 to 77.89	B2.3.2
BSA	Normal	1.85	1.83 to 1.87	1.83	1.81 to 1.85	B2.3.2
Dose intensity						
Selinexor	Beta	78.89%	77.32% to 80.42%	78.89%	77.32% to 80.42%	B3.6.1
Bortezomib	Beta	88.36%	86.57% to 90.03%	88.36%	86.57% to 90.03%	B3.6.1

		3L analysis		2L analysis		
Variable	**Distribution**	**Value**	**Confidence interval range**	**Value**	**Confidence interval range**	**Reference to section in submission**
Dexamethasone	Beta	100.00%	100.00% to 100.00%	100.00%	100.00% to 100.00%	B3.6.1
SVd clinical effectiveness						
OS parameterisation	Fixed	Joint fit – Lognormal	N/A	Joint fit – gamma	N/A	B3.4.1.1 B3.4.2.1
PFS parameterisation	Fixed	Joint fit – Lognormal	N/A	Independent fit – gamma	N/A	B3.4.1.2 B3.4.2.2
ToT parameterisation	Fixed	Joint fit – Log-logistic	N/A	Joint fit - gamma	N/A	B3.4.1.3 B3.4.2.3
Subsequent Therapies						
Proportion receiving subsequent therapy	Beta	0.79	0.62 – 0.93	Beta	0.79	0.62 – 0.93
Subsequent threrapy duration (weeks)	Normal	39.13	31.46 to 46.80	39.13	31.46 to 46.80	B3.6.2
Health-related quality of life: utilities and utility decrements						
Progression-free	Multivariate normal	0.70	N/A	0.70	N/A	B3.5.1
Progressed	Multivariate normal	0.66	N/A	0.66	N/A	B3.5.1
Anaemia	Beta	-0.31	-0.25 to -0.37	-0.31	-0.25 to -0.37	B3.5.4
Asthenia	Beta	-0.12	-0.09 to -0.14	-0.12	-0.09 to -0.14	B3.5.4
Cataract	Beta	-0.14	-0.11 to -0.17	-0.14	-0.11 to -0.17	B3.5.4
Diarrhoea	Beta	-0.10	-0.08 to -0.12	-0.10	-0.08 to -0.12	B3.5.4
Fatigue	Beta	-0.12	-0.09 to -0.14	-0.12	-0.09 to -0.14	B3.5.4
Febrile neutropenia	Beta	-0.15	-0.12 to -0.17	-0.15	-0.12 to -0.17	B3.5.4
Hypertension	Beta	0.00	NA	0.00	NA	B3.5.4
Hypophosphataemia	Beta	0.00	NA	0.00	NA	B3.5.4
Leukopenia	Beta	0.00	NA	0.00	NA	B3.5.4
Lymphopenia	Beta	-0.07	-0.05 to -0.08	-0.07	-0.05 to -0.08	B3.5.4
Lower respiratory tract infection	Beta	-0.19	-0.15 to -0.23	-0.19	-0.15 to -0.23	B3.5.4
Nausea	Beta	-0.10	-0.08 to -0.12	-0.10	-0.08 to -0.12	B3.5.4
Neutropenia	Beta	-0.15	-0.12 to -0.17	-0.15	-0.12 to -0.17	B3.5.4
Hyperglycaemia	Beta	0.00	N/A	0.00	N/A	B3.5.4
Peripheral neuropathy	Beta	-0.07	-0.05 to -0.08	-0.07	-0.05 to -0.08	B3.5.4
Pneumonia	Beta	-0.19	-0.15 to – 0.23	-0.19	-0.15 to – 0.23	B3.5.4
Thrombocytopenia	Beta	-0.31	-0.25 to -0.37	-0.31	-0.25 to -0.37	B3.5.4
Adverse Events (duration of AE in weeks)						
Anaemia	Normal	1.53	1.23 to 1.83	1.53	1.23 to 1.83	B3.5.4
Asthenia	Normal	2.09	1.68 to 2.49	2.09	1.68 to 2.49	B3.5.4
Cataract	Normal	26.09	20.98 to 31.20	26.09	20.98 to 31.20	B3.5.4
Diarrhoea	Normal	1.00	0.80 to 1.20	1.00	0.80 to 1.20	B3.5.4
Fatigue	Normal	2.09	1.68 to 2.49	2.09	1.68 to 2.49	B3.5.4
Febrile neutropenia	Normal	1.89	1.52 to 2.26	1.89	1.52 to 2.26	B3.5.4

		3L analysis		2L analysis		
Variable	**Distribution**	**Value**	**Confidence interval range**	**Value**	**Confidence interval range**	**Reference to section in submission**
Hypertension	N/A	0.00	N/A	0.00	N/A	B3.5.4
Hypophosphataemia	N/A	0.00	N/A	0.00	N/A	B3.5.4
Leukopenia	N/A	0.00	N/A	0.00	N/A	B3.5.4
Lymphopenia	Normal	2.21	1.78 to 2.65	2.21	1.78 to 2.65	B3.5.4
Lower respiratory tract infection	Normal	1.71	1.38 to 2.05	1.71	1.38 to 2.05	B3.5.4
Nausea	Normal	1.00	0.80 to 1.20	1.00	0.80 to 1.20	B3.5.4
Neutropenia	Normal	1.89	1.52 to 2.26	1.89	1.52 to 2.26	B3.5.4
Hyperglycaemia	Normal	0.00	N/A	0.00	N/A	B3.5.4
Peripheral neuropathy	Normal	25.7	20.67 to 30.75	25.7	20.67 to 30.75	B3.5.4
Pneumonia	Normal	1.71	1.62 to 2.41	1.71	1.62 to 2.41	B3.5.4
Thrombocytopenia	Normal	2.01	1.62 to 2.41	2.01	1.62 to 2.41	B3.5.4
Cost assumptions						
Oral administration		£0	Fixed	£0	Fixed	
SC administration	Normal	£119	£96 to £142	£119	£96 to £142	B3.6.1
IV administration (first)	Normal	£441	£354 to £527	£441	£354 to £527	B3.6.1
IV administration (subsequent)	Normal	£326	£262 to £390	£326	£262 to £390	B3.6.1
Progression-free resource use (weekly)	Normal	£63	£51-£76	£63	£51-£76	B3.6.3
Progressed disease resource use (weekly)	Normal	£63	£51-£76	£63	£51-£76	B3.6.3
Anaemia	Normal	£4,178	£3,359 to £4,996	£4,178	£3,359 to £4,996	B3.6.4
Asthenia	Normal	£42	£34 to £50	£42	£34 to £50	B3.6.4
Cataract	Normal	£3,955	£3,180 to £4,730	£3,955	£3,180 to £4,730	B3.6.4
Diarrhoea	Normal	£3,339	£2,684 to £3,993	£3,339	£2,684 to £3,993	B3.6.4
Fatigue	Normal	£42	£34 to £50	£42	£34 to £50	B3.6.4
Febrile neutropenia	Normal	£6,357	£5,111 to £7,602	£6,357	£5,111 to £7,602	B3.6.4
Hypertension	Normal	£1,171	£942 to £1,401	£1,171	£942 to £1,401	B3.6.4
Hypophosphataemia	Normal	£141	£113 to £168	£141	£113 to £168	B3.6.4
Leukopenia	Normal	£141	£113 to £168	£141	£113 to £168	B3.6.4
Lymphopenia	Normal	£141	£113 to £168	£141	£113 to £168	B3.6.4
Lower respiratory tract infection	Normal	£1,893	£1,522 to £2,264	£1,893	£1,522 to £2,264	B3.6.4
Nausea	Normal	£42	£34 to £50	£42	£34 to £50	B3.6.4
Neutropenia	Normal	£6,357	£5,111 to £7,602	£6,357	£5,111 to £7,602	B3.6.4
Hyperglycaemia	Normal	£141	£113 to £168	£141	£113 to £168	B3.6.4
Peripheral neuropathy	Normal	£3,671	£2,951 to £4,390	£3,671	£2,951 to £4,390	B3.6.4

		3L analysis		2L analysis		
Variable	**Distribution**	**Value**	**Confidence interval range**	**Value**	**Confidence interval range**	**Reference to section in submission**
Pneumonia	Normal	£5,080	£4,084 to £6,075	£5,080	£4,084 to £6,075	B3.6.4
Thrombocytopenia	Normal	£4,288	£3,447 to £5,128	£4,288	£3,447 to £5,128	B3.6.4
Cost of end-of-life care	Normal	£4,823	£3,878 to £5,769	£4,823	£3,878 to £5,769	B3.6.5

Abbreviations: AE, adverse event; BSA, body surface area; Dara, daratumumab; ECOG, Eastern Cooperative Oncology Group; EQ-5D-3L, EuroQol five dimension 3 levels; IsaPD, isatuximab plus pomalidomide and dexamethasone; IV, intravenous; IxaRd, ixazomib plus lenalidomide and dexamethasone; mg, milligram; N/A, not applicable; OS, overall survival; PanoVd, Panobinostat plus bortezomib and dexamethasone; Pd, pomalidomide plus dexamethasone; Rd, lenalidomide plus dexamethasone; IV, intravenous; NA, not applicable; IxaRd, ixazomib plus lenalidomide and dexamethasone; PFS, progression-free survival; SC, subcutaneous; ToT, time on treatment; Vd, bortezomib plus dexamethasone; 2L, second-line; 3L, third-line

B3.10.2 Assumptions

Key model assumptions are described in Table 47.

Table 47 Description of key model assumptions

Assumption	Justification
Model approach	
Model structure: A PSM model structure is appropriate for estimating incremental costs and QALYs relevant to the decision problem, given the nature and availability of data	PSM is well-established as a modelling approach for CEA in cancers. The approach makes direct use of OS and PFS data from BOSTON study data and allows for comparative efficacy estimates to be incorporated from aggregate evidence
Time horizon: A time horizon of 35 years is sufficient for capturing lifetime costs and QALYs relevant to decision-making	Fewer than 1% of patients remain alive in any arm in the base case and key scenario analyses
Clinical effectiveness	
BOSTON parameterisation approach: OS, PFS and ToT endpoints for SVd are estimated from joint analyses of SVd and Vd arms of the BOSTON trial unless incompatible with landmark estimates obtained from clinical experts	Although not considered as a comparator in the CEA, Vd fulfils a role to bridge clinical evidence between SVd and comparators in the NMA. Jointly-fitted estimates make use of evidence available from both arms and directly address relativities between SVd and Vd. Independently-fitted curves are explored in scenario analyses
Comparator relative effectiveness: Random effects (RE) hazard ratios are the most appropriate estimate of the direction and magnitude of clinical effectiveness relative to comparators	The interpretation and validation of results was sought from clinical experts who stated likely differences across trials (particularly when comparing against less recent studies), and

Assumption	Justification
	identified RE model results as the most appropriate to use in the base case. It was also highlighted that CI ranges crossing a HR value of 1 was expected when considering a large network, but that NMA point estimate results provide the best available synthesis of evidence across the range of studies available. Equivalence assumptions are explored in scenario analyses to understand sensitivity. FE models are also explored in scenario analysis.
Comparator time on treatment: The PFS hazard ratio for comparators relative to SVd is generalisable to time on treatment	Stopping rules for most comparator therapies align with selinexor (treatment to disease progression or discontinuation due to toxicity). However, scenario analyses are performed to consider the impact of treatment without early discontinuation among comparators
Treatment waning: The clinical efficacy of SVd is maintained beyond the BOSTON study period	BOSTON study data are relatively mature and show no substantial decrease in efficacy over time relative to comparators. Myeloma expert opinion sought in advisory boards suggested no clinical rationale for the efficacy of SVd to vary over time relative to comparators.
Costs	
Wastage: Contents from partially-used vials / tablets are wasted with costs incurred.	Aligned with NICE reference case
Health-related quality of life	
Health state utilities: Patient utilities by health state (progression-free or progressed) are generalisable across treatments. (0.697 for progression free and 0.660 for progressed disease)	Aligned with NICE reference case and approaches identified in previous MM submissions
Adverse events: AEs are ongoing throughout the period of active treatment	AEs are applied as one-off events on treatment initiation as a scenario analysis.

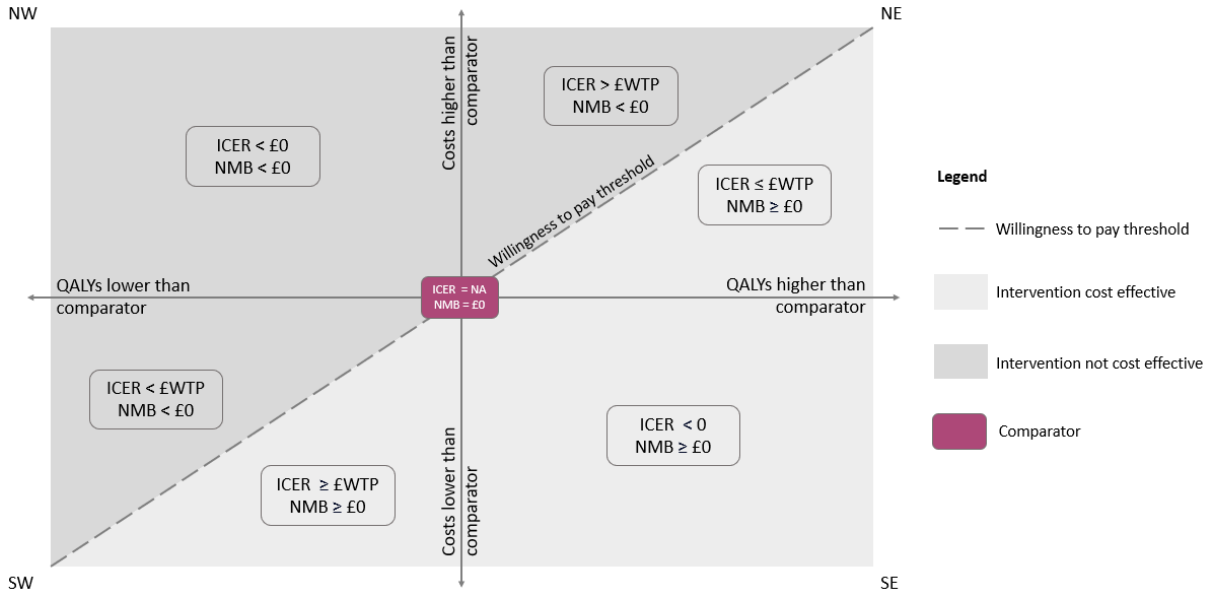
Abbreviations: AE, adverse event; CEA, cost-effectiveness analysis; CI, confidence interval; HR, hazard ratio; MM, multiple myeloma; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PSM, partitioned survival model; QALY, quality-adjusted life-year; RE, random effects; SVd, selinexor plus bortezomib and dexamethasone; ToT, time on treatment; Vd, bortezomib plus dexamethasone

B3.11 Base-case results

B3.11.1 Note on the interpretation of ICER results

As a measure of the incremental cost per QALY gained, ICERs are most easily interpreted in the context of interventions that are more effective and more costly than their comparator (the intervention lies to the North-East of the comparator, when plotted on a cost-effectiveness plane as shown in Figure 28). In this context, ICERs below the willingness-to-pay threshold are generally considered cost-effective.

Figure 28 Illustration of ICER interpretations on a cost-effectiveness plane



Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; NMB, net monetary benefit; NE, North-East; NW, North-West; QALY, quality-adjusted life year; SE, South-East; SW, South-West; WTP, willingness to pay

Where estimates are not contained within the North-East quadrant, ICERs can be less informative and potentially ambiguous. Negative ICERs are produced in the North-West quadrant (intervention is dominated) or South-East quadrant (the intervention achieves a QALY gain at a lower cost, and is therefore dominant). Interventions in the South-West quadrant (lower QALYs at lower cost) produce a positive ICER result, but are considered cost-effective at ICERs *above* the willingness-to-pay threshold, as a higher ICER implies a larger saving per QALY foregone. These differences in interpretation can be particularly problematic for distinguishing whether sensitivity and scenario results correspond to an improvement or a worsening of cost-effectiveness results.

To assist with interpretation, base case and scenario results are presented in terms of net monetary benefit (NMB) and net health benefit (NHB) as well as ICER estimates. By assigning a monetary value to each QALY gained or lost (£20,000 and £30,000 thresholds in the results shown, in keeping with NICE recommendations), NMB expresses the overall value of both cost and QALY effects in monetary terms, and NHB in purely QALY terms. Using either measure, results greater than zero always denote cost-effectiveness at the given willingness-to-pay threshold. and interpretation therefore does not vary according to the relative positioning of the intervention and comparator.

B3.11.2 Base case results versus 3L comparators

Base-case results comparing SVd to IxaRd and PanoVd after two prior therapies (3L) are summarised in Table 48 (ICER results) and Table 49 (NMB and NHB).

Pairwise results show a net QALY gain for SVd relative to either comparator (0.09 incremental QALYs *versus* IxaRd and 0.35 incremental QALYs *versus* PanoVd). Applying the published list prices for comparator therapies and a PAS discount of [redacted] to the list price for selinexor, SVd dominates both treatments with an ICER estimate of -£487,802 per QALY gained versus IxaRd and -£32,692 per QALY gained *versus* PanoVd. As QALY gains are achieved at a lower cost than either comparator (SVd lies to the South-East, as shown in Figure 29), SVd is considered cost-effective regardless of the willingness-to-pay threshold assumed.

Table 48 Base-case results *versus* pairwise comparators – 3L (selinexor at PAS price, comparators at list price)

Comparator	Total			Incremental (SVd *vs.* comparator)				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/ QALY)	ICER interpretation
SVd	£134,119	3.91	2.62					
IxaRd	£179,740	3.75	2.53	-£45,621	0.16	0.09	-£487,802	Dominant
PanoVd	£145,686	3.36	2.27	-£11,567	0.55	0.35	-£32,692	Dominant

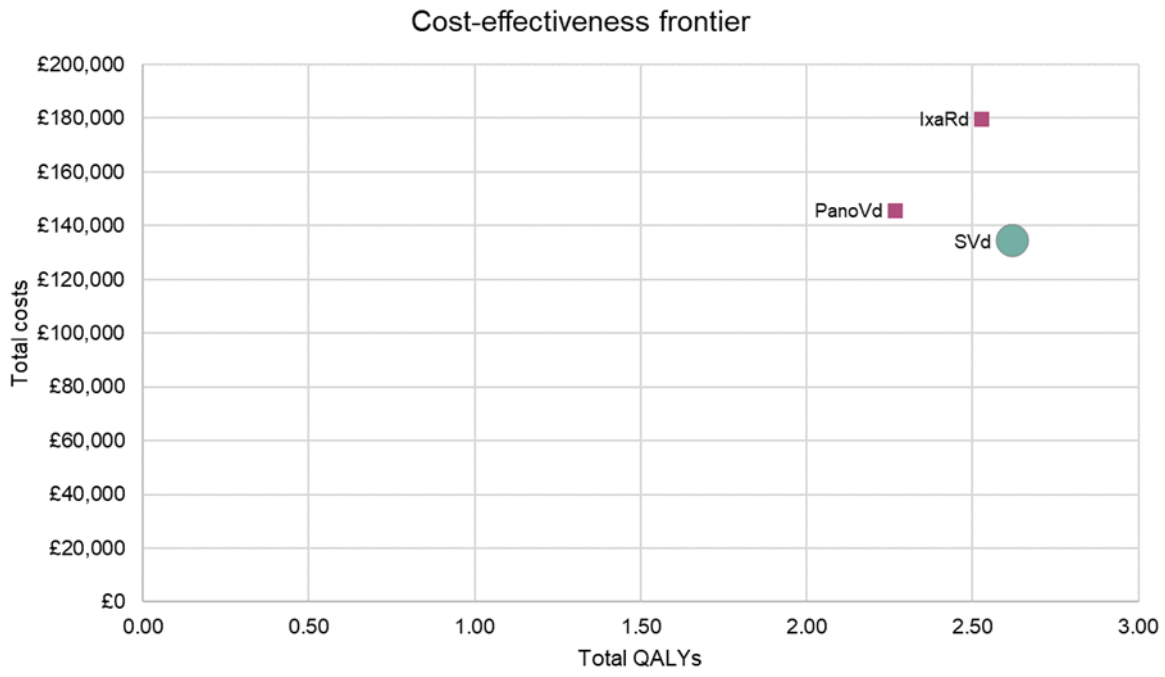
Abbreviations; ICER, incremental cost-effectiveness ratio; IxaRd, ixazomib plus lenalidomide and dexamethasone; LYG, life years gained; PanoVd, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; 3L, third-line.

Table 49 Base-case net monetary benefit and net health benefit results *versus* pairwise comparators – 3L (selinexor at PAS price, comparators at list price)

	Net monetary benefit (£) (SVd *vs.* comparator)		Net health benefit (QALYs) (SVd *vs.* comparator)	
	WTP £20,000	**WTP £30,000**	**WTP £20,000**	**WTP £30,000**
IxaRd	£47,492	£48,427	2.37	1.61
PanoVd	£18,643	£22,181	0.93	0.74

Abbreviations; IxaRd, ixazomib plus lenalidomide and dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; WTP, willingness to pay; 3L, third-line.

Figure 29 Cost effectiveness frontier - SVd *versus* IxaRd and PanoVd at 3L (selinexor at PAS price, comparators at list price)



Both ixazomib and Panobinostat have confidential PAS arrangements in place that are not reflected in the results presented. Cost-effectiveness results generated using the list price for selinexor are shown in Table 50, with ICERs of [redacted] *versus* IxaRd and [redacted] *versus* PanoVd.

Table 50 Base-case results *versus* pairwise comparators – 3L (selinexor at list price, comparators at list price)

Comparator	Total			Incremental (SVd *vs.* comparator)				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/ QALY)	ICER interpretation
SVd	[redacted]	3.91	2.62					
IxaRd	£179,740	3.75	2.53	[redacted]	0.16	0.09	[redacted]	[redacted]
PanoVd	£145,686	3.36	2.27	[redacted]	0.55	0.35	[redacted]	[redacted]

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

Table 51 Base-case net monetary benefit and net health benefit results *versus* pairwise comparators – 3L (selinexor at list price, comparators at list price)

	Net monetary benefit (£) (SVd *vs.* comparator)		Net health benefit (QALYs) (SVd *vs.* comparator)	
	WTP £20,000	WTP £30,000	WTP £20,000	WTP £30,000
IxaRd	[redacted]	[redacted]	[redacted]	[redacted]
PanoVd	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations; IxaRd, ixazomib plus lenalidomide and dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; WTP, willingness to pay; 3L, third-line.

B3.11.3 Base case results *versus* 2L comparators

Base-case results reflecting a 2L positioning *versus* Kd, assuming a PAS discount of [redacted] for Selinexor and applying the list price for carfilzomib, are summarised in Table 52. As shown in Figure 30, SVd lies to the South-West of Kd when plotted on a cost-effectiveness plane, demonstrating a lower QALY estimates but at lower cost.

Although the QALY estimate for SVd is lower than for its comparator, the ICER estimate of £580,849 suggests a substantial cost saving relative to that difference. Correspondingly, the NHBs for SVd *versus* Kd are greater than zero in both instances, suggesting that provision of SVd in the 2L population is a cost-effective use of resources.

Table 52 Base-case results versus comparator – 2L analysis (selinexor at PAS price, comparators at list price)

Comparator	Total			Incremental (SVd *vs.* comparator)				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	ICER interpretation
SVd	£137,595	3.85	2.59					
Kd	£319,918	4.28	2.91	-£182,324	-0.43	-0.31	£580,849	South-West Quadrant

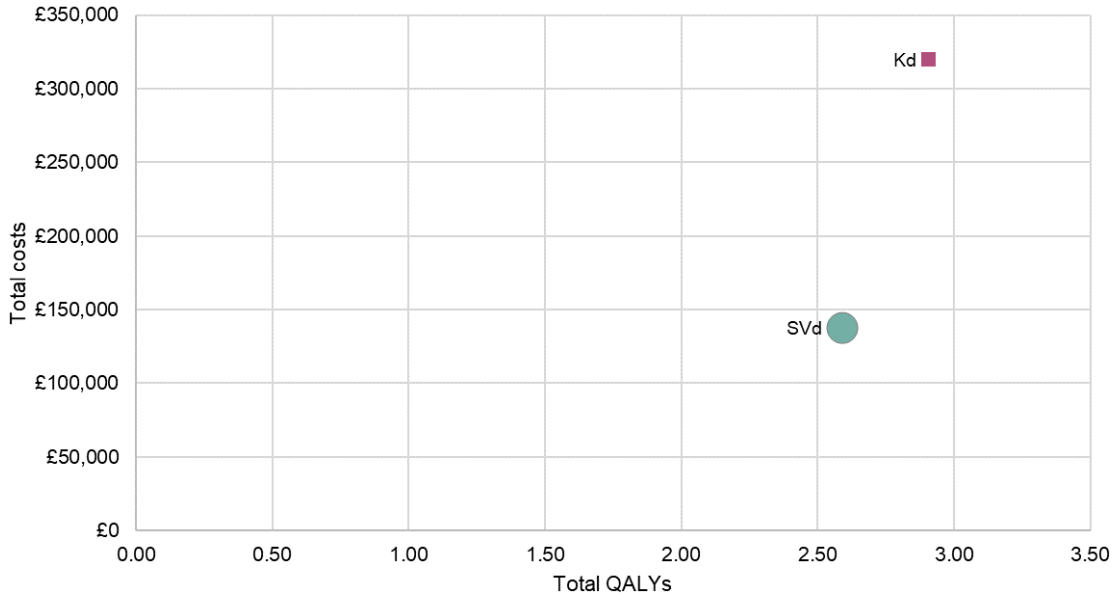
Abbreviations; ICER; incremental cost-effectiveness ratio; Kd,,carfilzomib plus dexamethasone; LYG, life years gained; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; 2L, second-line

Table 53 Base-case net monetary benefit and net health benefit results *versus* comparator – 2L analysis (selinexor at PAS price, comparators at list price)

	Net monetary benefit (£) (SVd *vs.* comparator)		Net health benefit (QALYs) (SVd *vs.* comparator)	
	WTP £20,000	WTP £30,000	WTP £20,000	WTP £30,000
Kd	£176,046	£172,907	8.80	5.76

Abbreviations: Kd, carfilzomib plus dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; WTP, willingness to pay; 2L, second-line

Figure 30 Cost effectiveness frontier - SVd *versus* Kd at 2L (selinexor at PAS price, comparators at list price)



While cost-effectiveness results cannot be compared against Kd at the commercial PAS price for carfilzomib and the level of discount is not known, Table 54 and Table 55 suggest that a substantial cost saving exists when assuming list prices for both SVd and Kd.

Table 54 Base-case results versus comparator – 2L analysis (selinexor at list price, comparators at list price)

Comparator	Total			Incremental (SVd *vs.* comparator)				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	ICER interpretation
SVd	[redacted]	3.85	2.59					
Kd	£319,918	4.28	2.91	[redacted]	-0.43	-0.31	[redacted]	[redacted]

Abbreviations; ICER; incremental cost-effectiveness ratio; Kd,,carfilzomib plus dexamethasone; LYG, life years gained; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; 2L, second-line

Table 55 Base-case net monetary benefit and net health benefit results *versus* comparator – 2L analysis (selinexor at list price, comparators at list price)

	Net monetary benefit (£) (SVd *vs.* comparator)		Net health benefit (QALYs) (SVd *vs.* comparator)	
	WTP £20,000	WTP £30,000	WTP £20,000	WTP £30,000
Kd	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Kd, carfilzomib plus dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; WTP, willingness to pay; 2L, second-line

B3.12 Exploring uncertainty

The impact of uncertainty on cost-effectiveness estimates was explored using probabilistic and deterministic sensitivity and scenario analyses.

B3.12.1 Probabilistic sensitivity analysis

A probabilistic analysis was conducted for both 3L and 2L base cases to account for the joint uncertainty of the underlying parameter estimates, using the approach suggested in NICE guidance. The choice of distribution (beta, gamma, log-normal, normal, and Dirichlet) applied to parameters was selected based on recommendations outlined in Briggs *et al*. (2008).[102]

Standard errors (SEs) were taken directly from source data if reported, or calculated from published standard deviations (SD), sample size and/ or 95% confidence interval data. If none were reported, SE is estimated as 20% of the default value. The probabilistic base case was run with 1,000 iterations, following a visual assessment to ensure adequate convergence of mean ICER estimates.

B3.12.1.1 PSA results – SVd *vs. 3L* comparators

The probabilistic results for 3L are reported in Table 56, alongside scatterplots illustrating the spread of PSA iterations against each comparator (Figure 31 and Figure 32).

In pairwise comparisons against both PanoVd and IxaRd, the deterministic base case and probabilistic mean estimates lie in close proximity on the cost effectiveness plane, but are sufficiently different that the ICER interpretation changes for SVd versus each comparator. Differences are driven primarily by uncertainty around the comparator estimate: SVd total costs and QALYs are closely aligned between the deterministic and the probabilistic results, whereas a larger difference is seen in the IxaRd and PanoVd results. The scatterplots show a number of extreme outlying results, driven primarily by extremities of HR assumptions derived from iterations of the NMA analysis that have a large influence on the mean probabilistic result.

For SVd versus IxaRd, the mean probabilistic ICER lies in the South-West quadrant where SVd is associated with lower costs and QALYs. For SVd versus PanoVd, the mean probabilistic ICER lies in the North-East quadrant of the cost effectiveness plane, indicating greater incremental costs and QALYs associated with SVd.

Table 56 PSA cost-effectiveness results – SVd *versus* 3L comparators

Comparator	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER interpretation
SVd	£122,560	2.61				
IxaRd	£185,984	2.85	-£63,424	-0.23	£274,089	South-West Quadrant
PanoVd	£122,180	2.36	£380	0.25	£1,525	North-East Quadrant

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

Figure 31 Scatterplot of PSA incremental estimates for SVd *versus* IxaRd at 3L

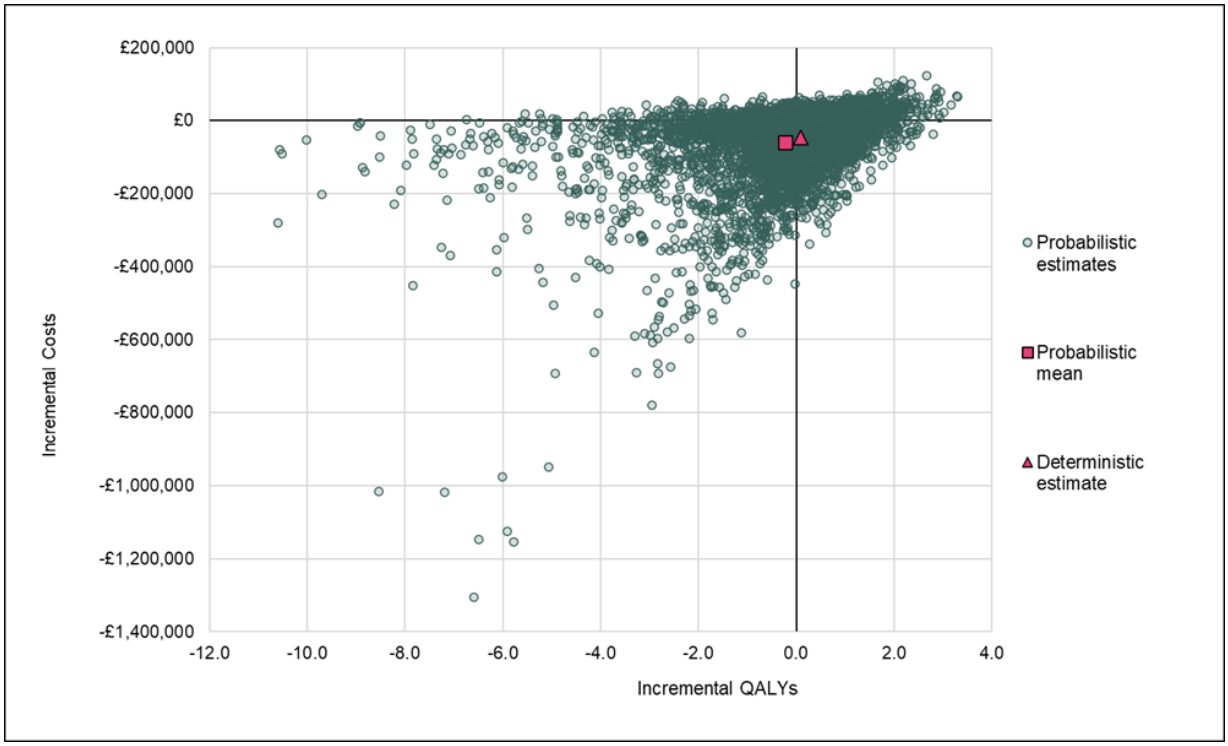
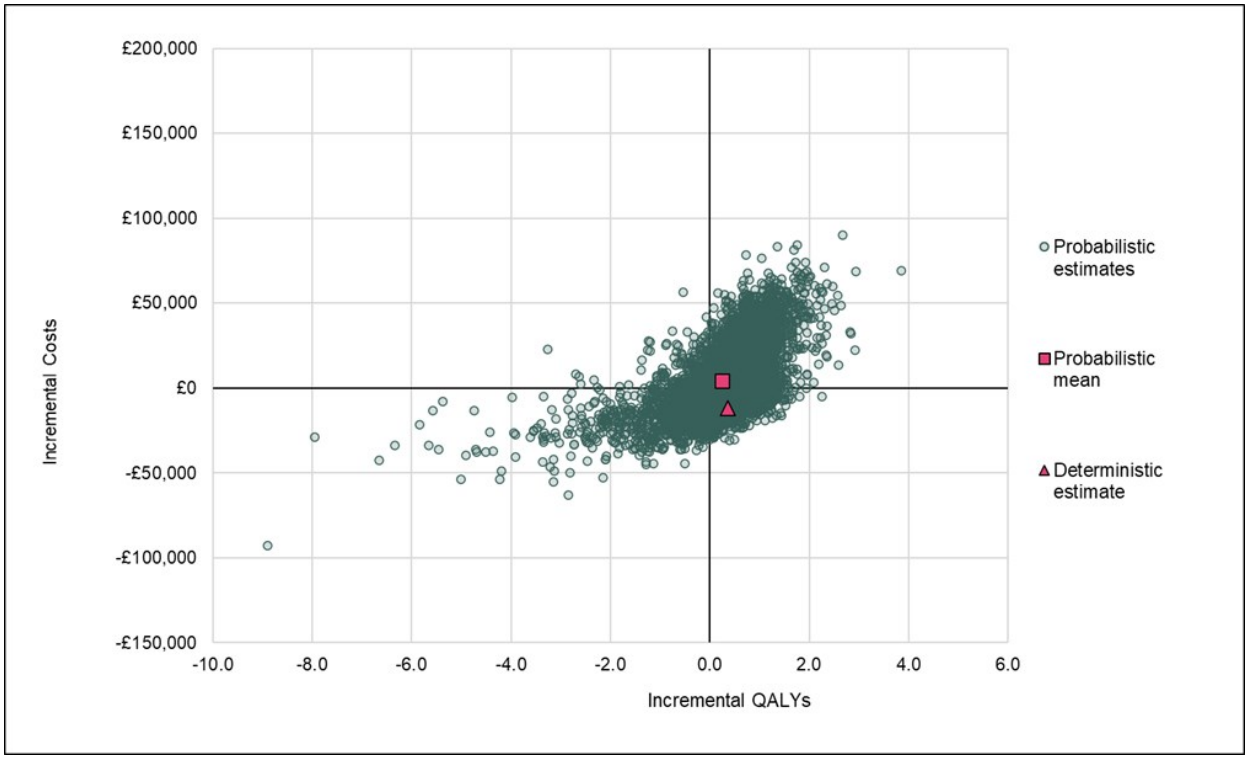


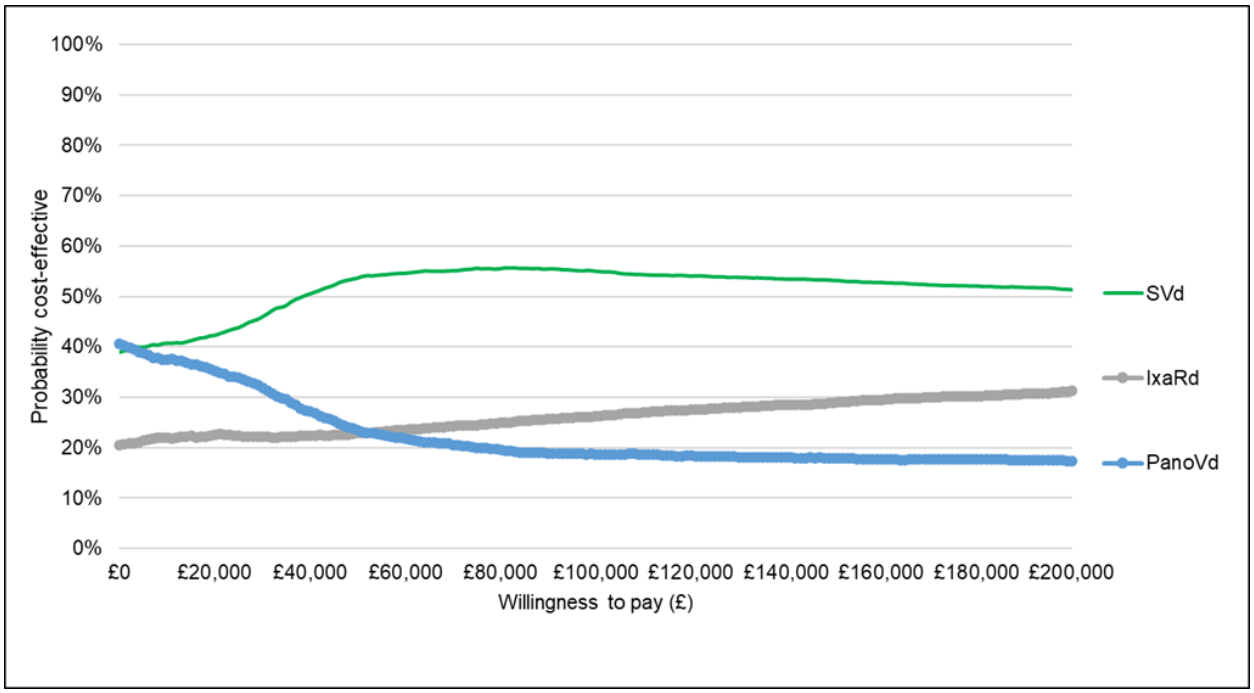
Figure 32 Scatterplot of PSA incremental estimates for SVd *versus* PanoVd at 3L



CEACs for SVd versus both 3L therapies show that for all WTP thresholds below £200,000/ QALY, including the NICE reference case of £20,000-£30,000/ QALY, SVd

has the highest probability (40%-50%) of being cost effective versus IxaRd and PanoVd (Figure 33).

Figure 33 Cost-effectiveness acceptability curves for SVd, IxaRd and PanoVd at 3L



B3.12.1.2 PSA results – SVd versus 2L comparators

Mean probabilistic results *versus* Kd at 2L are reported in Table 57, with a scatterplot of PSA iterations shown in Figure 34. The mean probabilistic ICER remains in the South-West quadrant, signifying a cost saving but lower expected QALYs than estimated for Kd. The CEAC highlights that for all WTP thresholds below £100,000/ QALY, including the NICE reference case £20,000-£30,000/ QALY, SVd has a high probability (90%-100%) of being cost effective *versus* Kd (Figure 35).

Table 57 PSA cost-effectiveness results – 2L

Comparator	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER interpretation
SVd	£136,271	2.62				
Kd	£316,708	3.16	-£180,437	-0.54	£334,280	South-West Quadrant

Abbreviations: ICER, incremental cost-effectiveness ratio; Kd, carfilzomib plus dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; 2L, second-line.

Figure 34 Scatterplot of PSA estimates on a cost-effectiveness plane SVd *versus* Kd at 2L

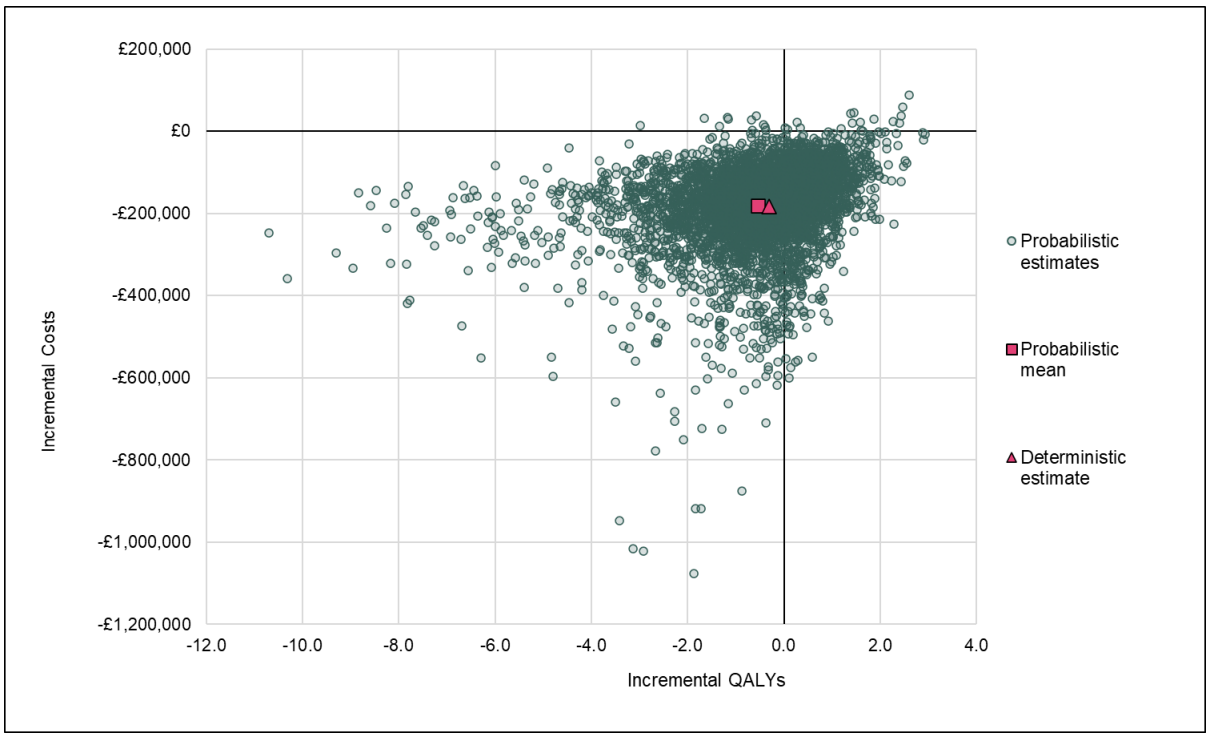
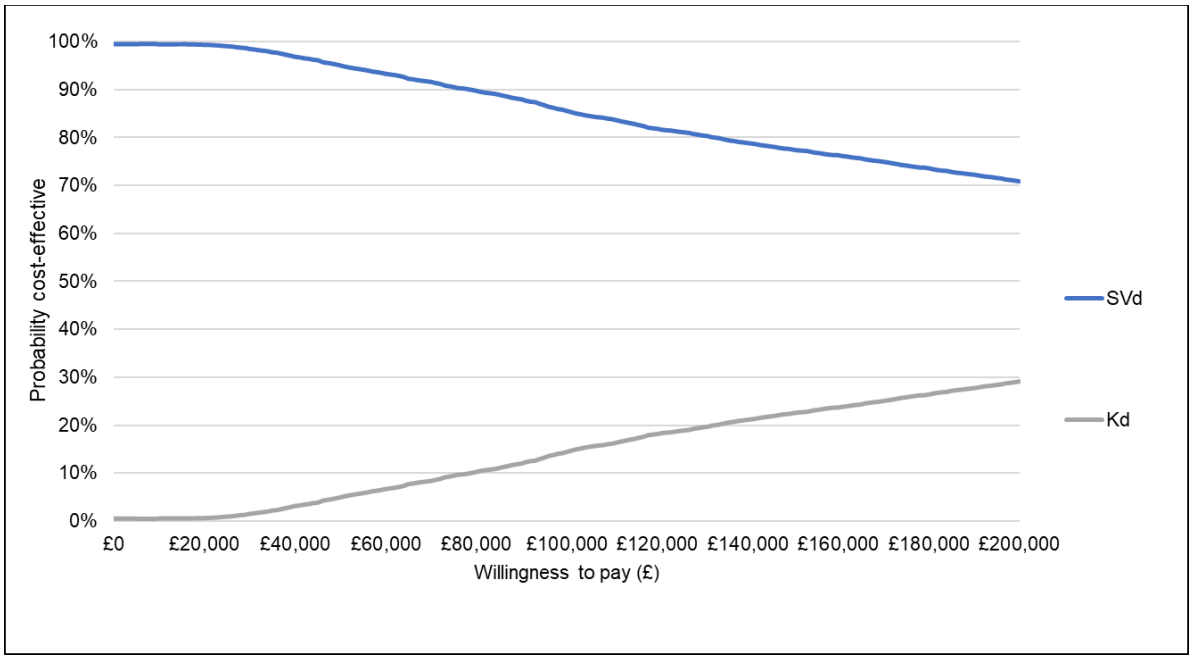


Figure 35 Cost-effectiveness acceptability curve for SVd *versus* Kd at 2L



The results of the PSA are broadly consistent across the 2L population in base case analysis. However, some numerical differences exist, even across 5000 simulations. This is likely driven by the small incremental QALYs in the ICER calculations, causing

the ICER to fluctuate when parameters are varied. Results are shown to be robust to changes in model parameters and assumptions in the OWSA and scenario analyses; with the biggest drivers of results identified as sensitivity with OS, PFS and ToT parameters.

B3.12.2 Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) was performed to identify key model drivers based on their relative influence on results. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available or using standard errors estimated based on ±20% variation around the mean where measures of variance around the base case values were not available. Pairwise one way sensitivity analyses were performed separately for each comparator and are reported for the 10 most influential parameters on the ICER. Survival model parameters were excluded due to the covariance between these parameters, which would lead to misleading or uninformative results when varying these estimates individually.

B3.12.2.1 OWSA results – 3L

Pairwise OWSA results for PanoVd and IxaRd *versus* SVd are presented in Figure 36 and Figure 37, showing the 10 most influential parameters on the cost-effectiveness results. Since estimates may span across quadrants of the cost-effectiveness plane (making ICER estimates difficult to interpret), results are reported in terms of net monetary benefit at a WTP of £30,000, such that SVd can be considered cost-effective if the NMB estimate is greater than zero.

For both 3L comparators, OS and PFS hazard ratio estimates were the parameter with the largest influence on results based on assumed levels of parameter uncertainty. Sensitivity results for SVd *versus* IxaRd (Figure 36) showed that upper and lower hazard ratio estimates for both OS and PFS yielded negative NMB estimates. This is due to the fact that OS HRs drive incremental cost and QALY results in opposing directions, but do not necessarily do so proportionally to one another. Whether the net impact on cost-effectiveness is positive or negative depends on the WTP assumed: in the OS example, the upper and lower HRs (IxaRd *versus* Sd) worsen and improve NMB, respectively, at a WTP <£5,000, whereas upper and lower HRs (IxaRd *versus* Sd) improve and worsen NMB, respectively, at a WTP >£50,000). Between these

values, the value assigned to QALYs is too low to offset cost increases when applying the more optimistic OR HR, but too high for cost savings to offset QALY losses when applying the pessimistic HR estimate.

Other than OS and PFS HRs, all OWSA results showed SVd to be cost-effective when varying parameters to upper and lower estimates.

Figure 36 3L OWSA NMB Results (SVd *versus* IxaRd)

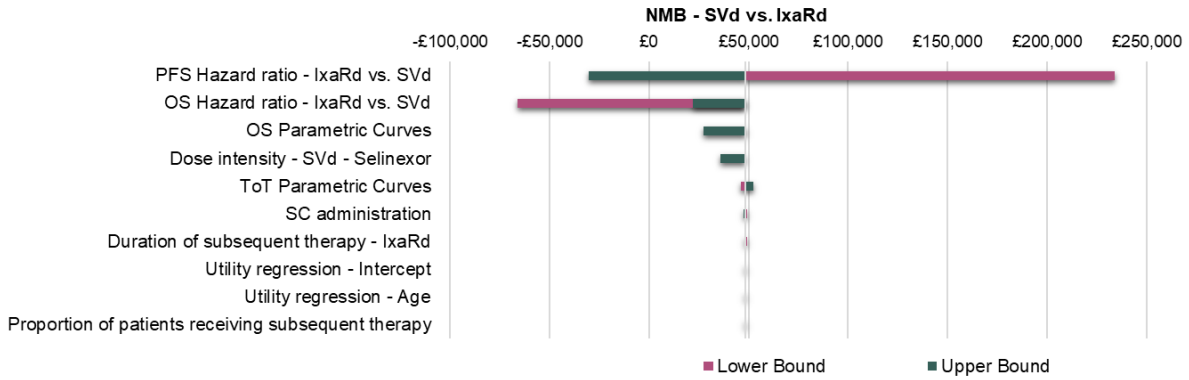
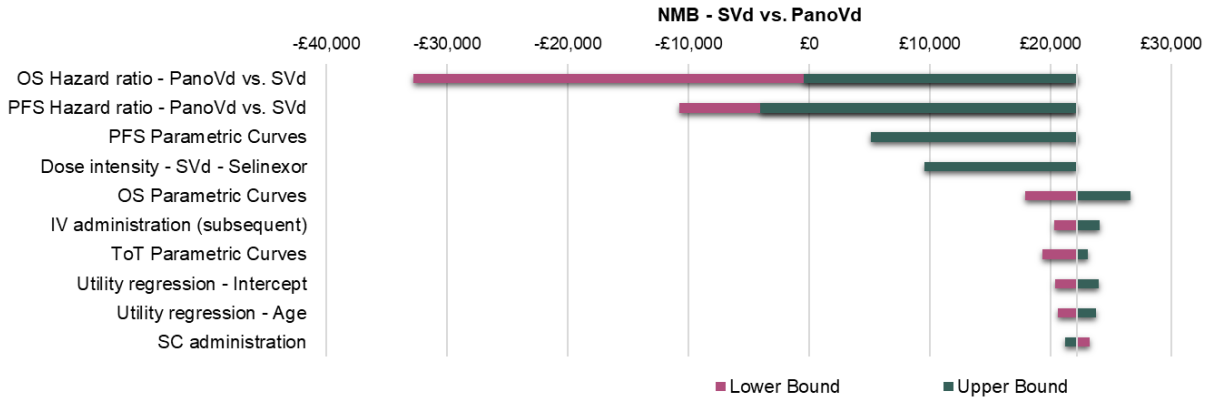


Figure 37 3L OWSA NMB Results (SVd *versus* PanoVd)



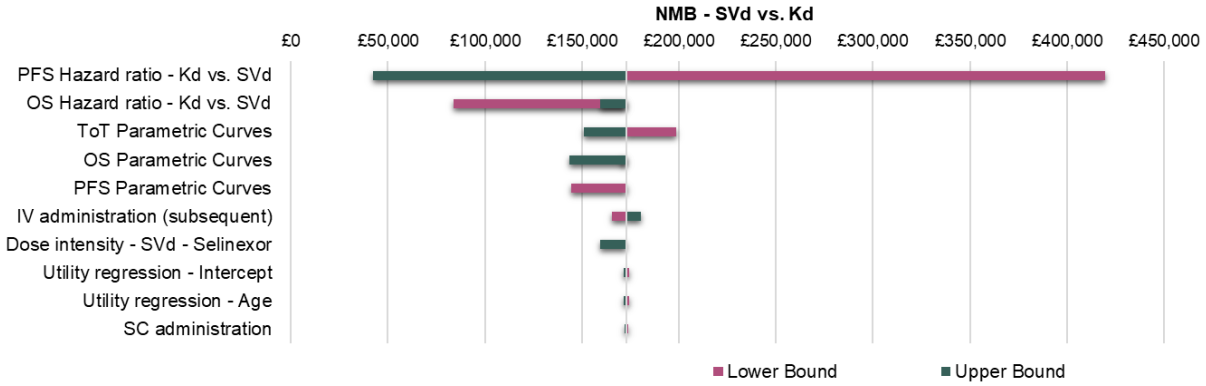
B3.12.2.2 OWSA results – 2L

OWSA results for SVd *versus* Kd are presented in Figure 38, indicating the top 10 most influential parameters on the cost effectiveness results. Results are presented in terms of impact on the ICER, but also the impact on the NMB to aid with interpretation of results and effects on cost-effectiveness.

The PFS Hazard ratio for Kd *versus* SVd has the largest impact on the ICER and NMB when adjusted to the upper and lower bounds. The sensitivity of results to this scenario

are driven by substantial differences in the drug acquisition and administration costs assumed for Kd, as comparator ToT is estimated using the PFS hazard ratio as a proxy for relative treatment duration. OS hazard ratio results by comparison are less sensitive, as scenarios in which lower/ higher costs are incurred are also associated with the same directional change in QALYs. The 2L results are also sensitive to the parametric curves, OS hazard ratios, and utility regression model variables.

Figure 38 2L NMB Results (SVd *versus* Kd)



B3.12.3 Scenario analysis

A series of scenario analyses were explored to assess the sensitivity of results to key areas of uncertainty outlined throughout the submission, applying alternative assumptions or estimates from published literature or expert opinion where available.

B3.12.3.1 Scenario analyses – 3L

For the 3L scenario pairwise analyses comparing SVd with IxaRd and PanoVd (Table 58), cost-effectiveness results were similar whether using estimates from random-effects or fixed-effects models from the NMAs.

To explore uncertainty around OS and PFS hazard ratios further, two additional scenario analyses were conducted. The first assumed equivalence between comparators in terms of OS, on the basis that data are less mature than for PFS, and more influenced by other factors such as subsequent therapies. This reduced the QALY gains associated with SVd to near-equivalence to both comparators, due to the small utility impact assumed for progressed *versus* progression-free health states. Incremental cost results, however, were relatively unchanged from base case estimates, since the largest component of cost was that of treatment, much of which

was incurred prior or close to disease progression. Because of the small QALY differences involved, the NMB estimate provides a more meaningful metric of cost-effectiveness than ICER for decision-making. In the second exploratory scenario, SVd and its comparators were assumed to be equally effective in terms of both OS and PFS endpoints. Since no QALY difference is assumed between treatment arms (other than disutilities associated with adverse events), ICER estimates have not been generated. Net monetary benefit in this scenario is lower than in the base case, due to the lack of substantive QALY gain, but remains positive due to the lower total costs applied.

Cost-effectiveness results were relatively robust to curve selection for both PFS and ToT, reflecting the maturity of data for both endpoints from the BOSTON study. By contrast, OS curve selection can be seen to have a large influence on results in keeping with expectations given the range of extrapolations illustrated in Figure 17 of Section B3.4.1.1.

Scenarios surrounding utility values were also explored. Although BOSTON utility estimates are considered most suitable for the base case analysis, being sourced directly from trial data and collected using the EQ-5D, a potential shortcoming is that line-specific estimates have not been applied. To assess the sensitivity of results to potential differences between 2L and 3L utility estimates, values specific to patients in each line were applied from Hatswell *et al.* 2019.[86] A further scenario included adjustment for an age-related utility decrement based on the UK general population, using the algorithm developed by Ara and Brazier (2010).[85] Neither scenario had a significant impact on NMB or changed the interpretation of cost-effectiveness results. Incremental QALYs ranged from 0.07-0.012 comparing SVd with IxaRd, while the incremental QALYs for SVd *versus* PanoVd range from 0.27-0.36.

Removing the dose adjustment assumption for selinexor, assuming a full 100mg weekly dose throughout treatment, reduced estimated NMB from base case levels of £48,427 to £35,810 *versus* IxaRd and from £22,181 to £9,564 v*ersus* PanoVd. Importantly, however, this scenario did not consider the likely increases in clinical effectiveness outcomes that might be associated with higher levels of treatment than were applied in the BOSTON trial used for base case estimates of dosage.

Table 58 Scenario analysis results for SVd *versus* IxaRd and PanoVd at 3L

Scenario dimension	Scenario	SVd *vs.* IxaRd incremental results			SVd *vs.* PanoVd incremental results		
		Costs (£)	QALYs	NMB at £30,000 (£)	Costs (£)	QALYs	NMB at £30,000 (£)
Base Case	Base Case Results	-£45,621	0.09	£48,427	-£11,567	0.35	£22,181
Time horizon	10 years	-£44,670	0.08	£47,138	-£13,484	0.32	£23,128
	20 years	-£45,623	0.09	£48,427	-£11,581	0.35	£22,191
Comparative efficacy	PFS: ITC hazard ratios (FE) OS: ITC hazard ratios (FE)	-£43,334	0.13	£47,224	-£11,697	0.35	£22,269
	PFS: ITC hazard ratios (RE) OS: HR=1 (equal efficacy)	-£46,362	-0.01	£46,035	-£13,223	-0.01	£13,052
	PFS: HR=1 (equal efficacy) OS: HR=1 (equal efficacy)	-£39,195	-0.01	£38,999	-£7,465	0.01	£7,697
PFS parametric curve	Fitted jointly with Vd: Exponential	-£45,456	0.09	£48,277	-£11,232	0.35	£21,830
	Fitted jointly with Vd: Weibull	-£45,260	0.09	£48,099	-£9,707	0.36	£20,388
	Fitted jointly with Vd: Log-logistic	-£45,613	0.09	£48,426	-£11,523	0.35	£22,159
	Fitted jointly with Vd: Gompertz	-£45,633	0.09	£48,437	-£11,534	0.35	£22,097
	Fitted jointly with Vd: Generalised gamma	-£45,620	0.09	£48,425	-£11,562	0.35	£22,168
	Fitted jointly with Vd: Gamma	-£45,267	0.09	£48,108	-£9,768	0.36	£20,453
	Fitted independently: Exponential	-£45,456	0.09	£48,277	-£11,232	0.35	£21,830
	Fitted independently: Weibull	-£45,223	0.09	£48,066	-£9,442	0.36	£20,137
	Fitted independently: Log-normal	-£45,612	0.09	£48,421	-£11,529	0.35	£22,128
	Fitted independently: Log-logistic	-£45,611	0.09	£48,425	-£11,514	0.35	£22,147
	Fitted independently: Gompertz	-£45,611	0.09	£48,413	-£11,513	0.35	£22,098
	Fitted independently: Generalised gamma	-£45,621	0.10	£48,475	-£11,559	0.36	£22,374

Scenario dimension	Scenario	SVd *vs.* IxaRd incremental results			SVd *vs.* PanoVd incremental results		
		Costs (£)	QALYs	NMB at £30,000 (£)	Costs (£)	QALYs	NMB at £30,000 (£)
	Fitted independently: Gamma	-£45,220	0.09	£48,065	-£9,431	0.36	£20,136
OS parametric curve	Fitted jointly with Vd: Exponential	-£46,916	0.20	£52,936	-£8,770	0.71	£30,036
	Fitted jointly with Vd: Log-normal	-£46,780	0.26	£54,486	-£7,671	0.93	£35,481
	Fitted jointly with Vd: Log-logistic	-£47,049	0.21	£53,405	-£8,879	0.75	£31,289
	Fitted jointly with Vd: Gompertz	-£41,568	0.04	£42,692	-£15,497	0.17	£20,455
	Fitted jointly with Vd: Generalised gamma	-£42,119	0.05	£43,475	-£15,039	0.19	£20,854
	Fitted jointly with Vd: Gamma	-£46,626	0.12	£50,291	-£10,522	0.45	£23,915
	Fitted independently: Exponential	-£46,916	0.20	£52,936	-£8,770	0.71	£30,036
	Fitted independently: Weibull	-£44,395	0.07	£46,422	-£12,782	0.27	£20,779
	Fitted independently: Log-normal	-£47,204	0.19	£52,804	-£9,545	0.65	£29,148
	Fitted independently: Log-logistic	-£47,297	0.17	£52,466	-£10,002	0.60	£28,054
	Fitted independently: Gompertz	-£41,401	0.04	£42,475	-£15,669	0.16	£20,452
	Fitted independently: Generalised gamma	-£47,366	0.16	£52,020	-£10,088	0.55	£26,536
	Fitted independently: Gamma	-£45,228	0.09	£47,946	-£11,274	0.34	£21,530
ToT parametric curve	Fitted jointly with Vd: Exponential	-£41,896	0.09	£44,711	-£13,046	0.35	£23,616
	Fitted jointly with Vd: Weibull	-£40,573	0.09	£43,391	-£16,202	0.35	£26,753
	Fitted jointly with Vd: Log-normal	-£47,927	0.09	£50,722	-£9,471	0.35	£20,103
	Fitted jointly with Vd: Gompertz	-£44,588	0.09	£47,396	-£9,992	0.35	£20,596
	Fitted jointly with Vd: Generalised gamma	-£43,887	0.09	£46,696	-£13,461	0.35	£24,055
	Fitted jointly with Vd: Gamma	-£40,147	0.09	£42,966	-£17,416	0.35	£27,962
	Fitted independently: Exponential	-£41,896	0.09	£44,711	-£13,046	0.35	£23,616
	Fitted independently: Weibull	-£40,547	0.09	£43,365	-£16,288	0.35	£26,838

Scenario dimension	Scenario	SVd *vs.* IxaRd incremental results			SVd *vs.* PanoVd incremental results		
		Costs (£)	QALYs	NMB at £30,000 (£)	Costs (£)	QALYs	NMB at £30,000 (£)
	Fitted independently: Log-normal	-£41,637	0.09	£44,454	-£16,332	0.35	£26,907
	Fitted independently: Log-logistic	-£42,472	0.09	£45,289	-£15,164	0.35	£25,752
	Fitted independently: Gompertz	-£49,983	0.09	£52,772	-£3,630	0.35	£14,279
	Fitted independently: Generalised gamma	-£53,655	0.09	£56,426	-£1,171	0.36	£11,839
	Fitted independently: Gamma	-£39,766	0.09	£42,586	-£18,410	0.35	£28,951
Comparator ToT	Treatment to progression	-£132,883	0.09	£135,730	-£24,583	0.37	£35,631
Adverse event application	Applied as one-off events	-£46,953	0.09	£49,714	-£8,163	0.33	£18,093
Discounting	No discounting (cost and benefits)	-£46,781	0.10	£49,781	-£10,399	0.38	£21,691
Selinexor weekly dosage	Full (100mg)	-£33,004	0.09	£35,810	£1,050	0.35	£9,564
Subsequent therapies	Costed after discontinuation	-£45,868	0.09	£48,673	-£11,456	0.35	£22,071
Drug Wastage	Excluded	-£46,564	0.09	£49,370	-£11,542	0.35	£22,156
Utility Source	BOSTON (arm specific)	-£45,621	0.12	£49,321	-£11,567	0.36	£22,474
	Hatswell *et al.* (2019)	-£45,621	0.07	£47,735	-£11,567	0.27	£19,781
Utility decrements	Adjusted using model coefficient	-£45,621	0.09	£48,316	-£11,567	0.34	£21,808

Abbreviations: FE, fixed effects; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; IxaRd, ixazomib plus lenalidomide and dexamethasone; mg, milligrams; NMB, net monetary benefit; OS, overall survival; PanoVd, panobinostat plus bortezomib and dexamethasone; PFS, progression-free survival; QALY, quality-adjusted life year; mg, milligrams; RE, random effects; SVd, selinexor in combination with bortezomib and dexamethasone; ToT, time on treatment ; SVd, selinexor plus bortezomib and dexamethasone; Vd, bortezomib plus dexamethasone; 3L, third-line.

B3.12.3.2 Scenario analyses – 2L

For the 2L scenario analyses comparing SVd with Kd (Table 59), the ICER results remain in the South-West quadrant for all scenarios, where SVd is associated with fewer costs and QALYs. Scenarios surrounding the probabilistic function for independent and dependent OS, PFS, and ToT curves, as well as including shorter model time horizons have the highest absolute impact on the ICER. All of the scenarios explored result in a positive (cost-effective) NMB *versus* Kd based on a list price assumption for carfilzomib.

Similar to the 3L comparisons, assuming equivalence with between SVd and Kd in overall survival rates has a minimal impact on cost-effectiveness result that is driven mainly by differences in incremental QALYs. The NMB for SVd *versus* Kd increases from £172,907 in the base case to £179,847 when assuming an OS HR of 1. Assuming equivalence in terms of both OS and PFS, time on treatment assumed for Kd is reduced more substantially, resulting in a decrease in incremental cost estimates and a reduction in the level of NMB to £117,613. This decrease occurs despite the beneficial impact on the incremental QALY estimate because of the reduced treatment duration assumed for Kd (derived on the basis of the PFS hazard ratio). Assuming Kd treatment to progression (rather than the relativity between PFS and ToT generalised from the SVd arm) yielded a substantially increased cost saving, due to the increased drug costs assumed for Kd.

Table 59 Scenario analysis results for SVd *versus* Kd at 2L

Dimension	Scenario	SVd *vs.* Kd incremental results		
		Costs (£)	QALYs	NMB at £30,000 (£)
Base case	N/A	-£182,324	-0.31	£172,907
Time horizon	10 years	-£179,044	-0.24	£171,891
	20 years	-£181,863	-0.31	£172,668
Comparative efficacy	PFS: ITC hazard ratios (FE) OS: ITC hazard ratios (FE)	-£181,298	-0.32	£171,746
	PFS: ITC hazard ratios (RE) OS: HR=1 (equal efficacy)	-£181,011	-0.04	£179,847
	PFS: HR=1 (equal efficacy) OS: HR=1 (equal efficacy)	-£117,834	-0.01	£117,613
PFS parametric curve	Fitted jointly with Vd: Exponential	-£182,321	-0.31	£172,907
	Fitted jointly with Vd: Weibull	-£182,404	-0.32	£172,924

	Fitted jointly with Vd: Log-normal	-£166,243	-0.32	£156,792
	Fitted jointly with Vd: Log-logistic	-£170,159	-0.32	£160,697
	Fitted jointly with Vd: Gompertz	-£156,722	-0.31	£147,368
	Fitted jointly with Vd: Generalised gamma	-£164,702	-0.31	£155,275
	Fitted jointly with Vd: Gamma	-£182,320	-0.31	£172,908
	Fitted independently: Exponential	-£182,321	-0.31	£172,907
	Fitted independently: Weibull	-£182,423	-0.32	£172,931
	Fitted independently: Log-normal	-£161,056	-0.31	£151,643
	Fitted independently: Log-logistic	-£165,015	-0.31	£155,583
	Fitted independently: Gompertz	-£156,038	-0.31	£146,714
	Fitted independently: Generalised gamma	-£158,793	-0.31	£149,510
OS parametric curve	Fitted jointly with Vd: Exponential	-£182,580	-0.39	£170,967
	Fitted jointly with Vd: Weibull	-£182,316	-0.29	£173,643
	Fitted jointly with Vd: Log-normal	-£183,406	-0.54	£167,232
	Fitted jointly with Vd: Log-logistic	-£183,169	-0.50	£168,082
	Fitted jointly with Vd: Gompertz	-£173,345	-0.21	£167,038
	Fitted jointly with Vd: Generalised gamma	-£182,456	-0.36	£171,551
	Fitted independently: Exponential	-£182,580	-0.39	£170,967
	Fitted independently: Weibull	-£182,328	-0.31	£172,935
	Fitted independently: Log-normal	-£183,480	-0.55	£166,981
	Fitted independently: Log-logistic	-£183,262	-0.52	£167,756
	Fitted independently: Gompertz	-£182,249	-0.26	£174,301
	Fitted independently: Generalised gamma	-£182,750	-0.43	£169,935
	Fitted independently: Gamma	-£182,365	-0.33	£172,414
ToT parametric curve	Fitted jointly with Vd: Exponential	-£188,523	-0.31	£179,104
	Fitted jointly with Vd: Weibull	-£184,020	-0.31	£174,602
	Fitted jointly with Vd: Log-normal	-£267,161	-0.31	£257,713
	Fitted jointly with Vd: Log-logistic	-£267,742	-0.31	£258,295
	Fitted jointly with Vd: Gompertz	-£218,698	-0.31	£209,274
	Fitted jointly with Vd: Generalised gamma	-£203,059	-0.31	£193,640
	Fitted independently: Exponential	-£188,523	-0.31	£179,104
	Fitted independently: Weibull	-£188,174	-0.31	£178,756
	Fitted independently: Log-normal	-£257,514	-0.31	£248,074
	Fitted independently: Log-logistic	-£273,135	-0.32	£263,683
	Fitted independently: Gompertz	-£272,281	-0.32	£262,826
	Fitted independently: Generalised gamma	-£258,742	-0.31	£249,300
	Fitted independently: Gamma	-£184,060	-0.31	£174,642
Comparator ToT	Treatment to progression	-£451,988	-0.31	£442,629

Adverse event application	Applied as one-off events	-£183,754	-0.32	£174,119
Discounting	No discounting (cost and benefits)	-£187,855	-0.34	£177,780
Selinexor weekly dosage	Full (100mg)	-£168,824	-0.31	£159,408
Subsequent therapies	Costed after discontinuation	-£182,308	-0.31	£172,891
Drug wastage	Excluded	-£169,673	-0.31	£160,256
Utility source	BOSTON (arm specific)	-£182,324	-0.28	£173,858
	Hatswell line-specific utilities	-£182,324	-0.30	£173,245
Utility decrements	Adjusted using model coefficient	-£182,324	-0.30	£173,351

Abbreviations: FE, fixed effects; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; Kd, carfilzomib plus dexamethasone; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; mg, milligrams; RE, random effects; SVd, selinexor plus bortezomib and dexamethasone; ToT, time on treatment; Vd, bortezomib plus dexamethasone; 3L, third-line.

B3.13 Subgroup analysis

No subgroups within the 2L and 3L populations were considered in the analysis.

B3.14 Benefits not captured in the QALY calculation

Additional benefits of therapy

QALY calculations included in the analysis comprise two main components: health state utilities (those corresponding to patients' disease progression status, assumed in this analysis to be generalisable across treatments); and treatment-specific disutilities due to adverse events.

An implicit assumption of this approach is that the only mechanism by which treatments can positively influence QALY outcomes is via the proportion remaining in more favourable (progression-free/ alive) health states, according to OS/ PFS estimates. Treatment-specific HRQoL effects (over and above progression-based utilities) are captured in terms of adverse events, but these can only have a subtractive effect on QALY estimates. This asymmetry potentially overlooks several *positive* treatment benefits identified by patients and clinicians as important in choosing between treatment options (and/ or whether to pursue further active therapy). A particular added value of SVd, particularly over comparators delivered via IV in a hospital setting (Kd at 2L, PanoVd at 3L) is its oral route of administration, providing a means to continued treatment that is both convenient and minimally invasive.

Carer health-related quality of life

The quality of life of carers has not been included in QALY calculations, but is likely to be substantial given the physical symptoms common in relapse. Carer quality of life impact has not been included in ICER estimates for previous MM appraisals, but is commonly factored in to cost-effectiveness cases in other disease areas. Incorporating quantitative estimates of the impact on informal carers of patients with MM would be expected to increase the estimated level of cost-effectiveness considerably.

B3.15 Validation

B3.15.1 Validation of cost-effectiveness analysis

The company engaged with key stakeholders including myeloma experts and patient representatives throughout the development and interpretation of the cost-effectiveness analysis to inform and validate estimates. Central to the myeloma expert engagement process were two advisory boards with UK MM experts to inform and validate assumptions about the current and evolving treatment landscape in MM across both indications, each with a different focus: Market Access (26th January 2023), Market Access and Health Economics (3rd May 2023).[36,37] Where evidence obtained through the expert engagement process was relevant to specific clinical or health economic aspects of the submission (such as the validation of survival extrapolation choices), these are also referred to in the corresponding sections of this document. A validation and clinical interpretation of NMA results was also conducted with clinical experts on 28th June 2023.

A technical quality control (QC) of the cost-effectiveness model has been performed, using internally-developed checklists aimed to assess the model in terms of face validity and perform a range of pressure and consistency checks to identify technical errors.

The company has also engaged with NHS Digital to seek access to Systemic Anti-Cancer Therapy (SACT) registry data as a potential source of validation or supportive evidence. At the time of submission, communications with NHS Digital have suggested the SACT registry to be a potential source of OS data, with the caveat that due to the limited data fields collected (particularly around patient history – therefore

refractoriness to prior lines), it may not be possible to isolate patients that are in 2L or 3L, or those receiving SVd rather than other selinexor-based combinations.

B3.16 Interpretation and conclusions of economic evidence

Base results, reflecting PAS pricing for selinexor, show SVd as a highly cost-effective treatment option when compared against current 3L comparators as well as an expected 2L positioning.

In a 3L setting, in which NMA results demonstrate a clinical benefit *versus* both IxaRd and PanoVd, SVd is shown to be dominant based on list price assumptions for either comparator, with a net monetary benefit of £48,427 *versus* IxaRd and £22,181 *versus* PanoVd. Corresponding ICERs are both negative (South-East quadrant), suggesting savings of £487,802 per QALY gained against IxaRd and £32,692 per QALY gained against PanoVd. In the 2L setting, where future unmet need is expected by clinical experts in MM patients that have received DRd as frontline therapy, base estimates demonstrate a high level of cost-effectiveness against Kd, with a net monetary benefit of £172,907 (South-West quadrant).

An extensive range of scenario analyses have been conducted to explore the sensitivity of results to the main sources of uncertainties that are inevitable in the context of a heterogeneous and continually evolving treatment landscape. Of those explored, the magnitude of net monetary benefit was shown to vary from base case estimates under the same cost assumptions, but did not imply a change in the cost-effectiveness decision.

A key uncertainty is around the relative efficacy of SVd *versus* treatment options for which head-to-head data are not available. The MM treatment landscape is, by necessity, a busy one, meaning that no single data source provides direct evidence against all relevant therapies. Vd, the comparator arm of the BOSTON study, is not itself a current UK comparator but fulfils an important function in bridging SVd evidence to that of comparators in the 3L and 2L settings via NMAs. As the number of studies informing each pairwise estimate is typically small, NMA HR results are associated with confidence interval ranges that overlap one in most comparisons. Despite this expected limitation, assessment of the NMA results by UK clinical experts suggests

that point estimate results have face validity and provide the most reliable and robust estimate of relative efficacy available regardless of implied statistical significance.

While the NMA does not provide the mechanism to control fully for differences in trial designs and populations, bias is expected to be in the favour of less recent comparator studies. As the treatments available at different lines have changed over time, so too has the profile of patients, with recent study cohorts more heavily pre-treated than those in earlier studies, and therefore likely to have benefitted from better frontline treatment and extended time in remission, but also presenting with disease that is more difficult to treat effectively due to prior exposure/refractoriness. This is particularly true for patients exposed and refractory to IMiDs and lenalidomide, who are the most difficult-to-treat patients in RRMM and present in substantially higher numbers in BOSTON than in past studies. The presence and likely impact of this unavoidable imbalance is suggested by NMA subgroup analyses specific to lenalidomide-refractory and PI-naïve patients, which demonstrate superior results to Kd at 2L and IxaRd and PanoVd at 3L based on a more balanced group of patients than is considered in the broader NMA comparisons.

Importantly, the cycle of remission and subsequent relapse as the disease becomes refractory to treatments is a characteristic of the MM treatment pathway that requires novel drug classes to be applied over the course of a patient's treatment to maximise the continued efficacy of therapy. A priority, therefore, in improving and extending the lives of MM patients is to consider the value of therapies not only in their clinical and cost-effectiveness compared directly to adjacent options in the treatment pathway but also provide potential for the number of successive drug classes and hence effective lines of therapy available over a patient's course of treatment to be extended.

Base case and scenario results demonstrate the high potential cost-effectiveness of SVd relative to comparators at both 3L and 2L settings. In the context of a highly individualised and dynamic treatment landscape, the company proposes that the recommendation of SVd as a treatment option at either positioning would provide clinicians with best means to make appropriate and adaptive decisions around the most beneficial timing for inclusion in the treatment pathway of both current and future patient cohorts.

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Appendices

The following appendices are provided as separate documents:

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection, and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: BOSTON utility analysis report

Appendix N: NMA validation

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Notes for authors: Please complete the template using plain language, taking time to explain all scientific terminology. As you draft your response, please do not delete the intro text included in each section. It might be a useful reference for patient reviewers.

However, any text preceded by the words '**Notes for authors**' simply contains additional prompts for the company to advise them on the type of information that may be most relevant, and the level of detail they need to include. **You may delete this text where indicated.**

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Nexpovio® (Selinexor)

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

The main population being appraised by NICE are myeloma patients requiring treatment in the second line (2L) and third line (3L) settings of the UK treatment pathway (i.e., for adult patients who have received one or two prior lines of treatment). Please see section 2c for details of the positioning of SVd in the treatment pathway. This positioning has been informed by and is supported by UK myeloma experts (Clinicians, clinical nurse specialists and pharmacists) and patients/patient representatives (Myeloma UK), 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 in the first line (1L) treatment setting.

Additionally, the company sought input and received supportive feedback on the proposed positioning of SVd in the treatment pathway from NHS England.

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Selinexor received EU marketing authorisation on 26th March 2021 (latest renewal date 13th May 2022). It was approved in two myeloma combinations in different treatment lines.

Both combinations are being appraised by NICE in parallel. However, this SIP relates to the combination of selinexor with bortezomib and dexamethasone.

The marketing authorisation wording of this combination is as follows:

Selinexor in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy[1].

Selinexor received MHRA marketing authorisation in February 2023 for the same indication[2].

https://mhraproducts4853.blob.core.windows.net/docs/b1f81c7ef0d562a5abefa7e9924be8df30157f85

Specific details of the marketing authorisation will be explained throughout this SIP, and details of each prior treatment or treatment class are included.

A separate SIP is available for the second treatment combination.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

In January 2023, a representative from Myeloma UK attended a Menarini-Stemline Advisory Board meeting with myeloma clinicians, clinical nurse specialists, pharmacists and health economists to ensure the needs and views of the myeloma patient community were represented in the discussions. Myeloma UK were paid for their participation at fair market value rates.

The company is also reviewing a voluntary contribution request from Myeloma UK to support general patient information and education services.

Section 2: current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen. **You may delete this note text.**

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Myeloma is a form of cancer arising from plasma cells found in the bone marrow. Plasma cells are a type of white blood cell that forms part of the body's immune system, and under normal circumstances, 'normal' plasma cells produce 'normal' proteins that help fight infection.

However, in myeloma, a higher number of abnormal plasma cells (abnormal plasma cells are myeloma cells) are produced, which in turn produce large quantities of an abnormal protein (also called an antibody) known as a paraprotein. Unlike normal proteins, paraprotein has no useful function and cannot fight infection.

In addition, myeloma cells suppress the development of other blood cells that are also responsible for fighting infection (white blood cells), carrying oxygen around the body (red blood cells) and blood clotting (platelets). Multiple myeloma refers to the presence of more than one site of affected bone at diagnosis.

Approximately 5,000 people are diagnosed with myeloma in England each year (2016 to 2018 data)[3]. It is most frequently diagnosed in older people, with about 43% of new cases in England in people 75 years or older[4]. The ten-year survival rate in England is estimated to be 29%, meaning that 29% of people diagnosed with myeloma are still alive after ten years[5].

In England, the number of people diagnosed is reported to be lower in the Asian ethnic group, higher in the Black ethnic group, and similar in people of mixed or multiple ethnicity, compared with the White ethnic group (2013-2017 data)[6]. The reasons for these differences are largely unknown.

At the time of diagnosis, most myeloma patients are likely to have bone pain in multiple areas of the body and are more susceptible to fractures and breaks. They are also susceptible to infections that take longer to resolve. A loss of appetite and

nausea is common, along with fatigue and breathlessness caused partly by anaemia.

Due to an accumulation of calcium in the bloodstream, hypercalcaemia causes patients to feel thirsty, tired and sick whilst passing a higher volume of urine than usual.

Spinal cord compression is another severe symptom causing severe back, neck, leg, and foot pain and loss of feeling (numbness) and is treated as a medical emergency[1].

These symptoms and complications affect many aspects of patient's lives, including reduced ability to perform activities of daily living, reduced participation in social activities and family life, and reduced likelihood of maintaining employment (for those still of active working age), thereby potentially impacting financial status[3].

The primary goal of treatment is to achieve an early, deep, and durable response with acceptable treatment-related side effects and improve quality of life. However, myeloma affects each patient differently, resulting in varying responses to treatment and impact on quality of life and survival. Survival can range from a few months to over ten years[7]. Quality of life is seen to deteriorate with disease progression[8].

Despite advances in treatment, myeloma remains incurable with a significant physical and emotional burden, fear of recurrence and overall impact on quality of life[9,10].

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Evidence shows that myeloma patients experience some of the longest delays in receiving a diagnosis compared overall with other cancers, and this remains the case despite national referral guidelines for suspected cancer and several campaigns from patient organisations. This is in part due to the vague and non-specific nature of symptoms.

Laboratory tests are essential for the diagnosis of myeloma. These include a bone marrow biopsy (to look for abnormal plasma cells in the bone marrow), a full blood count (to look at the number of other blood cells whose production may have been impacted by the higher number of plasma cells in the bone marrow), X-rays of the skeleton (to look for evidence of bone damage), and a specialised blood test to detect the presence of paraprotein in the blood.

A myeloma diagnosis is confirmed if at least 10 per cent of the cells in a bone marrow biopsy are abnormal plasma cells, evidence of organ damage such as bone damage or kidney failure, and evidence of abnormal protein in the blood[11].

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:

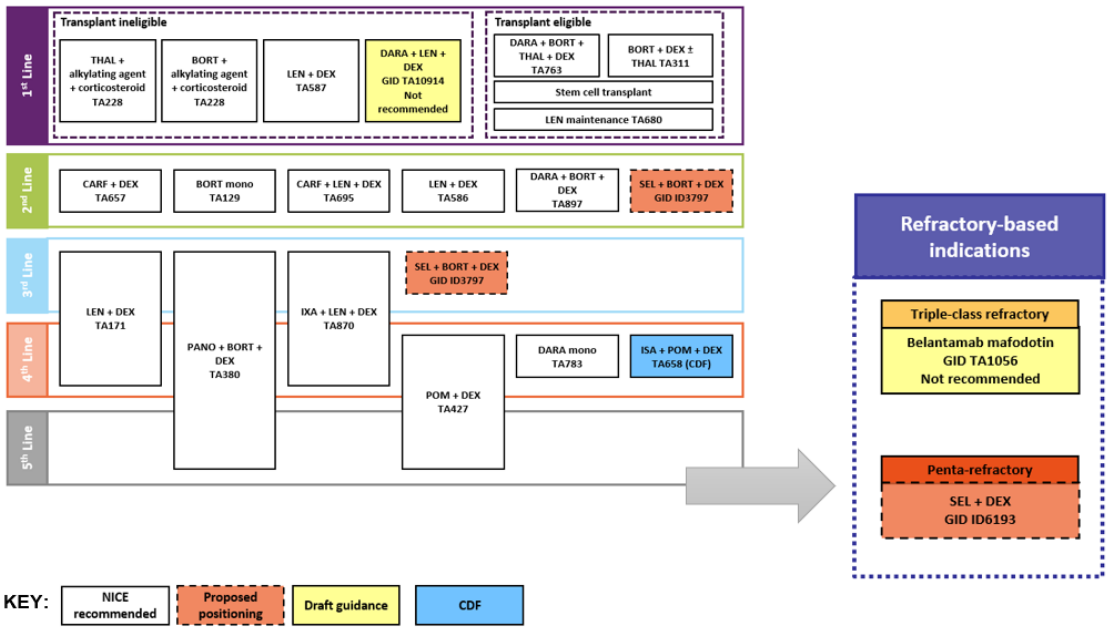
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The myeloma treatment pathway is complex and evolving rapidly. Myeloma patients often require multiple lines of treatment throughout the course of their disease.

Clinicians and patients place a high value on having access to safe and effective treatment combinations at different points in the treatment pathway. This includes access to differing but complementary and synergistic mechanisms of action (MoA), which are required as patients become increasingly refractory to different classes of treatment (drugs) as they progress through treatment lines.

The treatment pathway below reflects current published NICE guidance for the routine treatment of myeloma (correct to August 2023), including the anticipated position of selinexor:



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Myeloma patients usually have a lower quality of life than those without the cancer. They experience significant emotional and physical burdens, knowing this is an incurable cancer. Patients and their families constantly fear recurrence, which impacts their health-related quality of life, increasing the effect with each relapse[9,10].

Data collected from a survey of myeloma patients across 18 UK hospital clinics described the impact of myeloma-related symptoms on health-related quality of life. The survey reported that patients experienced decreased physical functioning, decreased cognitive functioning, severely decreased role functioning and severe financial difficulties[12].

Patients may experience a negative impact on their quality of life due to complicated treatment schedules. These schedules may involve different methods and frequency of administration and varied requirements for in-person hospital visits[13,14]. The humanistic burden is further exacerbated by treatment-related side effects, and caregiver stress and absenteeism can be significant[15].

However, while myeloma inevitably has a significant quality of life impact, especially in the later stages of the disease, patients receiving active treatment have been shown to have a better health-related quality of life (HRQoL) score than those receiving only supportive care, supporting the idea that patients benefit from further treatment options, particularly those with a new mechanism of action with which they have previously not been exposed to, maintaining hope for the future despite relapsing[15].

Section 3: the treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly. **You may delete this note text.**

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Selinexor is the first in a new family of drugs known as 'Selective Inhibitor of Nuclear Export' (SINE) compounds. There are other SINE compounds in development. However, selinexor is the first to be approved.

Selinexor works by blocking the action of a protein called Exportin 1, or XPO1 for short, within the nucleus of cancer cells. The nucleus is a cell's control centre[15]. By blocking the action of XPO1, selinexor prevents cancer cells from multiplying out of control, leading to their death. XPO1 is not myeloma or cancer-specific but is present in all cancer cells.

XPO1 is a protein in the nucleus of all cells that moves other proteins in and out of the nucleus. Some proteins only work when they are moved to a specific part of the cell. This means that XPO1 is important in helping move some proteins from the nucleus into the cytoplasm (the area of the cell surrounding the nucleus). In healthy (normal) cells, this is an essential process for cells to survive and carry out their intended function.

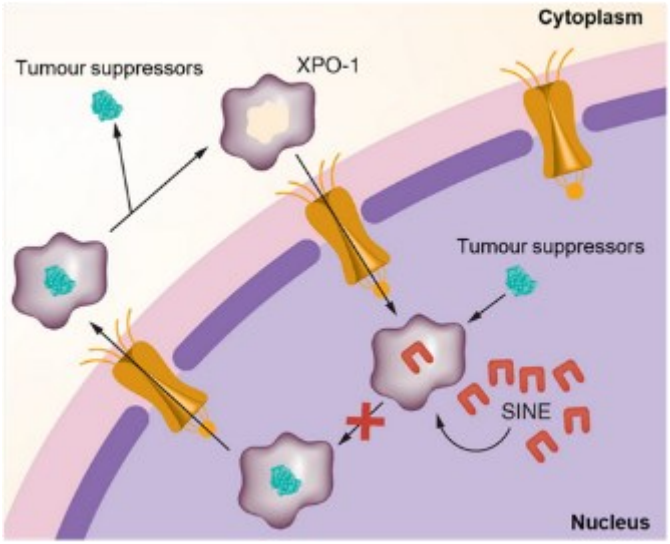
However, myeloma cells have higher than normal levels of XPO1. These higher levels of XPO1 are required by all myeloma cells to survive. Myeloma cells need XPO1 to remove proteins from the cell nucleus, where they are active and threaten myeloma cell survival, to the cytoplasm, where they pose no threat, allowing myeloma cells to grow and multiply. As mentioned above, Selinexor blocks this process, causing the myeloma cells to die.

Selinexor is given orally (by mouth) in tablet form. However, as with all anti-myeloma treatments, Selinexor is associated with several treatment-related side effects, the most common of which are described in section 3g.

It is considered a novel treatment for myeloma, given that it brings a new mechanism of action compared to existing treatments. This is important to

overcome myeloma cell treatment resistance, especially in the relapsed, refractory disease setting.

The picture below illustrates the mechanism of action of selinexor.



Summary of Product Characteristics (SPC) - Microsoft Word - 3334728241490700642_spc-doc.doc (windows.net)

Patient Information Leaflet (PIL) - Package leaflet: Information for the patient (windows.net)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☒Yes

☐No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Clinicians and patients place a high value on having access to safe and effective treatment combinations at different points in the treatment pathway, which include differing but complementary and synergistic mechanisms of action, as patients become increasingly refractory to different classes of treatment (drugs) as they progress through treatment lines.

In the context of this appraisal, selinexor is given in combination with bortezomib dexamethasone.

Bortezomib (Velcade) is a proteasome inhibitor (PI). It works by blocking the actions of proteasomes. Proteasomes are large molecules found in all cells of the body, and they are involved in the breakdown of damaged or unwanted proteins. Bortezomib temporarily blocks their function, stopping them from breaking down unwanted proteins. This causes proteins to build up to toxic levels, killing the myeloma cell.

Myeloma cells rely more heavily on proteasomes, as they produce more proteins than normal healthy cells. They are, therefore, much more sensitive to bortezomib[16].

As part of the SVd treatment combination, bortezomib is administered subcutaneously (injection under the skin) once weekly on day one of each week for four weeks, followed by one week off as part of a 35-day cycle.

Dexamethasone is a glucocorticoid drug. It mimics the action of a naturally occurring hormone in the body. It is effective at killing myeloma cells and can make other anti-myeloma treatments work better. It can also prevent inflammation and reduce pain associated with myeloma bone disease[17].

Dexamethasone is commonly available on the NHS and used in the treatment of multiple conditions.

As part of the SVd treatment combination, dexamethasone is taken orally (by mouth) twice weekly on days one and two of each week.

Please see section 3g for information about the possible side effects associated with selinexor, bortezomib and dexamethasone treatment.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

SVd treatment is given as a 35-day cycle of:

Selinexor 100mg taken as tablet, orally (by mouth), once weekly, on day one of each week.

The tablet should be swallowed whole with water. It should not be crushed, chewed, broken, or divided to prevent the risk of skin irritation from the active substance. It can be taken with or without food.

If a selinexor dose is missed or delayed or a patient vomits after a dose of selinexor, the patient should not repeat the dose. Patients should take the next dose on the next regularly scheduled day.

Dose modifications for selinexor in response to adverse events should be made by health care professionals as follows when in combination with bortezomib and dexamethasone:

- First reduction of 80mg once weekly
- Second reduction of 60mg once weekly
- Third reduction of 40mg once weekly

If symptoms do not resolve, treatment should be discontinued.

As part of the SVd treatment combination, bortezomib is administered subcutaneously (injection under the skin) once weekly on day one of each week for four weeks, followed by one week off, and dexamethasone is taken orally (by mouth) twice weekly on days one and two of each week.35-day cycle.

The SVd treatment does not involve additional visits to clinics or hospitals compared to current standard treatments. Information about bortezomib can be found in section 3b above.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

<u>Completed Trials</u>

The BOSTON (NCT03110562) phase 3 clinical trial provides a comprehensive and reliable data source on the effectiveness and safety of Selinexor when combined with bortezomib and dexamethasone (SVd). This trial compared the treatment combination of SVd with bortezomib and dexamethasone (Vd).

402 patients participated in the trial, with 195 patients given SVd and 207 given Vd.

The trial took place globally across 21 countries, including the UK.

The key inclusion and exclusion criteria were as follows[18]:

Key inclusion criteria (Patients considered suitable to be included in the trial)	**Key exclusion criteria** (Patients considered unsuitable to be included in this trial)
• Patients aged 18 years or older • Myeloma patients who have previously had one to three lines of anti-myeloma treatments • Patients with moderate or severe renal (kidney) impairment **when** the kidneys are not working properly. This is excluding patients requiring dialysis • ECOG status score of 0-2 (ECOG is a scale from 0-5 which is used to assess how a patient's disease is progressing and affecting the patient's daily life) • Adequate hepatic (liver) and haematopoietic (blood cell) functions	• Grade 2 neuropathy (nerve damage) or ≥ Grade 2 neuropathy with pain at baseline • Prior treatment with a Selective Inhibitor of Nuclear Export (SINE) drug, including selinexor • Patients who have previously required treatment for cancer or had evidence of recurrence • Patients with another medical condition, disease or active infection • Active plasma cell leukaemia • Myeloma patients with involvement of the central nervous system

The Boston trial started on 7th June 2017. The first data analysis was completed on 18th February 2020, and an updated data analysis was completed on 15th February 2021. There are no ongoing trials relevant to this submission.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?

- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Selinexor received marketing authorisation from the MHRA in February 2023. To be approved, the MHRA must be satisfied that the potential benefits of a new treatment outweigh its potential risks.

The BOSTON trial outcomes were[19]:

- Patients who received SVd experienced an increase of 4.47 months in progression-free survival compared to Vd. This means that they remained stable without any signs of the disease progressing for longer.
- This produced a 30% reduction in the risk of the disease progressing.
- SVd patients had a significantly improved overall response rate to the treatment compared with the Vd group.
- The SVd group had a higher number of patients with a deep response (a very good response to treatment or better) compared with the Vd group.
- SVd patients had a significant increase of 5.3 months in the time to the next treatment in comparison with the Vd group.

One limitation of this trial is that it had an open-label design. This means that both patients and researchers were aware of which treatment the patient was receiving. To prevent any bias, the efficacy of the treatment was only evaluated based on laboratory test results. These results were reviewed by an independent committee that was unaware of the patient's treatment group[19].

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life was improved by reducing the frequency and severity of nerve damage (peripheral neuropathy) when taking SVd compared to Vd.

The treatment known as SVd is more convenient for patients because it only needs to be administered once a week, whereas Vd and some other anti-myeloma treatment combinations require twice weekly administration. As a result, SVd patients have experienced a decrease in clinic visits by approximately 37%[19].

Quality of life was measured in BOSTON using the EORTC QLQ-CIPN20 and EORTC QLQ-C30 scales. These are questionnaires developed to assess the quality of life of cancer patients.

Another measure used was the EQ-5D-5L questionnaire. This measures a patient's quality of life by scoring their mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The most common adverse events that may occur with SVd and Vd treatments are[3]:

Treatment-related side effect	Patients that were affected during treatment with SVd and Vd in BOSTON trial
Thrombocytopenia (low-level of platelets in the blood. Can cause prolonged or excessive bleeding)	60% SVd, 27% Vd
Nausea (feeling sick with an urge to vomit)	50% SVd, 10% Vd
Fatigue (extreme tiredness)	42% SVd, 18% Vd
Anaemia (a lack of red blood cells or haemoglobin)	36% SVd, 23% Vd

Many of the negative effects on blood such as low platelet count can be fixed by adjusting the dosage and/or trying other treatments like growth factor and platelet transfusions. In most cases, these effects are reversible[20]. Patients should have their full blood counts monitored regularly during treatment and more frequently in the first two months of treatment.

To manage gastrointestinal side effects like nausea during selinexor treatment, anti-nausea medication is provided before starting the treatment and continued throughout. If necessary, the dose may be adjusted, and other anti-emetic medication may be added[20].

The safety of SVd was in line with the safety profiles of selinexor and Vd, with no new harmful effects observed. Any negative events were temporary and could be treated with adjustments in dosage and supportive care.

Treatment discontinuations were similar between the two treatment combinations.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of selinexor in combination with bortezomib (Velcade) and dexamethasone include:

- SVd is a triple combination treatment which includes a new mode of action, making it a potentially attractive prospect for patients and clinicians in areas of unmet need.
- The treatment has manageable side effects that are mostly reversible.
- SVd is a treatment that only needs to be administered once a week. This reduces the number of clinic visits required in comparison to other treatment options.
- In comparison to other bortezomib-containing combinations, the once-weekly combination has demonstrated a decrease in peripheral neuropathy, a common and debilitating treatment-related side effect of bortezomib.
- SVd treatment significantly prolongs progression-free survival compared to Vd
- The use of SVd resulted in a higher overall response rate, a better response, and a longer interval until the next treatment compared to Vd.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

While SVd aims to improve quality of life and survival, it is not curative and may not work in every patient. Although manageable and reversible, SVd is associated with several treatment-related side effects.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Note to authors:

Response:

The bullets below give a suggestion of structure, subheadings and key points to give the context of how the cost effectiveness of the treatment has been modelled. Addressing each of the bulleted points below should be kept to a few sentences.

How the model reflects the condition

What is the structure of the model? Explain how the model reflects the experience of having the condition over time.

Modelling how much a treatment extends life

- Does the treatment extend life? If so, please explain how (for example. by delaying disease progression, reducing disease severity or complications, reducing disease relapses or life-limiting side effects).

- Describe briefly which trial outcomes feed into the economic model. If trial data used for a certain length of time followed by extrapolation, please note how long the trial data was used for and briefly how the data has been extrapolated.

Modelling how much a treatment improves quality of life

- How is the treatment modelled to change a person's quality of life compared with the treatments already in use? This should include after stopping treatment if relevant. For example, say if the treatment improves quality of life because of improving symptoms or decreases quality of life because of side effects.

- Which quality of life measure(s) did you use to estimate a person's quality of life over time and on treatments? Are there any aspects of the condition or its treatments affecting quality of life which may not have been fully captured by the methods used to estimate quality of life?

Modelling how the costs of treatment differ with the new treatment

- Does the medicine lead to any cost implications (positive or negative) for the health service (e.g., drug costs, number of days in hospital)?

- Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g., where it is given or the monitoring that is needed)?

Uncertainty

- Are there any key assumptions you have made in your model about the medicine's benefits or costs because of lack of data?

- Did you test using alternative assumptions or data in your model? Which had the largest effect on your cost effectiveness estimates?

- Are there any data you have presented to support your modelled outcomes being plausible?

Cost effectiveness results

- What is the modelled benefit in overall survival, quality adjusted life years and the incremental cost effectiveness ratio? Please do not include statements giving your conclusions on whether the medicine is cost effective, this I s because the appraisal committee will make this decision.

Additional factors

- Have you made a case for a severity modifier being relevant for this condition? If so, please summarise the data presented

- Are there any benefits or disadvantages of the treatment not captured in the modelling?

You may delete this note text.

Selinexor represents a potential step-change in treatment for myeloma patients in the 3L treatment setting, where there is currently a lack of approved treatments.

Over time, as frontline treatment changes, it also has the potential to benefit specific patients at 2L.

Whilst associated with uncertainty, the relative efficacy of the SVd treatment combination compared to most currently available treatments suggests that it has the potential to improve patient outcomes.

The company designed a cost-effectiveness model to demonstrate the cost-effectiveness of SVd compared to the current standard of care. The results confirmed that this treatment combination is potentially cost-effective and represents a cost-effective use of scarce NHSE resources, particularly when reflecting the nature and severity of myeloma.

The quality of life of carers has not been included in QALY estimates but is likely to be substantial given the high frailty and physical dependency common in many patients at all stages of the disease.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Selinexor is a new and innovative treatment. It is a first-in-class drug, meaning it is the first in a new family of drugs known as Selective Inhibitor of Nuclear Export (SINE) compounds.

Selinexor has a novel mechanism of action, representing a significant advancement in the treatment of myeloma. It provides a promising alternative for patients in the key areas of unmet need in the myeloma treatment pathway.

A particular added value of selinexor is its oral route of administration which is minimally invasive and potentially more convenient for many patients.

The quality of life of carers has not been included in QALY estimates but is likely to be substantial given the high frailty and physical dependency common in many patients at all stages of the disease.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Several risk factors are 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 or lead to recommendations that will have an adverse impact on people with a particular disability or disabilities.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Selinexor (Nexpovio®) Horizons Infosheet (myeloma.org.uk)

Myeloma UK Treatment Guide

Myeloma symptoms | Cancer Research UK

What is myeloma? - Myeloma UK

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Term	Definition
AE	Adverse Events
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
HRQoL	Health-related quality of life
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple myeloma
PI	Proteosome inhibitor
RRMM	Relapsed and/ or refractory multiple myeloma
Sd	Selinexor plus dexamethasone
SLR	Systematic literature review
SVd	Selinexor plus bortezomib and dexamethasone

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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18. PowerPoint Presentation (karyopharm.com)
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions company response

September 2023

File name	Version	Contains confidential information	Date
ID3797 Sel+Bort+dex RR-MM EAG clarification questions company response	V2	Yes	28/01/24

Table of drug combination abbreviations

DRd	Daratumumab in combination with lenalidomide and dexamethasone
DVd	Daratumumab in combination with bortezomib and dexamethasone
IsaPd	Isatuximab in combination with pomalidomide and dexamethasone
IxaRd	Ixazomib in combination with lenalidomide and dexamethasone
Kd	Carfilzomib with dexamethasone
KRd	Carfilzomib in combination with lenalidomide and dexamethasone
PanoVd	Panobinostat in combination with bortezomib and dexamethasone
Pd	Pomalidomide with dexamethasone
Rd	Lenalidomide and dexamethasone
SVd	Selinexor in combination with bortezomib and dexamethasone
SVdX	Selinexor in combination with bortezomib and dexamethasone crossover population (crossed over from Vd to SVd)
Vd	Bortezomib and dexamethasone

Section A: Clarification on effectiveness data

Key clinical issue: The External Assessment Group (EAG) considers the indirect treatment comparisons (ITCs) provided by the company to be highly uncertain and recognises the difficulties in performing ITCs in relapsed/refractory multiple myeloma. In particular, the EAG considers the network meta-analysis (NMA) comparisons between SVd and lenalidomide containing comparators (KRd, Rd, IxaRd) to be flawed, and considers it highly unlikely that changes to the NMA methods could resolve this. Therefore, alternative analyses from the company are requested in questions A19, A20 and A21, which the EAG considers is crucial to exploring the uncertainty and robustness of the provided NMA. As such, the EAG requests that the company provides responses to Section B using both the company NMA estimates and the key analyses requested by the EAG. An overview of these requested analyses is presented below. The EAG has highlighted what it anticipates the preferred analysis for each comparator will be in green but notes this is subject to assessing the methods and conduct

of the additional analyses. Currently, the EAG has no clear preference between the requested analyses for PANO + BORT + DEX.

Line	Comparator	Analysis/ITC provided by company	Additional key analysis requested by EAG	Additional validation analyses requested by EAG
2L	CARF + DEX (Kd)	NMA	NMA (smaller network) /Bucher ITC	Unanchored and anchored MAICs (A22)
	BORT + DEX (Vd)	Direct trial evidence	—	—
	CARF + LEN + DEX (KRd)	NMA (via observational matched pairs analysis)	Unanchored MAICs (A20)	—
	LEN + DEX (Rd)	NMA (via observational matched pairs analysis)	Unanchored MAICs (A20)	—
	DARA + BORT + DEX (DVd)	NMA	NMA (smaller network) /Bucher ITC	Unanchored and anchored MAICs (A22)
3L+	PANO + BORT + DEX (PanoVd)	NMA (via common control arm with different dosing regimens)	1) Unanchored MAICs (A21) 2) NMA (smaller network) /Bucher ITC	—
	IXA + LEN + DEX (IxaRd)	NMA (via observational matched pairs analysis)	Unanchored MAICs (A20)	—

BOSTON Trial

The company thanks the EAG for recognising the difficulties in performing Indirect Treatment Comparisons on data for patients with relapsed/refractory multiple myeloma. We have followed the NICE Methods Guide and guidance from the NICE Decision Support Unit as the basis for the Company Submission including the Network Meta-Analysis (NMA). The outputs of the NMA have then been reviewed and validated

by leading UK multiple myeloma experts to ensure clinical plausibility of the results specifically in the UK context and NHS treatment pathway.

The recent positive recommendation for DRd as first-line treatment for transplant-ineligible patients (NICE GID-TA10914/ NICE ID4014)[1] will give rise to a significant unmet need at 2L for an effective treatment combination for a population of patients who are both daratumumab and lenalidomide relapsed and/ or refractory. The company is positioning SVd, in the 2L, in patients who have received daratumumab and lenalidomide in the front-line setting; based on the current reimbursed pathway, this would be in transplant-ineligible patients receiving DRd at 1L. Therefore, the company considers Kd the only relevant comparator at 2L and does not consider Vd, KRd, Rd or DVd; this has been validated by UK multiple myeloma experts.

The company positioning of SVd at 3L is not contingent on a specific prior treatment combination. This positioning was based on clinical feedback of a significant unmet need for a reimbursed treatment at this point in the clinical pathway. UK multiple myeloma experts state that patients receiving selinexor in the 3L will already be lenalidomide exposed and / or refractory and have been exposed and / or refractory to daratumumab. Therefore, the company considers PanoVd and IxaRd the only relevant comparator at 3L.

The company has explored the methodologies requested by the EAG for these comparators and are addressed in the responses to the specific questions. Based on this work the company base case has been updated to reflect a new 3L+ NMA, for both PFS and OS, where the link via the Dimopoulous matched-pairs analysis has been removed and replaced with an unanchored MAIC between Pd and Vd, using the ICARIA-MM trial and BOSTON IPD.

In addition to this document, the company also provide the following:

- A Supplementary Appendix of the updated 3L+ NMA
- Code for the 2L and the updated 3L+ NMAs
- A revised Microsoft Excel cost-effectiveness model (v1.1), containing both original and revised company base case analyses and a log of model changes subsequent to v1.0 .
- A Microsoft Word summary of revised company base case results
- Additional data on file to support A4 and A28

A1. Company submission (CS), Table 7. In BOSTON, the proportion of participants who have a prior stem cell transplant (SCT) appears imbalanced between the SVd arm in the intention-to-treat (ITT) population (39.0%) and 2L subgroup (39.4%), compared to the Vd arm in the ITT population (30.4%) and 2L subgroup (23.2%). Given that patients eligible for stem cell transplant (SCT) are exposed to different first line (1L) therapies and are, on average, younger and fitter than those ineligible for SCT:

a) Please comment on whether the presence of more SCT eligible patients in the SVd than Vd arm of BOSTON may lead to an overestimation of the SVd treatment effects relative to Vd.

Company response: Once patients demonstrate disease progression following an SCT, the benefit of the SCT does not impact the efficacy of future lines of treatment and clinical expert feedback is that prior SCT is not expected to influence PFS and OS in RRMM. Clinical expert feedback also confirmed that age and comorbidities are prognostic factors to response. SCT is likely to be seen in younger patients with a better performance status but, overall, it is age and comorbidities that influence PFS and OS, not the SCT itself. Participant age and baseline disease severity data (ECOG and R-ISS) were collected independently in BOSTON. They were well-balanced between arms in the ITT, as well as in the 2L and 3L subgroups. Thereby, it is not likely that the imbalance in SCT-eligible patients between arms will have influenced the reported treatment effect of SVd relevant to Vd.

b) Please provide an updated progression-free survival (PFS) and overall survival (OS) analysis for each group (ITT, second-line [2L], third-line [3L], 3L+), including prior SCT as a covariate in the stratified Cox proportional hazards model. Please also provide plots to assess the proportional hazards assumption for each analysis.

Company response: Since the Cox Proportional Hazards models for both PFS and OS endpoints (ITT, 2L, 3L) were stratified based on R-ISS score, the company feels it is not appropriate to also stratify based on prior SCT eligibility as a further proxy for disease severity.

A2. CS, section B.2.3.1. Please clarify why a different Vd dosing regimen was used in the SVd and Vd arms of BOSTON.

Company response: The Vd dosing used in each arm of the BOSTON trial are summarised in Table 16.

Dosing for SVd was based on the results from the dose-escalation phase of the phase 1b/ 2 trial, STOMP. The once-weekly (QW) recommended dosing of SVd in STOMP uses 40% less bortezomib and 25% less dexamethasone compared with standard twice weekly (BIW; for 2 of every 3 weeks) Vd combinations. Consequently, it is expected to have significantly less peripheral neuropathy and other significant AEs than standard Vd in addition to being more convenient for patients than standard Vd and the majority of Vd combinations, which require QW clinic visits for SC (or IV) administration of bortezomib.

Dosing in the Vd arm was in line with the SmPC, which is for up to eight 21-day cycles.[2] Following these eight cycles, patients in the Vd arm moved onto 35-day cycles consistent with the SVd dosing regimen.

A3. Priority question B.3.4.1. In BOSTON, the EAG notes that several different approaches of adjusting for crossover were considered, or performed, for overall survival. In the company submission, two-stage estimation with re-censoring was applied, however two-stage estimation without re-censoring was applied in the BOSTON clinical study report (CSR), with the justification that, [redacted] **In the CSR, a switch-adjusted hazard ratio (HR) using** [redacted] **was also presented, and, in the statistical analysis protocol, the only pre-specified method for adjusting for crossover was that an adjustment based** [redacted] **"may" be performed.**

Please clarify which methods have been implemented to adjust for treatment switching, and present and compare the outcomes of each, where performed, in

the ITT, 2L, 3L, and 3L+ settings. Please provide a discussion of and direction of any prediction biases in each analysis.

Company response: Two-stage estimation methods were implemented with re-censoring, following the recommendations described in Latimer *et al*. 2017[3] and in line with the approach used for the analyses submitted to EMA and MHRA. Other options were explored, but as demonstrated in Figure 1-

Figure 4, OS curves show little sensitivity to adjustment method. With this in mind, there is not a significant risk of bias in any direction.

Figure 1 [redacted]

Figure 2 [redacted]

Figure 3 [redacted]

Figure 4 [redacted]

A4. CS, Table 4. Progression-free survival on first post SVd/Vd/SVdX treatment (PFS2) was defined as a non-key secondary efficacy endpoint in the CSR, but does not appear to have been reported. Please provide PFS2 by arm, for the ITT, 2L, 3L

and 3L+ populations, including the number of patients receiving each subsequent therapy.

Company Response: PFS2 in the BOSTON trial was calculated from the date of first dose of post-SVd/ Vd/ SVdX treatment to the date of first progressive disease on post-SVd/ Vd/ SVdX treatment or death due to any cause. Patients who did not have an event were censored at the date of the last disease assessment or the database cut-off date, whichever occurred first.[4]

PFS2 data from the 2020 and 2021 data cuts of BOSTON are summarised in Table 1.[5] The number of patients receiving each subsequent therapy are summarised in Table 2.

Table 1 PFS2 data from the BOSTON trial

Analysis set	Intervention	Patients who received any post-SVd/ Vd/ SVdX therapy, n	Patients with events, n (%)	Patients censored, n (%)	Median PFS2 (CI), months
Primary Analysis (2020 data cut)					
ITT	SVd	[redacted]	[redacted]	[redacted]	[redacted]
	SVdX	[redacted]	[redacted]	[redacted]	[redacted]
	Vd (no crossover)	[redacted]	[redacted]	[redacted]	[redacted]
2L	SVd	[redacted]	[redacted]	[redacted]	[redacted]
	SVdX	[redacted]	[redacted]	[redacted]	[redacted]
	Vd (no crossover)	[redacted]	[redacted]	[redacted]	[redacted]
3L	SVd	[redacted]	[redacted]	[redacted]	[redacted]
	SVdX	[redacted]	[redacted]	[redacted]	[redacted]
	Vd (no crossover)	[redacted]	[redacted]	[redacted]	[redacted]
3L+	SVd	[redacted]	[redacted]	[redacted]	[redacted]
	SVdX	[redacted]	[redacted]	[redacted]	[redacted]
	Vd (no crossover)	[redacted]	[redacted]	[redacted]	[redacted]
Updated Analysis (2021 data cut)					
ITT	SVd	[redacted]	[redacted]	[redacted]	[redacted]
	SVdX	[redacted]	[redacted]	[redacted]	[redacted]
	Vd (no crossover)	[redacted]	[redacted]	[redacted]	[redacted]
2L	SVd	[redacted]	[redacted]	[redacted]	[redacted]
	SVdX	[redacted]	[redacted]	[redacted]	[redacted]

	Vd (no crossover)	[redacted]	[redacted]	[redacted]	[redacted]
3L	SVd	[redacted]	[redacted]	[redacted]	[redacted]
	SVdX	[redacted]	[redacted]	[redacted]	[redacted]
	Vd (no crossover)	[redacted]	[redacted]	[redacted]	[redacted]
3L+	SVd	[redacted]	[redacted]	[redacted]	[redacted]
	SVdX	[redacted]	[redacted]	[redacted]	[redacted]
	Vd (no crossover)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITT, intention-to-treat; PFS2, progression-free survival 2; SVd, selinexor in combination with bortezomib and dexamethasone; SVdX, Selinexor in combination with bortezomib and dexamethasone crossover population (crossed over from Vd to SVd); Vd, bortezomib plus dexamethasone

PFS2 in the BOSTON trial was calculated from the date of first dose of post-SVd/ Vd/ SVdX treatment to the date of first progressive disease on post-SVd/ Vd/ SVdX treatment or death due to any cause

Source: Data on file.[6]

Table 2 Subsequent therapies in BOSTON

	PI-based regimens	IMiD-based regimens	Anti-CD38-based regimens	Chemotherapy
ITT (N = 182)				
SVd	[redacted]	[redacted]	[redacted]	[redacted]
Vd	[redacted]	[redacted]	[redacted]	[redacted]
SVdX / SdX	[redacted]	[redacted]	[redacted]	[redacted]
2L only (N = 95)				
SVd	[redacted]	[redacted]	[redacted]	[redacted]
Vd	[redacted]	[redacted]	[redacted]	[redacted]
SVdX / SdX	[redacted]	[redacted]	[redacted]	[redacted]
3L only (N = 61)				
SVd	[redacted]	[redacted]	[redacted]	[redacted]
Vd	[redacted]	[redacted]	[redacted]	[redacted]
SVdX / SdX	[redacted]	[redacted]	[redacted]	[redacted]
3L+ (N = 87)				
SVd	[redacted]	[redacted]	[redacted]	[redacted]
Vd	[redacted]	[redacted]	[redacted]	[redacted]
SVdX / SdX	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IMiD, immunomodulatory drug; ITT, intention-to-treat; PI, proteosome inhibitor; SdX, selinexor plus dexamethasone crossover population (crossed over from Vd to Sd); SVd, selinexor in combination with bortezomib and dexamethasone; SVdX, Selinexor in combination with bortezomib and dexamethasone crossover population (crossed over from Vd to SVd); Vd, bortezomib plus dexamethasone.

Comparators

A5. Priority question. CS, section B.1.3.3. In the company submission, it is stated that: "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." Please clarify exactly where the company is positioning

SVd at 2L. It is currently unclear whether the company is positioning SVd for all relapsed/refractory multiple myeloma patients at 2L, or any of the following subgroups at 2L:

- **SCT ineligible patients only;**
- **LEN-refractory patients only;**
- **SCT ineligible patients who are LEN-refractory only, or;**
- **SCT ineligible patients who have received DRd at 1L only.**

Company response: The company recognises that the treatment pathway for multiple myeloma is rapidly evolving. The recent positive recommendation for DRd as first-line treatment for transplant-ineligible patients (NICE GID-TA10914/ NICE ID4014)[1] will give rise to a significant unmet need at 2L for an effective treatment combination for a population of patients who are both daratumumab- and lenalidomide-relapsed and/ or refractory. The company is positioning SVd, in the 2L, in patients who have received daratumumab and lenalidomide in the front-line setting, based on clinical feedback received during the development of the submission. Based on the current reimbursed pathway, this would be in transplant-ineligible patients receiving DRd at 1L.

A6. Priority question. CS, section B.1.3.3. As above, please clarify exactly where the company is positioning SVd at 3L, and whether this is contingent on treatment history.

Company response: The company positioning of SVd at 3L is not contingent on a specific prior treatment combination. This positioning was based on clinical feedback of a significant unmet need for a reimbursed treatment at this point in the clinical pathway. However, UK myeloma experts stated at an Advisory Board that patients receiving selinexor in the 3L will already be lenalidomide-exposed and/ or refractory and have been exposed and/ or refractory to daratumumab.

A7. Priority question. CS, section B.1.3.3. The EAG considers the following comparators to be relevant at 2L:

- **Kd;**

- **Vd (The EAG's clinical experts noted that bortezomib monotherapy is rarely given in UK clinical practice, and instead Vd is used. The EAG's clinical experts also noted that while Vd is used infrequently in current clinical practice, if DRd were approved for routine commissioning in 1L, the use of Vd at 2L would likely increase);**
- **KRd (for example, for a SCT ineligible patient receiving a bortezomib containing regimen at 1L);**
- **Rd (for example, for a SCT ineligible patient receiving a bortezomib containing regimen at 1L);**
- **DVd (for example, for patients who are not refractory to daratumumab after 1L).**

The EAG considers these comparators to be relevant at 2L even if DRd is approved for routine commissioning at 1L, as the EAG's clinical experts suggested that not all SCT ineligible patients would receive DRd at 1L, and, given the PFS benefit associated with DRdmay be around 5 years, many incident 2L patients in the years following a hypothetical approval of DRd at 1L would not have received DRd *[N.B. the EAG confirmed the regimen referred to throughout this paragraph should be DRd and not DVd as originally requested*

a) **If the company does not consider 1 or more of these as relevant comparators, please provide further justification outlining why for each.**

Company Response: Given the clarification provided in A5, that the company positioning of SVd at 2L is for patients who have received DRd at 1L, the company does not consider the following comparators relevant:

- **Vd** – not a NICE-reimbursed treatment combination and, therefore, not relevant to the NICE treatment pathway.
- **KRd** – UK clinical experts consulted by the company confirmed that following DRd, patients would be lenalidomide-relapsed and/ or refractory and, therefore, would not receive a lenalidomide-containing combination at 2L.
- **Rd** – UK clinical experts consulted by the company confirmed that following DRd, patients would be lenalidomide-relapsed and/ or refractory and, therefore, would not receive a lenalidomide-containing combination at 2L.

- **DVd** – UK clinical experts consulted by the company confirmed that following DRd, patients would be daratumumab-relapsed and/ or refractory and therefore would not receive another daratumumab-containing combination at 2L.

Therefore, the Company considers the only relevant comparator in this 2L setting to be Kd, as included in the company submission. This was validated with clinical feedback during the submission process.

b) Please clarify if the comparative efficacy analyses presented in the ITC report for PFS and OS for each of the comparators listed above at 2L are the company's preferred comparative efficacy analyses for these comparators. If not, please provide alternative analyses for PFS and OS.

Company Response: As per the response to A7a, the company considers Kd the only relevant comparator for SVd in the proposed 2L setting. The efficacy analyses from the presented 2L NMA are still the company's preferred estimates.

Indirect Treatment Comparisons

A8. Table 9 in Appendix D includes 2 different populations for the ENDEAVOR study. Please clarify which of these were used in the NMA, with justification.

Company response: In the 2L NMA for PFS and OS, data from Moreau 2017 and Orlowski 2019 were used, respectively.[7,8]

PFS data from Dimopoulos 2016 and Moreau 2017 were similar, and differences appear to be due to rounding (both sources of data were based on a data cut from November 2014); data from the most recent publication (Moreau 2017) were selected for inclusion in the PFS NMA.[8,9]

OS data from Orlowski 2019 were based on approximately 44 months of follow-up compared to Dimopoulos 2017, which was based on approximately 37 months of follow-up. Therefore, data from the latest data cut were selected for inclusion in the OS NMA.[7,10]

A9. Please provide the estimated 95% CIs generated from the digitised pseudo-IPD (individual patient data) for APEX.

Company Response: No uncertainty around the hazard ratio (HR) was presented for either PFS or OS outcomes in the 2L population of the APEX trial. Therefore, 2L Kaplan-Meier curves were digitised using an algorithm published by Guyot *et al.* (2012),[11] and pseudo individual patient data (IPD) were recreated to provide an estimate of the uncertainty. The 95% CI estimated from the pseudo-IPD is presented in Table 3.

Table 3 95% confidence intervals estimated from APEX pseudo individual patient data

Population	HR (reported by Richardson *et al.* 2005)[12]		Estimated 95% CI (using digitised pseudo IPD)	
	PFS	OS	PFS	OS
2L	0.56	0.42	[0.43, 0.73]	[0.24, 0.73]

Abbreviations: 2L, second-line; CI, confidence interval; HR, hazard ratio; IPD, individual patient data; OS, overall survival; PFS, progression-free survival.

The standard error (SE) in the 2L population was used to estimate of the 95% CI in the 3L+ population (in the absence of reported Kaplan-Meier curves for the 3L+ population).

However, it should be noted that the updated 3L+ network, summarised in the Supplementary Appendix, omits APEX.

A10. Please provide an updated version of **Table 10 in Appendix D** to include the outcome data from the matched pairs analysis of bortezomib vs bortezomib + dexamethasone.

Company Response: Please find an updated version of Table 10 from Appendix D (outcome data used in the 3L+ NMA**)** shown in Table 4 below**,** with the additional requested data highlighted in grey cells.

It should be noted that given the uncertainties around the matched-pairs analysis, an updated 3L+ NMA was performed which omits Dimopoulos 2015 and APEX (as described in A18, and the Supplementary Appendix).[12,13] Since a link was created between Pd and Vd through an unanchored MAIC using the ICARIA-MM trial and the BOSTON IPD, ICARIA-MM has been added to the tables in line with the updated 3L+

NMA network. Similarly, MM-003 has also been included in the table below given that it allowed to link Pd to Rd, and consequently to IxaRd (comparator of interest). Please note that the hazard ratios from the original and updated 3L+ NMAs are similar, further validating the results.

Table 4 Outcome data used in the 3L+ NMA

Trial name/ ID	Intervention	n	Median PFS (months)	PFS HR (95% CI)	Median OS	OS HR (95% CI)
BOSTON[5]	SVd	96	11.76	0.805 (0.559, 1.159)	31.74	0.829 (0.518, 1.328)
	Vd	108	9.43		NR	
APEX Richardson 2005[12] (omitted from the updated 3L+ NMA network)	BORT	200	4.9	0.55 (NR)	NR	0.63
	Dex	217	2.9		NR	
ICARIA-MM Richardson 2022[14]	IsaPd	154	11.1	0.599 (0.460, 0.780)	24.6	0.76 (0.57, 1.01)
	Pd	153	5.9		17.7	
MM-003 San Miguel 2015[15]	Pd	302	4.0	0.49 (0.4, 0.61)	13.1	0.72 (0.56, 0.92)
	Dex	153	1.9		8.1	
MM-009[a] Weber 2007[16]	Rd	109	10.2	NR	29.6	0.44 (0.30, 0.65)
	Dex	109	4.6		20.2	
MM-010[b] Dimopoulos 2007[17]	Rd	120	11.1	NR	NR	0.66 (0.45, 0.96)
	Dex	118	4.7		20.6	
MMY-2045, APEX, DOXIL-MMY3001 matched pairs analysis Dimopoulos 2015[13] (omitted from the updated 3L+ NMA network)	Vd	109	11.9	0.595 (0.351, 1.008)	NR	0.958 (0.541, 1.698)
	BORT	109	6.4		NR	
PANORAMA-1 San Miguel 2014[18]	PanoVd	188	12	0.64 (0.5, 0.83)	NR	NR
	Vd	182	7.6		NR	
PANORAMA-1 San Miguel 2016[19]	PanoVd	188	NR	NR	34.6	0.96 (0.74, 1.26)
	Vd	182	NR		30	
TOURMALINE-MM1 Mateos 2017[20]	IxaRd	148	NR	0.58 (0.401, 0.838)	NR	NR
	Rd	149	12.9		NR	
TOURMALINE-MM1 Richardson 2021[21]	IxaRd	148	NR	NR	53	0.845 (0.642, 1.114)
	Rd	149	NR		43	

Abbreviations: Bort, bortezomib monotherapy; CI, confidence interval; dex, dexamethasone; HR, hazard ratio; IxaRd, Ixazomib + lenalidomide + dexamethasone; NMA, network meta-analysis; NR, not reported; OS, overall survival; PanoVd, panobinostat + bortezomib + dexamethasone; PFS, progression-free survival; Rd, lenalidomide + dexamethasone; SVd, selinexor in combination with bortezomib plus dexamethasone; Vd, bortezomib plus dexamethasone; 3L+, third-line plus.

[a] Data reported for PFS was time to progression; OS data reported for the 2L+ population comprising 38.2% 2L and 61.8% 3L+

Trial name/ ID	Intervention	n	Median PFS (months)	PFS HR (95% CI)	Median OS	OS HR (95% CI)
[b] Data reported for PFS was time to progression; OS data reported for the 2L+ population comprising 32.2% 2L and 67.8% 3L+ Source: Data on file[5]						

A11. Appendix D. Please specify for which studies median PFS or median OS was included by arm in the NMAs, when HRs were not available. Please comment on whether the assumption of a constant hazard in each arm is likely to have held for each arm, and the likely magnitude and direction of any bias introduced if the assumption is violated.

Company Response: Median values were used in the NMA in the 3L+ PFS network to connect dexamethasone (D) with lenalidomide plus dexamethasone (Rd) using data from two studies (MM-009 and MM-010). Median data were included in the network (in the absence of a reported HR), using the methodology proposed by Woods *et al*. 2010.[22] It is not possible to assess the proportional hazards (PH) assumption in the 3L+ population as no Kaplan-Meier curves are reported for this population. Therefore, the PH assumption cannot be robustly interpreted for these two studies.

However, the PH assumption has been assessed in the 2L+ population from MM-009 and MM-010 since Kaplan-Meier curves are available. These curves were digitised and pseudo IPD were created using the algorithm published by Guyot *et al.* (2012).[11]

Table 5 indicates that the null hypothesis of PH is rejected within the 2L+ population in the MM-009 study for the PFS outcome, but cannot be rejected within the 2L+ population in the MM-010 study for the PFS outcome. Figure 5 and Figure 6 depict the log-cumulative hazards and Schoenfeld residuals, respectively. Although the Schoenfeld residuals indicate a non-horizontal line (suggesting a potential violation of the PH assumption), the log-cumulative hazard plot indicates parallel curves for Rd and D in both studies.

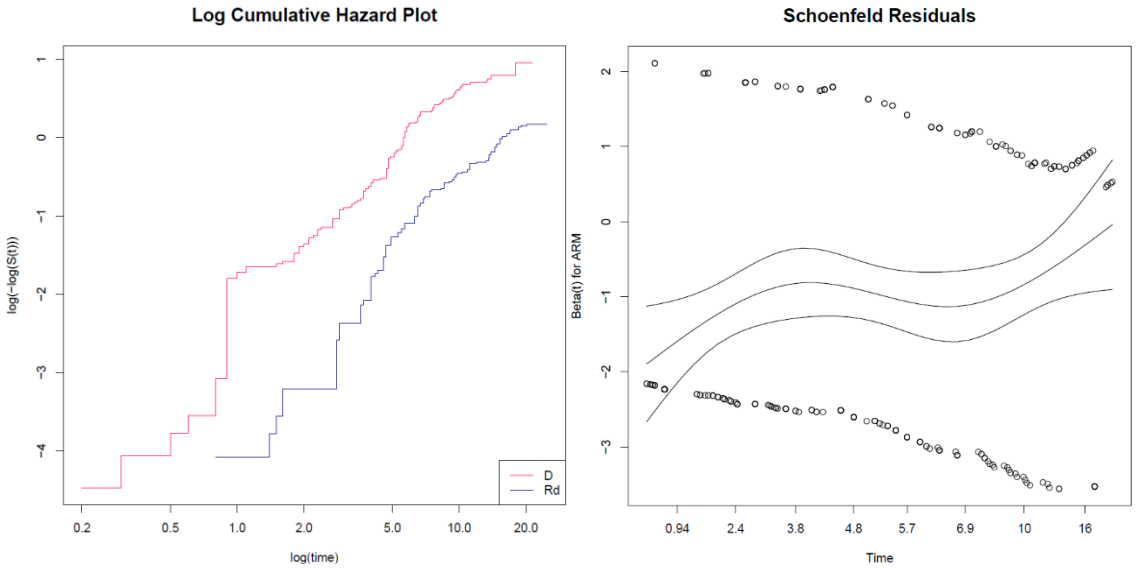
Whilst these results are based on an evaluation of the 2L+ population, it is not possible to comment on the applicability of this finding to the 3L+ population due to the limited data available. In addition, as only median values are available for the 3L+ population, exploring alternative methods which relax the PH assumption is not possible.

The networks informing the relative efficacy estimates for PFS and OS attempt to synthesise all available data in both the 2L and 3L+ populations; some studies support the assumption of PH, whilst others do not (see response A16). To reflect the totality of the data, an NMA was considered the optimal approach. However, it is not possible to synthesise all these data within a more complex framework which relaxes the PH assumption without including data across different populations and using data from older data cuts. The NMA are the most robust indirect treatment comparison approach reflecting all available data in these populations.

Table 5 Proportional hazards testing MM-009 and MM-010 (2L+, PFS)

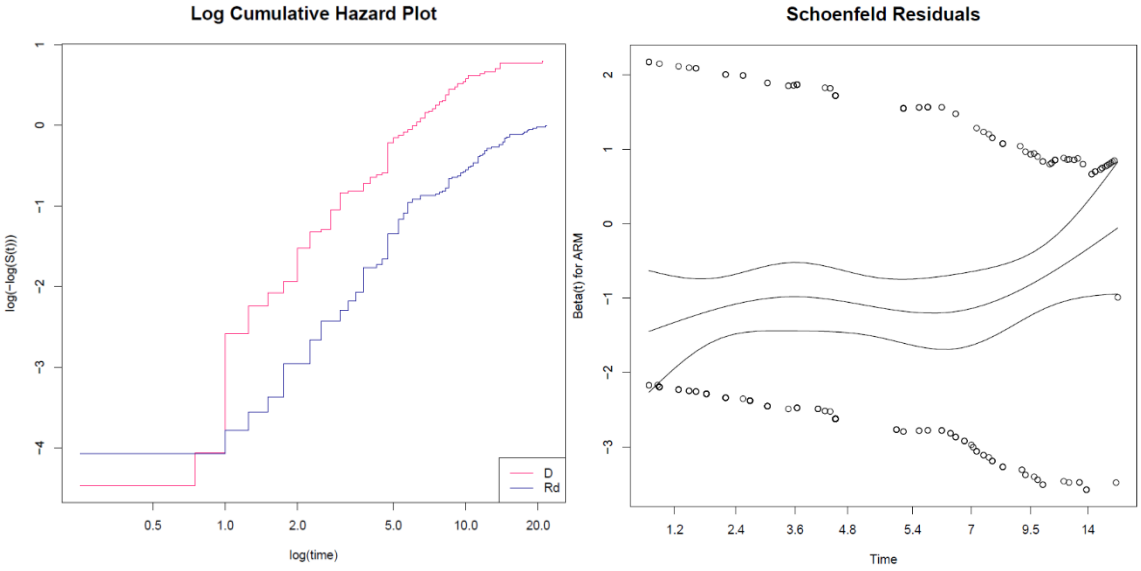
Trial	Comparison	Chi-squared	DF	P-Value
MM-009	Rd versus D	5.6465	1	0.0175
MM-010	Rd versus D	3.0837	1	0.0791
Abbreviations: D, dexamethasone; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone; SE, standard error.				

Figure 5 Proportional hazards testing MM-009 (2L+, PFS)



Abbreviations: D, dexamethasone; PFS, progression-free survival; Rd, lenalidomide + dexamethasone

Figure 6 Proportional hazards testing MM-010 (2L+, PFS)



Abbreviations: D, dexamethasone; PFS, progression-free survival; Rd, lenalidomide + dexamethasone

A12. Please clarify how the informative prior distribution for between-study standard deviation was selected.

Company Response: The informative prior distribution based on a half-normal (HN) distribution was selected due to the paucity of data for each treatment contrast in all networks (for all treatment comparisons, there is a maximum of two studies available).

This informative prior distribution was selected based on guidance published by the NICE Decision Support Unit (DSU).[23]

A13. Please provide the posterior distribution of the between-study standard deviation, and comment on the amount of posterior updating that has occurred.

Company response: A summary of the estimates obtained from the posterior distribution of the between-study standard deviation (SD) for each NMA are presented in Table 6, which shows there is heterogeneity present in each of the networks. The results reported for the 3L+ NMA are based on the updated network.

Table 6 Summary estimates from the posterior distribution of the between-study standard deviation

Line	PFS	OS
	Median SD [95% CrI]	Median SD [95% CrI]

2L	0.134 [0.005, 0.566]	0.208 [0.011, 0.658]
3L+	0.132 [0.004, 0.556]	0.210 [0.011, 0.651]
Abbreviations: 2L, second-line; 3L+, third-line onwards; CrI, credible interval; OS, overall survival; PFS, progression-free survival; SD, standard deviation.		

Posterior updating was observed for PFS in both 2L and 3L+ populations. However, for OS, only limited posterior updating was observed. This could be due to the paucity of data in all networks (a maximum of two studies were available for any treatment comparison).

A14. Please provide a sensitivity analysis of each NMA using wider prior distributions for the between-study standard deviation, for example, HN(0,0.5^2) or HN(0,1^2)

Company response: The NMA results from sensitivity analyses using a HN(0,0.5^2) distribution for the between-study standard deviation are presented in Table 7. These results are similar to the NMA results using the prior distributions recommended by the NICE Decision Support Unit (DSU)[23] and hence larger prior distributions are not likely to affect the overall NMA results, further validating the results of the company's NMA. The results reported for the 3L+ NMA are based on the updated network.

Table 7 NMA results using HN(0,0.5^2) distribution for the between-study standard deviation

Line	**Comparator**	**PFS**	**OS**
		HR [95% CrI]	**HR [95% CrI]**
2L	Kd *versus* SVd	0.729 [0.253, 2.239]	0.886 [0.233, 3.488]
3L+	IxaRd *versus* SVd	0.695 [0.075, 6.216]	1.086 [0.136, 8.035]
	PanoVd *versus* SVd	0.802 [0.177, 3.645]	1.246 [0.312, 4.983]
Abbreviations: 2L, second-line; 3L+, third-line onwards; CrI, credible interval; HR, hazard ratio; IxaRd, ixazomib plus lenalidomide plus dexamethasone; Kd, carfilzomib plus dexamethasone; OS, overall survival; PanoVd, panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival; SVd, selinexor plus dexamethasone.			

A15. Priority question. Appendix D. The EAG notes that there is considerable heterogeneity between the studies informing the NMA. At the time of writing the clarification letter, the EAG has not received the requested systematic

literature review (SLR) report from the Company. The EAG notes that baseline characteristics have only been provided for the ITT populations of studies included in the NMA, and that key study details have not been included in the study characteristics tables of the CS. Please complete the following tables of study characteristics, patient baseline characteristics, and outcomes, for the following studies and subgroups:

- **BOSTON (2L subgroup, 3L subgroup, 3L+ subgroup);**
- **ASPIRE, CASTOR and ENDEAVOR (2L subgroup if available, ITT population if not);**
- **APEX, MM-09, MM-010, PANORAMA-1 and TOURMALINE-MM1 (3L subgroup, 3L+ subgroup where appropriate);**
- **The Dimopoulos 2015 matched pairs analysis.[13]**

Please ensure relevant health technology appraisals have been searched for subgroup data relating to relevant treatment lines.

a) **Study characteristics**

- **Please update Table 6 of Appendix D to include the following additional trials: CASTOR; ASPIRE; MMY-2045; DOXIL-MMY-3001.**
- **Please also include full details of the dosing regimen for all trials in Table 6, including whether dosing was for a fixed period or until disease progression for each arm.**
- **Please include the stratification factors used in randomisation for each trial, specifically whether and how randomisation was stratified by prior lines of therapy.**
- **Please include whether crossover was permitted, at which time points and using which criteria.**
- **Please include blinding and the method and criteria for assessing PFS.**

b) **Baseline characteristics**

- **Please provide versions of Tables 6 and 7 from the Company submission for each of the studies included in the NMAs relevant to this appraisal (including CASTOR; ASPIRE; and the Dimopoulos 2015 matched pairs analysis). Please provide these for the subgroups used in the NMAs (e.g., 2L, 3L+), and only for the ITT population if no subgroup data are available.**

Please ensure relevant HTA submissions have been searched for relevant subgroup data.

Outcomes

- **For each study population included in the NMAs, (including CASTOR; ASPIRE; and the Dimopoulos 2015 matched pairs analysis), please complete the following table of outcomes. Please provide data using the relevant line subgroup (2L, 3L or 3L+) where available, and where data are not available for the subgroup, please provide the ITT data, flagging where ITT data are used.**

	Intervention	Comparator
Analysis population/subgroup		
n		
Median follow-up time, months (95% CI)		
Median PFS, months (95% CI)		
Hazard ratio PFS, (95% CI)		
Median OS, unadjusted for crossover, months (95% CI)		
Hazard ratio OS, unadjusted for crossover, (95% CI)		
Median OS, adjusted for crossover, months (95% CI)		
Hazard ratio OS, adjusted for crossover, (95% CI)		
N (%) of participants crossing over		
Method of adjustment for crossover		
Subsequent therapies received		
Therapy 1		
Therapy 2		
…		
Therapy N		

Company response: The study design of all trials included in the NMA are summarised in Table 8 with the required additional information highlighted in grey cells. CASTOR and ASPIRE, trials of DVd and KRd respectively, were not included since neither intervention were considered relevant comparators at 2L, as per

questions A5 and A7. MM-003 and ICARIA-MM have been added to the tables in line with the updated 3L+ NMA network, described in the Supplementary Appendix.

The baseline characteristics of the participants in all trials included in the NMA are summarised in Table 9 and Table 10 in the requested format. The equivalent tables for BOSTON are included in the company submission (Document B, Table 6 and Table 7). As above, CASTOR and ASPIRE were not included as the company does not consider DVd and KRd relevant comparators for the intended positioning. The only trial to report line-specific baseline characteristics was ENDEAVOR, thereby, the baseline characteristics of the populations of other trials are reported for the ITT population. MM-003 and ICARIA-MM have been added to the tables in line with the updated 3L+ NMA network, described in the Supplementary Appendix.

The outcome data used in the NMAs are reported in the requested format in Table 11.

Table 8 Study design of all trials included in the NMA

Trial	Primary publication	Study design	Study sites	N participants randomised	Stratification factors	Intervention	Comparator	Crossover	Inclusion criteria (prior treatment)	Data cuts identified	Primary outcome	Other endpoints	PFS assessment criteria
Trials used in both networks													
BOSTON	Grosicki 2020[24]	Phase 3 open-label (crossover permitted)	165 sites; 21 countries	402; 1 prior = 198 2 prior = 129 3 prior = 75	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	SVd 35-day cycles Selinexor 100mg orally on Days 1, 8, 15, 22 and 29 Bortezomib 1.3mg/m^2 SC on Days 1, 8, 15, and 22 Dexamethasone 20mg orally on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 Patients were treated until IRC-confirmed PD, investigator or patients decision, pregnancy, unacceptable toxicity, withdrawal of consent, death, or study termination	Vd Cycles 1 through 8; 21-day cycles: Bortezomib 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 Dexamethasone 20mg orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 Cycles ≥9; 35-day cycles: Bortezomib 1.3 mg/m^2 SC on Days 1, 8, 15, and 22. Dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 Patients were treated until IRC-confirmed PD, investigator or patients decision, pregnancy, unacceptable toxicity, withdrawal of consent, death, or study termination	Crossover was permitted at the point of IRC-confirmed objective PD per IMWG criteria, for patients in the Vd arm	1-3 prior lines	February 2020 February 2021	PFS by IRC	ORR; VGPR; CR; sCR; MRD-negative; OS; DOR; TTNT; TTR; PFS2; PN; HRQoL; safety	IRC-confirmed, per IMWG response criteria
Trials used only in the 2L network													
ENDEAVOR	Dimopoulos 2016[9]	Phase 3 open-label	241 sites across 27 countries	929	Previous PI therapy (yes *vs.* no), previous lines of treatment (1 *vs.* 2/3), ISS	Kd Carfilzomib (20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² given	Vd Bortezomib (1.3 mg/m²; 3–5 s IV or SC) on days 1, 4, 8, and 11.	Not permitted	1-3 prior treatments	November 2014 January 2017 July 2017	PFS	OS; ORR; DOR; PN; safety	IRC assessed according to the IMWG-uniform

Trial	Primary publication	Study design	Study sites	N participants randomised	Stratification factors	Intervention	Comparator	Crossover	Inclusion criteria (prior treatment)	Data cuts identified	Primary outcome	Other endpoints	PFS assessment criteria
					stage (I vs II–III), and planned route of bortezomib administration (IV or SC)	thereafter; 30 min IV infusion) on days 1, 2, 8, 9, 15, and 16. Dexamethasone (20 mg oral or IV) on days 1, 2, 8, 9, 15, 16, 22, and 23 28-day cycles until disease progression, withdrawal of consent, or unacceptable toxic effects	Dexamethasone (20 mg oral or IV) on days 1, 2, 4, 5, 8, 9, 11, and 12 21-day cycles until disease progression, withdrawal of consent, or unacceptable toxic effects			August 2017			response criteria
Trials used only in the 3L+ network													
APEX (omitted from the updated 3L+ NMA network)	Richardson 2005[12]	Phase 3 open-label	93 sites; 13 countries	669	Number of previous treatments (1 vs. >1), time to progression after the last treatment (≤6 months *vs.* >6 months), and β2-microglobulin values (≤2.5 mg per litre *vs.* >2.5 mg per litre)	Bort monotherapy Bortezomib 1.3mg/m^2 IV on days 1, 4, 8, and 11 of cycles 1 through 8 (21-day cycles) and on days 1, 8, 15, and 22 of cycles 9 to 11 35-day cycles, for a maximum treatment period of 273 days. Patients with a CR continued to receive treatment for 2 cycles after the confirmation of the response	Dex Dexamethasone 40mg orally on days 1 to 4, 9 to 12, and 17 to 20 of cycles 1 through 4 (35-day cycles) and on days 1 to 4 of cycles 5 through 9 (28-day cycles), for a maximum treatment period of 280 days. Patients with a CR continued to receive treatment for 2 cycles after the confirmation of the response	Patients in the dexamethasone group with confirmed PD were permitted to cross over to receive bort in a companion study	1-3 prior therapies that did not include bortezomib	Final analysis Updated analysis Dates not reported	TTP	OS; ORR; DOR; TTR	Disease response determined by a computer-programmed algorithm according to the European Blood and Marrow Transplant (EBMT) Group
DOXIL-MMY3001 (omitted from the updated	Orlowski 2007[25]	Phase 3 open-label	123 sites across 10 countries	646	β2-microglobulin levels (≤2.5, >2.5 and ≤5.5, or >5.5 mg/L) at	PLD+Bort 21-day cycles PLD 30mg/m^2 IV on day 4	Bort monotherapy 21-day cycles Bortezomib 1.3mg/m^2 IV on	Crossover was not permitted	Progressed after a response to 1 or more lines of therapy, or have been refractory	NR	TTP	OS; PFS; ORR; safety	NR for PFS; TTP and response rates were determined by

Trial	Primary publication	Study design	Study sites	N participants randomised	Stratification factors	Intervention	Comparator	Crossover	Inclusion criteria (prior treatment)	Data cuts identified	Primary outcome	Other endpoints	PFS assessment criteria
3L+ NMA network					screening, and response to prior treatment (response followed by progression, or primary refractory)	Bortezomib 1.3mg/m^2 IV on days 1, 4, 8, and 11 Study treatment continued until PD, unacceptable treatment-related toxicity, or for 8 cycles, although patients who were still responding after 8 cycles could continue, provided that treatment was tolerated	days 1, 4, 8, and 11 Study treatment continued until PD, unacceptable treatment-related toxicity, or for 8 cycles, although patients who were still responding after 8 cycles could continue, provided that treatment was tolerated		to initial treatment				a computerised algorithm according to EBMT criteria
ICARIA-MM	Attal 2019[26]	Phase 3 open-label	102 sites across 24 countries	307	Number of previous lines of treatment (2-3 *vs.* >3) and age (<75 years *vs.* ≥75 years)	IsaPd Isatuximab 10mg/kg IV (on days 1, 8, 15, and 22 in the first 28-day cycle; and days 1 and 15 in subsequent cycles), in combination with the approved dosing and schedules of pomalidomide 4mg orally (on days 1 to 21 in each cycle), and dexamethasone 40mg (20 mg for ≥75 years old) orally or IV (on days 1, 8, 15, and 22 in each cycle).	Pd Pomalidomide 4mg orally (on days 1 to 21 in each cycle), and dexamethasone 40mg (20 mg for ≥75 years old) orally or IV (on days 1, 8, 15, and 22 in each cycle).	Not crossover occured	At least 2 previous lines of treatment and had not responded to therapy with lenalidomide and a PI (bortezomib, carfilzomib, or ixazomib).	October 2018 (Primary analysis) October 2020 (Efficacy analysis update) October 2020 (Safety analysis updated)	PFS	Objective response; OS. Additional: ORR (VGPR or better, CR, and sCR), TTR, DoR, TTP, HRQoL, PK, and safety	Response and disease progression were determined by the IRC using the IMWG response criteria

Trial	Primary publication	Study design	Study sites	N participants randomised	Stratification factors	Intervention	Comparator	Crossover	Inclusion criteria (prior treatment)	Data cuts identified	Primary outcome	Other endpoints	PFS assessment criteria
MM-003	San Miguel 2013[27]	Phase 3 open-label	93 sites across 16 countries	455	Age (≤75 years *vs.* >75 years), disease status (refractory *vs.* relapsed and refractory *vs.* bortezomib intolerant), and number of previous treatments (2 *vs.* ≥3)	Pd Pomalidomide 4 mg + 40mg low-dose dexamethasone (20 mg in subjects > 75 years). Pomalidomide on days 1–21, orally + low-dose dexamethasone on days 1, 8, 15, and 22, orally.	Dex 40 mg/day dexamethasone (20 mg in subjects > 75 years). Dexamethasone days 1–4, 9–12, and 17–20.	Patients were able to crossover following progression via a companion study or at the time of final analysis for PFS when the IDMC recommended patients receiving Dex be permitted to crossover, irrespective of whether or not they had PD.	Refractory to previous treatment and had to have received at least two previous consecutive cycles of bortezomib and lenalidomide, alone or in combination.	September 2012 (prespecified final PFS) March 2013 September 2013 August 2017 (OS and safety)	PFS	OS, ORR, TTP, DOR, safety, QoL	2012 data cut was based on investigator's assessment of response in accordance with IMWG criteria. March 2013 data cut was assessed by IRAC. September 2013 data cut was assessed by the study investigator.
MM-009	Weber 2007[16]	Phase 3 double-blind	48 sites; US and Canada	353	Level of serum β2-microglobulin (<2.5 mg per litre *vs.* ≥2.5 mg per litre), previous SCT (none *vs.* ≥1), and the number of previous antimyeloma therapies (1 *vs.* ≥2)	Rd Lenalidomide 25 mg oral on days 1 to 21 of each 28-day cycle Dexamethasone 40mg on days 1 to 4, 9 to 12, and 17 to 20. After the fourth cycle, administered only on days 1 to 4. Treatment was continued until the occurrence of PD or unacceptable toxic effects	Placebo+dex 25 mg placebo orally on days 1 to 21 of each 28-day cycle Dexamethasone 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20. After the fourth cycle, administered only on days 1 to 4. Treatment was continued until the occurrence of PD or unacceptable toxic effects.	Following an interim analysis, the study was unblinded and patients were allowed to cross over to open-label administration of lenalidomide at progression or at the investigator's discretion	At least 1 prior treatment	January 2005 December 2005 July 2008	TTP	OS; ORR; safety	The response of patients was assessed according to the criteria of the EBMT.
MM-010	Dimopoulos 2007[17]	Phase 3 blinded	50 sites; 15 countries	351	Baseline serum β2-microglobulin level (<2.5mg per litre or ≥2.5mg per litre), previous SCT (none or ≥1), and	Rd Lenalidomide 25mg orally on days 1 to 21 of each 28-day cycle	Placebo+dex Placebo 25mg orally on days 1 to 21 of each 28-day cycle Dexamethasone 40 mg orally on	Following an interim analysis, the study was unblinded, and patients were	At least 1 prior treatment	August 2005	TTP	OS; ORR; safety	The response of patients was assessed according to the criteria of the EBMT

Trial	Primary publication	Study design	Study sites	N participants randomised	Stratification factors	Intervention	Comparator	Crossover	Inclusion criteria (prior treatment)	Data cuts identified	Primary outcome	Other endpoints	PFS assessment criteria
					the number of previous antimyeloma regimens (1 or ≥2)	Dexamethasone 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20. After the fourth cycle, administered only on days 1 to 4. Treatment was continued until PD or unacceptable toxic effects	days 1 to 4, 9 to 12, and 17 to 20. After the fourth cycle, administered only on days 1 to 4. Treatment was continued until PD or unacceptable toxic effects	allowed to receive lenalidomide at the time of disease progression or at the investigator's discretion					
MMY-2045 (omitted from the updated 3L+ NMA network	Dimopoulos 2013[28]	Phase 2 open-label	49 sites across 10 countries	163	NR	Vd All patients received four 21-day cycles of Vd: bortezomib 1.3 mg/m^2 IV on Days 1, 4, 8, and 11, and dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 Patients achieving at least PR received a further 4 cycles of Vd Patients with PD during/after the initial 4 cycles of Vd discontinued study treatment	Vd/ VDC/ VDR Patients with SD following the first four 21-day cycles were randomized (1:1:1), for cycles 5-8, to receive: a further 4 cycles of Vd, 4 cycles of Vd plus cyclophosphamide 500 mg orally on Days 1, 8, and 15, or 4 cycles of Vd plus lenalidomide 10mg orally on Days 1-14 (VDR) Patients with PD during/after the initial 4 cycles of Vd discontinued study treatment	NA	Relapsed/ progressed following, or who were refractory to, 1 previous line of therapy	NR	ORR	PFS; OS; safety	Response was assessed using the IMWG uniform response criteria and validated by an Independent Data Monitoring Committee
PANORAMA-1	San-Miguel 2014[18]	Phase 3 double-blind	215 sites across 34 countries	768	Number of previous treatment lines (1 *vs.* 2 to 3) and previous use of bortezomib treatment (yes *vs.* no)	PanoVd Treatment Phase 1 (eight 3-week cycles): Panobinostat 20mg orally 3 times/ week for the first 2 weeks	Placebo+Vd Treatment Phase 1 (eight 3-week cycles): Placebo orally 3 times/ week for the first 2 weeks	Crossover was not permitted	1-3 prior treatments	September 2013 August 2014 June 2015	PFS by INV	OS; ORR; CR; DOR; TTR; TTP; HRQoL; safety	Investigator assessed by modified EBMT criteria

Trial	Primary publication	Study design	Study sites	N participants randomised	Stratification factors	Intervention	Comparator	Crossover	Inclusion criteria (prior treatment)	Data cuts identified	Primary outcome	Other endpoints	PFS assessment criteria
						Bortezomib 1.3mg/m^2 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 pano 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	Bortezomib 1.3mg/m^2 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						
TOURMALINE-MM1	Moreau 2016[29]	Phase 3 double-blind	147 sites across 26 countries	722	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	IxaRd Ixazomib 4mg orally on days 1, 8, and 15 Lenalidomide 10-25 mg orally on days 1 through 21	Rd Placebo 4mg orally on days 1, 8, and 15 Lenalidomide 10-25 mg orally on days 1 through 21	Not permitted	1-3 prior therapies	October 2014 July 2015 September 2020	PFS by IRC	OS; ORR; CR; VGPR; DOR; TTP; safety; HRQoL	Double-blinded and assessed by IRC using IMWG Uniform Response Criteria

Trial	Primary publication	Study design	Study sites	N participants randomised	Stratification factors	Intervention	Comparator	Crossover	Inclusion criteria (prior treatment)	Data cuts identified	Primary outcome	Other endpoints	PFS assessment criteria
						Dexamethasone 40 mg orally on days 1, 8, 15, and 22 Treatment was continued until PD or unacceptable toxic effects	Dexamethasone 40 mg orally on days 1, 8, 15, and 22 Treatment was continued until PD or unacceptable toxic effects						

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; IDMC, Independent Data Monitoring 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; PLD+Bort, pegylated liposomal doxorubicin + bortezomib; 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.

Table 9 Baseline characteristics of participants in trials included in the NMA

		ENDEAVOR[8]		APEX[12,30,31] (omitted from the updated 3L+ NMA network		ICARIA-MM[26]		MM-003[27,32,33]		MM-009[16]		MM-010[17]		PANORAMA-1[18]		TOURMALINE-MM1[29]		Dimopoulos 2015[13] (omitted from the updated 3L+ NMA network	
		Kd	Vd	BORT	Dex	IsaPd	Pd	Pd	Dex	Rd	Dex	Rd	Dex	PanoVd	Vd	IxaRd	Rd	Vd	BORT
Population		1 prior line		ITT		ITT (3L+)		ITT (3L+)		ITT		ITT		ITT		ITT		Matched pairs	
n		232	232	333	336	154	153	302	153	177	176	176	175	387	381	360	362	109	109
Baseline demographics																			
Age, years	Median (range)	66 (36-89)	63.5 (39-88)	62 (48-74)[a]	61 (47-73)	68 (36-83)	66 (41-86)	64.0 (35-84)	65 (35-87)	64 (36-86)	62 (37-85)	63 (33-84)	64 (40-82)	63 (28-84)	63 (32-83)	66 (38-91)	66 (30-89)	62 (42-86)	64 (38-84)
Gender, n (%)	Male	NR	NR	188 (56)	200 (60)	89 (58)	70 (46)	181 (60)	87 (57)	106 (59.9)	104 (59.1)	104 (59.1)	103 (58.9)	202 (52)	205 (54)	207 (58)	202 (56)	NR	NR
Race, n (%)	White	NR	NR	267 (80)[b]	262 (78)	118 (76.6)	126 (82.4)	244 (80.8)	113 (73.9)	NR	NR	NR	NR	249 (64)	250 (66)	310 (86)	301 (83)	NR	NR
	Black-Af/Am	NR	NR	18 (5)	24 (7)	1 (0.6)	3 (2.0)	4 (1.3)	3 (2.0)	NR	NR	NR	NR	5 (1)	17 (4)	NR	NR	NR	NR

		ENDEAVOR[8]		APEX[12,30,31] (omitted from the updated 3L+ NMA network		ICARIA-MM[26]		MM-003[27,32,33]		MM-009[16]		MM-010[17]		PANORAMA-1[18]		TOURMALINE-MM1[29]		Dimopoulos 2015[13] (omitted from the updated 3L+ NMA network	
		Kd	Vd	BORT	Dex	IsaPd	Pd	Pd	Dex	Rd	Dex	Rd	Dex	PanoVd	Vd	IxaRd	Rd	Vd	BORT
Population		1 prior line		ITT		ITT (3L+)		ITT (3L+)		ITT		ITT		ITT		ITT		Matched pairs	
n		232	232	333	336	154	153	302	153	177	176	176	175	387	381	360	362	109	109
	Asian	NR	NR	NR	NR	21 (13.6)	15 (9.8)	4 (1.3)	0	NR	NR	NR	NR	128 (33)	104 (27)	NR	NR	NR	NR
	Other	NR	NR	11 (3)[c]	16 (5)	2 (1.3)[o]	1 (0.7)[o]	2 (0.7)	2 (1.3)	NR	NR	NR	NR	5 (1)	10 (3)	NR	NR	NR	NR
	Missing	NR	NR	37 (11)	34 (10)	12 (7.8)	8 (5.2)	48 (15.9)	35 (22.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baseline ECOG performance	0	110 (47.4)	131 (56.5)	NR	NR	55.0 (35.7)	69.0 (45.1)	110 (36.4)	36 (23.5)	74 (41.8)	83 (47.2)	78 (44.3)	65 (37.1)	175 (45)	162 (43)	180 (51)	170 (47)	26 (24)	25 (23)
	1	104 (44.8)	92 (39.7)	NR	NR	83.0 (53.9)	68.0 (44.4)	138 (45.7)	86 (56.2)	83 (46.9)	80 (45.5)	72 (40.9)	79 (45.1)	191 (49)	186 (49)	156 (44)	164 (46)	71 (65)	73 (67)
	2	18 (7.8)	9 (3.9)	NR	NR	16.0 (10.4)	16.0 (10.5)	52 (17.2)	25 (16.3)	14 (7.9)	6 (3.4)	23 (13.1)	27 (15.4)	19 (5)	29 (8)	18 (5)	24 (7)	12 (11)[d]	4 (4)[d]
Time since initial diagnosis (years)	Median (range)	NR	NR	3.5 (1.3-7.8)[a]	3.1 (1.4-7.2)	4.46 (0.6-18.4)	4.09 (0.5-20.5)	5.3 (0.6-30.0)	6.1 (0.9-21.1)	3.1 (0.5-14.7)	3.1 (0-19.7)	3.4 (0.4-15.7)	4.0 (0.3-26.6)	NR	NR	44.2 (3-281)[e]	42.2 (4-306)[e]	NR	NR
R-ISS stage at study entry	R-I	109 (47.0)[f]	115 (49.6)	139 (43)	139 (43)	39 (25.3)	31 (20.3)	197 (65)[f,n]	93 (61)[f, n]	NR	NR	11 (6.3)[f]	8 (4.6)	156 (40)[f]	152 (40)	226 (63)[f]	233 (64)	NR	NR
	R-II	68 (29.3)[f]	62 (26.7)	NR	NR	99 (64.3)	98 (64.1)	NR	NR	NR	NR	50 (28.4)[f]	57 (32.6)	104 (27)[f]	92 (24)	89 (25)[f]	87 (24)	NR	NR
	R-III	55 (23.7)[f]	55 (23.7)	NR	NR	16 (10.4)	24 (15.7)	93 (31)[f]	54 (35)[f]	NR	NR	115 (65.3)[f]	110 (62.9)	77 (20)[f]	86 (23)	45 (12)[f]	42 (12)	NR	NR
	Missing	0	0	NR	NR	0	0	12 (4)[f]	6 (4)[f]	NR	NR	0	0	50 (13)[f,g]	51 (13)	NR	NR	NR	NR
Baseline creatinine clearance (mL/ min)	<30	14 (6.0)	17 (7.3)	8 (2)[m]	5 (2)	NR	NR	2 (0.7)	3 (2.0)	NR	NR	NR	NR	NR	NR	5 (1)	5 (1)	22 (20)[k]	21 (19)[k]
	30-60	26 (11.2)[h]	27 (11.6)	NR	NR	55 (35.7)[p]	49 (32.0)[p]	93 (30.8)[b, i]	56 (36.6)[b, i]	NR	NR	NR	NR	NR	NR	74 (21)[i]	95 (26)	NR	NR

		ENDEAVOR[8]		APEX[12,30,31] (omitted from the updated 3L+ NMA network		ICARIA-MM[26]		MM-003[27,32,33]		MM-009[16]		MM-010[17]		PANORAMA-1[18]		TOURMALINE-MM1[29]		Dimopoulos 2015[13] (omitted from the updated 3L+ NMA network	
		Kd	Vd	BORT	Dex	IsaPd	Pd	Pd	Dex	Rd	Dex	Rd	Dex	PanoVd	Vd	IxaRd	Rd	Vd	BORT
Population		1 prior line		ITT		ITT (3L+)		ITT (3L+)		ITT		ITT		ITT		ITT		Matched pairs	
n		232	232	333	336	154	153	302	153	177	176	176	175	387	381	360	362	109	109
	>60	192 (82.8)[b,j]	188 (81.0)	NR	NR	87 (56.5)[l]	96 (62.7)[l]	205 (67.9)[b,l]	93 (60.8)[b,l]	NR	NR	NR	NR	387 (100)[k]	381 (100)[b]	281 (78)[b,l]	261 (72)	NR	NR
Cytogenetic abnormalities, n (%)	del(17p)/p53	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	t(14;16)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	t(4;14)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	1q21	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	All high-risk cytogenetic	44 (19.0)	53 (22.8)	NR	NR	24 (16)	36 (24)	130 (43)	57 (37.3)	NR	NR	NR	NR	79 (66)	88 (71)	75 (21)	62 (17)	NR	NR

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

[a] 10th and 90th percentiles, not range; [b] Self-calculated; [c] Hispanic and other, together; [d] ≥ 2; [e] Months; [f] ISS; [g] not assessed; [h] 30-50; [i] 30-<60; [j] >50; [k] <50; [l] ≥60; [m] ≤20; [n] ISS I/II; [o] Native Hawaiian or other Pacific Island; [p] <60

Table 10 Anti-MM treatment history of participants in trials included in the NMA

	ENDEAVOR[8]		APEX[12] (omitted from the updated 3L+ NMA network		ICARIA-MM[26,34,35]		MM-003[27,36]		MM-009[16]		MM-010[17]		PANORAMA-1[18]		TOURMALINE-MM1[29]		Dimopoulos 2015[13] (omitted from the updated 3L+ NMA network	
	Kd	Vd	BORT	Dex	IsaPd	Pd	Pd	Dex	Rd	Dex	Rd	Dex	PanoVd	Vd	IxaRd	Rd	Vd	BORT
	1 prior line		ITT		ITT (3L+)		ITT (3L+)		ITT		ITT		ITT		ITT		Matched pairs	
n	232	232	333	336	154	153	302	153	177	176	176	175	387	381	360	362	109	109
Prior anti-MM therapies																		

		ENDEAVOR[8]		APEX[12] (omitted from the updated 3L+ NMA network		ICARIA-MM[26,34,35]		MM-003[27,36]		MM-009[16]		MM-010[17]		PANORAMA-1[18]		TOURMALINE-MM1[29]		Dimopoulos 2015[13] (omitted from the updated 3L+ NMA network	
		Kd	Vd	BORT	Dex	IsaPd	Pd	Pd	Dex	Rd	Dex	Rd	Dex	PanoVd	Vd	IxaRd	Rd	Vd	BORT
		1 prior line		ITT		ITT (3L+)		ITT (3L+)		ITT		ITT		ITT		ITT		Matched pairs	
n		**232**	**232**	**333**	**336**	**154**	**153**	**302**	**153**	**177**	**176**	**176**	**175**	**387**	**381**	**360**	**362**	**109**	**109**
Number of prior LOT	Median (range)	NR	NR	2 (1-4)	2 (1-4)	3 (2-11)	3 (2-10)	5 (2-14)	5 (2-17)	NR	NR	NR	NR	1 (1-4)	1 (1-3)	NR	NR	NR	NR
	1 prior, n (%)	232 (100)	232 (100)	132 (40)	119 (35)	0	0	0	0	68 (38.4)	67 (38.1)	56 (31.8)	57 (32.6)	197 (51)	198 (52)	224 (62)	217 (60)	NR	NR
	2 priors, n (%)	NR	NR	NR	NR	97 (63.0)[d]	103 (67.3)[d]	17 (5.6)	8 (5.2)	NR	NR	NR	NR	124 (32)	108 (28)	97 (27)	111 (31)	NR	NR
	3 priors, n (%)	NR	NR	NR	NR	NR	NR	285 (94.4)[c]	145 (94.8)[c]	NR	NR	NR	NR	64 (17)	75 (20)	39 (11)	34 (9)	NR	NR
Prior SCT, n (%)		NR	NR	222 (67)[a]	229 (68)	83 (53.9)	90 (58.8)	214 (71)	105 (69)	109 (61.6)	108 (61.4)	97 (55.1)	95 (54.3)	215 (56)	224 (59)	212 (59)	199 (55)	44 (40)	51 (47)
Exposure to prior anti-MM drug classes, n (%)	PIs	NR	NR	NR	NR	154 (100)	153 (100)	NR	NR	NR	NR	NR	NR	NR	NR	249 (69)	253 (70)	NR	NR
	IMiDs	NR	NR	NR	NR	154 (100)	153 (100)	NR	NR	NR	NR	NR	NR	NR	NR	193 (54)	204 (56)	45 (41)[b]	38 (35)
Exposure to prior anti-MM drugs, n (%)	Bortezomib	96 (41.4)	101 (43.5)	NR	NR	150 (97.4)	150 (98.0)	302 (100)	153 (100)	19 (10.7)	20 (11.4)	8 (4.5)	7 (4.0)	169 (44)	161 (42)	248 (69)	250 (69)	NR	NR
	Carfilzomib	NR	NR	NR	NR	34 (22.1)	44 (28.8)	NR	NR	NR	NR	NR	NR	NR	NR	1 (<1)	4 (1)	NR	NR
	Ixazomib	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Daratumumab	NR	NR	NR	NR	1 (0.6)	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Lenalidomide	51 (22)	47 (20.3)	NR	NR	154 (100)	153 (100)	302 (100)	153 (100)	NR	NR	NR	NR	72 (19)	85 (22)	44 (12)	44 (12)	NR	NR
	Pomalidomide	NR	NR	NR	NR	NR	NR	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: BORT, bortezomib; Dex, dexamethasone; IsaPd, isatuximab + pomalidomide + dexamethasone; IMiD, immunomodulatory imide drug; IxaRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; LOT, line of therapy; mAbs, monoclonal antibodies; MM, multiple myeloma n, number of patients; NR, not reported; PanoVd, panobinostat + bortezomib + dexamethasone; Pd, pomalidomide +

	ENDEAVOR[8]		APEX[12] (omitted from the updated 3L+ NMA network		ICARIA-MM[26,34,35]		MM-003[27,36]		MM-009[16]		MM-010[17]		PANORAMA-1[18]		TOURMALINE-MM1[29]		Dimopoulos 2015[13] (omitted from the updated 3L+ NMA network	
	Kd	Vd	BORT	Dex	IsaPd	Pd	Pd	Dex	Rd	Dex	Rd	Dex	PanoVd	Vd	IxaRd	Rd	Vd	BORT
	1 prior line		ITT		ITT (3L+)		ITT (3L+)		ITT		ITT		ITT		ITT		Matched pairs	
n	232	232	333	336	154	153	302	153	177	176	176	175	387	381	360	362	109	109

dexamethasone; PIs, proteasome inhibitors; Rd, lenalidomide + dexamethasone; SCT, stem cell transplant; SdX, selinexor + low-dose dexamethasone (crossover); STD, standard deviation; SVd, selinexor + bortezomib + dexamethasone; SVdX, selinexor + bortezomib + dexamethasone (crossover); Vd, bortezomib + dexamethasone

[a] SCT or other high-dose therapy; [b] Immunomodulatory drugs; [c] >2; [d] 2 or 3

Table 11 Trial outcomes used in the NMAs

	BOSTON[5]		BOSTON[5]		ENDEAVOR[7,8]		MM-003[15]		MM-009[16]		MM-010[17]		PANORAMA-1[18,19]		TOURMALINE-MM1[20,21]		ICARIA-MM[14]		APEX[12]		Dimopoulos 2015[13]	
	SVd	Vd	SVd	Vd	Kd	Vd	Pd	Dex	Rd	Dex	Rd	Dex	PanoVd	Vd	IxaRd	Rd	IsaPd	Pd	BORT	Dex	Vd	d
Population	2L only		3L+		2L only		3L+		3L+		3L+		3L+		3L+		3L+		3L+		2L only	
n	99	99	96	108	232	232	302	153	109	109	120	118	188	183	148	149	154	153	200	217	109	109
Median follow-up time, months (95% CI) - latest datacut	28.71* (27.24, 29.90)	28.65* (27.63, 29.67)	28.71* (27.24, 29.90)	28.65* (27.63, 29.67)	44.3*	43.7*	15.4	15.4	26.2*	12.9*	16.4*	16.4*	NR	NR	85.0*	85.1*	35.3	35.3	12	12	26.1	18.4
Median PFS, months (95% CI)	21. 03 (13.24, NE)	10.68 (7.26, 16.39)	11.76 (7.39, 15.38)	9.43 (6.83, 9.69)	22.2	10.1	4.0	1.9	10.2^	4.6^	11.1	4.7	12 (9.5, 13.7)	7.6 (6.0, 8.7)	NR	12.9	11.1 (7.8, 13.8)	5.9 (4.5, 7.9)	4.9	2.9	11.9	6.4
Hazard ratio PFS, (95% CI)	0.621 (0.407, 0.950)		0.805 (0.559, 1.159)		0.447 (0.330, 0.606)		0.49 (0.40, 0.61)		NR		NR		0.64 (0.50, 0.83)		0.580 (0.401, 0.838)		0.599 (0.460, 0.780)		0.55		0.595 (0.351, 1.008)	

Median OS, unadjusted for crossover, months (95% CI)	NE (26.68, NE)	[redacted]	31.74 (30.19, NE)	[redacted]	51.3	43.7	13.1	8.1	29.6*	20.2*	NE*	20.6*	34.6 (27.73, 41.95)	30.0 (24.80, 39.92)	53.0	43.0	24.6 (20.3, 31.3)	17.7 (14.4, 26.2)	NR	NR	NR	NR
Hazard ratio OS, unadjusted for crossover, (95% CI)	[redacted]		[redacted]		0.771 (0.583, 1.018)		0.72 (0.56, 0.92)		0.44 (0.30, 0.65)*		0.66 (0.45, 0.96)*		0.96 (0.74, 1.26)		0.845 (0.642, 1.114)		0.76 (0.57, 1.01)		0.63		0.958 (0.541, 1.698)	
Median OS, adjusted for crossover, months (95% CI)	NE (26.68, NE)	32.76 (24.97, NE)	31.74 (30.19, NE)	NE (22.48, NE)	NA	NA	NR	NR	NR	NR	NR	NR	NA	NA	NA	NA	NA	NA	NR	NR	NA	NA
Hazard ratio OS, adjusted for crossover, (95% CI)	0.909 (0.570, 1.450)		0.829 (0.518, 1.328)		NA		NR		NR		NR		NA		NA		NA		NR		NA	
N (%) of participants crossing over	NA	30 (30.3%)	NA	47 (43.5%)	NA	NA	NA	85 (55.6%)	NR	NR	NR	NR	NA	NA	NA	NA	NA	NA	NA	147 (43.8%)*	NA	NA
Method of adjustment for crossover	Two-stage method	Two-stage method	Two-stage method	Two-stage method	NA	NA	NR		NR	NR	NR	NR	NA	NA	NA	NA	NA	NA	NR	NR	NA	NA
Subsequent therapy received																						
PI-based regimens	[redacted]				118*	57*	NR	NR	NR	NR	NR	NR	42*	48*	122**	141**	61	60	NR	NR	NR	NR
IMiD-based regmens	[redacted]				258*	332*	NR	NR	NR	NR	NR	NR	78*	111*	NR	NR	31	34	NR	NR	NR	NR
anti-CD38-based regimens	[redacted]				NR	NR	NR	NR	NR	NR	NR	NR	12*	5*	63*	86*	22	64	NR	NR	NR	NR
Chemotherapy	[redacted]				NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alkylating agents	[redacted]				152*	170*	NR	NR	NR	NR	NR	NR	58*	83*	NR	NR	64	52	NR	NR	NR	NR

Abbreviations: NA, not applicable; NE, not evaluable (i.e. not reached); NR, not reported
** Based on ITT population*
*** Receiving PI-based regimens in the next-line therapy*
^ Time to progression

A16. Priority question. For each study included in question A14, please extract whether the proportional hazards assumption has been tested or validated for HRs calculated for PFS and OS. Please comment on the validity of the NMA, should proportional hazards not be found to hold across studies in the network.

Company response: An assessment of the PH assumption for each connection in the 2L and 3L+ networks connecting BOSTON with relevant interventions (i.e., relevant connections) is provided below for PFS and OS. Comparator data were digitised and pseudo IPD were created using the algorithm published by Guyot *et al.* (2012).[11]

The networks informing the relative efficacy estimates for PFS and OS attempt to synthesise all available data in the 2L and 3L+ populations; some studies support the assumption of PH, whilst others do not. It is impossible to synthesise all these data within a more complicated framework which relaxes the PH assumption. Furthermore, there are some limitations in assessing the PH assumption due to data availability. For example, a broader population or an older data cut have been assessed in some cases to enable a commentary on the PH assumption. Where alternative data are used, this is specified in the footnotes under the tables presenting the results of the PH testing. The NMA are the most robust indirect treatment comparison approach, reflecting all available data in these populations.

<u>2L NMA</u>

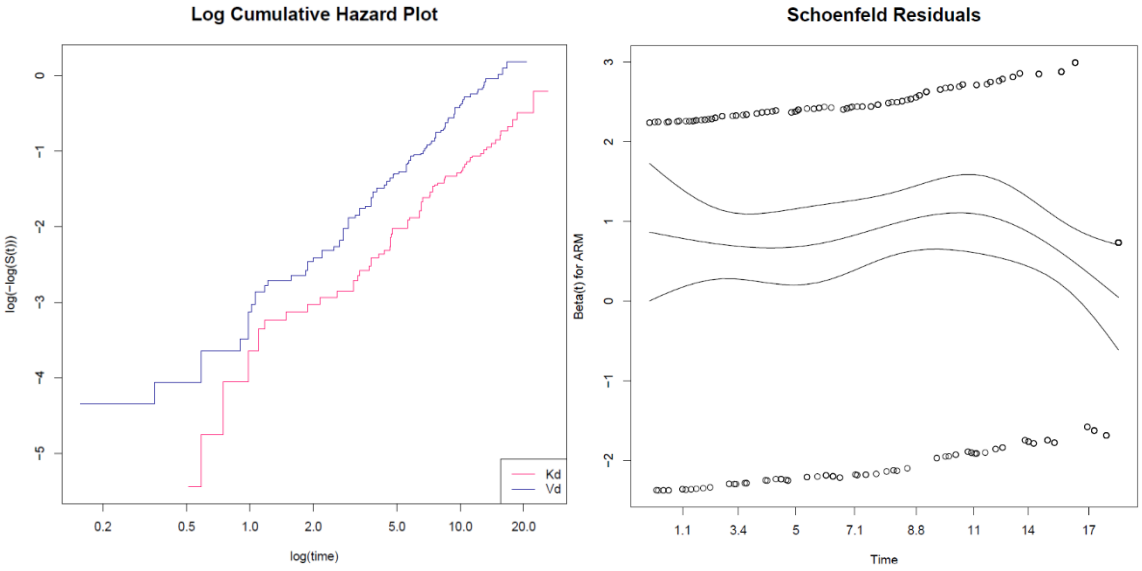
Table 12 indicates that the null hypothesis of PH cannot be rejected within the 2L population in the ENDEAVOR study for the PFS outcome. This is the only relevant connection in the 2L population, aside from the BOSTON clinical data. Figure 7 presents the log-cumulative hazard plot and the Schoenfeld residuals for PFS. The log-cumulative hazard plot for PFS indicates parallel curves for Vd and Kd for most of the follow-up.

Table 12 Proportional hazards testing ENDEAVOR (2L, PFS)

Trial	Comparison	Chi-squared	DF	P-Value
ENDEAVOR	Vd *versus* Kd	0.9026	1	0.3421

Abbreviations: Kd, carfilzomib plus dexamethasone; PFS, progression-free survival; SE, standard error; Vd, bortezomib plus dexamethasone.

Figure 7 Proportional hazards testing ENDEAVOR (2L, PFS)



Abbreviations: Kd, carfilzomib plus dexamethasone; PFS, progression-free survival; SE, standard error; Vd, bortezomib plus dexamethasone.

Table 13 indicates that the null hypothesis of PH cannot be rejected within the 2L population in the ENDEAVOR study for the OS outcome. This is the only relevant connection in the 2L population, aside from the BOSTON clinical data.

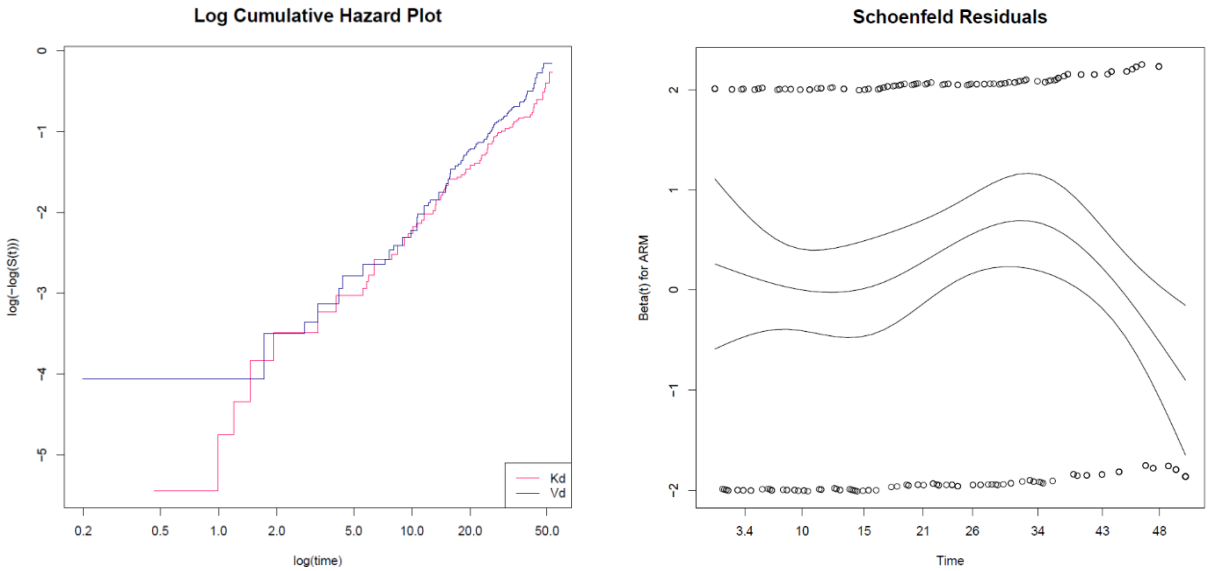
Figure 8 presents the log-cumulative hazard plot and the Schoenfeld residuals for OS. The log-cumulative hazard plot for OS indicates similar outcomes for Vd and Kd.

Table 13 Proportional hazards testing ENDEAVOR (2L, OS)

Trial	Comparison	Chi-squared	DF	P-Value
ENDEAVOR	Vd *versus* Kd	0.5185	1	0.4715

Abbreviations: Kd, carfilzomib plus dexamethasone; OS, overall survival; SE, standard error; Vd, bortezomib plus dexamethasone.

Figure 8 Proportional hazards testing ENDEAVOR (2L, OS)



Abbreviations: Kd, carfilzomib plus dexamethasone; OS, overall survival; SE, standard error; Vd, bortezomib plus dexamethasone.

3L+ NMA (updated NMA)

Table 14 indicates that the null hypothesis of PH cannot be rejected across the majority of studies (PANORAMA-1, ICARIA-MM *versus* the Vd data from BOSTON, MM-003, MM-010 and TOURMALINE-MM1). The only study where the PH assumption may not hold is the MM-009 study; note this study requires the use of the 2L+ Kaplan-Meier data as 3L+ data are unavailable.

Figure 9-Figure 12 present the log-cumulative hazard plots and Schoenfeld residuals for each study for PFS. The log-cumulative hazard plots for PFS indicate parallel curves for Vd versus PanoVd (PANORAMA-1), Pd versus D (MM-003), Rd versus D (MM-009 and MM-010) and Rd versus IxaRd (TOURMALINE-MM1) for most of the follow-up period. The log-cumulative hazard plots for Pd from ICARIA-MM versus the Vd data from BOSTON indicate similar outcomes.

Table 14 Proportional hazards testing (3L+, PFS)

Trial	Comparison	Chi-squared	DF	P-Value
PANORAMA-1	Vd *versus* PanoVd	2.2990	1	0.1295
ICARIA-MM*	Vd (BOSTON) *versus* Pd	2.1219	1	0.1452
MM-003†	Pd *versus* D	3.1419	1	0.0763
MM-009‡	Rd *versus* D	5.6465	1	0.0175
MM-010‡	Rd *versus* D	3.0837	1	0.0791
TOURMALINE-MM1	Rd *versus* IxaRd	0.3947	1	0.5298

Abbreviations: D, dexamethasone; IxaRd, ixazomib plus lenalidomide plus dexamethasone; Kd, carfilzomib plus dexamethasone; PanoVd, panobinostat plus bortezomib plus dexamethasone; Pd, pomalidomide plus dexamethasone; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone; SE, standard error; Vd, bortezomib plus dexamethasone.

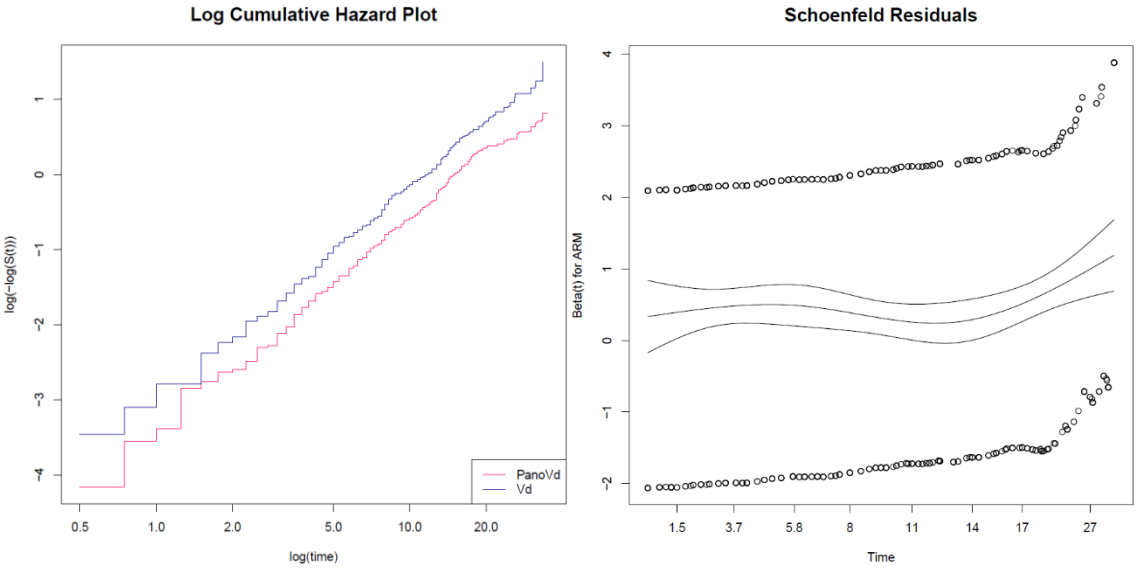
Notes:

**Proportional hazards in the ICARIA-MM connection is based on data from the Pd arm in ICARIA-MM and the Vd arm in BOSTON. The Vd arm is BOSTON reflects the 3L+ population, for patients with a non-missing R-ISS stage and patients who had received a prior proteasome inhibitor and immunomodulatory drug – in line with the MAIC assumptions (N=66).*

†Proportional hazards in the MM-003 connection is based on an older data cut than the hazard ratio used in the NMA. This is because Kaplan-Meier data are unavailable for the data corresponding to the latest hazard ratio.

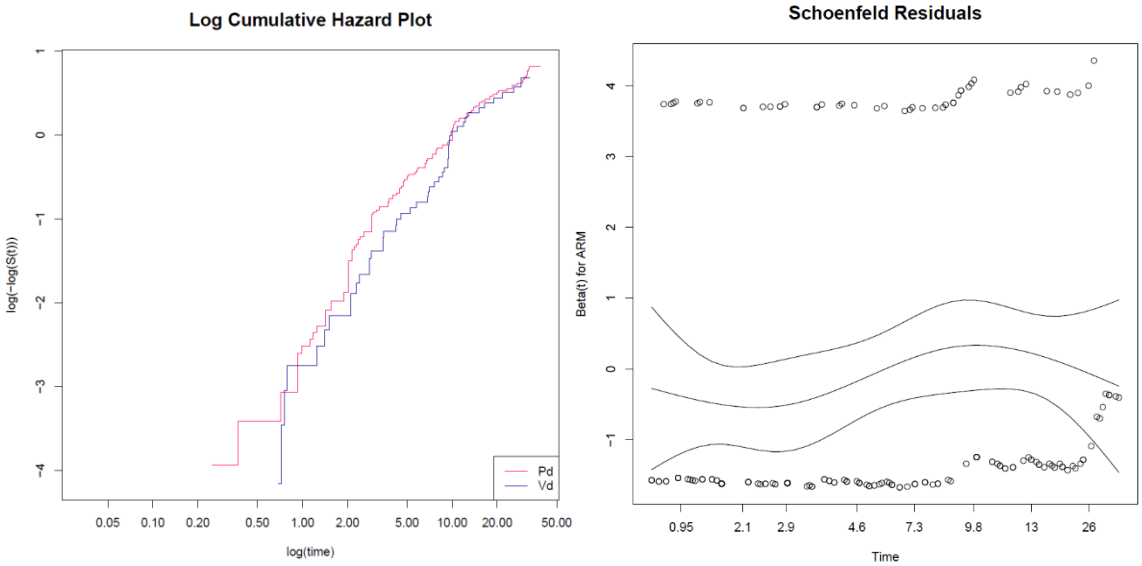
‡Proportional hazards in the MM-009 and MM-010 connections are based on the 2L+ population due to absence of Kaplan-Meier data in the 3L+ population – see response to clarification question A11.

Figure 9 Proportional hazards testing PANORAMA-1 (3L+, PFS)



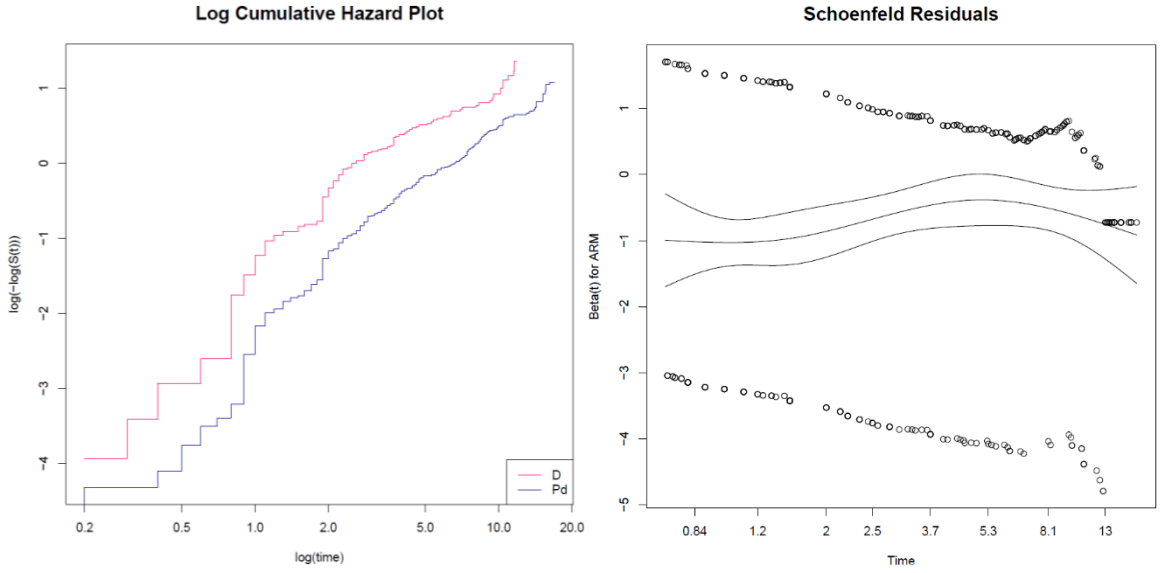
Abbreviations: PanoVd, panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival; SE, standard error; Vd, bortezomib plus dexamethasone

Figure 10 Proportional hazards testing ICARIA-MM vs BOSTON (3L+, PFS)



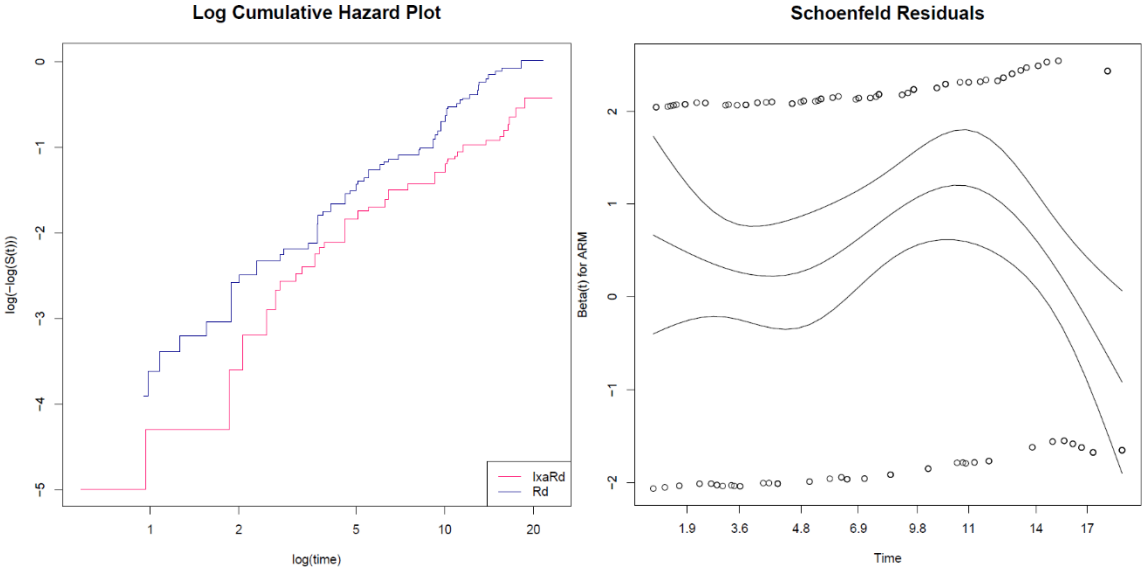
Abbreviations: Pd, pomalidomide plus dexamethasone; PFS, progression-free survival; SE, standard error; Vd, bortezomib plus dexamethasone

Figure 11 Proportional hazards testing MM-003 (3L+, PFS)



Abbreviations: D, dexamethasone; Pd, pomalidomide plus dexamethasone; PFS, progression-free survival; SE, standard error.

Figure 12 Proportional hazards testing TOURMALINE-MM1 (3L+, PFS)



Abbreviations: IxaRd, ixazomib plus lenalidomide plus dexamethasone; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone; SE, standard error.

Table 15 indicates that the null hypothesis of PH is rejected within the 3L+ population in the PANORAMA-1, MM-003, and MM-010 studies for the OS outcome. The assumption of PH cannot be rejected in the comparison of Pd from ICARIA-MM with the Vd BOSTON data in the MM-009 nor in the TOURMALINE-MM1 studies.

Figure 13-Figure 18 present the log-cumulative hazard plots and the Schoenfeld residuals for each study for OS. Although the Schoenfeld residuals indicate a violation in the PH assumption in the PANORAMA-1, MM-003 and MM-010 studies, the log-cumulative hazard plots indicate similar outcomes in PANORAMA-1 and parallel curves in MM-003 and MM-010 for most of the follow-up.

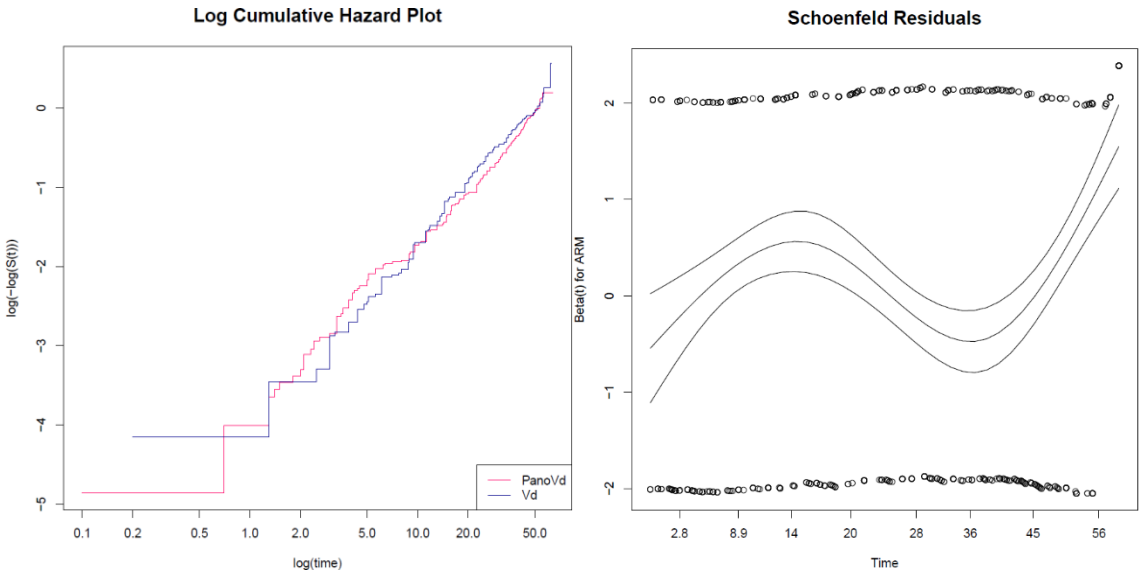
Table 15 Proportional hazards testing (3L+, OS)

Trial	Comparison	Chi-squared	DF	P-Value
PANORAMA-1	Vd *versus* PanoVd	8.4513	1	0.0036
ICARIA-MM*	Vd (BOSTON) *versus* Pd	0.1996	1	0.6551
MM-003†	Pd *versus* D	42.1585	1	0.0000
MM-009‡	Rd *versus* D	0.2837	1	0.5943
MM-010‡	Rd *versus* D	26.4091	1	0.0000
TOURMALINE-MM1§	Rd *versus* IxaRd	2.0848	1	0.1488

Abbreviations: D, dexamethasone; IxaRd, ixazomib plus lenalidomide plus dexamethasone; Kd, carfilzomib plus dexamethasone; PanoVd, panobinostat plus bortezomib plus dexamethasone; Pd, pomalidomide plus dexamethasone; PFS, progression-free survival; Rd, lenalidomide plus dexamethasone; SE, standard error; Vd, bortezomib plus dexamethasone
**Proportional hazards in the ICARIA-MM connection are based on data from the Pd arm in ICARIA-MM and the Vd arm in BOSTON. The Vd arm is BOSTON reflects the 3L+ population for OS adjusted using the two-stage methodology with re-censoring, for patients with a non-missing R-ISS stage and patients who had received a prior proteasome inhibitor and immunomodulatory drug – in line with the MAIC assumptions (N=66).*
†Proportional hazards in the MM-003 connection are based on an older data cut than the hazard ratio used in the NMA. This is because Kaplan-Meier data are unavailable for the data corresponding to the latest hazard ratio.

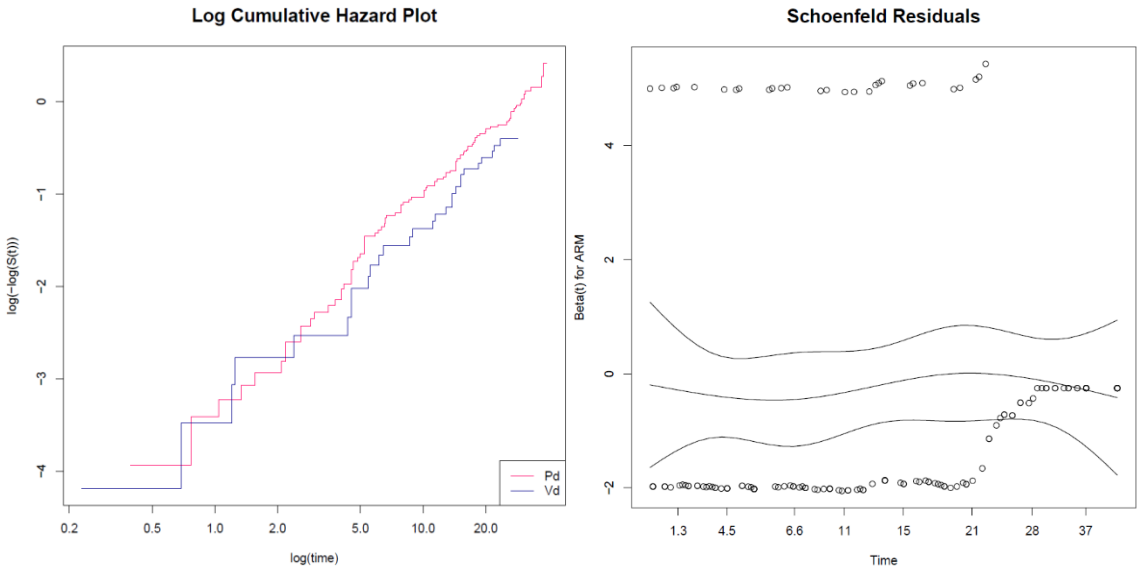
‡*Proportional hazards in the MM-009 and MM-010 connections are based on the 2L+ population due to lack of Kaplan-Meier data in the 3L+ population – see response to A11.*
§*Proportional hazards in the TOURMALINE-MM1 connection is based on the 2L+ population due to lack of Kaplan-Meier data in the 3L+ population.*

Figure 13 Proportional hazards testing PANORAMA-1 (3L+, OS)



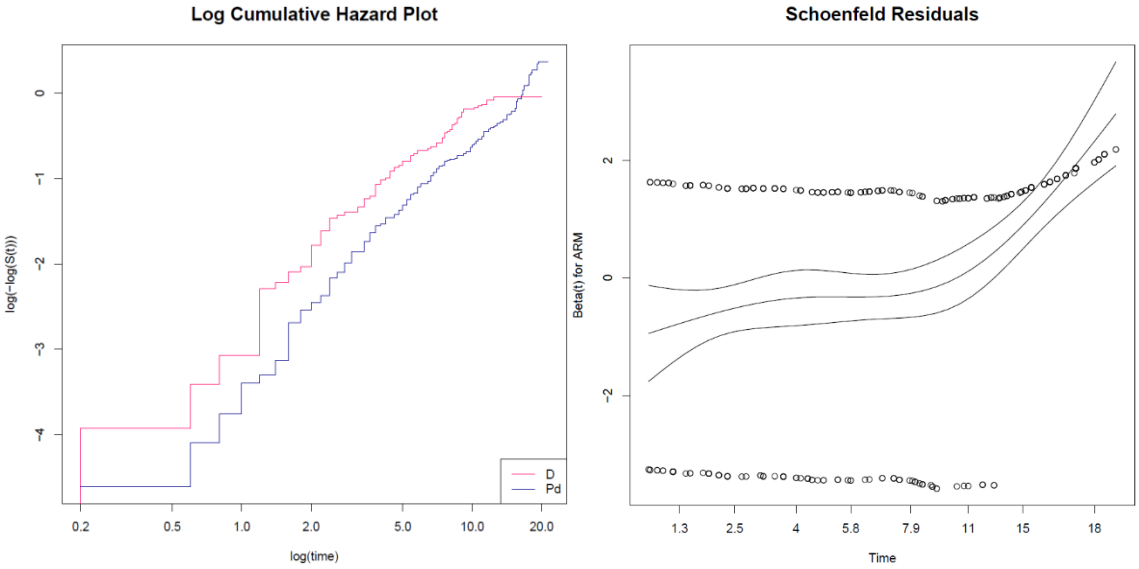
Abbreviations: OS, overall survival; PanoVd, panobinostat plus bortezomib + dexamethasone; SE, standard error; Vd, bortezomib plus dexamethasone.

Figure 14 Proportional hazards testing ICARIA-MM vs BOSTON (3L+, OS)



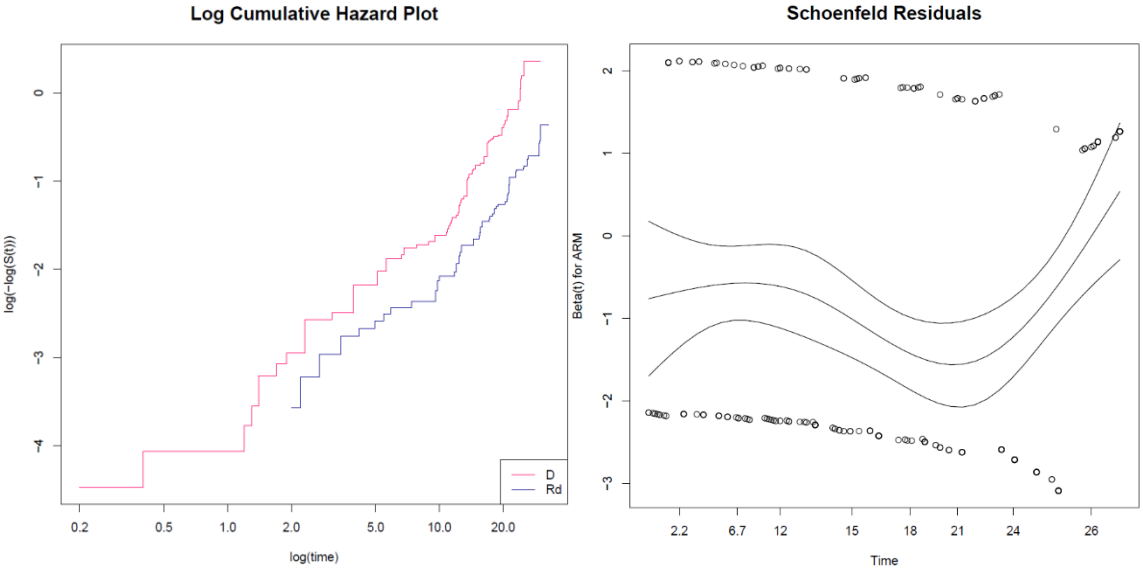
Abbreviations: OS, overall survival; Pd, pomalidomide plus dexamethasone; SE, standard error; Vd, bortezomib plus dexamethasone.

Figure 15 Proportional hazards testing MM-003 (3L+, OS)



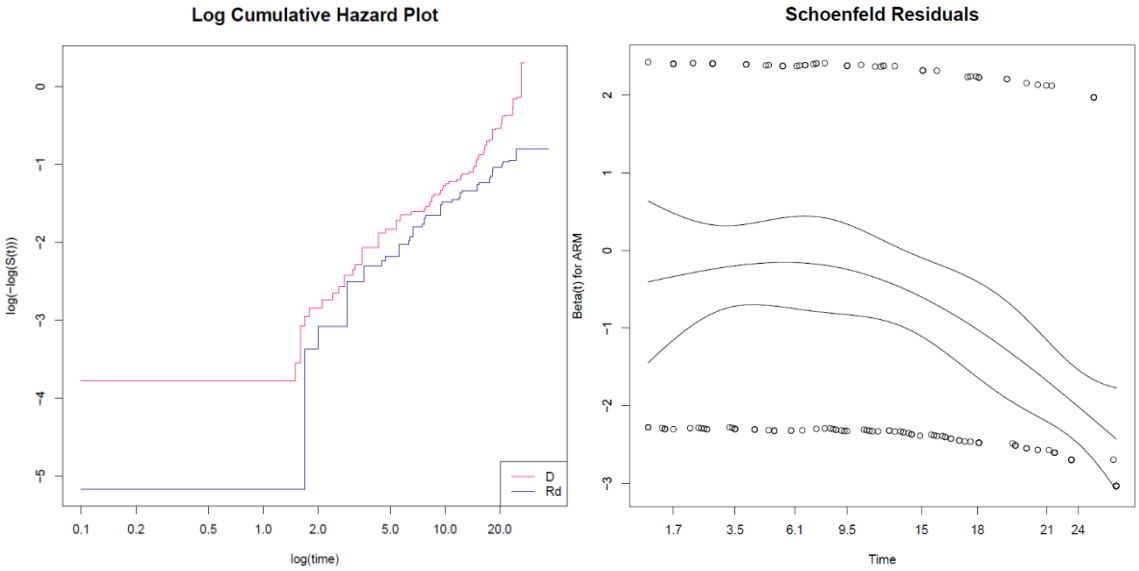
Abbreviations: D, dexamethasone; OS, overall survival; Pd, pomalidomide plus dexamethasone; SE, standard error.

Figure 16 Proportional hazards testing MM-009 (3L+, OS)



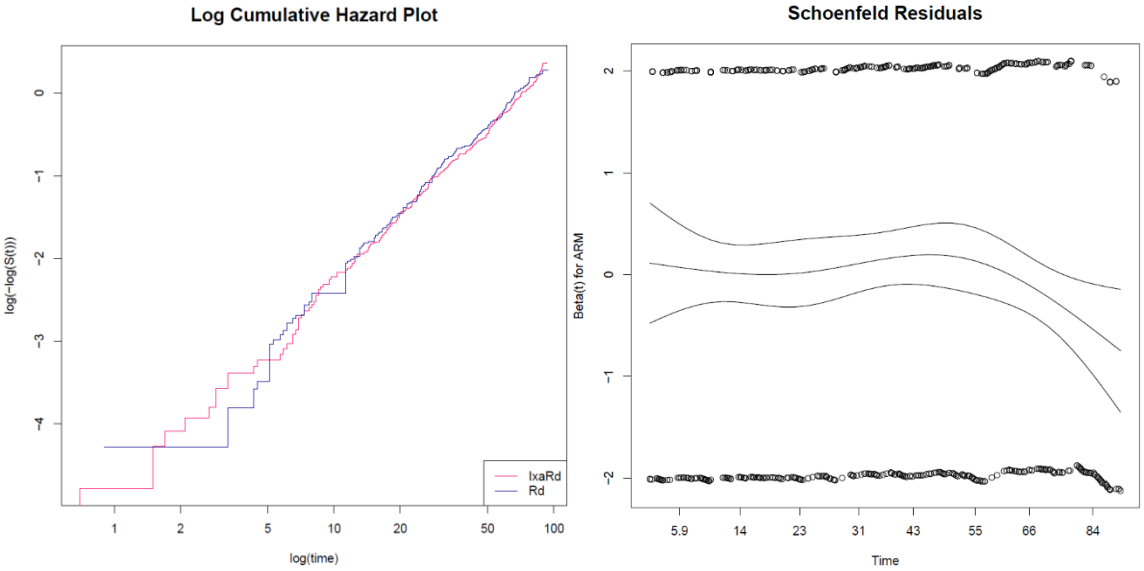
Abbreviations: D, dexamethasone; OS, overall survival; Pd, pomalidomide plus dexamethasone; SE, standard error.

Figure 17 Proportional hazards testing MM-010 (3L+, OS)



Abbreviations: D, dexamethasone; OS, overall survival; Pd, pomalidomide plus dexamethasone; SE, standard error.

Figure 18 Proportional hazards testing TOURMALINE-MM1 (3L+, OS)



Abbreviations: IxaRd, ixazomib + lenalidomide plus dexamethasone; OS, overall survival; Rd, lenalidomide plus dexamethasone; SE, standard error.

To reflect the totality of the data, an NMA based on HRs was still considered the optimal approach, however, moving to a more complex approach which relaxes the PH assumption comes with the caveat that data from different (potentially older) data cuts and different populations would be required to fill potential gaps in the network.

A17. Please report the differences in Vd dosing between the Vd arms of BOSTON, PANORAMA-1, ENDEAVOR and the Vd patients included in Dimopoulos 2015. Please comment on the appropriateness of using the Vd arms of these trials as a

common comparator arm in the NMAs, given the differences in dosing regimens across the trials.

Company response: The Vd dosing across trials are summarised in Table 16**.** The Vd dosing of bortezomib 1.3mg/m^2 on day 1, 4, 8 and 11 of a 21-day cycle and dexamethasone on day 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle is used in all the studies included in the NMA; however, deviations from this dosing schedule were reported in the PANORAMA-1 (from cycle 9 to 12), the BOSTON trial (starting from cycle 9) and the APEX study (from cycle 9 to 11). Considering that the same Vd dosing is administered for the first 8 cycles across all studies, and that the median time to treatment discontinuation in these studies does not exceed these 8 cycles, we believe that the different Vd dosing does not represent a relevant source of bias for the results of the NMA.

Table 16 Vd regimens across trials included in the relevant NMA networks

Trial		**Vd regimen**	
		V	**d**
BOSTON[37]	*SVd arm*	5-week [35-day] cycle Bortezomib 1.3 mg/m^2 SC on Days 1, 8, 15, and 22.	5-week [35-day] cycle Dexamethasone 20mg oral on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30.
	Vd arm	**Cycles 1 - 8** (3-week [21-day] cycle) Bortezomib 1.3 mg/m^2 SC on Days 1, 4, 8, and 11. **Cycles ≥ 9** (5-week [35-day] cycle) Bortezomib 1.3 mg/m^2 SC on Days 1, 8, 15, and 22	**Cycles 1 - 8** (3-week [21-day] cycle) Dexamethasone 20-mg oral on Days 1, 2, 4, 5, 8, 9, 11, and 12. **Cycles ≥ 9** (5-week [35-day] cycle) Dexamethasone oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30.
ENDEAVOR[9]	*Vd arm*	21-day cycle Bortezomib (1·3 mg/m^2; 3–5 s IV bolus or SC) on days 1, 4, 8, and 11.	21-day cycle Dexamethasone 20mg oral or IV on days 1, 2, 4, 5, 8, 9, 11, and 12.
PANORAMA-1[18]	*Both arms*	**Cycles 1-8** (3-week cycles) Bortezomib 1.3mg/m^2 IV on days 1, 4, 8, and 11. **Cycles 9-12** (6-week cycles) Bortezomib was given once per week during weeks 1, 2, 4, and 5.	**Cycles 1-8** (3-week cycles) Dexamethasone 20mg oral was given on days 1, 2, 4, 5, 8, 9, 11, and 12. **Cycles 9-12** (6-week cycles) Dexamethasone was given on the same and subsequent days as bortezomib.
Dimopoulos 2015 matched-pairs analysis			
MMY-2045[28]	*Vd arm*	21-day cycles Bortezomib 1.3 mg/m^2 IV bolus on Days 1, 4, 8, and 11.	21-day cycles Dexamethasone 20 mg oral on Days 1, 2, 4, 5, 8, 9, 11, and 12.
APEX[12]	*V arm*	**Cycles 1-8** (3-week cycles) Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11. **Cycles 9-11 (5-week cycles)**	NA

Trial		Vd regimen	
		V	d
		Bortezomib 1.3 mg/m^2 IV on days 1, 8, 15, and 22.	
	d arm	NA	**Cycles 1-4 (5-week cycles)** Dexamethasone 40 mg oral on days 1 through 4, 9 through 12, and 17 through 20 **Cycles 5-9 (4-week cycles)** Dexamethasone 40 mg oral on days 1 through 4.
DOXIL-MMY3001[25]	*V arm*	21-day cycles Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 of an every 21-days cycle.	NA
Abbreviations: d, dexamethasone; IV, intravenously; NMA, network meta-analysis; NA, not applicable; SC, subcutaneously; SVd, selinexor + bortezomib + dexamethasone; V, bortezomib; Vd, bortezomib + dexamethasone.			

A18. Please clarify exactly what degree of overlap there are between the patient populations labelled as “studies include some of the same patients” in the NMAs.

Company response: Two studies (APEX and the matched pairs analysis reported by Dimopoulos *et al.* 2015)[12,13] included in the original NMA were affected by the potential overlap of patients. Dimopoulos *et al.* 2015 state that *“only patients with one prior line in … APEX …were considered… and 242 patients from APEX and DOXIL-MMY-3001…. who had received one prior line of therapy were used for identification of matched pairs”.*[13] The DOXIL-MMY-3001 study evaluated 110 patients receiving bortezomib who had received one prior treatment, and the APEX study evaluated 132 patients receiving bortezomib who had received one prior therapy.[12,25] This suggests that the entire 2L cohort from the APEX trial receiving bortezomib were used for the identification of matched pairs in Dimopoulos *et al.* 2015. However, results from the matched pairs analysis are based on *“a total of 109 matched pairs of patients (n=218) treated with bortezomib plus dexamethasone and bortezomib who were identified by the propensity score matching model”.* Therefore, it is impossible to establish the extent of overlap of bortezomib patients in the APEX trial and the final matched pairs analysis reported by Dimopoulos *et al.* 2015. The overlap of patients from both studies included in the network has been noted as a limitation of the NMA presented.

However, upon further investigation of these two studies, there does not appear to be any overlap of patients from the APEX trial and the matched pairs analysis published

by Dimopoulos *et al.* 2015 in the 3L+ networks. This is because APEX data were based on a 3L+ population, whereas Dimopoulos *et al.* 2015 evaluated only 2L patients within the propensity scoring analysis. As a result of this finding, the NMA conducted for the 3L+ population has been updated based on the exclusion of the Dimopoulos *et al.* 2015 study; further details of the NMA update are provided in the Supplementary Appendix.

A19. Priority question. The EAG considers the NMA comparisons between SVd and IxaRd (3L), KRd (2L) and Rd (2L) to be at very high risk of bias due to:

- **The large amount of between study-heterogeneity in the evidence network connecting SVd to the comparators, including patient characteristics and dosing regimens;**
- **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 and;**
- **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.**

In light of these concerns, the EAG notes that unanchored matching adjusted indirect comparisons (MAICs) may provide an alternative estimate of the relative treatment effect of SVd vs comparators that avoids the uncertainties associated with the NMAs, with a different set of limitations to the NMA analysis. The EAG considers unanchored MAICs feasible due to the reasonable overlap of patient characteristics in key comparator studies, and notes that most heterogeneity may be introduced into the network through the use of older studies and observational data, in particular to link studies including Rd with those

including Vd. Please provide unanchored MAICs estimating what the SVd or Vd treatment effect would have been after matching to:

- **KRd at 2L (The EAG notes baseline characteristics are available for the KRd 2L group of ASPIRE in Table 19 of the company submission in the committee papers of TA695, and efficacy outcomes for the 2L subgroup are available in the primary publication);**
- **Rd at 2L;**
- **IxaRd at 3L**.

Please conduct the following 2 approaches:

a) **Matching the Vd IPD from BOSTON to the aggregate data of the DRd, IxaRd and Rd arms from the comparator trials to produce adjusted survival curves for Vd in the comparator trial population. Please provide hazard ratios for PFS and OS between Vd and DRd, IxaRd and Rd in the comparator trial population and provide a test for proportional hazards. Please provide cost-effectiveness analysis based on these results as outlined in B1 and B5?**

b) **Matching the SVd IPD from BOSTON to the KRd (DRd), IxaRd and Rd aggregate data from the comparator trials to produce adjusted survival curves for SVd in the comparator trial population, to provide a comparison between KRd (DRd), IxaRd and Rd in the comparator trial populations, providing hazard ratios for PFS and OS in the comparator trial population and a test for proportional hazards. Please provide cost-effectiveness analysis based on these results as outlined in B1 and B5?**
[N.B. the EAG confirmed that in this paragraph DRd should be KRd

Please provide fully adjusted analyses including all available baseline characteristics that are reported in both trials. Please also provide naive unadjusted comparisons alongside each analysis.

Company response: As per the response to A5 and A7, and based on UK clinical expert opinion, Rd and KRd are not considered relevant comparators at 2L since,

following DRd at 1L, patients would be lenalidomide-relapsed and/ or refractory and, therefore, would not receive a lenalidomide-containing combination at 2L.

No MAIC analysis could be performed to compare SVd *versus* IxaRd. Whilst a Kaplan-Meier curve is available for the 3L+ population for PFS in the TOURMALINE-MM1 study (published by Mateos *et al.* 2017),[20] no baseline characteristics are reported for this 3L+ cohort. Therefore, matching would only be possible using the 2L+ patient population characteristics from TOURMALINE-MM1. Matching 3L+ patients in the BOSTON trial to the 2L+ population of TOURMALINE-MM1 is not considered appropriate, and therefore, in the absence of suitable data, no MAIC analysis has been performed.

A20. Priority question. The EAG notes that the dosing of Vd in PANORAMA-1 was for a limited duration (eight 3-week cycles followed by four 6-week cycles), whereas in BOSTON patients were treated until disease progression. As such, it is unclear if the Vd arms between PANORAMA-1 are appropriately labelled as common comparators to perform anchored comparisons from. In light of this concern, please also perform the unanchored MAIC and cost-effectiveness analyses requested in question A19 for Vd and SVd IPD matched to PANORAMA-1 trial participants.

Company response: No MAIC analysis could be performed to compare SVd to PanoVd due to the absence of KM curves on the 3L+ population from PANORAMA-1. The studies by Richardson *et al.* (2016)[38] and San-Miguel *et al.* (2016)[19] report PFS and OS KM curves, respectively; however, these are only for a subgroup of the 3L+ population in PANORAMA-1, i.e., patients with at least two prior regimens including bortezomib and an IMiD. This is clear by comparing the number of 3L+ patients in PANORAMA-1 (N = 371) and the number of 3L+ patients previously exposed to bortezomib and an IMiD (N = 147). For this reason, the population for which KM curves are available in PANORAMA-1 differs from the 3L+ population on which the NMA performed by the company is based.

A21. Priority question. For DVd and Kd the EAG consider anchored comparisons to be feasible, but note the large heterogeneous network informing the between study heterogeneity in the company's NMA may overestimate

uncertainty for these comparisons. Please provide either, i) NMAs restricted to the clinical trials containing a Vd arm, or ii) Bucher ITCs or anchored MAICs comparing DVd and Kd with SVd. Please also provide these analyses for PanoVd compared to SVd, if the company considers the differences in Vd dosing between PANORAMA-1 and BOSTON unlikely to bias the results of these comparisons to a large degree.

Company response: As per the responses to A5 and A7, based on UK clinical expert opinion, DVd is not considered a relevant comparator at 2L since, following DRd treatment at 1L, patients would be daratumumab-relapsed and/ or refractory and, therefore would not receive another daratumumab-containing combination at 2L. Additionally, as per the response to A20, no MAIC analysis could be performed to compare SVd to PanoVd due to the absence of KM curves on the 3L+ population from PANORAMA-1.

A restricted NMA has been performed, informed only by studies containing a Vd arm for both 2L and 3L+ populations for PFS and OS.

Results are presented for comparisons between Kd *versus* SVd (in the 2L population) and PanoVd *versus* SVd (in the 3L+ population) and are summarised in Table 17. These results from the restricted NMAs for 2L and 3L+ are similar to the results from the full NMAs for 2L and 3L+ provided by the company, further validating the NMAs performed by the company.

Note: no comparison between IxaRd and SVd is possible as TOURMALINE-MM1 is not included in the restricted network.

Table 17 NMA results based on a restricted network of studies containing a Vd arm

Line	Comparator	PFS Restricted NMA HR [95% CrI]*	OS Restricted NMA HR [95% CrI]*
2L	Kd versus SVd	0.727 [0.249, 2.198]	0.883 [0.307, 2.530]
3L+	PanoVd versus SVd	0.801 [0.281, 2.336]	1.253 [0.421, 3.643]

Abbreviations: 2L, second-line; 3L+, third-line onwards; CrI, credible interval; HR, hazard ratio; Kd, carfilzomib plus dexamethasone; NMA, network meta-analysis; OS, overall survival; PanoVd, panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival; SVd, selinexor plus bortezomib plus dexamethasone;

**Random-effects NMA results are based on a HN(0,0.32^2) prior distribution.*

An anchored MAIC was also performed between SVd and Kd, using Vd as the common comparator arm. Matching to the ENDEAVOR 2L population has been performed using data for 2L population from the BOSTON trial (i.e., both arms have been included in the matching). A MAIC-HR has been estimated between SVd *versus* Vd, and a Bucher indirect comparison has been performed to estimate a HR between Kd *versus* SVd (i.e., anchoring on Vd) using the MAIC-HR.

In an attempt to overcome differences in study populations, matching on a number of factors has been undertaken. The selection of the baseline characteristics for the matching process was based on previous clinical validation of prognostic factors in MM, and on the availability of these baseline characteristics from the ENDEAVOR trial for the 2L+ population. A total of six factors were selected for inclusion in the matching, including age, ECOG PS, R-ISS, cytogenetic risk, receipt of prior bortezomib, and receipt of prior lenalidomide.

Table 18 Summary of baseline characteristics in Moreau *et al.* 2017 and BOSTON trial prior to- and after MAIC weighting

Factor	ENDEAVOR – Moreau *et al.* 2017[8]	BOSTON IPD[5]	
		Prior to matching	Post matching
Number of patients	464	198	(ESS) [redacted]
Arms	Kd & Vd	SVd & Vd	SVd & Vd
Line	2L	2L	2L
Age Median (range)	 64.8 (36.0-89.0)	 68.0 (44-90)	 64.8
ECOG PS, n (%) 0 1 2	 51.9% 42.2% 5.8%	 38.9% 54.0% 7.1%	 51.9% 42.2% 5.8%
R-ISS, n (%) 2-3‡	 51.7%†	 69.7%*	 51.7%
Cytogenetic risk, n (%) High	 24.9%*	 23.2%	 24.9%
Prior therapies, n (%) Bortezomib Lenalidomide	 42.5% 21.1%	 65.2% 21.7%	 42.5% 21.1%

Abbreviations: 2L, second-line; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IPD, individual patient data; ISS, International Staging System; Kd, carfilzomib plus dexamethasone; PS, performance status; R-ISS, Revised International Staging System; SVd, selinexor plus bortezomib plus dexamethasone; Vd, bortezomib plus dexamethasone.

Notes:

**Missing values were excluded prior to calculating %*

†Reported as ISS

‡R-ISS=2 and R-ISS=3 combined due to <8% patients in BOSTON with R-ISS=3

Results from the anchored MAIC analyses for PFS are presented in Table 19, which show the HR of Kd *versus* SVd (anchored on Vd). SVd is numerically superior to Kd

after weighting (HR estimate is greater than 1.0). However, no statistically significant differences are identified either prior to- or after weighting (95% CI include a HR estimate of 1.0).

Table 19 Anchored PFS MAIC results ENDEAVOR (Kd) *versus* BOSTON (SVd)

Comparator study	Matching	BOSTON sample size	ESS	ESS %	HR [95% CI] – Kd *versus* Vd	HR [95% CI] – SVd *versus* Vd	Bucher ITC – HR [95% CI] – Kd *versus* SVd
ENDEAVOR (Moreau *et al.* 2017)[8]	Unweighted	198	NA	NA	0.447 [0.330, 0.606]	0.600 [0.403, 0.893]	0.745 [0.452, 1.230]
	MAIC-weighted	185*	[redacted]	[redacted]		0.425 [0.247, 0.731]	1.052 [0.583, 1.898]

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; PS, performance status; R-ISS, Revised International Staging System.
Factors included in the matching: age, sex, ECOG PS, R-ISS, cytogenetic risk, prior bortezomib and prior lenalidomide.
*Notes: *13 patients did not report R-ISS and were therefore excluded from the analysis based on the Full set of factors.*

Results from the anchored MAIC analyses for OS are presented in Table 20, which shows the HR of Kd *versus* SVd (anchored on Vd). SVd is numerically superior to Kd after weighting (HR estimate is greater than 1.0). However, no statistically significant differences are identified either prior to- or after weighting (95% CI including a HR estimate of 1.0).

Table 20 Anchored OS MAIC results ENDEAVOR (Kd) *versus* BOSTON (SVd)

Comparator study	Matching	BOSTON sample size*	ESS	ESS %	HR [95% CI] – Kd versus Vd	HR [95% CI] – SVd versus Vd	Bucher ITC – HR [95% CI] – Kd versus SVd
ENDEAVOR (Moreau *et al.* 2017)[8]	Unweighted	198	NA	NA	0.771 [0.583, 1.018]	0.873 [0.546, 1.395]	0.884 [0.512, 1.525]
	MAIC-weighted	185*	[redacted]	[redacted]		0.557 [0.306, 1.014]	1.385 [0.726, 2.642]

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; PS, performance status; R-ISS, Revised International Staging System.
Factors included in the matching: age, sex, ECOG PS, R-ISS, cytogenetic risk, prior bortezomib and prior lenalidomide.
*Notes: *13 patients did not report R-ISS and were therefore excluded from the analysis based on the Full set of factors.*

A22. To provide an assessment of the unanchored MAIC approach, please provide unanchored MAICs as requested in question A19 for DVd and Kd compared to SVd.

Company response: As per the responses to A5 and A7, DVd is not considered a relevant comparator at 2L since following DRd patients would be daratumumab-

relapsed and/ or refractory and therefore would not receive another daratumumab-containing combination at 2L.

No unanchored MAIC analysis has been performed to compare Kd to SVd. A MAIC analysis comparing SVd versus Kd has been presented in response to clarification question A21 and is based on an anchored comparison, which is considered to be a more robust approach and is advocated by the NICE DSU.[39] Technical Support Document 18 states that *"when connected evidence with a common comparator is available, only "anchored" forms of population adjustment may be used. "Unanchored" population adjustment may only be considered in the absence of a connected network of randomised studies, or where there are single-arm studies involved."* As SVd is connected to Kd via a common comparator arm (i.e., Vd), only an anchored MAIC approach has been performed, consistent with this guidance.

Furthermore, because no unanchored MAIC was considered feasible to compare SVd *versus* IxaRd in the 3L+ population (in the absence of appropriate comparator data), the company believes that no validation of the unanchored approach is required.

A23. Priority question. Following the requested analyses in questions A19 to A22, please complete the following tables comparing the results of the NMA, MAIC and naive unadjusted analyses for SVd versus each comparator.

Line	Comparator	Random Effects NMA HR (95% CI)	Naive unanchored unadjusted HR (95% CI)	Fully adjusted unanchored MAIC HR (95% CI)	Restricted NMA/Bucher ITC HR (95% CI)
2L	**Kd**				
	Vd	**NA**	**NA**	**NA**	**NA**
	KRd				**NA**
	Rd				**NA**
	DVd				
3L	**PanoVd**				
	IxaRd				**NA**

Company response: A summary of results from all ITC analyses is presented in Table 21 and

Table 22 for PFS and OS, respectively.

Table 21 NMA, MAIC and naive unadjusted analyses for each comparator versus SVd – PFS

Line	Comparator	Random Effects NMA* HR [95% CrI]	Restricted Random-Effects NMA HR*‡ [95% CrI]	Anchored MAIC HR [95% CI]	Naive unanchored unadjusted HR [95% CI]	Fully adjusted unanchored MAIC HR [95% CI]
2L	Kd *versus* SVd	0.727 [0.308, 1.673]	0.727 [0.249, 2.198]	1.052 [0.583, 1.898]	**NA**	**NA**
3L+	IxaRd *versus* SVd	0.692 [0.118, 3.291]	**NA**	**NA**	**NA**	**NA**
	PanoVd *versus* SVd	0.797 [0.262, 2.281]	0.801 [0.281, 2.336]	**NA**	**NA**	**NA**

Abbreviations: 2L, second-line; 3L+, third-line onwards; CI, confidence interval; CrI, credible interval; HR, hazard ratio; IxaRd, ixazomib plus lenalidomide plus dexamethasone; Kd, carfilzomib plus dexamethasone; MAIC, matching-adjusted indirect comparison; NA, not applicable; NMA, network meta-analysis; PanoVd, panobinostat plus bortezomib plus dexamethasone; SVd, selinexor plus bortezomib plus dexamethasone.
Notes:
**Random-effects NMA results are based on a HN(0,0.32^2) prior distribution*
‡Based on studies containing a Vd arm.

Table 22 NMA, MAIC and naive unadjusted analyses for each comparator versus SVd – OS

Line	Comparator	Random Effects NMA* HR [95% CrI]	Restricted Random-Effects NMA*‡ HR [95% CrI]	Anchored MAIC HR [95% CI]	Naive unanchored unadjusted HR [95% CI]	Fully adjusted unanchored MAIC HR [95% CI]
2L	Kd versus SVd	0.887 [0.321, 2.452]	0.883 [0.307, 2.530]	1.385 [0.726, 2.642]	**NA**	**NA**
3L+	IxaRd versus SVd	1.094 [0.236, 5.181]	**NA**	**NA**	**NA**	**NA**
	PanoVd versus SVd	1.240 [0.454, 3.462]	1.253 [0.421, 3.643]	**NA**	**NA**	**NA**

Abbreviations: 2L, second-line; 3L+, third-line onwards; CI, confidence interval; CrI, credible interval; HR, hazard ratio; IxaRd, ixazomib plus lenalidomide plus dexamethasone; Kd, carfilzomib plus dexamethasone; MAIC, matching-adjusted indirect comparison; NA, not applicable; NMA, network meta-analysis; PanoVd, panobinostat plus bortezomib plus dexamethasone; SVd, selinexor plus bortezomib plus dexamethasone.
Notes:
**Random-effects NMA results are based on a HN(0,0.32^2) prior distribution*
‡Based on studies containing a Vd arm.

A24. The EAG considers the results of the NMAs to provide results that are potentially implausible, without accounting for meaningful treatment effect modification or

sampling bias. Please comment on the clinical plausibility of each of the following results:

a) The estimated HR for KRd vs Kd in the ITT population for PFS being 1.34 (95% CrI: 0.40 to 4.17), i.e., numerically better outcomes for Kd than KRd, but the opposite direction for OS (HR: 0.75 [95% CrI: 0.17 to 3.32]).

b) The estimated HR for Rd vs Vd in the ITT population for PFS to be 1.03 (95% CrI 0.40 to 2.56), 1.03 (95% CrI 0.39 to 2.54) in the 2L population and 1.30 (95% CrI 0.38 to 4.22) in the 3L population. The EAG's clinical experts expected that, all else being equal, Rd would be associated with a longer PFS than Vd. In Appendix N, the company's clinical experts agreed there would be expected efficacy difference between Rd and Vd.

Company response: Further discussion with KOLs confirmed that the OS results from the NMA are more in line with clinical expectations than the PFS results. However, it was highlighted that the PFS HRs favouring Kd over KRd in the ITT population, and Vd over Rd in the ITT, 2L, and 3L+ populations, should not undermine the clinical plausibility of the entire NMA when considering the following aspects:

- The PFS HRs are close to 1, implying that there is not a large and statistically significant PFS improvement with Kd over KRd, and with Vd over Rd.
- Prior exposure and refractoriness to different classes of myeloma treatments cannot be fully controlled for when performing an NMA for the ITT population (i.e. 2L+ population). This is supported by the results of the ITT (2L+) NMA performed in the PI-naïve population (trial populations are more aligned by being not previously exposed to PI) where the PFS results are in line with the clinical expectations and with the OS results, i.e., HR favours KRd over Kd, and Rd over Vd.[40]

Systematic Literature Review

A25. Please provide further details on how the searches of relevant conferences were undertaken, including search strategies and conference years searched.

Company response: The abstract books of key conferences were hand-searched against the predefined PICOS condition. Handsearching involves a manual, page-by-page, examination of the contents of conference proceedings and abstracts, and it does not rely upon key-word searches.[41] It is the gold-standard approach to search conference materials.[42]

Conferences were searched by years 2021-2023 and included:

- American Society of Clinical Oncology (ASCO), https://www.asco.org/;
- American Society of Hematology (ASH), https://www.hematology.org/;
- British Society for Haematology (BSH), https://b-s-h.org.uk/;
- Controversies in Multiple Myeloma (COMy), https://comylive.cme-congresses.com/;
- European Hematology Association (EHA), https://ehaweb.org/;
- European Myeloma Network (EMN), https://www.myeloma-europe.org/emn/about-emn/;
- European Society of Medical Oncology (ESMO), https://www.esmo.org/;
- International Myeloma Society (IMS) annual events, https://www.myelomasociety.org/.

Conference search annex

Embase search	1932
CPCI-S Search	369
ASCO	94
Handsearching ASH	759
BSH	39
COMy	Access not achieved – could not search
EHA	232
EMN	0
ESMO	11
IMS	Access not achieved – could not search
	3436

Embase
Database:
Host: Ovid
Data parameters: 1980 to 2023 Week 05

Date of search: 4 Feb 2023

#	Searches	Results
1	exp *multiple myeloma/	54598
2	(myelom* or ((Penta or triple-class) adj1 refractory)).ti,ab,kw,kf,ot.	111816
3	kahler*.ti,ab,kw,kf,ot.	188
4	*plasmacytoma/	5642
5	(plasm?cytom* or plasm?zytom* or plasma cytoma* or plasma zytoma*).ti,ab,kw,kf,ot.	8922
6	(plasm* adj3 (neoplas* or leukaem* or leukem* or tumor* or tumour* or dyscrasia)).ti,ab,kw,kf,ot.	19426
7	((plasmacytic* or plasmocytic* or plasmocyte*) adj1 (leukem* or leukaem*)).ti,ab,kw,kf,ot.	37
8	(myelomatoses or myelomatosis).ti,ab,kw,kf.	365
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	132932
10	selinexor/	1430
11	(selinexor* or nexpovio* or xpovio* or "ATG 010" or ATG010 or "ATG-010" or "KPT 330" or KPT330 or "KPT-330" or "ONO 7705" or ONO7705 or "ONO-7705" or 31TZ62FO8F or "1393477-72-9").ti,ab,kw,kf,ot.	1106
12	bortezomib/	37690
13	(bortezomib* or velcade* or "BXCL 101" or BXCL101 or "BXCL-101" or "LDP 341" or LDP341 or "LDP-341" or "mg 341" or mg341 or "mg-341" or "PS 341" or PS341 or "PS-341" or "jnj 26866138" or jnj26866138 or "jnj-26866138" or 69G8BD63PP or "179324-69-7").ti,ab,kw,kf,ot.	23552
14	dexamethasone/	172546
15	(Dexamethason* or Dexam?thason* or "aeroseb dex*" or "aeroseb−d*" or "aeroseb−dex*" or "Apo Dexam?thason*" or "Apo-Dexamethason*" or "bisu ds*" or "dacortina fuerte*" or "dacortine fuerte*" or "de−sone la*" or "dexa cortisyl*" or "dexa dabrosan*" or "dexa korti*" or "dexa scherosan*" or "dexa scherozon*" or "dexa scherozone*" or "dexa−p*" or "dexacen 4*" or "dexacen−4*" or "dexpak taperpak*" or "ex s1*" or "fluormethyl prednisolone*" or "isopto dex*" or "isopto maxidex*" or "isopto−dex*" or "lokalison f*" or "methazon ion*" or "methazone ion*" or "metisone lafi*" or "oftan−dexa*" or "predni f tablinen*" or "predni−f*" or "prednisolone f*" or Adrecort* or Adrenocot* or Aflucoson* or Alfalyl* or Anaflogistico* or Aphtasolon* or Apo Dexam?thason* or Apo-Dexamethason* or Arcodexan* or Artrosone* or Auxiron* or Azium* or Baycadron* or Bidexol* or Calonat* or Cebedex* or Cetadexon* or Colofoam* or Corsona* or Corsone* or Cortastat* or Cortidex* or Cortidexason* or Cortidrona* or Cortidrone* or Cortisumman* or Dalalone* or Danasone* or Decacortin* or Decadeltosona* or Decadeltosone* or Decaderm* or Decadion* or Decadran* or Decadron* or Decadronal* or Decadrone* or Decaesadril* or Decagel* or Decaject* or Decalix* or Decamethasone* or Decasone* or Decaspray* or Decasterolone* or Decdan* or Decilone* or Decofluor* or Dectancyl* or Dekacort* or Delladec* or Deltafluoren* or Deltafluorene* or Dergramin* or Deronil* or Desacort* or Desacortone* or Desadrene* or Desalark* or Desameton* or Desametone* or Desigdron* or Dexachel* or Dexacort* or Dexacortal* or Dexacorten* or Dexacortin* or Dexacortisyl* or Dexadabroson* or Dexadecadrol* or Dexadrol* or Dexagel* or Dexagen* or Dexahelvacort* or Dexakorti* or Dexalien* or Dexalocal* or Dexame* or Dexamecortin* or Dexameson* or Dexamesone* or Dexametason* or Dexameth* or Dexamethasone* or Dexamethasone* or Dexamethasone* or Dexamethasone* or Dexamethazon* or Dexamethonium* or Dexamonozon* or Dexan* or Dexane* or Dexano* or Dexapot* or Dexascheroson* or Dexascherozon* or Dexascherozone* or Dexason* or Dexasone* or Dexinoral* or Dexionil* or Dexmethsone* or Dexona* or Dexone* or Dextelan* or Dextenza* or Dextrasone* or Dexycu* or Dezone* or Dibasona* or Esacortene* or Exadion* or Exadione* or Firmalone* or Fluormethylprednisolon* or Fluormethylprednisolone* or Fluormone* or Fluorocort* or Fluorodelta* or Fluoromethylprednisolone* or Fortecortin* or Gammacorten* or Gammacortene* or Grosodexon* or Grosodexone* or Hemady* or Hexadecadiol* or Hexadiol* or Hexadrol* or Isnacort* or Isoptodex* or Isoptomaxidex* or Loverine* or Luxazone* or Marvidione* or Maxidex* or Mediamethasone* or Megacortin* or Mephameson* or Mephamesone* or Metasolon* or Metasolone* or Methazonion* or Methazonione* or Mexasone* or Millicorten* or Millicortenol* or Mymethasone* or Neoforderx* or Neofordex* or Nisomethasona* or Novocort* or Opticorten* or Opticortinol* or Oradexan* or Oradexon* or Oradexone* or Orgadrone* or Ozurdex* or Pidexon* or Policort* or Posurdex* or Prodexona* or Prodexone* or Sanamethasone* or Santenson* or Santeson* or Sawasone* or Solurex* or Spoloven* or Sterasone* or Thilodexine* or Triamcimetil* or Vexamet* or Visumetazone* or Visumethazone* or "isv 305" or isv305 or "isv-305" or "mk 125" or mk125 or "mk-125" or "nsc 34521" or nsc34521 or "nsc-34521" or "oto 104" or oto104 or "oto-104" or "sk 0503" or sk0503 or "sk-0503" or "spt 2101" or spt2101 or "spt-2101" or 7S5I7G3JQL or "50-02-2").ti,ab,kw,kf,ot.	93079
16	lenalidomide/	25117
17	(lenalidomid* or "apo-lenalidomide" or ladevina* or revlimid* or "CC 5013" or CC5013 or "CC-5013" or "CDC 501" or CDC501 or "CDC-501" or "ENMD 0997" or ENMD0997 or "ENMD-0997" or "imid 3" or imid3 or "imid-3" or "SYP 1512" or SYP1512 or "SYP-1512" or F0P408N6V4 or "191732-72-6").ti,ab,kw,kf,ot.	16040

18	carfilzomib/	6347
19	(carfilzomib* or kyprolis* or "ono 7057" or ono7057 or "ono-7057" or "PR 171" or PR171 or "PR-171" or 72X6E3J5AR or "868540-17-4").ti,ab,kw,kf,ot.	4047
20	panobinostat/	4850
21	(panobinostat* or farydak* or "lbh 589*" or lbh589* or "lbh-589*" or "mtx 110" or mtx110 or "mtx-110" or 9647FM7Y3Z or "404950-80-7").ti,ab,kw,kf,ot.	2316
22	daratumumab/	5554
23	(daratumumab* or dalinvi* or darasarex* or darzalex* or Faspro* or "hlx 15" or hlx15 or "hlx-15" or "HuMax-CD 38" or "JNJ-54767414" or 4Z63YK6E0E or "945721-28-8").ti,ab,kw,kf,ot.	3909
24	pomalidomide/	5086
25	(pomalidomid* or actimid* or imnovid* or pomalyst* or "CC 4047" or CC4047 or "CC-4047" or "cdc 394" or cdc394 or "cdc-394" or D2UX06XLB5 or "19171-19-8").ti,ab,kw,kf,ot.	3253
26	ixazomib/	2346
27	(Ixazomib* or ninlaro* or "MLN 2238" or MLN2238 or "MLN-2238" or "MLN 9708" or MLN9708 or "MLN-9708" or 71050168A2 or "1072833-77-2").ti,ab,kw,kf,ot.	1550
28	belantamab/	53
29	(belantamab* or BLENREP or "gsk 2857914" or gsk2857914 or "gsk-2857914" or "GSK 2857916" or GSK2857916 or "GSK-2857916" or "WHO 10754" or WHO10754 or "WHO-10754" or DB1041CXDG or "2050232-20-5" or "2061894−48−0").ti,ab,kw,kf,ot.	333
30	ciltacabtagene autoleucel/	185
31	(ciltacabtagen* or carvykti* or "jnj 4528" or jnj4528 or "jnj-4528" or "JNJ 68284528" or JNJ68284528 or "JNJ-68284528" or "LCAR B38M" or LCARB38M or "LCAR-B38M" or 0L1F17908Q).ti,ab,kw,kf,ot.	151
32	elotuzumab/	1652
33	(elotuzumab* or empliciti* or "BMS 901608" or BMS901608 or "BMS-901608" or "PDL 063" or PDL063 or "PDL-063" or huluc63 or 1351PE5UGS or "915296-00-3").ti,ab,kw,kf,ot.	915
34	idecabtagene vicleucel/	327
35	(idecabtagen* or abecma* or "BB 2121" or BB2121 or "BB-2121" or "id cel" or idecel or "ide−cel" or 8PX1X7UG4D).ti,ab,kw,kf,ot.	212
36	isatuximab/	839
37	(isatuximab* or sarclisa* or "Hu 38SB19" or Hu38SB19 or "Hu-38SB19" or "SAR 650984" or SAR650984 or "SAR-650984" or R30772KCU0 or "1461640-62-9").ti,ab,kw,kf,ot.	533
38	melphalan flufenamide/	175
39	(melphalan* or melflufen* or pepaxti* or pepaxto* or ygalo* or "j 1" or j1 or "ck 1535" or ck1535 or "ck-1535" or F70C5K4786 or "380449-51-4" or "380449−54−7").ti,ab,kw,kf,ot.	19282
40	teclistamab/	130
41	(teclistamab* or tecvayli* or "JNJ 64007957" or JNJ64007957 or "JNJ-64007957" or "jnj 7957" or jnj7957 or "jnj-7957" or 54534MX6Z9 or "2119595-80-9").ti,ab,kw,kf,ot.	68
42	venetoclax/	8549
43	(venetoclax* or venclexta* or "a 11954250" or a11954250 or "ABT 199" or ABT199 or "ABT-199" or "GDC 0199" or GDC0199 or GDC-0199 or "RG 7601" or RG7601 or "RG-7601" or "ro 5537382" or ro5537382 or N54AIC43PW or "1257044-40-8").ti,ab,kw,kf,ot.	6590
44	Cyclophosphamide/	229549
45	(Cyclophosphamid* or Alkyroxan* or Carloxan* or Ciclofosfamida* or Ciclolen* or Cicloxal* or Clafen* or "cyclo−cell*" or Cycloblastin* or Cycloblastin* or "cyclofos amide*" or Cyclofosfamid* or Cyclofosfamid* or Cyclophar* or Cyclophosphamid* or Cyclophosphamid* or Cyclophosphamid* or Cyclophosphan* or Cyclophosphan* or Cyclostin* or Cyclostin* or Cycloxan* or Cyphos* or Cyrevia* or Cytophosphan* or Cytophosphan* or Cytophosphan* or cytoxan lyophilized* or Cytoxan* or Endoxan* or Endoxon* or Enduxan* or "endocyclo phosphat*" or Genoxal* or Ledoxan* or Ledoxina* or "lyophilized Cytoxan*" or Mitoxan* or Neosan* or Neosar* or Noristan* or Procytox* or Procytoxide* or Semdoxan* or Sendoxan* or Syklofosfamid* or "b 518" or "b518" or "b-518" or "nsc 26271" or "nsc-26271" or "nsc26271" or "nsc 2671" or "nsc2671 pr nsc-2671" or 6UXW23996M or "50-18-0").ti,ab,kw,kf,ot.	92178
46	chemo*.af.	1675536
47	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46	1982059
48	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	0
49	Randomized Controlled Trial/	755138
50	exp Randomized Controlled Trials as Topic/	246980
51	"Randomized Controlled Trial (topic)"/	246872

52	Controlled Clinical Trial/	467822
53	exp Controlled Clinical Trials as Topic/	256400
54	"Controlled Clinical Trial (topic)"/	13233
55	Randomization/	97448
56	Random Allocation/	93577
57	Double-Blind Method/	176829
58	Double Blind Procedure/	201726
59	Double-Blind Studies/	162253
60	Single-Blind Method/	47675
61	Single Blind Procedure/	49742
62	Single-Blind Studies/	49742
63	Placebos/	324924
64	Placebo/	381700
65	Control Groups/	110772
66	Control Group/	110772
67	(random* or sham or placebo*).ti,ab,hw,kf,kw.	2434550
68	((singl* or doubl*) adj (blind* or dumm* or mask* or arm or arms)).ti,ab,hw,kf,kw.	370032
69	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	1972
70	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	1650007
71	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	67069
72	allocated.ti,ab,hw.	104620
73	((open label or open-label) adj5 (study or studies or trial* or extension)).ti,ab,hw,kf,kw.	85734
74	((sub* and (group adj2 anal*)) or (subgroup adj2 anal*)).ti,ab,kw,kf.	113006
75	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	17377
76	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	851
77	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	8153
78	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	18259
79	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf.	596041
80	(trial or trail).ti,ab,kw,kf.	1108589
81	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80	4394242
82	Clinical study/	117016
83	Case control study/	198089
84	Family study/	25666
85	Longitudinal study/	183606
86	Retrospective study/	1376303
87	Prospective study/	834133
88	Randomized controlled trials/	246872
89	87 not 88	823878
90	Cohort analysis/	959124
91	(Cohort adj (study or studies)).mp.	448732
92	(Case control adj (study or studies)).tw.	162882
93	(follow up adj (study or studies)).tw.	69214
94	(observational adj (study or studies)).tw.	239673
95	(epidemiologic$ adj (study or studies)).tw.	117597

96	(cross sectional adj (study or studies)).tw.	318450
97	82 or 83 or 84 or 85 or 86 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96	3667254
98	"systematic review"/	405604
99	(Systematic* adj2 Review*).ti,ab,kw,kf,ot.	367074
100	Meta-Analysis/	275276
101	(meta anal* or (MAIC or (indirect* adj3 comparison*))).ti,ab,kw,kf.	337490
102	98 or 99 or 100 or 101	667819
103	81 or 97 or 102	7528631
104	9 and 47 and 103	21680
105	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5445560
106	104 and 105	12134
107	(2021* or 2022* or 2023*).yr.	3715827
108	106 and 107	1932

CPCI-S

Database: Conference Proceedings Citation Index – Science (CPCI-S)
Host: Clarivate
Data parameters: 1990-Current
Date of search: 5 Feb 2023

#	Syntax	N
1	**"Multiple Myeloma"** (Topic)	13,559
2	**(myelom* or ((Penta or triple-class) NEAR/1 refractory))** (Topic)	18,271
	TS=((kahler* or plasmcytom* or plasma cytoma* or plasma zytoma* or myelomatoses or myelomatosis))	551
	(plasm* NEAR/3 (neoplas* or leukaem* or leukem* or tumor* or tumour* or dyscrasia)) (Topic)	1,210
	#1 OR #2 OR #3 OR #4 OR #5	3
	#1 OR #2 OR #3 OR #4 OR #5 and **2023** or **2022** or **2021** (Publication Years)	369

American Society of Clinical Oncology (ASCO)

Date of search: 4 Feb
Searched via: https://meetings.asco.org/abstracts-presentations
Searcher location: London, UK.

We searched ASCO Annual meetings via the ASSCO abstract presentation database/interface. We limited our searches to: Annual Meetings, by years 2021-2023, and Media: Abstracts or Posters.

Year	Route of access	N
2021	As above	38
2022	As above	56
2023 (DEC)	(out of scope)	N/A
		94

American Society of Hematology (ASH)
Date of search: 2-4 Feb 2023

Year	Route of access	N
2021	https://ashpublications.org/blood/issue/138/Supplement%201	454
2022	https://ashpublications.org/blood/issue/140/Supplement%201	305
2023 (DEC)	(out of scope)	N/A
		759

British Society for Haematology (BSH)
Date of search: 4 Feb 2023

Year	Route of access	N
2021	https://onlinelibrary.wiley.com/toc/13652141/2021/193/S1	19
2022	https://onlinelibrary.wiley.com/toc/13652141/2022/197/S1	20
2023 (23-25 April)	(out of scope)	N/A
		39

Controversies in Multiple Myeloma (COMy)
Access not achieved – could not search

European Hematology Association (EHA)
Date of search: 5 Feb 2023
We searched EHA abstract via their online portal: https://library.ehaweb.org/eha/?menu=16&browseby=9&sortby=1&trend=4016#!*menu=16*browseby=9*sortby=1*trend=4016
2021: Virtual
2022: Vienna
2023: June 8-11 (out of scope)

Year	Route of access	N
2021:	Portal	114
2022: 9-13 Sept 2022 (Paris)	Portal	118
2023 (June 8-11)	(out of scope)	N/A
		232

European Myeloma Network (EMN)
11 Feb 2023

We searched EMN via their publications library, filtering publications to those reported at EMN-22 and EMN-23. There was no EMN-21 (but we searched EMN-COVID, in case this covered 2021).

European Society of Medical Oncology (ESMO)
5 Feb 2023

Year	Route of access	N
2021: 16-21 Sept 2021 (Paris)	https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021	4

2022: 9-13 Sept 2022 (Paris)	https://oncologypro.esmo.org/meeting-resources/esmo-congress	7
2023 (20-24 October)	(out of scope)	N/A
		11

International Myeloma Society (IMS) annual events
Access not achieved – could not search

A26. Priority question. The quality assessment for each study included in the NMAs was conducted at the overall study-level, however the outcome data used in the NMAs usually came from subgroup analyses (2L or 3L+). Please provide an outcome-level assessment of risk-of-bias for each study included in the NMA for PFS and for OS, specifically focusing on the subgroup analysis (2L or 3L+) used in the NMA.

Company response: An updated summary of the risk of bias assessment of trials included in the NMA is provided in Table 23, including outcome-level and subgroup-level analyses for relevant domains. These additional assessments were constrained by limited reporting across comparator trials. MM-003 and ICARIA-MM have been added to the tables in line with the updated 3L+ NMA network, described in the Supplementary Appendix.

Table 23 Risk of bias assessment of the trials included in the NMA

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Did the authors of the study publication declare any conflicts of interest?
BOSTON[4,5,24,37]	Yes - Patients were randomised 1:1 using interactive response technology. Randomisation was stratified based on prior PI therapies, number of prior anti-MM regimens, and R-ISS stage	Yes - BOSTON was an open-label study but an interactive response technology was used during randomisation	Yes - Baseline characteristics of the study populations in both treatment groups were well balanced	Overall: No - There was no blinding in this study, therefore presenting a potential risk of bias PFS: Unclear – there was no blinding of care providers, or participants in this study however disease responses were IRC-confirmed OS: Unclear - There was no blinding in this study, therefore presenting a potential risk of bias however this is unlikely to impact on OS	No - Discontinuations were similar between arms – 81% in both arms at the primary analysis and 89% and 91% for SVd and Vd respectively, in the updated analysis	No - All outcomes reported	Overall: Yes - The primary efficacy analyses were performed in the ITT population. In general, missing baselines were not imputed. Methods for missing data thoroughly described PFS: Yes – PFS analyses were performed in the ITT population; appropriate censoring was applied including for patients who withdrew, were lost to follow-up, or had no PFS event before data-cut. OS: Yes – OS analyses were performed in the ITT population; if an event did not occur during the follow-up period, the patient was censored at the date of discontinuation from the study, or the	Yes - Conflicts of interest were declared
BOSTON 2L[4,5,37]			Yes – Prior SCT treatment was higher in the SVd arm compared to Vd (39.4% *vs.* 23.2%), however this is not considered a prognostic factor		No - Discontinuations were similar between arms – 79% in both arms in the primary (2020) analysis, and 88% and 93% for SVd and Vd respectively, in the updated (2021) analysis			
BOSTON 3L[4,5,37]			Yes - Baseline characteristics of the study populations in		No - Discontinuations were similar between arms –			

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Did the authors of the study publication declare any conflicts of interest?
			both treatment groups were well balanced		89% and 94% for SVd and Vd respectively, in the updated analysis		last participating visit on or before database cut-off date, whichever occurred first.	
APEX[12] (omitted from the updated 3L+ NMA network)	Yes - Patients were randomized 1:1 with randomisation stratified by number of prior treatments, TTP after the last treatment, and β2-microglobulin	Yes - An interactive voice recognition system was utilised to assign treatment	Yes - baseline demographic and other characteristics of the two groups were balanced	Overall: Unclear - Open-label; however, TTP and response rates were determined by a computer-programmed algorithm (validated by a three-member IRC) TTP: Unclear - There was no blinding of care providers or participants in this study, however the TTP was determined using a computer-programmed algorithm, validated by an IRC	Unclear - Discontinuations due to AEs were similar between arms (37% vs. 29%). Overall discontinuation rate not reported but at the time of the final analysis, 85 (26%) in the bortezomib group and 55 (17%) patients in the dex group were still receiving a study drug	No - All outcomes reported	Overall: Yes - Efficacy analyses were based on the ITT population, defined as all patients who were randomised to treatment; patients in this population were analysed according to the treatment to which they were randomised. No imputation of values for missing data was to be performed, with the exception of QOL subscales TTP: Yes - analyses performed in the ITT population; data for patients who started alternative chemotherapy (including crossover to bortezomib), who were lost to follow-up, or who died before documentation of PD	Yes - Conflicts of interest were declared
APEX 3L+[12] (omitted from the updated 3L+ NMA network)			Unclear – baseline demographics not reported by subgroup		Unclear – discontinuation data not reported by subgroup			

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Did the authors of the study publication declare any conflicts of interest?
				OS: Unclear - There was no blinding in this study, therefore presenting a potential risk of bias however this is unlikely to impact on OS			were censored at the last assessment OS: Yes - analyses performed in the ITT; data for patients were censored before data cut-off, on the date they were last known to be alive, regardless of disease progression or alternative therapy.	
ENDEAVOR[9]	Yes – Patients were randomly assigned 1:1. using an interactive voice and web response system. Randomisation was stratified by previous PI therapy, previous lines of treatment, ISS stage, and planned route of bortezomib administration. Patients were randomly assigned using	Yes – The study was open label and patients were randomly assigned (1:1) using an interactive voice and web response system	Yes – baseline characteristics of patients in the ITT population were well balanced between the study groups.	Overall: Unclear – Open-label but potential bias in the assessment of the primary endpoint was mitigated by using an IRC, masked to treatment allocation, for the determination of disease status PFS: Unclear – Open-label but potential bias was mitigated by using an IRC, masked to treatment	No – Discontinuation due to progressive disease was the most common reason for discontinuation in both treatment groups (44% in the Kd group and 47% in the Vd group)	No – All outcomes reported	Overall: Unclear – Efficacy assessments were based on the ITT population (consisting of all randomly assigned patients). The safety analysis included patients who received at least one dose of study treatment. However, it was not clear how missing data was accounted for PFS: Unclear: analyses performed in the ITT population however it was	Yes – Conflicts of interest declared
ENDEAVOR 2L[8,9]			Yes – baseline characteristics of participants in the 2L subgroup were well balanced		No – Discontinuation of treatment due to AEs was reported for the 2L subgroup and was similar			

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Did the authors of the study publication declare any conflicts of interest?
	a block randomisation scheme (block size of four)		between the study groups.	allocation, for the determination of disease status OS: Unclear - There was no blinding in this study, therefore presenting a potential risk of bias however this is unlikely to impact on OS	across both arms (17.2% in the Kd group and 18.5% in the Vd group)		unclear how missing data was handled OS: Unclear: analyses performed in the ITT population however it was unclear how missing data was handled	

ICARIA-MM (ITT was 3L+)[26]	Yes – Randomisation was done using interactive response technology to assign treatment based on a permuted blocked randomisation scheme with a block size of four and stratified according to the number of previous lines of treatment and age.	Yes – Randomisation was done using interactive response technology	Yes – Yes, baseline characteristics of patients in the ITT population were well balanced between the study groups.	Overall: Unclear – the study was open-label however an IRC, who were masked to treatment assignment, was implemented to ensure consistency in the assessment of disease response. PFS: Unclear – the study was open-label however an IRC, who were masked to treatment assignment, was implemented to ensure consistency in the assessment of disease response. OS: Unclear - There was no blinding in this study, therefore presenting a potential risk of bias however this is unlikely to impact on OS.	Unclear – Discontinuation was higher in the Pd arm compared with the IsaPd arm (76% *vs.* 57%) however this was explained as being due to more patients in the Pd arm discontinuing due to progressive disease.	No – All outcomes reported	Overall: Yes – all efficacy analyses were done in the ITT population and appropriate censoring rules were applied. PFS: Yes – all efficacy analyses were done in the ITT; patients without an event were censored at last assessment not showing PD prior to initiating a new treatment or analysis cut-off date. OS: Yes – all efficacy analyses were done in the ITT population; patients without an event were censored at the last date they were known to be alive or the cut-off date.	Yes – Conflicts of interest declared

MM-003 (ITT was 3L+)[27]	Yes – Patients were assigned in a 2:1 ratio with a validated interactive voice and internet response system using a randomly permuted block within strata. Patients were stratified by age, disease status, and number of previous treatments.	Yes – Randomisation was validated interactive voice and internet response system using a randomly permuted block within strata.	Yes – Yes, baseline characteristics of patients in the ITT population were well balanced between the study groups.	Overall: Unclear – The study was open-label, however the sponsor's study team was blinded to the study treatment code until the final analysis of the primary endpoint. An independent Response Adjudication Committee IRAC reviewed all efficacy data in a blinded manner, independent of investigator response to ensure an unbiased assessment of the data. PFS: Unclear – The study was open-label, however the sponsor's study team was blinded to the study treatment code until the final analysis of the primary endpoint. An independent Response Adjudication Committee IRAC reviewed all efficacy data in a	No – discontinuations were balanced between the groups (61% and 62%).	No – All outcomes reported	Overall: Yes – all efficacy analyses were done in the ITT population and appropriate censoring rules were applied. PFS: Yes – all efficacy analyses were done in the ITT population and appropriate censoring rules were applied. Missing assessments or discontinuations due to reasons other than progressive disease were handled by censoring rules based on the EMA guidelines. OS: Yes – all efficacy analyses were done in the ITT population and appropriate censoring rules were applied. Missing assessments or discontinuations due to reasons other than progressive disease were handled by censoring rules based on the EMA guidelines.	Yes – Conflicts of interest declared

				blinded manner, independent of investigator response to ensure an unbiased assessment of the data. OS: Unclear - There was no blinding in this study, therefore presenting a potential risk of bias however this is unlikely to impact on OS.				

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Did the authors of the study publication declare any conflicts of interest?
MM-009 (no subgroup data reported)[16]	Yes – Central randomisation was performed with a block size of 4. The assignment of patients was stratified according to the level of serum β2-microglobulin and the number of previous antimyeloma therapies	Yes – The trial was double-blinded, and allocation was performed by an integrated voice-response system	Yes – Baseline characteristics of the patients in the ITT population were well balanced between the study groups	Overall: Yes – the trial was double-blinded TTP: Yes – the trial was double-blinded OS: Yes – the trial was double-blinded	Yes – Discontinuations due to disease progression or adverse events were described however more participants discontinued from the placebo group than the lenalidomide group (71.6% *vs*. 38.4% due to disease progression and 19.8% *vs*. 10.2% due to Aes)	No – All outcomes reported	Overall: Unclear – the main analysis group was ITT, however it was not fully clear how missing data was accounted for TTP: Unclear: analyses performed in the ITT population; patients who died before evidence of PD were censored at the time of last evaluation; it was unclear how other missing data was handled OS: Yes: analyses performed in the ITT population; OS was calculated up to death from any cause or date of last visit	Yes – Conflicts of interest declared
MM-010 (no subgroup data reported)[17]	Unclear - Randomisation method was not described	Unclear - Blinded trial but not clear that allocation was adequately concealed	Yes - Baseline characteristics of the patients in the ITT population were well balanced between the study groups	Overall: Unclear - Only described as blinded TTP: Unclear - Only described as blinded Yes – the trial is described as	Unclear – discontinuation due to adverse events was reported for both lines combined (31 patients (8.8%). Disease	No - All outcomes reported	Overall: Unclear - the main analysis group was ITT, however it was not clear how missing data was accounted for TTP: Unclear - the main analysis group	Yes - Conflicts of interest declared

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Did the authors of the study publication declare any conflicts of interest?
				blinded and disease response was determined by a blinded IRC OS: Unclear - Only described as blinded	progression was reported as the most common reason for discontinuation, but number of events were not reported		was ITT, however it was not clear how missing data was accounted for OS: Unclear - the main analysis group was ITT, however it was not clear how missing data was accounted for	
PANORAMA-1[18]	Yes - Patients were randomised in a 1:1 ratio. An interactive web-based and voice response system was used, and stratification was by number of previous treatment lines and previous use of bortezomib treatment.	Yes – Randomisation used a system that automated the random assignment of patient numbers to randomisation numbers, which were linked to the two treatment groups.	Yes - Baseline characteristics of the patients in the ITT population were well balanced between the study groups.	Overall: Yes - Patients, physicians, and clinical trial team were masked to treatment allocation; the statisticians who did data analysis were masked to treatment allocation until unblinding at the time of the analysis of the primary endpoint. Matching panobinostat and placebo tablets were used to ensure masking	No - Discontinuation rate overall was similar across both arms	No – All outcomes reported	Overall: Unclear - All endpoints were based on investigator's assessment and analyses by ITT; however, it was not fully described how missing data were dealt with PFS: Yes - Assessed in the ITT population and was censored at the date of the last adequate assessment before the analysis cut-off date or start of new anti-neoplastic treatment for patients who had not progressed or who had received a new treatment.	Yes - Conflicts of interest declared
PANORAMA-1 3L+[18]			Unclear – baseline demographics not reported by subgroup.		Unclear – discontinuation rates not reported by subgroup			

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Did the authors of the study publication declare any conflicts of interest?
				PFS: Yes - Patients, physicians, and clinical trial team were masked to treatment allocation OS: Yes - Patients, physicians, and clinical trial team were masked to treatment allocation			OS: Unclear – Analyses by ITT however, it was not fully described how missing data were dealt with	
TOURMALLINE-MM1[29]	Yes - Patients were randomly assigned in a 1:1 ratio, stratified according to the number of prior therapies, previous exposure to PIs, and ISS disease stage	Unclear - Double-blind trial, but not clear that allocation was adequately concealed	Yes - Baseline characteristics of the patients in the ITT population were well balanced between the study groups	Overall: Yes - This trial was double-blind, so the participants and outcome assessors were blind to treatment allocation. It has to be assumed that the care providers were also blind to treatment PFS: Yes - This trial was double-blind, so the participants and	No - Patients that withdrew from the trial, had a protocol violation, lost to follow-up, or for other reasons equally balanced between the two study groups	No - All outcomes reported	Overall: Unclear - The trial included an ITT population which included all patients who underwent randomisation and were evaluated for all primary and secondary efficacy analyses. Patients were analysed according to the treatment actually received, regardless of which treatment they were randomised to received. However, it was not fully	Yes - Conflicts of interest declared
TOURMALLINE-MM1 3L+[29]			Unclear – baseline demographics not reported by subgroup		Unclear – discontinuation rates not reported by subgroup			

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Did the authors of the study publication declare any conflicts of interest?
				outcome assessors were blind to treatment allocation. It has to be assumed that the care providers were also blind to treatment OS: Yes - This trial was double-blind, so the participants and outcome assessors were blind to treatment allocation. It has to be assumed that the care providers were also blind to treatment			reported how missing data were dealt with PFS: Yes - Assessed in the ITT population; time-to-event parameters will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the events OS: Yes - Assessed in the ITT population; time-to-event parameters will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the events	

Abbreviations: AEs, adverse events; dex, dexamethasone; IRC, independent review committee; ISS, international staging system; ITT, intention-to-treat; IVRS, interactive voice response system; Kd, carfilzomib plus dexamethasone; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; QoL, quality of life; R-ISS; revised - international staging system; SVd, selinexor + bortezomib + dexamethasone; TTP, time to progression; V, bortezomib; Vd, bortezomib + dexamethasone.
Risk of bias assessment performed using the NICE checklist for RCTs (adapted from CRD guidance).

A27. No quality assessment of the Dimopoulos 2015 matched-pairs analysis was provided. Please provide a critical appraisal of Dimopoulos 2015,[13] making reference to the company's clinical expert concerns highlighted in Appendix N that using Dimopoulos et al. (2015), "might be an issue when going into subgroups" that were not the ITT population, and that, "this study included totally different patients, as the study is quite remote".

Company response: A request was sent to ask the EAG to clarify which tool they recommended using for this analysis. However, the updated 3L+ NMA (Supplementary Appendix) has been applied as the company's base case and this network omits the matched-pairs analysis reported in Dimopoulos *et al.* (2015).

A28. The EAG notes that the following median follow-up times for PFS based on IRC assessment were reported in **Table 11 of the CS**:

- Primary analysis, 18th February 2020: SVd 13.17 months; Vd 16.53 months
- Updated analysis, 15th February 2021: SVd 13.47 months; Vd 24.48 months

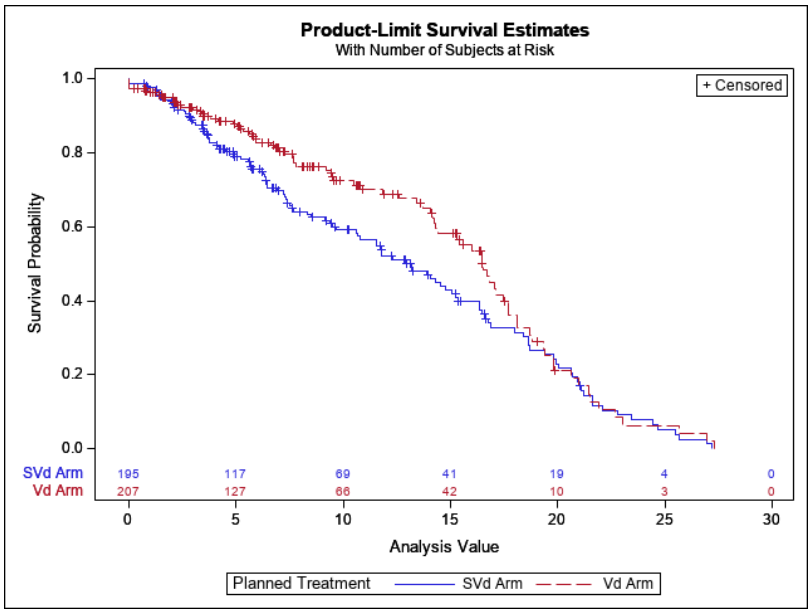
Between the primary and updated analyses, median follow-up time is very similar for SVd, but increases by around 8 months for Vd. Please could the Company:

a) Verify whether these follow-up time data are correct;
b) If they are correct, explain why median follow-up only increased substantially in the Vd arm in a data cut approximately 1 year after the primary analysis;
c) Comment on the validity of the presented PFS and OS analyses, given the asymmetry in follow-up times and the possibility that proportional hazards do not hold.

Company Response: These follow-up times are correct. The median PFS and OS are usually estimated by deriving for each patient the time from randomisation / first treatment dose to the last date a patient has been tracked and then calculating the median across all patients. However, Karyopharm Therapeutics implemented a different method called 'Reverse KM'. With this method the follow-up time is calculated in the same way as the Kaplan-Meier estimate of the survival function but with the meaning of the status indicator reversed so that the event of interest becomes the censor. So here, the censor becomes event (S=0) data and the event of interest becomes subjects censored (S=1) in the study. For example, the death of a subject is

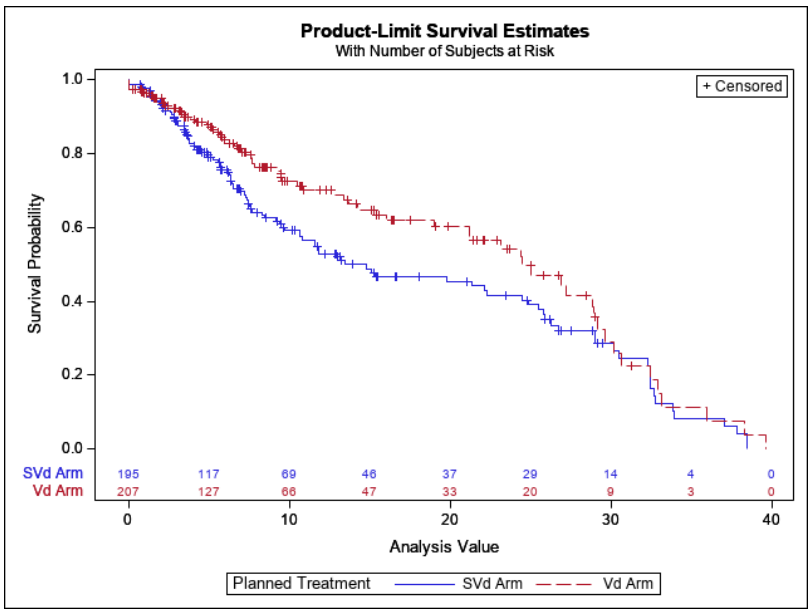
censored with unknown observation time. This way, the unobservable follow-up time of that subject is interpreted as the follow-up time. For this reason, the reverse KM curves are included in Figure 19 and Figure 20 below for PFS, from both BOSTON data cuts.

Figure 19 Reverse KM curves (2020 data cut)



Median follow-up time: SVd - 13.17 (95% CI: 10.64, 15.34); Vd - 16.53 (95% CI: 14.39, 17.71).
Source: data on file[5]

Figure 20 Reverse KM curves (2021 data cut)



Median follow-up time: SVd - 13.47 (95% CI: 10.64, 24.87); Vd - 24.48 (95% CI: 21.16, 29.17).
Source: data on file[5]

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model so that these can be combined. Furthermore, if the company chooses to update its base-case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base-case assumptions are provided with the response along with a log of changes made to the company base-case.

Questions in Section B are highly linked to the clinical analyses requested in Section A. Therefore, the EAG requests that the clarification questions presented in this document be considered holistically and where possible, key aspects of re-analysis should filter through to all requested scenarios.

Revised base case results using the updated NMA results and EAG recommended amendments (B9, B12, B16, B17, B20, B22) are shown below.

Table 24: Revised base case cost effectiveness results

Comparator	Original company submission ICER	NHB	Incremental Costs	Incremental QALYs	Updated ICER implementing combined scenario (new base case)	Incremental Costs (new base case)	Incremental QALYs (new base case)	NHB (new base case)
Kd	£580,849	5.76	-£182,324	-0.31	£605,630	-£182,607	-0.30	5.79
IxaRd	-£487,802	1.61	-£45,621	0.09	-£867,308	-£96,381	0.11	3.32
PanoVd	-£32,692	0.74	-£11,567	0.35	-£13,631	-£4,501	0.35	0.48

Key issues relating to the approach to the cost-effectiveness of SVd versus relevant comparators at 2L and 3L.

B1. Priority question. Please explore scenarios where the cost effectiveness of SVd versus the additional relevant comparators listed in Question A6 A7 (summarised below) is evaluated. When performing the requested cost-effectiveness analyses, please provide a set of analyses using the EAG's

preferred method of estimated comparator treatment effects, as outlined in the table at the start of Section A.

- **Vd. Please note that the dosing of Vd is different in the UK compared to the regimen used in BOSTON. Based on the bortezomib SmPC, in combination with dexamethasone bortezomib 2.5 mg/ml solution for injection is administered via subcutaneous and, after dilution, also for intravenous injection at the recommended dose of 1.3 mg/m2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. Dexamethasone is administered orally at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the bortezomib treatment cycle. 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.**
    - **Please conduct one scenario using the Vd regimen in BOSTON (taking into account RDI from the trial) and another using the Vd regimen outlined in the SmPC for bortezomib;**
- **KRd;**
- **Rd;**
- **DVd.**

Company response: Please note that the company assumes in this response that the question relates to the therapies listed in Question A7 (rather than A6). As outlined in response to A7, the treatments listed above are not considered relevant comparators since they are not reimbursed regimens relevant to the NICE pathway (Vd) or not relevant comparators to the company positioning of SVd at 2L for patients that have received DRd at 1L. Analyses comparing SVd against these treatments, therefore, have not been explored.

B2. Priority question. The EAG's clinical experts considered after one prior line of treatment, patients' overall survival (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 6L. As such, improvements in progression-free survival (PFS) at each line are potentially more clinically relevant. The EAG considers that OS from BOSTON includes the survival impact of subsequent

treatments for patients who progress to 3L and beyond. The EAG notes that the company has provided scenario analyses in the CS exploring an OS HR of 1 for all comparators.

Building upon the analyses requested in B1, please provide scenarios for each of the comparisons using an OS hazard ratio (HR) of 1.

Company response: As no additional comparators have been explored in response to B1, the requested scenario analyses do not apply.

B3. Priority question. Based on the jointly-fitted models included in the company base case for OS (2L and 3L), PFS (2L) and time on treatment (ToT) (2L and 3L), please provide the treatment group covariates and discuss the appropriateness of the underlying assumptions of the distributions selected, specifically:

a) **PFS 3L - the acceleration factor (lognormal is an acceleration failure time [AFT] model);**
b) **OS 2L and 3L - the HRs generated from the model and compare with the HRs obtained from BOSTON (gamma and Weibull are PH models);**
c) **ToT 2L - the HR generated from the model and compare with the HR obtained from BOSTON (gamma is a PH model);**
d) **ToT 3L - the HR or acceleration factor (log-logistic may be either proportional odds or accelerated failure time).**

Company response: During a clarification call held between the company, NICE and EAG on 20th September 2023, it was confirmed by the EAG that parts b) and c) of this question relate to a comparison of the SVd *versus* Vd hazard ratios estimated in the Cox regression analyses of BOSTON patient-level data against those derived from the NMA. Additionally, please note that both gamma and Weibull are characterised as AFT models under the default parameterisations of the R *flexsurv* package used for covariate estimation, as outlined in the package's reference manual (pp.21-22). [43]

Table 24 provides a summary of the SVd *vs.* Vd hazard ratios estimated from survival analyses of BOSTON patient-level data and (where available), the corresponding estimates from the NMA.

a) An SVd *vs.* Vd acceleration factor of -0.432 is estimated for PFS in a 3L population using a lognormal distribution.
b) Point estimate hazard ratios for OS in a 2L population are identical to the BOSTON cox regression analysis and that estimated from the NMA, with a wider confidence interval range estimated from the NMA (CI 0.40-1.86, compared to CI 0.54-1.40 as estimated from the Cox model). OS 3L hazard ratios estimates differ between the BOSTON model and NMA due to differences in the subgroup population definitions (HR 0.55, CI 0.28-1.08 from the Cox model, corresponding to a 3L population; HR 0.77 (0.36-1.67) from the NMA, corresponding to a 3L+ population).
c) The point estimate hazard ratio for ToT in a 2L population generated by the BOSTON cox regression analysis is HR 0.90 (CI 0.81-1.52). Due to the limited reporting of ToT in comparator studies, ToT hazard ratios were not estimated in the NMA and PFS hazard ratios used as a proxy HR for ToT in the economic analysis. The SVd vs. Vd HR for PFS in a 2L population as estimated in the BOSTON analysis is 0.62 (CI 0.41-0.95) and as estimated from the NMA is 0.62 (CI 0.33-1.15).
d) An SVd *vs.* Vd acceleration factor of -0.068 is estimated for ToT in a 3L population using a log-logistic distribution.

Table 25 Summary of hazard ratios for SVd *versus* Vd as estimated from Cox regression analyses of BOSTON patient data and as estimated in the NMA.

	Hazard ratios	
	BOSTON (Cox model)	NMA
2L population		
OS**	0.87 (0.54-1.40)	0.87 (0.40-1.86)
PFS	0.62 (0.41-0.95)	0.62 (0.33-1.15)
ToT	0.90 (0.81-1.52)	(Not estimated)
3L[a]		
OS[b]	0.55 (0.28-1.08)	0.77 (0.36-1.67)
PFS	0.75 (0.46-1.22)	0.80 (0.37-1.75)
ToT	0.95 (0.66-1.39)	(Not estimated)

[a] BOSTON results correspond to '3L only' subgroup; NMA results correspond to '3L+' estimates
[b] OS hazard ratios reflect 'adjusted with censoring' OS adjustment for patients switching from Vd to SVd

B4. Priority question. In the NICE Decision Support Unit technical support document 14 (DSU TSD 14), it is stated that, "when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption" and fitting separate parametric models to individual treatment arms

(independent models) may be preferable. Furthermore, the EAG considers that fitting an independent model for SVd, given it is the baseline curve for which comparator HRs are applied, more accurately captures the hazards over time and the shape of the curve for SVd and removes the underlying assumptions associated with the treatment effect covariate in the jointly fitted models.

The EAG considers that based on the log-log plots (lines are not parallel and/ or straight) and Schoenfeld residuals plots (lines are not straight) for OS, PFS and ToT for 2L and 3L, the PH assumption is violated.

The EAG notes that company scenarios which explored independent models for all distributions have been provided. Of the independent models for PFS, OS and TOT for both 2L and 3L, please advise which would be the company's preferred choices based on statistical and visual fit, as well as clinical validity, filling in the table below. Please provide any useful information, such as explanations, plots, and landmark estimates to support the curve selections.

Company response: As outlined in the original submission, the company believes that jointly-fitted curves applied in the company base case provide the most robust estimate for capturing not the hazard profile for SVd and also the profile of comparator therapies once hazard ratios have been applied. Of the independent curves available for SVd and for Vd, selections using the same criteria as the company base case in terms of alignment with clinical expert estimates, statistical and visual fit are provided in Table 26 below.

Table 26 Curve selections for independently-fitted curves

Treatment arm	PFS	OS	ToT
2L			
Vd	Gamma	Gamma	Gamma
SVd	Gamma	Gamma	Gamma
Rationale	Progression-free rates consistent with OS (no overlap in extrapolations); close visual fit to mature data. Low impact on cost-effectiveness results.	10-year survival extrapolations (SVd 8%, Vd 3%) fall within 1-10% range suggested by clinical expert opinion	Consistent with PFS; close visual fit to mature data. Low impact on cost-effectiveness results.

3L			
Vd	Lognormal	Gamma	Lognormal
SVd	Lognormal	Gamma	Lognormal
Rationale	Progression-free rates consistent with OS (no overlap in extrapolations); close visual fit to mature data. Low impact on cost-effectiveness results.	10-year survival extrapolations (SVd 4%, Vd 3%) fall within 1-10% range suggested by clinical expert opinion	Consistent with PFS; close visual fit to mature data. Low impact on cost-effectiveness results.

B5. Priority question. As the EAG considers that the PH assumption does not hold between SVd and Vd in BOSTON, applying comparator HRs to extrapolated SVd PFS, OS and ToT curves may not be appropriate. Instead, please explore scenarios where the Vd PFS, OS and ToT preferred independent curves are used as the baseline.

Please provide one set of analyses using the EAG's preferred method of estimated comparator treatment effects, as outlined in the table at the start of Section A.

Company response: Functionality has been added to optionally use Vd as the reference arm for comparator efficacy estimates, whereby parametric curves fitted independently to SVd and Vd are used, and HR estimates for pairwise comparators *versus* Vd, estimated using the 2L and 3L+ NMAs, are applied.

Scenario results applying independent curve selections and comparator hazard ratios relative to Vd are provided in below.

Table 27 Scenario results using independent curve selections and comparator hazard ratios *versus* Vd

Comparator	Original company submission ICER	Scenario ICER	ICER change relative to company base case	Original company submission NHB	Scenario NHB	NHB change relative to company base case
Kd	£580,849	-£15,695,580 (SVd is dominant)	-£16,276,429	5.76	9.20	+3.44
IxaRd	-£487,802	-£643,972	-£156,170	1.61	2.95	1.34
PanoVd	-£32,692	-£38,222	-£5,531	0.74	1.02	0.28

Survival analysis

B6. Priority question. The Weibull distribution was selected for the extrapolation of SVd OS for the 3L population. The log-cumulative hazard plot presented in Figure 16 of the CS is not straight therefore the Weibull PH model is not suitable. Additionally, the estimated shape parameter is less than 1, indicating that hazards are decreasing over time. Please discuss if the underlying assumption of decreasing hazards of death over time for the 3L population is clinically plausible and whether an alternative distribution is more plausible.

Given the need to extrapolate survival curves over a cohort lifetime, curve selection placed a greater emphasis on the clinical plausibility of extrapolations relative to the viability of hazard plots. This approach is consistent with the guidance provided in NICE TSD 14 ("*when the survival data require substantial extrapolation it is important to attempt to validate the predictions made by the fitted models by other means*"),[44] and is considered less likely to over- or under-estimate area under the curve than extrapolations that rank more highly in terms of hazard profile but lower agreement with landmark survival estimates.

Landmark survival estimates for 2/ 3L populations, provided by clinicians at the health economic advisory board following presentation of the BOSTON data, suggested that 10-year OS in the patient population would be expected fall within a 1% to 10% range. Of the jointly-fitted OS curves, only two fell within these bounds (Weibull, 4% 10-year OS; gamma, 9% 10-year OS). Of the two, the Weibull fell closest to the midpoint of the range and was therefore considered the most representative of the estimate provided.

Although flexible or piecewise methods present an alternative approach that circumvents the immediate issue of decreasing hazards in individual curves, overall results are likely to be similar to those achieved by fitting standard curves from baseline.

Adverse events

B7. Priority question. CS, section B.2.10. The CS outlines that 54.4% of SVd patients had treatment-emergent serious adverse events (SAEs).

a) Please provide a breakdown and proportions of the treatment-emergent SAEs in BOSTON.

b) For any SAEs that are not included in the model, please explore a scenario which includes their incidence per treatment arm.

Company response:

a) In BOSTON, a serious adverse event (SAE) was defined as any untoward medical occurrence that, at any dose, results in death; is life-threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/ incapacity; or is a congenital anomaly/birth defect. The incidence of serious TEAEs by preferred term is summarised in Table 28.

Table 28 Serious TEAEs from BOSTON (safety population; 2021 datacut)

	SVd (n=195) n (%)	Vd (n=204) n (%)	Total (N=399) n (%)
Patients with at least one serious TEAE	106 (54.4)	79 (38.7)	185 (46.4)
Pneumonia	24 (12.3)	25 (12.3)	49 (12.3)
Anaemia	6 (3.1)	3 (1.5)	9 (2.3)
Cataract	9 (4.6)	0	9 (2.3)
Diarrhoea	7 (3.6)	0	7 (1.8)
Lower respiratory tract infection	4 (2.1)	3 (1.5)	7 (1.8)
Vomiting	7 (3.6)	0	7 (1.8)
Acute kidney injury	4 (2.1)	2 (1.0)	6 (1.5)
Atrial fibrillation	4 (2.1)	2 (1.0)	6 (1.5)
Bronchitis	3 (1.5)	2 (1.0)	5 (1.3)
Gastroenteritis	4 (2.1)	1 (0.5)	5 (1.3)
Asthenia	2 (1.0)	2 (1.0)	4 (1.0)
Influenza	3 (1.5)	1 (0.5)	4 (1.0)
Nausea	4 (2.1)	0	4 (1.0)
Pyrexia	3 (1.5)	1 (0.5)	4 (1.0)
Septic shock	4 (2.1)	0	4 (1.0)
Thrombocytopenia	3 (1.5)	1 (0.5)	4 (1.0)
Upper respiratory tract infection	3 (1.5)	1 (0.5)	4 (1.0)
Urinary tract infection	4 (2.1)	0	4 (1.0)
Chronic obstructive pulmonary disease	1 (0.5)	2 (1.0)	3 (0.8)
Constipation	1 (0.5)	2 (1.0)	3 (0.8)

	SVd (n=195) n (%)	Vd (n=204) n (%)	Total (N=399) n (%)
Deep vein thrombosis	1 (0.5)	2 (1.0)	3 (0.8)
Dehydration	3 (1.5)	0	3 (0.8)
Dyspnoea	2 (1.0)	1 (0.5)	3 (0.8)
Epistaxis	3 (1.5)	0	3 (0.8)
Fatigue	2 (1.0)	1 (0.5)	3 (0.8)
Femur fracture	2 (1.0)	1 (0.5)	3 (0.8)
General physical health deterioration	3 (1.5)	0	3 (0.8)
Pulmonary embolism	2 (1.0)	1 (0.5)	3 (0.8)
Respiratory syncytial virus infection	2 (1.0)	1 (0.5)	3 (0.8)
Urosepsis	3 (1.5)	0	3 (0.8)
Abdominal pain	0	2 (1.0)	2 (0.5)
Bone pain	1 (0.5)	1 (0.5)	2 (0.5)
Cardiac failure congestive	1 (0.5)	1 (0.5)	2 (0.5)
Cellulitis	1 (0.5)	1 (0.5)	2 (0.5)
Cerebral infarction	0	2 (1.0)	2 (0.5)
Chest pain	1 (0.5)	1 (0.5)	2 (0.5)
Clostridium difficile colitis	0	2 (1.0)	2 (0.5)
Corona virus infection	2 (1.0)	0	2 (0.5)
Fall	2 (1.0)	0	2 (0.5)
Febrile neutropenia	1 (0.5)	1 (0.5)	2 (0.5)
Hypokalaemia	1 (0.5)	1 (0.5)	2 (0.5)
Infection	1 (0.5)	1 (0.5)	2 (0.5)
Myocardial infarction	1 (0.5)	1 (0.5)	2 (0.5)
Neuropathy peripheral	0	2 (1.0)	2 (0.5)
Pneumonia pneumococcal	2 (1.0)	0	2 (0.5)
Pulmonary oedema	1 (0.5)	1 (0.5)	2 (0.5)
Staphylococcal sepsis	1 (0.5)	1 (0.5)	2 (0.5)
Syncope	1 (0.5)	1 (0.5)	2 (0.5)
Transient ischaemic attack	1 (0.5)	1 (0.5)	2 (0.5)
Acute myocardial infarction	0	1 (0.5)	1 (0.3)
Acute respiratory failure	1 (0.5)	0	1 (0.3)
Affect lability	1 (0.5)	0	1 (0.3)
Angina pectoris	0	1 (0.5)	1 (0.3)
Atrioventricular block	1 (0.5)	0	1 (0.3)
Back pain	0	1 (0.5)	1 (0.3)
Blood glucose abnormal	1 (0.5)	0	1 (0.3)
Blood pressure fluctuation	1 (0.5)	0	1 (0.3)
Bradycardia	1 (0.5)	0	1 (0.3)
Brain oedema	1 (0.5)	0	1 (0.3)
Bronchiectasis	1 (0.5)	0	1 (0.3)
Bronchospasm	1 (0.5)	0	1 (0.3)
Cachexia	1 (0.5)	0	1 (0.3)
Cardiac arrest	1 (0.5)	0	1 (0.3)
Cardiac failure	0	1 (0.5)	1 (0.3)
Cardiac failure acute	1 (0.5)	0	1 (0.3)
Cardiac tamponade	1 (0.5)	0	1 (0.3)
Cardio-respiratory arrest	1 (0.5)	0	1 (0.3)
Cardiomyopathy	0	1 (0.5)	1 (0.3)
Cardiovascular disorder	1 (0.5)	0	1 (0.3)
Carotid artery aneurysm	1 (0.5)	0	1 (0.3)
Cerebral haemorrhage	1 (0.5)	0	1 (0.3)
Cerebral ischaemia	1 (0.5)	0	1 (0.3)

	SVd (n=195) n (%)	Vd (n=204) n (%)	Total (N=399) n (%)
Cervical vertebral fracture	0	1 (0.5)	1 (0.3)
Chest wall abscess	0	1 (0.5)	1 (0.3)
Cholecystitis acute	1 (0.5)	0	1 (0.3)
Cholelithiasis	1 (0.5)	0	1 (0.3)
Circulatory collapse	0	1 (0.5)	1 (0.3)
Clostridium difficile infection	1 (0.5)	0	1 (0.3)
Colitis	1 (0.5)	0	1 (0.3)
Colitis ischaemic	1 (0.5)	0	1 (0.3)
Death	1 (0.5)	0	1 (0.3)
Decreased appetite	1 (0.5)	0	1 (0.3)
Delirium	1 (0.5)	0	1 (0.3)
Dementia Alzheimer’s type	1 (0.5)	0	1 (0.3)
Dyspepsia	0	1 (0.5)	1 (0.3)
Embolism	0	1 (0.5)	1 (0.3)
Encephalopathy	1 (0.5)	0	1 (0.3)
Escherichia bacteraemia	1 (0.5)	0	1 (0.3)
Femoral neck fracture	0	1 (0.5)	1 (0.3)
Gangrene	0	1 (0.5)	1 (0.3)
Gastroenteritis norovirus	1 (0.5)	0	1 (0.3)
Glaucoma	1 (0.5)	0	1 (0.3)
H1N1 influenza	0	1 (0.5)	1 (0.3)
Haematuria	1 (0.5)	0	1 (0.3)
Hepatic cirrhosis	0	1 (0.5)	1 (0.3)
Hepatic encephalopathy	0	1 (0.5)	1 (0.3)
Hip fracture	1 (0.5)	0	1 (0.3)
Hyperkalaemia	0	1 (0.5)	1 (0.3)
Hypotension	1 (0.5)	0	1 (0.3)
Injury	1 (0.5)	0	1 (0.3)
Ischaemic stroke	0	1 (0.5)	1 (0.3)
Laryngitis	0	1 (0.5)	1 (0.3)
Left ventricular dysfunction	1 (0.5)	0	1 (0.3)
Left ventricular failure	0	1 (0.5)	1 (0.3)
Liver disorder	1 (0.5)	0	1 (0.3)
Lower gastrointestinal haemorrhage	1 (0.5)	0	1 (0.3)
Meningitis tuberculous	1 (0.5)	0	1 (0.3)
Metabolic encephalopathy	1 (0.5)	0	1 (0.3)
Mixed anxiety and depressive order	1 (0.5)	0	1 (0.3)
Mobility decreased	1 (0.5)	0	1 (0.3)
Multiple organ dysfunction syndrome	1 (0.5)	0	1 (0.3)
Myelodysplastic syndrome	0	1 (0.5)	1 (0.3)
Myocardial ischaemia	0	1 (0.5)	1 (0.3)
Neuralgia	0	1 (0.5)	1 (0.3)
Neutropenia	1 (0.5)	0	1 (0.3)
Non-cardiac chest pain	1 (0.5)	0	1 (0.3)
Orchitis	1 (0.5)	0	1 (0.3)
Orthostatic hypotension	0	1 (0.5)	1 (0.3)
Osteoarthritis	1 (0.5)	0	1 (0.3)
Osteochondrosis	0	1 (0.5)	1 (0.3)
Ovarian neoplasm	0	1 (0.5)	1 (0.3)
Overdose	1 (0.5)	0	1 (0.3)
Pancreatic carcinoma metastatic	0	1 (0.5)	1 (0.3)
Paraesthesia	0	1 (0.5)	1 (0.3)

	SVd (n=195) n (%)	Vd (n=204) n (%)	Total (N=399) n (%)
Pelvic fracture	1 (0.5)	0	1 (0.3)
Pelvic prolapse	1 (0.5)	0	1 (0.3)
Peripheral ischaemia	0	1 (0.5)	1 (0.3)
Personality change	1 (0.5)	0	1 (0.3)
Pneumonia bacterial	1 (0.5)	0	1 (0.3)
Pneumonia fungal	1 (0.5)	0	1 (0.3)
Pneumonia influenzal	1 (0.5)	0	1 (0.3)
Pneumonia parainfluenzae viral	1 (0.5)	0	1 (0.3)
Pneumonia respiratory syncytial viral	0	1 (0.5)	1 (0.3)
Pneumonitis	1 (0.5)	0	1 (0.3)
Postoperative respiratory failure	1 (0.5)	0	1 (0.3)
Presyncope	0	1 (0.5)	1 (0.3)
Pulmonary sepsis	0	1 (0.5)	1 (0.3)
Reactive psychosis	1 (0.5)	0	1 (0.3)
Respiratory failure	0	1 (0.5)	1 (0.3)
Rib fracture	1 (0.5)	0	1 (0.3)
Sepsis	1 (0.5)	0	1 (0.3)
Shock haemorrhagic	1 (0.5)	0	1 (0.3)
Sinus tachycardia	1 (0.5)	0	1 (0.3)
Spinal pain	1 (0.5)	0	1 (0.3)
Subdural haemorrhage	0	1 (0.5)	1 (0.3)
Tumour lysis syndrome	0	1 (0.5)	1 (0.3)
Vascular dementia	1 (0.5)	0	1 (0.3)
Ventricular arrhythmia	1 (0.5)	0	1 (0.3)

Abbreviations: SVd, selinexor in combination with bortezomib and dexamethasone; TEAE, treatment-emergent adverse events; Vd, bortezomib plus dexamethasone.
For patients who cross over, AEs that occur after the crossover are not included.
Source: data on file (Table 14.3.1.1.4.2) [5]

b) As recommended in NICE TSD12,[45] the economic analysis aims to capture the cost and utility impact of adverse events of grades 3 and above (denoting a high expected impact on patients' quality of life and/or resource use, but do not necessarily pose a risk to patients' life or functioning). By contrast, SAEs as reported in the response to part B7a correspond to events that carry an increased risk of severe outcomes (such as death or disability). Although some overlap is expected, the two are not synonymous and therefore it has not been considered appropriate or feasible to incorporate SAEs alongside the events already modelled, especially in the absence of appropriate cost and disutility estimates and/or equivalent data for comparator therapies.

B8. In the economic model, the impact of Grade 3-4 AEs is accounted for the entire duration patients are on treatment (i.e underlying assumption of recurrence of AEs or AEs not managed well). 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. The EAG notes that the company has already supplied a scenario exploring a one-off impact of AEs. As such, please justify the assumption weekly impact of Grade 3-4 AEs while on treatment.

Company response: The company agrees with the assumption that grade 3-4 AEs will have a fixed duration rather than persisting across the period of treatment. As summary data tables do not describe the time at AEs occur, the model uses two alternative approaches in terms of when they are applied in the model. In the first, all AEs are incurred at the outset of the model. In the second approach, the costs and disutilities associated with each AE are distributed across the time of treatment. This second approach is not intended to reflect an assumption that the AE itself will last for a longer time or incur a greater cost/ utility impact than the first approach, but merely to provide a less prescriptive approach to the timing of events.

B9. CS, sections B.2.10 and B.3.4.4. The EAG notes that the list of Grade 3 and above treatment-emergent AEs in 5% or more of patients in the SVd arm of BOSTON in Table 20 and Table 32 of the CS is different. Notably, a broader range of AEs experienced by less than 5% of SVd patients is considered for the economic model. As such, please clarify if all Grade 3 and above treatment-emergent AEs in the SVd arm of BOSTON has been used for the model.

Company response: Thank you for highlighting the discrepancies between adverse events reported in the company submission. A model scenario has been tested, including only the grade 3 and above treatment-emergent AEs in 5% or more of patients in the SVd arm of BOSTON, as per Table 20 in the original company submission. Table 29 reports the change in ICER and NHB when comparing the original company base case to this scenario, results are minimally impacted, cost effectiveness interpretations remain the same as the original company base case.

Table 29: Cost effectiveness results implementing B9 EAG revision

Comparator	Original company submission ICER	Updated ICER implementing this scenario	ICER change relative to company base case	Original company submission NHB	Updated NHB implementing this scenario	NHB change relative to company base case
Kd	£580,849	£581,187	+£338	5.76	5.76	+0.00
IxaRd	-£487,802	-£487,598	£204	1.61	1.62	0.00
PanoVd	-£32,692	-£32,778	-£86	0.74	0.74	0.00

B10. Please validate the adverse event rates from the TOURMALINE, ENDEAVOUR and PANORAMA studies included in the economic model. The EAG has identified differences between the study sources and those quoted. For example, there were 94 Grade 3+ incidences of neutropenia in the TOURMALINE study not 81 as included in the model and anaemia was recorded in the PANORAMA study.

Company response: The company agrees with the finding that 94 incidences of grade 3+ neutropenia were identified in the TOURMALINE study. This value has been applied in cell S16 of the AEs sheet of the economic model: this discrepancy therefore could not be identified.

Event rates corresponding to the PANORAMA study were derived from Table 3 of San Miguel *et al.* 2016.[19] The company notes that anaemia is not among the adverse events reported: the same source provides a list of newly-reported or worsing haematological abnormalities that may be consistent with, but could not be directly corresponded to, adverse events including anaemia.

Health related quality of life

B11. Priority question. The utility values presented in Table 8 of Appendix M do not match the utility values presented in cells D27:E29 in the "Utilities" worksheet of the economic model.

a) **Are the utilities presented in Appendix M based on the ITT population of BOSTON? If so, is there a version of Appendix M that is for only the 2L and 3L populations?**
b) **Please clarify why line of therapy was not considered as a covariate for the regression model.**
c) **Please clarify why treatment arm was included as a covariate to estimate progression-free (PF) and progressed disease (PD) utility values for SVd and Vd that were then averaged to get "treatment independent" utility values.**
d) **Please provide PF and PD utility values for 2L and 3L based on a regression model where the treatment arm covariate is not included and line of therapy is included as a covariate (present the final regression**

model) and provide a scenario analysis in the economic model using these values.

Company response: The utility values originally calculated from BOSTON patient data and presented in Appendix M correspond to the ITT population. The scope of this original analysis focused on a combined (2L/ 3L) patient population and therefore did not include line of therapy as a covariate or subgroup for utility estimates. Treatment arm was explored as a covariate to assess generalisability across comparators: since utility estimates by progression status were found to be highly consistent across treatment arms, the mean of values was applied to all arms in the economic evaluation.

Additional analyses including line of therapy as a covariate, are included as requested in Table 30.

Table 30 Utility regression model output (line of therapy covariate model)

	Coefficient	Standard Error	F-value	Pr(>F)
Intercept	0.4126111	0.0597638		
Age	-0.0020421	0.0007482	7.4499	0.006635
Baseline ECOG	-0.0340228	0.0119743	8.0732	0.004726
Baseline EQ-5D-3L	0.5919885	0.0314484	354.3484	<0.0001
PFS Status (Y)	0.0375982	0.0060916	38.0951	<0.0001
Prior lines of therapy	-0.0102553	0.0090637	1.2802	0.258564
AIC: -4025.22		BIC: -3968.634		Log-likelihood: 2021.61

Corresponding estimates of values for 2L and 3L patients, calculated using the mean baseline characteristics in each group, are provided in Table 31.

Table 31 Utility estimates by progression status and line of therapy (line of therapy covariate model)

	2L	3L
Pre-Progression Utility (95% CI)	0.706 (0.687, 0.725)	0.696 (0.681, 0.712)
Post-Progression Utility (95% CI)	0.668 (0.648, 0.689)	0.659 (0.641, 0.676)

A scenario analysis with these utility values have been performed and are presented in Table 32 below. Comparison against utility values used in the original submission

show that the incorporation of line of therapy as an additional covariate has low impact on cost-effectiveness against 2L or 3L comparators.

Table 32 Comparison of cost effectiveness results between original company base utility estimates and scenario utility estimates using treatment line covariate

Comparator	Original company submission ICER	Scenario ICER	ICER change relative to company base case	Original company submission NHB	Scenario NHB	NHB change relative to company base case
Kd	£580,849	£574,879	-£5,970	5.76	5.76	-0.00
IxaRd	-£487,802	-£489,221	-£1,419	1.61	1.61	0.00
PanoVd	-£32,692	-£32,775	-£84	0.74	0.74	0.00

B12. Priority question. For the general population utility values, the NICE methods guide recommends using the Health Survey for England (HSE) 2014 dataset, as recommended by the DSU (Hernández Alava *et al.* 2022).[2] Please update the general population utility values used for age adjustment in the model to use the HSE 2014 dataset.

Company response: Hernández Alava *et al*. 2022 has now been included in the model as the basis for estimating age-related disutilities.[46,47] Impact on ICER and NHB results relative to the original company base case are presented below.

Table 33 Cost effectiveness results implementing B12 EAG request

Comparator	Original company submission ICER	Updated ICER implementing this scenario	ICER change relative to company base case	Original company submission NHB	Updated NHB implementing this scenario	NHB change relative to company base case
Kd	£580,849	£604,454	+£23,605	5.76	5.78	+0.01
IxaRd	-£487,802	-£503,521	-£15,720	1.61	1.61	0.00
PanoVd	-£32,692	-£33,627	-£935	0.74	0.73	-0.01

Please note that Hernández Alava *et al*. estimates were already used in the company submission to derive general population quality-adjusted life expectancy (QALE) values for severity modifier calculations.

B13. Please provide the confidence intervals for the utility values in Table 34 in the CS.

Company response: Utility values for 2L and 3L patient groups and corresponding confidence intervals, calculated from the CS utility regression model, are provided in Table 34.

Table 34 Utility estimates and confidence intervals (original CS regression model)

	2L only		3L only	
	SVd	**Vd**	**SVd**	**Vd**
Pre-Progression Utility (95% CI)	0.702 (0.682, 0.723)	0.696 (0.677, 0.716)	0.703 (0.683, 0.723)	0.697 (0.677, 0.716)
Post-Progression Utility (95% CI)	0.665 (0.643, 0.686)	0.658 (0.637, 0.679)	0.665 (0.643, 0.686)	0.659 (0.638, 0.680)
Abbreviations: SVd, selinexor plus bortezomib plus dexamethasone; Vd, bortezomib plus dexamethasone				

Table 35 Utility regression model output (original CS regression model)

	Coefficient	**Standard Error**	**F-value**	**Pr(>F)**
Intercept	0.3885292	0.0554050		
Arm (Vd)	-0.0060605	0.0136660	0.1967	0.6577
Age	-0.0018686	0.0007403	6.3708	0.0120
Baseline ECOG	-0.0355510	0.0119660	8.8269	0.0032
Baseline EQ-5D-3L	0.5913469	0.0315365	351.6078	<0.0001
PFS Status (Y)	0.0377237	0.0060849	38.4348	<0.0001
AIC: -4024.96		BIC: -3968.37		Log-likelihood: 2021.48

Costs and resource use

B14. Priority question. The EAG considers there are several issues with the assumptions related to the inclusion of subsequent treatments as a weighted-basket in the model. The weighted-basket approach fails to consider the sequence of treatments a patient may have, contingent on treatment received in their previous line of therapy. For example, it is unlikely a patient failing on a 3L

lenalidomide-based regimen will go on to receive further treatment with lenalidomide plus dexamethasone.

Furthermore, duration of subsequent treatments assumed to be nine months based on an assumption used in TA897 (daratumumab with bortezomib and dexamethasone [DVd] for previously treated multiple myeloma) is not appropriate. 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. For the current appraisal, the company is assuming multiple lines of treatment in the subsequent treatment basket.

The EAG's clinical experts outlined that there would be a difference in the subsequent treatments provided to patients depending on what treatment they had in their previous line of therapy. Additionally, the EAG's clinical experts commented that;

- **only a small proportion of patients would receive chemotherapy as a subsequent treatment;**
- **bendamustine is no longer available in the NHS and isa+pom+dex is not routinely commissioned (still in the Cancer Drugs Fund [CDF]);**
- **no patient would receive Rd after progressing on IxaRD;**
- **the proportion of patients receiving daratumumab monotherapy is unlikely to be more than 10%.**

Given the above issues and the fact that costs of subsequent treatments are a substantial proportion of total costs in the model, the EAG requests the company to provide an alternative approach to subsequent treatments in the model that more appropriately captures the NHS treatment pathway. Additionally, please consider the following points:

a) **Please provide the subsequent treatments, proportions and duration of treatments provided to 2L and 3L patients in the BOSTON trial.**
b) **As proportion of treatments received may change depending on treatment received in the previous line, please fill out the table below for plausible proportions of each subsequent treatment, utilising BOSTON**

data where available and also taking into consideration the treatment pathway outlined in Figure 2 of the CS.

c) **In TA897, the submitting company assumed that patients typically receive treatment until death and that is why median OS at 3L+ was assumed for duration of subsequent treatment. The EAG considers that as patients may receive multiple lines of subsequent treatment, duration of treatment cannot exceed the life-years estimated for the PD health state. Furthermore, the duration of each line of subsequent treatment is anticipated to get shorter upon each progression (i.e duration on 4L treatment is likely to be shorter than 3L treatment). As such, consider how time spent in the PD health state can be split to estimate duration of subsequent treatments by line of treatment.**
d) **Please clarify why bendamustine has been included for the cost of chemotherapy even though it is not available in the NHS. Instead, please explore using a cyclophosphamide-based chemotherapy regimen for the cost of chemotherapy.**
e) **IsaPd is currently only available in the CDF and thus is not routinely commissioned in the NHS. Please remove IsaPd from subsequent treatments considered in the economic model.**

Company response: Please see a breakdown of subsequent treatments received by patients in the BOSTON study that align with the current NICE recommended treatment pathway in breakdown of Table 36.

The company agrees with the EAG's statement that subsequent treatment decisions will be influenced by current as well as earlier lines of therapy, and that lifetime treatment profiles can therefore be expected to differ by arm. Due to the considerable heterogeneity in patient journeys in both real world and NICE pathway settings, however, it is unlikely that BOSTON or other available data sources provide a suitable basis for estimating such differences accurately. Further, the separation of subsequent treatment assumptions by line potentially introduces further forms of bias whereby, for example, cost differences may be unduly influenced by the choice of final line assigned to each arm. The opinion of the company is that a simplified approach in which similar weekly costs of subsequent therapy are assumed across treatments is more

transparent and presents less overall risk of misrepresentation of differences across arms.

Part c of question B14 addresses the length of receipt assumed for subsequent therapies. The company wishes to point out that the median treatment length of 9 months generalised from TA897 is used solely for estimating the mean weighted cost for each subsequent therapy, where dosing for initial and later treatment cycles may vary. A scenario analysis exploring the impact of IsaPd from the list of available subsequent therapies has been conducted and has a small impact on overall cost-effectiveness ( ).

Table 36 Subsequent treatments in BOSTON patients by arm (UK pathway therapies only)

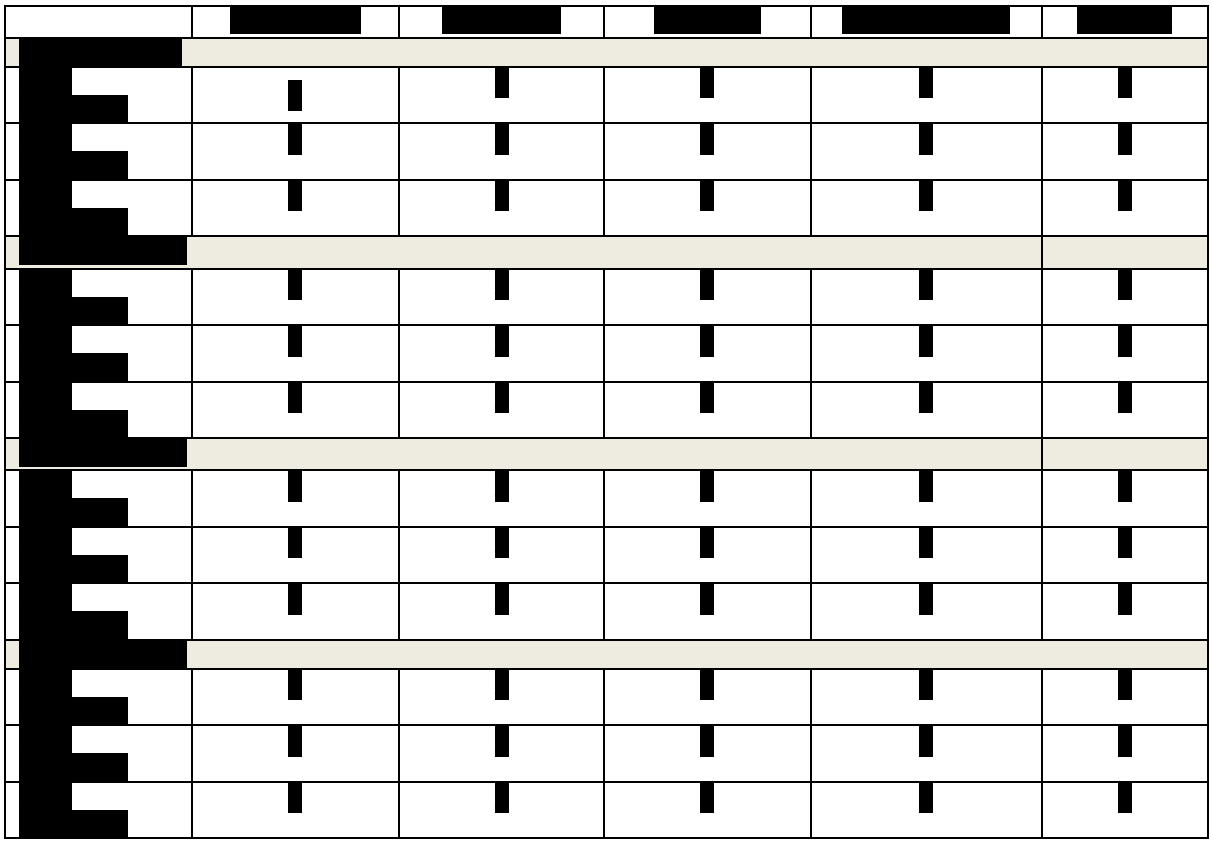


Table 37 Impact on cost-effectiveness results of removal of IsaPd from list of available subsequent therapy

Comparator	Original company submission ICER	Updated ICER implementing this scenario	ICER change relative to company base case	Original company submission NHB	Updated NHB implementing this scenario	NHB change relative to company base case

Kd	£580,849	£580,874	+£25	5.76	5.76	+0.00
IxaRd	-£487,802	-£486,405	£1,397	1.61	1.61	0.00
PanoVd	-£32,692	-£32,556	£136	0.74	0.74	0.00

B15. Priority question. In the model, 79.5% of PD patients receive subsequent treatments. However, for the 20.5% of PD patients who come off treatment, health state resource use is the same as PF and PD patients who are on treatment. Please justify, with supporting evidence, why health state resource use assumptions are not different for PD patients off treatment?

Company response: In the absence of resource use estimates specific to treatment (in addition to progression) status, and as treatment-free intervals between adjacent lines of therapy were not considered as model health states, no assumption was made as to the level of reduction made in background monitoring or care while off treatment.

B16. Priority question. The EAG's clinical experts stated that the resource use associated with routine monitoring used in the CS was not reflective of clinical practice. The EAG's clinical experts considered that:

- **All patients on active treatment (including chemotherapy) would be seen once a month by a consultant. This consultant visit would also include complete blood, blood chemistry, protein electrophoresis and immunoglobulin.**
- **Serum light chain excretion is standard of care rather than urinary light chain excretion.**
- **Patients would receive G-CSF injections, which would be around six per year.**

a) **Therefore, please conduct a scenario analysis which explores the EAG's clinical experts resource use assumptions (monthly use) for routine monitoring, shown in the table below, for the PF and PD health states in the model.**

b) **Please clarify if the data used to estimate the resource use for red blood cell and platelet transfusions is from BOSTON? If so, please provide more detail on the data, such as the patient characteristics, progression status, line of therapy, etc.**

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 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

***Please note in the model, as whole numbers are used for weekly use, the yearly estimates do not result in whole numbers. As such, the EAG recommends starting with the annual resource use and then calculating the weekly estimate.**

Company response:

a) A scenario analysis has been conducted in the model as per the table above, with the sensitivity of ICER results relative to the original company base case presented in Table 38. Relative to the original company base case, this scenario decreases background resource costs in all arms. Due to differences between arms in the distribution of progression-free relative to progressed disease states, this results in an increase in estimated cost-effectiveness against Kd and PanoVd, and a decrease *versus* IxaRd.

Table 38: Cost effectiveness results implementing B16 EAG scenario

Comparator	Original company submission ICER	Updated ICER implementing this scenario	ICER change relative to company base case	Original company submission NHB	Updated NHB implementing this scenario	NHB change relative to company base case
Kd	£580,849	£588,570	+£7,721	5.76	5.84	+0.08
IxaRd	-£487,802	-£478,069	£9,733	1.61	1.58	-0.03
PanoVd	-£32,692	-£23,887	£8,805	0.74	0.64	-0.10

b) Red blood cell and platelet transfusion resource frequencies were not identified from BOSTON data but generalised from levels reported in TA897 (Daratumumab with bortezomib and dexamethasone for previously-treated multiple myeloma).[48]

B17. Priority question. The CS outlines that the adverse event cost codes were taken from NHS reference costs 2021/2022, while the technical report outlines they were taken from NHS reference costs 2020/2021.

a) **Please confirm the source of the adverse event costs used in the model and use NHS reference costs 2021/2022 if not already being used.**
b) **Please provide the NHS reference costs codes used to cost the adverse events in secondary care in Table 43. Please note that cost codes for AEs are not provided in the economic model.**

Company response: Thank you for highlighting these discrepancies. A model scenario has been conducted sourcing all adverse event costs from the NHS reference costs 21/ 22.[49] Updated model results are reported in Table 39. There is minimal impact on the ICER and NHB results, and running this scenario does not change cost-effectiveness interpretations for SVd versus each comparator.

Table 39 Cost effectiveness results implementing B17 EAG request

Comparator	Original company submission ICER	Updated ICER implementing this scenario	ICER change relative to company base case	Original company submission NHB	Updated NHB implementing this scenario	NHB change relative to company base case
Kd	£580,849	£581,443	+£594	5.76	5.77	+0.01
IxaRd	-£487,802	-£489,155	-£1,353	1.61	1.62	0.00
PanoVd	-£32,692	-£35,351	-£2,659	0.74	0.77	0.03

NHS reference cost codes used are reported in Table 40 below.

Table 40: Adverse event NHS reference cost codes used in the economic model

Adverse Event	NHS reference cost codes
Anaemia	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA03G & SA03H
Asthenia	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA17H
Cataract	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, BZ33Z, BZ32B, BZ32A, BZ31B, BZ31A, BZ30A

Diarrhoea	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA17H
Fatigue	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA17H
Febrile neutropenia	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA30E, SA30D, SA30C, SA30B, SA30A
Hypertension	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, EB04Z
Hypophosphataemia	National Schedule of NHS Costs - Year 2021-22, Directly Accessed Pathology Services, DAPS03, Outpatient Care, Medical oncology service, WF02A
Leukopenia	National Schedule of NHS Costs - Year 2021-22, Directly Accessed Pathology Services, DAPS03, Outpatient Care, Medical oncology service, WF02A
Lymphopenia	National Schedule of NHS Costs - Year 2021-22, Directly Accessed Pathology Services, DAPS03, Outpatient Care, Medical oncology service, WF02A
Lower respiratory tract infection	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, DZ22Q, DZ22P, DZ22N, DZ22M, DZ22L, DZ22K
Nausea	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA17H
Neutropenia	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA30E, SA30D, SA30C, SA30B, SA30A
Hyperglycaemia	National Schedule of NHS Costs - Year 2021-22, Directly Accessed Pathology Services, DAPS03, Outpatient Care, Medical oncology service, WF02A
Peripheral neuropathy	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, DZ22Q, DZ22P, DZ22N, DZ22M, DZ22L, DZ22K
Pneumonia	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, DZ11V, DZ11U, DZ11T, DZ11S, DZ11R, DZ11Q, DZ11P, DZ11N, DZ11M, DZ11L, DZ11K
Thrombocytopenia	National Schedule of NHS Costs - Year 2021-22, Admitted Patient Care, SA12K, 2-4 SA12J, 5-7 SA12H, 8+ SA12G

B18. Priority question. The EAG's clinical experts noted that in clinical practice the majority of AEs would be managed in secondary care. As such, conduct a scenario in which all AEs are managed in secondary care.

Company response: A scenario has been conducted in the model assuming that all AEs are managed in secondary care. Results are presented in Table 41. There is minimal impact on the ICER and NHB results, and running this scenario does not change cost effectiveness interpretations for SVd versus each comparator.

Table 41: Cost effectiveness results implementing B18 EAG request

Comparator	Original company submission ICER	Updated ICER implementing this scenario	ICER change relative to company base case	Original company submission NHB	Updated NHB implementing this scenario	NHB change relative to company

						base case
Kd	£580,849	£579,080	-£1,769	5.76	5.75	-0.02
IxaRd	-£487,802	-£481,232	£6,570	1.61	1.59	-0.02
PanoVd	-£32,692	-£38,085	-£5,394	0.74	0.80	0.06

B19. The CS states that all patients receiving selinexor require 5-hydroxytryptamine (5-HT3) antagonists (ondansetron 8mg or equivalent) prior to the first dose of SVd and then two to three times daily, as needed. Therefore, in the model, the company assumed that ondansetron was given 2.5 times per day to 100% of patients while on selinexor treatment. In the CSR, it states that [redacted] of SVd patients received a 5-HT3 antagonist.

a) Please clarify if BOSTON patients received other 5-HT3 antagonists besides ondansetron in the trial;
b) Cost the appropriate concomitant proportions and type of treatments in the model (or alternatively, justify why doing so would not be relevant if, for example, different 5-HT3 antagonists have similar prices to the NHS).

Company response: UK clinical practice will follow SmPC guidance around the use of concomitant medication ("Prophylaxis with 5HT3 antagonists and/or other anti-nausea agents should be provided prior to and during treatment with selinexor").[50]

The expectation is that clinicians will apply the most cost-effective of the options available in line with NHS Trust policy. Therefore, the use of ondansetron as a proxy cost source for all 5-HT3 antagonists in the economic model will be consistent with or over-estimate the cost applied to the selinexor arm should lower-cost alternatives be provided in clinical practice.

B20. According to the SmPC for panobinostat, bortezomib is given as a subcutaneous injection and not an IV infusion, as assumed in the company base case. Please amend the model so that bortezomib as part of PanoVd (both as a comparator and subsequent treatment) is an SC injection.

Company response: A model scenario has been implemented to include bortezomib as an SC injection as part of the PanoVd treatment regimen. Results are presented in Table 42. There is minimal impact on the ICER and NHB results for SVd *versus* Kd

and IxaRd. For SVd *versus* PanoVd, the absolute change in ICER is ~£24,000, and the NHB decreases by 0.28, SVd remains cost effective *versus* PanoVd in this scenario.

Table 42: Cost effectiveness results implementing B20 EAG request

Comparator	Original company submission ICER	Updated ICER implementing this scenario	ICER change relative to company base case	Original company submission NHB	Updated NHB implementing this scenario	NHB change relative to company base case
Kd	£580,849	£580,850	+£1	5.76	5.76	+0.00
IxaRd	-£487,802	-£487,747	£55	1.61	1.61	0.00
PanoVd	-£32,692	-£9,048	£23,643	0.74	0.46	-0.28

B21. Please explore a scenario which includes the cost of oral administration for chemotherapy included in subsequent treatments using the NHS cost code SB11Z.

Company response: In clinical practice, subsequent treatments may include a range of chemotherapies with differing methods of delivery. Use of chemotherapy is assumed to be comparable across arms, and associated costs associated with changing the route of administration would have a low impact on ICER results.

B22. An eMIT price is available for ondansetron of £0.76. Please update the economic model to incorporate this price.

Company response: The model has been updated with an ondansetron unit cost of £0.76, sourced from eMIT 2022.[51] Results showing a minimal impact on ICER relative to the original company base case are presented in Table 43.

Table 43: Cost effectiveness results implementing B22 EAG request

Comparator	Original company submission ICER	Updated ICER implementing this scenario	ICER change relative to company base case	Original company submission NHB	Updated NHB implementing this scenario	NHB change relative to company base case
Kd	£580,849	£581,036	+£187	5.76	5.77	+0.00
IxaRd	-£487,802	-£488,387	-£585	1.61	1.62	0.00
PanoVd	-£32,692	-£32,846	-£155	0.74	0.74	0.00

B23. The company applied a one-off terminal care cost to all patients at the point of death. This value was sourced from a study by Round *et al.* (2015), which estimated end of life care across four cancer types (breast, colorectal, lung and prostate).

a. Please clarify exactly which costs were used from the Round *et al.* (2015) study.
b. Please clarify if the company conducted a literature search for more recent estimates of cancer end of life care.

Company response: The average end-of-life health care cost across the four cancer types has been applied in the cost-effectiveness model, described in Table 5 of the Round *et al*. 2015.[52] The cost and resource use component of the economic SLR did not identify any more recent, appropriate end-of-life care costs in myeloma.

Section C: Textual clarification and additional points

C1. Priority question. If they have not been provided by the time of receipt of the clarification letter, please provide the EAG with the SLR report and the machine-readable data files and the code used to perform the NMAs, such that the EAG can directly reproduce the NMA results.

Company response: The company has provided the SLR report, as well as the additional machine-readable files and code required to reproduce the NMA.

C2. Priority question. For each population where there are multiple comparators, please present incremental analysis.

Company response: Fully incremental results have been included for the 3L positioning where multiple comparators are considered.

C3. Priority question. Please present the one-way sensitivity analysis tornado plots using the ICER.

Company response: Functionality to show tornado plots reflecting ICER results has been included in the model. Please note that where base results are not in the North-East cost-effectiveness quadrant (and hence ICER is negative, or ICERs above the willingness-to-pay threshold are considered cost-effective), these have not been included in the submission or the reporting of updated results due to ambiguity around the direction or interpretation of values but can be explored within the Excel model.

C4. Priority question. The EAG considers that scenario analyses presented in Tables 58 and 59 should present the ICER in addition to the NMB (please note that net health benefits should be presented according to the NICE methods guide).

Company response: Updated scenario results show both NHB and ICER results. Please note caveats around the interpretation of ICER results outside the North-East cost-effectiveness quadrant, as noted in the response to question C3.

C5. Please provide updated tables which include the ICER. The duration of peripheral neuropathy is different in Table 37 of company submission and model. Please clarify which is correct and amend where if necessary.

Company response: Updated base case results are provided in an accompanying Microsoft Word document, and include ICER and NHB results *vesus* 2L and 3L comparators. The duration for peripheral neuropathy remains unchanged from the original company model, derived from Brown 2013.

C6. Please clarify if Tables 48, 49, 52 and 53 should be confidentially marked up and if Tables 50, 51, 54 and 55 should be unredacted.

Company response: Thank you for your question but the company took the decision to show the "with PAS" ICER results as these will be used as the primary results for decision making. The list price costs and ICER have therefore been redacted. We believe this maintains the confidentiality of the PAS, but should the EAG have a different view we will look to amend.

C7. Please provide the sources of relative dose intensity (RDI) used for comparator treatments in Table 38 of the CS.

Company response: Sources of RDI used for comparator treatmentrs in Table 38 of the CS are as follows:

- IxaRd: Moreau *et al*. 2016 (supplementary information provides the breakdown for all of the components)[29]
- PanoVd: EMA Public Assessment Report for panobinostat (Farydak)[53]
- Kd: Dimopoulos *et al*. 2017,[10] in the absence of data, 100% was assumed for dexamethasone

C8. Column BM in the "PtFlowSVd" tab of the model needs to be corrected to include ToT.

Company response: Thank you for highlighting this. The lookup array referenced by the formulae in Column BM has been expanded to include ToT as intended. The affected cells serve as a source for chart data and do not affect model results.

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B1.1.1 Revised base case results *versus* 3L comparators

Revised company base-case results comparing SVd (assuming a simple PAS discount of [redacted] to IxaRd and PanoVd (list prices) after two prior therapies (3L) are summarised in Table 1 (ICER results) and Table 2 (NMB and NHB).

Table 1 Base-case results *versus* pairwise comparators – 3L (selinexor at PAS price, comparators at list price)

Comparator	Total			Incremental (SVd *vs.* comparator)				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/ QALY)	Incremental ICER
SVd	£133,706	3.91	2.58					
IxaRd	£230,087	3.68	2.47	-£96,381	0.23	0.11	-£867,308	Comparator strictly dominated
PanoVd	£138,207	3.38	2.25	-£4,501	0.53	0.33	-£13,631	Comparator strictly dominated

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

Table 2 Base-case net monetary benefit and net health benefit results *versus* pairwise comparators – 3L (selinexor at PAS price, comparators at list price)

	Net monetary benefit (£) (SVd *vs.* comparator)		Net health benefit (QALYs) (SVd *vs.* comparator)	
	WTP £20,000	WTP £30,000	WTP £20,000	WTP £30,000
IxaRd	£98,604	£99,715	4.93	3.32
PanoVd	£11,106	£14,408	0.56	0.48

Abbreviations; IxaRd, ixazomib plus lenalidomide and dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; WTP, willingness to pay; 3L, third-line.

Figure 1 Cost effectiveness frontier - SVd *versus* IxaRd and PanoVd at 3L (selinexor at PAS price, comparators at list price)

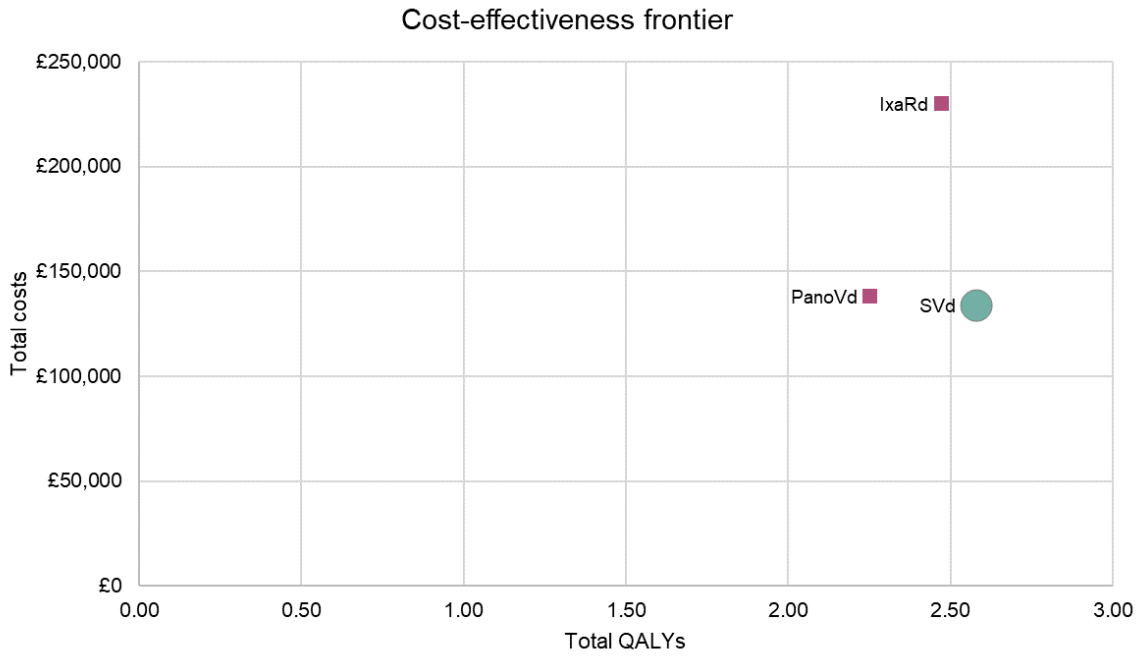


Table 3 Base-case results *versus* pairwise comparators – 3L (selinexor at list price, comparators at list price)

Comparator	Total			Incremental (SVd *vs.* comparator)				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/ QALY)	Incremental ICER
SVd	[redacted]	3.91	2.58					
IxaRd	£230,087	3.68	2.47	[redacted]	0.23	0.11	[redacted]	[redacted]
PanoVd	£138,207	3.38	2.25	[redacted]	0.53	0.33	[redacted]	[redacted]

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

Table 4 Base-case net monetary benefit and net health benefit results *versus* pairwise comparators – 3L (selinexor at list price, comparators at list price)

	Net monetary benefit (£) (SVd *vs.* comparator)		Net health benefit (QALYs) (SVd *vs.* comparator)	
	WTP £20,000	WTP £30,000	WTP £20,000	WTP £30,000
IxaRd	[redacted]	[redacted]	[redacted]	[redacted]

	Net monetary benefit (£) (SVd *vs.* comparator)		Net health benefit (QALYs) (SVd *vs.* comparator)	
	WTP £20,000	**WTP £30,000**	**WTP £20,000**	**WTP £30,000**
PanoVd	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations; IxaRd, ixazomib plus lenalidomide and dexamethasone; PanoVd, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; WTP, willingness to pay; 3L, third-line.				

B1.1.2 Base case results *versus* 2L comparators

Base-case results reflecting a 2L positioning *versus* Kd, assuming a PAS discount of [redacted] for Selinexor and applying the list price for carfilzomib, are summarised in Table 5.

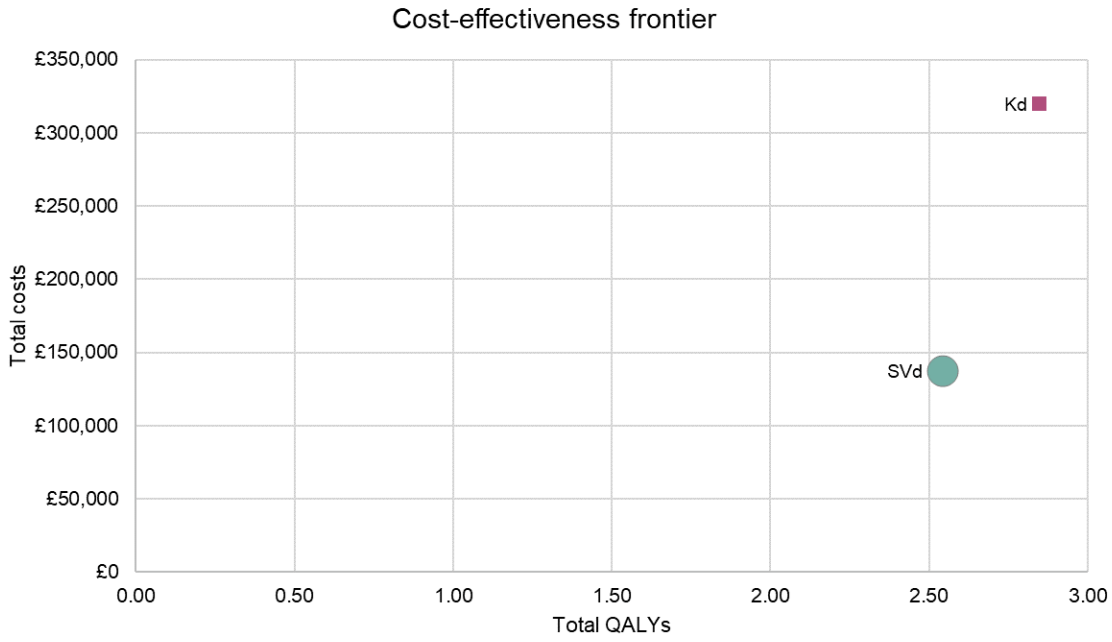
Table 5 Base-case results versus comparator – 2L analysis (selinexor at PAS price, comparators at list price)

Comparator	Total			Incremental (SVd *vs.* comparator)				
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**	**Incremental ICER**
SVd	£137,162	3.85	2.54					
Kd	£319,769	4.28	2.85	-£182,607	-0.43	-0.30	£605,630	£605,630 (SW quadrant)
Abbreviations; ICER; incremental cost-effectiveness ratio; Kd,,carfilzomib plus dexamethasone; LYG, life years gained; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; 2L, second-line								

Table 6 Base-case net monetary benefit and net health benefit results *versus* comparator – 2L analysis (selinexor at PAS price, comparators at list price)

	Net monetary benefit (£) (SVd *vs.* comparator)		Net health benefit (QALYs) (SVd *vs.* comparator)	
	WTP £20,000	**WTP £30,000**	**WTP £20,000**	**WTP £30,000**
Kd	£176,577	£173,561	8.83	5.79
Abbreviations: Kd, carfilzomib plus dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; WTP, willingness to pay; 2L, second-line				

Figure 2 Cost effectiveness frontier - SVd *versus* Kd at 2L (selinexor at PAS price, comparators at list price)



While cost-effectiveness results cannot be compared against Kd at the commercial PAS price for carfilzomib and the level of discount is not known, Table 7 and Table 8 suggest that a substantial cost saving exists when assuming list prices for both SVd and Kd.

Table 7 Base-case results versus comparator – 2L analysis (selinexor at list price, comparators at list price)

Comparator	Total			Incremental (SVd *vs.* comparator)				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	Incremental ICER
SVd	[redacted]	3.85	2.54					
Kd	£319,769	4.28	2.85	[redacted]	-0.43	-0.30	[redacted]	[redacted]

Abbreviations; ICER; incremental cost-effectiveness ratio; Kd,,carfilzomib plus dexamethasone; LYG, life years gained; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; 2L, second-line

Table 8 Base-case net monetary benefit and net health benefit results *versus* comparator – 2L analysis (selinexor at list price, comparators at list price)

	Net monetary benefit (£) (SVd *vs.* comparator)		Net health benefit (QALYs) (SVd *vs.* comparator)	
	WTP £20,000	**WTP £30,000**	**WTP £20,000**	**WTP £30,000**
Kd	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Kd, carfilzomib plus dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; WTP, willingness to pay; 2L, second-line

B1.2 Exploring uncertainty

B1.2.1 Probabilistic sensitivity analysis

B1.2.1.1 PSA results – SVd *vs. 3L* comparators

The probabilistic results for 3L are reported in Table 9, alongside scatterplots illustrating the spread of PSA iterations against each comparator (Figure 3 and Figure 4).

Table 9 PSA cost-effectiveness results – SVd *versus* 3L comparators

Comparator	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER interpretation
SVd	£135,193	2.60				
IxaRd	£225,416	2.66	-£90,223	-0.07	£1,293,485	South-West Quadrant
PanoVd	£125,546	2.35	£9,647	0.24	£39,743	North-East Quadrant

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

Figure 3 Scatterplot of PSA incremental estimates for SVd *versus* IxaRd at 3L

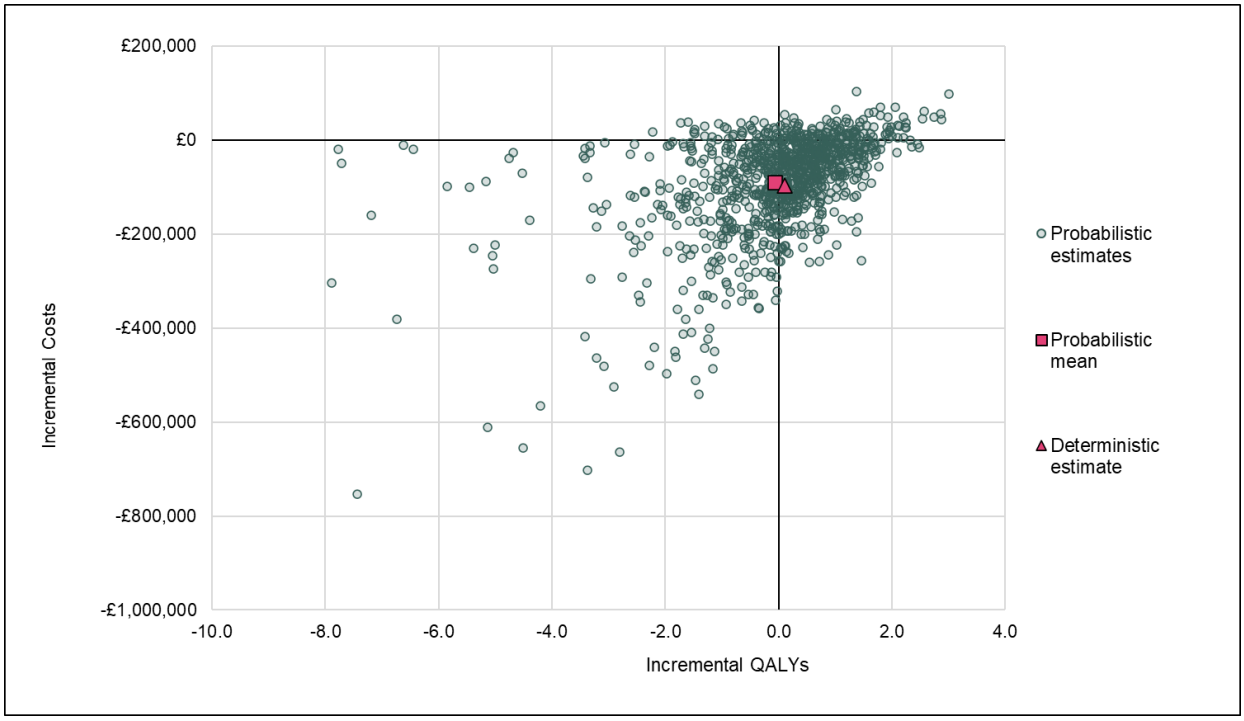
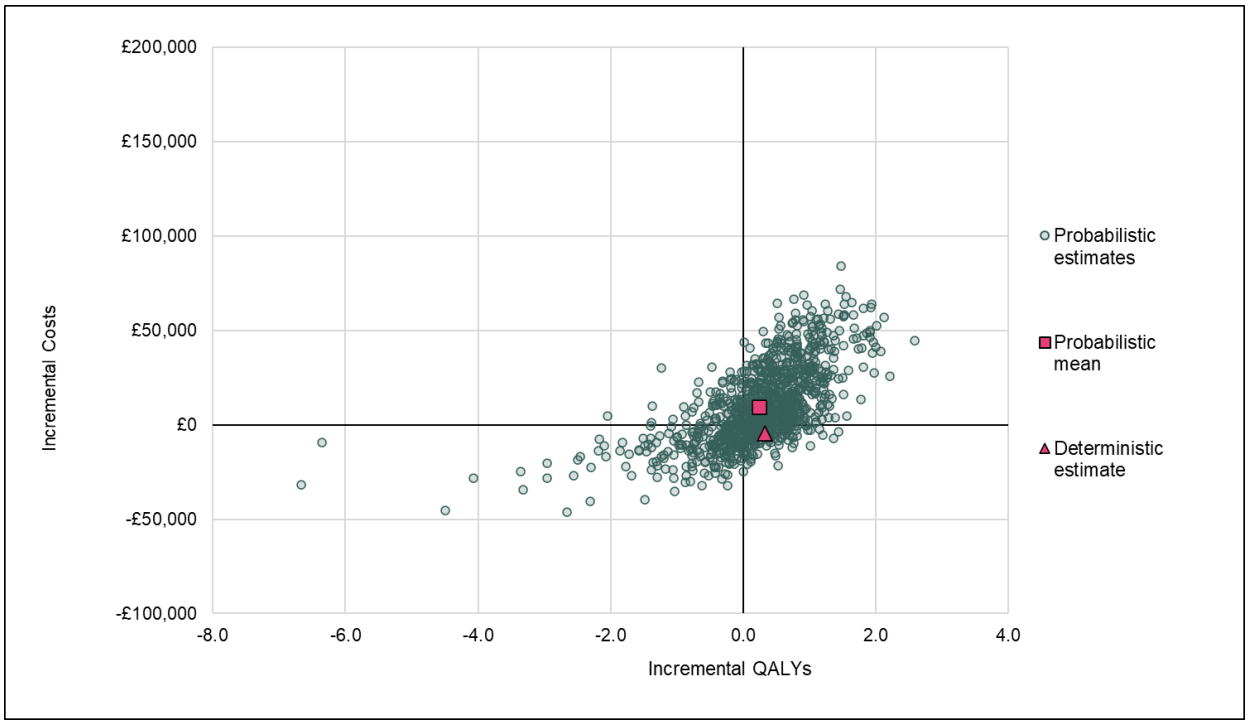


Figure 4 Scatterplot of PSA incremental estimates for SVd *versus* PanoVd at 3L



CEACs for SVd *versus* both 3L therapies show that for all WTP thresholds below £200,000/ QALY, including the NICE reference case of £20,000-£30,000/ QALY, SVd

has the highest probability (40%-50%) of being cost effective *versus* IxaRd and PanoVd (Figure 5).

Figure 5 Cost-effectiveness acceptability curves for SVd, IxaRd and PanoVd at 3L

B1.2.1.2 PSA results – SVd versus 2L comparators

Mean probabilistic results *versus* Kd at 2L are reported in Table 10, with a scatterplot of PSA iterations shown in Figure 6.

Table 10 PSA cost-effectiveness results – 2L

Comparator	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER interpretation
SVd	£136,410	2.57				
Kd	£316,740	3.11	-£181,330	-0.54	£334,464	South-West Quadrant

Abbreviations: ICER, incremental cost-effectiveness ratio; Kd, carfilzomib plus dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; 2L, second-line.

Figure 6 Scatterplot of PSA estimates on a cost-effectiveness plane SVd *versus* Kd at 2L

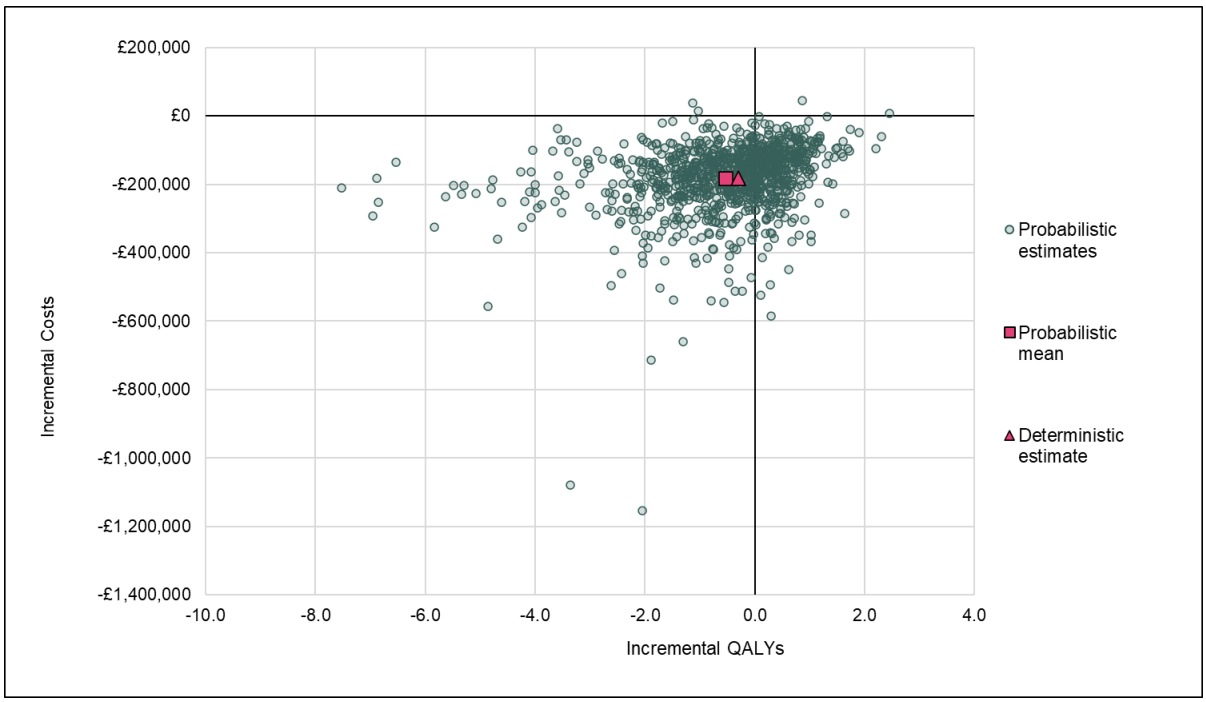


Figure 7 Cost-effectiveness acceptability curve for SVd *versus* Kd at 2L

B1.2.2 Deterministic sensitivity analysis

B1.2.2.1 OWSA results – 3L

Figure 8 3L OWSA NMB Results (SVd *versus* IxaRd)

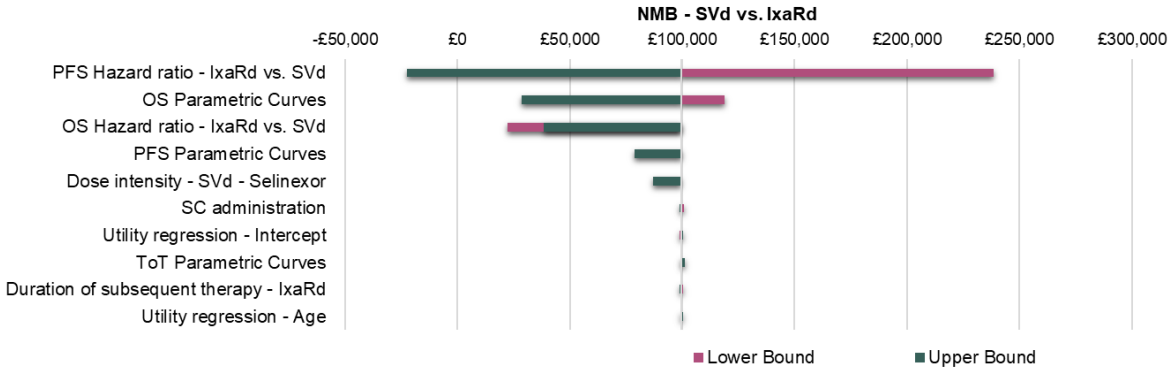
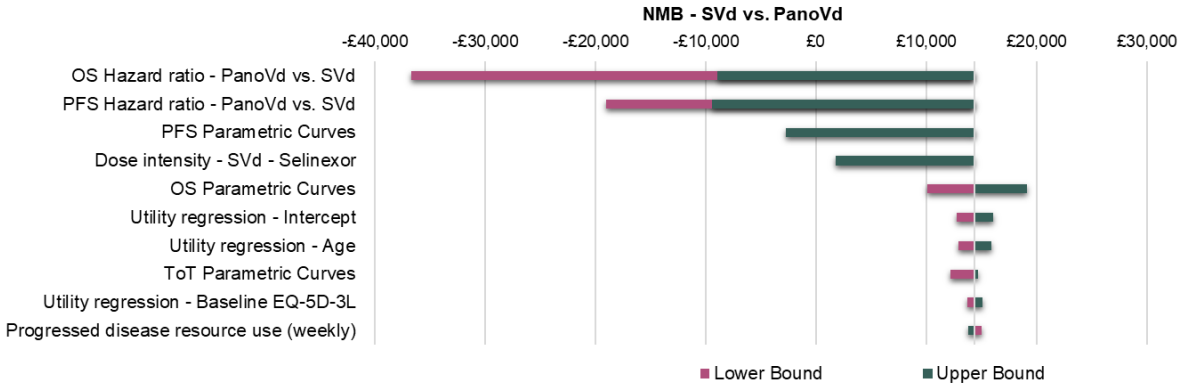
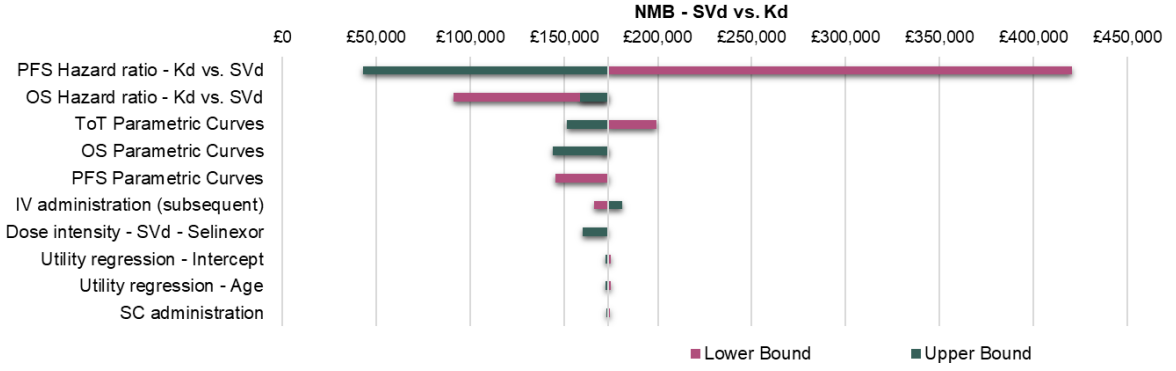


Figure 9 3L OWSA NMB Results (SVd *versus* PanoVd)



B1.2.2.2 OWSA results – 2L

Figure 10 2L NMB Results (SVd *versus* Kd)



B1.2.3 Scenario analysis

B1.2.3.1 Scenario analyses – 3L

Table 11 Scenario analysis results for SVd *versus* IxaRd at 3L

Scenario dimension	Option	SVd		IxaRd			
				Incremental Costs (£)	Incremental QALYs	ICER	NHB at £30,000
		Total cost	total QALYs				
Base case	**N/A**	**£133,706**	**2.58**	**-£96,381**	**0.11**	**-£867,308**	**3.32**
Time horizon	5 years	£112,902	2.12	-£84,143	0.04	-£1,996,842	2.85
	10 years	£131,511	2.53	-£93,281	0.10	-£968,506	3.21
	20 years	£133,691	2.58	-£96,386	0.11	-£867,960	3.32
	Lifetime (35 years)	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
Comparative efficacy	PFS: ITC hazard ratios (RE) OS: ITC hazard ratios (RE)	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
	PFS: ITC hazard ratios (FE) OS: ITC hazard ratios (FE)	£133,706	2.58	-£43,547	0.13	-£346,017	1.58
	PFS: ITC hazard ratios (RE) OS: HR=1 (equal efficacy)	£133,706	2.58	-£98,979	-0.04	£2,749,870	3.26
	PFS: HR=1 (equal efficacy) OS: HR=1 (equal efficacy)	£133,706	2.58	-£39,412	-0.01	£6,212,357	1.31
PFS parametric curve	Fitted jointly with Vd: Exponential	£132,835	2.57	-£95,670	0.11	-£850,516	3.30
	Fitted jointly with Vd: Weibull	£132,361	2.57	-£92,992	0.12	-£791,906	3.22
	Fitted jointly with Vd: Log-normal	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
	Fitted jointly with Vd: Log-logistic	£133,724	2.58	-£96,334	0.11	-£860,127	3.32
	Fitted jointly with Vd: Gompertz	£133,457	2.58	-£96,349	0.11	-£876,018	3.32
	Fitted jointly with Vd: Generalised gamma	£133,690	2.58	-£96,375	0.11	-£868,761	3.32
	Fitted jointly with Vd: Gamma	£132,387	2.57	-£93,119	0.12	-£791,679	3.22
	Fitted independently: Exponential	£132,835	2.57	-£95,670	0.11	-£850,516	3.30
	Fitted independently: Weibull	£132,257	2.57	-£92,552	0.12	-£782,246	3.20
	Fitted independently: Log-normal	£133,653	2.58	-£96,335	0.11	-£867,290	3.32
	Fitted independently: Log-logistic	£133,711	2.58	-£96,324	0.11	-£860,056	3.32

	Fitted independently: Gompertz	£133,554	2.58	-£96,341	0.11	-£874,010	3.32
	Fitted independently: Generalised gamma	£133,991	2.60	-£96,388	0.12	-£822,872	3.33
	Fitted independently: Gamma	£132,247	2.57	-£92,566	0.12	-£779,006	3.20
OS parametric curve	Fitted jointly with Vd: Exponential	£140,169	3.74	-£114,675	0.24	-£483,145	4.06
	Fitted jointly with Vd: Weibull	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
	Fitted jointly with Vd: Log-normal	£145,207	4.70	-£116,566	0.31	-£377,237	4.19
	Fitted jointly with Vd: Log-logistic	£140,046	3.72	-£116,617	0.25	-£467,637	4.14
	Fitted jointly with Vd: Gompertz	£127,272	1.96	-£76,076	0.04	-£1,753,142	2.58
	Fitted jointly with Vd: Generalised gamma	£128,111	2.06	-£79,125	0.05	-£1,504,682	2.69
	Fitted jointly with Vd: Gamma	£135,772	2.87	-£103,781	0.14	-£718,663	3.60
	Fitted independently: Exponential	£140,169	3.74	-£114,675	0.24	-£483,145	4.06
	Fitted independently: Weibull	£131,471	2.29	-£88,592	0.08	-£1,101,872	3.03
	Fitted independently: Log-normal	£138,446	3.39	-£116,097	0.22	-£535,499	4.09
	Fitted independently: Log-logistic	£137,408	3.18	-£116,245	0.20	-£587,264	4.07
	Fitted independently: Gompertz	£127,029	1.94	-£75,379	0.04	-£1,822,044	2.55
	Fitted independently: Generalised gamma	£137,010	3.08	-£113,163	0.18	-£626,247	3.95
	Fitted independently: Gamma	£133,591	2.52	-£96,261	0.11	-£891,740	3.32
ToT parametric curve	Fitted jointly with Vd: Exponential	£130,609	2.58	-£78,293	0.11	-£704,098	2.72
	Fitted jointly with Vd: Weibull	£129,700	2.58	-£71,379	0.11	-£641,938	2.49
	Fitted jointly with Vd: Log-normal	£136,981	2.58	-£99,222	0.11	-£895,667	3.42
	Fitted jointly with Vd: Log-logistic	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
	Fitted jointly with Vd: Gompertz	£132,957	2.58	-£91,055	0.11	-£819,410	3.15
	Fitted jointly with Vd: Generalised gamma	£132,667	2.58	-£87,304	0.11	-£785,853	3.02
	Fitted jointly with Vd: Gamma	£129,301	2.58	-£70,056	0.11	-£629,891	2.45
	Fitted independently: Exponential	£130,609	2.58	-£78,293	0.11	-£704,098	2.72
	Fitted independently: Weibull	£129,690	2.58	-£71,203	0.11	-£640,361	2.48
	Fitted independently: Log-normal	£130,049	2.58	-£82,426	0.11	-£740,417	2.86

	Fitted independently: Log-logistic	£130,058	2.58	-£89,217	0.11	-£800,597	3.09
	Fitted independently: Gompertz	£138,898	2.58	-£105,473	0.11	-£953,051	3.63
	Fitted independently: Generalised gamma	£144,272	2.58	-£111,061	0.11	-£1,008,429	3.81
	Fitted independently: Gamma	£129,021	2.58	-£68,265	0.11	-£613,769	2.39
Comparator ToT	PFS HR relative to SVd ToT	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
	Treatment to progression	£133,706	2.58	-£196,139	0.11	-£1,740,791	6.65
Adverse event application	Applied as one-off events	£131,922	2.57	-£97,259	0.11	-£894,671	3.35
	Applied as weekly rates while on treatment	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
Discounting	No discounting (cost and benefits)	£138,798	2.69	-£99,904	0.12	-£839,699	3.45
	3.5% discounting (costs and benefits)	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
Selinexor weekly dosage	Full (100mg)	£146,323	2.58	-£83,764	0.11	-£753,771	2.90
	Mean (78.9mg)	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
Subsequent therapies	Costed after progression	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
	Costed after discontinuation	£122,080	2.58	-£96,454	0.11	-£867,959	3.33
Drug wastage	Included (tablet wastage)	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
	Excluded	£132,152	2.58	-£97,321	0.11	-£875,766	3.36
Utility source	BOSTON (treatment independent)	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
	BOSTON (arm specific)	£133,706	2.60	-£96,381	0.14	-£691,357	3.35
	Hatswell	£133,706	2.13	-£96,381	0.06	-£1,563,999	3.27
Utility decrements	Adjusted using model coefficient	£133,706	2.58	-£96,381	0.11	-£867,308	3.32
	Adjust utilities using Ara and Brazier (2011)	£133,706	2.58	-£96,381	0.11	-£867,308	3.32

Table 12 Scenario analysis results for SVd *versus* PanoVd at 3L

Scenario dimension	Option	SVd	PanoVd			

		Total cost	total QALYs	Incremental Costs (£)	Incremental QALYs	ICER	NHB at £30,000
Base case	**N/A**	**£133,706**	**2.58**	**-£4,501**	**0.33**	**-£13,631**	**0.48**
Time horizon	5 years	£112,902	2.12	-£18,055	0.16	-£111,517	0.76
	10 years	£131,511	2.53	-£6,383	0.30	-£21,232	0.51
	20 years	£133,691	2.58	-£4,515	0.33	-£13,679	0.48
	Lifetime (35 years)	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
Comparative efficacy	PFS: ITC hazard ratios (RE) OS: ITC hazard ratios (RE)	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
	PFS: ITC hazard ratios (FE) OS: ITC hazard ratios (FE)	£133,706	2.58	-£4,358	0.34	-£12,716	0.49
	PFS: ITC hazard ratios (RE) OS: HR=1 (equal efficacy)	£133,706	2.58	-£6,112	-0.01	£1,041,168	0.20
	PFS: HR=1 (equal efficacy) OS: HR=1 (equal efficacy)	£133,706	2.58	-£378	0.01	-£48,624	0.02
PFS parametric curve	Fitted jointly with Vd: Exponential	£132,835	2.57	-£4,137	0.33	-£12,539	0.47
	Fitted jointly with Vd: Weibull	£132,361	2.57	-£2,560	0.33	-£7,696	0.42
	Fitted jointly with Vd: Log-normal	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
	Fitted jointly with Vd: Log-logistic	£133,724	2.58	-£4,457	0.33	-£13,468	0.48
	Fitted jointly with Vd: Gompertz	£133,457	2.58	-£4,468	0.33	-£13,596	0.48
	Fitted jointly with Vd: Generalised gamma	£133,690	2.58	-£4,497	0.33	-£13,627	0.48
	Fitted jointly with Vd: Gamma	£132,387	2.57	-£2,624	0.33	-£7,884	0.42
	Fitted independently: Exponential	£132,835	2.57	-£4,137	0.33	-£12,539	0.47
	Fitted independently: Weibull	£132,257	2.57	-£2,287	0.33	-£6,865	0.41
	Fitted independently: Log-normal	£133,653	2.58	-£4,463	0.33	-£13,531	0.48
	Fitted independently: Log-logistic	£133,711	2.58	-£4,449	0.33	-£13,446	0.48
	Fitted independently: Gompertz	£133,554	2.58	-£4,448	0.33	-£13,506	0.48
	Fitted independently: Generalised gamma	£133,991	2.60	-£4,496	0.34	-£13,358	0.49

	Fitted independently: Gamma	£132,247	2.57	-£2,277	0.33	-£6,827	0.41
OS parametric curve	Fitted jointly with Vd: Exponential	£140,169	3.74	-£1,878	0.65	-£2,911	0.71
	Fitted jointly with Vd: Weibull	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
	Fitted jointly with Vd: Log-normal	£145,207	4.70	-£809	0.83	-£972	0.86
	Fitted jointly with Vd: Log-logistic	£140,046	3.72	-£1,971	0.68	-£2,916	0.74
	Fitted jointly with Vd: Gompertz	£127,272	1.96	-£8,279	0.16	-£53,094	0.43
	Fitted jointly with Vd: Generalised gamma	£128,111	2.06	-£7,841	0.18	-£42,939	0.44
	Fitted jointly with Vd: Gamma	£135,772	2.87	-£3,509	0.41	-£8,481	0.53
	Fitted independently: Exponential	£140,169	3.74	-£1,878	0.65	-£2,911	0.71
	Fitted independently: Weibull	£131,471	2.29	-£5,659	0.25	-£22,622	0.44
	Fitted independently: Log-normal	£138,446	3.39	-£2,615	0.59	-£4,398	0.68
	Fitted independently: Log-logistic	£137,408	3.18	-£3,062	0.55	-£5,584	0.65
	Fitted independently: Gompertz	£127,029	1.94	-£8,444	0.15	-£56,114	0.43
	Fitted independently: Generalised gamma	£137,010	3.08	-£3,130	0.50	-£6,227	0.61
	Fitted independently: Gamma	£133,591	2.52	-£4,456	0.32	-£13,963	0.47
ToT parametric curve	Fitted jointly with Vd: Exponential	£130,609	2.58	-£6,134	0.33	-£18,659	0.53
	Fitted jointly with Vd: Weibull	£129,700	2.58	-£8,953	0.33	-£27,288	0.63
	Fitted jointly with Vd: Log-normal	£136,981	2.58	-£2,391	0.33	-£7,226	0.41
	Fitted jointly with Vd: Log-logistic	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
	Fitted jointly with Vd: Gompertz	£132,957	2.58	-£3,279	0.33	-£9,940	0.44
	Fitted jointly with Vd: Generalised gamma	£132,667	2.58	-£6,270	0.33	-£19,028	0.54
	Fitted jointly with Vd: Gamma	£129,301	2.58	-£10,036	0.33	-£30,604	0.66
	Fitted independently: Exponential	£130,609	2.58	-£6,134	0.33	-£18,659	0.53
	Fitted independently: Weibull	£129,690	2.58	-£9,028	0.33	-£27,520	0.63
	Fitted independently: Log-normal	£130,049	2.58	-£8,987	0.33	-£27,325	0.63
	Fitted independently: Log-logistic	£130,058	2.58	-£7,970	0.33	-£24,197	0.60
	Fitted independently: Gompertz	£138,898	2.58	£2,840	0.33	£8,571	0.24
	Fitted independently: Generalised gamma	£144,272	2.58	£5,713	0.33	£17,206	0.14

	Fitted independently: Gamma	£129,021	2.58	-£10,923	0.33	-£33,328	0.69
Comparator ToT	PFS HR relative to SVd ToT	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
	Treatment to progression	£133,706	2.58	-£17,170	0.34	-£49,836	0.92
Adverse event application	Applied as one-off events	£131,922	2.57	-£69	0.31	-£225	0.31
	Applied as weekly rates while on treatment	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
Discounting	No discounting (cost and benefits)	£138,798	2.69	-£3,310	0.35	-£9,424	0.46
	3.5% discounting (costs and benefits)	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
Selinexor weekly dosage	Full (100mg)	£146,323	2.58	£8,116	0.33	£24,577	0.06
	Mean (78.9mg)	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
Subsequent therapies	Costed after progression	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
	Costed after discontinuation	£122,080	2.58	-£4,366	0.33	-£13,220	0.48
Drug wastage	Included (tablet wastage)	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
	Excluded	£132,152	2.58	-£4,475	0.33	-£13,551	0.48
Utility source	BOSTON (treatment independent)	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
	BOSTON (arm specific)	£133,706	2.60	-£4,501	0.34	-£13,255	0.49
	Hatswell	£133,706	2.13	-£4,501	0.25	-£17,702	0.40
Utility decrements	Adjusted using model coefficient	£133,706	2.58	-£4,501	0.33	-£13,631	0.48
	Adjust utilities using Ara and Brazier (2011)	£133,706	2.58	-£4,501	0.33	-£13,631	0.48

B1.2.3.2 Scenario analyses – 2L

Table 13 Scenario analysis results for SVd *versus* Kd at 2L

Scenario dimension	**Option**	**SVd**		**Kd**			
				Incremental Costs (£)	**Incremental QALYs**	**ICER**	**NHB at £30,000**
		Total cost	**total QALYs**				

Base case	**N/A**	**£137,162**	**2.54**	**-£182,607**	**-0.30**	**£605,630**	**5.79**
Time horizon	5 years	£108,074	1.95	-£171,409	-0.12	£1,419,769	£6
	10 years	£129,508	2.42	-£179,333	-0.23	£772,862	£6
	20 years	£136,747	2.54	-£182,147	-0.30	£617,166	£6
	Lifetime (35 years)	£137,162	2.54	-£182,607	-0.30	£605,630	£6
Comparative efficacy	PFS: ITC hazard ratios (RE) OS: ITC hazard ratios (RE)	£137,162	2.54	-£182,607	-0.30	£605,630	£6
	PFS: ITC hazard ratios (FE) OS: ITC hazard ratios (FE)	£137,162	2.54	-£181,581	-0.31	£593,753	£6
	PFS: ITC hazard ratios (RE) OS: HR=1 (equal efficacy)	£137,162	2.54	-£181,294	-0.04	£4,809,995	£6
	PFS: HR=1 (equal efficacy) OS: HR=1 (equal efficacy)	£137,162	2.54	-£118,125	-0.01	£16,414,913	£4
PFS parametric curve	Fitted jointly with Vd: Exponential	£137,161	2.54	-£182,604	-0.30	£605,794	£6
	Fitted jointly with Vd: Weibull	£137,200	2.55	-£182,688	-0.30	£601,918	£6
	Fitted jointly with Vd: Log-normal	£137,921	2.57	-£166,561	-0.30	£550,410	£5
	Fitted jointly with Vd: Log-logistic	£137,875	2.56	-£170,469	-0.30	£562,664	£5
	Fitted jointly with Vd: Gompertz	£138,166	2.57	-£157,060	-0.30	£524,372	£5
	Fitted jointly with Vd: Generalised gamma	£137,984	2.57	-£165,023	-0.30	£546,701	£5
	Fitted jointly with Vd: Gamma	£137,161	2.54	-£182,604	-0.30	£605,876	£6
	Fitted independently: Exponential	£137,161	2.54	-£182,604	-0.30	£605,794	£6
	Fitted independently: Weibull	£137,208	2.55	-£182,707	-0.30	£601,239	£6
	Fitted independently: Log-normal	£138,021	2.57	-£161,385	-0.30	£535,448	£5
	Fitted independently: Log-logistic	£137,964	2.57	-£165,336	-0.30	£547,425	£5
	Fitted independently: Gompertz	£137,020	2.58	-£156,377	-0.30	£523,889	£5
	Fitted independently: Generalised gamma	£133,070	2.58	-£159,127	-0.30	£535,415	£5
	Fitted independently: Gamma	£137,162	2.54	-£182,607	-0.30	£605,630	£6
OS parametric curve	Fitted jointly with Vd: Exponential	£138,653	2.89	-£182,864	-0.37	£496,409	£6
	Fitted jointly with Vd: Weibull	£136,842	2.46	-£182,599	-0.28	£655,019	£6
	Fitted jointly with Vd: Log-normal	£143,599	3.88	-£183,690	-0.51	£363,686	£6

	Fitted jointly with Vd: Log-logistic	£141,408	3.46	-£183,452	-0.47	£388,572	£6
	Fitted jointly with Vd: Gompertz	£135,945	2.20	-£173,646	-0.21	£847,031	£6
	Fitted jointly with Vd: Generalised gamma	£137,897	2.73	-£182,739	-0.35	£527,345	£6
	Fitted jointly with Vd: Gamma	£137,162	2.54	-£182,607	-0.30	£605,630	£6
	Fitted independently: Exponential	£138,653	2.89	-£182,864	-0.37	£496,409	£6
	Fitted independently: Weibull	£137,244	2.56	-£182,612	-0.30	£606,774	£6
	Fitted independently: Log-normal	£144,566	4.06	-£183,763	-0.51	£356,961	£6
	Fitted independently: Log-logistic	£142,225	3.62	-£183,545	-0.48	£378,583	£6
	Fitted independently: Gompertz	£136,768	2.43	-£182,532	-0.26	£711,047	£6
	Fitted independently: Generalised gamma	£139,237	3.02	-£183,033	-0.40	£453,021	£6
	Fitted independently: Gamma	£137,500	2.63	-£182,648	-0.32	£574,605	£6
ToT parametric curve	Fitted jointly with Vd: Exponential	£137,846	2.54	-£188,808	-0.30	£626,115	£6
	Fitted jointly with Vd: Weibull	£137,424	2.54	-£184,304	-0.30	£611,218	£6
	Fitted jointly with Vd: Log-normal	£149,268	2.54	-£267,502	-0.30	£884,309	£9
	Fitted jointly with Vd: Log-logistic	£147,749	2.54	-£268,083	-0.30	£886,432	£9
	Fitted jointly with Vd: Gompertz	£141,044	2.54	-£218,997	-0.30	£725,772	£7
	Fitted jointly with Vd: Generalised gamma	£138,967	2.54	-£203,348	-0.30	£674,253	£6
	Fitted jointly with Vd: Gamma	£137,162	2.54	-£182,607	-0.30	£605,630	£6
	Fitted independently: Exponential	£137,846	2.54	-£188,808	-0.30	£626,115	£6
	Fitted independently: Weibull	£137,810	2.54	-£188,460	-0.30	£624,964	£6
	Fitted independently: Log-normal	£147,011	2.54	-£257,843	-0.30	£853,053	£8
	Fitted independently: Log-logistic	£149,148	2.54	-£273,484	-0.30	£903,802	£9
	Fitted independently: Gompertz	£149,575	2.54	-£272,633	-0.30	£900,718	£9
	Fitted independently: Generalised gamma	£147,236	2.54	-£259,072	-0.30	£857,050	£8
	Fitted independently: Gamma	£137,345	2.54	-£184,344	-0.30	£611,369	£6
Comparator ToT	PFS HR relative to SVd ToT	£137,162	2.54	-£182,607	-0.30	£605,630	£6
	Treatment to progression	£137,162	2.54	-£452,237	-0.30	£1,509,369	£15

Adverse event application	Applied as one-off events	£135,250	2.53	-£183,817	-0.31	£594,985	£6
	Applied as weekly rates while on treatment	£137,162	2.54	-£182,607	-0.30	£605,630	£6
Discounting	No discounting (cost and benefits)	£142,728	2.66	-£188,144	-0.32	£583,529	£6
	3.5% discounting (costs and benefits)	£137,162	2.54	-£182,607	-0.30	£605,630	£6
Selinexor weekly dosage	Full (100mg)	£150,661	2.54	-£169,108	-0.30	£560,859	£5
	Mean (78.9mg)	£137,162	2.54	-£182,607	-0.30	£605,630	£6
Subsequent therapies	Costed after progression	£137,162	2.54	-£182,607	-0.30	£605,630	£6
	Costed after discontinuation	£125,837	2.54	-£182,591	-0.30	£605,578	£6
Drug wastage	Included (tablet wastage)	£137,162	2.54	-£182,607	-0.30	£605,630	£6
	Excluded	£135,514	2.54	-£169,957	-0.30	£563,674	£5
Utility source	BOSTON (treatment independent)	£137,162	2.54	-£182,607	-0.30	£605,630	£6
	BOSTON (arm specific)	£137,162	2.56	-£182,607	-0.27	£675,176	£6
	Hatswell	£137,162	2.22	-£182,607	-0.29	£627,607	£6
Utility decrements	Adjusted using model coefficient	£137,162	2.54	-£182,607	-0.30	£605,630	£6
	Adjust utilities using Ara and Brazier (2011)	£137,162	2.54	-£182,607	-0.30	£605,630	£6

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions company response

October 2023

File name	Version	Contains confidential information	Date
ID3797 company response follow up questions 061023(ACIC)	V2	Yes	28 Januay 2024

Table of drug combination abbreviations

DRd	**Daratumumab in combination with lenalidomide and dexamethasone**
DVd	**Daratumumab in combination with bortezomib and dexamethasone**
IsaPd	**Isatuximab in combination with pomalidomide and dexamethasone**
IxaRd	**Ixazomib in combination with lenalidomide and dexamethasone**
Kd	**Carfilzomib with dexamethasone**
KRd	**Carfilzomib in combination with lenalidomide and dexamethasone**
PanoVd	**Panobinostat in combination with bortezomib and dexamethasone**
Pd	**Pomalidomide with dexamethasone**
Rd	**Lenalidomide and dexamethasone**
SVd	**Selinexor in combination with bortezomib and dexamethasone**
SVdX	**Selinexor in combination with bortezomib and dexamethasone crossover population (crossed over from Vd to SVd)**
Vd	**Bortezomib and dexamethasone**

Section A: Clarification on effectiveness data

A29. Priority. The EAG notes the Company did not conduct an unanchored MAIC directly comparing Vd or SVd from BOSTON with IxaRD from TOURMALINE-MM1 because, while the Company identified a Kaplan-Meier **curve is available for the 3L+ population for PFS in the TOURMALINE-MM1 study, the Company could not identify a Kaplan-Meier curve for OS for the 3L+ population, or baseline characteristics for the 3L+ population.**

The EAG has been able to identify complete baseline characteristics for the 3L+ population, and a Kaplan-Meier curve for OS for the 3L+ population in the following sources:

- **Complete baseline characteristics for 2 or 3 prior lines of therapy are available in Table 8 of the Response to Clarification Questions in the Committee Papers for Ixazomib citrate for treating relapsed or refractory multiple myeloma (ID807, Committee papers ACD 1 Draft guidance: TA505 ACD, page 31 of the Clarification Response, page 440 of the overall document).**
- **An OS Kaplan-Meier curve for patients with 2 or 3 prior therapies in TMM1 at the final analysis is available in Figure 1 of the Company Evidence Submission of Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505, ID1635, Committee papers, page 15 of the Company Evidence Submission, page 18 of the overall document)**

Please conduct fully adjusted unanchored MAICs for PFS and OS for Vd and SVd against IxaRd using these data. Please provide complete details of the MAICs, including:

- **Patient characteristics before and after matching;**
- **A histogram of weights;**
- **Effective sample size;**
- **Plots of the unadjusted and adjusted KM curves;**
- **The code used to conduct the MAICs.**

Company response: An unanchored MAIC has been performed to compare SVd and Vd *versus* IxaRd in the 3L+ population, matching on a subset of baseline characteristics (for the cohort receiving 2 or 3 prior lines of therapy) reported in Table

8 of the Response to Clarification Questions in the Committee Papers for Ixazomib citrate for treating relapsed or refractory multiple myeloma (TA870).[1]

The selection of the baseline characteristics for the matching process was based on previous clinical validation of prognostic factors in MM and on the availability of these baseline characteristics from the TOURMALINE-MM1 trial for the 2L and 3L population. A total of eight factors were selected for inclusion in the matching: age (matching on both the mean and standard deviation [SD]), gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), Revised International Staging System (R-ISS), high cytogenetic risk, receipt of prior stem cell transplant (SCT), prior proteasome inhibitor (PI) and prior immunomodulatory drug (IMiD) exposure.

Comparison between IxaRd and SVd

A summary of the patient characteristics prior to, and after weighting are presented in Table 1 based on both the Full and Reduced sets of factors.

Table 1 Summary of baseline characteristics in TOURMALINE-MM1 (IxaRd) and BOSTON trial (SVd) prior to, and after MAIC weighting

Factor	TOURMALINE-MM1[1]	BOSTON IPD[2]	
		Prior to matching	Post matching
Number of patients	148	96	[redacted]
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%

Factor	TOURMALINE-MM1[1]	BOSTON IPD[2]	
		Prior to matching	Post matching

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

Weights (including the rescaled weights) based on matching on the selected set of factors are presented in the histograms in Figure 1.

Figure 1 [redacted]

[redacted]

A summary of the PFS HR estimates for IxaRd *versus* SVd prior to and after weighting are presented in Table 2.

Table 2 Unanchored PFS MAIC results – IxaRd (TOURMALINE-MM1) versus SVd (BOSTON)

Comparator study	BOSTON SVd sample size	ESS	ESS %	HR naïve [95% CI]	HR weighted [95% CI]
TOURMALINE-MM1	91*	[redacted]	[redacted]	0.53 [0.35, 0.81]	0.66 [0.34, 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.*

Plots of the unadjusted and adjusted SVd Kaplan-Meier curves, as well as the digitised IxaRd curve are presented in Figure 2 for PFS.

Figure 2 [redacted]

A summary of the OS HR estimates for IxaRd versus SVd prior to- and after weighting are presented in Table 3.

Table 3 Unanchored OS MAIC results – IxaRd (TOURMALINE-MM1) *versus* SVd (BOSTON)

Comparator study	BOSTON SVd sample size	ESS	ESS %	HR naïve [95% CI]	HR weighted [95% CI]
TOURMALINE-MM1	91*	[redacted]	[redacted]	0.60 [0.38, 0.95]	1.29 [0.63, 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.*

Plots of the unadjusted and adjusted SVd Kaplan-Meier curves, as well as the digitised IxaRd curve are presented in Figure 3 for OS.

Figure 3 [redacted]

Comparison between IxaRd and Vd

A summary of the patient characteristics prior to- and after weighting are presented in Table 4.

Table 4 Summary of baseline characteristics in TOURMALINE-MM1 (IxaRd) and BOSTON trial (Vd) prior to- and after MAIC weighting

Factor	TOURMALINE-MM1[1]	BOSTON IPD[2]	
		Prior to matching	Post matching
Number of patients	148	108	[redacted]
Arm	IxaRd	Vd	Vd
Age Mean (SD)	65.9 (9.46)	65.0 (9.98)	65.9
Sex, n (%) Male	54.7%	57.4%	54.7%
ECOG PS, n (%) 0 1 2	 40.4%* 52.7%* 6.8%*	 36.1% 54.6% 9.3%	 40.4% 52.7% 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

Weights (including the rescaled weights) based on matching to the selected set of factors are presented in the histograms in

Figure 4.

Figure 4 [redacted]

A summary of the PFS HR estimates for IxaRd versus Vd prior to- and after weighting are presented in Table 5.

Table 5 Unanchored PFS MAIC results – IxaRd (TOURMALINE-MM1) *versus* Vd (BOSTON)

Comparator study	BOSTON Vd sample size	ESS	ESS %	HR naïve [95% CI]	HR weighted [95% CI]
TOURMALINE-MM1	102*	[redacted]	[redacted]	0.37 [0.25, 0.53]	0.37 [0.23, 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.*

Plots of the unadjusted and adjusted Vd Kaplan-Meier curves as well as the digitised IxaRd curve are presented in Figure 5 for PFS.

Figure 5 [redacted]

A summary of the OS HR estimates for IxaRd versus Vd prior to- and after weighting are presented in Table 6.

Table 6 Unanchored OS MAIC results – IxaRd (TOURMALINE-MM1) *versus* Vd (BOSTON)

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, 0.74]	0.48 [0.29, 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.*

Plots of the unadjusted and adjusted Vd Kaplan-Meier curves, as well as the digitised IxaRd curve are presented in

Figure 6 for OS.

Figure 6 [redacted]

An example R code has been provided in the associated file ("R code for CQ A29 MAIC vs IxaRd").

The results from these unanchored MAIC analyses are supportive of the results presented in the updated 3L+ NMA (which was submitted in response to an earlier clarification question). Especially for the comparison of SVd *versus* IxaRd, the direction of the estimates and conclusions drawn from the analyses remain unchanged.

A30. The EAG notes that several details of the unanchored MAIC used in the Company 3L+ between Vd and Pd were not reported in the supplementary appendix. Please provide the following details of this MIAC:

- Patient characteristics before and after matching;
- A histogram of weights;
- Effective sample size;
- Plots of the unadjusted and adjusted KM curves;
- The code used to conduct the MAICs.

Company response: Further details regarding the unanchored MAIC comparing pomalidomide plus dexamethasone (Pd) with Vd are presented in the following paragraphs.

A total of 70 patients (out of 108) from the Vd arm of the BOSTON trial were available for inclusion in the MAIC analysis; these patients had received at least two prior regimens and had also received prior exposure to IMiD and PI. This initial equalisation step was required because 100% of patients in the Pd arm of the ICARIA-MM trial had received prior exposure to IMiD and PI.[3]

The following baseline characteristics were included in the matching (based on the clinical input collected for other indirect treatment comparisons performed by the company): age, sex, prior SCT, R-ISS stage, high cytogenetic risk and time since diagnosis.

A summary of the patient characteristics prior to- and after weighting are presented in Table 7.

Table 7 Summary of baseline characteristics in ICARIA-MM (Pd) and BOSTON trial (Vd) prior to- and after MAIC weighting

Factor	ICARIA-MM	BOSTON IPD	
		Prior to matching	Post matching
Number of patients	153	70	[redacted]
Arm	Pd	Vd	Vd
Age Median (range)	66.0 (NR)	65.0 (38-85)	66.0
Sex, n (%) Male	45.8%	50.0%	45.8%

Stem cell transplant, n (%) Yes	58.8%	40.0%	58.8%
R-ISS, n (%)‡ 2-3	66.0%*†	72.7%*	66.0%
Cytogenetic risk, n (%) High	31.6%*	25.7%	31.6%
Time since diagnosis, years Median (range)	4.1 (2.9-7.0)	4.4 (1.2-11.9)	4.1
Abbreviations: ESS, effective sample size; IPD, individual patient data; ISS, International Staging System; Pd, pomalidomide plus dexamethasone; R-ISS, Revised International Staging System; Vd, bortezomib plus dexamethasone. *Notes: *Missing values were excluded prior to calculating %* *†Reported as ISS ‡R-ISS=2 and R-ISS=3 combined due to only 10% patients in BOSTON with R-ISS=3*			

Weights (including the rescaled weights) are presented in the histograms in Figure 7.

Figure 7 [redacted]

[redacted]

A summary of the PFS HR estimates for Pd versus Vd prior to- and after weighting are presented in Table 8.

Table 8 Unanchored PFS MAIC results Pd (ICARIA-MM) *versus* Vd (BOSTON)

Comparator study	BOSTON Vd sample size	ESS	ESS %	HR naïve [95% CI]	HR weighted [95% CI]
ICARIA-MM	66*	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; Pd, pomalidomide plus dexamethasone; PS, performance status; R-ISS, Revised International Staging System; prior SCT, stem cell transplant; Vd, bortezomib plus dexamethasone.

*Notes: *Four patients did not report R-ISS and were therefore excluded from the analysis.*

Plots of the unadjusted and adjusted KM Vd curves as well, as the digitised Pd curve for PFS are presented in Figure 8.

Figure 8 [redacted]

[redacted]

A summary of the OS HR estimates for Pd versus Vd prior to- and after weighting are presented in Table 9.

Table 9 Unanchored OS MAIC results Pd (ICARIA-MM) versus Vd (BOSTON)

Comparator study	BOSTON Vd sample size	ESS	ESS %	HR naïve [95% CI]	HR weighted [95% CI]
ICARIA-MM	66*	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; Pd, pomalidomide plus dexamethasone; PS, performance status; R-ISS, Revised International Staging System; prior SCT, stem cell transplant; Vd, bortezomib plus dexamethasone.
*Notes: *Four patients did not report R-ISS and were therefore excluded from the analysis.*

Plots of the unadjusted and adjusted KM Vd curves, as well as the digitised Pd curve for OS are presented in Figure 9.

Figure 9 [redacted]

An example R code has been provided in the associated file ("R code for CQ A30 MAIC vs Pd)".

A31. The Company noted that multiple approaches were explored to adjust for crossover for overall survival:

- Please clarify if Figure 1 to Figure 4s in the response to A3 represent the two-stage estimation approach results only;

- Please provide details and results of each other method that was performed.

Company Response: Two-stage estimation methods were implemented with re-censoring, following the recommendations described in Latimer *et al.* 2017,[4] and in line with the approach used for the analyses submitted to EMA and MHRA. The figures provided in the response to A3 represent the two-stage estimation methods results with and without re-censoring. Adjustments based on Rank Preserving Structural Failure Time (RPSFT) and Inverse probability of censoring weighted analysis (IPCW) were also explored. The RPSFT analyses supported the outcomes related to the TSE method and the IPCW KM curves lacked external validity.

A32. The EAG notes that, in the Company response to Clarification Question A5, the Company stated that:

"The company is positioning SVd, in the 2L, in patients who have received daratumumab and lenalidomide in the front-line setting, based on clinical feedback received during the development of the submission. Based on the current reimbursed pathway, this would be in transplant-ineligible patients receiving DRd at 1L."

Please clarify whether the Company is positioning SVd in the 2L for all patients who have received daratumumab and lenalidomide in the front-line setting (i.e., those SCT-ineligible receiving DRd at 1L and those SCT-eligible receiving DVTd and LEN maintenance at 1L), or only those who are transplant-ineligible who have received daratumumab and lenalidomide in the front-line setting (i.e., only those receiving DRd in the current pathway). The EAG notes that the efficacy and safety data provided in the BOSTON trial are from a mixed population of SCT eligible and SCT ineligible patients.

Company response: The choice of treatment in myeloma is based on the clonal nature of the disease. During treatment, malignant plasma cell clones acquire cytogenetic alterations or mutations that can become resistant to treatment. It is therefore important when choosing regimens to utilise multiple modes of action in a treatment regimen, but also to utilise alternative modes of actions in subsequent lines of therapy for patients progressing on treatment. However, stem cell transplantation, as a treatment modality, is utilised in order to be able to rescue patients following

myeloablative chemotherapy, with the aim of clearing the bone marrow of the disease. Once a patient relapses, whether with or without a prior SCT, the choice of treatment is completely driven by the agents and response received in the first line and maintenance setting and is not related to the SCT 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, based on clinical feedback received during the development of the submission. 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. The positioning of SVd is not related in any way to the prior use of stem cell transplantation, but purely on the modes of actions of treatments previously received as clinical feedback has been absolutely clear that SVd would only be used in patients not suitable for lenalidomide and daratumumab.

A33. Please provide:

A) The baseline age for patients in BOSTON by prior SCT, for the ITT population and 2L and 3L subgroups;
B) The Company's best estimate of the average age of patients at 2L and 3L by SCT status in clinical practice in England.

Company response: As described in A32, prior SCT status of trial participants is not considered to be relevant since the company positioning of SVd is based on prior treatment with daratumumab and lenalidomide, and not SCT. Therefore, given our response to A32 we do not believe this question to be relevant. If we have

misinterpreted the rationale for this question, please could the EAG provide more clarification.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model so that these can be combined. Furthermore, if the company chooses to update its base-case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base-case assumptions are provided with the response along with a log of changes made to the company base-case.

B24. Priority. The EAG thanks the company for providing clarification on the positioning of SVd in the second-line position. The EAG notes that the company's justification for not including Vd as a relevant comparator is due to it not being a "NICE-reimbursed" treatment combination. However, as part of the guidance review of TA129, it is noted in the Guidance Executive document that, "*NICE is aware of the widespread use of off label combination therapy with dexamethasone. Therefore, the impact of any potential NICE recommendation for combination therapy could only be limited, and therefore NICE guidance could not be considered to add value*".

Furthermore, as acknowledged by the Company, the introduction of DRd at first-line is likely to change the second-line treatment pathway but the EAG's experts consider that it might result in an increase in the usage of Vd at second-line as patients are likely to have been exposed or refractory to regimens containing daratumumab and lenalidomide. Therefore, the EAG considers that Vd is a relevant comparator and anticipates that the appraisal committee will want to see cost-effectiveness analysis for SVd versus Vd for the 2L subgroup.

The EAG is aware that the model has functionality to produce cost-effectiveness estimates. However, the EAG recommends the Company presents the cost-effectiveness results for the comparison with SVd, including fully incremental

analysis of SVd, Vd and Kd for the 2L population, with an appropriate discussion of these findings.

Company response: The recent recommendation of DRd for treatment of transplant ineligible patients has provided MM patients in England and Wales access to guidelines-recommended treatment and provides a significant step forward for these patients. The use of DRd at 1L will still allow the use of Kd at 2L since the use of this regimen permits a switch in the mode of action. Kd was included in the NICE-issued final scope for this appraisal, and the company believe that this remains the most relevant comparator, given the absence of other appropriate treatments. In relation to the comment from the EAG highlighting the publication of the Guidance Executive document for TA129 (published 2012), Kd has been reimbursed at 2L (TA657; 2020) since this time, again highlighting the relevance of this comparator. Vd was not included in the final scope by NICE, is not recommended by NICE, and based on clinical feedback is not used in established routine clinical practice in the 2L setting. By recommending a comparison to this regimen, which is now considered obsolete as a doublet therapy in 2L treatment of RRMM, it only highlights the huge unmet need that remains, and the need for new agents which allow a switch in the mode of action.

Although we do not believe it is appropriate to include Vd as a comparator, given that the EAG has requested the company run this analysis, clinical advice was to use 2L lenalidomide-refractory data from the BOSTON trial as patients treated with DRd, would be consider lenalidomide-refractory. The lenalidomide-refractory data for 2l+ is presented in the appendices of the company submission.

The PFS and OS curves for 2L lenalidomide-refractory patients are presented in Figure 10 and 11, respectively. These data were not used in the original modelling due to the lack of 2L lenalidomide-refractory data for comparators, but as Vd data are available from the BOSTON study it was considered to be appropriate in this setting.

Figure 10 – [redacted]

Figure 11 [redacted]

Results presented below provide cost-effectiveness estimates for SVd *vs.* Vd corresponding to the 2L lenalidomide-refractory subgroup of BOSTON. As estimates for this population are not available from the NMA, fully incremental results against comparators beyond Vd are not considered.

For this analysis, independently fitted curves for OS, PFS and ToT have been applied, with a gamma distribution applied to each based on consistency with landmark estimates applied in the base analysis. It should be noted that clinical validation of appropriate curve selection specific to a lenalidomide-refractory population has not been explored.

All other settings applied in the exploratory analysis below are consistent with the revised company base case approach as outlined in the company response dated 2nd October 2023.

Table 10 Exploratory cost-effectiveness results *versus* Vd, 2L lenalidomide-refractory patients

Comparator	Costs (£)	LYs	QALYs
SVd	£106,222	3.62	2.40
Vd	£77,873	2.20	1.48
Incremental (SVd *vs.* Vd)	£28,349	1.41	0.92
ICER (£ / QALY)	£30,769		
NHB at £30,000 (QALYs)	-0.02		

B25. Priority. In response to B14, the Company acknowledges the challenges with modelling subsequent treatments but does not supply an alternative approach to overcome issues with the base case approach highlighted by the EAG. The EAG requests the Company to explore a scenario 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.

Company response: Given the time frame in which the company were required to respond, market share data were sourced from existing market research for the 3L and 4L. For the 5L setting, clinical feedback was that chemotherapy would be used in the setting and market share is based on that proposed by the EAG for ID6193. Table 11 summarises confidential estimates of market share from this internal market research. As part of the company's earlier responses, at the request of the EAG, IsaPd (estimated based on the company's research to account for [redacted] of 4L treatments) has been removed due to being in the CDF rather than routine commissioning currently.

Table 11 [redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

*Cyclophosphamide plus dexamethasone assumed

As an exploratory analysis, market share estimates have been combined with assumptions from Yong *et al.* 2016 around attrition rates and the mean duration of each line of therapy (Table 12) to derive a treatment-agnostic weekly cost estimate for subsequent therapies (Figure 10 and Table 13).[6]

Table 12 Relative proportion of diagnosed patients reaching later lines of therapy and mean duration of subsequent therapies based on published estimates

	3L	*Interval*	4L	*Interval*	5L
Estimated proportion of diagnosed patients reaching line of therapy (Yong *et al.* 2016)[5]					
Proportion of patients (%)	38%		*15%*		1%
Estimated duration of treatment / interval by line of therapy (Yong *et al.* 2016)[5]					
Mean duration (months)	8	7	6	3	4
Median duration (months)	6	3	5	1	4

Figure 10 [redacted]

[redacted]

Table 13: Weighting estimates used to inform mean weekly treatment cost assumptions

	IxaRd	PanoVd	Pd	Chemotherapy
Relative weighting of subsequent therapies following 2L	[redacted]	[redacted]	[redacted]	[redacted]
Relative weighting of subsequent therapies following 3L	[redacted]	[redacted]	[redacted]	[redacted]

Where chemotherapy is received, this is assumed to be a regimen of cyclophosphamide plus dexamethasone (Table 14).

Table 14 Cost and dosage assumptions for cyclophosphamide plus dexamethasone applied to scenario analysis

Treatment	Cost per pack (£)	Dose per administration (mg)	Administrations per week	Source	Acquisition cost per week (£)
Cyclophosphamide 100 x 50mg	£52.65	200	7	emit 2022[6]	£14.74
Dexamethasone 50 x 2mg	£2.46	40	1	emit 2022[6]	£0.98
Total					£15.73

Results based on this exploratory analysis are shown in Table 15. As these results demonstrate, the limitation of this simplified approach is that OS gains are assumed to incur a cost distribution that is in keeping with current market share estimates, rather than increasing survival time spent in receipt of less costly later-line therapies or best supportive care. This is a particular issue in the 3L setting with the costs of pomalidomide being maintained and this simplified approach does not represent a realistic assessment of subsequent treatment costs. It should also be noted that the cost of pomalidomide was calculated at list price, which is not representative of the cost of pomalidomide to the NHS, and that treatment-free intervals have not been factored in to cost estimates. Concerns with the plausibility of this approach can be seen further when comparing the 3L and 2L scenario results for SVd shown in Table 15, whereby the total subsequent therapy cost for 3L is substantially larger than in the 2L analysis due to the increased influence of Pd on mean cost estimates. The results have therefore been included to demonstrate that this alternative scenario does not provide plausible subsequent cost estimates and the company does not consider this to be an appropriate alternative to the base case submission.

Table 15: Scenario results exploring application of a universal weekly treatment cost applied across post-progression survival

	Subsequent therapy costs	Total costs	ICER (SVd *vs.* comparator)	NHB at £30,000 (SVd *vs.* comparator)
2L analysis (company approach)				
SVd	£55,508	£137,162		
Kd	£55,332	£319,769	£605,630	5.79
2L analysis (scenario)				
SVd	£86,948	£168,602		

Kd	£63,461	£327,898	£528,318	5.01
3L analysis (company approach)				
SVd	£56,075	£133,706		
IxaRd	£54,992	£230,087	-£867,308	3.32
PanoVd	£56,134	£138,207	-£13,631	0.48
3L analysis (scenario)				
SVd	£134,350	£211,980		
IxaRd	£67,471	£242,566	-£275,235	1.13
PanoVd	£71,402	£153,476	£177,168	-1.62

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Myeloma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Myeloma UK is the only organisation in the UK dealing exclusively with myeloma and its associated conditions. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We are not a membership organisation and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	We have not received any funding from the manufacturer of the technology (Menarini-Stemline) in the last 12 months. In 2022, 5.7% of Myeloma UK's income came from pharmaceutical companies. The table below shows the 2022 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work, and gifts, honoraria, or sponsorship.

Company	Core grant	Research / Project	Donation	Honoraria	Fundraising Events	Total (£)
AbbVie Ltd			10,000			**10,000**
Amgen Ltd		25,000			10,000	**35,000**
Amgen (Europe) GmbH					8,000	**8,000**
The Binding Site Ltd	20,000					**20,000**
Celgene Ltd					15,000	**15,000**
Bristol Myers Squibb - Celgene	20,000					**20,000**
GSK		20,444		1,386	12,000	**33,830**
ITECHO		6,600				**6,600**
Janssen-Cilag Ltd				180		**180**
Janssen Pharmaceutica JW		25,000				**25,000**
Pfizer		19,259				**19,259**
Sanofi					48,980	**48,980**
Takeda UK Limited		40,000			17,000	**57,000**

	<table><tr><td></td><td>40,000</td><td>136,303</td><td>10,000</td><td>1,566</td><td>110,980</td><td>298,849</td></tr></table>
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission came from the myeloma patients and carers we engage with through our research and services programmes, including: • Structured interviews in July and August 2023 with relapsed/refractory myeloma patients. These interviews provide valuable experience and insight data from patients who are multiply relapsed and view this technology as a potential next step in their treatment pathway. • A Myeloma UK-funded, multi-criteria decision analysis study of 560 myeloma patients run by the European Medicines Agency (EMA) and the University of Groningen. The study explored patient preferences for different benefit and risk outcomes in myeloma treatment. • Analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays, posts to our online Discussion Forum and earlier appraisals.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. There is no cure, but treatment can halt its progress and improve the quality of life. The complications of myeloma can be significant, debilitating, and painful; and include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system that can lead to increased infections. ***"Before I was diagnosed, I was quite active. I was working abroad, teaching at one of the universities in Holland. I had to stop all that because the treatment was far too much. I was immediately put on chemo, and I was quite poorly in hospital. I had lots and lots of infections, that seems to be my thing that I get infections. I did try going back and doing a couple of four months contracts, but I just knew it wasn't right for me. It was just too much, and it wasn't fair on my employer and on the students and stuff because I wasn't able to do my job as well as I wanted to."*** In a survey of 1324 patients and carers, 72% of respondents reported that their myeloma had a high or moderate impact on their quality of life.[1] ***"Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of the simplest tasks become impossible to undertake such as going to the bathroom or making a cup of tea… things we take for granted."*** It is an incurable, relapsing and remitting cancer. The aim of treatment is to control the myeloma, slowing its progression, and reducing symptom burden. The constant possibility of relapse has a huge psychological impact on patients. ***"Emotionally, the most difficult point was when I went into remission, which sounds crazy, but I've since spoken to quite a few other people, and it is a really tough time. When you go into remission because. You think? Yay, I'm in remission. I'm fine. And everybody says. Oh great, you're in remission. You're well again, and actually you're not and physically your body is in a good place, but mentally you're in a whole different place."*** ***"There's this sort of the immediate effect in your day-to-day life in terms of side effects and things like that. But then also there is the fact that, you know, you have a more limited future. The fatigue the hardest to live with in the short term and its frustration of all the things that are not going to happen. The things I was looking forward to in my life. They are the two hardest things."*** The individual and heterogeneous nature of myeloma means that some patients may respond to or tolerate treatment well, and others may not. How well patient responds to or tolerates a drug impacts future treatment options. In general, a drug

	that did not work or caused serious side effects would not be offered again, even when administered in a different combination. "***Velcade gave me heart failure, that put me in hospital, I only had two or three sub cuts and was really unwell. They took me in, couldn't work out what it was so they thought, let's do a heart scan and saw that I'd had heart failure. My heart's recovered, but they swapped from VCD to CTD. So, I had CTD really as my first line although it was my second line because I'd had the Velcade. They've said that I should avoid having a proteosome inhibitors in future."*** Relapsed patients, the population covered in this appraisal, often experience a more significant disease burden due to the progressive nature of the disease and the cumulative effects of treatment, which can result in reduced quality of life.[2] Later lines of treatment are associated with worse outcomes; remission times decrease, and side effects increase. [3]Treatments often become less effective and harder to tolerate with every relapse. Over time, myeloma evolves, becoming more resistant to treatment, and patients get older, frailer and have more comorbidities. The best, most effective option should be given as early as possible. At every, relapse patients are faced with the uncertainty of whether the new treatment will be effective and tolerable. Patients are aware that every time they must change treatment their options and life expectancy decreases. Treatment side effects and frequent hospital visits have a social and practical impact on patient's lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members also affect patients' sense of control. Living with myeloma is often extremely physically and emotionally challenging for carers, and family members. They are affected in many ways because of both caring and dealing with the day-to-day implications of myeloma. Many in this situation mention changes in their social life, relationships, income, and wider family dynamics. ***"Fortunately, my husband's very supportive and he was driving me to and from hospital appointments. It just takes over because you have so many hospital appointments and spells in hospital that my husband put his life on hold as well."***

[1] Myeloma UK (2022) A Life Worth Living The impact of a delayed diagnosis on myeloma patients' quality of life. Available at https://www.myeloma.org.uk/library/a-life-worth-living/ (Accessed September 2023)

[2] Ramsenthaler, C., Osbourne, T.R. et al (2016) The impact of disease related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study. BMC cancer 16:1 P.427

[3]Yong, K., et. al. (2016). Multiple myeloma: patient outcomes in real-world practice. British journal of haematology, 175(2), 252–264.

	"We have had to jointly think about her future. I mean, she's older than me and I've always assumed that we would die much the same time, or she would die before me. And so, you know, my pension will be halved when I die. So, there's all sorts of things to think about." ***"I think it is harder for family. At the beginning anyway. It is happening to you, you have a treatment plan, milestones to reach. Induction, stem cell transplant etc. But they don't. The are watching you go through everything – infections, losing hair, weight- that's difficult."*** A Myeloma UK study into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social, and practical impact: - 94% of carers are emotionally impacted and found the uncertainty of myeloma a major factor - 25% of those in work had been unable to work or had to retire early to care for the person with myeloma - 84% always put the needs of their relative or friend with myeloma before their own - Only 42% of carers were not given enough information at diagnosis about how myeloma may affect them[4] ***"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo."*** ***"Sometimes it's tiring. Sometimes I feel sad. Sometimes I think about all the hours I have spent at the hospital and how I might have used that time otherwise. But it's all the price of love".***

[4] Myeloma UK (2012) A Life in Limbo: A Myeloma UK research report on the experience of myeloma carers in the UK. Available at https://www.myeloma.org.uk/documents/a-life-in-limbo/ (Accessed September 2023

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers feel fortunate that although myeloma is incurable, it is treatable in most cases. However, patients and carers, especially those who have already experienced relapse, are acutely aware that the range of treatment options and the chance of deep responses with long remissions decreases every time they relapse. They know about treatment resistance and that an effective treatment will stop working at some point. They also know that the range of treatment options available later in the pathway is markedly narrower than those available at first line. As combination treatments with better efficacy are introduced earlier into the treatment pathway it is also increasingly common for patients to be refractory to key backbone treatments much earlier in the course of their myeloma. This means that even at earlier lines in the pathway, while there may be approved treatments they will not be effective in some patients who have become refractory to certain drugs with a particular mechanism of action. Patients also know that every myeloma patient is different. They know every patient's experience of a treatment is different and sometimes unpredictable. They know that the level of effectiveness or side effects can differ, either from direct experience of treatments not working or causing unbearable side effects or through discussions with peers. Understandably, this can cause a great deal of worry for myeloma patients and their families. There is uncertainty about the future, whether the next treatment will work and if it will negatively affect their quality of life and the fear of reaching the 'end' of treatment options for their cancer. ***"You don't know how you're going to react to particular drugs until you've had. I guess it's a bit of a lottery."*** All anti-myeloma treatments have side effects which affect quality of life. The most impactful side effects are the ones which limit daily activities or reduce independence. These include fatigue, peripheral neuropathy, and gastrointestinal disturbances. ***For me fatigue and peripheral neuropathy had the biggest impact on my daily life.*** The mood swings, irritability and mania caused by dexamethasone is also very challenging for patients and their families. ***"On Mondays when I took my dex, I'd be, really buzzing and bouncing off the walls and the rest of the week could be like, really dozy and falling asleep about 7:00 o'clock in the evening."***

	Treatments which can be taken at home are generally seen as an advantage, especially for patients who live further away from the hospital. ***"My preference would be tablets and I'd be happy to take tablets. We're 26 miles from the nearest hospital and when you get to this age, getting there, getting parked and getting into the hospital is an absolute pain, so I wouldn't be keen on having to go, say every week for some sort of treatment."***
8. Is there an unmet need for patients with this condition?	There is a clear need for innovative anti-myeloma treatments. Myeloma is heterogenous and a range of treatments are needed throughout the treatment pathway to ensure there are effective treatments available to all patients when they need it. Relapse is caused by resistance to existing treatment. Myeloma is still incurable, and even after successful treatment, almost all patients eventually become resistant to existing treatment. Treatments that have worked well at earlier lines are no longer effective. Patients are all too familiar with this scenario. Their disease is resistant to existing treatments, and innovative treatments are needed to control their myeloma. New drugs are urgently needed to overcome treatment resistance. It is also important to note that more than a quarter of myeloma patients have high-risk disease at diagnosis. They either don't respond to existing treatments or relapse shortly after successful treatment and as a result move through the myeloma treatment pathway more quickly than standard risk patients. Treatments with new mechanisms of action are often a lifeline for high-risk patients, delivering significant remission times when other more established classes of anti-myeloma drugs have not.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We know from our research that patients value treatments which put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy a normal day-to-day life. [5] In the large-scale BOSTON trial, selinexor combined with bortezomib and dexamethasone (SVd) was compared with bortezomib and dexamethasone (Vd). This trial included 402 patients. Half were given SVd weekly, and half were given Vd twice weekly. The patients had relapsed and refractory myeloma and had all had 1–3 previous treatment lines. The average time before the myeloma became active again was significantly longer for the SVd group (14 months) than in the Vd group (9.5 months). The overall response rate was also significantly higher in the SVd group (76%) than in the Vd group (62%).[6] The proportion of patients with a very good partial response or better was 44·6% in the selinexor, bortezomib, and dexamethasone group and 32·4% in the bortezomib and dexamethasone group. ***"For people at high risk, the average progression free was nearly 50% more so that's what you that's worth having. 12/13 months as opposed to 9. However, that's an average. It could well turnout to give you another year or two."*** ***"It does seem to increase your period of remission above all remission. A few more months in great discomfort doesn't appeal very much, but if it's actually going to give you another year or two in remission. That's obviously very attractive."*** The patients we interviewed liked that selinexor was a new type of drug with a unique way of killing myeloma cells. They were also happy to see that this treatment combination was being approved for multiply relapsed, refractory patients, giving them hope that something would be available for them when their current treatment stopped working. ***"I thought it was really interesting because it is a totally different type of a drug it has completely different approach and I think that's always good because that's how we get to a cure by finding lots of different ways in."*** ***"It sounds pretty exciting to have a new treatment on the market."*** Some of the patients who had already self-administered bortezomib thought it would an advantage if the bortezomib injections could be taken at home along with the tablets. Taking the treatment at home would reduce the number of hospital visits. at home. However, this might not be suitable for all patients. The absence of lenalidomide in this triplet combination is a significant patient benefit. There is an increase in lenalidomide refractory patients at second line and beyond following the approval of lenalidomide maintenance and its increased use earlier in the pathway.

	The triplet combination is also an advantage. Combination treatments are typically more effective than monotherapies. Myeloma has genetically distinct clones, and the variation in treatment susceptibility between clones is one of the main causes of relapse and treatment resistance in myeloma. Therefore, it is best practice to use combination treatments containing multiple drugs with different mechanisms of action to treat myeloma with triplet and quadruplet combinations are now standard therapy in myeloma.

[5] Postmus, D., et. al. (2018). Individual Trade-Offs Between Possible Benefits and Risks of Cancer Treatments: Results from a Stated Preference Study with Patients with Multiple Myeloma. The oncologist, 23(1), 44–51.

[6] Grosicki, S.,et. all. (2020). Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. The Lancet, 396(10262), 1563-1573

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	There are three main factors that patients typically consider when thinking about treatments – efficacy, side effect profile and ease of administration. The order of priority varies based on personal preference.[7] The patients we interviewed felt that the treatment administration could be a disadvantage if patients needed go into hospital for regular bortezomib injections. This could mean weekly hospital visits for the duration of treatment. The treatment is given until disease progression and therefore could result in weekly visits for more than a year. Home administration of bortezomib is possible and is available at some hospitals but not all. ***"It would be better is it was all tablets that could be taken at home, not only for the patient not having to go to the hospital, every hospital as parking issues, and time and money getting there, catching public transport is a nightmare. It would be easier for patients and easier for the staff. They're not having to do sub cut injections."*** As with all anti-myeloma treatments, side effects are seen as a big disadvantage to treatment. Patients value treatments with few, mild side effects which stop when treatment ends. However, in practice patients will accept varying levels of toxicity in a treatment depending on the stage of their myeloma and whether it delivers a good survival benefit. Most of the patients we interviewed felt that the side effects associated with selinexor were like those they have experienced whilst taking other treatments. The main side effect patients would worry about was the risk of cataracts. Patients felt this was something that couldn't be easily reversed by reducing dose, taking supportive treatment, or stopping treatment. They were also concerned about the impact cataracts would have on their daily life and independence. ***"I would be concerned about the risk of cataracts. It's your eyesight, your independence. The others feel like standard."*** The use of dexamethasone in the combination is considered a disadvantage by several patients. Dexamethasone is commonly used in myeloma treatment combinations and is known to cause insomnia and mood changes. This has a huge impact on patients and their families. **"The side effects are probably the hardest part. I know they affect people a different wat. I mean the dexamethasone was something I find difficult to deal with all the way along and, I don't look forward to it again if I have to have that."** **"Every time I came off dex, I felt rotten. And so, unless there was a good reason for it, I'm happy to avoid dex."**

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who are refractory to proteosome inhibitors and immunomodulatory drugs. Data has shown that the life expectancy for multiply relapsed myeloma patients who are refractory to a proteasome inhibitor, an immunomodulatory drug and a anti-CD38 monoclonal antibody is typically less than 12 months.[8] Patients who are refractory to both a proteosome inhibitor and an immunomodulatory drug have median life expectancy of 8-9 months, and patients who are refractory to three or four of the common proteosome inhibitors and immunomodulatory drugs have a median life expectancy of only 3-5 months.[9]

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

[7] Fifer, S, et. al. (2020) Myeloma Patient Value Mapping: A Discrete Choice Experiment on Myeloma Treatment Preferences in the UK, Patient Preference and Adherence, 14, 1283-1293
[8] Lee, H. C.,et.al.. (2023). Treatment Patterns, Survival, Quality of Life, and Healthcare Resource Use Among Patients With Triple-Class Refractory Multiple Myeloma in US Clinical Practice: Findings From the Connect MM Disease Registry. Clinical lymphoma, myeloma & leukemia, 23(2), 112–122. https://doi.org/10.1016/j.clml.2022.11.008
[9] Gooding S, Lau IJ, Sjeikh M et al, Double Relapsed and/or Refractory Multiple Myeloma: Clinical Outcomes and Real World Healthcare Costs. PLoS ONE. 2015. 10 (9): e0136207)

Other issues

13. Are there any other issues that you would like the committee to consider?	No
14. Where would selinexor in combination with bortezomib and dexamethasone be used in the treatment pathway for relapsed or refractory multiple myeloma?	As with all other treatments, selinexor should be available to all patients who can benefit from it. There needs to be flexibility in the pathway to ensure patients can access the most effective option when they need it not when they reach the right line. Later lines of treatment are associated with reduced response rate, higher symptom burden and increased side effects. As a result, the number of patients receiving treatment decreases with every line of treatment. A real-world analysis of myeloma patient outcomes found that 95% of patients received first-line treatment, but only 61%, 38%, and 15% received second, third and fourth-line treatments, respectively. Therefore, patients should be given the most effective treatment at the earliest opportunity.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There is an unmet need for this technology as it will give patients a greater choice of options. The individual and heterogeneous nature of myeloma means that some patients may respond to or tolerate treatment well, and others may not. How well patient responds to or tolerates a drug impacts future treatment options. In general, a drug that did not work or caused serious side effects would not be offered again, even when administered in a different combination. • There is currently no treatment with this mechanism of action licensed for routine commissioning at this point in the treatment pathway. • Patients should be given the most effective treatment as early as possible in the treatment pathway, giving them the best opportunity to achieve deep remission and maintain a good quality of life. For this, patients need combination treatments with as many different mechanisms of action as possible. • Clinical trial data and insights from our patient interviews confirm that selinexor can deliver benefits which are most important to patients, improved OS and PFS with manageable side effects.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	Dr Neil Rabin
2. Name of organisation	UK Myeloma Society (Formerly UK Myeloma Forum)
3. Job title or position	Chair and Executive Member of the UK Myeloma Society
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? **Yes** or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	UK Myeloma Society (UKMS) is the only organisation that represents Physicians, Nursing staff, Pharmacists and Healthcare professional who are directly involved with providing clinical care or research for patients with myeloma. Membership is free by application and members of the executive are elected by the membership. It aims to improve the care of myeloma patients through the development and promotion of trials and provides education about myeloma to healthcare professionals.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	UKMS has received an unrestricted educational grant from Menarini Stemline of £14,000. UKMF has also received unrestricted educational grants from other pharmaceutical companies.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Myeloma is currently incurable. Most people diagnosed with myeloma will die as a result of complications of the disease. Symptoms and signs associated with active myeloma include bone pain, fractures secondary to bone deposits, fatigue, anaemia, recurrent infections, renal failure, high calcium levels and occasionally spinal cord compression. Treatment is primarily aimed at reducing these symptoms by controlling the disease. There is a direct association between how well the myeloma is controlled and the improvement in quality of life. Patients are clinically better if in complete response rather than partial response. Additional aims of treatment are to control the disease (and thereby symptoms) for as long as possible (i.e. lengthen the progression free survival / duration of response), lengthen life associated with the disease (i.e. increase overall survival) and prevent significant morbidity associated with progression of the disease.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	There are internationally agreed criteria for assessing response (International Myeloma Working Group Rajkumar et al. Blood 2011;117:4691-4695) These are based on the proportional reduction of serum paraprotein / serum free light chains (serological markers of myeloma), urine monoclonal protein and the bone marrow proportion of myeloma plasma cells. Generally, a Partial Response (PR) or better is considered clinically significant. Increasingly with more efficacious treatments the aim of the therapy is to achieve Complete Response (CR) or Very Good Partial Response (VGPR) for as many patients as possible. It is apparent in many studies that the greater the depth of response the longer the duration of the response (CR>VGPR>PR). Patients who achieve a CR have a longer survival than those who do not. Achieving minimal residual disease (MRD) is associated with an even longer duration of response and overall survival.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Myeloma is incurable with current therapy for the majority of patients. Therapy should be aimed at achieving the highest possible response rates and the deepest possible responses leading to the longest / most durable responses which thereby reduces the morbidity and mortality associated with the myeloma. Currently available second line and subsequent therapies are correctly listed in the scope. Although the majority of patients do respond to these therapies, there is a significant group that do not respond. Importantly the duration of response is often limited to 1-2 years, before a change in therapy is required. Gaining a good response with maximal disease control that is durable is imperative to limit complications related to myeloma and improve quality of life. It will also allow patients to be well enough to receive further treatment at relapse. This is often not possible with the current therapies for this elderly and often frail group of patients. There is therefore a clear unmet need to provide better treatments to induce a longer and more durable period of remission and limit, or prevent, myeloma associated complications.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	This scope is very broad and correctly identifies treatments that are available for patients who have received between 1 and 3 prior therapies. Outside clinical trials, transplant eligible patients receive Daratumumab VTD/ASCT and Lenalidomide maintenance, whilst non transplant-eligible patients receive Lenalidomide or Bortezomib based regimens. Daratumumab Lenalidomide dexamethasone has just been approved by NICE for non-transplant eligible patients. In future most patients are likely to be Lenalidomide and Daratumumab exposed/refractory following initial treatment. 2nd line includes: • Carfilzomib Dex, Bortezomib Dex (assuming PI sensitive without any toxicity issues) • Daratumumab Bortezomib Dex (assuming PI sensitive and Daratumumab naïve/sensitive) • Carfilzomib Lenalidomide Dex or Lenalidomide Dex (assuming the patient is not refractory to Lenalidomide). 3rd line includes: • Panobinostat with Bortezomib Dex (assuming PI sensitive without any toxicity issues) • Ixazomib Lenalidomide Dex (assuming the patient is not refractory to Lenalidomide). 4th line: • As listed in the scope
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are several options available to clinicians. Treatments offered to patients would be based on NICE approved treatments; toxicities from prior therapies and prior response to therapies (see 9.)
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	There are several options available to clinicians. Treatments offered to patients would be based on NICE approved treatments; toxicities from prior therapies and prior response to therapies (see 9.)

experience is from outside England.)	
9c. What impact would the technology have on the current pathway of care?	Selinexor is an oral therapy with manageable toxicities. It would easily fit into the current treatment algorithm and delivered in combination with an established treatment (bortezomib and dexamethasone).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The addition of an oral therapy (Selinexor) to an established treatment (bortezomib) would easily fit into the current treatment algorithm. Clinicians have a lot of experience in delivering bortezomib with either an oral (Panobinostat) or subcut (Daratumumab) medication.
10a. How does healthcare resource use differ between the technology and current care?	Patients already receive Bortezomib on a weekly basis to receive a subcutaneous injection. The healthcare resource for these patients would be similar, except patients would also receive an oral drug (Selinexor) to take at home with some additional supportive care medication to manage expected side effects.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. Guidance would need to be provided on how to manage expected side effects.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Based on the BOSTON trial, the addition of Selinexor to bortezomib and dexamethasone lead to objective treatment responses in patients with relapsed myeloma.
11a. Do you expect the technology to increase	Yes. Based on the BOSTON trial, the addition of Selinexor to bortezomib and dexamethasone lead to objective treatment responses in patients with relapsed myeloma.

length of life more than current care?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Based on the BOSTON trial, the addition of Selinexor to bortezomib and dexamethasone lead to objective treatment responses in patients with relapsed myeloma. This is a well-tolerated regimen with a manageable side effect profile.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Selinexor is well tolerated with potential side effects including loss of appetite, nausea and weight loss. There would need to be guidance of on how to manage these side effects to limit the impact on quality of life. There are no other concerning side effects.
14. Will any rules (informal or formal) be used to start or stop treatment with the	Response is based on clinical response to treatment after between 2 and 4 cycles of treatment.

technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. Quality of life is likely to be improved due to reduced myeloma associated complications.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Selinexor, a selective inhibitor of nuclear export compound that blocks exportin 1 (XPO1) and forces nuclear accumulation and activation of tumour suppressor proteins, inhibits nuclear factor κB, and reduces oncoprotein messenger RNA translation, is a potential novel treatment for myeloma that is refractory to current therapeutic options.
16a. Is the technology a 'step-change' in the management of the condition?	Yes because it improves depth of response which correlates with improved survival. This will lead to reduced myeloma associated complications.
16b. Does the use of the technology address any particular unmet need of the patient population?	Myeloma remains an incurable cancer. There is an unmet need to provide better treatments to induce a longer and more durable period of remission and limit, or prevent, myeloma associated complications.
17. How do any side effects or adverse effects of the technology affect the management of the	Selinexor is well tolerated with potential side effects including loss of appetite, nausea and weight loss. There would need to be guidance of on how to manage these side effects to limit the impact on quality of life. There are no other concerning side effects.

condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The BOSTON trial reflected UK based practice when it was devised. Treatment options have changed over time, as mentioned in the scope document. These include alternative proteosome inhibitors (Carfilzomib), addition of immunomodulatory drugs (Carfilzomib Lenalidomide Dexamethasone) or anti-CD38 monoclonal antibodies (Daratumumab with Bortezomib and Dexamethasone).
18a. If not, how could the results be extrapolated to the UK setting?	See comment above.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Depth of response. sCR, CR were measured in this trial. Survival has been assessed using PFS and OS. Toxicity was assessed and no concern has been highlighted.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	sCR, CR and MRD were measured in this trial as surrogates for long term survival. There is a wealth of data to support depth of response correlating with long term survival.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that	No

might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA171, TA380, TA427, TA586, TA657, TA658, TA695, TA783, TA870 and TA897]?	No
21. How do data on real-world experience compare with the trial data?	Outcomes are as expected. There is limited real world data with this combination.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No

Topic-specific questions

23. Where would selinexor in combination with bortezomib and dexamethasone be used in the treatment pathway for relapsed or refractory multiple myeloma?	Selinexor with Bortezomib Dex would be used in those with relapsed myeloma where treatment with a proteosome inhibitor is appropriate. This would be most suitable at 2nd or 3rd line.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Unmet need • Oral therapy • Novel mechanism of action • Expected side effects that are manageable in most patients •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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BMJ TAG

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

STA Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report.
Ben Farrar	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and drafted the summary, background and clinical results sections.
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; and drafted the economic sections

All authors read and commented on draft versions of the EAG 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	Proteosome 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	[redacted]	[redacted]	**605,630 (SW)**
EAG preferred treatment effectiveness assumptions	[redacted]	[redacted]	Dominant
OS for comparators equal to Vd	[redacted]	[redacted]	10,017,804 (SW)
Utility values by line of therapy and progression status	[redacted]	[redacted]	10,036,592 (SW)
EAG preferred subsequent treatments	[redacted]	[redacted]	8,601,271 (SW)
Administration cost for oral chemotherapy	[redacted]	[redacted]	8,400,870 (SW)
EAG preferred – AE costs*	[redacted]	[redacted]	6,612,455 (SW)
EAG clinical expert resource use assumptions*	[redacted]	[redacted]	6,612,455 (SW)
End of life care cost from the PSSRU*	[redacted]	[redacted]	6,612,455 (SW)
EAG's preferred deterministic base case - combination of all scenarios	[redacted]	[redacted]	**6,612,455 (SW)**
EAG's preferred probabilistic base case - combination of all scenarios	[redacted]	[redacted]	**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 (£)	[redacted]	431,480	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]

	PSA ICER (£/QALY)	-	-	8,694,817 (SW)
	Deterministic ICER (£/QALY)	-	-	6,612,455 (SW)
1	OS for comparators equal to SVd			
	PSA total costs (£)	[redacted]	490,202	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	475,592	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]
	PSA ICER (£/QALY)	-	-	Dominant
	Deterministic ICER (£/QALY)	-	-	Dominant
3	Use of utility values from Hatswell et al.[1]			
	PSA total costs (£)	[redacted]	432,400	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]
	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	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]	**Dominant**
EAG preferred treatment effectiveness assumptions	[redacted]	[redacted]	171,605 (SW)	[redacted]	[redacted]	6,024
OS for comparators equal to Vd	[redacted]	[redacted]	2,577,373 (SW)	[redacted]	[redacted]	Dominated
Utility values by line of therapy and progression status	[redacted]	[redacted]	2,583,364 (SW)	[redacted]	[redacted]	Dominated
EAG preferred subsequent treatments	[redacted]	[redacted]	2,324,202 (SW)	[redacted]	[redacted]	Dominated
Administration cost for oral chemotherapy	[redacted]	[redacted]	2,569,239 (SW)	[redacted]	[redacted]	Dominated

EAG preferred – AE costs*	[redacted]	[redacted]	2,445,681 (SW)	[redacted]	[redacted]	Dominated
EAG clinical expert resource use assumptions*	[redacted]	[redacted]	2,445,681 (SW)	[redacted]	[redacted]	Dominated
End of life care cost from the PSSRU*	[redacted]	[redacted]	2,445,681 (SW)	[redacted]	[redacted]	Dominated
EAG's preferred deterministic base case - combination of all scenarios	[redacted]	[redacted]	**2,445,681 (SW)**	[redacted]	[redacted]	**Dominated**
EAG's preferred probabilistic base case - combination of all scenarios	[redacted]	[redacted]	**2,457,260 (SW)**	[redacted]	[redacted]	**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 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 (£)	[redacted]	272,739	154,929	[redacted]	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	315,972	177,410	[redacted]	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	364,847	156,864	[redacted]	[redacted]

	PSA QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	275,666	155,321	[redacted]	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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.

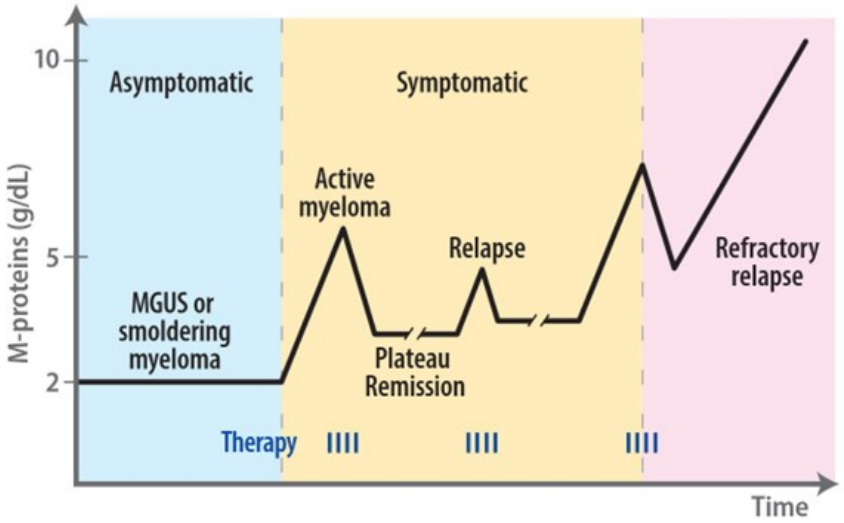
2.2 Background

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 immunoglobin 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.

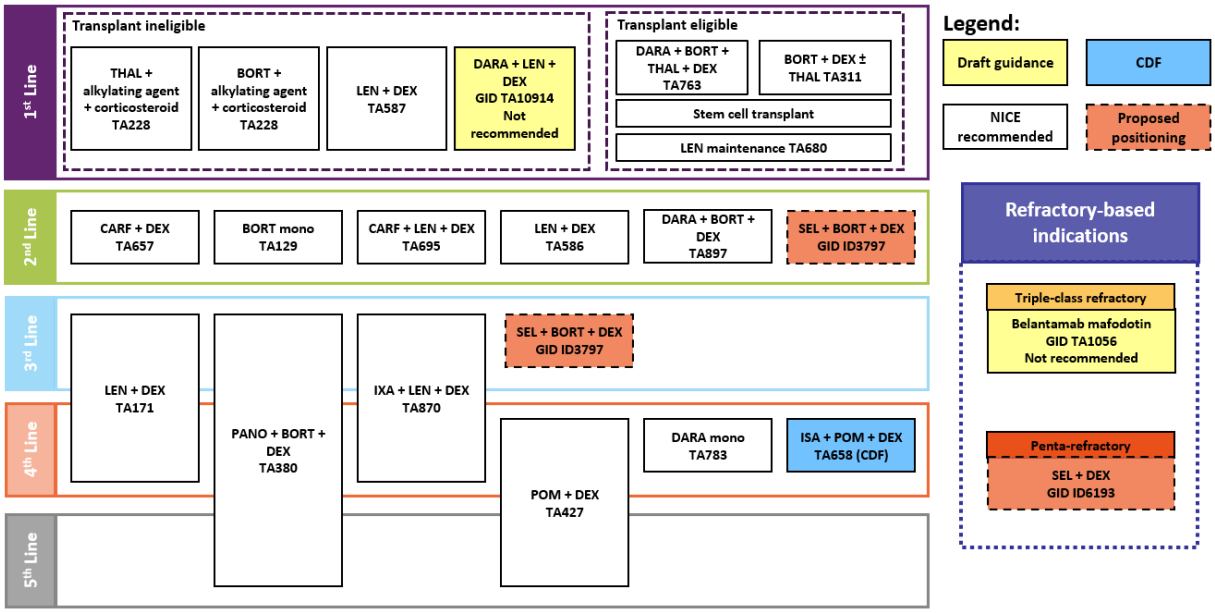
Table 11. Names and common abbreviations of drugs used in UK clinical practice for the treatment of MM.

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	Isa

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 clincial expert comments on the treatment pathway for RR-MM outlined by the Copmany.

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

	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.		

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: m^2, 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/m2 (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/m2 (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

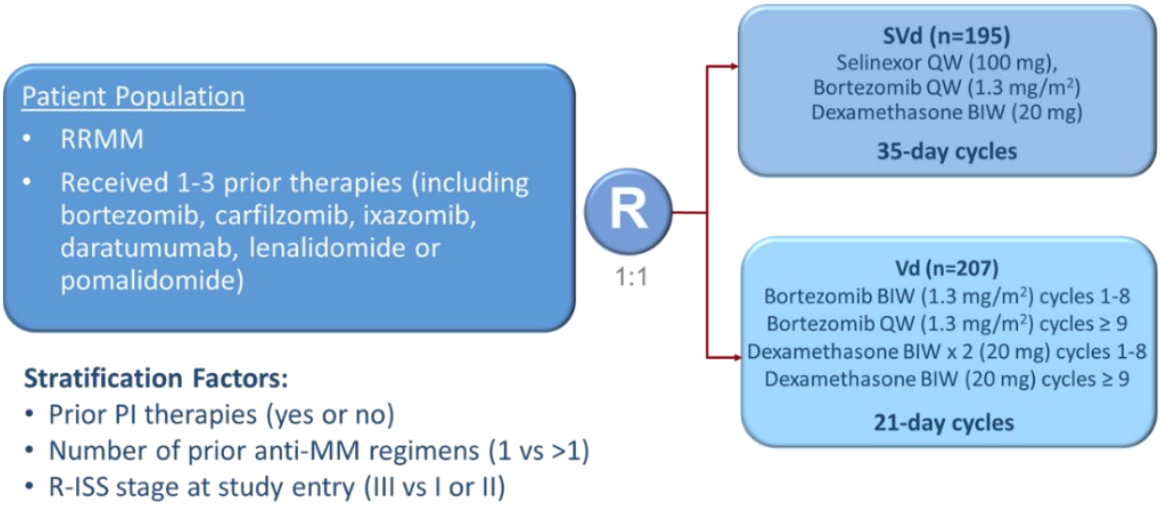
study or studies		bias for each line-of-therapy subgroup analysis used in the indirect treatment comparisons, in addition to the overall ITT populations. The EAG considers this to have been conducted appropriately, and free-text justifications for each decision were presented.

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 receive lenalidomide maintenance therapy at 1L, and around half of SCT-ineligible patients would have received a lenalidomide containing regiment 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 ≥ partial response (PR) and with last PI therapy (alone or in combination) was ≥ PR and;
- Participant did not discontinue bortezomib due to Grade ≥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 regiment 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/m^2 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), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis;
- ≥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] (CSR page 87) and;
- When discontinuation was treated as PFS event then: [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] (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 (18th February 2020)						Updated analysis (15th 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

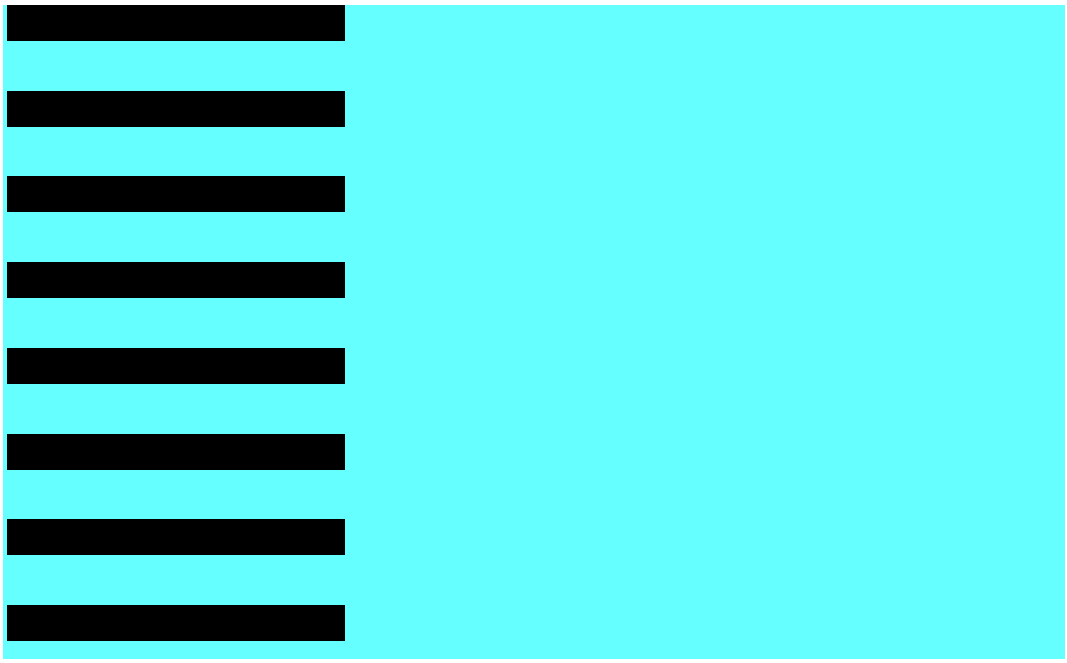
[c] Stratified for prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at screening

[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]
- In the BOSTON CSR, an adjusted HR was also presented [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] 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-effectives 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 ≥ complete response (CR) response rate was higher in SVd (≥ CR 24.%) than the Vd arm (≥ 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 be 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: 15th 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)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	11 (5.6)	3 (1.5)	14 (3.5)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Nausea	15 (7.7)	0 (0.0)	15 (3.8)
Neutropenia	18 (9.2)	7 (3.4)	25 (6.3)
[redacted]	[redacted]	[redacted]	[redacted]
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.

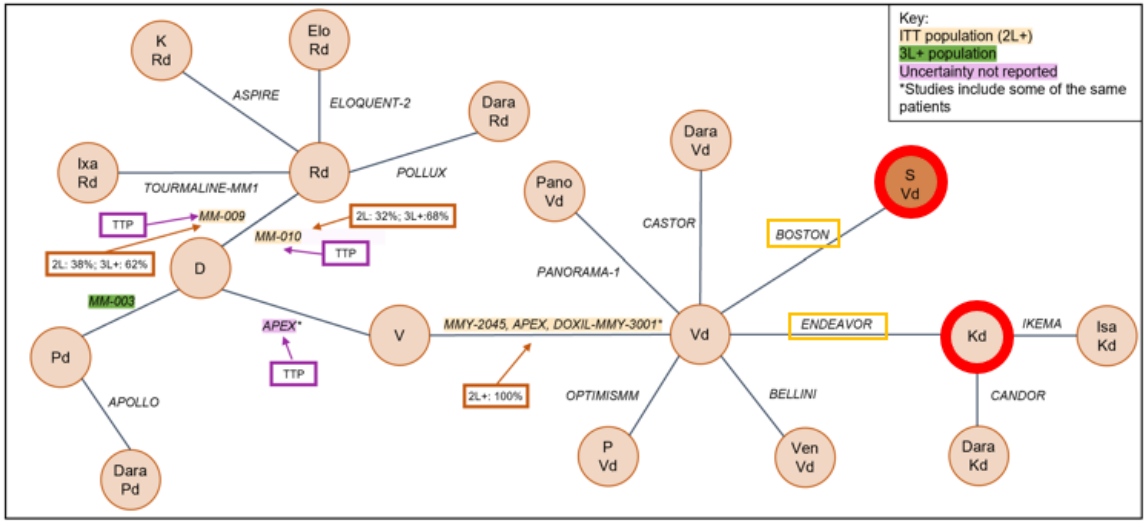
3.4.2 2L NMA

3.4.2.1 Comparison of included studies

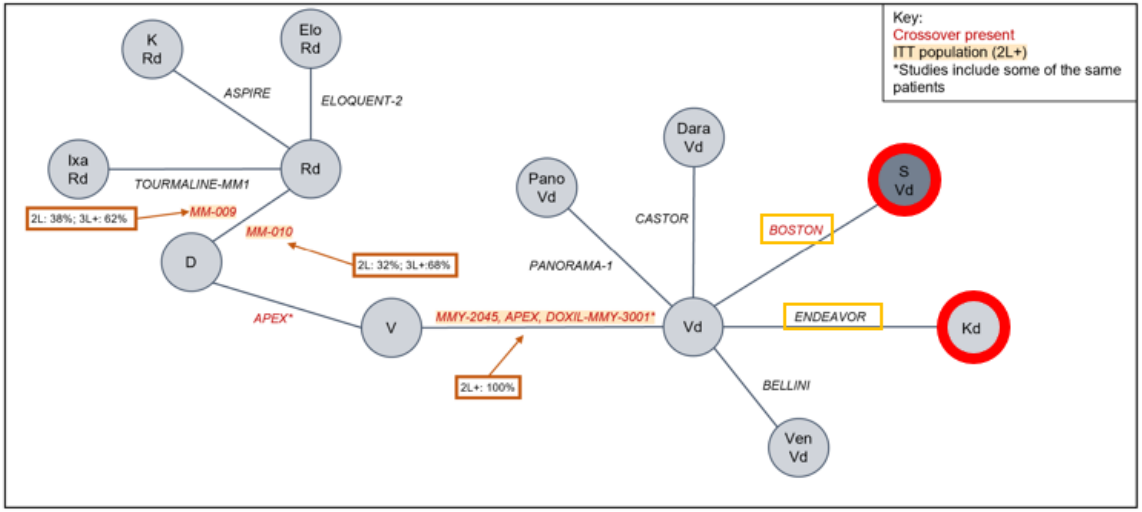
The network diagram of the Company's 2L NMA is presented in Figure 4. The EAG notes that the network simplifies when considering either the Company's preferred comparator (Kd) or the EAG's preferred comparators (Kd and Vd). The simplified network consists of two trials: BOSTON (SVd) and ENDEAVOR (Vd).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



OS, 2L

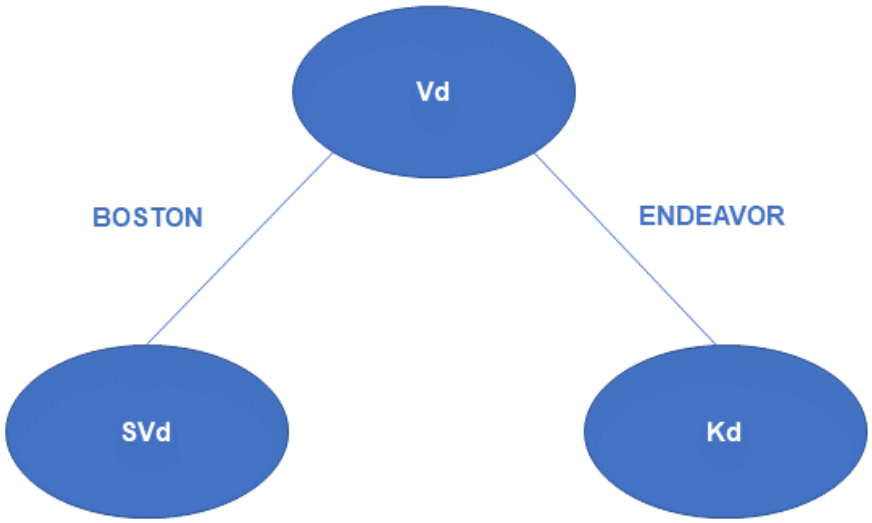


Legend:

Relevant intervention

Relevant connection

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/m2; 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: 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 MIAC, in its base case.

3.4.3 3L+ NMA and unanchored MAICs

3.4.3.1 Comparison of included studies

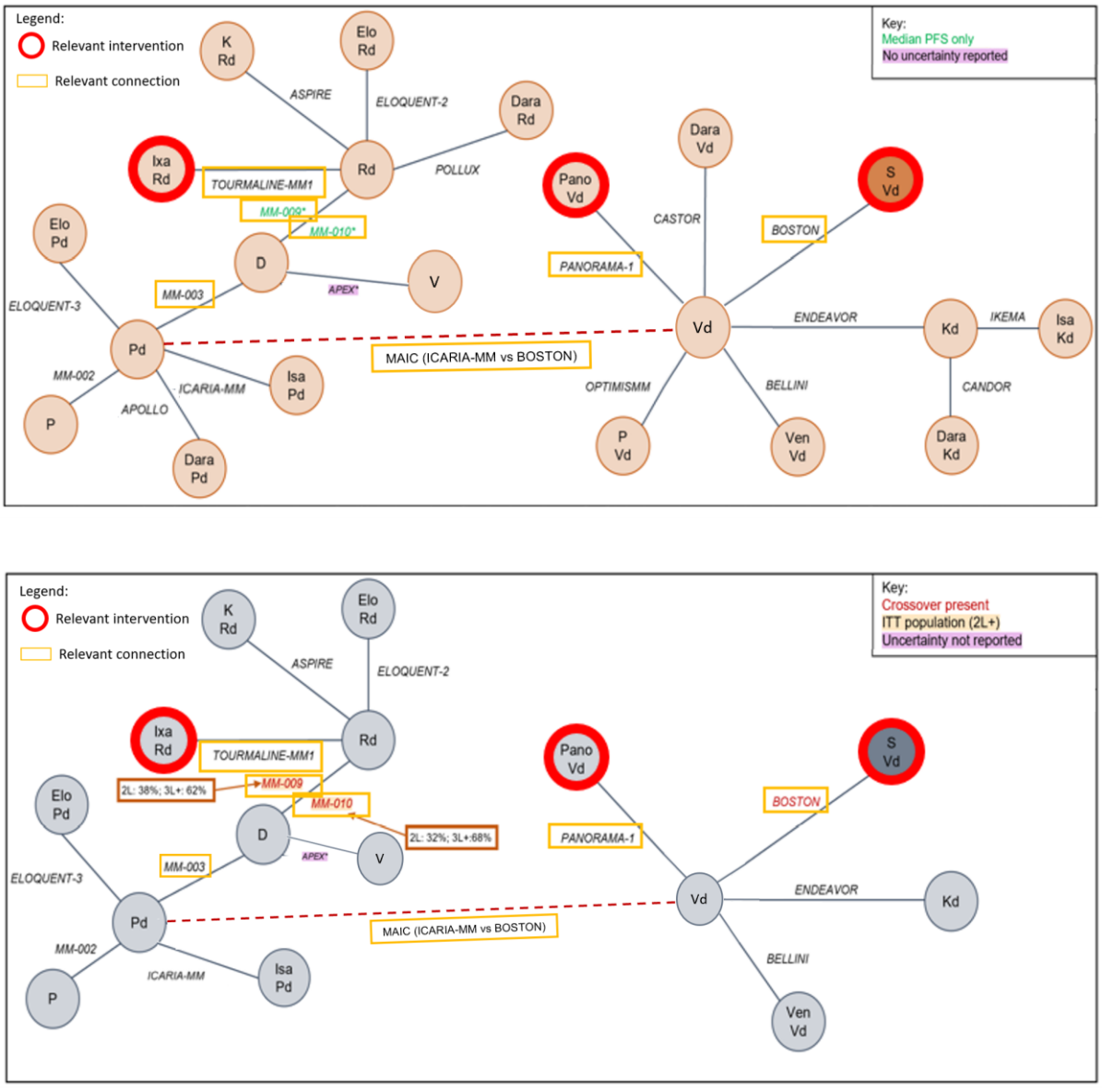
In the initial submission, the Company presented a 3L+ NMA that the EAG critiqued in Clarification Question A19 based on the following points:

- 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] (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]

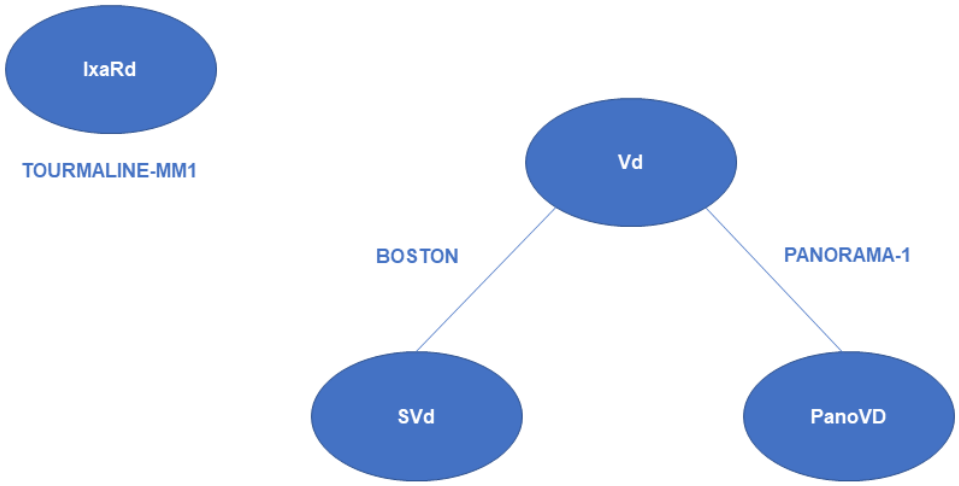
- For patients with one prior line of therapy: from 33.6 months (observed) to 19.5 months (adjusted);
- For patients with two or more prior therapies: estimated OS reduced from 27.3 months (observed) to 11.6 months (adjusted).

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

	BOSTON		PANORAMA-1		TOURMALINE-MM1	
	SVd	Vd	PanoVd	Vd	IxaRd	Rd
Population	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)	[redacted]	34.6 (27.73 to 41.95)	30.0 (24.80 to 39.92)	53	43
Hazard ratio OS, unadjusted for crossover, (95% CI)	[redacted]		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);
- Cytogenic 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 [redacted], a loss of [redacted] 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	[redacted]
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*	[redacted]	[redacted]	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] (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] (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] (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 1 2	 40.4%* 52.7%* 6.8%*	 36.1% 54.6% 9.3%	 40.4% 52.7% 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*	[redacted]	[redacted]	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] (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.

Figure 10. [redacted] (Reproduced from Company Response to Clarification Question A30)

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 influence 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	[redacted]	[redacted]	[redacted]	[redacted]	118*	57*	42*	48*	122**	141**
IMiD-based regmens	[redacted]	[redacted]	[redacted]	[redacted]	258*	332*	78*	111*	NR	NR
anti-CD38-based regimens	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	12*	5*	63*	86*
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Alkylating agents	[redacted]	[redacted]	[redacted]	[redacted]	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	[redacted]	[redacted]	-	-	-
PanoVd	138,207	[redacted]	[redacted]	[redacted]	Dominated by SVd
IxaRd	230,087	[redacted]	[redacted]	[redacted]	Dominated by SVd
Probabilistic results					
PanoVd	125,546	[redacted]	-	-	-
SVd	[redacted]	[redacted]	[redacted]	[redacted]	39,743
IxaRd	225,416	[redacted]	[redacted]	[redacted]	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 Hernadez-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.

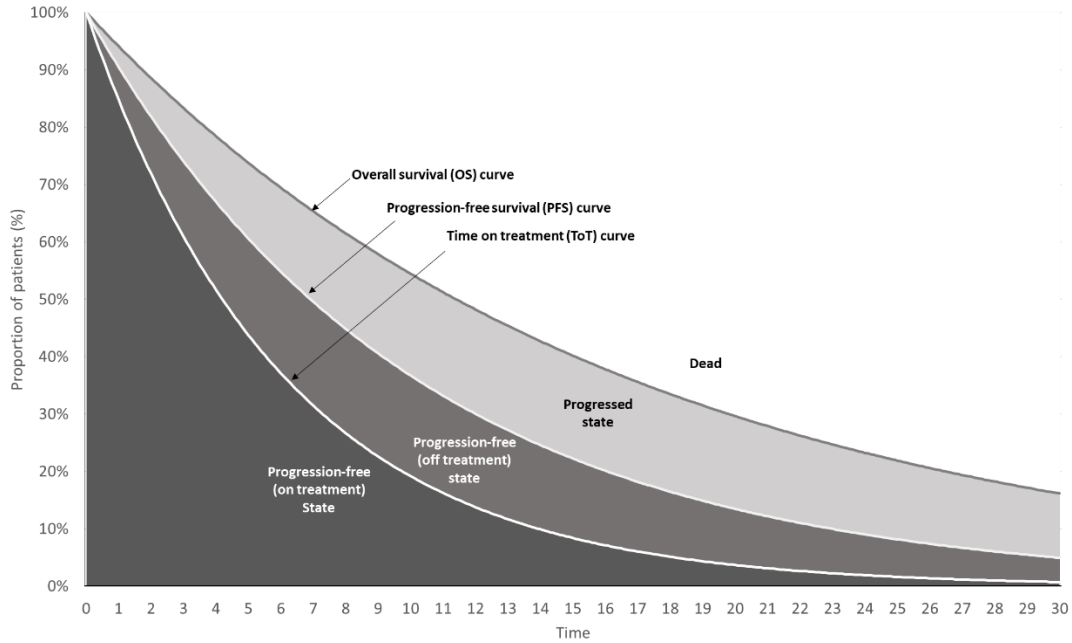
Abbreviations: EAG, External Assessment Group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

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 that determining if PH hold. 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

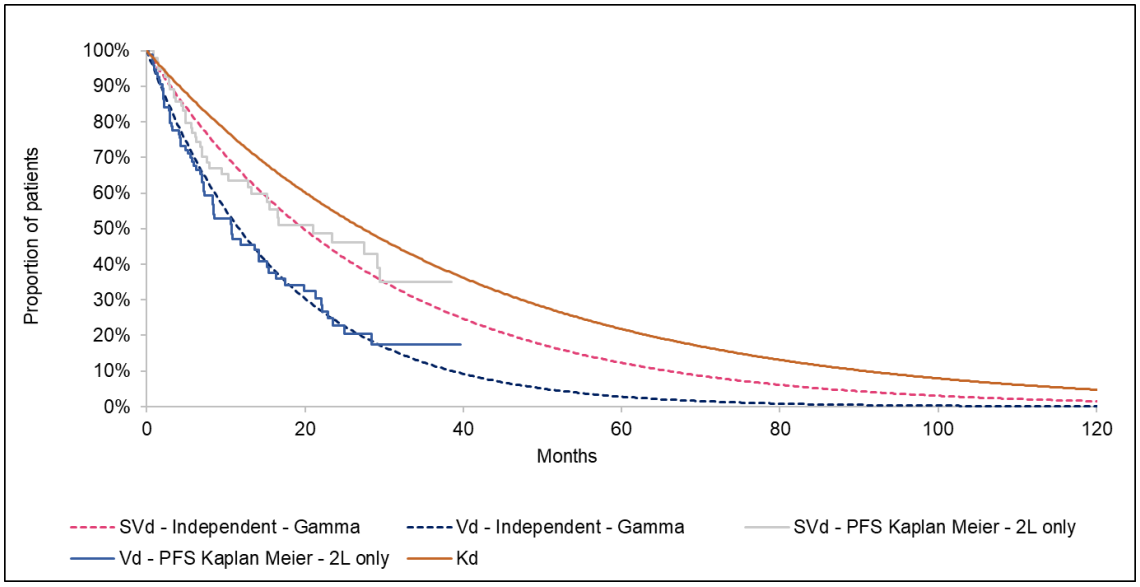
Based on the log-cumulative hazard plots and Schoenfeld residuals (Figure 18 and Figure 24 of the CS for the 3L and 2L subgroups, respectively), the company considered that the PH assumption held for PFS for the 3L subgroup from BOSTON and decided to use jointly fitted survival curves for SVd and Vd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

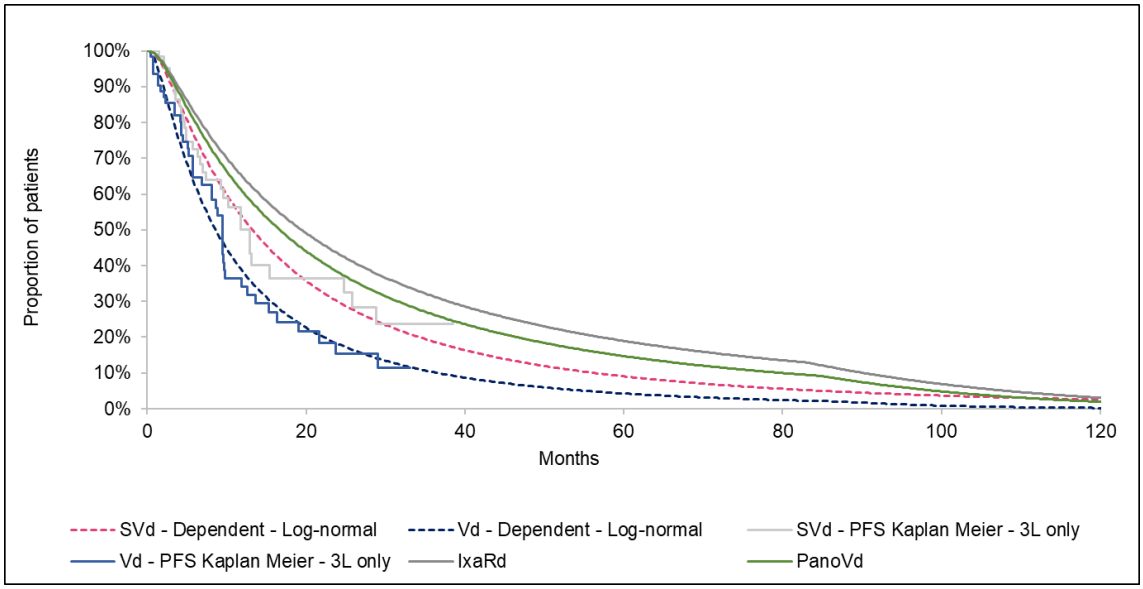
treatments for the 2L and 3L subgroups are presented in Figure 12 and Figure 13 and landmark estimates of PFS for treatments by subgroups are presented in Table 51.

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.

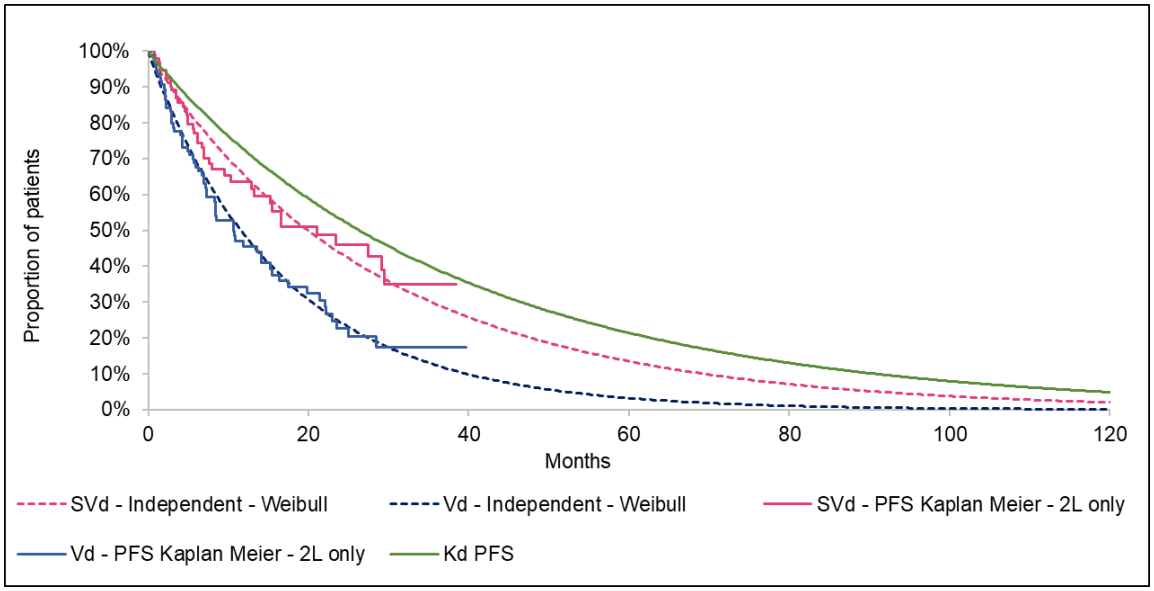
During the clarification stage, the EAG requested the company to present its preferred independent extrapolation of PFS for the 3L subgroup and they selected the lognormal curve for both SVd and Vd, stating that estimated PFS is consistent with OS (i.e. the OS cap is not implemented) and had a good visual 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.

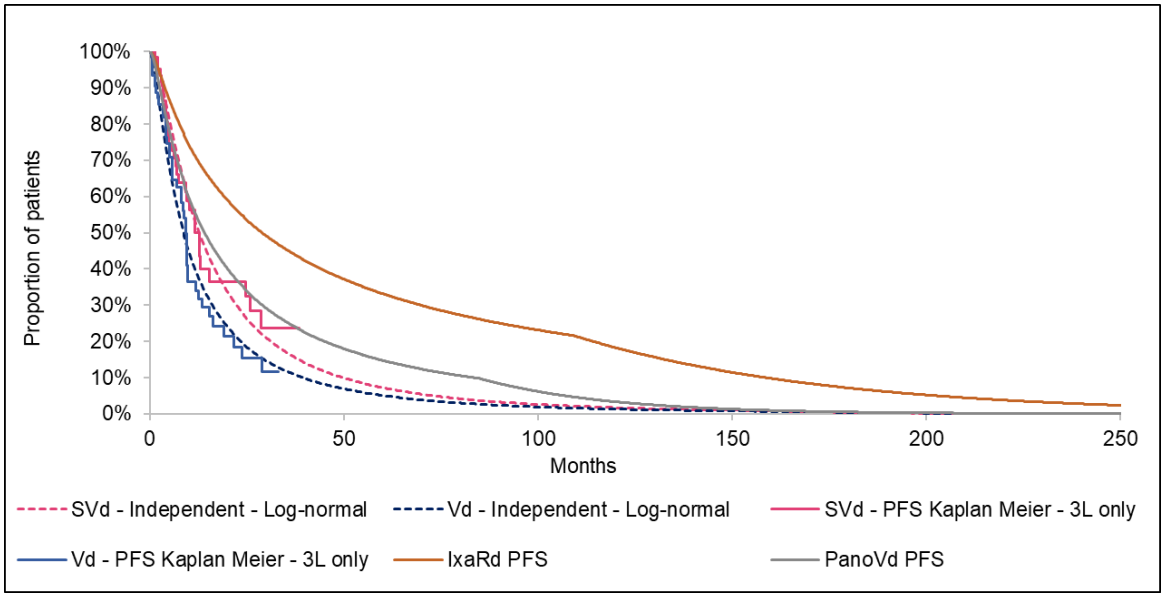
As mentioned in Section 4.2.3.2, the EAG prefers to use the Vd curve as the baseline to apply comparator HRs from the ITC for all outcomes, including PFS (see Table 46 for comparator HRs vs Vd). Therefore, for its preferred assumptions (presented in Section 6.3), the EAG considers that independently 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

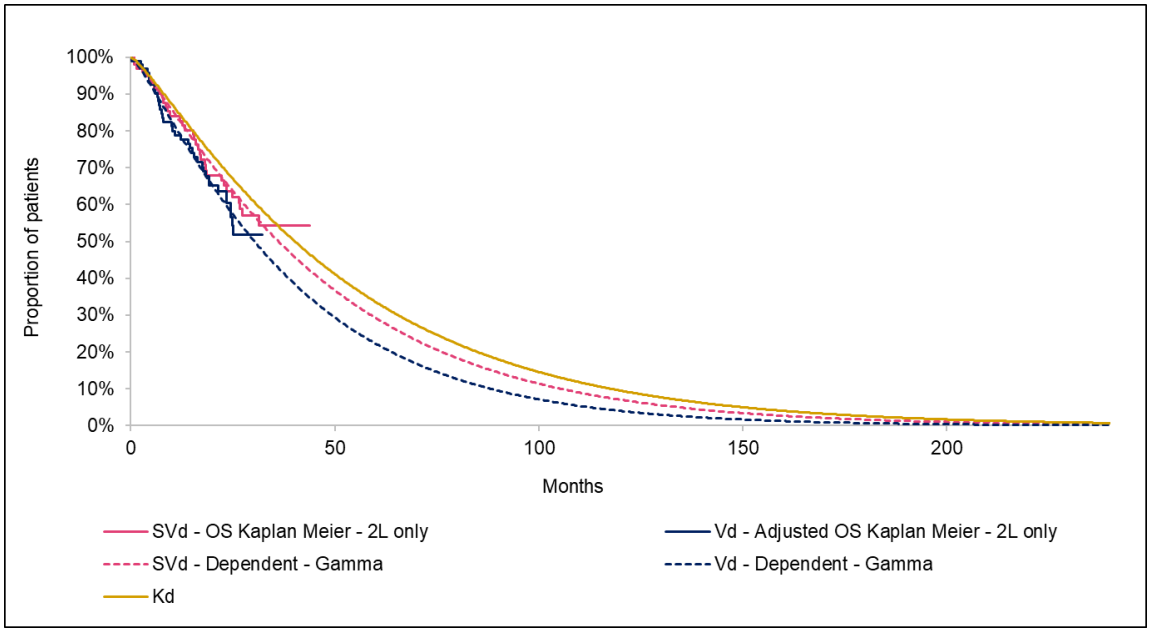
In BOSTON, patients in the Vd arm of the trial could crossover to SVd or selinexor with low-dose dexamethasone (Sd) upon disease progression. In the clinical study report (CSR) for BOSTON, independent review committee (IRC) confirmation of progressed disease for those patients in the Vd arm was required 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.

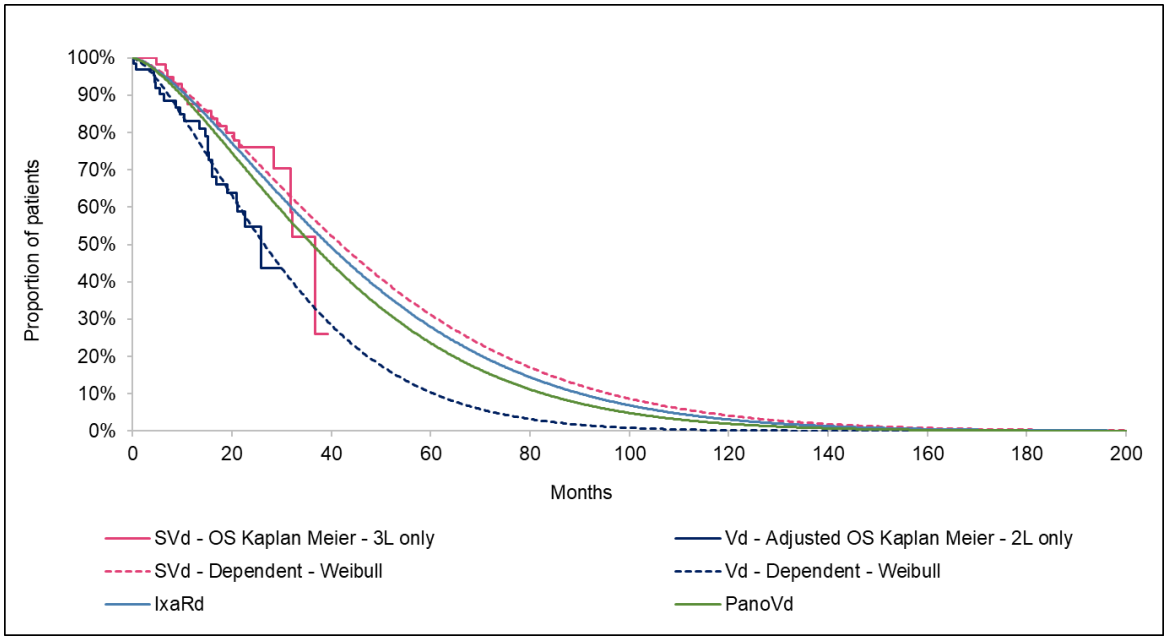
The company used the extrapolation of SVd OS as the baseline curve to apply comparator treatment effects obtained from the indirect treatment comparisons described in Section 3.4 and presented earlier in Table 44. For the extrapolation of SVd OS, the company selected the gamma distribution for the 2L 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

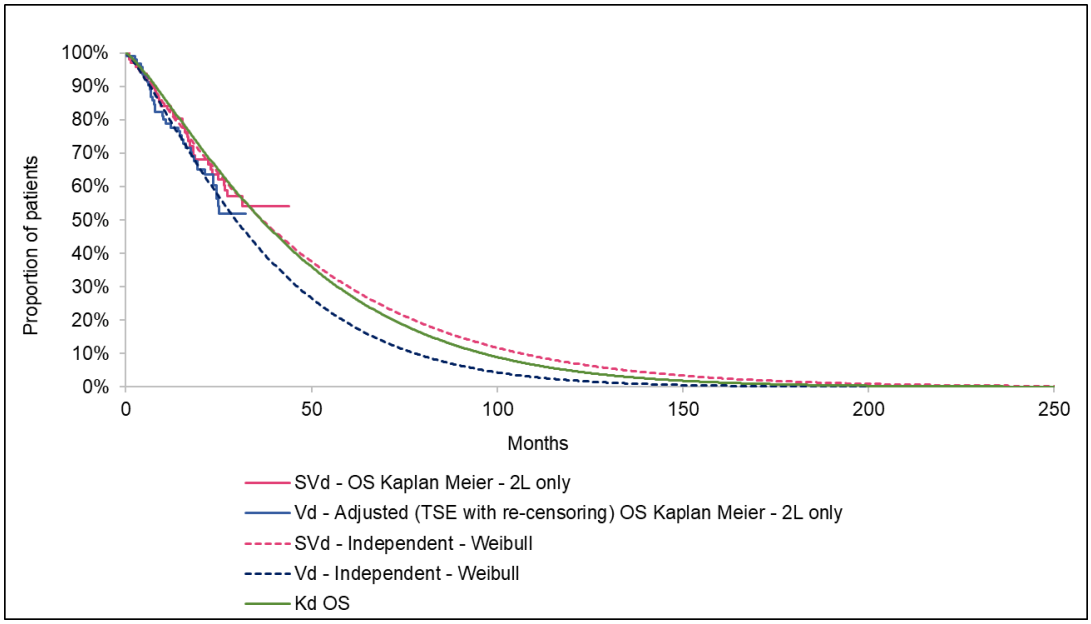
As mentioned in Section 4.2.3.2, the EAG considers that diagnostic plots for OS for both the 2L and 3L subgroups showed a violation of the PH assumption and thus joint modelling of OS for SVd and Vd is inappropriate and independent models are preferred. During the clarification stage, the EAG requested 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.

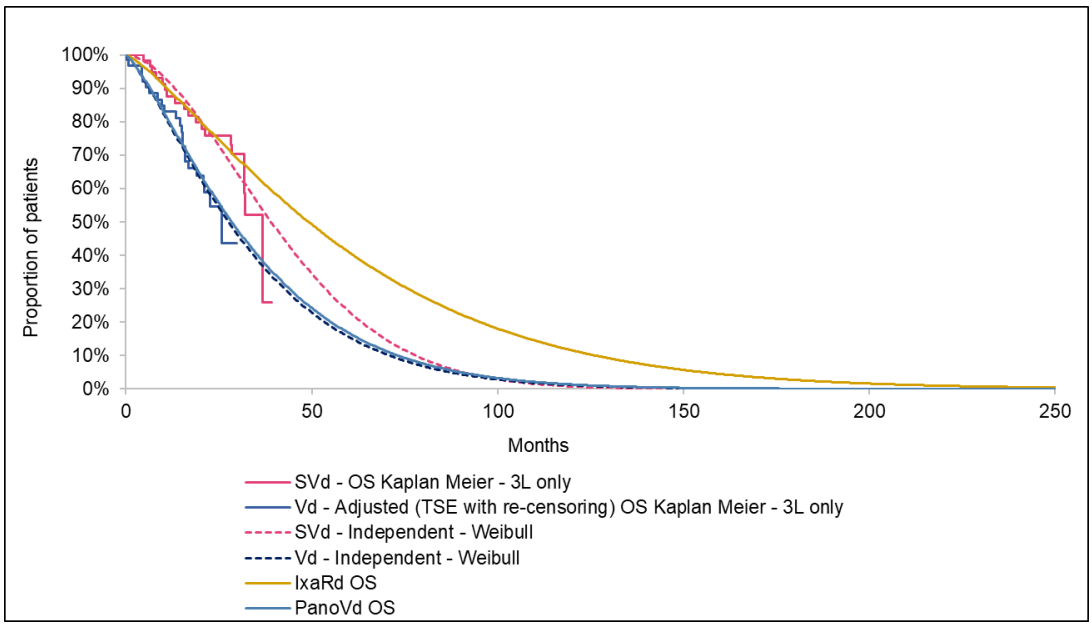
For the 3L subgroup, the EAG considered the Weibull curve provided a good fit to the observed data, with 10-year survival for SVd, IxaRd and PanoVd estimated to be under 1% for all treatments. Figure 18 and Figure 15 presents the independently fitted OS curves for the 2L and 3L subgroups, with Vd used 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

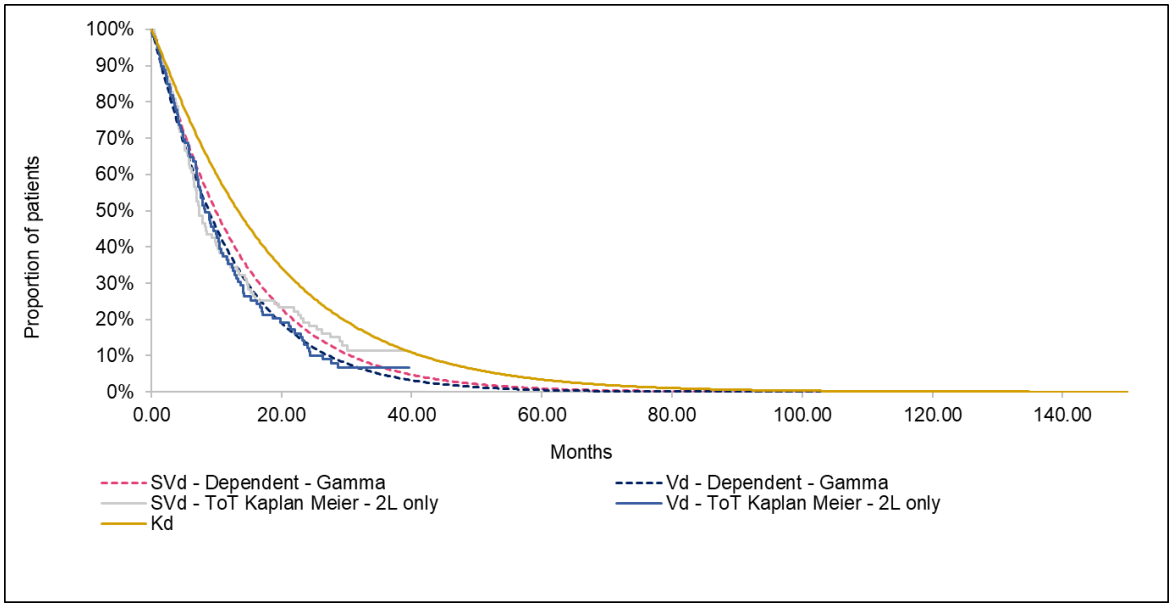
Based on the log-cumulative hazard plots and Schoenfeld residuals (Figure 20 and Figure 26 of the CS for the 3L and 2L subgroups, respectively), the company considered that the PH assumption held for TTD for both the 2L and 3L subgroups from BOSTON and decided to use jointly fitted survival curves for 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.

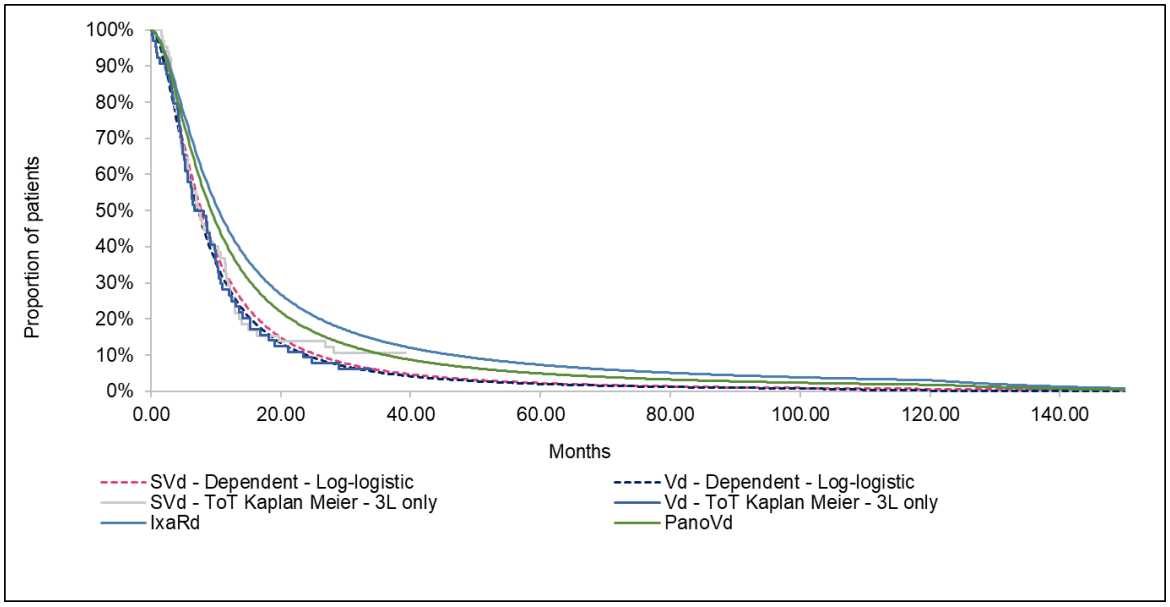
Plots of all the assessed distributions compared with the KM data and AIC/BIC statistics can be found in Figure 21 and Table 26 of the CS for the 3L subgroup and Figure 27 and Table 29 of the CS for the 2L subgroup. In the CS, the company explored all jointly and independently fitted standard parametric 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.

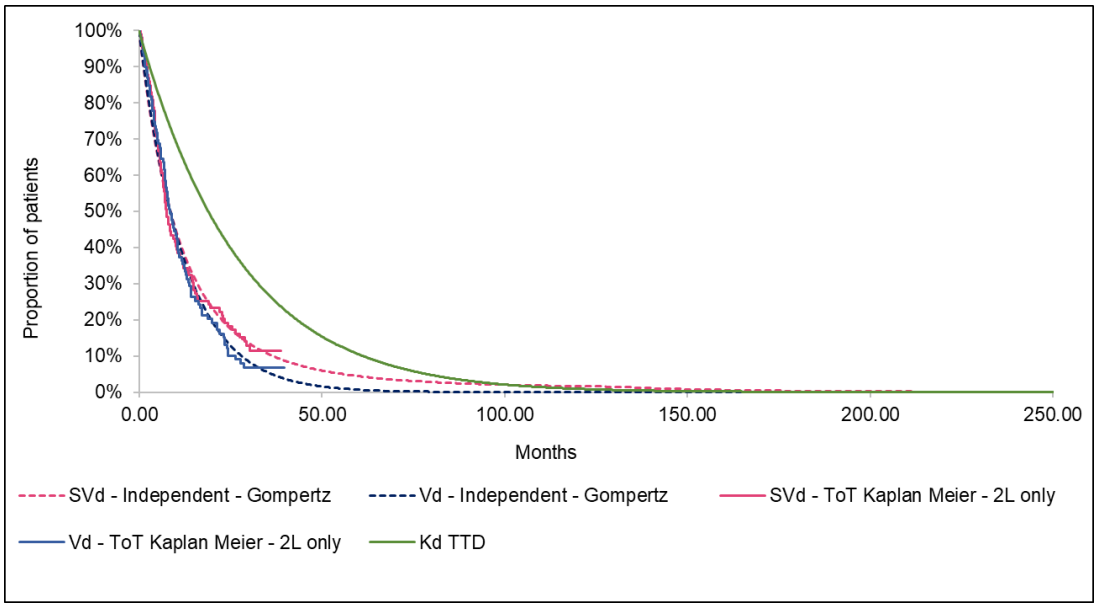
The EAG investigated the exponential, Weibull and Gompertz models to see if they provided a good fit to the observed 3L data but found that none were suitable. The EAG considers that the generalised gamma curve had a better visual to the observed data and ranked second best in terms of statistical fit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

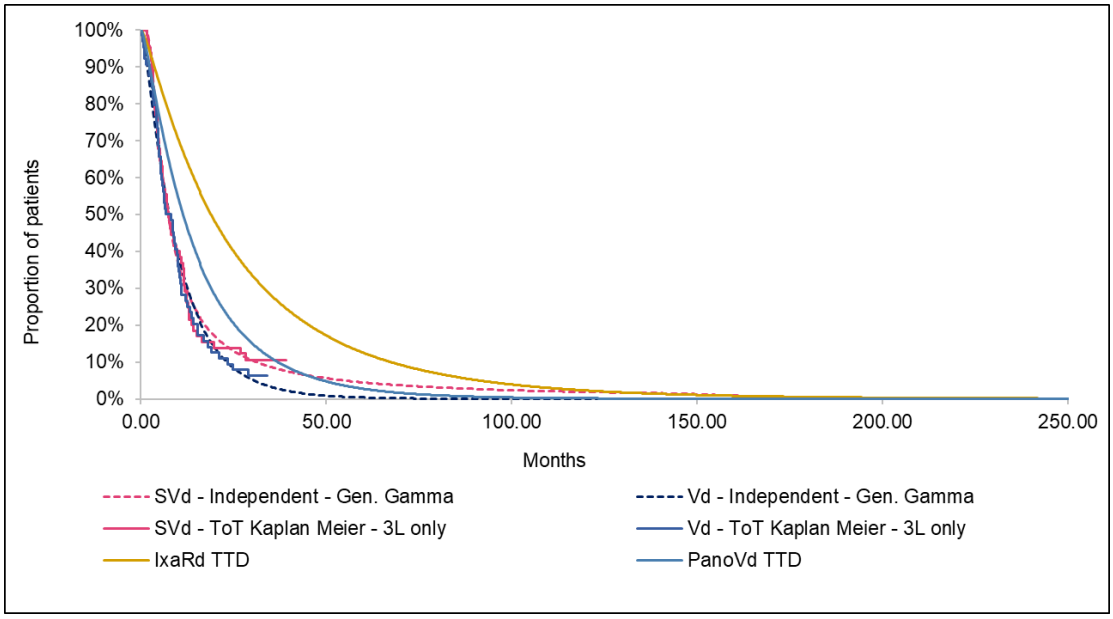
The EAG has included the independently fitted Gompertz curve for the 2L subgroup and the generalised gamma curve for the 3L subgroup (with the acknowledgement of the limitations of estimating comparators curves using an HR applied to an AFT model) along with TTD capped to PFS (Figure 22 and Figure 23) 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[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.

4.2.4.1 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 Hernadez-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 (Pr[>F]) but was retained in all models regardless.

Table 54. Mixed effects model coefficients. Reproduced form 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.

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

$\beta_1 = Arm\ (Vd)$

$\beta_2 = Age$
$\beta_3 = Baseline\ ECOG$

$\beta_4 = Baseline\ EQ - 5D - 3L$

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

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.

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

$\beta_1 = Age$
$\beta_2 = Baseline\ ECOG$

$\beta_3 = Baseline\ EQ - 5D - 3L$

$\beta_4 = PFS\ Status\ (Y)$

$\beta_5 = Prior\ line\ of\ therapy$

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 *et al.* (2016),[65] NICE TA783[66]	1.00	Assumption
Fatigue	-0.12	NICE GID-TA11060,[62] NICE TA897 [previously TA573],[61] NICE TA695,[63] Nikolaou *et al.* 2021[67]	2.09	NICE GID-TA11060,[62] NICE TA897 [previously TA573],[61] NICE TA695[63] Jakubowiak *et al.* 2016[65]
Febrile neutropenia	-0.15	Jakubowiak *et al.* 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 *et al.* 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 *et al.* 2016[65]
Lower respiratory tract infection	-0.19	NICE TA783 [lower respiratory infection][66]	1.71	Assumed equal to pneumonia
Nausea	-0.10	Jakubowiak *et al.* 2016,[65] NICE TA658,[64] NICE TA783[66]	1.00	Assumption
Neutropenia	-0.145	NICE TA897 [previously TA573],[61] Nikolaou *et al.* 2021[67]	1.89	NICE TA897 [previously TA573][61]
Peripheral neuropathy	-0.065	NICE TA897 [previously TA573],[61] NICE GID-TA11060,[62] Jakubowiak *et al.*(2016[65]	1.14	NICE TA897 [previously TA573],[61] NICE GID-TA11060,[62] Jakubowiak *et al.* 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]

Abbreviations: AE, adverse event; GID, guidance in development; NICE, National Institute for Health and Care Excellence; TA, technology appraisal

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 [redacted] per tablet) with the proposed PAS discount of [redacted] 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%	[redacted]	-	-
	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	Carflizomib	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; m^2, 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	[redacted]	-	-
PanoVd	[redacted]	-	-
Pd	-	[redacted]	-
Chemotherapy*	[redacted]	[redacted]	[redacted]
Best supportive care	-	-	[redacted]
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; SVd, 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	[redacted]	[redacted]	[redacted]	[redacted]
3L	[redacted]	[redacted]	[redacted]	[redacted]

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	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A
PanoVd	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A
4L										
IxaRd*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PanoVd*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pd†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5L										
PanoVd‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pd‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	[redacted]	[redacted]	N/A	N/A	N/A
PanoVd	[redacted]	[redacted]	N/A	N/A	N/A
Chemotherapy	[redacted]	[redacted]	N/A	N/A	N/A
4L					
IxaRd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PanoVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5L					
PanoVd	-	-	[redacted]	[redacted]	-
Pd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total weighted weekly cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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 TA897 [61]

†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 of 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 IxaRd 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	[redacted]	-	[redacted]	-	-	-	-
IxaRd	225,416	-	[redacted]	[redacted]	-	[redacted]	1,293,485 (SW quadrant)
PanoVd	125,546	-	[redacted]	[redacted]	-	[redacted]	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	[redacted]	[redacted]	-	-	-
PanoVd	138,207	[redacted]	[redacted]	[redacted]	Dominated by SVd
IxaRd	230,087	[redacted]	[redacted]	[redacted]	Dominated by SVd
Probabilistic results					
PanoVd	125,546	[redacted]	-	-	-
SVd	[redacted]	[redacted]	[redacted]	[redacted]	39,743
IxaRd	225,416	[redacted]	[redacted]	[redacted]	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 IxaRd

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 2021/22[55] - 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 PSSRU[57] - 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	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	413,520	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
B11	BOSTON Utility values by line of therapy and progression status			
	Total costs (£)	[redacted]	319,769	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	599,403 (SW)
B14	Removal of IsaPd from subsequent treatment costs			
	Total costs (£)	[redacted]	317,285	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	605,656 (SW)
B16	EAG clinical experts' health state resource use estimates			
	Total costs (£)	[redacted]	344,082	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	613,668 (SW)
B18	Adverse events managed only in secondary care			
	Total costs (£)	[redacted]	319,993	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	603,273 (SW)
B25	Company's alternative estimation of subsequent treatment costs using market share data			
	Total costs (£)	[redacted]	332,280	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	522,939 (SW)
EAG scenarios				
1	Combined scenario implementing the EAG's preferred assumption for treatment effectiveness in the model			
	Total costs (£)	[redacted]	415,266	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			Dominant
2	Scenario 1 + OS for comparators equal to Vd			
	Total costs (£)	[redacted]	379,426	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	10,017,804 (SW)
3	Scenario 1 + OS for comparators equal to SVd			
	Total costs (£)	[redacted]	425,200	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	460,604	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	Dominant
5	HSUV for the progressed health state equal to HSUV for the 3L progression-free health state (BOSTON data)			
	Total costs (£)	[redacted]	319,769	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	621,054 (SW)
6	Administration cost for oral chemotherapy			
	Total costs (£)	[redacted]	327,557	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	602,882 (SW)
7	EAG preferred AE unit costs + one-off impact of AEs + all AEs managed in secondary care			
	Total costs (£)	[redacted]	319,061	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	595,024 (SW)
8	End of life care cost from the PSSRU[57]			
	Total costs (£)	[redacted]	328,212	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	230,087	138,207	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	212,469	138,844	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	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 (£)	[redacted]	280,281	139,810	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B11	BOSTON Utility values by line of therapy and progression status					
	Total costs (£)	[redacted]	230,087	138,207	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B14	Removal of IsaPd from subsequent treatment costs					
	Total costs (£)	[redacted]	227,427	135,643	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B16	EAG clinical experts' health state resource use estimates					
	Total costs (£)	[redacted]	250,995	157,426	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B18	Adverse events managed only in secondary care					
	Total costs (£)	[redacted]	230,223	141,892	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	Dominant	Dominant
B25	Company's alternative estimation of subsequent treatment costs using market share data					
	Total costs (£)	[redacted]	246,150	157,268	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	Dominant	187,293
EAG scenarios						
1	Combined scenario implementing the EAG's preferred assumption for treatment effectiveness					
	Total costs (£)	[redacted]	301,409	137,321	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	171,605 (SW)	6,024
2	Scenario 1 + OS for comparators equal to Vd					
	Total costs (£)	[redacted]	240,084	132,618	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	2,577,373 (SW)	Dominated
3	Scenario 1 + OS for comparators equal to SVd					
	Total costs (£)	[redacted]	272,885	140,363	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	313,936	150,412	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	172,112 (SW)	3,384
6	Administration cost for oral chemotherapy					
	Total costs (£)	[redacted]	247,488	146,733	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	Dominant	Dominant
7	EAG preferred AE unit costs + one-off impact of AEs + all AEs managed in secondary care					
	Total costs (£)	[redacted]	229,174	131,964	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	Dominant	Dominant
8	End of life care cost from the PSSRU[57]					
	Total costs (£)	[redacted]	238,546	146,683	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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	-	[redacted]	[redacted]	**605,630 (SW)**
EAG scenario 1 – treatment effectiveness assumptions	4.2.3	[redacted]	[redacted]	Dominant
EAG scenario 2 – OS for comparators equal to Vd	4.2.3.6	[redacted]	[redacted]	10,017,804 (SW)
Company scenario B11 – utility values by line of therapy and progression status	4.2.5.2	[redacted]	[redacted]	10,036,592 (SW)
EAG scenario 4 – subsequent treatments	4.2.6.4	[redacted]	[redacted]	8,601,271 (SW)
EAG scenario 6 – administration cost for oral chemotherapy	4.2.6.24.2.6.8	[redacted]	[redacted]	8,400,870 (SW)

EAG scenario 7 – AE costs*	4.2.6.8	[redacted]	[redacted]	6,612,455 (SW)
Company scenario B16 – EAG clinical expert resource use assumptions*	4.2.6.6	[redacted]	[redacted]	6,612,455 (SW)
EAG scenario 8 – End of life care cost from the PSSRU*	4.2.6.9	[redacted]	[redacted]	6,612,455 (SW)
EAG preferred base case	-	[redacted]	[redacted]	**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	[redacted]	-	-	-	-	-
SVd	[redacted]	2.98	[redacted]	[redacted]	0.00	[redacted]	6,612,455 (SW)	[redacted]
Probabilistic results								
Kd	431,480	-	[redacted]	-	-	-	-	-
SVd	[redacted]	-	[redacted]	[redacted]	-	[redacted]	8,694,817 (SW)	[redacted]

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 (£)	[redacted]	431,480	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]
	PSA ICER (£/QALY)	-	-	8,694,817 (SW)
	Deterministic ICER (£/QALY)	-	-	6,612,455 (SW)
1	OS for comparators equal to SVd			
	PSA total costs (£)	[redacted]	490,202	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	475,592	[redacted]

	PSA QALYs	[redacted]	[redacted]	[redacted]
	PSA ICER (£/QALY)	-	-	Dominant
	Deterministic ICER (£/QALY)			Dominant
3	Use of utility values from Hatswell et al.[1]			
	PSA total costs (£)	[redacted]	432,400	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]
	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	-	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]	**Dominant**
EAG scenario 1 – treatment effectiveness assumptions	4.2.3	[redacted]	[redacted]	171,605 (SW)	[redacted]	[redacted]	6,024
EAG scenario 2 – OS for comparators equal to Vd	4.2.3.6	[redacted]	[redacted]	2,577,373 (SW)	[redacted]	[redacted]	Dominated
Company scenario B11 – utility values by line of therapy and progression status	4.2.5.2	[redacted]	[redacted]	2,583,364 (SW)	[redacted]	[redacted]	Dominated
EAG scenario 4 – subsequent treatments	4.2.6.4	[redacted]	[redacted]	2,324,202 (SW)	[redacted]	[redacted]	Dominated

EAG scenario 6 – administration cost for oral chemotherapy	4.2.6.24.2.6.8	[redacted]	[redacted]	2,569,239 (SW)	[redacted]	[redacted]	Dominated
EAG scenario 7 – AE costs*	4.2.6.8	[redacted]	[redacted]	2,445,681 (SW)	[redacted]	[redacted]	Dominated
Company scenario B16 – EAG clinical expert resource use assumptions*	4.2.6.6	[redacted]	[redacted]	2,445,681 (SW)	[redacted]	[redacted]	Dominated
EAG scenario 8 - End of life care cost from the PSSRU*	4.2.6.9	[redacted]	[redacted]	2,445,681 (SW)	[redacted]	[redacted]	Dominated
EAG preferred base case	**-**	[redacted]	[redacted]	**2,445,681 (SW)**	[redacted]	[redacted]	**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 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	[redacted]	2.75	[redacted]	-	-	-	-	-
IxaRd	284,753	2.75	[redacted]	[redacted]	0.00	[redacted]	2,445,681 (SW)	[redacted]
PanoVd	171,299	2.75	[redacted]	[redacted]	0.00	[redacted]	Dominated	[redacted]
Probabilistic results								
SVd	[redacted]	-	[redacted]	-	-	-	-	-
IxaRd	272,739	-	[redacted]	[redacted]	-	[redacted]	2,457,260 (SW)	[redacted]
PanoVd	154,929	-	[redacted]	[redacted]	-	[redacted]	Dominated	[redacted]

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 (£)	[redacted]	272,739	154,929	[redacted]	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	315,972	177,410	[redacted]	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	364,847	156,864	[redacted]	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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 (£)	[redacted]	275,666	155,321	[redacted]	[redacted]
	PSA QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	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 experience 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 accumulates 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 is 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.

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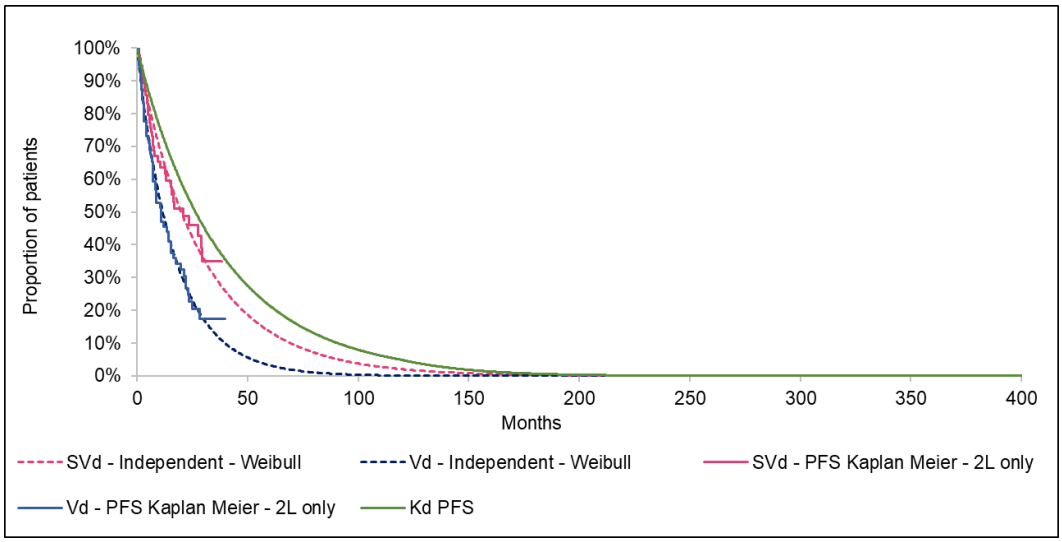
8 Appendices

8.1 Summary of EAG preferred treatment effectiveness extrapolations

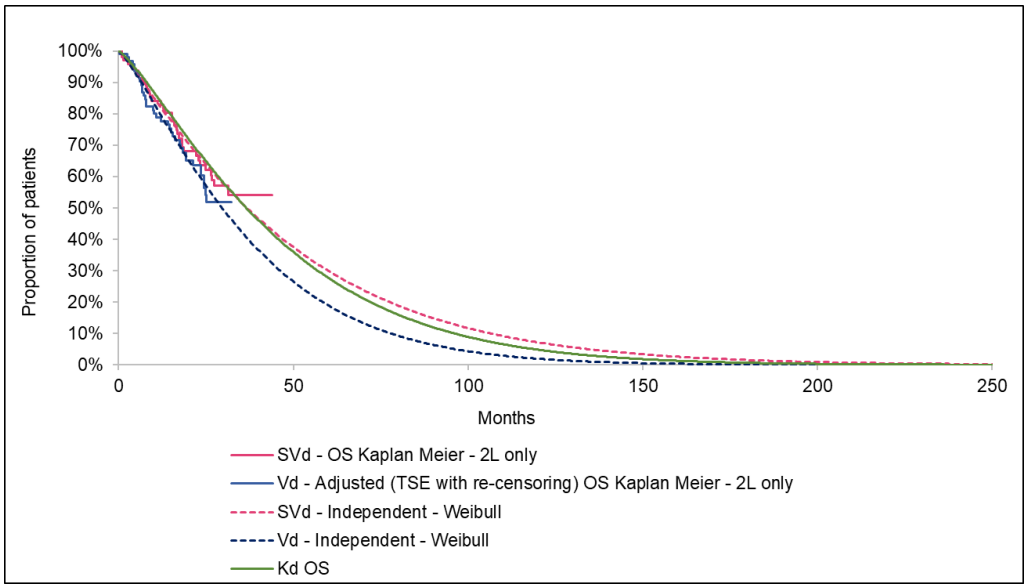
8.1.1 Second-line subgroup

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



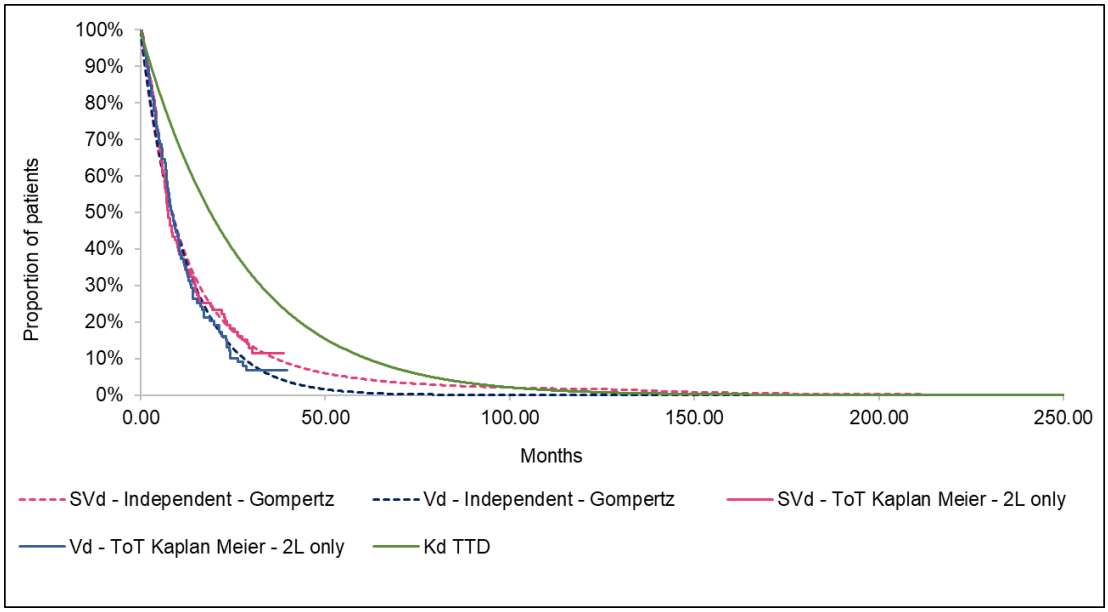
Abbreviations: 2L, second-line; Kd, carfilzomib with dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone

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

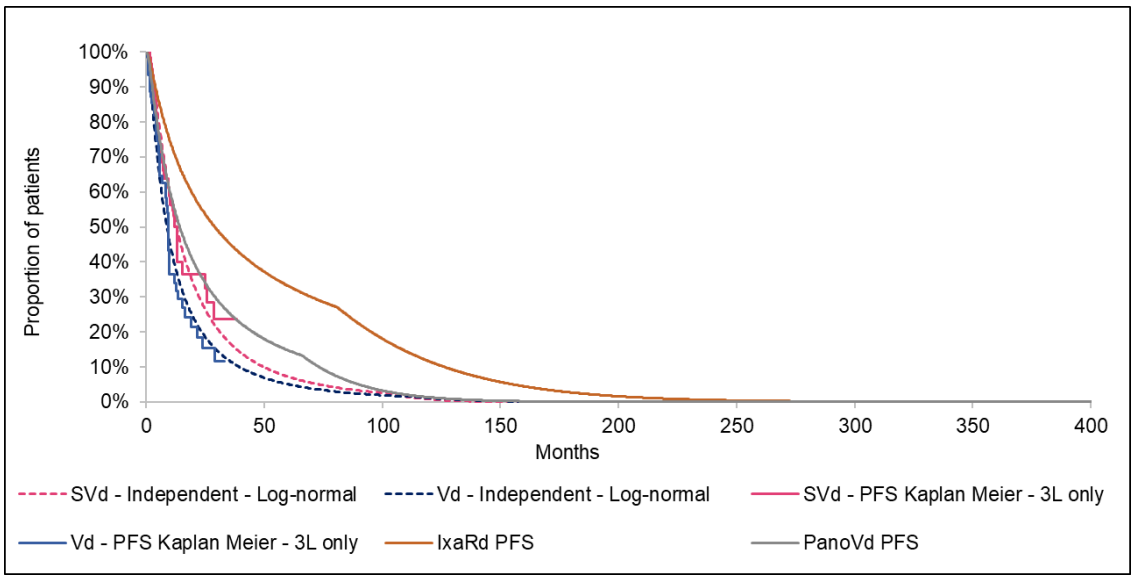
Figure 34. EAG Gompertz preferred extrapolation of TTD for SVd, Vd and Kd – 2L subgroup



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

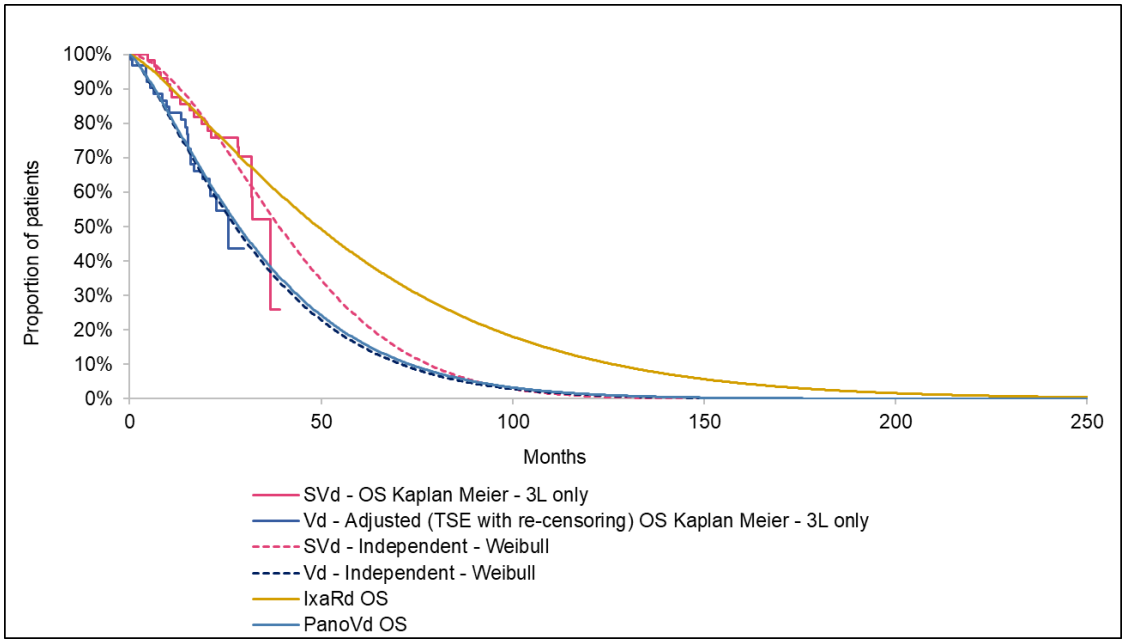
8.1.2 Third-line subgroup

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



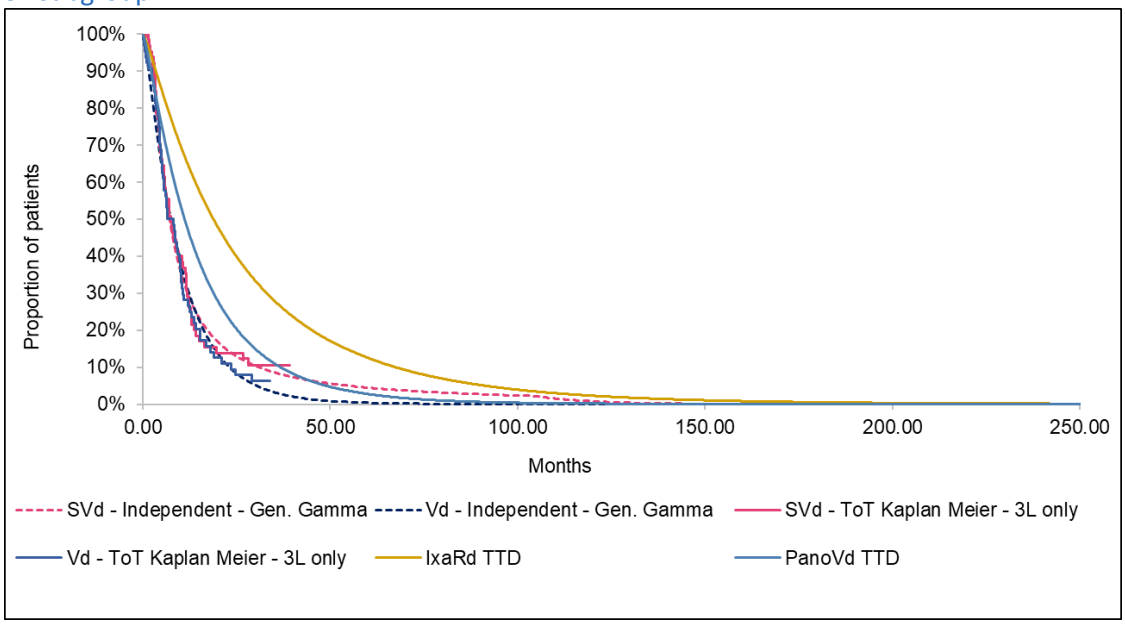
Abbreviations: 3L, third-line; IxaRd, ixazomib with lenalidomide and dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival; PanoVd, panobinostat with bortezomib and dexamethasone; SVd, selinexor with bortezomib and dexamethasone; Vd, bortezomib with dexamethasone.

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]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 9 November 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Kd dosing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 47 in table 16, the dose per administration of K in the Kd combination lacks detail on specific posology of the regimen	K in the combination of Kd should read as per the Kyprolis SmPC - administered at a 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).[1]	Missing essential posology detail	Thank you for highlighting the missing details. This has been updated in the EAG report.

Issue 2 Vd dosing in BOSTON

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 56 of the EAG report it states - The dosing regimen of Vd in BOSTON was Vd dosing regimen was "bortezomib 1.3mg/m^2 twice weekly for the first 24 weeks and once per week thereafter, and dexamethasone jan20mg four times per week for the	**Cycles 1 - 8** (3-week [21-day] cycle) Bortezomib 1.3 mg/m^2 SC on Days 1, 4, 8, and 11. **Cycles ≥ 9** (5-week [35-day] cycle) Bortezomib 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 Table 5 Company Submission	Error	Unclear if a factual inaccuracy. The EAG has updated the wording of this section to match that of Table 5 of the CS as requested by the Company, but the EAG notes that the original sentence was a direct

first 24 weeks and twice per week thereafter”			quote of page 32 of the Company Submission.

Issue 3 Vd dosing in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 57 of the EAG report states - 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	The posology for Velcade when in combination with dexamethasone is twice weekly for previously treated MM in the SmPC [Velcade SmPC; EMA].[2]	Error	Not a factual inaccuracy. No change required.

Issue 4 Crossover adjustment for OS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 67 of the EAG report states - No details on whether an RPSFT model was implemented were provided, and the only results provided using IPCW was a HR, which, in	In response to the EAG clarification questions, the Company confirmed that other options were explored but that OS curves showed little sensitivity to adjustment method.	Clarification that additional methods were explored, as confirmed in the response to EAG clarification questions.	Not a factual inaccuracy. No change required.

light of potential non-PH, is difficult to interpret			

Issue 5 Unanchored MAIC of IxaRd *vs.* Vd

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.4, 3.4.3, the EAG prefer an unanchored MAIC of IxaRd *vs*. Vd whereas the company believe the unanchored MAIC of IxaRd *vs.* SVd is more appropriate	The Company extends its gratitude to the EAG for commending its transparency around the uncertainty and limitations of the proposed NMA and recognises that the proposed updated 3L+ NMA only resolves some of the highlighted limitations. However, the Company disagrees with the reasons provided by the EAG to support the choice of the unanchored MAIC *vs*. Vd: • The EAG highlighted that baseline characteristics are more aligned between the IxaRd and Vd arm, given the differences in R-ISS and ECOG between the IxaRd and SVd arms. However, when appraising the anchored MAIC of Kd *vs.* SVd, the EAG highlighted how treatment effect modifiers, such as line of	Clarification	Not a factual inaccuracy. No change required.

	treatment and prior exposure and/or refractoriness to specific drug classes, should be preferred over prognostic factors in the MAIC. In the IxaRd comparison, while the proportion of PI-exposed patients is relatively similar across all three arms, prior exposure to IMiD differs between IxaRd and both BOSTON arms, with the proportion being much higher in both the SVd and Vd arm, than in the IxaRd arm. • The EAG highlighted that the adjusted OS SVd KM curve crosses the OS IxaRd KM curve, suggesting that the PH assumption is violated. At inspection, the adjusted OS curve for SVd remains above and parallel to the IxaRd curve for the first 30 months when the two curves cross. However, the number at risk for the adjusted SVd curve is 23 at 24 months, and it drops to 0 at 36 months, unlike the numbers at risk for the unadjusted SVd curve and the IxaRd curve. This suggests there is a high level of uncertainty after 24 months, and inspection of the PH		

	assumption should be based on the initial 24 months only. The Company maintains that the results from the updated 3L+ NMA should be used in the CEA. As presented in the EAG report, the updated 3L+ NMA estimated a PFS HR for IxaRd *vs*. Vd of 0.56 for PFS and an OS HR of 0.85, while the PFS and OS HRs of IxaRd *vs*. Vd from the unanchored MAIC are 0.37 and 0.48, respectively. In the EAG report of TA505, the EAG performed an NMA for 3L+ using studies such as APEX, MM-009, MM-010 and Dimopoulos *et al.* (2015), for which the current EAG highlighted some limitations. The EAG's NMA in TA505 estimated a PFS HR of IxaRd *vs*. Vd of 0.75 (Committee papers ACD 1 Draft guidance: TA505 ACD,[3] page 109 of the EAG report, page 717 of the overall document) and an OS HR of 0.91 (Committee papers ACD 1 Draft guidance: TA505 ACD,[3] page 115 of the EAG report, page 723 of the overall document), and was considered the best source of comparative effectiveness by the EAG. Results from the EAG's NMA of TA505 are more in		

	line with the results of the updated company NMA, suggesting that using the HRs of IxaRd *vs.* Vd from the unanchored MAIC might lead to an overestimation of the efficacy of IxaRd *vs.* Vd.		

Issue 6 Regimen error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In the last bullet point on page 85, the wrong regimen is referenced for MM-009 and MM-010 trials	The correct treatment should be 'Rd' instead of 'Kd' in MM-009 and MM-010 trials	Error	Thank you for highlighting this error. The EAG report has been amended.

Issue 7 Regimen error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In the first paragraph on page 86, the wrong treatment is referred to	The correct treatment should be 'Rd' instead of 'Kd'	Error	Thank you for highlighting this error. The EAG report has been amended.

Issue 8 Regimen

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In the second paragraph on page 86, the wrong treatment is referred to	The correct treatment should be ‘Rd’ instead of ‘Kd’	Error	Thank you for highlighting this error. The EAG report has been amended.

Issue 9 Regimen

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In the second paragraph on page 86, the wrong treatment is referred to	“Conversely, the lack of OS adjustment in MM-003 would bias results in the opposite direction, i.e., in favour of IxaRd” - the correct treatment should be ‘SVd’ instead of ‘IxaRd’	Error	Thank you for highlighting this error. The EAG report has been amended.

Issue 10 Curve fitting

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 113 of the EAG report states ‘However, the EAG notes, that of the models	This sentence appears to be incomplete. If this sentence aims to differentiate between proportional	Sentence needs completion for interpretability, but potentially also a correction to	Thank you for highlighting this error. The EAG report has

explored, only the exponential, Weibull and Gompertz distributions.'	hazard (PH) and accelerated failure time (AFT) distributions, please note that all distributions other than the exponential and Gompertz are AFT using the R *flexsurv* package used for curve fitting.	characterise parametric curves according to the survival analysis tools used. The potential impact depends on how curve type (AFT/PH) is factored into decision-making around appropriate curve selection.	been updated so that the sentence reads, "However, the EAG notes, that of the models explored, only the exponential, Weibull and Gompertz distributions supports the proportional hazards assumption". The EAG is unclear if the company is stating that their approach to the Weibull, was to specify this an AFT model using the R *flexsurv* package and requests further clarification. As per DSU TSD 14, the Weibull is a proportional hazards model and not an AFT model. Thus, if when using R, the Weibull has been specified as an AFT model even though the company asserts that the proportional hazards assumption holds for the data from BOSTON, this

			is an inconsistency that needs explanation and justification from the company.

Issue 11 Proportional hazards (PH) assessment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The company disagrees with the assertion on Page 115 that the PH assumption (for BOSTON SVd *vs.* Vd comparisons) 'was violated for PFS, OS and TTD for both the 2L and 3L subgroups'.	The Company feels that it is important to convey the subjectivity of this assessment and that the EAG's interpretation is not supported by statistical tests. Schoenfeld residual tests for PH violations were not statistically significant at the 5% level for 3L OS (p=0.16), 3L PFS (p=0.10), 3L TTD (p=0.62), 2L OS (p=0.49) or 2L TTD (p=0.49): the only statistically significant test result (suggesting violation of proportional hazards assumptions) was for 2L PFS (p=0.003).	The interpretation of proportional hazards assumptions has a critical bearing on the appropriateness of joint or independent curve fitting approaches, the use of SVd or Vd as a referent arm for comparator estimates, and cost-effectiveness results overall. The Company feels strongly that the EAG's rejection of proportional hazards assumptions is not supported and has an undue influence on results and that uncertainty around the EAG's assessment	Not a factual inaccuracy. No change required. The EAG notes that visual inspection of the log-cumulative hazards and Schoenfeld residual plots provided in the company submission indicated that the proportional hazards assumption was violated. For the log-cumulative hazards plots, curves which are not straight, crossing, overlapping or non-parallel indicated a violation of the

		of proportional hazards should be conveyed clearly.	proportional hazards assumption and this was seen for OS (3L, curves were not straight, 2L curves were crossing). For 3L PFS, the log-cumulative hazard plots showed curves which were non-parallel and slightly curved. TTD for both subgroups, curves on the log-cumulative hazards plots were overlapping and crossing. All Schoenfeld residual plots produced lines which were not straight, suggesting visually that the PH assumption did not hold. This detail has been added to the EAG report for clarity. The EAG further notes that the Company's argument is based on interpreting non-significant results as evidence in favour of the

			null, without providing evidence that the tests are powered to detect PH violations.

Issue 12 Discrepancy between NMA assumption for PFS and OS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The company believe there is inconsistency in the EAG approach to the NMA for PFS and OS. The EAG statement is that *'there is evidence of inferiority of SVd relative to Kd (2L), IxaRd and PanoVd (3L) in terms of PFS. […*] But at the same time for OS: *The EAG considers there to be reasonable evidence of similar effect on OS for all comparators.'* (Sections 3.5, page 106)	The Company wish to highlight that a different approach is taken by the EAG when considering PFS and OS comparative results, despite similar uncertainty in both endpoints. Results from the 2L NMA have demonstrated that SVd is numerically inferior to Kd in terms of both PFS and OS. On the other hand, results from the updated 3L+ NMAs, along with the unanchored MAIC of SVd vs IxaRd, have shown that SVd is numerically inferior to IxaRd and PanoVd in terms of PFS, while numerically superior in terms of OS. The PFS HRs from the 2L NMA and updated 3L+ NMA were considered appropriate by the EAG and hence	Clarification	Not a factual inaccuracy. No change required. The EAG's view is not inconsistent because, while the point estimates and uncertainty intervals were a similar distance from 1 for PFS and OS, the EAG noted the OS results were additionally confounded by differences in treatments at later lines both within and between trials. Hence, the EAG considered the evidence for between treatment differences in PFS to be stronger and less

	used as the source of comparative efficacy in the model, although they are not statistically significant (i.e. confidence intervals cross 1) due to high uncertainty, which has always been associated to large NMAs as in myeloma. On the other hand, a similar benefit is assumed for OS across all treatments, although the level of uncertainty and the statistical insignificance of OS HRs from the NMAs are similar to those in the PFS setting. However, in this instance, these have not been used by the EAG as a source of comparative efficacy. Given the similar uncertainty across both results, including PFS and not OS is counterintuitive.		confounded than the evidence for between treatment differences in OS.

Issue 13 Proportional hazards applied to curves

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 126 states that the 'gamma distribution does not support the assumption of PH to apply HRs from the	When applying a hazard ratio to an AFT curve (a gamma in this instance), the resultant comparator curve cannot be characterised as a gamma curve.	Presenting this as a technical issue is inconsistent with precedent submission	Not a factual inaccuracy. No change required.

ITC for the comparators to the selected curve'.	However, this does not invalidate the approach of applying hazard ratios to AFT distributions, which is commonplace in company and EAG-preferred scenarios.	approaches and artificially reduces the available curves.	

Issue 14 Relative importance of PFS and OS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 4 page 24 and section 5.2.3.6 page 131 states '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.	The Company wish to discuss and highlight that this assumption starkly contrasts with the expert opinions it gained from clinicians and patient organisations during the submission process. **OS in early RRMM treatment lines** Disease control and survival rates in myeloma patients decrease rapidly from their first line of treatment and continue to decrease over subsequent lines of treatment. The measurement of both PFS and OS outcomes is essential for guiding treatment decisions for patients and clinicians, especially in an ageing population, and therefore, it is not accurate to state that	Clinical and patient organisation opinion does not support the EAG assumption.	Not a factual inaccuracy. No change required.

	improvement in PFS at each line is more clinically relevant than OS – they are of equal importance. **Treatment-free intervals** Substantial treatment-free intervals have been recorded in BOSTON and published sources examining myeloma treatment pathways more broadly (see Yong *et al.* 2016).[4] In addition, feedback from myeloma clinical and patient experts during the submission process highlighted the importance of treatment-free intervals. Therefore, it is inaccurate to state that patients will be unlikely to be off treatment until they reach the sixth line. **Importance of PFS** The Company does recognise the importance of PFS being clinically relevant. As DRd becomes SoC in the frontline treatment of transplant-ineligible patients, patients refractory to both treatment classes will present a priority medical unmet need in coming years. In addition, this will mean that many		

	patients who are not eligible for these treatments will not be exposed to a PI and at the point of 1st relapse, will be PI Naïve. The subgroup analysis of the Lenalidomide refractory population within the BOSTON ITT population showed SVd had PFS gains of 10.2 months compared to 7.1 months with Vd. The median OS for SVd was 26.7 months compared to 18.6 months for Vd. The subgroup analysis of PI Naïve patients demonstrated a statistically significant and clinically meaningful ~20-month median PFS improvement compared to Vd (29.5 months *vs*. 9.7 months respectively).		

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**
No issues identified	NA	NA

We would also like to take this opportunity to point out the following typographical errors that we noticed during our review

EAG report page number	**Inaccuracy**	**EAG response**
19	SVD in the first paragraph under 1.1, should be SVd to be consistent with the rest of the document	Thank you for highlighting this error. The EAG report has been amended.
31	“Fourty-three” should be “Forty-three”	Thank you for highlighting this error. The EAG report has been amended.
33	The word indelible should be ineligible	Thank you for highlighting this error. The EAG report has been amended.
50	In the data extraction row of Table 17, the word trail should be trial	Thank you for highlighting this error. The EAG report has been amended.
55	In the first paragraph of 3.2.1.2, we believe the word “naïve” is missing following “bortezomib”.	Thank you for highlighting this error. The EAG report has been amended.
70	“The Company, in contrast, sates” instead of states	Thank you for highlighting this error. The EAG report has been amended.
95	In the first paragraph of 3.4.3.3.1, ‘BOSON’ should be ‘BOSTON’	Thank you for highlighting this error. The EAG report has been amended.

In addition to the issues highlighted by the Company, the EAG has revised a sentence on page 55 of the EAG report following feedback from a clinical expert highlighting a potential inaccuracy. The following sentence has been revised:

Original: "…considering **all** patients who had prior SCT (31.3% 2L, 43.4% 3L) would have receive lenalidomide maintenance therapy at 1L,"

Revised: "…considering **the majority of** patients who had prior SCT (31.3% 2L, 43.4% 3L) would have receive lenalidomide maintenance therapy at 1L,"

References

1. *European Medicines Agency (EMA). Kyprolis: Summary of product characteristics 2022;*
2. *European Medicines Agency (EMA). Velcade: Summary of product characteristics.*
3. *National Institute for Health and Care Excellence. TA505: Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. 2018.*
4. *Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. Oct 2016;175(2):252-264. doi:10.1111/bjh.14213*

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5:00pm** on **Wednesday 20 December 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating relapsed refractory multiple myeloma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Neil Rabin and [redacted]
2. Name of organisation	UK Myeloma Society
3. Job title or position	[redacted] Consultant Haematologist (NR) [redacted] Executive members of the UK Myeloma Society
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed refractory multiple myeloma? ☐ A specialist in the clinical evidence base for relapsed refractory multiple myeloma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

8. What is the main aim of treatment for relapsed refractory multiple myeloma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Prolonged survivorship with improved quality of life through minimal treatment-related toxicity and maximal impact associated with limited disease-related morbidity.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Achievement of at least a Partial Remission(>50% reduction in blood-borne markers), optimally better than a Very Good Partial Remission (>90% reduction in blood-borne markers) that is sustained and associated with improved quality of life.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed refractory multiple myeloma?	There are many unmet needs in caring for patients with myeloma, relevant to this HTA. Myeloma remains an incurable illness associated with significant morbidity. Advances in therapy-related survivorship with Selinexor allows for disease control, reduced health burden and potential for prolonged survival compared to current treatments.
11. How is relapsed refractory multiple myeloma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The treatment "pathway" is delineated by multiple, non-linked NICE HTA decisions, including drug combination availability through the CDF. This has led to a some-what rigid artificial pathway that limits individualised patient treatment decision and clinical judgment in many cases. Consequentially there are differences of opinion from what we (the professionals) wish to do versus what we are allowed to do (dictated by NICE HTAs). Add to this the dogma of "one size does not fit all" and myeloma therapy is a complicated landscape that is well placed to become the beacon of personalised anti-cancer medicine. The current technology under consideration allows patients to benefit from a drug with a unique mechanism of action, giving added benefit compared to standard treatments currently on offer.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	The proposed regimen is a triplet, given in combination with an existing therapy (Bortezomib). Seliexor is an oral medication. Bortezomib is an established treatment given as a subcut injection. There is no change in how this administered currently. There will have limited impact on pharmacy and no impact on oncology day units.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	We fully expect the technology to improve significant disease control, limiting disease-related morbidity and improving survivorship myeloma patients with relapsed/refractory disease. This will translate into meaningful gains in quality of life for our patients.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	We expect all patients to gain benefit from this technology.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	There is no issue about regimen delivery. Selinexor is an oral therapy that does have some expected toxicities associated with it (nausea, vomiting, diarrhoea, anorexia, dysgeusia, fatigue, thrombocytopenia). This are manageable. There will need to support given to healthcare professionals on how to manage these.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Only standard of care stop/start rules with no extra investment needed.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	We think the health-related benefits are mostly captured.

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This technology improves disease control for patients with myeloma with relapsed disease, limiting disease-related morbidity and improving survivorship. It offers a novel mechanism of action (First-in-Class Nuclear Export Inhibitor)
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Selinexor is an oral therapy that does have some expected toxicities associated with it (nausea, vomiting, diarrhea, anorexia, dysgeusia, fatigue, thrombocytopenia). This are manageable. There will need to support given to healthcare professionals on how to manage these.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Bortezomib is given sc and weekly as part of standard of care. BOSTON trial reports given Bortezomib weekly as the current standard of care: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32292-3/fulltext.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	There is limited real world data for this technology.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	None

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Oral therapy

Manageable side effects

Novel mechanism of action (First-in-Class Nuclear Export Inhibitor)

Myeloma remains an incurable disease

Easy to deliver

Thank you for your time.

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Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with relapsed refractory multiple myeloma or caring for a patient with relapsed refractory multiple myeloma. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

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Thank you for your time.

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Part 1: Living with this condition or caring for a patient with relapsed refractory multiple myeloma

Table 1 About you, relapsed refractory multiple myeloma, current treatments and equality

1. Your name	Rosemary Dill
2. Are you (please tick all that apply)	☒ A patient with relapsed refractory multiple myeloma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with relapsed refractory multiple myeloma? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with relapsed refractory multiple myeloma? **If you are a carer (for someone with relapsed refractory multiple myeloma) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for relapsed refractory multiple myeloma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for relapsed refractory multiple myeloma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of Selinexor with bortezomib and low-dose dexamethasone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	

9c. Does Selinexor with bortezomib and low-dose dexamethasone help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of Selinexor with bortezomib and low-dose dexamethasone over current treatments on the NHS please describe these. For example, are there any risks with Selinexor with bortezomib and low-dose dexamethasone? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from Selinexor with bortezomib and low-dose dexamethasone or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering relapsed refractory multiple myeloma and Selinexor with bortezomib and low-dose dexamethasone? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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