NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]

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 submission** from:
   a. Myeloma UK
   b. UK Myeloma Society

4. **Expert personal perspectives** from:
   a. Neil Rabin – Clinical expert, nominated by UK Myeloma Society
   b. Rosemary Dill – Patient expert, nominated by Myeloma UK

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

6. **External Assessment Group response to factual accuracy check of EAR**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after four or more treatments [ID6193]

Document B

Company evidence submission

July 2023

File name	Version	Contains confidential information	Date
[ID6193] Sel+dex PR-MM Doc B [NoAICorDPD_CICmarked]	FINAL v1 amended	**Yes**	22/01/2024

Contents

Tables and Figures

Glossary of abbreviations

Term	Definition
1L	First-line
2L	Second-line
3L	Third-line
4L	Fourth-line
5L	Fifth-line
5-HT3	5-hydroxytryptamine
ADC	antibody-drug conjugates
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criterion
ASCT	Allogenic stem cell transplant
AUC	Area under curve
BCLPD	Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
BaAbs	Bi-specific antibodies
BSC	Best supportive care
CASP	Critical Appraisal Skills Programme
CAR-T	Chimeric antigen receptors cell therapy
CBR	Clinical benefit rate
CCT	Conventional chemotherapy
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability
CEM	Cost-effectiveness model
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination (University of York)
DCB	Duration of clinical benefit
DCR	Double-class refractory
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DVd	Daratumumab plus bortezomib and dexamethasone
ECOG	Eastern Cooperative Oncology Group

Term	Definition
EHA	European Haematology Association
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life 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
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-MM	Functional Assessment of Cancer Therapy–Multiple Myeloma
FLC	Free light chain
G-CSF	Granulocyte colony-stimulating factor
GID	Guidance in development
HCHS	Hospital and Community Health Services
HCP	Healthcare professional
HCRU	Healthcare resource use
HDACi	Histone deacetylase inhibitors
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
INV	Investigator (assessed)
IRC	Independent Review Committee
IsaPd	Isatuximab plus pomalidomide and dexamethasone
ITC	Indirect treatment comparison
IxaRd	Ixazomib plus lenalidomide and dexamethasone
KM	Kaplan-Meir
LY	Life year
LYG	Life year gained
MA	Marketing authorisation
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intent-to-treat
MM	Multiple myeloma
MoA	Mechanism of action

Term	Definition
MR	Minimal response
MyPOS	Myeloma patient outcome scale
MUK	Myeloma UK
MVH	Measurement and valuation of health
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NHB	Net health benefit
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NICE	National Institute for Health and Care Excellence
NFkB	nuclear factor κB
NR	Not reported
OLS	Ordinary least squares
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PanoVd	Panobinostat plus bortezomib and dexamethasone
PAR	Public assessment report
Pd	Pomalidomide plus dexamethasone
PD	Progressive disease
PFS	Progression-free survival
PI	Proteosome inhibitor
PP	Per protocol
PR	Partial response
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services (Research Unit)
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QoL	Quality of life
RBC	Red blood cell
RCT	Randomised controlled trial
R-ISS	Revised International Staging System
RNA	Ribonucleic acid
RRMM	Relapsed and/ or refractory multiple myeloma

Term	Definition
SACT	Systemic Anti-Cancer Therapy (Dataset)
SAE	Serious adverse event
sCR	Stringent complete response
Sd	Selinexor plus dexamethasone
SD	Stable disease/ standard deviation
SE	Standard error
SINE	Selective inhibitor of nuclear export
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SPEP	Serum protein electrophoresis
STC	Simulated treatment comparison
SVd	Selinexor plus bortezomib and dexamethasone
TCR	Triple-class refractory
TEAE	Treatment-emergent adverse event
TOI	Trial Outcome Index
ToT	Time on treatment
TRAE	Treatment-related adverse event
TSP	Tumour suppressor proteins
TTNT	Time to next treatment
TTP	Time to progression
UPEP	Urine protein electrophoresis
US	United States (of America)
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. One example of this would be “BCLPD-refractory.”
BCLPD-refractory	Refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, one example of penta-refractory
Penta-exposed	Has been exposed to two proteasome inhibitors, two immunomodulatory drugs, and an anti-CD38 monoclonal antibody
Triple-class refractory	Refractory to one proteasome inhibitor, one immunomodulatory drug, and an anti-CD38 monoclonal antibody
Refractory	Usually interpreted as ≤25% response to therapy or progression during or within 60 days after completion of therapy
Proteosome inhibitors	Including: bortezomib, carfilzomib and ixazomib
Immunomodulatory drugs	Including: lenalidomide, pomalidomide, and thalidomide
Anti-CD38 monoclonal antibodies	Including: daratumumab, and isatuximab

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 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 in the majority of patients. MM patients often require multiple lines of treatment throughout the course of their disease. Clinicians, nurses and patients place a high value on having access to safe and effective treatment combinations throughout the treatment pathway, which includes different but complementary and synergistic mechanisms of action (MoA), as patients often become increasingly refractory to different classes of drug.

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 in two different indications.[2,3] NICE is appraising both treatment combinations 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]
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**
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**

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors; mAb, monoclonal antibody; 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. have requested 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 moving into 2L as the treatment landscape evolves, particularly the first-line (1L) treatment paradigm
- Sd in the later line 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 clinical experts (clinicians, nurses and patients) and where the evidence base for the medicine best supports its use.

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

Table 2 The decision problem

	Final scope issued by NICE (ID6193, June 2023)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with relapsed or refractory multiple myeloma who have had 4 or more treatments and whose disease is refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy.	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, and who have demonstrated disease progression on the last therapy.	This wording aligns with the MHRA MA for Sd.[3] Pivotal evidence for this penta-refractory population is from STORM Part 2, the penta-refractory efficacy population (referred to as BCLPD-refractory in STORM).
Intervention	Selinexor with dexamethasone	Selinexor with low-dose dexamethasone	N/A
Comparator(s)	● Pomalidomide in combination with low-dose dexamethasone ● Panobinostat in combination with bortezomib and dexamethasone ● Belantamab mafodotin (subject to ongoing NICE appraisal) ● Conventional chemotherapy regimens ● Best supportive care	For patients that are penta-refractory, best supportive care (BSC) – proxied standard of care.	The NICE final scope lists a number of comparator therapies. However, none of these interventions are licensed for penta-refractory MM and are not likely to be viable treatment options for penta-refractory patients for the reasons detailed below, which have been validated with UK myeloma clinical experts: Pomalidomide + dexamethasone (Pd): to be penta-refractory, patients must have documented refractoriness to two IMiDs; therefore, even if patients are not already Pd exposed/ refractory, treatment with a further IMiD would likely be unsuitable. Panobinostat + bortezomib + dexamethasone (PanoVd): to be penta-refractory, patients must have documented refractoriness to two PIs; therefore, treatment with a further bortezomib regimen would be unsuitable, and myeloma clinical experts describe limited use of PanoVd, regardless.

	Final scope issued by NICE (ID6193, June 2023)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Belantamab mafodotin: was recently appraised by NICE for triple-class refractory (TCR) MM (not penta-refractory, and thereby be indicated for a different population). However, draft guidance states it is not recommended for use.[6] Conventional chemotherapy (CCT): UK myeloma clinical experts described that while there may be limited use of agents such as cyclophosphamide, they would not consider this to be a major comparator for penta-refractory patients. Any limited use of CCT agents they would class under the umbrella of BSC. Therefore, considering all of the above, UK myeloma clinical experts' input suggests BSC as the only comparator.
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 outcome measures to be considered include: ● overall survival ● progression-free survival ● response rates ● adverse effects of treatment ● health-related quality of life	N/A
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	Costs are considered from an NHS and Personal Social Services perspective. The cost effectiveness of the treatments is expressed in terms of incremental cost per quality-adjusted life year, as per the reference case. The cost-effectiveness model uses a partitioned survival analysis approach,	N/A

	Final scope issued by NICE (ID6193, June 2023)	Decision problem addressed in the company submission	Rationale if different from the final NICE 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 considered.	whereby extrapolated OS, PFS and ToT outcomes are used to estimate the distribution of patients across health states over time. The health states in the model are progression-free, progressed disease and death, with the progression-free and progressed disease health states subdivided into on and off treatment. A lifetime horizon of 30 years is considered, with modelled overall survival of approximately 0.1% after 30 years, in keeping with the reference case.	
Subgroups to be considered	If evidence allows, the following subgroups will be considered: cytogenetic risk factors	Numbers do not support meaningful analysis of subgroups within the penta-refractory population.	The MA for Sd is based on the penta-refractory group of patients forming one pre-defined efficacy population of Part 2 of the pivotal STORM trial (n=83), which forms the pivotal evidence for this submission. Numbers do not support meaningful analysis of subgroups within the penta-refractory population.
Special considerations including issues related to equity or equality		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 nor lead to recommendations that will have an adverse impact on people with a particular disability or disabilities.	N/A

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; BSC, best supportive care; HCP, healthcare professional; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; MM, multiple myeloma; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; OS, overall survival; PFS, progression free survival; Sd, selinexor plus dexamethasone; ToT, time on treatment

B.1.2 Description of the technology being appraised

Table 3 provides a summary of the technology being appraised, selinexor. 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 and dexamethasone 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 one prior line of therapy.[3]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Selinexor, in combination with dexamethasone 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 selinexor combination and corresponding indication is addressed in this company submission (ID6193). Selinexor, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. This selinexor combination and corresponding indication are addressed in a separate company submission, submitted to NICE simultaneously (ID3797).[3]
Method of administration and dosage	Selinexor is for oral use. The recommended selinexor and dexamethasone starting doses in the Sd combination are as follows: ● Selinexor 80mg taken orally on Days 1 and 3 of each week.

	• Dexamethasone 20mg taken orally on Days 1 and 3 of each week with selinexor. Treatment with Sd 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. 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 as follows when in combination with dexamethasone: • First reduction 100mg once weekly • Second reduction 80mg once weekly • Third reduction 60mg 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.
Additional tests or investigations	No additional test or investigations are required to initiate treatment, or to identify the eligible licensed population.
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: GI, gastrointestinal; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National institute for Health and Care Excellence; PAS, patient access scheme; Sd, selinexor plus dexamethasone; SINE, selective inhibitor of nuclear export; SmPC, summary of product characteristics; SVd, selinexor plus bortezomib and dexamethasone; TSPs, tumour suppressor proteins; XPO1, exportin 1

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Overview of the health condition

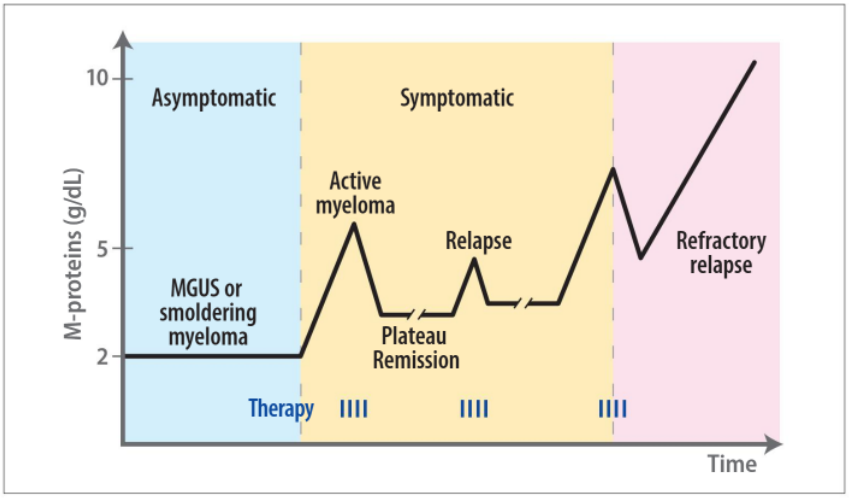
Multiple myeloma (MM) is a rare, clonal B-cell malignant neoplasm characterised by the accumulation of abnormal clonal plasma cells (myeloma cells) in the bone marrow microenvironment.[7] MM can be caused by several genetic plasma cell abnormalities which modify the expression of adhesion molecules on the cell surface and the cellular response to growth stimuli within the bone marrow, promoting cell growth, survival, and migration.[8] 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 MGUS and smouldering myeloma.[9,10] The acronym CRAB summarises the most typical clinical manifestations of multiple myeloma: 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 and direct toxicity from hypercalcaemia. Hypercalcaemia can also lead to GI symptoms such as thirst, nausea and constipation, as well as neurological effects including confusion, drowsiness, and neuropathy.[9-14]

In the plasma cells of MM patients, levels of XPO1, a key nuclear export receptor, are higher than in healthy people.[7,15] 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.[7,15]

Despite advances in treatment, MM remains incurable in the majority of patients; most patients relapse on treatment and require multiple lines of therapy. The primary goal of MM treatment is to achieve an early, deep, and durable response with an acceptable level of toxicity. However, MM is clinically and pathologically heterogeneous, resulting in variability in both responses to treatment and survival. Survival can range from a few months to over 10 years.[16] The MM disease trajectory will vary for each patient; however, as described above, relapses after treatment are inevitable, and the depth and duration of response following each relapse are generally diminished (Figure 1).[17] For patients in later treatment lines, symptom frequency increases as disruption of normal bone marrow function leads to the increasing risk of bone damage, pain, and reduced immune function, while treatment-related comorbidities also impair performance status and QoL, and there is an increasing risk of death.[11,14,17,18]

Figure 1 Graphical representation of MM disease progression phases



Source: Durie *et al*. 2018 (International Myeloma Foundation)[17]

By the time MM patients reach later lines of treatment, they have often relapsed on and become refractory to the major classes of drugs used to treat MM, and prognosis is poor.[8,11,19] Mechanisms of drug resistance include genetic and epigenetic abnormalities in tumour suppressor genes, changes in bone marrow environment, and clonal evolution of MM cells.[20] Drug resistance is a major limitation of current MM treatments, including newer treatments, where patients may become refractory to multiple drug classes. When patients are considered penta-refractory, treatment options become severely limited, and re-treatment with drug classes are inappropriate.

B.1.3.1.1 Epidemiology

The median age of MM diagnosis is ~70 years, with the 2020 global incidence at 176,404, in Europe.[21] Incidence of MM is increasing (136% increase between 1990-2019) worldwide due to the ageing population. The 2020 global mortality from MM was 117,077, with a median survival of 5-7 years.[21] Risk factors for MM include age and frailty, male sex, and family history.[8,22-26]

In the UK, approximately 5,800 people are diagnosed with MM every year, and there are currently around 17,600 people living with MM in the UK.[27] MM accounts for approximately 1% of all cancers and 10% of haematologic cancers. In Europe, around 95% of those diagnosed with MM receive 1L treatment, but given the increasing challenges for patients with each line of treatment, attrition is significant, resulting in an estimated drop to 1% of diagnosed MM patients receiving 5L treatment.[28] There are no specific data on the number of patients with penta-refractory disease due to the continuously changing treatment landscape, however a conservative estimate is to assume it equates to the number reaching 5L, while acknowledging this to be an over-estimate.

B.1.3.2 Clinical pathway of care

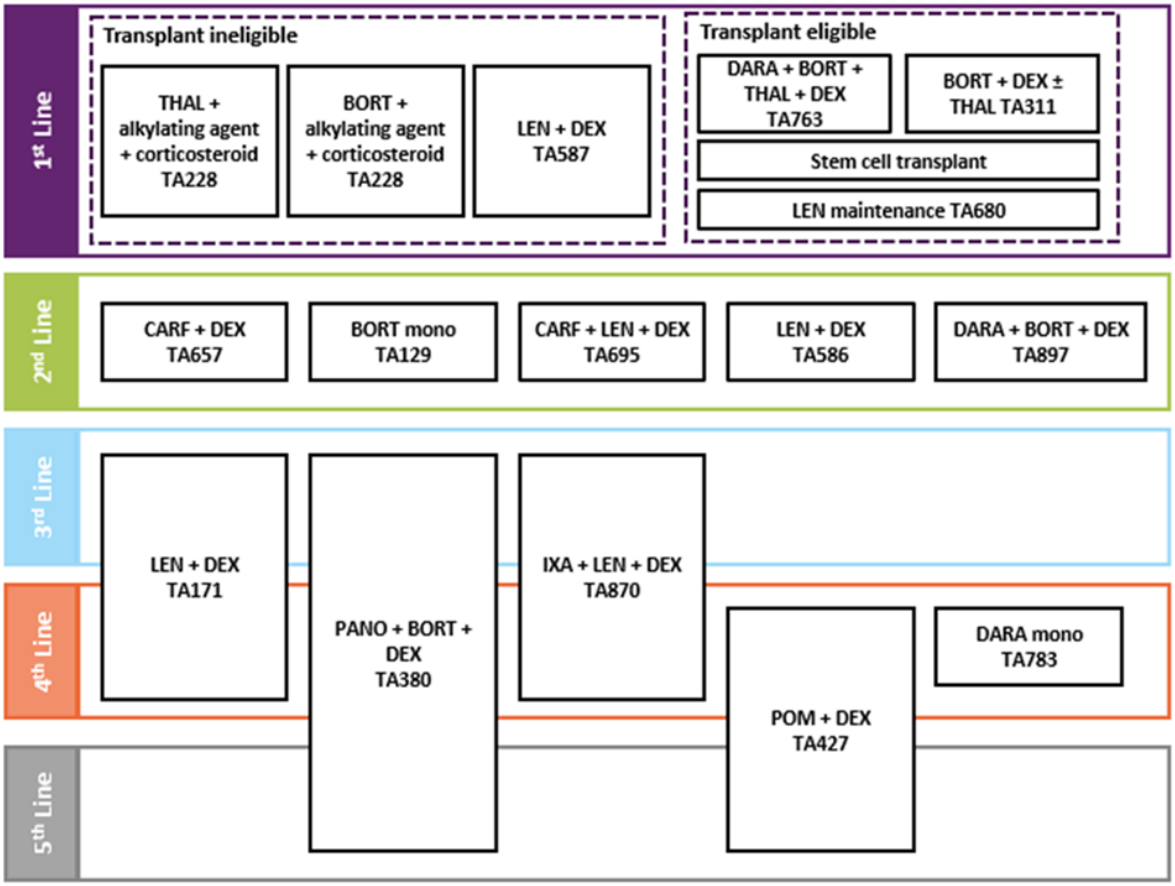
B.1.3.2.1 Current treatment landscape

The aims of MM treatment are multifactorial; effective treatment should manage the disease by offering a deep and durable response that reduces disease burden, maintains/ improves the quality of life, and extends survival. The treatment landscape for MM is complex, with various interventions and combination regimens recommended across different treatment lines. The treatment strategy is personalised where possible, taking into account age, frailty, and comorbidities whilst managing the side effects of treatments.[29,30] As patients pass through lines of treatment, previous class/ drug exposure and refractoriness also play a key part in decision-making.

NICE guideline 35 (NG35), '*Myeloma: diagnosis and management'*, was last updated in 2018, since when multiple NICE guidance from technology appraisals of new treatments have been published.[31] A treatment pathway devised to reflect current published NICE guidance for the routine treatment of MM is presented in Figure 2, (correct to July 2023). Despite increasing numbers of patients reaching later lines of

MM treatment with penta-refractory disease who remain suitable for active treatment and not yet at the point of palliative, end-of-life care, there are currently no treatments available in the UK that are licensed and reimbursed in this setting.

Figure 2 Devised pathway to represent current interventions with routine NICE guidance in MM, correct to 22 June 2023



The company conducted two Advisory Boards with UK MM clinical experts and patients to inform and validate assumptions about the current and evolving treatment landscape in MM across both indications.[32,33] Feedback from these Advisory Boards emphasised the need to treat patients at a later line as difficult; shared decision-making with the MM patient and their family is critical. Patients may be suitable for active treatment with Pd, PanoVd, or CCT (such as cyclophosphamide plus dexamethasone) at 5L, but for those who are also penta-refractory and with sufficient performance status to tolerate active treatment, options are more limited. Input from UK myeloma clinical experts and patients suggests these interventions are not routinely used in penta-refractory patients since they would likely have already been exposed and refractory to the treatments recommended at 5L (as detailed in Table 2), or these treatment

combinations would not be clinically appropriate at this stage in their treatment. Instead, many penta-refractory MM patients currently enrol in clinical trials or use compassionate use programmes to receive active treatment.

B.1.3.2.2 Future treatment landscape

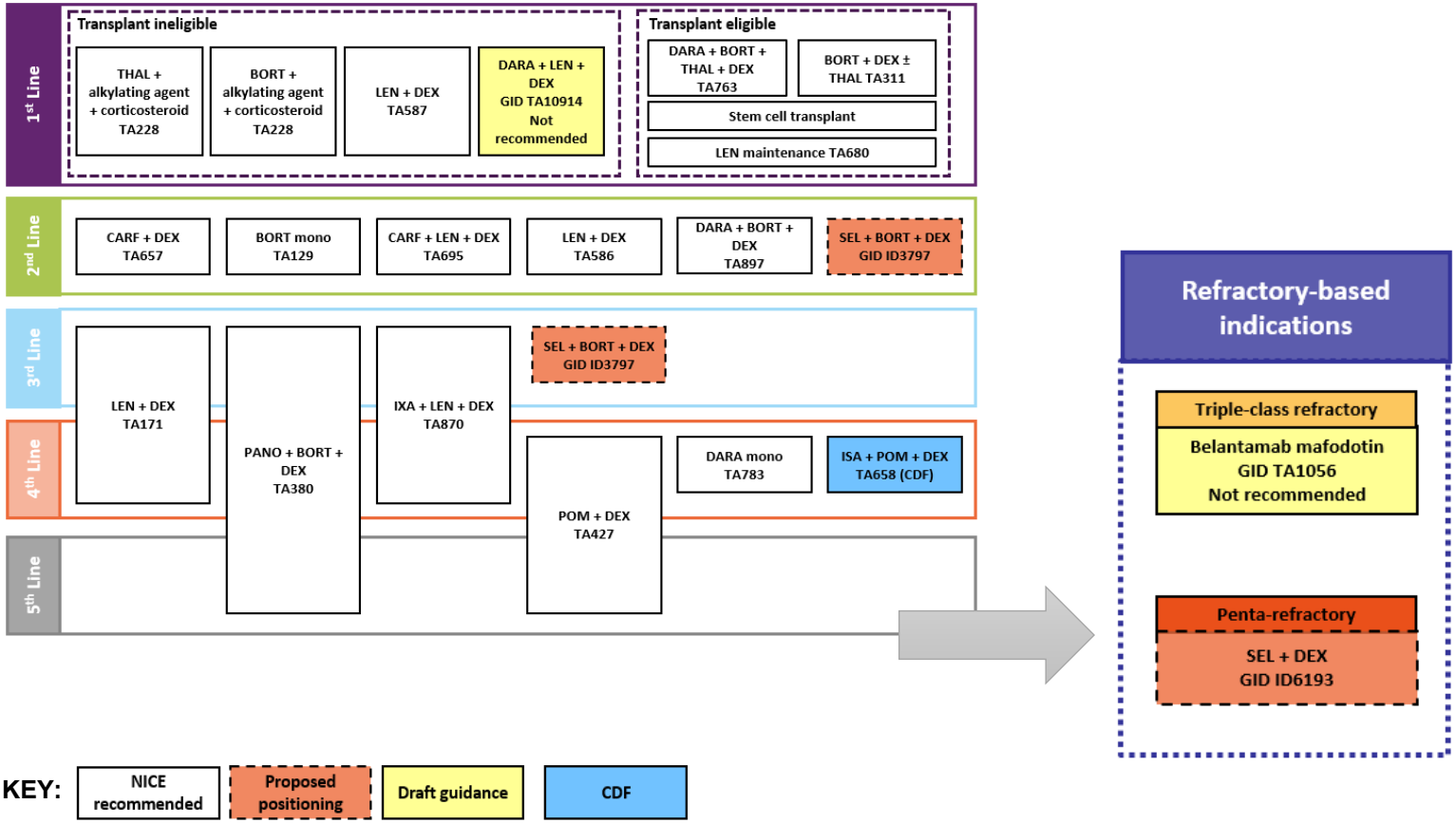
The Sd licensed indication relevant to this submission specifies that eligible MM patients should have at least four prior therapies **and** be refractory to at least two PIs, two IMiDs and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy, making the Sd combination the first licensed treatment specifically for penta-refractory MM.[3] Expert clinical input has aided the understanding of how Sd could be integrated into current UK clinical practice to optimise patient access.

Since the current treatment landscape, as described in Section B.1.3.2.1, includes no specific treatment options for penta-refractory MM, the clinical experts consulted suggested that BSC represents the only relevant comparator from the NICE scope for this decision problem although it may be seen as a proxy for the actual standard of care in the UK. Treatment approaches that were described collectively as 'BSC' included cyclophosphamide, melphalan, prednisolone, dexamethasone, thalidomide, and bendamustine and other supportive care to manage symptoms and comorbidities.

The refractoriness of patients in clinical practice has also been considered in the context of the penta-refractory license, which was based on the STORM BCLPD-refractory population (that is those that have documented refractoriness to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab), described in Section B.2.3.1. There are a number of treatment pathways a patient could currently take in order to become penta-refractory by 5L and beyond, with the number of permutations increasing with published guidance for daratumumab combinations earlier in the treatment pathway, and other mechanisms of access to treatment such as via the CDF, or in clinical trials and compassionate use/ early access programmes.

A potential future treatment pathway is presented in Figure 3, which takes into account the licensed penta-refractory indication of Sd with positioning that sits outside of the convention for routine lines of MM treatment.

Figure 3 Devised future pathway inclusive of interventions with routine NICE guidance in MM, draft guidance, those in the CDF, and proposed selinexor positioning, correct to 22 June 2023



B.1.3.3 Unmet need

The treatment landscape in MM has evolved dramatically over the last two decades with the introduction of PIs, IMiDs, histone deacetylase inhibitors (HDACi), and more recently anti-CD38 mAbs, chimeric antigen receptor T-cell therapy (CAR-T), antibody-drug conjugates (ADC), and bi-specific antibodies (BsAbs). Efficacious treatment combinations have resulted in extended time to relapse, a greater number of patients reaching later lines of treatment and ultimately extended overall survival after initial diagnosis with MM. However, MM remains incurable and patients will eventually relapse with increased refractoriness to available classes of drugs. There is no preferred treatment choice for patients with penta-refractory disease. BSC options outlined above (Section B.1.3.2.2) for patients with penta-refractory disease are associated with limited efficacy, issues with safety and tolerability, and drug resistance.[34-37] These patients have a poor prognosis.

There is a paucity of published natural history data, specifically in patients with penta-refractory MM. TCR disease is more widely reported, estimating OS as between 3.5 - 5.6 months.[7,38] It is widely acknowledged that as MM becomes more refractory (especially to anti-CD38 mAbs), the median PFS, DOR, and OS diminishes with each line of treatment Therefore, the median OS for patients with penta-refractory disease is likely to be lower than that reported for TCR MM.[7,34]

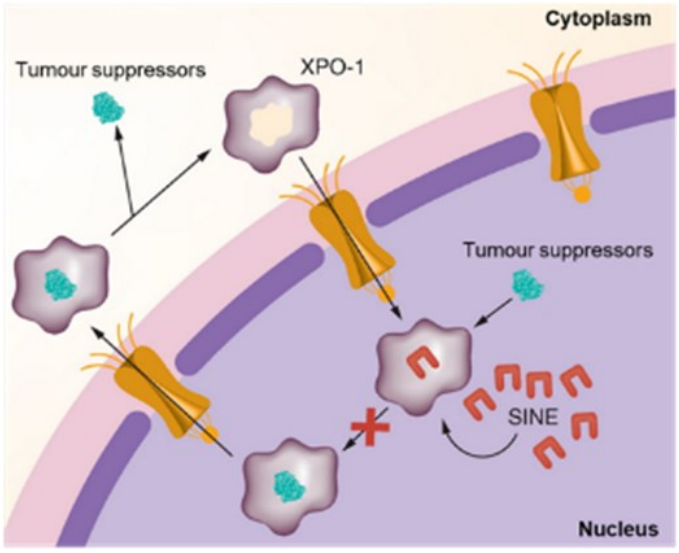
Whilst the number of patients reaching the later lines of MM treatment was traditionally very small, and the proportion fit enough to receive further active disease-modifying treatment even smaller, this is increasing as the treatment landscape evolves in earlier treatment lines. Expert clinical input suggests high proportions of MM patients at later lines enrol in clinical trials or utilise early access/ compassionate use programmes without other options. Therefore, unmet need remains for a licensed, active, efficacious, and tolerable treatment for penta-refractory patients. In addition, orally administered treatments are of additional value, given the advanced age, multiple comorbidities, and concomitant treatments in penta-refractory patients.

B.1.3.4 The introduction of selinexor

Selinexor is an oral, bioavailable, first-in-class, selective inhibitor of nuclear export (SINE) compound that specifically blocks the activity of exportin 1 (XPO-1), which is involved in cytoplasmic translocation of some tumour suppressor proteins (TSPs;

Figure 4).[1,39] Nuclear export of these TSPs leads to their inactivation, allowing malignant cells to evade apoptosis and 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.[40,41]

Figure 4 Mechanism of action of selinexor



Abbreviations: SINE, selective inhibitor of nuclear export (selinexor); XPO-1, exportin-1.
Source: Adapted from Talati (2018)[39]

Currently, the penta-refractory population have no specific treatment options with known clinical benefit available in the UK, despite Sd being recommended by key international guidelines (NCCN, EHA-ESMO).[42,43] The Sd combination in penta-refractory MM offers patients with multi-drug resistance an oral, active, life-extending treatment option with a novel MoA. The introduction of Sd in the treatment pathway represents a step-change in late-line RRMM treatment, providing patients with renewed hope when they may feel that they have exhausted all treatment options.

B.1.3.5 Impact of the condition on the quality of life of patients, their families and carers

Although the treatment paradigm for MM has evolved dramatically, MM remains an incurable disease with a significant physical and emotional burden, fear of recurrence and overall impact on HRQoL increasing for patients and their families with each relapse.[24,44] The symptoms and complications of MM affect many aspects of patients' and their carers 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 that are still of active working age), thereby impacting financial status.

Furthermore, patients with RRMM report worse HRQoL, as measured by the MDASI-MM symptom scores, than those with MM pre-first relapse.[45] First and subsequent relapse have a highly detrimental effect on patients' HRQoL, and although this is observed to recover during treatment-free intervals of subsequent treatment lines, in general, there is a progressive decline, and HRQoL does not return to pre-first relapse levels.[46]

A multi-centre cross-sectional study into the impact of disease-related symptoms on HRQoL sampled two cohorts of MM patients across 18 UK centres.[47] Data collection for HRQoL included the EORTC QLQ-C30, EORTC-QLQ-MY20, EQ-5D-3L, and 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=123 [22.1%] had received ≥3 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%), and severe financial difficulties (43.3%).[47]

There is also a substantial treatment administration burden on the HRQoL of MM patients and their caregivers.[48,49] Treatment combinations may require a complex schedule with different methods and frequency of administration and varied requirements for in-person hospital visits. The humanistic burden is further exacerbated by treatment-related side effects, and caregiver stress and absenteeism can be significant.[44]

However, while RRMM inevitably has a significant HRQoL impact, in the later line setting, patients with RRMM receiving active treatment have been shown to have better HRQoL scores than those receiving only supportive care,[44] supporting the premise that patients benefit from further treatment options, particularly those with new MoA with which they have previously not been challenged, maintaining hope for the future despite relapsing.

B.1.4 Equality considerations

MM is more common in:

- Men than women;
- Older people (43% of new cases of MM in England are in people aged ≥75 years [Cancer Research UK]);
- People of African and Caribbean family backgrounds.

Stakeholders have raised no potential equality issues. It is not expected that this evaluation will exclude any people protected by equality legislation nor leads to recommendations that will have an adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

To identify evidence of the clinical efficacy and safety of selinexor and relevant comparator treatments for RRMM patients, a systematic literature review (SLR) was conducted to support this company submission for Sd, but also the simultaneous company submission of SVd in the 2L and 3L setting (NICE ID3797).[50] The SLR research question related to the scope of this submission is:

What is the relative clinical efficacy and safety of selinexor in combination with dexamethasone versus comparators, 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 proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last 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.[51,52] The SLR search strategy and study selection methods are described in Appendix D.[50]

B.2.2 List of relevant clinical effectiveness evidence

One trial was identified, which included evidence of the clinical benefits of the technology relevant to the decision problem, the pivotal phase 2b STORM trial of Sd. STORM is a non-comparative trial; therefore, evidence of comparator efficacy and safety in penta-refractory patients was also informed by the SLR, which in turn informed subsequent indirect treatment comparisons (ITC; Section B.2.9).

The phase 2 single-arm MARCH trial of Sd was also identified by the SLR. MARCH was conducted at 17 sites in China and included 82 Chinese RRMM patients who were refractory to a PI and an IMiD, of which 20 were TCR.[53] However, given that the trial did not evaluate Sd in penta-refractory patients, it irrelevant to this decision problem.

Table 4 Clinical effectiveness evidence: The STORM trial

Study	Selinexor Treatment of Refractory Myeloma (STORM; NCT02336815)
Study design	Phase 2b, single-arm, 2-part, open-label, multicentre study
Population	Part 1: included patients with penta-exposed, triple class refractory MM, and a subset of patients with quad-exposed (lenalidomide, pomalidomide, bortezomib, carfilzomib) double class refractory (least 1 PI and 1 IMiD) MM. Part 2: Patients with penta-exposed MM, defined as patients who have MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (and an alkylating agent), and triple-class-refractory MM, defined as patients whose disease is refractory to prior treatment with at least one IMiD, at least one PI, and the anti-CD38 mAb, daratumumab (and glucocorticoids). **STORM Part 2 penta-refractory efficacy population (n=83; referred to as BCLPD-refractory in the trial), a pre-specified subset of the mITT, provides the clinical effectiveness data applicable to the decision problem addressed by this submission in penta-refractory MM**
Intervention(s)	Selinexor plus low-dose dexamethasone
Comparator(s)	N/A
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	STORM is the pivotal trial of Sd in the penta-refractory setting, providing key efficacy and safety outcome data utilised in the economic model.
Reported outcomes specified in the decision problem	● **Overall survival** ● **Progression-free survival** ● Response rates ● **Adverse effects of treatment** ● **Health-related quality of life** (FACT-MM mapped to EQ-5D-3L for CEA)

Abbreviations: CEA, cost-effectiveness analysis; EQ-5D-3L, EuroQoL 5 dimensions; FACT-MM, Functional Assessment Of Cancer Therapy-Multiple Myeloma; MM, multiple myeloma; mAb, monoclonal antibody PI, proteosome inhibitor; IMiD, immunomodulatory drug.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Section summary

- The phase 2b, single-arm, two-part STORM trial of Sd provides the only evidence for Sd, relevant to this decision problem
- Participants in STORM Part 2 were penta-exposed and triple-class refractory (enrolled n=123, mITT n=122)
- **STORM Part 2 penta-refractory efficacy population (n=83; referred to as BCLPD-refractory in the trial), a pre-specified subset of the mITT, provides the clinical effectiveness data applicable to the decision problem addressed by this submission in penta-refractory MM**

B.2.3.1 Trial methodology of relevant trials

STORM is a multicentre, phase 2b, single-arm, 2-part, open-label study to evaluate the efficacy and safety of Sd in patients with quad-exposed, double-class-refractory (DCR), or penta-exposed, triple-class-refractory MM.[5,54,55] STORM was initially designed to include patients with quad-exposed, DCR MM, based on the available and commonly used treatments for RRMM when the protocol was developed.[54-56] In that design, a subset of patients with penta-exposed, TCR MM was included as an exploratory endpoint only, as treatment with anti-CD38 mAbs was not yet common. With a change in the treatment landscape following the first approval of daratumumab in 2017, Part 2 of STORM was refined to include patients with penta-exposed TCR MM, defined as quad-refractory plus prior treatment with daratumumab.[54-56]

STORM Part 2 enrolled patients with both (i) TCR MM, defined as patients whose disease is refractory to prior treatment with at least 1 IMiD, at least 1 PI, and the anti-CD38 monoclonal antibody (mAb) daratumumab (and glucocorticoids), and (ii) penta-exposed MM, defined as MM patients previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (and an alkylating agent). A majority (68%) of enrolled penta-exposed patients were penta-refractory. Patients in Part 2 received oral selinexor 80mg (or 45mg/m^2) twice-weekly on Days 1 and 3 until disease progression, death, or unacceptable toxicity.

Enrolment was 123 patients in Part 2 and 79 patients in Part 1. **In STORM Part 2, 83 participants were penta-refractory and made up the pre-specified BCLPD-refractory efficacy population**, where refractoriness was defined as ≤25% response to treatment or progression during or within 60 days after completion of treatment. This BCLPD-refractory efficacy population of 83 penta-refractory participants is the population directly relevant to the decision problem addressed by this submission.

Table 5 summarises the overall trial design of both parts of the STORM trial for context, although as described, only the Part 2 pre-specified BCLPD-refractory efficacy population is relevant to the decision problem addressed by this submission. Patient disposition in STORM Part 2 is shown in Figure 5.

Table 5 Summary of methodology of the STORM trial

Trial	**STORM (NCT02336815)[5,54-56]**
	Part 2
Trial design	Phase 2b, open-label, single-arm, 2-part trial
Location	USA, Austria, Belgium, France, Germany, Greece
Settings and location where data were collected	The study enrolled patients at 60 sites across 6 countries. Most patients in Part 2 were enrolled in the US (n=84; 68.9%), followed by France (n=13; 10.7%), Germany (n=10; 8.2%), Belgium (n=7; 5.7%), Greece (n=7; 5.7%), and Austria (n=1; 0.8%).
Key dates	Date first patient enrolled: 26 May 2015 Date last patient last visit: 26 July 2019
Data cut offs	24 April 2018[54] 7 September 2019[55]
Patient disposition & follow-up	As of 7 September 2019, all patients had discontinued treatment, with disease progression (56.9%) and AEs (31.7%) being the most common reasons for discontinuation. Of the 123 patients treated, 35 (28.5%) completed 1 year of survival follow-up.
Eligibility criteria for participants	Previously received ≥3 anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid Refractory to previous anticancer treatments: glucocorticoids, PI (i.e., bortezomib and/or carfilzomib), IMiD (i.e., lenalidomide and/ or pomalidomide), and daratumumab Refractory to most recent anti-MM regimen Measurable disease based on IMWG guidelines[a] ECOG PS ≤2 Adequate hepatic function Adequate renal function Adequate haematopoietic function Haemoglobin ≥8.5g/dL.

Trial drugs Intervention	Selinexor (80mg PO) + low-dose dexamethasone (20mg PO) Part 2 dose schedule: Twice weekly on Days 1 and 3 continuously. A dose-modification protocol was used for the management of adverse events.[3,56] Treatment was continued until disease progression, death, or unacceptable toxicity.
Permitted and disallowed concomitant medication	Supportive care to mitigate selinexor side effects, including anti-nausea agents, appetite stimulants, and anti-fatigue agents (based on NCCN Guidelines), as well as blood product transfusions and/ or growth factors including granulocyte colony-stimulating factors for neutropenia, erythropoietins for anaemia, and/ or platelet-stimulating factors for thrombocytopenia. To minimise nausea, all patients received 5-HT3 antagonists (ondansetron 8mg or equivalent) prior to the first dose of Sd and continued 2 to 3 times daily as needed. Alternative antiemetic agents may have been used if the patient did not tolerate or had persistent nausea on 5-HT3 antagonists.
Primary outcomes	ORR (confirmed) by IRC
Other outcomes	Key secondary: DOR, CBR, DCB, PFS, TTP, DCR, TTNT, OS, QoL. Exploratory: MRD, correlative studies,
Disease response assessment	Responses assessed using IMWG criteria,[22] adjudicated by IRC. Efficacy assessments were repeated at the time of disease progression or suspected response to confirm response/ progression. For patients who achieved CR or sCR per the local laboratory, response was confirmed by a central laboratory using portions of the samples collected.
Assessment schedule	Screening, then Day 1 of every 4-week treatment cycle, and every 3 months after discontinuation. Responses may also have been captured on Day 15 of Cycle 1 or any non-scheduled visits during each cycle while on treatment. Two consecutive samples were required to confirm the response; the time period between sample collection may have occurred on the same day as long as the samples were analysed separately.
Pre-planned subgroups	Pre-planned efficacy population for Part 2 as subsets of the mITT include: **BCLPD-ref population (n=83)**, CLPD-ref population (m=101), BCPD-ref population (n=94), CPD-ref population (n=117).[56,57] Subgroup analyses were also planned for: R-ISS stage (I, II, III); patients with free light chain (FLC) MM/ non-FLC MM; high-risk MM; age (18-64, 65-74, ≥75 years of age); US patients/ non-US patients; prior use of daratumumab.

Abbreviations: 5-HT3; 5-hydroxytryptamine; AE, adverse events; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; BCPD, bortezomib, carfilzomib, pomalidomide, daratumumab; CBR, clinical benefit rate; CLPD, carfilzomib, lenalidomide, pomalidomide, daratumumab; CPD, carfilzomib, pomalidomide, daratumumab; CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FLC, free light chain; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group ; IRC, independent review committee; mITT, modified intent-to-treat; MM, multiple myeloma; MRD, minimal residual disease; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PI, proteasome inhibitor; QoL, quality of life; TTNT, time to next treatment; TTP, time to progression.

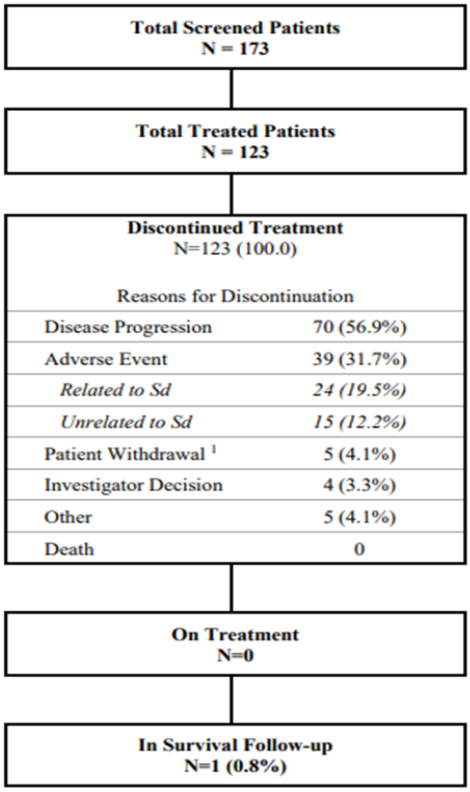
[a] Measurable disease based on IMWG guidelines as defined by at least 1 of the following:

−Serum M-protein ≥0.5 g/dL by SPEP or quantitative IgA

−Urinary M-protein excretion ≥200 mg/24 hours

−FLC ≥100 mg/L, provided that the FLC ratio is abnormal

Figure 5 Disposition of patients in STORM Part 2



[1]Includes 3 patients lost to follow-up

Source: Clinical Study Report (KCP-330-012; Data cut-off 7 September 2019)[55]

B.2.3.2 Demographics and baseline characteristics of participants of relevant trials

STORM Part 2 mITT population included n=122 patients who were penta-exposed and TCR. The BCLPD-refractory population is the focus of this submission and is a pre-specified efficacy subpopulation of the mITT, with n=83 penta-refractory patients. At baseline, the 83 penta-refractory patients enrolled in STORM Part 2 were a median of 65 years, with 51.8% being 65 years of age or older, with rapidly progressive MM at study entry, and were heavily pre-treated (median of 8 prior systemic anti-MM therapies) with multiple comorbidities (median of 10) and concomitant medications (median of 11). In addition, 57% of patients had a high-risk mutation; del(17p)/ p53, t(4;14), t(4;16), or 1q21 amplification.[55]

The baseline demographics and characteristics of penta-refractory participants in PART 2 of the STORM trial are summarised in Table 6, and the prior-drug exposure and refractoriness are detailed in Table 7.

Table 6 Characteristics of participants in the STORM trial

		STORM Part 2[55]
Eligible patients		**Penta-refractory (BCLPD)**
Baseline demographics		
N		83
Age, years	Median (range)	65.3 (40-86)
Gender, n (%)	Male	51 (61.4)
Race, n (%)	White	58 (69.9)
	Black or Af/Am	13 (15.7)
	Asian	2 (2.4)
	Native Hawaiian or other Pacific islander	1 (1.2)
	Other	6 (7.2)
	Missing	3 (3.6)
Baseline ECOG performance	0	27 (32.5)
	1	47 (56.6)
	2	7 (8.4)
	Missing	2 (2.4)
Time since initial diagnosis (years)	Median (range)	7.05 (1.2-23.4)
R-ISS stage at study entry	R-I	10 (12.0)
	R-II	56 (67.5)
	R-III	17 (20.5)
Baseline creatinine clearance (mL/ min)	<30	4 (4.8)
	30-<60	23 (27.7)
	≥60	56 (67.5)
	Mean (STD)	78.7 (34.59)
	Median (range)	75.5 (25-186)
Cytogenetic abnormalities, n (%)	del (17p)/p53	27 (32.5)
	t(14;16)	4 (4.8)
	t(4;14)	12 (14.5)
	1q21	27 (32.5)
	del(13)/ del(q13)	15 (18.1)
	All high-risk	47 (56.6)

	STORM Part 2[55]
Eligible patients	**Penta-refractory (BCLPD)**
Baseline demographics	
N	83

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; DCR, double-class refractory; ECOG, Eastern Cooperative Oncology Group ; R-ISS, Revised Multiple Myeloma International Staging System; STD, standard deviation; TCR, triple-class refractory

Table 7 Prior treatment with anti-MM therapies of patients within the STORM trial

		STORM Part 2[55]
Eligible patients		**Penta-refractory (BCLPD)**
N		**83**
Number of prior anti-MM regimens	Mean (STD)	**8.2 (2.84)**
	Median (range)	**8.0 (4.0-18.0)**
	<5 priors, n (%)	**4 (4.8)**
	5 priors, n (%)	**11 (13.3)**
	6 priors, n (%)	**11 (13.3)**
	7 priors, n (%)	**12 (14.5)**
	8 priors, n (%)	**15 (18.1)**
	≥9 priors, n (%)	**30 (36.1)**
Prior SCT, n (%)		**67 (80.7)**
Exposure to prior anti-MM drug classes, n (%)	PIs	**83 (100.0)**
	IMiDs	**83 (100.0)**
	mAbs	**83 (100.0)**
Refractoriness to anti-MM drugs, n (%)	Bortezomib	**83 (100.0)**
	Carfilzomib	**83 (100.0)**
	Daratumumab	**83 (100.0)**
	Lenalidomide	**83 (100.0)**
	Pomalidomide	**83 (100.0)**
Penta-refractory, n (%)		**83 (100.0)**

Abbreviations: anti-MM, anti-multiple myeloma; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; BCPD, bortezomib, carfilzomib, pomalidomide, daratumumab; CLPD, carfilzomib, lenalidomide, pomalidomide, daratumumab; CPD, carfilzomib, pomalidomide, daratumumab; DCR, double-class refractory; IMiD, immunomodulatory drugs; mAb, monoclonal antibody; PI, proteosome inhibitor; SCT, stem cell transplant; STD, standard deviation; TCR, triple-class refractory

There is a paucity of published natural history data on penta-refractory MM patient populations across Europe and the UK. Therefore, discussions with UK myeloma experts, both HCPs and patient organisations, have been relied upon to assess the generalisability of the STORM trial participant population to those seen in UK clinical

practice. Outside of the commonly observed differences between in-trial and out-of-trial populations (such as age and race demographics), we believe that the penta-refractory participants in STORM are clinically relevant and plausible in an NHS England context.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis populations

The efficacy populations detailed by the study protocol were aligned to each part of the study, with the primary efficacy endpoints based on the modified intent-to-treat (mITT) population from Part 2. Several subpopulations of the Part 2 mITT population based on prior treatment and cytogenetic abnormalities were evaluated to further support the efficacy in Part 2. Results for patients treated in Part 1 were summarised and analysed separately.[57]

The primary statistical efficacy analysis was performed on ORR (proportion of patients who achieved sCR, CR, VGPR, or PR) using the mITT population. The primary analysis was performed on the Part 2 patients with penta-exposed, triple-class-refractory MM only. The per-protocol (PP) population was used for supportive inferences concerning efficacy. Secondary and exploratory endpoints were assessed using the mITT population. Time-to-event endpoints (including DOR) were assessed using Kaplan-Meier methods. QoL was assessed using the FACT-MM. The trial outcomes index is the primary measurement of interest, comprising the physical and functional subscales plus the MM-specific subscale only performed on the Part 2 patients with penta-exposed, triple-class-refractory MM.[57]

Safety analyses were performed on the overall population of patients who received any amount of study treatment, presented overall and by study part, and separately for Part 1 patients with penta-exposed, TCR MM, Part 1 patients with quad-exposed, DCR MM, and Part 2 patients with penta-exposed, TCR MM.

Efficacy was also examined by refractoriness to specific previous treatments. The following populations are included for primary and secondary efficacy variables and

include subsets of the mITT population from Part 2. To be included in a specific subset, documentation of refractoriness to the relevant treatment(s) was required.[57]

Pre-specified analysis populations are detailed in Table 8.

Table 8 Key populations for analysis in the STORM trial

Analysis set	Description
Modified ITT (mITT) Part 2	Patients with penta-exposed, TCR MM who met all eligibility criteria and received at least 1 dose of Sd. Includes patients who discontinued therapy due to toxicity or PD or died from any cause. To be used for the primary efficacy analyses. mITT analysis set includes 122 of 123 patients treated with Sd in Part 2 of the study. One patient did not receive prior carfilzomib and was not included in the mITT analysis set.
	n=122
All penta-exposed TCR patients	This includes all penta-exposed, TCR patients from Part 2 (mITT) and Part 1 who received at least 1 dose of Sd.
	n=152
Per-protocol (PP)	PP analysis population included 119 patients in Part 2 who received ≥70% of their prescribed Sd doses and had ≥1 adequate post-baseline response assessment.
	n=119
Part 2 high-risk patients	This includes all patients from Part 2 (mITT) who received at least 1 dose of Sd and had at least 1 of the following chromosomal abnormalities: del(17p)/p53, t(14; 16), t(4; 14), or 1q21.
	n=65
Part 2 efficacy-evaluable	This includes all patients in the mITT population with at least 1 adequate post-baseline IRC-based MM response assessment.
	n=112
Total safety population	Safety population included any patients who received any amount of Sd across Part 1 and Part 2 of the study
	n=202
Part 1 safety population	This includes all patients treated with Sd on Part 1: - Penta-exposed, TCR MM Patients in Part 1 (n=31) - Quad-exposed, double-class-refractory MM Patients in Part 1 (n=48)
	n=79
Part 2 safety population	This includes all patients treated with Sd on Part 2.
	n=123
BCLPD-refractory (penta-refractory) population (MHRA Licensed population)	**Includes all patients whose MM was documented to be refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab.**
	n=83

Analysis set	Description
Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; , MHRA, Medicines and Healthcare Products Regulatory Agency; IRC, independent review committee; mITT, modified intent-to-treat; MM, multiple myeloma; PP, per protocol; RCT, triple-class refractory, Sd, Selinexor plus dexamethasone	
Source: Statistical Analysis Plan (KCP-330-012) Version 2.0. 2018.[57]	

B.2.4.2 Determination of sample size

The sample size was based on assumptions for penta-exposed, TCR MM with a minimal threshold of 10% of patients with a partial response or better. For the primary efficacy analysis, a sample of 122 patients allowed for a one-sided test at an alpha level of 0.025 to detect a minimum of 20% of patients with a partial response or better against a value of 10% under the null hypothesis with 90% power.[57]

B.2.4.3 Overview of statistical methods

All summary statistics were computed and displayed for each of the defined analysis populations and by each assessment timepoint whenever applicable. Summary statistics for continuous variables minimally included: n (number), mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages are presented. For time-to-event variables, the Kaplan-Meier method was used for descriptive summaries. Graphical displays were generated as appropriate. Adjustments for covariates were considered for the analysis of primary and key secondary endpoints.[57]

Subgroup analysis on selected efficacy endpoints was conducted by:

- Revised International Staging System (R-ISS) for MM (Stage I, II, and III);
- Region (US *vs*. non-US);
- Serum free light chain (FLC) MM patient (yes *vs*. no): defined as patients without measurable disease by serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP), but with measurable disease in FLC, at baseline.

The primary analysis of ORR was designed to determine the superiority of Sd to the minimal threshold for ORR. The analysis used a 2-sided, exact 95% CI, calculated for the rate of ORR among the mITT population, and statistical significance to be declared if the lower bound of this interval is >10%. No formal hypothesis testing was conducted to compare the ORR rates in the subgroup analyses.

Definitions of key endpoints as used in analyses are presented in Table 9.

Table 9 Definitions and analysis overview of key STORM efficacy endpoints

Efficacy endpoints	Definition	Analysis information
ORR	Overall response rate included patients who experienced partial response (PR), very good partial response (VGPR), CR, or sCR, based on IMWG response criteria.	The primary analysis of ORR was designed to determine the superiority of Sd to the minimal threshold for ORR. The analysis used a 2-sided, exact 95% CI, calculated for the rate of ORR among the mITT population, and statistical significance to be declared if the lower bound of this interval is >10%.
PFS	Duration from start of study treatment to time of PD (per IRC) or death from any cause, whichever occurs first.	Median PFS with 95% CI are estimated based on the Kaplan-Meier method.
TTP	Duration from start of study treatment to time of PD or death due to PD (per IRC), whichever occurs first.	Median TTP with 95% CI was estimated based on the Kaplan-Meier method.
DOR	Duration from first response (at least PR) to time of PD or death due to PD (per IRC), whichever occurs first.	DOR is summarised descriptively. Median DOR with 95% CI is estimated based on the Kaplan-Meier method.
TTNT	Duration from the start of study treatment to the start of the next MM treatment or death due to disease progression, whichever occurs first.	Median TTNT with 95% CI was estimated based on the Kaplan-Meier method.
OS	Duration from start of study treatment to death from any cause. If death event did not occur during the follow-up period, the patient was censored at the date of discontinuation from the study, or database cut date, whichever was earlier.	Median OS time with 95% CI was estimated based on the Kaplan-Meier method.
FACT-MM	This instrument combines the general version of the FACT (FACT-G) with a MM-specific subscale (14 items). [a]	The QoL analysis is based on changes in the total TOI score from Baseline using paired T-tests.

Abbreviations: CBR, clinical benefit rate; CI, confidence intervals; CR, complete response; DCB, duration of clinical benefit; DOR, duration of response; FACT-G, Functional Assessment of Cancer Therapy - General; IMWG, International Myeloma Working group; IRC, Independent Review Committee; mITT, modified intent-to-treat; MR, minimal response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; TOI, treatment outcome index; TTNT, time to next treatment; VGPR, very good partial response

[a] The subscales for the FACT-G are Physical Well-Being (7 items), Social/ Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; total of 41 items) is the primary measurement of interest, comprised of the Physical and Functional subscales plus the MM-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 ("Not at all") to 4 ("Very much"), therefore the TOI has a score ranging from 0 to 120.

Source: Statistical Analysis Plan (KCP-330-012) Version 2.0. 2018[57]

B.2.5 Critical appraisal of relevant clinical effectiveness evidence

Quality assessment of the STORM trial was performed according to the criteria set out in the Critical Appraisal Skills Programme (CASP), as summarised in Table 10.[58] The

risk-of-bias judgement overall for STORM was LOW in the context of STORM as a single-arm non-RCT. The full table of quality assessment is presented in Appendix D. The STORM trial quality assessment CASP tool has an overall LOW risk of bias, although one domain was assessed as 'NO' due to three patients detailed as lost to follow-up. However, it is recognised that this is in the context of STORM as a single-arm, open-label, non-RCT and overall methods and practices that were detailed in the protocol and implemented were as expected for a well-conducted non-RCT.

Table 10 Quality assessment of non-RCTs summary: STORM

	STORM (yes/ no/ not clear/ N/A)
Was the cohort recruited in an acceptable way?	**YES**
Was the exposure accurately measured to minimise bias?	**YES**
Was the outcome accurately measured to minimise bias?	**YES**
Have the authors identified all important confounding factors?	**NOT CLEAR**
Have the authors taken account of the confounding factors in the design and/or analysis?	**YES**
Was the follow-up of patients complete?	**NO**
How precise (for example, in terms of confidence interval and p-values) are the results?	**YES**
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study[52,58,59]	

B.2.6 Clinical effectiveness results of the relevant trials

Section summary

- STORM provides pivotal evidence of clinical effectiveness for Sd, as indicated to treat MM in adults who received ≥4 prior therapies, whose disease is refractory to ≥2 PIs, ≥2 IMiD agents, and an anti-CD38 mAb (penta-refractory), and have disease progression on the last therapy;
- Clinical effectiveness data applicable to the decision problem is in the penta-refractory population which is the STORM BCLPD-refractory population.
- For n=83 patients in the mITT whose disease was BCLPD-refractory (penta-refractory), Sd had an ORR of 25.3%, median DOR of 3.8 months, median PFS of 2.8 months, and median OS of 8.4 months;

- Sd provides an efficacious, oral treatment option with a novel MoA in heavily pre-treated penta-refractory RRMM patients who are frequently elderly and frail.

Clinical efficacy data for Sd is presented in Sections B.2.6.1-B.2.6.40, from the primary and updated analyses of key efficacy endpoints from STORM. The data cut-off dates for the primary and updated analyses were 24th April 2018 and 7th September 2019, respectively.[3,54,55] Data are shown for the pre-planned penta-refractory (BCLPD-refractory) efficacy population from STORM, the population directly relevant to this decision problem.

B.2.6.1 STORM: response data

The penta-refractory population (n=83) had an IRC-ORR of 25.3% with 21 patients responding to therapy. Of these 21 responders, one had a complete response (CR), four had a very good partial response (VGPR), and 16 had a partial response (PR). In addition, ten patients had a minimal response (MR), 32 had stable disease (SD), and 20 had progressive disease (PD) or were not evaluable. Of the 21 responders in the penta-refractory population, the median time to response was 4.0 weeks; disease control could be achieved as early as 2 weeks. In the penta-refractory population, the median DOR was 3.8 months, with the longest DOR being 10.8 months.[3,55]

Table 11 presents IRC-ORR and INV-ORR data from the primary and updated analysis of STORM for the BCLPD-refractory population.

Table 11 ORR per IRC and INV assessment in STORM Part 2 BCLPD-refractory population

	Primary analysis[54] (data cut-off: 24th April 2018)	**Updated analysis[55] (data cut-off: 7th September 2019)**
	STORM Part 2: BCLPD-refractory population	**STORM Part 2: BCLPD-refractory population**
N	**83**	**83**
	IRC assessment	
ORR,[a] n (%)	21 (25.3)	21 (25.3)
Exact 95% CI	16.4, 36.0	16.4, 36.0

	Primary analysis[54] (data cut-off: 24th April 2018)	Updated analysis[55] (data cut-off: 7th September 2019)
	STORM Part 2: BCLPD-refractory population	**STORM Part 2: BCLPD-refractory population**
N	**83**	**83**
CBR,[b] n (%)	31 (37.3)	31 (37.3)
Exact 95% CI	27.0, 48.7	27.0, 48.7
Best overall response		
sCR/ CR, n (%)	1 (1.2)	1 (1.2)
Exact 95% CI	0.0, 6.5	0.0, 6.5
VGPR, n (%)	4 (4.8)	4 (4.8)
Exact 95% CI	1.3, 11.9	1.3, 11.9
PR, n (%)	16 (19.3)	16 (19.3)
Exact 95% CI	11.4, 29.4	11.4, 29.4
MR, n (%)	10 (12.0)	10 (12.0)
Exact 95% CI	5.9, 21.0	5.9, 21.0
SD, n (%)	32 (38.6)	32 (38.6)
Exact 95% CI	28.1, 49.9	28.1, 49.9
PD/ NE, n (%)	20 (24.1)	20 (24.1)
Exact 95% CI	15.4, 34.7	15.4, 34.7
Duration of response		
Median DOR, months (95% CI)	3.8 (2.3, NE)	3.8 (3.7, 10.8)
	Investigator assessment	
ORR,[a] n (%)	19 (22.9)	20 (24.1)
Exact 95% CI	14.4, 33.4	15.4, 34.7
CBR,[b] n (%)	27 (32.5)	27 (32.5)
Exact 95% CI	22.6, 43.7	22.6, 43.7
Best overall response		
sCR/ CR, n (%)	0 (0.0)	0 (0.0)
Exact 95% CI	NE, NE	NE, NE
VGPR, n (%)	6 (7.2)	6 (7.2)
Exact 95% CI	2.7, 15.1	2.7, 15.1
PR, n (%)	13 (15.7)	14 (16.9)
Exact 95% CI	8.6, 25.3	9.5, 26.7
MR, n (%)	8 (9.6)	7 (8.4)
Exact 95% CI	4.3, 18.1	3.5, 16.6

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; mITT, modified intent-to-treat population; MR, minimal response; n, number of patients; NE,

	Primary analysis[54] (data cut-off: 24th April 2018)	Updated analysis[55] (data cut-off: 7th September 2019)
	STORM Part 2: BCLPD-refractory population	STORM Part 2: BCLPD-refractory population
N	**83**	**83**

not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response

[a] ORR was defined as the proportion of patients with a confirmed PR or better

[b] CBR was defined as the proportion of patients with a confirmed MR or better

B.2.6.2 STORM: PFS/ TTP data

IRC-assessed PFS and TTP per IMWG were secondary endpoints in STORM. The median IRC-PFS was 2.8 (95% CI: 1.9, 4.3) in the BCLPD-refractory population, while the median IRC-TTP was 3.0 months (95% CI: 2.0, 4.7).

Table 12 and Table 13 present PFS and TTP by IRC and INV from the primary and updated analysis of STORM, respectively, for the BCLPD-refractory population. Kaplan-Meir curves for PFS by IRC and INV for the BCLPD-refractory population, are presented in

Figure 6 and Figure 7, respectively.

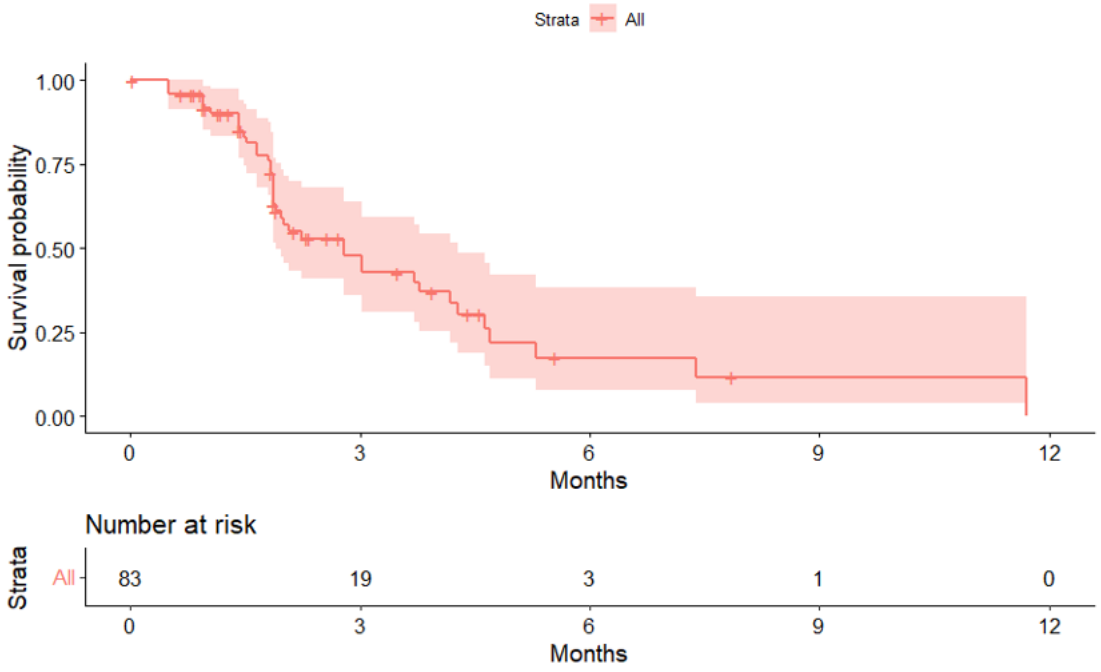
Table 12 PFS per IRC and INV in STORM BCLPD-refractory population

	Primary analysis[54] (data cut-off: 24th April 2018)	Updated analysis[55] (data cut-off: 7th September 2019)
	STORM Part 2: BCLPD-refractory population	STORM Part 2: BCLPD-refractory population
n	**83**	**83**
	IRC assessment	
Median PFS, months (95% CI)	2.8 (2.1, 4.3)	2.8 (1.9, 4.3)
Patients with events, n (%)	36 (43.4)	40 (48.2)
Progressive disease, n (%)	34 (41.0)	36 (43.4)
Death, n (%)	2 (2.4)	4 (4.8)
Patients censored, n (%)	47 (56.6)	43 (51.8)
	Investigator assessment	

	Primary analysis[54] (data cut-off: 24th April 2018)	Updated analysis[55] (data cut-off: 7th September 2019)
	STORM Part 2: BCLPD-refractory population	STORM Part 2: BCLPD-refractory population
n	**83**	**83**
Median PFS, months (95% CI)	3.8 (2.2, 5.3)	3.0 (2.2, 4.7)

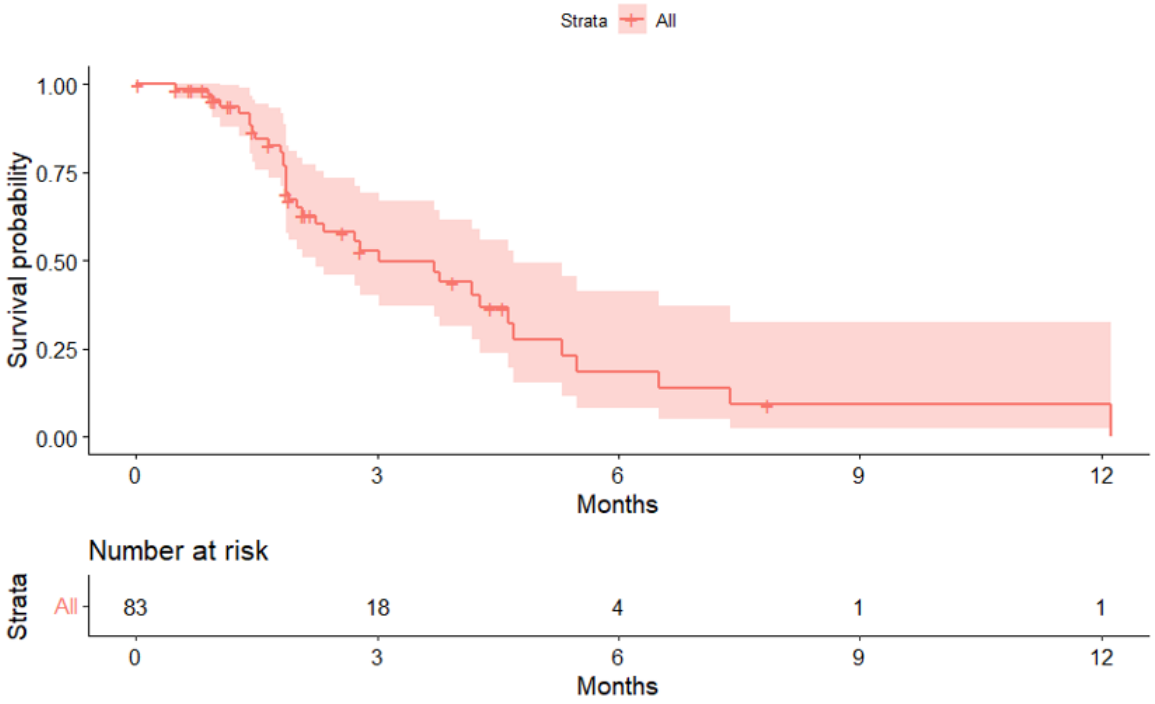
Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; CI, confidence interval; IRC, independent review committee; mITT, modified intent-to-treat population; n, number of patients; PFS, progression-free survival

Figure 6 PFS by IRC for BCLPD-refractory patients in STORM



Source: Menarini-Stemline data on file.[60]

Figure 7 PFS by INV for BCLPD-refractory patients in STORM



Source: Menarini-Stemline data on file.[60]

Table 13 TTP per IRC and INV assessment for STORM Part 2 BCLPD-refractory population

	Primary analysis[54] (data cut-off: 24th April 2018)	Updated analysis[55] (data cut-off: 7th September 2019)
	STORM Part 2: BCLPD-refractory population	STORM Part 2: BCLPD-refractory population
N	**83**	**83**
TTP based on IRC assessment		
Median time to progression, months (95% CI)	3.0 (2.2, 4.6)	3.0 (2.0, 4.7)
Patients with events, n (%)	34 (41.0)	36 (43.4)
Progressive disease, n (%)	34 (41.0)	36 (43.4)
Death due to disease progression, n (%)	0 (0.0)	0 (0.0)
Patients censored, n (%)	49 (59.0)	47 (56.6)
TTP based on Investigator assessment		
Median time to progression, months (95% CI)	3.8 (2.8, 5.9)	3.8 (2.7, 5.5)

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; CI, confidence interval; IRC, independent review committee; mITT, modified intent-to-treat population; n, number of patients; TTP, time to progression

B.2.6.3 STORM: overall survival data

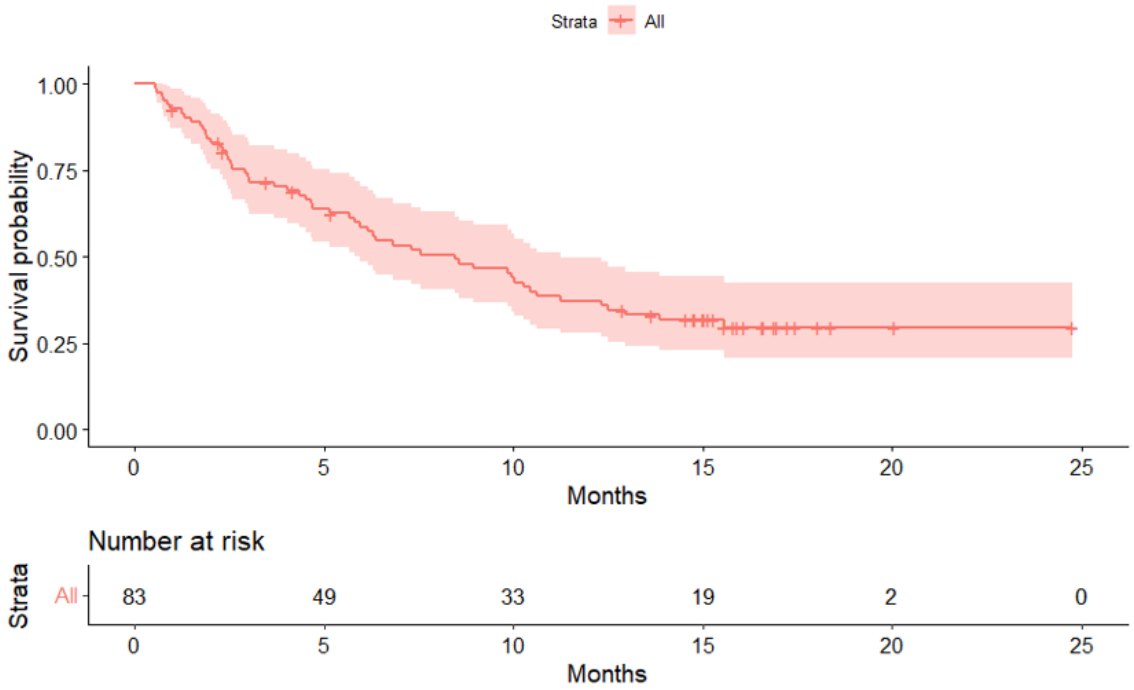
The median OS in the BCLPD-refractory population was 8.4 months (95% CI: 5.9, 11.2) with an estimated 6- and 12-month survival probability of 58.6% and 37.3%, respectively (Table 14, Figure 8). Patients with a response of PR or better had a longer median OS than those with either SD or PD/ NE (not evaluable, 6.4 months, and 2.1 months, respectively; Figure 9), further demonstrating the clinical benefit of Sd treatment.

Table 14 OS based on IRC assessment in STORM Part 2 BCLPD-refractory population

	Primary analysis[54] (data cut-off: 24th April 2018)	**Updated analysis[55] (data cut-off: 7th September 2019)**
	STORM Part 2: BCLPD-refractory population	**STORM Part 2: BCLPD-refractory population**
N	83	83
Median OS, months (95% CI)	7.6 (5.9, NE)	8.4 (5.9, 11.2)
Death, n (%)	36 (43.4)	54 (65.1)
Estimated 6-month survival probability, %	60.0	58.6
Estimated 12-month survival probability, %	26.2	37.3

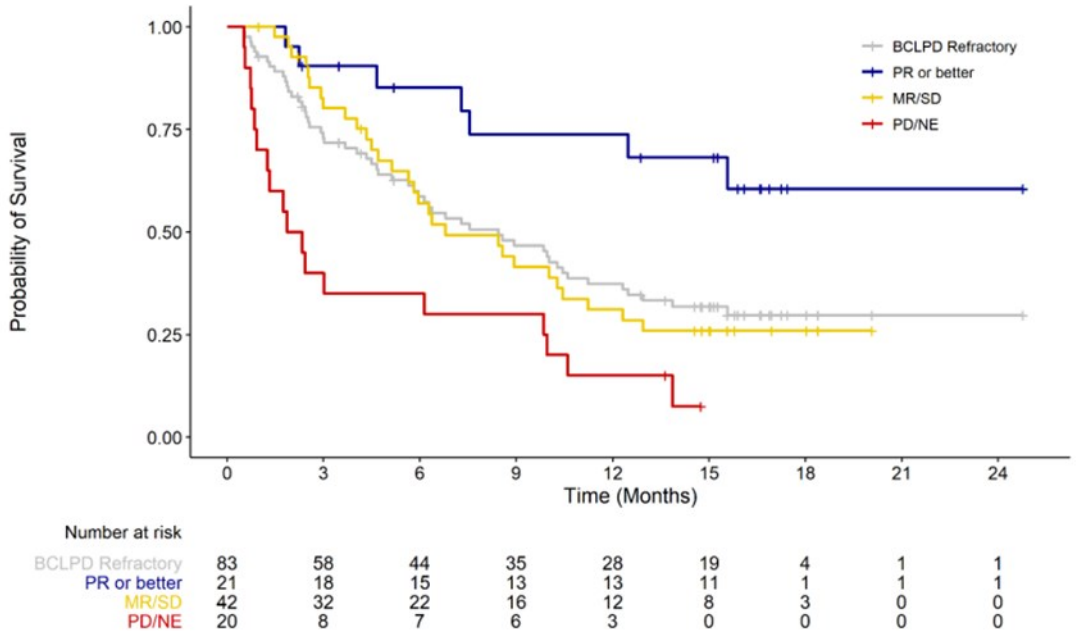
Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; CI, confidence interval; IRC, independent review committee; mITT, modified intent-to-treat population; n, number of patients; OS, overall survival

Figure 8 Overall survival for the BCLPD-refractory population in STORM



Source: Menarini-Stemline data on file.[60]

Figure 9 Overall survival for the BCLPD-refractory population in STORM, by response



Source: Menarini-Stemline data on file.[60]

B.2.6.4 HRQoL

In the STORM trial HRQoL and potential for improvement over the course of the study were assessed using the Functional Assessment of Cancer Therapy–Multiple Myeloma (FACT-MM) patient-reported outcome (PRO) questionnaire.[56] This instrument combines the 27-item general FACT (FACT-G) version with an MM-specific subscale (14 items). The subscales for the FACT-G are Physical Well-Being (7 items), Social/ Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; 41 items) is the primary measurement of interest, comprised of the Physical and Functional subscales plus the MM-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 (“Not at all”) to 4 (“Very much”). Therefore, the TOI has a score ranging from 0 to 120. The Q

oL assessment was performed at Baseline (prior to first dose of study treatment), on Day 1 of each cycle on or after the second, and at the Final visit. The primary analysis for QoL was based on the change from baseline to the TOI score at each assessment time point.

The FACT-MM was administered to patients in both parts of the STORM study. Overall, treatment with Sd led to median decreases (-4 to -25) from baseline in the FACT-MM Total TOI Score, starting as early as Cycle 2 and continuing to Cycle 8. FACT-MM score reductions are associated with improvements in patients' perceptions of their disease.[56]

Of the 5 subscales that make up the FACT-MM QOL assessment, two showed consistent median decreases compared with the baseline. The decreases seen in the FACT-MM Physical Well-Being Subscale Score were the largest of the subscales and included median decreases from the baseline of -3 to -7 through to Cycle 8. The FACT-MM Functional Well-Being Subscale Score also showed median decreases from baseline, ranging from 0 to -4. The FACT-MM-Specific Subscale Score, Social Well-Being Subscale Score, and Emotional Well-Being Subscale Score stayed relatively consistent across all time points measured.[55]

Most patients with MM receiving Sd in STORM maintained HRQoL in the 5L penta-refractory setting, based on validated patient-reported FACT-G, FACT-MM, and FACT-MM TOI scores.

B.2.7 Subgroup analysis

The licensed population for Sd is penta-refractory MM, represented by the BCLPD-refractory population in STORM. The BCLPD-refractory population was a pre-specified efficacy population of Part 2 of the STORM trial. Further subgroup analysis within the BCLPD-refractory efficacy population was not pre-specified.

Beyond the pre-planned efficacy populations, such as the BCLPD-refractory population, that are subsets of the mITT by refractoriness (see B.2.4.1 0 for definitions of these populations), subgroup analyses were also planned for R-ISS stage (I, II, III); patients with FLC MM/ non-FLC MM; high-risk MM; age (18-64, 65-74, ≥75 years of age); US patients/ non-US patients; prior use of daratumumab. However, these were not combined to take account of refractoriness.[56,57]

B.2.8 Meta-analysis

As only one trial evaluating Sd was identified in the SLR, meta-analysis was not required.

B.2.9 Indirect and mixed treatment comparisons

No RCTs were identified from the SLR of Sd or comparators for the treatment of penta-refractory MM. The single-arm STORM trial provided pivotal efficacy data for Sd, and several observational studies provided data on penta-refractory MM outcomes with standard of care (SoC) treatment.

A feasibility assessment was conducted to identify studies with sufficient reporting to allow the matching of populations *versus* STORM in the ITC.[61] Therefore, studies identified in the SLR would be excluded from the ITC if patients' characteristics were poorly reported, did not report OS or PFS, or where the population size was too small (<30). Two interventional trials and five real-world observational studies were included following the feasibility assessment of the ITC, from which only one interventional trial, STORM, and three observational real-world studies were included in relevant analyses to inform this submission. These were the STORM trial of Sd, MAMMOTH,

LocoMMotion, and Kim *et al*. 2021, RWE observational studies, summarised in Appendix D.[5,35,62,63]

Unanchored matching-adjusting indirect comparisons (MAICs) were conducted of STORM against three data sets relevant to the decision problem addressed by this submission. However, despite the inclusion of LocoMMotion and Kim *et al*., robust MAICs were not possible since the number of penta-refractory patients in Kim *et al*. was only 25, and LocoMMotion did not publish separate OS and PFS KM curves for the n=44 penta-refractory patients alone. The remaining study of SoC, MAMMOTH, did not publish PFS curves since the study was not designed to report the PFS of current SoC, where some participants did not receive further treatment.[35,61-63]

The selection of MAMMOTH as the best available source of evidence to inform the ITC *versus* STORM was validated by myeloma clinical experts in the UK and from other European countries. Therefore, OS MAIC of STORM *versus* MAMMOTH are the only analyses to potentially inform this decision problem.

The MAIC models tested, “must have”, “full”, and “must have + nice to have”, were based on the number of prognostic factors and effect modifiers included, with the prognostic factors being validated by UK myeloma clinical experts. However, no conclusions were drawn from the MAIC of STORM Part 2 BCLPD *versus* MAMMOTH as all models tested produced effective sample sizes (ESS) too small, which led to high uncertainty (Table 15). Where limited ESS were present from MAICs, largely due to the lack of overlap in key patient baseline characteristics, a simulated treatment comparison (STC) was performed as a secondary analysis for affected studies, as this approach mitigates the large loss of ESS.

Table 15 MAIC results STORM BCLPD *versus* MAMMOTH: overall survival

	Model	Original sample size	ESS	ESS %	HR naïve (95% CI)	HR weighted (95% CI)	AIC (weighted)	BIC (weighted)	Comments
MAMMOTH (penta-refractory)	Must have	80	13.5	17%	0.627 (0.435-0.904)	0.757 (0.268-1.883)	598.603	601.407	ESS n<30
	Full	80	10.4	13%	0.627 (0.435-0.904)	0.681 (0.327-2.095)	555.86	558.664	ESS n<30

	Must have + nice to have	-	-	-	-	-	-	-	Population cannot be matched

In the STC of STORM BCLPD-refractory population *versus* the penta-refractory subpopulation of MAMMOTH for OS, the best fitting distribution (based on AIC and BIC), log-normal, resulted in a HR of 0.585, favouring Sd over SoC (Table 16 and Table 17).

Table 16 Detailed results of STC of OS: STORM BCLPD-refractory population *vs*. MAMMOTH penta-refractory population

Month	Survival %						
	STORM Part 2 (BCLPD)						MAMMOTH
	Weibull	GenGamma*	Exp	Llogis	Lnorm	Gompertz	
0	100%		100%	100%	100%	100%	100%
1	95%		94%	96%	97%	93%	96%
2	90%		89%	91%	91%	87%	87%
3	85%		84%	85%	84%	82%	77%
4	81%		80%	80%	78%	77%	66%
5	76%		75%	74%	72%	72%	56%
6	72%		71%	69%	66%	68%	49%
7	68%		67%	64%	61%	64%	44%
8	64%		63%	59%	57%	61%	33%
9	60%		60%	55%	53%	58%	31%
10	57%		56%	52%	50%	55%	24%
11	54%		53%	48%	46%	52%	21%
12	50%		50%	45%	44%	49%	20%
13	48%		47%	42%	41%	47%	20%
14	45%		45%	40%	39%	45%	17%
15	42%		42%	37%	36%	43%	16%
16	40%		40%	35%	34%	41%	16%
17	37%		38%	33%	33%	39%	16%
18	35%		36%	32%	31%	37%	13%
19	33%		34%	30%	29%	36%	10%
20	31%		32%	29%	28%	35%	10%
21	29%		30%	27%	26%	33%	10%
HR	**0.568**		**0.597**	**0.573**	**0.585**	**0.652**	

Month	Survival %						
	STORM Part 2 (BCLPD)						MAMMOTH
	Weibull	GenGamma*	Exp	Llogis	Lnorm	Gompertz	

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; Exp, exponential; GenGamma, generalised gamma; HR, hazard ratio; llogis, log-logistic; lnorm, log-normal

**Model could not converge for generalised gamma*

Table 17 STC OS AIC/ BIC ranking: STORM BCLPD-refractory population *vs*. MAMMOTH penta-refractory population

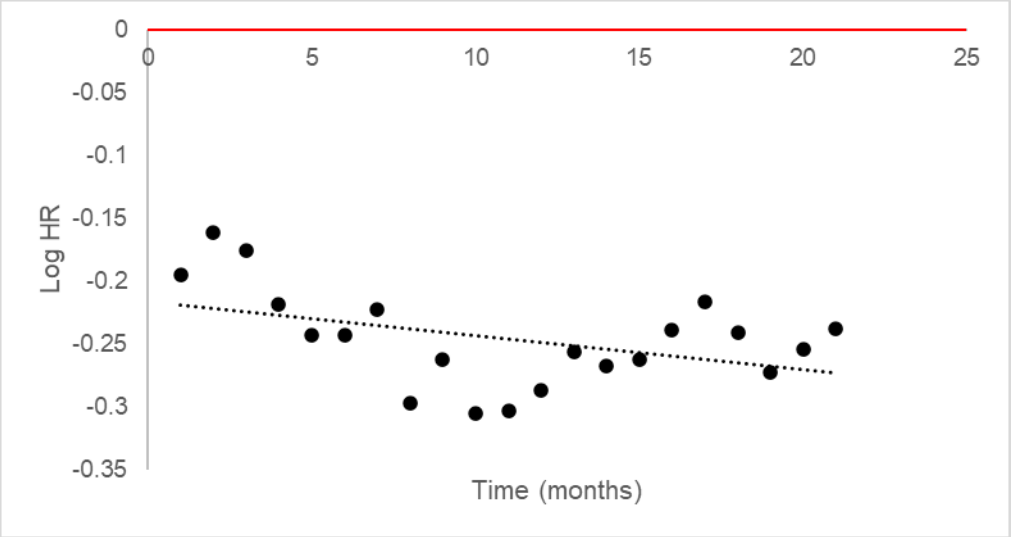
Distribution	AIC	BIC	AIC+BIC	Ranking
Weibull	367.03	390.47	757.50	5
GenGamma*	356.11	381.89	738.00	NA
Exp	365.19	386.29	751.48	3
Llogis	362.87	386.31	749.19	2
Lnorm	360.86	384.30	745.17	1
Gompertz	366.44	389.87	756.31	4

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion ; Exp, exponential; GenGamma, generalised gamma; llogis, log-logistic; lnorm, log-normal; NA, not applicable

**Model could not converge for generalised gamma distribution. Model was excluded from ranking.*

Based on Figure 10, the hazard rate for Sd relative to the comparator arm improved slightly over time (the log HR remained below 0 and decreased over time). This suggests that the proportional hazard assumption may not hold for this comparison. Additional methods were considered, such as accelerated failure time (AFT), independent parameterisations and piecewise approaches, and the advantages and limitations of each. However, the nature of the data from STORM and MAMMOTH and myeloma expert clinical opinion sought on an advisory board (Appendix M) suggested these additional analyses would introduce further uncertainty since it seemed likely that there was no clinically plausible explanation for the apparent proportional hazard violation; the effect observed was an artefact of the quality and limited size of the data set.

Figure 10 Simulated treatment comparison LOG HR for overall survival: STORM BCLPD-refractory population *vs*. MAMMOTH penta-refractory population



Source: ITC report[61]

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

The primary analysis of the ITC was conducted through a MAIC. In certain populations and comparisons, the MAIC produced a low ESS (n<30), resulting in high uncertainty. In such instances, STC was used to produce results with higher certainty (as STC is not prone to ESS loss). The matching process inherently estimates the treatment effect of Sd in the comparator's study's population.[61]

Whilst comparator studies were exclusively TCR (or with a majority TCR population), each assessed study included populations with varying characteristics and variable reporting of penta-refractoriness. Therefore, it is important to consider the target population when interpreting the results from each analysis.

Conclusions for SoC for when the OS data is sourced from MAMMOTH could not be drawn decisively from the MAIC for OS, as the resulting ESS was insufficient. Based on the STC, the adjusted HR favoured Sd over SoC when the latter's efficacy data was sourced from MAMMOTH for OS. This is likely to be a highly conservative estimate of the comparable efficacy of Sd versus BSC; despite MAMMOTH being the best data source available for penta-refractory patients in the real-world and therefore used as the best available proxy for BSC in UK clinical practice, there are limitations. MAMMOTH collected data at US clinical sites where penta-refractory patients who

received further treatment (63/ 70) received several treatment combinations that would not be available to penta-refractory patients in UK clinical practice, thereby overestimating the SoC/ BSC treatment effect that would likely be observed in penta-refractory patients in the UK.

Although further comparisons were explored in the wider ITC, they are not judged directly relevant to the decision problem addressed by this submission as while the originating studies all included a proportion of penta-refractory patients, they did not report sufficiently on that patient group independently; just wider populations inclusive of penta-refractory patients.

B.2.10 Adverse reactions

Section summary

- STORM provides evidence of tolerability and adverse reactions associated with treatment with Sd;
- Most safety data were analysed for the overall safety analysis set for STORM Part 1 and STORM Part 2. These data are presented predominantly, with limited data presented that were analysed for the BCLPD-refractory population, separately;
- Selinexor is well tolerated: the most common AEs (all ≤Grade 2) were nausea, fatigue, and decreased appetite, all of which are reversible and managed with dose adjustments without compromising efficacy and avoiding the need for treatment discontinuations;
- As selinexor is not associated with major organ toxicities and Sd maintains QoL, most treatment-related GI disorders associated with selinexor (e.g., nausea, decreased appetite) were Grade ≤2 events and were generally manageable and reversible;
- Sd results in durable PFS, longer DoR and longer time-to-next-treatment when safety concerns are managed with appropriate dose reductions of selinexor.

Safety and tolerability data for Sd is presented from the STORM trial in Sections B.2.10.1-B.2.10.2, below. Most safety data were analysed for the overall safety

analysis set (SAS) for STORM Part 1 and STORM Part 2, separately and combined. These data are presented predominantly, with limited data presented that were analysed for the BCLPD-refractory population separately.

B.2.10.1 Extent of study drug exposure

The median duration of treatment in STORM Part 2 mITT population, was 9.0 weeks (range: 1-76), with 37.4% of patients receiving selinexor ≥12 weeks, 29.3% ≥16 weeks, 13.8% ≥24 weeks, and 4.9% ≥32 weeks. The median total dose of selinexor received was 920 mg (range: 160-6220), with a median of 113.6 mg (range: 22-240) received per week. Median overall treatment compliance (>70% of prescribed doses) for selinexor of 100%. Most patients had a dose modification of selinexor on study, which included 98.4% with a dose hold/ interruption and 62.3% with a dose reduction.[55]

Of the patients who had a selinexor dose reduction in Part 2, 50.4% had their selinexor dose reduced to between 120 mg and 100 mg total per week (i.e., Dose Levels -1 and -2); 9.8% had their total weekly dose reduced to <100 mg (i.e., Dose Levels -3 and -4). The median time to dose reduction was 36.0 days (range: 8-126).

In the BCLPD-refractory population, exposure was consistent with the full mITT: the median duration of treatment was 9,0 weeks (range: 1-61), with 37.3% of patients receiving selinexor for >12 weeks, 26.5% >16 weeks, 10.8>24 weeks, and 3.6% >32 weeks. The median total dose of selinexor received in the BCLPD-refractory population was 880mg (range 160 mg to 6,220 mg), with a median dose of 104.6mg (range: 22 to 180mg) received per week. Most BCLPD-refractory patients had a dose modification of selinexor on study which included 98.8% with a dose hold/ interruption and 59.0% with a dose reduction.[55]

Of the BCLPD-refractory patients who had a selinexor dose reduction in Part 2, 45.8% had their selinexor dose reduced to between 120 mg and 100 mg total per week (i.e., Dose Levels -1 and -2); 12.0% had their total weekly dose reduced to <100 mg (i.e., Dose Levels -3 and -4). The median time to dose reduction was 36.0 days (range: 8-120).

For all patients treated in Part 1, the median duration of study treatment, overall compliance and average dosing, was consistent with Part-2, and the BCLPD-refractory population.

B.2.10.2 Adverse events

Table 18 presents an overview of treatment-emergent adverse events (TEAEs) for STORM Part 1 and Part 2. All patients (100%) treated with Sd across both parts of the study experienced a TEAE, and 199 patients (98.5%) experienced a TEAE assessed as related to Sd. Just over half (60.9%) of the patients had a serious TEAE (TESAE). Most patients (78.2%) had a dose modification due to a TEAE, and dose holds/ interruptions due to TEAEs occurred in 62.4% of patients and dose reductions in 53.0%. [55]

Twenty patients (9.9%) had a TEAE with an outcome of death (12 patients [9.8%] in Part 2 and 8 [10.1%] in Part 1), with 4 (2.0%) patients having a fatal event assessed as related to treatment (3 patients [2.4%] in Part 2 and 1 [1.3%] in Part 1). Results were consistent across both parts of the study. The median number of unique events (by preferred term [PT]) per patient on study was 13.0, while the median number of unique events assessed as related to Sd was 8.0.

Available safety data for the BCLPD-refractory population is consistent with that seen overall for the wider STORM population, as expected.

Table 18 Summary of TEAEs in the STORM safety analysis population

	STORM Part 1	**STORM Part 2**	
	Updated analysis 7th September, 2019[55]		
	SAS	**SAS**	**BCLPD**
n	**79**	**123**	**83**
Treatment-emergent adverse event [a]	79 (100.0)	123 (100.0)	**83 (100)**
Grade 3/ 4 TEAE	75 (94.9)	115 (93.5)	**NR**
Serious TEAE	45 (57.0)	78 (63.4)	**NR**
TEAE leading to dose modification[b]	61 (77.2)	97 (78.9)	**NR**
TEAE leading to dose reduction	46 (58.2)	80 (65.0)	**NR**
TEAE leading to dose interruption	35 (44.3)	72 (58.5)	**NR**
TEAE leading to study discontinuation	20 (25.3)	39 (31.7)	**25 (30)**

	STORM Part 1	STORM Part 2	
	Updated analysis 7th September, 2019[55]		
	SAS	SAS	BCLPD
n	**79**	**123**	**83**
TEAE leading to death	8 (10.1)	12 (9.8)	**8 (9.6)**
Treatment-emergent treatment-related adverse event [b]	78 (98.7)	121 (98.4)	**NR**
Grade 3/ 4 TRAE	69 (87.3)	110 (89.4)	**NR**
Serious TRAE	21 (26.6)	38 (30.9)	**NR**
TRAE leading to dose modification	54 (68.4)	88 (71.5)	**NR**
TRAE leading to dose reduction	37 (46.8)	64 (52.0)	**NR**
TRAE leading to dose interruption	32 (40.5)	70 (56.9)	**NR**
TRAE leading to study discontinuation	13 (16.5)	24 (19.5)	**NR**
TRAE leading to death	1 (1.3)	3 (2.4)	**2 (2.4)**

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; NR, not reported; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TRAE treatment-emergent treatment-related adverse event

Note: Percentages are based on the number of all-treated patients in each treatment group. A TEAE is defined as an AE that emerged or worsened from first dose to 30 days after last dose.

[a] The number of patients with dose modification(s) is not necessarily equal to the sum of the patients who had a modified dose or a drug interruption as the same patient could fall into more than one of these categories

[b] TEAEs with a relationship of Possible, Probably, or Definite to either selinexor or dexamethasone per Investigator are considered related to study treatment

Most treated patients (89.1%) had a severe (≥Grade 3), treatment-related TEAE. The most frequently occurring (>5% of patients) severe TEAEs assessed as related to Sd included the haematologic events of thrombocytopenia (58.9%), anaemia (31.2%), neutropenia (19.8%), leukopenia (12.9%), and lymphopenia (8.9%). Several gastrointestinal events also occurred in >5% of patients, including nausea (8.9%) and diarrhoea (5.9%). The only other related severe events occurring in ≥5% of patients were hyponatraemia (17.8%), fatigue (18.8%), and hyperglycaemia (7.4%). Table 19 details severe treatment-related TEAEs occurring in ≥5% of patients in STORM (Part 1 and Part 2).

Table 19 Treatment-related Grade 3+ (3/4/5) AEs by maximum severity, occurring in ≥5% (all patients in safety analysis populations)

	STORM Part 1 and Part 2 N=202
	Updated analysis 7th September, 2019[55]
Patients with ≥1 TRAE Grade 3+	180 (89.1)
Blood and lymphatic system disorders:	143 (70.8)
Thrombocytopenia	119 (58.9)
Anaemia	63 (31.2)
Neutropenia	40 (19.8)
Leukopenia	26 (12.9)
Lymphopenia	18 (8.9)
Gastrointestinal disorders:	33 (16.3)
Nausea	18 (8.9)
Diarrhoea	12 (5.9)
General disorders and administration site conditions:	45 (22.3)
Fatigue	38 (18.8)
Infections and infestations	13 (6.4)
Metabolism and nutrition disorders:	65 (32.2)
Hyponatraemia	36 (17.8)
Hyperglycaemia	15 (7.4)
Decreased appetite	10 (5.0)
Psychiatric disorders:	12 (5.9)
Abbreviations: TRAE, treatment-related adverse event	

In the penta-refractory population of STORM Part 2, the most commonly reported haematological AEs were thrombocytopenia (76%), anaemia (66%), neutropenia (42%), and leukopenia (36%). The most common non-haematological AEs were nausea (68%), fatigue (60%), decreased appetite (55%), diarrhoea (51%), weight decreased (46%), hyponatremia (39%), and vomiting (39%). The majority of AEs were Grade 1 or 2, reversible and manageable with dose modifications and standard supportive care. Importantly, these management guidelines include the use of two anti-emetics and body weight monitoring; the education appears to be effective in the post-marketing setting, where the rate of discontinuation of Sd due to AEs is ~13%, which is more than 50% lower than that observed in the clinical trial itself.

Of the 83 patients in the penta-refractory population of STORM Part 2, 30% discontinued treatment due to an AE. Consistent with the heavily pre-treated and medically complex patient population, the reasons for discontinuing treatment due to an AE were variable and not due to major organ toxicity, neuropathy, or infection. Fatigue, nausea, and pneumonia were the most common AE's leading to discontinuation. Of note, the most commonly reported haematologic AEs (thrombocytopenia, neutropenia, and anaemia) did not lead to patients discontinuing selinexor. The overall frequency of non-haematologic AEs reported was substantially higher than the number leading to discontinuation, indicating that while selinexor is associated with several AEs, the majority of patients can tolerate them.

B.2.11 Ongoing studies

No additional ongoing or planned studies are expected to provide data relevant to the decision problem.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Unmet need

There is currently no licensed treatment for penta-refractory MM in the UK; patients may receive supportive symptom management and perhaps palliative care when appropriate, or those who are fit enough often enrol on clinical trials or compassionate use programmes to access active treatment, despite them often lacking proven efficacy in penta-refractory patients. Despite significant evolution in MM treatment, an unmet need exists in penta-refractory disease for an efficacious and tolerable treatment option, particularly one with a new MoA with which they have not already been challenged and developed resistance.

B.2.12.2 Clinical effectiveness

Selinexor is a novel, oral SINE compound which induces apoptosis in myeloma cells, inferring anti-tumour activity, a new MoA compared to current MM treatments. The mITT population of the phase 2b STORM trial included 83 penta-refractory participants in the BCLPD-refractory efficacy population, which formed the basis of the MHRA MA. Headline outcomes in the penta-refractory population include an ORR of 25.3%, median DOR of 3.8 months, and median OS of 8.4 months.

Interpretation of data from STORM should focus on clinically significant gains in the context of the population which has rapidly progressing disease, limited OS expectations, and limited if any, current treatment options.

Of the 21 responders in the penta-refractory population, the median time to respond was 4.0 weeks, with disease control being achieved as early as 2 weeks in some patients. This rapid response is key in these patients with very rapid disease progression, where a median 22% increase in disease burden occurred in the 12 days between screening and initiating treatment with selinexor, in STORM. Without rapid disease control, these patients can develop rapid end-organ failure (especially renal failure), progressive pancytopenia, infection, and death, evident in the STORM trial where the OS was only ~8 weeks in patients with PD or NE response. This highlights the particular importance of being able to control the disease in these heavily pre-treated patients rapidly. In addition, the rapid time to response observed in patients treated with selinexor allows the physician and the patient to quickly evaluate the benefits of therapy, thereby limiting the time on treatment and associated AEs if they are not benefitting.

Similar to ORR, the length of DOR decreases with each line of treatment, as the disease becomes increasingly refractory. While the median DOR was 3.8 months, the longest DOR was 10.8 months, and the overall median time on treatment for the responding patients was almost 5 months. A DOR of 3.8 months observed in the penta-refractory population of STORM Part 2 is clinically meaningful in the context of very limited expected survival in this patient population.

As with ORR and DOR, OS should also be evaluated in the context of the patient population being studied. As such, the 8.4 months median OS achieved in penta-refractory patients in STORM Part 2 is clinically significant and meaningful to patients and their families. It is also noteworthy that observed OS was greater for patients achieving PR or better.

As described in Section B.1.3.2, in the context of Sd being the first licensed treatment specifically for penta-refractory MM, UK myeloma clinical experts consulted suggest that in terms of the NICE final scope, BSC is the only relevant comparator for this decision problem, where in reality patients may currently have experimental regimens

in trials, unlicensed/ off-license agents in compassionate use programmes, or some kind of supportive care including CCT agents such as cyclophosphamide, where appropriate.

There is a paucity of data collected in penta-refractory MM. Outside of the STORM trial, the SLR identified only observational evidence of data reported for penta-refractory MM separately. Following a feasibility assessment, three observational studies of real-world SoC were included in initial unanchored MAIC analyses, but due to concerns over resulting ESS and lack of reporting of necessary KM curves for penta-refractory patients separately, an STC *versus* the MAMMOTH study was performed, for OS as the only relevant analysis. Sd in STORM compared favourably to real-world SoC from MAMMOTH (HR 0.585).

This is likely to be a highly conservative estimate of the comparable efficacy of Sd *versus* BSC; despite MAMMOTH being the best data source available for penta-refractory patients in the real-world and therefore used as the best available proxy for BSC in UK clinical practice, there are limitations. MAMMOTH collected data at US clinical sites where penta-refractory patients who received further treatment (63/70), received treatment combinations that would not be available to penta-refractory patients in UK clinical practice, thereby overestimating the SoC/ BSC treatment effect that would likely be observed in penta-refractory patients in the UK.

With the MM treatment pathway evolving dramatically in earlier lines, more patients are reaching later treatment lines. Overall, oral Sd represents a life-extending treatment option with a novel mechanism of action for penta-refractory patients who currently have no licensed treatment options with known clinical benefits. Furthermore, since Sd is an oral regimen, it also provides a convenient treatment for patients with the most severe disease in critical need of new treatments.

B.2.12.3 Safety and tolerability

Death from MM itself is commonly due to infection, cardiac failure, renal failure, or other major organ dysfunctions.[64] The tolerability of any MM treatment regimen in penta-refractory MM is compromised by the patient's advanced age, multiple common comorbidities, and highly advanced stage of disease with associated end-organ damage. Other compromising factors that should be considered are the cumulative

effects of several previous treatment combinations, in and the side effects of the concomitant treatments required to treat these comorbidities. Consequently, patients with penta-refractory MM are at very high risk for AEs, regardless of causality to MM treatments.

Overall, the safety profile of selinexor is predictable and manageable. Most AEs in STORM were haematologic, gastrointestinal, or associated with constitutional symptoms. Haematologic AEs were generally reversible with dose modification and treatment with growth factors and were not associated with clinical sequalae. The gastrointestinal and constitutional side effects were primarily low-grade and tended to be reversible with supportive care. Overall, the safety profile of Sd did not limit treatment duration.

The UK Myeloma Society nurses subgroup is leading the development of an educational support programme to support nurses, pharmacists, and patients to mitigate the adverse event profile of selinexor.

Its implementation throughout the UK considers supportive care measures alongside dose reductions/ optimisation. The focus is ensuring appropriate prophylactic anti-emetics are implemented from the start of therapy, with appropriate dose modification as recommended in the SmPC if required. In countries where this programme has been implemented, it appears to be effective as the discontinuation rate in the post-marketing setting is around half of what was seen in the clinical trial (13% *vs*. 30%, respectively). A further benefit of selinexor is that it does not require adjustment of doses of concomitant medications, and there are no known drug-drug interactions. There is no evidence of clinically significant cumulative toxicities and major organ toxicities or of peripheral neuropathy, alopecia, mucositis, thromboembolism, or secondary malignancies. Both febrile neutropenia and opportunistic infections are not typically observed with Sd therapy and no specific anti-microbial prophylaxis is required. The AE profile was also consistent across the whole trial, Part 1, and Part 2, and across all populations despite different refractoriness – i.e., penta-refractory patients did not fare worse.

In summary, penta-refractory MM patients are prone to AEs as a feature of their advanced age, frailty, disease burden and cumulative effect of prior treatment.

However, the AEs associated with selinexor are predictable and manageable, particularly with a prophylactic approach. Most AEs are dose- and schedule-dependent and are reversible and manageable with dose modifications and/ or supportive care, and when supportive care measures are utilised, the rate and severity of the AEs may be diminished. Overall, selinexor demonstrates a positive benefit-risk profile.

B.2.12.4 Conclusion

Penta-refractory MM patients have a high disease burden and built-up drug resistance and likely significant treatment-related comorbidities. Despite this, with the evolution of new MM treatments earlier in the treatment pathway, more patients are reaching 5L and with penta-refractory status, who need an alternative treatment with a new MoA which confers favorable efficacy to extend survival coupled with a manageable safety profile. Selinexor in combination with dexamethasone is the first EMA and MHRA licensed treatment specifically for penta-refractory MM, with data from the pivotal STORM trial demonstrating clinically meaningful response rates with impactful survival gains for these heavily pre-treated patients for whom clinical trials, compassionate use programs and other sub-optimal treatments are often the only options available to them, ahead of palliative care.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

B.3.1.1 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 Sd, but also the simultaneous company submission of SVd in a 2L and 3L setting (NICE ID3797). 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 RRMM, who have received greater than 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?

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.[51,52,65] The SLR search strategy and study selection methods are described in Appendix G.

B.3.1.2 Description of identified studies

There were no identified studies that reported cost-effectiveness evidence, specifically in penta-refractory MM. In the absence of penta-refractory data, two studies (reported over three records) in proxy patient populations were identified that reported evidence from international cost-effectiveness analyses (CEAs) in patients with TCR MM (n=1), from the US (Nikolaou *et al*. 2021), and 5L+ RRMM (n=1), from Italy (Speranza *et al*. 2021/ 22).[66-68] One NICE technology appraisals currently with guidance in development (GID), '*Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]*', was also identified in a 5L+ TCR population, reporting available cost-effectiveness evidence using DREAMM-2, though currently is not recommended at NICE with final publication expected August 2023.[6] A

summary of published cost-effectiveness evidence from the two international studies and the NICE ongoing appraisal is summarised in Table 20.

All of the studies identified used a partitioned survival, four-health state model structure (where reported), whereby patient health states correspond to OS and PFS study endpoints and estimated treatment duration. The US study and NICE TA reported health states of progression-free on-treatment, progression-free off-treatment, progressed disease, and death. A weekly cycle length and a lifetime time horizon were applied in all three analyses, varying between 10 and 25 years across models, where duration was reported. QALYs, total treatment costs and ICERs varied across the studies.

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

Table 20 Summary of identified cost-effectiveness studies

Study / Year	Summary	Interventions	Efficacy source	Model structure	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Nikolaou *et al.* (2021)[66]	CEA from US commercial payer perspective	Belamaf *vs.* Sd	DREAMM-2 (Belamaf), MAIC *vs.* STORM Part 2 (Sd)	PSM with 4 health states (PF on tx, PF off tx, PD, death)	TCR MM with ≥4 prior therapies	Belamaf 1.11 QALYs, Sd 0.62 QALYs	Belamaf: $212,535, Sd: $226,802	Belamaf *vs. S*d: Belamaf dominant
Speranza *et al.* (2021/22)[67,68]	CEA from Italian health service perspective	Belamaf *vs.* SoC	NR ['literature and clinical studies' cited]	PSM (number of health states NR)	RRMM with ≥4 prior therapies	Belamaf 1.97 QALYs, SoC 0.41 QALYs	Belamaf: €74,449, SoC: €16,526	Belamaf *vs*. SoC[b]: €31,023 per QALY
NICE ID2701 (2023)[6]	CEA from UK NHS/ PSS perspective	Belamaf *vs.* Pd	DREAMM-2	PSM with 4 health states (PF on tx, PF off tx, PD, death)	RRMM with ≥4 prior therapies	Redacted	Redacted	Belamaf *vs.* Pd: Belmaf dominant

Abbreviations: Belamaf, Belantamab mafodotin; CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; MAIC, matching-adjusted indirect comparison; MM, multiple myeloma; NICE, National Institute for Health and Care Excellence; NR, not reported; Pd, pomalidomide + dexamethasone; PD, progressive disease; PF, progression free; PSM, partitioned survival model; PSS, Personal Social Services; QALYs, quality-adjusted life years; RRMM, relapsed and/ or refractory multiple myeloma; Sd, selinexor plus dexamethasone; SoC, standard of care; TCR, triple-class refractory; tx, treatment; UK, United Kingdom; US, United States; vs., versus

[a] 5L studies have been considered in lieu of evidence in penta-refractory patients

[b] SoC reported as: pomalidomide + dexamethasone; carfilzomib + dexamethasone; ixazomib + lenalidomide + dexamethasone; cyclophosphamide

B.3.2 Economic analysis

Section summary

- The CEA considers the cost-effectiveness of Sd *vs.* BSC, as a proxy standard of care comparator. Based on UK myeloma expert clinical input, 20% of penta-refractory BSC patients are assumed to receive chemotherapy, and the remainder symptomatic or palliative care only.
- A *de novo* four-state partitioned survival model was developed in Microsoft Excel to estimate total and incremental lifetime costs and QALYs.
- Progression and survival among patients receiving Sd are estimated using parametric curves fitted to Kaplan-Meier curves of penta-refractory patients from the single-arm, pivotal, phase 2b STORM study. UK myeloma clinical expert input was sought to validate appropriate curve selection alongside evaluations of statistical/ visual fit.
- Comparator efficacy is estimated using hazard ratios derived from an ITC (STA and MAIC analyses) of STORM *versus* MAMMOTH, a US real-world study used as a proxy for BSC as the only source with sufficient reporting in a penta-refractory population. Because many patients in MAMMOTH received active regimens that would not be available in UK clinical practice, indirect comparisons using the study as a proxy comparator are likely to underestimate the true treatment effect of Sd *vs.* BSC.
- A pre-progression utility value of 0.59 is applied, estimated based on mapped FACT-MM data collected in STORM. As the STORM study collected limited evidence beyond progression, a post-progression utility decrement sourced from published literature is applied.
- Base and scenario cost-effectiveness results are reported as ICERs (costs per incremental QALY) and net health benefit (NHB) for Sd *versus* BSC.
- A severity modifier of 1.7 is applied, according to the QALY shortfall in the BSC arm relative to general population norms. Cost-effectiveness results are presented both with and without the modifier applied.
- Base case results show Sd to be cost-effective *vs.* BSC (ICER £27,408), despite active therapies in the proxy comparator source. Scenario analyses show cost-effectiveness to be largely robust to key data uncertainties.

In the absence of a previous NICE evaluation for Sd in a MM patient population, a *de novo* cost-utility model was developed in Microsoft Excel with the primary aim of estimating the incremental lifetime costs and QALYs associated with Sd relative to BSC in a penta-refractory MM population.

B.3.2.1 Patient population

The economic analysis considers the cost-effectiveness of Sd relative to BSC for the treatment of MM in adult patients whose disease is penta-refractory (refractory to at least two PIs, two IMiDs and an anti-CD38 mAb). This patient population aligns with the MA for Sd as a treatment of MM in adult patients whose disease is penta-refractory, as outlined in section B.1.2.[3]

Where possible, evidence used to inform the CEA is derived from sources specific to penta-refractory MM populations. For the Sd arm, the primary source of clinical effectiveness evidence is the BCLPD-refractory population of Part 2 of the single-arm, pivotal, phase 2b STORM trial. The baseline characteristics of BCLPD-refractory patients from STORM which are applied at model baseline are described in Table 21. Inclusion and exclusion criteria for the overall STORM trial are provided in Section B.2.3.1.

Table 21 Patient characteristics used in the economic analysis

Population	**STORM Part 2 BCLPD-refractory (n=83)[55]**
Mean age (years)	64.5
Proportion male (%)	61.5%
Weight (kg)	78.4
BSA (m^2)	1.89
Median (range) prior lines	8 (4-18)

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; BSA, body surface area; kg, kilogram; m^2, metre squared; n, number

B.3.2.2 Model structure

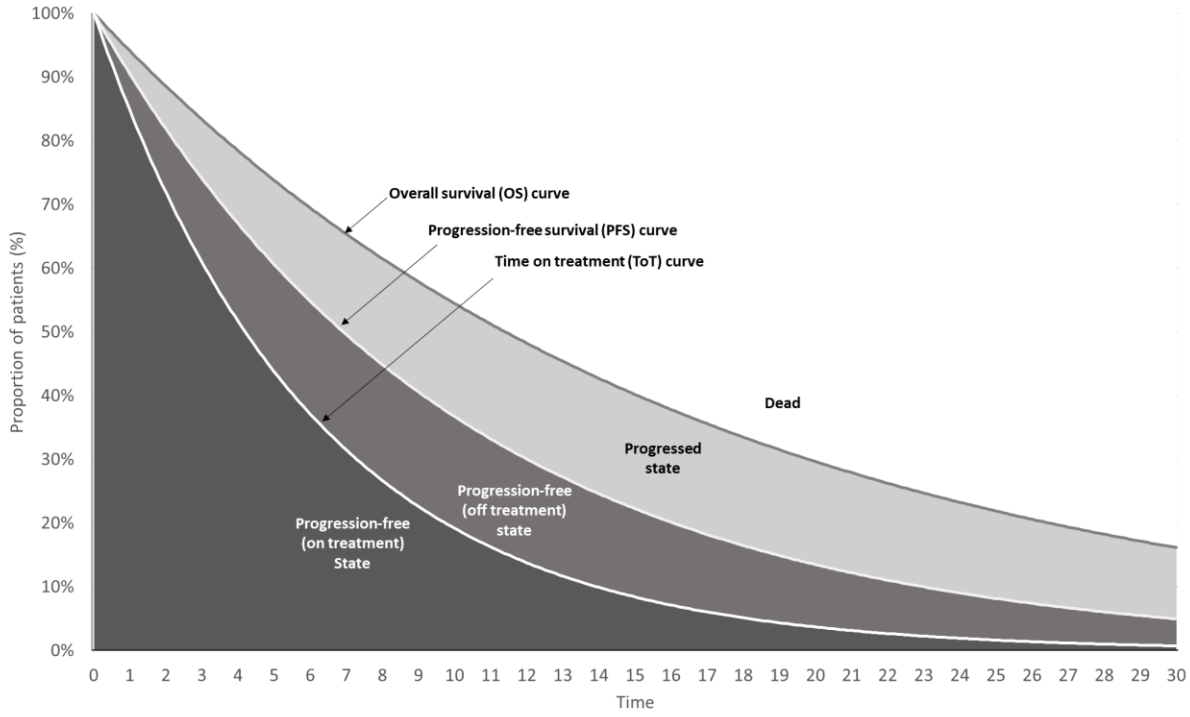
Appropriate model structure was explored with reference to NICE Decision Support Unit (DSU) guidance (specifically NICE TSDs 14, 15, 16 and 19).[69-72] A key consideration was how different approaches could accommodate the features and

limitations of evidence available for Sd and BSC (in particular the use of single-arm data for Sd and reliance upon comparator evidence reported at the aggregate level). Publicly available documentation on the NICE website was also examined to identify learnings generalisable from EAG and NICE committee responses to the approaches explored in previous MM appraisals.

The PSM structure employed in the studies described in Table 20 is a well-established approach for evaluating the cost-effectiveness of oncology therapies. In common with state transition approaches (the most frequently used alternative), the PSM typically categorises patients into three main health states: progression-free, progressed, and dead.

The time-on-treatment endpoint can be used to subdivide the progression-free state (Figure 11) and/ or progressed disease states to distinguish between patients that are on or off treatment. In contrast to Markov-based approaches, which estimate the distribution of patients across health states based on observed *transitions* at specific time intervals, the PSM does so directly from the area between OS and PFS survival curves (illustrated in Figure 11), known as the Area Under the Curve (AUC) method.

Figure 11 Illustrative partitioned survival model diagram with on/ off-treatment progression-free health states



As discussed in NICE TSD 19, a particular advantage of the PSM approach is that estimates of health state membership can be derived directly from aggregate estimates without the need for patient-level data to inform transition probabilities.[72]

This is a benefit when indirect comparisons are required against comparator treatments for which patient data are unavailable: study publications commonly report Kaplan-Meier curves for OS and PFS as primary or secondary trial endpoints, but patient-level transitions cannot be inferred from these.

Given these advantages and strong precedents in MM evaluations, and in considering STORM as a single-arm trial, a PSM structure was considered appropriate.

In addition to OS and PFS endpoints, estimated time on treatment was used to divide the progression-free health state into separate on-treatment and off-treatment states to reflect an assumption that some patients may discontinue treatment prior to disease progression.

The model applies a cycle length of one week, to align model cycles with the dosing schedule for Sd (administrated on a 35-day/5- week cycle). A half-cycle correction has been applied in the base case analysis.

Cost and QALY estimates are calculated over a 30-year period from model baseline, to represent a lifetime horizon (whereby fewer than 1% of patients in either arm remain alive at model end in any main scenarios). The economic analysis perspective is that of the NHS and Personal Social Services (PSS) in the UK healthcare system, with costs and benefits discounted at 3.5% per annum in keeping with standard assumptions recommended by the NICE health technology evaluations manual.[52]

A summary of the model's structure, settings and inputs and comparison against previous NICE technology appraisals in RRMM is presented in Table 22.

Table 22 Features of the economic analysis

	Previous evaluations					Current evaluation	
	TA658 (2020)[73]	**TA783 (2022)[74]**	**TA427 (2017)[75]**	**TA870 (2023)[76]**	**TA380 (2016)[77]**	**Chosen values**	**Justification**
Intervention	IsaPd	Dara mono	Pd	IxaRd	PanoVd	Sd	-
Model structure	PSM	PSM	PSM	PSM	PSM	PSM	Suitability for the trial endpoints and use of aggregate comparator data
Time horizon	5-15 years	15 years	15 years	25 years	Lifetime (99% patients died)	Lifetime	Consistent with the NICE reference case
Cycle length	1 week	1 week	1 week	1 week	3 weeks	1 week	Coterminous with Sd 5-weekly dosing cycle
Treatment waning effect?	Not applied	Not applied	Not applied	Not applied. Committee thought treatment waning would be largely captured in the trial.	Not applied	Not applied in the base case	Patients are only treated to progression, and data are sufficiently mature that the likelihood of uncaptured waning is minimal.
Source of utilities	EQ-5D from the ICARIA-MM trial	EQ-5D from the MM-003 trial	EQ-5D from the MM-003 trial	EQ-5D from the TMM1 trial	EORTC-30 from the PANORAMA-1 trial mapped to EQ-5D	STORM FACT-MM mapped to EQ-5D-3L for progression-free; decrement from TA658	STORM data mapped from the FACT-MM are preferred as direct study data but only suitable for estimating progression-free utilities. Applying a relative decrement from TA658 (rather than an absolute estimate) allows for wider evidence to be

	Previous evaluations					Current evaluation	
	TA658 (2020)[73]	**TA783 (2022)[74]**	**TA427 (2017)[75]**	**TA870 (2023)[76]**	**TA380 (2016)[77]**	**Chosen values**	**Justification**
						for progressed disease	incorporated while maintaining the assumed association between states.
Source of unit costs	BNF, eMIT, NHS reference costs	BNF, NHS reference costs	MIMS, eMIT, NHS reference costs	BNF, eMIT, NHS reference costs	BNF, NHS reference costs	BNF, eMIT, NHS reference costs	Relevant given the perspective and in keeping with precedent
Perspective	NHS & Personal Social Services	NHS & Personal Social Services	NHS & Personal Social Services	NHS & Personal Social Services	NHS & Personal Social Services	NHS & Personal Social Services	Consistent with the NICE reference case

Abbreviations: BNF, British National Formulary; Dara mono, daratumumab monotherapy; eMIT, electronic market information tool; EQ-5D/-3L, EuroQol five dimension/ 3 level; FACT-MM, Functional Assessment of Cancer Therapy - Multiple Myeloma; IsaPd, isatuximab with pomalidomide and dexamethasone; IxaRd, ixazomib with lenalidomide and dexamethasone; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PanoVd, Panobinostat plus bortezomib and dexamethasone Pd, pomalidomide; PSM, partitioned survival model; Sd, selinexor plus dexamethasone; TA, technology appraisal

B.3.2.3 Intervention technology and comparators

The cost-effectiveness analysis (CEA) considers the intervention, Sd, in line with its marketing authorisation as outlined in section B.1.2: for the treatment of multiple myeloma in adult patients that 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).[3]

The intervention technology considered in the analysis is selinexor plus dexamethasone. Patients are assumed to receive selinexor in accordance with marketing authorisation guidance at an initial starting dose of selinexor 80mg plus dexamethasone 20mg orally twice per week, with dose modifications applied in response to adverse events if appropriate. To preserve the expected relationship between dosage and clinical efficacy and adverse event outcomes, the mean dose of 114.4mg per week observed in the STORM trial is applied. Patients receiving Sd are assumed to remain on treatment until disease progression or unacceptable toxicity, as captured by treatment duration data in the STORM trial.

As no therapy is currently recommended for penta-refractory patients, BSC is the sole comparator considered in the analysis. No published data source has been identified that directly represents BSC in a UK penta-refractory population. Instead, publications from international registry sources, representing the standard of care in different global settings, have been explored as potential proxy sources of evidence (section B.2.12.2). Of the sources considered, the US MAMMOTH study was the only source from which sufficient evidence specific to a penta-refractory cohort of patients had been published for robust indirect comparisons to be made. Since the study included patients receiving treatment that would not be recommended as a component of the UK standard of care, estimates of comparator efficacy using MAMMOTH as a proxy for BSC are presented with the caveat that they expected to substantially understate the overall effectiveness and hence cost-effectiveness of Sd relative to BSC.

B.3.3 Clinical parameters and variables

B.3.3.1 STORM time-to-event data

Key time-to-event endpoints relating to penta-refractory patients receiving Sd were obtained from patient-level data corresponding to the 83 BCLPD-refractory in the STORM trial (described in section B.2.6).

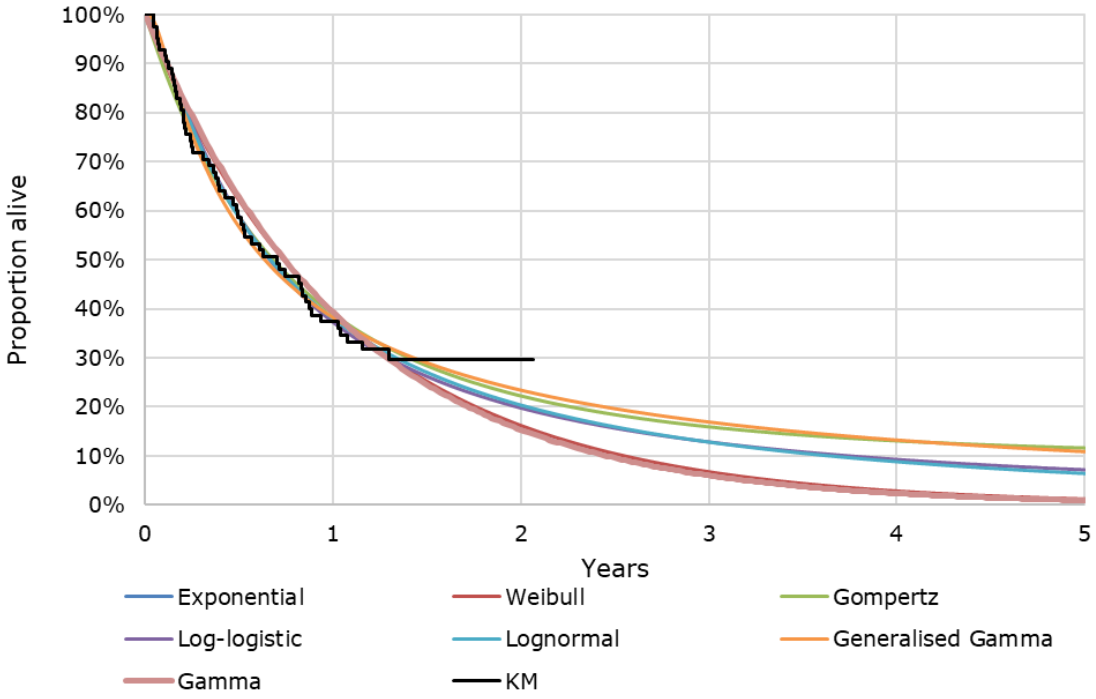
Data from the updated analysis of STORM (September 2019 data cut), from secondary endpoints PFS and OS, were used to estimate health state membership by progression status, using the PSM approach outlined in section B.3.2.2. To approximate and extrapolate these estimates over the time horizon of the model, seven alternative parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic, generalised gamma and gamma) were fitted to patient-level data for each endpoint. The optimal choice of parametric function was determined based on the following criteria, as recommended in NICE TSD 14:

- Statistical goodness of fit (according to Akaike Information Criterion (AIC) statistics, whereby a smaller absolute number indicates a better statistical fit);
- Visual goodness of fit (To assess how closely parametric curves align with Kaplan-Meir curves over the observed period);
- Expert clinical opinion (the extent to which curve choices align with clinical expectations, especially regarding cross-sectional estimates of cumulative progression and survival rates at landmark time points).[69]

B.3.3.1.1 Overall survival

Parametric distributions fitted to OS in the BCLPD-refractory STORM population are shown in Figure 12 below, with landmark survival estimates corresponding to each curve summarised in Table 23.

Figure 12 Parametric curves fitted to OS: STORM BCLPD-refractory population



Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; IRC, Independent Review Committee; OS, Overall survival
Source: Menarini Stemline data on file

Table 23 Landmark estimates of proportion of patients estimated to be alive corresponding to OS parametric functions fitted: STORM BCLPD-refractory population

Year	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised Gamma	Gamma
1	39.30%	39.40%	38.96%	37.26%	37.99%	38.21%	39.27%
2	15.44%	16.21%	22.25%	19.79%	20.37%	23.41%	15.34%
5	0.94%	1.22%	11.63%	7.17%	6.43%	10.88%	0.89%
10	0.01%	0.02%	9.91%	3.11%	2.06%	5.69%	0.01%
20	0.00%	0.00%	9.79%	1.32%	0.52%	2.84%	0.00%
30	0.00%	0.00%	9.79%	0.79%	0.21%	1.87%	0.00%

Of the parametric curves explored, the log-normal distribution provides the closest statistical fit to observed OS data based on AIC statistics (Table 24), although the close range of AIC values (381 to 387) suggests little meaningful difference from a statistical standpoint. All curves correspond well to the Kaplan-Meier curve in terms of visual fit

also, suggesting that more flexible curve-fitting approaches such as spline or piecewise fitting would offer no clear improvement while adding undue complexity.

With little to distinguish between them in terms of visual or statistical fit, base OS curve selection focused on clinical expert opinion regarding the plausibility of extrapolated survival rates and level of agreement with clinical expectations. Presented with the OS curves shown in Figure 12 at an advisory board,[32] two myeloma clinical experts (UK Consultant Haematologists) suggested that approximately five percent of patients might be expected to be alive at five years beyond baseline. Gompertz and generalised gamma curves, estimating overall survival >10% at 5 years and >5% at 10 years from baseline, were singled out as likely overestimates.

The log-normal distribution (6.4% alive at 5 years) was chosen as the base case OS curve for Sd, on the basis that it corresponded most closely to clinical estimates. The log-normal curve also aligned with the expectation that small numbers of patients survive to 10 years beyond baseline (2.1% as estimated from a log-normal distribution). All curves fitted were explored in model scenario analyses.

Table 24 Parametric curve coefficients and goodness-of-fit statistics for OS: STORM BCLPD-refractory population

Function	Parameter	Model parameter	SE	Covariance			AIC	BIC
Exponential	Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	385.39	387.81
Weibull	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	387.30	392.14
	Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Gompertz	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	385.23	390.07
	Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Log-logistic	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	382.97	387.81
	Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Log-normal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	380.84	385.68
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Generalised gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	381.77	389.03
	sigma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Q	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Gamma	Shape	[redacted]	[redacted]	[redacted]	[redacted]		387.39	392.22
	Scale	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; SE, standard error

B.3.3.1.2 Progression-free survival

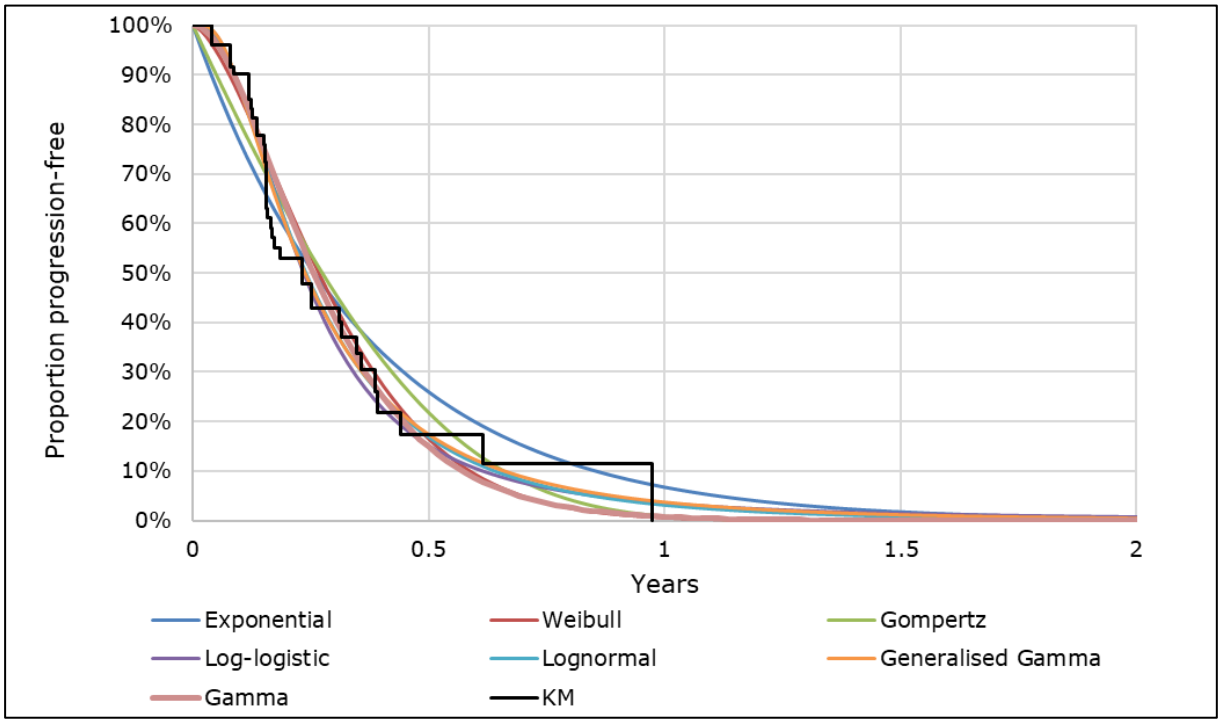
Progression-free survival (IRC assessed)

Parametric distributions fitted to PFS (based on IRC assessment) are shown to two years in Figure 13 with corresponding landmark estimates to model end in Table 25. Curve coefficients and statistical fit information are provided in Table 26.

In keeping with the OS extrapolation, the log-normal distribution had the best statistical fit to the Kaplan-Meier curve for PFS, with AIC values ranging from 184.7 (log-normal) to 201.1 (exponential). Clinicians consulted at the advisory board meeting identified no clear distinction between PFS curves regarding clinical plausibility since all provided similar estimates whereby less than one per cent of patients remained progression-free at two years.

As the curve with the best statistical fit, the log-normal distribution was selected as the most appropriate base case approximation of PFS. The log-normal also avoids overlap between OS and PFS curves seen in other extrapolation choices which, although not a methodological challenge, would suggest some incompatibility between the underlying distributions assumed for each endpoint. Results for all other parametric curves fitted to the Kaplan-Meier curve were explored in scenario analyses.

Figure 13 Parametric curves fitted to PFS (IRC assessed): STORM BCLPD-refractory population



Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; IRC, Independent Review Committee; PFS, progression free survival
Source: Menarini Stemline data on file

Table 25 Landmark estimates of proportion of patients estimated to be progression free corresponding to PFS (IRC assessed) functions fitted: STORM BCLPD-refractory population

Year	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised Gamma	Gamma
1	6.73%	0.56%	0.85%	3.52%	3.12%	3.72%	0.76%
2	0.45%	0.00%	0.00%	0.74%	0.28%	0.46%	0.00%
5	0.00%	0.00%	0.00%	0.09%	0.00%	0.01%	0.00%
10	0.00%	0.00%	0.00%	0.02%	0.00%	0.00%	0.00%
20	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
30	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; IRC, Independent Review Committee; PFS, progression free survival

Table 26 Parametric curve coefficients and goodness-of-fit statistics for PFS (IRC assessed): STORM BCLPD-refractory

Function	Parameter	Model parameter	SE	Covariance			AIC	BIC
Exponential	Rate	[redacted]	[redacted]	[redacted]			201.12	203.54
Weibull	Shape	[redacted]	[redacted]	[redacted]	[redacted]		191.63	196.47
	Scale	[redacted]	[redacted]	[redacted]	[redacted]			
Gompertz	Shape	[redacted]	[redacted]	[redacted]	[redacted]		199.63	204.46
	Rate	[redacted]	[redacted]	[redacted]	[redacted]			
Log-logistic	Shape	[redacted]	[redacted]	[redacted]	[redacted]		185.42	190.26
	Scale	[redacted]	[redacted]	[redacted]	[redacted]			
Log-normal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]		184.74	189.58
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]			
Generalised gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	186.67	193.93
	sigma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Q	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Gamma	Shape	[redacted]	[redacted]	[redacted]	[redacted]		188.28	193.12
	Scale	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; IRC, Independent Review Committee; PFS, progression-free survival; SE, standard error

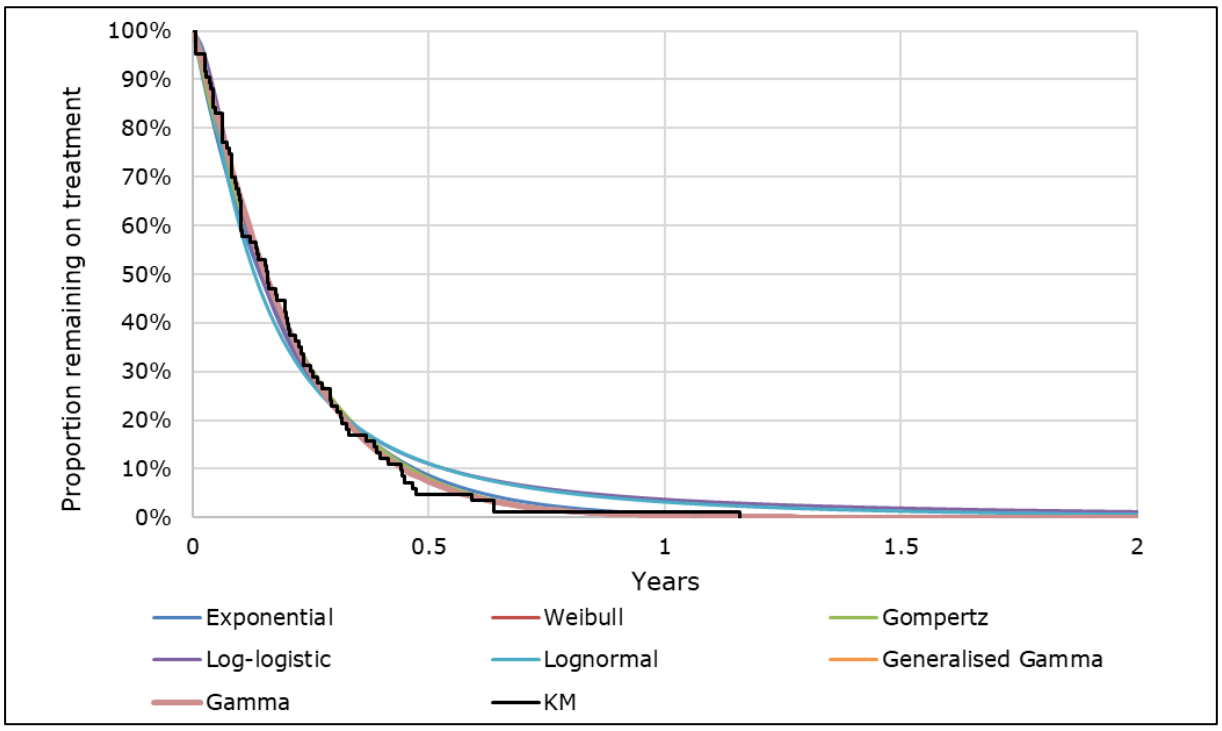
B.3.3.1.3 Time on treatment (ToT)

Time on treatment (ToT) was defined as the date of starting a medication to the date of treatment discontinuation or death, whichever occurred first. ToT was not measured as an endpoint in the STORM trial; therefore, the outcome was derived from subtracting the treatment start date from the end date. The median ToT was 1.9 months in the BCLPD-refractory population. ToT was capped by PFS within the model, such that the number of patients on treatment could not exceed the number that were progression-free at any point in time.

An exponential distribution has been applied in the base case for ToT, based on AIC ranking (AIC score of 316.6, from a range of 316.2 to 329.2 across all curves), and reflecting the clinical expectation that ToT would not asymptote to zero ahead of PFS (i.e., as long as patients' disease has not progressed, at least some will remain on

treatment). Log-logistic and log-normal ToT extrapolations exceed the base (log-normal) PFS estimate of 3.12% at 12 months and can therefore be regarded as likely overestimates contingent on other base assumptions. Results using each of the alternative parametric curve choices were applied as sensitivity analyses.

Figure 14 Parametric curves fitted to ToT: STORM BCLPD-refractory population



Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; ToT, time on treatment
Source: Menarini Stemline data on file

Table 27 Landmark estimates of proportion of patients estimated to remain on treatment corresponding to ToT parametric functions fitted: STORM BCLPD-refractory population

Year	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised Gamma	Gamma
1	0.75%	0.30%	0.33%	3.75%	3.21%	0.37%	0.40%
2	0.01%	0.00%	0.00%	1.21%	0.65%	0.00%	0.00%
5	0.00%	0.00%	0.00%	0.26%	0.05%	0.00%	0.00%
10	0.00%	0.00%	0.00%	0.08%	0.00%	0.00%	0.00%
20	0.00%	0.00%	0.00%	0.03%	0.00%	0.00%	0.00%
30	0.00%	0.00%	0.00%	0.01%	0.00%	0.00%	0.00%

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; ToT, time on treatment

Table 28 Parametric curve coefficients and goodness-of-fit statistics for ToT: STORM BCLPD-refractory population

Function	Parameter	Model parameter	SE	Covariance			AIC	BIC
Exponential	Rate	[redacted]	[redacted]	[redacted]	[redacted]		316.55	318.97
Weibull	Shape	[redacted]	[redacted]	[redacted]	[redacted]		316.22	321.06
	Scale	[redacted]	[redacted]	[redacted]	[redacted]			
Gompertz	Shape	[redacted]	[redacted]	[redacted]	[redacted]		317.77	322.61
	Rate	[redacted]	[redacted]	[redacted]	[redacted]			
Log-logistic	Shape	[redacted]	[redacted]	[redacted]	[redacted]		325.25	330.09
	Scale	[redacted]	[redacted]	[redacted]	[redacted]			
Log-normal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]		329.21	334.05
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]			
Generalised gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	318.11	325.37
	sigma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Q	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Gamma	Shape	[redacted]	[redacted]	[redacted]	[redacted]		316.12	320.96
	Scale	[redacted]	[redacted]	[redacted]	[redacted]			
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; IRC, Independent Review Committee; SE, standard error; ToT, time on treatment								

B.3.3.2 Indirect treatment comparison

Overall survival for the BSC arm of the CEA was using a hazard ratio from the STORM *versus* MAMMOTH penta-refractory ITC described in section B.2.9 and Appendix D. As the MAIC analysis reduced ESS to a level that was considered too small to provide a robust estimate of relative efficacy, the base case analysis used the HR of 0.585 (in favour of Sd) estimated from the STC. HRs derived from the MAICs (estimated using 'full' and 'must-have' lists of covariates — 0.757 and 0.681 *versus* MAMMOTH, respectively) were applied as model scenarios.

The receipt of active therapies among patients included in the MAMMOTH study is expected to have led to higher survival rates than found among patients receiving BSC alone. Since it has not been possible to quantify the size of such an effect from aggregate data nor to control for its influence, HR estimates derived using the

MAMMOTH represent a pessimistic or conservative estimate of the impact of Sd on survival rates *versus* BSC.

Overall survival

Of the comparator studies identified through searches and guidance from clinical experts, MAMMOTH was the only source with published OS results specific to a penta-refractory MM population that could be incorporated into an ITC. MAIC estimates based on both 'full' and 'must-have' variable lists identified by clinical experts led to reductions in ESS from 80 patients to 13.5 and 10.4 patients, respectively. As this level of reduction suggests MAIC-based estimates may not be reliable, the base case OS hazard ratio was instead taken from the STC (a regression-based method with lower requirements for overlapping covariate distributions) of the same populations. A hazard ratio of 0.585, favouring Sd over BSC, was estimated from the log-normal estimate identified as the best-fitting distribution (based on AIC) in the STC analysis.

Progression-free survival

No PFS estimate specific to penta-refractory patients was reported in the MAMMOTH study. As a conservative assumption, a PFS hazard ratio of 1 for Sd *vs.* BSC (denoting no superiority in terms of progression rate) was assumed in the base case. To explore sensitivity to this assumption, a HR of 0.585 (equivalent to the HR for Sd *vs.* BSC, favouring Sd), was applied.

B.3.3.3 Adverse events

Adverse event rates applied in the CEA as the base case and scenario assumptions are listed in Table 29. AE rates were not reported separately for the BCLPD-refractory population of STORM but are assumed to be equivalent to those reported in the overall Part 2 population of the study, based on the comparable levels of treatment adherence and dose adjustment observed in the two groups.

As a conservative assumption, no adverse events have been assumed in the base case for patients receiving BSC. Although the expectation is that BSC would present AEs (especially where chemotherapy is received), the assumption is that Sd would more likely delay than displace alternative forms of therapy, and associated event rates would be similar.

To explore uncertainty around the prevalence of AEs in the BSC further, a scenario analysis applies estimated AE rates to the 20% of patients that are assumed to receive chemotherapy in the BSC arm.

Since no suitable studies in penta-refractory populations were identified from the clinical SLR, assumptions for this scenario are derived from AE rates reported among patients receiving cyclophosphamide and dexamethasone in the control arm of the MUK eight trial (median 4 prior lines of therapy).[78]

Table 29 Adverse event rates used in cost-effectiveness analysis

Adverse events, Grade 3-4	STORM Part 2[55]	MAMMOTH[63]	MUK eight[78]	No AEs (assumption)
Anaemia	45.1%	33.0%	22.6%	0.0%
Asthenia	5.7%	3.7%	0.0%	0.0%
Back pain	2.5%	5.0%	0.0%	0.0%
Bone pain	0.8%	7.0%	0.0%	0.0%
Decreased appetite	6.6%	0.7%	0.0%	0.0%
Dehydration	3.3%	0.0%	0.0%	0.0%
Diarrhoea	7.4%	1.0%	1.9%	0.0%
Dyspnoea	4.1%	5.0%	0.0%	0.0%
Fatigue	21.3%	5.3%	1.9%	0.0%
Hyperglycaemia	6.6%	0.0%	3.8%	0.0%
Hypokalaemia	6.6%	0.0%	0.0%	0.0%
Hyponatraemia	22.1%	0.0%	0.0%	0.0%
Infections and infestations	0.0%	30.3%	13.2%	0.0%
Leukopenia	14.8%	8.7%	0.0%	8.7%
Lymphopenia	11.5%	0.0%	0.0%	0.00%
Nausea	9.8%	0.7%	1.9%	0.7%
Neutropenia	22.1%	47.7%	0.0%	47.7%
Pneumonia	9.0%	12.7%	0.0%	12.7%
Sepsis	7.4%	0.0%	0.0%	0.0%

Thrombocytopenia	62.3%	22.3%	24.5%	22.3%
Vision blurred	1.6%	0.0%	0.0%	0.0%

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL data were collected in the STORM trial using the Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM), a patient-reported outcome (PRO) measure that comprised the 27-item FACT-G (a four-domain HRQoL measure developed for cancers) and a 14-item MM-specific subscale.

Data were collected at baseline and every 4-week treatment cycle from cycle 2 until treatment discontinuation. As the FACT-MM is not a preference-based measure and cannot be used directly to estimate utilities, mapping was required to derive estimated utility scores.

B.3.4.2 Mapping

No algorithm has been published for mapping directly from the FACT-MM to the EQ-5D-3L (the preferred utility measure recommended in the NICE manual).[52] As the FACT-MM includes questions from the FACT-General (FACT-G), published algorithms were used to map FACT-G data to the EQ-5D-3L (valued using the UK tariff).[79] Full methods and analysis results are described in a standalone report as Appendix M.

Tobit and ordinary least squares (OLS) methods were explored as alternative mapping approaches. The OLS mapping model provided a superior statistical fit of the two and a higher level of mapping precision (using size FACT-MM questions *versus* four in the tobit model) and was used as the primary set of estimates.

Predicted utility scores for the BCLPD-refractory patient population of STORM using the OLS model were 0.589 for pre-progression and 0.607 in post-progression (Table 30). The implied increase in utility score with disease progression, although not statistically significant, is likely an artifact of low numbers of observations in post-progression states (HRQoL was measured up to the end of treatment, and therefore seldom in progressed states) as potential imbalances due to patients with lower

baseline utility being more likely to discontinue treatment than those in better overall health.

Table 30 Health State Utility Values Across Optimal Models

Health State	OLS Mapping Method	Tobit Mapping Method
	STORM Part 2 BCLPD-refractory population	STORM Part 2 BCLPD-refractory population
Pre-Progression (SE)	0.5894 (0.0202)	0.5775 (0.0375)
Post-Progression (SE)	0.6067 (0.0208)	0.6105 (0.0365)

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; OLS, ordinary least squares; SE, standard error

B.3.4.3 Health-related quality-of-life studies

The economic SLR conducted in RRMM, described in Section B.3.1 (and Appendix G), did not identify HRQoL data or utility estimates reported specifically for penta-refractory MM. Two published records of the pivotal STORM trial were identified, reporting HRQoL data in the wider penta-exposed MM trial population rather than the BCLPD-refractory subgroup considered in the regression analysis described in section B.3.4.2. These records reported FACT-G/ MM/ MM-TOI baseline scores and change from baseline by cycle.

Due to the paucity of utility data in penta-refractory MM, HRQoL data from four studies in alternative patient populations reporting utility values have been considered potential proxy data. Across the four studies, utility values are reported for MM patients described as triple-class refractory (TCR; n=2), triple-class exposed (TCE; n=1), and a heavily pre-treated RRMM population with a median of 5 prior lines (n=1).[6,66,80,81] Utility estimates applied in additional NICE TAs across later lines of RRMM, relevant to the decision problem, have been examined as a further source of validation for the model base case utilities as well as sensitivity analysis in the economic model, due to the low number of utility studies identified. Utility values identified in the identified studies and NICE TAs in 4L RRMM are summarised in Table 31.

Table 31 Utility values identified relevant to the economic model

PF utility values	PD utility values	Source

5L+ TCR		
PF On-treatment range: 0.647 - 0.759 PF: 0.731 (95% CI: 0.693-0.770, SD = 0.020) PF Off-treatment range: 0.621 - 0.650	0.664 (95% CI: 0.613-0.716, SD = 0.026)	NICE GID-TA10568 (2023), Nikolaou *et al.* (2021)
5L+ TCE		
0.730	0.66	Yang *et al.* (2022)
Heavily pre-treated (3L+ with median 5 prior lines [6L])		
0.730 (95% CI: 0.700-0.760; SE: 0.017)	0.676 based on PD state decrement [-0.054 (95% CI: -0.084 - -0.025; SE: 0.015)]	Pelligra *et al.* (2017)
Additional NICE TA utility values – 4L		
PF range: 0.61 (CI: 0.59, 0.63) – 0.65 PF On-treatment range: 0.717 (95% CI: 0.677, 0.758) (SE: 0.021) - 0.731 (95% CI: 0.695, 0.768) (SE: 0.018) PF Off-treatment range: 0.473 (95% CI: 0.288, 0.658) (SE: 0.095) - 0.621 (95% CI: 0.527, 0.714) (SE: 0.048	PD: 0.57 (CI: 0.55, 0.59) PD On-treatment: 0.649 (95% CI: 0.591, 0.707) (SE: 0.030) PD Off-treatment: 0.553 (95% CI: 0.478, 0.629) (SE: 0.038))	NICE TA658 (2020), NICE TA783 (2022) [CDF review of TA510]
Abbreviations: CDF, Cancer Drugs Fund; CI, confidence interval; GID, guidance in development; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, progression-free; SD, standard deviation; SE, standard error; TA, technology appraisal; TCE, triple-class exposed; TCR, triple-class refractory; 3L, third-line; 5L, fifth-line; 6L, sixth-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 B.3.4.4 and the disutilities applied in the economic model reported in Section B.3.4.5.

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

The health state utility values applied in the base case and scenario analyses and the source data used for each are described in Table 32. In the base case, the mapped utility estimate of 0.589 for progression-free BCLPD-refractory patients in the STORM study is applied to progression-free patients in both model arms.

As data collection beyond treatment discontinuation in STORM was too limited for post-progression utilities to be estimated robustly, the base case draws on published evidence to estimate PD utility based on a relative decrement to the PFS value of 0.589. A decrement of 9.2% is assumed in the base case, corresponding to the proportional decrease observed on progression in DREAMM-2. Although the source of this estimate is not a penta-refractory population, its application as a relative decrement rather than an absolute utility value relaxes the need for equivalence, as the only generalisation made is in terms of the relationship between progression-free and progressed HRQoL. Scenarios considering both STORM, DREAMM-2 and TA658 estimates as absolute values are also explored; an additional scenario using the PFS utility value from STORM and the PD utility value as the PFS utility value minus a decrement derived from the utility values in TA658.

Table 32 Summary of health state utility approaches and sources explored for cost-effectiveness analysis

Health State	Utility value: mean (standard error)	Source	Approach
Base case			
Progression-free	0.589 (0.020)	STORM (BCLPD-refractory population)	PFS value applied as point estimate
Progressed	0.535 (0.107)	DREAMM-2	PD:PFS ratio from DREAMM-2 applied as relative decrement
Scenario: STORM			
Progression-free	0.589 (0.020)	STORM (BCLPD-refractory population)	PFS value applied as point estimate
Progressed	0.607 (0.021)	STORM (BCLPD-refractory population)	PD value applied as point estimate
Scenario: DREAMM-2			

Health State	Utility value: mean (standard error)	Source	Approach
Progression-free	0.731 (0.146)	DREAMM-2	PFS value applied as point estimate
Progressed	0.664 (0.133)	DREAMM-2	PD value applied as point estimate
Scenario: TA658			
Progression-free	0.718 (0.144)	TA658 (ICARIA-MM)	PFS value applied as point estimate
Progressed	0.611 (0.122)	TA658 (ICARIA-MM)	PD value applied as point estimate
Scenario: STORM + TA658 PD relative decrement			
Progression-free	0.589 (0.020)	STORM	PFS value applied as point estimate
Progressed	0.535 (0.100)	TA658 (ICARIA-MM)	PD:PFS ratio from TA658 applied as relative decrement

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; PD, progressed disease; PFS, progression-free survival

B.3.4.5 Adverse events

To capture the impact of adverse reactions associated with treatment, utility decrements were assumed to apply to Grade 3 or 4 adverse events. Estimates of the level and duration of disutilities for each event were sourced from published literature, precedents in previous HTA appraisals and NICE reports, or by assumption, as detailed in Table 33.

Table 33 Summary of adverse event utility decrements and mean duration

Adverse event	Utility decrement	Utility decrement source	AE duration (weeks)	Duration source
Anaemia	-0.310	NICE TA897 [previously TA573], NICE TA695[82,83]	1.53	NICE TA897 [previously TA573], NICE TA695[82,83]
Asthenia	-0.12	NICE TA658[73]	2.09	Assumed equal to fatigue
Back pain	-0.070	NICE TA873[74]	2.00	Assumed 2-week duration
Bone pain	-0.070	Assumed equivalent to back pain	2.00	Assumed 2-week duration
Decreased appetite	-0.034	Sullivan *et al*. (2011)[84]	2.00	Assumed 2-week duration
Dehydration	-0.103	Assumed equivalent to Diarrhoea	2.00	Assumed 2-week duration

Diarrhoea	-0.103	Jakubowiak *et al*. (2016), NICE TA783[74,85]	1.71	Jakubowiak *et al*. (2016)[85]
Dyspnoea	-0.12	NICE TA783[74]	1.57	Jakubowiak *et al*. (2016)[85]
Fatigue	-0.115	NICE TA897 [previously TA573], NICE TA695, Nikolaou *et al.* (2021)[66,82,83]	2.09	NICE TA897 [previously TA573], NICE TA695 Jakubowiak *et al*. (2016)[82,83,85]
Hyperglycaemia	-0.060	NICE TA695[82]	0.57	NICE TA695[82]
Hypokalaemia	-0.200	NICE TA695, NICE TA783[74,82]	0.003	NICE TA695, NICE TA783[74,82]
Hyponatraemia	-0.200	Assumed as hypokalaemia [NICE TA695, NICE TA783]	0.003	Assumed as hypokalaemia [NICE TA695, NICE TA783]
Infections and infestations	-0.140	Jakubowiak *et al*. (2016)[85]	1.71	Jakubowiak *et al*. (2016)[85]
Leukopenia	-0.070	NICE TA783, Nikolaou *et al.* (2021)[66,74]	2.21	Jakubowiak *et al*. (2016)[85]
Lymphopenia	-0.065	NICE TA695, NICE TA897 [previously TA573][82,83]	2.21	NICE TA695, NICE TA897 [previously TA573], Jakubowiak *et al*. (2016)[82,83]
Nausea	-0.103	Jakubowiak *et al*. (2016), TA658, NICE TA783[73,83,85]	3.47	Jakubowiak *et al*. (2016)[85]
Neutropenia	-0.145	NICE TA897 [previously TA573], Nikolaou *et al.* (2021)[66,83]	1.89	NICE TA897 [previously TA573][83]
Pneumonia	-0.190	NICE TA897 [previously TA573][83]	1.71	NICE TA897 [previously TA573][83]
Sepsis	-0.20	NICE TA658[73]	4	NICE TA783[74]
Thrombocytopenia	-0.310	NICE TA897 [previously TA573][83]	2.01	NICE TA897 [previously TA573][83]
Vision blurred	-0.004	Sullivan *et al*. (2011)[84]	2.00	Assumed 2-week duration
Abbreviations: AE, adverse event; NICE, National Institute for Health and Care Excellence; TA, technology appraisal				

Age-related utility decrements applied over and above those corresponding to health state and adverse events were applied using the approach identified by Ara and Brazier (2010),[86] and described in Table 34.

Table 34 Additional utility increments/ decrements applied in the model

Utility adjustment factor	Coefficient	Justification/ assumption
Baseline	0.9508566	

Utility adjustment factor	Coefficient	Justification/ assumption
Male	0.0212126	To capture declining utility with age, using the regression equation from Ara and Brazier (2010).[86]
Age	-0.0002587	
Age^2	-0.0000332	

B.3.5 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) and electronic Market Information Tool (eMIT) 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). Where resource and/ or cost estimates were identified from previous MM NICE appraisals (eg.TA783 and TA427,)[74,75] the cost codes reported for each estimate were used to match against updated reference costs.

Costs considered in the cost-effectiveness analysis include drug acquisition, drug administration, 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 have been inflated using PSSRU 2022 Hospital and Community Health Services (HCHS) pay and price indices.

As described in Section B.3.1, an economic SLR was conducted to identify publications reporting cost-effectiveness studies, cost and resource use and HRQoL/ utility data, in patients with RRMM.[87] Further detail relating to identifying cost and healthcare resource data from the SLR can be found in Appendix I.

Of the records identified reporting cost and/ or resource use, none reported evidence specifically in penta-refractory MM. Of the other studies and sources identified across various countries in populations with varying levels of exposure and refractoriness to MM treatments, the most appropriate inputs were sourced from those most relevant to this decision problem.[6,88-91] Details of the sources selected for each cost input are presented in Sections B.3.5.3-B.3.5.5.

B.3.5.1 Intervention and comparators' costs and resource use

Costs have been considered from a UK NHS perspective and include the following main categories:

- **Treatment costs** - including the acquisition and administration costs associated with intervention and comparator treatments;
- **Health state costs** – background disease costs including routine care and monitoring costs;
- **Adverse event costs –** costs associated with the treatment of AEs;
- **Miscellaneous costs** – including the costs of concomitant and subsequent treatments and terminal care.

B.3.5.2 Treatment costs

The dosing schedule for Part 2 of the STORM study, outlined in Table 35, was for twice-weekly receipt of oral selinexor 80mg (or 45mg/m^2) with low-dose dexamethasone until disease progression, unacceptable toxicity or death.

As outlined in Section B.2.10.1, a dose-modification protocol allowed for dose reductions to be applied to managing adverse events. More than half of the patients underwent a dose reduction during the study; the mean weekly dose within the BCLPD population is 114.4mg (range 22mg to 180mg per week). This mean dosage has been applied in the CEA to provide consistency with other key evidence from the STORM trial used to inform model estimates of treatment duration, clinical efficacy, and adverse event rates. As a conservative approach, the mean value has been rounded up to the nearest 20mg tablet (i.e., a weekly dose of 120mg is assumed across all patients).

Table 35 Drug scheduling and dosing assumptions for Sd

	STORM Part 2 study protocol			CEA dosing assumption	
	Dose per admin (mg)	Admins week (N)	Dose per week (mg)	Relative dose intensity	Mean weekly dose (mg)
Selinexor	80	2	160	71%	114.4
Dexamethasone	20	2	40	0%	40
Abbreviations: CEA, cost-effectiveness analysis; mg, milligram; N, number; Sd, Selinexor plus dexamethasone					

Table 36 Drug acquisition costs associated with Sd (list price)

Treatment	Strength per unit (mg)	Units per pack	Cost per pack	Cost source
Selinexor	20	20	£9,200	Menarini Stemline data on file[60]
Dexamethasone	2	50	£2.46	eMIT, 2022
Abbreviations: eMIT electronic Market Information Tool; mg, milligram; Sd, Selinexor plus dexamethasone				

No active treatment is assumed in the BSC arm. However, based on UK myeloma clinical expert input received in the January 2023 Advisory Board, 20% of penta-refractory patients are assumed to receive chemotherapy as a part of BSC. Costs have been approximated based on the dosing and unit costs of cyclophosphamide plus dexamethasone (Table 37 and Table 38).

Table 37 Drug scheduling and dosing assumptions for cyclophosphamide plus dexamethasone

Treatment	Dose per administration	Unit	Administrations per weekly cycle
Cyclophosphamide	200.00	mg	7.00
Dexamethasone	4.75	mg	7.00

Table 38 Drug acquisition costs associated with cyclophosphamide plus dexamethasone

Treatment	Unit size / strength per unit(mg)	Units per pack	Cost per pack (£)	Discount / PAS	Cost per mg (£)	Comments
Cyclophosphamide	50.00	100.00	52.46	0%	0.01	BNF costs, 2022
Dexamethasone	2.00	50.00	2.46	0%	0.02	BNF costs, 2022

B.3.5.3 Health-state unit costs and resource use

Estimates of resource use and costs associated with background disease, comprising haematological physician visits, blood count tests and biochemistry costs, are presented in Table 39.

Levels of resource use are expressed as weekly volumes (the mean number of times each resource is assumed to be used per patient per model cycle). Estimates were sourced from the NICE technology appraisal for daratumumab with bortezomib and dexamethasone for previously treated myeloma (NICE TA897, previously TA573)[83] and applied consistently to both model arms by progression status.

Table 39 Health state resource use and cost assumptions

		Progression-free		Progressed		
	Unit cost	Units per week	Cost per week	Units per week	Cost per week	Source
Physician visit	£232.78	0.23	£40.11	0.08	£13.94	NICE TA897 (Tables 51&52). Chemotherapy (Consultant led) Services Code 303: Clinical Haematology, NHS Reference cost 2022[83,92]
Complete blood count	£2.96	0.21	£0.56	0.39	£1.05	NICE TA897 (Tables 51&52). Chemotherapy (Consultant led) Services Code 303: Clinical Haematology. NHS Reference cost 2022[83,92]
Blood chemistry	£2.39	0.19	£0.24	0.33	£0.42	NICE TA897 (Tables 51&52). DAPS05 - Haematology. NHS Reference cost 2022[83,92]
Protein electrophoresis	£1.55	0.13	£0.16	0.18	£0.23	NICE TA897 (Tables 51&52). DAPS05 -

						Haematology. NHS Reference cost 2022[83,92]
Immunoglobin	£7.61	0.12	£0.15	0.19	£0.24	NICE TA897 (Tables 51&52). DAPS05 - Haematology. NHS Reference cost 2022[83,92]
Urinary light chain excretion	£8.53	0.05	£0.06	0.09	£0.11	NICE TA897 (Tables 51&52). DAPS05 - Haematology. NHS Reference cost 2022[83,92]
Total per week	-	-	**£56.19**	-	**£23.06**	-
Abbreviations: DAPS, directly accessed pathology services; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; TA, technology appraisal						

B.3.5.4 Adverse reaction unit costs and resource use

The costs associated with each Grade 3 or 4 adverse event included in the economic analysis (listed in Table 40) were sourced from the 2020/21 NHS Reference Costs database and inflated to 2022 prices using the HCHS pay and prices index published by PSSRU.[92] Adverse events costs were estimated in the CEA as one-off events and costed in the first model cycle. Based on the event rates reported in STORM, this equated to a total discounted AE cost estimate of £3,092 per patient in the Sd arm.

Table 40 Adverse event costs per event

Adverse event	Cost per Grade 3-4 event	NHS code	Description
Anaemia	£862.75	SA04G, SA04H, SA04J, SA04K, SA04L	*Iron Deficiency Anaemia, all scores*
Asthenia	£683.01	SA01G, SA01H, SA01J, SA01K	*Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC (all scores) [TAKEN FROM TA416 - SCLC]*
Back pain	£1,004.89	HC32H, HC32J, HC32K	*Low Back Pain without Interventions*
Bone pain	£1,279.38	WH08A, WH08B	*Unspecified pain with CC score 1+ and 0*
Decreased appetite	£1,522.19	FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10F, FD10G, FD10H, FD10J, FD10K, FD10L, FD10M	*Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions, with CC Score 8+, 5-7, 3-4, 0-2, 9+, 5-8, 3-4, 0-2, 11+, 6-10, 3-5, 0-2*
Dehydration	£1,399.85	KC05G, KC05H, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N	*Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+, 0-4, 10+, 7-9, 4-6, 2-3, 0-1*
Diarrhoea	£1,232.54	FD10J, FD10K, FD10L, FD10M	*Non-Malignant Gastrointestinal Tract Disorders with single intervention.*

Adverse event	Cost per Grade 3-4 event	NHS code	Description
Dyspnoea	£683.01	SA01G, SA01H, SA01J, SA01K	*Assume as asthenia: Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC (all scores) [TAKEN FROM TA416 - SCLC]*
Fatigue	£683.01	SA01G, SA01H, SA01J, SA01K	*Assume as asthenia: Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC (all scores) [TAKEN FROM TA416 - SCLC]*
Hyperglycaemia	£1,231.30	KB02G, KB02H, KB02J, KB02K	*Diabetes with Hyperglycaemic Disorders*
Hypokalaemia	£1,284.63	KC05J, KC05K, KC05L, KC05M, KC05N	*Fluid or Electrolyte Disorders, without Interventions*
Hyponatraemia	£1,284.63	KC05J, KC05K, KC05L, KC05M, KC05N	*Fluid or Electrolyte Disorders, without Interventions*
Infections and infestations	£3,683.61	WH07D	*Infections or Other Complications of Procedures, with Single Intervention, with CC*
Leukopenia	£1,139.64	SA08G, SA08H, SA08J	*Other Haematological or Splenic Disorders*
Lymphopenia	£1,139.64	SA08G, SA08H, SA08J	*Other Haematological or Splenic Disorders*
Nausea	£1,522.19	FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10F, FD10G, FD10H, FD10J, FD10K, FD10L, FD10M	*Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions, with CC Score 8+, 5-7, 3-4, 0-2, 9+, 5-8, 3-4, 0-2, 11+, 6-10, 3-5, 0-2*
Neutropenia	£1,139.64	SA08G, SA08H, SA08J	*Other Haematological or Splenic Disorders*
Pneumonia	£3,042.19	DZ11K-DZ11V	*Lobar, Atypical or Viral Pneumonia with single Interventions (all scores); Bronchopneumonia with single interventions (all scores)*
Sepsis	£3,683.61	WH07D	*Infections or Other Complications of Procedures, with Single Intervention, with CC*
Thrombocytopenia	£811.45	SA12G, SA12H, SA12J, SA12K	*Thrombocytopenia (all scores)*
Vision blurred	£1,036.80	EB08A, EB08B, EB08C, EB08D, EB08D, EB08E	*Syncope or collapse, with CC Score 13+, 10-12, 7-9, 4-6, 0-3*

Abbreviations: CC, complications, and comorbidities; NHS, National Health Service; SCLC, small-cell lung cancer; TA, technology appraisal

B.3.5.5 Miscellaneous unit costs and resource use

Administration costs

As Sd is an orally administered product, no administration costs were applied. No administration costs were applied to patients assumed to receive chemotherapy as a component of BSC or as a subsequent therapy to Sd, given an understanding that cyclophosphamide is most commonly used for MM in its oral form.[93]

One-off concomitant therapy costs

All patients receiving Sd require 5-hydroxytryptamine (5-HT3) antagonists (ondansetron 8mg or equivalent) prior to the first dose of Sd and then two to three times daily, as needed. This cost for ondansetron is considered in the model as part of the weekly cycle cost for Sd, with the cost of ondansetron sourced from BNF and assumed as being required 2.5 times per day while on selinexor treatment. This cost is presented in Table 41.

Table 41 Concomitant therapy costs

Intervention	Concomitant medication	Cost per mg (£)	Dose per administration mg)	Administrations per weekly cycle	Cost source
Selinexor	Ondansetron	0.02	8.00	17.50	BNF costs, 2022
Abbreviations: BNF, British National Formulary					

One-off disease progression costs

Transfusion-related resources required occasionally by MM patients are included in the model as one-off costs applied at the first model cycle. These costs were based on G-CSF, red blood cell (RBC) transfusions, and platelet transfusions, as displayed in the below table. Resource levels are based on the reported values in NICE TA783,[74] and were considered equal to all comparators except Pano + Bort +Dex (PanoVd), which required fewer administrations. These additional costs were considered in previous NICE submissions (e.g., NICE TA897 and TA427).[75,83] Costs were based on the BNF (2022) for G-CSF and NHSBT Pricing Proposals (2020) for RBC and platelet transfusions.

Table 42 Resource costs associated with disease progression

Resource	Cost per unit (£)	Units	Source
G-CSF	£56.68	0.43	*NICE TA510: Neupogen Singleject 30 million units/0.5mL solution for injection pre-filled syringes (Amgen Ltd), BNF 2022*[74]
RBC transfusion	£695.00	1.47	*NICE TA510, NHS Reference costs 2022*[74]
Platelet transfusion	£695.00	0.96	*NICE TA510, NHS Reference costs 2022*[74]
Abbreviations: BNF, British National Formulary; GCSF, Granulocyte colony stimulating factor (G-CSF); NICE, National Institute for Health and Care Excellence; RBC, red blood cell; NHSBT, NHS Blood and Transplant			

Subsequent therapy costs

Subsequent therapy costs are applied to 20% of Sd patients, reflecting an assumption that an equivalent proportion will receive chemotherapy as in the BSC arm. Only background care and terminal care costs are applied after progression in the BSC arm.

Terminal care costs

A one-off terminal care cost of £4,823.20 is applied at death, based on mean estimates from a multi-cancer study of end-of-life care reported in Round *et al.* (2015) and updated to 2022 prices.[92,94]

B.3.6 Severity

Absolute and relative QALY shortfalls were estimated by comparing the estimated quality-adjusted life expectancy (QALE) of patients receiving best supportive care (the sole comparator relevant to a penta-refractory population) against that expected in an age- and gender-matched general population (Table 43).

Table 43 summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Proportion male at baseline (%)	61.5%	Table 21
Starting age (years)	64.5	Table 21
Abbreviations: QALY, quality-adjusted life year		

QALE in the general population was estimated using the approach and sources recommended by Schneider *et al* (2021)[95]:

- Life tables: England, 2018-2020 (pooled)[96];
- Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study;[97]
- Health state profiles: EQ-5D-3L from the Health Survey for England (2014);[98]
- Model: ALDVMM by Hernandez Alava, *et al*. (2022).[99]

For a population aged 64.5 years and 61.5% male, as assumed in the base case, a general population quality-adjusted life expectancy (QALE) of 11.1 was estimated. The QALE in the BSC arm using base model settings was 0.4: a shortfall of 10.8 QALYs (96.6%) relative to QALE in the general population (Table 44).

Table 44 Summary of QALY shortfall analysis

Expected total QALE for the general population	Total QALE that people living with a condition would be expected to have with current treatment	QALY shortfall
11.1	0.4	10.8 (97%)
Abbreviations: QALY, quality-adjusted life year		

As the proportional shortfall estimate exceeds the upper threshold of 95%, a severity modifier of 1.7 has been applied when estimating incremental QALY, ICER and NHB results. For transparency, all results tables and figures that reflect modified QALY estimates have titles that identify them as such, and base deterministic results are reported both with and without the modifier applied. All QALY estimates reported by arm (rather than incrementally) are unmodified.

Comparison against previous evaluations

Severity modifiers were introduced by NICE in 2022 alongside the updated Methods Guide, with no precedents that have explored their applicability in later-line RRMM.[52] However, end-of-life criteria (applied to certain life-extending treatments for people with short life expectancies and a loose predecessor to the severity modifier) were considered applicable by the then-called evidence review groups (ERGs) assessing 4L appraisals for pomalidomide (TA427), daratumumab monotherapy (TA783) and isatuximab plus pomalidomide and dexamethasone (TA658).[73-75]

To frame results in the context of historical end-of-life criteria, Table 45 provides a breakdown of the BSC QALE estimate into the utility values applied to progression-free and progressed disease health states and the undiscounted life year expectancy in each state.

Table 45 Summary of health state utility values and BSC arm life expectancy for QALY shortfall analysis

State	Utility value: mean	Undiscounted life years
Progression-free	0.589	0.319
Progressed disease	0.535	0.369
Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year		

B.3.7 Uncertainty

Treatment options for patients with penta-refractory MM are currently very limited. In the absence of any active treatment as standard practice, care for many patients - particularly those for whom clinical trials or compassionate use programmes are not viable - is focused mainly on symptom management and palliative support.

Besides representing a high unmet need for patients, the lack of an active comparator also presents a challenge in demonstrating the relative cost-effectiveness of novel treatments. Whereas the characteristics and outcomes of patients in earlier lines of therapy can be sufficiently well-evidenced to support various methods of direct and indirect comparison, extracting relevant comparator evidence from trial or registry data at later lines, where numbers are small and pathways substantially more varied become increasingly complex.

In the absence of a current data source representative of BSC in the UK penta-refractory MM population, as a proxy the CEA compares Sd efficacy against that of a penta-refractory subgroup of the MAMMOTH study. The patients in the MAMMOTH study are substantially more heavily treated than the BSC, which creates uncertainty regarding estimating representative BSC outcomes. In the absence of any adjustment to counter this likely imbalance and potential over-estimation of the benefit of BSC in practice, the base analysis is therefore expected to reflect a conservative estimate of the cost-effectiveness of Sd *versus* BSC.

B.3.8 Managed access proposal

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

B.3.9 Summary of base-case analysis inputs and assumptions

Base case parameter values, distributions used for PSA, and confidence interval ranges for OWSA are provided in Table 46.

Table 46 Summary of variables applied in the economic model

Variable	Distributio	Value	Range
Model settings			
Time horizon	Fixed	30	-
Half-cycle correction	Fixed	Yes	-
Discount rate (costs)	Fixed	3.5%	-
Discount rate (outcomes)	Fixed	3.5%	-
Severity modifier	Fixed	1.7	-
AE approach	Fixed	One-off	-
Wastage applied	Fixed	Yes	-
Baseline characteristics			
Population	Fixed	Penta-refractory	-
Age (years)	Lognormal	64.5	39.2 - 89.8
Proportion male (%)	Beta	61.5%	52.8%-70.1%
Weight (kg)	Lognormal	78.4	47.7 - 109.1
BSA (m^2)	Lognormal	1.89	1.15 - 2.63
Sd outcomes			
OS source	Fixed	MAMMOTH	-
OS curve	Fixed	Lognormal	-
PFS source	Fixed	IRC assessed	-
PFS curve	Fixed	Lognormal	-
TTD source	Fixed	TTD	-
TTD curve	Fixed	Exponential	-
Comparator outcomes			
Source for OS HR: Sd *vs.* BSC	Fixed	STC	-
OS HR: Sd *vs*. BSC	Lognormal	0.59	0.56 - 0.95
Source for PFS HR: Sd *vs*. BSC	Fixed	Equivalence assumed	-
PFS HR: Sd *vs*. BSC	Lognormal	1	1.00 - 1.00
BSC AE source	Fixed	No AEs	BSC AE source
Cost inputs			
Sd acquisition cost per cycle (£)	Fixed	[redacted]	-
Sd admin cost per cycle (£)	Fixed	£0.00	-
Sd compliance	Beta	98.4%	96.2% - 100.0%
Sd adverse event total cost (£)	Gamma	£3,092.19	£1,880.05 – £4,304.33
Sd subsequent treatment cost (£)	Gamma	£58.09	£35.32 - £80.87
BSC chemotherapy use	Beta	20%	17%-23%

Variable	Distributio	Value	Range
BSC acquisition cost per active cycle (£)	Fixed	£15.51	-
BSC admin cost per active cycle (£)	Fixed	£0.00	-
BSC adverse event total cost (£)	Gamma	£0.00	£0.00 - £0.00
BSC subsequent treatment cost (£)	Gamma	£0.00	£0.00 - £0.00
PFS resource cost (£)	Gamma	£56.19	£34.16 - £78.21
PD resource cost (£)	Gamma	£23.06	£14.02 - £32.10
PFS one-off cost (£)	Gamma	£1,711.83	£1,040.79 - £2,382.87
Terminal care cost (£)	Gamma	£4,823.20	£2,932.51 - £6,713.90
Health-related quality of life			
PFS Utility approach	Fixed	STORM BCLPD mapped estimate	-
PD utility approach	Fixed	DREAMM-2 relative decrement	-
PFS utility value	Beta	0.59	0.55 - 0.63
PD utility value	Beta	0.54	0.33 - 0.75
Ara and Brazier utility adjustment	Fixed	Included	-
Sd adverse event total disutility	Beta	0.02	0.01 - 0.03
BSC adverse event total disutility	Beta	0.00	0.00 - 0.00

Abbreviations: AE, adverse event, BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; BSA, body surface area; BSC, best supportive care; HR, hazard ratio; IRC, independent review committee; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression free survival; PSM, partitioned survival model; QALY, quality-adjusted life year; QoL, quality of life; Sd, selinexor plus low-dose dexamethasone; TTD, time to discontinuation; UK, United Kingdom

B.3.9.1 Assumptions

An overview of key model assumptions is provided in Table 47.

Table 47 Model assumptions

Assumption	Justification
Model approach	
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 and directly uses OS and PFS endpoints of the STORM study. PSM is also less reliant on patient-level data than transition-based approaches, making it well-suited for indirect comparisons from single-arm data sources such as STORM.
A 30-year time horizon is sufficient proxy for a patient lifetime in fifth line setting.	Fewer than 1% of patients remain alive in either arm in base case estimates or key scenario analyses.
A one-week cycle length is appropriate for accurately reflecting the costs of treatment	A one-week cycle length is sufficiently short to allow for dosing schedules for Selinexor to be represented accurately and in keeping with previous MM CEAs.
Patient population	
The BCPLD-refractory population of STORM part 2 is representative of penta-refractory patients in the UK.	All patients in the BCPLD subgroup would be classed as penta-refractory in a UK clinical pathway. The dosing schedule and dosing modification practices in the

Assumption	Justification
	STORM study were consistent with expected practices in a UK real-world clinical setting.
Clinical effectiveness	
The OS benefit associated with Sd relative to BSC is equal to or greater than the HR suggested by ITC results *versus* MAMMOTH.	MAMMOTH[63] provides proxy comparator data in a relevant penta-refractory population but is likely to report superior results to an actual BSC comparator in clinical practice due to the inclusion of patients receiving active treatments.
Proportional hazards are appropriate to assume when estimating the overall survival benefit of Sd relative to BSC as proxied using MAMMOTH data.	Although visual analyses conducted as part of indirect treatment comparisons suggested some potential time variance in hazard rates, clinical expert opinion received in advisory boards suggested no clinical rationale and that proportional hazards were the most reasonable assumption.
PFS outcomes in patients receiving Sd are non-inferior to those receiving BSC.	Owing to the lack of PFS data available from the indirect comparison, PFS equivalence is assumed as a conservative base case approach. Published research suggests that the correlation between OS and PFS in MM is greater at later lines of therapy, where there is less potential for OS to be influenced by subsequent pathways.[100] The sensitivity of results using the OS HR as a proxy for the PFS HR is explored as a scenario.
Concomitant therapies have no impact on treatment efficacy for the intervention or comparators.	Concomitant therapies, such as ondansetron (used to manage symptoms of nausea), treat the symptoms of adverse events and have a negligible or no direct effect on progression or survival outcomes.
Cost and resource use	
Patients are not treated with Sd beyond disease progression	According to the STORM trial, Sd was administered until disease progression, death or discontinuation.
Drug costs for Selinexor reflect mean dosage observed during the STORM period rather than the planned starting dose.	Dose adjustment to find an optimal balance between efficacy and tolerability is expected to be commonplace in a real-world setting. Further, applying observed STORM dosages in the CEA ensures consistency with corresponding efficacy and adverse event rate estimates.
Doses are rounded up to the nearest tablet, with the remainder discarded as wastage. Unused tablets are assumed to roll over to the next treatment cycle.	Selinexor dosages vary in 20mg (single tablet) increments. Upwards adjustment of the mean dosage across the sample to the next full 20mg dose ensures that the model does not apply patient-level dosage that would not apply in a real-world setting and is expected to provide a slight overestimate of acquisition costs.
Subsequent therapies reflect the UK treatment pathway rather than STORM study data. In the BSC arm, 20% of which is assumed to chemotherapy, no further treatment is assumed. In the Sd arm, 20% are assumed to receive subsequent chemotherapy.	Costs of subsequent therapies, where available, are included based on the treatments contributing to BSC as estimated by clinical experts.
Health-related quality of life	

Assumption	Justification
In the absence of EQ-5D data collected in the STORM study, FACT-G scores collected from progression-free patients and mapped to the EQ-5D-3L are the most appropriate source of utility estimates for progression-free disease.	Mapped PFS utility estimates use HRQoL collected from STORM study data and published mapping algorithms and have face validity when compared to published estimates for earlier-line RRMM patients. Health state utilities from published literature / previous MM NICE submissions are included in scenario analyses.
Given the limited collection HRQoL from patients with progressed disease in the STORM study, the relative utility decrement associated with progression is derived from published evidence. It is the most appropriate method for estimating utility in progression-free disease.	The small number of observations and the potential bias associated with missing data present challenges as to the validity of utility estimates derived from STORM PD observations. Applying a progression decrement (relative to PFS) based on published studies as a proportional (rather than absolute) effect is a cautious approach to incorporating external evidence to address uncertainties around the STORM estimate.
Health state-specific utilities are equivalent across treatment arms	Differences in the HRQoL of patients due to utility decrements associated with adverse events are applied separately and should not be double counted.
No unpaid caregiver disutilities are included	There is a paucity of data on caregiver burden specifically related to MM, and unpaid carer disutilities have not been applied. However, it is reasonable to assume that informal provision of supportive care also negatively impacts the QoL of family and friends of patients, and so the ICER estimates are therefore likely to underestimate overall impact.

Abbreviations: AE, adverse event; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; BSC, best supportive care; CEA, cost-effectiveness analysis; CEM, cost-effectiveness model; EQ-5D, EuroQoL 5 dimension; FACT-G, functional assessment of cancer therapy – general; HR, hazard ratio; HRQoL, health related quality of life; ICER, incremental cost-effectiveness ratio; MM, multiple myeloma; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD, progressive disease; PFS, progression free survival; PSM, partitioned survival model; QALY, quality-adjusted life year; QoL, quality of life; Sd, selinexor plus low-dose dexamethasone; UK, United Kingdom

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

Base case cost-effectiveness results for Sd versus BSC are shown in Table 48 and Table 49. Results reflect a confidential PAS discount of [redacted] to the list price for selinexor. Unless otherwise stated, all cost, QALY and LY results are discounted at a rate of 3.5% per annum.

Base case results demonstrate a substantial positive impact on patient HRQoL outcomes, despite the likely influence of active treatments in the BSC proxy comparator arm and the absence of any claimed PFS benefit. Under this conservative base scenario, the incremental cost-effectiveness ratio with a 1.7 severity modifier is estimated to be £27,408 per QALY gained.

Table 48 Base-case ICER results (Sd PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
No severity modifier applied							
Sd	£26,295	1.429	0.771	-	-	-	-
BSC	£7,859	0.672	0.376	£18,435	0.757	0.396	£46,593
Severity modifier (1.7) applied							
Sd	£26,295	1.429	1.311	-	-	-	-
BSC	£7,859	0.672	0.639	£18,435	0.757	0.673	£27,408
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; Sd, selinexor plus low-dose dexamethasone							

Table 49 Base case net health benefit results (Sd PAS price)

Technologies compared	NHB at WTP threshold of £20,000/ QALY (no modifier) (QALYs)	NHB at WTP threshold of £30,000/ QALY (no modifier) (QALYs)
No severity modifier applied		
Sd *vs.* BSC	-0.526	-0.219
Severity modifier (1.7) applied		
Sd *vs.* BSC	-0.249	0.058
Abbreviations: BSC, best supportive care; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years; Sd, selinexor plus low-dose dexamethasone; WTP, willingness-to-pay		

For reference, base case cost-effectiveness results at the list price for selinexor (no PAS discount applied) are reported in Table 50 and Table 51.

Table 50 Base-case ICER results (Sd list price)

Technologies	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/ QALY)
No severity modifier applied							
Sd	[redacted]	1.429	0.771	-	-	-	-
BSC	£7,859	0.672	0.376	[redacted]	0.757	0.396	[redacted]
Severity modifier (1.7) applied							

Technologies	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/ QALY)
Sd	[redacted]	1.429	1.311	-	-	-	-
BSC	£7,948	0.672	0.639	[redacted]	0.757	0.673	[redacted]
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; Sd, selinexor plus low-dose dexamethasone							

Table 51 Net health benefit (discounted; list prices)

Technologies compared	NHB at WTP threshold of £20,000/ QALY (no modifier) (QALYs)	NHB at WTP threshold of £30,000/ QALY (no modifier) (QALYs)
No severity modifier applied		
Sd *vs*. BSC	[redacted]	[redacted]
Severity modifier (1.7) applied		
Sd *vs*. BSC	[redacted]	[redacted]
Abbreviations: BSC, best supportive care; NHB, net health benefit; QALYs, quality-adjusted life years; Sd, selinexor plus low-dose dexamethasone; WTP, willingness-to-pay		

B.3.11 Exploring uncertainty

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

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic analysis was conducted 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.* (2006).[101]

Where available, standard errors (SEs) were taken from source data or calculated from published standard deviations (SD) and sample sizes or 95% confidence intervals (CIs). When none were reported, the SE was 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. Probabilistic

results were highly consistent with those derived from the deterministic base analysis, with an estimated ICER (based on a 1.7 severity modifier) of £28,227 compared to £27,408 as the deterministic result).

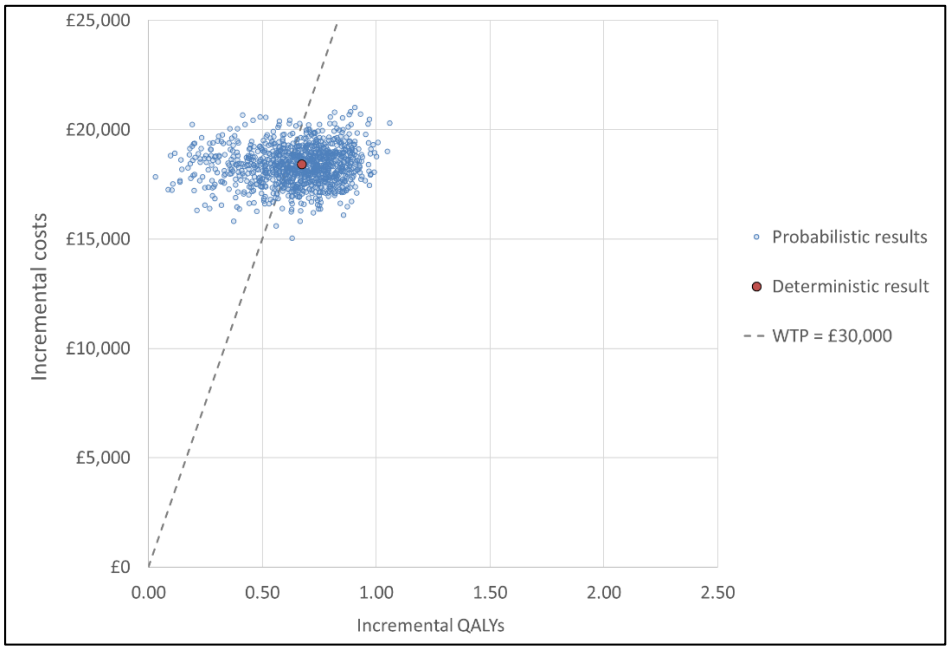
Table 52 Base-case probabilistic ICER results (Sd PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/ QALY)
No severity modifier applied							
Sd	£26,250	1.417	0.772	-	-	-	-
BSC	£7,896	0.695	0.389	£18,354	0.722	0.382	£47,986
Severity modifier (1.7) applied							
Sd	£26,250	1.417	1.312	-	-	-	-
BSC	£7,896	0.695	0.662	£18,354	0.722	0.650	£28,227

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; Sd, selinexor plus low-dose dexamethasone

A scatterplot of PSA iterations on a cost-effectiveness plane, with the deterministic estimate overlaid, is shown in Figure 15. All points resided in the North-East quadrant of the cost-effectiveness plane (denoting positive incremental costs and positive incremental QALYs relative to BSC).

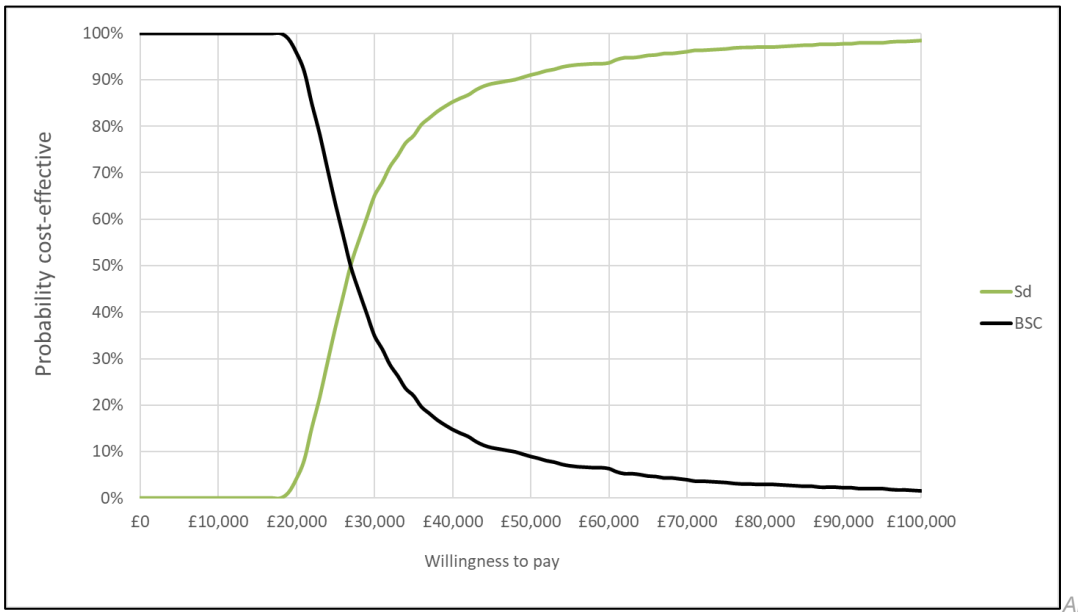
Figure 15 Cost-effectiveness plane showing probabilistic and deterministic cost-effectiveness results in relation to a £30,000 per QALY ICER threshold (1.7 severity modifier applied to incremental QALY values)



Abbreviations: ICER: Incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 16 presents a cost-effectiveness acceptability (CEAC) curve based on the PSA, illustrating the probability of each treatment option (Sd or BSC) being the most cost-effective resource use at a given level of willingness-to-pay per QALY gained. CEACs for the two arms cross at 50% (denoting the point of indifference, at which either is considered equally effective) at a similar point to the base ICER estimate, further illustrating the accordance between the results.

Figure 16 Cost-effectiveness acceptability curve (PAS price, 1.7 severity modifier applied)



Abbreviations: BSC, best supportive care; Sd, selinexor plus dexamethasone

B.3.11.2 **Deterministic sensitivity analysis**

A one-way deterministic sensitivity analysis (DSA) was performed to identify key model drivers. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available or standard errors estimated based on ±20% variation around the mean where measures of variance around the base case values were unavailable.

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.

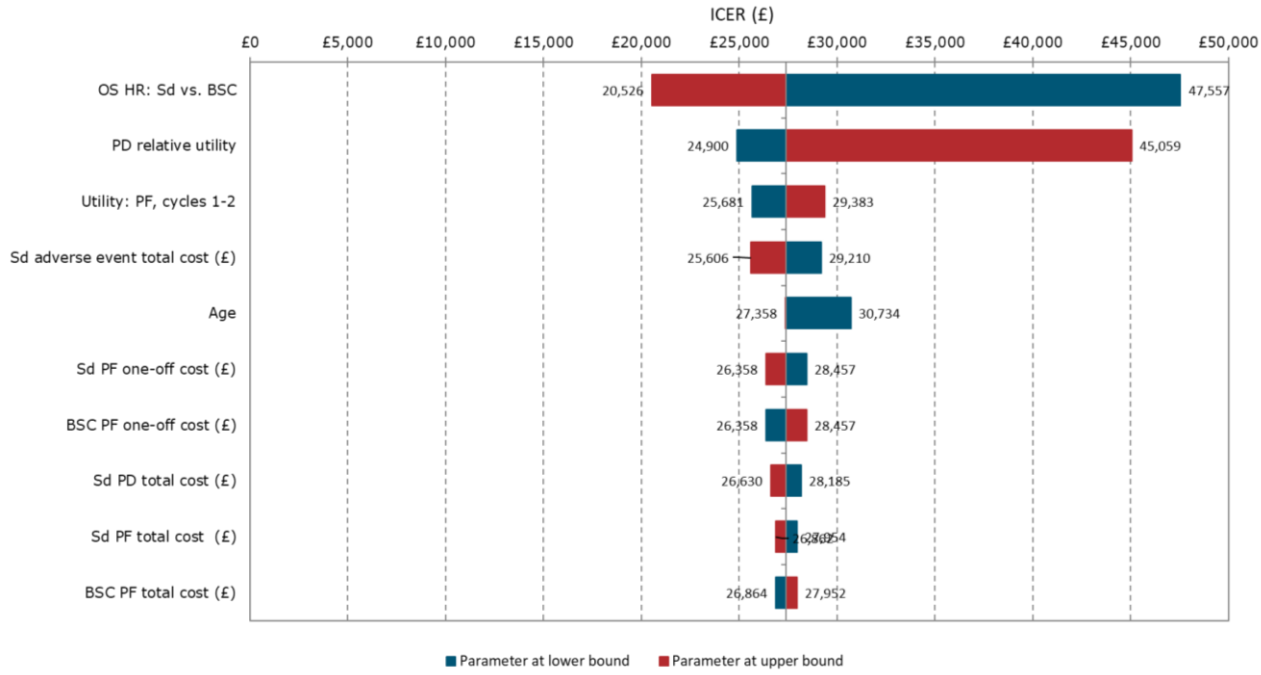
The top 10 most influential parameters on the ICER from the OWSA are presented in Table 53. ICER estimates for all OWSA were below £50,000, and in all but two analyses (varying the OS HR applied and the utility score assumed for patients with progressed disease), the ICER was below £30,000. Importantly, while the distributional assumptions applied to parameters in the economic model prevent impossible values from being generated (e.g., by bounding probabilities between values of zero and one), the analyses do not otherwise impose any assumptions around the relative plausibility of uncertainty in either direction.

Table 53 Deterministic one-way sensitivity analysis results (Sd PAS price)

Parameter	ICER (£)		ICER Difference (£)
	Lower parameter estimate	Upper parameter estimate	
OS HR: Sd vs. BSC	£47,556.95	£20,526.43	£27,030.53
PD relative utility	£24,899.68	£45,059.23	£20,159.55
Utility: PF, cycles 1-2	£25,681.09	£29,383.31	£3,702.23
Sd adverse event total cost (£)	£29,209.82	£25,605.67	£3,604.15
Age	£30,733.74	£27,358.39	£3,375.36
Sd PF one-off cost (£)	£28,457.07	£26,358.42	£2,098.65
BSC PF one-off cost (£)	£26,358.42	£28,457.07	£2,098.65
Sd PD total cost (£)	£28,185.40	£26,630.08	£1,555.32
Sd PF total cost (£)	£27,953.77	£26,861.72	£1,092.05
BSC PF total cost (£)	£26,863.52	£27,951.96	£1,088.44

Abbreviations: BSC, best supportive care; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; OS, overall survival; PD, progressed disease; PF, progression-free; QALYs, quality-adjusted life years; Sd, selinexor plus low-dose dexamethasone; WTP, willingness-to-pay

Figure 17 Tornado diagram (discounted results; Sd PAS price)



Abbreviations: BSC, best supportive care; HR, hazard ratio; PAS, patient access scheme; OS, overall survival; PD, progressed disease; PF, progression-free; Sd, selinexor plus low-dose dexamethasone

B.3.11.3 Scenario analysis

A series of scenario analyses were explored to assess the sensitivity of results to key areas of uncertainty outlined throughout the submission. Scenario results, described in Table 54 and discussed below, show ICER results to be robust to several key areas of uncertainty. Of the key uncertainties explored, assumptions around OS extrapolation and comparative efficacy had the largest effect on ICER estimates; across all scenarios, ICER estimates scenarios were contained within a range of £15,225 to £47,449.

PFS reported in the STORM study was mature and approximated closely by each of the standard parametric curves explored, meaning that choice of curve of the several explored has little impact on total cost and QALY estimates. A more key PFS-related uncertainty is the relative estimate applicable to BSC: a limitation of reporting in the MAMMOTH study is that a PFS hazard ratio specific to the penta-refractory population could not be derived. The base case handles this uncertainty conservatively, modelling clinical superiority in terms of OS but no difference in PFS. A scenario assuming instead that the HR for PFS is equal to that estimated for OS (i.e., 0.585, favouring Sd over BSC) has only a marginal impact on the ICER result (£27,302 compared to the base case ICER of £27,408). This relatively small impact highlights the importance of OS as a main driver of QALY gains, due to the size of decrement associated with progression (whether from literature or trial sources), as well as the opposing influence of reduced resource costs when off treatment. The use of MAIC OS estimates derived from the ITC increased ICER estimates to £34,100 and £43,296 (using ‘full’ and ‘must-have’ covariates); this demonstrates the importance of OS HR as a key driver, although due to extreme sample size constraints (discussed in Section B.3.3.2) MAIC results are unlikely to be a reliable source of estimates.

Scenarios exploring adverse events also had a small impact on overall cost-effectiveness, with ICERs ranging from £26,549 to £29,713 according to assumptions around AE rates in the BSC arm and the approach to distributing AEs over the course of treatment (Table 54). Due to the limited number of treatments expected at or beyond the penta-refractory setting, the impact of assumptions around costs (for subsequent therapies, routine monitoring, etc.) were small.

When using a single data source to estimate both progression-free and progressed utility scores (either STORM, DREAMM-2 or ICARIA-MM (TA658))[6,73], the ICER for Sd versus BSC improved compared to the base case analysis. This result is consistent with *a priori* expectations, given that clinical benefit in the Sd arm is driven by OS rather than PFS, and will therefore achieve a higher incremental QALY difference when a higher overall utility is assumed.

Key scenarios in which ICER was seen to increase relative to base estimates were when estimating treatment duration from the PFS curve (imposing an assumption that patients were treated until progression, with no early discontinuation) (£39,487) and when assuming a weekly dosage of 160mg selinexor when estimating drug costs for Selinexor (£34,602) (Table 54). As outlined in Section B.2.12.3, Sd dosing in a real-world setting is highly patient-centred to achieve an optimal balance in minimising side effects associated with treatment (thus also minimising treatment discontinuation) while maintaining clinical effectiveness. Given the likely correlation between drug dosage, time on treatment and adverse event rates, results when varying each of these parameters in isolation should be interpreted with caution.

Table 54 Scenario analysis cost-effectiveness results (discounted; Sd PAS price)

Scenario dimension	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
BASE CASE	**Not applicable**	**£18,435**	**0.67**	**£27,408**
Time horizon	10 years	£18,292	0.61	£29,989
PFS source	Investigator assessment	£18,439	0.67	£27,405
PFS hazard ratio	Same as OS	£18,638	0.68	£27,302
PFS extrapolation	Parametric: Weibull	£18,366	0.67	£27,308
	Parametric: Exponential	£18,427	0.67	£27,400
	Parametric: Gen. Gamma	£18,435	0.67	£27,407
	Parametric: Log Logistic	£18,436	0.67	£27,409
	Parametric: Gompertz	£18,380	0.67	£27,330
	Parametric: Gamma	£18,412	0.67	£27,375
OS hazard ratio source	MAMMOTH MAIC (full)	£18,272	0.54	£34,100
	MAMMOTH MAIC (must have)	£18,132	0.42	£43,296
OS extrapolation	Parametric: Weibull	£18,146	0.40	£45,253

Scenario dimension	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
	Parametric: Exponential	£18,121	0.38	£47,201
	Parametric: Gen. Gamma	£18,840	1.02	£18,560
	Parametric: Log Logistic	£18,555	0.76	£24,427
	Parametric: Gompertz	£19,185	1.26	£15,225
	Parametric: Gamma	£18,118	0.38	£47,449
ToT assumption for comparators	Treated to progression (PFS)	£26,561	0.67	£39,487
ToT extrapolation	Parametric: Weibull	£18,421	0.67	£27,386
	Parametric: Gen. Gamma	£18,402	0.67	£27,358
	Parametric: Log Normal	£20,118	0.67	£29,910
	Parametric: Log Logistic	£20,722	0.67	£30,807
	Parametric: Gompertz	£18,421	0.67	£27,387
	Parametric: Gamma	£18,407	0.67	£27,365
Comparator AE source	Auner *et al.* (2022)	£18,237	0.67	£27,111
	MAMMOTH	£17,860	0.67	£26,549
Adverse event application	Per cycle	£19,974	0.67	£29,713
Discounting	No benefit discounting	£18,435	0.77	£23,919
	No cost discounting	£18,691	0.67	£27,788
	No discounting (cost or benefit)	£18,691	0.77	£24,252
	6% discounting	£18,297	0.62	£29,476
Selinexor weekly dosage	Full (160mg)	£23,275	0.67	£34,602
Chemotherapy use as part of BSC	100%	£18,400	0.67	£27,355
Health state utilities	PFS: STORM absolute value PD: TA658 relative decrement	£18,435	0.63	£29,254
	PFS: STORM absolute value PD: STORM absolute value	£18,435	0.74	£24,897
	PFS: DREAMM2 absolute value PD: DREAMM2 absolute value	£18,435	0.83	£22,095
	PFS: TA658 absolute value PD: TA658 absolute value	£18,435	0.77	£24,010

Abbreviations: AE, adverse event; BSC, best supportive care; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; mg, milligrams; OS, overall survival; PAS, patient access

Scenario dimension	Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
scheme; PFS, progression-free survival; QALY, quality-adjusted life year; Sd, selinexor plus dexamethasone; TA, technology appraisal; ToT, time on treatment				

B.3.12 Subgroup analysis

No subgroups within the penta-refractory population were considered in the analysis.

B.3.13 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 Sd, especially given the advanced age and level of comorbidity common in patients with penta-refractory MM, 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 estimates but is likely to be substantial given the high frailty and physical dependency common in patients at later lines of treatment for RRMM. Carer quality of life is not understood to have been incorporated into ICER estimates for previous MM NICE appraisals but has been accepted as a component of total QALY estimates in other disease areas.

Incorporating quantitative estimates of the impact on informal carers of patients with MM could be expected to increase the estimated level of cost-effectiveness considerably.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The company engaged with key stakeholders including clinical 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.[32,33] 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 technical QC of the cost-effectiveness model has been performed. It was carried out using internally developed checklists 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 supportive or validating evidence. At the time of submission, communications with NHS Digital are ongoing: it appears the SACT registry could be a potential source of OS data for current standard of care (as a proxy for BSC), with the caveat that data limitations may make it difficult to single out patient groups by the line of treatment, refractoriness to prior therapies and use of steroids (i.e. it is likely it will not be possible to derive data for patients receiving Sd specifically from other selinexor-based combinations).

B.3.15 Interpretation and conclusions of economic evidence

The potential for Sd as a life-extending treatment using a novel MoA at a stage of disease where multi-drug resistance has exhausted traditional options has a clear and direct impact on addressing current unmet needs in the management of later line RRMM. For MM patients, the opportunity to extend the pathway of viable treatment

options delivers benefits not only through the LY and QALY gains considered directly in the CEA but also through the hope it provides both at the point of delivery and in earlier stages of treatment.

The analysis shows that Sd is likely to produce meaningful life year and QALY gains (controlling for the adverse events associated with continued treatment) in a population that does not have active treatment options. Estimating incremental cost-effectiveness in MM, especially at later lines of treatment, is complicated by several factors: in particular, the lack of head-to-head data from the single-arm STORM study as the primary evidence source for Sd, and the limited proxy evidence available for BSC in a UK penta-refractory setting. Where uncertainties exist, the analysis adopts a conservative set of base case assumptions and show Sd to be highly cost-effective against BSC with an ICER of £27,408 per QALY gained.

The MM treatment landscape is complex and is impacted by the influence of patients' prior exposure or refractoriness to drug classes, general health and tolerance of adverse events on treatment options. It is also dynamic, meaning that successive patient cohorts with similar characteristics may present at later lines with substantially different treatment histories and, therefore, eligibility for ongoing treatments. Consequently, the number of lines after which penta-refractory status is reached can vary substantially between patients. Treatment options for patients with penta-refractory MM in the current treatment pathway are extremely limited. In the absence of any recommended active therapies, care options are limited largely to chemotherapy, supportive/ palliative care or (where available and eligible) clinical trials or compassionate use programmes. For this reason, BSC has been selected as the comparator to Sd in the economic analysis performed for the later line penta-refractory patient population being considered in the economic analysis.

An area of uncertainty is the lack of direct data to estimate BSC outcomes in a UK treatment setting. The variety of treatments used within and outside the pathway of NICE-recommended therapies presents challenges in defining 'best supportive care' as received by a real-world penta-refractory MM population and identifying robust evidence of the clinical and economic outcomes associated with such a group. UK registry data (including SACT) will likely include patients relevant to the decision

problem. However, exploratory discussions with data holders and clinical experts have suggested that the limited data collected around treatment history will likely present a substantial challenge in positively identifying comparator patients. Furthermore, the limited range of endpoint data beyond OS collected is likely to leave uncertainties around progression rates and resource use unaddressed.

Hence, the base case results in the economic analysis for the BSC comparator are based on data from the MAMMOTH study, which has limitations to its proxy BSC estimates for OS, and could not be used to estimate PFS outcomes. The MAMMOTH study is a retrospective, observational review of RRMM patients at 14 academic institutions in the US, and presents aggregate results for patients overall and within a subgroup of 70 patients with penta-refractory MM. Within this cohort, 63/70 patients received active therapies, many of which would not be routinely available in the UK to patients with similar treatment histories, making that cohort more heavily treated than would be the case in a current UK penta-refractory BSC patient cohort. Although this presents a probable source of bias in the analysis, an important consideration is that the direction (if not the magnitude) of that bias is expected to be in favour of the BSC comparator. The potential cost-effectiveness of Sd in clinical practice, therefore, may be substantially higher than shown suggested by comparisons against MAMMOTH.

A severity modifier of 1.7 has been identified as applicable to the penta-refractory population, highting the extent of QALY losses in the patient population. With this taken into account and assuming a PAS discount of [redacted] on the list price for selinexor, base case ICER results of £27,408 and comprehensive scenario analyses demonstrate that Sd provides a clinically effective and cost-effective treatment option for penta-refractory MM patients with high current unmet needs.

B.4 References

1. Peterson TJ, Orozco J, Buege M. Selinexor: A First-in-Class Nuclear Export Inhibitor for Management of Multiply Relapsed Multiple Myeloma. *The Annals of pharmacotherapy*. Jun 2020;54(6):577-582. doi:10.1177/1060028019892643
2. Medicines and Healthcare products Regulatory Agency (MHRA). *Public Assessment Report: Nexpovio 20mg*. 2021. 26 May 2021. https://mhraproducts4853.blob.core.windows.net/docs/ed27f53b3b5404611d1940fb4bc2a7a649b1237d
3. Medicines and Healthcare products Regulatory Agency (MHRA). *Summary of Product Characteristics: Nexpovio*. 2023. 2 February 2023.
4. Grosicki S, Simonova M, Spicka I, et al. 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*. 2020;396(10262):1563-1573. doi:10.1016/s0140-6736(20)32292-3
5. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma. *New England Journal of Medicine*. 2019;381(8):727-738.
6. National Institute for Health and Care Excellence (NICE). *GID-TA10568: Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies*. 2023.
7. Gandhi UH, Senapedis W, Baloglu E, et al. Clinical Implications of Targeting XPO1-mediated Nuclear Export in Multiple Myeloma. *Clin Lymphoma Myeloma Leuk*. May 2018;18(5):335-345. doi:10.1016/j.clml.2018.03.003
8. Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood*. Mar 26 2015;125(13):2068-74. doi:10.1182/blood-2014-12-615187
9. Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. *Mayo Clinic proceedings*. Jan 2016;91(1):101-19. doi:10.1016/j.mayocp.2015.11.007
10. Sive J, Cuthill K, Hunter H, et al. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. *Br J Haematol*. Apr 2021;193(2):245-268. doi:10.1111/bjh.17410
11. Ocio EM, Montes-Gaisán C, Bustamante G, et al. Clinical and Sociodemographic Characteristics of Patients With Relapsed and/or Refractory Multiple Myeloma and Their influence on Treatment in the Real-World Setting in Spain: The CharisMMa Study. *Clin Lymphoma Myeloma Leuk*. Apr 2022;22(4):e241-e249. doi:10.1016/j.clml.2021.10.001
12. Ramsenthaler C, Kane P, Gao W, et al. Prevalence of symptoms in patients with multiple myeloma: a systematic review and meta-analysis. *Eur J Haematol*. Nov 2016;97(5):416-429. doi:10.1111/ejh.12790
13. Seesaghur A, Petruski-Ivleva N, Banks VL, et al. Clinical features and diagnosis of multiple myeloma: a population-based cohort study in primary care. *BMJ Open*. 2021;11(10):e052759. doi:10.1136/bmjopen-2021-052759
14. Sverrisdóttir IS, Rögnvaldsson S, Thorsteinsdottir S, et al. Comorbidities in multiple myeloma and implications on survival: A population-based study. *Eur J Haematol*. Jun 2021;106(6):774-782. doi:10.1111/ejh.13597

15. Benkova K, Mihalyova J, Hajek R, Jelinek T. Selinexor, selective inhibitor of nuclear export: Unselective bullet for blood cancers. *Blood Reviews*. 2021/03/01/ 2021;46:100758.
16. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. *Leukemia*. 2012/01/01 2012;26(1):149-157. doi:10.1038/leu.2011.196
17. International Myeloma Foundation (Durie B, . *Concise Review of the Disease and Treatment Options: Multiple Myeloma*. 2018.
18. Hari P, Romanus D, Luptakova K, et al. The impact of age and comorbidities on practice patterns and outcomes in patients with relapsed/refractory multiple myeloma in the era of novel therapies. *J Geriatr Oncol*. Mar 2018;9(2):138-144. doi:10.1016/j.jgo.2017.09.007
19. Toppila I, Miettinen T, Lassenius MI, Lievonen J, Bauer M, Anttila P. Characteristics and survival trends in Finnish multiple myeloma patients—a nationwide real-world evidence study. *Annals of Hematology*. 2021/07/01 2021;100(7):1779-1787. doi:10.1007/s00277-021-04481-4
20. Yang WC, Lin SF. Mechanisms of Drug Resistance in Relapse and Refractory Multiple Myeloma. *Biomed Res Int*. 2015;2015:341430. doi:10.1155/2015/341430
21. IARC. GLOBOCAN 2020: Estimated cancer incidence, mortality and prevalence worldwide in 2020. Accessed May 13, 2022. https://gco.iarc.fr/
22. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. Aug 2016;17(8):e328-e346. doi:10.1016/s1470-2045(16)30206-6
23. IARC. GLOBOCAN 2020: Multiple Myeloma Fact Sheet. Accessed 13 June 2022, https://gco.iarc.fr/today/data/factsheets/cancers/35-Multiple-myeloma-fact-sheet.pdf
24. Hulin C, Hansen T, Heron L, et al. Living with the burden of relapse in multiple myeloma from the patient and physician perspective. *Leuk Res*. Aug 2017;59:75-84. doi:10.1016/j.leukres.2017.05.019
25. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. Mar 17 2011;364(11):1046-60. doi:10.1056/NEJMra1011442
26. Verelst S, Blommestein H, De Groot S, et al. Long-term Outcomes in Patients With Multiple Myeloma: A Retrospective Analysis of the Dutch Population-based HAematological Registry for Observational Studies (PHAROS). *Hemasphere*. Aug 2018;2(4):e45. doi:10.1097/hs9.0000000000000045
27. Myeloma UK (MUK). *Myeloma bone disease: Symptoms and Compications Infoguide*. 2021.
28. 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
29. Cook G, Zweegman S, Mateos MV, Suzan F, Moreau P. A question of Class: Treatment Options for Patients With Relapsed and/or Refractory Multiple Myeloma. *Crit Rev Oncol Hematol*. 2018;121:74-89. doi:10.1016/j.critrevonc.2017.11.016 Accessed Jan. https://www.sciencedirect.com/science/article/pii/S1040842817302214?via%3Dihub

30. Jeryczynski G, Bolomsky A, Agis H, Krauth MT. Stratification for RRMM and Risk-Adapted Therapy: Sequencing of Therapies in RRMM. *Cancers (Basel)*. 2021;13(23). doi:10.3390/cancers13235886 PMC8657274, Accessed Nov 23.
31. National Institute for Health and Care Excellence (NICE). *Myeloma: diagnosis and management (NG35)*. 2018.
32. Tolley Health Economics. Selinexor HE Advisory Board Report. 2023.
33. Menarini-Stemline. Selinexor Market Access Advisory Board Report. 2023.
34. Cornell R, Hari P, Tang S, et al. Overall survival of patients with triple-class refractory multiple myeloma treated with selinexor plus dexamethasone vs standard of care in MAMMOTH. *Am J Hematol*. Jan 2021;96(1):E5-e8. doi:10.1002/ajh.26010
35. Mateos M, Weisel K, De Stefano V, et al. LocoMMotion: A Prospective, Non-Interventional, Multinational Study of Real-Life Current Standards of Care in Patients with Relapsed and/or Refractory Multiple Myeloma. *Leukemia*. 2022;36(5):1371-1376. doi:10.1038/s41375-022-01531-2 Accessed May.
36. Pozzi S, Bari A, Pecherstorfer M, Vallet S. Management of Adverse Events and Supportive Therapy in Relapsed/Refractory Multiple Myeloma. *Cancers (Basel)*. 2021;13(19). doi:10.3390/cancers13194978 PMC8508369, Accessed Oct 4. https://www.mdpi.com/2072-6694/13/19/4978
37. Robak P, Drozdz I, Szemraj J, Robak T. Drug resistance in multiple myeloma. *Cancer Treatment Reviews*. 2018/11/01/ 2018;70:199-208. doi:https://doi.org/10.1016/j.ctrv.2018.09.001
38. Pick M, Vainstein V, Goldschmidt N, et al. Daratumumab resistance is frequent in advanced-stage multiple myeloma patients irrespective of CD38 expression and is related to dismal prognosis. *Eur J Haematol*. May 2018;100(5):494-501. doi:10.1111/ejh.13046
39. Talati C, Sweet K. Nuclear transport inhibition in acute myeloid leukemia: recent advances and future perspectives. *International Journal of Hematologic Oncology*. 2018;7(3):IJH04.
40. Mo CC, Jagannath S, Chari A, et al. Selinexor for the treatment of patients with previously treated multiple myeloma. *Expert review of hematology*. Aug 2021;14(8):697-706. doi:10.1080/17474086.2021.1923473
41. Richard S, Jagannath S. Targeting Nuclear Export Proteins in Multiple Myeloma Therapy. *BioDrugs*. Jan 2022;36(1):13-25. doi:10.1007/s40259-021-00514-6
42. Callander NS, Baljevic M, Adekola K, et al. NCCN Guidelines Insights: Multiple Myeloma, Version 3. *J Natl Compr Canc Netw*. Jan 2022;20(1):8-19. doi:10.6004/jnccn.2022.0002
43. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(†). *Ann Oncol*. Mar 2021;32(3):309-322. doi:10.1016/j.annonc.2020.11.014
44. Despiégel N, Touboul C, Flinois A, et al. Health-Related Quality of Life of Patients With Multiple Myeloma Treated in Routine Clinical Practice in France. *Clin Lymphoma Myeloma Leuk*. Jan 2019;19(1):e13-e28. doi:10.1016/j.clml.2018.08.019
45. Kamal M, Wang XS, Shi Q, et al. Symptom burden and its functional impact in patients with "symptomatic" relapsed or refractory multiple myeloma. *Support Care Cancer*. Jan 2021;29(1):467-475. doi:10.1007/s00520-020-05493-y
46. Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma:

a UK cross-sectional survey. *Support Care Cancer*. Feb 2013;21(2):599-607. doi:10.1007/s00520-012-1548-y
47. Ramsenthaler C, Osborne TR, Gao W, et al. 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*. Jul 7 2016;16:427. doi:10.1186/s12885-016-2410-2
48. Lassalle A, Thomaré P, Fronteau C, et al. Home administration of bortezomib in multiple myeloma is cost-effective and is preferred by patients compared with hospital administration: results of a prospective single-center study. *Ann Oncol*. Feb 2016;27(2):314-8. doi:10.1093/annonc/mdv563
49. Nathwani N, Bell J, Cherepanov D, et al. Patient perspectives on symptoms, health-related quality of life, and treatment experience associated with relapsed/refractory multiple myeloma. *Support Care Cancer*. Jul 2022;30(7):5859-5869. doi:10.1007/s00520-022-06979-7
50. Tolley Health Economics Ltd. *Selinexor versus comparators for the treatment of RRMM: a clinical systematic review*. 2023.
51. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions (version 6.0)*. Updated July 2019. www.training.cochrane.org/handbook
52. National Institute for Health and Care Excellence (NICE). *PMG36: NICE health technology evaluations: the manual*. 2022. 31 January. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation
53. Qiu L, Xia Z, Fu C, et al. Selinexor plus low-dose dexamethasone in Chinese patients with relapsed/refractory multiple myeloma previously treated with an immunomodulatory agent and a proteasome inhibitor (MARCH): a phase II, single-arm study. *BMC Med*. Apr 5 2022;20(1):108. doi:10.1186/s12916-022-02305-4
54. Karyopharm Therapeutics Inc. *Clinical Study Report (KCP-330-012; Data cut-off 24 April 2018)*. 2018.
55. Karyopharm Therapeutics Inc. *Clinical Study Report (KCP-330-012; Data cut-off 7 September 2019)*. 2019.
56. Karyopharm Therapeutics Inc. *Clinical Study Protocol (KCP-330-012) Version 6.0*. 2017.
57. Karyopharm Therapeutics Inc. *Statistical Analysis Plan (KCP-330-012) Version 2.0*. 2018.
58. Critical Appraisal Skills Programme. CASP Cohort Study Checklist. Critical Appraisal Skills Programme. 2022, https://casp-uk.net/casp-tools-checklists/
59. National Institute for Health and Care Excellence (NICE). *Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template (Instructions for companies)*. 2022. 10 February 2022.
60. Menarini Stemline. *Data on file*. 2023.
61. Cytel. *Indirect treatment comparison of selinexor for the treatment of triple-class refractory multiple myeloma: feasibility analysis & ITC Report*. 2023.
62. Kim C, Braunlin M, Mehta B, Payne R. Outcomes of Triple-Class (proteasome inhibitor, immunomodulator, CD38 monoclonal antibody) Exposed Relapsed or Refractory Multiple Myeloma (RRMM) in United States (US) Real-World Practice. *Blood*. 2021;138(Supplement 1):3042-3042. doi:10.1182/blood-2021-145588

63. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;33(9):2266-2275.
64. Terebelo H, Srinivasan S, Narang M, et al. Recognition of early mortality in multiple myeloma by a prediction matrix. *Am J Hematol*. Sep 2017;92(9):915-923. doi:10.1002/ajh.24796
65. Centre for Reviews and Dissemination (CRD). *Systematic reviews: CRD's guidance for undertaking reviews in health care.* 2009. http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf
66. Nikolaou A, Ambavane A, Shah A, et al. Belantamab mafodotin for the treatment of relapsed/refractory multiple myeloma in heavily pretreated patients: a US cost-effectiveness analysis. *Expert review of hematology*. 2021;14(12):1137-1145.
67. Speranza G, Diliberto MJ, Fattore C, et al. POSB74 Belantamab Mafodotin as the First-in-Class Anti-BCMA Treatment for Relapsed/Refractory Multiple Myeloma: A Budget Impact and Cost-Effectiveness Analysis. *Value in Health*. 2022;25(1 Supplement):S74-S75.
68. Speranza G., Diliberto MJ., Fattore C., et al. Belantamab Mafodotin as the First-in-Class Anti-BCMA Treatment for Relapsed/Refractory Multiple Myeloma: A Budget Impact and Cost-Effectiveness Analysis. *Value in Health, Volume 24, Issue 12, S2 December 2021*.
69. Latimer N. *NICE DSU TSD 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data*. June 2011 (Updated March 2013):52. http://nicedsuNa.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf
70. Davis S, Stevenson M, Tappenden P, Wailoo A. NICE DSU TSD 15: Cost-effectiveness modelling using patient-level simulation. TSD 15. National Institute for Health and Care Excellence; April 2014:62. April 2014. http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD15_Patient-level_simulation.pdf
71. Latimer N, Abrams K. NICE DSU TSD 16: Adjusting survival time estimates in the presence of treatment switching. TSD 16. National Institute for Health and Care Excellence; July 2014:57. July 2014. http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD16_Treatment_Switching.pdf
72. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU TSD 19: Partitioned Survival Analysis as a decision modelling tool. National Insitute for Health and Care Excellence; 2017:72. 2nd June 2017. http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf
73. National Institute for Health and Care Excellence (NICE). TA658: Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma. https://www.nice.org.uk/guidance/ta658/history
74. National Institute for Health and Care Excellence (NICE). TA783: Daratumumab monotherapy for treating relapsed and refractory multiple myeloma.
75. National Institute for Health and Care Excellence (NICE). TA427: Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib. https://www.nice.org.uk/guidance/ta427/history

76. National Institute for Health and Care Excellence (NICE). TA870: Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. https://www.nice.org.uk/guidance/ta870
77. National Institute for Health and Care Excellence (NICE). TA380: Panobinostat for treating multiple myeloma after at least 2 previous treatments. https://www.nice.org.uk/guidance/ta380/history
78. Auner HW, Brown SR, Walker K, et al. Ixazomib with cyclophosphamide and dexamethasone in relapsed or refractory myeloma: MUKeight phase II randomised controlled trial results. *Blood Cancer Journal*. 2022/04/01 2022;12(4):52. doi:10.1038/s41408-022-00626-4
79. Young TA, Mukuria C, Rowen D, Brazier JE, Longworth L. Mapping Functions in Health-Related Quality of Life: Mapping from Two Cancer-Specific Health-Related Quality-of-Life Instruments to EQ-5D-3L. *Medical decision making : an international journal of the Society for Medical Decision Making*. 2015;35(7):912-926.
80. Yang J BD. Cost-Effectiveness of Belantamab Mafodotin (BELAMAF) VS. Melphalan Flufenamide in Combination with Dexamethasone (MEL+DEX) in Heavily PRE-Treated Relapsed/Refractory Multiple Myeloma Patients: A U.S. Payer Perspective. *Value in Health, Volume 25, Issue 6, S1 (June 2022)*.
81. Pelligra CG, Parikh K, Guo S, et al. Cost-effectiveness of Pomalidomide, Carfilzomib, and Daratumumab for the Treatment of Patients with Heavily Pretreated Relapsed-refractory Multiple Myeloma in the United States. *Clinical Therapeutics*. 2017;39(10):1986-2005.e5.
82. National Institute for Health and Care Excellence (NICE). TA695: Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma.
83. National Institute for Health and Care Excellence (NICE). TA897: Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma. https://www.nice.org.uk/guidance/ta897
84. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. Nov-Dec 2011;31(6):800-4. doi:10.1177/0272989x11401031
85. Jakubowiak AJ, Campioni M, Benedict A, et al. Cost-effectiveness of adding carfilzomib to lenalidomide and dexamethasone in relapsed multiple myeloma from a US perspective. *J Med Econ*. Nov 2016;19(11):1061-1074. doi:10.1080/13696998.2016.1194278
86. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2010;13(5):509-18. doi:10.1111/j.1524-4733.2010.00700.x
87. Tolley Health Economics . *Selinexor versus comparators for the treatment of RRMM: an economic systematic review*. 2023.
88. Decaux O, Frenzel L, Royer B, et al. Therapeutic Management of Multiple Myeloma and Healthcare Resource Assessment By Matching the Emmy Cohort to the Data of the National Health Data System (SNDS) in France. *Value in Health*. 2022;25(1 Supplement):S259-S260.
89. Decaux O, Frenzel L, Royer B, Belhadj K, Perrot A, Caillot D. Therapeutic Management of Multiple Myeloma and Healthcare Resource Assessment By Matching the Emmy Cohort to the Data of the National Health Data System (SNDS) in France. 2021;

90. Dhanasiri S, Hollier-Hann G, Stothard C, Dhanda DS, Davies FE, Rodriguez-Otero P. Treatment Patterns and Outcomes in Triple-Class Exposed Patients with Relapsed and Refractory Multiple Myeloma: Findings From the Multinational ITEMISE Study. *Clin Ther*. 2021;43(11):1983-1996.e3. doi:10.1016/j.clinthera.2021.09.013 Accessed Nov. https://www.clinicaltherapeutics.com/article/S0149-2918(21)00386-6/pdf
91. Rodriguez Otero P, Dhanasiri S, Hollier-Hann G, Stothard C, Davies F, Dhanda D. Healthcare Resource Utilization Burden in the Management of Triple-Class Exposed Patients With Relapsed/Refractory Multiple Myeloma: Results From the ITEMISE Study. 2021;
92. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care Manual 2022. https://www.pssru.ac.uk/unitcostsreport/
93. Myeloma UK (MUK) . *Cyclophosphamide: treatment guide*. 2022.
94. Round J, Jones, L. and Morris, S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. *Palliative Medicine*. 2015;29(10):899-907.
95. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. 2021;doi:10.1101/2021.12.13.21267671
96. Office for National Statistics (ONS). National Life Tables, United Kingdom, period expectation of life, based on data for the years 2018-2020. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables
97. MVH Group Centre for Health Economics (University of York). *Final Report on the Modelling of Valuation Tariffs*. 1995.
98. NatCen Social Research UCL, Department of Epidemiology and Public Health., . *Health Survey for England, 2014. [data collection]*. 2014.
99. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *PharmacoEconomics*. 2022/11/30 2022;doi:10.1007/s40273-022-01218-7
100. Etekal T, Koehn K, Sborov DW, et al. Time-to-event surrogate end-points in multiple myeloma randomised trials from 2005 to 2019: A surrogacy analysis. *Br J Haematol*. Mar 2023;200(5):587-594. doi:10.1111/bjh.18568
101. Briggs A CK, Sculpher M. Decision Modelling for Health Economic Evaluation; Chapter 4: Making decision models probabilistic (Section 4.3). In: Oxford University Press., ed. 2008.

B.5 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 - NA

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: STORM utility analysis report

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:

Selinexor (Nexpovio®) in combination with dexamethasone (Sd) is being appraised by NICE 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. To understand and explain what this means in clinical practice, the following definitions included in the submission document may be helpful. Additionally, the treatment pathway included in section 2c may be helpful in showing the proposed position of Sd in the treatment pathway.

Term	Description
Penta-refractory	Refractory to two proteasome inhibitors, two immunomodulatory drugs, and an anti-CD38 monoclonal antibody. One example of this would be “BCLPD-refractory.”
BCLPD-refractory	Refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, one example of penta-refractory
Penta-exposed	Has been exposed to two proteasome inhibitors, two immunomodulatory drugs, and an anti-CD38 monoclonal antibody
Triple-class refractory	Refractory to one proteasome inhibitor, one immunomodulatory drug, and an anti-CD38 monoclonal antibody
Refractory	Usually interpreted as ≤25% response to therapy or progression during or within 60 days after completion of treatment.
Proteosome inhibitors	For example, bortezomib, carfilzomib and ixazomib
Immunomodulatory drugs	For example, lenalidomide, pomalidomide and thalidomide
Anti-CD38 monoclonal antibodies	For example, daratumumab and isatuximab

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 multiple 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 dexamethasone.

The marketing authorisation wording of this combination is as follows:

Selinexor in combination with dexamethasone 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, and who have demonstrated disease progression on the last therapy.[1]

Selinexor received MHRA marketing authorisation on 26th May 2021 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 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.[8,9]

Despite advances in treatment, myeloma remains incurable with a significant physical and emotional burden, fear of recurrence and overall impact on quality of life.[10,11]

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 compared to diagnosing all cancer patients, 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 diagnosis of myeloma is confirmed if at least 10 per cent of the cells in a bone marrow biopsy are abnormal plasma cells (abnormal plasma cells are myeloma cells) plus evidence of organ damage such as bone damage or kidney failure, and evidence of abnormal protein in the blood.[12]

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:

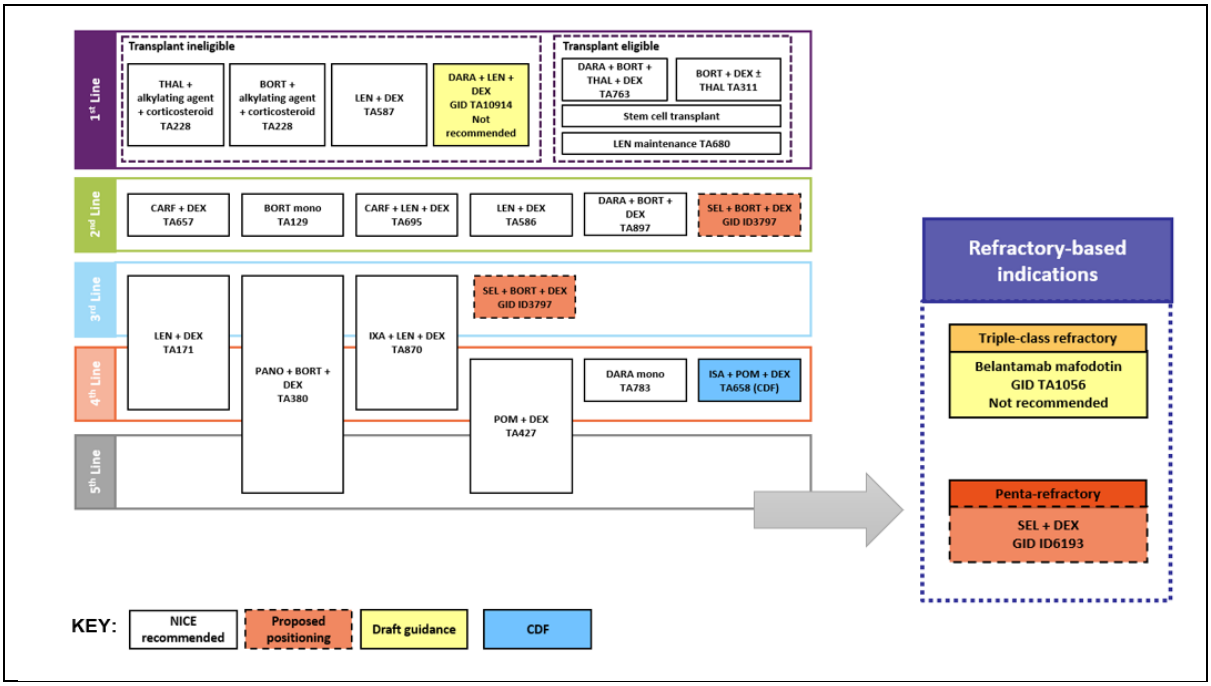
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

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

Advice the company received from myeloma clinicians, pharmacists, nurses, and patient representatives indicated that the optimum positioning of the selinexor + dexamethasone combination is for penta-refractory myeloma beyond the 5th line setting where there are currently no approved treatments. However, myeloma clinical experts confirmed that several chemotherapy-based options, corticosteroids including cyclophosphamide, melphalan, dexamethasone, and/or supportive care options, are used.

Patients may access treatment via a clinical trial and/or compassionate use scheme if no alternative options are suitable in this setting. Compassionate use is a treatment option that allows unlicensed treatment, under strict conditions, treatments in development can be made available to groups of patients with a disease with no satisfactory approved treatments and who cannot enter clinical trials. Additionally, chemotherapy-based palliation and other supportive care options may be considered.

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 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.[10, 11]

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, financial difficulties, severely decreased role functioning and severe financial difficulties.[13]

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.[14, 15] The humanistic burden is further exacerbated by treatment-related side effects, and caregiver stress and absenteeism can be significant.[16]

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,[16] 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.

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.[16] 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.

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.

Further information can be found in the links below.

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.

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

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 is relatively cheap and used in the treatment of multiple conditions. Please see section 3g for a description of the possible side effects associated with 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?

Selinexor is given as a 28-day cycle of 80mg orally on Day 1 and 3 of each week, plus dexamethasone 20mg orally twice weekly on Day 1 and Day 3. Treatment should be continued until disease progression or unacceptable treatment-related toxicity.

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, 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 treatment-related side effects be made as follows when in combination with dexamethasone:

- First reduction of 100mg once weekly
- Second reduction of 80mg once weekly
- Third reduction of 60mg once weekly

If symptoms do not resolve, treatment should be discontinued.

Many myeloma treatments involve in-patient visits to community or hospital clinics for infusions. In comparison, selinexor with dexamethasone is an all-oral treatment combination providing a convenient treatment for most patients.

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.

The pivotal phase 2b, single-arm, two-part STORM trial, represents the most robust source of clinical effectiveness and safety data for selinexor combined with dexamethasone. It was a non-comparative trial, meaning selinexor was not compared to any other treatment in the trial.

Part two of the STORM trial included n=123 patients with both:

1. triple-class-refractory myeloma, defined as patients whose disease is refractory to prior treatment with at least one IMiD, at least one PI, and the anti-CD38 mAb, daratumumab (and glucocorticoids)

2. penta-exposed myeloma, defined as myeloma patients previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (and an alkylating agent), glucocorticoids).

Of the n=123 participants in STORM Part 2, n=83 were penta-refractory, that is, refractory to previous treatment with bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab (sometimes referred to as BCLPD-refractory, denoting which five drugs they were refractory too). This Penta-refractory patient group is reflected in the MA wording (see section one), forming the submission's basis.

The primary outcome measure of part two of the STORM trial was the percentage of participants with an Overall Response Rate (ORR) per the International Myeloma Working Group (IMWG) definition and assessed by an Independent Review Committee (IRC). Secondary endpoints included overall survival (OS), progression-free survival (PFS) and duration of response (DOR).

All trials have eligibility criteria, which are the conditions patients need to meet to participate safely in a trial. The STORM trial included the following criteria.

- Previously received ≥3 anti-myeloma treatment combinations, including an alkylator (cyclophosphamide or melphalan), lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid (dexamethasone).
- Refractory to previous treatments: glucocorticoids, proteasome inhibitor (i.e., bortezomib and/or carfilzomib), immunomodulatory drug (i.e., lenalidomide and/ or pomalidomide), and daratumumab
- Refractory to the most recent anti-myeloma treatment
- Measurable disease based on International Myeloma Working Group (IMWG) guidelines
- Eastern Oncology Cooperative Group (ECOG)PS ≤2
- Adequate kidney function
- Adequate renal function
- Adequate bone marrow function
- Haemoglobin ≥8.5g/dL.

Patients were recruited into the trial from the USA, Austria, Belgium, France, Germany, and Greece from 60 hospitals. No hospitals in the UK participated.

A dose-modification protocol was used for the management of adverse events.[18,19]

Treatment was continued until disease progression, death, or unacceptable toxicity. The first patient enrolled on 26 May 2015, and the last patient visit in the trial was on 26 July 2019.

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.

For n=83 patients treated with Selinexor plus dexamethasone in part two of the STORM trial and whose disease was BCLPD-refractory (penta-refractory), headline efficacy data included an ORR of 25.3%, with a median DOR of 3.8 months, median PFS of 2.8 months, and median OS of 8.4 months. The 21 responders had a median time to respond of 4 weeks, with disease control being achieved as early as two weeks. A rapid response is key in patients with very rapid disease progression. Clinical interpretation of data from STORM focuses on gains for patients in the population with rapidly progressing disease, limited OS expectations, and limited or no available treatment options.

The extent to which patients place importance on various treatment outcomes will depend on several individual and disease-related factors. However, generally, patients want to live for as long as possible, with the best quality of life with the minimum level of treatment and side effects. All these efficacy outcomes are important to patients, especially in the relapsing refractory myeloma setting.

Further information on efficacy can be found in section B.2.6 of the submission.

Limitations to the data were the single-arm trial design and the limited sample size. No patients were recruited from the UK.[20]

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.

In the STORM trial, health-related quality of life HRQoL and potential for improvement over the course of the trial were assessed using the Functional Assessment of Cancer Therapy–Multiple Myeloma (FACT-MM), a patient-reported outcome (PRO) measure that comprised the 27-item FACT-G (a four-domain HRQoL measure developed for cancers) and a 14-item MM-specific subscale.[18]

From these assessments, most patients maintained their HRQoL at the same level since the start of the trial. When patients are considered penta-refractory, treatment options become severely limited, and re-treatment with drug classes are inappropriate, making the quality of life a high priority for these patients and their families.

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.

Almost all myeloma treatments have treatment-related side effects. Most are mild and short-lasting, although some can be serious and have a long-lasting or permanent impact on patients. Consequently, preventing and managing treatment-related side effects is an important component of the care patients (and their families) receive.

The safety and tolerability of any myeloma treatment in penta-refractory myeloma is affected or compromised by:

- the patient's advanced age
- multiple other diseases (comorbidities)
- highly advanced stage of disease
- many previous combinations of treatments
- side effects of the medicines used to treat these other comorbidities

Hence, it is important to note that penta-refractory patients are already highly susceptible to adverse events and treatment-related side effects even before receiving selinexor in combination with dexamethasone.

The most common side effects that may occur with Selinexor treatment are:[21]

Thrombocytopenia - can be managed with dose interruptions, modifications, platelet transfusions, and/or other treatments as clinically indicated.

Anaemia - can be managed with dose modifications (see section 4.2), blood transfusions, and/or erythropoietin administration.

Neutropenia - can be managed with dose interruptions, modifications, and colony-stimulating factors as per medical guidelines.

Digestive effects - prophylactic concomitant treatment with a 5-HT3 antagonist and/or other anti-nausea treatments should be provided prior to and during treatment with selinexor

The main potential side effects of dexamethasone treatment are [22, 23]:

- Stomach pain and indigestion
- Increased appetite and weight gain
- Insomnia
- Mood changes
- Swelling of face, hands, and feet
- Increased risk of infection

Further information can be found in the links below.

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)

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 dexamethasone include:

- As newer treatments are introduced earlier in the treatment pathway, an increasing number of myeloma patients are reaching a penta-refractory status. Very few treatment options are available for patients with penta-refractory myeloma beyond 5th line in the treatment pathway. It is crucial for these patients and their families to have access to a new treatment with a different approach. Selinexor, when combined with dexamethasone, offers such a treatment option.
- Selinexor is associated with a new mechanism of action, an important feature of any new treatments in the relapsed refractory setting where resistance to previous treatments is common.
- The treatment has manageable side effects that are mostly reversible.
- Selinexor, in combination with dexamethasone, is the first EMA and MHRA-licensed treatment specifically for penta-refractory myeloma.
- The STORM trial data reveals meaningful response rates and extended survival benefits to patients and their families. This is a valuable benefit for these individuals, as their only remaining options are clinical trials, compassionate care programs, and other less-than-ideal treatments before turning to palliative care.
- Selinexor and dexamethasone are taken orally (by mouth), which for many patients, is more convenient, less invasive and easier for the patient and their caregiver to administer.

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 the treatment aims to improve quality of life and survival, it is not curative and does not work in all patients. Although manageable and reversible, the treatment can cause some serious side effects. This is true of all myeloma treatments.

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.

Selinexor represents a potential step-change in treatment for myeloma patients with penta-refractory myeloma beyond the 5th line treatment setting, where there is currently a lack of approved treatments.

Whilst associated with uncertainty, the relative efficacy of selinexor and dexamethasone compared to currently available treatments suggests that the combination has the potential to improve patient outcomes.

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 medicine. It is a first-in-class drug, the first in a new family of drugs known as Selective Inhibitor of Nuclear Export (SINE) compounds.

The potential for selinexor in combination with dexamethasone as a life-extending treatment using a novel mode of action at a stage of the disease where multi-drug resistance has exhausted traditional options has a clear and direct impact on addressing current unmet needs in the management of later-line relapsing and refractory myeloma.

A particular added value of selinexor in combination with dexamethasone, especially given the advanced age and level of comorbidity common in patients with penta-refractory myeloma, is its oral route of administration, providing a means to continued treatment that is both convenient and minimally invasive.

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 patients at later lines of treatment.

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 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.

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

(PDF) Quality of life analyses in patients with multiple myeloma: results from the Selinexor (KPT-330) Treatment of Refractory Myeloma (STORM) phase 2b study (researchgate.net)

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

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:

1. Nexpovio, INN-selinexor (europa.eu)
2. Microsoft Word - 4620829376420294057_spc-doc.doc (windows.net)
3. Myeloma incidence statistics | Cancer Research UK
4. 826-united-kingdom-fact-sheets.pdf (iarc.fr)
5. Cancer Statistics Review, 1975-2016 - SEER Statistics
6. Myeloma statistics | Cancer Research UK
7. Myeloma statistics | Cancer Research UK
8. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. *Leukemia*. 2012/01/01 2012;26(1):149-157. doi:10.1038/leu.2011.196
9. Quality of life in multiple myeloma: considerations and recommendations - PubMed (nih.gov)
10. Myeloma symptoms | Cancer Research UK
11. Myeloma UK nurse learning programme
12. Hulin C, Hansen T, Heron L, et al. Living with the burden of relapse in multiple myeloma from the patient and physician perspective. *Leuk Res*. Aug 2017;59:75-84. doi:10.1016/j.leukres.2017.05.019
13. Despiégel N, Touboul C, Flinois A, et al. Health-Related Quality of Life of Patients With Multiple Myeloma Treated in Routine Clinical Practice in France. *Clin Lymphoma Myeloma Leuk*. Jan 2019;19(1):e13-e28. doi:10.1016/j.clml.2018.08.019
14. Ramsenthaler C, Osborne TR, Gao W, et al. 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*. Jul 7 2016;16:427. doi:10.1186/s12885-016-2410-2
15. Lassalle A, Thomaré P, Fronteau C, et al. Home administration of bortezomib in multiple myeloma is cost-effective and is preferred by patients compared with hospital administration: results of a prospective single-center study. *Ann Oncol*. Feb 2016;27(2):314-8. doi:10.1093/annonc/mdv563
16. Nathwani N, Bell J, Cherepanov D, et al. Patient perspectives on symptoms, health-related quality of life, and treatment experience associated with relapsed/refractory multiple myeloma. *Support Care Cancer*. Jul 2022;30(7):5859-5869. doi:10.1007/s00520-022-06979-7
17. Despiégel N, Touboul C, Flinois A, et al. Health-Related Quality of Life of Patients With Multiple Myeloma Treated in Routine Clinical Practice in France. *Clin Lymphoma Myeloma Leuk*. Jan 2019;19(1):e13-e28. doi:10.1016/j.clml.2018.08.019
18. Selinexor (Nexpovio®) Horizons Infosheet (myeloma.org.uk)
19. Myeloma UK Treatment Guide
20. (PDF) Quality of life analyses in patients with multiple myeloma: results from the Selinexor (KPT-330) Treatment of Refractory Myeloma (STORM) phase 2b study (researchgate.net)
21. Medicines and Healthcare Products Agency (MHRA). Summary of Product Characteristics: Nexpovio. 2023. 2 February 2023
22. Chari et al, N Engl J Med 2019; 381:727-738, Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma, Oral

Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma | NEJM
23. Dexamethasone | Drugs | BNF | NICE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after four or more treatments [ID6193]

Clarification questions company response

[September 2023]

File name	Version	Contains confidential information	Date
[ID6193] Sel+Dex rrMM EAG clarification questions company response	**1**	**Yes**	**15/09/2023**

The company wishes to thank the EAG for their comments and questions.

In running the additional analyses to respond to the clarification questions on the ITC (A17-A21), a number of corrections were made to the original analyses versus MAMMOTH, with updated results presented as a response to clarification question A17. These supersede the respective STC results presented in the Section B2.9 of the company submission, as well as the results presented for the comparison with MAMMOTH included in the ITC report. These are fully detailed in the company response to A17.

The company base case has been updated to reflect the result of the updated ITC as well as a number of changes suggested by the EAG, described in Section B. For transparency, the impact on ICER results of amendments or scenarios suggested by the EAG in Section B are all stated as one-way analyses relative to the original company base case, and with the modifier corresponding to each scenario applied. A table is provided at the top of section B detailing the impact of each scenario on the ICER and highlighting the changes that have been incorporated into the revised company base case.

In addition to this document, the company also provide the following:
- Example R code ("R code for CQ A17")
- 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.

Section A: Clarification on effectiveness data

Prior therapies

A1. Priority question. The EAG notes that the MHRA marketing authorisation for Selinexor in combination with dexamethasone (Sd) requires patients to be refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody ('penta-refractory'). Please clarify:

a. **the definition of 'penta-refractory' in the marketing authorisation;**
b. **the definition of 'penta-refractory' used in STORM Part 2 BCLPD subgroup including the criteria used to define 'refractory' for each of the five treatments; and**
c. **how the definition 'penta-refractory' used in the STORM Part 2 BCLPD subgroup compares with the definition of 'penta-refractory' expected to be used in clinical practice in England.**

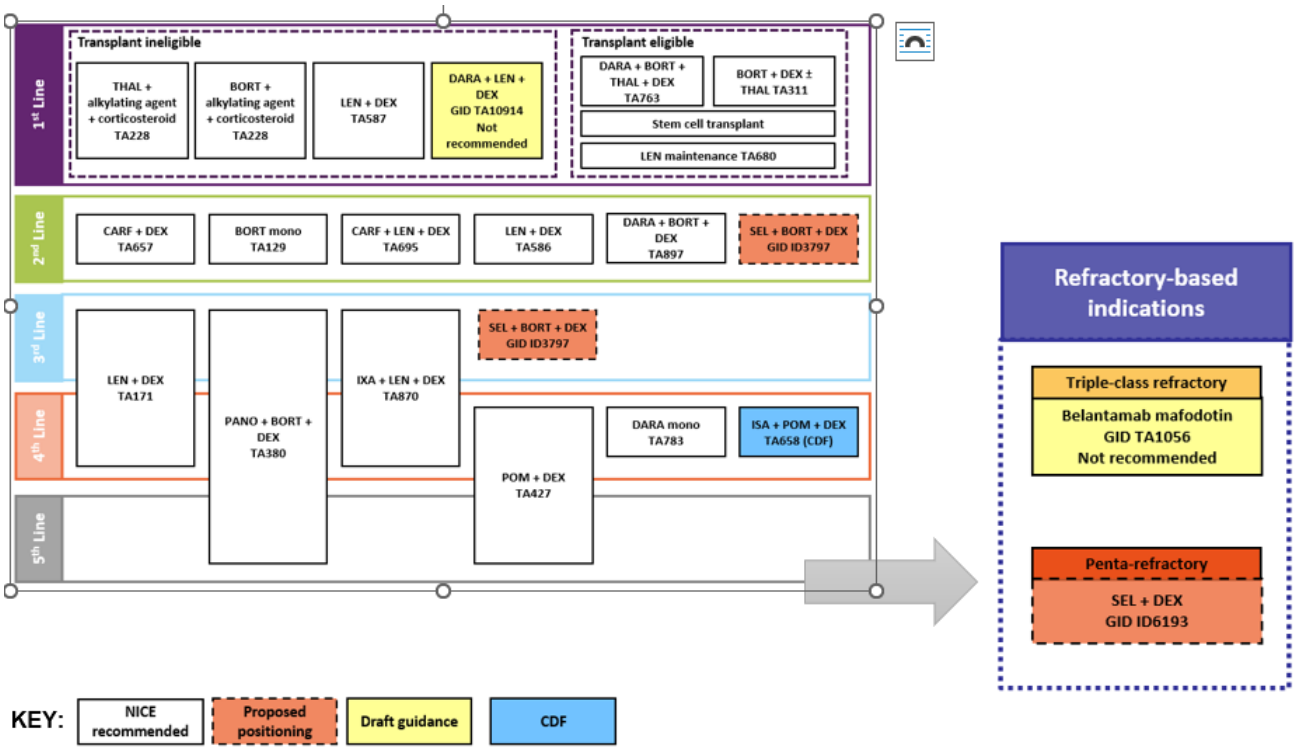
Company response:

a) As detailed in the company submission (CS; B.1.1, B.1.2), the therapeutic indication described in the marketing authorisation for selinexor plus dexamethasone (Sd) is: *in combination with dexamethasone 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, and who have demonstrated disease progression on the last therapy.*[1,2] Being refractory to at least two PIs, two IMiDs and an anti-CD38 mAb is known as penta-refractory. Table 1 below details specific drugs routinely available in UK clinical practice in each of the three drug classes that form part of the definition of penta-refractory. It is important to note that most of the drugs listed are available in more than one position in the UK pathway and in combination with different drugs (see pathway presented in Figure 3, CS B.1.3.2.1).

Table 1 PIs, IMiDs and anti-CD38 mAbs currently routinely available in clinical practice

Proteosome inhibitors (PIs)	Immunomodulatory drugs (IMiDs)	Anti-CD38 monoclonal antibody (mAb)
Bortezomib Carfilzomib Ixazomib	Lenalidomide Thalidomide Pomalidomide	Daratumumab Isatuximab (CDF)

Figure 1 Devised pathway to represent current interventions with routine NICE guidance in MM, correct to July 2023



b) The STORM trial included penta-refractory patients. In the BCLPD-refractory efficacy population it was also specified how patients were penta-refractory – the two PIs were bortezomib and carfilzomib, two IMiDs were lenalidomide and pomalidomide, and the anti-CD38 mAb was daratumumab. As described in B.2.3.1 of the CS, refractoriness in the STORM trial was defined as ≤25% response to treatment or progression during or within 60 days after completion of treatment.[3]

c) Although the marketing authorisation for Sd is based on the BCLPD-refractory population from the STORM trial, the marketing authorisation does not dictate the specific agents in each class that defines penta-refractory, specifying only that it is at least two PIs, two IMiDs and an anti-CD38 mAb. As discussed in CS B.1.3.2.2, there are a number of treatment pathways a patient could currently take in order to become penta-refractory by fifth-line and beyond (5L+), with the number of permutations increasing with NICE guidance for daratumumab combinations earlier in the treatment pathway, and other mechanisms of access to treatment such as via the CDF, or in clinical trials and compassionate use/ early access programmes.

A2. Priority question. Please confirm:

a) **how the MHRA marketing authorisation wording for Sd of "*at least four prior therapies*" relates to the number of lines of therapy in the treatment of patients with multiple myeloma (MM). For example, is Sd expected to be used from the fifth line of therapy and onwards? If not, at what line or lines would it be used in the treatment pathway?**

b) **if any difference in comparators is expected for patients who have had a prior stem cell transplant (SCT) compared to for patient's ineligible for SCT.**

Company response:

a) The MA wording of "at least four prior therapies" should be interpreted as four prior lines of therapy, as is reflected in the STORM trial which was the pivotal evidence supporting the MA. Based on clinical expert feedback, the interpretation in the UK is that Sd would be used in the 5L+ setting, with selinexor plus bortezomib and dexamethasone (SVd) being the choice of therapy within its licensed indication at 2L or 3L (submitted simultaneously as NICE ID3797).
b) Additional UK clinical experts, beyond those consulted by the company prior to submission, confirmed that although the UK treatment pathway for patients is different in earlier lines depending on eligibility for SCT, when patients are penta-refractory and have received ≥ four prior lines of therapy, the choice of therapy is not dependent on prior transplant status. Therefore, no difference in comparator is expected. As described in the CS, for penta-refractory 5L+ patients, there is no current SoC, and clinical expert opinion suggested BSC is the only appropriate comparator.

A3. Priority question. Clinical experts advising the EAG have highlighted that patient eligible for SCT are likely to be younger and healthier than those ineligible for SCT and also that they may receive Sd at an earlier line of therapy. Please comment on the likely age that each patient group might be expected to be at the time they become penta-refractory to treatments and thus eligible for Sd?

Company response: As discussed in the response to question A2 b), feedback from UK clinical experts is that prior SCT will not impact the choice of therapy at 5L+ in

penta-refractory patients. In addition, as described in A2 a), the licensed indication for Sd intends that patients must be penta-refractory and have received at least four prior lines of therapy, therefore any patients achieving penta-refractory status prior to 5L would not be eligible for Sd, regardless of their age and/ or status with regards to prior SCT. In fact, patients at earlier lines receiving selinexor are expected to do so as part of the other licensed selinexor combination, SVd, at 2L or 3L (submitted simultaneously as NICE ID3797).

Additionally, it was not considered appropriate to use age to define when patients would become penta-refractory to treatments. Clinical experts agreed that those patients eligible for SCT are a younger cohort, but given the outcomes associated with SCT compared to no SCT, it would not be appropriate to infer that these patients reach 5L+ penta-refractory at a younger age in clinical practice.

In the absence of natural history data specific to penta-refractory MM patients in the UK, patient demographic data from the 83 BCLPD-refractory participants of the STORM trial were reviewed to understand the mean age at trial entry. [redacted][4]

A4. Priority question. Please clarify how the number of prior anti-MM regimens at baseline in STORM Part 2 BCLPD-refractory subgroup (Table 7 of company submission [CS] document B) compares with the anticipated use of Sd in clinical practice in England as patients in the trial received a median of 8 regimens (range 4 to 18).

Company response: Based on clinical feedback and the availability of reimbursed treatments in the treatment pathway in MM in England, Sd is anticipated to be used in the 5L+ setting, available once patients are penta-refractory, aligned to both the STORM trial and the licensed indication. Use of Sd prior to 5L+ would be off-license, with SVd being the appropriate therapy if selinexor were to be used in earlier treatment lines, in line with its licensed indication (submitted simultaneously as NICE ID3797). Despite a paucity of natural history data in penta-refractory MM patients in England,

UK clinical experts expect the STORM population to be generalisable to the patients seen in clinical practice.

A5. Please clarify what impact the wide range in number of prior therapies in STORM Part 2 BCLPD-refractory subgroup (Table 7 of company submission [CS] document B) has on the interpretation of the results for the efficacy outcomes with Sd as patients in the trial had received between 4 and 18 prior anti-MM regimens.

Company response: At the time of commencement, STORM was the largest trial conducted in penta-refractory MM, in response to huge unmet need amongst these heavily pre-treated patients. The penta-refractory patient population are heterogeneous in light of the lack of a standard of care (SoC). Historically, upon refractoriness to the major drug classes (PIs, IMiDs, and more recently anti-CD38 mAbs), MM patients have been challenged with a variety of interventions not specific to penta-refractory MM, as reflected in the range observed in the number of prior anti-MM regimens in the STORM trial. Penta-refractory status is more clinically significant to patient treatment outcomes then the number of prior lines (i.e., exposure), therefore interpretation on the basis of prior number of regimens was not conducted.

Comparators

A6. Priority question. Please provide a comparison of the efficacy of Sd compared to panobinostat in combination with bortezomib and dexamethasone (PanoVd) for all outcomes specified in the NICE final scope.

Company response: As described in the CS (Table 2, B.1.1), UK clinical expert input elicited by the company suggests that PanoVd is not an appropriate comparator for the treatment of penta-refractory patients at 5L+, therefore a comparison has not been made. Moreover, UK clinical experts confirmed that PanoVd is a more appropriate comparator for SVd at 3L (NICE ID3797).

A7. Priority question. Please provide a comparison of the adverse events associated with selinexor in combination with dexamethasone (Sd) compared

with those associated with panobinostat in combination with bortezomib and dexamethasone (PanoVd).

Company response: In line with company response to A6., UK clinical expert input elicited by the company suggests that PanoVd is not an appropriate comparator for the treatment of penta-refractory patients at 5L+, therefore a comparison has not been made.

A8. Priority question. Please provide an analysis comparing Sd from the STORM Part 2 BCLPD-refractory subgroup to conventional chemotherapy using the penta-refractory subgroup from Gill *et al.* 2021[1] for overall survival (OS) using data available in Gill *et al.* 2022[2].

Company response: The study published by Gill *et al*. in the 2021 abstract and further in a 2022 correspondence,[5,6] was evaluated for appropriateness as a proxy for BSC in the absence of other data, during the feasibility assessment for the ITC. Based on the 2021 publication, the Gill *et al*. study conducted in one US centre was an outlier amongst the observational studies, did not fully report baseline characteristics, and did not define outcomes. Furthermore, on the basis of the 2022 correspondence, the treatments used for penta-refractory disease do not make it a suitable data set to estimate OS. In particular, there are 7 patients who received selinexor (median OS not reached), and 4 patients receiving CAR-T (median PFS 18.7 months and OS not reached). This confirmed the Gill *et al.* (2021/ 2022) study is clinically inappropriate as a proxy for comparator effectiveness, as proxy for BSC and/ or conventional chemotherapy.A9. Priority question. The EAG considers that patients who have received a SCT may become penta-refractory, and thus eligible for Sd, at an earlier line in the treatment pathway based on initially receiving DAR+BORT+THAL+DEX and LEN maintenance followed by CARF+DEX (as depicted in Figure 3 of CS document B). Clinical experts have advised the EAG that IXA+LEN+DEX would therefore be a valid treatment option, despite patients being refractory to LEN. The EAG thus considers that ixazomib plus lenalidomide and dexamethasone could be a potential comparator for Sd. Please provide a comparison of the efficacy of Sd with ixazomib plus

lenalidomide and dexamethasone for all outcomes specified in the NICE final scope.

Company response: As described in A2a), the licensed indication for Sd intends that patients must be penta-refractory and have received at least four prior lines of therapy, therefore any patients achieving penta-refractory status prior to 5L would not be eligible for Sd.

Clinical expert opinion elicited by the company suggests that IxaRd is currently used at 3L or 4L in the UK. Therefore, while IxaRd is a comparator for the other licensed selinexor combination, SVd at 3L (submitted simultaneously as NICE ID3797), it is not an appropriate comparator for the treatment of penta-refractory patients at 5L+, therefore a comparison has not been made *versus* Sd.

A10. Priority question. The EAG considers that patients could receive treatment with the immunomodulators, thalidomide and lenalidomide, to become penta-refractory and therefore pomalidomide plus dexamethasone would be a potential comparator for Sd. Please provide a comparison of the efficacy of Sd compared to pomalidomide plus dexamethasone for all outcomes specified in the NICE final scope.

Company response: As described in the CS (Table 2, B.1.1), clinical expert input elicited by the company suggests that Pd is not an appropriate comparator for the treatment of penta-refractory patients at 5L+, therefore a comparison has not been made. This has been further clarified with additional UK clinical expert input in response to the clarification questions which confirmed that while patients may receive thalidomide at 1L and lenalidomide at 2L, these patients may still be challenged with pomalidomide but in the 4L setting. Therefore, Pd was not considered an appropriate comparator as Sd would be used in the 5L+ penta-refractory setting, post-Pd.

STORM subgroup analyses

A11. Please provide the results for the primary outcome for the STORM Part 2 BCLPD-refractory subgroup for the following subgroups:

a) age (18-64, 65-74, ≥75 years of age);

b) prior SCT (yes/no);

c) ECOG status (0, 1 and 2);

d) number of prior anti-MM regimens; and

e) R-ISS stage (I, II, III).

Company response: Table 2 presents a summary of overall response rate (ORR; proportion of patients who achieve a confirmed partial response or better) data based on IRC assessment, by subgroup factors within the BCLPD-refractory analysis population (Table 2). Results should be interpreted with caution due to the small numbers of participants when stratified.

Table 2 ORR by IRC in the BCLPD-refractory analysis population by age, prior SCT, ECOG, prior anti-MM regimens, and R-ISS

	n	ORR, n (%)	Exact 95% CI
Age[3]			
18-64 years	40	10 (25.0)	12.7-41.2
65-74 years	31	7 (22.6)	9.6-41.1
≥75 years	12	4 (33.3)	9.9-65.1
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
R-ISS stage[3]			

	n	ORR, n (%)	Exact 95% CI
I	10	3 (30.0)	6.7-65.2
II	56	15 (26.8)	15.8-40.3
III	17	3 (17.6)	3.8-43.4

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; R-ISS, Revised International Staging System; SCT, stem cell transplant

Notes:

Two patients have missing ECOG at baseline information

Data cut: September 2019 (updated analysis)

STORM adverse events

A12. Priority question. Please provide a breakdown of the adverse events for the STORM Part 2 BCLPD-refractory subgroup including the equivalent data for treatment-related Grade 3+ (3/4/5) AEs by maximum severity, occurring in ≥5% reported in Table 19 of CS document B.

a) Based on the results provided in the first part of the question, please consider (if relevant) including a scenario analysis in the model where the AE for the Part 2 BCLPD-refractory subgroup are used instead of those for the ITT population.

Company response: Table 3 presents a summary of TRAEs ≥ Grade 3, occurring in ≥5% of participants in either analysis set. Given the consistency of adverse event rates between the mITT (n=202) and the BCLPD-refractory population (n=83), it was not considered necessary to include a scenario analysis on of the BCLPD-refractory population data.

Table 3 TRAEs ≥ Grade 3 in STORM Part 1 and Part 2 combined, and BCLPD-refractory population

	STORM Part 1 & 2 BCLPD-refractory n=202[3]	STORM Part 2 BCLPD-refractory n=83[4]
	Updated analysis: 7th September 2019	
Patients with ≥1 TRAE Grade 3+	180 (89.1)	[redacted]
Blood and lymphatic system disorders:	143 (70.8)	[redacted]
Thrombocytopenia	119 (58.9)	[redacted]
Anaemia	63 (31.2)	[redacted]
Neutropenia	40 (19.8)	[redacted]

	STORM Part 1 & 2 BCLPD-refractory n=202[3]	STORM Part 2 BCLPD-refractory n=83[4]
	Updated analysis: 7th September 2019	
Leukopenia	26 (12.9)	[redacted]
Lymphopenia	18 (8.9)	[redacted]
Gastrointestinal disorders:	33 (16.3)	[redacted]
Nausea	18 (8.9)	[redacted]
Diarrhoea	12 (5.9)	[redacted]
General disorders and administration site conditions:	45 (22.3)	[redacted]
Fatigue	38 (18.8)	[redacted]
Asthenia	6 (3.0)	[redacted]
Infections and infestations	13 (6.4)	[redacted]
Metabolism and nutrition disorders:	65 (32.2)	[redacted]
Hyponatraemia	36 (17.8)	[redacted]
Hyperglycaemia	15 (7.4)	[redacted]
Decreased appetite	10 (5.0)	[redacted]
Psychiatric disorders:	12 (5.9)	[redacted]
Abbreviations: TRAE, treatment-related adverse event		

Health-related quality of life

A13. Please provide the health-related quality of life (HRQoL) outcome data from STORM Part 2 for the BCLPD-refractory subgroup.

Company response: The primary analysis for QoL was based on the change from baseline on the TOI score at each assessment time point, which was summarised using descriptive statistics. The total score considering all 5 subscales as well as the 5 individual subscale sums of scores was summarised similarly. Table 4 presents the FACT-MM TOI and individual subscale scores, for the BCLPD-refractory efficacy population, based on Table 34 of the CSR which present data for the full mITT of STORM Part 2.[3] Median decrease from baseline is observed in the FACT-MM TOI score, and across most of the individual domains, which is consistent with the whole Part 2 mITT population.

Table 4 Fact MM scores for BCLPD-refractory population (STORM Part 2 mITT)

	STORM Part 2 mITT BCLPD-refractory[3]	
	n	**Median**
FACT-MM: Total trial outcomes index total score		
Baseline	75	68
Δ at C2D1	53	-4
Δ at C3D1	34	-8
Δ at C4D1	21	-7
Δ at C5D1	19	-5
Δ at C6D1	11	-14
Δ at C7D1	8	-9
Δ at C8D1	3	-27
FACT-MM: MM-specific subscale score		
Baseline	75	34
Δ at C2D1	53	-1
Δ at C3D1	34	0
Δ at C4D1	20	-2
Δ at C5D1	19	0
Δ at C6D1	11	0
Δ at C7D1	8	-1
Δ at C8D1	3	-5
FACT-MM: Physical well-being subscale score		
Baseline	75	20
Δ at C2D1	53	-3
Δ at C3D1	34	-3
Δ at C4D1	21	-5
Δ at C5D1	19	-3
Δ at C6D1	11	-2
Δ at C7D1	8	-5
Δ at C8D1	3	-18
FACT-MM: Social/ family well-being subscale score		
Baseline	75	24
Δ at C2D1	52	0
Δ at C3D1	34	0
Δ at C4D1	21	-1
Δ at C5D1	19	0
Δ at C6D1	11	0
Δ at C7D1	8	-3
Δ at C8D1	3	-1
FACT-MM: emotional well-being subscale score		
Baseline	75	17
Δ at C2D1	53	0
Δ at C3D1	34	1
Δ at C4D1	21	1
Δ at C5D1	19	1
Δ at C6D1	11	0

	STORM Part 2 mITT BCLPD-refractory[3]	
Δ at C7D1	8	0
Δ at C8D1	3	4
Abbreviations: Δ, change; C, cycle; D, day; MM, multiple myeloma		

Subsequent treatments in STORM

A14. Priority Question. Please provide a breakdown of the "new" anti-MM therapies received by the [redacted] % of Sd patients in the STORM Part 2 BCLPD-refractory subgroup.

Company response: Table 5 presents the number of patients from the STORM Part 2 BCLPD-refractory population receiving each group of "new" anti-MM subsequent therapies, at any time after Sd.

Table 5 Subsequent therapies received any time after Sd in STORM Part 2 BCLPD-refractory population

Subsequent therapy	Number of participants
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

A15. Please provide by mean and median OS including Kaplan-Meier curves by class of subsequent therapy after Sd in the STORM Part 2 BCLPD-refractory subgroup. (e.g., proteasome inhibitor, immunomodulatory drug, anti-CD38 monoclonal antibody and chemotherapy).

Company response: Please see below in OS data by class of subsequent therapy after Sd in STORM Part 2 BCLPD-refractory population (**Error! Reference source n ot found.**-

Figure 9).

Figure 2 [redacted]

[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]

[redacted]

Figure 3 [redacted]

[redacted]		[redacted]	
[redacted]		[redacted]	
[redacted]		[redacted]	
[redacted]		[redacted]	
[redacted]		[redacted]	
[redacted]		[redacted]	
[redacted]		[redacted]	
[redacted]		[redacted]	

[redacted]

Source: Data on file

Figure 4 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

Figure 5 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Figure 6 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Source: Data on file

Figure 7 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Figure 8 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Figure 9 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

A16. Please provide by mean and median OS including Kaplan-Meier curves for the subgroup of patients who received no subsequent anti-MM therapies after Sd in the STORM Part 2 BCLPD-refractory subgroup.

Company response: Figure 10 presents OS data for patients who received no subsequent therapy after Sd, in STORM Part 2 BCLPD-refractory population.

Figure 10 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

STC methods

A17. Priority question. The EAG notes that the STC methods were only briefly reported in the submission and the ITC report, however the R code for the STCs was provided in Appendix D. From this code, the EAG recognises that the STC method was to, i) fit parametric survival curves to the STORM BCLPD IPD and then, ii) substitute the mean covariate values into this model using the

MAMMOTH baseline characteristics. The EAG notes that little validation or exploration of uncertainty in the STC was presented. Please:

a) **Provide a full written methods section of the STC;**
b) **Present the full model output of the fitted models, including coefficients and uncertainty intervals for each covariate;**
c) **Perform an assessment of the model fit and assumptions of each survival model;**
d) **Assess the likely robustness of the fitted models to out-of-sample predictions, i.e., assess the amount of bias likely when extrapolating beyond the STORM BCLPC population - for example by assessing the model predictions across a range of covariate values and assessing the clinical plausibility of the results;**
e) **Present the uncertainty intervals of the simulated survival curves in the MAMMOTH population, which should be available using the summary() function in the R code; and**
f) **Clarify further why 95% confidence intervals could not be generated around the estimated HRs, and, if they cannot be provided, interpret the likely uncertainty of the STC results acknowledging the 95% CIs generated for the individual survival curves, and given the possibility that these 95% CIs may undercover the true 95% confidence interval.**

Company response:

(a) STC methods have been explored to provide an estimate of a HR between Sd and SoC using data from the MAMMOTH study using the 'Must have + Nice to have' set of factors. The steps of the approach adopted for the STC are as described as follows:

(1) Bootstrap of the STORM BCLPD IPD: Non-parametric bootstrap to re-sample the STORM BCLPD IPD

(2) Outcome regression model: A standard parametric survival model is fitted to the bootstrapped IPD. The model includes all prognostic factors and effect modifiers in the 'Must have + Nice to have' covariate set.

(3) Prediction step: Survival probabilities for the aggregate-level data (AgD) population (i.e., the MAMMOTH study) when treating with Sd are predicted using the regression model from step (2) and the reported covariates from the AgD study. To obtain the correct marginal effect, covariates are sampled using a Gaussian copula based on the marginal mean values reported by the AgD study, and the correlation structure calculated using the bootstrapped IPD.

(4) Pseudo IPD are reconstructed for the AgD study (based on digitisation of the Kaplan-Meier curve) as well as the Sd arm within the AgD population (based on the survival probabilities predicted in step (3)), using methods proposed by Guyot *et al.* 2012.[7]

(5) Estimation of HR: A Cox regression model is fitted to the pseudo IPD obtained in step (4) to estimate the HR.

(6) Estimation of uncertainty around the HR: Step (1) to (5) are repeated 2,000 times. The 95% CI are calculated based on the 2.5th and 97.5th percentiles from 2,000 bootstrapped results.

The above process was repeated for each selected parametric survival model (including exponential, Weibull, lognormal, loglogistic and Gompertz distributions). Note: there were convergence issues when attempting to fit the generalised gamma model. Hence, this model was not used in the STC.

Results from the STC analyses are presented in Table 6, which show the HR (and corresponding 95% CI) of Sd versus SoC (evaluated in the MAMMOTH study) for each parametric model. Sd is statistically significantly superior to SoC (HR and 95% CI is estimate are less than 1.0) across all of the models.

Table 6 STC results – STORM BCLPD versus MAMMOTH for each parametric survival model: overall survival

Distribution	HR	95% CI	Mean (SD)
Exponential	0.388	[0.191, 0.790]	0.414 (0.153)
Weibull	0.389	[0.185, 0.787]	0.413 (0.154)
Lognormal	0.433	[0.229, 0.795]	0.455 (0.146)
Loglogistic	0.420	[0.208, 0.789]	0.442 (0.152)
Gompertz	0.392	[0.198, 0.760]	0.417 (0.151)

Distribution	HR	95% CI	Mean (SD)
Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation. *Notes: HR is based on a comparison of Sd versus standard of care.*			

(b) A summary of the full model output from each parametric model fitted to the STORM BCLPD IPD is presented in Table 7 to Table 11

Table 7 Summary of model output from the exponential parametric model fitted to the STORM BCLPD IPD

Estimates:

	data mean	est	L95%	U95%	se	exp(est)	L95%	U95%
rate	NA	0.007122	0.000387	0.131232	0.010588	NA	NA	NA
AGE	64.000000	0.022732	-0.010765	0.056228	0.017090	1.022992	0.989293	1.057839
factor(SEXN)1	0.632911	0.281798	-0.321545	0.885141	0.307834	1.325511	0.725028	2.423327
factor(HCRN)1	0.607595	-0.345345	-1.056417	0.365727	0.362799	0.707976	0.347699	1.441562
REGIMN	8.088608	0.122504	-0.016084	0.261092	0.070710	1.130324	0.984044	1.298347
factor(STEMCT)1	0.810127	-0.078431	-0.948129	0.791268	0.443732	0.924566	0.387465	2.206192
factor(RISSN)2	0.683544	0.952236	-0.156920	2.061392	0.565906	2.591498	0.854773	7.856901
factor(RISSN)3	0.189873	0.730227	-0.519357	1.979811	0.637555	2.075551	0.594903	7.241372
IDIAGYR	7.506806	-0.066814	-0.172246	0.038617	0.053793	0.935369	0.841772	1.039373
DURMM	18.264014	-0.014088	-0.034833	0.006658	0.010585	0.986011	0.965767	1.006680

Abbreviations: DURMM, duration of last multiple myeloma treatment; est, estimate; HCRN, high cytogenetic risk; IDIAGYR, time since diagnosis; L95%, lower 95% confidence interval; NA, not applicable; REGIMN, number of regimens; RISSN, Revised International Staging System; se, standard error; SEXN, sex; STEMCT, stem cell transplant; U95%, upper 95% confidence interval

Table 8 Summary of model output from the Weibull parametric model fitted to the STORM BCLPD IPD

Estimates:

	data mean	est	L95%	U95%	se	exp(est)	L95%	U95%
shape	NA	1.10364	0.87488	1.39223	0.13080	NA	NA	NA
scale	NA	123.11717	8.49082	1785.20297	167.97956	NA	NA	NA
AGE	64.00000	-0.02128	-0.05183	0.00927	0.01559	0.97895	0.94949	1.00932
factor(SEXN)1	0.63291	-0.27817	-0.82646	0.27013	0.27975	0.75717	0.43760	1.31013
factor(HCRN)1	0.60759	0.34918	-0.30124	0.99961	0.33186	1.41791	0.73990	2.71722
REGIMN	8.08861	-0.12046	-0.24658	0.00566	0.06435	0.88651	0.78147	1.00568
factor(STEMCT)1	0.81013	0.07280	-0.72317	0.86877	0.40611	1.07551	0.48521	2.38397
factor(RISSN)2	0.68354	-0.91609	-1.92631	0.09412	0.51543	0.40008	0.14568	1.09870
factor(RISSN)3	0.18987	-0.68693	-1.82785	0.45399	0.58211	0.50312	0.16076	1.57458
IDIAGYR	7.50681	0.06487	-0.03136	0.16109	0.04909	1.06702	0.96913	1.17479
DURMM	18.26401	0.01322	-0.00573	0.03216	0.00967	1.01330	0.99429	1.03269

Abbreviations: DURMM, duration of last multiple myeloma treatment; est, estimate; HCRN, high cytogenetic risk; IDIAGYR, time since diagnosis; L95%, lower 95% confidence interval; NA, not applicable; REGIMN, number of regimens; RISSN, Revised International Staging System; se, standard error; SEXN, sex; STEMCT, stem cell transplant; U95%, upper 95% confidence interval

Table 9 Summary of model output from the lognormal parametric model fitted to the STORM BCLPD IPD

Estimates:

	data mean	est	L95%	U95%	se	exp(est)	L95%	U95%
meanlog	NA	4.33700	1.41624	7.25775	1.49021	NA	NA	NA
sdlog	NA	1.17200	0.95356	1.44048	0.12334	NA	NA	NA
AGE	64.00000	-0.02819	-0.06430	0.00792	0.01842	0.97220	0.93773	1.00795
factor(SEXN)1	0.63291	-0.20800	-0.80922	0.39322	0.30675	0.81221	0.44520	1.48175
factor(HCRN)1	0.60759	0.14040	-0.53060	0.81140	0.34235	1.15073	0.58825	2.25105
REGIMN	8.08861	-0.06020	-0.19795	0.07754	0.07028	0.94157	0.82041	1.08062
factor(STEMCT)1	0.81013	0.20097	-0.64098	1.04292	0.42958	1.22259	0.52678	2.83750
factor(RISSN)2	0.68354	-0.78903	-1.80150	0.22343	0.51657	0.45428	0.16505	1.25036
factor(RISSN)3	0.18987	-0.73258	-1.90782	0.44266	0.59962	0.48067	0.14840	1.55684
IDIAGYR	7.50681	0.05299	-0.04549	0.15146	0.05024	1.05442	0.95553	1.16353
DURMM	18.26401	0.01226	-0.00856	0.03308	0.01062	1.01233	0.99147	1.03363

Abbreviations: DURMM, duration of last multiple myeloma treatment; est, estimate; HCRN, high cytogenetic risk; IDIAGYR, time since diagnosis; L95%, lower 95% confidence interval; NA, not applicable; REGIMN, number of regimens; RISSN, Revised International Staging System; se, standard error; SEXN, sex; STEMCT, stem cell transplant; U95%, upper 95% confidence interval

Table 10 Summary of model output from the loglogistic parametric model fitted to the STORM BCLPD IPD

Estimates:

	data mean	est	L95%	U95%	se	exp(est)	L95%	U95%
shape	NA	1.44343	1.14674	1.81688	0.16946	NA	NA	NA
scale	NA	94.31867	5.58436	1593.02225	136.02874	NA	NA	NA
AGE	64.00000	-0.03031	-0.06629	0.00568	0.01836	0.97015	0.93586	1.00569
factor(SEXN)1	0.63291	-0.22747	-0.83164	0.37669	0.30825	0.79654	0.43534	1.45746
factor(HCRN)1	0.60759	0.18612	-0.46405	0.83630	0.33173	1.20457	0.62873	2.30781
REGIMN	8.08861	-0.08461	-0.22972	0.06050	0.07404	0.91887	0.79476	1.06237
factor(STEMCT)1	0.81013	0.30540	-0.54557	1.15638	0.43418	1.35717	0.57951	3.17840
factor(RISSN)2	0.68354	-0.80117	-1.84253	0.24019	0.53132	0.44880	0.15842	1.27149
factor(RISSN)3	0.18987	-0.75705	-1.94920	0.43511	0.60825	0.46905	0.14239	1.54513
IDIAGYR	7.50681	0.06146	-0.03874	0.16166	0.05112	1.06339	0.96200	1.17546
DURMM	18.26401	0.01075	-0.00989	0.03138	0.01053	1.01080	0.99016	1.03188

Abbreviations: DURMM, duration of last multiple myeloma treatment; est, estimate; HCRN, high cytogenetic risk; IDIAGYR, time since diagnosis; L95%, lower 95% confidence interval; NA, not applicable; REGIMN, number of regimens; RISSN, Revised International Staging System; se, standard error; SEXN, sex; STEMCT, stem cell transplant; U95%, upper 95% confidence interval

Table 11 Summary of model output from the Gompertz parametric model fitted to the STORM BCLPD IPD

Estimates:

	data mean	est	L95%	U95%	se	exp(est)	L95%	U95%
shape	NA	-0.012817	-0.077171	0.051538	0.032834	NA	NA	NA
rate	NA	0.008232	0.000414	0.163819	0.012561	NA	NA	NA
AGE	64.000000	0.022444	-0.011100	0.055988	0.017114	1.022698	0.988962	1.057585
factor(SEXN)1	0.632911	0.266764	-0.340084	0.873611	0.309622	1.305732	0.711711	2.395546
factor(HCRN)1	0.607595	-0.325303	-1.039513	0.388907	0.364400	0.722308	0.353627	1.475368
REGIMN	8.088608	0.116974	-0.024202	0.258150	0.072030	1.124091	0.976089	1.294533
factor(STEMCT)1	0.810127	-0.081144	-0.946072	0.783784	0.441298	0.922061	0.388263	2.189743
factor(RISSN)2	0.683544	0.915063	-0.208582	2.038707	0.573299	2.496932	0.811735	7.680673
factor(RISSN)3	0.189873	0.710549	-0.540063	1.961162	0.638079	2.035109	0.582711	7.107581
IDIAGYR	7.506806	-0.064286	-0.170159	0.041587	0.054018	0.937737	0.843531	1.042464
DURMM	18.264014	-0.013849	-0.034618	0.006919	0.010596	0.986246	0.965974	1.006943

Abbreviations: DURMM, duration of last multiple myeloma treatment; est, estimate; HCRN, high cytogenetic risk; IDIAGYR, time since diagnosis; L95%, lower 95% confidence interval; NA, not applicable; REGIMN, number of regimens; RISSN, Revised International Staging System; se, standard error; SEXN, sex; STEMCT, stem cell transplant; U95%, upper 95% confidence interval

(c) The assessment of model fit was based on the AIC and BIC scores. Assumptions underpinning each model could not be assessed due to the inclusion of a large set of covariates in the regression model. Since the sample size of the BCLPD-refractory population is small, data are split too sparse across each level of the factors, therefore, it was not possible to evaluate the assumptions of each survival model for each combination of stratums. Hence, the AIC and BIC values were used to help identify the best-fitting model.

A summary of model fit is presented in Table 12, which shows that the lognormal distribution provided the best model fit according to the AIC and BIC.

Table 12 AIC/BIC ranking for parametric models fitted to the STORM BCLPD-refractory OS IPD

Distribution	AIC	BIC	AIC+BIC	Ranking
Lognormal	**368.99**	**395.05**	**764.04**	**1**
Exponential	371.53	395.23	766.76	2
Loglogistic	371.11	397.17	768.28	3
Weibull	372.87	398.93	771.80	4
Gompertz	373.38	399.44	772.82	5

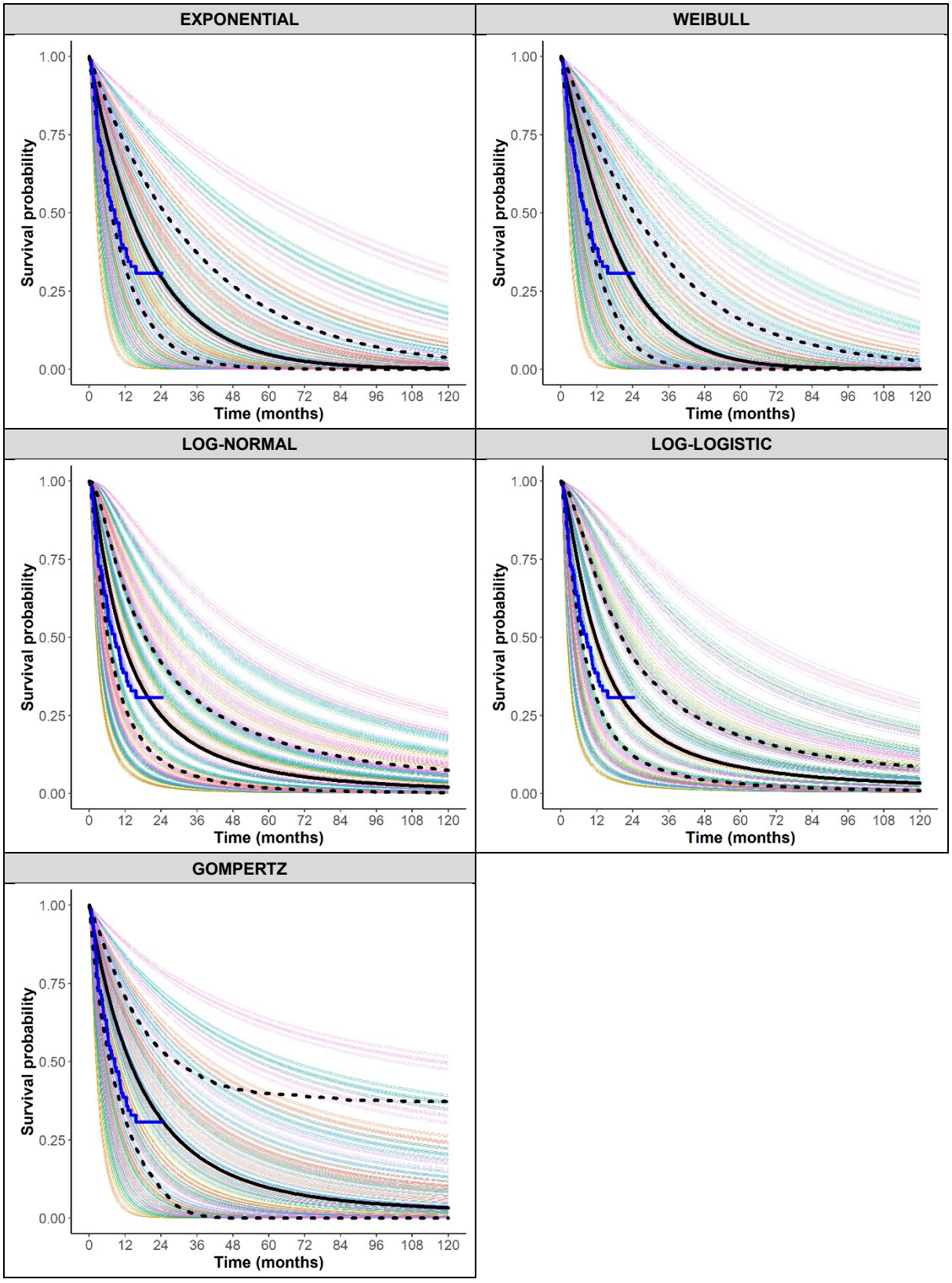
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

(d) Consistent with the robustness assessment performed as part of the response to clarification question A8, the unadjusted Kaplan-Meier curve (based on the STORM BCLPD-refractory population) along with the simulated survival curve (and associated 95% CI) for Sd within the MAMMOTH population (using the mean of covariates approach using values reported by MAMMOTH) is presented in Figure 11. Whilst the model predictions show variation, the curves with the greatest survival probabilities over time are based on a simulation using a low age value (lower than may be plausible in the BCLPD-refractory population).

The details on how the range of covariates were chosen are consistent with the approach detailed as part of the response to clarification question A8. To explore model predictions, a range of covariate values have been explored by considering a population which is different to the 'average' STORM BCLPD-refractory population. To do this, different values of covariates included in the model were explored and all and a combinations of covariate values were used to inform model predictions.

To determine the values of covariates, an age range of 35-90 was used, and the values for dichotomous covariates were based on 10 percentage points either side of the mean value in the STORM BCLPD-refractory population. For continuous covariates (with the exception of age), the lower and upper quartiles in the STORM BCLPD-refractory population values were used.

Figure 11 Parametric survival curves using on a range of covariate values, along with the simulated Sd survival curve (and 95% CI bands) in the MAMMOTH population



(e) A summary of the mean and 95% CI values for the simulated Sd curve (based on each of the five parametric survival models) in the MAMMOTH population are presented in the associated Excel file ("Simulated_Sd_MAMMOTH_population.xlsx") (based on extrapolation up to 120 months), along with the corresponding estimates for SoC based on the digitised Kaplan Meier curve reported by Gandhi *et al.* (2019).[8]

(f) The STC versus MAMMOTH has been updated and therefore, 95% CIs have been estimated using bootstrapping techniques and are presented in Table 6 as part of a response to question A17.

Additional clarification questions [received 4 Sept 2023]

A18. Priority question. Please provide the Kaplan-Meier survival curves for OS of the STORM Part 2 BCLPD population vs MAMMOTH from the fully adjusted MAIC, including the unadjusted Sd curve, the MAMMOTH curve and the adjusted Sd curve.

Company response: The unadjusted and MAIC-weighted Sd Kaplan-Meier curves are presented in Figure 12

Figure 12 Kaplan-Meier Survival Curve for OS - STORM BCLPD vs MAMMOTH – unadjusted Sd, MAIC-weighted Sd and digitised data from MAMMOTH based on 'Must have' modelFigure 13 Kaplan-Meier Survival Curve for OS - STORM BCLPD vs MAMMOTH – unadjusted Sd, MAIC-weighted Sd and digitised data from MAMMOTH based on 'Must have' model

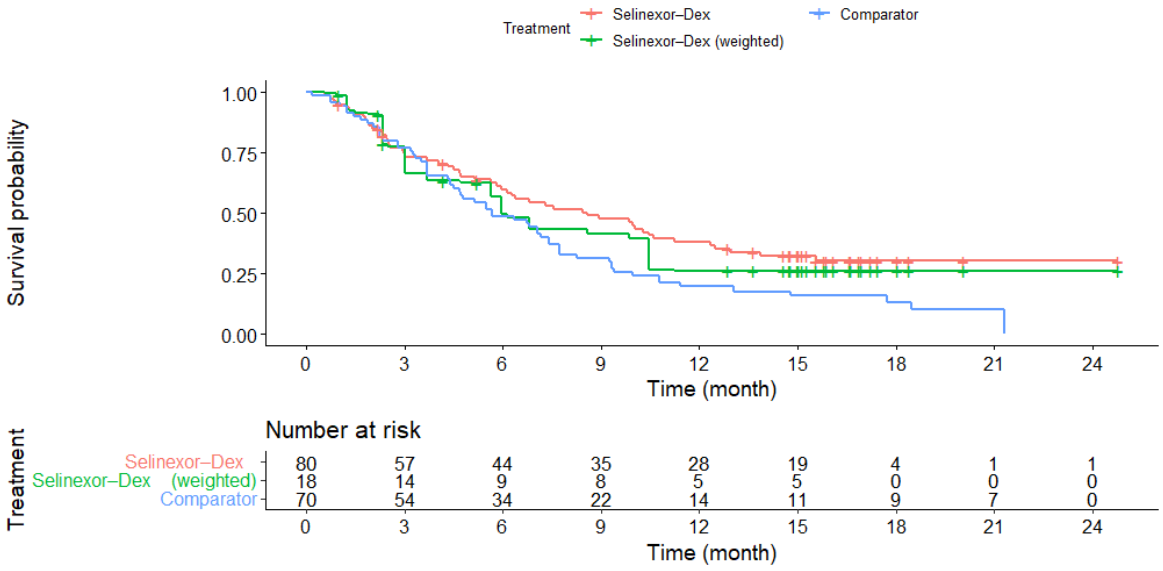


Figure 14Figure 13 and Figure 14 along with the MAMMOTH Kaplan-Meier curve (reconstructed from the digitised data) for the 'Must have' set of covariates and 'Full' set of covariates, respectively.

Figure 13 Kaplan-Meier Survival Curve for OS - STORM BCLPD vs MAMMOTH – unadjusted Sd, MAIC-weighted Sd and digitised data from MAMMOTH based on 'Must have' model

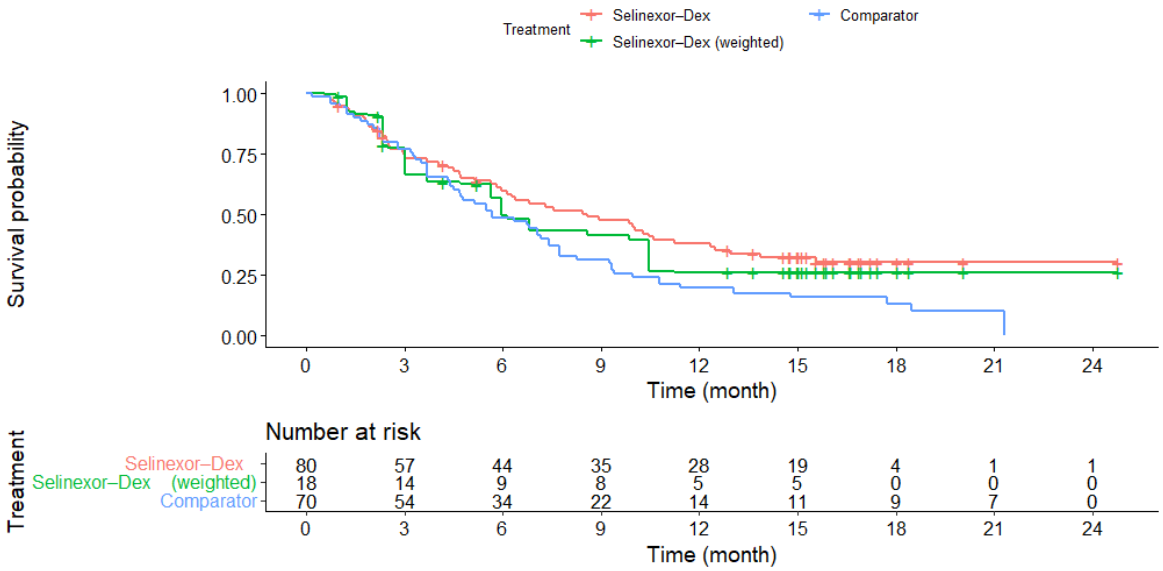
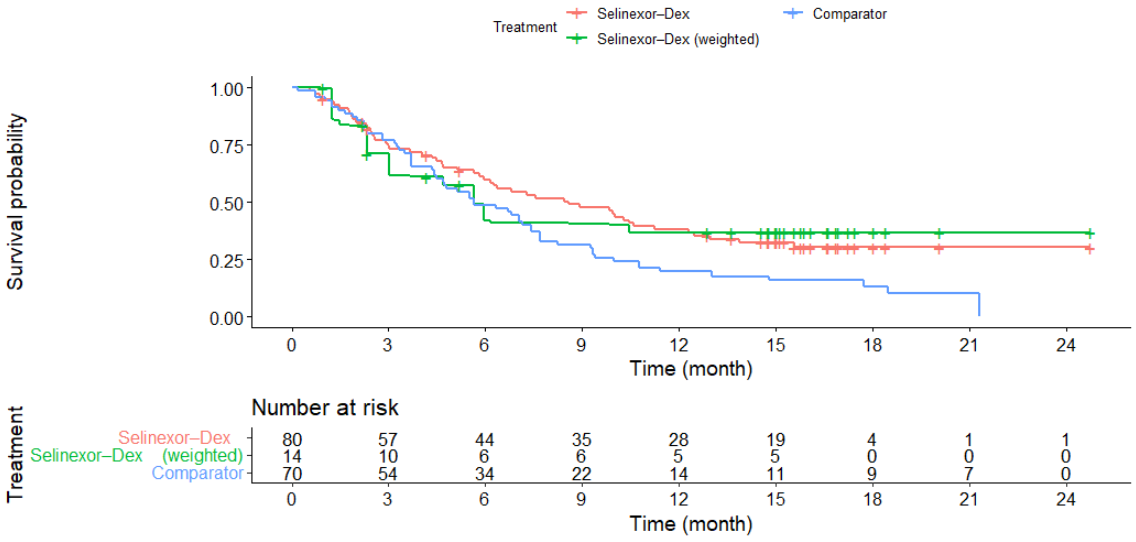


Figure 14 Kaplan-Meier Survival Curve for OS - STORM BCLPD vs MAMMOTH – unadjusted Sd, MAIC-weighted Sd and digitised data from MAMMOTH based on 'Full' model



A19. For the STC, please clarify how hazard ratios were calculated between the simulated Sd curves and the MAMMOTH survival curve, and provide any code used to calculate this.

Company response: As described as part of the response to question A17, estimates of the HR were calculated using Cox regression model fitted to pseudo IPD reconstructed for the AgD study (based on digitisation of the Kaplan-Meier curve), as well as the Sd arm within the AgD population. Example R code has been provided in the associated file ("R code for CQ A17").

A20. Please confirm that the data provided in Tables 35, 36 and 37 of the ITC report, and Table 16 of the Company submission, present the simulated survival curves based on parametric survival models fitted with the STORM data but with the MAMMOTH covariate values substituted in ("STORM" columns), and the MAMMOTH common is the digitised survival curve of the MAMMOTH penta-refractory population.

Company response: The STC analysis versus MAMMOTH has been updated, with results presented as a response to clarification question A17, which have superseded the respective STC results presented in the Section B2.9 of the submission dossier, as well as the results presented for the comparison with MAMMOTH included in the ITC report.

A21. Please clarify why the values for MAMMOTH are different between Tables 35 and 36 of the ITC report compared to Table 37 of the ITC report.

Company response: The STC analysis versus MAMMOTH has been updated, with results presented as a response to clarification question A17, which have superseded the respective STC results presented in the Section B2.9 of the submission dossier, as well as the results presented for the comparison with MAMMOTH included in the ITC report.

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.

Treatment effectiveness in the model

A summary of model changes and implications on base case ICER results for EAG questions that required model updates are detailed in Table 13.

Table 13 Summary of model changes and impact on ICER estimate

EAG Question	Description	Severity Modifier	ICER	Change in ICER (relative to original company base case)	Incorporated into revised company base case
A17	Revised OS HR (MAMMOTH STC)	1.7	£21,626	-£5,781.83	Yes
B5	Piecewise OS options	1.7	£45,104	+£17,696.73	No – scenario only
B8	Age-related disutility (Hernandez)	1.7	£27,282	-£126.15	Yes
B9	AE disutility (amended values)	1.7	£27,408	+£0.62	Yes
B10	AE disutility durations (amended values)	1.7	£27,408	-£0.12	Yes
B13	Chemotherapy uptake 65%	1.7	£27,378	-£30.12	Yes
B15a	Resource use frequencies	1.7	£33,514	+£6,106.26	No – scenario only
B15b	Resource use varied by treatment status	1.7	£27,405	-£2.74	No – scenario only
B16	NHS 21/22 ref costs for AEs	1.7	£29,509	+£2,101.26	Yes
B17	Oral delivery cost SB117 £217/cycle	1.7	£28,059	+£651.17	No – scenario only
B18	Cyclophosphamide dose (alternative value)	1.7	£27,438	+£30.02	No
B20	Cyclophosphamide cost (amended value)	1.7	£27,408	-£0.17	Yes
B21	Ondansetron cost (amended value)	1.7	£27,392	-£15.77	Yes
A17+B8+B9+ B10+B13+ B16+B18+ B20+B21	Revised base case combining EAG questions	1.7	£23,135	-£4,273	Yes

B1. Priority question. Please include a scenario analysis in the model where the cost-effectiveness of PanoVd vs Sd is evaluated (using the clinical analysis requested in Question A6).

Company response: As described in A6, PanoVd is not an appropriate comparator for the treatment of penta-refractory MM patients at 5L+. A scenario comparing Sd against PanoVd therefore has not been explored.

B2. Priority question. Please include a scenario analysis in the model where the effectiveness of the BSC arm in the model is estimated using the results from Question A8. The EAG acknowledges that the treatments included in the Gill *et al*. study are not chemotherapy regimens, and these would be assumed to provide a proxy for the treatment effectiveness of chemotherapy for penta-refractory patients.

Company response: As described in A8, Gill *et al*. (2021/ 2022) study is not a suitable data set for providing estimates of relative effectiveness for BSC and/ or chemotherapy.[5,6], with only 7.7% (4 out of 91) penta-refractory patients receiving chemotherapy for penta-refractory disease, bendamustine. In addition, 7.7% of patients received selinexor as treatment for penta-refractory disease with OS not reached. Four patients received CAR-T therapy, with OS not being reached and PFS being 18.7 months.[5,6]

B3. Priority question. Please include a scenario analysis in the model where the cost-effectiveness of IXA+LEN+DEX vs Sd is evaluated (using the clinical analysis requested in Question A9). Please consider what inputs would need to be changed in the model to reflect the SCT-eligible population who could receive IXA+LEN+DEX, such as baseline age; subsequent treatments in both treatment arms; etc.

Company response: As described in A9, IxaRd is not an appropriate comparator for the treatment of penta-refractory MM patients at 5L+. A scenario comparing Sd against IxaRd therefore has not been explored.

B4. Priority question. Please include a scenario analysis in the model where the cost-effectiveness of POM+DEX vs Sd is evaluated (using the clinical analysis

requested in Question A10). Please consider what inputs would need to be changed in the model to reflect the population eligible to receive POM+DEX.

Company response: As described in A10, Pd is not an appropriate comparator for the treatment of penta-refractory MM patients at 5L+. A scenario comparing Sd against Pd therefore has not been explored.

B5. Priority question. The EAG's clinical experts considered that OS is likely to be overestimated in the BSC arm of the model. One expert advised that all penta-refractory patients are expected to be dead at 3 years after initiation of treatment (vs 3% in the company's model), with 3% of patients alive being a more likely survival estimate for 2 years in the model (vs 7% in the company's model). Furthermore, the experts commented that given the treatment duration with Sd (mean 2.5 months, with a PFS of 3.83 months in the model), it is implausible that 6% of Sd patients would be alive at 5 years in the model. The experts confirmed that at 5 years all patients would be expected to have died. In light of this, the EAG notes that the tails of the exponential or Weibull curves extrapolated from the fitted OS KM STORM provide more realistic predictions for the BSC and the Sd long-term OS extrapolations in the model. The EAG, however, acknowledges that the latter provide a worse fit to the KM OS data from STORM compared with the company's base case lognormal curve. Therefore, can the company please explore a more flexible modelling option with a lognormal curve fitted to the observed KM OS data from STORM, where the tails of the curve are varied to provide more clinical plausible long-term survival predictions.

Company response: As described in section B.3.3.1 of the CS, given there was little to distinguish between the parametric curves for the OS data in terms of visual or statistical fit, clinical expert opinion was used to determine the most appropriate distribution, with log-normal determined as the most appropriate. Further clinical input has been elicited during the response to the EAG questions and it was considered feasible by clinical experts that patients could remain alive at three years on best supportive care and therefore an assumption of all patients being dead by 3 years would be pessimistic. Additional feedback was also received that in the penta-refractory setting, we are considering only 1% of the diagnosed population and when choosing the most appropriate extrapolation, we are considering very tiny patient numbers at this point of the extrapolation.

Although the company believes that the base-case presented in the CS remains the most appropriate, a flexible modelling approach has been undertaken in response to the question from the EAG. Functionality has been added to run scenarios in which an initial OS parametric curve is applied from model baseline before switching to an alternative OS curve from a user-specified time point. Secondary OS curve choices are as fitted to the original Kaplan-Meier curves (as opposed to separate curves fitted to the tails of distributions only). A prompt is provided in the model listing the time points at which the selected OS curves cross to inform time point selection.

Applying a lognormal OS curve from baseline and a Weibull curve from 63 weeks (at which the two curves cross), ICER increases by £17,696 to £45,104 relative to the lognormal curve being applied throughout (using original company base assumptions). It should be noted that this result is broadly equivalent to applying the Weibull throughout, since the area under the curve is broadly similar across curves during the observed period. Applying the piecewise scenario in conjunction with the corrected hazard ratio for STORM *versus* MAMMOTH and other corrections suggested by the EAG (questions A17, B8, B9, B10, B13, B16, B20, B21) provides an ICER of £35,865.

Population in the model

B6. Priority question. The incidence rates published at Cancer Research UK for MM indicate that 43% of new cases are diagnosed in people aged 75 and over (which would correspond to a first-line treatment instead of a penta-refractory population as for this STA) and that the highest rates are in the 85 to 89 age group for females and males. Therefore, can the company include a scenario analysis in the model (with the severity modifier changed accordingly) considering a population of 75 years at baseline.

Company response: As discussed in A3, clinical expert input has confirmed that the age at diagnosis should not be used as a proxy for reaching penta-refractory status and that a scenario analysis utilising a population of 75 years at baseline would not be appropriate.

Clinical expert feedback is that it is expected that it would be a younger cohort that would reach penta-refractory status. Patients over 75 years of age at diagnosis receive fewer lines of therapy, with patients over 80 years of age receiving potentially only 3-

4 lines of therapy. This is supported by Yong *et al.* 2016, which identifies older age as a negative predictor of continued treatment ("*One contributing factor* [to the small proportion of patients reaching fifth-line treatment] *may be the old age of many of these patients, who will accumulate comorbidities unrelated to MM. Thus, patients who are younger at diagnosis (i.e., those who were eligible for SCT) may be more likely to reach later lines)".*[9] This should also be considered in the context that only 1% of patients diagnosed with MM reach 5L+ lines of therapy.

This is further supported by the age distribution reported in the penta-refractory subgroup of the MAMMOTH study; median age among n=70 penta-refractory patients was 58.5 years (range: 35-76 years).[8]

Health related quality of life

B7. Priority question. The CS reports that no algorithm has been published for mapping directly from the FACT-MM to the EQ-5D-3L, therefore questions from the 27-item FACT-General (FACT-G) questions included in the FACT-MM were used to map FACT-G data to the EQ-5D-3L (with published algorithms using the UK tariff). Can the company please:

1. **Discuss the likelihood that using the FACT-G questions only (as opposed to the FACT-MM) might have misrepresented patients' quality of life.**

2. **Provide the FACT-MM scores (detailed by FACT-MM and FACT-G items) for mean baseline and change from baseline values for each subscale score for the BCLPD Part 2 population in STORM (the EAG notes that similar results are provided in Table 14.2.4.2 of the 2019 TLFs report, however, the EAG could not find a description/explanation for the meaning of each of the 20 CD1 subscales).**

Company response:

1. The FACT-G is a 27-item patient-reported outcome measure designed specifically to collect health-related quality of life outcomes from cancer patients. The measure includes four domains of health-related quality of life: physical wellbeing, social/family wellbeing, emotional wellbeing and functional wellbeing. The FACT-

G is a standalone instrument, supporting comparisons across cancer types, but can also be used alongside bolt-on domains. The FACT-MM includes the 27 items of the FACT-G alongside an additional 14-question subdomain specific to multiple myeloma.

NICE's recommendation, described in the 2022 methods guide, 2020 Task and Finish group report and NICE TSD 11,[10-12] is that patient utilities are estimated where possible from generic preference-based measures to maximise consistency across evaluations, with the EQ-5D-3L as NICE's preferred measure. A trade-off in terms of achieving this consistency is that some aspects specific to each disease may be captured less sensitively than can be achieved by condition-specific measures.

Following the evidence hierarchy implied by NICE's recommendations, utility estimates are derived from the FACT-G since (unlike the FACT-MM) a validated mapping algorithm has been developed allowing for EQ-5D utilities to be estimated. Although the additional 14 items included in the FACT-MM may capture some aspects of disease more sensitively than the base measure, this limitation does not apply to any greater an extent than would be the case were direct EQ-5D measurements to have been collected in the study, as per the NICE reference case.

2. A list of questions included in each domain of the FACT-G and FACT-MM is available online from FACIT.[13] Please note that the total number of items collected in the FACT-MM are 27 (FACT-G) plus 14 (MM-specific); the 'C*n*D*n'* rows of table 14.2.4.2 referred to in the question relate to the cycle and day number at which the measure was administered.

B8. 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).[3] Please update the general population utility values used for age adjustment in the model to use the HSE 2014 dataset.

Company response: Functionality has been added to apply age-related disutilities using Hernández Alava *et al*. 2022 in place of the Ara and Brazier 2010 estimates applied in the company submission.[14,15] Relative to the company submission, applying this modification reduces the ICER by £126 to £27,282.

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.

B9. Priority question. The EAG notes that there are a number of discrepancies between the adverse event disutility values reported in Table 33 of the company submission (Summary of adverse event utility decrements and mean duration) and the values used in the economic model (Sheet "Quality of Life inputs"). Please clarify the correct values and amend the economic model if necessary:

Adverse event	Disutility reported in company submission	Disutility reported in economic model
Asthenia	0.12	0.012
Dyspnoea	0.12	0.012
Infections and infestations	0.14	0.218
Sepsis	0.20	0.218

Company response: Disutility values for asthenia, dyspnoea, infections and infestations, and sepsis are correctly reported in the company submission (values of -0.12, -0.12, -0.14, -0.20 respectively), where asthenia, dyspnoea, and infections and infestations are sourced from NICE TA783 (previously TA510), and the sepsis disutility has been taken from Jakubowiak *et al*. (2016).[16,17]

Thank you for highlighting these discrepancies between the submission and the model. The economic model has been amended to reflect the correct values as above. Relative to the original company model, this increases the base ICER estimate by <£1 to £27,408.

B10. Priority question. The EAG notes that there are a number of discrepancies between the duration of AEs reported in Table 33 of the company submission (reported in weeks) and those values calculated in months in the model (Sheet

"Quality of Life inputs"). Please clarify the correct values and amend the economic model as required:

a. **Asthenia - Company submission reports that duration used is assumed equal to fatigue, however this is not the value used in the model calculation. Asthenia is applied for 22 days whereas fatigue is applied for 14.6 days**
b. **Hyperglycaemia - Company submission reports that duration is 0.57 weeks but calculation in economic model applied for 11.4 days.**
c. **Hypokalaemia and Hyponatramia - Company submission reports that duration is 0.003 weeks but calculation in the economic model applied for 11.4 days.**
d. **Sepsis - Company submission reports that duration is 4 weeks but calculation in the economic model applied for 12 days**

Company response: Thank you for highlighting the discrepancies. The responses for each part of the question are reported below. All lengths of time are stated in days for consistency.

a. The cost effectiveness model has been amended to reflect the assumption reported in the submission that the duration of asthenia is equal to duration of fatigue at 14.6 days.
b. The cost effectiveness model has been amended to reflect the assumption reported in the company submission that the duration of hyperglycaemia is 3.99 days.
c. The duration of hyperkalaemia and hyponatremia are assumed to be equal at 11.4 days, the model is currently correct, and the cost effectiveness results reflect this – the company submission needs to be amended to reflect the correct AE durations.
d. The duration of sepsis is assumed to be 12 days, the model is currently correct and the cost effectiveness results reflect this – the company submission needs to be amended to reflect the correct AE duration

With these discrepancies corrected in the model for part a and b, the ICER result increases by <£1 relative to the original base case (ICER remains at £27,408).

B11. The published study by Hatswell *et al.* (2018) [4] presented a systematic review and meta-regression of health state utilities for multiple myeloma. Please discuss if any of the utility values presented in this study, particularly those for fourth line (classified as receiving four classes of treatment) could be representative of patients who are eligible to receive Sd based on previous treatments received.

Company response: The company response here relates to Hatswell *et al*. (2019), which, reports health state utility values for MM patients by line of therapy, up to the 4L.[18] This study was identified in the economic systematic literature review. Utility values that are directly applicable to a penta-refractory population, i.e., the licensed RRMM population for Sd, are not reported in the publication. The utility values are also not separated by disease progression, therefore assumptions regarding application to progression free and progressed disease health states would need to be considered when applying the 4L utility value.

While not directly corresponding to the penta-refractory population, the 4L utility values presented in the models reported by Hatswell *et al. (2019)* are a useful benchmark to determine face validity for utility values applied in base case cost effectiveness analyses.

Costs and resource use

B12. Priority question. The company used the mean weekly dose of selinexor of 114.4mg in the model to estimate treatment costs (which the company has rounded up to assume a weekly dose of 120 mg in the model). However, the 2019 TLFs reports a wide distribution of the weekly dose used in the trial, [redacted] Therefore, please conduct a scenario analysis in the model where the weekly dose of selinexor is estimated based on the distribution of patients receiving different doses of treatment reported in the 2019 TLFs in order to capture the different cost categories associated with selinexor treatment.

Company response: As determined on the clarification call between the company, EAG and NICE on 7th September 2023, the data referred to in this question relate to

the BCLPD-refractory subgroup column of Table 14.1.3.1 (rather than the mITT population column, from which the values above are derived).

Table 14 shows the distribution of BCLPD-refractory patients across average dose ranges as described in Table 14.1.3.1, with additional columns to show the mean, median, minimum and maximum values within each range. By applying the mean dosage to patients in each range, the weighted mean dose across patients is 114.41mg/week. Rounding this figure up to the nearest 20mg (in keeping with the company submission) as a conservative approach, this equates to 120mg/week and therefore does not change cost-effectiveness results relative to the company base case.

Table 14: [redacted]

Average selinexor dose received per week (mg/ week)	N	%	Mean	Median	Minimum	Maximum
[redacted]						

Source: Menarini Stemline Data on file[4]

B13. Priority question. The EAG's clinical experts advised that about 65% of patients receiving BSC in the UK would receive conventional chemotherapy (instead of the 20% assumed in the company's base case). Therefore, can the company please:

1. **Conduct a scenario analysis where 65% of BSC patients in the model receive chemotherapy and 65% of Sd patients in the model receive chemotherapy as a subsequent treatment after selinexor+dex;**
2. **Using the treatment effectiveness results requested in Question B1 to estimate the effectiveness of BSC, conduct a scenario analysis on the estimated treatment costs where 65% of BSC patients in the model receive chemotherapy and 65% of Sd patients in the model receive chemotherapy as a subsequent treatment after selinexor+dex.**

Company response:

1. The cost-effectiveness analysis has been updated to incorporate a revised assumption that 65% of BSC patients receive chemotherapy, and 65% of Sd patients receive chemotherapy as a subsequent treatment. Relative to the original company base case, the ICER result decreases by £30 to £27,378.
2. As determined on the clarification call between the company, EAG and NICE on 7th September 2023, this question relates to analyses of Gill *et al* 2022[2] referred to in Question B2 (rather than B1). As discussed in responses to questions A8 and B2, the Gill study is not considered a suitable proxy comparator and therefore has not been used as a source for comparative model estimates.

B14. Priority question. The EAG's clinical experts noted that both cyclophosphamide and melphalan are given as conventional chemotherapy as part of BSC in the UK. Please include a scenario in the model where the treatments making up the conventional chemotherapy in the BSC arm are a mix of melphalan and cyclophosphamide (or alternatively justify that due to cost similarity this would not have an impact on the model results).

Company response: The suggested dose of 0.15mg per kg bodyweight for melphalan would equate to a 12mg dose based on the STORM baseline population (weight 78.4kg) and rounded up to the nearest tablet. Assuming that this is prescribed for the first 4 days of a 6-week cycle, this would equate to an average weekly dose of 8mg (4x2mg tablet) per week across the period received. Given the low cost of melphalan as a generic medicine (£17.12 per 25x2mg tablets, from eMIT 2022),[19] this would not be expected to substantially influence results.

B15. Priority question. The EAG's clinical experts stated that the resource used associated with routine monitoring used in the company submission was not reflective of clinical practice. It was stated that:

- **All patients on active treatment (including chemotherapy) would be seen once a month by a physician. This physician visit would include complete blood, blood chemistry, protein electrophoresis and immunoglobulin.**
- **Patients not on active treatment (PFS or PD) would instead be seen every other month and have the same tests as above.**
- **Serum light chain excretion is standard of care rather than urinary light chain excretion.**

Therefore, can the company please:

a. **Conduct a scenario analysis which uses the resource use assumptions (monthly use) for routine monitoring, shown in the table below, for PFS and PD.**

b. **Implement a scenario in which the updated resource use for PFS is instead applied for all patients "on active treatment" and the PD resource use is instead applied to all patients "not on active treatment". Please note that patients on conventional chemotherapy after Sd should incur the "on active treatment" costs in the model.**

	Monthly use	
Resource	**PFS**	**PD**
Physician visit	1.000	0.500
Complete blood count test	1.000	0.500
Blood chemistry	1.000	0.500
Protein electrophoresis	1.000	0.500
Immunoglobulin	1.000	0.500
Serum light chain excretion	0.217	0.390

Company response:

a. Resource use estimates in the company submission were aligned with those assumed in previous MM NICE submissions.[20-22] A scenario analysis has been applied using the monthly healthcare resource use estimates described in the table above. Replacing urinary light chain excretion has with serum light chain excretion, the same unit cost (£8.53) is applied, based on an assumption that the 2021/22 NHS reference cost for directly accessed pathology services (microbiology DAPS07) remains the most appropriate unit cost source. Updating resource use as per part a. increases the ICER by £6,106.26 relative to the base case, to an ICER of £33,514.

b. A scenario has also been considered that applies resource usage on the basis of treatment status, such that resource estimates labelled 'PD' in the table above are applied to patients that are off-treatment rather than with progressed disease. Updating resource use as per part b. decreased the ICER by £3 relative to the base

case, to an ICER of £27,405. Combining the results of part a. and part b. together increases the ICER by £6,096 relative to the base case, to an ICER of £33,504.

B16. Priority question. Please clarify why costs associated with adverse events were taken from the NHS Reference Costs 2020/21 and inflated to 2022 prices using the HCHS pay and prices index, rather than using NHS Reference Costs 2021/22.

Please provide an updated analysis using the most recent NHS Reference Costs for adverse events. In addition, when providing these updated costs, please clarify the exact unit costs description used for each adverse event costs. For example, do the NHS codes refer to total HRG costs, elective inpatient, day case, etc.

Company Response: An updated analysis has been performed using the adverse event costs below, taken from the most recent NHS reference costs (Table 15). Updating adverse event costs as per the table below increases the ICER by £2,101.26 relative to the base case, resulting in an ICER of £29,509.

Table 15: Adverse event unit costs and codes

Adverse event	Unit cost	Source	Code
Anaemia	£1,214	Total HRGs sheet	SA04G, SA04H, SA04J, SA04K, SA04L
Asthenia	£764	Non-elective short stay	SA01G, SA01H, SA01J, SA01K
Back pain	£1,413	Total HRGs sheet	HC32H, HC32J, HC32K
Bone pain	£1,360	Total HRGs sheet	WH08A, WH08B
Decreased appetite	£4,466	Total HRGs sheet	FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10F, FD10G, FD10H, FD10J, FD10K, FD10L, FD10M
Dehydration	£2,230	Total HRGs sheet	KC05G, KC05H, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N
Diarrhoea	£2,211	Total HRGs sheet	FD10J, FD10K, FD10L, FD10M
Dyspnoea	£764	Non-elective short stay	SA01G, SA01H, SA01J, SA01K
Fatigue	£764	Non-elective short stay	SA01G, SA01H, SA01J, SA01K
Hyperglycaemia	£1,469	Total HRGs sheet	KB02G, KB02H, KB02J, KB02K
Hypokalaemia	£1,292	Total HRGs sheet	KC05J, KC05K, KC05L, KC05M, KC05N
Hyponatraemia	£1,292	Total HRGs sheet	KC05J, KC05K, KC05L, KC05M, KC05N
Infections and infestations	£4,142	Non-elective long stay	WH07D
Leukopenia	£1,372	Total HRGs sheet	SA08G, SA08H, SA08J

Adverse event	Unit cost	Source	Code
Lymphopenia	£1,372	Total HRGs sheet	SA08G, SA08H, SA08J
Nausea	£4,466	Total HRGs sheet	FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10F, FD10G, FD10H, FD10J, FD10K, FD10L, FD10M
Neutropenia	£1,372	Total HRGs sheet	SA08G, SA08H, SA08J
Pneumonia	£5,857	Non-elective long stay	DZ11K-DZ11V
Sepsis	£4,407	Non-elective long stay	WH07D
Thrombocytopenia	£1,122	Total HRGs sheet	SA12G, SA12H, SA12J, SA12K
Vision blurred	£1,407	Total HRGs sheet	EB08A, EB08B, EB08C, EB08D, EB08D, EB08E

B17. No administration costs are assumed to apply for patients receiving chemotherapy as a component of BSC or subsequent treatment due to cyclophosphamide being most commonly used in its oral form. NHS reference costs provide a unit cost for delivering oral chemotherapy (Currency code SB11Z). Please clarify why this cost was not included and provide a scenario analysis with this cost included in the BSC arm as a comparator and as a subsequent treatment in the model.

Company response: Administration costs were not applied to oral therapies, aligning with the assumption with those applied in previous myeloma submissions (e.g., TA587).[23] Applying an administration cost of £217 per cycle for oral therapies (corresponding to NHS cost code SB11Z, NHS reference costs 2022), the ICER estimate increases by £651 to £28,059 relative to the company base case.

B18. Priority question. Clinical experts to the EAG suggested that the dose used in clinical practice for cyclophosphamide would be 500mg once weekly. This dose has also been used in previous technology appraisals for multiple myeloma (ID2701 and TA338). Please confirm if the dose used in the economic model (200mg daily) has therefore overestimated the dose used in UK clinical practice.

1. **Please provide a scenario analysis in the model where the 500mg once weekly dose is used for cyclophosphamide as a BSC and a subsequent treatment.**

Company response: The model has been updated to include a scenario using the suggested dosing schedule for cyclophosphamide administered as BSC and as a subsequent treatment. This increases the ICER by £30 relative to the company base case, resulting in an ICER of £27,438.

B19. Table 39 of the company submission (Health state resource use and cost assumptions) states that:

a. the source for the unit cost of complete full blood count is "Chemotherapy (Consultant led) Services Code 303: Clinical Haematology". However, the cost used in the model does not match this code.
b. the source for all remaining tests was "DAPS05 - Haematology", despite these having different unit costs.

Please clarify if these sources have been incorrectly referenced. If so, please provide an updated table which details the specific NHS Reference Costs currency code and currency description used for each resource stated in Table 39.

Company response: An updated table with correct NHS reference costs currency codes, descriptions, costs, and weekly resource use is provided below (Table 16).

Table 16 Updated healthcare resource use and costs

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 - DAPS04	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

Resource description	Unit cost	NHS reference cost code	Weekly resource use (units): progression-free[a]	Weekly resource use (units): progressed[b]
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, TA427

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

B20. Table 38 of the company submission (Section B 3.5.2) states that the cost of cyclophosphamide, reported as £52.46, is sourced from BNF. The BNF price for cyclophosphamide (50mg tablets/ Packsize 100) is £139. An eMIT price is available for cyclophosphamide (50mg tablets/ Packsize 100 [£52.65]). Please clarify the exact source used for cyclophosphamide and update as required.

Company response: The model has been updated with a cyclophosphamide unit cost of £52.65, sourced from eMIT 2022.[24] This increases the ICER by <£1 relative to the base case ICER.

B21. A 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.[24] This decreases the ICER by £16 relative to the base case ICER, resulting in an ICER of £27,392.

B22. 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.[25] The cost and resource use component of the economic SLR did not identify any more recent, appropriate end of life care costs in MM.

B23. The CS states that all patients receiving selinexor require 5-hydroxytryptamine (5-HT3) antagonists (ondansetron 8mg or equivalent) prior to the first dose of Sd 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. Nonetheless, the 2019 TLFs report shows that only [redacted] of BCLPD Part 2 patients received ondansetron before treatment, with [redacted] of patients receiving it concomitantly with selinexor. Therefore, can the company please:

a) Confirm if STORM 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").*[2]

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-HT_3 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.

B24. Table 42 in the CS is labelled as "*Resource costs associated with disease progression*" however, these costs are applied as one-off costs to progression-free patients (i.e., all patients) in both arms of the model (therefore, cancelling out in the model results). Please clarify if these costs are intended to be applied to patients experiencing disease progression, and if that is the case please apply these accordingly in the model.

Company response: The one-off costs referred to are intended to account for transfusion-related resources (G-CSF, red blood cell transfusions and platelet transfusions) which may be required in some patients. These are applied at model initiation rather than aligned to any modelled event. As such, labelling in Table 42

should read as “Additional one-off resource costs associated with disease” rather than referring to disease progression specifically.

Additional clarification questions [received 4 Sept 2023]

B25. Please clarify whether the compliance rate observed in the clinical trial resulted in fewer packs of Selinexor being prescribed? Please also comment on how Selinexor would be prescribed in usual practice; i.e. would it be prescribed as needed (when the patient has run out) or according to a fixed prescribing schedule?

Company response: Selinexor tablets are prescribed to patients as needed. There is only one strength of selinexor tablet, which is 20mg. Dose adjustment is made by changing the number of tablets that a patient would need to take each day. Therefore, patients continue with the same strength tablet irrespective of dose.

B26. Table 54 of the company submission provides the results of scenario analyses conducted by the company, with a severity modifier of 1.7 applied in each scenario. Please provide an updated table with the ICERs presented without a severity modifier applied. In addition, in an additional column in the table please clarify if each scenario qualifies for the severity modifier to be applied based on the scenario analysis results.

Company response: An updated model version (v1.1), provided alongside this response document, includes additional columns in the scenario sheet detailing the modifier applicable to each scenario, and ICER results for each scenario with and without the relevant modifier applied. Scenarios may be run according to the original company submission or using the revised inputs addressed in this response. A version of Table 54 provided in the company submission, including ICER results both with and without modifiers, is provided below. Please note that results in the table below correspond to the original company base case rather than the updated estimates outlined in this report.

Table 17: ICER results both with and without modifiers

Scenario dimension	Scenario	Incremental costs	Incremental QALYs (no modifier)	Modifier applicable to scenario	ICER with modifier (£/mQALY)	ICER without modifier (£/QALY)
BASE CASE	**Not applicable**	**£18,435**	**0.40**	**1.7**	**£27,408**	**£46,593**
Time horizon	10 years	£18,292	0.36	1.7	£29,989	£50,980
PFS source	Investigator assessment	£18,439	0.40	1.7	£27,404	£46,588
PFS hazard ratio	Same as OS	£18,638	0.40	1.7	£27,302	£46,413
PFS extrapolation	Parametric: Weibull	£18,366	0.40	1.7	£27,308	£46,424
	Parametric: Exponential	£18,427	0.40	1.7	£27,400	£46,579
	Parametric: Gen. Gamma	£18,435	0.40	1.7	£27,407	£46,592
	Parametric: Log Logistic	£18,436	0.40	1.7	£27,409	£46,596
	Parametric: Gompertz	£18,380	0.40	1.7	£27,329	£46,460
	Parametric: Gamma	£18,412	0.39	1.7	£27,375	£46,538
OS hazard ratio source	MAMMOTH MAIC (full)	£18,272	0.32	1.7	£34,100	£57,970
	MAMMOTH MAIC (must have)	£18,132	0.25	1.7	£43,296	£73,603
OS extrapolation	Parametric: Weibull	£18,146	0.24	1.7	£45,253	£76,929
	Parametric: Exponential	£18,121	0.23	1.7	£47,201	£80,241
	Parametric: Gen. Gamma	£18,840	0.60	1.7	£18,560	£31,552
	Parametric: Log Logistic	£18,555	0.45	1.7	£24,426	£41,525
	Parametric: Gompertz	£19,185	0.74	1.7	£15,225	£25,882
	Parametric: Gamma	£18,118	0.22	1.7	£47,449	£80,663

Scenario dimension	Scenario	Incremental costs	Incremental QALYs (no modifier)	Modifier applicable to scenario	ICER with modifier (£/mQALY)	ICER without modifier (£/QALY)
ToT assumption for comparators	Treated to progression (PFS)	£26,561	0.40	1.7	£39,487	£67,128
ToT extrapolation	Parametric: Weibull	£18,421	0.40	1.7	£27,386	£46,556
	Parametric: Gen. Gamma	£18,402	0.40	1.7	£27,358	£46,509
	Parametric: Log Normal	£20,118	0.40	1.7	£29,909	£50,846
	Parametric: Log Logistic	£20,722	0.40	1.7	£30,807	£52,372
	Parametric: Gompertz	£18,421	0.40	1.7	£27,387	£46,557
	Parametric: Gamma	£18,407	0.39	1.7	£27,365	£46,521
Comparator AE source	Auner *et al.* (2022)	£18,237	0.40	1.7	£27,111	£46,089
	MAMMOTH	£17,860	0.40	1.7	£26,549	£45,132
Adverse event application	Per cycle	£19,974	0.40	1.7	£29,712	£50,511
Discounting	No benefit discounting	£18,435	0.45	1.7	£23,919	£40,663
	No cost discounting	£18,691	0.40	1.7	£27,788	£47,240
	No discounting (cost or benefit)	£18,691	0.45	1.7	£24,251	£41,227
	6% discounting	£18,297	0.37	1.7	£29,476	£50,110
Selinexor weekly dosage	Full (160mg)	£23,275	0.40	1.7	£34,602	£58,823
Chemotherapy use as part of BSC	100%	£18,400	0.40	1.7	£27,354	£46,502

Scenario dimension	Scenario	Incremental costs	Incremental QALYs (no modifier)	Modifier applicable to scenario	ICER with modifier (£/mQALY)	ICER without modifier (£/QALY)
Health state utilities	PFS: STORM absolute value PD: TA658 relative decrement	£18,435	0.37	1.7	£29,254	£49,732
	PFS: STORM absolute value PD: STORM absolute value	£18,435	0.44	1.7	£24,897	£42,325
	PFS: DREAMM2 absolute value PD: DREAMM2 absolute value	£18,435	0.49	1.7	£22,095	£37,561
	PFS: TA658 absolute value PD: TA658 absolute value	£18,435	0.45	1.7	£24,010	£40,817

Abbreviations: AE, adverse event; BSC, best supportive care; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; mg, milligrams; mQALY, modified quality-adjusted life year; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year; Sd, selinexor plus dexamethasone; TA, technology appraisal; ToT, time on treatment

Section C: Textual clarification and additional points

C1. Table 36 of the company submission (Section B 3.5.2) states that the cost of dexamethasone is sourced from eMIT whereas Table 38 states it is sourced from BNF 2022. Please clarify which source was used for unit costs for dexamethasone?

Company response: Thank you for highlighting this discrepancy. Dexamethasone costs applied in the economic model are sourced from eMIT 2022 (£2.46 per 50x2mg tablet pack) as described correctly in Table 36.21 Table 38 of the submission should also cite eMIT 2022 as the data source.

C2. Please clarify if the PFS and OS data presented in Tables 6, 7 and 8 of the CS Document B relate to the updated analysis (data cut-off: 7th September 2019) of the STORM Part 2: BCLPD-refractory population. If not, please provide equivalent Kaplan-Meir curves for the updated analysis for all three outcomes (PFS by IRC and INV assessment, and OS).

Company response: It was confirmed in the clarification call with NICE and the EAG that this question relates to with Tables 12, 13, and 14 of the CS. Figures 6, 7, 8 and 9 (coordinating with Tables 12, 13, and 14) presented in the CS relate to the updated analysis of the STORM trial, data cut-off 7th September 2019.

REFERENCES

1. Medicines and Healthcare products Regulatory Agency (MHRA). *Public Assessment Report: Nexpovio 20mg*. 2021. 26 May 2021. https://mhraproducts4853.blob.core.windows.net/docs/ed27f53b3b5404611d1940fb4bc2a7a649b1237d
2. Medicines and Healthcare products Regulatory Agency (MHRA). *Summary of Product Characteristics: Nexpovio*. 2023. 2 February 2023.
3. Karyopharm Therapeutics Inc. *Clinical Study Report (KCP-330-012; Data cut-off 7 September 2019)*. 2019.
4. Menarini Stemline. *Data on file*. 2023.
5. Gill SK, Unawane R, Wang S, et al. Inferior outcomes of patients with quad and penta-refractory multiple myeloma (MM) compared to those of patients who have been quad and penta exposed. *Blood*. 2021;138(SUPPL 1):4742.
6. Gill SK, Unawane R, Wang S, et al. I-OPen: inferior outcomes of penta-refractory compared to penta-exposed multiple myeloma patients. *Blood Cancer J*. Sep 23 2022;12(9):138. doi:10.1038/s41408-022-00733-2
7. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. Feb 1 2012;12:9. doi:10.1186/1471-2288-12-9
8. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;33(9):2266-2275.
9. 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
10. National Institute for Health and Care Excellence (NICE). PMG36: NICE health technology evaluations: the manual. Updated 31 January. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation
11. Brazier J, Rowen D. NICE DSU TSD 11: Alternatives to EQ-5D for generating health state utility values. TSd 11. National Institute for Health and Care Excellence; 2011:31. March 2011. http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD11-Alternatives-to-EQ-5D_final.pdf
12. National Institute for Health and Care Excellence (NICE). *CHTE methods review: Health-related quality of life (Task and finish group report)*. 2020.
13. FACIT.org. FACT-MM (Version 4). Accessed September 2023, https://www.facit.org/_files/ugd/626819_b33daf602f3c45feb203ff1a467a507b.pdf
14. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2010;13(5):509-18. doi:10.1111/j.1524-4733.2010.00700.x
15. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *PharmacoEconomics*. 2022/11/30 2022;doi:10.1007/s40273-022-01218-7
16. Jakubowiak AJ, Campioni M, Benedict A, et al. Cost-effectiveness of adding carfilzomib to lenalidomide and dexamethasone in relapsed multiple myeloma

from a US perspective. *J Med Econ*. Nov 2016;19(11):1061-1074. doi:10.1080/13696998.2016.1194278
17. National Institute for Health and Care Excellence (NICE). TA783: Daratumumab monotherapy for treating relapsed and refractory multiple myeloma.
18. Hatswell AJ, Burns D, Baio G, Wadelin F. Frequentist and Bayesian meta-regression of health state utilities for multiple myeloma incorporating systematic review and analysis of individual patient data. *Health Economics (United Kingdom)*. 2019;28(5):653-665.
19. EMC. Melphalan 2mg tablets Accessed September 2023, https://www.medicines.org.uk/emc/product/3806/pil#about-medicine
20. National Institute for Health and Care Excellence (NICE). TA658: Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma. https://www.nice.org.uk/guidance/ta658/history
21. National Institute for Health and Care Excellence (NICE). TA870: Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. https://www.nice.org.uk/guidance/ta870
22. National Institute for Health and Care Excellence (NICE). TA897: Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma. https://www.nice.org.uk/guidance/ta897
23. National Institute for Health and Care Excellence (NICE). TA587: Lenalidomide plus dexamethasone for previously untreated multiple myeloma. https://www.nice.org.uk/guidance/ta587
24. Gov.UK. Drugs and pharmaceutical electronic market information tool (eMIT ; 2022 data).
25. Round J, Jones, L. and Morris, S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. *Palliative Medicine*. 2015;29(10):899-907.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after four or more treatments [ID6193]

Additional clarification questions company response

22 September 2023

File name	Version	Contains confidential information	Date
ID6193 Sel+dex rrMM EAG additional clarification questions 22.09.23 [CiC]	V3	Yes	25th January 2024

1) The EAG would like to thank the company for their additional work on the STC. The EAG is, however, concerned that the company were unable to assess the assumptions of the fitted outcome regression models, and did not provide any other validation. The EAG is concerned that the results of the regression models: i) are highly uncertain, and ii) potentially clinically implausible. For example, the EAG notes that:
   a) The 95% confidence interval around the estimated meanlog is 4.33 (95% CI: 1.42 to 7.46). It is unclear to the EAG whether or how this uncertainty around the lognormal survival distribution parameters are propagated through to the final HRs;
   b) The clinical plausibility of the coefficients from the outcome regression is unclear. For example, the point estimate of the coefficient associated with R-ISS Stage 3 is closer to 0 than the R-ISS Stage 2 coefficient;
   c) The magnitude of the effect estimate for sex is around 150% of the magnitude of the effect for high risk cytogenetics.

   The EAG recognises that the estimated coefficients are conditional estimates, but considers it necessary to assess the clinical plausibility of the each of the effect estimates to assess whether applying this regression model in the STC is likely to produce valid results - for instance by justifying the unexpected relationship observed between the R-ISS point estimates. If the outcome regression provides clinically implausible predictions between, e.g., R-ISS 2 and R-ISS 3 patients, then it is likely unsuitable to conduct an STC using this model. Please:
   a) Comment on whether and how the uncertainty in the meanlog and sdlog from the outcome regression propagates through the STC;
   b) Comment on the clinical plausibility of each of the effect estimates from the outcome regression model;
   c) Comment on the appropriateness of applying results from an STC where it is “not possible to evaluate the assumptions of each survival model for each combination of stratums”;
   d) Confirm the factor levels for SEX, HCRN and STEMCT, e.g., what 1 and 0 correspond to in Tables 7 through 11 in the clarification response;
   e) Explain how missing demographic data were handled in the MAMMOTH AgD, e.g., the 7.1% missing cytogenetic risk scores and 22.9% NA for ISS at diagnosis. Please outline any assumptions that follow from how the missing data were handled.[1]

Company Response: In the context of performing population-adjusted indirect treatment comparisons (ITC) with individual patient-level data (IPD) available for only one study under investigation, the current ITC methodology includes matching-adjusted indirect comparisons (MAIC) or simulated treatment comparisons (STC). The MAIC yielded very low effective

sample size (ESS) in this case and therefore the STC was conducted as an alternative approach to obtain the estimate for the treatment effect, which was considered preferable to a naïve comparison, due to the observed differences in baseline characteristics between the STORM trial and the comparator trials.

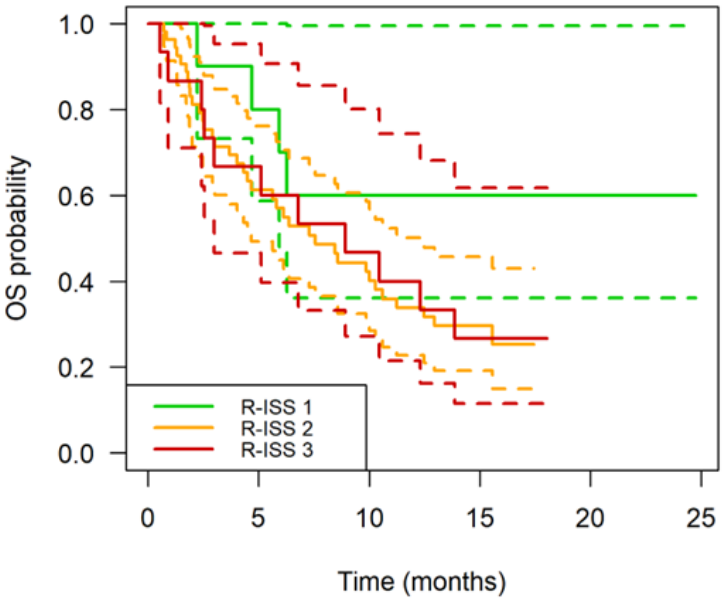
The point estimates of the coefficients from the fitted outcome regression model in the STC are reflective of trends observed in the STORM trial data (see response to question (b) below). Given the wide 95% confidence interval (CI) associated with the estimated model coefficients, the fitted model from STC is not suggesting any statistically significant association between the included covariates and outcome. The large uncertainty associated with the coefficients is reflective of the small size of the BCLPD-refractory population from the STORM trial as well as the inclusion of a large set of covariates in the regression model. To correctly propagate this uncertainty in the estimated relative treatment effect, bootstrapping was applied to obtain the final hazard ratio (HR) and its standard error (SE).

a. The point estimate and the CI of the coefficients from the fitted model were not directly used to derive the final HR. The uncertainty associated with the fitted outcome regression model are dealt with using non-parametric bootstrapping. The SE of the final HR was obtained based on bootstrapping of 2,000 samples of the STORM data. The steps are described as follows: (1) Outcome regression step: A lognormal distribution was fitted to each of the 2,000 samples. (2) Prediction step: Survival probabilities were predicted based on each of the 2,000 fitted lognormal distribution. (3) Obtaining the relative treatment effect: A HR was derived for each of the fitted lognormal distributions. Hence, in total, 2,000 bootstrapped HRs were obtained. The SE was calculated based on the 2,000 bootstrapped HRs. In summary, bootstrapping of 2,000 samples of the STORM data has taken into account of uncertainty in the fitted outcome regression model. Uncertainty from the lognormal distribution has been propagated through the final HR using bootstrapping methods.

b. The estimated model coefficients are reflective of the STORM data. For example, patients with R-ISS Stage 3 show slightly improved overall survival (OS) compared to R-ISS Stage 2, which would explain why the point estimate of the coefficient associated with R-ISS 3 is closer to 0 than the R-ISS 2 coefficient (see Figure 1). The company notes that these effects are not statistically significant in the regression model (also reflected by the overlap of 95% CI from the Kaplan-Meier [KM] curves). As the STORM trial is not designed or powered to show subgroup effects, trends observed (-0.73 for R-ISS 3 *vs*. -0.79 for R-ISS 2) may be due to chance. As explained in the

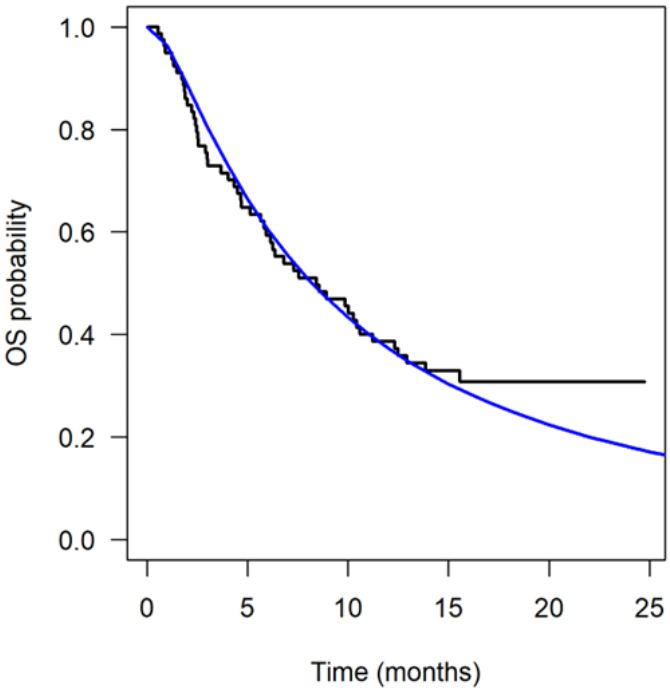
response to part (a), the STORM data were bootstrapped 2,000 times and this trend is not always observed in the bootstrapped samples, which correctly reflects the uncertainty associated with the effects of R-ISS and the effects not being statistically significant. When assessing OS based on cytogenetic risk, there is minimal difference between the two groups, which could explain why the point estimate of the coefficient for sex (for example) in the regression model is larger than coefficient for cytogenetic risk. However, these effects are not statistically significant in the regression model.

Figure 1: OS by R-ISS in the STORM BCLPD population



c. As the shape of the hazard function cannot be assessed robustly for each combination of stratums due to the sparse nature of the data, alternative validations of the base case model (lognormal) were evaluated based on the statistical goodness-of-fit (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]), as well as visual assessment of the fitted model against KM data. The lognormal model fitted to the STORM data fits the observed OS KM curve well, as shown in Figure 2. This is based on lognormal parameter estimates presented in the clarification response document.

Figure 2: OS Kaplan-Meier curve from the STORM BCLPD population with overlaid lognormal model



d. The factor levels for SEX, HCRN and STEMCT are summarised in Table 1.

Table 1: Summary of factor levels

Factor	Name	Levels
Sex	SEX	0: Female 1: Male
High cytogenetic risk	HCRN	0: No 1: Yes
Receipt of stem cell transplant	STEMCT	0: No 1: Yes

e. Missing demographic data for ISS were excluded from the MAMMOTH AgD prior to calculating the percentages of patients with ISS 1, ISS 2 and ISS 3. This is equivalent to complete case analysis assuming missing completely at random. However, for cytogenetic risk, no recalculation was made based on missing values because a small percentage were missing (<10%). This is equivalent to assuming that all the missing patients belong to the reference category. Applying the complete case analysis approach made no change to the estimated HR.

2) The company states in the submission and in the clarification response that the STC uses the "Must have + Nice to have" set of factors. However, in the code, the outcome regression is fit using the following predictors:

AGE+SEXN+HCRN+REGIMN+STEMCT+RISSN+IDIAGYR+DURMM

This is missing ECOG performance status, creatinine clearance at baseline and haemoglobin at baseline.

a. Please provide a table detailing the exact covariates adjusted for in the STC, and the rationale for not including others from the "Must have + Nice to have" set of factors.

Company response: MAMMOTH did not report ECOG performance status nor haemoglobin at baseline. However, creatinine clearance was reported at diagnosis and at the start of the index regimen, but the latter was reported in different units (mg/dL) compared to how this factor was measured in the STORM trial (mL/min/1.73m^2). Therefore, these three factors were not included in the STC.

A summary of the 'Must have + Nice to have' factors reported by each of the comparator studies is presented in Table 2, which have been included in the STC analyses.

Table 2: Summary of factors reported by each comparator study

Set of factors – 'Must have + Nice to have'	MAMMOTH
Age	✓
Sex	✓
ECOG performance status	×
R-ISS	✓
High cytogenetic risk	✓
No. prior regimens	✓
Prior SCT	✓
Duration of last therapy	✓
Time since initial diagnosis	✓
Creatinine clearance at baseline	× (reported using different units)
Haemoglobin at baseline	×

Abbreviations: ECOG, Eastern Cooperative Oncology Group; No., number; R-ISS, Revised International Staging System; SCT, stem cell transplant.

3) Due to the potential concerns highlighted above with the company's STC and the inability of the STC to appropriately account for the initial overlapping of KM curves (depicted in the naive comparison of the OS KM curves and exacerbated in the MAIC-adjusted curves), the EAG prefers to use the results of the MAIC in the economic analysis. Please can the company fit independent curves to the OS results of the fully adjusted MAIC for the BCLPD subpopulation of STORM 2 versus MAMMOTH. The EAG appreciates that this entails fitting survival curves to the MAMMOTH digitised OS KM data and the MAIC-adjusted STORM 2 OS data, as opposed to estimating a hazard ratio. The EAG considers a "hazard ratio-based approach" to be inappropriate in the presence of initially overlapping KM curves followed by a subsequent change in hazards.

Please note that the EAG considers this may require the use of more flexible survival curves than the standard parametric curves. Please see NICE DSU TSD 21.

Company Response: The company is concerned that the EAG's suggested approach is based on the unsuitable MAIC analysis which is associated with a very low effective sample size (ESS) (<13% of the BCLPD-refractory population) and only adjusts for a limited number of covariates (fewer than included in the STC). Based on the differences observed in the baseline characteristics between the STORM trial and the comparator trial, it was also deemed that the STC adjustment was aligned with clinical expectation, but not the MAIC adjustment. For example, from an assessment of the baseline characteristics, the MAMMOTH population looks to be relatively healthier cohort than the STORM BCLPD-refractory population and therefore after adjustment, a downwards shift in the HR estimate would be expected (compared to the naïve comparison); the MAIC analyses presented do not reflect this.

Updated response 22nd November 2023

The company acknowledge the EAG request to provide independently fitted curves to the MAIC-adjusted OS KM curve for Sd, as per EAG's proposed approach, considering the overlapping of the KM curves for the first 7 months followed by a potential subsequent change in hazards when using the MAIC-adjusted curves, as noted at page 77 of EAG report.

Firstly, the company reiterates that the EAG's approach is based on an unsuitable MAIC analysis that excludes some key prognostic factors and treatment effect modifiers identified by the EAG, such as prior SCT and duration of last therapy. This MAIC is associated with a very low effective sample size (ESS) (N = 10, corresponding to < 13% of the initial BCLPD-refractory population), which would generate very uncertain and unrobust statistical results.

Secondly, the company believes that using the adjusted OS KM curve for Sd, after matching the BCLPD-refractory patients to the MAMMOTH population, would move the Sd population even further away from the population expected in the UK. This is mainly because the EAG raised concerns that patients included in the MAMMOTH study would differ from the population expected in the UK clinical practice.

Moreover, the company does not agree that the pattern of 'overlapping KM curves followed by a subsequent change in hazards' noted in page 77 is more likely a consequence of the low ESS associated with the MAIC analysis rather than being aligned with clinical evidence to suggest that a treatment effect would emerge only after several months have passed.

Although the company does not agree with the robustness of the suggested approach for the reasons listed above, functionality to explore the use of curves fitted independently to MAIC-adjusted STORM data and to digitised MAMMOTH curves have been added for transparency. Standard parametric models were fitted to both KM curves and AIC and BIC, as well as survival estimates at 3 years, and are reported in Table 1 below. Please note that the company does not believe that advanced survival modelling (e.g. spline models or piecewise models) could be robustly implemented given the extremely low ESS and the lack of clarity around the time at which the knot for spline models and the KM cut-off for the piecewise models should be located.

Table 1 – AIC and BIC and survival estimates at 3 years

	STORM (MAIC adjusted)			**MAMMOTH (unadjusted)**		
	AIC	**BIC**	**Survival at 3 years**	**AIC**	**BIC**	**Survival at 3 years**
Exponential	66.8	71.5	7.15%	424.1	428.6	0.93%
Weibull	65.5	67.9	12.53%	427.3	429.6	0.18%
Gompertz	63.5	68.3	35.28%	425.2	429.7	0.03%
Log-logistic	64.8	69.6	14.73%	430.0	434.5	3.14%
Log-normal	64.1	68.9	15.08%	431.8	436.3	2.49%
Generalised Gamma	61.3	68.5	25.89%	425.9	432.6	0.30%
Gamma	67.2	71.9	10.15%	423.9	428.4	0.32%

For the MAMMOTH KM curve, considering the 3-year survival estimate of 0.87% assumed in the company base case, all the parametric curves generated similar estimates, except for the log-normal and log-logistic distribution which led to unrealistic results. An exponential curve fitted to MAMMOTH is selected as it has the lowest AIC and BIC and provides the closest 3-year survival estimate (0.93%) to the 0.87% estimate assumed in the company base case. A lognormal distribution is considered the best fitting curve to the adjusted OS KM curve for Sd, based on the AIC and BIC and clinical plausibility. Using these two independent curves for each treatment yields a ICER estimate broadly in line with the company submission (£23,133).

4) Please can the company provide further explanation of why they were unable to match the BCLPD subpopulation of STORM 2 versus MAMMOTH for the "Must have + Nice to have" MAIC (Table 15 of CS Document B).

Company Response: The result of the matching process for the "Must have + Nice to have" MAIC led to an ESS equal to 0, i.e., the BCLPD-refractory subpopulation of STORM Part 2 could not be matched to the MAMMOTH population. Compared to the "Full" MAIC where the populations were matched against six factors resulting in an ESS of 10.4 patients, adding prior SCT and duration of last therapy to the list of matching factors made the re-weighting of the BCLPD-refractory subpopulation of STORM Part 2, impossible (

Table 4). However, considering all the eight factors of the "Must have + Nice to have" model in the STC is still a viable option. The STC uses an outcome regression model to compute the treatment effect in a simulated sample, where the mean patient characteristics mirror those in the MAMMOTH population to predict the outcomes that would have been observed in the BCLPD-refractory subpopulation of STORM Part 2.

Table 3: Summary of factors reported by each comparator study

Set of factors	Must have	Full	Must have + Nice to have
Age	✓	✓	✓
Sex	✓	✓	✓
ECOG performance status	×	×	×
R-ISS		✓	✓
High cytogenetic risk	✓	✓	✓
No. prior regimens	✓	✓	✓

Prior SCT	✓		✓
Duration of last therapy			✓
Time since initial diagnosis		✓	✓
Creatinine clearance at baseline	× (reported using different units)	× (reported using different units)	× (reported using different units)
Haemoglobin at baseline	×	×	×
ESS	13.5	10.4	0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; No., number; R-ISS, Revised International Staging System; SCT, stem cell transplant.

5) The EAG notes that adverse events from STORM Part 2 were used in the economic model. Please provide:

   a) the equivalent of Table 3 (TRAEs ≥ Grade 3 in STORM Part 1 and Part 2 combined, and BCLPD-refractory population) from the response to clarification questions for the STORM Part 2 population;

Company Response:

Table 4 presents a summary of TRAEs ≥Grade 3, occurring in ≥5% of participants in any analysis set. Results are consistent between the Part 1 and Part 2 mITT (n=202), Part 2 mITT (n=123), and the BCLPD-refractory population (n=83), analysis sets.

Table 4 TRAEs ≥ Grade 3 in STORM Part 1 and Part 2 combined, Part 2 only, and in the Part 2 BCLPD-refractory population

	STORM Part 1 & 2 BCLPD-refractory	**STORM Part 2 BCLPD-refractory**	**STORM Part 2**
	n=202	[redacted]	[redacted]
	Updated analysis: 7th September 2019		
Patients with ≥1 TRAE Grade 3+	180 (89.1)	[redacted]	[redacted]
Blood and lymphatic system disorders:	143 (70.8)	[redacted]	[redacted]
Thrombocytopenia	119 (58.9)	[redacted]	[redacted]
Anaemia	63 (31.2)	[redacted]	[redacted]
Neutropenia	40 (19.8)	[redacted]	[redacted]

	STORM Part 1 & 2 BCLPD-refractory	STORM Part 2 BCLPD-refractory	STORM Part 2
	n=202	[redacted]	[redacted]
	Updated analysis: 7th September 2019		
Leukopenia	26 (12.9)	[redacted]	[redacted]
Lymphopenia	18 (8.9)	[redacted]	[redacted]
Gastrointestinal disorders:	33 (16.3)	[redacted]	[redacted]
Nausea	18 (8.9)	[redacted]	[redacted]
Diarrhoea	12 (5.9)	[redacted]	[redacted]
General disorders and administration site conditions:	45 (22.3)	[redacted]	[redacted]
Fatigue	38 (18.8)	[redacted]	[redacted]
Asthenia	6 (3.0)	[redacted]	[redacted]
Infections and infestations:	13 (6.4)	[redacted]	[redacted]
Metabolism and nutrition disorders:	65 (32.2)	[redacted]	[redacted]
Hyponatraemia	36 (17.8)	[redacted]	[redacted]
Hyperglycaemia	15 (7.4)	[redacted]	[redacted]
Decreased appetite	10 (5.0)	[redacted]	[redacted]
Psychiatric disorders:	12 (5.9)	[redacted]	[redacted]
Abbreviations: TRAE, treatment-related adverse event			

b) the number of patients/events for STORM Part 2 for the adverse events reported as percentages in Table 29 (Adverse event rates used in cost-effectiveness analysis) of the Company submission, document B.

Company Response: The STORM data from Table 29 from the CS document B has been updated below to include the n as well as %, for STORM Part 2, as included in the cost-effectiveness analysis.

Table 5: Treatment emergent adverse events used in cost-effectiveness analysis

Adverse events	STORM Part 2	
	[redacted]	%
Anaemia	[redacted]	45.1%
Asthenia	[redacted]	5.7%
Back pain	[redacted]	2.5%
Bone pain	[redacted]	0.8%
Decreased appetite	[redacted]	6.6%

Adverse events	STORM Part 2	
Dehydration	[redacted]	3.3%
Diarrhoea	[redacted]	7.4%
Dyspnoea	[redacted]	4.1%
Fatigue	[redacted]	21.3%
Hyperglycaemia	[redacted]	6.6%
Hypokalaemia	[redacted]	6.6%
Hyponatraemia	[redacted]	22.1%
Leukopenia	[redacted]	14.8%
Lymphopenia	[redacted]	11.5%
Nausea	[redacted]	9.8%
Neutropenia	[redacted]	22.1%
Pneumonia	[redacted]	9.0%
Sepsis	[redacted]	7.4%
Thrombocytopenia	[redacted]	62.3%
Vision blurred	[redacted]	1.6%

References

1. Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019; **33**: 2266-75.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]

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].

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 10 pages.

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**

	<table><tr><td>Takeda UK Limited</td><td></td><td>40,000</td><td></td><td></td><td>17,000</td><td>**57,000**</td></tr><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; they include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system that can lead to increased infections. ***"Fatigue. I have it because of my low blood cell counts. My energy levels are poor. I'm OK walking on the flat but anything that involves hills, I do struggle to get up. I like play golf but have to use a buggy."*** 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. ***"There is a constant pressure of wondering what's going to happen to me next because myeloma is like that, it's not curable and it's going to come back, I'm sure every month there's the possibility of relapse and it's hard to ignore that. It's a massive relief every month when I'm told that my paraproteins haven't risen."*** 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. ***"When I saw my consultant, I think it was last November. She told me there wasn't anything else at that time for me to go on. I was on the last thing so. I don't know.*** **Hopefully there's a couple of other treatments in the pipeline or in the works."** 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. Over time, myeloma evolves, becoming more resistant to treatment, and patients get older, frailer and have more comorbidities. Treatments become less effective and harder to tolerate with every relapse.[3]

	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 need to change treatment their options and life expectancy decrease. 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. 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."***

[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.
[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 at the fifth line and beyond is markedly narrower than those available at first or second line. ***"It would be nice to have some more options. Particularly given the fact that CAR-T and teclistamab were withdrawn by the drug company and belantamab was refused authorization by NICE. This is the biggest issue for me. There was a range of potentially life extending treatments out there that have all been taken off the table for one reason or another. I would be keen to see something more out there for people like me who are young - I can't say healthy, but I feel healthy technically - and who are active. It wouldn't be nice not to give me some more treatment, given what I can contribute generally to society and my family. That's how I feel."*** Multiply relapsed 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. ***"I think the most difficult thing, and this trumps fatigue by miles, is the relapsing and remitting nature of the disease. You never quite know what's around the corner. It's always in the back of my mind. And I'm sure it's the same for my family - How long is this treatment going to work and what is going to happen next? Once you get further down the lines of treatment like I am, that question becomes a bit more serious. When your options are becoming more limited."*** Patients at the fourth or fifth line of treatment also know that they are in the minority and that most patients will not need or reach fifth line. Whilst patients feel fortunate that they have received several treatments, they are frustrated when effective treatments available in other countries are not available in the UK. This is particularly true for patients who have never had a complete response or significant time in remission. A new type of drug with an innovative mechanism could be the drug that works for them. ***"I would understand if it was because of massive expense, but it does seem that. Other parts of the world can afford it. And there aren't many of us, so it wouldn't be a massive part of the NHS budget. To give those few people who have got through to the 4th or fifth line of treatment, it wouldn't be a massive expense I don't think."*** 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.

	"I don't have a lot of symptoms. If I have problems. It's to do with the medication, the chemo. And I don't know which drug. Well, probably they all are prone to give you peripheral neuropathy. But the thalidomide and the lenalidomide certainly do. So, I have gradually had an increase in peripheral neuropathy which started with a slightly numb feeling in the toes and it has now spread to the shins, the lower leg and my fingers. I fumble a bit more than I used to. So that's kind of annoying because it means I can't climb rocks anymore." The mood swings, irritability and mania caused by dexamethasone are also very challenging for patients and their families. Multiply relapsed patients see side effects as an inevitable part of their treatment, which can be managed by added medication, dose reductions, or changing their routine. However, it is a balance, and many patients acknowledge that the extra time a treatment could deliver must be bearable. ***"You really want treatments that work, and the longer they work, the better. And then it is a balance because it's all a trade-off, a balance about side effects."*** Treatments which can be taken at home are generally seen as an advantage, especially for patients who live further away from the hospital. ***"Tablet form or even injections you can take at home are hugely preferable. Getting to the hospital, and parking at the hospital is an absolute nightmare. It turns things into a really big deal."*** ***"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 ss an absolute pain, so I wouldn't be keen on having to go, say every week for some sort of treatment."*** ***"I've seen people distressed about travelling to the hospital when I've been in the waiting room. In the middle of winter there's snow on the ground, there's ice on the ground and it's imperative they have the treatment. They're putting their life at risk just to get there. To me, that's not satisfactory."***

8. Is there an unmet need for patients with this condition?	There is a clear need for innovative anti-myeloma treatments for patients who are refractory to available treatments and for patients at fifth line and beyond. Patients can be successfully retreated at relapse, but the probability of deep, durable responses decreases with every relapse. A retrospective study of patient outcomes across Europe showed that 74% of patients achieved at least a very good partial response (VGPR) in the first-line setting, compared with 11% at fifth line or later. It also showed a decrease in overall response rates (ORR) with each line of treatment with 3 in 5 patients not responding to available treatments at fifth line. (ORR = 92% at first line, 84% at 2nd line, 73% at 3rd line, 64% at 4th line and 41% fifth line).[3] 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 with relapsed and refractory myeloma are all too familiar with this scenario. Their disease is resistant to most existing treatments, and innovative treatments are needed to control their myeloma. New drugs are urgently needed to overcome treatment resistance. 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.[5] 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.[6] 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. Overall, there is a need for a wide range of options at each stage of the treatment pathway given the heterogeneous and evolving nature of myeloma. However, treatment options are extremely limited and, in some cases, non-existent at the more advanced stages of this pathway. Although clinical trials and compassionate use programmes may be available at later stages of the pathway, they are not accessible to all patients. Clinical trials and compassionate use programmes are often limited to a few large, specialist, inner-city hospitals. ***"There is luck involved and that luck is often impacted by geography. I have no doubt that certain groups of patients in certain areas get better access to trials. It's really unfair."***

[5] 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

[6] 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)

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.[7] The STORM clinical trial assessed the use of selinexor plus dexamethasone in relapsed myeloma patients. Among patients enrolled in STORM Part 2 (n=123), 83 relapsed myeloma patients were refractory to two proteasome inhibitors (bortezomib, carfilzomib), two immunomodulators (lenalidomide, pomalidomide) and an anti-CD38 monoclonal antibody (daratumumab).[8] The results from the trial show that, 26% of patients in this group achieved a partial response or better following treatment. Response to treatment significantly improved overall survival rates with patients who achieved a partial response of better having a median overall survival of 15.6 months compared to 5.9 months for patients with stable disease following treatment and 1.7 months for patient with progressive disease following treatment. This suggests that the treatment has the potential to increase the median life expectancy of multiply relapsed, penta-refractory patients by 10-14 months. For many of these patients the alternative treatment choice would be end of life care. ***"The idea of a selective inhibitor of nuclear export looks good to me. I'd be prepared to have a go at it…. If it's extending life expectancy, then it's probably worth it."*** ***"Survival improved with treatment, greatly. I'd prefer it to be more, but it is encouraging."*** 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. ***"The new way of working sounds pretty impressive to me. It sounds like a branch rather than a piece of grass I can hold on to and keep me floating for a little bit longer. That would be good because I've got a lot to live for. grandchildren and working with friends and people really are on most important. I'm not bothered about going to the Seychelles or the Maldives, I just want to see people that I know and love and spend time with."*** The all-oral treatment regimen was also seen as an advantage. The treatment could be taken at home, reducing the number of hospital visits. ***"Tablet form or even if you can do injections at home because I've done that. Those are hugely preferable. Because getting to the hospital and parking is an absolute nightmare. It turns things into a really big deal."***

[7] 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.
[8] Chari, A., et. al. (2019). Oral selinexor–dexamethasone for triple-class refractory multiple myeloma. New England Journal of Medicine, 381(8), 727-738.

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.[9] When looking at the clinical trial data for selinexor some of the patients felt that the response rate was lower than they would like. They would need to rely on luck, hoping they would be one of the lucky ones. It would increase their anxiety whilst starting treatment. However, whilst they would prefer an option with a higher chance of success, the low response rate would not put them off receiving the treatment if it was recommended. Choices towards the end of the pathway are limited. They also noted that myeloma is an individual and complex the cancer with patients experiencing varying response rates at every line of treatment. It is important that selinexor is made available to allow doctors the flexibility to prescribe this treatment to multiply relapsed/refractory patients who they think will benefit clinically. ***"I would be happier if the response rate was at least 50-60%. I think that's low in my opinion, I think, it just needs to be higher. If I'm going to start something new, I would like to know that I'd be in remission if possible but if there was nothing else better, then I'd go with it. But if there was something better, then I would look at that one first. Maybe if it had a better result."*** 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. ***"Well, look, all those, all those side effects I've had them in various shapes and forms previously and they can all be managed. That's what I would say about the more common things. But the cataract one is probably off the ones there that's the one that's unusual.*** ***"When I see cataract that sounds like to me another procedure that you might need. Whereas all those other side effects, you can just pop a few more pills."*** Whilst cataract was listed as one of the side effects on the patient leaflet for selinexor it should be noted that cataracts were not commonly observed in the STORM trial. They were mainly observed when used in combination with bortezomib and dexamethasone. 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"***

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.	No

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

[9] 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

Other issues

13. Are there any other issues that you would like the committee to consider?	The patient cohort eligible for this treatment is small. Data shows that the numbers of patients reaching 5th line could be as small as 1 in 10 patients. Many patients needing effective treatment at fifth line and beyond are still fit and active, particularly patients who were diagnosed when they were younger or who have quickly moved through treatment lines due side effects or poor response rates.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a clear unmet need for this technology as it will give refractory patients a greater choice of options. • The patient cohort eligible for this treatment is small. Data shows that the numbers of patients reaching 5th line could be as small as 1 in 10 patients. • There is currently no treatment with this mechanism of action licensed for routine commissioning at this point in the treatment pathway. • Clinical trial data and insights from our patient interviews confirm that selinexor can deliver benefits which are most important to patients, good OS and good PFS with manageable side effects. • Patients consider the all-oral regime a distinct advantage of this treatment.

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.

NICE National Institute for Health and Care Excellence

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]

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.

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. For patients with relapsed/refractory myeloma Stable Disease (SD) is considered an appropriate outcome.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Myeloma is incurable with current therapy. Although the majority of patients do respond to therapies early on, only a minority of patients will respond from 5th line (at least 4 prior therapies) onwards. Maintaining disease control is imperative to limit complications related to myeloma and improve quality of life and potentially receive further treatment at relapse. 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?	Currently available 5th line therapies include Pomalidomide Dexamethasone (TA427); Panobinostat in combination with bortezomib and dexamethasone (TA380); and Best supportive care. If the patient was refractory (or had significant toxicity) related to a proteosome inhibitor, it would not be appropriate to treat the patient with Panobinostat in combination with bortezomib and dexamethasone.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Treatments are based on NICE approved treatments and other available therapies
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 experience is from outside England.)	There are limited options available to clinicians to treat patient patients who have received at least 4 or more prior lines of therapies including 2 proteosome inhibitors, 2 immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory). Options are listed above, with concerns about re-treating with bortezomib (together with Panobinostat) if the patient is refractory to a proteosome inhibitor. The only option would be access to clinical trials. I do not think there would be differences in opinion across the NHS.
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 would be easily delivered.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Selinexor would be given as an oral therapy, prescribed from outpatient clinics. It would easily fit into the current treatment algorithm and would be easily delivered.
10a. How does healthcare resource use differ between the technology and current care?	Selinexor would be given as an oral therapy, prescribed from outpatient clinics. This is similar to delivering Pomalidomide Dexamethasone (TA380).
10b. In what clinical setting should the technology be	Specialist clinics.

used? (For example, primary or secondary care, 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 STORM trial, Selinexor–dexamethasone resulted in objective treatment responses in patients with myeloma refractory to currently available therapies.
11a. Do you expect the technology to increase length of life more than current care?	Based on the STORM trial, Selinexor–dexamethasone resulted in objective treatment responses in patients with myeloma refractory to currently available therapies. These patients do not have other available therapies.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. This is a well-tolerated regime with limited and 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 an oral therapy. It will be easy to deliver from outpatient clinics. This will not be more difficult for patients or healthcare professionals.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Response is based on clinical response to treatment after between 2 and 4 cycles.
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	Selinexor is 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

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?	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?	There are limited other treatment options.
17. 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 well tolerated with potential side effects including loss of appetite, nausea and weight loss. There would need to be guidance on how to manage these side effects to limit the impact on quality of life. There are no other concerning side effects.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	STORM data reflects the patient group that is refractory to 2 proteosome inhibitors, 2 immunomodulatory agents and an anti-CD38 monoclonal antibody.
18a. If not, how could the results be extrapolated to the UK setting?	See comments above.

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Depth of response and survival has been assessed using PFS and OS.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS and OS are important outcomes that have been measured.
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 might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No
21. How do data on real-world experience	No

compare with the trial data?	

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 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Unmet need, patients have limited other options • Oral therapy (easy to deliver) • Novel mechanism of action • Expected side effects that are manageable for most patients •
	•

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.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]

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.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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.

NICE National Institute for Health and Care Excellence

Part 1: Treating relapsed or 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) both 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 or refractory multiple myeloma? ☐ A specialist in the clinical evidence base for relapsed or 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	☒ Yes

do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	
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 or 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	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. For patients who have relapsed/refractory disease and exhausted all conventional therapies, Stable Disease is a positive outcome as well.

reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or 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 or 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	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. These patients have exhausted all conventional treatment options.

is from outside England.) • What impact would the technology have on the current pathway of care?	
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? • 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	Seliexor is an oral medication and will delivered in hospital based haematology/oncology clinics. This will have limited impact on pharmacy and no impact on oncology day units.

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. This therapy is given at a stage where there are no other treatment options.
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	We think the health-related benefits are mostly captured.

substantial health-related benefits that 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	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)

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?	
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	The reported trial reflects UK clinical practice.

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?	
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,	None

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. 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.	

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 with no other treatment options at this stage of the illness

Easy to deliver

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]

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 or refractory multiple myeloma or caring for a patient with relapsed or 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.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

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, 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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with relapsed or refractory multiple myeloma

Table 1 About you, relapsed or refractory multiple myeloma, current treatments and equality

1. Your name	Rosemary Dill
2. Are you (please tick all that apply)	☒ A patient with relapsed or refractory multiple myeloma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with relapsed or 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

Patient expert statement

	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 or refractory multiple myeloma? **If you are a carer (for someone with relapsed or 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 or 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 or 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 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 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 dexamethasone over current treatments on the NHS please describe these. For example, are there any risks with Selinexor with 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 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 or refractory multiple myeloma and Selinexor with 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.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

BMJ TAG

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136082.

Title:	Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Victoria Wakefield, Principal Health Technology Assessment Analyst, BMJ-TAG, London Mariana Bacelar, Principal Health Economist, BMJ-TAG, London Melina Vasileiou, Clinical Evidence Analyst, BMJ-TAG, London Kate Ennis, Senior Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	03/11/2023
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136082.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Faye Sharpley (Consultant Haematologist, The Christie NHS Foundation Trust, Macclesfield) and Dr Michael Chapman (MRC Investigator and Honorary Consultant Haematologist, MRC Toxicology Unit, Cambridge for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Wakefield V, Bacelar M, Vasileiou M, Ennis K. Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]: A Single Technology Appraisal. BMJ Technology Assessment Group, 2023.

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
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Melina Vasileiou	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Mariana Bacelar	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
Kate Ennis	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

All authors read and commented on draft versions of the EAG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

5L	Fifth line
AIC	Akaike information criterion
AE	Adverse event
AFT	Accelerated Failure Time
BCLPD	Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
BIC	Bayesian inflation criterion
BSC	Best supportive care
CASP	Critical Appraisal Skills Programme
CCT	Conventional chemotherapy
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
ESS	Effective sample size
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-MM	Functional Assessment of Cancer Therapy – Multiple Myeloma
HCP	Health-care professional
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IMiD	Immunomodulatory imide drug
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meir
MA	Marketing authorisation
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple myeloma
NICE	National Institute of Health and Care Excellence
NHS	National Health Service
NMA	Network meta-analysis
OS	Overall survival
PanoVd	Panobinostat plus bortezomib and dexamethasone
PAS	Patient access scheme
Pd	Pomalidomide plus dexamethasone

PD	Progressed disease
PI	Proteosome inhibitor
PFS	Progression-free survival
PH	Proportional hazards
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
RCT	Randomised controlled trial
RDI	Relative dose intensity
RRMM	Relapsed and/or refractory multiple myeloma
QALY	Quality-adjusted life years
QoL	Quality of life
SCT	Stem cell transplant
Sd	Selinexor plus dexamethasone
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SoC	Standard of care
STC	Simulated treatment comparison
TCR	Triple-class refractory
TOT	Time on treatment
TSD	Technical support document
TTD	Time to treatment discontinuation
WTP	Willingness to pay

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.

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 1.5 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 with (low-dose) dexamethasone (Sd) for the treatment of relapsed or refractory multiple myeloma (RRMM) in penta-refractory adult patients.

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Omission of clinical and cost-effectiveness analyses for PanoVd	2.3.3
2	Generalisability of the clinical data to the population eligible for Sd in clinical practice in England	2.3.1, 3.2, 3.4
3	Uncertainty in the results of the company ITC comparison of Sd versus SoC and subsequent modelling of overall survival	3.4, 4.2.6

Abbreviations: EAG, External Assessment Group; Sd, selinexor plus dexamethasone; ITC, indirect treatment comparison

Due to the uncertainties in the evidence available, the EAG was unable to provide a preferred base case. However, the key difference between the company's preferred assumptions and the EAG's preferred assumptions is surrounding the modelling of overall survival (OS).

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, the technology is modelled to affect QALYs by:

- Increasing OS for all patients
- Adverse events (AE) experienced by patients receiving Sd

Overall, the technology is modelled to affect costs by:

- Higher treatment acquisition costs than currently available treatments for penta-refractory patients
- Management of AEs related to treatment

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

- The estimation of OS for Sd and standard of care (SoC)

1.3 Summary of the EAG's key issues

Table 2. Issue 1: Omission of clinical and cost-effectiveness analyses for PanoVd

Report section	2.3.3
Description of issue and why the EAG has identified it as important	Comparisons listed in the NICE final scope were Pd, PanoVd, belantamab mafodotin, conventional chemotherapy regimens; and BSC. However, BSC (proxied by SoC) was the only comparator considered relevant by the company for the population in which they chose to position Sd for (penta-refractory MM patients at 5L+). The company reported that its clinical experts suggested PanoVd is not an appropriate comparator for the treatment of penta-refractory patients at 5L+ and therefore the company has not provided a comparison versus Sd for either clinical or cost-effectiveness. However, the EAG clinical experts indicated that PanoVd is a potentially relevant comparator for Sd as it is a current treatment option for patients at 5L+. Therefore, the EAG is concerned that the company has not provided a comparison of Sd with PanoVd in the CS, as conclusions about the clinical and cost-effectiveness of Sd over the treatment options currently available to the population of interest cannot effectively be drawn.
What alternative approach has the EAG suggested?	Inclusion of PanoVd as a comparator for Sd at 5L+.
What is the expected effect on the cost-effectiveness estimates?	Without any comparative evidence between Sd and PanoVd in the population of interest, the EAG is unable to comment on the expected clinical and cost-effectiveness of Sd compared to PanoVd.
What additional evidence or analyses might help to resolve this key issue?	A comparison of the clinical and cost-effectiveness of Sd compared to PanoVd for the outcomes specified in the NICE final scope.

Abbreviations: 5L, fifth-line; BSC, best supportive care; CS, company submission; EAG, External Assessment Group; MM, multiple myeloma; NICE, National Institute of Health and Care Excellence; PanoVd: panobinostat plus bortezomib and dexamethasone; Pd pomalidomide plus dexamethasone; Sd, selinexor plus dexamethasone; SoC: standard of care

Table 3. Issue 2: Generalisability of the clinical data to the population eligible for Sd in clinical practice in England

Report section	2.3.1, 3.2, 3.4
Description of issue and why the EAG has identified it as important	Based on clinical expert advice, the EAG considers the baseline characteristics of the STORM Part 2 BCLPD-refractory population likely to differ from the penta-refractory RRMM patients in clinical practice in England. In particular, the median age (65.3 years) in the STORM Part 2 BCLPD-refractory population was possibly lower than the average age at which patients would be expected to reach a penta-refractory status in the UK. Also, the ECOG status was probably better than seen in clinical practice, and prior SCT and number of prior anti-MM regimens in the STORM Part 2 BCLPD-refractory population were potentially higher than expected in clinical practice in England. Penta-refractory status can also be achieved using different prior therapies than those received by the BCLPD-refractory population in STORM Part 2 and the potential impact of this on the efficacy of Sd is unknown. The EAG is also concerned that [redacted] In addition, the EAG notes that there are differences between the patient characteristics and treatments received in the MAMMOTH study used to inform BSC in the CS, compared with SoC in clinical practice in England. The EAG notes that SoC in MAMMOTH is being used as a proxy for BSC and that BSC is deemed by the company to include a mix of no further active treatments and CCT. However, the EAG notes that 90% of patients in MAMMOTH received further treatments and the EAG's clinical experts reported that this proportion is higher compared to expected in clinical practice in England (up to 70%). Moreover, the EAG notes that some patients in MAMMOTH received IMiDs, PIs and other drugs which are not consistent with clinical practice in England. The EAG considers that the discrepancies between the studies: STORM Part 2 BCLPD-refractory subgroup and MAMMOTH penta-refractory subgroup, compared with patients with penta-refractory RRMM in clinical practice in England, as well as the differences in treatments and subsequent treatments, may limit the generalisability of the findings for Sd to clinical practice. However, the EAG considers that the treatments used in MAMMOTH [redacted]
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	The EAG considers the impact of the potential differences in the population and subsequent treatments on the cost-effectiveness estimates to be unknown.
What additional evidence or analyses might help to resolve this key issue?	An alternative source of data for SoC that more closely reflects the combination of BSC + CCT used in clinical practice in England. However, the EAG agrees with the company that MAMMOTH appears to be the most reasonable source of the studies identified from the company's current SLRs.

Abbreviations: 5L, fifth-line; BCLPD: bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; CCT: conventional chemotherapy EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; IMiD,

Immunomodulatory imide drug; MM, multiple myeloma; PI, proteosome inhibitor; RRMM, relapsed and/or refractory multiple myeloma; SCT, stem-cell transplant; Sd, Selinexor plus dexamethasone; SoC: standard of care

Table 4. Issue 3: Uncertainty in the results of the company ITC comparison of Sd versus SoC and subsequent overall survival modelling

Report section	3.4, 4.2.6.1
Description of issue and why the EAG has identified it as important	The EAG is concerned about the robustness of both the company MAICs and STC analyses for the comparison of Sd versus SoC. The EAG notes that the MAIC analyses result is small ESSs, with the EAG preferred 'Full' adjusted MAIC resulting in an ESS of 10.3 for Sd. For the STC, the EAG is concerned that the simple proportional hazards (PH) approach utilised by the company lacks face validity given the multiple overlaps seen in the initial 3.5 months of the underlying unadjusted KM curves for Sd and SoC from STORM Part 2 BCLPD refractory patients and the MAMMOTH penta-refractory subgroup. Therefore, the subsequent use of a hazard ratio (HR) when the PH assumption has been violated to model OS for the SoC arm is inappropriate. Furthermore, the HR has been applied to a parametric curve (lognormal) which does not support the PH assumption.
What alternative approach has the EAG suggested?	Given the complex nature of the underlying KM curves for Sd and SoC, as illustrated in the naive comparisons and MAICs, the EAG's preferred approach would be to fit independent curves to the adjusted Sd KM curve and the SoC KM curve from MAMMOTH as this would not require estimating a HR (which would not appear to have face validity given the crossing curves). The EAG appreciates that this would essentially mean that the OS estimates are for the MAMMOTH population rather than the STORM Part 2 BCLPD-refractory population, but considers this the "least biased" of the options available.
What is the expected effect on the cost-effectiveness estimates?	As the EAG was not provided with independently fitted curves the impact on cost-effectiveness could not be estimated. However, based on the EAG's illustrative scenarios for OS (see Section 6.3), it is expected that the ICER will increase and have a large impact on the cost-effectiveness conclusions.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers independent complex curve fitting is required to more accurately reflect the data for Sd and SoC and enable more robust estimates of the cost-effectiveness of Sd versus SoC.

Abbreviations: BCLPD: bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, EAG, External Assessment Group; ESS, effective sample size; HR, hazard ratio; KM, Kaplan-Meir; MAIC, matching-adjusted indirect comparison; OS, overall survival; Sd, selinexor plus dexamethasone; STC, simulated treatment comparison; SoC: standard of care

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

Secondary issues identified for committee consideration include the following:

- Resource use assumptions that are more reflective of the NHS – Section 4.2.8.2
- An administration cost for oral chemotherapy should be included in the cost-effectiveness analysis – Section 4.2.8.1
- Cyclophosphamide 500mg dose used as part of conventional chemotherapy – Section 4.2.8.1

- Adverse event unit costs calculated by weighted average of included healthcare resource group (HRG) as opposed to average only used by the company – Section 4.2.8.3
- End of life care cost from the PSSRU should be used in the economic model – Section 4.2.8.4

1.5 Summary of EAG's preferred assumptions and resulting ICER

Table 5 presents the EAG's preferred assumptions. The EAG was unable to provide a preferred base-case ICER as the requested analyses for OS were not provided to the EAG. Therefore, The EAG presents the cumulative impact of their preferred assumptions (scenarios 1–5) and an illustrative scenario for OS to show the potential impact on the ICER.

Table 5. EAG preferred assumptions and cumulative impact on the ICER

Preferred assumption	Incremental costs (£)	Incremental QALYs	Cumulative ICER (£/QALY)	Cumulative ICER (£/QALY) severity modifier (1.7) applied
Company base case post clarification	[redacted]	[redacted]	£39,285	£23,109
EAG scenario 1 - EAG clinical expert resource use assumptions	[redacted]	[redacted]	£39,901	£23,471
EAG scenario 2 - inclusion of administration cost for oral chemotherapy	[redacted]	[redacted]	£40,412	£23,772
EAG scenario 3 - Cyclophosphamide 500mg dose	[redacted]	[redacted]	£40,474	£23,808
EAG scenario 4 - Updated adverse event costs	[redacted]	[redacted]	£38,738	£22,787
EAG scenario 5 - End of life care cost from the PSSRU	[redacted]	[redacted]	£38,282	£22,519
EAG scenario 6 – OS illustrative example	[redacted]	[redacted]	£121,088	£71,228
EAG scenarios 1–5, probabilistic	[redacted]	[redacted]	**£38,979**	**£22,929**
EAG scenarios 1–6, probabilistic	[redacted]	[redacted]	**£124,450**	**£73,206**

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; PSSRU, Personal Social Services Resource Use; OS, overall survival

For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.3.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost-effectiveness of selinexor (Nexpovio®; Menarini-Stemline UK Ltd.) with (low-dose) dexamethasone (Sd) in the treatment of multiple myeloma (MM) in penta-refractory patients. The term penta-refractory in the company submission (CS) refers to people with relapsed and/or refractory multiple myeloma (RRMM) who have had four or more treatments and whose disease is refractory to at least two proteasome inhibitors (PIs), two immunomodulatory agents (IMiDs) and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. Selinexor has marketing authorisation in the UK in combination with dexamethasone for this population (Medicines and Healthcare products Regulatory Agency [MHRA], May 2021).[1] The External Assessment Group (EAG) notes that the term penta-refractory is not used within the MHRA approval but it is mentioned in the National Institute for Health and Care Excellence (NICE) final scope for this STA, and it is used in the CS to describe the population that selinexor plus dexamethasone (Sd) is indicated for use in.[2] The EAG's clinical experts reported that penta-refractory is not a term that is currently widely used in UK clinical practice but agreed the definition appears consistent with the MHRA marketing authorisation for Sd.

2.2 Background

Multiple myeloma (MM) is a form of cancer characterised by the build-up of abnormal plasma cells (a type of white blood cell) in the bone marrow, the tissue in the body's larger bones that produces blood cells.[3] DNA damage during the development of plasma cells leads to abnormal plasma cells (myeloma cells) which, unlike normal plasma cells, produce large quantities of the abnormal antibody paraprotein and supress the development of normal blood cells also responsible for carrying oxygen around the body and blood clotting.[3, 4] Myeloma typically affects multiple places in the body and is therefore often referred to as MM. The symptoms of MM often include bone pain, fatigue, recurring infections, and kidney problems.[4]

MM has been estimated to occur in 5,000 people per year in England, being more prevalent in males than females and accounting for 2% of all new cancers[5]. In the UK, incidence rates are highest in people aged 85 to 89 years with 43% of all new myeloma cases diagnosed in people aged 75 and over each year. Incidence rates in England are higher in the Black ethnic group, lower in the Asian ethnic group and similar in people of mixed or multiple ethnicities compared to the White ethnic group. Overall, 1 in 3 (29.1%) people diagnosed with MM survive for 10 years or more.[5]

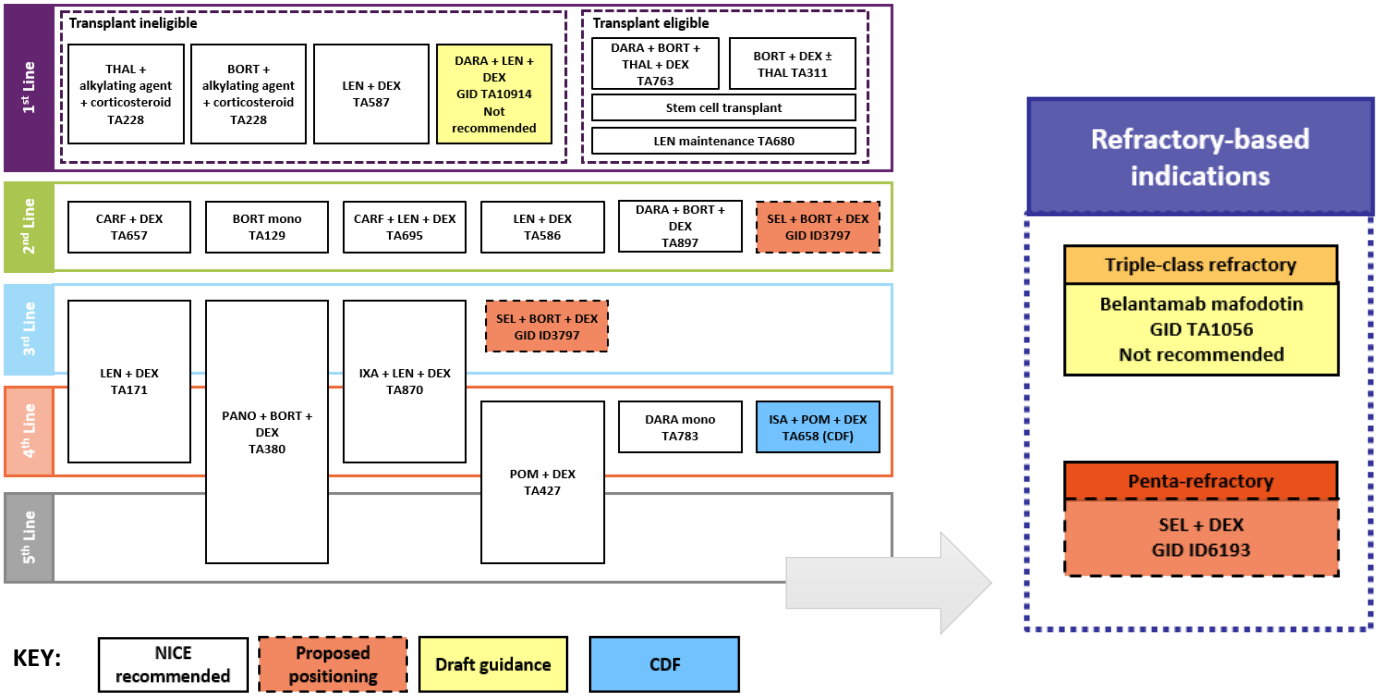
Section B.1 of the CS provides an overview of MM. Based on advice from the EAG's clinical experts, the CS presents an accurate overview of the health condition, clinical presentation, its progression, disease burden and epidemiology. However, the EAG notes that the focus of the NICE final scope and the MHRA marketing authorisation for Sd is relapsed and/or refractory MM (RRMM) patients in particular, and not just MM. As defined by the International Myeloma Working Group (IMWG), RRMM is disease nonresponsive to the chosen line of therapy in patients who had achieved a minimal response or better at some point previously in their disease.[6] The company does not provide an overview that is particularly relevant to this diverse group of patients experiencing progressive disease despite previous treatment.

2.2.1 Positioning of Selinexor with dexamethasone in the UK treatment pathway

MM to date remains incurable, with relapses inevitably occurring at different stages during the course of the disease.[7] The main aim of treatment for MM is to reduce the disease burden, maintain a good quality of life and extend survival.[8] The company highlights that the treatment landscape for MM is complex and treatment strategies are personalised to account for individual factors including age, frailty, comorbidities, and previous drug exposure. It highlights the limited availability of treatment options for penta-refractory patients as they are more likely to have been exposed to, and be refractory to, many of the current treatments recommended by NICE.

The company presented an overview of the current treatment pathway for MM (CS, Figure 1) and also provided a figure depicting the proposed positioning of Sd in the treatment pathway (Figure 1 [CS, Figure 3]).

Figure 1. Company's proposed future treatment pathway for RRMM including Sd based on NICE guidance available up to 22 June 2023 (Reproduced from CS, Figure 3)



Abbreviations: BORT, bortezomib; CARF, carfilzomib; CDF, Cancer Drugs Fund; DARA, daratumumab; DEX, dexamethasone; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PANO, Panobinostat; POM, pomalidomide; SEL, Selinexor; and THAL, thalidomide.

As discussed above, eligibility for treatment with Sd requires a patient to be penta-refractory and there are strict requirements on the drug classes for which refractoriness must be demonstrated: at least two PIs, two IMiDs and one anti-CD38 monoclonal antibody. Table 6 provides a summary of the most commonly used drugs in each of these classes in the UK along with the common abbreviations for these drugs.

Table 6. 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 or BORT
		carfilzomib	K or CARF
		ixazomib	Ixa
Immunomodulatory drugs	—lidomide	lenalidomide	R or LEN
		thalidomide	T or THAL
		pomalidomide	P or POM
Anti-CD38 monoclonal antibodies	—mab	daratumumab	D or DARA
		isatuximab	Isa

The company reported that their treatment pathways were informed and validated through two advisory boards with UK MM clinical experts and patients. The EAG notes that the company's treatment pathways differentiate between stem-cell transplant (SCT) ineligible patients and SCT eligible patients at the start of the treatment pathway (Figure 1) but there is no further

differentiation beyond the first-line of therapy. The company stated in their response to clarification questions (CQs) that although the UK treatment pathway for RRMM patients differs in earlier lines of therapy depending on eligibility for SCT, when patients are penta-refractory and have received ≥ four prior lines of therapy, the choice of therapy does not differ based on prior SCT status. The company's proposed positioning of Sd is therefore relevant for all RRMM patients at ≥5L of therapy regardless of prior SCT status.

The EAG's clinical experts reported that the treatments given at each line of therapy are likely to differ depending on whether a patient has received a prior SCT and also depending on what prior treatments and response has been. However, the EAG's clinical experts broadly agreed with the company's outline of the treatment pathway for RRMM patients but highlighted patients who receive SCTs tend to be younger and fitter compared to those who do not.

Current treatment options at 5L in the company's treatment pathway are pomalidomide (POM) plus dexamethasone (DEX) or panobinostat plus bortezomib plus dexamethasone (PanoVd), although the EAG notes that both can also be given earlier in the treatment pathway. The EAG notes that the company is positioning Sd as an alternative treatment at 5L, for those patients who meet the penta-refractory eligibility criteria.

The EAG's clinical experts reported that patients are likely to have received POM+DEX at 4th Line (4L) or prior to meeting the definition of penta-refractory. Subsequently, at 5L, treatment options would be very limited, with PANO+BORT+DEX being a potential option for a limited number of patients due to the potential side-effects. The EAG's clinical experts reported that patients would occasionally go back to a regime from a previous line of therapy such as thalidomide, although it would generally be of limited efficacy at this stage. The EAG's clinical experts also reported that chemotherapy drugs would be used as an alternative treatment option at 5L and for some patients no further active treatment would be appropriate and thus best supportive care (BSC) would be given.

The EAG also considers it important to highlight that its experts noted that based on the number of drugs patients receive in the initial lines of therapy, they could become penta-refractory earlier than 5L (if the definition of penta-refractory is based on resistance to drugs rather than line of therapy). However, the EAG notes that the company confirmed in their response to clarification questions that their proposed positioning of Sd is for penta-refractory patients at 5L and beyond (5L+). In addition, the EAG notes that the MHRA marketing authorisation for Sd is for patients who have received at least four prior therapies.

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

A summary of the final scope issued by NICE, together with the company's rationale for any deviation from this, is provided in Table 7. Key differences between the decision problem addressed in the CS and the final scope are discussed in greater detail in the sections that follow below. The EAG considers the main difference between the decision problem specified by the company and the NICE final scope is in the comparators - the company considered BSC to be the only relevant comparator for Sd. The EAG also notes that the company included conventional chemotherapy as a part of BSC rather than a separate standalone comparator.

Table 7. 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 relapsed or refractory multiple myeloma who have had 4 or more treatments and whose disease is refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy.	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, and who have demonstrated disease progression on the last therapy.	This wording aligns with the MHRA MA for Sd.[9] Pivotal evidence for this penta-refractory population is from STORM Part 2, the penta-refractory efficacy population (referred to as BCLPD-refractory in STORM).	The key clinical efficacy data for selinexor plus dexamethasone (Sd) are from a subgroup of the STORM Part 2 trial – the BCLPD-refractory population. This subgroup matches the penta-refractory population defined in the NICE final scope, although the EAG's clinical experts reported that in UK clinical practice penta-refractory status could be achieved using different prior therapies and the impact of this on the efficacy of Sd is unknown. In addition, clinical experts reported that patients could become penta-refractory at an earlier line of therapy than 5th line (5L), although the EAG notes that the company is positioning Sd to be used only from 5L onwards and the marketing authorisation requires patients to have received at least four prior therapies. In terms of baseline characteristics, the EAG's clinical experts considered patients in the STORM Part 2 BCLPD-refractory population potentially comprised a younger population with a higher proportion of ECOG performance status 0 and 1, and a higher number of prior anti-MM

				regimens compared to that expected in clinical practice in England. See Section 2.3.1 for further details.
Intervention	Selinexor with dexamethasone	Selinexor with low-dose dexamethasone	N/A	The treatment regimen for Sd in the STORM Part 2 BCLPD-refractory population is consistent with the MHRA marketing authorisation for Sd. See Section 2.3.2 below for further discussion.
Comparators	• Pomalidomide in combination with low-dose dexamethasone • Panobinostat in combination with bortezomib and dexamethasone • Belantamab mafodotin (subject to ongoing NICE appraisal) • Conventional chemotherapy regimens • Best supportive care	For patients that are penta-refractory, best supportive care (BSC) – proxied standard of care.	The NICE final scope lists a number of comparator therapies. However, none of these interventions are licensed for penta-refractory MM and are not likely to be viable treatment options for penta-refractory patients for the reasons detailed below, which have been validated with UK myeloma clinical experts: • Pomalidomide + dexamethasone (Pd): to be penta-refractory, patients must have documented refractoriness to two IMiDs; therefore, even if patients are not already Pd exposed/ refractory, treatment with a further IMiD would likely be unsuitable. • Panobinostat + bortezomib + dexamethasone (PanoVd):	The EAG notes that the company considers BSC to be the only relevant comparator for Sd and that in the CS it is proxied by Standard of Care (SoC). The EAG notes that the company also considered conventional chemotherapy (CCT) to comprise a treatment given as part of BSC. Based on clinical expert advice, the EAG agrees that pomalidomide + dexamethasone is unlikely to be relevant a comparator at 5L+. In addition, the EAG notes that belantamab mafodotin is not currently recommended for use in RRMM in NHS clinical practice and clinical experts reported that it is not routinely used. However, the EAG is concerned that panobinostat + bortezomib + dexamethasone (PanoVd) is a potential comparator as it is a current treatment option at 5L+ and clinical

			to be penta-refractory, patients must have documented refractoriness to two PIs; therefore, treatment with a further bortezomib regimen would be unsuitable, and myeloma clinical experts describe limited use of PanoVd, regardless. • Belantamab mafodotin: was recently appraised by NICE for triple-class refractory (TCR) MM (not penta-refractory, and thereby be indicated for a different population). However, draft guidance states it is not recommended for use.[10] • Conventional chemotherapy (CCT): UK myeloma clinical experts described that while there may be limited use of agents such as cyclophosphamide, they would not consider this to be a major comparator for penta-refractory patients. Any limited use of CCT agents they would class under the umbrella of BSC. Therefore, considering all of the above, UK myeloma clinical	experts reported that it is a current treatment option. The EAG agrees with the company that BSC is a comparator for Sd at 5L+ but the EAGs clinical experts also considered CCT to be an important comparator. See Section 2.3.3 below for further discussion.

			experts' input suggests BSC as the only comparator.	
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 outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	N/A	The EAG considers that all outcomes specified in the NICE final scope were covered in the CS with clinical data reported for Sd from the STORM Part 2 BCLPD-refractory population. The results for these outcomes in the STORM Part 2 BCLPD-refractory population are discussed in Section 3.3. The EAG notes that data for the comparator considered by the company (BSC) is not available for all outcomes. Outcome data for comparators is discussed in Section 2.3.3 below.
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 are considered from an NHS and Personal Social Services perspective. The cost effectiveness of the treatments is expressed in terms of incremental cost per quality-adjusted life year, as per the reference case. 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	N/A	The economic analysis adheres to the reference case and reflects the final scope. The EAG notes that there are concerns with the modelling of OS and the resulting survival benefit estimated for Sd. This is discussed in further detail in Section 4.2.6.1.

	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 considered.	health states over time. The health states in the model are progression-free, progressed disease and death, with the progression-free and progressed disease health states subdivided into on and off treatment. • A lifetime horizon of 30 years is considered, with modelled overall survival of approximately 0.1% after 30 years, in keeping with the reference case.		
Subgroups to be considered	If evidence allows, the following subgroups will be considered: • cytogenetic risk factors.	Numbers do not support meaningful analysis of subgroups within the penta-refractory population.	The MA for Sd is based on the penta-refractory group of patients forming one pre-defined efficacy population of Part 2 of the pivotal STORM trial (n=83), which forms the pivotal evidence for this submission. Numbers do not support meaningful analysis of subgroups within the penta-refractory population.	The EAG notes that the key clinical efficacy data for Sd are from a subgroup of the STORM Part 2 trial – the BCLPD-refractory population which comprises only n=83 patients and thus further subgroup analysis is limited by small patient numbers. The EAG also notes that cytogenetic risk factors were not a prespecified subgroup in the STORM Part 2 trial. In response to clarification question A11, the company provided subgroup data from the BCLPD-refractory population for the following subgroups: • age (18-64, 65-74, ≥75 years of age); • prior SCT (yes/no); • ECOG status (0, 1 and 2);

				• number of prior anti-MM regimens; and • R-ISS stage (I, II, III). The results of these are discussed in Section 3.3.5.
Special considerations, including issues related to equity or equality		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 nor lead to recommendations that will have an adverse impact on people with a particular disability or disabilities.	N/A	None listed in the NICE final scope.

Abbreviations: 5L, fifth-line; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; BSC, best supportive care; CCT: conventional chemotherapy EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; HCP, healthcare professional; IMiD, immunomodulatory imide drug; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; MM, multiple myeloma; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; OS, overall survival; PanoVd, Panobinostat plus bortezomib and dexamethasone; Pd, pomalidomide plus dexamethasone; PFS, progression free survival; RRMM, relapsed and/or refractory multiple myeloma; Sd, selinexor plus dexamethasone; SoC: standard of care; TCR, triple-class refractory; ToT, time on treatment.

2.3.1 Population

The STORM Part 2 trial (n=123) was a single arm phase 2b open-label, multi-centre trial evaluating the efficacy and safety of Sd in patients with both triple-class refractory multiple myeloma (TCR-MM) (defined as patients whose disease is refractory to prior treatment with at least 1 IMiD, at least 1 PI and the anti-CD38 monoclonal antibody daratumumab [and glucocorticoids]) and penta-exposed MM (defined as quad-refractory plus prior treatment with daratumumab; i.e. MM patients previously treated with lenalidomide, pomalidomide, bortezomib and daratumumab [and an alkylating agent]).

The subgroup of STORM Part 2 defined as the BCLPD-refractory population (refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab [n=83]) comprised the main source of clinical evidence for Sd in the CS. The EAG's clinical experts considered the BCLPD-refractory population to meet the criteria for penta-refractory but also highlighted that not all penta-refractory patients are likely to be BCLPD-refractory. For example, patients in England who have received a prior stem cell transplant (SCT) could have received the IMiD thalidomide, and SCT ineligible patients may not have received the PI carfilzomib in previous lines of therapy but have received ixazomib. The EAG considers the impact on the efficacy of Sd for these potential differences in prior therapies between the STORM Part 2 trial and clinical practice in England is unknown.

Based on clinical expert advice, the EAG considers that some of the characteristics of the STORM Part 2 BCLPD-refractory population differ to those expected in a penta-refractory RRMM population in clinical practice in England. The EAG's clinical experts reported that the median age (65.3 years) in the STORM Part 2 BCLPD-refractory population was possibly lower than the average age at which patients would be expected to reach a penta-refractory status in the UK. The EAG's clinical experts also reported that they would typically see a lower proportion of penta-refractory patients with ECOG 0 compared to in the STORM Part 2 BCLPD-refractory population (32.5%). In addition, the EAG's clinical experts reported that there would be a proportion of penta-refractory patients in clinical practice in England that could be eligible for Sd and have an ECOG performance status of 2 or higher although these patients were excluded from the STORM Part 2 trial.

Another potential discrepancy between the penta-refractory population in STORM Part 2 and clinical practice in England is the proportion of patients with a prior stem cell transplant: in the STORM Part 2 BCLPD-refractory population, prior SCT (80.7%) was higher than expected in UK clinical practice

according to the EAG's clinical experts. In response to clarification question A3, the company specified that [redacted] The EAG notes that considering that the proportion of patients with a prior SCT is likely to be lower in UK clinical practice, the age of the population eligible for Sd is [redacted] compared to the penta-refractory population in STORM Part 2. The EAG's clinical experts also noted the number of prior anti-MM regimens in the STORM Part 2 BCLPD-refractory population varied widely, ranging from 4 to 18 and is potentially higher than expected in clinical practice in England. The company acknowledged in response to clarification question A5 that patients in STORM Part 2 were heavily pre-treated but they considered penta-refractory status is more clinically significant to patient treatment outcomes then the number of prior lines (i.e., exposure). In response to clarification question A11, the company provided subgroup results for the primary outcome of objective response rate by number of prior therapies and these are discussed in Section 3.3.5.

In addition to the EAG's concerns about the STORM Part 2 BCLPD-refractory subgroup, the EAG is concerned that the penta-refractory subgroup in the MAMMOTH study used in the indirect treatment comparison between Sd and SoC does not reflect patients in clinical practice in England either. The EAG considers that in MAMMOTH patients have a lower mean age (58.5 years), higher rate of prior SCT (67.1%) and a lower and greater number of prior lines of therapy (median 5, range 2 to 16). Moreover, the EAG notes that MAMMOTH was a USA based study and required that patients index regimen included a CD38 MoAB to which they were deemed to be refractory to. The EAG considers that clinical practice and availability of treatments in the USA is likely to differ with UK clinical practice and considers that with the 5L+ positioning of Sd, patients in clinical practice in England may not receive a CD38 MoAB in their final regimen prior to receiving Sd. The generalisability of the SoC data from MAMMOTH to current clinical practice in England is therefore questionable.

In summary, the EAG considers the BCLPD-refractory subgroup from STORM Part 2 to be consistent with the penta-refractory population specified in the NICE final scope and consistent with the MHRA marketing authorisation for Sd. However, the EAG considers there are some potential discrepancies between the STORM Part 2 BCLPD-refractory population, the penta-refractory subgroup from MAMMOTH and the penta-refractory RRMM population potentially eligible for Sd in clinical practice in England. The EAG considers the impact of these potential differences to be unknown.

2.3.2 *Intervention*

Selinexor (Nexpovio®) is an oral, first-in-class, reversible covalent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). The inhibition of XPO1 by selinexor leads to the accumulation of tumour suppressor proteins (TSPs) and apoptosis of cancer cells. The combination of selinexor and dexamethasone have demonstrated synergistic cytotoxic effects in multiple myeloma *in vitro* and increased antitumour activity *in vivo*.[9]

Selinexor received marketing authorisation from the MHRA in May 2021 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 (PIs), two immunomodulatory agents (IMiDs) and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy. This selinexor combination and corresponding indication is consistent with the company submission for this NICE single technology appraisal (ID6193).

In February 2023, the MHRA also approved selinexor in combination with bortezomib and dexamethasone (SVd) after one prior line of therapy.[9] This selinexor combination and corresponding indication are being appraised separately by NICE as part of a different single technology appraisal (ID3797).[9]

The recommended starting doses for selinexor and dexamethasone in the Sd combination are as follows:

- selinexor 80mg taken orally on Days 1 and 3 of each week; and
- dexamethasone 20mg taken orally on Days 1 and 3 of each week with selinexor.

The company reported that it is not expected that any additional test or investigations will be required to initiate treatment with Sd, or to identify the eligible population.

Treatment with Sd is recommended to be continued until disease progression or unacceptable toxicity.

The EAG considers that the dosing regimen of Sd in the STORM Part 2 trial is consistent with the marketing authorisation for Sd. However, the EAG notes that [redacted]% of patients in STORM Part 2 BCLPD-refractory population received subsequent treatments following Sd and the EAG is concerned that

[redacted] The EAG's clinical experts reported that they would expect patients to receive chemotherapy if further active treatment was deemed appropriate at this stage of MM, and the EAG notes that [redacted]. Based on the advice from its clinical experts, the EAG considers the proportion of patients receiving subsequent therapies in the STORM Part 2 BCLPD-refractory population to be reasonable [redacted]

2.3.3 Comparators

The NICE final scope lists the following as comparators of interest:

- pomalidomide in combination with low-dose dexamethasone;
- panobinostat in combination with bortezomib and dexamethasone;
- belantamab mafodotin (subject to ongoing NICE appraisal);
- conventional chemotherapy regimens; and
- best supportive care (BSC).

The EAG notes that the company considers the only relevant comparator for Sd to be BSC and that this also includes a proportion of patients on conventional chemotherapy (CCT). In addition, the EAG notes that the company reported that BSC is proxied by standard of care (SoC) in the CS and model.

The EAG notes that the marketing authorisation for Sd is for patients with RRMM who have who have received at least four prior therapies and, in response to clarification question A2a, the company confirmed that Sd is anticipated to be used after four prior lines of therapy. The EAG's clinical experts reported that some patients could become penta-refractory earlier than 5L and the EAG considers additional comparators could potentially be of relevance if Sd was to be approved as a treatment option earlier than 5L+.

However, based on the company's proposed 5L+ positioning of Sd and advice from the EAG's clinical experts, the EAG agrees with the company that POM+DEX is unlikely to be relevant a comparator at 5L+ as patients are likely to have already received it. In addition, the EAG notes that belantamab

mafodtin is not currently recommended for use in RRMM in NHS clinical practice and clinical experts reported that it is not routinely used although it is available via a compassionate access scheme. The EAG thus considers it reasonable that the company has not considered belantamab mafodtin to be a relevant comparator for Sd at 5L+.

In contrast, the EAG is concerned that PanoVd is a potentially relevant comparator for Sd as the EAG's clinical experts confirmed that it is a current treatment option at 5L+. The EAG is therefore concerned that the company has not provided a comparison of Sd with PanoVd in the CS and due to the lack of clinical evidence, the EAG is unable to comment on the likely efficacy of Sd versus PanoVd.

Finally, the EAG agrees with the company that BSC is a comparator for Sd at 5L+ and the EAG's clinical experts also considered CCT to be an important comparator. The EAG notes that in the CS CCT has been incorporated within the BSC comparator and considers this not to be unreasonable, although the EAG considers this to be a part of standard of care (SoC; [BSC including a proportion of patients receiving CCT]). The EAG also notes that the use of SoC data as a proxy for BSC in the model is due to the availability of comparator clinical data, which originates from the MAMMOTH study.

MAMMOTH is a USA-based retrospective cohort study and focused on patient's refractory to an anti-CD38 monoclonal antibody with a subgroup of penta-refractory patients (N=70; hereafter referred to as MAMMOTH). The EAG notes that treatments in MAMMOTH included PIs, IMiDs, anti-CD38 monoclonal antibodies, chemotherapy drugs and/or potentially other drugs as it is unclear if all drugs are detailed in the study publication. The EAG is concerned that MAMMOTH includes patients on a wider variety of drugs than CCT and therefore is not reflective of clinical practice in England. The EAG also notes that 10% of penta-refractory patients in MAMMOTH received no further treatment regimens, which is potentially lower than the proportion expected to receive BSC in clinical practice in England according to the EAG's clinical experts.

In summary, the EAG considers the CS has omitted a potentially relevant comparator (PanoVd) for the 5L positioning of Sd and that SoC is used in the company's economic model as a proxy for BSC, but the treatments used in the MAMMOTH study used to inform SoC do not align with clinical practice in England.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify clinical evidence for their company submission (CS), which covered randomised controlled trial (RCTs) and non-randomised/observational studies. Methods and search results for the SLR are provided in Section B.2.1, B.2.2. and Appendix D of the CS. The company reported that searches were conducted according to the methods published in the Cochrane Handbook and the NICE Methodology Process and Methods guide.[11, 12] The EAG considers the references for the published methods cited by the company to be incorrect but does not have concerns that the methods referred to were not followed. The search strategy was developed by a trained information scientist and checked by the research team using the PRESS checklist.[13]

The EAG's critique of the company's SLR methods is outlined in Table 8 below. Overall, the EAG considers it unlikely that the company would have missed relevant evidence (RCTs and non-randomised/observational studies) involving selinexor plus dexamethasone (Sd).

The search for the SLR was broader than the positioning described by the company in the decision problem (Section 2.3). It covered adults with relapsed and/or refractory multiple myeloma (RRMM) as a whole without limiting to a particular line of therapy. This was partially because a single SLR was undertaken for two separate research questions examining the clinical efficacy and effectiveness of selinexor for patients with RRMM at different lines of therapy, one in the 2L/3L setting and one in the penta-refractory (≥ 5L) setting; the penta-refractory one relates to the scope of this appraisal. The EAG does not consider this to be a concern.

The company conducted a wide search combining different search terms for the condition and interventions. The company applied study design filters using established search filters but some of these were amended to increase the sensitivity of the searches and to ensure single arm studies and studies reporting subgroups of interest were identified. In particular, the SLR used the CADTH RCT/CCT filter (amended to aid the identification of single arm trials, subgroups, and studies reported as Phase 2 or 2b) and the SIGN search filter for observational studies.[14, 15] The EAG is concerned by the use of non-standard study design filters as potentially relevant single-arm data may have been missed but the EAG and its clinical experts are not aware of any specific studies of relevance that have been omitted from the CS.

The database searches were conducted in February 2023 and no relevant RCTs were identified of Sd or comparators for the treatment of penta-refractory MM. The company's PRISMA diagram indicates that n=948 records were ultimately identified for inclusion after primary and secondary screening, but the final number of included studies cannot be inferred from the company's PRISMA diagram. The single-arm phase 2b STORM trial was identified and used as the key clinical evidence source for Sd in the CS.

The company conducted indirect treatment comparisons (ITCs) for Sd versus standard of care (SoC), which were informed by observational real-world studies identified through what appears to be an additional two SLRs (one for interventional studies and the second for real world evidence), with searches run in April 2022. The EAG notes that a feasibility assessment was conducted to identify studies with sufficient reporting to allow matching of populations versus STORM, in the ITC. Therefore, studies identified in the SLR were excluded from the ITC if: patient characteristics were poorly reported, if they did not report overall survival (OS) or progression-free survival (PFS), or where the population size was deemed to be too small (<30). Two interventional trials and five real-world observational studies were included following the feasibility assessment of the ITC, of which only one interventional trial, STORM, and three observational real-world studies (MAMMOTH, LocoMMotion, and Kim *et al.* 2021) were included in analyses deemed relevant by the company.[16-19] The SoC studies and ITCs are discussed further in Section 3.4.

Table 8. 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	**The EAG considers the sources and dates searched to be comprehensive, although limited details were provided for non-database searches.** Databases searched: • MEDLINE • Embase • Cochrane: CDSR & CENTRAL • CRD: DARE, HTA & NHS EED Registries searched: ClinicalTrials.gov, ICTRP & EUCTR. Web searching of resources including NICE, SMC, NIRIO tech briefings, EMA, MHRA. Conference searching including: Embase, CPCI-S, ASCO and handsearching ASH. Other sources:

		• Gray literature • Reference checking of clinical guidelines The database and grey literature searches were conducted in February 2023. The company searched across a variety of sources in line with guidance in the Cochrane Handbook.
Search strategies	Appendix D1.1	**The EAG considers the search strategies used likely to be appropriate and unlikely that the company would have missed any evidence (RCT or non-randomised/observational) involving Sd.** The search strategies for the SLR used free-text search words and MeSH terms for the condition, population and interventions of interest. The EAG notes that the company states the condition search structure and terms were compared and were in agreement with Cochrane reviews in a similar population but no further details on this are provided. The EAG notes that the company used filters developed by SIGN to search for a range of study designs but amended them to increase the sensitivity of the searches and ensure single arm studies and studies reporting subgroups of interest are identified.
Inclusion criteria	Appendix D1.1 (Table 1)	**The EAG considers the inclusion criteria of the SLR to be reasonable, although much broader than applicable for the positioning described by the company in the decision problem.** For inclusion, studies were required to comprise adults with (≥18 years) with RRMM with ≥1 prior line of therapy. Studies that reported on newly diagnosed/untreated MM were excluded. All interventions listed in the treatment pathway, alone or in different combinations were deemed suitable for inclusion. Inclusion of studies was not limited by comparator. Outcomes were in line with those defined by NICE in the final scope. Records were not limited to English language studies with the aim for records to be translated to assess eligibility. Conference abstracts were limited to those published from 2021 to present. The rationale for this was unclear, but the EAG does not consider it to have impacted studies included in the CS. Studies identified in the SLR were excluded from the indirect treatment comparisons (ITC) if patient characteristics were poorly reported, which the EAG considers to be reasonable as it would not be possible to accurately match them to the population of the relevant Sd trial identified. Studies were also excluded from ITC if the population size was <30 as they would result in too small effective sample sizes, leading to high uncertainty in the results.
Screening	Appendix D1.1	**The EAG considers the reporting of methods for screening to be adequate.** Dual screening was conducted by two independent reviewers with any disagreement between them regarding the inclusion or exclusion of a record resolved through discussions with a third reviewer. Full-text papers deemed relevant, based on the screening of titles and abstracts of identified records against the SLR inclusion criteria, were obtained and reviewed independently by two reviewers. Results of the study selection process were summarised in a PRISMA diagram.
Data extraction	Appendix D1.1	**The EAG considers the methods of data extraction to be adequate although the template used to facilitate this was unclear.**

		Eligible studies were independently extracted by one reviewer with a cell-by-cell data quality check conducted by a second reviewer. Where there were multiple publications of a study, reports were grouped together, and the primary publication was used in synthesis and supplemented by additional records where relevant outcomes were only reported in different publication versions. Any discrepancy between published versions were highlighted. However, there were no explicit details on any software or data extraction template used.
Tool for quality assessment of included study or studies	Appendix D1.3,	**The EAG has concerns about the company's choice of quality assessment tool for non-RCTs.** The company used a checklist adapted from CASP ('Making sense of evidence 12 questions to help you make sense of a cohort study') to assess the quality of the non-RCTs STORM and MAMMOTH. The STORM trial was considered to be a well-conducted non-RCT with an overall LOW risk of bias. However, the EAG has not been able to validate the appropriateness of the use of an adapted CASP checklist for the single-arm, non-randomised STORM trial and the retrospective, observational MAMMOTH trial. The ROBINS-I tool may have been a more appropriate choice. This is discussed further in section 3.2 below.

Abbreviations: CASP, Critical Appraisal Skills Programme; CS, company submission; EAG, External Assessment Group; ITC, indirect treatment comparisons; NICE, National Institute for Health and Care Excellence; RRMM, relapsed and/or refractory multiple myeloma; RCT, randomised controlled trial; SIGN, Scottish Intercollegiate Guidelines Network; SLR, systematic literature review

3.2 Critique of trials of the technology of interest

There were two trials relating to Sd identified in the company's SLR (Section 3.1). However, only one of them was considered to include evidence of the clinical benefits of Sd in penta-refractory patients, the population relevant for this appraisal, and was therefore included in the CS. This was STORM (NCT02336815), a single arm phase 2b open-label, multi-centre trial evaluating the efficacy and safety of Sd in patients with quad-exposed, double-class-refractory, or penta-exposed, triple-class refractory multiple myeloma (TCR-MM).[19]

The STORM trial comprised of two parts. Part 1 of the STORM trial included patients with quad-exposed (lenalidomide, pomalidomide, bortezomib, carfilzomib) double class refractory (at least 1 proteosome inhibitor [PI] and 1 immunomodulatory imide drug [IMiD]) multiple myeloma (MM) and a subset of patients with penta-exposed TCR-MM included as an exploratory endpoint only. Following a change in the treatment landscape after the approval of daratumumab in 2017, Part 2 of the STORM trial (n=123) was refined to comprise patients with both TCR-MM (defined as patients whose disease is refractory to prior treatment with at least 1 IMiD, at least 1 PI and the anti-CD38 monoclonal antibody daratumumab [and glucocorticoids]) and penta-exposed MM (defined as quad-refractory plus prior treatment with daratumumab; i.e. MM patients previously treated with

lenalidomide, pomalidomide, bortezomib and daratumumab [and an alkylating agent]). Patients enrolled in Part 2 received oral selinexor 80mg (or 45 mg/m^2) twice weekly on Days 1 and 3 until disease progression, death or unacceptable toxicity.

Data from the penta-refractory efficacy population (n=83), which comprised the majority (68%) of patients included in Part 2 of the STORM trial and referred to as the BCLPD-refractory population (refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib daratumumab), was deemed relevant for the decision problem and hence formed the focus of the CS (STORM Part 2 BCLPD-refractory population). The EAG's clinical experts agreed it was appropriate to focus on this sub-set (and not the overall population of STORM Part 2 which included penta-exposed and triple-class refractory patients) but highlighted that although the BCLPD-refractory population does meet criteria for penta-refractory, it would be incorrect to assume that all penta-refractory patients are BCLPD-refractory. For example, the EAG's clinical experts noted stem cell transplant (SCT) eligible patients could have received thalidomide and SCT ineligible patients may not have received carfilzomib in previous lines of therapy.

Applicability of the STORM Part 2 trial to the decision problem is discussed throughout Section 2.3 and the trial methodology is described in Section B.2.3 of the CS, with statistical analysis and critical appraisal described in Sections B.2.4 and B.2.5, respectively. The EAG notes that the company's quality assessment of STORM was performed using an adaptation of the questions set out in the Critical Appraisal Skills Programme (CASP): 'Making sense of evidence 12 questions to help you make sense of a cohort study'.[20] Therefore, the EAG has not been able to validate the appropriateness of the use of an adapted CASP checklist for the single-arm, non-randomised STORM trial. A different checklist, such as ROBINS-I checklist for assessing risk of bias in non-randomised studies of interventions, listed in NICE health technology evaluations: the manual, may have been more appropriate.[12, 21]

The overall risk of bias of the STORM trial, based on the adaptation of the CASP checklist, was deemed LOW. However, considering this was a single-arm, open-label non-randomised controlled trial and the lack of clarity over the identification of all important confounding factors associated with this type of study design, the EAG is not confident that the overall risk-of-bias judgment should be LOW. The EAG highlights that being a single-arm trial is a limitation as it does not provide direct comparative evidence and requires the use of indirect techniques such as matching-adjusted indirect

comparisons (MAICs) and simulated treatment comparisons (STC) to enable comparison of Sd with standard of care (SoC), which introduces additional uncertainty (see section 3.4).

The EAG's assessment of the design, conduct internal validity of the STORM Part 2 trial and the representativeness of the trial population is summarised in Table 9 below.

Based on clinical expert advice, the EAG considers that some of the characteristics of BCLPD-refractory patients in the STORM Part 2 trial, including the age of participants, the time since diagnosis during which they have become penta-refractory, Eastern Cooperative Oncology Group (ECOG) status, proportion with a SCT-transplant and the number of prior anti-MM regimes are not consistent with penta-refractory patients seen in UK clinical practice. The EAG is also concerned that the sample size from STORM Part 2 relevant to this appraisal is relatively small (BCLPD-refractory population, a pre-specified subset of the modified intent-to-treat [mITT] population, n=83) making it difficult to draw robust conclusions on the efficacy of Sd.

In addition, the EAG is notes that [redacted] of patients in the STORM Part 2 BCLPD-refractory population received subsequent therapies after Sd and that these subsequent therapies included treatments not expected to be given in clinical practice in England (e.g. PIs, IMiDs and anti-CD38 monoclonal antibodies). The EAG is therefore concerned and unclear what impact subsequent therapies may have had on the results from STORM, in particular for OS which is a key clinical efficacy outcome used in the economic model. The subsequent therapies received by patients in the STORM Part 2 BCLPD-refractory population are summarised in Table 10.

Table 9. EAG's summary of the design, conduct and analysis of STORM Part 2

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Section B.2.3.1 in CS	**N/A** The trial was single-arm, thus randomisation was not applicable. This is considered a limitation given that it does not provide direct comparative evidence and indirect comparisons via MAICs and STC had to be performed instead, introducing uncertainty (see Section 3.4)
Concealment of treatment allocation	Section B.2.3.1 in CS	**N/A** Given this was an open-label, single arm non-randomised trial, concealment of allocation was not applicable. Participants were allocated to only one treatment.

Eligibility criteria	Section B.2.3.1 in the CS	**Appropriate but penta-refractory efficacy population (BCLPD-refractory) deemed applicable to decision problem, not representative of the whole population eligible for Sd in UK clinical practice.** Full details of the eligibility criteria for STORM Part 2 overall trial population are available in the CS Table 5. Key inclusion criteria for the BCLPD-refractory efficacy population relevant to the decision problem were: • All patients whose MM was documented to be refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab. The EAG notes that although BCLPD-refractory patients do meet criteria for penta-refractory patients described in the CS and NICE final scope, not all penta-refractory patients are BCLPD-refractory. Hence, BCLPD-refractory patients are not likely to be representative of the whole spectrum of penta-refractory patients likely to be eligible for Sd in UK clinical practice.
Blinding	Section B.2.3.1 in CS	**N/A; The study was open-label and Investigators, site staff, Sponsor and Sponsor designees had access to individual patient data.** Assessment of objectively measured outcomes such as OS are unlikely to be impacted by knowledge of the intervention received by patients and outcome assessors. Outcomes entailing a more subjective element, such as ORR, PFS and DOR were well defined and assessed by the IMWG response criteria or an independent review committee, thus the EAG did not have concerns over the impact of lack of blinding.
Baseline characteristics	Section B.2.3.2 in the CS	**The EAG considers the baseline characteristics of the STORM Part 2 BCLPD-refractory population potentially indicate a younger population with a better ECOG performance status than the expected UK penta-refractory patients.** • The EAG's clinical experts noted the median age (range): 65.3 (40-86) years was possibly lower than the average age at which patients would be expected to reach the penta-refractory stage in the UK clinical practice. • Baseline ECOG performance status in BCLPD-refractory patients was better than expected for patients in the UK. The EAG's clinical experts estimated that whilst the majority of penta-refractory patients in the UK would fall under ECOG performance status 2 a number of penta-refractory patients expected to be worse than ECOG 2 classification and a smaller proportion than in the STORM trial are likely to be ECOG 0. The EAG notes that the trial eligibility criteria required patients to have ECOG performance status of ≤2 and considers this may be an important limitation considering the proposed treatment positioning is for all penta-refractory patients regardless of baseline ECOG status. • The EAG's clinical experts noted that the proportion of BCLPD-refractory patients in STORM Part 2 (80.7%) with a prior SCT was higher than expected in UK clinical practice.

		• The EAG noted the number of prior anti-MM regimens STORM Part 2 BCLPD-refractory patients had received varied widely, ranging from 4 to 18. The EAG considers this potentially is a higher number of therapies than expected for penta-refractory patients in clinical practice in the UK. The EAG also notes that BCLPD-refractory patients may not be representative of the whole spectrum of penta-refractory patients likely to be eligible for Sd in UK clinical practice, as discussed in Section 2.3.1.
Dropouts	Section B.2.3.1 in CS	**Reasonable, although discontinuation data specific for the BCLPD-refractory population were not provided.** Data on discontinuation were provided for the overall population enrolled in STORM Part 2 (n=123). The company notes that all patients had discontinued treatment as of 7 September 2019 (data cut-off), the most common reasons being disease progressions (56.9%) and adverse events (31.7%), part of which (19.5%) were related to Sd, followed by patient withdrawal (4.1%, including patients lost at follow-up). Of the 123 patients treated in STORM Part 2, 28.5% completed 1 year of survival follow-up.
Statistical analysis		
Sample size and power	Section B.2.4.2 in CS & kcp-330-012 CSR 2018	**Small sample size in STORM Part 2 penta-refractory (BCLPD-refractory) efficacy population may limit the robustness of any conclusions.** The company reported that the sample size of the overall population of STORM Part 2 was based on assumptions for penta-exposed, TCR-MM using an assumed minimal threshold of 10% of patients with a partial response or better. They reported that a sample of 122 patients, the number used in the primary efficacy analysis, "allowed for a one-sided test at an alpha level of 0.025 to detect a minimum of 20% of patients with a partial response or better against a value of 10% under the null hypothesis with 90% power." The EAG considers the BCLPD-refractory subgroup of the overall STORM Part 2 population to be appropriate for addressing the decision problem but is concerned about its small sample size (n=83).
Handling of missing data	KCP-330-012-statistical & kcp-330-012-protocol	**Reasonable although no detail of handling of missing data were reported in the CS; detail has been obtained from the protocol and statistical analysis plan.** There was no imputation of missing efficacy data. Patients with no response recorded post-baseline were planned to be reported as failures in the analysis of ORR. For efficacy data including PFS, TTP, DOR patients with missing data due to having no disease progression or being non-evaluable at the final analyses, were to be censored on the day they were last evaluated for response assessment and omitted from the analysis. For OS, if death event did not occur during the follow-up period, patients were to be censored at the date of discontinuation from the study or date of last participating visit or database cut date, whichever was earlier.

		The EAG notes that the procedures for handling missing data outlined in the company's statistical analysis plan and protocol were reasonable, however it was not possible to confirm that the procedures were followed.
Outcome assessment	Section B.2.4.1 in the CS	**Reasonable** Analysis of primary efficacy endpoints was performed on the modified intent-to-treat (mITT) population from STORM Part 2, including patients with penta-exposed, triple-class-refractory MM who met all eligibility criteria and received at least 1 dose of Sd. Data for the pre-planned penta-refractory (BCLPD-refractory) efficacy population, including all patients whose MM was documented to be refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab, were the focus of the CS. Safety analyses included patients who received at least 1 dose of study treatment. Safety data reported were Treatment-emergent adverse events and Treatment-emergent treatment-related adverse events (including Grade 3 or 4, serious TEAEs/TRAEs and TAEs/ TRAEs leading to dose modifications, discontinuation and leading to death). These comprised analyses of the overall STORM Part 1 and Part 2 population, and by study part and separately for Part 1 patients with penta-exposed, TCR MM, Part 1 patients with quad-exposed, DCR MM, and Part 2 patients with penta-exposed TCR MM. A breakdown of the adverse events for the Part 2 BCLPD-refractory subgroup including the equivalent data for treatment-related Grade 3+ (2/4/5) AEs by maximum severity occurring in ≥5% was requested and provided by the company.

Abbreviations: AEs, adverse events; BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; CS, company submission; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; DOR, duration of response; IMWG, International Myeloma Working group; MAIC, matching-adjusting indirect comparisons; mITT, modified intention to treat; ORR, overall response rate; OS, Overall survival; PFS, Progression-free survival; QoL, quality of life; Sd; Selinexor plus dexamethasone; SCT, stem cell transplant; TEAEs, treatment-emergent adverse events; TCR, triple-class refractory; TTP, time-to-progression

Table 10. Subsequent therapies received any time after Sd in STORM Part 2 BCLPD-refractory population (Reproduced from clarification response A14, Table 5)

Subsequent therapy	STORM Part 2 BCLPD-refractory population N = 83
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

3.3 Clinical efficacy results of STORM Part 2 BCLPD-refractory population

Clinical efficacy data for Sd presented in the CS for the penta-refractory (BCLPD-refractory) efficacy population of STORM Part 2 were from the primary and updated analyses with the EAG focus on the updated analyses as these data were used in the indirect treatment comparison (ITC) and analyses of cost-effectiveness. The data cut-off dates for the primary and updated analyses were 24 April 2018 and 7 September 2019, respectively.[9, 22, 23]

3.3.1 Overall survival

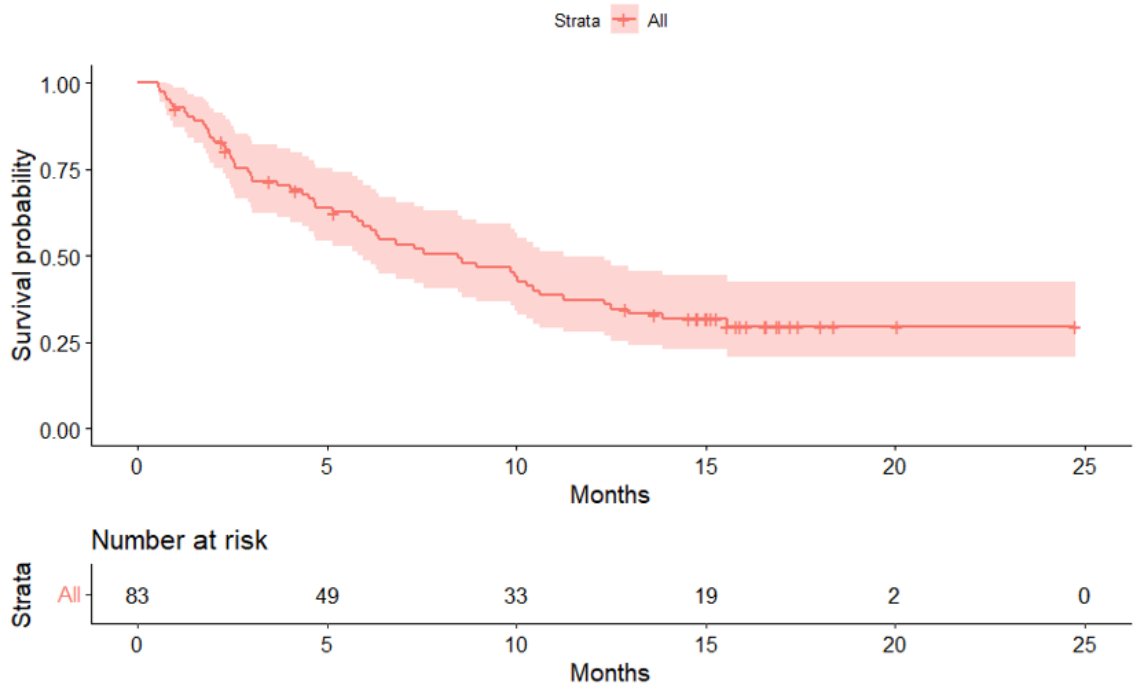
Overall survival in STORM Part 2 was defined as the duration from the start of study treatment to death from any cause. If a death event did not occur during the follow-up period, the patient was censored at the date of discontinuation from the study or database cut date, using whichever occurred earliest.[24] The EAG notes that the median OS in the updated analysis for Sd in the BCLPD-refractory population was 8.4 months (95% CI: 5.9 to 11.2) with an estimated 6- and 12-month survival probability of 58.6% and 37.3%, respectively (Table 11, Figure 2). As discussed in Section 3.2, the EAG is concerned that the results for OS may be confounded by the use of subsequent therapies not routinely used in clinical practice in England and therefore OS may potentially be overestimated for Sd in STORM Part 2.

Table 11. OS based on IRC assessment in STORM Part 2 BCLPD-refractory population (Reproduced from CS, Table 14)

	Primary analysis[22] (data cut-off: 24 April 2018)	Updated analysis[23] (data cut-off: 7 September 2019)
	STORM Part 2: BCLPD-refractory population	STORM Part 2: BCLPD-refractory population
N	83	83
Median OS, months (95% CI)	7.6 (5.9, NE)	8.4 (5.9, 11.2)
Death, n (%)	36 (43.4)	54 (65.1)
Estimated 6-month survival probability, %	60.0	58.6
Estimated 12-month survival probability, %	26.2	37.3

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; CI, confidence interval; IRC, independent review committee; mITT, modified intent-to-treat population; n, number of patients; OS, overall survival.

Figure 2. Overall survival for the BCLPD-refractory population in STORM from the updated analysis with data cut-off 7 September 2019 (Reproduced from CS, Figure 8)



Source: Menarini-Stemline data on file.[25]

3.3.2 *Progression free survival and time-to-progression*

Progression-free survival (PFS) in STORM Part 2 was defined as the duration from start of study treatment to disease progression (PD) or death from any cause whichever occurred first. Time-to-progression (TTP) was the duration from the start of study treatment to the time of progressive disease (PD) or death due to PD, whichever occurred first.

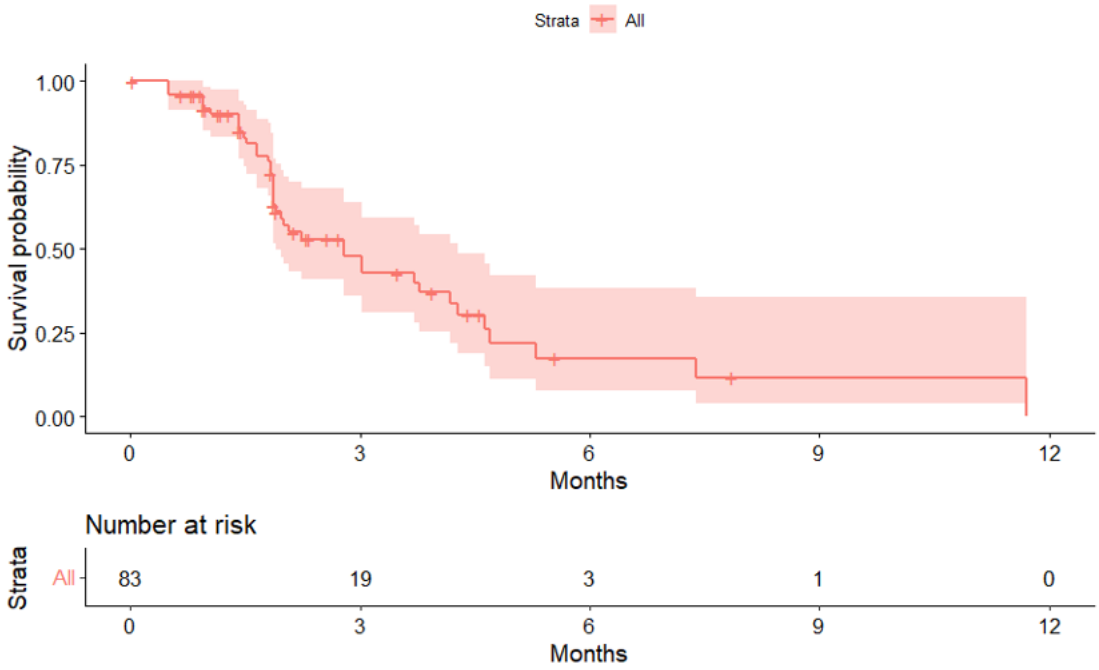
The median independent review committee (IRC) assessed PFS was 2.8 months (95% CI: 1.9 to 4.3) in the STORM Part 2 BCLPD-refractory population and the median IRC-TTP was slightly longer at 3.0 months (95% CI: 2.0, 4.7); both based on the updated analysis data-cut. Table 12 presents PFS and TTP by IRC and investigator (INV) assessment from the updated analysis of the STORM Part 2 BCLPD-refractory population. Kaplan-Meier curves for PFS by IRC and INV for the STORM Part2 BCLPD-refractory population updated analyses are presented in Figure 3 and Figure 4, respectively.

Table 12. PFS and TTP per IRC and INV in STORM BCLPD-refractory population STORM from the updated analysis with data cut-off 7 September 2019 (Adapted from CS, Table 12 and 13)

PFS	Updated analysis[23] (data cut-off: 7 September 2019)	TTP	Updated analysis[23] (data cut-off: 7 September 2019)
	STORM Part 2: BCLPD-refractory population		STORM Part 2: BCLPD-refractory population
N	83	N	83
IRC assessment			
Median PFS, months (95% CI)	2.8 (1.9, 4.3)	Median time to progression, months (95% CI)	3.0 (2.0, 4.7)
Patients with events, n (%)	40 (48.2)	Patients with events, n (%)	36 (43.4)
Progressive disease, n (%)	36 (43.4)	Progressive disease, n (%)	36 (43.4)
Death, n (%)	4 (4.8)	Death due to disease progression, n (%)	0 (0.0)
Patients censored, n (%)	43 (51.8)	Patients censored, n (%)	47 (56.6)
Investigator assessment			
Median PFS, months (95% CI)	3.0 (2.2 to 4.7)	Median time to progression, months (95% CI)	3.8 (2.7 to 5.5)

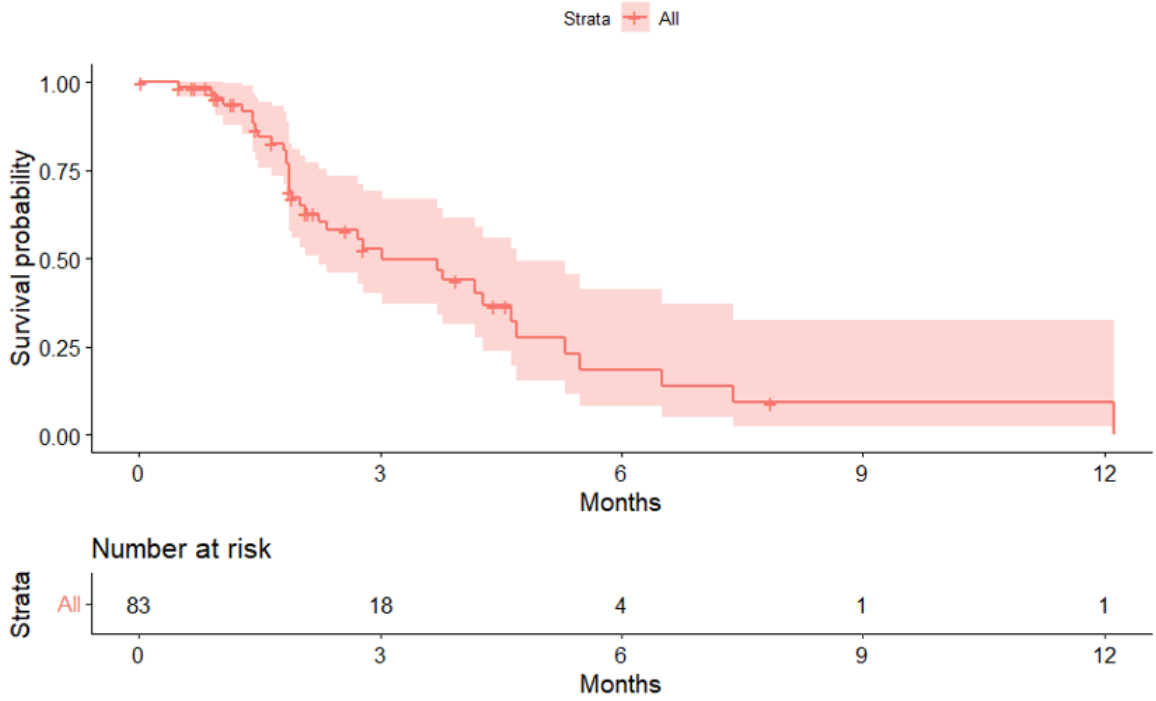
Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; CI, confidence interval; IRC, independent review committee; mITT, modified intent-to-treat population; n, number of patients; PFS, progression-free survival.

Figure 3. PFS by IRC for BCLPD-refractory patients in STORM, updated analysis with data cut-off 7 September 2019 (Reproduced from CS, Figure 6)



Source: Menarini-Stemline data on file.[25]

Figure 4. PFS by INV for BCLPD-refractory patients in STORM, updated analysis data cut-off 7 September 2019 (Reproduced from CS, Figure 7)



Source: Menarini-Stemline data on file.[25]

3.3.3 Response

Overall response rate was the primary efficacy outcome in STORM Part 2 and included patients who experienced partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), based on IMWG response criteria. The BCLPD-refractory population (n=83) had an IRC-ORR of 25.3% and an INV-ORR of 24.1% (Table 13). The EAG notes that the median DOR by IRC assessment was 3.8 months in the BCLPD-refractory population and the company reported that the longest DOR was 10.8 months.[9, 23]

Table 13. ORR per IRC and INV assessment in STORM Part 2 BCLPD-refractory population (Adapted from CS, Table 11)

	Updated analysis[23] (data cut-off: 7 September 2019)	
	IRC assessment	Investigator assessment
N	83	83
ORR,[a] n (%)	21 (25.3), 95% CI: 16.4 to 36.0	20 (24.1), 95% CI: 15.4 to 34.7
CBR,[b] n (%)	31 (37.3), 95% CI: 27.0 to 48.7	27 (32.5), 95% CI: 22.6 to 43.7
Best overall response		
sCR/ CR, n (%)	1 (1.2), 95% CI: 0.0 to 6.5	0 (0.0), 95% CI: N to NE
VGPR, n (%)	4 (4.8), 95% CI: 1.3 to 11.9	6 (7.2), 95% CI: 2.7 to 15.1
PR, n (%)	16 (19.3), 95% CI: 11.4 to 29.4	14 (16.9), 95% CI: 9.5 to 26.7
MR, n (%)	10 (12.0), 95% CI: 5.9 to 21.0	7 (8.4), 95% CI: 3.5 to 16.6
SD, n (%)	32 (38.6), 95% CI: 28.1 to 49.9	NR
PD/ NE, n (%)	20 (24.1), 95% CI: 15.4 to 34.7	NR
Duration of response		
Median DOR, months (95% CI)	3.8 (3.7 to 10.8)	NR

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; mITT, modified intent-to-treat population; MR, minimal response; n, number of patients; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a] ORR was defined as the proportion of patients with a confirmed PR or better

[b] CBR was defined as the proportion of patients with a confirmed MR or better

3.3.4 HRQL

Health-related quality of life (HRQL) was measured in the STORM trial using the Functional Assessment of Cancer Therapy–Multiple Myeloma (FACT-MM) patient-reported outcome (PRO) questionnaire.[26] This instrument combines the 27-item general FACT (FACT-G) version with an MM-

specific subscale (14 items). The FACT-G HRQL data from the STORM trial was used in a mapping procedure to generate EQ-5D-3L data for use in the economic model.

The company reported that the trial outcomes index (TOI) is the primary measurement of interest and that it comprised physical and functional subscales plus the MM-specific subscale, and it has a score ranging from 0 to 120. The HRQL assessments in STORM were performed at baseline (prior to first dose of study treatment), on Day 1 of each treatment cycle on or after the second, and at the Final visit. The EAG considers there to be limited reporting of the HRQL data from STORM Part 2 BCLPD-refractory population in the CS but additional detail on the FACT-MM and FACT-MM TOI scores was provided in response to clarification question A13. In summary, the company reported that most patients in the BCLPD-refractory population maintained HRQL, based on validated patient-reported FACT-G, FACT-MM, and FACT-MM TOI scores.

3.3.5 Subgroup analysis

The BCLPD-refractory population was a pre-specified efficacy population of Part 2 of the STORM trial and further subgroup analysis within the BCLPD-refractory efficacy population was not pre-specified.

In the overall population of STORM Part 2 subgroup analyses were also planned for R-ISS stage (I, II, III); patients with FLC MM/non-FLC MM; high-risk MM; age (18-64, 65-74, ≥75 years of age); US patients/non-US patients; prior use of daratumumab. In addition, in response to clarification question A11 the company provided ORR-INV results from the BCLPD-refractory population for the subgroups of age (18-64, 65-74, ≥75 years of age); prior SCT (yes/no); ECOG status (0, 1 and 2); number of prior anti-MM regimens; and R-ISS stage (I, II, III). The EAG notes that some of the subgroups in the BCLPD-refractory population comprise of small patient numbers and does not consider it appropriate to draw conclusions from these results.

3.3.6 Safety

A summary of the adverse events (AEs) associated with Sd from the STORM trial based on the updated analysis (data-cut 7 September 2019) is provided in Table 14 below. Analyses of AEs were performed using the safety analysis sets, which comprised all patients treated with Sd in Part 1 (n=79) and Part 2 of the STORM trial (n=123), and the BCLPD-refractory subgroup (n=83). The company reported that the median duration of study treatment, overall compliance and average dosing were consistent between the Part 1, Part 2 and the BCLPD-refractory populations.

All patients (100%) across both parts of the STORM trial experienced a treatment emergent adverse event (TEAE) and 98.5% experienced a TEAE assessed as related to the study treatment (TRAE) (Table 14). The company highlighted that available safety data for the BCLPD-refractory population, the primary focus of the CS, was consistent with the overall STORM trial population. In the BCLPD-refractory sub-group, 30% experienced a TEAE leading to study discontinuation, 9.6% a TEAE leading to death and 2.4% a TRAE leading to death. These results were comparable with that for the STORM Part 1 and overall Part 2 population.

Most (89.1%) treated patients in the overall STORM Part 1 and Part 2 population (n=202) had a severe ≥Grade 3 treatment related TEAE. The EAG notes that a breakdown of the ≥Grade 3 treatment related TEAEs occurring in ≥5% of participants was only given for the overall population of STORM Part 1 and Part 2 combined (including the BCLPD-refractory subgroup) in the CS, although in the company's response to clarification questions equivalent data were provided separately for the BCLPD-refractory population and the overall STORM Part 2 including the BCLPD-refractory population. Results were generally consistent between the Part 1 and 2, Part 2 and the BCLPD-refractory population analysis sets. The most frequently occurring (>5% of patients) severe TEAEs across populations included haematologic events such as thrombocytopenia, anaemia, neutropenia, leukopenia and lymphopenia, gastrointestinal events such as nausea and diarrhoea, and other severe events such as hyponatremia, fatigue, hyperglycaemia and hypokalaemia.

The EAG notes that the rates of Grade 3 and 4 AEs associated with Sd in STORM Part 2 were used in the company's economic model rather than the AEs for the BCLPD-refractory population (Table 15). In addition, the EAG notes that the economic model includes the rate of all Grade 3 and 4 AEs in the STORM Part 2 population whereas the data presented in the clinical section of the CS are limited to those occurring in ≥ 5% of patients in each population presented. Additional Grade 3 and 4 AEs included in the economic model were back pain, bone pain, dehydration, dyspnoea, hypokalaemia, pneumonia, sepsis, and vision blurred. The EAG assumes that the rate of AEs is based directly on the occurrences observed in the clinical trial, of which the company has IPD data for. Therefore, the EAG deems it appropriate to use the reported rates in the model as opposed to the incident data (CS, Table 29). However, the EAG notes that if any additional active comparators were to be included in the model, the use of rates would be inappropriate unless the equivalent IPD data was available.

Table 14. Summary of TEAEs in the STORM safety analysis population (Reproduced from CS, Table 18)

	STORM Part 1	STORM Part 2	
	Updated analysis 7th September, 2019[23]		
	SAS	SAS	BCLPD
n	**79**	**123**	**83**
Treatment-emergent adverse event [a], n (%)	79 (100.0)	123 (100.0)	83 (100)
Grade 3/ 4 TEAE, n (%)	75 (94.9)	115 (93.5)	NR
Serious TEAE, n (%)	45 (57.0)	78 (63.4)	NR
TEAE leading to dose modification[b], n (%)	61 (77.2)	97 (78.9)	NR
TEAE leading to dose reduction, n (%)	46 (58.2)	80 (65.0)	NR
TEAE leading to dose interruption, n (%)	35 (44.3)	72 (58.5)	NR
TEAE leading to study discontinuation, n (%)	20 (25.3)	39 (31.7)	25 (30)
TEAE leading to death, n (%)	8 (10.1)	12 (9.8)	8 (9.6)
Treatment-emergent treatment-related adverse event [b], n (%)	78 (98.7)	121 (98.4)	NR
Grade 3/ 4 TRAE, n (%)	69 (87.3)	110 (89.4)	NR
Serious TRAE, n (%)	21 (26.6)	38 (30.9)	NR
TRAE leading to dose modification, n (%)	54 (68.4)	88 (71.5)	NR
TRAE leading to dose reduction, n (%)	37 (46.8)	64 (52.0)	NR
TRAE leading to dose interruption, n (%)	32 (40.5)	70 (56.9)	NR
TRAE leading to study discontinuation, n (%)	13 (16.5)	24 (19.5)	NR
TRAE leading to death, n (%)	1 (1.3)	3 (2.4)	2 (2.4)

Abbreviations: BCLPD, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; NR, not reported; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TRAE treatment-emergent treatment-related adverse event

Note: Percentages are based on the number of all-treated patients in each treatment group. A TEAE is defined as an AE that emerged or worsened from first dose to 30 days after last dose.

[a] The number of patients with dose modification(s) is not necessarily equal to the sum of the patients who had a modified dose or a drug interruption as the same patient could fall into more than one of these categories

[b] TEAEs with a relationship of Possible, Probably, or Definite to either selinexor or dexamethasone per Investigator are considered related to study treatment

Table 15. Grade 3 and 4 treatment-emergent adverse events used in cost-effectiveness analysis (Reproduced from company response to additional clarification questions, Table 5)

Adverse events	STORM Part 2	
	[redacted]	%
Anaemia	[redacted]	45.1%
Asthenia	[redacted]	5.7%
Back pain	[redacted]	2.5%

Bone pain	[redacted]	0.8%
Decreased appetite	[redacted]	6.6%
Dehydration	[redacted]	3.3%
Diarrhoea	[redacted]	7.4%
Dyspnoea	[redacted]	4.1%
Fatigue	[redacted]	21.3%
Hyperglycaemia	[redacted]	6.6%
Hypokalaemia	[redacted]	6.6%
Hyponatraemia	[redacted]	22.1%
Leukopenia	[redacted]	14.8%
Lymphopenia	[redacted]	11.5%
Nausea	[redacted]	9.8%
Neutropenia	[redacted]	22.1%
Pneumonia	[redacted]	9.0%
Sepsis	[redacted]	7.4%
Thrombocytopenia	[redacted]	62.3%
Vision blurred	[redacted]	1.6%

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

Two interventional trials and five real-world observational studies were included from the SLRs following the feasibility assessment of the ITC, of which only one interventional trial, STORM, and three observational real-world studies (MAMMOTH, LocoMMotion, and Kim *et al.* 2021) were included in analyses deemed relevant by the company.[16-19, 27]

The EAG notes that the interventional trial that was deemed not to be relevant was of belantamab mafodotin and the two real-world studies were FHAD and Gill *et al*. 2021.[27-29] The FHAD study included 64 patients in the USA with triple-class-refractory MM but did not report on the proportion of patients (if any) who were penta-refractory.[28] Gill *et al*. 2021 comprised of 112 penta-refractory patients from a single centre but had limited reporting, with publications only comprising of an abstract (2021) and a letter (2022).[29, 30] The EAG considers it reasonable to exclude FHAD due to the lack of detail on penta-refractory status of patients in the study, but the EAG considers the data from Gill *et al*. 2021 could have potentially been used in an ITC with STORM for OS. However, in response to clarification question A8, the company reported that based on the additional detail from the 2022 publication relating to Gill *et al*. 2021, the treatments used for penta-refractory disease do not make it a suitable data set to estimate OS. In particular, there were 7 patients who received selinexor and

4 patients who received CAR-T, therefore the company did not consider the Gill *et al*. study to be a clinically appropriate proxy for BSC and/or conventional chemotherapy (CCT).

The EAG notes that despite the inclusion of LocoMMotion and Kim *et al*., they were subsequently dismissed by the company as being unsuitable for use in unanchored matching-adjusting indirect comparisons (MAICs) because the number of penta-refractory patients in Kim *et al*. was only 25, and LocoMMotion did not publish separate OS and PFS KM curves for the n=44 penta-refractory patients. The one remaining study of SoC, MAMMOTH, was selected by the company as the best available source of evidence for SoC for use in an unanchored MAIC versus STORM. However, MAMMOTH does not report PFS and so only analyses of OS were possible.

3.4.1 Overview of MAMMOTH

MAMMOTH is a USA-based retrospective cohort study and focused on patient's refractory to an anti-CD38 monoclonal antibody with a subgroup of penta-refractory patients (N=70; hereafter referred to as MAMMOTH). Patients enrolled in the penta-refractory subgroup of MAMMOTH were required to have penta-refractory RRMM and to be refractory to daratumumab or isatuximab, administered alone or in combination following at least 4 weeks of treatment with evidence of progressive disease (PD), as defined by the International Myeloma Working Group (IMWG) Response Criteria, having progressed while on therapy or within 60 days after last dose of the treatment regimen. The EAG considers that the first subsequent treatment received following this progression is detailed in Table 16 and notes that these treatments included PIs, IMiDs, anti-CD38 monoclonal antibodies, chemotherapy drugs. The EAG considers it to be unclear if all drugs received at first subsequent treatment are detailed in the MAMMOTH study publication but nevertheless, the EAG is concerned that MAMMOTH includes patients on a wider variety of drugs than CCT and includes drugs not routinely used in penta-refractory patients in clinical practice in England (e.g. PIs, IMiDs and elotuzumab). The EAG also notes that 10% of penta-refractory patients in MAMMOTH received no further treatment regimens which is potentially lower than the proportion expected to receive BSC in clinical practice in England according to the EAGs clinical experts (approximately 30%).

Based on clinical expert advice, the EAG considers that similar to the STORM Part 2 BCLPD-refractory population, there are differences between the MAMMOTH patients and the penta-refractory RRMM patients seen in clinical practice in England. In MAMMOTH patients have a lower mean age (58.5 years), higher rate of prior SCT (67.1%) and a lower and greater number of prior lines of therapy (median 5, range 2 to 16) compared to penta-refractory RRMM patients in clinical practice in

England. In addition, the EAG notes that MAMMOTH was a USA-based study that required patients index regimen to include an anti-CD38 monoclonal antibody to which they were deemed to be refractory to. The EAG considers that clinical practice and availability of treatments in the USA is likely to differ with UK clinical practice and considers that with the 5L+ positioning of Sd, patients in clinical practice in England may not receive an anti-CD38 monoclonal antibody in their final regimen prior to receiving Sd. The EAG also notes that subsequent treatments received in MAMMOTH following the first therapy in Table 16 were not detailed in the study publication and so it is unclear if they are any more consistent with clinical practice than the subsequent treatments received in the STORM Part 2 BCLPD-refractory population. However, the EAG does consider the treatments in MAMMOTH to be broadly consistent with the subsequent treatments received by patients in the STORM Part 2 BCLPD-refractory population, as both studies involved the further treatment of penta-refractory patients with PIs, IMiDs and anti-CD38 monoclonal antibodies. However, the EAG considers that the generalisability of the SoC data from MAMMOTH to current clinical practice in England is questionable.

Table 16. Summary of treatment regimens used in MAMMOTH

Treatment regimen*	MAMMOTH N= 70
Any	63 (90.0%)
Chemotherapy: Any alkylator 'PACE' like Bendamustine	 29 (41.4%) 5 (7.1%) 6 (8.6%)
IMiD plus daratumumab, elotozumab or carfilzomib	11 (15.7%)
Any carfilzomib (PI) Carfilzomib + IMiD Carfilzomib + alkylator	8 (11.4%) 2 (2.9%) 2 (2.9%)
Any daratumumab (mAb) Daratumumab + IMiD Daratumumab + PI	9 (12.9%) 3 (4.3%) 5 (7.1%)
Elotuzumab + IMiD	6 (8.6%)

* Regimen categories are not mutually exclusive.
Abbreviations: IMiD, immunomodulatory drug; mAb, monoclonal antibody; PI, proteosome inhibitor.

3.4.2 *Methods and results for the indirect treatment comparisons*

The company explored the use of three different sets of variables in the MAIC models: "must have", "full", and "must have + nice to have". These variables comprised of prognostic factors and effect

modifiers, with the prognostic factors validated by the company's clinical experts. The EAG notes that the "full" set excluded prior SCT and in naïve comparison there is a difference between prior SCT in STORM (80.7%) and MAMMOTH (67.1%).

Table 17. Summary of variables used in the ITC analyses and variables reported in MAMMOTH

Set of factors – 'Must have + Nice to have'	Must Have	Full	Must Have + Nice to Have	MAMMOTH
Age	✓	✓	✓	✓
Sex	✓	✓	✓	✓
ECOG performance status	✓	✓	✓	×
R-ISS	✓	✓	✓	✓
High cytogenetic risk	✓	✓	✓	✓
No. prior regimens	✓	✓	✓	✓
Prior SCT	✓		✓	✓
Duration of last therapy			✓	✓
Time since initial diagnosis		✓	✓	✓
Creatinine clearance at baseline		✓	✓	× (reported using different units)
Haemoglobin at baseline		✓	✓	×

Abbreviations: ECOG, Eastern Cooperative Oncology Group; No., number; R-ISS, Revised International Staging System; SCT, stem cell transplant.

The company reported that no conclusions could be drawn from the MAIC of STORM Part 2 BCLPD *versus* MAMMOTH as all models tested produced low effective sample sizes (ESS) and were associated with high uncertainty (Table 18). The EAG notes that the "must have + nice to have" set of variables were not fully reported in MAMMOTH and therefore the EAG considers the "Full" set to be the most appropriate for the MAIC of the remaining analyses. The EAG notes the resulting ESS from the MAIC using the "Full" model is only 10 but considers it more appropriate to adjust for all variables rather than use the model with fewer variables. The EAG also notes that there are potentially additional variables (prior SCT and duration of last therapy) that could have been included in the MAIC but that the company reported that the inclusion of these in the "must have + nice to have" MAIC resulted in an ESS of 0. The EAG also considers it important to highlight that the low ESS in the MAICs reflects the lack of overlap in key patient baseline characteristics between the STORM Part 2 BCLPD refractory

population and the MAMMOTH penta-refractory population. The company reported that due to this low ESS, a simulated treatment comparison (STC) was performed as a secondary analysis, as this approach mitigates the large loss of ESS. The EAG does not consider the company's methods of using an STC fully addresses the underlying reason for the low ESS: the poor overlap in patient characteristics between the two studies and so questions the validity of using a regression analysis based on STORM Part 2 BCLPD refractory IPD to estimate the treatment effects of SoC from MAMMOTH, without providing strong evidence that the outcome regression model is correctly specified and provides reasonable predictions when extrapolating beyond the training data.

Table 18. MAIC results STORM BCLPD *versus* MAMMOTH: overall survival (Reproduced from CS, Table 15)

Model	Original sample size	ESS	ESS %	HR naïve (95% CI)	HR weighted (95% CI)	AIC (weighted)	BIC (weighted)	Comments
Must have	80	13.5	17%	0.627 (0.435-0.904)	0.757 (0.268-1.883)	598.603	601.407	ESS n<30
Full	80	10.4	13%	0.627 (0.435-0.904)	0.681 (0.327-2.095)	555.86	558.664	ESS n<30
Must have + nice to have	-	-	-	-	-	-	-	Population cannot be matched

Figure 5 and Figure 6 show the MAMMOTH Kaplan-Meier (KM) curves (reconstructed from the digitised data) with the Sd data from the unadjusted and adjusted MAIC analyses for the 'Must have' set of covariates and 'Full' set of covariates, respectively. The EAG notes that in both the "Must have" and the "Full" analyses the first 7 months of the curves are overlapping for Sd and SoC and beyond this there are few patients (8 and 6, respectively) left in the analyses. The EAG also notes that a naïve comparison of the unadjusted Sd KM curve also overlaps with the MAMMOTH SoC digitised data curves in Figure 5 and Figure 6.

Figure 5. Kaplan-Meier Survival Curve for OS - STORM BCLPD vs MAMMOTH – unadjusted Sd, MAIC-weighted Sd and digitised data from MAMMOTH based on 'Must have' model (Reproduced from company response to clarification questions, Figure 12)

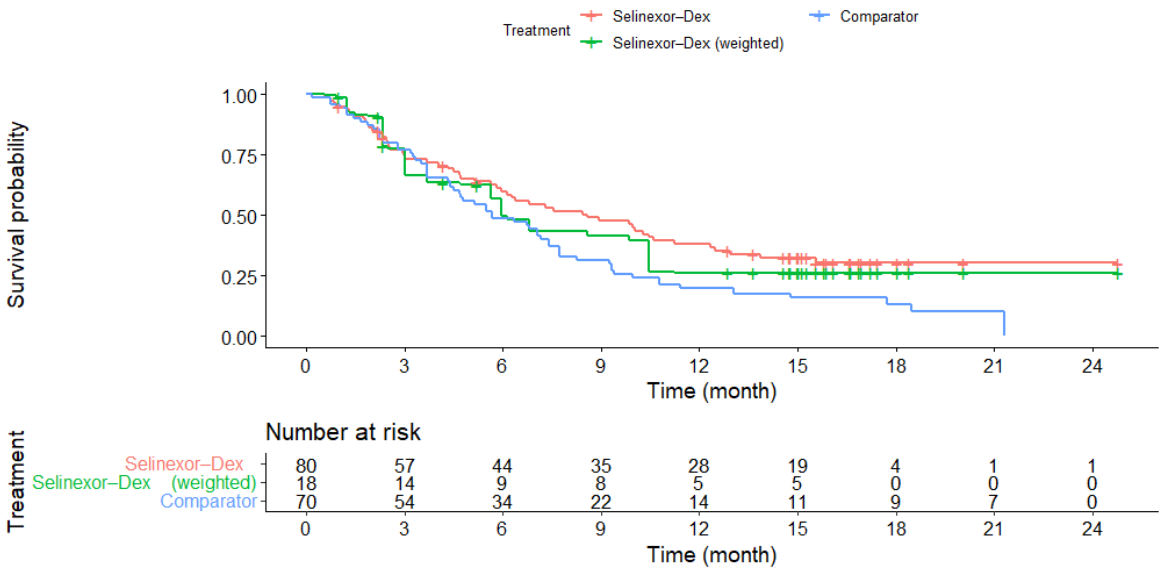
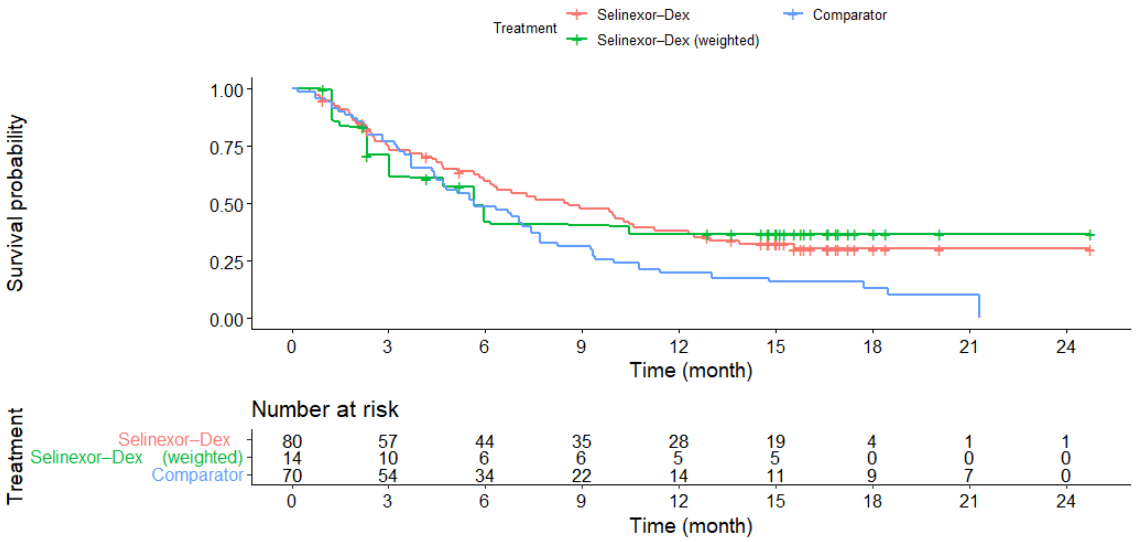


Figure 6. Kaplan-Meier Survival Curve for OS - STORM BCLPD vs MAMMOTH – unadjusted Sd, MAIC-weighted Sd and digitised data from MAMMOTH based on 'Full' model (Reproduced from company response to clarification questions, Figure 14)



In the company response to clarification questions, the company provided additional detail on the STC methods they had used to provide an estimate of a HR between Sd and SoC using data from the STORM Part 2 BCLPD refractory population and the penta-refractory subgroup from the MAMMOTH study. The company reported that standard parametric survival models including all prognostic factors and effect modifiers in the 'Must have + Nice to have' covariate set were fit to the STORM Part 2 BCLPD refractory IPD. The reported covariate values from the penta-refractory subgroup of

MAMMOTH were inputted into the resulting survival model, and survival probabilities simulated from this model. A HR was then calculated between the digitised KM data of the MAMMOTH penta-refractory subgroup and the simulated survival data. Further details of the STC methods can be found in the company response to clarification question A17.

The company reported that the above process was repeated for each selected parametric survival model (including exponential, Weibull, lognormal, loglogistic and Gompertz distributions) but due to convergence issues when attempting to fit the generalised gamma model it could not be used in the STC.

The results from the STC analyses are provided in Table 19 and suggest Sd is associated with statistically significantly longer OS compared to SoC (HR and 95% CI are less than 1.0) across all of the models.

Table 19. STC results – STORM BCLPD versus MAMMOTH for each parametric survival model: overall survival (Reproduced from company response to clarification questions, Table 6)

Distribution	HR	95% CI	Mean (SD)
Exponential	0.388	0.191 to 0.790	0.414 (0.153)
Weibull	0.389	0.185 to 0.787	0.413 (0.154)
Lognormal	0.433	0.229 to 0.795	0.455 (0.146)
Loglogistic	0.420	0.208 to 0.789	0.442 (0.152)
Gompertz	0.392	0.198 to 0.760	0.417 (0.151)

Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation.
Notes: HR is based on a comparison of Sd versus standard of care.

The company assessment of model fit suggested that the lognormal distribution provided the best model fit according to the AIC and BIC.

The EAG is concerned that there are several limitations of the company's STC, including the following:

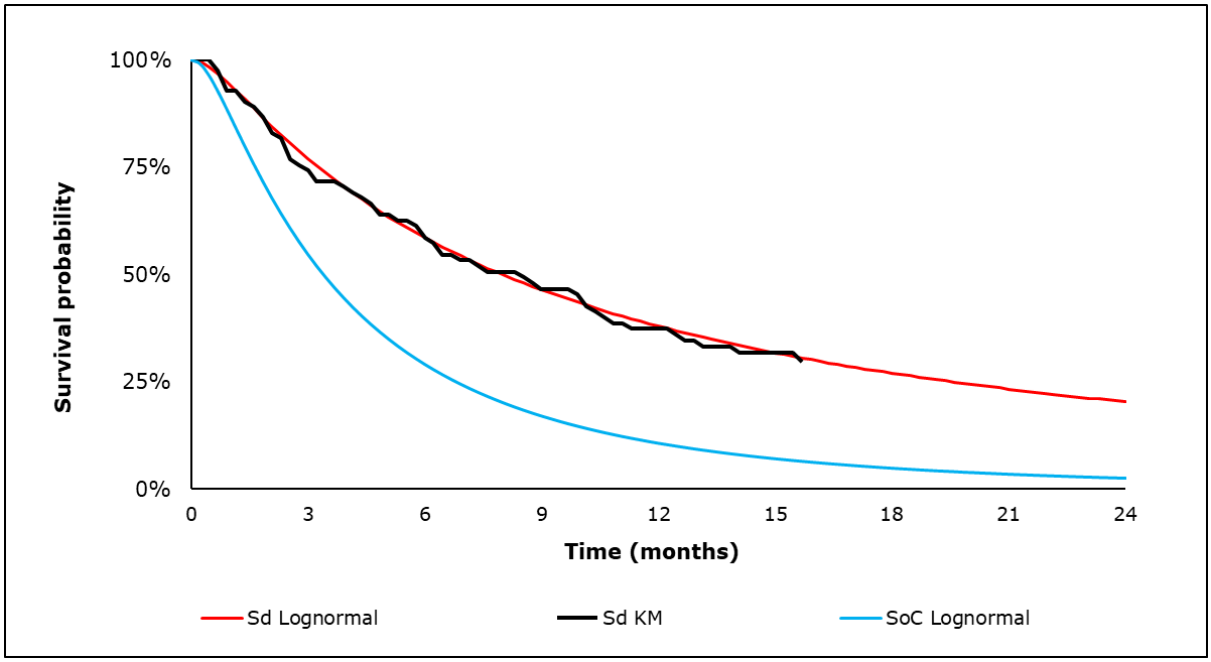
- The company accepted there was “large uncertainty associated with the coefficients” of the outcome regression model, which was performed on data from a study “not designed or powered to show subgroup effects”. While the company captured this uncertainty through bootstrap resampling, the point estimate of the HR from the STC is likely to be very unstable and could change substantially if the study was replicated;
    - The company did not validate the clinical plausibility of the results of the outcome regression. For example, the EAG noted that the point estimate of the coefficient

associated with R-ISS Stage 3 was closer to 0 than the R-ISS Stage 2 coefficient, which is unexpected if R-ISS Stage 3 represents a worse prognosis than R-ISS Stage 2. In response to additional clarification questions, the company outlined that, "The estimated model coefficients are reflective of the STORM data. For example, patients with R-ISS Stage 3 show slightly improved overall survival (OS) compared to R-ISS Stage 2, which would explain why the point estimate of the coefficient associated with R-ISS 3 is closer to 0 than the R-ISS 2 coefficient". However, the EAG considers this to be evidence that the outcome regression may lack clinical plausibility, and therefore be unsuitable to simulate new data. For example, these simulations will assume that, on average, R-ISS Stage 3 will show improved overall survival compared to R-ISS Stage 2 – which the EAG considers clinically implausible.[31]

- The company did not provide an assessment of the overall fit of the model, nor an assessment of whether the model was correctly specified. Instead, the company validated a series of parametric survival models using relative measures of model fit (AIC and BIC). However, that the lognormal model provided a better fit to the data than each other model does not provide any evidence of the absolute fit, i.e., the lognormal model may have been the best fitting of a series of poorly fitting models.

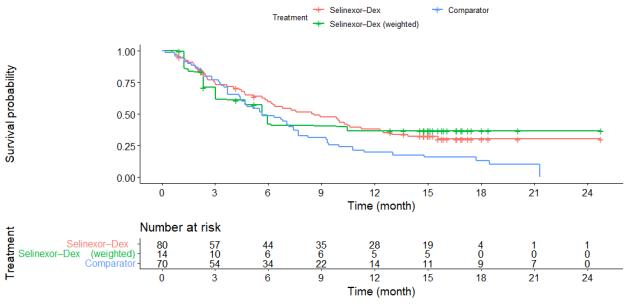
The extrapolated OS survival curve for Sd from the company's preferred model (lognormal) is shown alongside the STORM Part 2 BCLPD refractory observed trial KM data and the SoC curve, estimated from applying the HR derived from the STC, in Figure 7 below.

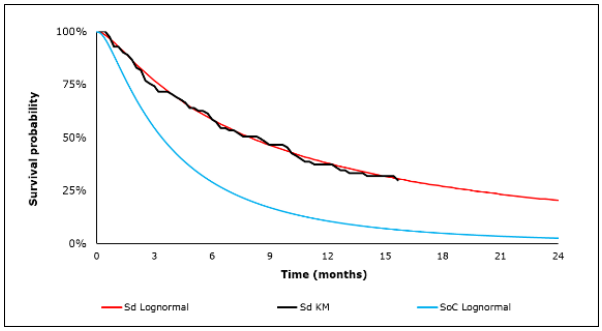
Figure 7. OS Kaplan-Meier curve for Sd from the STORM BCLPD population with overlaid lognormal extrapolation and the SoC survival curve (produced from the company model)



The EAG notes from the naïve and adjusted (MAIC) comparisons of Sd and SoC using the STORM Part2 BCLPD refractory population and the MAMMOTH penta-refractory subgroup that there are multiple overlaps in the initial 3.5 and 7 months of the overall survival KM curves, respectively, and that this is not captured in the STC (Figure 8). The STC instead considers the efficacy of Sd and SoC is entirely separate as it assumes proportional hazards holds. The EAG does not consider this to be appropriate and therefore does not consider it valid to use the results of the company's current STC for drawing conclusions on the efficacy of Sd versus SoC or for use in the analysis of cost-effectiveness. The EAG also does not consider the company's MAICs to be robust for drawing conclusions given the resulting low ESS but of the ITCs presented by the company, the EAG considers the "Full" MAIC to be the most reasonable as it provides adjustment for the most variables.

Figure 8. OS KM curves from the "Full" MAIC (left) and OS extrapolations from the STC(right) (Reproduced from Figure 6 and Figure 7)





Given the complex nature of the underlying KM curves for Sd and SoC, as illustrated in the naive comparisons and MAICs, the EAG's preferred approach would be to fit independent curves to the adjusted Sd KM curve and the SoC KM curve from MAMMOTH as this would not require estimating a HR (which would not appear to have face validity given the crossing curves). The EAG appreciates that this would essentially mean that the OS estimates are for the MAMMOTH population rather than the STORM Part 2 BCLPD population, but considers this the "least biased" of the options available.

3.5 Conclusions of the clinical effectiveness section

The EAG considers the key evidence submitted by the company in support of the clinical efficacy and safety of selinexor with (low-dose) dexamethasone (Sd) in the treatment of multiple myeloma (MM) in penta-refractory patients to be from the STORM Part 2 BCLPD-refractory (refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib daratumumab) subgroup (n=83) of the STORM trial.[19] STORM (NCT02336815) was a single arm phase 2b open-label, multicentre trial evaluating the efficacy and safety of Sd in patients with quad-exposed, double-class-refractory, or penta-exposed, triple-class refractory multiple myeloma (TCR-MM). The EAG considers the STORM Part 2 BCLPD-refractory subgroup to align well with the NICE final scope in terms of intervention and outcomes but considers there to be potential limitations in relation to its generalisability to the penta-refractory RRMM population in England and in terms of the subsequent treatments received not aligning with clinical practice (Section 2.3.1 and Section 2.3.2).

Based on clinical expert advice, the EAG considers the baseline characteristics of the STORM Part 2 BCLPD-refractory population differ to the penta-refractory RRMM patients in clinical practice in England. In particular, the median age (65.3 years) in the STORM Part 2 BCLPD-refractory population was possibly lower than the average age at which patients would be expected to reach a penta-refractory status in the UK. Also, the ECOG status was probably better than seen in clinical practice, and prior SCT and number of prior anti-MM regimens in the STORM Part 2 BCLPD-refractory population were potentially higher than expected in clinical practice in England. Penta-refractory status can also be achieved using different prior therapies than those received by the BCLPD-refractory population in STORM Part 2 and the potential impact of this on the efficacy of Sd is unknown. The EAG is also concerned that the subsequent treatments received in the STORM Part 2 BCLPD refractory trial population following Sd ([redacted]) are not fully reflective of subsequent treatments likely to be received in clinical practice in England. The subsequent treatments in STORM include

[redacted]

[redacted]

In addition, the EAG notes that there are differences between the patient characteristics and treatments received in the MAMMOTH study used to inform BSC in the CS, compared with SoC in clinical practice in England. The EAG notes that SoC in MAMMOTH is being used as a proxy for BSC and that BSC is deemed by the company to include a mix of no further active treatments and CCT. However, the EAG notes that 90% of patients in MAMMOTH receive further treatments and the EAG's clinical experts reported that this proportion is higher compared to expected in clinical practice in England (up to 70%). In addition, the EAG notes that some patients in MAMMOTH received IMiDs, PIs and other drugs which are not consistent with clinical practice in England.

The EAG considers that the discrepancies between the studies: STORM Part 2 BCLPD-refractory subgroup and MAMMOTH penta-refractory subgroup, compared with patients with penta-refractory RRMM in clinical practice in England, as well as the differences in treatments and subsequent treatments, may limit the generalisability of the findings for Sd to clinical practice. However, the EAG considers that the treatments used in MAMMOTH and

[redacted]

The NICE final scope describes the population of interest for Sd as people with RRMM who have had four or more treatments and whose disease is refractory to at least two proteasome inhibitors (PIs), two immunomodulatory agents (IMiDs) and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy. Selinexor has marketing authorisation in the UK in combination with dexamethasone for this population (Medicines and Healthcare products Regulatory Agency [MHRA], May 2021) although the EAG notes that the term penta-refractory is not used within the MHRA approval.[1] The key clinical efficacy data for Sd are from the BCLPD-refractory subgroup of STORM Part 2 that also matches the penta-refractory population defined in the NICE final scope. However, the EAG is concerned that the term penta-refractory does not directly align with a line of therapy but the company clarified in their response to clarification questions that they are seeking approval of Sd for use at fifth line and beyond (5L+). The EAG's clinical experts reported that patients could become penta-refractory at an earlier line of therapy than fifth line. However, the EAG notes that the wording of the MHRA marketing

authorisation restricts the use of Sd to patients who have received at least four prior therapies and the company confirmed in response to clarification question A2, that this relates to four prior lines of therapy. The EAG thus considers the company's proposed positioning of Sd for penta-refractory RRMM patients at 5L+ to be reasonable.

The EAG considers additional comparators would be of relevance if Sd was to be considered as a treatment option earlier than ≥5L, such as Pd, and considers it important to highlight that these have not been considered in the CS or the EAG report as the focus has been on the use of Sd in the 5L+ positioning proposed by the company.

Comparisons listed in the NICE final scope were Pd, PanoVd, belantamab mafodotin, conventional chemotherapy (CCT) regimens; and BSC. However, BSC (proxied by SoC) was the only comparator considered relevant by the company for the population in which they chose to position Sd for (penta-refractory MM patients at 5L+). The EAG notes that BSC in the CS includes CCT but all other comparators were omitted from the CS. The EAG's clinical experts consider it not to be unreasonable to exclude Pd and belantamab mafodotin as comparators for Sd in the 5L+ setting. However, the EAG's clinical experts indicated that PanoVd is a potentially relevant comparator for Sd as it is a current treatment option for patients at 5L+. Therefore, the EAG is concerned that the company has not provided a comparison of Sd with PanoVd in the CS, as conclusions about the clinical and cost-effectiveness of Sd over the treatment options currently available to the population of interest cannot effectively be drawn.

The EAG notes that there is an absence of head-to-head data comparing Sd with BSC or CCT and that the company has conducted a MAICs and STCs to enable a comparison between the Sd and SoC (proxy for BSC). However, the EAG is concerned about the robustness of both the company MAICs and STC analyses for the comparison of Sd versus SoC. The EAG notes that the MAIC analyses result is small ESSs, with the EAG preferred 'Full' adjusted MAIC resulting in an ESS of 10.3 for Sd.

For the STC, the EAG is concerned that the simple proportional hazards approach utilised by the company lacks face validity given the multiple overlaps seen in the initial 3.5 months of the underlying KM curves for Sd (unadjusted curve) and SoC from STORM Part 2 BCLPD-refractory patients and the MAMMOTH penta-refractory subgroup.

Given the complex nature of the underlying KM curves for Sd and SoC, as illustrated in the naïve comparisons and MAICs, the EAG's preferred approach would be to fit independent curves to the

adjusted Sd KM curve and the SoC KM curve from MAMMOTH as this would not require estimating a HR (which would not appear to have face validity given the crossing curves). The EAG appreciates that this would essentially mean that the OS estimates are for the MAMMOTH population rather than the STORM Part 2 BCLPD-refractory population, but considers this the "least biased" of the options available.

The EAG notes that the median OS in the updated analysis for Sd in the STORM Part 2 BCLPD-refractory population was 8.4 months (95% CI: 5.9 to 11.2) with an estimated 6- and 12-month survival probability of 58.6% and 37.3%, respectively. [redacted]% of patients had ≥1 Grade 3+ TRAE. Analysis of overall survival from the MAIC for Sd versus SoC using MAMMOTH and the 'Full' set of covariates resulted in a HR of 0.681 (95% confidence interval: 0.327 to 2.095), suggesting longer OS with Sd than SoC. However, as discussed above the EAG considers the results from both STORM and the indirect treatment comparisons with MAMMOTH should be interpreted with caution.

In summary, the EAG is concerned that PanoVd is a potentially relevant comparator (Section 2.3.3), and that this has not been considered in the clinical or cost-effectiveness analyses presented in the CS. Additionally, the EAG is concerned that there is a lack of robust clinical data to enable a robust comparison of Sd with SoC, and therefore any estimates of clinical efficacy should be interpreted with caution. The EAG also considers independent complex curve fitting is required to more accurately reflect the data for Sd and SoC and to enable more robust estimates of the cost-effectiveness of Sd versus SoC.

4 Cost effectiveness

Table 20 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.

Table 20. Company's base case results post clarification

Interventions	Total Costs (£)	Total LY*	Total QALYs	Inc. costs (£)	Inc. LYs*	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) severity modifier applied
Deterministic results								
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,285	£23,109
Probabilistic results								
BSC	[redacted]	-	[redacted]	-	-	-	-	-
Sd	[redacted]	-	[redacted]	[redacted]	-	[redacted]	£40,350	£23,735

*Undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; BSC, best supportive care; Sd, Selinexor plus dexamethasone

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

The company conducted a systematic literature review (SLR) which used a single search strategy to identify: (i) published cost-effectiveness studies; (ii) health-related quality of life (HRQoL) studies and (iii) cost and resource use studies for patients with relapsed and/or refractory multiple myeloma (RRMM) who have received greater than 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. Searches were performed between 5–11 February 2023 and used disease terms for multiple myeloma combined with economic and HRQoL search filters, sourced from the InterTASC Information Specialists' Sub-Group (ISSG) Search Filter Resource. A summary of the EAG's critique of the company's SLR is provided in Table 21.

Table 21. EAG's critique of company's systematic literature review

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	Appendix G	Appendix G	**Appropriate** Electronic database searches included: MEDLINE ALL (via Ovid); Embase (via Ovid); Econlit; CDSR; CENTRAL; CRD DARE; CRD HTA database and CRD EED. A comprehensive range of conference abstract websites was searched for the years 2021-2023. Additional grey literature searches included: HTA and regulatory websites (see Table 15, Appendix G of company submission); EconPapers within Research Papers in Economics; ScHARRHUD utility database and EuroQoL website.
Inclusion/ exclusion criteria	Appendix G	Appendix G	Appendix G	**Appropriate.** Date limits were applied only to healthcare cost and resource use studies (2013 to present) to represent the most up-to-date cost data. The EAG considers this appropriate.
Screening	Appendix G	Appendix G	Appendix G	**Appropriate.**
Data extraction	Appendix G and Table 20 in the CS. No studies in penta-refractory population identified so extracted data from three studies with a broader population.	Appendix H and Table 31 in the CS. No studies in penta-refractory population identified so extracted data from wider populations, considered as proxies.	Appendix I. Data only extracted from one previous NICE TA. Unclear why TA897 was deemed relevant but other NICE TAs were not also extracted.	**Appropriate for cost-effectiveness and HRQoL searches**. In light of a lack of available data for the penta-refractory population, the EAG considers it appropriate to extract data from studies with the most relevant population. Unclear to the EAG from the information provided why NICE TA897 was the only TA extracted for cost and resource use when data in CS for "one-off disease progression costs" is described as being sourced from TA510.
Quality assessment of included studies	Appendix G using the Drummond checklist.	Appendix H, quality discussed in narrative write up.	Not included.	**Appropriate.**

Abbreviations: CS, company submission; CDSR, Cochrane Database of Systematic Reviews; CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; EAG, External Assessment Group; EED, Economic Evaluation Database; HRQoL, health related quality of life; ScHARRHUD, School of Health and Related Research Health Utilities Database; TA, technology appraisal;

The company's SLR identified 15,024 papers after de-duplication, based on the whole RRMM population. A total of 13,686 studies were excluded based on title and abstract screening, leaving 1,338 papers for full text review. A further 996 papers were excluded following full text review, leaving 358 papers for inclusion across the three SLR components. These included studies were relevant to the whole RRMM population and not specifically to the penta-refractory population. Due to a lack of specific papers in the penta-refractory population, studies using a similar patient population were extracted by the company, including: four cost-effectiveness papers (three unique studies), 12 HRQoL papers and one cost and resource use paper.

Of the three unique cost-effectiveness papers included, one was in triple-class refractory (TCR) patients based in the United States of America (USA),[32] one in heavily treated (5L+) RRMM patients,[33] based in Italy and one in 5L+ TCR population, based on NICE TA10568 (guidance in development at time of publication).[10] All studies reported used a partitioned survival model.

Of the 12 HRQoL studies, four reported utility values for proxy populations which the company considered could support the economic model. These were in 5L TCR RRMM, 5L triple-class exposed (TCE) RRMM patients and patients with RRMM that were heavily pre-treated. The remaining eight studies extracted were previous NICE TAs conducted in RRMM populations to show the range of utility values used in previous submissions in different RRMM subgroups. The company also extracted a range of disutility values for adverse events included in the economic model, identified during the SLR. Please refer to Section 4.2.7 for details on the HRQoL data applied in the economic model.

Only one study was extracted for cost and resource use data (NICE TA897)[34] as it was deemed by the company to be the most appropriate source of data in the absence of penta-refractory populations identified. The EAG notes that resource use and cost data from other NICE TAs also informed the economic model (please see Section 4.2.8), even though these were not described in the SLR sections of the CS.

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

4.2.1 NICE reference case checklist

Table 22 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case[12] checklist for the base-case analysis, with reference to the NICE final scope[2] outlined in Section 2.

Table 22. 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 (30 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 FACT-G, 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	FACT-G data obtained directly from patients in STORM Part 2 BCPLD refractory patients.[23]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	As noted in Section 3.2, the EAG notes that the population of the STORM trial may not be fully reflective 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,[35] BNF,[36] PSSRU,[37] 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 Population

The population in the company's base case analysis is based on the BCPLD-refractory subgroup from the STORM Part 2 clinical trial.[23] At model entry, patients are therefore assumed to have a mean age of 64.5 years and 61.5% of patients are male. As discussed in Section 2.3.1, the EAG notes that there are potential discrepancies between the STORM Part 2 BCLPD-refractory population and the penta-refractory rrMM population potentially eligible for Sd in clinical practice in England. Incidence rates published by Cancer Research UK for MM indicate that 43% of new cases are diagnosed in people aged 75 and over,[5] suggesting that patients could be older than that suggested in the economic model if age at diagnosis is older than the mean age of penta-refractory patients. In addition, [redacted].[25] As discussed in Section 2.3.1, a lower proportion of patients in UK clinical practice are expected to have prior SCT than that observed in STORM Part 2, [redacted] As the EAG consider the mean age of patients eligible to receive Sd in the economic model to be a source of uncertainty, this is explored in scenario analyses in Section 6.

4.2.3 Intervention and comparator

The intervention evaluated in the economic model is selinexor (80mg) plus dexamethasone (20mg), administered orally. Based on dose reductions observed in the STORM trial due to adverse events, the modelled dose uses the average dose taken by trial participants (see Section 4.2.8 for further detail). Upon discontinuation of Sd or disease progression, patients receive standard of care (SoC), the only comparator included in the economic model. SoC comprises of best supportive care (BSC) which is assumed to consist of no active treatments, but a proportion of patients will receive treatment with conventional chemotherapy (CCT), described in further detail in upcoming Section 4.2.8. In the economic model, the MAMMOTH study, based in the USA, is used to represent BSC for penta-refractory patients.[18] The company states that patients in MAMMOTH received active treatments as part of BSC that would not be available in UK clinical practice and therefore any indirect comparisons undertaken using MAMMOTH as a proxy for BSC are likely to underestimate the treatment effect of Sd versus SoC. The EAG notes that while it is true that a large proportion of patients (90%) received additional active subsequent treatments in MAMMOTH that would not be received in UK clinical practice, 59% of patients in STORM Part 2 BCLPD refractory trial population

also received additional subsequent treatments.[22, 23] Therefore, the magnitude of any underestimation of the treatment effect of Sd versus SoC is unclear (Section 3.4.1).

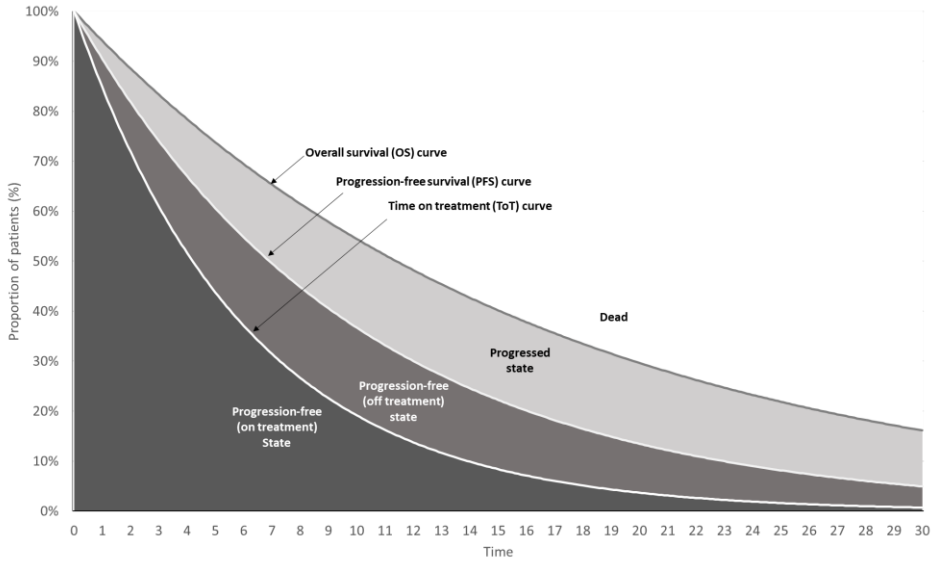
As discussed in Section 2.3.3, the EAG considers panobinostat in combination with bortezomib and dexamethasone (PanoVd) to be a potentially relevant comparator to Sd. As the company's response to clarification questions (CQs) A6 and B1 was that they do not consider PanoVd a relevant comparator, this was not able to be explored in the economic model.

4.2.4 Modelling approach and model structure

The company developed a *de novo* model in Microsoft Excel®. The model adopts a partitioned survival approach comprising of three health states: progression-free survival (PFS); disease progression (PD); and death - Figure 9. Patients enter the model in the PFS state at a mean age of 64.5 years and receive treatment either with Sd or SoC. Patients occupying the PFS state are at risk of disease progression or death and can also discontinue treatment before disease progression. The probability of being alive and free from disease progression was calculated using the cumulative PFS distribution in the model, while the probability of being alive was calculated from the cumulative overall survival (OS) curve. The difference between the OS and the PFS curves was used to estimate the proportion of patients with disease progression at every cycle of the model as a partition survival approach does not explicitly model transitions between health states. Time on treatment was estimated in the model through the use of a time to treatment discontinuation (TTD) distribution.

The distributions used to estimate OS, PFS and TTD are modelled using treatment-specific approaches which are discussed in detail in Section 4.2.4.

Figure 9. Company's model (reproduced from Figure 11 in CS)



4.2.5 *Perspective, time horizon and discounting*

A lifetime horizon of 30 years was adopted in the model and time was discretised into weekly cycles, with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.[12]

4.2.5.1 *EAG critique*

The EAG is generally satisfied with the company's modelling approach.

4.2.6 *Treatment effectiveness*

In order to estimate survival outcomes (PFS; OS; and TTD) for Sd, the company used the Kaplan-Meier (KM) observed data for each outcome from the STORM Part 2 trial, for the 83 patients who were refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab (BCLPD-refractory), with a September 2019 data-cut (hereafter referred to as the STORM Part 2 trial for the effect of the company's economic analysis).[23]

The company fitted different parametric survival models to KM data from STORM Part 2. In order to assess the relative goodness-of-fit of the different models for each population, the company: (1) generated Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics for the Sd arm; (2) visually assessed the parametric curves against the KM curves; (3) used clinical expert opinion to assess the clinical plausibility of model extrapolations. Standard parametric distributions,

including the exponential, Weibull, Gompertz, log-logistic, lognormal, generalised gamma and the gamma distributions were tested.

In order to generate measures of relative treatment effectiveness for OS outcomes for Sd vs SoC, the company used the hazard ratio (HR) derived from the simulated treatment comparison (STC) undertaken using STORM and MAMMOTH and described in detail in Section 3.4. For PFS and TTD, the company assumed that these outcomes would be the same in the SoC arm as those estimated with the fitted parametric models for Sd. These outcomes are discussed in detail in the following sections.

4.2.6.1 Overall survival

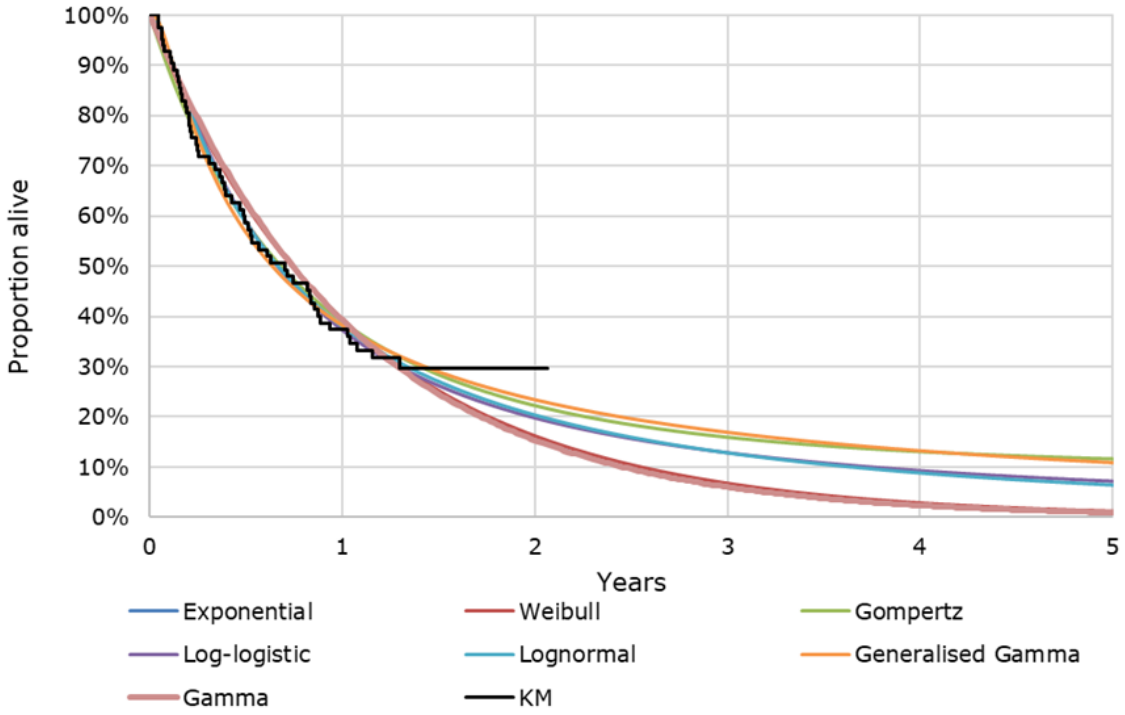
The company chose the lognormal distribution to model OS for Sd as this provided the best statistical fit (as per the AIC and BIC statistics reported in Table 24 of the CS) and aligned with the company's clinical experts' views on the plausibility of long-term survival. The company reported that all alternative models provided a good visual fit to the KM data, suggesting that more flexible curve-fitting approaches such as spline or piecewise fitting would offer no improvement while adding modelling complexity. The company's clinical experts suggested that approximately 5% of Sd patients might be expected to be alive at five years beyond baseline in the model.

The long-term survival predictions of all the company's fitted models for Sd are reported in Table 23 and the fitted survival curves for Sd are shown in Figure 10. All alternative models were explored in scenario analyses conducted by the company.

Table 23. Landmark estimations of survival in the company's model for Sd (reproduced from Table 23 in the CS).

Year	Exponential	Weibull	Gompertz	Log-logistic	Lognormal	Generalised Gamma	Gamma
1	39.30%	39.40%	38.96%	37.26%	**37.99%**	38.21%	39.27%
2	15.44%	16.21%	22.25%	19.79%	**20.37%**	23.41%	15.34%
5	0.94%	1.22%	11.63%	7.17%	**6.43%**	10.88%	0.89%
10	0.01%	0.02%	9.91%	3.11%	**2.06%**	5.69%	0.01%
20	0.00%	0.00%	9.79%	1.32%	**0.52%**	2.84%	0.00%
30	0.00%	0.00%	9.79%	0.79%	**0.21%**	1.87%	0.00%

Figure 10. Parametric curves fitted to OS Kaplan-Meier data from STORM BCPLD population (Figure 12 from company submission)



After clarification, the company updated the HR used to estimate OS for the SoC arm of the model, to 0.43 (in favour of Sd) estimated from the STC. Alternative HRs derived from the matching-adjusted indirect comparisons (MAICs) (estimated using the full list of available covariates and what the company considered to be a 'must-have' list of covariates), were provided in scenario analysis in the model where the HRs of 0.757 and 0.681 were used, respectively, to estimate OS for SoC. The MAICs conducted by the company are reported in detail in Section 3.4.

Table 24. Landmark estimations of survival in the company's model for Sd and SoC with updated HR from STC (before and after clarification)

Year	Sd Lognormal	SoC Lognormal with HR applied (after clarification)	SoC Lognormal with HR applied (before clarification)
1	37.99%	11.70%	19.12%
2	20.37%	2.54%	6.59%
3	12.83%	0.87%	2.99%
5	6.43%	0.18%	0.92%
10	2.06%	0.01%	0.13%
20	0.52%	0.00%	0.01%

Abbreviations: Sd, selinexor plus dexamethasone; SoC, standard of care; HR, hazard ratio; STC, simulated treatment comparison

In their CS, the company noted its concern that active therapies given in MAMMOTH are expected to have led to higher survival rates than found among patients receiving SoC in the UK. The company added that it has not been possible to quantify the size of such an effect from aggregate data nor to control for its influence, however, caveated that the HR estimates derived using the MAMMOTH study represent a conservative estimate of the impact of Sd on survival rates vs SoC.

4.2.6.2 EAG critique

At clarification, the EAG noted that its clinical experts considered that OS was likely to be overestimated in the SoC arm of the model. One expert advised that all penta-refractory patients are expected to have died 3 years after initiation of treatment (vs 3% in the company's model before clarification), with 3% of patients alive being a more likely survival estimate for 2 years in the model (vs 7% in the company's model before clarification). Nonetheless, the EAG notes that given the company's change in HR to be used to estimate the OS curve for SoC after clarification, the survival predictions in the SoC arm are now more aligned with the EAG's clinical experts' expectations (Table 24).

Nonetheless, the EAG's clinical experts also noted that given the treatment duration with Sd (mean 2.5 months, with a PFS of 3.83 months in the model), it was implausible that 6% of Sd patients would be alive at 5 years in the model. The experts confirmed that at 5 years all patients would be expected to have died. The EAG also raised this issue at clarification and noted that the tails of the exponential or Weibull curves extrapolated from the fitted OS KM STORM provided more realistic predictions for Sd long-term OS extrapolations in the model, as shown in Figure 10. The EAG also acknowledged that the latter distributions provided a worse fit to the KM OS data from STORM compared with the company's base case lognormal curve. As a result, the EAG asked that the company explored a more flexible modelling option with a lognormal curve fitted to the observed KM OS data from STORM, where the tails of the curve were varied to provide more clinical plausible long-term survival predictions.

The company did not comment on the EAG's issue around the plausibility of 6% of Sd patients being alive at 5 years given the mean treatment duration of 2.5 months and mean PFS of 3.83 months. However, as a result of an EAG request at clarification, the company also provided an alternative, piecewise modelling approach as a scenario analysis, in which an initial lognormal OS parametric curve was applied from model baseline before switching to a Weibull OS curve from a user-specified time point. The company noted that the OS curves available to be chosen after the user-specified time point

were fitted to the entire KM OS curves (as opposed to separate curves fitted to the tails of distributions only, from a pre-specified timepoint). The same hazard ratio applied in the company's base case, derived from the STC using the lognormal distribution, is then applied to the new survival estimates (combination of lognormal and Weibull) to estimate survival for the SoC OS. The company noted that applying a lognormal OS curve from baseline and a Weibull curve from 63 weeks (the point at which the Weibull and lognormal curves cross), increased the ICER by £17,696 to £45,104 per QALY gained, relative to the lognormal curve being applied throughout (i.e., using the company's base case assumption). The EAG notes that the flexible modelling approach used by the company does not use the standard methods to flexible modelling as described by NICE decision support unit (DSU) technical support document 21.[38] The piecewise approach should instead fit parametric curves to each separate piece of the KM it is being used for. The choice of the cut point used should be determined by evaluating the underlying hazards and the sensitivity on the results of the cut point chosen should be explored in scenario analysis. Table 25 shows a comparison of the landmark estimates for OS using the company's base case of a lognormal compared to the flexible approach provided by the company.

Table 25. Landmark estimations of survival in the company's model for Sd and SoC versus using company estimated flexible curve fitting approach

Year	Company base case		Flexible modelling approach	
	Sd survival	SoC survival	Sd survival	SoC survival
1	37.99%	11.70%	37.99%	10.70%
2	20.37%	2.54%	16.21%	1.50%
3	12.83%	0.87%	1.22%	0.00%
5	6.43%	0.18%	0.02%	0.00%
10	2.06%	0.01%	0.00%	0.00%
20	0.52%	0.00%	0.00%	0.00%

Abbreviations: Sd, selinexor plus dexamethasone; SoC, standard of care

The EAG notes that the flexible modelling approach employed by the company leads to estimates of survival for Sd more in line with the EAG clinical experts' opinions. As the landmark estimates of the flexible model, shown in Table 25 from 2 years onwards, is based on the Weibull curve (as the company use the Weibull model from 63 weeks), which supports proportional hazards, the Weibull produces estimates more in line with the EAG's clinical opinion. The company also noted how the results of their flexible modelling approach is broadly in line with applying the Weibull throughout as the area under the curve is broadly similar during the observed period. As noted above, the EAG has concerns on the techniques used to employ the flexible modelling approach. The application of a HR to estimate OS for the SoC arm would need to ensure that each parametric curve fit to the flexible model supports

proportion hazards; it is methodologically inappropriate to apply a HR to a parametric curve that does not support proportional hazards (and the lognormal does not).

As discussed in Section 3.4, the EAG has concerns with the company's STC and the inability to appropriately account for the initial overlapping of KM curves (depicted in the naive comparison of the OS KM curves, up to approximately 3.5 months, and exacerbated in the MAIC-adjusted curves, up to approximately 7 months, Figure 5 and Figure 6, respectively), suggesting that proportional hazards (PH) does not hold. During the clarification stage, the EAG requested that the company fit independent curves to the OS results of the fully adjusted MAIC for the BCLPD subpopulation of STORM 2 versus MAMMOTH, as opposed to estimating a hazard ratio. The EAG considers a "hazard ratio-based approach" to be inappropriate in the presence of initially overlapping KM curves followed by a subsequent change in hazards, and believes this will overestimate the survival benefit of Sd.

Despite the request from the EAG, the company did not provide independently fitted curves as they stated that no conclusions could be drawn from the MAIC of STORM Part 2 BCLPD *versus* MAMMOTH as all models tested produced low effective sample sizes (ESS) and were associated with high uncertainty. The EAG notes that even if the company deem the MAICs to be unreliable due to low ESS, the unadjusted KMs for Sd and SoC from MAMMOTH still show crossing of the curves up to approximately 3.5 months, suggesting that PH assumption does not hold. The initial period where crossing curves is observed is also where the most patients are available to inform the adjustment. A hazard ratio derived from a Cox regression model should only be applied to parametric curves that satisfy the PH property, which the lognormal distribution does not. Therefore, the EAG deems applying a HR to the lognormal curve to estimate SoC OS to be inappropriate. In addition, it is uncertain if a HR derived using a Cox regression model from the lognormal STC is appropriate when PH does not hold. The company noted that they considered an accelerated failure time (AFT) model but stated that it would likely introduce additional uncertainty as they considered the observed PH violation to be an artefact of the quality and limited size of the data set. As noted in Section 3.4 the EAG's preference to modelling survival in the economic model would be independently fitted curves and does not consider the company's argument for not providing these to be sufficient and believe these would be useful for the NICE committee to have access to. Without these, the EAG considers that the modelling of overall survival in the economic model is a key source of uncertainty. While independently fitted curves means that survival for SoC is based on a comparator trial, in which

differences in the populations have been observed, the EAG considers this to be a more reliable approach to modelling survival that the use of a hazard ratio used by the company.

As noted in Section 3.4.1 and 4.2.3, the company stated that the use of active therapies as subsequent treatments in MAMMOTH that would not be used in UK clinical practice is likely to overestimate survival in the SoC arm. Therefore, using a hazard ratio derived from MAMMOTH versus STORM represents a conservative estimate of the impact of Sd OS compared to SoC. The EAG notes that active treatments as part of subsequent therapies not used in the UK were also used in the STORM clinical trial. The EAG agrees that the use of active subsequent treatments is not representative of UK clinical practice; however, as these are being used in both MAMMOTH and STORM, it is unknown whether this results in a conservative estimate of OS for Sd when compared to SoC as the overall impact may be mitigated by the use of active treatments in STORM. In addition, as previously discussed, the EAG does not agree with the use of a hazard ratio to estimate SoC OS, particularly when derived from a lognormal distribution which does not support PH.

4.2.6.3 Progression-free survival

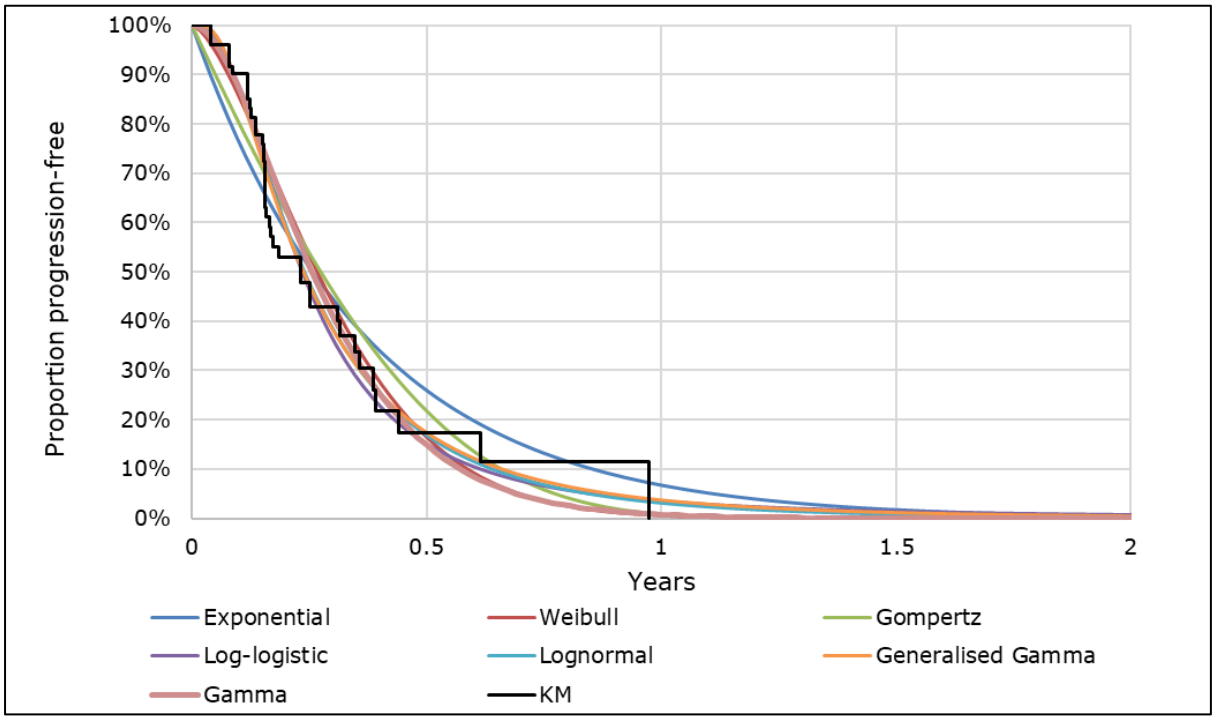
The company also selected a lognormal distribution to model PFS for Sd based on best statistical fit. In addition, clinicians consulted during an advisory board meeting suggested that there was no clear distinction between any of the fitted curves in terms of clinical plausibility as all parametric curves resulted in less than 1% of patients' progression free at 2 years, as shown in Table 26. Extrapolated curves based on standard parametric curves are shown in Figure 11

Table 26. Landmark estimations of patients estimated to be progression free (IRC assessed) in the company's model (reproduced from Table 25 in the CS).

Year	Exponential	Weibull	Gompertz	Log-logistic	Lognormal	Generalised Gamma	Gamma
1	6.73%	0.56%	0.85%	3.52%	3.12%	3.72%	0.76%
2	0.45%	0.00%	0.00%	0.74%	0.28%	0.46%	0.00%
5	0.00%	0.00%	0.00%	0.09%	0.00%	0.01%	0.00%
10	0.00%	0.00%	0.00%	0.02%	0.00%	0.00%	0.00%

Abbreviations: IRC, independent review committee; CS, company submission

Figure 11. Parametric curves fitted to IRC assessed PFS from STORM BCPLD population (taken from Figure 13 of the CS)



As the MAMMOTH trial showed no specific PFS benefit in the penta-refractory population, the company applied the same lognormal curve to the SoC arm, which assumes no treatment benefit for Sd in relation to PFS.

4.2.6.4 EAG critique

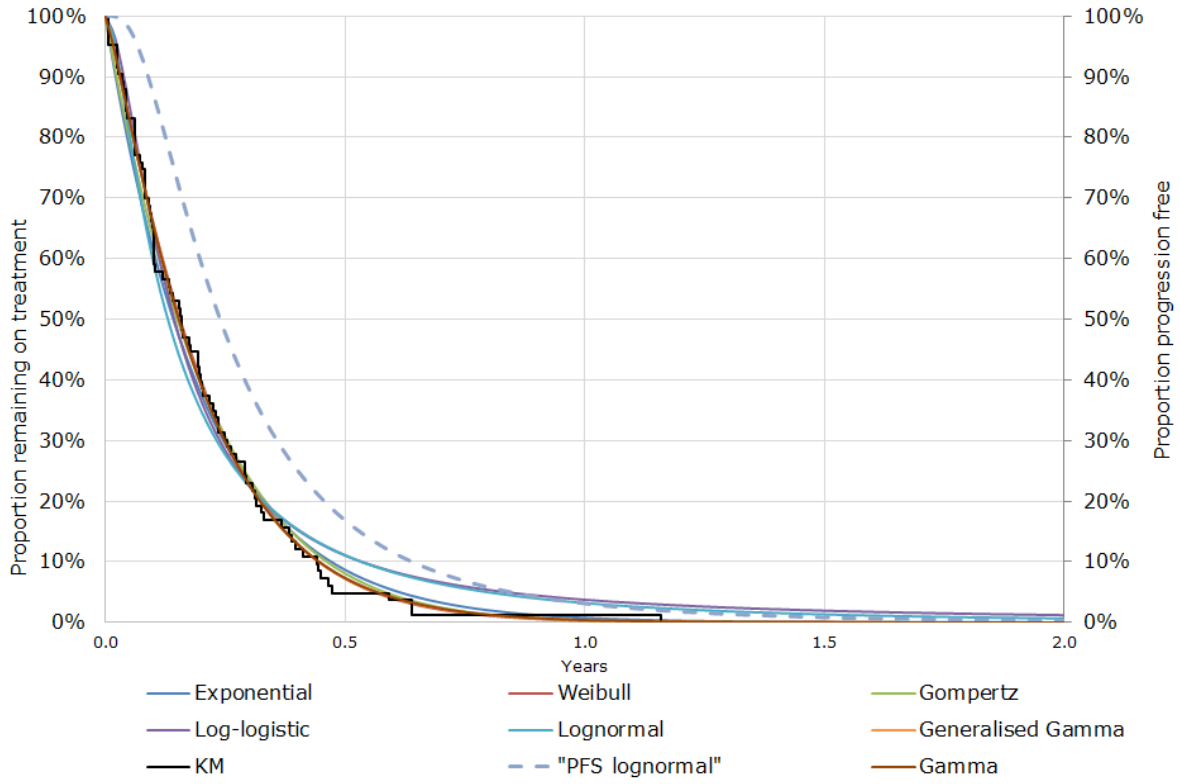
The EAG notes that in light of the evidence showing no PFS benefit for Sd, this is a conservative approach and is satisfied with this assumption. However, the EAG notes that based on visual fit, none of the fitted curves provide a good fit to the tail of the KM. However, due to little differences observed between the curves, the company's scenario analyses showed that the use of an alternative distribution for PFS had a very minimal impact on the ICER.

4.2.6.5 Time to treatment discontinuation

Time to treatment discontinuation (TTD) was not measured as an endpoint in the STORM trial and was therefore measured as end of treatment minus treatment start date. The company fit a range of standard parametric curves to the TTD KM. Based on statistical fit and clinical expert advice that while

patients had not progressed some would remain on treatment, the company chose the exponential curve in their base case. Although the use of the exponential curve ensures that TTD does not exceed PFS (when modelled using the company's base case assumption of a lognormal), a TTD to PFS cap is applied in the model to ensure that patients are not accruing treatment costs if they have disease progression. This is in line with the marketing authorisation,[39] stating that patients will remain on treatment until disease progression or unacceptable toxicity. The company noted that both the log-normal and log-logistic curves result in the number of patients remaining on treatment at 1 year (3.21% and 3.75%, respectively) being greater than the number of patients who are progression-free (3.12%), as shown in Figure 12. As patients discontinue treatment on or before progression, the company stated that both the log-normal and log-logistic may overestimating the number of patients remaining on treatment.

Figure 12. Parametric curves fit to time on treatment for Sd patients versus PFS survival estimates, produced from the company's model



4.2.6.6 EAG critique

The EAG notes that based on statistical and visual fit, the gamma and Weibull also provide a close fit to the observed data, with the AIC for the gamma being the lowest of all parametric curves (see

Table 28 of CS). In addition, the Weibull predicted median TTD is equal to the observed median TTD from the BCLPD-refractory population of the STORM trial (2.07 months). Based on the similarity between the curves and the short time patients remain on treatment, the use of alternative parametric curves (Weibull and gamma) had a very minimal impact on the ICER.

The company's model provided the option to base time on treatment to PFS. Due to the high toxicity of Sd and the marketing authorisation stipulating that patients will remain on treatment until disease progression or unacceptable toxicity, the EAG agrees that TTD should be based on that observed in the clinical trial.

4.2.7 Health-related quality of life

4.2.7.1 Health state utility values

Health state utility values used in the model were informed by health-related quality of life (HRQoL) data collected in the STORM trial using the Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM), which includes the 27-item FACT-General (FACT-G) and an additional 14-item MM-specific subscale. HRQoL data was collected every four weeks, from baseline until treatment discontinuation.

As the NICE Reference Case[12] recommends the use of the EQ-5D-3L for the measurement of utility data, the company used a published mapping algorithm. No mapping algorithm is available for FACT-MM to EQ-5D-3L, therefore the company used the FACT-G questions included in the FACT-MM, for which a published mapping algorithm to EQ-5D-3L is available.

The company used the mapping algorithm taken from Longworth *et al.* 2014.[40] This study aimed to estimate mapping functions from FACT-G to EQ-5D-3L and test the applicability of different mapping approaches commonly applied in the literature. Longworth *et al.*[40] used a USA dataset which included 530 participants who had one of 11 cancers at stage 3 or 4 and completed EQ-5D and FACT-G. The study tested models estimated by ordinary least squares (OLS), tobit, two-part model (TPM), splining and response mapping model. After assessing for model performance to select the best fitting model, Longworth *et al*.[40] concluded that OLS followed by the tobit model (both using significant items only – model 6) gave the best model predictions based on mean predictions for the overall sample. Due to this, the company therefore used the OLS model (model 6) to map patient level data on FACT-G from the STORM trial to predict EQ-5D-3L utility values in their primary analysis, with the tobit model explored as a secondary analysis. The OLS mapping model used

included six significant items from FACT-G (lack of energy, trouble meeting the needs of family, pain, feeling sad, losing hope, and able to work) whereas the tobit model included four significant items (lack of energy, pain, able to work, and enjoy life).

Following the mapping of FACT-G patient level data from STORM to EQ-5D-3L, the company then used the mapped EQ-5D-3L values in mixed effects OLS and tobit regression models applied to three different patient groups from STORM to generate final utility values to be used in the economic model. The three populations from the STORM trial explored were Part 2 patients only (triple-class refractory [TCR] MM and penta-exposed MM), Part 1 +2 patients (quad-exposed double class refractory + Part 2 patients) and Part 2 BCLPD population (penta-refractory patients from Part 2, refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab).

Data from the Part 2 BCLPD-refractory population in the STORM trial was deemed the most relevant for the economic model, which included 62 patients with full data to be used in the regression models. The OLS mixed effects model was used as the final model after being deemed as ranking superior in model performance and fit and used for the primary analysis. Patient-level characteristics included in the initial regression model were sex, age, race, years since diagnosis, number of previous regimens, fluorescence in situ hybridisation (FISH) indicator, Eastern Cooperative Oncology Group (ECOG) score, Revised-International Staging System (R-ISS), and baseline EQ-5D-3L. A backwards stepwise regression approach using statistical goodness-of-fit according to Akaike and Bayesian information criteria (AIC and BIC) and log-likelihood statistics was used to determine the final regression model.

[redacted]

[redacted] The final utility regression used for the Part 2 BCLPD OLS model is shown below:

[redacted]

Based on the final regression model for the Part 2 BCLPD population, the estimated EQ-5D-3L utilities for both progression free survival (PFS) and progressed disease (PD) health states are shown in Table 27.

Table 27. Mapped utility values for STORM Part 2 BCLPD-refractory population

Health state	Mapped utility value for STORM Part 2 BCLPD-refractory population (95% CIs*)
Progression-free survival	0.5894 (0.550 to 0.629)
Progressed disease	0.6067 (0.566 to 0.647)

* 95% confidence intervals calculated by the EAG based on standard errors

Abbreviations: BCLPD, Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; CI, confidence interval

As shown in Table 27, utility values for the PD health state were higher than those estimated for the PFS health state. This was the case for all OLS and tobit regressions ran using the different populations (Part 1+2, Part 2 and Part 2 BCLPD, see Table 26 of CS Appendix M). The company state that this is due to small patient numbers as data collection in STORM beyond treatment discontinuation was too limited to produce reliable estimates of PD utility values. The number of patients informing the utility estimates for PD was not available to the EAG to assess if the reasons provided by the company were plausible or if there may be other reasons for the increase in utility values between health states. The company also stated that patients in poorer health with lower baseline utility values will have discontinued treatment quicker than those with higher baseline utility values. Therefore, the patients remaining in the trial will have had higher overall utility values, resulting in a higher utility estimate for the PD health state.

Due to the higher utility values in the PD health state derived from the STORM study, the company applied an alternative utility value for the PD health state. The relative decrement between the PFS and PD utility values observed in the DREAMM-2 study was applied to the estimated PFS utility value from the STORM trial. DREAMM-2 included patients who were triple-refractory RRMM, had received ≥3 prior therapies and were refractory to an immunomodulatory agent and a proteasome inhibitor, and refractory or intolerant to an anti-CD38 monoclonal antibody. Despite not being the same population as patients from the STORM trial, from which the PFS health state utility was derived, the company stated that as data are being used as a relative decrement rather than absolute, this relaxes the need for populations to be equivalent. The values used to calculate the relative decrement and the final utility values applied in the company model are shown in Table 28. The company explored a range of alternative utility values sourced from previous NICE TAs for MM in scenario analyses, however no values were identified for the penta-refractory population.

Table 28. Health state utility values applied in company model base-case

Health state	Utility values estimated from STORM - PART 2 BCLPD refractory population (SE)	Utility values from DREAMM-2 (SE)	Relative decrement from DREAMM-2 (SE)	Utility values used in company model (SE)
PFS	0.589 (0.0202)	0.731 (0.146)	0.908 (0.182)	0.589 (0.020)
PD	0.607 (0.0208)	0.664 (0.133)		0.535 (0.107)

Abbreviations: PFS, progression-free survival; PD, progressed disease; BCPLD, Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; SE, standard error

4.2.7.1.1 EAG critique

Overall, the EAG generally agrees with the company's approach to use mapping for obtaining health state utility values, due a lack of available directly measured EQ-5D data in the penta-refractory population. During the clarification stage (question B7.1) the EAG asked the company to discuss the likelihood that using the FACT-G questions only (as opposed to the FACT-MM) might have misrepresented patients' quality of life. Although the FACT-MM asks 14 additional questions to the FACT-G, the EAG is satisfied that these questions are already covered within the four subscales of the FACT-G (physical, social/family, emotional and functional) and therefore using the FACT-G responses as a standalone instrument to measure patients' quality of life will still capture MM patients HRQoL appropriately. For example, the MM subscale of FACT-MM ask patients to score "I get tired easily" and the physical subscale of FACT-G already asks patients to score "I have a lack of energy".

The choice of mapping model (Longworth *et al.* 2014)[40] was chosen by the company based on alignment of the population of STORM and the dataset used by Longworth *et al.* The Part 2 BCPLD population of STORM had an average age of 64.5 years and 61.5% male, whereas the dataset used to create the mapping algorithm had an average of 59 and 52% male. Table 1 of Appendix M of the CS shows the average FACT-G scores of the patients enrolled in STORM compared against mapping sample. Although the patients in the mapping sample had a slightly higher overall FACT-G total score on average compared to STORM Part 2 BCPLD patients (78 versus 70.3, respectively), the EAG notes

that the ranges of the values observed are very similar and the EAG considers the population in Longworth *et al.* to be generalisable to the STORM trial and relevant for mapping. The company notes that a mapping algorithm developed in Singapore was excluded for consideration due to lack of geographical representation. While the EAG considers the mapping algorithm used by the company to be reputable, it is noted that this was published in 2014 and the company did not provide details of how mapping algorithms were searched for. Therefore, it is unknown if any other mapping algorithms may have been available and more appropriate.

The company discuss how the utility values generated from the mapping exercise and subsequent regression models showed an increase of quality of life from the PFS to PD health state and therefore used a relative decrement from the DREAMM-2 study. The EAG notes that as the mean EQ-5D-3L values obtained directly from mapping the STORM trial data for both PFS and PD patients were not presented prior to being used in the mixed effects regression models, it is unclear if the increase in the utility values is a consequence of the data available or of the methods used. Without seeing these data, the EAG is unable to assess this. The EAG does note, however, that the six mixed effects models (three STORM populations applied to both OLS and tobit) examined by the company using the mapped EQ-5D-3L data all observed the same pattern.

The EAG also noted that the patients in the STORM trial were from the USA, Austria, Belgium, France, Germany, and Greece and therefore may not be fully reflective of HRQoL of patients with RRMM in the UK.

In light of the mapped trial data from the STORM study showing an increase in quality of life from the PFS to PD health state, which clinical experts agreed did not have face validity, the company used a relative decrement applied from the DREAMM-2 study in the base-case. The DREAMM-2 study was undertaken in a triple refractory RRMM population and therefore using the absolute values from this trial for the PFS and PD health states may underestimate the utility values in the penta-refractory population. The EAG's clinical experts confirmed that patients' quality of life declines with further progressions and further lines of treatment, and thus, would expect PFS patients on 4th line treatment to have better quality of life than PFS patients on 6th line treatment. The company also provided a range of alternative absolute utility values for PFS and PD used in previous NICE TAs (TA658,[41] TA427[42] and TA573)[43], identified from the systematic literature review (SLR). Table 31 of the CS provides alternative absolute values identified during the SLR. The company

also provided results of a scenario analysis using the absolute values for PFS and PD observed in DREAMM-2 and those used in TA658.[41]

The EAG notes that if the relative decrement had been taken from the alternative NICE TAs (TA658,[41] TA427[42] and TA573[43]) instead of DREAMM-2 then the resulting utility value for the PD health state would be lower than that applied in the model. Therefore, as a relative decrement, the DREAMM-2 study could be considered the conservative choice. A systematic review and meta-regression of health state utilities for multiple myeloma by Hatswell *et al.* 2018[44] reported utility values by line of treatment for patients with MM. Although this study did not report on utility values by progression status that could be directly used in the model, the estimated utility value using the results of the meta-analysis (Bayesian EQ-5D model) for patients who have received four treatment classes (described as all classes available) is 0.469, showing that utility values are very low in patient populations for whom there are no further alternative treatment options.

The company's model used Ara and Brazier 2010[45] to apply age-related utility decrement. As a result of a clarification request, the company updated the model to use the Health Survey for England (HSE) 2014 dataset, as recommended by the NICE decision support unit (DSU) (Hernández Alava *et al.* 2022).[46]

4.2.7.2 Disutility associated with adverse events

The company applied a one-off utility decrement in the first model cycle to account for the disutility of adverse events associated with Sd. The company included adverse events observed in the STORM part 2 population (see Section 3.3.6). The accompanying utility decrement and duration of AEs were sourced from previous NICE TAs, published literature or assumptions when required. As a response to a clarification request, the company updated some disutility values and durations initially applied in the model due to discrepancies observed by the EAG between the report and economic model. The disutilities and duration of AEs applied in the final economic model are shown in Table 29. Combined with the reported rate from STORM PART 2, this generated a total one-off utility decrement of 0.019 applied to Sd patient's in the first model cycle.

Table 29. Disutility and duration of adverse events, adapted from the company's model

Adverse event	Disutility	Disutility source	Duration of AE (months)	Duration source
Anaemia	0.310	NICE TA510	0.35	NICE TA510

Asthenia	0.120	NICE TA510	0.48	Jakubowiak *et al.* 2016
Back pain	0.070	NICE TA510	0.46	Assumed 2-week duration
Bone pain	0.070	Assumed to be equivalent to back pain	0.46	Assumed 2-week duration
Decreased appetite	0.034	Sullivan et al 2011	0.46	Assumed 2-week duration
Dehydration	0.103	Assumed equivalent to Diarrhoea	0.46	Assumed 2-week duration
Diarrhoea	0.103	NICE TA510	0.39	Jakubowiak *et al.* 2016
Dyspnoea	0.120	NICE TA510	0.36	Jakubowiak *et al.* 2016
Fatigue	0.115	NICE TA510	0.48	NICE TA510
Hyperglycaemia	0.060	Wehler et al 2018	0.13	Jakubowiak *et al.* 2016
Hypokalaemia	0.200	NICE TA510	0.37	Jakubowiak *et al.* 2016
Hyponatraemia	0.200	Assumed equal to hypokalaemia NICE TA510	0.37	Jakubowiak *et al.* 2016
Infections and infestations	0.140	Wehler et al 2018	0.39	Jakubowiak *et al.* 2016
Leukopenia	0.070	NICE TA510	0.51	Jakubowiak *et al.* 2016
Lymphopenia	0.070	NICE TA510	0.51	NICE TA510
Nausea	0.103	NICE TA510	0.80	Jakubowiak *et al.* 2016
Neutropenia	0.145	Brown et al. 2013	0.43	NICE TA510
Pneumonia	0.190	NICE TA510	0.39	NICE TA 510
Sepsis	0.200	Wehler et al 2018	0.39	Jakubowiak *et al.* 2016
Thrombocytopenia	0.310	NICE TA510	0.46	NICE TA510
Vision blurred	0.004	Sullivan et al 2011.	0.46	Assumed 2-week duration

Abbreviations: AE, adverse event; NICE, National Institute for Health and Care Excellence; TA, technical appraisal

4.2.8 Resource use and costs

The company's model includes costs related to drug acquisition and subsequent treatment, health state costs, adverse events (AEs), one-off disease related costs and terminal care. These are detailed further in the following subsections. Costs used in the model represent 2021/22 prices, with costs inflated using the PSSRU HCHS pay and prices index when required.[37]

4.2.8.1 Treatment costs

The list price for selinexor 20mg is £9,200 per pack of 20 tablets. A confidential patient access scheme (PAS) is in place for selinexor and all results presented in this report include the corresponding PAS. Selinexor is taken in combination with low dose dexamethasone, with a list price of £2.46 (2mg, pack size 50). Patients in the Sd arm of the model were also assumed to receive 5-hydroxytryptamine (5-HT3) antagonists as a concomitant medication, which the company assumed to be 8mg of ondansetron (2.5mg daily) for all patients while on treatment with Sd. Drug acquisition costs for Sd used in the model, including ondansetron used as concomitant medication, are shown in Table 30. The company assumed no administration costs associated with either selinexor or dexamethasone due to these being oral treatments.

Table 30. Treatment acquisition costs for Sd

Treatment	Pack size (number of units)	Unit size (mg)	List price per pack	PAS price per pack	PAS price per mg	Source
Selinexor	20	20	£9,200	[redacted]	[redacted]	Company internal pricing
Dexamethasone	50	2	£2.46	£2.46	£0.02	eMIT 2022[47]
Ondansetron	10	8	£0.76	£0.76	£0.01	eMIT 2022[47]

Abbreviations: PAS, patient access scheme; mg, milligrams

The SmPC has a recommended dose of selinexor of 80mg twice weekly, combined with dexamethasone 20mg twice weekly, with dose reductions for selinexor recommended as needed due to adverse events. Due to dose reductions observed in the STORM clinical trial, the company used the mean relative dose intensity (RDI) observed in the trial of 114.4mg weekly to calculate drug acquisition costs in the economic model. This was rounded up to 120mg weekly due to unit size (20mg per tablet). In addition, the company applied a reduction in treatment costs to reflect the

compliance rate of 98.4% observed in the STORM trial. The treatment cost of Sd applied in each weekly model cycle is shown in Table 31.

Table 31. Sd treatment costs applied in the economic model per cycle, PAS included

Treatment	Dose per weekly cycle (mg)	Compliance	Acquisition cost per weekly cycle
Selinexor	120	98.4%	[redacted]
Dexamethasone	40	100%	£0.98
Ondansetron	140	100%	£1.33
Total	-	-	[redacted]

Abbreviations: mg, milligrams

As a result of a clarification request by the EAG (clarification question B12), the company provided the distribution of BCLPD refractory patients of the STORM trial across the average weekly dose ranges of selinexor reported in the CSR, shown below in Table 32. Based on this, the weighted average dose was 114.41mg/week. When rounded to the nearest 20mg, as in the company's base case, this results in a dose of 120mg/week. As this is the equivalent to the dose used in the company base-case this does not affect the cost-effectiveness results.

Table 32. Average selinexor dose received per week in BCLPD-refractory population of STORM. Reproduced from company clarification response B12.

Average selinexor dose received per week (mg/ week)	N	%	Mean	Median	Minimum	Maximum
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Abbreviations: mg, milligrams; N, number

Patients on SoC receive no active treatments in the model, with the exception of a proportion of patients who receive conventional chemotherapy (cyclophosphamide) plus dexamethasone, while progression-free. Both treatments are assumed to be administered orally. The proportion of patients receiving conventional chemotherapy was updated in the company model following a clarification request by the EAG to 65%, based on clinical expert opinion.

Patients in the Sd arm of the model with disease progression, were assumed to start receiving SoC as subsequent treatment as a one-off cost. For patients receiving conventional chemotherapy as a

subsequent treatment to Sd (65% of SoC patients after Sd), an average treatment duration of 13.43 weeks was assumed. This was based on NICE TA510,[48] in which duration of subsequent therapy was sourced from a data review of the Haematological Malignancy Research Network (HMRN) for 2004-2013, in which average duration of fifth-line therapy in patients with rrMM was 94 days (13.43 weeks).

Table 33 and Table 34 shows the dosage and costs used in the economic model associated with conventional chemotherapy, applied to 65% of SoC and progressed Sd patients. The company's base case model assumes a daily dose of 200mg cyclophosphamide. The dose of dexamethasone was assumed to be 40mg once weekly.

Table 33. Unit costs of treatments used for SoC and subsequent treatment

Treatment	Pack size (number of units)	Unit size (mg)	List price per pack	Price per mg	Source
Cyclophosphamide	100	50	£52.65	£0.01	eMIT 2022[20]
Dexamethasone	50	2	£2.46	£0.02	eMIT 2022[20]

Abbreviations: eMIT, electronic market information tool; mg, milligrams; SoC, standard of care

Table 34. Dosage and costs applied in the economic model for SoC and subsequent treatment

Treatment	Dose per administration (mg)	Administrations per weekly cycle	Dose per weekly cycle (mg)	Acquisition costs per weekly cycle
Cyclophosphamide	200	7	1400	£14.74
Dexamethasone	40	1	40	£0.98
Total	-	-	-	**£15.73**

Abbreviations: mg, milligrams; SoC, standard of care

4.2.8.1.1 EAG critique

The company's model assumes that no administration costs apply for patients receiving chemotherapy as a component of SoC or subsequent treatment due to cyclophosphamide being most commonly used in its oral form. The EAG notes that NHS reference costs provide a unit cost for delivering oral chemotherapy (Currency code SB11Z), which has been applied in recent NICE TAs for MM (TA897).[34] As part of the clarification process the company provided a scenario including oral chemotherapy administration costs in the model. The EAG reports the results in Section 6.

As part of SoC and subsequent treatment, the company use a daily dose of 200mg cyclophosphamide. Clinical experts to the EAG noted that the dose for cyclophosphamide used as part of both SoC and subsequent treatment to Sd would be 500mg weekly in the UK NHS. The dose of 500mg weekly is also in line with the NHS chemotherapy protocol for MM[49] provided by the company to the EAG as part of the clarification process, in support of the dose to be used for dexamethasone in combination with cyclophosphamide. Therefore, it is unclear to the EAG why this dose was not used in the company's base case. As part of the clarification process, the company provided a scenario using a 500mg weekly cycle. However, this was only applied in the company's scenario as part of the SoC arm and not as a subsequent treatment. Therefore, the EAG corrected this and reports the results in Section 6.

Concomitant medication with ondansetron is used in the company's model as a 5-hydroxytryptamine (5-HT3) antagonist is required for patients receiving Sd. During the clarification process (question B23), the EAG requested the company to clarify if other 5-HT3 antagonists were used in the STORM trial and the implication of using alternatives in the economic model. The company did not confirm if any other 5-HT3 antagonists were used in the STORM trial but stated that they expect clinicians to apply the most cost-effective option available and therefore using ondansetron in the economic model will be consistent with clinical practice or over-estimate costs in the Sd arm if lower cost alternatives were used. The EAG is satisfied that applying ondansetron to all patients is a conservative approach.

4.2.8.2 Disease management costs

The company included health state costs related to routine monitoring for patients which included physician visits, blood count tests and biochemistry tests. The resource use differed between PFS and PD and was informed by a previous NICE submission for MM (NICE TA897).[34] The unit costs of routine monitoring were obtained from NHS Reference Costs 2021/22.[35] Weekly resource use and unit costs applied in the model for PFS and PD health states are reported in Table 35.

Table 35. Resource use and costs for routine monitoring used in the company model base case

Resource Use	PFS weekly resource use	PD weekly resource use	Unit cost	PFS weekly cost	PD weekly cost	Source

Haematologist clinical visit	0.23	0.08	£232.78	£40.11	£13.94	NHS Reference Costs 2021/22. CONSULTANT LED - Multi-professional Non-Admitted Face-to-Face Attendance, Follow-up - WF02A
Full blood count	0.21	0.39	£2.96	£0.56	£1.05	NHS Reference Costs 2021/22. DIRECTLY ACCESSED PATHOLOGY SERVICES - Haematology - DAPS05
Biochemistry	0.19	0.33	£2.39	£0.24	£0.42	NHS Reference Costs 2021/22. DIRECTLY ACCESSED PATHOLOGY SERVICES - Integrated blood services - DAPS03
Protein electrophoresis	0.13	0.18	£1.55	£0.16	£0.23	NHS Reference Costs 2021/22. DIRECTLY ACCESSED PATHOLOGY SERVICES - Clinical biochemistry - DAPS04
Immunoglobulin	0.12	0.19	£7.61	£0.15	£0.24	NHS Reference Costs 2021/22. DIRECTLY ACCESSED PATHOLOGY SERVICES - Immunology - DAPS06
Serum light chain excretion	0.05	0.09	£8.53	£0.06	£0.11	NHS Reference Costs 2021/22. DIRECTLY ACCESSED PATHOLOGY SERVICES - Microbiology - DAPS07
Total cost per weekly cycle	-	-	-	£56.19	£23.06	-

Abbreviations: PFS, progression free survival; PD, progressed disease; NHS, national health service

In addition to routine management costs, a one-off cost associated with blood transfusion (granulocyte colony-stimulating factor [G-CSF], red blood cell transfusion and platelet transfusion) was applied to all patients in the model. Resource used was based on NICE TA510 (Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma),[48] shown in Table 36. Associated costs were sourced from British National Formulary (BNF)[36] and NHS Reference Costs 2021/22.[35] The EAG notes that these costs are applied as one-off costs to progression-free patients (i.e., all patients) in both arms of the model during the first cycle of the model, therefore, cancelling out in the economic results.

Table 36. One-off blood transfusion related resource use and costs used in the company model

Resource	Proportion of patients receiving	Number required per patient	Resource use	Unit cost (£)	Source
G-CSF	0.43	1.00	0.43	£56.68	NICE TA510, Neupogen Singleject 30 million units/0.5mL solution for injection pre-filled syringes (Amgen Ltd), BNF 2022
RBC transfusion	0.49	3.00	1.47	£695.00	NICE TA510, NHS Reference costs 2021/22- SA44A, Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over
Platelet transfusion	0.20	4.79	0.96	£695.00	NICE TA510, NHS Reference costs 2021/22- SA44A, Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over
Total one- off cost applied	**£1,711.83**				

Abbreviations: BNF, British National Formulary; GCSF, Granulocyte colony stimulating factor (G-CSF); NICE, National Institute for Health and Care Excellence; RBC, red blood cell

4.2.8.2.1 EAG critique

Clinical expert opinion provided to the EAG suggested that all patients on active treatment would be seen by a physician once a month, regardless of progression status, during which all of the reported blood and biochemistry tests as part of routine management would take place. Clinical experts agreed that serum light chain excretion may not be undertaken each visit and the resource use in the company's base case for this resource looked appropriate. In addition, clinical experts stated that patients receiving chemotherapy would be seen on a monthly basis, regardless of if their disease having progressed or not. Clinical experts suggested that patients who have progressed and are not on any active treatment would be seen less frequently, with resource use equal to half of that applied to patients on active treatment. In response to a clarification request by the EAG, the company included two scenario analyses using the resource use shown in Table 37. One scenario assumed that resource use is dependent on patients' progression status (i.e., patients' resource use

changes when patients move from the PFS to the PD health state), while the second scenario assumed that the resource use reported in Table 22 depends on patients being on or off treatment (i.e., patients' resource use changes when patients stop treatment, regardless of disease progression). The EAG notes that these scenarios were incorrectly implemented in the company's model as monthly resource was not converted into weekly. Therefore, the results of the company's scenario analyses were implemented by the EAG and are reported in Section 6. The EAG notes that patients on SoC only receive chemotherapy in the PF health state and the majority of patients receive chemotherapy (65%), with no active treatments being received in the PD state. Therefore, the EAG's preferred approach is to apply resource use based on progression status, in line with the company's base case, but using the updated resource use informed by the clinicians in Table 37.

Table 37. Resource use applied in company scenario analysis based on EAG clinical expert advice.

Resource	Monthly use	
	PFS/on treatment	PD/off treatment
Physician visit	1.000	0.500
Complete blood count test	1.000	0.500
Blood chemistry	1.000	0.500
Protein electrophoresis	1.000	0.500
Immunoglobulin	1.000	0.500
Serum light chain excretion	0.217	0.390

Abbreviations: PFS, progression free survival; PD, progressed disease

4.2.8.3 Adverse event costs

The company applied a one-off cost in the first model cycle of the Sd treatment arm to account for the impact of managing AEs. The unit cost for the management of each AE is shown in Table 38, sourced from NHS Reference Costs 2021/22[35], following a clarification request from the EAG. Unit costs were combined with the rate of each AE occurring, taken from the STORM Part 2 trial, as discussed in Section 3.3.6, with a resulting one-off cost of £4,505.42 applied in the Sd arm of the model.

SoC patients were assumed to not incur any AE costs.

Table 38. Adverse event unit costs

Adverse event	Unit cost	Source
Anaemia	£1,214	Total HRGs. Currency code SA04G - SA04L
Asthenia	£764	Non-elective short stay. Currency code SA01G - SA01K

Back pain	£1,413	Total HRGs. Currency code HC32H - HC32K
Bone pain	£1,360	Total HRGs. Currency code WH08A - WH08B
Decreased appetite	£4,466	Total HRGs. Currency code FD10A - FD10M
Dehydration	£2,230	Total HRGs. Currency code KC05G – KC05N
Diarrhoea	£2,211	Total HRGs. Currency code FD10J – FD10M
Dyspnoea	£764	Non-elective short stay. Currency code SA01G -SA01K
Fatigue	£764	Non-elective short stay. Currency code SA01G -SA01K
Hyperglycaemia	£1,469	Total HRGs. Currency code KB02G – KB02K
Hypokalaemia	£1,292	Total HRGs. Currency code KC05J – KC05N
Hyponatraemia	£1,292	Total HRGs. Currency code KC05J – KC05N
Infections and infestations	£4,142	Non-elective long stay. Currency code WH07D
Leukopenia	£1,372	Total HRGs. Currency code SA08G – SA08J
Lymphopenia	£1,372	Total HRGs. Currency code SA08G – SA08J
Nausea	£4,466	Total HRGs. Currency code FD10A – FD10M
Neutropenia	£1,372	Total HRGs. Currency code SA08G – SA08J
Pneumonia	£5,857	Non-elective long stay. Currency code DZ11K-DZ11V
Sepsis	£4,407	Non-elective long stay. Currency code WH07D
Thrombocytopenia	£1,122	Total HRGs. Currency code SA12G – SA12K
Vision blurred	£1,407	Total HRGs. Currency code EB08A – EB08E
Abbreviations: HRG, Healthcare Resource Group		

4.2.8.3.1 EAG critique

Following a clarification request from the EAG, the company updated the unit costs used for AEs to reflect NHS Reference Costs 2021/22.[35] However, the EAG noted that company's reported unit costs had been incorrectly calculated as an average of the included currency codes rather than a weighted average, when more than one NHS Reference Costs currency code was included. Therefore, this failed to take into account the number of activities in the NHS Reference Costs corresponding to each currency code. The EAG updated the unit costs based on calculating the weighted average. The updated costs used in the EAG preferred assumptions are shown in Table 39. Results of the EAG analysis are reported in Section 6.

Table 39. Adverse event unit costs calculated by the EAG

Adverse event	Unit cost calculated by the company	Unit cost calculated by the EAG	Source

Anaemia	£1,214	£866	Total HRGs. Currency code SA04G - SA04L
Asthenia	£764	£770	Non-elective short stay. Currency code SA01G - SA01K
Back pain	£1,413	£1,102	Total HRGs. Currency code HC32H - HC32K
Bone pain	£1,360	£1,273	Total HRGs. Currency code WH08A - WH08B
Decreased appetite	£4,466	£1,844	Total HRGs. Currency code FD10A - FD10M
Dehydration	£2,230	£1,674	Total HRGs. Currency code KC05G – KC05N
Diarrhoea	£2,211	£1,422	Total HRGs. Currency code FD10J – FD10M
Dyspnoea	£764	£770	Non-elective short stay. Currency code SA01G -SA01K
Fatigue	£764	£770	Non-elective short stay. Currency code SA01G -SA01K
Hyperglycaemia	£1,469	£1,533	Total HRGs. Currency code KB02G – KB02K
Hypokalaemia	£1,292	£1,525	Total HRGs. Currency code KC05J – KC05N
Hyponatraemia	£1,292	£1,525	Total HRGs. Currency code KC05J – KC05N
Infections and infestations	£4,142	£4,408	Non-elective long stay. Currency code WH07D
Leukopenia	£1,372	£1,365	Total HRGs. Currency code SA08G – SA08J
Lymphopenia	£1,372	£1,365	Total HRGs. Currency code SA08G – SA08J
Nausea	£4,466	£1,844	Total HRGs. Currency code FD10A – FD10M
Neutropenia	£1,372	£1,365	Total HRGs. Currency code SA08G – SA08J
Pneumonia	£5,857	£3,624	Non-elective long stay. Currency code DZ11K-DZ11V
Sepsis	£4,407	£4,408	Non-elective long stay. Currency code WHO7D
Thrombocytopenia	£1,122	£993	Total HRGs. Currency code SA12G – SA12K
Vision blurred	£1,407	£1,353	Total HRGs. Currency code EB08A – EB08E
Total one-off cost when combined with probability of AE	**£4505.42**	**£3620.71**	-
Abbreviations: AE, adverse event, EAG, evidence review group; HRG, Healthcare Resource Group,			

4.2.8.4 End of life costs

A one-off cost of £4,823 is applied to all patients at death to reflect terminal care costs. This cost was sourced from a study by Round *et al.* 2015[50], which estimated the average end of life care health care costs across four cancer types (breast, colorectal, lung and prostate). The reported average cost for health care resource use was used and inflated by the company to 2022 prices using the Personal Social Services Research Unit (PSSRU)[37] HCHS pay and price indices.

4.2.8.4.1 EAG critique

In Round *et al.* 2015,[50] average costs were also estimated for social care resource use in addition to health care resource use, costed using PSSRU, which the EAG believe should have been included in the company's estimates. In addition, an end-of-life care cost is available directly from PSSRU 2022[37] for cancer which has been used in previous NICE TAs (TA897; TA870),[34, 51] with a cost per patient in their final year of life estimated at £13,113. The PSSRU cost of £13,113 is used in the EAG's base case model, with results of the EAG analysis shown in Section 6.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

In response to the EAG's clarification questions, the company submitted an updated model and cost-effectiveness results. All results include PAS prices (a simple discount of [redacted] The company's base-case also applies a severity modifier of 1.7. The company's updated deterministic and probabilistic base case results are presented in Table 40. As the company model only presented discounted life years for probabilistic results, undiscounted life years are not able to be presented by the EAG. Results from the company's probabilistic sensitivity analyses (PSA) are based on 1,000 simulations.

The probabilistic base case analysis results in an incremental cost-effectiveness ratio of £40,350, reducing to £23,735 when the severity modifier of 1.7 is applied. The deterministic and probabilistic analyses produce similar ICERs.

Table 40. Company's base case results, produced by the EAG

Interventions	Total Costs (£)	Total LY*	Total QALYs	Inc. costs (£)	Inc. LYs*	Inc. QALYs	ICER (£/QALY)	ICER (£/QALY) severity modifier (1.7) applied
Deterministic results								
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Sd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,285	£23,109
Probabilistic results								
SoC	[redacted]	-	[redacted]	-	-	-	-	-
Sd	[redacted]	-	[redacted]	[redacted]	-	[redacted]	£40,350	£23,735
*Undiscounted								

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care; Sd, Selinexor plus dexamethasone

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The PSA scatterplot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 13 and Figure 14, respectively. Based on the PSA, Sd has a 20.90% probability of being cost-effective at a willingness to pay (WTP) threshold of £20,000 and 83.90% probability at a WTP threshold of £30,000.

Figure 13. Scatterplot of PSA estimates on a cost-effectiveness plane for Sd versus BSC (PAS prices and 1.7 severity modifier applied) (produced from the company's model)

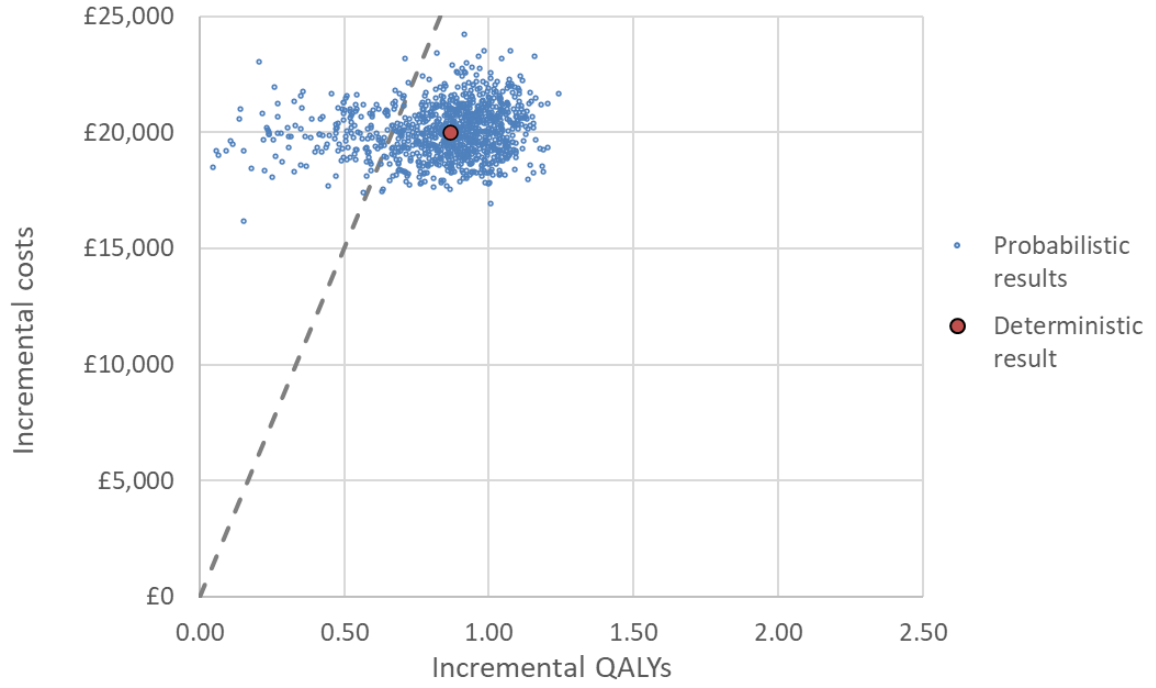
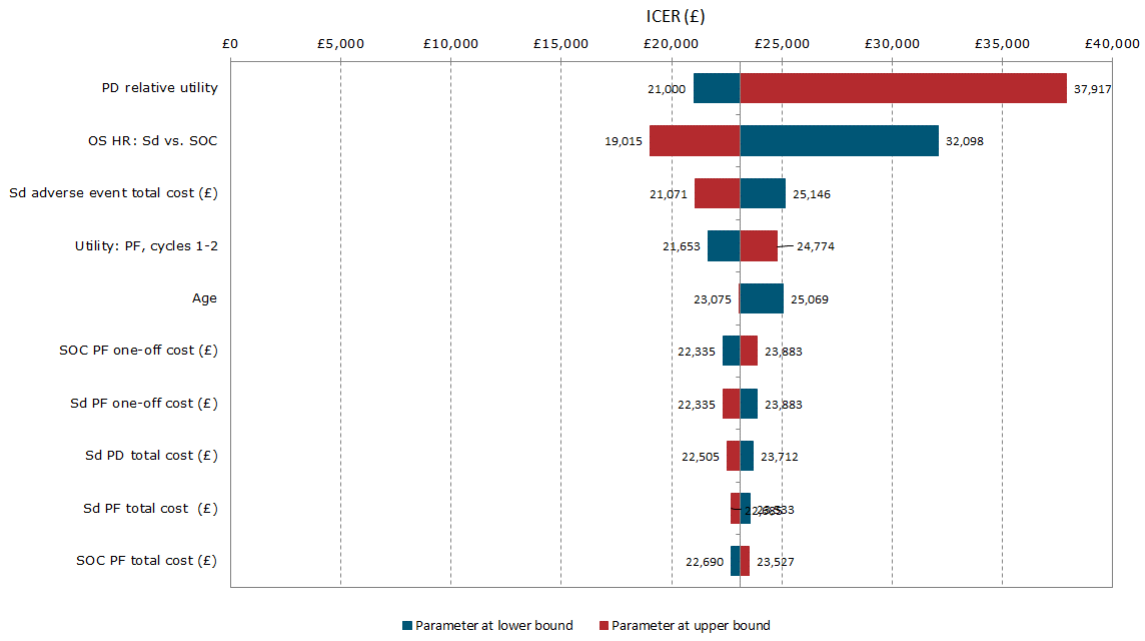


Figure 14. Cost-effectiveness acceptability curve for Sd versus BSC (PAS prices and 1.7 severity modifier applied) (produced from the company's model)

5.2.2 *Deterministic sensitivity analysis*

The company conducted one-way sensitivity analysis (OWSA) to assess the sensitivity of the model to individual parameter uncertainty. Parameters were varied by 95% confidence intervals (CIs) when available and ±20% when these were not available. The company provided a tornado diagram displaying the top 10 most influential parameters on the ICER. This diagram is reproduced below from the company's new base case results document. As shown in Figure 15, the ICER was most sensitive to changes in the relative decrement applied to obtain the PD health state utility value and the overall survival hazard ratio (HR). The EAG notes that the upper value used in the OWSA for the PD relative decrement is 1, which results in same utility values applied in both PFS and PD health states and hence has a large impact on the ICER.

Figure 15. OWSA tornado plot. (Reproduced from the company's new base case results document, Figure 3)



5.2.3 *Scenario analysis*

The company undertook a range of scenario analyses to explore the impact of alternative assumptions for key model parameters. Results of all scenarios conducted by the company are presented in Table 8 of the company's new base case results document.

5.3 Model validation and face validity check

Section B.3.14.1 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

During the clarification stage, the EAG requested a number of scenario analyses which were provided by the company. A number of these were incorporated into the company's updated base case analysis, as previously discussed. The remaining scenarios requested were applied to the company's original base case rather than the final base case post-clarification. Therefore, the EAG has re-run the requested scenarios and are presented in Table 41.

As discussed in Section 4, the EAG identified a number of uncertainties and further scenario analyses that are required to assess the impact of any changes on the incremental cost effectiveness ratio (ICER). The additional scenarios performed by the EAG are detailed below.

1. An illustrative example for modelling overall survival (OS). As noted in Section 4.2.6.2, the EAG's preference to model OS would be independently fitted curves to the OS results of the fully adjusted Matching-adjusted Indirect Comparison (MAIC) for the bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab (BCLPD) refractory subpopulation of STORM 2 versus MAMMOTH. As this was not available to the EAG, this scenario combines the EAG's preferences deemed to provide the best estimate from the currently available data. This includes:
    a. OS modelled using the Weibull parametric curve. As discussed in Section 4.2.6.2, in the absence of independently fitted curves and the application of a hazard ratio (HR) to estimate OS for standard of care (SoC), a parametric curve which supports the proportional hazards (PH) assumption should be used. The Weibull model provided estimates of survival most in line with those provided by the EAG's clinical experts.
    b. No treatment benefit on OS assumed up to 7 months, whereafter the HR derived from the "Full" MAIC is applied to estimate SoC OS. As noted in Section 3.4 and Section 4.2.6.1, based on visual inspection of the MAICs, the Kaplan-Meier (KM) curves are overlapping for Sd and SoC for the first 7 months and therefore it is difficult to infer any difference in OS between the two groups. The EAG cautions that they do not deem the company's MAICs to be robust for drawing conclusions given the resulting low ESS but of the indirect treatment comparisons (ITCs) presented by the company and data available, the EAG considers the "Full" MAIC to be the most reasonable as it provides adjustment for the most variables.

2. Company's base-case approach using a Weibull curve for OS. .
3. Start age in the model equal to that of patients who have received a previous stem cell transplant (SCT) in the STORM BCPLD refractory population, 63 years – Section 4.2.2.
4. Start age in the model equal to that of patients who had not received prior SCT in the STORM BCPLD refractory population, 72 years - Section 4.2.2.
5. Updated adverse event unit costs, calculated by the EAG – Section 4.2.8.3.1.
6. End of life care cost from the Personal Social Services Research Unit (PSSRU)[37] – Section 4.2.8.4.1.

6.2 EAG scenario analysis

Table 41 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]. Presented results are deterministic only. Based on the probabilistic sensitivity analysis (PSA) results presented in Section 5.1, the EAG expects the PSA results to be very similar to the presented deterministic results.

Table 41. Deterministic results of the EAG's scenario analyses

	Results per patient	Sd	SoC	Incremental value
0	**Company base case post clarification**			
	Total costs (£)	[redacted]	£7,700	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,285
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£23,109
Company scenarios in response to EAG clarification questions				
B15a	Updated resource use frequencies			
	Total costs (£)	[redacted]	£7,768	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,901
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£23,471
B15b	Updated resource use frequencies applied by treatment status			
	Total costs (£)	[redacted]	£7,605	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,890
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£23,465

B17	Administration cost of oral chemotherapy			
	Total costs (£)	[redacted]	£7,896	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,796
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£23,409
B18	Cyclophosphamide 500mg dose			
	Total costs (£)	[redacted]	£7,634	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,346
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£23,145
EAG scenarios				
1	Illustrative example for modelling OS (Weibull curve, no treatment effect until [redacted], MAIC "Full" HR)			
	Total costs (£)	[redacted]	£8,018	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£124,897
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£73,469
2	Company's OS approach with Weibull curve as base case			
	Total costs (£)	[redacted]	£7,596	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£60,901
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£35,824
3	Start age of SCT eligible patients			
	Total costs (£)	[redacted]	£7,700	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,251
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£23,089
4	Start age of SCT ineligible patients			
	Total costs (£)	[redacted]	£7,700	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£39,633
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£23,313
5	Updated adverse event costs			
	Total costs (£)	[redacted]	£7,700	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]

	ICER (£/QALY)	-	-	£37,550
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£22,088
6	PSSRU end of life care costs			
	Total costs (£)	[redacted]	£15,912	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	£38,828
	ICER (£/QALY) 1.7 severity modifier applied	-	-	£22,840

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; Sd, Selinexor plus dexamethasone; SoC, standard of care; OS, overall survival, SCT stem cell transplant; HR, hazard ratio

6.3 EAG preferred assumptions

In this section, the EAG presents its preferred assumptions for the cost-effectiveness of Sd for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who are penta-refractory. As noted in Section 6.1, the EAG did not have the available evidence to run their preferred assumptions for modelling OS. As this is such a key aspect of the cost-effectiveness results, it was not possible to produce an EAG preferred base-case ICER. Instead, the EAG presents the preferred assumptions for all other aspects of the cost-effectiveness below and the individual and cumulative impact on the ICER. The illustrative example on OS, described in Section 6.1 is added in last to show the potential impact on the ICER of alternative assumptions regarding the modelling of OS. The EAG preferred assumptions are detailed below, with corresponding results shown in Table 42.

- EAG scenario 1 – EAG clinical experts resource use assumptions. Company CQ response B15a;
- EAG scenario 2 – inclusion of administration cost for oral chemotherapy. Company CQ response B17;
- EAG scenario 3 – Cyclophosphamide 500mg dose. Company CQ response B18;
- EAG scenario 4 – Updated adverse event costs;
- EAG scenario 5 – End of life care cost from the PSSRU;[37]
- EAG scenario 6 – OS illustrative example. Weibull curve, no treatment effect until 7 months, MAIC "Full" HR.

Table 42. EAG's preferred model assumptions

Preferred assumption	Section in EAG report	ICER (£/QALY)	ICER (£/QALY) severity modifier (1.7) applied	Cumulative ICER (£/QALY)	Cumulative ICER (£/QALY) severity modifier (1.7) applied
Company base case post clarification	**-**	**£39,285**	**£23,109**	**£39,285**	**£23,109**
EAG scenario 1 - EAG clinical expert resource use assumptions	4.2.8.2	£39,901	£23,471	£39,901	£23,471
EAG scenario 2 - inclusion of administration cost for oral chemotherapy	4.2.8.1	£39,796	£23,409	£40,412	£23,772
EAG scenario 3 - Cyclophosphamide 500mg dose	4.2.8.1	£39,346	£23,145	£40,474	£23,808
EAG scenario 4 - Updated adverse event costs	4.2.8.3	£37,550	£22,088	£38,738	£22,787
EAG scenario 5 - End of life care cost from the PSSRU	4.2.8.4	£38,828	£22,840	£38,282	£22,519
EAG scenario 6 – OS illustrative example	4.2.6.2	£124,897	£73,469	£121,088	£71,228
EAG scenarios 1–5, probabilistic	-	-	-	**£38,979**	**£22,929**
EAG scenarios 1–6, probabilistic	-	-	-	**£124,450**	**£73,206**

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; PSSRU, Personal Social Services Resource Use; OS, overall survival

Due to the uncertainty associated with OS and the large impact on the ICER of the EAG's OS illustrative scenario, (EAG scenario 6) as shown above in Table 42, the EAG has also explored additional alternative OS assumptions. The first additional scenario employs the same assumptions as the company's base-case; however, OS is modelled using a Weibull curve as opposed to a lognormal. The second additional scenario employs the same assumptions as EAG scenario 6; however, treatment benefit on OS is assumed to apply from 3.5 months as opposed to 7 months.

This is based on the time point at which there was no further crossing of the naive OS KM curves, based on visual inspection.

The ICERs shown below in Table 43 also apply EAG scenarios 1–5 and are provided for information for the committee and do not represent the EAG's preference.

Table 43. Alternative OS assumptions, including EAG scenarios 1–5

Additional assumptions	Sd	SoC	Incremental value
Alternative assumption 1 - Company's OS approach with Weibull curve as base case			
Total costs (£)	[redacted]	£15,855	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	-	-	£59,541
ICER (£/QALY) 1.7 severity modifier applied	-	-	£35,024
Alternative assumption 2 - Weibull curve, no treatment effect until 3.5 months, MAIC "Full" HR			
Total costs (£)	[redacted]	£16,374	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	-	-	£108,814
ICER (£/QALY) 1.7 severity modifier applied	-	-	£64,008

Abbreviations: Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; OS, overall survival; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Sd, Selinexor plus dexamethasone; SoC, standard of care

6.4 Conclusions of the cost effectiveness sections

Generally, the EAG considers the company's submitted cost-effective evidence to adhere to the NICE decision problem defined in the NICE final scope.[2] However, as discussed in Section 4.2.3, the EAG is concerned that the company may have excluded a potential comparator listed in the NICE final scope,[2] as panobinostat + bortezomib + dexamethasone (PanoVd) is a current treatment option at 5L+. As the company did not include PanoVd in their clinical effectiveness literature searches or economic model, the EAG could not explore the impact of this being a comparator in the cost-effectiveness analysis.

Based on the company's analyses, the EAG considers there is considerable uncertainty in the cost-effectiveness results based on the modelling of OS. In the absence of head-to-head data comparing Sd with BSC or CCT, the company conducted MAICs and STCs to enable a comparison between Sd and SoC (proxy for BSC), using data from MAMMOTH.[18] The company's base case analysis used a

lognormal curve fit to STORM KM data to model OS for the Sd arm and applied a hazard ratio derived from the STC to estimate OS for SoC. The EAG considers there are a number of methodological flaws with this approach. Based on the plot of the log HR over time and comparison of the KM curves, the EAG considers that the proportional hazards (PH) assumption is violated. Therefore, the EAG deem the use of a HR to estimate OS for SoC to be inappropriate, particularly so when applied to a lognormal curve which does not support the PH assumption. The EAG's preference of independently fitted curves, to the "Full" adjusted MAIC, were not provided and therefore the impact of using these in the economic model could not be explored by the EAG, nor a EAG preferred base case ICER produced. To assess the uncertainty associated with OS in the economic model, the EAG therefore provided an illustrative scenario, using the preferred data of that which was available to the EAG, which was shown to have a substantial impact on the ICER.

The EAG explored a number of scenarios using EAG preferred assumptions around the resource use and costs used in the model. None of these had a substantial impact on the ICER, with the resulting ICERs ranging from £38,282–£40,474, reducing to £22,519–£23,808 when the severity modifier of 1.7 was applied.

The EAG also considers there to be uncertainty regarding the age at which patients are likely to receive Sd, as patients in UK clinical practice who will be eligible to start treatment may be older than those in the STORM trial. When the model start age was adjusted compared to the company's base case, this did not have a substantial impact on the ICER. However, as previously discussed, the EAG was not able to produce a preferred base case ICER which included their preference on OS. As changes in age and OS would impact the QALYs for the SoC arm this could have an impact on the severity modifier applied and therefore the resulting ICER (see Section 7).

Overall, the EAG believes that there is a substantial amount of uncertainty in the cost-effectiveness analysis due to the modelling of OS. The EAG was not able to produce a preferred base case ICER; however, exploratory scenarios around alternative assumptions for OS show the resulting increase in the ICER, driven largely by changes in the incremental QALYs.

7 Severity modifier

As outlined in the National Institute for Health and Care Excellence (NICE) manual,[12] "*the committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS*". The thresholds of quality-adjusted life-year (QALY) weightings for severity are reported in Table 44.

Table 44. QALY weighting for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18.

Abbreviations: QALY, quality-adjusted life-year

The company calculated the absolute and proportional QALY shortfall using the approach and sources recommended by Schneider *et al.* 2021 coded in their economic model.[52] This approach calculates the expected total QALYs for the general population matched to baseline age and sex distribution included in the economic model. The source of the general population EQ-5D data used in the calculator is from a study by the Health Survey for England 2014, as recommended by the NICE Decision Support Unit (DSU).[53] Table 45 presents the company's preferred assumptions for the general population QALY shortfall estimates.

Table 45. Summary of preferred assumptions for general population QALY shortfall estimates

Factor	Value or source	Reference to section in submission or rationale
Sex distribution - male	61.5%	Post clarification economic model – STORM Part 2 BCPLD refractory population[23]
Starting age (mean)	64.5	Post clarification economic model – STORM Part 2 BCPLD refractory population[23]
Expected total QALYs for the general population	11.14	Calculated in company's model based on approach by Schneider *et al*. 2021.[52] Estimated based on starting age and sex distribution at baseline
Discount rate	3.5%	NICE reference case[12]

Abbreviations: BCPLD, Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; QALY, quality-adjusted life-year

To calculate the absolute and proportional QALY shortfall in their economic model, the company used the base case total discounted QALYs estimated for the standard of care (SoC) arm, estimated to be [redacted]. The results of the company's QALY shortfall analysis is presented in Table 46. Table 47 presents a summary of the company's preferred assumptions that impact the SoC QALY shortfall estimates. Of the modelled inputs that affect the SoC QALY shortfall estimates listed in Table 47, OS is considered to be highly uncertain by the EAG and therefore changes may have an impact on the severity modifier applied.

Table 46. Summary of QALY shortfall analysis

Expected total QALYs for the general population	Expected total QALYs that people living with the condition would be expected to have on SoC	QALY shortfall	
		Proportional shortfall	Absolute shortfall
11.14	[redacted]	[redacted]	[redacted]

Abbreviations: SoC, standard of care; QALY, quality-adjusted life-year.

Table 47. Summary of company preferred assumptions affecting SoC QALY shortfall estimates

Modelled input	Assumption or value (reference to appropriate table or figure in submission)
OS curve for SoC	Section B.3.3.1 to B.3.3.2 of the CS. HR derived from the STC comparing STORM and MAMMOTH data, applied to the Sd lognormal OS curve.
PFS curve for SoC	Section B.3.3.1 to B.3.3.2 of the CS. Assumed the same as applied for Sd, based on a lognormal curve fit to PFS Kaplan-Meier data
TTD curve for SoC	Section B.3.3.1 to B.3.3.2 of the CS. Assumed the same as applied for Sd, based on an exponential curve fit to TTD Kaplan-Meier data
PFS utility value	Section B.3.4.4 of the company submission. 0.589 (SE: 0.020)
PD utility value	Section B.3.4.4 of the company submission. 0.535 (SE: 0.107)

Abbreviations: CS, company submission; HR, hazard ration; OS, overall survival; Sd, Selinexor plus dexamethasone; STC, simulated treatment comparator; SoC, standard of care; TTD, time to treatment discontinuation; PFS, progression free survival; PD, progressed disease, SE, standard error

7.1 Cost effectiveness estimates

Based on the QALY shortfall analysis, the company estimates that a severity modifier of 1.7 should apply as the resulting proportional shortfall was greater than 95%. Based on the absolute shortfall only, a severity modifier of 1 would apply as the resulting absolute shortfall was less than 12. Table 48 presents the company's preferred cost-effectiveness results with the severity modifier of 1.7 applied to the incremental QALYs.

Table 48. Company cost-effectiveness results with and without severity weighting applied

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
No severity modifier	[redacted]	[redacted]	39,285
1.7 severity modifier	[redacted]	[redacted]	23,109

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

7.2 EAG critique

The EAG considers the calculation of the QALY shortfall in the company's model based on the approach by Schneider *et al*.[52] to be appropriate. The EAG notes that there will be slight discrepancies between the company's estimates calculated directly in the model and the Schneider *et al*. calculator,[52] as the company has used the most recently available life tables for England (2018–2020 pooled), whereas the Schneider *et al*.[52] calculator uses 2017–2019 pooled. The EAG notes that this is a very small difference and considers the company's approach to be correct.

As noted in Section 6.3, the EAG was unable to provide a preferred base case ICER. However, an example exploratory scenario was provided which combined five of the EAG's preferred assumptions, related to costs and resource use, and an illustrative scenario for modelling OS. When the EAG's scenarios were applied in the economic model it resulted in an absolute QALY shortfall of [redacted] and a proportional QALY shortfall of [redacted], resulting in a severity modifier of 1.7. As previously discussed, the EAG considers the average age of penta-refractory patients who will receive selinexor plus dexamethasone (Sd) to be uncertain and potentially higher than the age used in the economic model. As the start age of patients influences the general population QALY shortfall estimates, the EAG examined the impact of applying a higher start age to the EAG's exploratory scenario, consisting of the EAG's five preferred assumptions and illustrative scenario for modelling OS. When the start age was set to 72, based on the average age of stem cell transplant (SCT) ineligible patients in the STORM trial, the resulting absolute QALY shortfall was [redacted] and a proportional QALY shortfall of [redacted], resulting in a severity modifier of 1.2. The resulting ICER for this scenario is £121,245, which reduces to £101,037 when the corresponding 1.2 severity modifier applied. Although this is not based on the EAG's preferred ICER, this exploratory scenario highlights the sensitivity of the severity modifier and resulting ICERs on alternative assumptions in the economic model that are considered uncertain.

8 References

1. Medicines and Healthcare products Regulatory Agency (MHRA). Public Assessment Report: Nexpovio 20mg. 2021.
2. National Institute for Health and Care Excellence. Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193] - Final Scope, 2023. Available from: https://www.nice.org.uk/guidance/gid-ta11223/documents/final-scope. Date accessed: 01 Nov 2023.
3. NHS. Overview Multiple Myeloma, 2021. Available from: https://www.nhs.uk/conditions/multiple-myeloma/. Date accessed: 03 Oct 2023.
4. (MUK). MU. What is myeloma, 2021. Available from: https://www.myeloma.org.uk/understanding-myeloma/what-is-myeloma/. Date accessed: 03 Oct 2023.
5. UK CR. Myeloma incidence statistics, 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-Zero. Date accessed: 03 Oct 2023.
6. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011; **117**: 4691-5.
7. Bhatt P, Kloock C, Comenzo R. Relapsed/Refractory Multiple Myeloma: A Review of Available Therapies and Clinical Scenarios Encountered in Myeloma Relapse. *Curr Oncol* 2023; **30**: 2322-47.
8. Bird SA, Boyd K. Multiple myeloma: an overview of management. *Palliat Care Soc Pract* 2019; **13**: 1178224219868235.
9. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Nexpovio. 2023.
10. National Institute for Health and Care Excellence (NICE). GID-TA10568: Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies. 2023.
11. Higgins JPT, Thomas J, Chandler J, cumpston M, Li T , Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4, 2023. Available from: https://training.cochrane.org/handbook/current. Date accessed: 03 Oct 2023.
12. NICE. NICE health technology evaluations: the manual (Process and methods [PMG36]), 2022. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. Date accessed: 03 Oct 2023.
13. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *Journal of clinical epidemiology* 2016; **75**: 40-6.
14. (SIGN) SIGN. Search filters, 2022. Available from: https://www.sign.ac.uk/what-we-do/methodology/search-filters/. Date accessed: 03 Oct 2023.
15. CADTH. RCT / CCT - MEDLINE, Embase, PsycInfo, 2021. Available from: https://searchfilters.cadth.ca/link/35. Date accessed: 03 Oct 2023.
16. Kim C, Braunlin M, Mehta B, Payne R. Outcomes of Triple-Class (proteasome inhibitor, immunomodulator, CD38 monoclonal antibody) Exposed Relapsed or Refractory Multiple Myeloma (RRMM) in United States (US) Real-World Practice. *Blood* 2021; **138**: 3042-.
17. Mateos M, Weisel K, De Stefano V, Goldschmidt H, Delforge M, Mohty M, et al. LocoMMotion: A Prospective, Non-Interventional, Multinational Study of Real-Life Current Standards of Care in Patients with Relapsed and/or Refractory Multiple Myeloma, 2022.
18. Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019; **33**: 2266-75.

19. Chari A, Vogl DT, Gavriatopoulou M, Nooka AK, Yee AJ, Huff CA, et al. Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma. *New England Journal of Medicine* 2019; **381**: 727-38.
20. Critical Appraisal Skills Programme. CASP Cohort Study Checklist. 2018. Available from: https://casp-uk.net/casp-tools-checklists/. Date accessed Sept 2023.
21. NICE. NICE real-world evidence framework (Corporate document [ECD9]), 2022. Available from: https://www.nice.org.uk/corporate/ecd9/chapter/methods-for-real-world-studies-of-comparative-effects#types-of-non-randomised-study-design. Date accessed: 05 Oct 2023.
22. Karyopharm Therapeutics Inc. Clinical Study Report (KCP-330-012; Data cut-off 24 April 2018). 2018.
23. Karyopharm Therapeutics Inc. Clinical Study Report (KCP-330-012; Data cut-off 7 September 2019). 2019.
24. Supplement to: Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor–dexamethasone for triple-class refractory multiple myeloma. N Engl J Med 2019;381:727-38. Available from: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1903455/suppl_file/nejmoa1903455_appendix.pdf. Date accessed: Oct 2023.
25. Menarini Stemline. Data on file. 2023.
26. Karyopharm Therapeutics Inc. Clinical Study Protocol (KCP-330-012) Version 6.0. 2017.
27. Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol* 2020; **21**: 207-21.
28. Richardson PG, Jagannath S, Chari A, Vogl DT, Dimopoulos MA, Moreau P, et al. Overall survival with oral selinexor plus low-dose dexamethasone versus real-world therapy in triple-class-refractory multiple myeloma. *EJHaem* 2021; **2**: 48-55.
29. Gill SK, Unawane R, Wang S, Aleman A, Serna M, Perez-Manon F, et al. Inferior Outcomes of Patients with Quad and Penta-Refractory Multiple Myeloma (MM) Compared to Those of Patients Who Have Been Quad and Penta Exposed. *Blood* 2021; **138**: 4742-.
30. Gill SK, Unawane R, Wang S, Ahn J, Aleman A, Siegel DS, et al. I-OPen: inferior outcomes of penta-refractory compared to penta-exposed multiple myeloma patients. *Blood Cancer J* 2022; **12**: 138.
31. Gopalakrishnan S, D'Souza A, Scott E, Fraser R, Davila O, Shah N, et al. Revised International Staging System Is Predictive and Prognostic for Early Relapse (<24 months) after Autologous Transplantation for Newly Diagnosed Multiple Myeloma. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation* 2019; **25**: 683-8.
32. Nikolaou A, Ambavane A, Shah A, Ma W, Tosh J, Kapetanakis V, et al. Belantamab mafodotin for the treatment of relapsed/refractory multiple myeloma in heavily pretreated patients: a US cost-effectiveness analysis. *Expert review of hematology* 2021; **14**: 1137-45.
33. Speranza G, Diliberto MJ, Fattore C, Fiorentino F, Prawitz T, Nikolaou A, et al. POSB74 Belantamab Mafodotin as the First-in-Class Anti-BCMA Treatment for Relapsed/Refractory Multiple Myeloma: A Budget Impact and Cost-Effectiveness Analysis. *Value in Health* 2022; **25(1 Supplement)**: S74-S5.
34. National Institute for Health and Care Excellence (NICE). TA897: Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma. 2023. Available from: https://www.nice.org.uk/guidance/ta897. Date accessed: September 2023.
35. NHS. National Cost Collection for the NHS 2021/22. 2023. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/. Date accessed: January 2023.
36. BNF. British National Formulary. 2021. Available from: https://bnf.nice.org.uk/. Date accessed Oct 2023.

37. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care Manual 2022. 2022. Available from: https://www.pssru.ac.uk/unitcostsreport/. Date accessed Oct 2023.
38. Rutherford M, Lambert, PC., Sweeting, MJ., Pennington, R., Crowther, MJ., Abrams, KR., Latimer, NR. NICE DSU Technical Support Document 21. Flexible Methods for Survival Analysis. 2020.
39. European Medicines Agency. Nexpovio. Assessment Report. 2022.
40. Longworth L, Yang Y, Young T, Mulhern B, Hernández Alava M, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. *Health Technol Assess* 2014; **18**.
41. National Institute for Health and Care Excellence (NICE). TA658: Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma. 2020. Available from: https://www.nice.org.uk/guidance/ta658/history. Date accessed: September 2023.
42. National Institute for Health and Care Excellence (NICE). TA427: Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib. 2017. Available from: https://www.nice.org.uk/guidance/ta427/history. Date accessed Oct 2023.
43. National Institute for Health and Care Excellence (NICE). TA573: Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma. 2019.
44. Hatswell AJ, Burns D, Baio G, Wadelin F. Frequentist and Bayesian meta-regression of health state utilities for multiple myeloma incorporating systematic review and analysis of individual patient data. *Health Economics (United Kingdom)* 2019; **28(5)**: 653-65.
45. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2010; **13**: 509-18.
46. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *PharmacoEconomics* 2022.
47. Department of Health and Social Care. eMIT national database, 2021. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Date accessed: Aug 2023.
48. National Institute for Health and Care Excellence (NICE). TA510: Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. 2018.
49. NHS. Chemotherapy Protocol- MULTIPLE MYELOMA-RCD-CYCLOPHOSPHAMIDE-DEXAMETHASONE-LENALIDOMIDE 2016. Available from: https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Myeloma/MyelomaRCDCyclophosphamideDexamethasoneLenalidomidelRCDVer1.pdf. Date accessed: Sept 2023.
50. Round J, Jones, L. and Morris, S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. *Palliative Medicine* 2015; **29**: 899-907.
51. Excellence NIfHaC. TA870: Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. 2023.
52. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. QALY shortfall calculator. 2021. Available from: https://shiny.york.ac.uk/shortfall/. Date accessed Oct 2023.
53. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU Report. 2022.

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]

Addendum: EAG response to additional company analyses

December 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136082.

1 EAG response to additional analyses

In the External Assessment Group (EAG) report, the EAG noted that in the naïve and adjusted (MAIC) comparisons of selinexor plus dexamethasone (Sd) and standard of care (SoC) using the STORM Part2 bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab (BCLPD) refractory population[1] and the MAMMOTH penta-refractory subgroup[2] there are multiple overlaps in the initial 3.5 and 7 months of the overall survival KM curves, respectively, and that this is not captured in the company's simulated treatment comparison (STC). In response to an additional clarification question, the company provided independently fitted curves to the MAIC adjusted STORM data and to digitised MAMMOTH curves. However, the EAG notes that the company does not consider the results of this analysis to be robust and provided three reasons for this which are summarised below:

1. The company consider it to be based on an unsuitable MAIC analysis that excludes some key prognostic factors and treatment effect modifiers identified by the EAG, such as prior stem cell transplant (SCT) and duration of last therapy. In addition, the MAIC is associated with a very low effective sample size (ESS) (N = 10, corresponding to < 13% of the initial BCLPD-refractory population).
2. The company considers that using the adjusted overall survival (OS) Kaplan-Meier (KM) curve for Sd, after matching the BCLPD-refractory patients to the MAMMOTH population, would move the Sd population even further away from the population expected in the UK.
3. The company considers that the pattern of 'overlapping KM curves followed by a subsequent change in hazards' noted in the EAG report (page 77) is "*more likely a consequence of the low ESS associated with the MAIC analysis rather than being aligned with clinical evidence to suggest that a treatment effect would emerge only after several months have passed*".

The EAG considers it important to highlight that the low ESS in the MAIC reflects the lack of overlap in key patient baseline characteristics between the STORM Part 2 BCLPD refractory population and the MAMMOTH penta-refractory population. However, as detailed in the EAG report, the EAG considers that the discrepancies between the studies: STORM Part 2 BCLPD-refractory subgroup and MAMMOTH penta-refractory subgroup, compared with patients with penta-refractory RRMM in

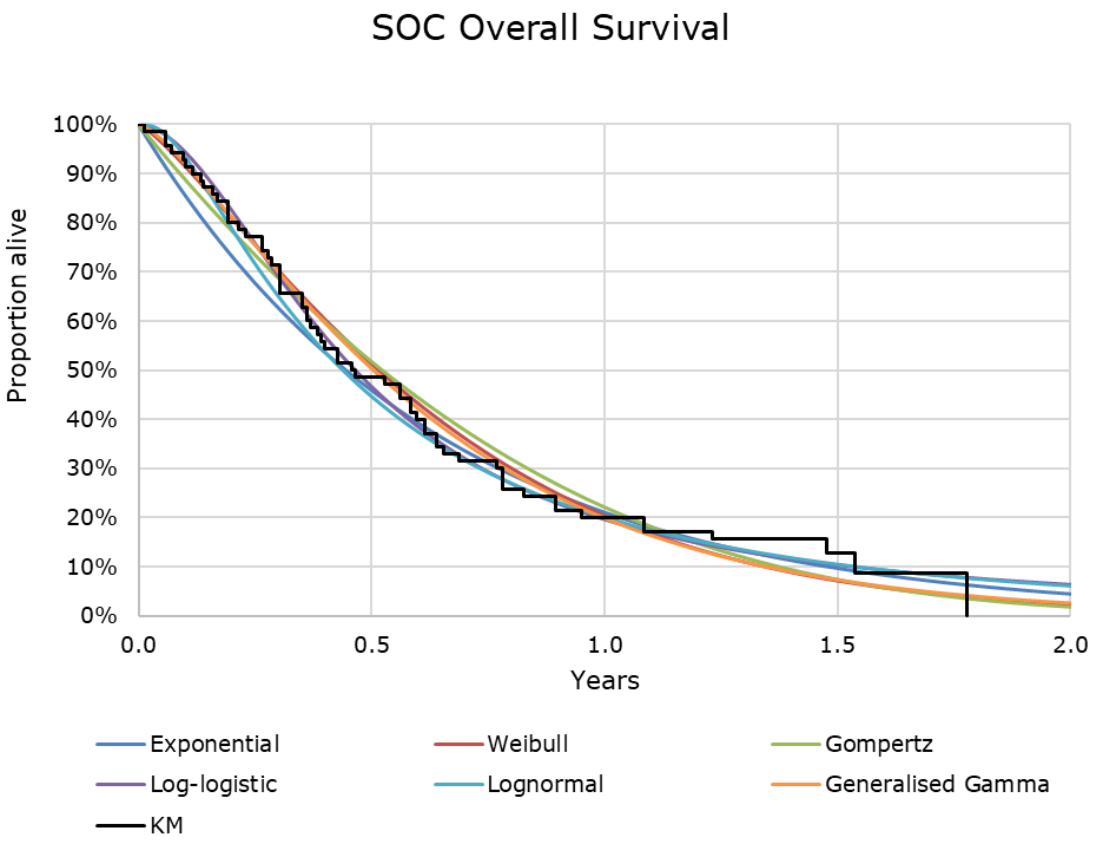
clinical practice in England, as well as the differences in treatments and subsequent treatments, may limit the generalisability of the findings for Sd to clinical practice.

With regards the company's statement asserting that the overlapping KM curves are due to the low ESS in the MAICs, the EAG notes that: this overlap is present in the naïve comparison of the KM OS curves for Sd and SoC, the "duration" of the overlap increases in all of the MAICs presented by the company, and the overlap occurs at the beginning of the KM curves (whether adjusted or not), where the ESS is at its highest and the curves diverge when the ESS drops.

Overall, the EAG considers there to be a paucity of clinical data to provide a robust comparison of Sd versus SoC and acknowledges that the EAG preferred 'Full' adjusted MAIC results in a low ESS. However, the same lack of overlap resulting in a low ESS in the MAIC similarly confounds the predictions from the STC, with the additional confounder of assuming proportional hazards holds. The EAG does not consider this to be appropriate and therefore does not consider it valid to use the results of the company's current STC for drawing conclusions on the efficacy of Sd versus SoC or for use in the analysis of cost-effectiveness. While the EAG considers the company's MAICs to be highly uncertain given the resulting low ESSs, the EAG considers the "Full" MAIC to be the most reasonable as it provides adjustment for the most variables.

The EAG thanks the company for providing the independently fitted curves to the MAIC-adjusted OS KM curve for Sd and digitised MAMMOTH data for SoC. The company selected the exponential as the best fitting curve for the SoC arm (digitised MAMMOTH data) based on AIC/BIC statistics and clinical plausibility regarding the predicted proportion of patients alive at 3 years. The EAG's clinical experts stated that they would expect all patients on SoC to have died by 3 years. The EAG notes that aside from the log-normal and log-logistic distributions, all other parametric curves predict less than 1% of patients alive at 3 years. The EAG notes that based on both visual fit (see Figure 1) and clinical plausibility, the Weibull model provides a superior fit to the data than the exponential, with 0.18% of patients predicted to be alive at 3 years and 0% at 5 years.

Figure 1. Parametric curves fitted to OS Kaplan-Meier data from MAMMOTH (produced from the company's model)

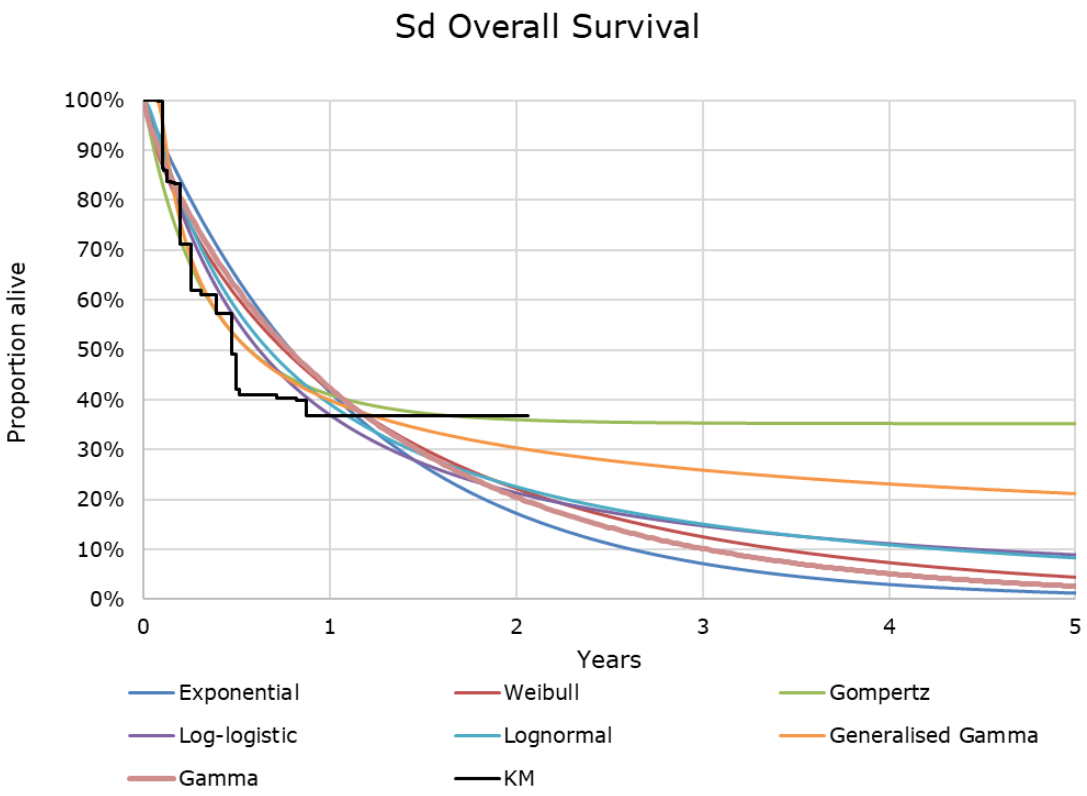


The company chose the log-normal distribution as the best fitting curve to the adjusted OS KM curve for Sd, based on the AIC and BIC and clinical plausibility. The EAG notes that the estimated survival at 5 years from the lognormal is 8.26%. As previously noted in the EAG report, clinical experts stated that given the average treatment duration of Sd being 2.5 months, it seems clinically implausible that 6% of patients (based on the company's base case OS analysis) would be alive at 5 years. Therefore, the 8% estimated from the log-normal fitted to the MAIC-adjusted OS KM curve also appears clinically implausible.

The EAG had requested that based on the overlapping KM curves up to 7 months, the company modelled the independently fitted curves allowing for a change in the underlying hazard. This would require the use of more flexible parametric curves.[3] The EAG notes that none of the standard parametric curves fitted by the company are sufficiently flexible to capture the underlying KM data and the AIC/BIC statistics suggest that all are equally ill fitting (see Figure 2). However, the EAG acknowledges that fitting more complex curves may not be appropriate due to the paucity of the

data. Therefore, based on the available data, the EAG considers the Weibull model fit to the MAIC-adjusted OS KM data to provide the most clinically plausible estimates of survival (3 year OS = 12.53%, 5 year OS = 4.39%).

Figure 2. Parametric curves fitted to OS Kaplan-Meier data from the full MAIC adjusted KM data (produced from the company's model)



Therefore, the EAG prefers the use of Weibull model fit in both arms. As shown in Figure 3, the use of the Weibull model fit to both the Sd and SoC data results in a crossing of the curves at approximately 3.5 months. As previously discussed in the EAG report, there was crossing of the naive KM curves until around 3.5 months in a naïve comparison of the KM curves, which was further exacerbated by the adjustment of the Sd OS KM curve in any of the MAICs conducted by the company. Therefore, the EAG considers that the use of the Weibull model fit to both the full MAIC adjusted KM and the MAMMOTH KM data to be the best reflection of the available data. The EAG notes, however, that the Weibull model is higher than the Sd KM beyond the crossing point, suggesting that survival is likely to be overpredicted. The EAG consider there to be unresolvable uncertainty in the OS estimates but provides the results of the EAG preferred assumptions previously discussed in the EAG report with OS modelled using the Weibull model fit to both

independent curves. The results of this scenario applied both separately to the company base case and including the EAG's preferred scenarios 1-5 are presented in Table 1. Due to the likely overestimate of survival for Sd, the EAG considers this to be an "optimistic" ICER for SD versus SoC.

Figure 3. Weibull parametric curve fit to both the OS Kaplan-Meier data from the full MAIC adjusted and MAMMOTH KM data (produced from the company's model)

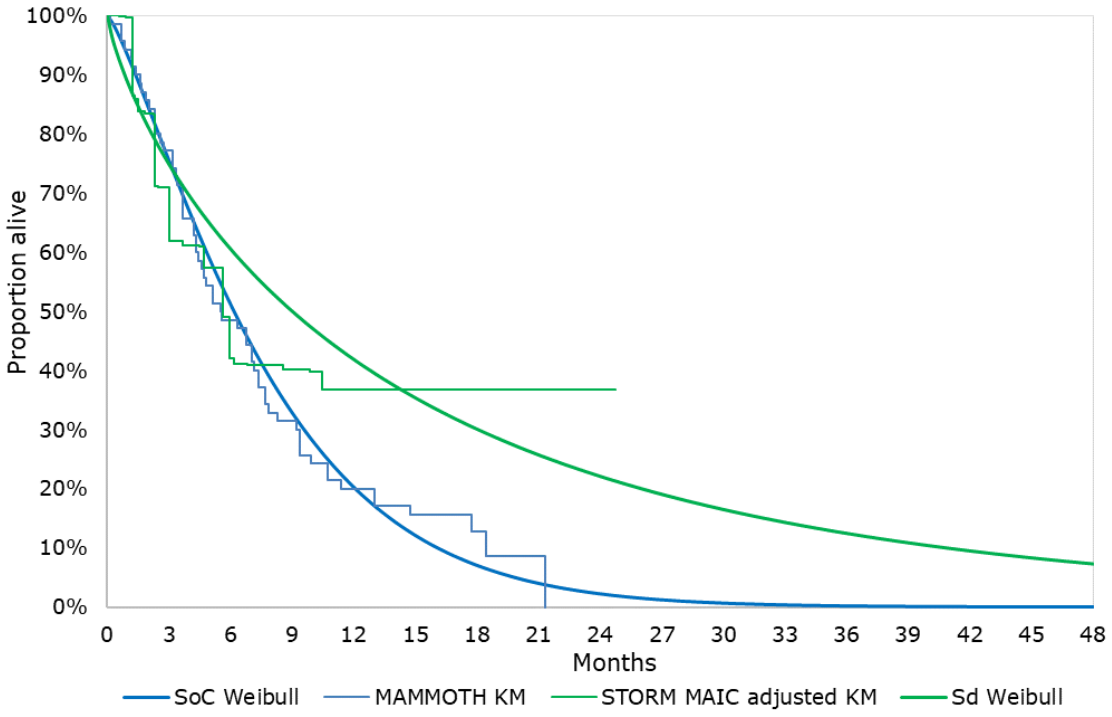


Table 1. Results of Weibull curve applied to both OS Kaplan-Meier data from the full MAIC adjusted and MAMMOTH KM data, probabilistic.

	Sd	SoC	Incremental value
Weibull curve applied to both OS Kaplan-Meier data from the full MAIC adjusted and MAMMOTH KM data			
Total costs (£)	[redacted]	£7,909	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	-	-	£56,308
ICER (£/QALY) 1.7 severity modifier applied	-	-	£33,122
Above scenario including EAG preferred assumptions 1–5			
Total costs (£)	[redacted]	£16,309	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	-	-	£53,892

ICER (£/QALY) 1.7 severity modifier applied	-	-	£31,701

Abbreviations: Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; OS, overall survival; MAIC, matching-adjusted indirect comparison; Sd, Selinexor plus dexamethasone; SoC, standard of care

As OS is the key driver in the assessment of cost-effectiveness of Sd compared to SoC and, given the unresolvable uncertainty in OS, the EAG suggests that committee might want to consider mitigating the decision risk in this appraisal with an appropriate adjustment to the ICER threshold used for decision making.

2 References

1. Chari A, Vogl DT, Gavriatopoulou M, Nooka AK, Yee AJ, Huff CA, et al. Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma. *New England Journal of Medicine* 2019; **381**: 727-38.

2. Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019; **33**: 2266-75.

3. Rutherford M, Lambert, PC., Sweeting, MJ., Pennington, R., Crowther, MJ., Abrams, KR., Latimer, NR. NICE DSU Technical Support Document 21. Flexible Methods for Survival Analysis. 2020.

Single Technology Appraisal

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]

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 Wednesday 15 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 Sd indication

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On a number of occasions throughout the EAG report it is suggested that Sd for the treatment of penta-refractory 5L+ MM is a selective positioning, narrower than the MHRA marketing authorisation (MA). The positioning with NICE is as per the MHRA MA indication. The company appreciate that the word penta-refractory does not appear in the indication but the indication does make clear that patients are refractory to 5 treatments - *in combination with dexamethasone 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, and who have demonstrated disease progression on the last therapy.* This positioning was detailed as such in the original company	The EAG report should make clear that the proposed positioning of Sd with NICE is as per the wording of the MHRA MA, and that this has been the case throughout the appraisal process.	The company is concerned that wording on several occasions throughout the report misrepresents the company's positioning, which is as per the MHRA MA and was in the initial company submission and has not wavered from this throughout the appraisal process.	The EAG thanks the company for highlighting this and has updated the text in the EAG report to clarify that the text in the marketing authorisation stating "four prior therapies" is considered by the company to be "four prior lines of therapy". The EAG has also updated the key issues in the EAG report and removed "Issue 1: Company positioning of Sd for penta-refractory patients at 5L+".

submission and clarified further during EAG clarification questions.			

Issue 2 Positioning of Sd

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 15, table 2, it states that clinical experts reported that patients could become penta-refractory at an earlier line of therapy than fifth line and thus could be eligible to receive Sd earlier than 5L+. Whilst the company agree that there may be potential to become penta-refractory in an earlier line of therapy than 5L+, patients would not become eligible for Sd as this is not in line with the MHRA indication and is not as per the STORM study, where patients had received a median of 8 prior treatments (range 4 – 18). In addition, SVd (selinexor in combination with bortezomib and dexamethasone) was studied in the BOSTON study in the 2L – 4L setting and is currently being assessed by NICE (ID3797) for use	The EAG report should make clear that the proposed positioning of Sd with NICE in the 5L+ is as per the wording of the MHRA MA and in line with the patient population in the STORM study.	Patients would not be eligible to receive Sd earlier than 5L+	The EAG thanks the company for highlighting this and has updated the EAG report to remove "Table 2. Issue 1: Company positioning of Sd for penta-refractory patients at 5L+" from the report as detailed in response to Issue 1 above.

earlier in the treatment pathway at 2L and 3L.			

Issue 3 PanoVd as a valid comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On a number of occasions throughout the EAG report it is stated that the EAG have received clinical input that PanoVd would be real-world comparator to Sd in penta-refractory patients who have received at least four prior lines of treatment (5L+). This is strongly at odds with all leading UK clinical expert opinion elicited by the company during submission preparation including two advisory boards and a number of semi-structured interviews. Based on the information provided by the UK clinical experts, the company believe that should a patient be suitable for treatment with PanoVd, with bortezomib still suitable, this would likely be earlier in the treatment pathway,	The EAG report should make clear that while PanoVd is available generally at 5L as per current NICE guidance, it is rarely used, and would not be clinically appropriate for 5L+ penta-refractory patients in the overwhelming majority of cases – as is consistent with page 23 of the EAG report where the EAG state: "*Subsequently, at 5L, treatment options would be very limited, with PANO+BORT+DEX being a potential option for a limited number of patients due to the potential side-effects"*.	The company is concerned that the appraisal committee may be misled by the EAG position of suggesting PanoVd as an appropriate comparator to Sd in 5L+ penta-refractory MM patients which, to the best of company knowledge, is not a commonly held clinical opinion amongst leading UK clinical experts.	Not a factual inaccuracy, no change required.

making SVd the appropriate Selinexor comparator (as per the SVd appraisal ID3797), not Sd which is only indicated as per the license for 5L+ MM patients who are penta-refractory. Moreover, it is highly unlikely that 5L+ penta-refractory patients would have myeloma disease that was still receptive to a bortezomib-based regimen.			

Issue 4 Clarification around OS evidence

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.2 describes its clinical assumption, based on expert engagement, that no penta-refractory patients receiving SoC will survive to three years beyond treatment initiation. As acknowledged by the EAG, this broadly aligns with the revised company estimate of 0.87% survival at three years. Nonetheless, the company believes that it is important to reiterate that	Although the level of discrepancy between the EAG estimate of 0% survival and the revised company estimate of 0.87% survival at three years is nominally small, the company believes that it is important to clarify that survival beyond three years is supported not only by studies in penta-refractory patients cohorts but also the individual profiles of	The company feels that this is a fundamentally important point to clarify both in terms of a potential driver of ICER and due to its narrative relevance in terms of the value impact of later-line therapies.	Not a factual inaccuracy, no change required.

survival beyond three years is supported both by studies described in the company submission as well as by the profiles of individual patients directly involved in patient engagement exercises.	patients directly involved in patient engagement as part of the submission process.		

Issue 5 Overlaps between KM curves for Sd and SOC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On pages 18 and 64 of the EAG report, the EAG states in relation to the STC that '*the simple PH approach utilised by the company lacks face validity given the multiple overlaps seen in the initial 7 months of the underlying KM curves for Sd and SOC from STORM Part 2 BCLPD refractory patients and the MAMMOTH penta-refractory subgroup'*.	The EAG should make it clear that the multiple overlaps in the initial 7 months are seen only when comparing the MAIC adjusted KM curve for Sd from STORM Part 2 BCLPD refractory patients and the KM curve from MAMMOTH penta-refractory population. When comparing instead the unadjusted KM curve for Sd and the KM curve from MAMMOTH, the overlaps are seen only for the first 3 months.	Clarification	The EAG thanks the company for highlighting this and has updated the text in the EAG report on page 18 to : "….given the multiple overlaps seen in the initial 3.5 months of the underlying unadjusted KM curves for Sd and SoC from STORM Part 2 BCLPD refractory patients and the MAMMOTH penta-refractory subgroup." and on page 64 to: "The EAG

			notes from the naïve and adjusted (MAIC) comparisons of Sd and SoC using the STORM Part2 BCLPD refractory population and the MAMMOTH penta-refractory subgroup that there are multiple overlaps in the initial 3.5 and 7 months of the overall survival KM curves, respectively, and that this is not captured in the STC".

Issue 6 Use of adjusted OS KM curve for Sd and independent curve fitting

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.4.2, the EAG concluded that 'the least biased' option to assess realtive efficacy between Sd and SOC is to fit independent curves over the adjusted KM curve for Sd and the OS KM curve from the MAMMOTH study. The company believes that	The EAG proposed apporach consists of fitting an indipendent survival curve on the adjusted KM OS curve for Sd, which was drawn on an ESS of 10 patients. At page 41, the EAG raised concerns about the relative small sample size of the	The company feels that this is a fundamentally important point to clarify the most reliable approach that generates the least biased results,	Not a factual inaccuracy, no change required.

the extremely small ESS resulting from the matching process (10 patients) would generate very uncertain statistical results. Moreover, the results from this approach, matching the BCLPD-refractory population to the MAMMOTH study population, would lead to biased results towards a population that is not fully representative of the UK population. The company does not agree that the pattern of 'overlapping KM curves followed by a subsequent change in hazards' noted in page 77 should be interpreted as a meaningful representation of the treatment effect given the uncertainties and low ESS associated with the MAIC analysis and the lack of narrative evidence to suggest that a treatment effect would emerge only after several months have passed.	BCLPD-refractory population (n = 83), since it would make it difficult to draw robust conclusions on the efficacy of Sd. Given the EAG's concerns on the initial trial sample size, the company believes that an higher level of uncertainty and a lack of robust statistical results arise when the independent survival curves for Sd would be based on an ESS of 10 patients, which correpponds to 12% of the initial trial population. Moreover, the EAG was concerned that the population from the MAMMOTH study differed from the population expected in the UK clinical practice. More specifically, the EAG highlighted that patients in the MAMMOTH study have a lower median age, an higher SCT rate, higher number of prior LOTs, as well as different subsequent therapies, than what is expected in the penta-refractory population of the UK clinical practice. The company believes that using the adjusted KM curve for Sd, which was derived from	given that this is one main driver of ICER.	

	matching the BCLPD-refractory patients to the MAMMOTH population, would move the population on which the efficacy of Sd was estimated even further away from the population expected in the UK. Although there might be uncertainty around the PH assumption, given the reasons highlighted above and the fact that the approach proposed by the EAG does not seem to be recommended by any NICE guidelines (TSD 18 and TSD 21), the company still believes that the STC is the best available approach to derive relative efficacy between Sd and SOC.		

Issue 7 Set of prognostic factors and treatment effect modifiers used in the MAICs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
At page 56, the EAG recognised that not all the prognostic factors	In its initial submission, the company performed three MAICs based on the	The company is concerned that the	The EAG thanks the company for highlighting

(PFs) and treatment effect modifiers (TEMs) included in the 'Must have + Nice to have' list is available from the MAMMOTH study and hence considered the 'Full' set of variables to be the most appropriate for the MAIC. Moreover, the EAG noted that 'there are potentially additional variables (prior SCT and duration of last therapy) that could have been included in the MAIC and is unclear what result this would have on the resulting ESS and overall results from the MAIC'.	three different set of PFs and TEMs and the availability of these factors from the MAMMOTH study. A complete list of factors included in each set is reported in Tale 18 of the EAG report. Results from the different MAICs were presented in the initial company submission and summarised in Table 19 of the EAG report. The first MAIC was conducting using the 'Must have' set of factors, which included all the PFs and TEMs listed in the second column of Table 18 with the exception of ECOG PS as it is not available from the MAMMOTH study. The ESS from this MAIC is 13.5. The second MAIC was conducting using the 'Full' set of factors, which include all the PFs and TEMs in the third column of Table 18 except for ECOG PS, creatinine clearance at baseline and haemoglobin at baseline, since they are not reported in the MAMMOTH study. The ESS resulting from this MAIC is 10.	EAG would have suggested that the company refused to provide results from a MAIC that includes all the potential PFs and TEMs.	this and has updated the text on page 56 in the EAG report to include details of the third MAIC that used the 'Must have + Nice to have' set of factors and the resulting ESS of 0.

	The third MAIC was conducting using the ‘Must have + Nice to have’ set of factors, which included all the potential PFs and TEMs with the exception of ECOG PS, creatinine clearance at baseline and haemoglobin at baseline, since they are not reported in the MAMMOTH study. This MAIC included prior SCT and duration of last therapy, which were highlighted by the EAG as additional potential variables to be included in the MAIC. The ESS from this MAIC is equal to 0 and hence no HRs could be derived.		

Issue 8 Incorrect results reported.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 97, the EAG report states ‘The probabilistic base case analysis results in an incremental cost-effectiveness ratio of £40,816, reducing to £24,009 when the severity modifier of 1.7 is applied’.	The results reported in the text at page 97 should reflect the results reported in table 41 at the same page. Therefore, the text should be amended to ‘The probabilistic base case analysis results in an incremental cost-effectiveness ratio	Factual inacurracy.	The EAG thanks the company for highlighting this and has amended the text in the report on page 97.

	of £40,350, reducing to £23,735 when the severity modifier of 1.7 is applied'.		

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**
51	However, the EAG notes that **is** any additional active – if?	The EAG thanks the company for highlighting this and has amended the text in the EAG report to "However, the EAG notes that if any additional active…".
69 (Table 23, row 8)	Section **X** – missing section number	The EAG thanks the company for highlighting this and has amended the text in the EAG report to 'Section 3.2'.