Medicinrådet

Bilag til Medicinrådets vurdering af belantamab mafodotin til behandling af recidiverende eller refraktær knoglemarvskræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. belantamab mafodotin
2. Amgros' forhandlingsnotat vedr. belantamab mafodotin
3. Ansøgning vedr. belantamab mafodotin

17. december 2025

Til Medicinrådet

GSK takker for det grundige udkast til vurderingen af BVd og for den omfattende proces omkring denne. Vi værdsætter den åbne dialog og den fleksibilitet, som er vist gennem vurderingsarbejdet. GSK anerkender, at behandling af myelomatose er kompleks og under hastig udvikling, med mange behandlingskombinationer, som vanskeligt lader sig direkte sammenligne. Vi vil gerne bidrage til vurderingen med følgende perspektiver:

Klinisk værdi og sammenligning

Blenrep er undersøgt i et omfattende studieprogram inkl. fase 3 studierne DREAMM-7 (BVd vs DVd i 2L+) og DREAMM-8 (BPd vs PVd i 2L+). DREAMM-7 har vist forlænget PFS og OS mod daratumumab som er uden fortilfælde. Vurderingsudkastet afspejler, at behandlingen giver et bedre respons end komparator. GSK forstår dog ikke, hvorfor Medicinrådet vurderer OS resultatet fra DREAMM-7 til at have høj grad af strukturel usikkerhed og parameterusikkerhed forbundet med analysens hovedresultater, når de samtidig bruger umodne OS til at drage konklusion om forskelle i subpopulationer (2L vs 3L+).

GSK fandt det ikke muligt at lave en indirekte sammenligning mod Cilta-Cel i 2L behandlingen. Omend vi gerne havde set Medicinrådets sekretariat og fagudvalg havde foretaget en naiv sammenligning, anerkender vi samtidig ønsket og behovet for at behandle relevante patienter med Cilta-Cel. Sammenlignes OS HR fra DREAMM-7 med OS HR fra CARTITUDE-4 er disse fuldt ud sammenlignelige til trods for mindre relevante komparatorer i CARTITUDE-4. GSK opfordrer til, at en eventuel anbefaling omfatter 2L+ myelomatose patienter, herunder len-refraktære patienter, der ikke kan eller ønsker at modtage Cilta-Cel.

[redacted]

[redacted]

Tilgang til dosering

Vi finder det positivt, at Medicinrådet vurderer, at brugen af IPD-dosering til beregning af lægemiddelomkostninger afspejler real-world praksis, og derfor er den rette tilgang til beregning af lægemiddelomkostningerne. I vurderingsrapporten er den meget lave RDI på 51% for belantamab anvendt i en følsomhedsanalyse for at undersøge usikkerheden i omkostningsestimaterne. Vi fremhæver resultatet af denne følsomhedsanalyse for at understrege vigtigheden af valg af metode til at beregne lægemiddelomkostninger for belantamab. Den mediane RDI skævvrider mod de tidligere tidspunkter i opfølgningen, hvor flere patienter endnu ikke er stoppet i behandlingen med belantamab, og afspejler ikke doseringen for patienter, der fortsætter i belantamab-behandling over en længere periode. Dermed vil lægemiddelomkostningerne være overestimerede ved brug af RDI. [redacted]

Anvendes den dosering og frekvens som en dansk klinisk ekspert[1] finder realistisk i dansk klinisk praksis (inspireret af doseringsstrategien i DREAMM-10 protokollen, 1L belantamab studie) vil den gennemsnitlige dosering og frekvens være 1.9 mg/kg hver 11. uge set over 38 måneders behandling. Dette tager dog ikke højde for yderligere dosisreduktioner eller længere intervaller mellem behandlingerne som følge af bivirkningshåndtering. Medicinrådet vurderer, at BVd-patienter mediant behandles i ca. 38 måneder (≈165 uger). Under de ovenfor angivne antagelser gives der 7 behandlinger det første år (hver 8. uge i uge 0–52) og herefter 9 behandlinger i de følgende år (hver 12. uge), dvs. i alt 16 behandlinger over 38 måneder. Det svarer til et gennemsnitligt interval på cirka 11 uger mellem behandlingerne (165 uger / 15 intervaller = 11 uger).

Hertil kan det nævnes, at BVd d. 8. december, 2025 er blevet færdigbehandlet af den norske HTA-institution og har modtaget en bred 2L+ anbefaling, baseret på en maksimaldosis på 2,5 mg/kg i de første 8 uger, efterfulgt af 1,9 mg/kg hver 8. uge. Dette fremgår ligeledes Norsk Myelomatosegruppes behandlingsguideline, som er lavet af 8 ledende norske eksperter[2].
[redacted]

GSK vil derfor anbefale, at der i den kommende opdaterede behandlingsvejledning bliver taget stilling til anbefalet maksimaldosis af belantamab. Denne kan dermed anvendes som evalueringskriterie i tender-sammenhæng.

[redacted] Ligeledes er sekretariatet i gang med at undersøge muligheden for at dele de tilpassede modeller med virksomhederne. GSK støtter dette, da modellens resultater er grundlaget for forhandlinger og anbefalinger. Det ville derfor være værdifuldt at få indsigt i de centrale forudsætninger, så alle parter får en fælles forståelse af beslutningsgrundlaget. Dette er et vigtigt skridt mod øget transparens.

Vi ser frem til at sagen behandles på rådsmødet den 21. januar 2026, og står naturligvis til rådighed for eventuelle spørgsmål eller behov for supplerende oplysninger.

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1 [redacted]

2

3 [redacted]

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

19.12.2025

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.01.2025
Leverandør	GSK
Lægemiddel	Blenrep (belantamab mafodotin)
Ansøgt indikation	Belantamab mafodotin i kombination med bortezomib og dexamethason til behandling af voksne patienter med recidiveret eller refraktær knoglemarvskræft, der har modtaget mindst én tidligere behandling.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Blenrep (belantamab mafodotin):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Blenrep	70 mg (1 stk.)	100.246,00	[redacted]	[redacted]
Blenrep	100 mg (1 stk.)	143.208,00	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder at hvis Medicinrådet ikke anbefaler Blenrep, indkøbes lægemidlet til AIP.

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der findes flere behandlingsalternativer til patientgruppen. Ifølge Medicinrådets lægemiddelrekommandation vedr. myelomatose er nuværende standardbehandling til patientpopulationen:

- Carvykti (ciltacabtagene autoleucel)
- Darzalex (daratumumab) i kombination med bortezomib og dexamethason (DaraBorDex)
- Nexpovio (selinexor) i kombination med bortezomib og dexamethason (SelBorDex)
- Darzalex i kombination med lenalidomid og dexamethason (DaraLenDex)
- Empliciti (elotuzumab) i kombination med lenalidomid og dexamethason (EloLenDex) *eller* Kyprolis (carfilzomib) i kombination med lenalidomid og dexamethason (CarLenDex)

Tabel 2 viser lægemiddeludgiften til Blenrep i relation til Darzalex, da det er disse behandlinger der er medtaget i Medicinrådets vurdering af Blenrep. Lægemiddeludgiften er udregnet for første års behandling. Det skal bemærkes, at Blenrep i det kliniske studie dosisreduceres markant sammenlignet med dosis oplyst i SmPC. Der er derfor opgjort to forskellige lægemiddeludgifter i tabel 2 for Blenrep: en udregning baseret på SmPCet, og en udregning baseret på den gennemsnitlige relative dosisintensitet (RDI) på 51%, jf. Medicinrådets vurdering af belantamab mafodotin i kombination med bortezomib og dexamethason til behandling af patienter med recidiverende og refraktær knoglemarvskræft, som har modtaget mindst en tidligere behandling.

Lægemiddeludgiften til bortezomib og dexamethason samt lenalidomid og dexamethason er ikke medtaget i udregning af de årlige lægemiddeludgifter, da de udgør en mindre del af den samlede lægemiddeludgift.

[redacted]

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Blenrep	100 mg (1 stk.)	2,5 mg/kg hver 3. uge, i.v.*,**	[redacted]	[redacted]
Darzalex	1800 mg (1 stk.)	1.800 mg hver uge i uge 1-9, 1.800 mg hver 3. uge i uge 10-24. Fra uge 25, 1.800 mg hver 4. uge indtil progression, s.c.	[redacted]	[redacted]

*Dosis er justeret for RDI på 51% i udregningen af den årlige lægemiddeludgift.
**Baseret på en legemsvægt på 73,4 kg jf. Medicinrådets omkostningsanalyse vedrørende lægemidler til knoglemarvskræft (myelomatose)

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Anbefalet	Anbefalet i Norge for følgende maksimaldosering: *Første syklus (56 dager): 2,5 mg/kg* *Andre syklus og videre (56 dager): Hver 8. uke 1,9 mg/kg*	Link til vurdering
England	Under vurdering		Link til status
Sverige	Under vurdering		Link til status

Opsummering

[redacted]

Application for the assessment of belantamab mafodotin in combination with bortezomib and dexamethasone for treatment of patients with relapsed or refractory multiple myeloma

Contact information

Contact information	
Name	**Christina Matzen, GSK**
Title	Patient Engagement & Market Access Manager
Phone number	+45 29 40 83 51
E-mail	Christina.l.matzen@gsk.com
Name	**Martin Jensen, GSK**
Title	Health economist
Phone number	+45 24 69 91 26
E-mail	martin.k.jensen@gsk.com

Table of contents

Tables and Figures

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[redacted] 136
[redacted] 147
[redacted] **Error! Bookmark not defined.**

Abbreviations

ADA	Antibody-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASCT	Autologous stem cell transplant
BCMA	B-cell maturation antigen
BM	Belantamab mafodotin
BSA	Body Surface Area
BsAb	Bispecific antibody
BVd	Belantamab mafodotin + bortezomib + dexamethasone
CAR-T	Chimeric antigen receptor T-cell
CI	Confidence interval
CrI	Credible Interval
CRR	Complete response rate
CTCAE	Common Terminology Criteria for Adverse Events
CyKd	Cyclophosphamide + high dose carfilzomib + dexamethasone
CyVd	Cyclophosphamide + bortezomib + dexamethasone
d	Dexamethasone
DMC	Danish Medicines Council
DMSG	Dansk Myelomatose Studie Gruppe
DoR	Duration Of Response
DRd	Daratumumab + Bortezomib + dexamethasone
DVd	Daratumumab + lenalidomide + dexamethasone
ECOG	Eastern Cooperative Oncology Group
EMD	Extramedullary disease
EVd	Elotuzumab + bortezomib + dexamethasone
FLC	Free light chains
hKd	High dose carfilzomib + dexamethasone
hKDd	High dose carfilzomib + daratumumab + dexamethasone
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IA	Interim analysis
IhKd	Isatuximab + high dose carfilzomib + daratumumab
IMiDs	Immunomodulatory drugs
IMWG	International Myeloma Working Group
IPD	Individual patient dosing
IRR	Infusion-related reaction
ITT	Intention to treat
Kd	Carfilzomib + dexamethasone
KM	Kaplan Meier
KVA	Keratopathy and Visual Acuity
LoT	Lines of Treatment
mAbs	Monoclonal antibodies

MECs	Microcyst-like epithelium changes (a type of keratopathy observed in patients receiving belantamab mafodotin)
MedDRA PTs	Medical Dictionary for Regulatory Activities Preferred Terms
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple Myeloma
MoA	Mode of Action
mOS	Median overall survival
mPFS	Median progression-free survival
M-protein	Monoclonal immunoglobulin protein
MRD	Minimal residual disease
NMA	Network Meta analysis
NR	Not reached
Off-tx	Off treatment
On-tx	On treatment
ORR	Objective response rate
OS	Overall Survival
PanoVd	Panobinostat + bortezomib + dexamethasone
PD	Progressed disease
PF	Progression-free
PFS	Progression-free Survival
PFS2	Progression-free survival on subsequent line of therapy
PIs	Proteasome inhibitors
PK	Pharmacokinetics
PH	Proportional hazards
PRO	Patient Reported Outcome
PSM	Partitioned survival model
Pd	Pomalidomide + dexamethasone
PVd	Pomalidomide + bortezomib + dexamethasone
QoL	Quality of life
Rd	Lenalidomide + dexamethasone
RDI	Relative dose intensity
R-ISS	Revised International Staging System
RRMM	Relapsed or Refractory Multiple Myeloma
SAE	Serious adverse event
SLR	Systematic literature review
SMM	Smoldering multiple myeloma
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SVd	Selinexor + bortezomib + dexamethasone
TEM	Treatment effect modifiers
TLR	Targeted literature review
TNF	Tumor necrosis factor
TTE	Time to event
TTD	Time to treatment discontinuation
TTP	Time to progression
TTR	Time to response

Tx	Treatment
Vd	Bortezomib + dexamethasone

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Blenrep
Generic name	Belantamab mafodotin
Therapeutic indication as defined by EMA	Belantamab mafodotin is indicated in adults for the treatment of relapsed or refractory multiple myeloma, 1. in combination with bortezomib and dexamethasone (BVd) in patients who have received at least one prior therapy; and 2. in combination with pomalidomide and dexamethasone (BPd) in patients who have received at least one prior therapy including lenalidomide.
Marketing authorization holder in Denmark	GSK Denmark Delta Park 37, 2665 Vallensbæk Strand, Denmark
ATC code	L01FX15
Combination therapy and/or co-medication	Bortezomib and dexamethasone
(Expected) Date of EC approval	29 July 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If no, why not? A high level of heterogeneity in the treatment landscape of multiple myeloma within the Nordic countries results in a joint Nordic assessment being unsuitable.

Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Vial containing 70 and 100 mg powder for concentrate for solution for infusion. After reconstitution with 1.4/2 mL of sterile water for injection, each mL of solution contains 50 mg belantamab mafodotin.

2. Summary table

Summary	
Indication relevant for the assessment	Belantamab mafodotin is indicated in adults for the treatment of relapsed or refractory multiple myeloma: • in combination with bortezomib and dexamethasone (BVd) in patients who have received at least one prior therapy
Dosage regiment and administration	Belantamab mafodotin will be available as a 70 mg and 100 mg powder for concentrate for solution for infusion. Belantamab mafodotin starting dose schedule (as per SmPC): 2.5 mg/kg administered once every 3 weeks. Dose modifications are required for nearly all patients to manage safety and tolerability. Dose modifications are described in SmPC. Bortezomib and dexamethasone are administered for the first 8 cycles.
Choice of comparator	Daratumumab in combination with bortezomib and dexamethasone (DVd) Daratumumab in combination with lenalidomide and dexamethasone (DRd)
Prognosis with current treatment (comparator)	According to the DMSG 2023 annual report, the 3-year survival rate of Danish patients with MM is estimated at 81% for younger patients (<70 years), 59% for older patients (>70 years) and 69% for the entire patient group. The 5-year survival rate for the same patient groups is 72%, 40% and 53%. Despite advances in therapeutic options, MM is still considered incurable, and although periods of remission can be achieved, the course of myeloma is characterized by recurring relapses leading to multi-refractory disease and death.
Type of evidence for the clinical evaluation	Head-to-head study: BVd vs. DVd [redacted]
Most important efficacy endpoints (Difference/gain compared to comparator)	**PFS** BVd vs DVd: 36.6 months (95% CI: 28.4–NR) versus 13.4 months (95% CI: 11.1–17.5). HR: 0.41 [95% CI: 0.31–0.53], p<0.001. [redacted] **OS** BVd vs DVd: The projected mOS for BVd is 84 months compared to 51 months for DVd. HR 0.58; 95% CI: 0.43-0.79; p=0.00023. [redacted]

Most important (treatment-related) serious adverse events for the intervention and comparator	BVd: pneumonia (4%) and thrombocytopenia (3%); all other treatment-related SAEs were reported in ≤1% of participants. DVd: pneumonia, thrombocytopenia, and IRR (2%, each); all other treatment-related SAEs were reported in ≤1% of participants. [redacted]
Impact on health-related quality of life	Clinical documentation: EQ-5D-3L Health economic model: Equal to comparator
Type of economic analysis that is submitted	Cost utility analysis De novo partitioned survival model
Data sources used to model the clinical effects	DREAMM-7 POLLUX
Data sources used to model the health-related quality of life	DREAMM-7
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	BVd vs DVd: 3,163,563 DKK [redacted]
ICER (DKK/QALY)	BVd vs DVd: 1,909,365 DKK/QALY [redacted]
Uncertainty associated with the ICER estimate	Top five parameters with the largest overall impact: • HRQL, Utility, BVd • HRQL, Utility, DVd • Dose per admin, DVd, Daratumumab (SC) • Price per pack for belantamab mafodotin 100 mg (AIP) • Price per pack for belantamab mafodotin 70 mg (AIP)
Number of eligible patients in Denmark	Approximately 300 new patients per year
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology of multiple myeloma

Multiple myeloma (MM) is an incurable, progressive, plasma cell malignancy. Plasma cells are B lymphocytes produced by the bone marrow that arise from hematopoietic stem cell progenitor cells [1]. Normal plasma cells reside in the bone marrow and produce immunoglobulins that function as a part of the adaptive immune system for recognizing foreign pathogens within the body [1]. In MM, genetic damage occurs to developing B lymphocytes that leads to clonal plasma cell proliferation and elevated production of abnormal immunoglobulin, otherwise known as monoclonal immunoglobulin protein (M-protein). M-protein is a harmful antibody, multiplying in the bloodstream, depositing in the tissues, and leading to organ dysfunction [1, 2]. Roughly 15 to 20% of patients with MM have myeloma cells that produce only part of the immunoglobulin, the free light chains (FLCs), whereas <3% secret no M-protein. In addition, B-cell maturation antigen (BCMA) expression is a hallmark of myeloma cells. BCMA is a member of the tumor necrosis factor (TNF) receptor family, which enhances both survival and proliferation [3].

MM is a complex, heterogeneous disease characterized by continued genomic evolution through multiple lines of therapy (LoT), leading to inevitable disease relapse despite previous deep remissions [2]. The development of MM is a multistep process, which includes the precursor disease states: monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) [2].

3.1.2 Clinical symptoms and diagnosis of multiple myeloma

The clinical manifestations of MM include fractures, bone pain, renal impairment, hypercalcemia, anemia, neuropathy, hyper viscosity, increased susceptibility to infections, and extramedullary disease (EMD) [4]. These clinical manifestations can be

driven by the M-protein, FLCs, malignant cells, or inflammatory cytokines secreted by malignant cells [5] . As such, the disease burden of MM is typically measured and followed by the presence of M-protein in serum or urine and by the degree of organ damage. The most common symptoms of MM are related to the underlying pathology of the CRAB features, i.e. calcium elevation, renal failure, anemia, and bone lesions [2].

Diagnosis of MM is typically made when patients present with symptoms relating to end-organ damage. These symptoms may include fatigue or dyspnea related to anemia, bone pain related to bone disease, and neurological symptoms related to hypercalcemia, hyper viscosity or spinal cord compression (due to spinal lesions) [6]. MM is then diagnosed based on the detection of serum M-protein levels, clonal plasma cell infiltration in bone marrow and assessment of biomarkers and CRAB features. These are the IMWG (International Myeloma Working Group) criteria for diagnosis, which are the most widely accepted criteria for diagnosis of MM [7]. The initial investigation of a patient with suspected MM includes clinical assessment, measurement of M-protein levels (blood and urine tests), bone marrow biopsy, and radiographic imaging [6]. In Denmark, MM is diagnosed based on the national clinical guidelines developed by the Danish Myeloma Study Group (DMSG), which align with the IMWG guidelines [8].

3.2 Current treatment options

The goal of MM therapies is to induce deep and lasting remissions to prolong PFS and OS, to relieve disease-related symptoms and to preserve QoL [9]. Choice of treatment depends on the effect of previous treatment, side effects of previous treatments, general level of function (performance status), comorbidity and patient preferences, including the number of treatment attendance. Any refractoriness to medicine that has been included in previous treatments is also considered [9, 10].

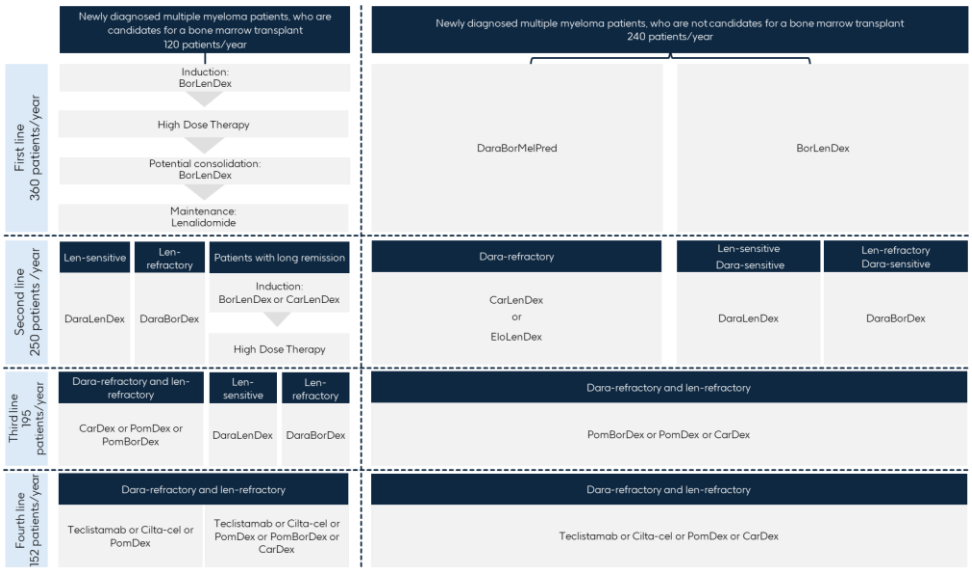
In Denmark MM treatment is based on national guidelines developed by the Danish Medicines Council (DMC) and the DMSG [11, 12]. Regardless of which treatment the newly diagnosed patient receives, a small proportion of patients will not respond (be refractory) to first-line treatment, and all patients will at some point have a relapse requiring new treatment.

When a patient relapses, there are several treatment options consisting of a combination medicine that attack the cancer cells in different ways [11]. In current clinical practice, approximately 80% of patients (corresponding to approximately 215

patients annually) are treated in the second line with a combination of daratumumab, lenalidomide and dexamethasone (DRd). However, this treatment is not possible in patients treated with lenalidomide in the first line who have disease progression during or within 60 days after completion of lenalidomide (lenalidomide refractory). This group of approximately 85 patients is treated predominantly with a combination of daratumumab, bortezomib and dexamethasone (DVd). There is also a third group of approximately 20 patients who are considered to be both lenalidomide-refractory and bortezomib-intolerant [11, 13].

The various treatment lines and the included treatment regimens are outlined in Figure 1 below.

Figure 1: Treatment algorithm for patients with multiple myeloma



Source: Created by GSK based on DMC guideline [11] and DMC recommendations of Teclistamab and Cilta-cel [14, 15]

3.2.1 Patient prognosis

MM is the second most common hematologic malignancy in Denmark with a total number of approximately 3,500 people living with the disease [16]. Each year approximately 380 people are diagnosed with treatment-emergent MM. The median age at diagnosis in Denmark is 71 years [14].

The risk of getting MM increases with age and occurs slightly more frequently in men than in women [8]. The prevalence is increasing due to an increase in average life expectancy of the Danish population and an improvement in the prognosis of the disease [8]. The prognosis has improved since the introduction of high-dose chemotherapy with

stem cell transplant in the early 1990s. Since then, many new treatments have been added that have gradually improved the prognosis for both younger and older patients each year [8, 17]. Introduction of new drugs such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs) and especially monoclonal antibodies (mAbs) have resulted in a 5-year survival rate that has increased by more than 10 %-points over the past 5 years [18].

According to the DMSG 2023 annual report, the 3-year survival rate of Danish patients with MM is estimated at 81% for younger patients (<70 years), 59% for older patients (>70 years) and 69% for the entire patient group. The 5-year survival rate for the same patient groups is 72%, 40% and 53% [18].

Despite advances in therapeutic options, MM is still considered incurable, and although periods of remission can be achieved, the course of myeloma is characterized by recurring relapses leading to multi-refractory disease and death [17]. As patients go through multiple relapses, the efficacy of the treatment regimens is reduced, which is associated with a reduced duration of response and increased resistance to available therapies (refractoriness) [2]. An increasing complexity of tumor genetics, accumulation of mutations and development in tumor microenvironment all lead to this reduced efficacy of treatments and refractoriness over time and increasing LoT, which highlights the need for more effective treatment modalities 2L+ [2].

In addition to specific drug refractoriness risks, patient characteristics that require attention due to the increased risk of progression and shorter OS include age, frailty, high-risk cytogenetics, renal impairment, comorbidities, and EMD [19].

3.2.2 Functioning and health-related quality of life

There is a substantial burden associated with RRMM and the associated symptoms. Physical and social functioning have been reported to be 15% and 19% worse respectively in RRMM patients compared to the general population [20]. Pain and fatigue have been reported to be the most debilitating symptoms for patients, and an international HRQoL and economic questionnaire found that 30.4% of patients with RRMM had moderate to severe pain and 70.6% reported fatigue [21]. As such, patients have a substantially reduced ability to perform daily activities. Patients with RRMM report more symptoms and poorer QoL than patients with MM (non-relapsed/refractory), and studies have reported decreased QoL scores with each additional LoT [22-24].

These findings were supported by a systematic review of health state utilities in MM which found that upon MM diagnosis, utility is low (approximately 0.55), increases to approximately 0.65 on 1L treatment and then declines with each subsequent line [24]. Likewise, an SLR on longitudinal studies evaluating QoL also concluded that "clinically beneficial improvements in HRQoL are far more likely during primary treatments compared to relapse treatment regimens" [23]. Patients generally reported improvements in mean score from baseline during 1L treatment in fatigue and pain; however, during relapse treatment fatigue stabilized or deteriorated while pain stabilized or improved [23]. A cross-sectional analysis of symptom burden utilizing PROs in 557 patients with MM treated at 18 hematological cancer centers in the UK showed that the number of symptoms increased with disease progression, and the severity scores for all the symptoms tended to be higher during treatment than at diagnosis [25].

Interestingly, despite several studies showing that HRQoL decreases with each subsequent LoTs, recent findings by Ribbands et. al (2023) suggest that HRQoL, functioning and MM symptoms remained consistent across patients in different LoTs [26]. One factor that might explain this is the increasing number of novel, well tolerated, therapies available in later LoTs [26].

3.3 Patient population

The relevant Danish patient population for this application is adult patients with RRMM, who have received at least one prior therapy. Treatment refractoriness is defined by disease progression during treatment at full dose or within 60 days after treatment discontinuation. Disease progression after more than 60 days from the end of treatment is called relapse [11].

The DMC estimates that yearly approx. 380 MM patients receive first line treatment and 320 receive second line treatment [11].

Table 1: Incidence and prevalence of MM in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	372	420	370	396	397
Prevalence in Denmark	1979	2085	2217	2306	2385

Source: [16, 27]

It is expected that approx. 20% of patients do not proceed to the next LoT. This is based on a Danish study and advice from clinical expert [17]. The estimated number of patients eligible for the BVd combination is as described in Table 2.

Table 2: Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	298	336	296	317	318

3.4 The intervention

Belantamab mafodotin (BM) is a humanized IgG1 kappa monoclonal antibody conjugated with a cytotoxic agent, mcMMAF. BM binds to cell surface BCMA and is rapidly internalized. Once inside the tumor cell, the cytotoxic agent (cys-mcMMAF) is released disrupting the 15 microtubule network, leading to cell cycle arrest and apoptosis. The antibody also enhances recruitment and activation of immune effector cells, killing tumor cells by antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP). Apoptosis induced by BM is accompanied by markers of immunogenic cell death, which may contribute to an adaptive immune response to tumor cells.

BM induces immune-independent ADC-mediated apoptosis, immune-dependent enhancement of ADCC and ADCP, and release of markers characteristic of ICD leading to an adaptive immune response with minimal interference with normal immune function [28, 29]. This MoA does not impact BCMA expression, allowing for future targeting by BCMA-directed agents. Further, unlike other BCMA-targeted therapies, BM does not cause T-cell exhaustion, removing the need for costly IV immunoglobulin administration, which has been used to reduce the risk of severe infection associated with BsAbs and CAR-T therapies [28-30].

Overview of intervention	
Indication relevant for the assessment	BM is indicated in adults for the treatment of relapsed or refractory multiple myeloma, 1. in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
ATMP	No
Method of administration	IV infusion over 30 minutes

Dosing	BM starting dose schedule (as per SmPC): 2.5 mg/kg administered once every 3 weeks. Dose modifications are required for nearly all patients to manage safety and tolerability. Dose modifications are described in SmPC.
Dosing in the health economic model (including relative dose intensity)	For BM dosing, the model has the following dosing options: • Dosing based on the label, using the median RDI from the IA1 data cut of the DREAMM-7 trial to account for dose reductions or delays. • Dosing based on the label, using time-varying median RDI from the IA2 data cut of the DREAMM-7 trial. RDI is reported in 12-week periods over the entire trial period. • Dosing based on individual patient data (IPD) from the IA2 data cut of the DREAMM-7 trial, without RDI, as IPD dosing is reflective of the doses actually received by patients including dose reductions and delays ○ IPD dosing includes the option to use the actual dose received; or closest SmPC dose.
Should the medicine be administered with other medicines?	Yes, in combination with 1.3 mg/m^2 bortezomib and 20 mg dexamethasone for eight cycles. From Cycle 9 onwards, BM should be administered as a monotherapy.
Treatment duration / criteria for end of treatment	Administration of BM is to be continued according to the recommended schedule until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	No monitoring during administration.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Patients should have an ophthalmic examination (including visual acuity and slit lamp examination) performed by an eye care professional before each of the first 4 doses of BM, and as clinically indicated thereafter.
Package size(s)	70 mg powder for concentrate for solution for infusion 100 mg powder for concentrate for solution for infusion

3.4.1 Description of ATMP

Not applicable.

3.4.2 The intervention in relation to Danish clinical practice

BM in combination with bortezomib and dexamethasone (BVd) is approved for the treatment of patients with RRMM, who have received at least one prior therapy. With the current Danish treatment guidelines this patient population corresponds to patients

reaching 2nd line therapy [11]. The standard of care at submission for patients in 2nd line is DVd or DRd.

While preparing the reimbursement dossier CAR-T (cilta-cel) was in progress in DMC for 2L reimbursement. However, we do not find a comparison with cilta-cel suitable, because of the factors listed below:

- Cilta-cel is only for lenalidomide refractory patients with a high performance status, this does not apply to BVd and the patient populations are therefore not the same.
- DRd has only recently been recommended in first line, meaning a lot of patients currently in first line treatment will not be treated with DRd. Because of the long PFS in first line, it is expected that at least for the next 4 years patients will still be eligible for DRd in 2L, making DRd a reasonable comparator for BVd.
- A feasibility assessment of DREAMM-7 and the relevant cilta-cel studies determined in line with regulatory guidance that they were not sufficiently comparable (study population, endpoints etc.) to conduct an indirect comparison in accordance with established scientific standards.
- Cilta-cel is not yet included in the treatment guidelines meaning it has not yet been implemented as primary standard of care. Furthermore, meanwhile a lot of eligible patients will benefit greatly from cilta-cel, there will still be lenalidomide refractory 2L patients who for various reasons (patient choice, eligibility criteria etc.) will not get CAR-T treatment. At the moment the alternative treatment for this group is DVd, a treatment that BVd outperforms in efficacy.

Cilta-cel is recommended by the Danish Medicines Council for a specific, selected patient group (len-refractory and previously bor-treated patients in good performance status), but not for the entire 2L+ population. Cilta-cel represents a treatment option for a clearly defined CAR-T eligible subgroup, and not necessarily for the broader population of patients for whom we seek reimbursement for. This distinction has direct implications for which comparisons are relevant and methodologically sound.

Patients deemed suitable for cilta-cel are typically younger and have better performance status. Strict inclusion criteria are applied, and many patients with comorbidities, reduced performance status, or certain risk profiles will not be candidates for CAR-T. BM, on the other hand, has been developed and evaluated in a broader range of patients

with relapsed/refractory myeloma, reflecting the heterogeneous clinical population often treated in 2L+ practice. These differences in patient characteristics mean that the populations in cilta-cel studies and BM studies are not interchangeable, and comparisons without further delineation risk being confounded by selection differences.

We conducted detailed feasibility analyses that considered the potential for anchored (standard NMA, ML-NMR, anchored MAIC, anchored STC) and unanchored ITCs (STC, MAIC). We judged that all ITCs were infeasible for the reasons summarized below. This approach is consistent with regulatory guidance, which advises that ITCs should only be performed when study populations, endpoints, and other critical features are sufficiently aligned to avoid biased or misleading results:

Anchored ITCs

1. Lack of a connected network (relevant to all anchored ITC approaches)

A connected network of intervention comparisons is required for any anchored ITC to be feasible. Since DREAMM-7 and CARTITUDE-4 trials do not have a common comparator, we assessed the feasibility of a broader range of interventions in an attempt to assemble a network that connected them. However, all scenarios were subject to substantial limitations. For example,

- there is no available RCT that connects PVd in the OPTIMISMM trial with DPd in the CARTITUDE-4 study.
- standard of care arm in the CARTITUDE-4 study included a mix of patients receiving DPd and PVd, with the majority receiving DPd (183 out of 211 patients received DPd, while 28 received PVd).

2. Limitations of a ‘standard’ NMA (even if we were to form a connected network)

A detailed assessment of treatment effect modifers (EMs) identified substantial differences across the included studies, violating the transitivity assumption (a key assumption of standard NMA). We are aware these limitations can be potentially addressed by population adjustment methods (e.g. ML-NMR, MAIC, STCs), feasibility of such methods is dealt with separately below.

3. Violation of the proportional hazards (PH) assumption and a lack of reconstructed individual participant data (RIPD)

The PH assumption, central to most time-to-event analyses of PFS, OS etc., is violated in the CARTITUDE-4 study. Although we are aware of methods that can address violation of

this assumption (e.g. ML-NMR, Cope's two-step multivariate NMA of survival parameters) these methods require RIPD. However, our feasibility assessment found that RIPD was not available for all interventions required to form connected networks or using subgroup analysis results from CARTITUDE-4.

Therefore, any anchored ITC analyses are subject to substantial limitations.

Unanchored ITCs

Difficulties in assembling a connected network of interventions identified above can theoretically be overcome by conducting an unanchored ITC (STC or MAIC are the main options). However, Phillippo et al (2016) and Faria et al (2015) point out population adjustment methods (such as STC and MAIC) require the 'overlap assumption', that is, for any combination of covariates, there must be sufficient overlap in participant characteristics across trials [31, 32]. Phillippo et al (2016) point out that a lack of overlap across trial populations constitutes a significant limitation to the validity of all population adjustment methods. Our feasibility analyses suggest this is a substantial problem for an ITC comparing BVd and cilta-cel:

- Lack of overlap of populations between BVd and cilta-cel is substantial (e.g. matching on prior exposure and refractory to lenalidomide alone would result to an ESS equal to 33% of the original sample size of DREAMM-7, and further adjustment on other effect modifiers would reduce the ESS further), MAIC was deemed infeasible. Phillippo et al (2016) points out that substantial reductions in ESS are evidence of a lack of overlap.
- STC could be a potential method in this context, but all population adjustment analyses perform poorly and are highly uncertain when there is limited overlap between populations and we did not think the overall argument would be persuasive to HTA agencies by the time the overlaps had been corrected for.

3.5 Choice of comparator(s)

As described above, the most relevant comparators for the evaluation of BVd are:

- Daratumumab in combination with bortezomib and dexamethasone (DVd)
- Daratumumab in combination with lenalidomide and dexamethasone (DRd)

Information on the comparators is presented in the following tables.

Overview of comparator

Generic name	Daratumumab
ATC code	L01FC01
Mechanism of action	Human monoclonal IgG1κ antibody that binds to the CD38 protein, expressed at a high level on the surface of multiple myeloma tumor cells. Binding inhibits the growth of CD38-expressing myeloma cells by various mechanisms.
Method of administration	Available as subcutaneous injection or solution for IV infusion
Dosing	Injection solution: 1800 mg IV infusion solution: 16 mg/kg

Dosing in the health economic model (including relative dose intensity)	For daratumumab, the model has the following dosing options:
	• Dosing based on the label, using the median RDI from the IA1 data cut of the DREAMM-7 trial to account for dose reductions or delays.
	• Dosing based on IPD from the IA2 data cut of the DREAMM-7 trial, without RDI, as IPD dosing is reflective of the doses actually received by patients including dose reductions and delays.
	  ○ IPD dosing for daratumumab includes the option to use the relative difference between the IV label dose and the average IV dose based on IPD to calculate an average dose for subcutaneous treatment, or;
	  ○ Use the label dose but still utilize IPD to guide the timing of administration.

Should the medicine be administered with other medicines?	In combination with either: a) Bortezomib and dexamethasone b) Lenalidomide and dexamethasone
Treatment duration/ criteria for end of treatment	Administered until progression, unacceptable toxicity or death.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	Solution for injection vial containing 1800 mg of daratumumab for subcutaneous use 5 mL vial containing 100 mg of daratumumab (20 mg/mL) concentrate for solution for infusion 20 mL vial containing 400 mg of daratumumab (20 mg/mL) concentrate for solution for infusion

Overview of comparator	
Generic name	Bortezomib
ATC code	L01XG01

Mechanism of action	Bortezomib is a proteasome inhibitor. Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. Bortezomib causes reduction of tumor growth in vivo in many preclinical tumor models.
Method of administration	3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration.
Dosing	Bortezomib is administered via sc injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle for a total of 8 cycles.
Dosing in the health economic model (including relative dose intensity)	Based on SmPC label with median RDI applied to account for dose reductions or delays. For bortezomib, RDI = 79.3%, sourced from DREAMM-7.
Should the medicine be administered with other medicines?	In combination with belantamab mafodotin and dexamethasone or daratumumab and dexamethasone.
Treatment duration/ criteria for end of treatment	Bortezomib is administered in cycles 1-8. Treatment will be ended before if unacceptable toxicity occurs.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	3.5 mg powder for solution for injection contains a glass 10 ml vial with a royal blue cap, in a transparent blister pack.

Overview of comparator	
Generic name	Dexamethasone
ATC code	H02AB02
Mechanism of action	Dexamethasone binds to glucocorticoid receptors. These receptors are responsible for initiating inflammatory reactions and, by blocking these, the body's natural responses are inhibited.
Method of administration	IV or orally
Dosing	20 mg, orally or IV, on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle for the first 8 cycles.
Dosing in the health economic model (including relative dose intensity)	Based on SmPC label with median RDI applied to account for dose reductions or delays. For dexamethasone, RDI = 89.1%, sourced from DREAMM-7.
Should the medicine be administered with other medicines?	In combination with either belantamab mafodotin and bortezomib, daratumumab and bortezomib or daratumumab and lenalidomide.

Treatment duration/ criteria for end of treatment	Dexamethasone is administered in cycles 1-8. Treatment will be ended before if unacceptable toxicity occurs.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	4 mg tablets (20 or 100 tablets in a blister pack) 4 mg/ml for iv use (multiple pack sizes)

Overview of comparator	
Generic name	Lenalidomide
ATC code	L04AX04
Mechanism of action	Lenalidomide inhibits proliferation and enhances apoptosis of certain hematopoietic tumor cells (including MM plasma tumor cells, follicular lymphoma tumor cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells.
Method of administration	Orally
Dosing	Lenalidomide (25 mg once daily orally on days 1-21 of repeated 28-day [4-week] cycles)
Dosing in the health economic model (including relative dose intensity)	The RDI in the model is based on the DREAMM-7 study. DREAMM-7 compares treatment with BVd and DVd. Since lenalidomide is not included in the study, we have assumed an RDI of 100%. As lenalidomide is an oral treatment and drug wastage is included in the base case analysis, the lenalidomide dose is not affected by RDI, because it is rounded up to a whole tablet per day. If drug wastage is excluded from the analysis, the lenalidomide dose will be adjusted according to the RDI input.
Should the medicine be administered with other medicines?	Yes. In combination with daratumumab and dexamethasone.
Treatment duration/ criteria for end of treatment	Treatment until progression, unacceptable toxicity or death.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	25 mg capsules in 21 unit blister packages

3.6 Cost-effectiveness of the comparator(s)

DVd and DRd were evaluated before the establishment of the DMC. Both combinations have been through KRIS. But the DMC has continuously assessed the combinations in

relation to the treatment guidelines, and the combinations continue to be SOC in 2nd line [11, 33, 34].

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 3 presents the outcome measures included in the present application and the definitions and method of measurement for each outcome. In the evaluation of BVd we will focus on OS, PFS and HRQoL. This has been decided in dialogue with the DMC. Further rationale for including each outcome is presented later in the section.

Table 3: Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival (PFS)	DREAMM-7 median follow-up: 28.2 months POLLUX median follow-up: 54.8 months	PFS is defined as the time from the date of randomization until the earliest date of documented disease progression or death due to any cause	Disease progression was assessed by an independent review committee with the use of International Myeloma Working Group criteria.
Overall survival (OS)	DREAMM-7 median follow-up: 39.4 months POLLUX median follow-up: 79.7 months	Time from the date of randomization until the date of death due to any cause.	Time measured from randomization until death from any cause.
Health-Related-Quality-of-Life (HRQoL)	DREAMM-7 Data cut-off: 7 October 2024 POLLUX: 79.7 months	Change from baseline in EQ-5D-3L and comparison between interventions.	The symptoms related to MM and its treatment, symptom severity, the impact of these symptoms on daily functioning, and side effects of treatment were assessed using the EQ-5D-3L questionnaire at baseline and Q6W hereafter.

Validity of outcomes

In recent previous applications on MM treatments the DMC considered PFS, OS and HRQoL sufficient for the evaluation of the effect [14, 15]. Therefore, this application focuses on these efficacy endpoints.

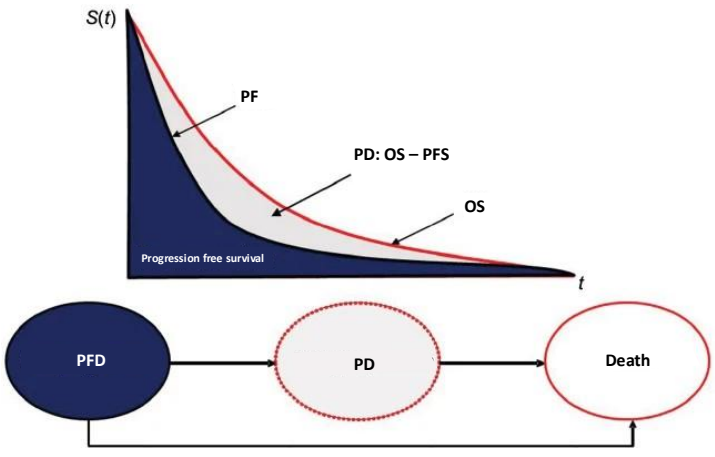
4. Health economic analysis

Treatment with BVd is considered to have an added benefit compared to the treatments that constitute current treatment options in Danish clinical practice. Therefore, a cost-utility analysis (CUA) was chosen. This is in line with the methods guide by the DMC.

4.1 Model structure

The model structure is that of a 3-state partitioned survival model (PSM). Patients enter the model and transition between progression-free (PF) and progressed disease (PD), with an absorbing state for death. State membership to the PF state is estimated from extrapolated curves fitted to progression-free survival (PFS) Kaplan-Meier (KM) curves. State membership of the dead state is estimated from extrapolated curves fitted to overall survival (OS) KM curves (Death=1-OS) and the PD state membership is estimated to be the difference between the OS and PFS curves (PD=OS-PFS). A visual representation of the model structure is depicted in Figure 2.

Figure 2: Diagram of model structure



4.2 Model features

Table 4 presents a summary of the model features.

Table 4: Features of the economic model

Model features	Description	Justification
Patient population	Adult MM patients, previously treated with at least one prior line of therapy, and with documented disease progression during or after their most recent therapy	Aligned with the DREAMM-7 trial population. The overall ITT population is assessed within the model, aligned with data presented in the clinical sections of the application.
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (30 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age of patients at baseline of 70 years in the Danish population, validated by Danish clinical expert
Cycle length	1 week	To account for differences in dosing schedules between comparators
Half-cycle correction	No	The one-week cycle length is assumed to be sufficiently short to capture model transitions
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	BVd	
Comparator(s)	DVd DRd	According to national treatment guidelines. Validated by Danish clinical expert
Outcomes	OS, PFS	In line with DMC methods guide

5. Overview of literature

In this section, the literature used in the application is presented. The application is primarily based on a head-to-head study comparing BVd with DVd both in terms of efficacy, safety and health-related quality of life. However, since we also present an indirect comparison, we have included a systematic literature review in Appendix H.

5.1 Literature used for the clinical assessment

Table 5: Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma, Vania Hungria et al.N Engl J Med 2024;391:393-407. DOI: 10.1056/NEJMoa2405090. [35]	DREAMM-7	NCT04246047	Start: 07/05/20 Completion: 19/06/26 Data cut-off: 02/10/23 Future data cut-off expected June 26	BVd vs DVd in patients with RRMM
Belantamab mafodotin plus bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (DREAMM-7): updated overall survival analysis from a global, randomized, open-label, phase 3 trial, Vania Hungria et al. Lancet Oncol. 2025 Aug;26(8):1067-1080. [36]	DREAMM-7	NCT04246047	Start: 07/05/20 Completion: 19/06/26 Data cut-off: 02/10/23 Future data cut-off expected June 26	BVd vs DVd in patients with RRMM
Results from the randomized phase III DREAMM-7 study of belantamab mafodotin + bortezomib, and	DREAMM-7	NCT04246047	Start: 07/05/20 Completion: 19/06/26	BVd vs DVd in patients with RRMM

dexamethasone (BVd) vs daratumumab, bortezomib, and dexamethasone (DVd) in relapsed/refractory multiple myeloma (RRMM), Mateos, M.-V., et al., Journal of Clinical Oncology, 2024. 42(36_suppl): p. 439572-439572. [37]			Data cut-off: 02/10/23 Future data cut-off expected June 26	
DREAMM-7 update: Subgroup analyses from a phase 3 trial of belantamab mafodotin + bortezomib and dexamethasone (BVd) vs daratumumab, bortezomib, and dexamethasone (DVd) in relapsed/refractory multiple myeloma (RRMM), Mateos, M.-V., et al., Journal of Clinical Oncology, 2024. 42(16_suppl): p. 7503-7503. [38]	DREAMM-7	NCT04246047	Start: 07/05/20 Completion: 19/06/26 Data cut-off: 02/10/23 Future data cut-off expected June 26	BVd vs DVd in patients with RRMM
Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma, Dimopoulos, M.A., et al., New England Journal of Medicine, 2016. 375(14): p. 1319-1331. [39]	POLLUX	NCT02076009	Start: 23/07/14 Completion: 21/11/24 Data cut-off: 20/12/16	BVd vs DRd in patients with RRMM
Overall Survival with Daratumumab, Lenalidomide, and Dexamethasone in Previously Treated Multiple Myeloma (POLLUX): A Randomized, Open-Label, Phase III Trial, Dimopoulos, M.A., et al., Journal of Clinical Oncology, 2023. 41(8): p. 1590-1599. [40]	POLLUX	NCT02076009	Start: 23/07/14 Completion: 21/11/24 Data cut-off: 20/12/16	BVd vs DRd in patients with RRMM

5.2 Literature used for the assessment of health-related quality of life

A SLR has been conducted to identify HRQoL studies of patients with MM who have received at least one prior line of therapy. See Appendix I for the methods used to identify relevant studies, and detailed description and of identified studies. Note that DREAMM-7 health state utility analysis results were not yet published at SLR conduction, and therefore not included in the results.

Table 6: Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma, Vania Hungria et al.N Engl J Med 2024;391:393-407. DOI: 10.1056/NEJMoa2405090. [35]	Health state/RRMM	Table 23: Overview of health state utility values and disutilities
NICE. Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy. Published 3 May 2020. TA695 Appraisal consultation committee papers, page 101-103. Accessed May 2025. [41]	Health state/sensitivity analysis Disutility/adverse events	Table 23: Overview of health state utility values and disutilities
NICE. Daratumumab monotherapy for treating relapsed or refractory multiple myeloma. Published September 2016. TA510 Appraisal consultation committee papers, page 203-204. Accessed May 2025. [42]	Disutility/adverse events	Table 23: Overview of health state utility values and disutilities
NICE. Daratumumab with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma. Published 11 August 2022. TA897 committee papers 20230606, page 114. Accessed May 2025. [43]	Health state/sensitivity analysis Disutility/adverse events	Table 23: Overview of health state utility values and disutilities
Utility assessment among patients with dry eye disease. Schiffman et al. Ophthalmology. 2003;110(7):1412-9. [44]	Disutility/adverse events	Table 23: Overview of health state utility values and disutilities
Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Brown RE et al. The European Journal of Health Economics. 2013 Jun 1; 14(3):507-14. [45]	Disutility/adverse events	Table 23: Overview of health state utility values and disutilities
Catalogue of EQ-5D scores for the United Kingdom. Sullivan PW et al. Med Decis Making. 2011;31(6):800-4. [46]	Disutility/adverse events	Table 23: Overview of health state utility values and disutilities

5.3 Literature used for inputs for the health economic model

A SLR has been conducted to identify literature on cost effectiveness and health costs of patients with MM who have received at least one prior line of therapy. See Appendix J for the methods used to identify relevant studies, and detailed description and of identified studies.

Table 7: Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma, Vania Hungria et al.N Engl J Med 2024;391:393-407. DOI: 10.1056/NEJMoa2405090. [35]	Overall survival Progression Free Survival	N/A	
Szabo et al. The Clinical Course of Multiple Myeloma in the Era of Novel Agents: A Retrospective, Single-Center, Real-World Study. Clinical Hematology International. 2019;1: 10.2991/chi.d.190805.002. [17]	Proportion of patients who progress and receive subsequent treatment	Targeted literature review	Section 8.3 and section 11.6
Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working	Median duration of subsequent treatments	Targeted literature review	Section 8.3

group study. Leukemia. 2012
Jan;26(1):149–57. [47]

6. Efficacy

6.1 Efficacy of Belantamab Mafodotin, Bortezomib and Dexamethasone compared to Daratumumab, Bortezomib and Dexamethasone for patients with Relapsed/Refractory Multiple Myeloma

To compare BVd with DVd the head-to-head trial DREAMM-7 was used. It will be described in the section below.

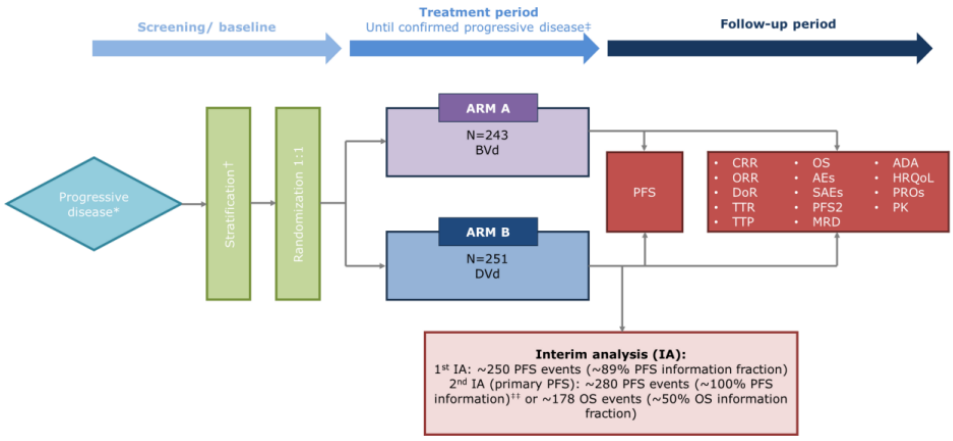
6.1.1 Relevant study: DREAMM-7

DREAMM-7 is an ongoing phase 3, open-label, global, randomized trial involving patients with MM who had received at least one LoT and had had disease progression during or after the most recent therapy. Patients were excluded from the trial if they had disease that was refractory to anti-CD38 therapy or had had exposure to anti-BCMA therapy.

In total 494 patients were randomly assigned in a 1:1 ratio to receive either BVd or DVd. Both treatment groups were to receive bortezomib and dexamethasone for the first eight cycles. The BVd group was to receive BM (administered intravenously at a dose of 2.5 mg/kg on day 1 of 21-day cycles [every 3 weeks]) until the occurrence of disease progression. The BM dose could be reduced to 1.9 mg/kg or delayed to manage AEs. The DVd group was to receive daratumumab (administered intravenously at a dose of 16 mg/kg every week in cycles 1 through 3, every 3 weeks in cycles 4 through 8, and every 4 weeks in cycle 9 and beyond) until the occurrence of disease progression.

Treatment was continued until the occurrence of progressive disease, unacceptable toxicity, withdrawal of consent, or death (whichever occurred first). Patients were stratified according to R-ISS at screening (I vs. II or III), previous exposure to bortezomib (yes vs. no), and the number of previous LoTs (one vs. two or three vs. four or more). Up to 50% of the patients enrolled could have received two or more previous LoT. Crossover between treatment groups was not permitted.

Figure 3: DREAMM 7 study overview



*Disease progression during or after the most recent therapy.
†Stratification factors used for the stratified analyses include number of prior LoT (1 versus 2/3 versus ≥4), prior bortezomib use (yes versus no) and the revised International Staging System (R-ISS) stage at screening (R-ISS I versus II/III).
‡Treatment until progressive disease, death, unacceptable toxicity, withdrawal of consent, or end of study.
‡‡Planned if PFS was not significant at IA1. However, as PFS was significant at IA2, the IA2 will be based on OS events.

The primary endpoint was PFS, defined as the time from randomization to the occurrence of documented disease progression or death from any cause. Disease progression was assessed by an independent review committee with the use of IMWG criteria.

Key secondary endpoints were OS, DoR, and MRD status, which was assessed by means of next-generation sequencing at a sensitivity of 10−5 or lower. Additional secondary endpoints were AEs, which were graded in accordance with the National Cancer Institute CTCAE, version 5.0, findings on ocular examination, which were graded with the use of the Keratopathy and Visual Acuity (KVA) scale and HRQoL. More information on DREAMM-7 can be found in Appendix A.

A total of 213 patients (88%) experienced dose delays on BM vs 178 patients (72%) on daratumumab. A total of 1,133 dose delays were reported for BM vs 436 for daratumumab. The median duration of dose delays was 54 days for BM vs 5 days for daratumumab [48].

Dose delays for bortezomib and dexamethasone were similar in both the BVd and DVd arms: 16% experienced bortezomib dose delays in the BVd arm vs 17% in the DVd arm, whereas 2% experienced dexamethasone dose delays in the B-Vd arm vs 4% in the DVd arm [48].

In total, 194 dose reductions were reported, with 167 patients (69%) experiencing dose reductions for BM. No dose reductions were reported for daratumumab.

A total of 155 patients receiving BVd (64%) and 121 patients receiving DVd (49%) experienced dose reductions for bortezomib, and 5 patients receiving BVd (2%) and 16 patients receiving DVd (7%) experienced dose reductions for dexamethasone.

6.2 Efficacy of Belantamab Mafodotin, Bortezomib and Dexamethasone compared to Daratumumab, Lenalidomide and Dexamethasone for patients with Relapsed/Refractory Multiple Myeloma

[redacted]

6.2.1 Relevant study: POLLUX

POLLUX is a randomized, open-label, multicenter, phase 3 trial. Patients who had RRMM and had received one or more previous LoT were assigned to receive either DRd (daratumumab group) or Rd (control group).

Of 569 patients enrolled, 286 were assigned to receive DRd and 283 to Rd. Patients received daratumumab IV at a dose of 16 mg/kg administered weekly (on days 1, 8, 15, and 22) for 8 weeks during cycles 1 and 2, every 2 weeks (on days 1 and 15) for 16 weeks (cycles 3 through 6), and every 4 weeks thereafter. Lenalidomide were dosed orally 25 mg on days 1 to 21 of each cycle if the creatinine clearance was more than 60 ml per minute (or a dose of 10 mg daily if the creatinine clearance was 30 to 60 ml per minute) and dexamethasone at a dose of 40 mg weekly. For the daratumumab group, the dose of dexamethasone was split. Dexamethasone was administered at a dose of 20 mg before infusion as prophylaxis for infusion-related reactions and 20 mg was administered the next day.

The primary endpoint was PFS, with progression determined with the use of a validated computer algorithm that combined laboratory results (e.g., M-protein level) and applicable imaging and generated the outcome according to IMWG criteria. Secondary endpoints included the time to disease progression in a time-to-event analysis, ORR, rate of very good partial response or better, rate of complete response or better, percentages

of patients with results below the threshold for MRD, time to response, DoR and OS. Safety assessments included evaluation of AEs, clinical laboratory tests, electrocardiograms, vital signs, and physical examinations. Follow-up was continued for patients who discontinued treatment. An independent data and safety monitoring committee was established to periodically review unblinded safety data.

More information on POLLUX can be found in Appendix A.

Table 8: Overview of study design for studies included in the comparisons

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
DREAMM-7 (NCT04246047)	Phase 3, open-label, global, randomized trial	The study is ongoing with a median follow-up of 28.2 months in the first data cut. The completion is estimated to 19-06-2026	N=494 Adults with RRMM, who have had at least one prior LoT, who had documented disease during, or after, their most recent therapy. Stratification factors used were Number of prior LoT (1 versus 2/3 versus ≥4), prior bortezomib (yes versus no) and score on the R-ISS (I versus II/III)	A total of 243 were randomly assigned to receive Belantamab mafodotin IV 2.5 mg/kg Q3W, Bortezomib 1.3 mg/m^2 SC on Days 1, 4, 8 and 11 of cycles 1-8 (21-day cycle) and Dexamethasone 20 mg on the day of and day after bortezomib for Cycles 1-8	A total of 251 were randomly assigned to receive Daratumumab IV 16 mg/kg (Cycle 1-3: Q1W, Cycle 4-8: Q3W and Cycle 9+: Q9+), Bortezomib 1.3 mg/m^2 SC on Days 1, 4, 8 and 11 of cycles 1-8 (21-day cycle) and Dexamethasone 20 mg on the day of and day after bortezomib for Cycles 1-8	**Primary endpoint:** PFS defined as the time from the date of randomization until the earliest date of documented disease progression or death due to any cause. **Key secondary endpoints:** OS defined as the time from the date of randomization until the date of death due to any cause. DoR defined as the time from first documented evidence of PR or better until PD or death due to any cause. MRD-negativity rate defined as the percentage of participants who are MRD-negative by next-generation sequencing (NGS). Follow-up period: Q3W from Cycle 1 Day 1 until PD
POLLUX (NCT02076009)	Open-label, multicenter, phase 3 trial	Study start: 23-07-2023 Study completion: 21-11-2024	N= 569 Patients who had RRMM and had received one or more LoT. Randomization (in a 1:1 ratio) was conducted by means of a central schedule and was	A total of 286 were randomly assigned to receive Daratumumab IV 16 mg/kg weekly (on days 1, 8, 15, and 22) for 8 weeks during cycles 1 and	A total of 283 were randomly assigned to receive Lenalidomide 25 mg orally on days 1 to 21 of each cycle	**Primary endpoint:** PFS defined as the time from the date of randomization until the earliest date of documented disease progression or death due to any cause.

	balanced with the use of randomly permuted blocks and stratified according to the number of lines of previous therapy (1 vs. 2 or 3 vs. >3), ISS (I vs. II vs. III)	2, every 2 weeks (on days 1 and 15) for 16 weeks (cycles 3 through 6), and every 4 weeks thereafter, Lenalidomide 25 mg orally on days 1 to 21 of each cycle Dexamethasone 40 mg weekly (20 mg before infusion as prophylaxis for infusion-related reactions and 20 mg was administered the next day)	Dexamethasone at a dose of 40 mg weekly	**Key secondary endpoints:** OS defined as the time from the date of randomization until the date of death due to any cause. DoR defined as the time from first documented evidence of PR or better until PD or death due to any cause. Time to disease progression defined as time from the date of randomization to the date of first documented evidence of PD Overall response rate defined as the proportion of subjects who achieve CR or PR according to the IMWG criteria, during or after the study treatment.

6.2.2 Comparability of studies

Both DREAMM-7 and POLLUX are phase 3, open-label, randomized trials. Both investigated the efficacy of study drug in a 2L+ setting, meaning patients had experienced at least one relapse before inclusion. The patient characteristics of the study populations are compared in Table 9. Overall, the study populations are very similar, however with some differences in prior therapies, that can be explained by the development in MM treatment that has happened from POLLUX was initiated until DREAMM-7 was. For the full assessment of comparability of efficacy in the studies please refer to Section 7.

6.2.2.1 Comparability of patients across studies

Table 9: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	DREAMM-7		POLLUX	
Characteristics	**BVd (N=243)**	**DVd (N=251)**	**DRd (N=286)**	**Rd (N=283)**
Median age (range) - yr	65 (34–86)	64 (32-89)	65 (34-89)	65 (42-87
Age category — no. (%)				
18 to <65 yr	121 (50)	126 (50)	133 (47)	141 (49.5)
65 to <75 yr	85 (35)	95 (38)	124 (43)	108 (38.2)
≥75 yr	37 (15)	30 (12)	29 (10)	35 (12.4)
Sex — no. (%)				
Male	128 (53)	144 (57)	N/A	N/A
Female	115 (47)	107 (43)	N/A	N/A
Race — no. (%)†				
White	206 (85)	203 (81)	207 (72)	186 (65.7)
Black	8 (3)	12 (5)	5 (2)	11 (3.9)
Asian	28 (12)	33 (13)	54 (19)	40 (16.3)
Weight – median/mean (kg)	73.10/76.25	79.30/78.15	N/A	N/A
BSA – median/mean (m2)	1.9/1.9	1.9/1.9	N/A	N/A
ECOG performance-status score ≤1 — no./total no. (%)‡	121/242 (50)	134/246 (54)	147/286 (51)	133/283 (47)
0	121 (50)	112 (46)	N/A	N/A
1	111 (46)	123 (50)	N/A	N/A
2	10 (4)	11 (4)	N/A	N/A
R-ISS stage at screening — no. (%)				
I	102 (42)	103 (41)	137 (48)	140 (49.5)
II	130 (53)	132 (53)	93 (33)	86 (30.4)

III	9 (4)	14 (6)	56 (20)	57 (20.1)
Unknown	2 (1)	2 (1)	N/A	
Median time since diagnosis (range) - yr	4.3 (0.2–26.0)	3.9 (0.1–23.4)	3.48 (0.4-27.0)	4.0 (0.4-21.7)
Cytogenetic risk — no. (%)§				
Standard	175 (72)	175 (70)	193 (84.6)	176 (83.4)
High	67 (28)	69 (27)	35 (15.4)	35 (16.6)
t(4;14)	41 (17)	42 (17)	10 (4.4)	15 (7.1)
t(14;16)	8 (3)	6 (2)	2 (0.9)	6 (2.8)
del(17p13)	30 (12)	35 (14)	25 (11.0)	20 (9.5)
Missing or not evaluable	1 (<1)	7 (3)	N/A	N/A
Other cytogenetic abnormalities — no. (%)				
del(13)	18 (7)	28 (11)	N/A	N/A
del(1p)	22 (9)	31 (12)	N/A	N/A
Hypodiploidy	33 (14)	28 (11)	N/A	N/A
t(11;14)	13 (5)	15 (6)	N/A	N/A
t(14;20)	1 (<1)	1 (<1)	N/A	N/A
1q21+	94 (39)	79 (31)	N/A	N/A
Other	30 (12)	24 (10)	N/A	N/A
Extramedullary disease — no. (%)				
Yes	13 (5)	25 (10)	N/A	N/A
No	230 (95)	226 (90)	N/A	N/A
Myeloma IgG — no. (%)	161 (66)	159 (63)	N/A	N/A
Previous LoT — no. (%)				
1	125 (51)	125 (50)	N/A	N/A
2 or 3	88 (36)	99 (39)	N/A	N/A
≥4	30 (12)	27 (11)	N/A	N/A
Median (range) number of prior LoT	1 (1-7)	2 (1-7)	1 (1—11)	1 (1-8)
Time to relapse after most recent therapy — no. (%)				
≤12 mo	49 (20)	50 (20)	N/A	N/A
>12 mo	194 (80)	201 (80)	N/A	N/A
Previous proteasome inhibitor — no. (%)				
Any	218 (90)	216 (86)	245 (86)	242 (85.5)
Bortezomib	210 (86)	211 (84)	241 (86)	238 (84.1)
Carfilzomib	31 (13)	35 (14)	6 (2)	6 (2.1)
Ixazomib	13 (5)	11 (4)	2 (0.7)	2 (0.7)
Previous immunomodulatory drugs — no. (%)				

Any	198 (81)	216 (86)	158 (55)	156 (55.1)
Lenalidomide	127 (52)	130 (52)	50 (17.5)	50 (17.7)
Thalidomide	121 (50)	144 (57)	122 (43)	125 (44.2)
Pomalidomide	25 (10)	19 (8)	2 (0.7)	0
Previous daratumumab treatment — no. (%)	3 (1)	4 (2)	N/A	N/A
Previous ASCT — no. (%)	164 (67)	173 (69)	180 (63)	180 (63.6)
Previous chemotherapy — no. (%)	198 (81)	206 (82)	268 (93.7)	270 (95.4)
Previous glucocorticoids — no. (%)	241 (>99)	247 (98)	280 (98)	281 (99.3)

* Percentages may not total 100 because of rounding
† Race was reported by the investigators.
‡ The Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ Standard cytogenetic risk was defined by negative results for all high-risk abnormalities: t(4;14), t(14;16), and del(17p13). High cytogenetic risk was defined by the presence of at least one high-risk abnormality. High-risk abnormalities were assessed by means of interphase fluorescence in situ hybridization with the following central laboratory thresholds: 2% for t(4;14), 2% for t(14;16), and 5% for del(17p13). Local laboratory thresholds were based on local standards
Sources: [35, 39]

Baseline characteristics for 2L, 3L and 3L+ separately are presented in Appendix B.

6.2.3 Comparability of the study population(s) with Danish patients eligible for treatment

GSK has consulted a clinical expert, who confirms that the study population is fully comparable to the Danish patient population eligible for treatment. Relevant characteristics used in the health economic model are presented in Table 10.

Table 10: Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	70	70
Gender	Comparable to study poulation	55% male
Patient weight	Comparable to study poulation	77.2 kg
BSA	Comparable to study poulation	1.9 m^2

6.2.4 Efficacy – results per DREAMM-7

6.2.4.1 Progression-free survival

BVd is the first and only regimen to show significantly superior and sustained mPFS in a head-to-head trial vs a daratumumab-based triplet, DVd. After a median follow-up of

28.2 months (range: 0.1 –40.0), BVd resulted in statistically significant improvement in PFS compared to DVd (HR: 0.41 [95% CI: 0.31–0.53], p<0.001) [35, 37]. BVd more than doubled mPFS vs DVd; 36.6 months (95% CI: 28.4–NR) vs 13.4 months (95% CI: 11.1–17.5) (Table - I). Landmark analysis of PFS at 18 months showed a higher PFS rate in the BVd group compared with the DVd group (69% vs 43%, respectively) [35, 37].

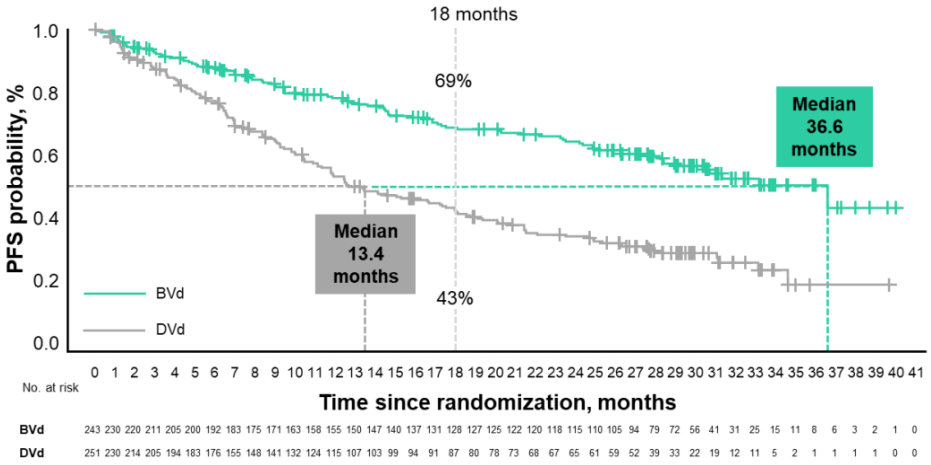
Table - I: PFS in DREAMM-7 (ITT population)

	BVd (N=243	DVd N=251
Number of participants, n (%)		
Progressed or died (event)	91 (37)	158 (63)
Censored, follow-up ended	44 (18)	41 (16)
Censored, follow-up ongoing	108 (44)	52 (21)
Estimates for PFS(months)*		
1st Quartile (95% CI)	14.5 (9.5–17.5)	6.4 (4.9–7.0)
Median (95% CI)	36.6 (28.4–NR)	13.4 (11.1–17.5)
3 rd Quartile (95% CI)	NR	33.1 (26.3–NR)
Hazard ratio†		
Estimate (95% CI)	0.41 (0.31–0.53)	
Stratified log-rank‡		
P-value	<0.00001	
PFS rate (95% CI)		
PFS rate at 6 months	0.88 (0.83–0.91)	0.77 (0.71–0.82)
PFS rate at 12 months	0.78 (0.72–0.83)	0.53 (0.47–0.60)
PFS rate at 18 months	0.69 (0.62–0.75)	0.43 (0.36–0.49)

*CIs were estimated using the Brookmeyer Crowley method. Hazard ratios were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 versus †2/3 versus ≥4), prior bortezomib (no, yes) and R-ISS at screening (I versus II/III), with a covariate of treatment. ‡P-value from 1-sided stratified log-rank test. **Sources**: [37, 48]

The KM curves for PFS showed clear and early separation between the treatment groups in favor of the BVd group (Figure 4). Follow-up is ongoing for the majority of censored participants/events (44% vs 21% in the BVd and DVd groups, respectively) [37]. For PFS censoring rules in DREAMM-7, see Table - X in Appendix B.

Figure 4: Kaplan-Meier Curves of PFS in DREAMM-7 (ITT population)



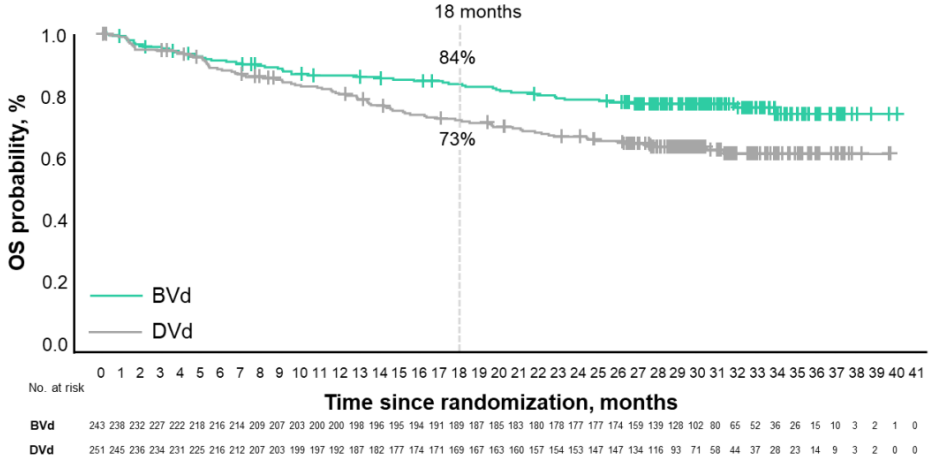
Source: [35]

PFS KM curves for 2L, 3L and 3L+ separately are presented in Appendix B.

6.2.4.2 Overall Survival

Treatment with BVd resulted in clinically meaningful improvements in all key secondary efficacy endpoints [37]. At IA1 (PFS data cut-off), a strong and clinically meaningful OS trend (nominal p=0.00049) was observed, with a 43% reduction in the hazard of death (HR: 0.57; 95% CI: 0.40–0.80) [35, 37]. OS trends showed an early separation favoring BVd vs DVd (Figure 5). At 12 months, OS probability is 87% in BVd arm vs 81% in DVd arm with the separation continuing to widen at 18 months (84% vs 73%, respectively) [37]. Over the study period, more deaths occurred due to DVd (35%) than BVd (22%) in the ITT arm, however, neither arm reached median OS [37].

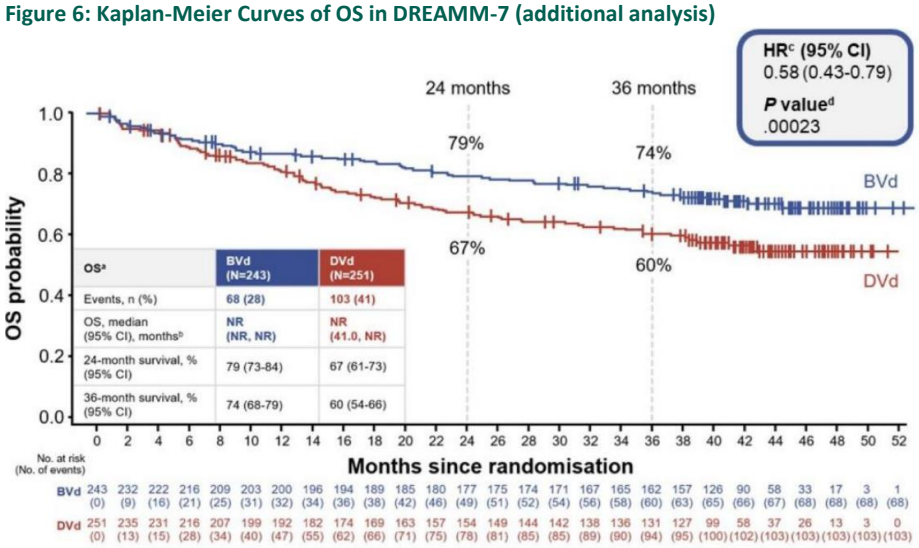
Figure 5: Kaplan-Meier Curves of OS in DREAMM-7 (ITT population)



Source: GSK data on file

After a further follow-up of 39.4 months, the risk of death among patients receiving BVd is significantly reduced (42%) (n=243) vs DVd (n=251) (HR 0.58; 95% CI: 0.43-0.79; p=0.00023) [36, 48]. The projected mOS for BVd is 84 months compared to 51 months for DVd. At this follow-up, the three-year OS rate was 74% in the BVd arm and 60% in the DVd arm. The survival benefit favoring BVd was seen as early as four months and was sustained over time (Figure 6) [36, 48]. As of November 2024, OS for BVd has reached the interim criteria for statistical significance of OS, with BVd significantly reducing risk of death vs DVd [36, 48]. The censoring rule for OS is the time from randomization until the date of death due to any cause. Patients who did not experience death will be censored at the date of last contact or the end of the study.

Figure 6: Kaplan-Meier Curves of OS in DREAMM-7 (additional analysis)



Source: [36]

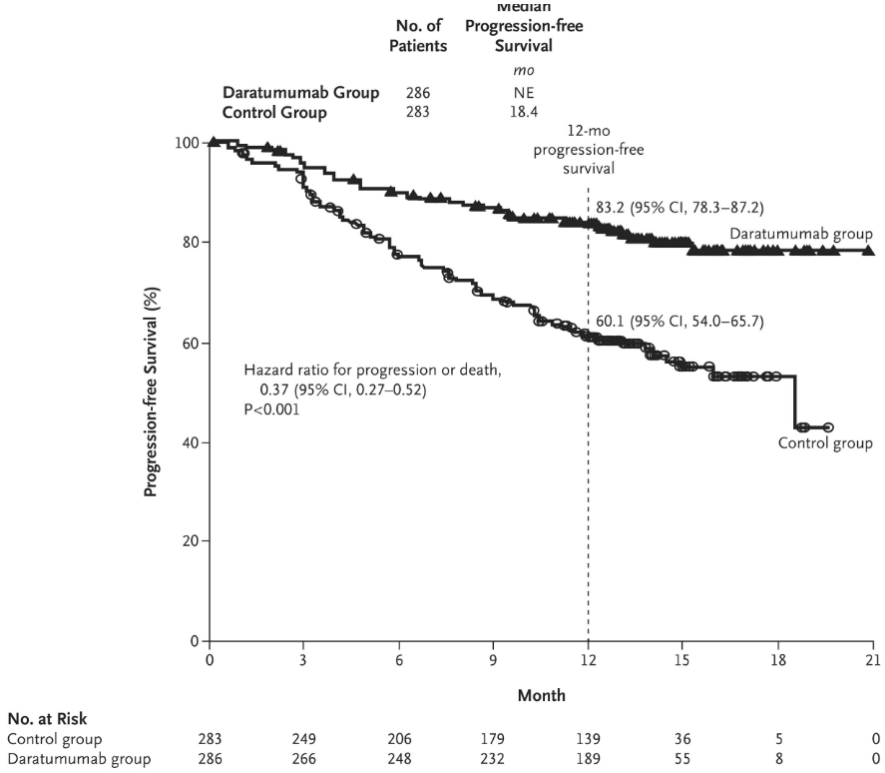
OS KM curves for 2L, 3L and 3L+ separately are presented in Appendix B.

6.2.5 Efficacy – results per POLLUX

6.2.5.1 Progression-free survival

At a median follow-up of 13.5 months, a total of 169 events of disease progression or death (in 53 patients [18.5%] in the DRd-group vs 116 [41.0%] in the Rd-group) were reported. The HR for disease progression or death in the daratumumab group vs the control group was 0.37 (95% confidence interval [CI], 0.27 to 0.52; P<0.001 by stratified log-rank test) (Figure 7) [39].

Figure 7: Kaplan-Meier Curves of PFS in POLLUX (ITT population)



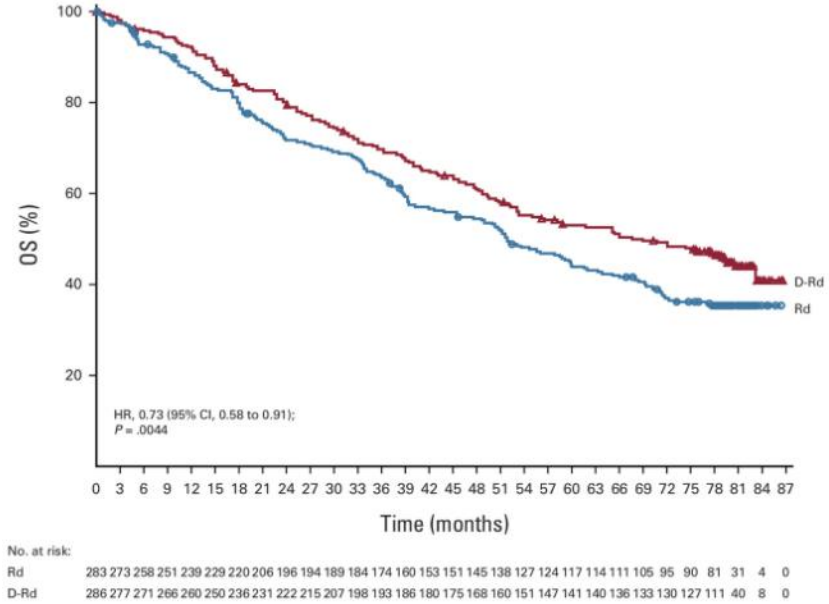
Source: [39]

At a median follow-up of 51.3 months median PFS for DRd vs Rd was 45.8 vs 17.5 months. The HR for disease progression or death in the DRd group vs Rd group was 0.43 (95% CI, 0.35-0.54; P<0.001) [49].

6.2.5.2 Overall Survival

153 (53.5%) of 286 patients in the DRd group and 175 (61.8%) of 283 patients in the Rd group had died at a median (range) follow-up of 79.7 months (0.0-86.5). The HR for death in the DRd group compared with the Rd group was 0.73 (95% CI, 0.58 to 0.91; P = .0044) (Figure 8), crossing the prespecified stopping boundary of P < .0331 and representing a 27% reduction in the risk of death. The median OS was 67.6 months (95% CI, 53.1 to 80.5) in the DRd arm vs 51.8 months (95% CI, 44.0 to 60.0) in the Rd arm [40].

Figure 8: Kaplan-Meier Curves of OS in POLLUX (ITT population)



Source: [40]

7. Comparative analyses of efficacy

A head-to-head study comparing BVd with DVd forms the basis of this application.

[redacted]

7.1 Differences in definitions of outcomes between studies

[redacted]

7.2 Method of synthesis

[redacted]

7.2.1 Systematic literature review

[redacted]

[redacted]

[redacted]

7.2.2 Comparability of studies: DRd vs BVd

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3 Results from the comparative analysis

[redacted] The results from the connecting pathway are presented in Appendix C.

Table 11: Results from the comparative analysis of BVd vs DRd for patients with RRMM

Outcome measure	BVd (N=243)	DRd (N=286)	Result
PFS	Median: 36.6 months (95% CI: 28.4–NR) HR: 0.46 (95 % CI: 0.35, 0.59)	Median: 45.8 months HR: 0.43 (95 % CI: 0.35, 0.54)	[redacted]
OS	Median: Not reached HR: 0.58 (95 % CI: 0.43, 0.79)	Median: 67.6 months (95% CI, 53.1 to 80.5) HR: 0.73 (95 % CI: 0.58, 0.91)	[redacted]

7.3.1 Efficacy – results per PFS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Scenario	Total residual deviance	DIC	pD	Data points
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.3.2 Efficacy – results per OS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Scenario	Total residual deviance	DIC	pD	Data points
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.4 Discussion of comparative analysis

[redacted]

[redacted]

[redacted]

[redacted]

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Efficacy data for BVd and DVd was sourced from the IA2 data cut of the DREAMM-7 trial.

[redacted]

8.1.1 Extrapolation of efficacy data

Parametric survival modelling was implemented to extrapolate the survival curves over a lifetime horizon. Survival analyses were carried out in line with the NICE technical support documents and the methods guide from the DMC [61, 62]. Multiple analyses were used to test proportional hazards (PH), including visual assessment of log-cumulative hazard plots, assessment of Schoenfeld residual plots and quantile-quantile (Q-Q) plots. The assessments suggest that the PH assumption is unlikely to hold, therefore independent parametric models were fit to both treatment arms. Extrapolations are described in section 8.1.1.1 and 8.1.1.2, and a further detailed description is presented in Appendix D.

Treatment discontinuation has been modelled as per each treatment's respective trial protocol-defined treatment discontinuation criteria. Where treatments are continued to progression, the extrapolated TTD has been capped by the modelled PFS for the respective treatments. The model also includes the functionality to set TTD equal to PFS. For the BVd and DVd arms of the model, discontinuation is informed by TTD data from the DREAMM-7 trial.

[redacted]

8.1.1.1 Extrapolation of PFS

To extrapolate PFS over the model time horizon for each treatment arm, survival distributions have been fitted to the KM data by treatment arm. The extrapolated PFS curves were used to inform the proportion of the model cohort in the PF health state and the PD health state (OS – PFS) and were capped by OS. The exponential function was applied in the base case analysis for both BVd and DVd, informed by input from a Danish clinical expert. The clinical expert suggested choosing the most conservative distribution for both treatment arms.

Table 12: Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	DREAMM-7 IA2 data cut
Model	Independent parametric models

Assumption of proportional hazards between intervention and comparator	No, likely violated
Function with best AIC fit	BVd: Exponential DVd: Log-logistic
Function with best BIC fit	BVd: Exponential DVd: Log-logistic
Function with best visual fit	BVd: Exponential DVd: Exponential
Function with best fit according to evaluation of smoothed hazard assumptions	BVd: Exponential DVd: Log-logistic
Validation of selected extrapolated curves (external evidence)	Danish clinical expert opinion
Function with the best fit according to external evidence	BVd: Exponential DVd: Exponential
Selected parametric function in base case analysis	BVd: Exponential DVd: Exponential
Adjustment of background mortality with data from Statistics Denmark	No
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 9: PFS – BVd KM and parametric distributions

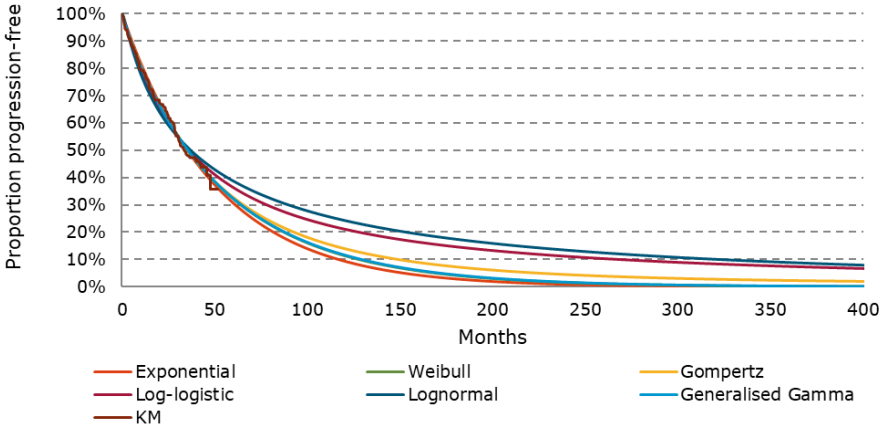


Figure 10: PFS – DVd KM and parametric distributions

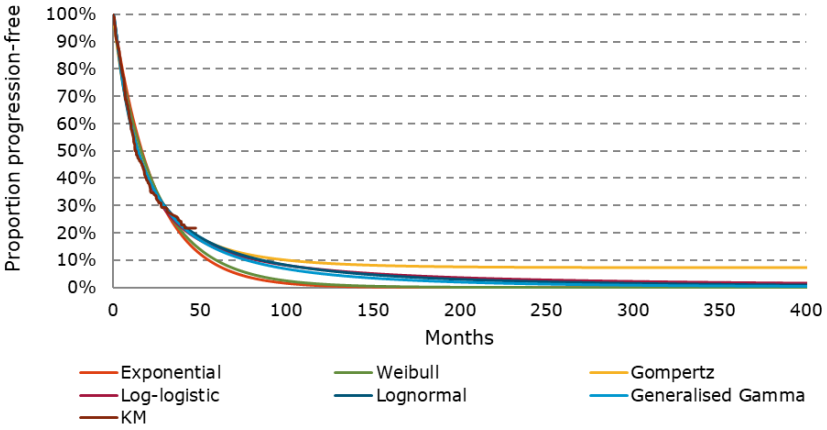
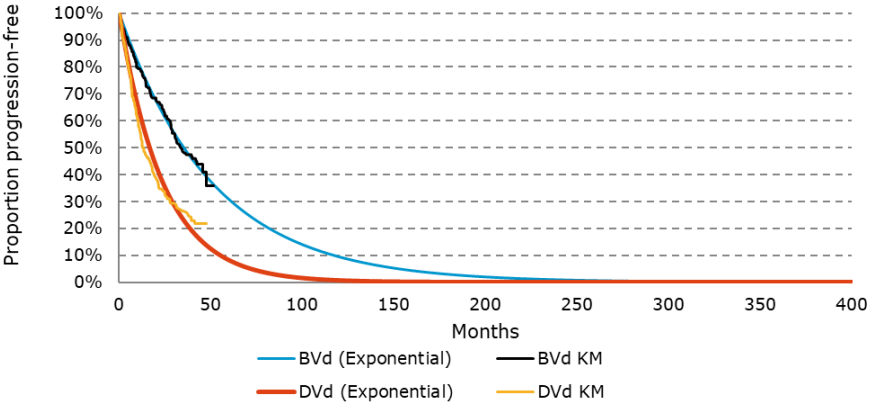


Figure 11: Base case PFS extrapolations for BVd and DVd with PFS KM data



8.1.1.2 Extrapolation of OS

To reflect the uncertainty around long-term survival benefits, the base case approach in the model fits parametric curves directly to the OS data from the IA2 data cut of the DREAMM-7 trial for both BVd and DVd. This method requires the assumption that the OS

hazard ratio observed in the DREAMM-7 trial represents the true longer-term OS treatment effect associated with BVd and DVd.

Table - II: Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	DREAMM-7 IA2 data cut
Model	Independent parametric models
Assumption of proportional hazards between intervention and comparator	No, likely violated
Function with best AIC fit	BVd: Log-normal DVd: Gompertz
Function with best BIC fit	BVd: Log-normal DVd: Gompertz
Function with best visual fit	BVd: Exponential DVd: Exponential
Function with best fit according to evaluation of smoothed hazard assumptions	BVd: Log-normal DVd: Gompertz
Validation of selected extrapolated curves (external evidence)	Danish Clinical Expert opinion
Function with the best fit according to external evidence	BVd: Exponential DVd: Exponential
Selected parametric function in base case analysis	BVd: Exponential DVd: Exponential
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 12: OS - BVd KM and parametric distributions

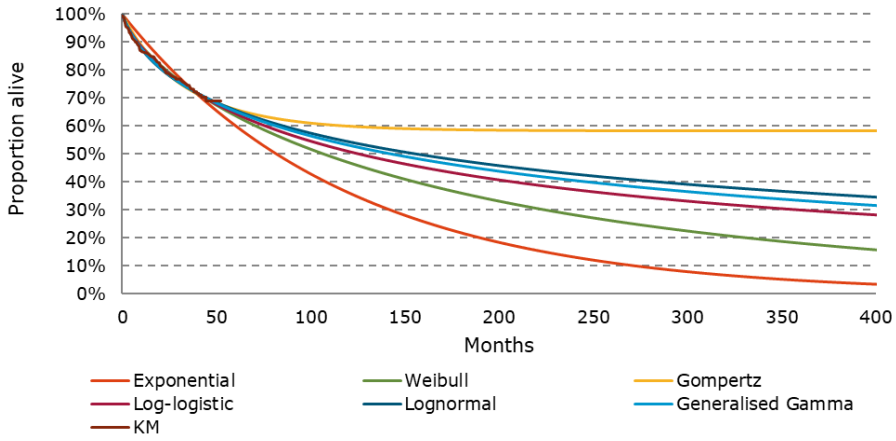


Figure 13: OS – DVd KM and parametric distributions

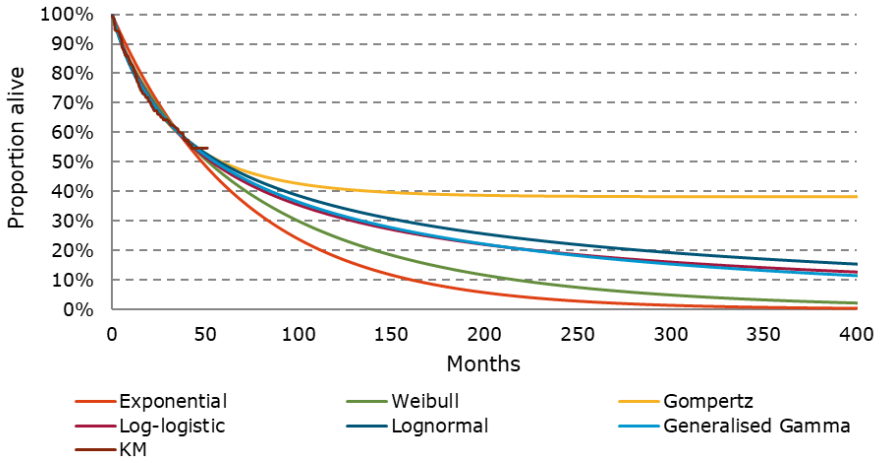
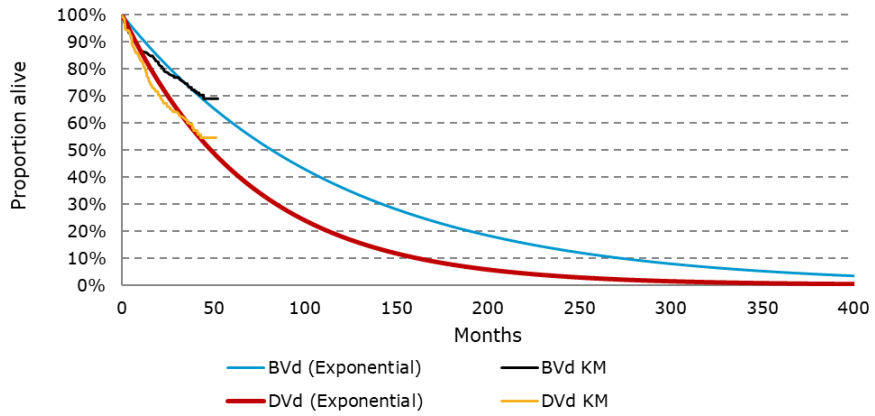


Figure 14: Base case OS extrapolations for BVd and DVd with OS KM data



8.1.2 Calculation of transition probabilities

Not applicable.

Table 13: Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

After treatment with the intervention or comparator patients may progress and be treated with a subsequent line of therapy. In line with previous HTA appraisals, a one-off cost was applied for up to two lines of subsequent therapy. The one-off subsequent treatment cost was calculated using the proportion of patients who required a first and second subsequent treatment, the distribution of first and second subsequent treatments required for each treatment arm, and the treatment cost of each subsequent treatment. Patients may start on subsequent treatment following the time of disease progression.

The proportion of patients on BVd and DVd who start a subsequent treatment (this is initiated once patients have experienced disease progression) was informed by Szabo et al. 2019, assuming a 22% median decrease in the number of patients per subsequent line of therapy [17]. This approach was chosen due to the limited follow-up period DREAMM-7, which impacts the observed proportions of patients receiving subsequent treatments. Specifically, DREAMM-7 reports that after treatment with BVd, 26% of patients receive a first subsequent treatment, and after treatment with DVd, 44% of patients receive a first subsequent treatment [48]. These proportions are likely to be lower than those observed in real-world clinical practice, as longer follow-up periods would capture additional patients progressing to subsequent lines of therapy, and are therefore not used.

As patients with MM typically receive treatment until death, median OS of 9 months for third and later line patients was assumed to be a reasonable proxy for the median duration of subsequent treatments, sourced from Kumar et al. (2012) [47].

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Table 14: PFS Estimates in the model, undiscounted

	Modelled average PFS ('Partitioned survival model D-Vd M21, M23' [redacted]	Modelled median PFS ('Partitioned survival model D-Vd M20, M22' [redacted]	Observed median from relevant study
BVd	50.88 months	35.42 months	36.6 months [35]
DVd	24.06 months	16.79 months	13.4 months [35]
[redacted]	[redacted]	[redacted]	[redacted]

Table - III: OS Estimates in the model, undiscounted

	Modelled average OS ('Partitioned survival model D-Vd N21, N23' [redacted]	Modelled median OS ('Partitioned survival model D-Vd N20, N22' [redacted]	Observed median from relevant study
BVd	107.51 months	81.87 months	Not reached [35]
DVd	69.19 months	48.53 months	Not reached [35]
[redacted]	[redacted]	[redacted]	[redacted]

Table 15: Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction)

Treatment	Treatment length [months]	PFS [months]	OS [months]
BVd	27.06	50.88	107.51
DVd	20.53	24.06	69.19
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

8.5.1.1 Median modelled PFS from RWE

Real-world studies have investigated the efficacy of DRd.

[redacted] The studies are presented in Table - IV below:

Table - IV: median modelled PFS from RWE

Country	Population receiving DRd	Median PFS (95% CI)	Source
Germany/ Canada	32 patients with MM who had relapsed on lenalidomide maintenance post-autologous stem cell transplant	21.7 months (11.6-NR)	[63]
Taiwan	31 patients with MM who had received one or more lines of therapy	24.1 months (14-33)	[64]
US	214 patients with relapsed and/or refractory MM	17.7 months (11.3-26.8)	[65]

9. Safety

In this section we present safety data from the DREAMM-7 trial on patients treated with BVd or DVd [35]. Furthermore, safety data from POLLUX will be presented for patients treated with DRd [39, 40].

9.1 Safety data from the clinical documentation

9.1.1 DREAMM-7

The safety analysis set for the DREAMM-7 trial consisted of all randomized subjects in the ITT analysis set, who received at least one dose of study treatment. Participants were analyzed according to the treatment they actually received.

The safety assessments included monitoring of AEs, clinical laboratory tests, vital signs, physical examinations, ECOG performance status, ocular examination, pregnancy, PRO, 12-lead ECG, and Visual Functioning Questionnaire. The AESIs were ocular events, thrombocytopenia, and IRRs. These AEs were coded using MedDRA PTs and graded for intensity/severity using CTCAE v5.0.

Overall, at the time of DREAMM-7 primary analysis, BVd showed a safety profile consistent with the known profiles of the individual agents. All patients in both arms of the safety analysis set (BVd: 242 patients; DVd: 246 patients) experienced ≥1 AE [35, 37]. The incidences of any AEs, AEs related to any study treatment, and fatal SAEs were similar in the BVd and DVd groups.

Because participants in the BVd group stayed in treatment longer than participants in the DVd group, a post-hoc analysis was performed to ascertain the effects of study treatment exposure on key safety parameters. After adjusting for time on study treatment, the exposure-adjusted rates were 68.8 and 62.4 events per 100 PYs for the BVd and DVd groups, respectively [38]. The incidence rate between the BVd and DVd group for any SAEs were 50% and 37%, respectively; after adjusting for time on study treatment, the exposure-adjusted rates were 36.3 and 30.0 events per 100 PYs, respectively [38].

In both treatment groups, nearly all participants experienced a dose modification due to any AE, with dose interruptions/delay being the most common dose modification in both treatment groups. The incidence of all AE-related dose modifications was higher in the BVd group compared with the DVd group. The most common AEs leading to treatment discontinuation in the BVd group were related to peripheral neuropathy, pneumonia, and infections. The most common AEs leading to treatment discontinuation in the DVd group were related to peripheral neuropathy and COVID-19 (with or without pneumonia). The number of participants who discontinued for neuropathic AEs was similar in both study groups. To see an overview of the most common AEs leading to dose discontinuation, dose reduction or dose interruption/delay refer to Appendix E.

The overall incidence of AEs by system organ class was generally similar across treatment groups, with few exceptions described below. In the BVd group, the system organ class of eye disorders had the highest percentage of participants with AEs, followed by blood and lymphatic system disorders, and infections and infestations. In the DVd group, the system organ class of infections and infestations had the highest percentage of participants with AEs, followed by nervous system disorders, and blood and lymphatic system disorders [35]. Eye-related AEs will be discussed separately in Section 9.2.

Table 16: Overview of safety events (DREAMM-7 and POLLUX)

	DREAMM-7 Median follow-up: 28.2 months			POLLUX Median follow-up: 25.4 months
	BVd (N=242)	DVd (N=246)	Difference, % (95 % CI)	DRd (N= 286)
Number of adverse events, n	[redacted]	[redacted]	[redacted]	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]	[redacted]	N/A
Number of serious adverse events, n	[redacted]	[redacted]	[redacted]	N/A
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	[redacted]	[redacted]	[redacted]	(48.8)
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	[redacted]	[redacted]	[redacted]	N/A
Grade ≥ 3 events, exposure-adjusted (events/PYs)	[redacted]	[redacted]	[redacted]	N/A
Number of treatment-related adverse events*, n	[redacted]	[redacted]	[redacted]	N/A
Number and proportion of patients with ≥ 1 treatment-related adverse events*, n (%)	[redacted]	[redacted]	[redacted]	N/A
Number and proportion of patients who had a dose reduction due to any AE, n (%)	[redacted]	[redacted]	[redacted]	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	[redacted]	N/A
Number and proportion of patients who discontinue treatment due to adverse events*, n (%)	[redacted]	[redacted]	[redacted]	(6.7)

Adverse events leading to permanent discontinuation of any study treatment, exposure-adjusted (events/PYs)	[redacted]	[redacted]	[redacted]	N/A

* 'Related to any Study Treatment' includes responses of 'Yes' and missing responses to the following question: 'Is there a reasonable possibility that the AE may have been caused by the study treatment?' § Includes subjects who have discontinued treatment or died prior to End of Treatment Visit.
Source: GSK Data on file, [39]

Table 17 shows SAEs occurring in ≥2% of each group. According to the DMC application template, a list of all SAEs with frequency of ≥5% recorded in the study should be presented. However, since a limited number of SAEs had a frequency of ≥5% we have expanded to ≥2%. A full list of SAEs reported in DREAMM-7 is presented in Appendix E.

Table 17: Serious adverse events reported in ≥ 2% of patients in the safety population for DREAMM-7

Adverse events	BVd (N=242)		DVd (N=246)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
Any event	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Anemia	[redacted]	[redacted]	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Overall, the incidence of SAEs was higher in the BVd group than in the DVd group. After adjusting for time on study treatment, the exposure-adjusted rates were 36.338 and 30.044 events per 100 person years for the BVd and DVd groups, respectively. The most frequently reported SAEs in both treatment groups were related to pneumonia, COVID 19, and pyrexia. Pneumonia was more frequently reported in the BVd group than in the DVd group.

Treatment-related SAEs were more frequent in the BVd group (19%) than in the DVd group (12%). The most frequently reported treatment-related SAEs in the BVd group were pneumonia (4%) and thrombocytopenia (3%); all other treatment-related SAEs were reported in ≤1% of participants. The most frequently reported treatment-related SAEs in the DVd group were pneumonia, thrombocytopenia, and IRR (2%, each); all other treatment-related SAEs were reported in ≤1% of participants. No participants in the BVd group had an SAE of infusion-related reaction [35].

9.1.2 POLLUX

The safety population in POLLUX consisted of all treated subjects. Safety evaluations included AE monitoring, physical examinations, electrocardiogram (ECGs) monitoring, clinical laboratory parameters (hematology and chemistry), blood pressure and temperature measurements, and ECOG performance status [39]. An overview of safety data is presented in Table 16.

AEs that occurred at a frequency of 10% or more in the DRd group versus the Rd group were neutropenia, diarrhea, upper respiratory tract infection, and cough, most of which resulted from longer exposure to treatment in the DRd group. Deep-vein thrombosis was reported in 1.8% of the patients in the DRd group and in 3.9% of those in the Rd group. In the DRd group, 51.9% of patients had neutropenia of grade 3 or 4, as compared with 37.0% of those in the Rd group; thrombocytopenia of grade 3 or 4 occurred in 12.7% and 13.5% of the patients, respectively [39].

With regard to non-hematologic AEs, incidences of grade 3 or 4 diarrhea, fatigue, nausea, and dyspnea were slightly higher in the DRd group than in the Rd group. The rate of infection of grade 3 or 4 was also slightly higher in the DRd group than in the Rd group (28.3% and 22.8%, respectively); the most common infection of grade 3 or 4 was pneumonia, which occurred at similar rates in the two groups.

SAEs were reported in 48.8% of the patients in the DRd group and in 42.0% of those in the Rd-group, among which pneumonia was the most common (in 8.1% of the patients in the DRd group and in 8.5% of those in the Rd-group) [39]. Since the POLLUX publications do not report SAEs in ≥5% of patients, we have listed Grade ≥3 AEs for both BVd, DVd and DRd in the Appendix E to allow for further comparison of safety between combinations.

The percentage of patients with AEs leading to the discontinuation of treatment was similar in the two groups: 6.7% in the DRd group and 7.8% in the Rd group. The most common AEs (in ≥1% of the patients in either group) that led to the discontinuation of treatment included pneumonia (in 1.1% of the patients in the DRd group and in 0.7% of those in the Rd group), pulmonary embolism (in 1.1% in the Rd group), and deterioration in general physical health (in 1.1% in the DRd group) [39].

9.2 Eye-related adverse events

Eye-related AEs, a known risk of treatment with BM, were generally reversible, manageable with dose modification, and led to low treatment discontinuations. The following section will elaborate on eye-related AEs because they are a novel treatment-emergent event specific to anti-drug conjugates that should be managed in patient with RRMM [66-68].

The cornea is the transparent, anterior most structure of the eye and plays an important role in focusing light onto the retina [69]. For BM keratopathy (MECs) is typically described as superficial bilateral, microcystlike lesions seen on slit lamp microscopy. For most patients, MECs are first observed in the corneal periphery and progress to the mid-periphery and subsequently the center. The presence of MECs in the corneal center can correlate with changes in vision, including subjective blurred vision, but not all people with registered MECs will have blurred vision [35]. Furthermore, since the cornea regenerates this state is not permanent, meaning people with vision disturbances will only experience it periodically. Similar findings have been commonly described with other ADCs, particularly for MMAF-containing ADCs [67, 68].

Over the DREAMM-7 study period, eye-related AEs were more frequent for BVd vs DVd (79% vs 29%). However, eye-related side effects across BM are generally resolved or managed with individualized dose modifications as per protocol, enabling patients to continue treatment without impacting efficacy [37, 48, 70]. Of the eye-related AEs for BVd, only 9% discontinued due to any ocular event [35].

Table - V summarizes eye-related AEs for both arms. Eye-related AEs (CTCAE Grade) occurred in 79% of the BVd group; vision blurred, and dry eye were reported in more than half of the participants in this group. In the DVd group, 29% experienced an eye-related AE, with vision blurred the most frequently reported event. Grade 3 or 4 eye-related AEs (CTCAE grade) were reported in more participants in the BVd group (34%) than in the DVd group (3%) [37, 48].

Table - V: Eye-related AEs occurring in ≥5% of the patient population in either cohort

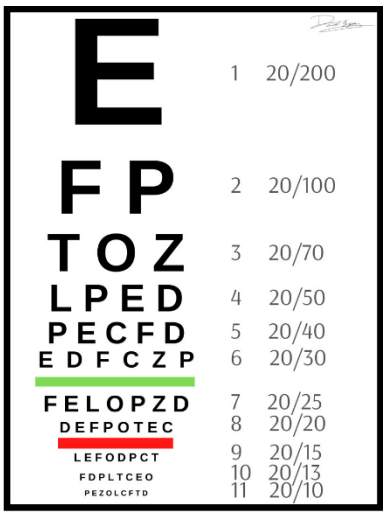
AE, n (%)	BVd (N=242)		DVd (N=246)	
	All grades	Grade ≥3	All grades	Grade ≥3
Ocular AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]

Eye irritation	[redacted]	[redacted]	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]	[redacted]	[redacted]
Photophobia	[redacted]	[redacted]	[redacted]	[redacted]
Foreign body sensation in eyes	[redacted]	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]	[redacted]
Lacrimation increased	[redacted]	[redacted]	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]	[redacted]	[redacted]
Diplopia	[redacted]	[redacted]	[redacted]	[redacted]

Source: GSK Data on File

Best corrected visual acuity (BCVA) is the clarity/sharpness of vision a patient can achieve with correction (e.g. glasses) measured using a Snellen chart (Figure 17) [71, 72].

Figure 15: Snellen Chart



Source: [73]

Determining BCVA necessitates refraction, a test that measures the strength of the corrective lens needed to achieve precise focus. Normal vision is a visual acuity score of 20/20 (if using feet as in DREAMM-7) or 6/6 (if using meters as in Danish clinical practice) [71, 73]. This means that at 20 feet or 6 meters from the chart, the patient can see what the average, healthy individual can see from that position. For example, a patient with BCVA of 20/50 or 6/15 can see at 20 feet/6 meters what the average individual can see at 50 feet/15 meters away. The smallest line read correctly represents the patient's BCVA [72, 73]. A person's visual acuity is expressed in either a decimal fraction or percentage [72]. In DREAMM-7 it is presented as a decimal fraction.

At the time of primary analysis, 82 patients (34%) with a BCVA score of 20/25 or better in ≥1 eye at baseline had a worsening in both eyes to 20/50 (40% vision) or worse, and a

decrease to 20/200 (10% vision) in both eyes occurred in 2% (Table - VI) [35, 37]. The median time to onset of first event was 73.5 days (105 days for events of worsening to bilateral 20/200) (Table - VI). In total, 98% of these events resolved at the time of analysis, with a median time to resolution of 22 days (19 days for visual impairment events) [37]. In a post-hoc analysis, the BCVA returned to the baseline level (20/25 or better in at least one eye) after the first occurrence of worsening in 94% of the patients who had a decrease to 20/50 in both eyes and in 80% of those who had a decrease to 20/200 in both eyes. The median time to resolution after the first occurrence was nine weeks in those with a decrease to 20/50 and 12 weeks in those with a decrease to 20/200 [35].

Table - VI: Changes in best visual acuity

BVd	Bilateral worsening of BCVA in patients with normal baseline 20/25 or better	
	20/50 or worse	20/200 or worse*
Patients, n/N (%)	82/242 (34)	5/242 (2)
Time to onset of first event, median (range), days	73.5 (16–753)	105 (47–304)
Time to resolution of first event to baseline, median (range), days†	64 (8-908)	86.5 (22–194)
Time to improvement of first event, median (range), days‡	22 (6-257)	19 (8–26)
First event resolved, n/N (%)†	77/82 (94)	4/5 (80)
First event improved, n/N (%)‡	80/82 (98)	5/5 (100)
Follow-up ended with event ongoing, n/N (%)	2/82 (2)	0

*Only patients with baseline visual acuity of 20/25 or better in ≥1 eye with on-trial worsening to 20/50 or 20/200 in each eye at the same visit.
†Resolution (post-hoc) was defined as returning to baseline visual acuity (20/25 or better in ≥1 eye).
‡Improvement was defined as bilateral improvement to better than 20/50 (or 20/200).
Source: [37]

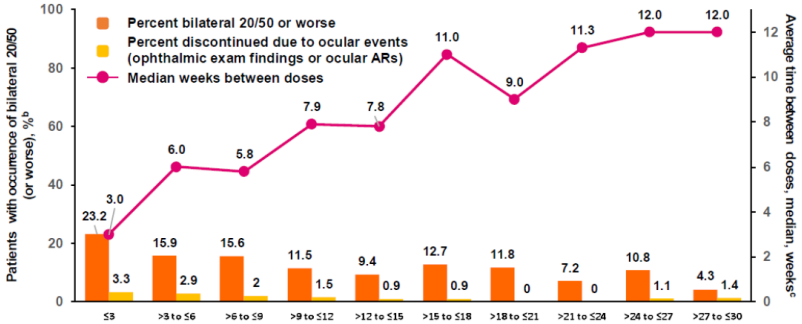
9.2.1 Impact of dose modifications on PFS and eye-related AE management

Efficacy was maintained in post-hoc analysis in DREAMM-7 in patients requiring extended dose delays (considering only patients receiving ≥6 months of treatment to exclude early discontinuation [e.g., rapid disease progression]). Patients receiving BVd with ≥1 dose delay of ≥12 weeks (N=126) had a mPFS of 36.6 months (33.2–not reached) [37, 38, 74]. Of patients with VGPR or better who experienced an extended dose delay, 95% maintained or deepened their response. Of patients with ≤ PR who received 1–2 doses, 95% reached, maintained or deepened their response after their first dose delay

[74]. In patients who had at least one Grade ≥2 ophthalmic finding, 91% continued BM following the first event and received a median of eight BM infusions, 93% had partial response or better and 75% had VGPR.

Median time between doses increased with treatment duration, but occurrence of BCVA worsening events decreased, and rates of treatment discontinuation due to ocular events were low [74]. Data on the prevalence of bilateral BCVA 20/50 or worse and time interval between doses by time on treatment are presented in Figure 16. Prevalence of ocular AEs (CTCAE) were generally lower after completion of the first three months of treatment [74].

Figure 16: Prevalence of bilateral BCVA 20/50 or worse and time between doses on treatment in DREAMM-7[a]



No. of patients on treatment[b]	211	170	147	131	117	110	102	97	93	69
No. of patients with bilateral 20/50 or worse[b]	49	27	23	15	11	14	12	7	10	3
Median days between doses[b]	21	42	41	55	54	77	63	79	84	84
No. of patients who discontinued due to KVA or ocular CTCAE event[b]	7	5	3	2	1	1	0	0	1	1

[a]Only the BM treatment period was considered in post-hoc analyses.
[b]Only patients with 20/25 or better in ≥1 eye at baseline is considered.
[c]Mean of days between doses for each patient per interval is used.
[d]Graph is truncated at 30 months because data beyond 30 months represented low number of patients on treatment (>30 to ≤33 months: N=42; >33 to ≤36 months: N=20; >36 to ≤39 months: N=8; >39 to ≤42 months: N=3).
Source: [74]

9.3 Adverse events in the health economic model

Table 18: Adverse events used in the health economic model

Adverse events	BVd	DVd	[redacted]		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator		Source	Justification

Neutropenia	30 (12)	15 (6)	[redacted]	DREAMM-7 [redacted]	Grade 3+ AE deemed requiring treatment by clinical expert
Anemia	20 (8)	25 (10)	[redacted]	DREAMM-7 [redacted]	Grade 3+ AE deemed requiring treatment by clinical expert
Febrile neutropenia	1 (<1)	1 (<1)	[redacted]	DREAMM-7 [redacted]	Grade 3+ AE deemed requiring treatment by clinical expert
Pneumonia	21 (9)	8 (3)	[redacted]	DREAMM-7 [redacted]	Grade 3+ AE deemed requiring treatment by clinical expert
Keratopathy*	4 (2)	0 (0)	[redacted]	DREAMM-7	Grade 3+ Eye-related adverse event relevant for BVd only
Blurred vision*	53 (22)	2 (<1)	[redacted]	DREAMM-7	Grade 3+ Eye-related adverse event relevant for BVd only
Dry eyes*	17 (7)	0 (0)	[redacted]	DREAMM-7	Grade 3+ Eye-related adverse event relevant for BVd only

*: In the base case analysis Grade ≥3 ocular-related AEs are included, however, given the specificity of corneal events to BM, the model includes the functionality to include Grade ≥2 ocular-related AEs to quantify the impact on costs and HRQoL.

9.4 Safety data from external literature applied in the health economic model

Not applicable.

Table 19: Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

In this section, the HRQoL data relevant for the assessment of BVd versus DVd is described. [redacted] Health related quality of life data was collected in the DREAMM-7 trial – including EQ-5D-3L, EORTC QLQ-C30, EORTC IL52, EORTC QLQ-MY20, FACT-GP5 and PGIS/PGIC. To support this submission, we are going to present EQ-5D-3L data.

Table 20: Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-3L	DREAMM-7	To determine the beneficial effect of belantamab mafodotin on RRMM symptoms, its impact on functioning and the impact of the treatment itself.

10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments]

10.1.1 Study design and measuring instrument

In the DREAMM-7 trial HRQoL data was collected using EQ-5D-3L. The instrument was used at baseline and at check-ups in the manner it is validated for. The data collection of EQ-5D-3L is described in the section below.

The EQ-5D-3L is a standardized instrument for use as a measure of health utility. It is designed for self-completion or interview administration and is cognitively simple, taking only a few minutes to complete. The EQ-5D-3L self-assessment questionnaire has 2 parts. The first part consists of 5 items covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point Likert scale (no problems, some or moderate problems, and unable or extreme problems). Respondents are asked to choose one level that reflects their "own health state today" for each of the 5 dimensions. Respondents can be then classified into 1 of 243 distinct health states. The second part is a 20-cm visual analogue scale (EQ-VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. EQ-5D-3L health states are

converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples. The instrument is validated and used across countries and patient population.

One important aspect of HRQoL, particular in cancer trials, is that the HRQoL can change rapidly after the disease has progressed. Therefore, it is essential to consider the pre- and post-progression states when analyzing the utility estimates. To determine whether patients in the study were in a pre- or post-progression health state, PFS was used. Progression was defined as the time from the date of randomization to the earliest date of PD or death by any cause in the absence of PD, whichever occurred first.

Overall, the demographics in DREAMM-7 are well-balanced between treatment arms and the population is representative of the expected population of Danish patients with RRMM, as presented in Table 9 and Table 10.

10.1.2 Data collection

All participants completed the self-administered version of the PRO questionnaires unless they were not able to complete the questionnaire on their own, then an interviewer-administered format will be used. The questionnaires were administered to participants in different regions based on the availability of translated versions. PRO questionnaires were completed by participants at the start of study visits before receiving any results and before discussing their health status with the study staff.

EQ-5D-3L were administered before first cycle (baseline) and hereafter Q6W on treatment. EQ-5D were collected at 3, 6 and 12 months during OS follow up (can be collected by phones using interviewer administration). EQ-5D-3L analyses are based on ITT analysis set.

Pattern of missing data and completion are presented in Table 21.

Table 21: Pattern of missing data and completion

	BVd				DVd			
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 67	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 121	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 127	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 139	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 163	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 169	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 175	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 181	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 187	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 193	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 199	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 205	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 211	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 217	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 223	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

10.1.3 HRQoL results

Error! Reference source not found. shows the change in the EQ-5D-3L utility index score.

Error! Reference source not found. shows the change in the score on the EQ-5D-3L visual analogue score (VAS).

[redacted]

[redacted]

[redacted] A similar table with EQ-5D VAS is found in Appendix F.

Table 22: Analysis of Change from Baseline in EQ-5D-3L Utility Score, Mixed Effects Model for Repated Measures, ITT population, Danish population weights

	BVd		DVd		BVd vs. DVd
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 67	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 121	[redacted]	[redacted]	[redacted]	[redacted]
Week 127	[redacted]	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]	[redacted]
Week 139	[redacted]	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]	[redacted]
Week 151	[redacted]	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]	[redacted]
Week 163	[redacted]	[redacted]	[redacted]	[redacted]
Week 169	[redacted]	[redacted]	[redacted]	[redacted]
Week 175	[redacted]	[redacted]	[redacted]	[redacted]
Week 181	[redacted]	[redacted]	[redacted]	[redacted]
Week 187	[redacted]	[redacted]	[redacted]	[redacted]
Week 193	[redacted]	[redacted]	[redacted]	[redacted]
Week 199	[redacted]	[redacted]	[redacted]	[redacted]
Week 205	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Last Follow-up	[redacted]	[redacted]	[redacted]	[redacted]

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

The EQ-5D-3L utility values were assigned to each health state in the model to reflect the health-related quality of life (HRQoL) associated with treatment and disease progression. An analytical dataset was constructed with one record per patient per visit, capturing time-dependent variables describing the patient's health status at each time point. To estimate the mean utility values associated with different health states (i.e., progression-

free on treatment, progression-free off treatment, and progressive disease), a generalized linear model was fitted using the generalized estimating equations (GEE) method. This approach incorporated all available EQ-5D-3L measurements across visits and accounted for within-subject correlation arising from repeated measures over time. A compound symmetry correlation structure was used as the base-case specification, and model fit was assessed before considering alternative working correlation structures such as unstructured, autoregressive of order 1 or m-dependent. The model included baseline utility value, health state, and treatment as covariates to adjust for individual differences in baseline HRQoL and treatment effects over time. The least square means along with 95% confidence intervals are presented.

According to the study design of DREAMM-7, patients who discontinued study treatment were assessed at the end of treatment and at the last follow-up visit. Although patients were allowed to continue completing PRO assessments per the protocol schedule after treatment discontinuation, there was a drop in PRO data collection beyond this point. As treatment discontinuation increased over time, the extent of missing data also naturally increased, especially at later visits. This pattern of missingness was expected and reflects the real-world progression of patients in the trial. Missing values were not imputed in the analyses, and although patient characteristics were not compared between those with and without missing EQ-5D data, a sensitivity analysis was conducted to assess the potential impact of missing data on QoL estimates. Since compliance with EQ-5D completion declined over time, the proportion of missing EQ-5D data was expected to increase. This may have introduced bias into the estimation of QoL, as EQ-5D utility scores could appear to improve over time if derived only from a subset of patients with an increasing proportion of healthier individuals. To address this potential bias, analyses were performed using data from visits with at least 50% of non-missing EQ-5D values. The mean utility scores obtained were consistent with those from the main analysis.

The utility estimates become unstable at later time points primarily due to a substantial reduction in sample size caused by treatment discontinuation, patient drop-out, or loss to follow-up. In this context, stability is defined by the precision of the estimate. The basis for this assessment is that estimates derived from smaller sample sizes are less precise and subject to greater uncertainty. The empirical observation supporting the assessment is the progressive widening of the 95% CIs at later time points, as shown in **Error! Reference source not found.** below. These wider CIs signify decreased precision and hence lower stability of the mean utility estimates.

[redacted]

The EQ-5D-3L data from DREAMM-7 have been indexed with Danish preference weights based on Wittrup-Jensen et al. 2009 [75]. The model applies age-adjustment to the HRQoL data in alignment with the method guidance from the DMC [76], and includes the functionality to use treatment-specific health state utility values for the PF state derived from DREAMM-7.

[redacted]

The resulting disease-specific utility values associated with the model health states are presented in Table 23:.

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

The impact of treatment-related AEs on HRQoL is incorporated in the model as a one-off QALY loss for each AE and applied on an absolute (rather than relative) basis.

AE disutilities are applied in the first model cycle for patients entering the model, under the assumption that AEs are likely to occur very soon after treatment initiation and only require acute care, except for eye-related AEs which are applied in the BVd arm only. For eye-related AEs, a QALY loss is applied to the proportion of patients on-treatment

experiencing eye-related AEs each cycle until BVd treatment discontinuation as eye-related AEs can continue over the course of BM treatment.

In the model base case, only Grade 3+ eye-related AEs are considered in the analysis, however the model includes functionality to consider Grade 2+ eye-related AEs. A summary of the AE disutility estimates (applied in the first model cycle) and eye-related AE disutility estimates (applied only to patients receiving BVd until discontinuation) are presented in Table 23:. The disutilities included are the ones deemed relevant by input from clinical expert.

10.2.3 HSUV results

The health state utility values and AE disutilities are listed in Table 23:. Individual patient EQ-5D utility scores reported in DREAMM-7 are analysed using mixed-effects linear regression, incorporating all available EQ-5D measurements across all visits. The estimated regression coefficients obtained from the best fitting model are used as an estimate of the disutility resulting from progression, relative to the mean utility associated with the 'baseline profile' of PF patients, allowing PF and PD health state utility values to be derived. Since the disutilities used to inform AEs are not based on Danish value tariffs, there are some uncertainties when comparing them to the observed results from DREAMM-7 that have been converted to the Danish value tariffs. However, due to the paucity of available data these values were included in the base case analysis. Only the disutilities that require treatment is included in the model and is informed by input from a Danish clinical expert. In the model, the incidences of AE disutilities presented in the 'Quality of life inputs' sheet is linked to the probability of experiencing an AE in the 'Costs inputs' sheet and are sourced from DREAMM-7 and POLLUX trial.

Table 23: Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff used	Comments
HSUV health state				
HSUV PFS (on-tx)	0.799 [0.790-0.810]	EQ-5D-3L	DK	Estimate is based on mean of both trial arms. DREAMM-7 data on file
HSUV PFS (off-tx)	0.800 [0.780-0.820]	EQ-5D-3L	DK	Estimate is based on mean of both trial arms. DREAMM-7 data on file
HSUV PD	0.775 [0.750-0.800]	EQ-5D-3L	DK	Estimate is based on mean of both trial arms. DREAMM-7 data on file

HSUV treatment specific (PFS on-tx and off-tx only)				
HSUV BVd	0.810 [0.790-0.830]	EQ-5D-3L	DK	Source: DREAMM-7 data on file
HSUV DVd	0.790 [0.770-0.810]	EQ-5D-3L	DK	Source: DREAMM-7 data on file
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility				
Neutropenia	0.15	EQ-5D	UK	[41]
Anemia	0.31	EQ-5D	UK	[41]
Thrombocytopenia	0.31	EQ-5D	UK	[41]
Lymphopenia	0.07	EQ-5D	UK	[43]
Fatigue	0.12	EQ-5D	UK	[41]
Keratopathy (grade 2 only)	0.07	EQ-5D	UK	Assumed to be the same as dry eyes. [44]
Blurred vision (grade 2 only)	0.07	EQ-5D	UK	Assumed to be the same as dry eyes. [44]
Dry eyes (grade 2 only)	0.07	EQ-5D	UK	[44]
Keratopathy (grade 3+)	0.16	EQ-5D	UK	Assumed to be the same as dry eyes. [44]
Blurred vision (grade 3+)	0.16	EQ-5D	UK	Assumed to be the same as dry eyes. [44]
Dry eyes (grade 3+)	0.16	EQ-5D	UK	[44]

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.3.1 Study design

10.3.2 Data collection

10.3.3 HRQoL Results

10.3.4 HSUV and disutility results

Table 24: Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 25: Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

To estimate the resource use and associated costs, data from DREAMM-7, the available SmPCs of all included medicines, input from a Danish clinical expert, assumptions and Danish clinical guidelines were included. A description of each cost element and how it was valued is presented in the following sections.

11.1 Medicines - intervention and comparator

For BM, 100 mg and 70 mg vials are available in the base case to minimize wastage. For comparators where multiple sizes are available, the pack size most aligned to the comparator dosing regimen are selected. The model includes functionality to include or exclude wastage. When wastage is assumed, Method of Moments (MoM) calculations derive the number of vials needed per cycle based on weight or BSA. Wastage is included in the model base-case. In the base case, wastage is applied to 100% of administrations.

For oral treatments, when wastage is not included, the acquisition cost is calculated by multiplying the listed price per capsule by the exact number of capsules per dose without RDI applied. When wastage is included, the acquisition cost is calculated by multiplying the cost per unit (capsule) by the number of capsules per dose without RDI applied rounded up to the nearest whole capsule.

For IV and SC treatments, when wastage is not included, the acquisition cost is calculated by multiplying the listed price per vial by the exact number of vials required per dose. When wastage is included, the model uses MoM. This uses the patients' weight and body surface area from the DREAMM-7 trial, and dose to determine the number of vials required for treatment. For BM and daratumumab, the dose is not adjusted by RDI as IPD are used to inform dosing, but for other comparators the dose is adjusted by RDI.

The MoM calculation assumes the patients' weight and BSA are distributed according to the log-normal distribution. Therefore, the dose patients receive per cycle is also

assumed to be log-normally distributed. The cost of vials for each dose is calculated by multiplying the number of whole vials required by the vial unit cost. For each dose, the cost of vials is weighed by multiplying the cost of vials by the distribution of each dose. The sum of the weighted costs per vial calculates the MoM acquisition cost per administration.

Table 26: Medicines used in the model

	Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
BVd	**Belantamab mafodotin**	Informed by IPD	N/A	Informed by IPD	No
	Bortezomib	1.3 mg	79 %	Treatment cycles 1-8: days 1,4,8 and 11	No
	Dexamethasone	20 mg	89 %	Treatment cycles 1-8: days 1, 2, 4, 5, 8, 9, 11 and 12	No
DVd	**Daratumumab**	Informed by IPD	N/A	Informed by IPD	No
	Bortezomib	1.3 mg	79 %	Treatment cycles 1-9: days 1, 4, 8 and 11	No
	Dexamethasone	20 mg	89 %	Treatment cycles 1-9: days 1, 2, 4, 5, 8, 9, 11 and 12	No
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

11.1.1 IPD calculation

IPD is used in the model base case for BM or daratumumab as the actual dose received. The IPD provide weekly data detailing the number of patients on-treatment, the number of patients receiving any BM/daratumumab dose and number of patients receiving each BM/daratumumab dose. The doses of BM administered in DREAMM-7 are: <1.7 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2.0 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg and >2.7 mg/kg. The doses of daratumumab administered in DREAMM- 7 are: <8 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 12 mg/kg, 13

mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg and >18 mg/kg. In Danish clinical practice, daratumumab is primarily administered subcutaneously. As a result of this, the distribution is used to adjust the subcutaneous dose of 1800 mg.

For each weekly cycle, the percentage of patients receiving each dose (listed above) as a proportion of the number of patients on-treatment is calculated to inform the BM/daratumumab acquisition cost per cycle. When the number of patients on BM/daratumumab is less than 50, the percentage of patients receiving each dose is calculated using the total number of patients on-treatment and the total number of patients receiving each dose in the remaining IPD weeks. This is used to extrapolate the dosing after the timepoint where there are less than 50 patients remaining on BM/daratumumab. This is because the percentage of patients receiving each dose as a proportion of the number of patients on treatment may destabilize when the number on-treatment is low. The percentage of patients receiving each dose as a proportion of number of patients is stable with 50 patients on-treatment, after which it becomes increasingly unstable. Using the total number of patients on-treatment and the total number of patients receiving each dose in the remaining IPD weeks ensure the percentage of patients receiving each dose is stable.

In the model, the 'Belamaf dosing data' tab, starting at cell AA33, provides the number of patients who received a specific dose during a given week for BM. For daratumumab, this is visible in the 'Daratumumab dosing data' tab, starting at cell AY62.

The percentage of patients receiving each dose is used to calculate the weighted BM/daratumumab acquisition cost per cycle for each dose, which is used to calculate the total BM/daratumumab acquisition cost per cycle. The per cycle BM/daratumumab acquisition cost X mg/kg is calculated as follows:

*X mg/kg acquisition cost per cycle = % of patients receiving X mg/kg * acquisition cost of X mg/kg*

11.1.2 Time-varying RDI and median RDI for BM

For BM, the model also includes the option to account for dose delays and reduction using median RDIs from the DREAMM-7 trial reported in 12-week intervals to capture the changes in dose intensity over time. The median BM RDIs for each of the 12-week periods are presented in Table - VII.

Table - VII: BM time-varying RDI

Week	RDI
1-12	69.1%
13-24	46.5%
25-36	47.1%
37-48	43.0%
49-60	41.2%
61-72	41.6%
73-84	40.3%
85-96	34.4%
97-108	35.8%
109-120	32.8%
121-132	34.5%
133-144	29.9%
145-156	35.8%
157-168	30.6%
169-180	34.1%
181-192	28.2%
193-204	32.3%
205-216	44.8%
217-228	37.3%

For each 12-week period the RDI is applied to the SmPC dose for BM to calculate the acquisition cost per administration which informs the BVd acquisition cost per cycle. When wastage is applied, each 12-week period uses independent method of moment calculations to estimate the average number of vials required for each 12-week RDI. Furthermore, the model also includes the option for dosing to be based on the label, using the median RDI for BM from the IA2 data cut of 51%.

While the model provides flexibility to incorporate dosing methodologies based on median RDI or time-varying RDI, these approaches are not selected as the base case for their inherent limitations in accurately capturing long-term dosing dynamics and treatment patterns observed in clinical practice. The median RDI is limited in its ability to represent the evolving dose intensity of BM over time. Specifically, median RDI reflects the dose intensity at discrete intervals during the trial period but is overly influenced by the earlier time points in follow-up, where a greater proportion of patients remain on treatment. This results in a skewed representation of dosing patterns that does not adequately account for the cumulative effects of dose delays, reductions and discontinuations that occur later in the treatment pathway. Similarly, the time-varying RDI approach offers a dynamic perspective by accounting for changes in dose intensity

over time. However, it does not sufficiently capture individual-level variability in dosing patterns that are fundamental to understanding real-world treatment practices. While it provides additional granularity compared to median RDI, it still relies on aggregated trial data that may fail to represent long-term trends in dose adjustments and discontinuations. Nevertheless, the inclusion of median RDI and time-varying RDI as alternative approaches serves as valuable exploratory insights and allow for transparency in evaluating how different dosing assumptions influence the model outcomes, while ultimately underscoring the appropriateness of the IPD approach as the most reliable and data-driven methodology.

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Administration costs were included for all IV and SC treatments at the hospital. The BM and daratumumab administration cost per cycle was calculated using IPD by multiplying the percentage of patients receiving a dose as proportion of the number of patients on-treatment by the BM and daratumumab administration unit cost.

Table 27: Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	Informed by IPD	2,136	17MA98 A: DC900 P: BWAA62	DRG 2025
SC injection	Informed by IPD	2,136	17MA98 A: DC900 P: BWAA31	DRG 2025

11.4 Disease management costs

The frequency and unit costs for disease management used in the model are presented in Table 28. The frequency of the activities was divided into PFS (on-tx), PFS (off-tx) and PD. The resource use for disease management from TA897 [43], which reported frequency of routine follow-up care for pre- and post-progression patients, was presented to the Danish clinical expert. The Danish clinical expert confirmed that the resource use for hematologist visits and blood tests was in line with Danish clinical practice, thus included in the model. The pre-progression resource use informed both the PFS (on-tx) and PFS (off-tx) in the model. The resource use of hematologist visits and

blood tests were assumed to be equal across the intervention and comparators. For BVd, the treatment specific resource use of eyesight tests and slit lamp tests were also included, informed by the SmPC for BM. No cost associated with the slit lamp test was included, as it was assumed to be examined during the same consultation as the eyesight test. For daratumumab, the treatment specific resource use of a blood test to determine blood type was also included.

Table 28: Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Haematologist visit	PFS (on-tx): Every month PFS (off-tx): Every month PD: Every third month	2,136	17MA98 Mand, 70år, planlagt, varighed <12 timer. A: DC900	DRG 2025
Blood test	PFS (on-tx): Every month PFS (off-tx): Every month PD: Every 18 days	1,494	23MA04*	DRG 2025
Eyesight test (BM only)	Before each of the first 4 doses (frequency depending on cycle length)	1,501	02PR02 Mand, 70år, planlagt, varighed <12 timer. A: DC900, P: UCXA	DRG 2025
Blood test to determine blood type (daratumumab only)	Singular event	1,494	23MA04*	DRG 2025

*: The DRG code for blood tests was selected in line with other applications. Alternatively, the cost of laboratory analysis of the blood test could have been applied (analysis code: NPU17675, DKK 577), however, this only covers the cost of the analysis and does not cover the cost of blood drawing in the clinic. Reducing the cost of the blood test would favor BM by reducing the ICERs slightly.

11.5 Costs associated with management of adverse events

The model considers how treatment-related AEs impact the cost and quality of life of patients. In line with existing cost-effectiveness analyses in MM, the model considered Grade ≥3 AEs only. AEs were incorporated as one-off events and the impact was

attributed to the first cycle of treatment for patients entering the model, under the assumption that AEs are likely to occur very soon after treatment initiation and not require long term care. As an exception, it is assumed that ocular-related AEs during BVd treatment continue for the duration of treatment and therefore disutilities for these AEs continue to accrue until treatment discontinuation. No unit cost has been assigned to the ocular AEs, as no resource use is expected to be required for treating these. The unit costs included in the model are presented in Table 29.

Table 29: Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Neutropenia	Mand, 70år, planlagt, varighed <12 timer. A:DD709 B: DC900	DKK 2,208 (16MA98)
Anemia	Mand, 70år, planlagt, varighed <12 timer. A: DC900 Procedure: BOQA0	DKK 4,221 (16PR02)
Febrile neutropenia	Mand, 70år, akut, varighed >12 timer. A: DD709 B: DC900	DKK 57,027 (17MA02)
Pneumonia	Mand, 70år, akut, varighed >12 timer. A: DJ139 B: DC900	DKK 57,027 (17MA02)

11.6 Subsequent treatment costs

After treatment with the intervention or comparator patients may progress and be treated with a subsequent line of therapy. In the model, a one-off cost was applied for up to two lines of subsequent therapy. The one-off subsequent treatment cost was calculated using the proportion of patients who required a first and second subsequent treatment, the distribution of first and second subsequent treatments required for each treatment arm, and the treatment cost of each subsequent treatment. The proportion of patients who progress and receive subsequent treatment was informed by a Danish clinical expert and Szabo et al. 2019, which assumes a 22% median decrease in the number of patients per subsequent line of therapy. This results in 78% of 2L patients were assumed to receive a 3L treatment (first subsequent treatment), and 61% of 2L patients were assumed to receive a 4L treatment (second subsequent treatment) [17]. The proportion of patients who progress and receive subsequent treatment was assumed to be equal across the intervention and comparators.

The distribution of first and second subsequent treatments was informed by a Danish clinical expert, presented in Table - VIII below:

Table - VIII: Distribution of subsequent treatments

Subsequent Treatments		Treatment Arm		
		BVd	DVd	[redacted]
First subsequent treatment	DRd	50%	0%	[redacted]
	Pd	25%	50%	[redacted]
	PVd	0%	0%	[redacted]
	Kd	25%	50%	[redacted]
	Teclistamab	0%	0%	[redacted]
Second subsequent treatment	Pd	20%	20%	[redacted]
	Kd	20%	20%	[redacted]
	Teclistamab	60%	60%	[redacted]

Table 30: Medicines of subsequent treatments

	Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
DRd	**Daratumumab**	1800 mg	100%	Cycle length: 28 days Treatment cycles 1 to 2: 4 administrations per cycle (days 1, 8, 15, 22) Treatment cycles 3 to 6: 2 administrations per cycle (days 1, 15) Treatment cycles 7+: 1 administration per cycle (day 1 only)	No
	Lenalidomide	25 mg	100%	Cycle length: 28 days All treatment cycles: 21 administrations (days 1-21)	No
	Dexamethasone	40 mg	100%	Cycle length: 28 days All treatment cycles: 4 administrations (days 1, 8, 15, 22)	No
DVd	**Daratumumab**	1800 mg	100%	Cycle length: 28 days Treatment cycles 1 to 3: 3	No

				administrations per cycle (days 1, 8, 15) Treatment cycles 4 to 9: 1 administration per cycle (day 1 only) Treatment cycles 10+: 1 administration per cycle (day 1 only)	
	Bortezomib	1.3 mg/m^2	100%	Cycle length: 21 days Treatment cycles 1-9: 4 administrations (days 1, 4, 8 and 11)	No
	Dexamethasone	20 mg	100%	Cycle length: 21 days Treatment cycles 1-9: 8 administrations (days 1, 2, 4, 5, 8, 9, 11 and 12)	No
Pd	**Pomalidomide**	4 mg	100%	Cycle length: 28 days All treatment cycles: 21 administrations per cycle	No
	Dexamethasone	40 mg	100%	Cycle length: 28 days All treatment cycles: 4 administrations per cycle	No
PVd	**Pomalidomide**	4 mg	100%	Cycle length: 21 days All treatment cycles: 14 administrations per cycle	No
	Bortezomib	1.3 mg/m^2	100%	Cycle length: 21 days Treatment cycles 1 to 8: 4 administrations per cycle (days 1, 4, 8 and 11) Treatment cycles 9+: 2 administrations per cycle (days 1 and 8)	No
	Dexamethasone	20 mg	100%	Cycle length: 21 days	No

				Treatment cycles 1 to 8: 8 administrations per cycle (days 1, 2, 4, 5, 8, 9, 11 and 12) Treatment cycles 9+: 4 administrations per cycle (days 1, 2, 8 and 9)	
Kd	**Carfilzomib**	First two administrations: 20 mg/m^2 Remaining administrations: 56 mg/m^2	100%	Cycle length: 28 days All treatment cycles: 6 administrations per cycle	No
	Dexamethasone	20 mg	100%	Cycle length: 28 days All treatment cycles: 8 administrations per cycle	No
Rd	**Lenalidomide**	25 mg	100%	Cycle length: 28 days All treatment cycles: 21 administrations per cycle	No
	Dexamethasone	40 mg	100%	Cycle length: 28 days All treatment cycles: 4 administrations per cycle	No
	Teclistamab	First administration: 0.06 mg/kg Second administrati	100%	Cycle length: 7 days Treatment cycle 1: 3 administrations (days 1, 3 and 5) Treatment cycle 2+: 1 administration per cycle	No

	on: 0.30 mg/kg Remaining administrations: 1.50 mg/kg

11.7 Patient costs

Patient-related time use and costs in relation to treatment and transportation were included in the model, in line with DMC guidelines. Inputs provided for patient-related time use was informed by a Danish clinical expert. The costs related to the time spent were based on the DMC catalogue for unit costs: The unit cost of 188 DKK was applied for the value of one patient hour, and a unit cost of 140 DKK was applied for transportation costs. The time of transportation for a hospital visit was assumed to be 1 hour, based on an assumed 30-minute drive back and forth to the hospital.

For treatment with BM during cycle 1-8, no transportation per administration was included, as administration was assumed to occur at the same visit as bortezomib. The average patient time was 2.75 hours with patient time for bortezomib coadministration considered. For treatment with BM during cycles 9+, transportation was included. No patient cost for dexamethasone was included, as it was assumed that the patient takes the treatment themselves at home.

For treatment with DVd, during cycles 1-3, only a single administration of daratumumab was assumed to not be given on the same day as administration of bortezomib, resulting in only 0.33 hours spent on transportation per administration. No transportation was included during cycles 4-9 for daratumumab to avoid double counting. For cycles 10+, transportation was included. The average patient time was 2.5 hours with patient time for bortezomib coadministration considered.

Patient costs used for the subsequent treatment with teclistamab were based on the DMC evaluation of teclistamab [15], with no transportation assumed at day 3, reflecting the extension of hospitalization on day 1.

Table 31: Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Treatment with belantamab mafodotin, cycle 1-8	2.75 hours
Treatment with belantamab mafodotin, cycle 9+	3.5 hours
Treatment with belantamab mafodotin, cycle 9+, transportation	1 hour
Treatment with bortezomib	0.75 hours
Treatment with bortezomib, transportation	1 hour
Treatment with daratumumab when combined with bortezomib and dexamethasone, cycle 1-3	2.5 hours
Treatment with daratumumab when combined with bortezomib and dexamethasone, cycle 1-3, transportation	0.33 hours
Treatment with daratumumab when combined with bortezomib and dexamethasone, cycle 4-9	2.25 hours
Treatment with daratumumab	3 hours
Treatment with daratumumab, transportation	1 hour
Treatment with carfilzomib	0.75 hours
Treatment with carfilzomib, transportation	1 hour
Treatment with teclistamab, cycle 1	48 hours
Treatment with teclistamab, cycle 1, transportation	1 hour
Treatment with teclistamab, cycle 2+	4 hours
Treatment with teclistamab, cycle 2+, transportation	1 hour
Hematologist visit	0.33 hours
Blood test	0.25 hours
Eyesight test	0.25 hours
Slit lamp test	0.25 hours
Inpatient stay	48 hours
Treatment of anemia	4 hours
Treatment of neutropenia	0.17 hours
Treatment of febrile neutropenia	48 hours
Treatment of febrile neutropenia, transport	1 hour
Treatment of pneumonia	48 hours
Treatment of pneumonia, transport	1 hour

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

Table 32: Base case overview

Feature	Description
Comparator	DVd [redacted]
Type of model	4-state partitioned survival model
Time horizon	30 years (life time)
Treatment line	2nd line (2L). First and second subsequent treatment lines included (3L and 4L).
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-3L in DREAMM-7. Danish population weights from Wittrup-Jensen et al. (2009) were used to estimate health-state utility values. The remaining utility values were derived from literature.
Costs included	Treatment acquisition costs Administration costs Disease management Costs of adverse events Patient costs Transportation costs
Dosage of medicine	Based on weight, BSA, RDI and IPD
Average time on treatment	BVd: Exponential DVd: Exponential [redacted]
Parametric function for PFS	BVd: Exponential DVd: Exponential
Parametric function for OS	BVd: Exponential DVd: Exponential
Inclusion of waste	Yes
Average time in model health state PFS OS	BVd / DVd / [redacted] 50.88 months / 24.06 months / [redacted] 107.51 months / 69.19 months / [redacted]

12.1.1 Base case results

Table 33: Base case results, BVd vs DVd, discounted estimates

	BVd	DVd	Difference
Medicine costs	4,317,112 DKK	1,155,310 DKK	3,161,802 DKK

Medicine costs – co-administration	-	-	-
Administration	98,038 DKK	126,112 DKK	-28,074 DKK
Disease management costs	298,009 DKK	199,986 DKK	98,023 DKK
Costs associated with management of adverse events	5,963 DKK	2,493 DKK	3,470 DKK
Subsequent treatment costs	554,959 DKK	619,530 DKK	-64,570 DKK
Patient costs	58,686 DKK	65,773 DKK	-7,087 DKK
Palliative care costs	-	-	-
Total costs	**5,332,768 DKK**	**2,169,205 DKK**	**3,163,563 DKK**
Life years gained (PFS on treatment)	2.127	1.641	0.486
Life years gained (PFS off treatment)	1.638	0.265	1.373
Life years gained (PD)	3.408	3.010	0.398
Total life years	**7.172**	**4.916**	**2.256**
QALYs (PFS on treatment)*	[redacted]	[redacted]	[redacted]
QALYs (PFS off treatment)*	[redacted]	[redacted]	[redacted]
QALYs (PD)*	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		**1,402,232 DKK**	
Incremental cost per QALY gained (ICER)		**1,909,365 DKK**	

*: Decrements in QALY are included in health states.

[redacted]

	[redacted]	[redacted]	[redacted]
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]

Palliative care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (PFS on treatment)	[redacted]	[redacted]	[redacted]
Life years gained (PFS off treatment)	[redacted]	[redacted]	[redacted]
Life years gained (PD)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (PFS on treatment)*	[redacted]	[redacted]	[redacted]
QALYs (PFS off treatment)*	[redacted]	[redacted]	[redacted]
QALYs (PD)*	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	
[redacted]		[redacted]	

*: Decrements in QALY are included in health states.

12.2 Sensitivity analyses

Deterministic one-way sensitivity analyses (OWSA) and probabilistic sensitivity analysis (PSA) were conducted to explore the level of uncertainty in the model results.

12.2.1 Deterministic sensitivity analyses

The OWSA involved varying one parameter at a time and assessing the subsequent impact on the incremental benefits and costs. By varying each parameter individually, the sensitivity of the model results to that parameter were assessed. The OWSA has been conducted by allocating a 'low' and a 'high' value to each parameter; the low value is the lower bound of the 97.5% CI, the high value is the upper bound of the 97.5% CI. In the absence of CI data, the standard error is assumed to be 20% of the mean for all variables. The estimated standard error is used to predict the upper and lower bound of the parameters' CI.

Table 34: One-way sensitivity analyses results

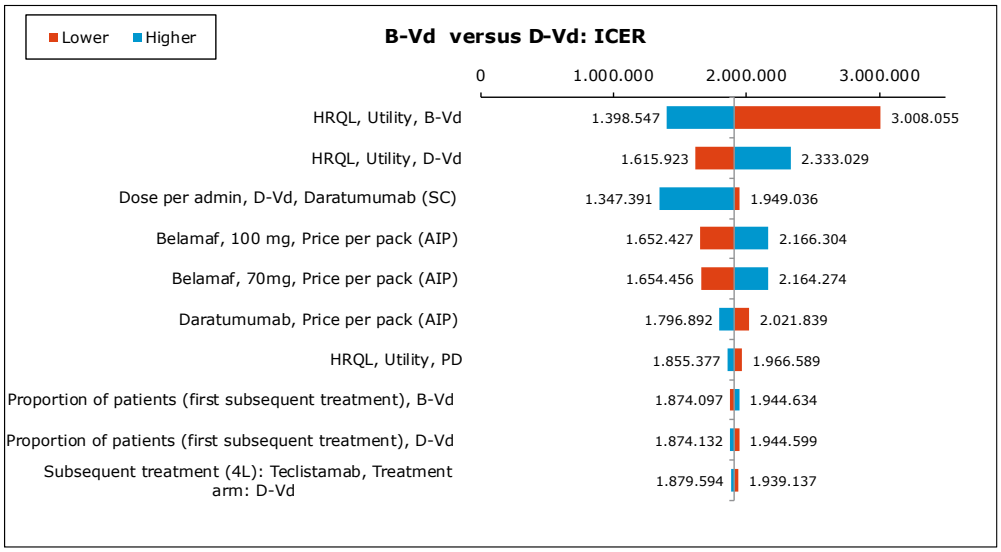
	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY) (Lower/higher)

Base case, BVd vs DVd			3,163,563	1.66	1,909,365
HRQL, Utility, BVd	-/+ 20%	See table note	3,163,563 / 3,163,563	1.05/2.26	3,008,055 / 1,398,547
HRQL, Utility, DVd	-/+ 20%	See table note	3,163,563 / 3,163,563	1.96/1.36	1,615,923 / 2,333,029
Dose per admin, DVd, Daratumumab (SC)	-/+ 20%	See table note	3,229,291 / 2,232,446	1.66/1.66	1,949,036 / 1,347,391
Belamaf, 100 mg, Price per pack (AIP)	-/+ 20%	See table note	2,737,850 / 3,589,276	1.66/1.66	1,652,427 / 2,166,304
Belamaf, 70 mg, Price per pack (AIP)	-/+ 20%	See table note	2,741,213 / 3,585,913	1.66/1.66	1,654,456 / 2,164,274
Daratumumab, Price per pack (AIP)	-/+ 20%	See table note	3,349,917 / 2,977,209	1.66/1.66	2,021,839 / 1,796,892
HRQL, Utility, PD	-/+ 20%	See table note	3,163,563 / 3,163,563	1.61/1.71	1,966,589 / 1,855,377
Proportion of patients (first subsequent treatment), BVd	-/+ 20%	See table note	3,105,128 / 3,221,998	1.66/1.66	1,874,097 / 1,944,634
Proportion of patients (first subsequent treatment), DVd	-/+ 20%	See table note	3,221,940 / 3,105,186	1.66/1.66	1,944,599 / 1,874,132
Subsequent treatment (4L): Teclistamab, Treatment arm: DVd	-/+ 20%	See table note	3,212,890 / 3,114,235	1.66/1.66	1,939,137 / 1,879,594
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

*: To perform impact assessment of reducing or increasing the value of this parameter.

Figure 17: Tornado diagram for OWSA with the ten most influential parameters, BVd vs DVd



[redacted]

[redacted]

12.2.2 [redacted]Probabilistic sensitivity analyses

The PSA involved drawing a value at random for each variable from its uncertainty distribution. This has been performed for each parameter simultaneously and the resulting incremental results recorded; this constitutes one 'simulation'. One thousand simulations (n=1000) were performed, which gave a distribution of incremental results, and consequently, an assessment of the robustness of the cost-effectiveness results. The beta distribution was used to vary parameters that needed to remain bounded between 0-1 (i.e. proportions, utilities and disutilities). The gamma distribution and normal distribution were used for values between 0-infinity. The normal distribution was used to vary the hazard ratios, and the gamma distribution was used to vary all other remaining

parameters. An overview of the PSA data and a description of how correlation between the model parameters was handled in the model is presented in Appendix G.

Figure 18: Cost-effectiveness plane, BVd vs DVd

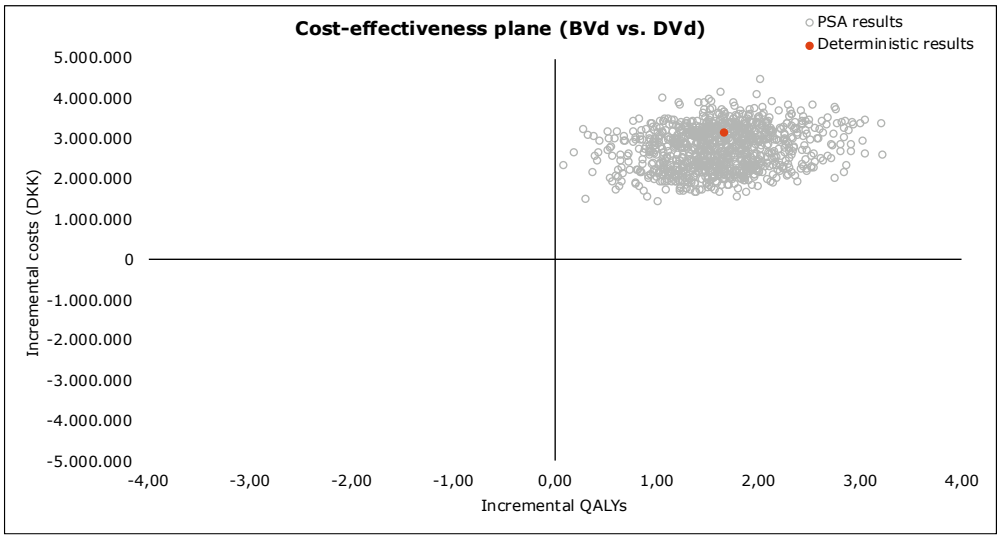
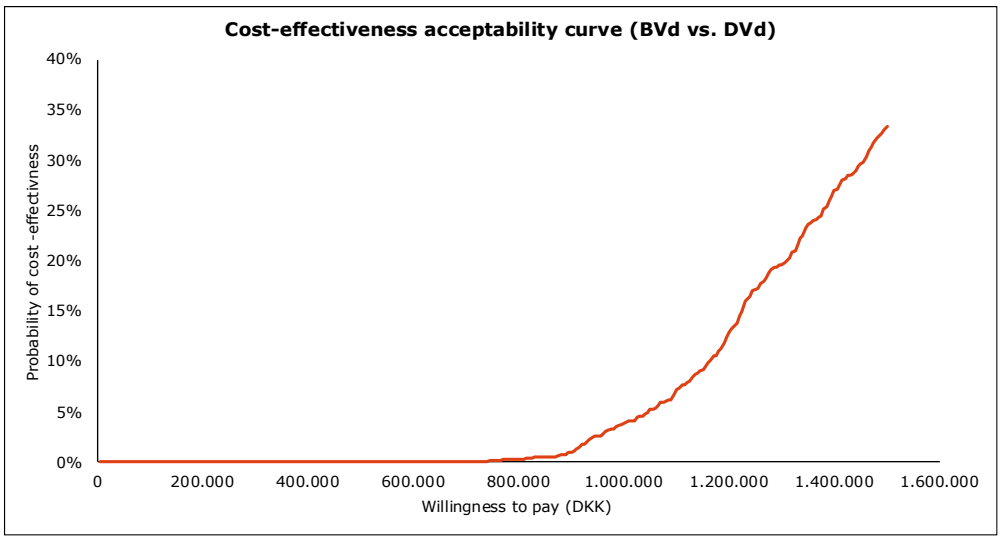


Figure 19: Cost-effectiveness acceptability curve, BVd vs DVd



[redacted]

[redacted]

[redacted]

13. Budget impact analysis

The budget impact analysis was performed using the same patient numbers described in section 3.3. Based on input from Danish clinical expert, the current market share is believed to be 30 % for DVd and 70 % for DRd for all five years. The proposed market share given a DMC recommendation of BVd is 65 % for BVd, 35 % for DRd and 0 % for

DVd for all five years. If the DMC does not recommend BVd as an option for standard treatment, the market share is assumed to be 0% for BVd.

Number of patients (including assumptions of market share)

Table 35: Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
BVd	193	218	192	206	206
DVd	0	0	0	0	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
BVd	0	0	0	0	0
DVd	89	101	89	95	95
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 36: Expected budget impact of recommending the medicine for the indication, not discounted, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 37: Main characteristic of DREAMM-7 and POLLUX

Trial name: DREAMM-7	NCT number: NCT04246047
Objective	To compare the efficacy of belantamab mafodotin in combination with bortezomib and dexamethasone (bor/dex) with that of daratumumab in combination with bor/dex in participants with RRMM
Publications – title, author, journal, year	Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma. Hungria et al. N Engl J Med. 2024;391 (5):393-407 Belantamab Mafodotin, Bortezomib, and Dexamethasone Vs Daratumumab, Bortezomib, and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Overall Survival Analysis and Updated Efficacy Outcomes of the Phase 3 Dreamm-7 Trial. Hungria et al. *Blood* (2024) 144 (Supplement 1): 772 (ASH congress 2024)
Study type and design	A multicenter Phase III, randomized, open-label study evaluating the efficacy and safety of the combination of belantamab mafodotin and bor/dex compared with the standard of care combination of daratumumab and bor/dex in participants with RRMM Following screening, participants were stratified based on the number of prior LoT (1 vs 2/3 vs ≥4), prior bortezomib (yes vs no), and the Revised International Staging System (R-ISS I vs II/III), and centrally randomized in a 1:1 ratio to either arm. No more than 50% of participants with 2 or more prior lines of treatment were enrolled. No cross-over was allowed
Sample size (n)	494 participants randomized

Main inclusion criteria	• Confirmed diagnosis of multiple myeloma as defined by the International Myeloma Working Group (IMWG) criteria.
	• Previously treated with at least 1 prior line of multiple myeloma (MM) therapy and must have documented disease progression during or after their most recent therapy.
	• Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
	• Must have at least 1 aspect of measurable disease, defined as one of the following:
	  ○ Urine M-protein excretion >=200 mg per 24-hour, or
	  ○ Serum M-protein concentration >=0.5 grams per deciliter (g/dL), or
	  ○ Serum free light chain (FLC) assay: involved FLC level >=10 mg per dL (>=100 mg per liter) and an abnormal serum free light chain ratio (<0.26 or >1.65).
	• All prior treatment-related toxicities (defined by National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] version 5.0) must be <=Grade 1 at the time of enrollment, except for alopecia.
	• Adequate organ function

Main exclusion criteria	• Intolerant to daratumumab. • Refractory to daratumumab or any other anti-CD38 therapy (defined as progressive disease during treatment with anti-CD38 therapy, or within 60 days of completing that treatment). • Intolerant to bortezomib, or refractory to bortezomib (defined as progressive disease during treatment with a bortezomib-containing regimen of 1.3 mg/m^2 twice weekly, or within 60 days of completing that treatment). Note: participants with progressive disease during treatment with a weekly bortezomib regimen are allowed. • Ongoing Grade 2 or higher peripheral neuropathy or neuropathic pain. • Prior treatment with anti-B-cell maturation antigen (anti-BCMA) therapy. • Prior allogenic stem cell transplant. • Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions, including renal, liver, cardiovascular, or certain prior malignancies. • Corneal epithelial disease.
Intervention	Belantamab mafodotin was administered intravenously (IV) at the dose of 2.5 mg/kg on Day 1 of every 21-day cycle. Prophylaxis to mitigate ocular events was instituted for all participants. Bortezomib 1.3 mg/m2 was administered subcutaneously (SC) on Days 1, 4, 8, and 11 of every 21-day cycle for a total of 8 cycles. Bortezomib was to be administered approximately 1 hour after the belantamab mafodotin infusion was complete. Dexamethasone 20 mg (orally [PO] or IV) was administered on the day of and the day after bortezomib treatment. Starting dose of dexamethasone was reduced to 10 mg for participants older than 75 years of age, who had a body-mass index of <18.5 kg/m2, who had previous unacceptable side effects associated with glucocorticoid therapy, or who were unable to tolerate the starting dose. On days where bor/dex administration coincided with administration of belantamab mafodotin, dexamethasone was to be administered PO or IV prior to the infusion of belantamab mafodotin. N = 243 patients
Comparator(s)	Daratumumab 16 mg/kg IV was administered according to the approved label schedule in combination with bor/dex weekly for Cycles 1 through 3 (Weeks 1 to 9) (21-day cycles, total of 9 doses), on Day 1 of Cycles 4 thorough 8 (Weeks 10 to 24) (21-day cycles, total of 5 doses), and then every 4 weeks from Cycle 9 (Week 25) onwards (28-day cycles). For the first dose of daratumumab dosing at Week 1 only, the single infusion of daratumumab could be split over 2 days. Bortezomib and dexamethasone dosing schedule in Arm B was same as that of Arm A N = 251 patients
Follow-up time	Median follow-up of 28.2 months (range, 0.1 to 40.0)
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	**Primary endpoints:** • Progression-Free Survival (PFS), defined as the time from the date of randomization until the earliest date of documented disease progression or death due to any cause **Secondary endpoints:** • Overall Survival (OS), defined as the time from the date of randomization until the date of death due to any cause • Duration of Response (DoR), defined as the time from first documented evidence of PR or better until progressive disease (PD) or death due to any cause • Minimal Residual Disease (MRD) negativity rate, defined as the percentage of participants who are MRD negative by next-generation sequencing • Complete Response Rate (CRR), defined as the percentage of participants with a confirmed complete response (CR) or better (i.e., CR, sCR) • Overall Response Rate (ORR), defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., PR, VGPR, CR, sCR) • Clinical Benefit Rate (CBR), defined as the percentage of participants with a confirmed minimal response (MR) or better per IMWG • Time to Response (TTR), defined as the time between the date of randomization and the first documented evidence of response (PR or better) among participants who achieve confirmed PR or better • Time to Progression (TTP), defined as the time from the date of randomization until the earliest date of documented PD or death due to PD • PFS2, defined as time from randomization to disease progression after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new antimyeloma therapy cannot be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier • Incidence of adverse events (AEs) and changes in laboratory parameters • Ocular findings on ophthalmic exam • Plasma concentrations of belantamab mafodotin, and cys-mcMMAF • Incidence and titers of ADAs against belantamab mafodotin • Maximum post-baseline PRO-CTCAE score for each item attribute • Change from baseline in HRQOL as measured by EORTC QLQC30 and EORTC IL52 (disease symptoms domain from the EORTC QLQ-MY20) **Exploratory endpoints:**

	• Time to Best Response (TTBR), defined as the interval of time between the date of randomization and the earliest date of achieving best response among participants with a confirmed PR or better • VGPR rate, defined as the percentage of participants with a confirmed Very Good Partial Response (VGPR) or better (i.e., VGPR, CR, sCR) • Sustained MRD negativity rate: defined as the percentage of participants with MRD negativity confirmed by NGS minimum of one year apart, per IMWG criteria • Changes in safety assessments, including vital signs • Changes from baseline in symptoms and related impacts as measured by OSDI • Change from baseline in EQ-5D-3L • Change from baseline in PGIS and change in PGIC over time • Change from baseline in FACT-GP5 • Imaging plus MRD-negativity rate, defined as the percentage of participants who are MRD negative by NGS and who have no evidence of disease on PET-CT • Number of office/outpatient/hospital clinic visits by specialty • Number of emergency room/urgent care facility visits • Number and duration of in-patient hospitalizations (total nights, including duration by wards [intensive care unit vs. general ward]) • Use of supportive care medication • Derived pharmacokinetic parameter values of belantamab mafodotin, and cys-mcMMAF, as data permit • Belantamab mafodotin exposure (e.g., concentration, Cmax, or AUC) vs. efficacy and safety endpoints (e.g., PFS, ORR, CRR, corneal events) • Assess various biomarkers at baseline and on-treatment, by tumor and blood-based analysis of DNA, RNA, and protein including but not limited to evaluating baseline BCMA expression and/or immune status in tumor tissue and in the tumor microenvironment and/or serum soluble BCMA levels, and their relationship to clinical response
Method of analysis	The Intent-to-Treat (ITT) analysis set will be used for all study population analyses and efficacy analyses, unless otherwise specified and Safety analysis set will be used for all safety analyses. The stratified log-rank test and stratified Cox proportional hazards models will include the randomization stratification factors as “strata”. Unless otherwise specified, the stratification factors entered for randomization will be used in the primary analysis. If there is any mis-stratification, a supplementary analysis will be performed using the stratification data based on the clinical database.

Subgroup analyses	The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered. • If the percentage of participants is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial. • If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup. Due to the expected low number of events per strata, subgroup analyses will not be stratified and analysis models will not include stratification factors as covariates. Otherwise, subgroup analyses will be performed similarly to the primary analysis method including only the participants within the relevant subgroup category. P-values will not be presented. All subgroup analyses will be based on the clinical database using eCRF or vendor data (and not randomized/RTSM strata). The following subgroup analyses (see below) will be performed to compare the primary estimand of PFS between treatments, based on IRC-assessed response, as well as the primary estimand of OS between treatments, if data permit.
Other relevant information	N/A

Subgroup	Categories
Prior Lines of Therapy	1 vs. 2/3 vs. ≥4, and 1 vs. >1
Prior Bortezomib	No, Yes
Prior Lenalidomide	No, Yes
Refractory to Lenalidomide	No, Yes
R-ISS Stage	I vs. II/III
Age	<65 years, 65-<75 years, ≥75 years
Gender	Female, Male
Ethnicity	Hispanic, non-Hispanic
Race	White, Black or African American, Other
Region	North America, Europe, North East Asia [Japan, China and Republic of Korea], Rest of World (ROW)
Time to Relapse with 1 Prior Line Of Therapy	Relapse <18 months vs >=18 months
Cytogenetic Risk[1]	High Risk, Standard Risk, Missing or Not Evaluable
Extramedullary Disease	No, Yes

Trial name: POLLUX	NCT number: NCT02076009
Objective	The purpose of this study is to compare the effectiveness of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd), in terms of progression-free survival in participants with relapsed or refractory multiple myeloma.
Publications – title, author, journal, year	Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. Dimopoulos MA et al. N Engl J Med 2016 Oct 6;375(14):1319-1331 Overall Survival with Daratumumab, Lenalidomide, and Dexamethasone in Previously Treated Multiple Myeloma (POLLUX): A Randomized, Open-Label, Phase III Trial, Dimopoulos, M.A., et al., J Clin Oncol, 2023. 41(8): 1590-1599. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Bahlis NJ et al. Leukemia. 2020 Jul;34(7):1875-1884
Study type and design	Open-label, multicenter, phase 3 trial with patients who had relapsed or refractory multiple myeloma and had received one or more lines of previous therapy. Randomization (in a 1:1 ratio) was conducted by means of a central schedule and was balanced with the use of randomly permuted blocks and stratified according to the number of lines of previous therapy (1 vs. 2 or 3 vs. >3), International Staging System disease stage (I vs. II vs. III, with higher stages indicating more advanced disease.
Sample size (n)	569
Main inclusion criteria	• Must have documented multiple myeloma and measurable disease • Must have received at least 1 prior line of therapy for multiple myeloma and achieved a response (partial response or better) to at least one prior regimen • Must have documented evidence of progressive disease as defined by the International Myeloma Working Group criteria on or after their last regimen • Must have an Eastern Cooperative Oncology Group Performance Status score of 0, 1, or 2 • If a participant has received subsequent anticancer therapy (salvage therapy), the participant must have a "wash-out period" defined as 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the planned start date of daratumumab monotherapy. The only exception is the emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 milligram per day for a maximum of 4 days) before Daratumumab monotherapy • 18 Years and older

Trial name: POLLUX	NCT number: NCT02076009
Main exclusion criteria	• Has received any of the following therapies: daratumumab or other anti-CD38 therapies • Has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment • Disease shows evidence of refractoriness or intolerance to lenalidomide or if previously treated with a lenalidomide-containing regimen the participant is excluded if he or she discontinued due to any adverse event related to prior lenalidomide treatment • Has received autologous stem cell transplantation within 12 weeks before the date of randomization, or previously received an allogenic stem cell transplant (regardless of timing), or planning to undergo a stem cell transplant prior to progression of disease • History of malignancy (other than multiple myeloma) within 5 years before the first dose of daratumumab monotherapy (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or breast, or other non-invasive lesion, that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 5 years)
Intervention	Daratumumab at a dose of 16 mg/kg iv weekly (on days 1, 8, 15, and 22) for 8 weeks during cycles 1 and 2, every 2 weeks (on days 1 and 15) for 16 weeks (cycles 3 through 6), and every 4 weeks thereafter Lenalidomide at a dose of 25 mg orally on days 1 to 21 of each cycle Dexamethasone at a dose of 40 mg weekly (20 mg before infusion as prophylaxis for infusion-related reactions and 20 mg was administered the next day) N = 286
Comparator(s)	Lenalidomide at a dose of 25 mg orally on days 1 to 21 of each cycle Dexamethasone at a dose of 40 mg weekly N = 283
Follow-up time	Median follow-up at 79,7 months

Trial name: POLLUX	NCT number: NCT02076009
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	The primary end point was progression-free survival, with progression determined with the use of a validated computer algorithm that combined laboratory results (e.g., M-protein level) and applicable imaging and generated the outcome according to IMWG criteria. Time to disease progression in a time-to-event analysis, overall response rate (ORR), rate of very good partial response (VGPR) or better (comprising very good partial, complete, and stringent complete responses), rate of complete response or better (comprising complete and stringent complete responses), minimal residual disease, time to response, duration of response, and overall survival.
Method of analysis	Efficacy analyses were based on the intention-to-treat population. Progression-free survival was compared between groups on the basis of a stratified log-rank test. The Kaplan–Meier method was used to estimate the distributions and 12-month rates of progression-free survival. Hazard ratios and 95% confidence intervals were estimated with the use of a Cox regression model, with treatment as the sole explanatory variable. Stratified Cochran–Mantel–Haenszel tests were used to compare overall response rates, rates of very good partial response or better, and other binary end points. Duration of response was assessed by means of the Kaplan–Meier method.
Subgroup analyses	Prespecified subgroup analysis of PFS, OS, ORR and safety endpoints where: Age (<65 years, 65-74 years, ≥75 years), ISS disease stage (I, II, III), number of previous lines of therapy (1, 2, 3, >3), previous lenalidomide (yes/no), refractory to proteasome inhibitor (yes/no), refractory to last line of therapy (yes/no), types of multiple myelomas (IgG, IgA, serum free light chain only)
Other relevant information	The safety population included all the patients who received at least one dose of trial treatment.

Trial name: CASTOR	NCT number: NCT02136134
Objective	To evaluate the efficacy and safety of daratumumab in combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone alone in patients with relapsed or relapsed and refractory multiple myeloma
Publications – title, author, journal, year	"Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma," Antonio Palumbo et al., The New England Journal of Medicine, 2016.
Study type and design	Multicenter, randomized, open-label, active-controlled, phase 3 trial. Patients were randomly assigned 1:1 to receive either daratumumab in combination with bortezomib and dexamethasone or bortezomib and

	dexamethasone alone. Randomization was stratified by ISS disease stage, number of previous lines of therapy, and prior bortezomib treatment.
Sample size (n)	498 patients (251 in the daratumumab group and 247 in the control group)
Main inclusion criteria	Patients with relapsed or relapsed and refractory multiple myeloma. At least one previous line of therapy. Measurable disease based on serum, urine, or serum free light-chain assay.
Main exclusion criteria	Disease refractory to bortezomib or another proteasome inhibitor. Grade 2 or higher peripheral neuropathy or neuropathic pain. Severe hematologic or organ dysfunction (e.g., neutrophil count ≤1000/mm³, hemoglobin ≤7.5 g/dL, platelet count <75,000/mm³).
Intervention	Daratumumab (16 mg/kg intravenously) administered weekly during cycles 1–3, every 3 weeks during cycles 4–8, and every 4 weeks thereafter. Bortezomib (1.3 mg/m² subcutaneously) and dexamethasone (20 mg orally or intravenously) were administered over 8 cycles.
Comparator(s)	Bortezomib (1.3 mg/m² subcutaneously) and dexamethasone (20 mg orally or intravenously) administered over 8 cycles.
Follow-up time	Median follow-up of 7.4 months.
Is the study used in the health economic model?	[redacted]
Primary, secondary and exploratory endpoints	Primary endpoint: Progression-free survival. Secondary endpoints: Overall response rate, time to disease progression, very good partial response or better, complete response or better, duration of response, overall survival. Exploratory endpoints: Time to subse
Method of analysis	Intention-to-treat analysis. Kaplan–Meier method was used to estimate progression-free survival and overall survival. Stratified log-rank tests and Cox proportional hazards regression were used for treatment comparisons.
Subgroup analyses	Prespecified subgroup analyses based on ISS disease stage, number of previous lines of therapy, prior bortezomib treatment, and other baseline characteristics.
Other relevant information	

Trial name: APEX study	NCT number: NCT00048230
Objective	To compare the efficacy and safety of bortezomib with high-dose dexamethasone in patients with relapsed multiple myeloma who had received one to three previous therapies.
Publications – title, author, journal, year	"Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma," Paul G. Richardson et al., The New England Journal of Medicine, 2005.
Study type and design	Randomized (1:1), open-label, phase 3 study conducted at 93 centers in the United States, Canada, Europe, and Israel. Randomization was stratified based on the number of prior treatments, time to progression after the last treatment, and β2-microglobulin levels. Patients in the dexamethasone group were allowed to cross over to bortezomib upon disease progression.
Sample size (n)	669 patients (333 in the bortezomib group and 336 in the dexamethasone group).
Main inclusion criteria	Measurable progressive disease after one to three previous treatments. Karnofsky performance scale score ≥60. Platelet count ≥50,000/mm³, hemoglobin ≥7.5 g/dL, absolute neutrophil count ≥750/mm³, and creatinine clearance ≥20 mL/min.
Main exclusion criteria	Prior treatment with bortezomib. Disease refractory to high-dose dexamethasone. Grade 2 or higher peripheral neuropathy. Clinically significant coexisting illnesses unrelated to myeloma.
Intervention	Bortezomib (1.3 mg/m² intravenously) administered on days 1, 4, 8, and 11 for eight 3-week cycles, followed by treatment on days 1, 8, 15, and 22 for three 5-week cycles.
Comparator(s)	High-dose dexamethasone (40 mg orally) administered on days 1–4, 9–12, and 17–20 for four 5-week cycles, followed by treatment on days 1–4 for five 4-week cycles.
Follow-up time	Median follow-up of 8.3 months.
Is the study used in the health economic model?	[redacted]
Primary, secondary and exploratory endpoints	**Primary endpoint:** Time to disease progression. **Secondary endpoints:** Overall survival, one-year survival rate, response rate (complete and partial), duration of response, time to first infection (grade 3 or higher), incidence of grade 3 or higher infections, and time to first skeletal event.

Method of analysis	Intention-to-treat analysis. Kaplan–Meier method was used to estimate time to progression and survival. Stratified log-rank tests and Cox proportional hazards regression were used for treatment comparisons.
Subgroup analyses	Subgroup analyses were performed based on the number of prior treatments, time to progression after the last treatment, and β2-microglobulin levels.
Other relevant information	

Trial name: MM009	**NCT number: NCT00056160**
Objective	To evaluate the efficacy and safety of lenalidomide plus dexamethasone compared to placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma.
Publications – title, author, journal, year	"Lenalidomide plus Dexamethasone for Relapsed Multiple Myeloma in North America," Donna M. Weber et al., The New England Journal of Medicine, 2007.
Study type and design	Multicenter, double-blind, placebo-controlled, randomized phase 3 trial. Patients were randomly assigned 1:1 using a stratified permuted block randomization scheme via an interactive voice-response system. Randomization was stratified by serum β2-microglobulin levels, prior stem-cell transplantation, and the number of previous antimyeloma therapies.
Sample size (n)	353 patients (177 in the lenalidomide group and 176 in the placebo group).
Main inclusion criteria	Age ≥18 years. Progressive multiple myeloma after at least one previous treatment. Measurable disease not resistant to dexamethasone. Serum monoclonal protein level ≥0.5 g/dL or urinary Bence Jones protein level ≥0.2 g/day. Adequate organ function and performance status (ECOG ≤2).
Main exclusion criteria	Disease resistant to dexamethasone. Serum creatinine ≥2.5 mg/dL. Severe hepatic dysfunction (AST/ALT >3x ULN, bilirubin >2x ULN). Severe neutropenia or thrombocytopenia
Intervention	Lenalidomide: 25 mg orally on days 1–21 of a 28-day cycle. Dexamethasone: 40 mg orally on days 1–4, 9–12, and 17–20 for the first 4 cycles, then days 1–4 thereafter. Patients: 177 received lenalidomide plus dexamethasone.

Comparator(s)	Placebo: orally on days 1–21 of a 28-day cycle. Dexamethasone: same dosing schedule as the intervention group. Patients: 176 received placebo plus dexamethasone.
Follow-up time	Median follow-up of 26.2 months for the lenalidomide group and 12.9 months for the placebo group.
Is the study used in the health economic model?	[redacted]
Primary, secondary and exploratory endpoints	Primary Endpoint: Time to disease progression. Secondary endpoints: Overall survival. Response rate (complete, near-complete, or partial). Exploratory endpoints: Safety and adverse events.
Method of analysis	Intention-to-treat analysis. Kaplan–Meier methods were used to estimate time-to-event variables (e.g., time to progression, overall survival). Stratified log-rank tests and Cox proportional hazards regression were used for treatment comparisons.
Subgroup analyses	Characteristics of included population: Stratified by serum β2-microglobulin levels (<2.5 mg/L vs. ≥2.5 mg/L), previous stem-cell transplantation (none vs. ≥1), and number of prior therapies (1 vs. ≥2).
Other relevant information	

Trial name: MM010	**NCT number: NCT00424047**
Objective	To evaluate the efficacy and safety of lenalidomide plus dexamethasone compared to placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma.
Publications – title, author, journal, year	Lenalidomide plus Dexamethasone for Relapsed Multiple Myeloma in North America. Donna M. Weber, Christine Chen, Ruben Niesvizky, et al. The New England Journal of Medicine. 2007
Study type and design	Double-blinded, randomized, placebo-controlled phase 3 study. Patients were randomly assigned 1:1 using a stratified permuted block randomization scheme via an interactive voice-response system. The investigators, patients, and sponsor were masked during treatment assignment.
Sample size (n)	353 patients (177 in the lenalidomide group and 176 in the placebo group).
Main inclusion criteria	Age ≥18 years. Progressive multiple myeloma after at least one previous treatment.

	Measurable disease not resistant to dexamethasone. Serum monoclonal protein level ≥0.5 g/dL or urinary Bence Jones protein level ≥0.2 g/day. Adequate organ function and performance status (ECOG ≤2).
Main exclusion criteria	Disease resistant to dexamethasone. Serum creatinine ≥2.5 mg/dL. Severe hepatic dysfunction (AST/ALT >3x ULN, bilirubin >2x ULN). Severe neutropenia or thrombocytopenia.
Intervention	Lenalidomide: 25 mg orally on days 1–21 of a 28-day cycle. Dexamethasone: 40 mg orally on days 1–4, 9–12, and 17–20 for the first 4 cycles, then days 1–4 thereafter. Patients: 177 received lenalidomide plus dexamethasone.
Comparator(s)	Placebo: orally on days 1–21 of a 28-day cycle. Dexamethasone: same dosing schedule as the intervention group. Patients: 176 received placebo plus dexamethasone.
Follow-up time	Median follow-up of 26.2 months for the lenalidomide group and 12.9 months for the placebo group.
Is the study used in the health economic model?	[redacted]
Primary, secondary and exploratory endpoints	Primary endpoint: Time to disease progression. Secondary endpoints: Overall survival. Response rate (complete, near-complete, or partial). Exploratory endpoints: Safety and adverse events.
Method of analysis	Intention-to-treat analysis. Kaplan–Meier methods were used to estimate time-to-event variables (e.g., time to progression, overall survival). Stratified log-rank tests and Cox proportional hazards regression were used for treatment comparisons.
Subgroup analyses	Stratified by serum β2-microglobulin levels (<2.5 mg/L vs. ≥2.5 mg/L), previous stem-cell transplantation (none vs. ≥1), and number of prior therapies (1 vs. ≥2).
Other relevant information	

Appendix B. Efficacy results per study

Table 38: Results per DREAMM-7

Results of DREAMM-7 (NCT number: NCT04246047)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median PFS	BVd	243	36.6 (28.4–NR) months	19.2 months	N/A	N/A	HR: 0.41	(0.31–0.53)	<0.000001	The median PFS is based on the Kaplan-Meier estimator. Hazards model stratified by the number of lines of prior therapy (1 versus †2/3 versus ≥4), prior bortezomib (no, yes) and R-ISS at screening (I versus II/III), with a covariate of treatment. P-value from 1-sided stratified log-rank test. Median follow-up of 28.2 months	[35]
	DVd	251	17.4 (15.0–19.8) months								
OS probability	BVd	243	74 (68-79)	14%	(5%, 22%)	N/A	HR 0.58	0.43-0.79	p=0.00023	Testing of OS and DOR was conditional on rejection of the null	[36]

36 months survival, %	DVd	251	60 (54-68)									hypothesis for PFS. Alpha was split such that 4/5 of alpha (ie, 2%) was initially allocated to testing OS and 1/5 of alpha (ie, 0.5%) was allocated to testing DOR (using RMDOR methods)

Table - IX: Results per POLLUX

Results of POLLUX (NCT number: NCT02076009)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Stud	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		

	arm		(CI)								
PFS	DRd	286	44.5 months	17 months	N/A	N/A	HR: 0.44	0.35-0.55	<0.00001	PFS was compared based on a stratified log-rank test. HRs and 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable, and the Kaplan–Meier method was used to estimate the distributions	[39]
	Rd	283	17.5 months								
OS	DRd	286	67.6 (53.1-80.5)	15.8	N/A	N/A	HR: 0.73	0.58-0.91	0.00044	N/A	[40]
	Rd	283	51.8 (44.0-60.0)								
Duration of Response (DoR)	DRd	286	92.9%	N/A	N/A	N/A	21.6%	N/A	< 0.00001	Duration of response was assessed by means of the Kaplan–Meier method	[40]
	Rd	283	76.4%								
MRD-neg	DRd	286	26.2%	N/A	N/A	N/A	N/A	N/A	< 0.0	Post-treatment for patients	[40]

activity rate	Rd	283	6.4%						001	achieving a complete response (CR) or stringent CR (sCR)	
CRR	DRd	286	43.1%	23.9%	N/A	N/A	N/A	N/A	< 0.0001	N/A	[40]
	Rd	283	19.2%								
ORR	DRd	286	92.9% (89.2-95.6)	N/A	N/A	N/A	N/A	N/A	< 0.001	Stratified Cochran–Mantel–Haenszel tests were used to compare overall response rates	[40]
	Rd	283	76.4% (71.0-81.3)								

Table - X: DREAMM-7 PFS censoring rules

#	Situation	Date of Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) or Censored
1	No (or inadequate) baseline assessments [1] and the participant has not died (if the participant has died follow the rules for death indicated at the bottom of the table)	Randomization	Censored
2	No adequate post-baseline assessments and the participant has not died (if the participant has died follow the rules for death indicated at the bottom of the table)	Randomization	Censored
3	Progression documented at scheduled visits and Progression documented without extended loss-to-follow-up time [4]	Date of assessment of progression	Event
4	Progression documented between scheduled visits and Progression documented without extended loss-to-follow-up time [4]	Date of assessment of progression	Event
		(S1) min (Date of next scheduled visit, date of death)	(S1) Event
5	With post-baseline assessment but no progression (or death)	Date of last 'adequate' assessment of response [2]	Censored
6	No adequate post-baseline assessment before start of new anti-myeloma therapy (prior to documented disease progression or death)	Random	Censored
		(S2) Date of starting new anti-myeloma therapy	(S2) Event

7	With adequate post-baseline assessment and new anti-myeloma treatment started (prior to documented disease progression or death) [3] .	Date of last 'adequate' assessment of response [2] (on or prior to starting anti-myeloma treatment)	Censored
		(S2) Date of starting new anti-myeloma therapy	(S2) Event
8	Death before first scheduled assessment (or death at Baseline or without any adequate assessments)	Date of death	Event
9	Death between adequate assessment visits	Date of death	Event
10	Death without extended loss-to-follow-up time [4]	Date of death	Event
11	Death or progression after an extended loss-to-follow-up time [4]	Date of randomization if no post-baseline assessments, or date of last 'adequate' assessment of response [2] prior to PD/death (prior to missed assessments): since disease assessment is every 3 weeks, a window of 49 days (6 weeks + 7-day window) will be used to determine whether there is extended time without adequate assessment. If the time difference between PD/death and max (last adequate disease assessment, randomization) is more than 49 days, PFS will be censored at the last adequate disease assessment prior to PD/death.	Censored
		(S3) Date of death or progression	(S3) Event
12	(S4) Treatment discontinuation due to clinical PD[5] before PD or death	(S4) Date of treatment discontinuation	(S4) Event

Note: (S1) (S2) (S3) (S4) Rules To Be Applied For PFS Supplementary Analysis.
Event or censored are based on confirmed responses.
[1]. Adequate baseline assessment is defined as at baseline, a patient has at least one of the following measurements: Serum M-protein ≥0.5 g/dL (≥5 g/L) or b. Urine M-protein ≥200 mg/24h or c. Serum FLC assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain ratio (1.65).
[2]. An adequate assessment is defined as an assessment where the response is sCR, CR, VGPR, PR, MR, or SD.
[3]. If PD or death and new anti-myeloma therapy occur on the same day assume the progression or death was documented first (e.g., outcome is progression or death, and the date is the date of the assessment of progression or death). If anti-myeloma therapy is started prior to any adequate assessments, censoring date should be the date of randomization.

Table - XI: Baseline characteristics in DREAMM-7 subpopulation (2L, 3L, 3L+)

	BVd (N=243)			DVd (N=251)		
Characteristics	2L (n=125)	3L (n=54)	3L+ (n=118)	2L (n=123)	3L (n=63)	3L+ (n=126)
Median age (range) - yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age category — no. (%)						
18 to <65 yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65 to <75 yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥75 yr	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sex — no. (%)						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race — no. (%)†						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight – Median/mean (kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSA – Median/mean (m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance-status score — no (%)‡						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-ISS stage at screening — no. (%)						
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median time since diagnosis (range) - yr	[redacted]	[redacted]		[redacted]	[redacted]	
Cytogenetic risk — no. (%)§						
Standard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
t(4;14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
t(14;16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
del(17p13)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing or not evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other cytogenetic abnormalities — no. (%)						

del(13)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
del(1p)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypodiploidy						
t(11;14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
t(14;20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1q21+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extramedullary disease — no. (%)						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myeloma IgG — no. (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous LoT — no. (%)						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 or 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range) number of prior LoT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to relapse after most recent therapy — no. (%)						
<12 mo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥12 mo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous proteasome inhibitor — no. (%)						
Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixazomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous immunomodulatory drugs — no. (%)						
Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous daratumumab treatment — no. (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous ASCT — no. (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous chemotherapy — no. (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous glucocorticoids — no. (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: GSK data on file

[redacted]

Source: GSK data on file

[redacted]

Source: GSK data on file

[redacted]

	BVd (N=124)	DVd (N=125)
Number of participants, n (%)		
Progressed or died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Estimates for PFS (months)		
1st Quartile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
3 rd Quartile (95% CI)	[redacted]	[redacted]
Hazard ratio		
Estimate (95% CI)	[redacted]	

[redacted]

	BVd (N=55)	DVd (N=63)

Number of participants, n (%)		
Progressed or died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Estimates for PFS (months)		
1st Quartile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
3 rd Quartile (95% CI)	[redacted]	[redacted]
Hazard ratio		
Estimate (95% CI)	[redacted]	

Source: GSK data on file

[redacted]

	BVd (N=119)	DVd (N=126)
Number of participants, n (%)		
Progressed or died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Estimates for PFS (months)		
1st Quartile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
3 rd Quartile (95% CI)	[redacted]	[redacted]
Hazard ratio		
Estimate (95% CI)	[redacted]	

[redacted]

Source: GSK data on file

[redacted]

Source: GSK data on file

[redacted]

Source: GSK data on file

[redacted]

	2L	3L	3L+
Hazard ratio			
Estimate (95% CI)	[redacted]	[redacted]	[redacted]
Stratified Log-Rank p-value	[redacted]	[redacted]	[redacted]

[redacted]

Source: GSK data on file

[redacted]

Source: GSK data on file

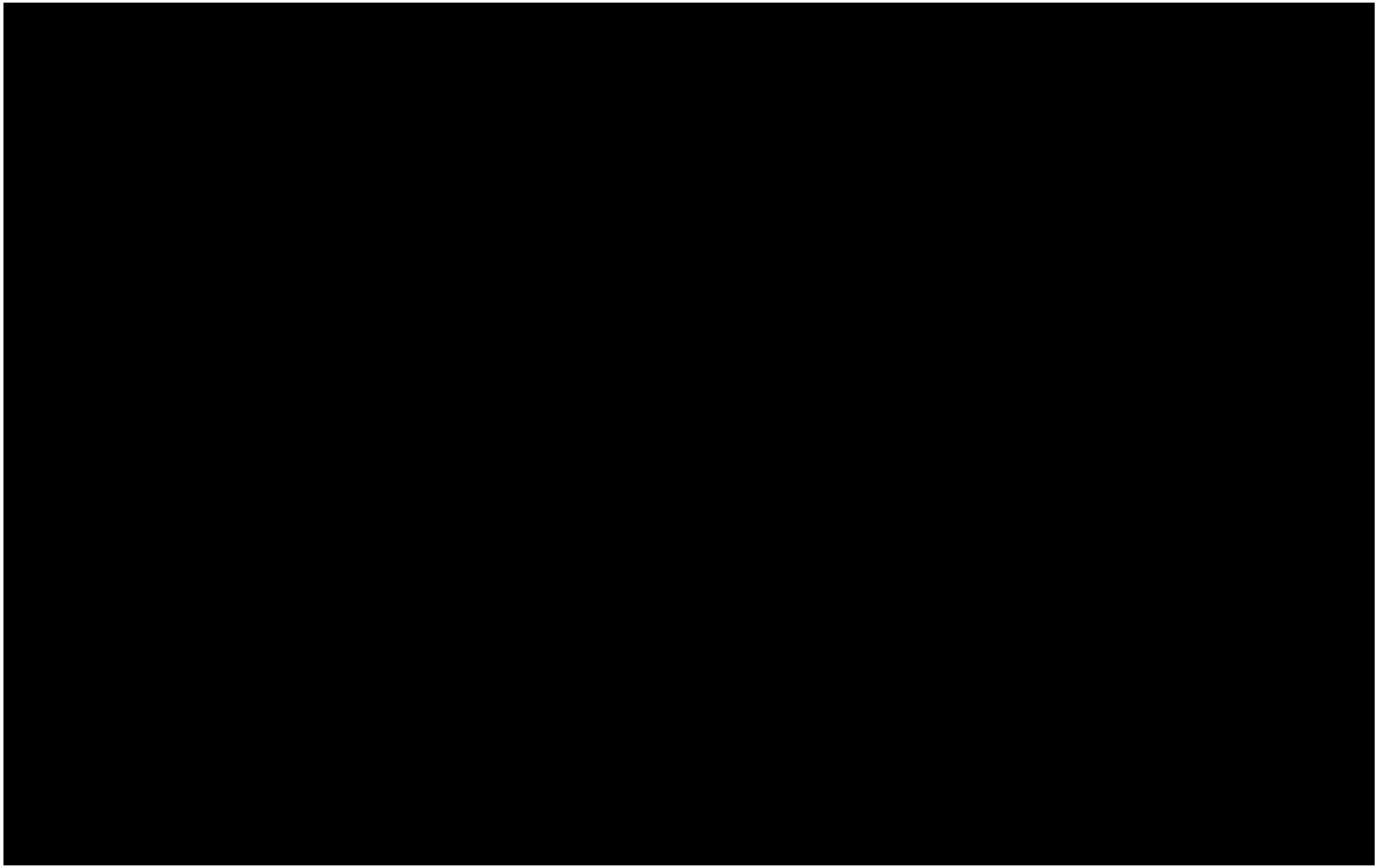
[redacted]

Source: GSK data on file

Appendix C. Comparative analysis of efficacy

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

Table - XII: Comparisons on the pathway for the NMA

Outcome measure	BVd (N=243)	DVd (N= 251) CASTOR	Result
PFS	Median: 36.6 months (95% CI: 28.4–NR) HR: 0.46 (95 % CI: 0.35, 0.59)	Median: 16.7 months HR: 0.31 (95 % CI: 0.25, 0.39)	[redacted]
OS	Median: Not reached HR: 0.58 (95 % CI: 0.43, 0.79)	Median: 49.6 months (95% CI: 42.2-62.3) HR: 0.74 (95 % CI: 0.59, 0.92)	[redacted]
Outcome measure	**BVd (N=243)**	**Vd (N= 333) APEX**	**Result**
PFS	Median: 36.6 months (95% CI: 28.4–NR) HR: 0.46 (95 % CI: 0.35, 0.59)	Median: 6.22 months HR: 0.55 (95 % CI: 0.44, 0.69)	[redacted]

OS	Median: Not reached HR: 0.58 (95 % CI: 0.43, 0.79)	Median: N/A HR: 0.57 (95 % CI: 0.32, 0.86)	[redacted]
Outcome measure	**BVd (N=243)**	**Rd (N=176) MM-009/MM-010**	**Result**
PFS	Median: 36.6 months (95% CI: 28.4–NR) HR: 0.46 (95 % CI: 0.35, 0.59)	Median: 11.3 months HR: 0.35 (95 % CI: 0.27, 0.46)	[redacted]
OS	Median: Not reached HR: 0.58 (95 % CI: 0.43, 0.79)	Median: N/A HR: 0.66 (95 % CI: 0.45, 0.96)	[redacted]

[redacted]

[redacted]

Outcome	Population	Intercept prior (fixed and random effects)	Fixed effects prior – treatment effects	Random effects prior – treatment effects	Random effects prior – heterogeneity variance*
PFS	ITT	[redacted]	[redacted]	[redacted]	[redacted]
OS	ITT	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]


[redacted]

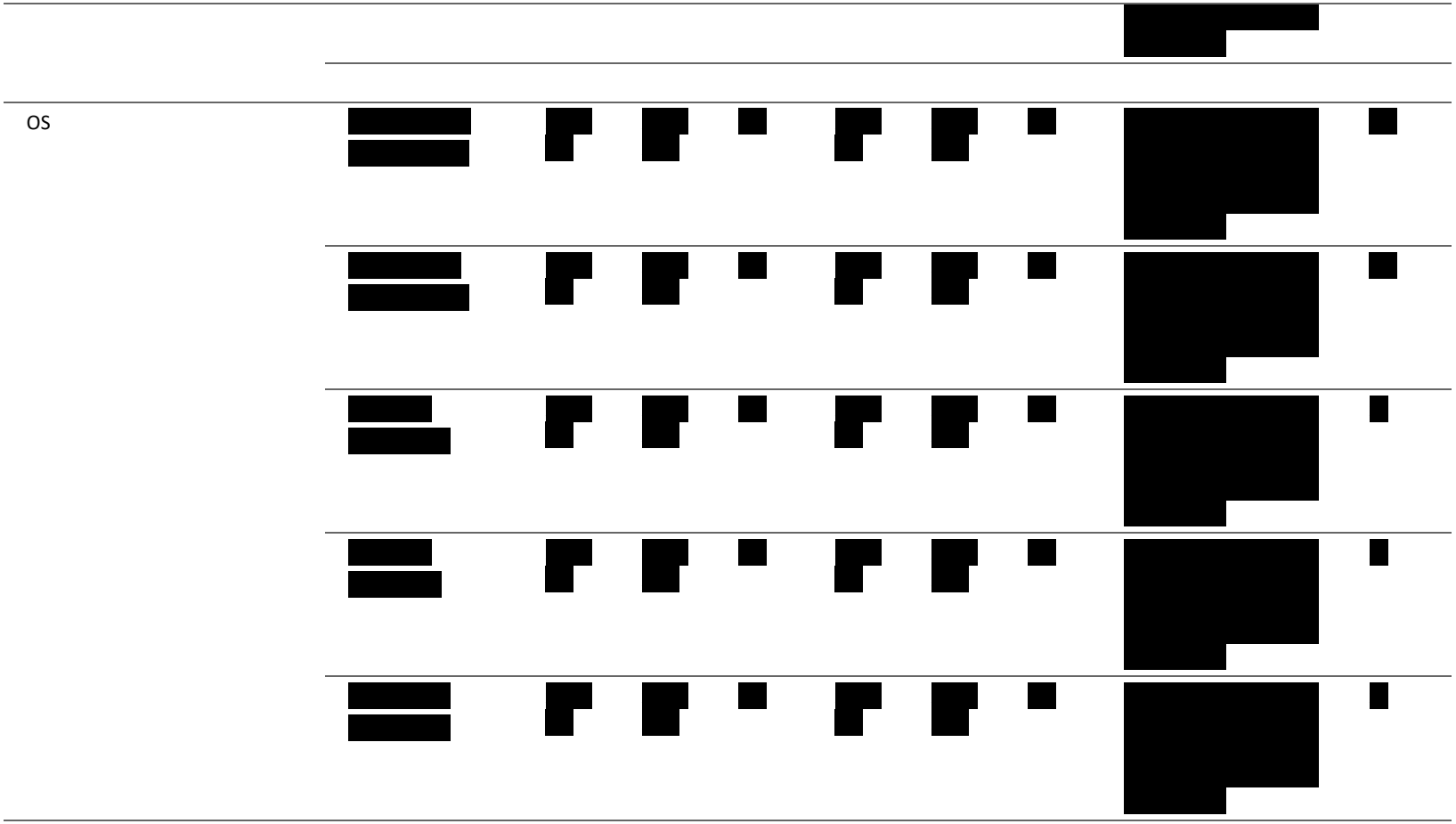
[redacted]

[redacted]

[redacted]

[redacted]

Outcome		Relative difference in effect (fixed effects)			Relative difference in effect (random effects)			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CrI	P value		
PFS	[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]


OS

Appendix D. Extrapolation

D.1 Extrapolation of PFS

D.1.1 Data input

DREAMM-7 IA2 data cut

D.1.2 Model

Six standard parametric distributions have been fitted to PFS KM data using the 'flexsurv' package in R (exponential, Weibull, log-logistic, log-normal, Gompertz and Generalized gamma).

D.1.3 Proportional hazards

The Schoenfeld plot, presented in Figure 20, shows residuals with a random pattern with a non-zero slope. It provides evidence for non-proportionality and therefore, that the PH assumption does not hold. The log-cumulative hazard plot of PFS, presented in Figure 21, shows that the curves cross several times early in the plot, indicating that the PH may not hold.

Figure 20: PFS – BVd and DVd Schoenfeld residuals plot

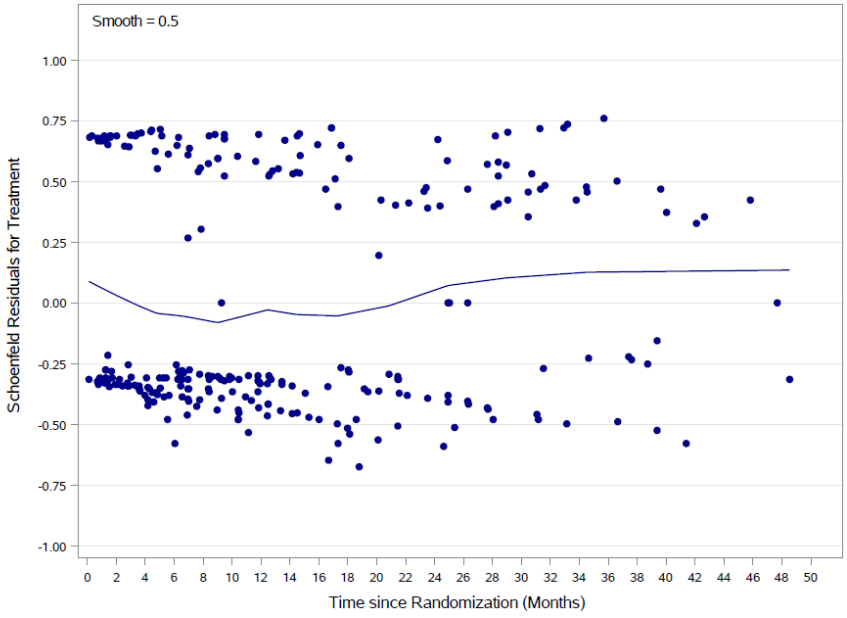
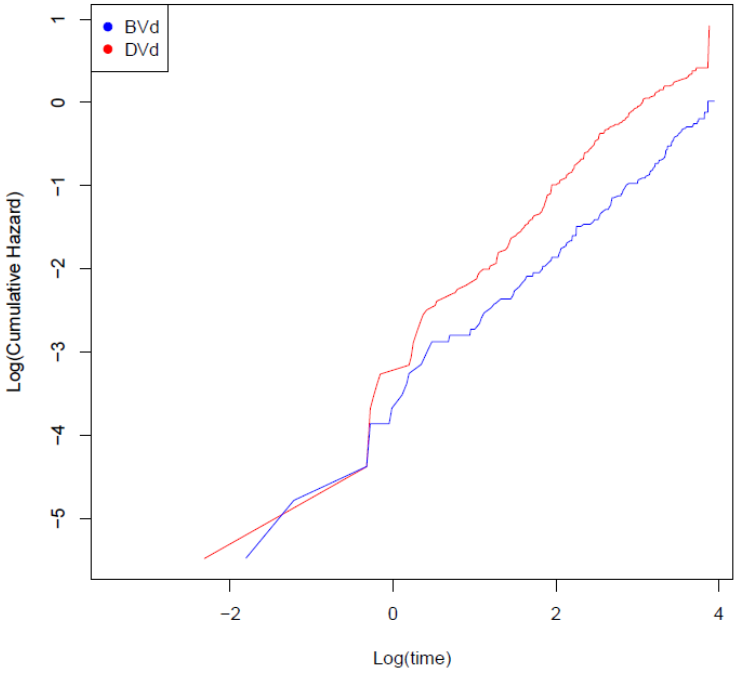
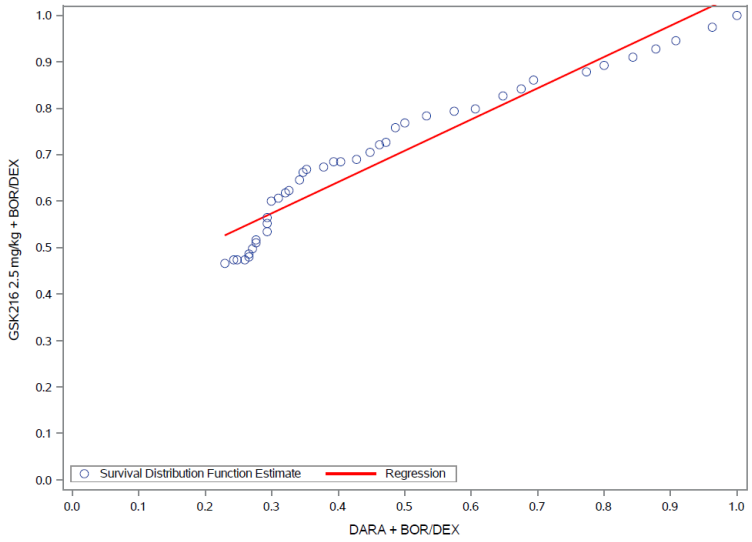


Figure 21: Plot of Log (PFS Cumulative Hazard) vs Log (Time)



The Q-Q plot for BVd and DVd in Figure 22 shows that the quantiles do not lie on a straight line, suggesting the treatment effect is not multiplicative with respect to time and therefore, a dependent AFT model would not be appropriate. Given the violation of the proportional hazard assumption in the Schoenfeld plot and the AFT assumption in the Q-Q plot independent parametric models are fit to both treatment arms.

Figure 22: PFS – BVd and DVd Q-Q plot



D.1.4 Evaluation of statistical fit (AIC and BIC)

According to the AIC and BIC presented in Table - XIII, the exponential distribution appeared to provide the best statistically fitting curve for BVd PFS. It is worth noting that the majority of distributions (apart from the lognormal distribution) are considered a comparable fit due to being within three points of each other for their AIC scores. Based on the AIC and BIC presented in Table - XIV, the best statistically fitting curve for DVd PFS is the log-logistic distribution, although there is little difference between all fits.

Table - XIII: PFS – BVd goodness of fit statistics for parametric distributions

Exponential	1,077.08	1	1,080.57	1
Weibull	1,078.47	2	1,085.45	2
Generalised gamma	1,080.47	5	1,090.95	5
Gompertz	1,078.75	3	1,085.73	3
Log-logistic	1,080.22	4	1,087.21	4
Log-normal	1,084.21	6	1,091.20	6

Table - XIV: PFS – DVd goodness of fit statistics for parametric distributions

Exponential	1,397.90	5	1,401.42	5
Weibull	1,398.03	6	1,405.08	6
Generalised gamma	1,389.65	3	1,400.22	4
Gompertz	1,391.28	4	1,398.33	3
Log-logistic	1,387.15	1	1,394.20	1
Log-normal	1,388.29	2	1,395.34	2

D.1.5 Evaluation of visual fit

Exponential was selected as the base-case because it aligns with clinical expectations of an approximately constant long-term hazard, ensuring survival approaches zero rather than plateauing at implausible levels. For DVd, while other distributions showed slightly better statistical fit to the short-term data, they produced long-term shapes inconsistent with expert opinion. The exponential curve is also the most parsimonious, reducing the risk of overfitting given a limited follow-up.

Figure 23: PFS for BVd, parametric curves

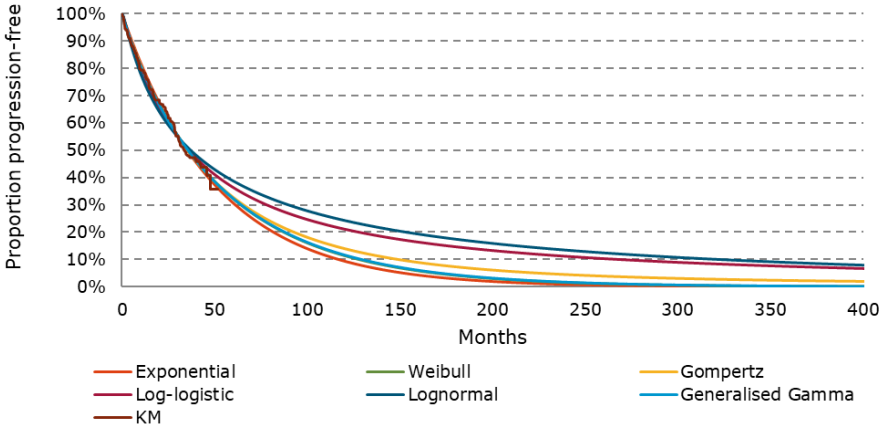
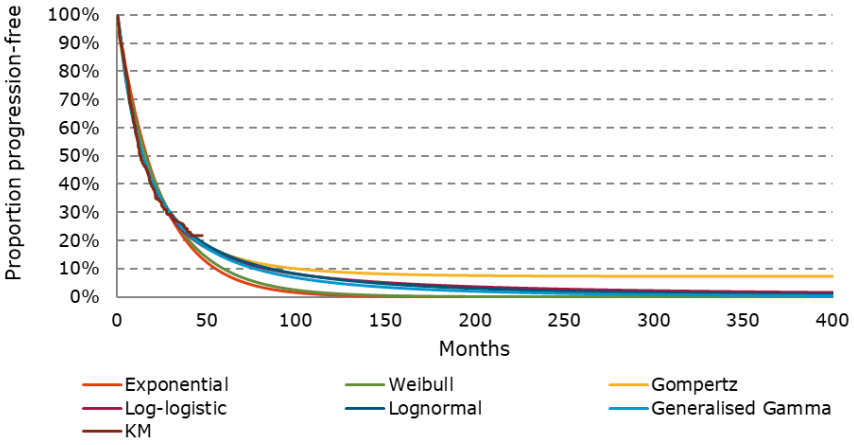


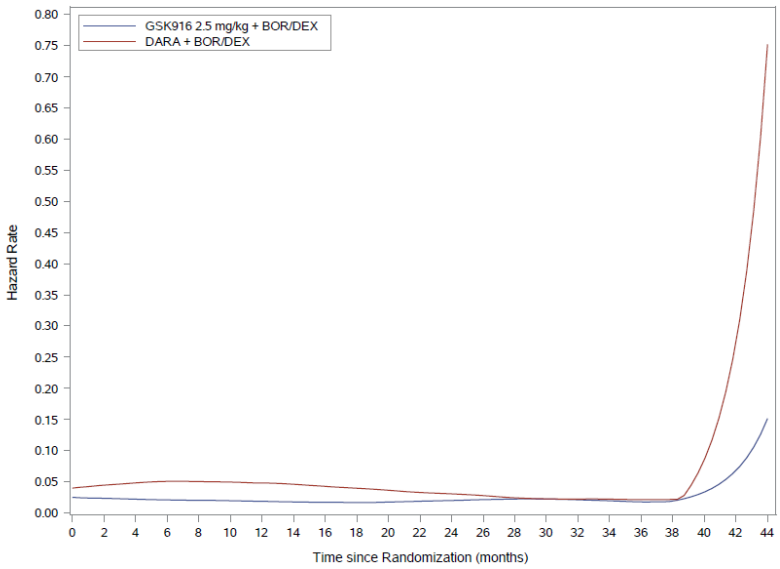
Figure 24: PFS for DVd, parametric curves



D.1.6 Evaluation of hazard functions

For DVd, the empiric hazard plot (Figure 25) includes a turning point of around 38 months that may be a change in hazard or an artifact of sparse tail data, which is also seen for BVd to a lesser extent.

Figure 25: PFS – BVd and DVd empiric hazard plot



D.1.7 Validation and discussion of extrapolated curves

Standard parametric distributions were fitted to the observed time-to-event data and compared using graphical fit to the KM-curve, AIC/BIC, and formal diagnostics. A Danish clinical expert reviewed the long-term plausibility of the extrapolations. Because follow-up was limited and late-term observations were sparse, we prioritized clinical plausibility over minimal improvements in short-term statistical fit.

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of OS

D.2.1 Data input

DREAMM-7 IA2 data cut.

D.2.2 Model

Six standard parametric distributions have been fitted to OS KM data using the 'flexsurv' package in R (exponential, Weibull, log-logistic, log-normal, Gompertz and Generalized gamma).

D.2.3 Proportional hazards

The Schoenfeld plot, presented in Figure 26, shows residuals with a random pattern with a non-zero slope. It provides evidence for non-proportionality and therefore, that the PH assumption does not hold. The log-cumulative hazard plot of OS is presented in Figure 27, and suggests that the PH assumption is questionable, particularly early in the time axis, due to crossing and non-parallel patterns.

Figure 26: Unadjusted OS – BVd and DVd Schoenfeld residuals plot

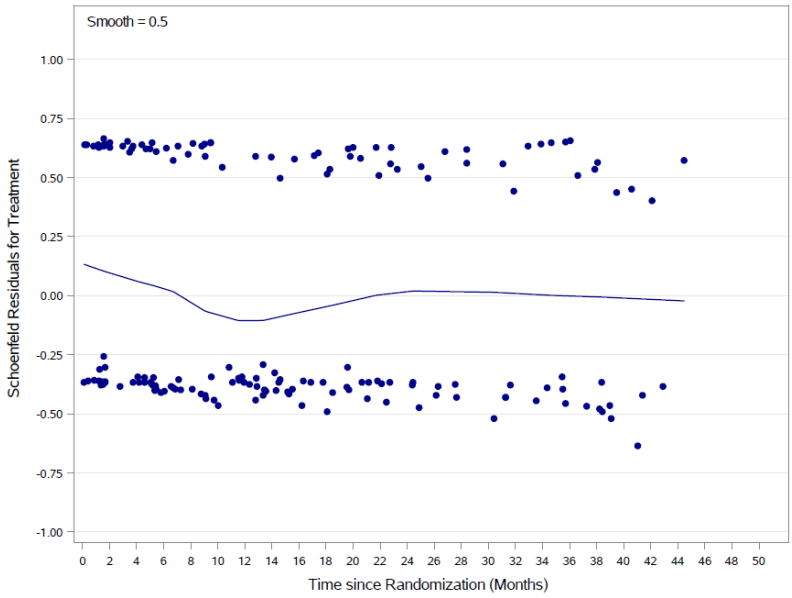


Figure 27: Plot of Log (OS Cumulative Hazard) Vs Log(Time)

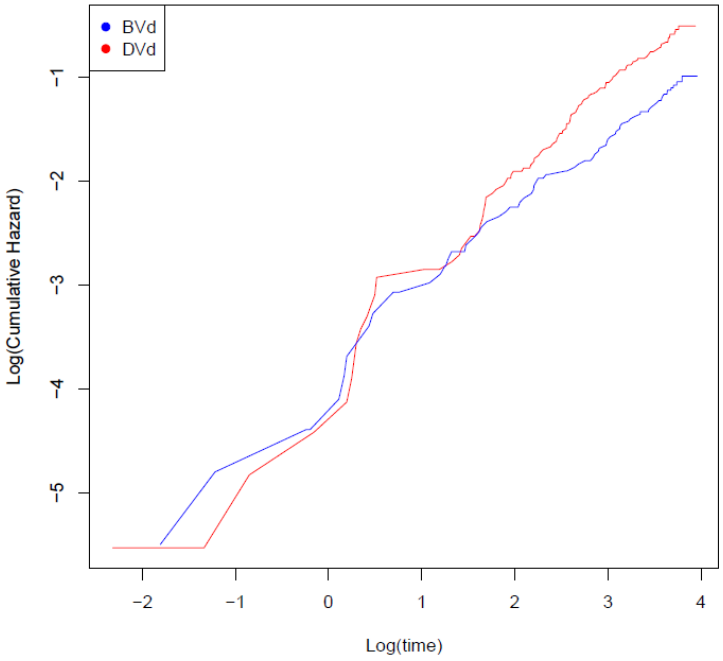
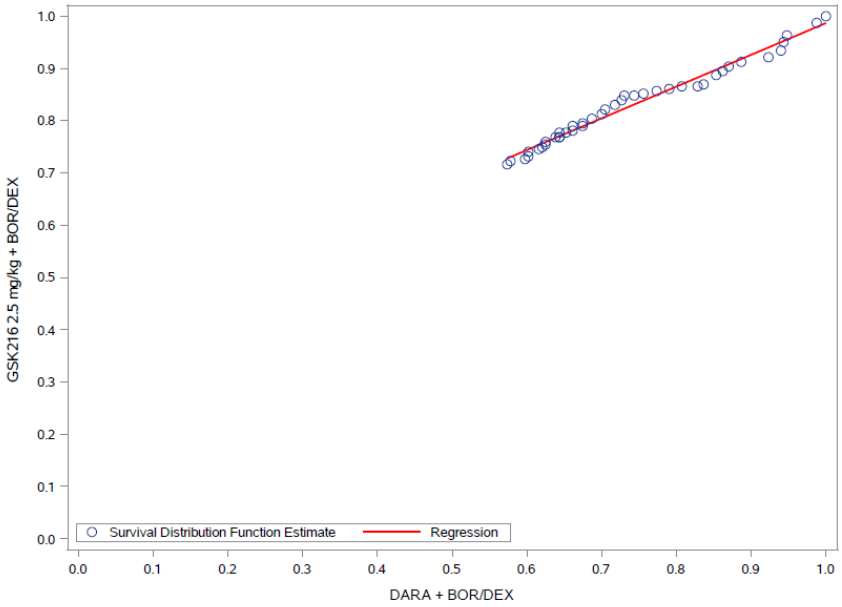


Figure 28: Unadjusted OS – BVd and DVd Q-Q plot



The Q-Q plot for BVd and DVd (Figure 28) shows that the quantiles do not lie on a straight line, suggesting the treatment effect is not multiplicative with respect to time and therefore, a dependent AFT model would not be appropriate. Given the Schoenfeld plot and the Q-Q plot do not support the PH or constant AF assumption, independent parametric models are fit to both treatment arms.

D.2.4 Evaluation of statistical fit (AIC and BIC)

Based on the AIC and BIC, the log-normal distribution is the best statistically fitting curve for BVd OS however, all distributions apart from exponential could be considered comparable as their AIC values are within three points. The Gompertz distribution is the best statistically fitting curves for DVd OS, however all distributions except exponential could also be considered comparable being within three points of the AIC score.

Table - XV: Unadjusted OS – BVd goodness of fit statistics for parametric distributions

Distribution	AIC	AIC Rank	BIC	BIC Rank
Exponential	787.21	6	790.70	4
Weibull	781.79	3	793.15	5
Generalised gamma	782.67	4	793.15	5
Gompertz	783.07	5	790.07	3
Log-logistic	781.46	2	788.45	2
Log-normal	780.76	1	787.75	1

Table - XVI: Unadjusted OS – DVd goodness of fit statistics for parametric distributions

Distribution	AIC	AIC Rank	BIC	BIC Rank
Exponential	1083.46	6	1086.99	4
Weibull	1081.36	5	1088.41	5
Generalised gamma	1080.49	4	1091.07	6
Gompertz	1078.52	1	1085.57	1
Log-logistic	1079.13	3	1086.18	3
Log-normal	1078.93	2	1085.99	2

D.2.5 Evaluation of visual fit

By visual inspection it appears that most of the curves plateau without approaching zero. The exponential distribution was chosen as the base-case based on clinical expert input, who judged that alternative distributions were less clinically plausible because of their rapid plateau.

Figure 29: OS for BVd, parametric curves

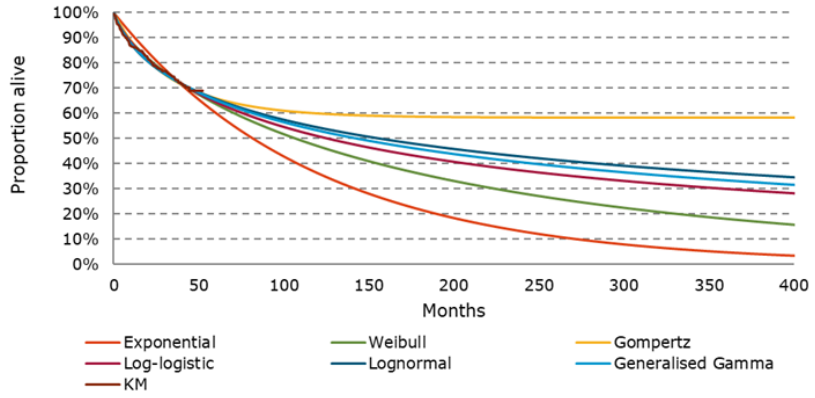
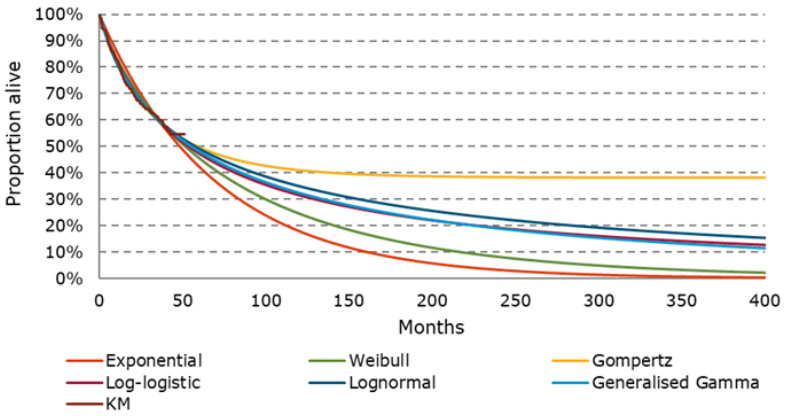
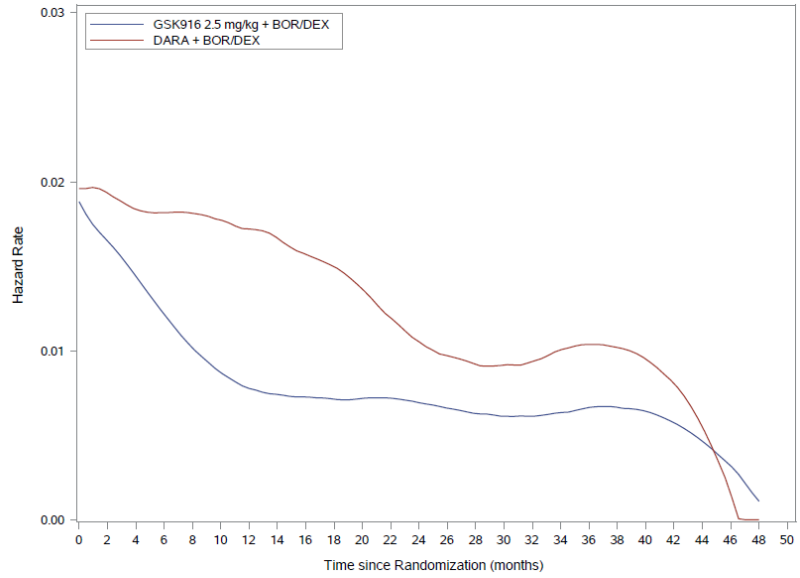


Figure 30: OS for DVd, parametric curves



D.2.6 Evaluation of hazard functions

Figure 31: Unadjusted OS – BVd and DVd empiric hazard plot



The empiric hazard plot for BVd and DVd, presented in Figure 31, shows a non-monotonic decrease for both BVd and DVd, indicating that the hazards are not constant.

D.2.7 Validation and discussion of extrapolated curves

Standard parametric distributions were fitted to the observed time-to-event data and compared using graphical fit to the KM-curve, AIC/BIC, and formal diagnostics. A Danish clinical expert reviewed the long-term plausibility of the extrapolations. Because follow-up was limited and late-term observations were sparse, clinical plausibility was prioritized over improvements to short-term statistical fit.

D.2.8 Adjustment of background mortality

For OS, background mortality was applied as per DMC guidelines in the model.

D.2.9 Adjustment for treatment switching/cross-over

N/A

D.2.10 Waning effect

N/A

D.2.11 Cure-point

N/A

D.3 Extrapolation of Time To Treatment Discontinuation (TTD)

D.3.1 Data input

DREAMM-7 IA2 data cut.

D.3.2 Model

Six parametric distributions have been fitted to the TTD KM curves to extrapolate TTD.

D.3.3 Proportional hazards

N/A

D.3.4 Evaluation of statistical fit (AIC and BIC)

Table - XVII: TTD – BVd goodness of fit statistics for parametric distributions

Distribution	AIC	AIC Rank	BIC	BIC Rank
Exponential	1566.20	6	1569.69	6
Weibull	1558.94	5	1565.92	5
Generalised gamma	1549.62	2	1560.09	3
Gompertz	1553.94	4	1560.92	4
Log-logistic	1551.40	3	1558.38	2
Log-normal	1547.64	1	1554.62	1

Table - XVIII: TTD – DVd goodness of fit statistics for parametric distributions

Distribution	AIC	AIC Rank	BIC	BIC Rank
Exponential	1674.24	4	1677.74	2
Weibull	1675.73	6	1682.74	6
Generalised gamma	1671.04	2	1681.55	4
Gompertz	1671.55	3	1678.57	3
Log-logistic	1667.89	1	1674.90	1
Log-normal	1674.61	5	1681.62	5

D.3.5 Evaluation of visual fit

Figure 32: TTD – BVd KM and parametric distributions, within trial fit

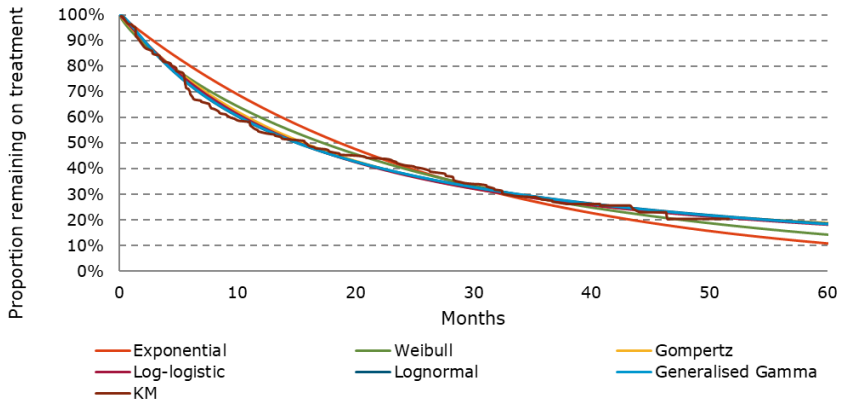


Figure 33: TTD – BVd KM and parametric distributions, long-term fit

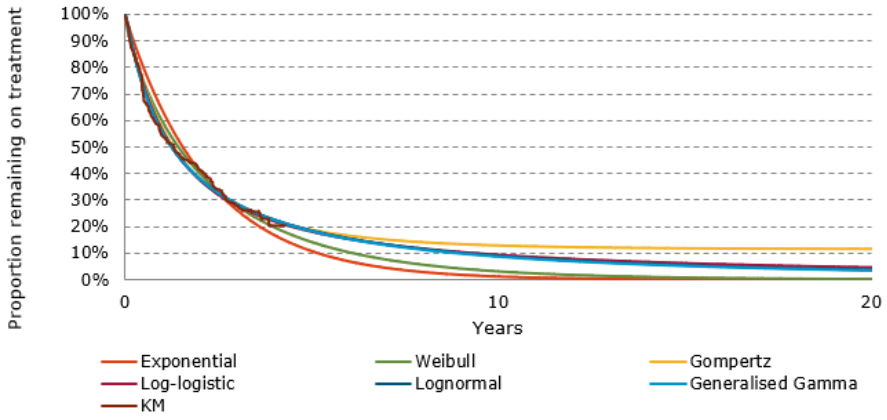


Figure 34: TTD – DVd KM and parametric distributions, within trial fit

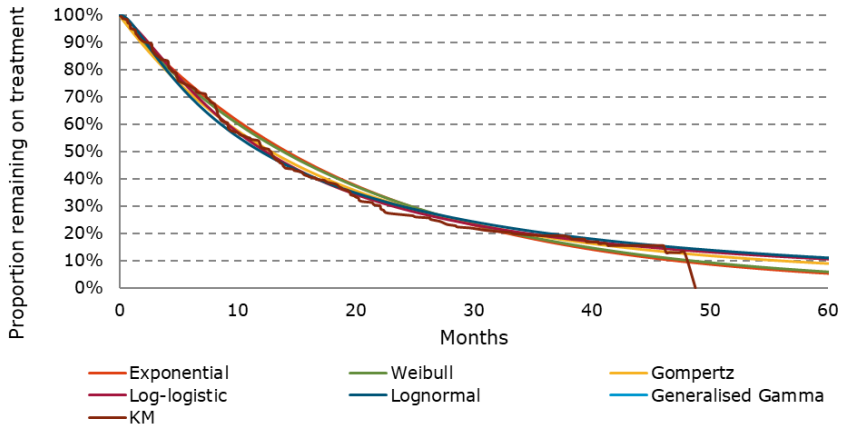
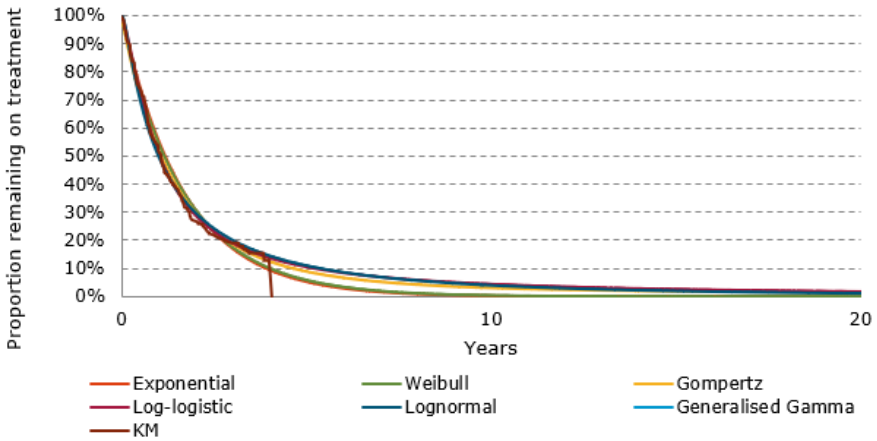


Figure 35: TTD – DVd KM and parametric distributions, long-term fit



D.3.6 Evaluation of hazard functions

N/A

D.3.7 Validation and discussion of extrapolated curves

Based on clinical expert opinion, exponential is selected for TTD extrapolation for both BVd and DVd.

D.3.8 Adjustment of background mortality

N/A

D.3.9 Adjustment for treatment switching/cross-over

N/A

D.3.10 Waning effect

N/A

D.3.11 Cure-point

N/A

Appendix E. Serious adverse events

[redacted]

Adverse events, n (%)	BVd (N=242)		DVd (N=246)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
[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]	[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]	[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]

Adverse events, n (%)	BVd (N=242)	DVd (N=246)
Discontinuation		

[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]
Dose reduction		
[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]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Dose interruption/delay		
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

	DREAMM-7		POLLUX
Adverse events, n (%)	BVd (N=242)	DVd (N=246)	DRd (N=283)
[redacted]			
[redacted]			
[redacted]			

[redacted]

Appendix F. Health-related quality of life

[redacted]

	BVd		DVd		BVd vs. DVd
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]				
Week 7					
Week 13					
Week 19					
Week 25					
Week 31					
Week 37					
Week 43					
Week 49					
Week 55					
Week 61					
Week 67					

Week 73	[redacted]	[redacted]	[redacted]	[redacted]
Week 79	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]
Week 91	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]
Week 103	[redacted]	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]	[redacted]
Week 115	[redacted]	[redacted]	[redacted]	[redacted]
Week 121	[redacted]	[redacted]	[redacted]	[redacted]
Week 127	[redacted]	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]	[redacted]
Week 139	[redacted]	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]	[redacted]
Week 151	[redacted]	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]	[redacted]
Week 163	[redacted]	[redacted]	[redacted]	[redacted]
Week 169	[redacted]	[redacted]	[redacted]	[redacted]
Week 175	[redacted]	[redacted]	[redacted]	[redacted]
Week 181	[redacted]	[redacted]	[redacted]	[redacted]
Week 187	[redacted]	[redacted]	[redacted]	[redacted]
Week 193	[redacted]	[redacted]	[redacted]	[redacted]
Week 199	[redacted]	[redacted]	[redacted]	[redacted]
Week 205	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Last Follow-up	[redacted]	[redacted]	[redacted]	[redacted]

Table - XIX: Summary descriptive statistics of EQ-5D-3L Utility Scores by Visits, Denmark Value Set

	BVd		DVd	
	n	Mean (SD)	n	Mean (SD)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Week 19	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]

Week 31	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]
Week 43	[redacted]	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]	[redacted]
Week 55	[redacted]	[redacted]	[redacted]	[redacted]
Week 61	[redacted]	[redacted]	[redacted]	[redacted]
Week 67	[redacted]	[redacted]	[redacted]	[redacted]
Week 73	[redacted]	[redacted]	[redacted]	[redacted]
Week 79	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]
Week 91	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]
Week 103	[redacted]	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]	[redacted]
Week 115	[redacted]	[redacted]	[redacted]	[redacted]
Week 121	[redacted]	[redacted]	[redacted]	[redacted]
Week 127	[redacted]	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]	[redacted]
Week 139	[redacted]	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]	[redacted]
Week 151	[redacted]	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]	[redacted]
Week 163	[redacted]	[redacted]	[redacted]	[redacted]
Week 169	[redacted]	[redacted]	[redacted]	[redacted]
Week 175	[redacted]	[redacted]	[redacted]	[redacted]
Week 181	[redacted]	[redacted]	[redacted]	[redacted]
Week 187	[redacted]	[redacted]	[redacted]	[redacted]
Week 193	[redacted]	[redacted]	[redacted]	[redacted]
Week 199	[redacted]	[redacted]	[redacted]	[redacted]
Week 205	[redacted]	[redacted]	[redacted]	[redacted]
Week 211	[redacted]	[redacted]	[redacted]	[redacted]
Week 217	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Last Follow-up	[redacted]	[redacted]	[redacted]	[redacted]
All Visits	[redacted]	[redacted]	[redacted]	[redacted]

Source: GSK data on file

Note: the n in the All Visits section represents the total number of subjects with a utility score multiplied by the number of visits. Elsewhere, n is number of subjects with a utility score at each visit.

Table - XX: Summary of descriptive statistics of EQ-5D-3L VAS Value by Visit

	BVd		DVd	
	n	Mean (SD)	n	Mean (SD)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Week 19	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]
Week 31	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]
Week 43	[redacted]	[redacted]	[redacted]	[redacted]
Week 49	[redacted]	[redacted]	[redacted]	[redacted]
Week 55	[redacted]	[redacted]	[redacted]	[redacted]
Week 61	[redacted]	[redacted]	[redacted]	[redacted]
Week 67	[redacted]	[redacted]	[redacted]	[redacted]
Week 73	[redacted]	[redacted]	[redacted]	[redacted]
Week 79	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]
Week 91	[redacted]	[redacted]	[redacted]	[redacted]
Week 97	[redacted]	[redacted]	[redacted]	[redacted]
Week 103	[redacted]	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]	[redacted]
Week 115	[redacted]	[redacted]	[redacted]	[redacted]
Week 121	[redacted]	[redacted]	[redacted]	[redacted]
Week 127	[redacted]	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]	[redacted]
Week 139	[redacted]	[redacted]	[redacted]	[redacted]
Week 145	[redacted]	[redacted]	[redacted]	[redacted]
Week 151	[redacted]	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]	[redacted]
Week 163	[redacted]	[redacted]	[redacted]	[redacted]

Week 169	[redacted]	[redacted]	[redacted]	[redacted]
Week 175	[redacted]	[redacted]	[redacted]	[redacted]
Week 181	[redacted]	[redacted]	[redacted]	[redacted]
Week 187	[redacted]	[redacted]	[redacted]	[redacted]
Week 193	[redacted]	[redacted]	[redacted]	[redacted]
Week 199	[redacted]	[redacted]	[redacted]	[redacted]
Week 205	[redacted]	[redacted]	[redacted]	[redacted]
Week 211	[redacted]	[redacted]	[redacted]	[redacted]
Week 217	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
Last Follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Worst Case Post-Baseline	[redacted]	[redacted]	[redacted]	[redacted]

Source: GSK data on file

Appendix G. Probabilistic sensitivity analyses

The model handles correlation between the parameters using the preferred Cholesky decomposition method, calculating multivariate normal sampled values. In Table 39, an overview of the data and assumptions for the included parameters and their selected probability distributions is presented.

Table 39: Parameters included in the PSA

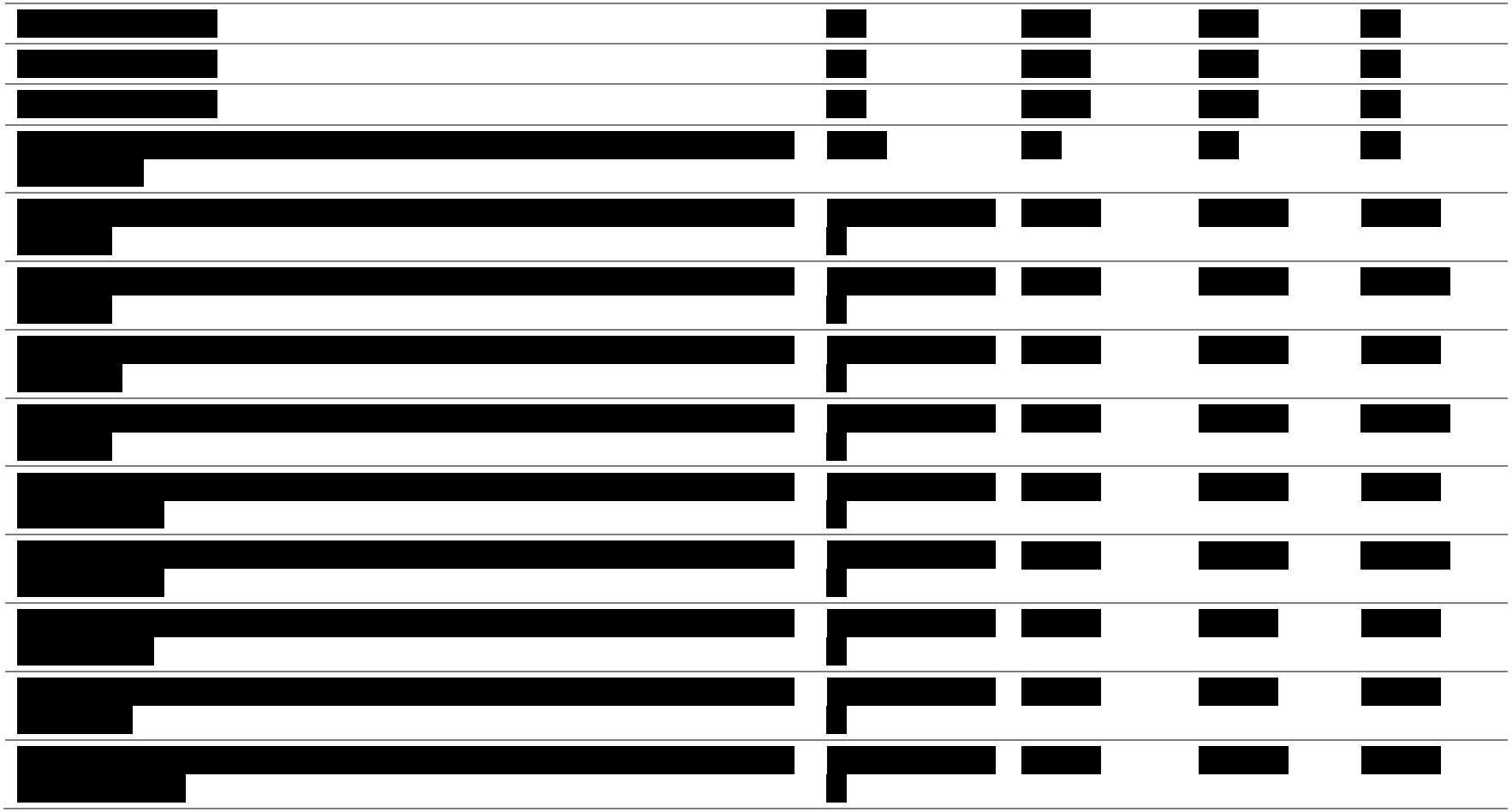
Input parameter	Probability distribution	Upper bound	Lower bound	Point estimate
Mean age at baseline (years)	Normal	70	3,50	67,76
Percentage male at baseline	Beta	179,45	146,82	0,58
Progression-free survival, D-Vd vs B-Vd, Hazard ratio	Normal	2,17	0,29	2,42
Progression-free survival, B-Vd vs D-Vd, Hazard ratio	Normal	0,46	0,06	0,52
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival, D-Vd vs B-Vd, Hazard ratio	Normal	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival, B-Vd vs D-Vd, Hazard ratio	Normal	0,58	0,09	0,52
Time to treatment discontinuation, D-Vd vs B-Vd, Hazard ratio	Normal	2,17	0,11	2,32
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to treatment discontinuation, B-Vd vs D-Vd, Hazard ratio	Normal	0,46	0,02	0,48
Dose per admin, B-Vd, Belamaf (IV)	Normal	2,50	0,13	2,35
Dose per admin, B-Vd, Bortezomib (SC)	Normal	1,30	0,07	1,17

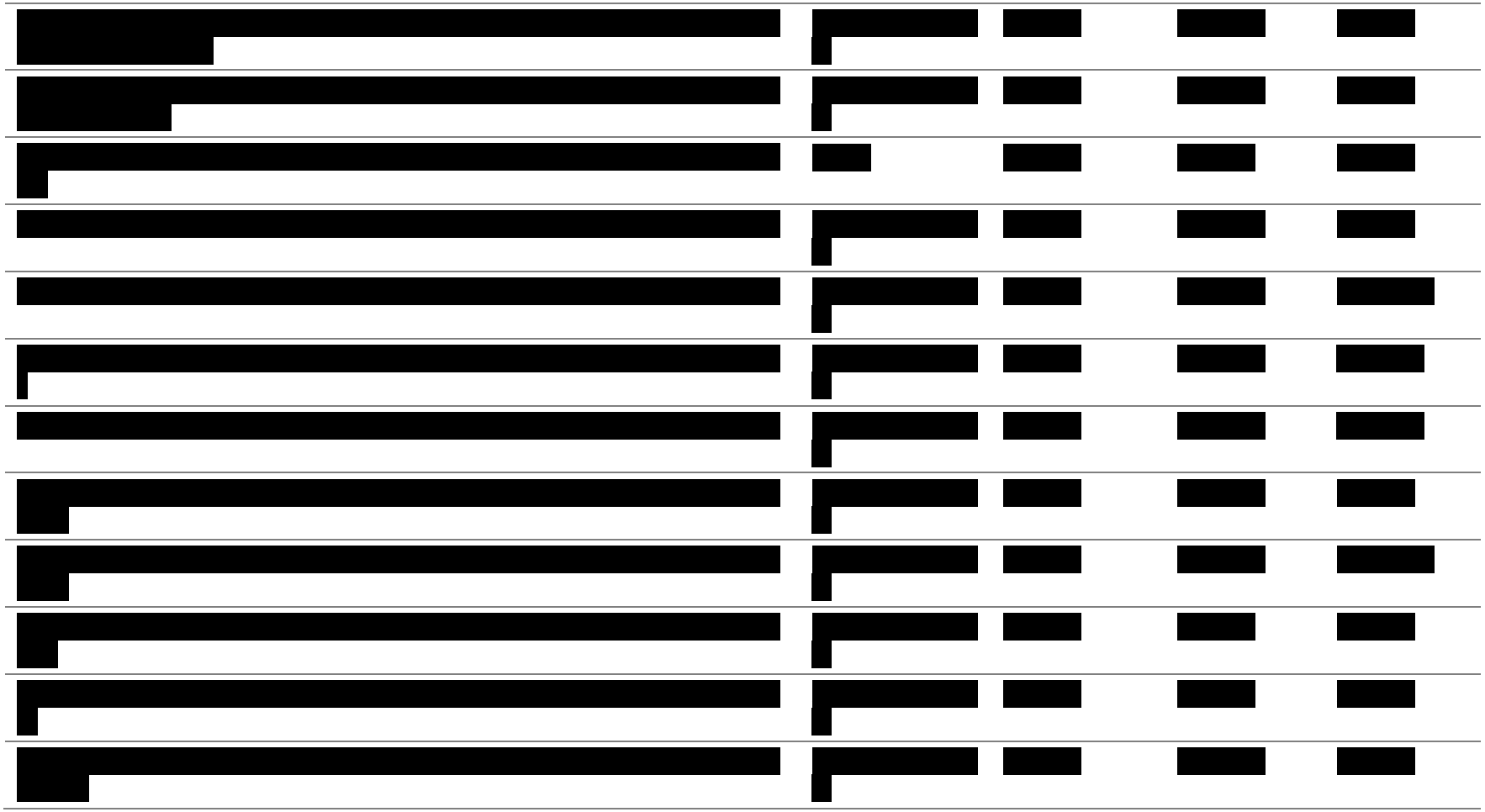
Dose per admin, B-Vd, Dexamethasone (Oral)	Normal	20,00	1,00	20,97
Dose per admin, D-Vd, Daratumumab (SC)	Normal	1800,00	90,00	1682,40
Dose per admin, D-Vd, Bortezomib (SC)	Normal	1,30	0,07	1,32
Dose per admin, D-Vd, Dexamethasone (Oral)	Normal	20,00	1,00	20,54
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematologist visit, Resource use per cycle, B-Vd, PFS (on treatment)	Gamma	400,00	0,00	0,23
Haematologist visit, Resource use per cycle, B-Vd, PFS (off treatment)	Gamma	400,00	0,00	0,23
Haematologist visit, Resource use per cycle, B-Vd, PD	Gamma	400,00	0,00	0,09
Blood test, Resource use per cycle, B-Vd, PFS (on treatment)	Gamma	400,00	0,00	0,22
Blood test, Resource use per cycle, B-Vd, PFS (off treatment)	Gamma	400,00	0,00	0,20
Blood test, Resource use per cycle, B-Vd, PD	Gamma	400,00	0,00	0,41
Haematologist visit, Resource use per cycle, D-Vd, PFS (on treatment)	Gamma	400,00	0,00	0,22
Haematologist visit, Resource use per cycle, D-Vd, PFS (off treatment)	Gamma	400,00	0,00	0,21
Haematologist visit, Resource use per cycle, D-Vd, PD	Gamma	400,00	0,00	0,08
Blood test, Resource use per cycle, D-Vd, PFS (on treatment)	Gamma	400,00	0,00	0,21
Blood test, Resource use per cycle, D-Vd, PFS (off treatment)	Gamma	400,00	0,00	0,21
Blood test, Resource use per cycle, D-Vd, PD	Gamma	400,00	0,00	0,37
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

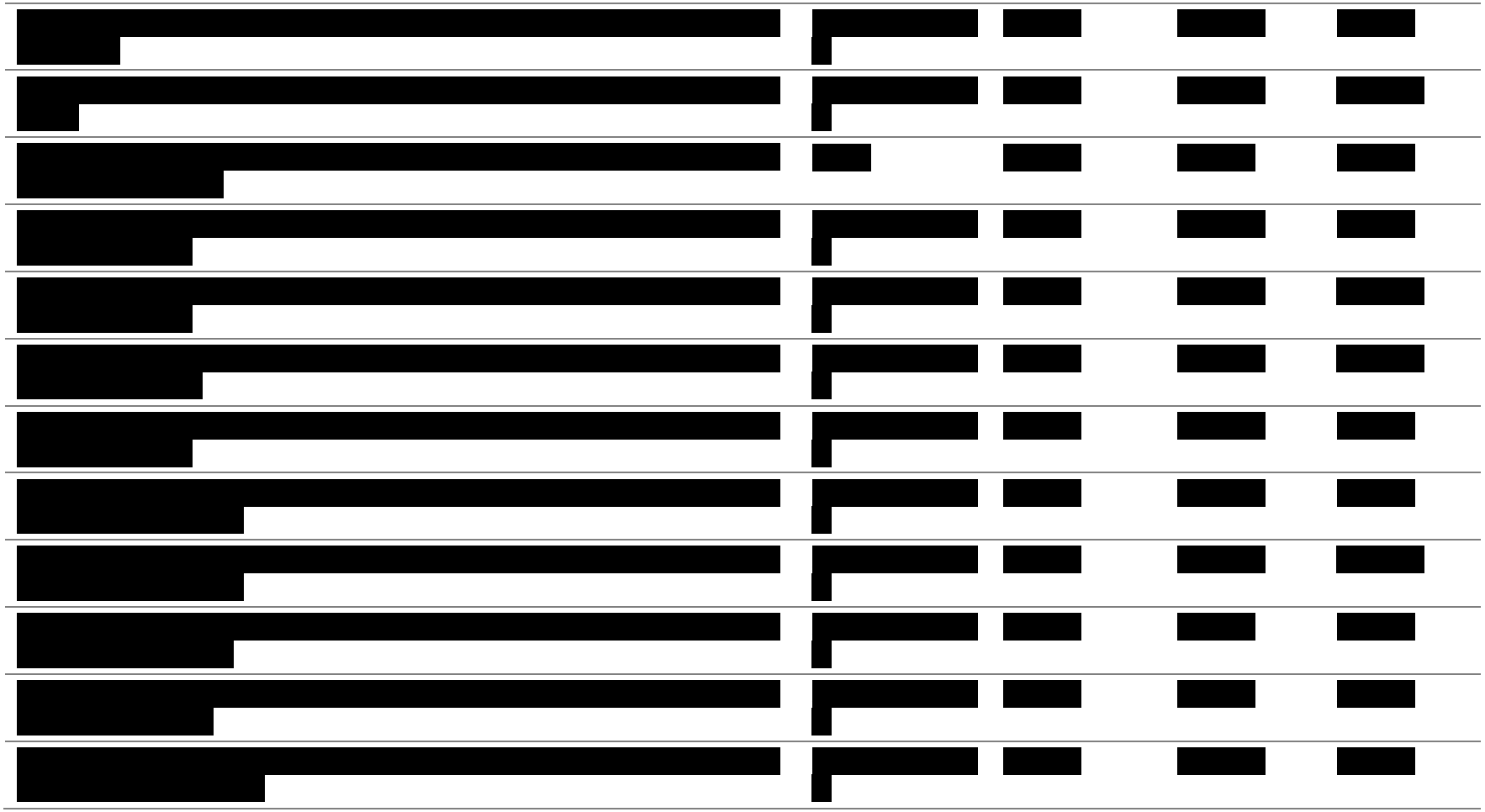
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Treatment duration (years), D-Vd, Daratumumab, Treatment cycles 10+ (days 1 only)	Normal	0,23	0,01	0,23
Treatment duration (years), D-Vd, Bortezomib, Treatment cycles 1-9 (days 1, 4, 8 and 11)	Normal	0,52	0,03	0,52
Treatment duration (years), D-Vd, Dexamethasone, Treatment cycles 1-9 (days 1, 2, 4, 5, 8, 9, 11, and 15)	Normal	0,52	0,03	0,51
Treatment duration (years), Pd, Pomalidomide, All treatment cycles	Normal	0,75	0,04	0,79
Treatment duration (years), Pd, Dexamethasone, All treatment cycles	Normal	0,75	0,04	0,73
Treatment duration (years), P-Vd, Pomalidomide, All treatment cycles	Normal	0,75	0,04	0,68
Treatment duration (years), P-Vd, Bortezomib, Treatment cycles 1-8 (days 1, 4, 8 and 11)	Normal	0,46	0,02	0,47
Treatment duration (years), P-Vd, Dexamethasone, Treatment cycles 9+ (days 1, 2, 8 and 9)	Normal	0,29	0,01	0,30

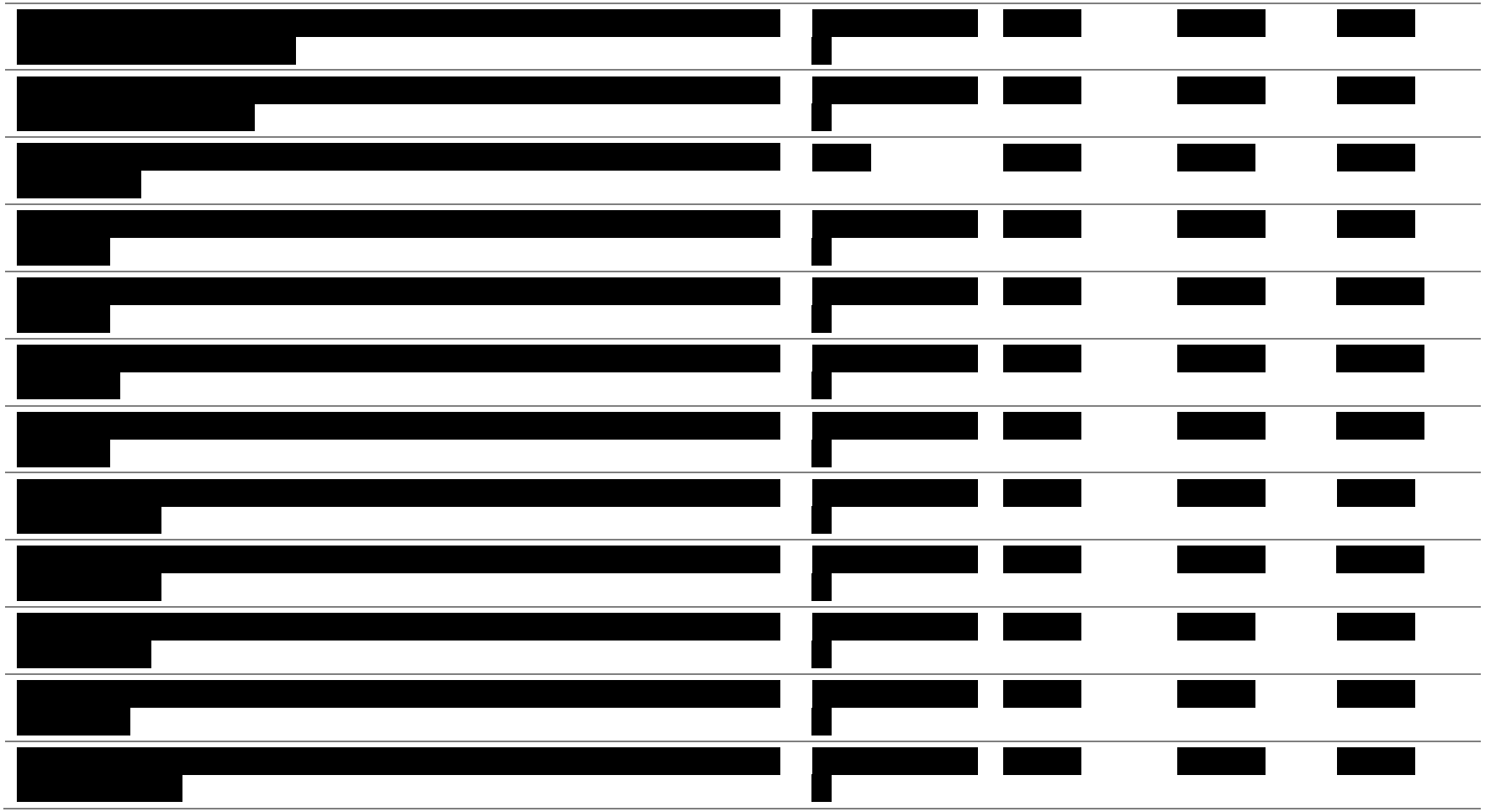
Treatment duration (years), Kd, Carfilzomib, Treatment cycle 2+	Normal	0,67	0,03	0,73
Treatment duration (years), Kd, Dexamethasone, All treatment cycles	Normal	0,75	0,04	0,79
Treatment duration (years), Rd, Lenalidomide, All treatment cycles	Normal	0,75	0,04	0,79
Treatment duration (years), Rd, Dexamethasone, All treatment cycles	Normal	0,75	0,04	0,71
Treatment duration (years), Teclistamab, Teclistamab, Treatment cycle 2+	Normal	0,73	0,04	0,69
Proportion of patients (first subsequent treatment), B-Vd	Beta	87,22	24,60	0,80
Proportion of patients (first subsequent treatment), D-Vd	Beta	87,22	24,60	0,76
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients (second subsequent treatment)	Beta	156,03	100,43	0,60
Subsequent treatment (3L): D-Rd, Treatment arm: B-Vd	Beta	199,50	199,50	0,51
Subsequent treatment (3L): Pd, Treatment arm: B-Vd	Beta	299,75	899,25	0,26
Subsequent treatment (3L): Kd, Treatment arm: B-Vd	Beta	299,75	899,25	0,26
Subsequent treatment (3L): Pd, Treatment arm: D-Vd	Beta	199,50	199,50	0,54
Subsequent treatment (3L): Kd, Treatment arm: D-Vd	Beta	199,50	199,50	0,51
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment (4L): Pd, Treatment arm: B-Vd	Beta	319,80	1279,20	0,19
Subsequent treatment (4L): Kd, Treatment arm: B-Vd	Beta	319,80	1279,20	0,20

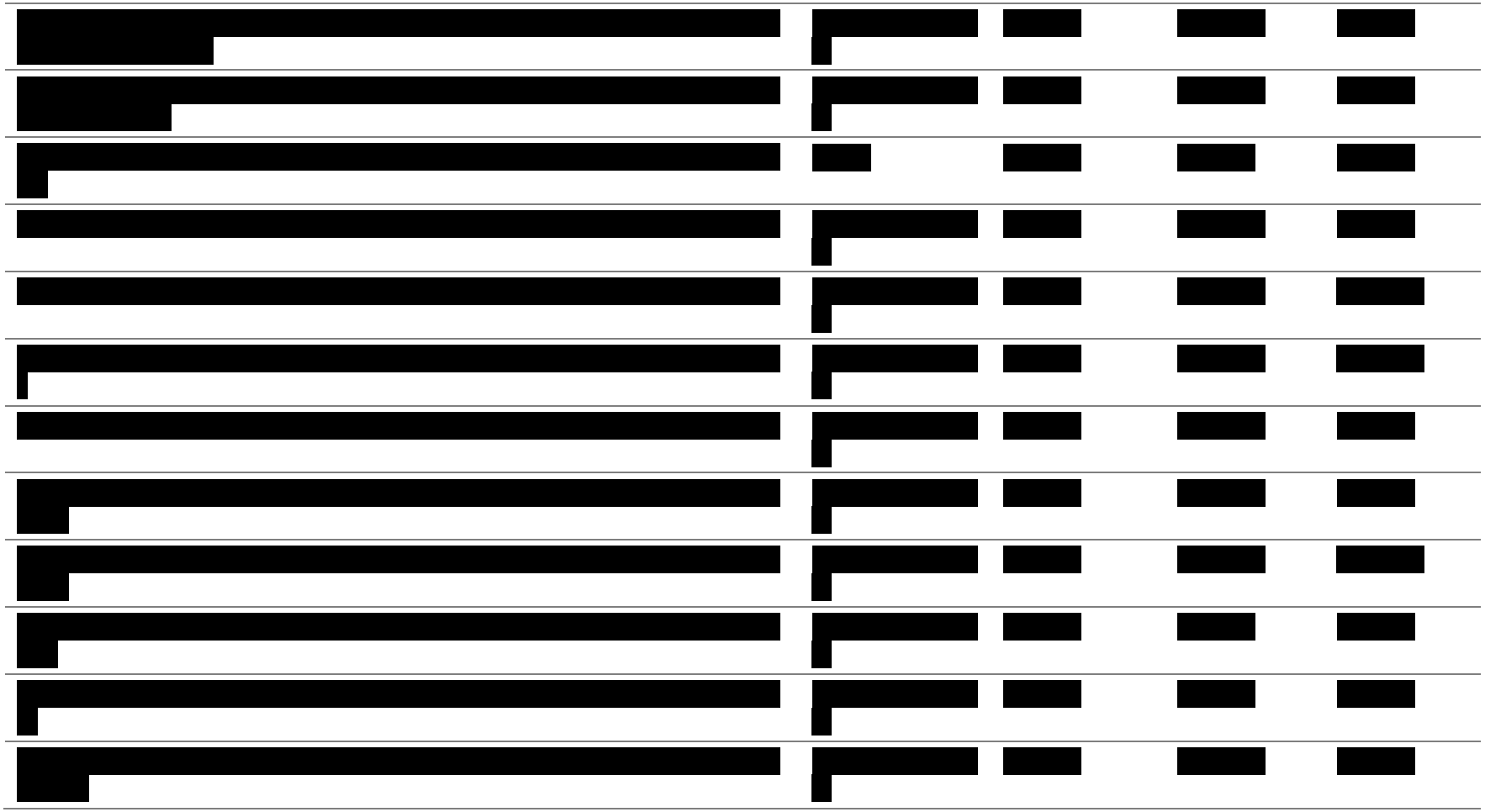
Subsequent treatment (4L): Teclistamab, Treatment arm: B-Vd	Beta	159,40	106,27	0,58
Subsequent treatment (4L): Pd, Treatment arm: D-Vd	Beta	319,80	1279,20	0,20
Subsequent treatment (4L): Kd, Treatment arm: D-Vd	Beta	319,80	1279,20	0,21
Subsequent treatment (4L): Teclistamab, Treatment arm: D-Vd	Beta	159,40	106,27	0,54
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events, Disutility, Neutropenia	Beta	341,86	2015,77	0,15
Adverse events, Disutility, Anaemia	Beta	275,69	613,63	0,29
Adverse events, Disutility, Febrile neutropenia	Beta	339,85	1925,82	0,16
Adverse events, Disutility, Pneumonia	Beta	323,81	1380,45	0,19
Disutility, Keratopathy (Grade 2 only)	Beta	371,93	4941,36	0,06
Disutility, Blurred vision (Grade 2 only)	Beta	371,93	4941,36	0,07
Disutility, Dry eyes (Grade 2 only)	Beta	371,93	4941,36	0,07
Disutility, Keratopathy (Grade 3+)	Beta	335,84	1763,16	0,15
Disutility, Blurred vision (Grade 3+)	Beta	335,84	1763,16	0,16
Disutility, Dry eyes (Grade 3)	Beta	335,84	1763,16	0,17
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

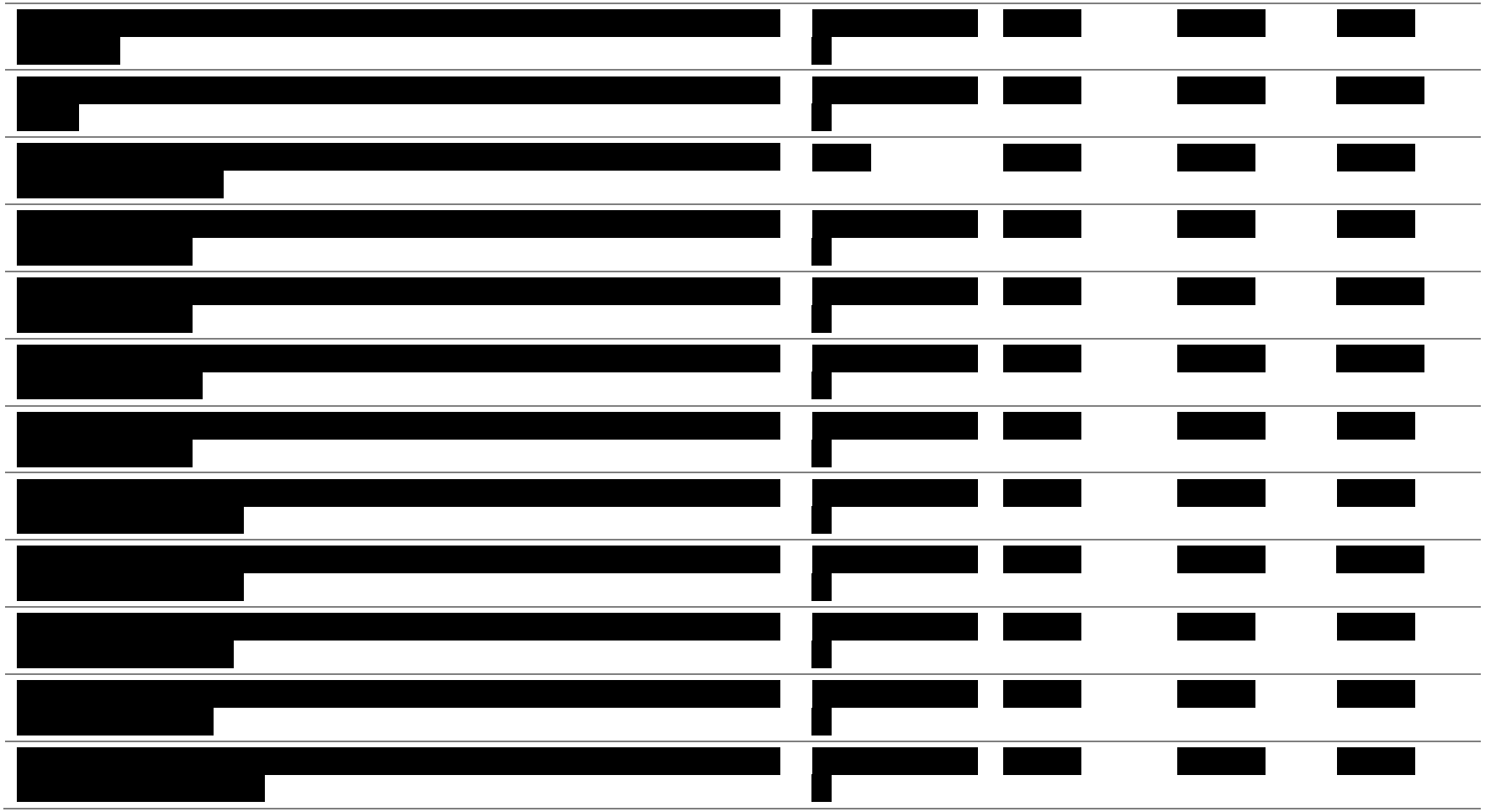












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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

The objective of the comprehensive global clinical SLR is to find clinical evidence to summarize the efficacy and safety data from RCTs for treatment regimens in RRMM. A SLR was conducted following the recommendations of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist. Comprehensive multi-string search strategies were used to search electronic databases. An adapted version of the published filters from the Scottish Intercollegiate Guidelines Network (SIGN) were used to target randomized controlled trials as a study design. The search strategies are provided in Section 0. The following electronic databases (Table 40 and Table 41) were searched from 2008 to December 2021 in the first iteration of the review and then December 2021 to March 2023 (cut-off date 26 March 2023) for the second iteration of the review, and from October 2023 for the last iteration (cut-off 4 March 2024).

Table 40: Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	2008 until latest search	04.02.2024
Medline	nlm.nih.gov	2008 until latest search	04.02.2024
CENTRAL	Cochranelibrary.com	2008 until latest search	04.02.2024

Table 41: Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search (latest)
Clinical Trials	Clinicaltrials.gov	Table - XXVII	04.02.2024
International Clinical Trials Registry Platform (ICTRP)	https://trialsearch.who.int/	Table - XXVIII	04.02.2024
The International Network of Agencies for Health	https://database.inahta.org/	Table - XXVI	04.02.2024

Technology Assessment database (INAHTA)			
Centre for Reviews and Dissemination (CDR) [Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessments (HTA)]	https://www.crd.york.ac.uk/CRDWeb/	Table - XXV	04.02.2024

Supplementary searching included screening of reference lists of recent and relevant SLRs and NMAs for additional trials not identified through the electronic database search. The following conference proceedings (Table 42) were also searched when not already indexed for the given year in Embase.

Table 42: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search (latest)
American Association for Cancer Research (AACR)	Conference website	Screening reference lists of recent and relevant SLRs and NMAs	Based on inclusion and exclusion criteria	04.02.2024
American Society for Clinical Oncology (ASCO)	Conference website	Screening reference lists of recent and relevant SLRs and NMAs	Based on inclusion and exclusion criteria	04.02.2024
American Society of Hematology (ASH)	Conference website	Screening reference lists of recent and relevant SLRs and NMAs	Based on inclusion and exclusion criteria	04.02.2024
European Society for Medical Oncology (ESMO)	Conference website	Screening reference lists of recent and relevant SLRs and NMAs	Based on inclusion and exclusion criteria	04.02.2024
Society of Hematologic Oncology (SOHO)	Conference website	Screening reference lists of recent and relevant SLRs and NMAs	Based on inclusion and exclusion criteria	04.02.2024

European Hematology Association (EHA)	Conference website	Screening reference lists of recent and relevant SLRs and NMAs	Based on inclusion and exclusion criteria	04.02.2024
International Myeloma Workshop (IMW)	Conference website	Screening reference lists of recent and relevant SLRs and NMAs	Based on inclusion and exclusion criteria	04.02.2024
Controversies in Multiple Myeloma (COMy)	Conference website	Screening reference lists of recent and relevant SLRs and NMAs	Based on inclusion and exclusion criteria	04.02.2024
European Myeloma Network (EMN)	Conference website	Screening reference lists of recent and relevant SLRs and NMAs	Based on inclusion and exclusion criteria	04.02.2024

*In cases when the conference was covered in Embase at the time of search for the indicated years, we relied on the search string to yield the relevant conference abstracts. In cases where the conference for the given year was not yet indexed in Medline at the time of search, we searched the conference by hand.
**Could not retrieve.
***Searched ASH database for the given year for "myeloma" and "clinical trials", subsequently for mention of relapsed or refractory.

H.1.1 Search strategies

The search strategies for the different places are described in the tables below.

Table - XXI: Medline search strategy (original search)

	Search #	Query	Number of Citations
Date of Search		**01 December 2021**	
Database Name		**Ovid MEDLINE(R) ALL: 1946 to November 30, 2021**	
Study population	#1	Multiple Myeloma/	**43401**
	#2	myelom*.ti,ab,kw.	**68409**
	#3	(kahler* adj3 (disease* or morbus)).ti,ab,ot,kw.	**243**
	#4	or/1-3	**75781**
	#5	(relaps* or refract* or recurren* or resist*).tw.	**2032052**
	#6	(prior treatment* or prior therap* or (previous* adj1 treat*)).tw.	**37726**
	#7	(second line or 2nd line).tw.	**26027**
	#8	(third line or 3rd line).tw.	**4781**
	#9	(fourth line or 4th line).tw.	**744**
	#10	(fail* adj3 (first line or 1st line)).tw.	**2097**

	#11	or/5-10	**2074025**
	#12	4 and 11	**12911**
Study design	#13	Randomized Controlled Trials as Topic/	**150719**
	#14	randomized controlled trial/	**150719**
	#15	Random Allocation/	**106258**
	#16	Double Blind Method/	**168663**
	#17	Single Blind Method/	**31274**
	#18	clinical trial/	**532529**
	#19	clinical trial, phase i.pt.	**22725**
	#20	clinical trial, phase ii.pt.	**36440**
	#21	clinical trial, phase iii.pt.	**19493**
	#22	clinical trial, phase iv.pt.	**2228**
	#23	controlled clinical trial.pt.	**94570**
	#24	randomized controlled trial.pt.	**552166**
	#25	multicenter study.pt.	**309717**
	#26	clinical trial.pt.	**532529**
	#27	exp Clinical Trials as topic/	**367195**
	#28	(clinical adj trial*).tw.	**418666**
	#29	((phase1 or phase i or phase one or phase 2 or phase ii or phase two or phase 3 or phase iii or phase three or phase 4 or phase iv or phase four) adj2 trial*).ti,ab.	**61490**
	#30	((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).tw.	**184578**
	#31	((single arm or single group or non-random*) adj2 (trial* or stud*)).ti,ab.	**15343**
	#32	PLACEBOS/	**35783**
	#33	placebo$.tw.	**230758**
	#34	randomly allocated.tw.	**32374**
	#35	(allocated adj2 random*).tw.	**35897**
	#36	or/13-35	**1796796**
Filters, combinations and limits	#37	case report.tw.	**349151**
	#38	letter/	**1160927**
	#39	historical article/	**366715**
	#40	Comment/	**940451**
	#41	Letter/	**1160927**
	#42	Editorial/	**588266**
	#43	or/37-42	**2700674**

	#44	36 not 43	**1730089**
	#45	animal/ not human/	**4889858**
	#46	44 not 45	**1632762**
	#47	12 and 46	**3168**
	#48	limit 47 to english language	**3046**
	#49	**limit 48 to yr="2008 -Current"**	**Final 2074**

Table - XXII: Embase search strategy (original search)

	Search #	Query	Number of Citations
Date of Search		**01 December 2021**	
Database Name		**Ovid Embase: 1974 to 2021 November 30**	
Study population	#1	multiple myeloma/	**84627**
	#2	myelom*.ti,ab,kw.	**105760**
	#3	(kahler* adj3 (disease* or morbus)).ti,ab,ot,kw.	**111**
	#4	or/1-3	**123528**
	#5	(relaps* or refract* or recurren* or resist*).tw.	**123528**
	#6	(prior treatment* or prior therap* or (previous* adj1 treat*)).tw.	**74565**
	#7	(second line or 2nd line).tw.	**49579**
	#8	(third line or 3rd line).tw.	**10885**
	#9	(fourth line or 4th line).tw.	**1871**
	#10	(fail* adj3 (first line or 1st line)).tw.	**3773**
	#11	or/5-10	**2814660**
	#12	4 and 11	**30656**
Study design	#13	Clinical Trial/	**1019596**
	#14	Randomized Controlled Trial/	**684894**
	#15	controlled clinical trial/	**464483**
	#16	multicenter study/	**307053**
	#17	phase 1 clinical trial/	**61272**
	#18	phase 2 clinical trial/	**92644**
	#19	Phase 3 clinical trial/	**57395**
	#20	Phase 4 clinical trial/	**4552**
	#21	exp RANDOMIZATION/	**92509**
	#22	Single Blind Procedure/	**44436**
	#23	Double Blind Procedure/	**189943**
	#24	Crossover Procedure/	**68765**

	#25	PLACEBO/	**373975**
	#26	randomi?ed controlled trial*.tw.	**271363**
	#27	rct.tw.	**44377**
	#28	(random* adj2 allocat*).tw.	**48237**
	#29	single blind*.tw.	**27883**
	#30	double blind*.tw.	**225237**
	#31	((treble or triple) adj blind*).tw.	**1461**
	#32	((phase1 or phase i or phase one or phase 2 or phase ii or phase two or phase 3 or phase iii or phase three or phase 4 or phase iv or phase four) adj2 trial*).ti,ab.	**117292**
	#33	((single arm or single group or non-random*) adj2 (trial* or stud*)).ti,ab.	**24485**
	#34	placebo*.tw.	**334723**
	#35	Prospective Study/	**728168**
	#36	or/13-35	**2681856**
Filters, combinations and limits	#37	Case Study/	**82414**
	#38	case report.tw.	**468108**
	#39	abstract report/ or letter/	**1217643**
	#40	Editorial.pt.	**708659**
	#41	Letter.pt.	**1198512**
	#42	Note.pt.	**873365**
	#43	or/37-42	**3409091**
	#44	36 not 43	**2548419**
	#45	12 and 44	**8268**
	#46	(conference paper or conference abstract).pt.	**5023486**
	#47	45 not 46	**2983**
	#48	limit 46 to yr="2019 -Current"	**879611**
	#49	45 and 48	**1904**
	#50	47 or 49	**4887**
	#51	exp animal/ or exp animal experiment/ or nonhuman/	**29761417**
	#52	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or animal or pig or pigs or porcine or rabbit or rabbits or animal or animals or dog or dogs or cat or cats or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.	**6466843**
	#53	or/51-52	**29961977**
	#54	exp human/ or exp human experiment/	**22970252**

	#55	53 not (53 and 54)	**6992762**
	#56	(editorial or letter or comment or note).pt.	**2780536**
	#57	50 not (55 or 56)	**4833**
	#58	limit 57 to english language	**4731**
	#59	**limit 58 to yr="2008 -Current"**	**Final 3749**

Table - XXIII: Combined Medline and Embase search strategy (Update 1)

Set#	Searched for	Results Update 1	Results Update 2**
S1	TI,AB("multiple myeloma")	123679*	133515*
S2	TI,AB,IF(myelom*)	217556*	208587*
S3	TI,AB(kahler* NEAR/3 (disease* OR morbus))	472°	473°
S4	S1 OR S2 OR S3	217604*	208862*
S5	TI,AB(relaps* or refract* or recurren* or resist*)	5326656*	5692874*
S6	TI,AB("prior treatment" OR "prior treatments" OR "prior therapy" OR "prior therapies" OR (previous* NEAR/1 (treat*)))	153249*	163010*
S7	TI,AB("second line" or "2nd line")	84651*	91959*
S8	TI,AB("third line" or "3rd line")	17924*	19710*
S9	TI,AB("fourth line" or "4th line")	2229°	2437°
S10	TI,AB(fail* NEAR/3 ("first line" OR "1st line"))	7499*	8092*
S11	S5 OR S6 OR S7 OR S8 OR S9 OR S10	5479745*	5856574*
S12	S4 AND S11	47441*	50643*
S13	TI,AB((clinical NEAR/1 trial*) OR ((doubl* OR treb* OR tripl*) NEAR/1 (blind[*3] OR mask[*3] OR dummy)) OR ((control* OR equivalence OR superiority OR non-inferiority OR noninferiority OR pragmatic OR practical OR quasiexperimental OR quasi-experimental OR experimental OR phase) NEAR/3 (study OR studies OR trial* OR group*)) OR sham OR placebo* OR random* OR RCT) OR EMB.EXACT("clinical trial" OR "multicenter study" OR "phase 1 clinical trial" OR "phase 2 clinical trial" OR "phase 3 clinical trial" OR "phase 4 clinical trial" OR "double blind procedure" OR "crossover procedure" OR "placebo" OR "control group" OR "prospective study") OR EMB.EXACT.EXPLODE("randomization" OR "randomized controlled trial as topic" OR "controlled clinical trial") OR MESH.EXACT("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial" OR "Random Allocation" OR "Double Blind Method" OR	8509314*	9089386*

	"Clinical Trial" OR "Placebos") OR MESH.EXACT.EXPLODE("Clinical Trials as Topic")		
S14	EMB.EXACT("case study" OR "case report" OR "abstract report" OR "letter" OR "note") OR DTYPE("Letter" OR "Historical Article" OR "Editorial" OR "Note" OR "Comment" OR "News" OR "Newspaper Article" OR "Review") OR TI,AB("case study" or "case studies" OR "case report" OR "case reports")	15349089*	16179242*
S15	(S12 AND S13) NOT S14	12632*	13942*
S16	S15 NOT ((exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or exp plant/ or exp fungus/) not exp human/)	11745*	12981*
S17	S16 AND LA(english)	11493*	12717*
S18	S17 AND PD (relevant date inserted here)	740°	817°

* Duplicates are removed from the search, but included in the result count.
° Duplicates are removed from the search and from the result count.
** Includes combined search from two time points as per the report

Table - XXIV: Cochrane search strategies

Search #		Query	Number of Citations		
			02 Dec 2021	26 Mar 2023	04 Feb 2024
Study population and combinations	*#1*	MeSH descriptor: [Multiple Myeloma] this term only	1713	2106	**2454**
	#2	:ti,ab,kw	6463	7024	**7571**
	#3	(kahler* near/3 (disease* or morbus)):ti,ab,kw	7	7	**7**
	#4	#1 or #2 or #3	5240	571	**7571**
	#5	(relaps* or refract* or recurren* or resist*):ti,ab,kw	195347	212124	**237351**
	#6	("prior treatment*" or "prior therap*" or (previous* near/1 treat*)):ti,ab,kw	11296	12480	**14178**
	#7	("second line" or "2nd line"):ti,ab,kw	6345	6907	**8030**
	#8	("third line" or "3rd line"):ti,ab,kw	1116	1231	**1461**
	#9	("fourth line" or "4th line"):ti,ab,kw	138	163	**201**
	#10	(fail* near/3 ("first line" or "1st line")):ti,ab,kw	674	723	**864**
	#11	#5 or #6 or #7 or #8 or #9 or #10	206644	224410	**250853**
Limits	***#12***	**#4 and #11 with Cochrane Library publication date Between Jan 2008 and Dec 2021 for original**	**Final 2240**	**Final 285**	**Final 119**

		search and Dec 2021 and Mar 2023 for the updated search			

Table - XXV: Centre for Reviews and Dissemination (CRD) search strategy*

	Search #	Query	Number of Citations
Date of Search		**02 Dec 2021**	
Database Name		**Database of Abstracts of Reviews of Effects (DARE): up to March 2015** **Heath Technology Assessments (HTA): up to March 2018**	
Study population and combinations	*#1*	MeSH DESCRIPTOR Multiple Myeloma EXPLODE ALL TREES	**180**
	#2	(myelom*) OR (Kahler and (disease* or morbus))	**274**
	#3	#1 OR #2	**274**
	#4	(relaps* or refract* or recurren* or resist*) OR ("prior treatment*" or "prior therap*" or "previous treat*") OR ("second line" or "2nd line")	**8864**
	#5	("third line" or "3rd line") OR ("fourth line" or "4th line") OR (fail* and ("first line" or "1st line"))	**505**
	#6	#4 OR #5	**9096**
	#7	#3 AND #6	**76**
Limits	***#8***	**(#7) IN DARE, HTA FROM 2008 TO 2021**	**Final 43**

*The specified database is no longer being updated. Relevant records are now being covered by INAHTA. This source was therefore not searched in the first update.

Table - XXVI: International Network of Agencies for Health Technology Assessment (INAHTA) Database search

	Search #	Query	Number of Citations		
Database Name		**International HTA Database (https://database.inahta.org/)**	**02 Dec 2021**	**26 Mar 2023**	**04 Feb 2024***
Study population and combinations	#1	"Multiple Myeloma"[mhe]	79	26	**14**
	#2	((myelom*) OR (Kahler and (disease* or morbus)))	91	26	**49**
	#3	#1 OR #2	99	26	**15**
	#4	((relaps* or refract* or recurren* or resist*) OR ("prior treatment*" or "prior therap*" or "previous treat*") OR ("second line" or "2nd line"))	1762	113	**59**
	#5	((("third line" or "3rd line") OR ("fourth line" or "4th line") OR	134	11	**7**

		(fail* and ("first line" or "1st line"))))			
	#6	#4 OR #5	1838	119	**65**
	#7	#6 AND #3	32	3	**6**
Limits			**Final 32**	**Final 3**	**Final 6**

*searched records available from 2023 to 2024

Table - XXVII: Clinicaltrials.gov search strategy

	Search #	Query	Number of Citations		
Database Name		**Clinicaltrials.gov**	**02 Dec 2021**	**26 Mar 2023**	**04 Feb 2023**
((relaps* OR refract* OR recurren* OR resist* OR EXPAND[Concept] "prior treatment*" OR EXPAND[Concept] "prior therap*" OR EXPAND[Concept] "previous treat*" OR EXPAND[Concept] "second line" OR EXPAND[Concept] "2nd line" OR EXPAND[Concept] "third line" OR EXPAND[Concept] "3rd line" OR EXPAND[Concept] "fourth line" OR EXPAND[Concept] "4th line" OR EXPAND[Concept] "treatment fail*" OR EXPAND[Concept] "failure of treatment*") AND AREA[ConditionSearch] Multiple Myeloma) OR AREA[ConditionSearch] Multiple Myeloma in Relapse AND AREA[ResultsFirstPostDate] RANGE[01/01/2008, MAX]			**221**	**168**	**68**

Table - XXVIII: International Clinical Trials Registry Platform (ICTRP) search strategy

	Search #	Query	Number of Citations		
Database Name		**International Clinical Trials Registry Platform (ICTRP)**	**02 Dec 2021**	**26 Mar 2023**	**04 Feb 2024**
(multiple myeloma AND relaps*) OR (multiple myeloma AND refract*) OR (multiple myeloma AND recurren*) OR (multiple myeloma AND prior treatment*) OR (multiple myeloma AND prior therap*) OR (multiple myeloma AND failed treatment*) OR (multiple myeloma AND previous treatment*) OR (multiple myeloma AND second line) OR (multiple myeloma AND line) In title			**713**	**91**	**29**

H.1.2 Systematic selection of studies

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnote, de-duplicated and then transferred to Covidence, an online SLR workflow platform for screening of title/abstracts/full-texts, and for review management.

Titles and abstracts identified by the search strategy were independently assessed for possible eligibility by two reviewers. Those studies that did not meet eligibility criteria were excluded. For those citations that were deemed potentially relevant, full texts were retrieved, and eligibility criteria applied. Any discrepancies between the two reviewers were resolved by a third senior reviewer. Reviewers documented all reasons for exclusion of full text articles.

To be included in the comprehensive global SLR, studies were required to meet all of the inclusion criteria presented in Table 43. The Eligibility criteria was applied following the Population-Intervention-Comparators-Outcomes-Study design (PICOS) framework, in line with PRISMA-P guidance.

Based on the selection made in the comprehensive global SLR, we have made some adjustments the selection to better fit Danish clinical practice. The modifications primarily focused on the PICOS framework, ensuring relevance to the local context. The primary adjustment involved the selection of interventions.

[redacted]

Table 43: Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	• Adults (aged ≥18 years) with documented MM, previously treated with at least 1 prior line of therapy, and with documented disease progression during or after most recent therapy	• Treatment-naïve patients	None
Intervention	Any treatment or combination of treatments, including but not restricted to: **Anti-BCMA ADC therapies:** Belantamab mafodotin (GSK 916) and other ADC therapy **Proteasome inhibitors:** Bortezomib, carfilzomib, ixazomib and other PIs **Immunomodulatory drugs:** Lenalidomide, pomalidomide, thalidomide and other IMiDs **Corticosteroids:** Dexamethasone and others **Alkylating agents:** Cyclophosphamide, cisplatin, melphalan, bendamustin and others **Peptide-drug conjugates:** Melphalan flufenamide and others **Other chemotherapeutic agents:** e.g., doxorubicin, etoposide and others **HDAC inhibitors:** Panobinostat and others **Anti-CD-38 therapies:** Daratumumab, Isatuximab and others	• Surgery • Palliative treatment • Radiotherapy • Autologous stem cell transplant (ASCT) alone	• [redacted] • [redacted]

Anti-SLAMF7 therapies (CS1/CD319/CRACC): Elotuzumab

Exportin1 (chromosome region maintenance 1) antagonists:

Selinexor

Programmed cell death protein 1 (PD-1)/ Programmed death ligand 1(PD-L1) inhibitors: Pembrolizumab, Nivolumab and others

Anti-CTLA4:

Ipilimumab

Anti-APRIL therapies:

BION-1301

BcL-2 inhibitors:

Venetoclax

eEF1A2 antagonists:

Plitidepsin

VEGFR inhibitors:

Vatalanib

HSP90 inhibitors:

Tanespimycin

Hypomethylating agents:

Azacytidine

Anti-BCMA-CAR-T cell therapies:

Idecabtagene vicleucel (Ide-cel)

T-cell therapies:

	Elotuzumab Bispec, Cilta-cel, REGN-5458, CC-93269, Letetresgene autoleucel (lete-cel) **Anti-BCMA CD3/BiTE therapies:** Elranatamab (PF-06863135), Teclistamab (JNJ-64007957), Talquetamab (JNJ-64407564) AMG 420, AMG 701, TNB-383B, Descartes-08 **CELMoD:** CC-92480, Iberdomide (CC-220) **Bromodomain and extra-terminal inhibitors:** RO6870810 **Radiopharmaceuticals:** CLR-131 and others		
Comparators	• Between above intervention comparisons • Standard of care / best supportive care • Placebo or no treatment	• Dose finding /single intervention comparisons	• Similar to intervention
Outcomes	**Efficacy outcomes, including but not restricted to:** OS, PFS, PFS2, CR, sCR, PR, VGPR, MR, SD, PD, PPS, MRD negativity, ORR, DoR, TTBR, TTR, TTP, TTTF, TTNT **Safety outcomes, including but not restricted to:** • Total AEs greater than 5%: Hematological AEs (total), Non-hematological AEs (total), Grade 3+ AEs, total TRAEs, grade 3+ TRAEs, total SAEs (≥5%), discontinuations due to AEs, time to treatment discontinuation, treatment-related deaths	• Studies not reporting any outcomes of interest • Studies that do not report outcomes of interest for the population (2L+ RRMM)	None

	• Target AE's (regardless of % reported): The following AEs will be included (total and grade 3+): anemia, constipation, CRS, diarrhea, dyspnea, fatigue, febrile neutropenia, HLH/MAS, ICANS, neutropenia, ocular toxicity, pneumonia, pyrexia, thrombocytopenia, URTI, hepatic toxicity, neurotoxicity, leukopenia		
Study design	Primary and post-hoc analyses of: • RCTs*	• Observational studies (retrospective, prospective, cohort studies, longitudinal studies, case series) • Non-randomized controlled trials • Single arm clinical trials • Pilot studies, Phase I or IIa trials reporting pharmacokinetic or pharmacodynamic outcomes • Case studies/case reports • Systematic reviews and meta-analyses** • *In vitro* and animal studies	None
Publication type	• Full-text peer-reviewed articles • Clinical trial records • Conference abstracts	• Narrative reviews, editorials, protocols,	None

	• Relevant GSK clinical study reports if available		letters, notes or comments	
Language restrictions	• English language only	•	Non-English language	None

Note:

**For studies with mixed patient populations, ≥80% of patients must have had ≥1 prior therapy for inclusion*

***Reference lists of systematic literature reviews were evaluated to identify any potential trial not captured through the database searches*

^Given the large amount of available evidence by the time of the second iteration of the review, in that iteration, we focused on primary reports of phase 3 RCTs, though phase 1 / 2 RCTs trials and non-primary reports of phase 3 RCTs were identified and collected separately.

In the initial iteration of the review, electronic searches were conducted on December 20, 2021, and returned 6300 potentially eligible publications after removal of duplicates. Of these, 4781 were excluded at the title and abstract screening stage as they did not meet the inclusion criteria, and 1519 were retrieved for full-text review. Supplementary searching of conferences and reference lists identified an additional 11 publications for inclusion when assessed against the eligibility criteria. A PRISMA flow diagram of the search process is provided in Figure 36, Figure 37 and Figure 38.

In total, 175 publications were included in the original review. Of the excluded studies 377 publications were excluded due to study design.

The search was re-applied for Update 1 on 26 March 2023 and yielded 1,286 records. After 360 duplicates were removed, we screened the titles and abstracts of 927 studies, of which 708 were excluded for miscellaneous reasons. The full texts of 219 records were screened against the PICOS criteria, and 207 studies were then excluded at this step. The most common reason for exclusion was the study design. A total of 179 studies qualified to be retained. Subsequently 12 studies were selected (representing 12 trials) for extraction and inclusion.

The search was then applied two additional times (October 18, 2023 [searching studies since March 26, 2023] and February 4, 2024 [searching studies since October 18, 2023]). The hits from these two searches were combined into a single update. A total of 193 studies qualified to be retained. Subsequently 14 studies were selected (representing 13 trials) for extraction and inclusion.

Figure 36: PRISMA flow diagram of identified publications (original search)

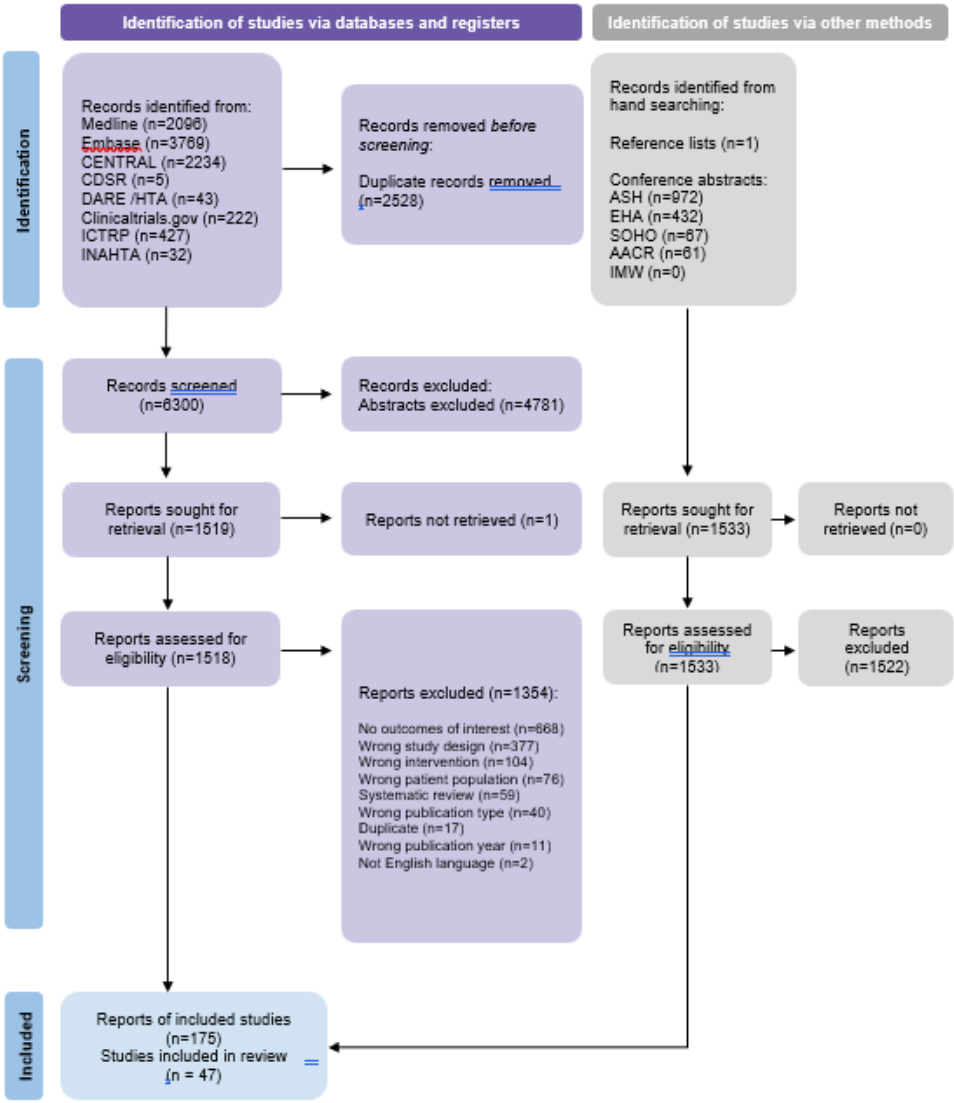
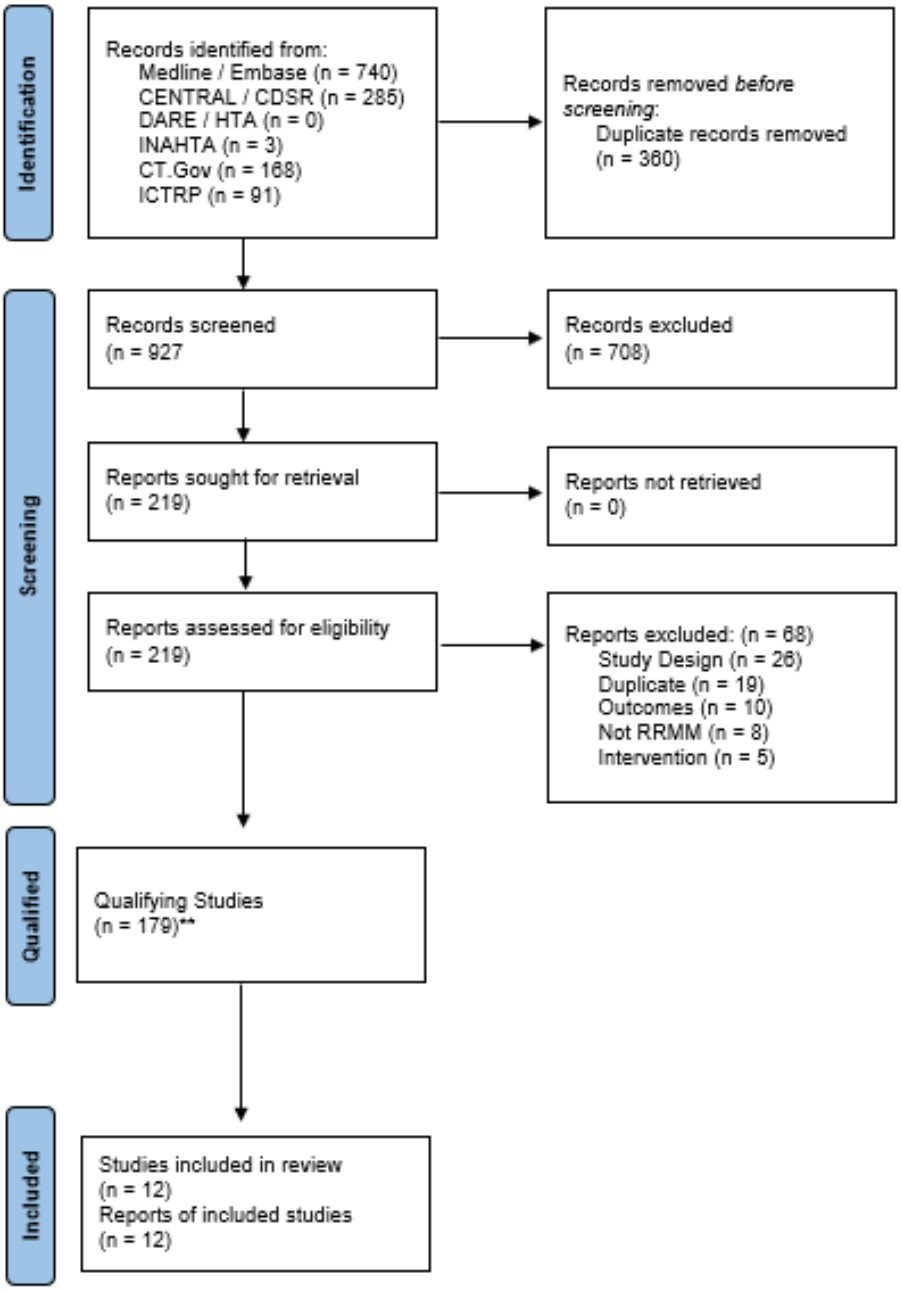
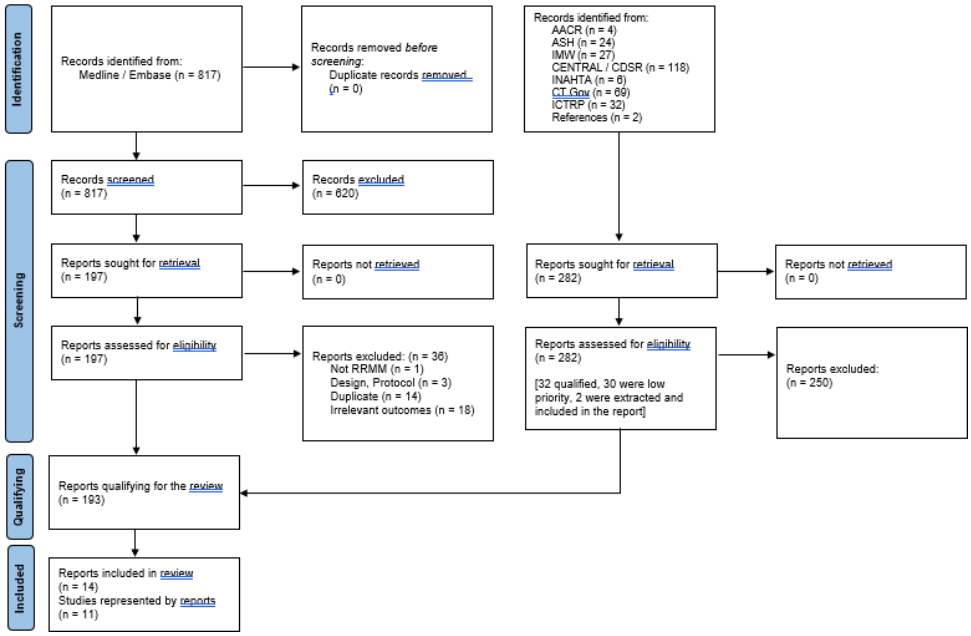


Figure 37: PRISMA flow diagram of identified publications (update 1)



**In the first review update, we continued to screen and select studies as per the protocol. However, we did not extract all qualifying studies but instead focused on extracting studies that were judged to be most relevant. A list of qualifying studies that were not extracted is given in Supplemental Appendix E. Most qualifying studies that were not included for extraction were Phase 1 or Phase 1/2 studies that were not randomized or were single arm.

Figure 38: PRISMA flow diagram of identified publications (update 2)



**In the second review update, we continued to screen and select studies as per the protocol. However, we did not extract all qualifying studies but instead focused on extracting studies that were judged to be most relevant. Most qualifying studies that were not included for extraction were Phase 1 or Phase 1/2 studies that were not randomized or were single-arm or were selected abstracts for which full text versions will be more useful once published.

The global comprehensive review included 163 Phase 3 study reports and 41 Phase 2 study reports. However, as described earlier we made some adjustments to the PICOS framework to guide the following selection of studies to fit Danish clinical practice. An overview of included studies that are used as clinical evidence in the current application to summarize the efficacy and safety data can be found in Table 44. The full list of studies found in the global comprehensive SLR can be found in the embedded excel file below.

AppendixC_Included_Studies.xlsx

Table 44: Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
DREAMM-7 (NCT04246047)	Evaluation of efficacy and safety of belantamab mafodotin in combination with bortezomib and dexamethasone compared to daratumumab in combination with bortezomib and dexamethasone	RCT, phase III	Patients with RRMM who have received at least one prior line of therapy	Belantamab mafodotin plus bortezomib and dexamethasone (n=243) vs daratumumab plus bortezomib and dexamethasone (n=251).	PFS (time frame: up to approx. 41 months)	CRR, ORR, CBR, DoR, TTR, TTP, OS, PFS2, MRD (time frame: up to 73 months)
CASTOR [78] (NCT01620879)	Evaluation of efficacy and safety of daratumumab in combination with bortezomib and dexamethasone compared to bortezomib and dexamethasone.	RCT, phase III	Patients with RRMM who have received at least one prior line of therapy	Daratumumab plus bortezomib and dexamethasone (n=251) vs bortezomib and dexamethasone (n=247).	PFS (time frame: approx. 1 year 4 months)	TTP, VGPR response, ORR, OS, MRD (time frame: up to6 years 9 months)
POLLUX [39, 40] (NCT02076009)	Evaluation of efficacy and safety of daratumumab in combination with lenalidomide and dexamethasone compared to lenalidomide and dexamethasone.	RCT, phase III	Patients with RRMM who have received at least one prior line of therapy	Daratumumab plus lenalidomide and dexamethasone (n=286) vs lenalidomide and dexamethasone (n=283).	PFS (time frame: up to 21 months)	TTP, VGPR response, MRD, ORR, OS, TTR, DoR (time frame: up to 21 months)

APEX [51] (NCT00048230)	Evaluation of efficacy and safety of bortezomib with high-dose dexamethasone.	RCT, phase III	Patients with RRMM who have received at least one prior line of therapy	Bortezomib (n=333) vs high-dose dexamethasone (n=336)	TTP (time frame: 39 weeks)	OS, one-year survival rate, VGPR response rate, DoR, time to first infection (grade 3 or higher), incidence of grade 3 or higher infections, and time to first skeletal event.
MM-009 [79] (NCT00056160)	Evaluation of efficacy and safety of lenalidomide plus dexamethasone with placebo plus dexamethasone.	RCT, phase III	Patients with RRMM who have received at least one prior line of therapy	Lenalidomide plus dexamethasone (177) vs place plus dexamethasone (176)	TTP (time frame: approx. 1 year)	OS, response rate, safety
MM-010 [79] (NCT00424047)	Evaluation of efficacy and safety of lenalidomide plus dexamethasone with placebo plus dexamethasone.	RCT, phase III	Patients with RRMM who have received at least one prior line of therapy	Lenalidomide plus dexamethasone (177) vs place plus dexamethasone (176)	TTP (time frame: approx. 1 year)	OS, response rate, safety

H.1.3 Excluded full text references

A list of all studies excluded in the comprehensive global SLR can be found in the embedded excel file below.

AppendixB_Excluded_
Full_Text_Studies.xlsx

H.1.4 Quality assessment

Assessment of study quality was undertaken using the Cochrane risk of bias assessment tool for randomized trials (RoB2) [80]; the tool assesses the internal validity of RCTs considering different types of bias such as selection, performance, detection, attrition and reporting bias. The assessment was conducted by two independent reviewers with any discrepancies resolved through consensus or the involvement of a senior reviewer. Guidance and algorithms published by the Cochrane Methods group were used to assist the assessment process. Only full text publications were assessed for quality, and where multiple publications were identified for a trial, only the primary publication was assessed.

H.1.5 Unpublished data

Not applicable.

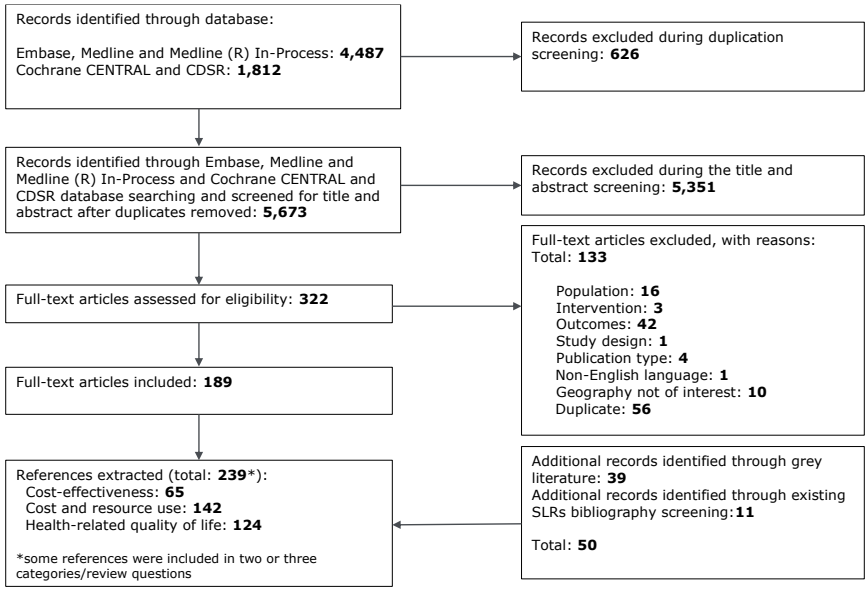
Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

The SLR was conducted according to the NICE guidelines, with respect to technology appraisal (TA) submissions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the Cochrane Handbook for Systematic Reviews of Interventions, to ensure methodological quality.

The SLR specified three review questions, which sought to identify cost-effectiveness, cost and resource use, and health-related quality of life references in patients with RRMM who have had at least one prior line of therapy. Searches were performed on January 31st 2023 (Figure 39) , using pre-defined search strategies in the following databases: Embase, Medline and Medline (R) In-Process (Embase interface 1947 to present), Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) (via Cochrane Library). References were reviewed and selected by two independent reviewers based on title and abstract (first pass) and then full-text articles (second pass). Disagreements were resolved by a third reviewer. In addition, grey literature searching was performed in AMCP/ Nexus, ASCO ASH, BSH, EBMT, EHA, EMN, ESMO, IMW, ISPOR conferences proceedings as well as the NICE, CADTH/pCODR, SMC, G-BA/IQWiG, HAS, and PBAC websites. References meeting the selection criteria were extracted by one reviewer and assessed for quality by a second reviewer.

Figure 39: PRISMA - January 2023 search



To capture all relevant publications, a 15-years' time limit (2008 - present) was applied in the database searches. However, for the previous HTA assessments, 10-years' time limit was applied. For the grey literature search, the time frame was limited to the past 3 years.

The first update of the search was run on January 8th 2024 (Figure 40), using the same methodology as the search ran on January 31st 2023. A second update of the search was run on April 15th 2024 (Figure 41), using the same methodology as the search ran on January 31st 2023. For this update, one additional website was screened (Haematological Malignancy Research Network [HMRN]) with the same time frame as all other grey literature (three years).

Figure 40: PRISMA January 2024 search

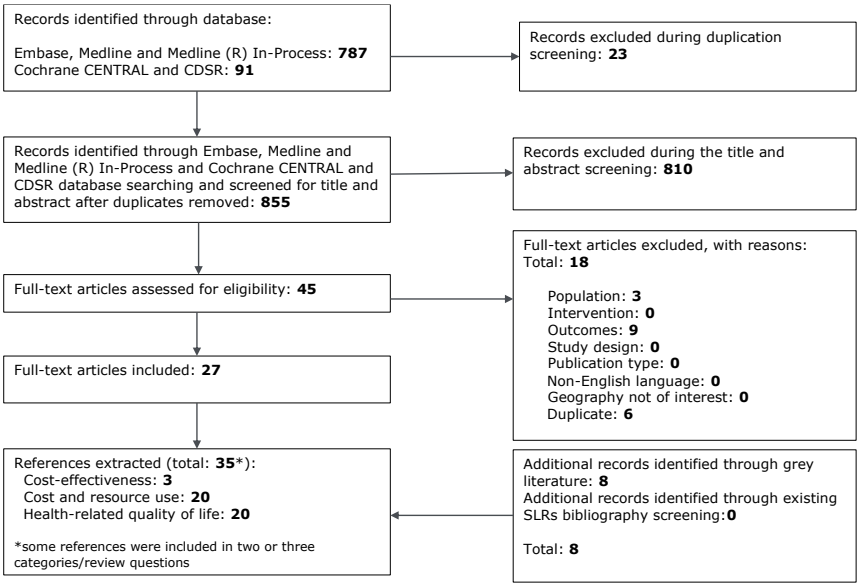
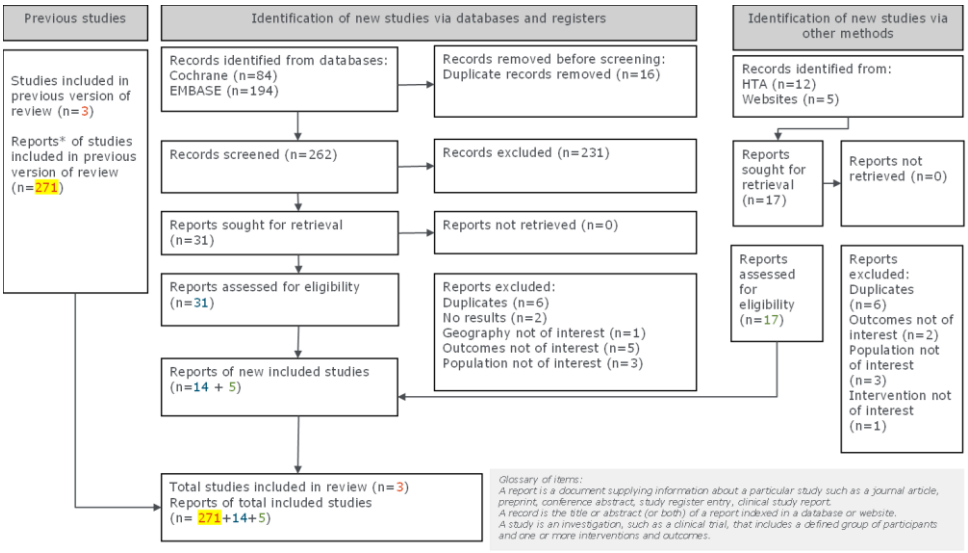


Figure 41: PRISMA April 2024 search



The SLR identified 151 HRQoL publications that reported PRO and utility data for patients with RRMM with at least one prior treatment. A total of 105 publications reported PRO data, with most of these studies using the EORTC QLQ-C30 questionnaire. A total of 34 studies reported utility data, with most eliciting values from the EQ-5D tool. There were 12 studies containing both PRO and utility data, which used the following questionnaires: EQ-5D, EORTC QLQ-MY20, and EORTC QLQ-C30.

Out of the 146 identified in the SLR, three were selected to inform HRQoL in the model. Note that DREAMM-7 health state utility analysis results are not published and they are

not included in the SLR results. The sources selected from the SLR to be included in the model from are deemed the most relevant to the decision problem based on population, interventions, and recency of publication. TA695 reported pre-progression and post-progression utility values for KRd and Rd. TA897 reported utility values for PFS and post-progression survival for DVd, Vd and Kd. TA695, TA897 and Brown 2013 all reported AE utilities. These AE utility decrements are used to inform the CEM base case.

Table 45: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	2008-present	31.01.2023
Medline	nlm.nih.gov	2008-present	31.01.2023
Cochrane Central Register of Controlled Trials	Cochranelibrary.com	2008-present	31.01.2023
Cochrane Database of Systematic Reviews	Cochranelibrary.com	2008-present	31.01.2023

Table 46: Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	N/A	31.01.2023
CADTH/pCODR	www.cda-amc.ca	N/A	31.01.2023
SMC	www.scottishmedicines.org.uk	N/A	31.01.2023
G-BA/IQWIG	www.iqwig.de/www.g-ba.de	N/A	31.01.2023
HAS	www.has.sante.fr	N/A	31.01.2023
PBAC	www.pbs.gov.au	N/A	31.01.2023
HMRN	www.hmrn.org	N/A	15.04.2024

Table 47: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
AMCP/Nexus	Conference website	Electronic search	N/A	31.01.2023
ASCO	Conference website	Electronic search	N/A	31.01.2023

ASH	Conference website	Electronic search	N/A	31.01.2023
BSH	Conference website	Electronic search	N/A	31.01.2023
EBMT	Conference website	Electronic search	N/A	31.01.2023
EHA	Conference website	Electronic search	N/A	31.01.2023
EMN	Conference website	Electronic search	N/A	31.01.2023
ESMO	Conference website	Electronic search	N/A	31.01.2023
IMW	Conference website	Electronic search	N/A	31.01.2023
ISPOR	Conference website	Electronic search	N/A	31.01.2023

I.1.1 Search strategies

Table - XXIX presents the selection criteria used for the comprehensive global economic and humanistic SLR. These were used to inform the inclusion of studies at the first and second pass stages of the reviews. For this application the selection criteria were narrowed on the intervention to only include BM and daratumumab.

Table - XXIX: Study selection criteria for the economic and humanistic SLR

Category	Inclusion Criteria	Exclusion Criteria
Population	**2L+ RRMM:** • Patients with MM who have received ≥1 prior line of therapy (LOTs) **Notes:** • Induction + stem cell transplant (SCT) + consolidation + maintenance were considered as one LOT	• Studies in patients who are treatment naïve • Studies in which LOT could not be definitively determined as 2L+ for ≥80% of the population[§]
Interventions	Any of these interventions either alone or in combination: • Belantamab mafodotin • Bortezomib • Carfilzomib • Cyclophosphamide • Ixazomib • Daratumumab • Isatuximab • Elotuzumab • Selinexor	• Surgery • Radiotherapy • Palliative care • Autologous SCT alone

	• Dexamethasone
	• Panobinostat
	• Lenalidomide
	• Pomalidomide
	• Thalidomide
	• CAR-T-cells therapy:
	  ○ Idecabtagene vicleucel,
	  ○ Ciltacabtagene autoleucel,
	• Teclistamab
	• Melflufen (Pepaxto, Pepaxti)
	• No intervention	

Comparisons	• Any of the above interventions and placebo • Head-to-head comparisons • Best supportive care (BSC) • No comparator	N/A
Outcomes	Economic evaluations: • Cost-effectiveness results such as ICER and QALYs • Cost-utility results • Cost-minimisation results • Cost-benefit results Economic burden (costs and resource use): • Direct or indirect costs of treatment and illness ○ Costs associated with adverse events (AEs) • Societal costs (productivity loss) • Resource use • Resource use associated with AEs • Drivers of cost/resource use (healthcare, hospital, drug-related) HRQoL outcomes: • BPI-SF • EORTC QLQ-C30 • EORTC IL52 • EQ-5D • FACT-Fatigue/FACIT-F • FACT-G • FACT-MM/ FACIT-MMMDASI • EORTC QLQ-MY20 • SF-36/12 • PRO-CTCAE • PROMIS- Physical functioning • Utility scores • HRQoL impact of AEs	Publications that do not report data on relevant outcomes
Study designs	• Economic evaluations such as cost-effectiveness or cost-utility analyses	N/A

	• Economic models • Observational studies (including utilities/disutilities studies) • Real-world data • Interventional investigations including RCTs/comparative studies as well as single-arm trials	
Publication types	N/A	Narrative publications Reviews* Case studies Case reports Editorials
Other criteria	English language	N/A
	Geographic region: US, EU5, Canada, Australia, Japan, China, South Korea and Taiwan	Studies conducted in geographic regions, not of interest
Timeframe	Databases (Embase, Cochrane) from 2008 to align with clinical SLR, HTAs last 10 years, conferences - last 3 years	N/A

Table - XXX: Embase, MEDLINE and Medline (R) In-Process (Embase interface), search date 31st January 2023

		Query	Yield
Efficacy search			
Population	1	('myeloma'/exp AND multiple) OR 'MM'/exp OR 'plasmacytoma'/de OR myelom* OR plasmacytom* OR (plasm* AND 'cells'/exp AND myelom*) OR (plasm* AND cell AND myelom*) OR ('plasma'/exp AND 'cells'/exp AND 'leukemia'/exp) OR (plasma* NEAR/3 neoplas*) OR 'plasma cell leukemia'/exp	169,724
	2	relaps*:ti,ab OR refract*:ti,ab OR recurren*:ti,ab OR 'resistant':ti,ab OR 'prior treatment':ti,ab OR 'prior treatments':ti,ab OR 'prior therapy':ti,ab OR 'prior therapies':ti,ab OR 'previously treated':ti,ab OR 'second line':ti,ab OR 'third line':ti,ab OR '2nd line':ti,ab OR '3rd line':ti,ab OR 'fourth line':ti,ab OR '4th line':ti,ab OR 'fifth line':ti,ab OR '5th line':ti,ab	2,222,129
	3	#1 AND #2	37,183
Economic Filter	4	'socioeconomics'/de OR 'cost-benefit analysis'/de OR 'cost-effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost-utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'healthcare cost'/de OR 'healthcare financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR 'cost-minimisation analysis'/de OR (cost NEXT/1 estimate*) OR (cost NEXT/1 variable*) OR (unit NEXT/1 cost*) OR resource*:ti OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti)	1,187,005

Societal Filter	5	‘absenteeism’/exp or ‘presenteeism’/exp or ‘medical leave’/exp or 'indirect costs':ti,ab or 'societal costs':ti,ab or ‘indirect burden’:ti,ab or 'burden of illness':ti,ab or 'illness cost':ti,ab or 'illness burden':ti,ab or 'patient burden':ti,ab or 'economic burden':ti,ab or 'disability':ti,ab or 'functional status':ti,ab or 'physical function':ti,ab or 'impairment':ti,ab or 'disabilities':ti,ab or productivity:ti,ab or employment:ti,ab or retirement:ti,ab or 'medical leave':ti,ab or 'work disability':ti,ab or absenteeism:ti,ab or presenteeism:ti,ab or 'work absence':ti,ab or 'productivity loss':ti,ab or 'work impairment':ti,ab or 'homebound':ti,ab or 'sick leave':ti,ab or 'sick day':ti,ab or 'worktime loss':ti,ab or 'opportunity loss':ti,ab or 'job performance':ti,ab or ('work' NEXT/2 'loss'):ti,ab	1,087,598
Quality of life Filter	6	‘EORTC QLQ C30’/de OR ‘EORTC QLQ MY20’/de OR (EORTC QLQ C30 OR EORTC QLQ MY20):ab,ti OR ‘quality adjusted life year’/de OR ‘value of life’:ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR ‘disability adjusted life’:ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR ‘health* year* equivalent*’:ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR (‘illness state*’ OR health state*):ab,ti OR (‘euro qual’ OR ‘euro qual5d’ OR ‘euro qol5d’ OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR ‘sf 36*’ OR ‘sf thirtysix’ OR ‘sf thirty six’):ab,ti OR (sf6 OR ‘sf 6’ OR sf6d OR ‘sf 6d’ OR ‘sf six’ OR sfsix OR sf8 OR ‘sf 8’ OR ‘sf eight’ OR sfeight):ab,ti OR (sf12 OR ‘sf 12’ OR ‘sf twelve’ OR sftwelve):ab,ti OR (sf16 OR ‘sf 16’ OR ‘sf sixteen’ OR sfsixteen):ab,ti OR (sf20 OR ‘sf 20’ OR ‘sf twenty’ OR sftwenty):ab,ti OR (15D OR 15-D OR ‘15 dimension’):ab,ti OR (‘standard gamble*’ OR sg):ab,ti OR (‘time trade off*’ OR ‘time tradeoff*’ OR tto OR timetradeoff*):ab,ti OR ‘EORTC IL52’/de OR (EORTC IL52):ab,ti	1,201,625
Measurement tool Filter	7	('eortc qlq c30' OR 'qlq' OR 'qlq my20' OR 'qlq-my20' OR 'fact-g' OR 'bpi-sf' OR 'bpi-sf' OR 'brief pain inventory short form' OR 'brief pain inventory' OR 'mdasi' OR ‘MDASI-MM’ OR ‘facit-mm’ OR ‘fact-f’ OR ‘facit-f’ OR 'md Anderson symptom inventory' OR 'PROMIS' OR 'patient-reported outcomes measurement information system' OR 'functional assessment of cancer	34,103

			therapy'):ti,ab OR ((fact or 'functional assessment') NEAR/3 (cancer* OR carcinoma*)):ab,ti	
Combine searches	all	8	#3 AND (#4 OR #5 OR #6 OR #7)	4,487

Table - XXXI: Cochrane CENTRAL and CDSR (via Cochranelibrary.com) search terms, search date 31st January 2023

	Query	Yield
1	MeSH descriptor: [MM] explode all trees	2,087
2	MeSH descriptor: [Plasmacytoma] explode all trees	91
3	(("multiple" and myelom*) or "plasma cell myeloma" or "Kahler's disease" or plasmacytom*):ti,ab,kw	6,076
4	(relaps* or refract* or recurren* or "resistant" or "prior treatment" or "prior treatments" or "prior therapy" or "prior therapies" or "previously treated" or "second line" or "third line" or "2nd line" or "3rd line" or "fourth line" or "4th line" or "fifth line" or "5th line"):ti,ab,kw	163,883
5	("quality adjusted life year" or "value of life" or "socioeconomics" or "module" or qaly* or qald* or qale* or qtime* or "quality adjusted" or "adjusted life year" or "disability adjusted life" or daly* or "wellbeing" or score* or "scoring" or valu* or "qaly" or measur* or evaluat* or scale* or instrument* or "weight" or "weights" or "weighting" or "information" or "utility" or "utilities" or disutil* or "HSUV" or "HSUVs" or health* or year* or equivalent* or "illness state" or "euro qual" or "euro qual5d" or "euro qol5d" or "eq-5d" or "euroqual" or "euroqol" or "euroqual5d" or "euroqol5d" or "EORTC QLQ C30" or "EORTC QLQ MY20" or "EORTC IL52" or "short form" or shortform* or sf36* or "sf 36" or "sf12" or "standard gamble" or "time trade off"):ti,ab,kw	1,417,152
6	#1 or #2 or #3	6,076
7	#4 AND #5 AND #6	1,812

Literature search results included in the model/analysis are presented in the table below.

Table - XXXII: literature search results included in the model

Reference (Full citation incl. reference number)	Health state/Disutility
Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma, Vania Hungria et al.N Engl J Med 2024;391:393-407. DOI: 10.1056/NEJMoa2405090. [35]	Health state/RRMM
NICE. Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy. Published 3 May 2020. TA695 Appraisal consultation committee papers, page 101-103. Accessed May 2025. [41]	Health state/sensitivity analysis Disutility/adverse events
NICE. Daratumumab monotherapy for treating relapsed or refractory multiple myeloma. Published September 2016. TA510 Appraisal consultation committee papers, page 203-204. Accessed May 2025. [42]	Disutility/adverse events
NICE. Daratumumab with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma. Published	Health state/sensitivity analysis

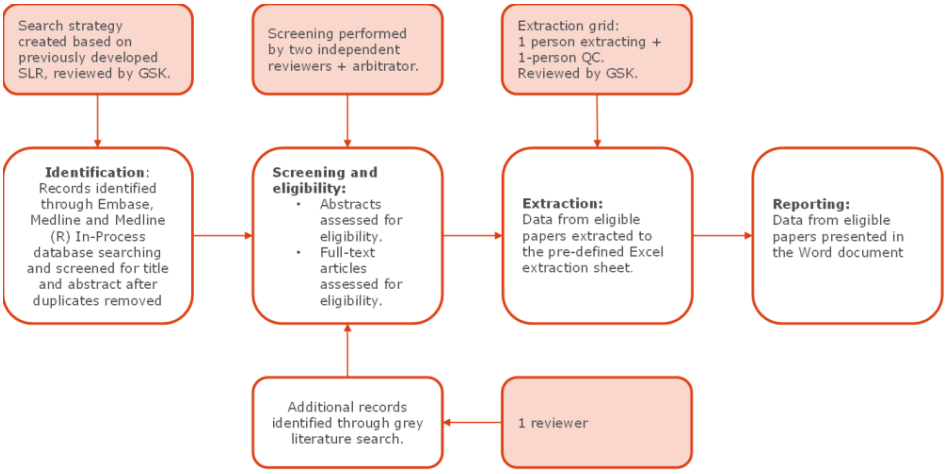
11 August 2022. TA897 committee papers 20230606, page 114. Accessed May 2025. [43]	Disutility/adverse events
Utility assessment among patients with dry eye disease. Schiffman et al. Ophthalmology. 2003;110(7):1412-9. [44]	Disutility/adverse events
Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Brown RE et al. The European Journal of Health Economics. 2013 Jun 1; 14(3):507-14. [45]	Disutility/adverse events
Catalogue of EQ-5D scores for the United Kingdom. Sullivan PW et al. Med Decis Making. 2011;31(6):800-4. [46]	Disutility/adverse events

I.1.2 Quality assessment and generalizability of estimates

The Drummond Checklist of Economic Evaluations was used to assess the quality of peer – reviewed economic evaluations as recommended by NICE.

An extensive quality control process was followed throughout the process of the SLR. Figure 42 provides a brief overview of the quality check (QC) assessment.

Figure 42: QC process summary



I.1.3 Unpublished data

Not applicable.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

J.1.1 Systematic search for costs and healthcare resources for 2L+ RRMM population

The objective of this economic SLR was to identify costs, healthcare resource use, existing economic models, and health utilities for the 2L+ RRMM population: patients with RRMM who have had at least one prior line of MM therapy.

The SLR was conducted according to the NICE guidelines, with respect to TA submissions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the Cochrane Handbook for Systematic Reviews of Interventions, to ensure methodological quality.

Table 51: Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion (latest)
Embase	Embase.com	2008-present	15.04.2024
Medline	nlm.nih.gov	2008-present	15.04.2024
CENTRAL	Cochranelibrary.com	2008-present	15.04.2024

J.1.2 Search strategies

Searches to identify relevant evidence were conducted on 31st January 2023 in the following databases:

- Embase
- Medline and Medline (R) In-Process (Embase interface 1947 to present)
- Cochrane Central Register of Controlled Trials (CENTRAL) and the CDSR (via Cochrane Library) [HRQoL only]

To capture all relevant publications, a 15-years' time limit (2008 - present) was applied in the database searches. However, for the previous HTA assessments, 10-years' time limit was applied. For the grey literature search, the time frame was limited to the past 3 years.

Supplementary searches of grey literature were performed in February 2023 to identify the most recent research that may not yet have been published in peer-reviewed journals (Table - XXXIII).

Table - XXXIII: SLR methodology – grey literature

Topic	Conference Proceedings	Other Grey Literature Sources
Economic and humanistic	• AMCP/Nexus • ASCO ASH • BSH • EBMT • EHA • EMN • ESMO • IMW • ISPOR	• NICE • CADTH/pCODR • SMC • G-BA/IQWiG • HAS • PBAC • HRMN

Table - XXXIV presents the search terms in Embase for the economic/humanistic SLR. Table - XXXV presents the search terms used in CENTRAL and CDSR. Both Table - XXXIV and Table - XXXV were search terms ran on 31st January 2023. Table - XXXVI represents the search terms and results from Embase ran on January 8th 2024. Table - XXXVII presents the search terms used for the Cochrane search ran on January 8th of 2024. Both Table - XXXVI and Table - XXXVII were search terms ran for the first updated search. Table - XXXVIII represents the search terms and results from Embase ran on April 15th 2024. Table - XXXIX presents the search terms used for the Cochrane search ran on April 15th of 2024. Both Table - XXXVIII and Table - XXXIX were search terms ran for the second updated search.

Table - XXXIV: Embase, MEDLINE and Medline (R) in-Process (Embase interface), search date 31st January 2023

		Query	Yield
Efficacy search			
Population	1	('myeloma'/exp AND multiple) OR 'MM'/exp OR 'plasmacytoma'/de OR myelom* OR plasmacytom* OR (plasm* AND 'cells'/exp AND myelom*) OR (plasm* AND cell AND myelom*) OR ('plasma'/exp AND 'cells'/exp AND 'leukemia'/exp) OR (plasma* NEAR/3 neoplas*) OR 'plasma cell leukemia'/exp	169,724
	2	relaps*:ti,ab OR refract*:ti,ab OR recurren*:ti,ab OR 'resistant':ti,ab OR 'prior treatment':ti,ab OR 'prior treatments':ti,ab OR 'prior therapy':ti,ab OR 'prior therapies':ti,ab OR 'previously treated':ti,ab OR 'second line':ti,ab OR 'third line':ti,ab OR '2nd line':ti,ab OR '3rd line':ti,ab OR 'fourth line':ti,ab OR '4th line':ti,ab OR 'fifth line':ti,ab OR '5th line':ti,ab	2,222,129
	3	#1 AND #2	37,183
Economic Filter	4	'socioeconomics'/de OR 'cost-benefit analysis'/de OR 'cost-effectiveness analysis'/de OR 'cost of illness'/de OR	1,187,005

		'economic evaluation'/de OR 'cost-utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'healthcare cost'/de OR 'healthcare financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR 'cost-minimisation analysis'/de OR (cost NEXT/1 estimate*) OR (cost NEXT/1 variable*) OR (unit NEXT/1 cost*) OR resource*:ti OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti)	
Societal Filter	5	'absenteeism'/exp or 'presenteeism'/exp or 'medical leave'/exp or 'indirect costs':ti,ab or 'societal costs':ti,ab or 'indirect burden':ti,ab or 'burden of illness':ti,ab or 'illness cost':ti,ab or 'illness burden':ti,ab or 'patient burden':ti,ab or 'economic burden':ti,ab or 'disability':ti,ab or 'functional status':ti,ab or 'physical function':ti,ab or 'impairment':ti,ab or 'disabilities':ti,ab or productivity:ti,ab or employment:ti,ab or retirement:ti,ab or 'medical leave':ti,ab or 'work disability':ti,ab or absenteeism:ti,ab or presenteeism:ti,ab or 'work absence':ti,ab or 'productivity loss':ti,ab or 'work impairment':ti,ab or 'homebound':ti,ab or 'sick leave':ti,ab or 'sick day':ti,ab or 'worktime loss':ti,ab or 'opportunity loss':ti,ab or 'job performance':ti,ab or ('work' NEXT/2 'loss'):ti,ab	1,087,598
Quality of life Filter	6	'EORTC QLQ C30'/de OR 'EORTC QLQ MY20'/de OR (EORTC QLQ C30 OR EORTC QLQ MY20):ab,ti OR 'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR	1,201,625

		timetradeoff*):ab,ti OR 'EORTC IL52'/de OR (EORTC IL52):ab,ti	
Measurement tool Filter	7	('eortc qlq c30' OR 'qlq' OR 'qlq my20' OR 'qlq-my20' OR 'fact-g' OR 'bpi-sf' OR 'bpi-sf' OR 'brief pain inventory short form' OR 'brief pain inventory' OR 'mdasi' OR 'MDASI-MM' OR 'facit-mm' OR 'fact-f' OR 'facit-f' OR 'md Anderson symptom inventory' OR 'PROMIS' OR 'patient-reported outcomes measurement information system' OR 'functional assessment of cancer therapy'):ti,ab OR ((fact or 'functional assessment') NEAR/3 (cancer* OR carcinoma*)):ab,ti	34,103
Combine all searches	8	#3 AND (#4 OR #5 OR #6 OR #7)	4,487

Table - XXXV: Cochrane CENTRAL and CDSR (via Cochranelibrary.com) search terms, search date 31st January 2023

	Query	Yield
1	MeSH descriptor: [MM] explode all trees	2,087
2	MeSH descriptor: [Plasmacytoma] explode all trees	91
3	(("multiple" and myelom*) or "plasma cell myeloma" or "Kahler's disease" or plasmacytom*):ti,ab,kw	6,076
4	(relaps* or refract* or recurren* or "resistant" or "prior treatment" or "prior treatments" or "prior therapy" or "prior therapies" or "previously treated" or "second line" or "third line" or "2nd line" or "3rd line" or "fourth line" or "4th line" or "fifth line" or "5th line"):ti,ab,kw	163,883
5	("quality adjusted life year" or "value of life" or "socioeconomics" or "module" or qaly* or qald* or qale* or qtime* or "quality adjusted" or "adjusted life year" or "disability adjusted life" or daly* or "wellbeing" or score* or "scoring" or valu* or "qaly" or measur* or evaluat* or scale* or instrument* or "weight" or "weights" or "weighting" or "information" or "utility" or "utilities" or disutil* or "HSUV" or "HSUVs" or health* or year* or equivalent* or "illness state" or "euro qual" or "euro qual5d" or "euro qol5d" or "eq-5d" or "euroqual" or "euroqol" or "euroqual5d" or "euroqol5d" or "EORTC QLQ C30" or "EORTC QLQ MY20" or "EORTC IL52" or "short form" or shortform* or sf36* or "sf 36" or "sf12" or "standard gamble" or "time trade off"):ti,ab,kw	1,417,152
6	#1 or #2 or #3	6,076
7	#4 AND #5 AND #6	1,812

Table - XXXVI: Embase, MEDLINE and Medline (R) In-Process (Embase interface), search date 8th January 2024

		Query	Yield
Efficacy search			
Population	1	('myeloma'/exp AND multiple) OR 'multiple myeloma'/exp OR 'plasmacytoma'/de OR myelom* OR plasmacytom* OR (plasm* AND 'cells'/exp AND myelom*) OR (plasm* AND cell AND myelom*) OR ('plasma'/exp AND 'cells'/exp AND 'leukemia'/exp) OR (plasma* NEAR/3 neoplas*) OR 'plasma cell leukemia'/exp	179,941
	2	relaps*:ti,ab OR refract*:ti,ab OR recurren*:ti,ab OR 'resistant':ti,ab OR 'prior treatment':ti,ab OR 'prior	2,354,005

		treatments':ti,ab OR 'prior therapy':ti,ab OR 'prior therapies':ti,ab OR 'previously treated':ti,ab OR 'second line':ti,ab OR 'third line':ti,ab OR '2nd line':ti,ab OR '3rd line':ti,ab OR 'fourth line':ti,ab OR '4th line':ti,ab OR 'fifth line':ti,ab OR '5th line':ti,ab	
	3	#1 AND #2	40,218
Economic Filter	4	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'healthcare cost'/de OR 'healthcare financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR 'cost minimisation analysis'/de OR (cost NEXT/1 estimate*) OR (cost NEXT/1 variable*) OR (unit NEXT/1 cost*) OR resource*:ti OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti)	1,261,936
Societal Filter	5	'absenteeism'/exp or 'presenteeism'/exp or 'medical leave'/exp or 'indirect costs':ti,ab or 'societal costs':ti,ab or 'indirect burden':ti,ab or 'burden of illness':ti,ab or 'illness cost':ti,ab or 'illness burden':ti,ab or 'patient burden':ti,ab or 'economic burden':ti,ab or 'disability':ti,ab or 'functional status':ti,ab or 'physical function':ti,ab or 'impairment':ti,ab or 'disabilities':ti,ab or productivity:ti,ab or employment:ti,ab or retirement:ti,ab or 'medical leave':ti,ab or 'work disability':ti,ab or absenteeism:ti,ab or presenteeism:ti,ab or 'work absence':ti,ab or 'productivity loss':ti,ab or 'work impairment':ti,ab or 'homebound':ti,ab or 'sick leave':ti,ab or 'sick day':ti,ab or 'worktime loss':ti,ab or 'opportunity loss':ti,ab or 'job performance':ti,ab or ('work' NEXT/2 'loss'):ti,ab	1,162,966
Quality of life Filter	6	'EORTC QLQ C30'/de OR 'EORTC QLQ MY20'/de OR (EORTC QLQ C30 OR EORTC QLQ MY20):ab,ti OR 'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR	1,287,736

		euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti OR 'EORTC IL52'/de OR (EORTC IL52):ab,ti	
Measurement tool Filter	7	('eortc qlq c30' OR 'qlq' OR 'qlq my20' OR 'qlq-my20' OR 'fact-g' OR 'bpi-sf' OR 'bpisf' OR 'brief pain inventory short form' OR 'brief pain inventory' OR 'mdasi' OR 'MDASI-MM' OR 'facit-mm' OR 'fact-f' OR 'facit-f' OR 'md Anderson symptom inventory' OR 'PROMIS' OR 'patient-reported outcomes measurement information system' OR 'functional assessment of cancer therapy'):ti,ab OR ((fact or 'functional assessment') NEAR/3 (cancer* OR carcinoma*)):ab,ti	37,574
Combine all searches	8	#3 AND (#4 OR #5 OR #6 OR #7)	5,269
Combine all searches	9	#3 AND (#4 OR #5 OR #6 OR #7) AND [31-01-2023]/sd NOT [18-12-2023]/sd	787

Table - XXXVII: Cochrane CENTRAL and CDSR (via Cochranelibrary.com) search terms, search date 8th January 2024

	Query	Yield
1	MeSH descriptor: [Multiple Myeloma] explode all trees	2,807
2	MeSH descriptor: [Plasmacytoma] explode all trees	148
3	(("multiple" and myelom*) or "plasma cell myeloma" or "Kahler's disease" or plasmacytom*):ti,ab,kw	6,370
4	(relaps* or refract* or recurren* or "resistant" or "prior treatment" or "prior treatments" or "prior therapy" or "prior therapies" or "previously treated" or "second line" or "third line" or "2nd line" or "3rd line" or "fourth line" or "4th line" or "fifth line" or "5th line"):ti,ab,kw	173,722
5	("quality adjusted life year" or "value of life" or "socioeconomics" or "module" or qaly* or qald* or qale* or qtime* or "quality adjusted" or "adjusted life year" or "disability adjusted life" or daly* or "wellbeing" or score* or "scoring" or valu* or "qaly" or measur* or evaluat* or scale* or instrument* or "weight" or "weights" or "weighting" or "information" or "utility" or "utilities" or disutil* or "HSUV" or "HSUVs" or health* or year* or equivalent* or "illness state" or "euro qual" or "euro qual5d" or "euro qol5d" or "eq-5d" or "euroqual" or "euroqol" or "euroqual5d" or "euroqol5d" or "EORTC QLQ C30" or "EORTC QLQ MY20" or "EORTC IL52" or "short form" or shortform* or sf36* or "sf 36" or "sf12" or "standard gamble" or "time trade off"):ti,ab,kw	1,527,526
6	#1 or #2 or #3	6,370
7	#4 AND #5 AND #6	1,909

8	#4 AND #5 AND #6 (with Cochrane Library publication date from Feb 2023 to Jan 2024)	91

Table - XXXVIII: Embase, MEDLINE and Medline (R) In-Process (Embase interface), search date 15 April 2024

		Query	Yield
Efficacy search			
Population	1	('myeloma'/exp AND multiple) OR 'multiple myeloma'/exp OR 'plasmacytoma'/de OR myelom* OR plasmacytom* OR (plasm* AND 'cells'/exp AND myelom*) OR (plasm* AND cell AND myelom*) OR ('plasma'/exp AND 'cells'/exp AND 'leukemia'/exp) OR (plasma* NEAR/3 neoplas*) OR 'plasma cell leukemia'/exp	183,647
	2	relaps*:ti,ab OR refract*:ti,ab OR recurren*:ti,ab OR 'resistant':ti,ab OR 'prior treatment':ti,ab OR 'prior treatments':ti,ab OR 'prior therapy':ti,ab OR 'prior therapies':ti,ab OR 'previously treated':ti,ab OR 'second line':ti,ab OR 'third line':ti,ab OR '2nd line':ti,ab OR '3rd line':ti,ab OR 'fourth line':ti,ab OR '4th line':ti,ab OR 'fifth line':ti,ab OR '5th line':ti,ab	2,394,329
	3	#1 AND #2	41,524
Economic Filter	4	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'healthcare cost'/de OR 'healthcare financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR 'cost minimisation analysis'/de OR 'cost comparison'/de OR 'cost comparison analysis'/de OR (cost NEXT/1 estimate*) OR (cost NEXT/1 variable*) OR (unit NEXT/1 cost*) OR resource*:ti OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti)	1,282,463
Societal Filter	5	'absenteeism'/exp or 'presenteeism'/exp or 'medical leave'/exp or 'indirect costs':ti,ab or 'societal costs':ti,ab or 'indirect burden':ti,ab or 'burden of illness':ti,ab or 'illness cost':ti,ab or 'illness burden':ti,ab or 'patient burden':ti,ab or 'economic burden':ti,ab or 'disability':ti,ab or 'functional status':ti,ab or 'physical function':ti,ab or 'impairment':ti,ab or 'disabilities':ti,ab or productivity:ti,ab or employment:ti,ab or retirement:ti,ab or 'medical leave':ti,ab or 'work disability':ti,ab or absenteeism:ti,ab or presenteeism:ti,ab or 'work absence':ti,ab or 'productivity loss':ti,ab or 'work impairment':ti,ab or 'homebound':ti,ab or 'sick leave':ti,ab or 'sick day':ti,ab or 'worktime loss':ti,ab or 'opportunity loss':ti,ab or 'job performance':ti,ab or ('work' NEXT/2 'loss'):ti,ab	1,184,369
Quality of life Filter	6	'EORTC QLQ C30'/de OR 'EORTC QLQ MY20'/de OR (EORTC QLQ C30 OR EORTC QLQ MY20):ab,ti OR 'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR	1,313,976

		qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti OR 'EORTC IL52'/de OR (EORTC IL52):ab,ti	
Measurement tool Filter	7	('eortc qlq c30' OR 'qlq' OR 'qlq my20' OR 'qlq-my20' OR 'fact-g' OR 'bpi-sf' OR 'bpisf' OR 'brief pain inventory short form' OR 'brief pain inventory' OR 'mdasi' OR 'MDASI-MM' OR 'facit-mm' OR 'fact-f' OR 'facit-f' OR 'md Anderson symptom inventory' OR 'PROMIS' OR 'patient-reported outcomes measurement information system' OR 'functional assessment of cancer therapy'):ti,ab OR ((fact or 'functional assessment') NEAR/3 (cancer* OR carcinoma*)):ab,ti	38,663
Combine all searches	8	#3 AND (#4 OR #5 OR #6 OR #7)	5,451
Combine all searches	9	#3 AND (#4 OR #5 OR #6 OR #7) AND [08-01-2024]/sd	194

Table - XXXIX: Cochrane CENTRAL and CDSR (via Cochranelibrary.com) search terms, search date 15 April 2024

	Query	Yield
1	MeSH descriptor: [Multiple Myeloma] explode all trees	2,434
2	MeSH descriptor: [Plasmacytoma] explode all trees	86
3	(("multiple" and myelom*) or "plasma cell myeloma" or "Kahler's disease" or plasmacytom*):ti,ab,kw	6,599
4	(relaps* or refract* or recurren* or "resistant" or "prior treatment" or "prior treatments" or "prior therapy" or "prior therapies" or "previously treated" or "second line" or "third line" or "2nd line" or	177,792

	"3rd line" or "fourth line" or "4th line" or “fifth line” or “5th line”):ti,ab,kw	
5	(“quality adjusted life year” or “value of life” or “socioeconomics” or “module” or qaly* or qald* or qale* or qtime* or “quality adjusted” or "adjusted life year" or “disability adjusted life” or daly* or “wellbeing” or score* or “scoring” or valu* or “qaly” or measur* or evaluat* or scale* or instrument* or “weight” or “weights” or “weighting” or ”information” or “utility” or “utilities” or disutil* or ”HSUV” or “HSUVs” or health* or year* or equivalent* or "illness state" or “euro qual” or “euro qual5d” or “euro qol5d” or “eq-5d” or “euroqual” or “euroqol” or “euroqual5d” or “euroqol5d” or “EORTC QLQ C30” or “EORTC QLQ MY20” or “EORTC IL52” or "short form" or shortform* or sf36* or "sf 36" or “sf12” or “standard gamble” or “time trade off”):ti,ab,kw	1,568,620
6	#1 or #2 or #3	6,599
7	#4 AND #5 AND #6	2,015
8	#4 AND #5 AND #6 (with Cochrane Library publication date from Jan 2024 to Dec 2024)	84

J.1.3 Systematic selection of studies

Table - XL presents the selection criteria used for the comprehensive global economic and humanistic SLR. These were used to inform the inclusion of studies at the first and second pass stages of the reviews. Only papers published in English were accepted. Studies published as abstracts, conference proceedings or press releases were considered eligible for inclusion if adequate data were provided (note: abstracts/conference proceedings were excluded if there is an associated peer-reviewed publication already included in the search). To capture all relevant publications, a 15-years' time limit (2008 - present) was applied in the database searches. However, for the previous HTA assessments, 10-years' time limit was applied. For the grey literature search the time frame was limited to the past 3 years. For this application the inclusion criteria category intervention has been narrowed to only include BM and daratumumab.

Table - XL: Inclusion and exclusion criteria used for assessment of studies

Category	Inclusion Criteria	Exclusion Criteria
Population	**2L+ RRMM:** • Patients with MM who have received ≥1 prior line of therapy (LOTs) **Notes:** • Induction + stem cell transplant (SCT) + consolidation + maintenance was considered as one LOT	• Studies in patients who are treatment naïve • Studies in which LOT could not be definitively determined as 2L+ for ≥80% of the population
Interventions	Any of these interventions either alone or in combination: • Belamaf	• Surgery • Radiotherapy • Palliative care

	• Bortezomib
	• Carfilzomib
	• Cyclophosphamide
	• Ixazomib
	• Daratumumab
	• Isatuximab
	• Elotuzumab
	• Selinexor
	• Dexamethasone
	• Panobinostat
	• Lenalidomide
	• Pomalidomide
	• Thalidomide
	• CAR-T-cells therapy:
	  ○ Idecabtagene vicleucel,
	  ○ Ciltacabtagene autoleucel,
	• Teclistamab
	• Melflufen (Pepaxto, Pepaxti)
	• No intervention
		• Autologous SCT alone

Comparisons	• Any of the above interventions and placebo • Head-to-head comparisons • Best supportive care (BSC) • No comparator	N/A

Outcomes	Economic evaluations:
	• Cost-effectiveness results such as ICER and QALYs
	• Cost-utility results
	• Cost-minimisation results
	• Cost-benefit results
	Economic burden (costs and resource use):
	• Direct or indirect costs of treatment and illness
	  ○ Costs associated with adverse events (AEs)
	• Societal costs (productivity loss)
	• Resource use
	  ○ Resource use associated with AEs
	• Drivers of cost/resource use (healthcare, hospital, drug-related)
	HRQoL outcomes:
	• BPI-SF
	• EORTC QLQ-C30
	• EORTC IL52
	• EQ-5D
	• FACT-Fatigue/FACIT-F
	• FACT-G
	• FACT-MM/ FACIT-MMMDASI
	• EORTC QLQ-MY20
	• SF-36/12
	• PRO-CTCAE
	• PROMIS- Physical functioning
		Publications that do not report data on relevant outcomes

	• Utility scores • HRQoL impact of AEs	
Study designs	• Economic evaluations such as cost-effectiveness or cost-utility analyses • Economic models • Observational studies (including utilities/disutilities studies) • Real-world data • Interventional investigations including RCTs/comparative studies as well as single-arm trials	N/A
Publication types	N/A	Narrative publications Reviews* Case studies Case reports Editorials
Other criteria	English language	N/A
	Geographic region: US, EU5, Canada, Australia, Japan, China, South Korea and Taiwan	Studies conducted in geographic regions, not of interest
Timeframe	Databases (Embase, Cochrane) from 2008 to align with clinical SLR, HTAs last 10 years, conferences - last 3 years	N/A

Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified studies based on title and abstract (first pass) for inclusion using the review questions and selection criteria. Differences in evaluation between the two initial reviewers were discussed, and a third reviewer was involved if required as an additional measure if differences remained.

Figure 43 presents a PRISMA flow diagram that details how references were reviewed and extracted during the original search run in January 2023. After conducting the database searches and removing duplicates, there were 5,673 unique references which underwent first pass screening. Of these, 5,351 did not meet the selection criteria and were consequently excluded, leaving 322 unique references to be assessed at the second pass stage. Of the 322 full texts assessed at the second pass stage, 189 were included for data extraction. Grey literature search and additional targeted searches provided another 50 eligible references. Therefore, a total of 239 unique references underwent data extraction, of which 65 met the cost-effectiveness inclusion criteria, 142 met the cost and resource use inclusion criteria, and 124 met the HRQoL inclusion criteria.

Figure 44 presents a PRISMA flow diagram that details the references identified during the search ran in January of 2024. After removal of duplicates, a total of 855 references were identified during database searches and 810 did not meet the selection criteria at first pass and were excluded. The 45 included studies were assessed for eligibility

through full-text screening, and a total of 27 were included for data extraction. Another eight papers were identified through grey literature searches. Therefore, a total of 35 unique references were extracted, of which three met the cost-effectiveness inclusion criteria, 20 met the cost and resource use inclusion criteria, and 20 met the HRQoL inclusion criteria.

Figure 45 presents a PRISMA flow diagram that details the references identified during the search ran in April of 2024. A total of 262 references were identified during database searches and 231 did not meet the selection criteria at first pass. Of these, 31 studies were assessed for eligibility through full-text screening, and a total of 14 were included for data extraction. Another five papers were identified through grey literature searches. Therefore, a total of 19 unique references were extracted, of which 2 met the cost-effectiveness inclusion criteria, 11 met the cost and resource use inclusion criteria, and 7 met the HRQoL inclusion criteria.

Figure 43: PRISMA - January 2023 search

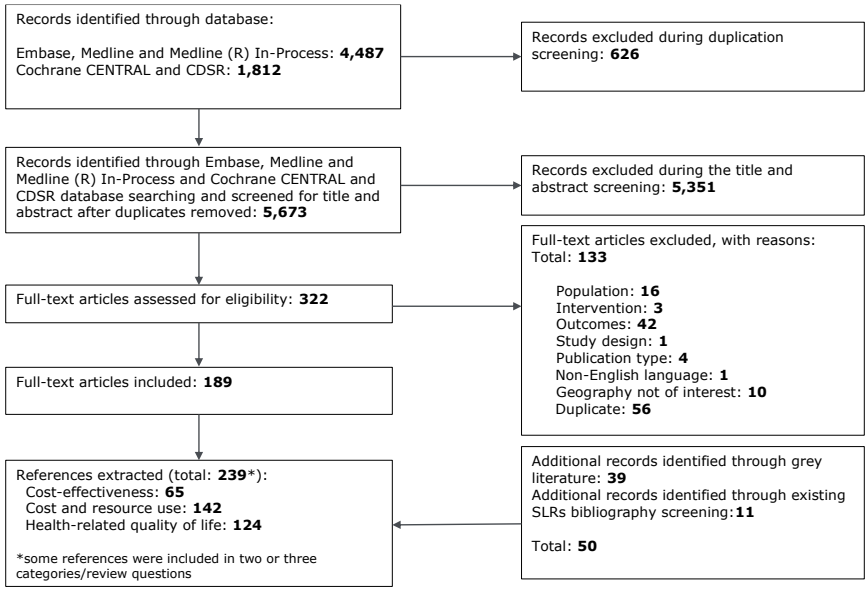


Figure 44: PRISMA - January 2024 search

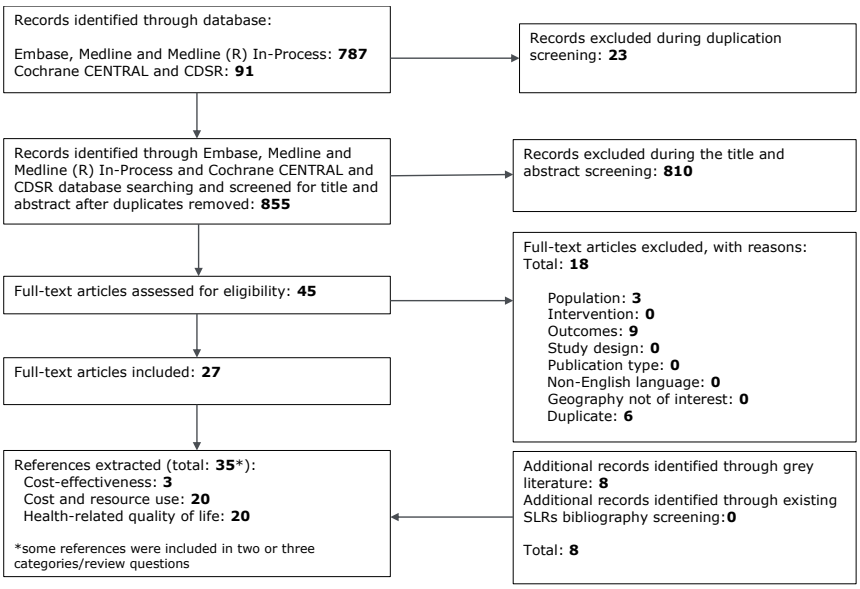
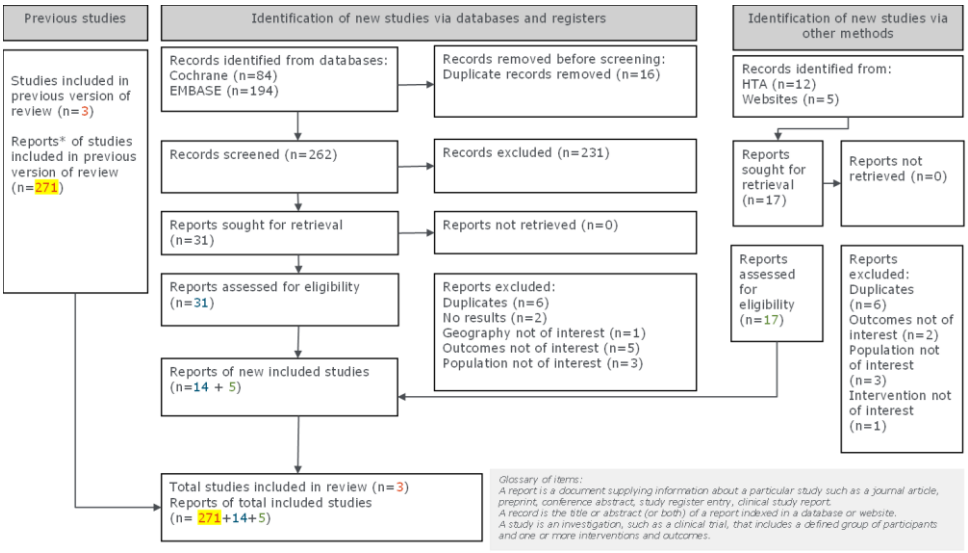


Figure 45: PRISMA - April 2024 search



Literature search results included in the model/analysis are presented in the table below.

Table - XLI: Literature search results included in the model

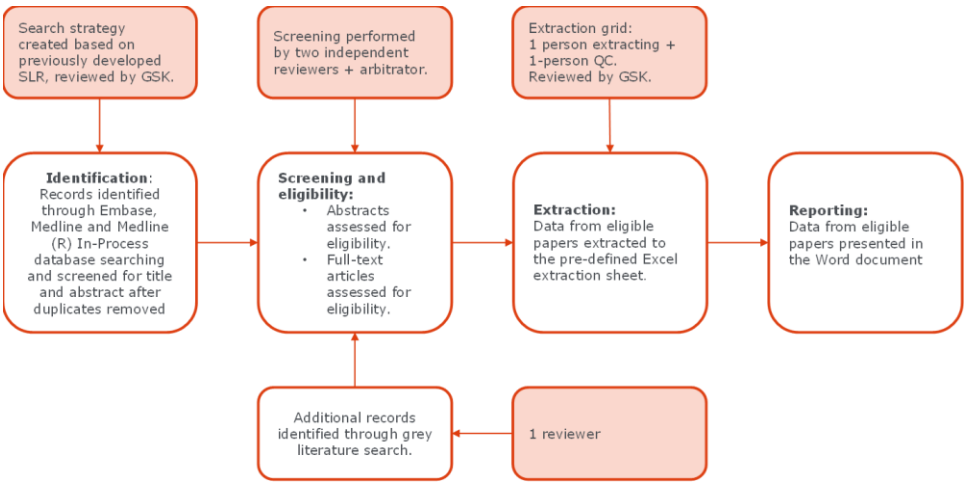
Reference (Full citation incl. reference number)	Input/estimate
Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma, Vania Hungria et al.N Engl J Med 2024;391:393-407. DOI: 10.1056/NEJMoa2405090 [35]	Overall survival Progression Free Survival

Szabo et al. The Clinical Course of Multiple Myeloma in the Era of Novel Agents: A Retrospective, Single-Center, Real-World Study. Clinical Hematology International. 2019;1: 10.2991/chi.d.190805.002 [17]	Proportion of patients who progress and receive subsequent treatment
Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, 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 Jan;26(1):149–57	Median duration of subsequent treatments

J.1.4 Quality assessment

The Drummond Checklist of Economic Evaluations was used to assess the quality of peer – reviewed economic evaluations as recommended by NICE. An extensive quality control process was followed throughout the process of the SLR. Figure 46 provides a brief overview of the quality check (QC) assessment.

Figure 46: QC process summary



J.1.5 Unpublished data

Not applicable.

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk