Medicinrådet

Bilag til Medicinrådets anbefaling vedr. daratumumab i kombination med lenalidomid og dexamethason til behandling af patienter med nydiagnosticeret myelomatose, som ikke er kandidater til autolog stamcelletransplantation

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. daratumumab i kombination med lenalidomid og dexamethason
2. Forhandlingsnotat fra Amgros vedr. daratumumab i kombination med lenalidomid og dexamethason
3. Ansøgers endelige ansøgning vedr. daratumumab i kombination med lenalidomid og dexamethason

Janssen-Cilag A/S

Bregnerødvej 133
DK-3460 Birkerød
www.janssen-cilag.dk

19. December 2022

Til Medicinrådet

Janssen-Cilags tilbagemelding på Medicinrådets udkast til anbefaling vedr. daratumumab i kombination med lenalidomid og dexamethason til behandling af patienter med nydiagnosticeret myelomatose, som ikke er kandidater til autolog stamcelletransplantation

Validiteten af datagrundlaget
Janssens oprindelige ansøgning til Medicinrådet viste en overall survival (OS) Hazard Ratio (HR) på 0,79 med et konfidensinterval (CI) på 0,50-1,23 når man sammenligner daratumumab i kombination med lenalidomid og dexamethason (DarLenDex) med daratumumab i kombination med bortezomib melphalan og prednison (DaraBorMelPred). I sammenligningen mellem DarLenDex og bortezomib i kombination med lenalidomid og dexamethason (BorLenDex) er HR 0,77 med et CI på 0,52-1,14.

Da der ikke findes studier der sammenligner lægemidlerne direkte, så er disse resultater genereret i en netværksmetaanalyse (NMA). Denne analysemetode er forbundet med visse usikkerheder, men er generelt anset som en acceptabel metode i medicinske teknologivurderinger og alternativet ville være en unanchored matching adjusted indirect comparison (MAIC) analyse med tilhørende større confounding problematikker og usikkerheder.

Sammenligningen mellem DarLenDex og DaraBorMelPred
Medicinrådet vælger at forkaste NMA'ens resultater pga. usikkerheden der knytter sig til disse og konkluderer at der ikke er forskel hvad angår OS. Medicinrådet anvender Kaplan Meier kurverne fra MAIA og ALCYONE studierne til at bekræfte denne antagelse, og benytter dermed en narrativ sammenligning til at forkaste resultatet af en NMA. Janssen finder det kritisabelt at Medicinrådet tilsyneladende tillægger en narrativ sammenligning af Kaplan Meier kurver mere vægt end NMA'ens resultater.

Sammenligning mellem DarLenDex og BorLenDex
Også i denne sammenligning vælger Medicinrådet at forkaste OS data, og konkludere at der ikke er forskel på lægemidlerne. Denne gang med begrundelsen at studiepopulationerne i MAIA og SWOG S0777 studierne ikke er sammenlignelige. Medicinrådet anerkender dog at NMA'en for denne sammenligning ellers er anvendelig, da DarLenDex og BorLenDex er sammenlignet med en fælles komparator (LenDex). Janssen mener ikke det er den optimale made at håndtere usikkerheden i NMA'en på og bemærker at forskellene i studiepopulationerne sandsynligvis medfører at BorLenDex klarer sig bedre overfor DarLenDex hvad angår OS. SWOG S0777 inkluderer ikke kun patienter der **ikke** er kandidater til autolog

stamcelletransplantation, som MAIA gør. Det håndteres ved at afgrænse populationen til patienter over 65 år, men disse patienter klarer sig sandsynligvis bedre end patienter der **ikke** er kandidater autolog stamcelletransplantation.

Håndtering af usikkerhed vedr. OS
Janssen er enig i at estimaterne er forbundet med usikkerhed, men stiller sig undrende overfor måden Medicinrådet håndterer usikkerheden på. Medicinrådet kunne for eksempel rådføre sig med fagudvalget som man gjorde med "de gamle metoder" (før 2021). Det er ikke til at udlede af vurderingen om fagudvalget er blevet spurgt til råds, og i det hele taget er det svært at læse hvad fagudvalget mener om DarLenDex.

Medicinrådet har valgt at acceptere NMA'ens resultater for progressionsfri overlevelse (PFS). Derfor kunne Medicinrådet have anvendt PFS som surrogatmål for PFS, eller i det mindste anvende PFS data til at bekræfte antagelsen at der er en OS forskel, i stedet for at anvende narrative sammenligninger til at afkræfte det. Janssen vil i denne sammenhæng gerne bemærke at man til vurdering af isatuximab i kombination med carfilzomib og dexamethason til myelomatose benyttede PFS som surrogatmål for OS, og at Medicinrådet i samme vurdering accepterede en unanchored MAIC som evidensgrundlag og med de gamle metoder vurderede at der var en moderat merværdi.

Fagudvalgets vurdering
Som nævnt, så bemærker Janssen at fagudvalget ikke har fået lov at konkludere noget i denne vurdering, hvilket Janssen finder uheldigt. Vi bemærker dog også antagelserne vedr. brugen af DarLenDex i tilfælde af en anbefaling. Vi formoder at Medicinrådet har brugt fagudvalget til validering af disse tal, og at DarLenDex her tager 60% af patienterne i første linje og BorLenDex slet ikke bruges i dette scenarie. Dette antyder at fagudvalget foretrækker DarLenDex og anser det som et bedre lægemiddel end både BorLenDex og DaraBorMelPred.

Budgetkonsekvenser
Janssen bemærker at Medicinrådet har justeret antagelserne vedr. patientoptaget. Vi mener ikke det er realistisk at patientoptaget sker så hurtigt som antaget (60% af alle første linje patienter i år 1). Denne antagelse har store konsekvenser for budgetkonsekvenserne i 2023 og 2024, og en mere realistisk antagelse vil nedbringe disse signifikant.

Janssen takker for en god dialog i processen og ser frem til afgørelsen d. 25. januar.

Med venlig hilsen
Jeppe S. Christensen
HEMAR manager Denmark

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

20. december 2022

MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25. januar 2023
Leverandør	Janssen-Cilag
Lægemiddel	Darzalex (daratumumab)
Ansøgt indikation	Daratumumab i kombination med lenalidomid og dexamethason (DaraLenDex) til behandling af patienter med nydiagnosticeret myelomatose, som ikke er kandidater til autolog stamcelletransplantation

Forhandlingsresultat

Amgros har opnået følgende pris på Darzalex (daratumumab):

Tabel 1: Forhandlingsresultat på Darzalex (daratumumab) ved kombinationen DaraLenDex til nydiagnosticeret myelomatose

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Tilbudt SAIP (DKK)	Rabatprocent ift. AIP
Darzalex (daratumumab)	1800 mg (SC)	1 stk.	38.192,76	[redacted]	[redacted]	[redacted]
Darzalex (daratumumab)	20 mg/ml (IV)	20 ml.	12.326,81	[redacted]	[redacted]	[redacted]
Darzalex (daratumumab)	20 mg/ml (IV)	5 ml.	3.147,97	[redacted]	[redacted]	[redacted]

Prisen er betinget af en anbefaling af Darzalex (daratumumab) til behandling af nydiagnosticeret myelomatose.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt mulighed for to andre behandlingsalternativer for patienter med nydiagnosticeret myelomatose, der ikke er egnede til højdosiskemoterapi med stamcellestøtte (HDT). Medicinrådets har tidligere anbefalet en kombination af BorLenDex eller DaraBorMelPred.

De årlige lægemiddeludgifter fremgår af tabel 2.

Tabel 2: Årlige lægemiddeludgifter for Darzalex (daratumumab)

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlige lægemiddeludgifter SAIP pr. år (DKK)
Darzalex (daratumumab) – opstartsår	1800 mg*	1 stk.	[redacted]	23	[redacted]
Darzalex (daratumumab) – vedligeholdelsesår	1800 mg**	1 stk.	[redacted]	13	[redacted]

*Styrke: 1800 mg. i uge 1-8, hver 2. uge i uge 9-24 efterfulgt af hver 4. uge indtil sygdomsprogression
**Styrke: 1800 mg. hver 4. uge indtil sygdomsprogression

Sarclisa (isatuximab) forventes at ansøge EMA i 2024 med godkendelse i Q1 2025, hvorefter der vil komme mere konkurrence på området[1].

Tabel 3: Sammenligning af lægemiddeludgifter

Lægemiddelkombination	Årlig lægemiddeludgift SAIP pr. år (DKK)
DaraLenDex (opstartsår)	[redacted]
DaraLenDex – (vedligeholdelsesår)	[redacted]
DaraBorMelPred (opstartsår)	[redacted]
DaraBorMelPred (vedligeholdelsesår)	[redacted]
BorLenDex (opstartsår)	[redacted]
LenDex* (vedligeholdelsesår)	[redacted]

*Patienter, der behandles med BorLenDex seponerer behandlingen med Bortezomib efter 8 serie, og fortsætter derefter i behandling med LenDex.

Status fra andre lande

Norge: Under vurdering[2].
Sverige: Anbefalet[3].
England: Forventes vurderet i marts 2023[4].
Andre lande: [redacted]

Konklusion

[redacted]

[1] https://www.sanofi.com/en/science-and-innovation/research-and-development/rd-pipeline
[2] https://nyemetoder.no/metoder/daratumumab-lenalidomid-og-deksametason-indikasjon-ii
[3] https://janusinfo.se/download/18.439eaa9418048fbb7c310d5a/1650529785060/Darzalex-(daratumumab)-220421.pdf
[4] https://www.nice.org.uk/guidance/awaiting-development/gid-ta10914

Application for the assessment of daratumumab (Darzalex®) in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation

DMC Version 3.0

Colour scheme for text highlighting	
	Confidential information

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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1 Basic information

Contact information	
Name	Jeppe Christensen
Title **Phone number** **E-mail**	Market Access Manager +45 29998267 jchris20@its.jnj.com

Overview of the pharmaceutical	
Proprietary name	Darzalex®
Generic name	Daratumumab
Marketing authorization holder in Denmark	Janssen-Cilag A/S Bregnerødvej 133 Birkerød, 3460 DK
ATC code	L01FC01
Pharmacotherapeutic group	Antineoplastic agents, monoclonal antibodies, CD38 inhibitors
Active substance(s)	Daratumumab
Pharmaceutical form(s)	Solution of injection, subcutaneous injection (SC); Concentrate for solution for infusion, intravenous infusion (IV)
Mechanism of action	Daratumumab is a fully human monoclonal IgG1 antibody expressed by genetically engineered Chinese Hamster Ovary (CHO) cells. It binds CD38 on multiple myeloma cells with high affinity and specificity, and it harbours several effector functions including CDC and ADCC. By attaching to CD38 on these cells, daratumumab activates the immune system to kill the abnormal white blood cells.
Dosage regimen	**Subcutaneous:** The recommended dose is 1,800 mg of Darzalex® solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule:

Weeks	Schedule
Weeks 1 to 8	weekly (total 8 doses)
Weeks 9 to 24[a]	every two weeks (total 8 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9

[b] First dose of the every-4-week dosing schedule is given at Week 25

Lenalidomide (25 mg) should be administered once daily orally on Days 1-21 of repeated 28-day [4-week] cycles).

Dexamethasone should be administered at 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years).

Intravenous: the recommended dosing of daratumumab administered by IV infusion is 16 mg/kg weekly on days 1, 8, 15 and 22 for two 28-day cycles, then every 2 weeks for the remaining induction and consolidation cycles based on treatment assignment.

Lenalidomide (25 mg) should be administered once daily orally on Days 1-21 of repeated 28-day [4-week] cycles).

Overview of the pharmaceutical	
	Dexamethasone should be administered at 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years).
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Daratumumab is indicated in patients with **newly diagnosed multiple myeloma** in combination with the medicines lenalidomide and dexamethasone. Lenalidomide is used for treating multiple myeloma and dexamethasone is used to suppress the immune system.
Other approved therapeutic indications	Daratumumab is indicated in patients with **newly diagnosed multiple myeloma** in combination with bortezomib, melphalan and prednisone in patients who cannot have autologous stem cell transplant. Daratumumab is indicated in patients with **newly diagnosed multiple myeloma** in combination with bortezomib, thalidomide (another medicine used to treat multiple myeloma), and dexamethasone, in patients who can have autologous stem cell transplant. Daratumumab is indicated in patients with **previously treated multiple myeloma** in combination with dexamethasone plus either lenalidomide or bortezomib Daratumumab is indicated in patients with **previously treated multiple myeloma** on its own when the disease has come back after treatment with cancer medicines (including medicines known as proteasome inhibitors) and immunomodulatory medicines (that act on the immune system), or when the disease has not improved with these medicines. (Initial authorized indication). Daratumumab is indicated for patients **newly diagnosed with the condition AL amyloidosis** and is used in combination with cyclophosphamide, bortezomib and dexamethasone.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Pre-infusion medications should be administered to reduce the risk of infusion-related reactions to all patients 1-3 hours prior to every infusion (or SC injection) of daratumumab as follows: • Corticosteroid (long-acting or intermediate-acting) Combination therapy: Dexamethasone 20 mg (or equivalent), administered prior to every Darzalex® infusion (or SC injection). When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on days daratumumab is administered. Additional background regimen specific corticosteroids (e.g., prednisone) should not be taken on days daratumumab is administered when patients have received dexamethasone as a pre-medication. • Antipyretics (oral paracetamol 650 to 1,000 mg) • Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent). Post-infusion medication • Post-infusion medications should be administered to reduce the risk of delayed infusion-related reactions as follows: Combination therapy: Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after daratumumab administration. However, if a background regimen-specific corticosteroid (e.g., dexamethasone, prednisone) is administered the day after the daratumumab infusion (or SC injection), additional post medications may not be needed.

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Overview of the pharmaceutical		
Packaging – types, sizes/number of units, and concentrations	Dispensing form and strength	**Packaging**
	Solution for subcutaneous injection 1800 mg	1 piece (15ml)
	Conc. for solution for IV infusion, 20 mg / ml	5ml
	Conc. for solution for IV infusion, 20 mg / ml	20ml
Orphan drug designation	Yes	

2 Abbreviations

2.1 Abbreviations (excluding drug regimens)

Abbreviation	Meaning
1PL	one prior line
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse events
AIC	Akaike Information Criterion
AIP	pharmaceutical purchasing price
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
ASH	American Society of Hematology
BIC	Bayesian Information Criterion
BIM	budget impact model
BSA	body surface area
BW	bodyweight
CBC	complete blood counts
CDC	complement-dependent cytotoxicity
CHO	Chinese hamster ovary
CI	confidence interval
COMP	Committee for Orphan Medicinal Products
CR	complete response
CRAB	hypercalcaemia, renal impairment, anaemia, and bone disease
CRI	credible interval
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUL4	cullin 4
DDB1	damage-binding protein 1
DIC	deviance information criterion
DKK	Danish kroner
DMC	Danish Medicines Council

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Abbreviation	Meaning
DNA	deoxyribonucleic acid
DRG	diagnosis-related group
DSA	deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	electrocardiogram
EHA	European Hematology Association
EHA-ESMO	European Hematology Association-European Society for Medical Oncology
EMA	European Medicines Agency
EPAR	European public assessment report
EMR	electronic medical records
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality-of-life questionnaire
EOT	end-of-treatment
EQ-5D-5L	EuroQoL Five-Dimension Five-Level
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration (US government)
GHS	Global Health Scale
HBV	Hepatitis B virus
HR	hazard ratio
HRQoL	health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFE	immunofixation
IgG1κ	immunoglobulin G1 kappa
IMWG	International Myeloma Working Group
IMWG	International Myeloma Working Group
IQR	interquartile range
ISS	International Staging System
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LS	least squares
LY	life year
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MRD	minimal residual disease
MRI	magnetic resonance imaging

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Abbreviation	Meaning
mSMART	Mayo Stratification for Myeloma and Risk-adapted Therapy
NCI	National Cancer Institute
NDMM	newly diagnosed multiple myeloma
NE	not evaluable
NICE	National Institute for Health and Care Excellence
NK	natural killer
NMA	network meta-analysis
OR	odds ratio
ORR	overall response rate
OS	overall survival
p.o.	per oral
PD	disease progression
PFLY	progression-free life year
PFS	progression-free survival
PFS2	time from randomisation to progression on the next line of therapy or death
PH	proportional hazards
PP	per-protocol
PP	post-progression
PPLY	post-progression life year
PPS	post-progression survival
PR	partial response
PSA	probabilistic sensitivity analysis
PSM	Partitioned survival model
QALY	quality-adjusted life year
QAPFLY	quality-adjusted progression-free life year
QAPPLY	quality-adjusted post-progression life year
RBC	red blood cell
RCT	randomized control trial
RDI	relative dose intensity
R-ISS	Revised International Staging System
Roc1	regulator of cullins 1
RWE	real world evidence
SAE	serious adverse event
SC	subcutaneous
sCR	stringent complete response
SCT	stem cell transplant
SD	standard deviation
SE	standard error
SEER	Surveillance Epidemiology and End Results
SMM	soldering multiple myeloma

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Abbreviation	Meaning
SPE	serum protein electrophoresis
TA	technology appraisal
TEAE	treatment-emergent adverse event
TIE	transplant-ineligible
TTD	time-to-treatment discontinuation
TTNT	time to next treatment
TTTD	time-to-treatment discontinuation
tx	treatment
UK	United Kingdom
US	United States
VAS	visual analogue scale
VGPR	very good partial response

2.2 Abbreviations for drug regimens

Drug regimen abbreviation(s)	Drugs
BorCycloDex / BCd / VCd	Bortezomib + cyclophosphamide + dexamethasone
BorDex / Bd / Vd	Bortezomib + dexamethasone
BorLenDex / BRd / RVd / VRd / VLd	Bortezomib + lenalidomide + dexamethasone
BorLenPred / BRP / VRP	Bortezomib + lenalidomide + prednisone
BorMelPred / BMP / VMP	Bortezomib + melphalan + prednisone
BorMelPredSil / BMPS / VMPS	Bortezomib + melphalan + prednisone + siltuximab
BorMelPredThal-BorThal / BMPT-BT / VMPT-VT	Bortezomib + melphalan + prednisone + thalidomide, followed by bortezomib + thalidomide
BorThalDex / BTd / VTd	Bortezomib + thalidomide + dexamethasone
BorThalPred / BTP / VTP	Bortezomib + thalidomide + prednisone
CycloLenDex / CLd / CRd	Cyclophosphamide + lenalidomide + dexamethasone
CycloLenPred / CRP / CLP	Cyclophosphamide + lenalidomide + prednisolone
CycloThalDex / CTD	Cyclophosphamide + thalidomide + dexamethasone
CarLenDex / CLd / CRd / KLd / KRd	Carfilzomib + lenalidomide + dexamethasone
CarMelPred / CMP / KMP	Carfilzomib + melphalan + prednisone
DaraBorDex / DBd / DVd	Daratumumab + bortezomib + dexamethasone
DaraBorMelPred / Dara+VMP / DVMP / Dara+VMP	Daratumumab + bortezomib + melphalan + prednisone
DaraBorThalDex / DBTd / DVTd	Daratumumab + bortezomib + thalidomide + dexamethasone
DaraLenDex / DRd / DRd / Dara+Rd	Daratumumab + lenalidomide + dexamethasone
Dex / d	Dexamethasone
Dex-IFN / IFN-dex	Dexamethasone + interferon alpha
EloLenDex / ELd	Elotuzumab + lenalidomide + dexamethasone
EloBorLenDex / Elo-VLd / VLd-Elo	Elotuzumab + bortezomib + lenalidomide + dexamethasone
IxaBorDex / IBd / IVd	Ixazomib + bortezomib + dexamethasone
IxaCycloDex / ICd	Ixazomib + cyclophosphamide + dexamethasone

Drug regimen abbreviation(s)	Drugs
IxaDex / Id	Ixazomib + dexamethasone
IxaLenDex / ILd / IRd	Ixazomib + lenalidomide + dexamethasone
IxaThalDex / ITd	Ixazomib + thalidomide + dexamethasone
LenDex / Ld / Rd	Lenalidomide + dexamethasone
MelDex / Md	Melphalan + dexamethasone
MelPred / MP	Melphalan + prednisone
MelPredLen / MPL / MPR	Melphalan + prednisone + lenalidomide
MelPredThal / MPT	Melphalan + prednisone + thalidomide
ThalDex / Td	Thalidomide + dexamethasone
PanBorDex	Panobinostat + bortezomib + dexamethasone
PembroLenDex / Pembro+Ld / Pembro+Rd	Pembrolizumab + lenalidomide + dexamethasone
VinMelCycloPred / VMCP	Vincristin + melphalan + cyclophosphamide + prednisolone

2.3 Terms considered interchangeable

Interchangeable terms for the subgroup of newly diagnosed patients with multiple myeloma not elegible for high-dose Melphalan with stem cell support
ASCT-ineligible
Ineligible for autologous stem-cell transplantation (ASCT)
Ineligible for high-dose chemotherapy with stem-cell transplant
Ineligible for transplant
Transplant-ineligible (TIE)

3 Tables and figures

3.1 Table of tables

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3.2 Table of figures

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4 Summary

This application is in support of the use of daratumumab in combination with lenalidomide and dexamethasone (Dara+Rd) as standard treatment for patients in Denmark with newly diagnosed multiple myeloma (NDMM) who are not eligible for autologous stem cell transplant (ASCT) (also referred to as transplant-ineligible, "TIE").

Multiple myeloma (MM) is an incurable blood cancer with orphan disease designation in Europe [1]. MM is genetically complex and develops from the continued accumulation of genetic abnormalities over time [2]. Prognosis in MM is dependent on many factors, including host factors (age, performance status, comorbidities, eligibility for ASCT) and tumour characteristics (molecular cytogenetic markers, stage, disease aggressiveness, response to therapy) [3, 4].

Patients are assessed for ASCT eligibility at diagnosis, based on a combination of factors that include age, performance status, comorbidities, frailty, and disability [3, 5]. Criteria varies between countries, but the European Medicines Agency (EMA) advises that ASCT eligibility eligibility should be determined based on the comorbidities and physiological age of an individual patient, rather than their chronological age [6]. According to the EMA, patients in Europe, aged between 65 years and 70 years, who are fit and without relevant comorbidities might be considered candidates for ASCT [6]. Therefore, the EMA suggests that an age threshold of ≥70 years may be more reflective of the ASCT eligibility/ineligibility criteria used in clinical practice [6].

The survival of patients with MM has improved dramatically over the past 20 years, a change that is primarily attributed to the introduction of more targeted therapies [7-14]. In a retrospective review of newly diagnosed patients with MM published in 2003, the median survival was only 33 months (2.8 years) and did not improve over the analysis period (January 1, 1985 to December 31, 1998) [13]. In contrast, a more recent review of newer anti-myeloma therapies reported a median survival of 73 months (6.1 years) and an 8-year survival rate of 57% [14-16]. Transplant-ineligible patients tend to be older than transplant-eligible patients at diagnosis, and do have lower survival expectancies than transplant eligible patients, but survival of both groups of multiple myeloma patients have improved as a result of improvements in treatments.

The relevant comparators for this application are the current treatment regimens recommended by the Danish Medicines Council (DMC) for newly diagnosed patients who are not candidates for high-dose chemotherapy (i.e., not eligible for autologous stem cell transplantation). The most-recent treatment guideline for multiple myeloma in Denmark, recommends a combination of bortezomib + lenalidomide + dexamethasone (VRd) as primary treatment for most patients who are not candidates for high-dose chemotherapy [17]; as well as 2) lenalidomide + dexamethasone (Rd) [17]; and 3) bortezomib + melphalan + prednisone (VMP) [17]; furthermore, the DMC has also more recently given a positive recommendation for 4) daratumumab + bortezomib + melphalan + prednisone (Dara+VMP) [18].

In this application, the main efficacy outcomes of interest are progression-free survival (PFS) and overall survival (OS). These endpoints are highly clincally relevant, enable the comparative assessments with comparators where no direct head-to-head evidence exists, and are critically important for the construction of the cost-effectiveness model. The analysis is based on data from the ongoing MAIA (MMY3008) trial, which compares Dara+Rd and Rd treatment regimens, with a recent update at a median follow-up of 56.2 months [19]. While as of the median follow-up of 56.2 data cut, the median progression-free survival has not been met for the Dara+Rd treatment arm in the MAIA trial, it

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

was 34.4 months in the Rd arm, indicating the clinical benefit of the Dara+Rd treatment regimen. Neither the Dara+Rd nor Rd treatment arms have met median overall survival as of the median 56.2 month follow-up data cut.

The ongoing MAIA trial is the only head-to-head trial considering newly diagnosed patients who are ineligible for ASCT which compares the Dara+Rd treatment regimen with any of the other relevant comparator treatment regimens in Denmark (i.e., Rd) [19]. To provide evidence of relative treatment efficacy between Dara+Rd and the other relevant treatment comparators where head-to-head evidence does not currently exist (i.e., VRd, VMP, Dara+VMP), a Bayesian Network Meta Analysis (NMA) has been conducted, using continuous lenalidomide/dexamethasone (Rd) as the referent comparator [20]. The evidence from the NMA indicates a statistically significantly lower (better) hazard ratio for both PFS (HR = 0.53, 95% CrI: 0.43, 0.66) and OS (HR = 0.68, 95% CrI: 0.54, 0.86) for the Dara+Rd treatment regimen compared to Rd. For Dara+VMP, a statistically significantly lower (better) hazard ratio for was found for PFS (HR = 0.58, CrI: 0.37, 0.93) compared to Rd, but no significant difference was found for OS hazard ratio. No significant differences were found for either PFS or OS hazard ratios considering VRd or VMP compared to Rd. This evidence for treatment of NDMM amongst patients who are ineligible for ASCT suggests that compared with the other available treatment regimens in Denmark, the Dara+Rd treatment regimen is likely to offer the greatest survival benefits.

In the MAIA (MMY3008) study, Dara+Rd was well tolerated, with a safety profile consistent with the known toxicity of the Rd regimen and the known AEs experienced with daratumumab as a single agent [19]. The overall incidence of TEAEs was comparable between treatment groups, reported by [redacted] of patients treated with Dara+Rd and Rd, respectively [21]. Discontinuation of study treatment (i.e., all study drugs) due to TEAEs occurred less frequently with Dara+Rd than with Rd (13% and 23%, respectively; statistical comparison not conducted) [19].

A cost-effectiveness model was developed in Microsoft Excel® to assess the cost-effectiveness of Dara+Rd vs. Rd, VRd, VMP and Dara+VMP patients with NDMM who are ineligible for ASCT. A three-health-state cohort model structure was implemented through a partitioned survival approach, partitioning the baseline patient cohort into progression-free, progressed, and dead, based on estimated PFS and OS curves informed by the survival data from the MAIA trial [19] and implementation of hazard ratios estimated from the NMA [20]. Model outcomes include life years (LYs), quality-adjusted life years (QALYs), disutility associated with adverse events (AEs), costs of drug acquisition, administration, medical resource use, AE management, cost per LY gained and cost per QALY gained. Deterministic sensitivity analyses (DSAs), probabilistic sensitivity analyses (PSAs) and scenario analyses were used to investigate uncertainty of the model parameters.

As per DMC guidance, the cost-effectiveness analysis takes a restricted societal perspective, using the best available clinical and economic evidence. Local Danish data inputs are used wherever available. The current model is based on results from the MAIA trial with median follow-up of 56.2 months [19] and hazard ratios for PFS and OS curves estimated from the NMA [20].

In the base case analysis, Dara+Rd resulted in increased QALYs gained incomparison to all relevant comparators: 1) Dara+Rd vs. Rd: 2.14; 2) Dara+Rd vs. VRd: 1.63; 3) Dara+Rd vs. VMP: 2.66; and 4) Dara+Rd vs. Dara+VMP: 1.63. Based on list prices of Darzalex, comparators and drugs used in combination, the costs associated with Dara+Rd were also higher vs. all comparators: 1) Dara+Rd vs. Rd: DKK 3,959,421; 2) Dara+Rd vs. Dara+VMP: DKK 1,575,922; 3) Dara+Rd vs. VRd: DKK 2,379,726; and 4) Dara+Rd vs. VMP: DKK 3,899,876.

Together, the base-case ICERs are: 1) Dara+Rd vs. Rd: 1,847,098 DKK/QALY; 2) Dara+Rd vs. Dara+VMP: 969,505 DKK/QALY; 3) Dara+Rd vs. VRd: 1,463,974 DKK/QALY; and 4) Dara+Rd vs. VMP: 1,468,509 DKK/QALY.

Based on the projected uptake of the Dara+Rd treatment in newly diagnosed MM in the case that Dara+Rd recieves a positive reimbursement recommendation (given current list prices), the annual budget impacts in the first five years are: Year 1) DKK 22,263,765; Year 2: DKK 60,746,630; Year 3: DKK 88,111,473; Year 4: DKK 115,443,545; Year 5: DKK 139,351,625.

This submission only considers the subgroup of patients with newly diagnosed MM who are ineligible for ASCT.

5 The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Disease

Multiple myeloma (MM) is a rare haematological cancer. The disease begins in the white blood cells that are responsible for the production of antibodies (i.e., immunoglobulins [Ig]). Being a clonal malignancy, MM arises when a single plasma cell undergoes an oncogenic event that leads to its over-proliferation and reduced apoptosis. This results in an abnormally high number of white blood cell clones in the bone marrow, which interfere with the production of other blood cells (i.e., red blood cells and platelets) [22].

Plasma cell clones are typically characterised by the overproduction of an abnormal immunoglobulin (i.e., an M-protein) which can accumulate in the kidney or blood, leading to renal failure or blood hyperviscosity, respectively. Additionally, plasma cell clones frequently migrate to adjacent bones, where their invasion and subsequent over-proliferation can destroy skeletal structures, causing bone pain and fractures. Malignant cells may also circulate in the blood and populate multiple organs throughout the body [22].

Multiple myeloma is diagnosed based on bone marrow examinations, imaging studies, tumor tissue biopsies, and examinations for M-component or free light chains in blood and urine. The diagnostic criteria used in Denmark [17] are those recommended by the International Myeloma Working Group (IMWG) [23].

MM is a treatment-sensitive, but incurable disease and all patients will eventually relapse [24].

5.1.2 Aetiology and aetiopathology

Multiple myeloma is a genetically complex disease that develops from the accumulation of genetic abnormalities in plasma cells over time. While the exact mechanism that triggers malignant transformation of these cells has not yet been identified, it is widely acknowledged that the pre-malignant, asymptomatic stage of MM, monoclonal gammopathy of undetermined significance (MGUS), develops from an initial (primary) oncogenic event in the form of either a hyperdiploidy (i.e., having more than 46 chromosomes) or a chromosomal translocation (i.e., switching of genetic material between two different chromosomes) [25, 26].

5.1.3 Natural history

Multiple myeloma is a highly heterogeneous disease with a variable clinical course. At the time of diagnosis, patients have a median age of approximately 65 to 70 years; rarely are patients younger than 40 years [8, 13, 27].

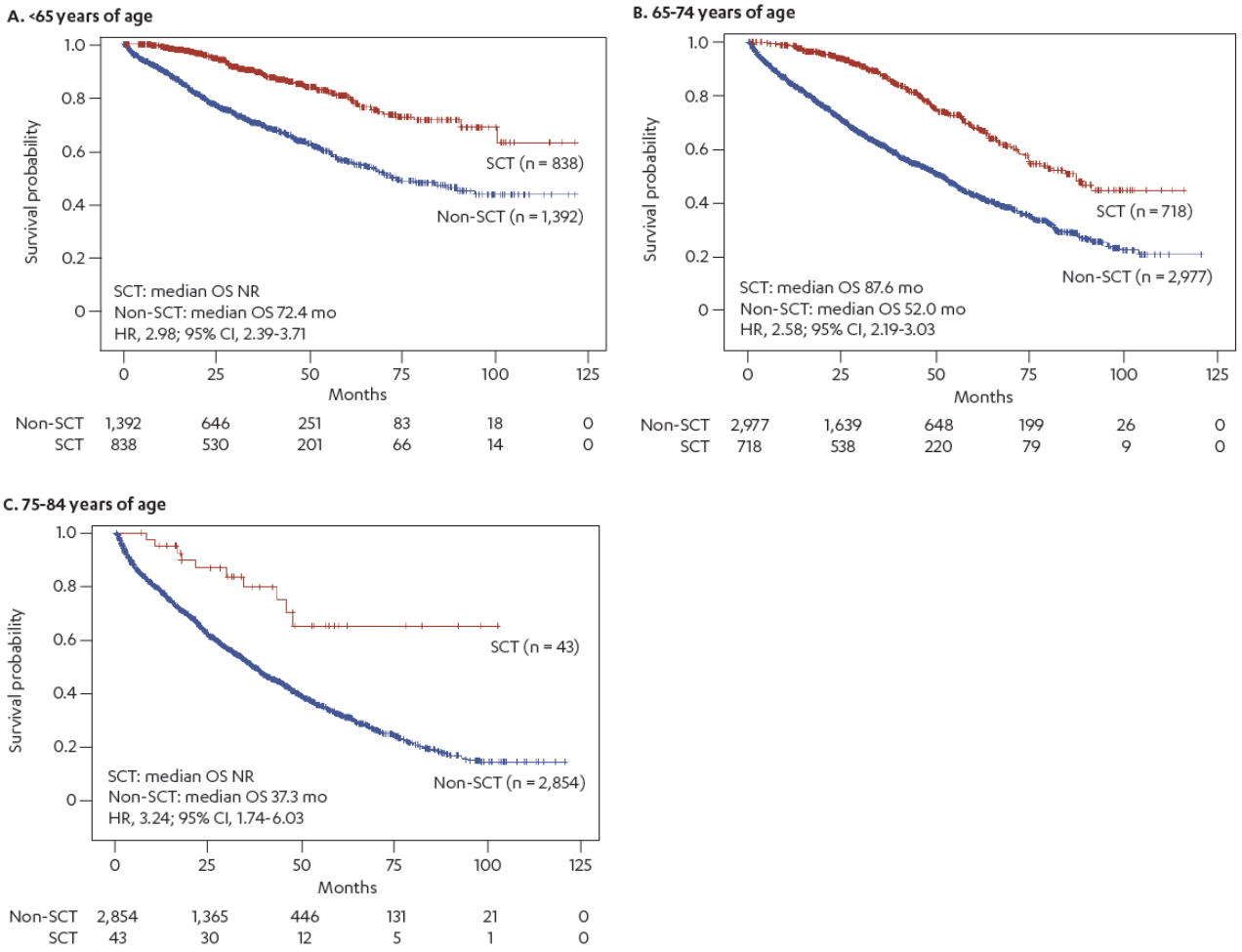
Patients with MM may or may not be eligible for ASCT. Patients are assessed for ASCT eligibility at diagnosis, based on a combination of different factors that vary between countries, including age, performance status, comorbidities, frailty and disability [3, 5]. Patients ≥65 years of age are commonly considered ineligible for ASCT due to a lack of evidence for the survival benefit of ASCT from studies focusing on this age group [28, 29]. Given a median age of 65 to 70 years at diagnosis, at least half of newly diagnosed patients with MM can therefore be considered ASCT-ineligible [8, 13, 27].

The survival of patients with MM has improved dramatically over the past 20 years, a change that is primarily attributed to the introduction of more targeted therapies [7-14]. In a retrospective review of newly diagnosed patients with MM published in 2003, the median survival was only 33 months (2.8 years) and did not improve over the analysis period (January 1, 1985 to December 31, 1998) [13]. In contrast, a recent review of newer anti-myeloma therapies reported a median survival of 73 months (6.1 years) and an 8-year survival rate of 57% [14-16]. This temporal improvement in survival is supported by other studies, which examined OS before and after the introduction of newer therapies. For example, in a retrospective Mayo Clinic study of patients with MM (N=1,038), those diagnosed between 2006 and 2010 had significantly prolonged OS compared with those diagnosed between 2001 and 2005 (6.1 vs. 4.6 years, respectively; p=0.002) [11]. Similarly, a large (N≈45,000 patients with MM) analysis of survival data from the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) Registries Database revealed that, across patient age groups under 80 years, cumulative five-year survival improved significantly over time, from 34% in the period of 1973 to 1979 to 68% in 2001 to 2009 (p<0.05) [9].

However, despite advances in the treatment of MM since 2000 that may have resulted in improved survival rates, ASCT-ineligible patients still have lower survival compared with ASCT-eligible patients [30, 31]. A real-world study of 9,323 MM patients was conducted in the US, to compare the characteristics and outcomes of stem cell transplant (SCT)-eligible and SCT-ineligible patients [31]. Data regarding 1,599 SCT-eligible patients (17.2%) and 7,724 SCT-ineligible patients (82.8%), dating from January 2000 to March 2017, was sourced from the three following US databases: the SEER Medicare Linked database (January 2007 to December 2014), the OPTUM Commercial Claims database (January 2000 to March 2017) and the OPTUM Electronic Medical Records (EMR) database (January 2007 to March 2016) [31]. At baseline, SCT-ineligible patients tended to be older (median age: 73 vs. 64 years), less commonly male (49.1% vs. 58.8%) and had a higher occurrence of comorbidities, such as chronic heart failure (19.3% vs. 6.6%) and renal disease (34.0% vs. 25.1%) than SCT-eligible patients [31]. Age, gender and presence of comorbidities, along with time to treatment initiation and year of treatment initiation, were all associated with OS [31].

After accounting for varying baseline characteristics, the adjusted HR for OS was 2.29 for SCT-ineligible patients vs. SCT-eligible patients (95% CI: 2.01-2.61; p<0.0001) [31]. For the SCT-eligible group, median OS was not reached (95% CI: 91.8-not estimable [NE]), whereas the median OS for SCT-ineligible patients was found to be 45.1 months (95% CI; 43.1-46.8) [31]. Furthermore, the OS rate at 18 months after front-line treatment was considerably lower in SCT-ineligible patients compared with SCT-eligible patients (74.7% vs. 96.7%) [31]. This disadvantage in terms of OS among SCT-ineligible patients compared with SCT-eligible patients was found across all age groups analysed (<65, 65-74, ≥75; Figure 1) and highlights the need for more effective treatment options for patients ineligible to receive SCT [31].

Figure 1. OS by age group and SCT eligibility



HR = hazard ratio; OS = overall survival; SCT = stem-cell transplant; Source: Chari, et al. 2018 [31]

An observational study (N=852) published in 2017 examined patients with MM diagnosed between January 2005 and December 2007 in five South American countries [30]. The ASCT-ineligible patients[1] in this study had an average age of 67.4 years, compared with 54.7 years for ASCT-eligible patients [30]. The OS of ASCT-ineligible patients was found to be shorter than that of ASCT-eligible patients: 43.0 months and 73.6 months, respectively [30].

The US prospective observational study of the Connect MM registry found that patients with ≥6-year OS were associated with the following patient- and disease-specific baseline characteristics: were more likely to have undergone ASCT, have higher rates of triple therapy treatment, maintenance therapy with or without SCT, and demonstrate higher response rates [32].

[1] Transplant eligibility was determined locally in each study centre; there were no centrally determined criteria for ASCT eligibility; however, prior to data collection the clinical condition of the patients was agreed upon as a major determinant of transplant eligibility.

A recent study assessed response to treatment in MM patients treated in various Swedish centres from 2000 to 2011 [33]. Within the study population, 1,125 of 1,616 patients did not receive an ASCT[2]. Within these patients who did not receive ASCT as a first-line treatment, both PFS and time to next treatment (TTNT) were substantially shorter than in patients who did receive ASCT [33].

Similarly, a retrospective New Zealand study (N=361) analysing data from patients with MM diagnosed between 2000 and 2009 found that patients ≥66 years of age, who generally received standard-dose chemotherapy without SCT, had significantly shorter median survival than those <66 years of age who received SCT[3] (25 vs. 78 months, respectively; p<0.0001). Relative survival, compared against an age- and sex-matched normative population, was calculated for both age groups (≥66 [older patients] and <66 years of age [younger patients]). Older patients were found to have a significantly shorter relative survival than younger patients at each time point (p<0.001), suggesting that differences in median OS between the groups were greater than that attributable to normal ageing [34].

5.1.4 Treatment and Prognosis

Treatment of multiple myeloma in Denmark is based in haematological departments [17], and usually consists of regimens using combinations of medicine to attacks cancer cells in several ways, which generally has a greater effect than monotherapy [35]. In certain cases, medical treatment is supplemented with radiotherapy and possibly surgery. Although the disease is incurable, symptom- and treatment-free periods are achievable for many patients. The goal of the treatment is to achieve the longest possible survival with the fewest possible side effects, prolonged treatment-free periods and the best possible quality of life [17].

Prognosis in MM is dependent on a number of factors, including patient factors (age, performance status, comorbidities, ASCT eligibility) and tumour characteristics (molecular cytogenetic markers, stage, disease aggressiveness, response to therapy) [3, 4, 32]. Patients have a considerably poorer prognosis once they have relapsed or become refractory to current treatments [36].

Prognostic factors that identify patients with a higher risk for achieving poorer outcomes (i.e., shortened survival) have not been comprehensively defined. Nonetheless, several groups of patients have been identified as having poorer outcomes. These include patients with [3, 5, 30, 37, 38]:

- High-risk disease:
- t(4;14) or t(14;16) translocations
- Deletion of chromosomes 17 or 13
- Hypodiploidy
- High β2 microglobulin

[2] No information on reasons for patients not receiving an ASCT is provided; no information on the characteristics of patients who did not undergo ASCT is provided

[3] Patients were categorised into two groups based on their age: 'young' patients <66 years and 'old' patients ≥66 years of age. 62% of 'young' patients received SCT, while 3% of 'old' patients received SCT. Therefore, the 'young' and 'old' patient groups from this study have been used in this GVD as proxy for ASCT-eligible and –ineligible patient groups, respectively.

- Low serum albumin
- Elevated serum lactate dehydrogenase (LDH)
- ASCT ineligibility (determined by age, performance status, comorbidities, frailty and disability)

Various combinations of these factors provide robust models for the risk stratification of patients newly diagnosed with MM including the International Myeloma Working Group (IMWG) Revised International Staging System (R-ISS) and the Mayo Stratification for Myeloma and Risk-adapted Therapy (mSMART) [38, 39]. The R-ISS classifies patients into one of three risk stages, each with progressively worsening median survivals [38].

While ASCT-ineligibility itself is a prognostic factor for poor outcomes, additional prognostic factors within the ASCT-ineligible population of patients with MM have been associated with shortened survival [40]. In a study with ASCT-ineligible patients with MM[4], univariate statistical analyses suggest that patient age, performance status and serum calcium levels are predictive of OS (p=0.033, p=0.025 and p=0.005, respectively), and multivariate analyses indicate that serum calcium >11.0mg/dL is a significant unfavourable prognostic factor for OS (p=0.009) [40].

5.1.5 Complications

The clinical complications of MM are complex and often involve multiple organ systems [41].

Differentiation of symptomatic MM from the asymptomatic stages of MGUS and smoldering multiple myeloma (SMM) requires the presence of end-organ damage that is exemplified by a distinct set of complications. These complications, which are common to patients with MM, are known by the acronym '**CRAB**': hypercalcaemia, renal impairment, anaemia and bone disease and are further discussed below [42]:

C: Up to 30% of patients with MM present with hypercalcaemia, or elevated blood calcium level. Patients may exhibit confusion, disorientation, muscle weakness, polyuria and cardiac arrhythmia [43, 44]. Hypercalcaemia is often a prominent feature late in the course of MM [44].

R: Renal impairment is a common and potentially serious complication of MM observed in approximately 20% to 25% of patients at MM presentation [45] and up to 50% of patients at one point during the course of the disease [46, 47].

A: Anaemia, or a low red blood cell count, is another common complication of MM. Approximately 60% to 70% of patients present with anaemia at diagnosis [48].

B: Bone disease is the most common complication of MM, affecting approximately 80% to 90% of patients [43, 49]. Invasion and expansion of plasma cell clones in the bone marrow weakens and damages the bone, leading to the formation of osteolytic bone lesions and the development of bone fractures, spinal cord compression, hypercalcaemia and osteoporosis [50].

More recently, diagnostic criteriain MM have been extended to consider 3 validated biomarkers: 1) ≥60% clonal bone marrow plasma cells; 2) serum free light chain ratio ≥100; and 3) > 1 focal bone lesion by MRI [23]. These are the so-

[4] Criteria for ASCT ineligibility were not defined in the study paper

called SLiM (e.g., Sixty, Light, MRI) criteria, which clinicians are used along with the CRAB criteria to make treatment decisions.

Less frequent complications of MM include hyper-viscosity syndrome (i.e., increased blood viscosity), infection, thrombosis and extramedullary disease [43, 51, 52].

5.1.6 Effects of MM on patients and caregivers

There is evidence that patients with MM report worse symptoms and health-related quality of life (HRQoL) than those with other haematological cancers, including lymphoma or leukaemia [53]. The clinical burden of MM is influenced by both progressive disease symptoms and treatment-associated complications such as weakness, fatigue, bone pain, weight loss, confusion, excessive thirst and constipation [54]. Patients with MM live in fear of relapse [55]. Uncertainty about the future causes ongoing anxiety and often affects patients' relationships with family and friends who may act as informal caregivers [55] [56]. This leads to decreased independence and increased social isolation [55]. Treatments that achieve a lasting remission offer maximum life expectancy and freedom from the emotional burden of the disease (to "not always think of the disease"), and are therefore highly valued by patients.

Achieving prolonged remission following first-line treatment is critical for improving and maintaining the HRQoL of patients. Indeed, the symptomatic burden for patients with relapsed/refractory disease is greater than NDMM due to the progressive nature of the disease and the cumulative adverse effects of subsequent treatment [57]. Observational data from a UK study, which included responses from 370 patients with MM, demonstrated that patient HRQoL is reduced following progression from their first treatment-free interval to second-line treatment and subsequent lines of therapy [58]. This study also showed that a longer treatment-free interval was significantly associated with improved HRQoL [58].

In a recent European study of patient perceptions regarding MM and its treatment in patients with newly diagnosed and relapsed/refractory MM (N=30), patient preferences on key efficacy and safety outcomes were elicited [59]. The results of qualitative interviews revealed increased life expectancy (87%), remission/response (80%) and reduced fatigue (80%) as the most important treatment preferences. Symptoms of fatigue and bone pain were most often discussed while, among patients with NDMM, cognitive impairment was the most frequently mentioned side-effect (94% of respondents). Duration of treatment was most often discussed in the context of treatment burden (mentioned by 83% of NDMM respondents), indicating that a sustained period of treatment-free remission would be highly valued by patients. This finding is consistent with results from a recent qualitative survey undertaken by NICE's Science Policy and Research programme in collaboration with Myeloma UK. In the survey of 97 UK MM patients, respondents were asked what the most important good effects (or characteristics) they would want from any treatment for myeloma with the joint top-ranked response being a longer remission / treatment-free period (Figure 2).

Figure 2. Treatment effects most desire by patients

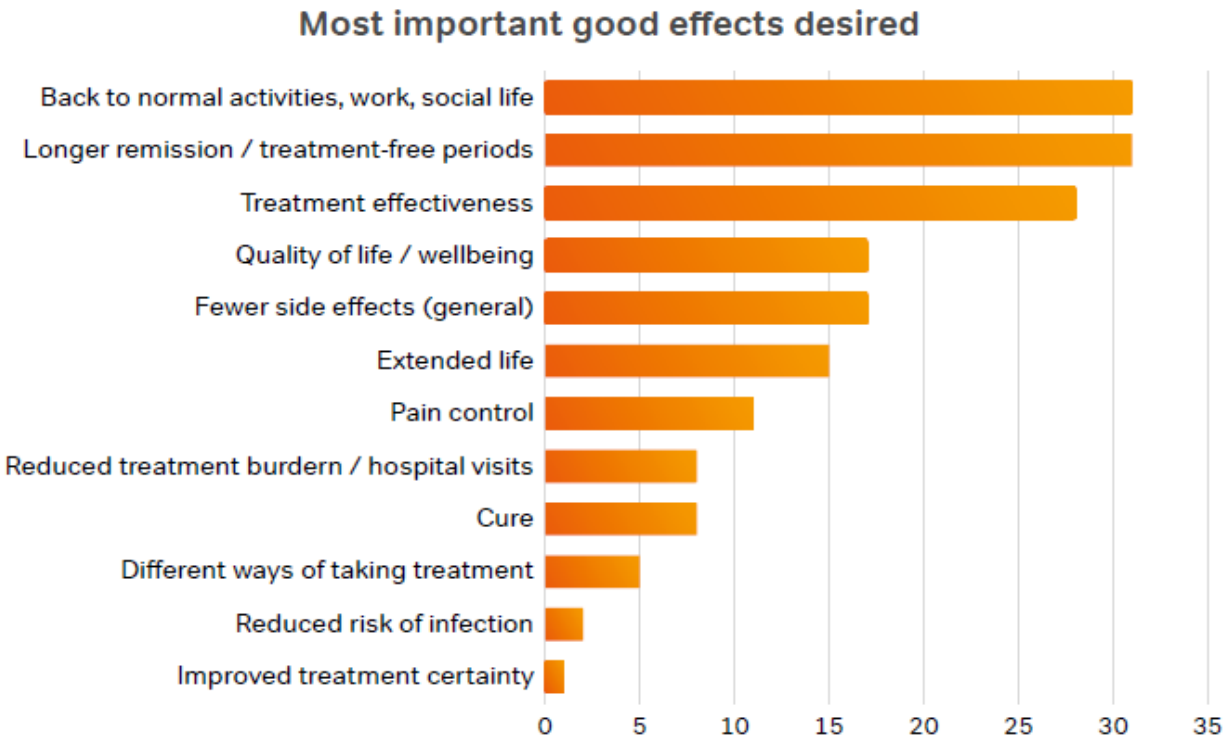


Figure reprinted from: Myeloma UK, Measuring Patient Preferences. 2019 [60].

The symptom burden associated with MM was also highlighted in the responses from this survey, with fatigue and tiredness; other symptoms and side effects; mobility and daily activities; and pain and discomfort, being reported by patients as the aspects of MM that has the greatest impact on their lives [60]. The negative effects of treatment that patients would most want to avoid were also assessed as part of the survey, highlighting the need for treatments that themselves have minimal disruption on patient's health (i.e., avoidance of adverse events) and normal activities. Across both studies, it is clear that longer remission and treatment-free intervals are goals of therapy that are highly valued by patients with MM, in addition to increased life expectancy and reduced symptom burden.

Most of the clinical management of MM is provided in the outpatient setting; therefore the bulk of care is informal and provided by caregivers [61]. Caregivers may perform complicated technical procedures (e.g., dressing changes, intravenous line care and injections), assist the patient with daily living, attend appointments and take in complex information [61]. Therefore, the detrimental effects of MM on working life are not only experienced by patients, but also their caregivers [62]. Almost half (49%) of the partners of patients with MM report symptoms of anxiety and 14% report symptoms of depression [62]. The emotional impact experienced by caregivers of patients with MM further hinders their ability to work. The unmet need in supportive care is considerable and caregivers have specifically reported a need for help to manage the side effects and complications experienced by patients due to treatment for MM [62].

5.1.7 Relevance of progression-free survival

Progression-free survival is used in the clinical part of the application as well as the cost-effectiveness analysis.

In addition to the extension of overall survival, another therapeutic goal is to prolong the progression free time and progression-free survival (PFS) [63]. PFS is a composite endpoint of the benefit categories of mortality (overall survival) and morbidity (occurrence of disease progression). In addition to the cure rate and overall survival, PFS is required by the EMA and The United States Food and Drug Administration (FDA) as one of the primary endpoints in cancer studies [64] [65]. EMA and FDA have approved drugs on the basis of PFS and currently accept it as a primary endpoint in clinical trials trial [64] [65] [66]. In MM, the EMA has accepted PFS as a suitable primary endpoint for marketing authorization, (e.g., carfilzomib [Kyprolis] [67], elotuzumab [Empliciti] [68], ixazomib [Ninlaro] [69], panobinostat [Farydak] [70], and pomalidomide [Imnovid] [71]). Similarly, daratumumab (Darzalex) was initially approved in the Relapsed/refractory multiple myeloma setting based on overall response rate (ORR) data (with PFS as a secondary endpoint) in 2016, and later the indication was extended to newly diagnosed MM (NDMM) using PFS data in 2018 [72].

PFS is particularly clinically relevant because it allows robust conclusions to be drawn about the effectiveness of a therapy even in studies with a small number of patients or studies of short follow-up [73].

In the published protocol for the MM evaluation conducted by the Medicines Council, PFS was stated to be a critical endpoint [17], [74] illustrating its importance in MM. PFS has been widely adopted as the primary endpoint in clinical trials. PFS is also a relevant endpoint in MM since time without progression provides patients with the possibility of achieving periods without active treatment course with potential side effects, affected quality of life and disadvantages in connection to hospital visits to receive treatment [74]. In addition, PFS reflects the duration of periods, where the patient achieve symptom-free periods thus presumed better quality of life [75].

Cartier et al. 2015 performed a meta-analysis of 21 myeloma randomized control trials (RCTs) (14 first-line, 4 maintenance, and 3 relapsed/refractory) using trial-level data and found positive correlation between treatment effects on PFS and treatment effects on OS [76]. Similarly, Félix et al. 2013 conducted a study focusing on time-dependent endpoints as predictors of overall survival in multiple myeloma with 152 studies where the majority of the studies were in the newly diagnosed setting) and PFS was found to predict OS in MM patients [77].

5.1.8 Relevance of response and MRD-negativity

Minimal Residual Disease (MRD)-negativity is reported in the efficacy section of this application. However, MRD-negativity is not used in the cost-effectiveness analysis.

Patients are increasingly demonstrating substantially better clinical responses with newer treatments, including increasing rates of complete remission [78]. However, complete response does not automatically translate to prolonged overall survival for all MM patients, as a small number of myeloma cells may remain in the body even in complete response. The absence of myeloma cells in bone marrow at the lowest level of detection is termed MRD-negativity at the level of sensitivity of the method used. The depth of response measured in MRD analyses is of prognostic relevance. In the following we provide evidence that achievement of MRD-negativity is a predictive factor for delayed progressive disease and prolonged survival:

For example, PFS is nearly twice as long in patients with complete response and evidence of MRD-negativity, and overall survival is also greatly extended compared to patients with complete response without MRD-negativity [79] [80] [81]. The reduced mortality risk is a patient-relevant endpoint which is directly linked to the depth of response [82] [83]. In

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

particular, evidence of early MRD-negativity has developed into an independent and important predictor of prolonged PFS and overall survival [84].

The EHA-ESMO guideline from 2021 [85] refers to two studies where MRD negativity in the bone marrow in patients who have achieved conventional complete response (CR) consistently correlates with prolonged PFS and OS in both NDMM and relapsed/refractory MM patients [79] [86]. In addition, the guideline refer to a study where MRD has been found to be a surrogate endpoint for PFS in patients receiving first-line treatment [87]. Therefore, MRD may be used as an endpoint to accelerate drug development. The guideline highlights that the use of MRD in relation to driving treatment decisions is under investigation and the results of several phase III trials will clarify the role of MRD in making decisions about therapy in MM [85].

As a result of the correlation between MRD-negativity and prolongation of PFS and OS [84], MRD-negativity is considered to be a valid surrogate for the duration of survival of MM patients.

In particular, across studies of drugs intended to be approved in first-line oncology or haematological indications, mature data for OS are challenging to realize (i.e., median OS). The EMA has issued a guideline supporting the use of the MRD-negativity endpoint as an intermediate endpoint in multiple myeloma randomized clinical trials. In these cases, studies must be designed to demonstrate the efficacy through relevant hard endpoints at a later date [88].

5.1.9 Patient populations relevant for this application

MM is the second most common haematological cancer in Denmark [17]. The median age at diagnosis is approx. 72 years, with incidence increasing with age [89]. Approximately 450 new patients are diagnosed with MM in Denmark annually, of which approximately 20% have smouldering (asymptomatic) multiple myeloma, and do not receive immediate treatment [17]. About 360 patients with newly diagnosed MM will receive primary treatment in Denmark (Table 1), and about two thirds (approx. 240) of these patients are considered ineligible for autologous stem cell transplant and will receive a first treatment (Table 2) [17]. The relevant patient population for this application (i.e., who will be candidates for first-line treatment with daratumumab in combination with lenalidomide and dexamethasone) are these approximately 240 Danish patients who are newly diagnosed with multiple myeloma (NDMM) and considered ineligible for autologous stem cell transplantation (ASCT).

Table 1. Estmated incidence and prevalence of treated MM in the past 5 years in Denmark

Year	2017	2018	2019	2020	2021
Incidence in Denmark	330	317	365	363	380[a]
Prevalence in Denmark	1850[a]	1870[a]	1890[a]	1916	1940[a]

Source: 2020 Annual Report of the Dansk Myelomatose Database [89]; [a] Missing values estimated

Table 2. Estimated number of ASCT-ineligible NDMM patients eligible for first-line treatment with Dara+Rd

Year	2022	2023	2024	2025	2026
Number of ASCT-ineligible patients in Denmark who are expected to be eligible for first-line treatment with Dara+Rd in the coming years	240	244	247	251	255

Source: Background for DMC treatment recommendations for bone marrow cancer (myeloma) [17], approximately 1% increase expected per year

5.2 Current treatment options and choice of comparators

5.2.1 Current treatment options

The most-recent treatment guideline for multiple myeloma in Denmark, recommends a combination of bortezomib + lenalidomide + dexamethasone (VRd) as primary treatment for most patients who are not candidates for high-dose chemotherapy (i.e., not eligible for autologous stem cell transplantation) [17]; as well as 2) lenalidomide + dexamethasone (Rd) [17]; and 3) bortezomib + melphalan + prednisone (VMP) [17]. Furthermore, the DMC has also more recently (2021) given a positive recommendation for 4) daratumumab + bortezomib + melphalan + prednisone (Dara+VMP) in the same indication of treatment for newly diagnosed patients with multiple myeloma who are ineligible for ASCT [18].

5.2.2 Choice of comparators

All four treatment regimens described in section 5.2.1 are considered relevant comparators. These are the three treatment regimens positively recommended in the DMC treatment guideline for multiple myeloma (VRd, Rd, and VMP) [17], as well as Dara+VMP which has been recommended more recently but not included in the current treatment guidelines [18]. Within the indication of treatment for newly diagnosed patients with multiple myeloma who are ineligible for ASCT, it is expected that the introduction of Dara+Rd will primarily take market share away from patients who would otherwise be treated with VRd, Dara+VMP, and Rd.

5.2.3 Description of the comparators

Key information regarding medications included in comparator treatment regimens are provided in Table 3. An overview of the four comparator treatment regimens, including details of details of dosing is provided in Table 4.

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Table 3. Key descriptive information of medications included in comparator treatment regimens

Drug (Brand name)	ATC code	Mechanism of action	Pharmaceutical form	Packaging
Bortezomib (Velcade®)	L01XG01, Antineoplastic agents, other antineoplastic agents	Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death.	Powder for solution for injection 3.5 mg	1 vial
Lenalidomide (Revlimid®)	L04AX04, Antineoplastic and immunomodulating agents, other immunosuppressants	Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In haematopoietic cells, lenalidomide binding to cereblon recruits substrate proteins Aiolos and Ikaros, lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in direct cytotoxic and immunomodulatory effects.	Hard capsule 2.5 mg	21 pieces
			Hard capsule 5 mg	21 pieces
			Hard capsule 7.5 mg	21 pieces
			Hard capsule 10 mg	21 pieces
			Hard capsule 15 mg	21 pieces
			Hard capsule 20 mg	21 pieces
			Hard capsule 25 mg	21 pieces
Melphalan	L01AA03, Antineoplastic and immunomodulating agents, alkylating agents	Melphalan is a bifunctional alkylating agent that prevents the separation and replication of DNA. Formation of carbonium intermediates from each of the two bis-2-chloroethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking the two DNA strands and thereby preventing cell replication	Tablets 2 mg	25 pieces
Dexamethasone	H02AB02, Corticosteroids for systemic use, glucocorticoids	Binds with glucocorticoid receptors. Anti-inflammatory and immunosuppressive effects.	Tablets 1 mg	20 pieces, 100 pieces
			Tablets 4 mg	20 pieces, 100 pieces
			Tablets 40 mg	10 pieces
Prednisolone	H02AB06, Corticosteroids for systemic use, glucocorticoids	Binds with glucocorticoid receptors. Anti-inflammatory and immunosuppressive effects.	Tablet 2.5 mg	100 pieces
			Tablet 5 mg	100 pieces
			Table 25 mg	10 pieces, 100 pieces

Sources: www.medicin.dk, SmPCs

Table 4. Overview of comparator treatment regimens

Regimen	Administration	Dose	Frequency	Duration
VRd (BorLenDex)				
Bortezomib	s.c.	1.3 mg/m2	Days 1, 4, 8 and 11 out of 21 days	Every three weeks, at least 6 series
Lenalidomide	p.o.	25 mg	Day 1-14 out of 21 days	Every three weeks, at least 6 series
Dexamethasone	p.o.	20 mg	Days 1, 2, 4, 5, 8, 9, 11 and 12 out of 21 days	Every three weeks, at least 6 series
Co-medications **Monitoring** **Diagnostic tests**	Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). Platelet counts should be monitored prior to each dose. Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment. Antiviral prophylaxis (for herpes zoster) is recommended in patients being treated with bortezomimb. Patients with renal impairment should be monitored closely. It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness in patients at risk of infection with HBV before initiation of treatment. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes. Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycemics. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Patients with risk factors for or existing heart disease should be closely monitored. When rituximab is used in combination with bortezomib, HBV screening must always be performed. Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics. Also as per Rd treatment.			
Rd (LenDex)				
Lenalidomide	p.o.	25 mg	Day 1-21 of 28 days	At least 18 series or until progression
Dexamethasone	p.o.	40 mg	Once a week	At least 18 series or until progression
Co-medications **Monitoring** **Diagnostic tests**	Women of childbearing potential: a medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 week. Patients with known risk factors for myocaridal infarction or thromoboembolims – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).			

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Regimen	Administration	Dose	Frequency	Duration
	Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during lenalidomide therapy. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias.			
VMP (BorMelPred)				
Bortezomib	s.c.	1.3 mg/m2	Days 1, 8, 15 and 22 of 5 weeks	9 series of 5 weeks
Melphalan	p.o.	9 mg/m2	Days 1-4 of 5 weeks	9 series of 5 weeks
Prednisolone	p.o.	100 mg	Days 1-4 of 5 weeks	9 series of 5 weeks
Co-medications **Monitoring** **Diagnostic tests**	Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). Platelet counts should be monitored prior to each dose. Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment Antiviral prophylaxis (for herpes zoster) is recommended in patients being treated with bortezomib. Patients with renal impairment should be monitored closely. It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness in patients at risk of infection with HBV before initiation of treatment. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes. Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycemics. Patients with risk factors for or existing heart disease should be closely monitored. When rituximab is used in combination with bortezomib, HBV screening must always be performed. Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.			
Dara+VMP (DaraBorMelPred)				
Daratumumab	s.c.	1,800 mg	Weekly in first series, every third week in series 2-9 and thereafter every fourth week until progression	9+ series of 4 weeks
Bortezomib	s.c.	1.3 mg/m2	Days 1, 4, 8 and 11 out of days	Every three weeks, at least 6 series
Melphalan	p.o.	9 mg/m2	Days 1-4 of 4 weeks	9 series of 4 weeks

Regimen	Administration	Dose	Frequency	Duration
Prednisolone	p.o.	60 mg	Days 1-4 of 4 weeks	9 series of 4 weeks
Co-medications **Monitoring** **Diagnostic tests**	As per Dara+Rd treatment regimen, and VMP treatment regimen.			

p.o. = per oral; i.v. = intravenous; s.c. = subcutaneous; VRd = Bortezomib + lenalidomide + dexamethasone; Rd = Lenalidomid + dexamethasone; VMP = Bortezomib + melphalan + prednisone; Dara+VMP = Daratumumab + bortezomib + melphalan + prednisone; Sources: Medicin.dk [90]; DMC drug recommendation and treatment guidelines regarding drugs for bone marrow cancer (multiple myeloma) [17]; DMC Dara+VMP recommendation background [18]; [91] [92, 93]

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5.3 The intervention

Daratumumab is a first-in-class, fully human[5] immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds to CD38, a cell surface glycoprotein found on the surface of many immune cells, including white blood cells [94, 95].

Daratumumab is a targeted immunotherapy that binds with high affinity to tumour plasma cells expressing CD38, a transmembrane glycoprotein; high levels of CD38 expression are found universally in the plasma cells of patients with MM [96]. Because of the clonal heterogeneity of MM, an immunotherapy approach targeting CD38+ cells is hypothesised to have broad therapeutic potential [96].

Data suggest that daratumumab is effective in vitro by killing CD38+ MM cells through multiple mechanisms (Table 5; Figure 3) [95] [96].

Table 5. Mechanisms of action of daratumumab

Mechanism of action	
Direct on-tumour actions	
Target immune proteins	Also known as complement-dependent cytotoxicity. Induction of myeloma cell death by activating immune proteins (complement) in the blood.
Target immune cells that engulf myeloma cells	Also known as antibody-dependent cell-mediated phagocytosis. Induction of myeloma cell death by activating immune cells in the blood that engulf and kill the myeloma cell.
Target immune cells that induce myeloma cell lysis	Also known as antibody-dependent cell-mediated cytotoxicity. Induction of myeloma cell death by activating immune cells in the blood that lyse the myeloma cell.
Cross-link with naturally occurring antibody	Induction of myeloma cell apoptosis by cross-linking with naturally occurring antibodies found in the blood.
Immunomodulatory actions	
Inhibition of myeloma cell proliferation	Modulation of cellular enzymatic activities associated with calcium mobilisation and signalling, thereby preventing the further proliferation of myeloma cells.

Sources: de Weers et al., 2011 [95]; Khagi & Mark, 2014 [96].

[5] Note: human mAbs are generally considered less immunogenic than humanised or fully animal-derived mAbs

Figure 3. The multiple mechanisms of action of daratumumab

Treatment of ASCT-ineligible NDMM patients in Denmark with daratumumab + lenalidomide + dexamethasone (i.e., Dara+Rd) in Denmark is expected to involve the subcutaneous administration of daratumumab. Details of the expected Dara+Rd treatment regimen of ASCT-ineligible NDMM patients in Denmark are presented in Table 6.

Table 6. Expected Dara+Rd treatment regimen of ASCT-ineligible NDMM patients in Denmark

Subject	Description	
Pharmaceutical formulation	Solution for injection	
Method of administration	Subcutaneous administration of daratumumab Oral administration of lenalidomide Oral administration of dexamethasone	
Dosing	Subcutaneous: The recommended dose is 1800 mg of Darzalex® solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule:	
	Weeks	**Schedule**
	Weeks 1 to 8	weekly (total 8 doses)
	Weeks 9 to 24[a]	every two weeks (total 8 doses)
	Week 25 onwards until disease progression[b]	every four weeks
	[a] First dose of the every-2-week dosing schedule is given at Week 9 [b] First dose of the every-4-week dosing schedule is given at Week 25 Lenalidomide (25 mg) should be administered once daily orally on Days 1-21 of repeated 28-day [4-week] cycles).	

Subject	Description
	Dexamethasone should be administered at 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years).
Concomitant medications	Pre-infusion medications should be administered to reduce the risk of infusion-related reactions to all patients 1-3 hours prior to every infusion (or SC injection) of daratumumab as follows: • Corticosteroid (long-acting or intermediate-acting) Combination therapy: Dexamethasone 20 mg (or equivalent), administered prior to every Darzalex® infusion (or SC injection). When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on days daratumumab is administered. Additional background regimen specific corticosteroids (e.g., prednisone) should not be taken on days daratumumab is administered when patients have received dexamethasone as a pre-medication. • Antipyretics (oral paracetamol 650 to 1,000 mg) • Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent). Post-infusion medication • Post-infusion medications should be administered to reduce the risk of delayed infusion-related reactions as follows: Combination therapy: Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after daratumumab administration. However, if a background regimen-specific corticosteroid (e.g., dexamethasone, prednisone) is administered the day after the daratumumab infusion (or SC injection), additional post medications may not be needed.
Diagnostic Testing and Monitoring	Neutropenia/Thrombocytopenia Darzalex® may increase neutropenia and thrombocytopenia induced by background therapy. Complete blood cell counts should be monitored periodically during treatment according to manufacturer's prescribing information for background therapies. Patients with neutropenia should be monitored for signs of infection. Interference with indirect antiglobulin test (indirect Coombs test) Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab administration. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time. In the event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests (see section 4.5). If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices. Interference with determination of complete response Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see section 4.5). This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein. Hepatitis B virus (HBV) reactivation

Subject	Description
	Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with Darzalex®. HBV screening should be performed in all patients before initiation of treatment with Darzalex®. For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of Darzalex® treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated. In patients who develop reactivation of HBV while on Darzalex®, suspend treatment with Darzalex® and institute appropriate treatment. Resumption of Darzalex® treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

The Dara+Rd treatment regimen is considered superior to the current treatment options for NDMM patients in Denmark [20]. However, if Dara+Rd is recommended as a standard treatment, it is expected that only a fraction of the incident cases of ASCT-ineligible MM will receive Dara+Rd as fist-line treatment in clinical practice. This is expected on the basis of preferences from the treating haematologists and the patients. Dara+Rd is already used for subsequent treatment lines amongst MM patients in Denmark. For ASCT-ineligible NDMM patients provided Dara+Rd as a first-line treatment, subsequent lines of treatment will no longer be treated with Dara+Rd (or potentially other CD38-targeting therapies that may be approved in Denmark in the future), but the recommendation of Dara+Rd as a first line-treatment would otherwise not be expected to alter the treatment pathway for MM patients in Denmark.

6 Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

An extensive systematic literature search has been conducted for relevant clinical studies addressing the questions: 1) what is the efficacy of Dara+Rd and relevant comparators in ASCT-ineligible patients with NDMM?; and 2) what is the safety of Dara+Rd and relevant comparators in ASCT-ineligible patients with NDMM? The initial literature review was conducted based on searches performed in 2017, which has been updated 5 times since then with the most recent searches being conducted on 24 March 2021.

Searches were performed in the following indexed databases:

- MEDLINE via Pubmed
- Embase
- Cochrane

The following conference websites were manually searched to capture potentially relevant studies:

- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)
- European Society for Medical Oncology (ESMO)
- European Hematology Association (EHA)

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The initial and subsequent clinical literature searches identified 122 relevant publications covering 45 trials. The literature search is extensively detailed in Appendix A – Literature search for efficacy and safety of intervention and comparators.

6.2 List of relevant studies

Although a large number of clinical trials were identified in the literature review, most did not discuss treatment regimens relevant to the treatment context in Denmark. For the patient population of newly diagnosed patients with multiple myeloma who are ineligible for ASCT, based on the relevant comparators in Denmark, three randomized controlled trials are included in this submission (Table 7). The primary study of interest is the MAIA (MMY3008) study which compared Dara+Rd and Rd treatment regimens [19]. The ALCYONE (MMY3007) compared Dara+VMP and VMP treatment regimen [98]. Evidence for the efficacy of VRd used in this submission comes from the SWOG S0777 study, which compared VRd and Rd treatment regimens [99]. It must be noted that the SWOG S0777 study population was broader than the relevant patient population for this application, so efficacy from the subgroup of patients 65+ was used as a proxy for efficacy evidence for newly diagnosed patients with multiple myeloma who are ineligible for ASCT.

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Table 7. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study	Used in comparison of
Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2021 Nov;22(11):1582-1596. doi: 10.1016/S1470-2045(21)00466-6. Epub 2021 Oct 13 [19].	MAIA (MMY3008)	NCT02252172	Start: 1 April 2008 Primary completion date: 1 July 2016 Ongoing	Dara+Rd vs. Rd
Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020 Jan 11;395(10218):132-141. doi: 10.1016/S0140-6736(19)32956-3. Epub 2019 Dec 10 [98]	ALCYONE (MMY3007)	NCT02195479	Start: 9 December 2014 Primary Completion: 21 November 2017 Ongoing	Dara+VMP vs. VMP
Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017 Feb 4;389(10068):519-527. doi: 10.1016/S0140-6736(16)31594-X. Epub 2016 Dec 23 [99]. **Durie BG, Hoering A, Sexton R, Abidi MH, Epstein J, Rajkumar SV, et al. Longer term followup of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J. 2020;10:1-11 [100]**	SWOG S0777 (relative efficacy evidence from 65+ subgroup)	NCT00644228	1 April 2008 – 1 July 2016	Rd vs. VRd

For detailed information about the three included studies, refer to Appendix B – Main characteristics of included studies. Of the 45 studies identified as relevant to the clinical context, 34 were excluded as irrelevant for the purpose of making an indirect treatment comparison between relevant comparators in Europe, which serves as the indirect comparison in of treatment regimens available in Denmark (Table 70) [20]. All the studies which were included in the indirect comparison are listed in Table 68, with baseline characteristics in Table 69. Nineteen planned or ongoing relevant studies were identifed without results available are identified in Table 8.

Table 8. Planned and ongoing relevant RCTs without results available

Trial ID	Study Name	Status
NCT03759093	CURATE.AI-optimized modulation for multiple myeloma: an N-of-1 randomised trial	Not yet recruiting
EUCTR2019-00304730-ES	A clinical trial of belantamab mafodotin plus standard of care treatments compared with standard of care treatments alone for patients with newly diagnosed multiple myeloma not eligible for transplant	No Results Available
EUCTR2018-002068-15-IT	A randomised trial that compare carfilzomib - lenalidomide - dexamethasone versus lenalidomide - dexamethasone in newly diagnosed myeloma patients not eligible for autologous stem cell transplantation (asct)	No Results Available
ChiCTR2000029863	A multicenter, prospective, randomised, study for Ixazomib plus Cyclophosphamide and Dexamethasone compared with Lenalidomide plus Cyclophosphamide and Dexamethasone in transplant-ineligible newly diagnosed multiple myeloma	No Results Available
CTRI/2019/07/020397	A comparison of Bortezomib, Pomalidomide with low-dose Dexamethasone and Bortezomib, Lenalidomide with low-dose dexamethasone for newly-diagnosed multiple myeloma patients- A randomised phase III study	Not yet recruiting
NCT04277845	Randomised phase II study of bortezomib, lenalidomide and dexamethasone versus lenalidomide and dexamethasone in elderly patients with newly diagnosed multiple myeloma	Not yet recruiting
NCT03993912	Compare Lenalidomide and Subcutaneous Daratumumab vs. Lenalidomide and Dexamethasone in Frail Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High Dose Therapy	No Results Available
NCT04091126	Bortezomib, Lenalidomide and Dexamethasone (VRd) With Belantamab Mafodotin Versus VRd Alone in Transplant Ineligible Multiple Myeloma	No Results Available
NCT04096066	A Trial That Compare Two Treatments in Newly Diagnosed Myeloma Patients Not Eligible for Transplant	No Results Available
NCT04009109	Study of Lenalidomide/Ixazomib/Dexamethasone/Daratumumab in Transplant-Ineligible Patients With Newly Diagnosed MM	Not yet recruiting
NCT02312258	Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Participants With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation (SCT)	No Results Available
NCT04277845	Randomised Phase II Study in Elderly Patients With Newly Diagnosed Multiple	Not yet recruiting
NCT04268498	A Study of Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma	No Results Available
NCT02891811	Patients With Newly Diagnosed Multiple Myeloma Comparing KTd vs. KRd Induction Therapy and Investigating a K-mono Maintenance Strategy	No Results Available
NCT04808037	Blmf, Lenalidomide and Dexamethasone in Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma (BelaRd)	No Results Available
NCT04717700	Selinexor With Alternating Bortezomib or Lenalidomide Plus Dexamethasone in TIE Newly Diagnosed MM Patients (SABLe)	Not yet recruiting
NCT04751877	Study of Isatuximab+Lenalidomide+Dexamethasone With/Without Bortezomib in de Novo Non Frail NTE Multiple Myeloma Elderly Patients (IFM2020-05)	Not yet recruiting
NCT04635189	Steroid Sparing Treatment With in Newly Diagnosed Transplant Ineligible Patients With Multiple Myeloma	Not yet recruiting
NCT03993912	Compare Lenalidomide and Subcutaneous Daratumumab vs. Lenalidomide and Dexamethasone in Frail Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High Dose Therapy (IFM2017_03)	No Results Available

7 Efficacy and safety

7.1 Efficacy and safety of Dara+Rd compared to Rd for NDMM ASCT-ineligible (TIE) patients

The MAIA (MMY3008, NCT02252172) study [19], which is the source of critical clinical evidence for the efficacy of the Dara+Rd treatment regimen amongst ASCT-ineligible NDMM patients and the study providing the evidence extending the marketing authorization of the Dara+Rd treatment regimen amongst ASCT-ineligible NDMM patients (EMA, 2019 [101]), is the only relevant study identified which compared Dara+Rd and Rd for the relevant patient population.

7.1.1 Relevant studies

MAIA (MMY3008, NCT02252172) study [19] is an ongoing randomized open-label multicentre phase 3 trial with 737 patients randomized, 368 to treatment with Dara+Rd, and 369 to treatment with Rd. Patients were considered transplant-ineligible if they were ≥65 years of age or if they were <65 years of age with comorbid conditions that would have a negative impact on tolerability to high-dose chemotherapy used in ASCT [102, 103].

Eligible patients were stratified by ISS (I, II or III), region (North America versus Other), and age (<75 versus ≥75 years) [102, 103]. Patients were randomised in a 1:1 ratio to treatment Arm A (Rd) or treatment Arm B (Dara+Rd) [103]. An overview of the MAIA study design is presented in Figure 4 [102]. The treatment administration schedule is described in detail in 5.2.3.

Figure 4. Overview of the MAIA study design

For detailed study characteristics refer to Appendix B – Main characteristics of included studies. For baseline characteristics of patients included in each study refer to Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.1.2 Efficacy and safety – MAIA (MMY3008, NCT02252172)

7.1.2.1 Overall survival

At a median follow-up of 56.2 months, median OS was not reached in either group [19]. There were a total of 273 deaths, with 117 deaths (31.8%) in the Dara+Rd group and 156 (42.3%) in the Rd group (HR: 0.68; 95% CI: 0.53, 0.86; p=0.0013; Table 9 and Figure 5) [19]. The risk of death was statistically significantly lower for Dara+Rd by 32% compared with Rd [19]. At 5 years (60 months) of treatment, the estimated OS rate in the Dara+Rd group was greater than that in the Rd group (66.3% vs. 53.1%, respectively, Table 9) [19].

Table 9. OS among patients treated with either Dara+Rd or Rd (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

Overall survival	Rd (n=369)	Dara+Rd (n=368)
Number of events, n (%)	156 (42.3%)	117 (31.8%)
Median, months (95% CI)	NE (55.7, NE)	NE (NE, NE)
Hazard ratio for Dara+Rd vs. Rd (95% CI)[a] **p-value[b]**	0.68 (0.53, 0.86) 0.0013	
12-month OS rate,% (95% CI)	91.3 (87.9, 93.8)	92.6 (89.4, 94.9)
24-month OS rate,% (95% CI)	83.4 (79.1, 86.9)	84.3 (80.2, 87.7)
36-month OS rate,% (95% CI)	72.3 (67.3, 76.6)	78.2 (73.6, 82.1)
48-month OS rate, % (95% CI)	62.4 (57.1, 67.3)	69.8 (64.8, 74.3)
60-month OS rate, % (95% CI)	53.1 (47.2, 58.6)	66.3 (60.8, 71.3)

CI = confidence interval; Dara+Rd = daratumumab, lenalidomide and dexamethasone; NE = not evaluable; Rd = lenalidomide and dexamethasone; [a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. A hazard ratio <1 indicates an advantage for Dara+Rd; [b] p-value is based on the log-rank test stratified with ISS staging (I, II or III), region (North America vs. Other) and age (<75 years vs. ≥75 years) as randomised Sources: Janssen, 263 OS update CSR, June 2021, Facon et al. 2021 [19, 104]

Figure 5. Kaplan-Meier plot for OS among patients treated with either Dara+Rd or Rd (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

7.1.2.2 Progression-free survival

The primary PFS analysis was the primary endpoint for MAIA, in accordance with the pre-specified statistical analysis plan. The primary PFS analysis demonstrated the superiority of Dara+Rd over Rd alone and was consistent with the PFS analysis at the interim OS analysis (Janssen, 2019i).

As of the data cut-off (19 February 2021), a total of 377 PFS events had been observed (160 [43.5%] and 217 [58.8%] events for the Dara+Rd and Rd groups, respectively) [19, 104]. Consistent with the primary PFS analysis, there was a statistically significant improvement in PFS for patients in the Dara+Rd group compared with those in the Rd group (HR 0.53; 95% CI: 0.43, 0.66; p<0.0001; Table 10), representing a 47% reduction in the risk of disease progression or death with Dara+Rd compared with Rd alone [19]. The median PFS was not reached in the Dara+Rd group and was 34.4 (95% CI: 29.6, 39.2) months in the Rd group (Table 10; Figure 6) [19].

[redacted]

Table 10. PFS among patients treated with Dara+Rd compared with Rd (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

Progression-free survival	Rd (n=369)	Dara+Rd (n=368)
Number of events, n (%)	217 (58.8%)	160 (43.5%)
Median, months (95% CI)	34.43 (29.6, 39.2)	NE (54.8, NE)
Hazard ratio for Dara+Rd vs. Rd (95% CI)[a] **p-value[b]**	0.53 (0.43, 0.66) <0.0001	
12-month PFS rate,% (95% CI)	78.4 (73.6, 82.4)	86.2 (82.2, 89.4)
24-month PFS rate,% (95% CI)	61.6 (56.1, 66.6)	76.0 (71.2, 80.1)
36-month PFS rate,% (95% CI)	48.4 (42.9, 53.8)	67.4 (62.3, 72.0)
48-month PFS rate, % (95% CI)	37.6 (32.2, 42.9)	59.4 (54.1, 64.4)
60-month PFS rate, % (95% CI)	28.7 (23.1, 34.6)	52.5 (46.7, 58.0)

CI = confidence interval; Dara+Rd = daratumumab, lenalidomide and dexamethasone; NE = not evaluable; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; [a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II or III), region (North America vs. Other) and age (<75 years vs. ≥75 years) as randomised. A hazard ratio <1 indicates an advantage for Dara+Rd; [b] p-value is based on the log-rank test stratified with ISS staging (I, II or III), region (North America vs. Other) and age (<75 years vs. ≥75 years) as randomised; Clinical cut-off date: 19 February 2021; Sources: Janssen, 263 OS update HEMAR report, July 2021 [21]; Facon et al. 2021 [19].

Figure 6. Kaplan-Meier plot for PFS among patients treated with Dara+Rd compared with Rd (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

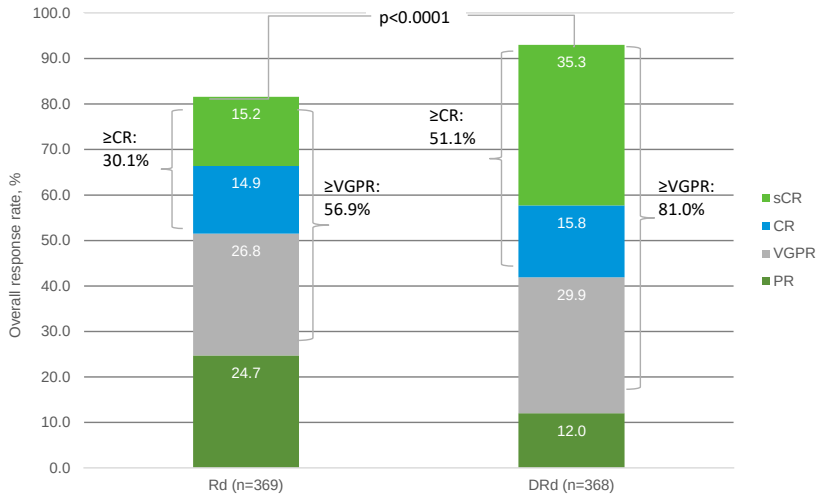
[redacted]

Subgroup analyses demonstrate consistent PFS advantage of treatment with Dara+Rd over Rd across the pre-specified, clinically relevant subgroups, including patients ≥75 years of age and those with poor prognosis, such as patients with advanced-stage disease, renal impairment, or high-risk cytogenetic abnormalities [19].

7.1.2.3 Overall response rate

At a median follow-up of 56.2 months, treatment with Dara+Rd was associated with a significantly higher proportion of patients achieving an overall response compared with Rd alone (ORR with Dara+Rd = 92.9%, Rd = 81.6%; OR: 3.00; 95% CI: 1.85, 4.86; p<0.0001; Figure 7) [19].

Figure 7. Overall response rate among patients treated with Dara+Rd compared with Rd (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)



CR = complete response; Dara+Rd = daratumumab, lenalidomide and dexamethasone; ORR = overall response rate; PR = partial response; Rd = lenalidomide and dexamethasone; sCR = stringent complete response; VGPR = very good partial response

Clinical cut-off date: 19 February 2021; Source: Facon et al., 2021 [19].

7.1.2.3.1 Very good partial response rate

Treatment with Dara+Rd was associated with a significantly higher proportion of patients achieving a VGPR or better compared with Rd alone (≥VGPR rate with Dara+Rd: 81%, Rd: 56.9%; OR: 3.28; 95% CI: 2.34, 4.59; p<0.0001; Figure 7) [19].

7.1.2.3.2 Complete response rate

Treatment with Dara+Rd was associated with a significantly higher proportion of patients achieving a CR or better compared with Rd alone (≥CR rate with Dara+Rd: 51.1%, Rd: 30.1%; OR: 2.44; 95% CI: 1.80, 3.30; p<0.0001; Figure 7) [19].

7.1.2.3.3 Duration of response

At a median follow-up of 56.2 months, the mediation duration of response was not reached for the Dara+Rd group, compared with 43.9 months (95% CI: 37.7, 52.9) in the Rd group (Table 11) [19, 21].

Table 11. Duration of response among patients treated with Dara+Rd compared with Rd (MAIA; response-evaluable analysis set; median follow-up 56.2 months)

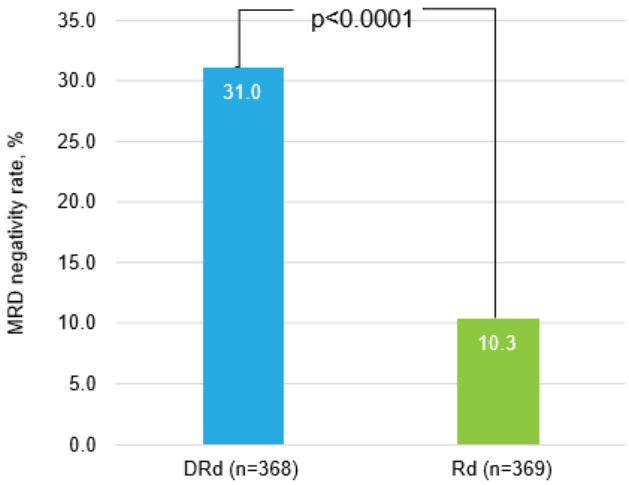
Duration of response[a]	Rd	Dara+Rd
Responders (≥PR) in the response-evaluable set	301	342
Number of events, n (%)	146 (48.5%)	109 (31.9%)
Median, months (95% CI)	43.9 (37.7, 52.9)	NE (NE, NE)

CI = confidence interval; Dara+Rd = daratumumab, lenalidomide and dexamethasone; NE = not evaluable; PR = partial response; Rd = lenalidomide and dexamethasone a First response PR or better Clinical cut-off date: 19 February 2021; Sources: Janssen, 263 OS update HEMAR report, July 2021 [21]; Facon et al. 2021 [19].

7.1.2.4 MRD-negativity

The latest evidence of MRD-negativity from the MAIA trial is based on the clinical cut-off date of 8 June 2020, and not on the interim analysis (i.e., data cut-off 19 February 2021). At a median follow-up of 47.9 months, treatment with Dara+Rd was associated with a significantly higher proportion of patients achieving MRD negativity (10–5) compared with Rd alone [19]. The MRD negativity rate was three-fold higher with Dara+Rd than Rd, Figure 8; MRD negativity rate with Dara+Rd = 31.0%, Rd = 10.3%, OR: 3.91, 95% CI: 2.62, 5.84, p<0.0001) [19].

Figure 8. Minimal residual disease negativity rate among patients treated with Dara+Rd compared with Rd (MAIA; intent-to-treat analysis set; median follow-up 47.9 months)



Dara+Rd = daratumumab; MRD = minimal residual disease; Rd = lenalidomide and dexamethasone; Source: Facon et al., 2021 (data from the CCO June 2020) [19]

[redacted]

Table 12. Summary of durable (6 and 12 month) MRD-negativity rate at 10^{-5} in bone marrow (MAIA; intent-to-treat analysis set; median follow-up 47.9 months)

[redacted]

[redacted]

7.1.2.5 Time to disease progression

Median time to disease progression was not reached for Dara+Rd and 40.9 months for Rd (HR: 0.48; 95% CI: 0.38, 0.61; p<0.0001; Figure 9) [19, 21].

Figure 9. Kaplan-Meier plot for time to disease progression among patients treated with Dara+Rd compared with Rd (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

7.1.2.6 Time to subsequent anti-cancer therapy

Time to subsequent antimyeloma therapy was significantly prolonged with Dara+Rd versus Rd (HR: 0.47; 95% CI: 0.37, 0.59; p<0.0001; Figure 10) [19, 21]. Median time to subsequent antimyeloma therapy was NE with Dara+Rd and 42.4 (95% CI: 33.5, 50.4) months with Rd [19].

Figure 10. Kaplan-Meier plot for time to subsequent anticancer therapy among patients treated with Dara+Rd compared with Rd (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

7.1.2.7 EORTC QLQ-C30

[redacted]

Table 13. Baseline values for all subscales of the EORTC QLQ-C30 (MAIA; intent-to-treat analysis set)

[redacted]

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Treatment benefit was assessed using mixed effects repeated measures analyses of LS mean change from baseline. A within-group change of 8 points on the 100-point scale was defined as representing a clinically meaningful change [102, 106].

Continuous improvement in the EORTC QLQ-C30-Global Health Scale (GHS) score was observed in both treatment groups during throughout the follow-up period. A numerically greater improvement from baseline in EORTC QLQ-C30 GHS with Dara+Rd compared with Rd was reported starting from treatment cycle 3 through to cycle 48. At cycle 12, an improvement in EORTC QLQ-C30 GHS was significantly greater among patients treated with Dara+Rd than among those treated with Rd [redacted]

Figure 11. LS mean change in baseline EORTC QLQ-C30 GHS score among patients treated with Dara+Rd or Rd (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

Table 14. Mixed Model for Repeated Measures for change in EORTC QLQ-C30 GHS among patients treated with Dara+Rd or Rd (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

[redacted]

[redacted]

Figure 12. Median time to improvement and worsening in EORTC-QLQ-C30 GHS (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

[redacted]

Changes consistent with these improvements in GHS were also observed with the EORTC QLQ-C30 functional scales (Table 15) [21].

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Table 15. EORTC QLQ-C30 Functional Scales change from baseline among patients treated with Dara+Rd or Rd (MAIA; mixed model for repeated measures; median follow-up 56.2 months)

[redacted]

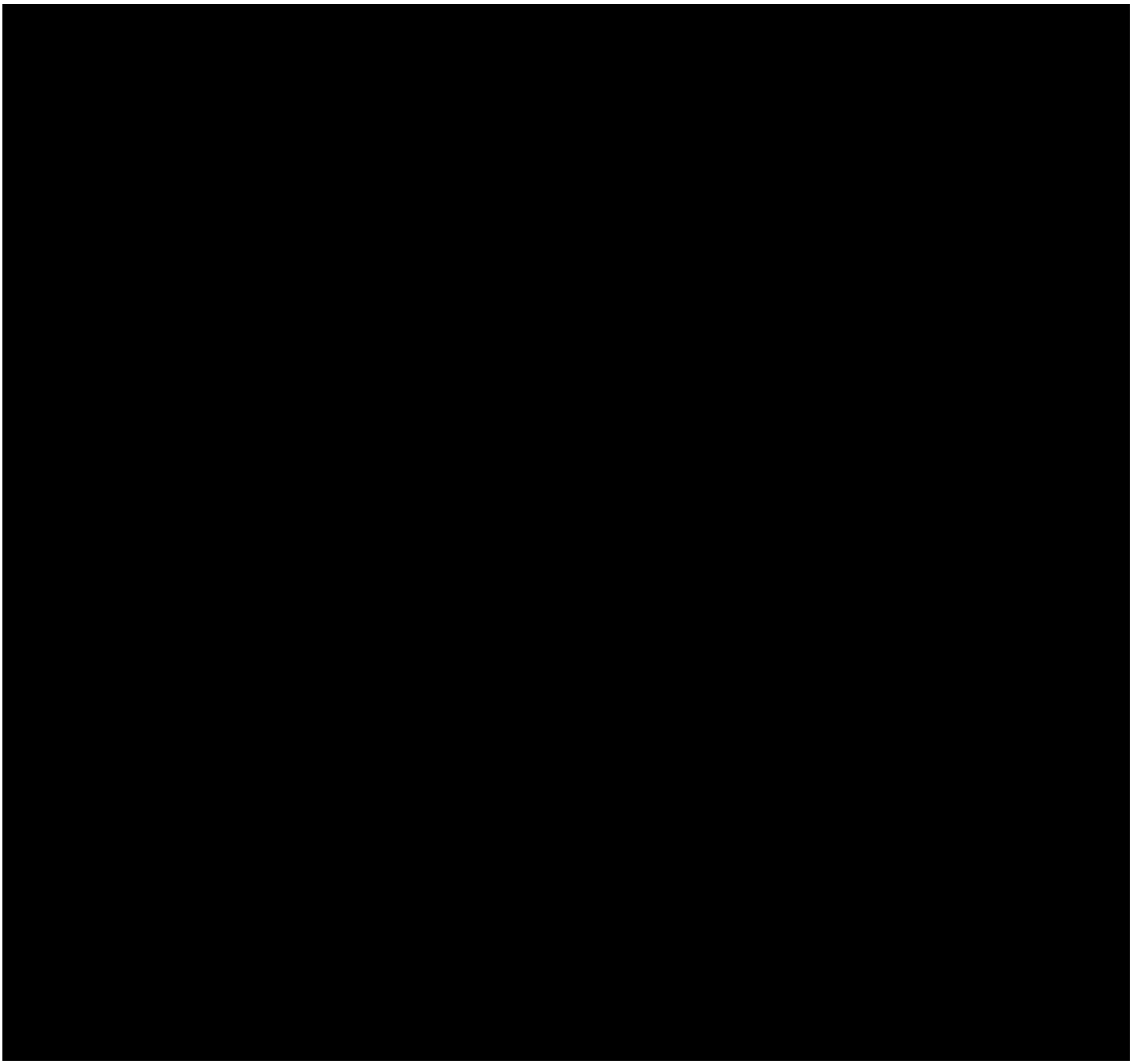

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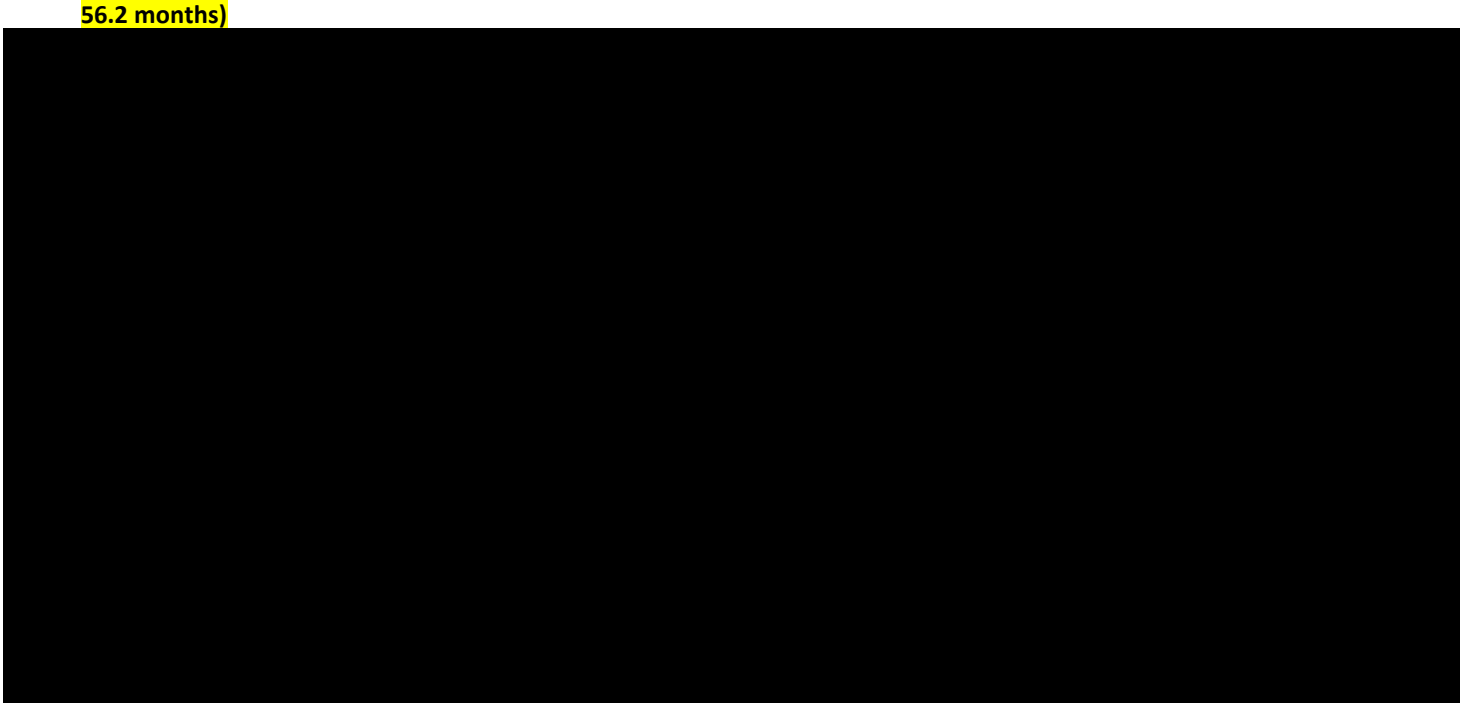
Figure 13. Mean change from baseline in EORTC QLQ-C30 pain scores in MAIA (median follow-up 56.2 months)

[redacted]

Figure 14. Mean change from baseline in EORTC QLQ-C30 physical functioning scores in MAIA (median follow-up 56.2 months)



7.1.2.8 EQ-5D-5L

[redacted]

At the interim OS analysis (data cut: 19 February 2021), a numerical improvement from baseline in EQ-5D-5L-VAS was reported during treatment through to Cycle 54 in both Dara+Rd and Rd groups. Significantly greater improvement in EQ-5D-5L VAS in Dara+Rd group compared with Rd group was observed at two timepoints: at Cycle 6 [redacted] and Cycle 12 ([redacted] [21].

Figure 15. Mean change from baseline in EQ-5D-5L VAS scores in MAIA (median follow-up 56.2 months)

[redacted]

Figure 16. Median time to improvement and worsening in EQ-5D-5L VAS (MAIA; intent-to-treat analysis set; median follow-up 56.2 months)

[redacted]

A clinically meaningful improvement in EQ-5D-5L utility score was observed with both treatment arms from baseline to Cycle 54. Significantly greater improvement in utility score in Dara+Rd group compared with Rd group was observed at two timepoints during the study: at Cycle 42 (and at Cycle 54 ( ) [21].

Figure 17. Mean change from baseline in EQ-5D-5L utility scores in MAIA (median follow-up 56.2 months)

Treatment with Dara+Rd was associated significantly longer (by 12 months) median time to worsening of utility score compared with Rd; ( ) [21].

Danish EQ-5D-5L tariffs were applied to generate Danish utility weights for progression-free and progressed-disease health states in the economic model (see Appendix I – Mapping of HRQoL data).

7.1.2.9 Safety

Data on the safety of daratumumab in ASCT-ineligible patients with MM (data cut-off 19 February 2021) is available for the safety population of MAIA, including all patients who received at least one dose of any study treatment (N=729) [19]. Of these 729 patients, 364 were treated with Dara+Rd and 365 were treated with Rd alone [19].

7.1.2.9.1 Exposure data

The median duration of treatment in MAIA was 47.5 months for the Dara+Rd group and 22.6 months for the Rd group (Table 16) [19].

Table 16. Treatment exposure and dose intensity (MAIA; safety analysis set; 56.2 months follow-up)

	Rd (n=365)	Dara+Rd (n=364)
Median duration of treatment (months)	22.6	47.5
Daratumumab relative dose intensity (mg/kg), median % (IQR)	-	98 (95-101)

	Rd (n=365)	Dara+Rd (n=364)
Lenalidomide relative dose intensity (mg), median % (IQR)	86 (61-99)	66 (46-93)
Dexamethasone relative dose intensity (mg), median % (IQR)	86 (65-99)	78 (56-96)

Dara+Rd = daratumumab, lenalidomide and dexamethasone; IQR = interquartile range; n/a = not applicable; Rd = lenalidomide and dexamethasone; Source: Janssen, 263 OS update HEMAR report, June 2021 (Facon, Kumar, et al., 2021)

7.1.2.9.2 Treatment-emergent adverse events

Overall, Dara+Rd was well tolerated, with a safety profile consistent with the known toxicity of the Rd regimen and the known AEs experienced with daratumumab as a single agent [19].

A summary of the most common (≥10%) TEAEs experienced by patients in the Dara+Rd and Rd groups is presented in Table 84 [19, 21]. The overall incidence of TEAEs was comparable between treatment groups, reported by [redacted] of patients treated with Dara+Rd and Rd, respectively [21].

Although the incidence of Grade 3 and Grade 4 TEAEs was higher with Dara+Rd than with Rd (96% and 88%, respectively), the incidence of discontinuation of study treatment due to TEAEs was lower with Dara+Rd than with Rd (13% and 23%, respectively; Table 85) [19, 21]. The incidence of serious TEAEs was similar between the Dara+Rd treatment group and the Rd treatment group (77% vs. 70%, respectively), as well as for TEAEs leading to death (9.3% vs. 8.8%, respectively) [19].

7.1.2.9.3 Grade 3 or 4 TEAEs

The most frequently reported Grade 3 or 4 TEAEs (≥10% in either study group) were haematological AEs (including neutropenia, anaemia, lymphopenia and leukopenia) and pneumonia (Table 17) [21]. Of these, Dara+Rd was associated with a higher incidence of Grade 3 or 4 neutropenia (Dara+Rd: 54%; Rd: 37%), lymphopenia (Dara+Rd: 17%; Rd: 11%), leukopenia (Dara+Rd: 12%; Rd: 6%) and pneumonia (Dara+Rd: 19%; Rd: 11%) than Rd, but a lower incidence of anaemia (Dara+Rd: 17%; Rd: 22%) [19].

Table 17. Most common (≥5% in either group) Grade 3 or 4 TEAEs by MedDRA system organ class and preferred term (MAIA; 56.2 months follow-up)

	Proportion of patients, n (%)	
	Rd (n=365)	Dara+Rd (n=364)
Patients with Grade 3 or 4 TEAEs	322 (88.2%)	348 (95.6%)
Blood and lymphatic system disorders	199 (54.5%)	246 (67.6%)
Neutropenia	135 (37.0%)	197 (54.1%)
Anaemia	79 (21.6%)	61 (16.8%)
Lymphopenia	41 (11.2%)	60 (16.5%)
Leukopenia	23 (6.3%)	42 (11.5%)
Thrombocytopenia	34 (9.3%)	32 (8.8%)
Infections and infestations	106 (29.0%)	151 (41.5%)
Pneumonia	39 (10.7%)	70 (19.2%)
Metabolism and nutrition disorders	80 (21.9%)	93 (25.5%)

	Proportion of patients, n (%)	
	Rd (n=365)	Dara+Rd (n=364)
Hypokalaemia	36 (9.9%)	46 (12.6%)
Hyperglycaemia	14 (3.8%)	28 (7.7%)
Gastrointestinal disorders	60 (16.4%)	83 (22.8%)
Diarrhoea	22 (6.0%)	32 (8.8%)
General disorders and administration site conditions	65 (17.8%)	70 (19.2%)
Fatigue	17 (4.7%)	32 (8.8%)
Respiratory, thoracic and mediastinal disorders	37 (10.1%)	59 (16.2%)
Pulmonary embolism	19 (5.2%)	26 (7.1%)
Vascular disorders	36 (9.9%)	54 (14.8%)
Hypertension	16 (4.4%)	31 (8.5%)
Eye disorders	44 (12.1%)	47 (12.9%)
Cataract	39 (10.7%)	40 (11.0%)

Dara+Rd = daratumumab, lenalidomide and dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; TEAE = treatment-emergent adverse event; Source: Janssen, 263 OS update, June 2021; Facon et al. 2021 [19, 21]

7.1.2.9.4 Serious TEAEs

The incidence of serious TEAEs was similar between the Dara+Rd and Rd groups (approximately 77% and 70%, respectively; Table 18) [19]. Pneumonia was the most frequently reported serious TEAE in each of the treatment groups and occurred at a higher rate in the Dara+Rd group than in the Rd group (18% vs. 11%, respectively) [19].

Table 18. Most common (≥2%) serious TEAEs by MedDRA system organ class and preferred term (MAIA; 56.2 months follow-up)

	Proportion of patients, n (%)	
	Rd (n=365)	Dara+Rd (n=364)
Total number of subjects with serious TEAE	257 (70.4%)	281 (77.2%)
Infections and infestations	98 (26.8%)	149 (40.9%)
Pneumonia	39 (10.7%)	66 (18.1%)
Influenza	8 (2.2%)	16 (4.4%)
Bronchitis	6 (1.6%)	15 (4.1%)
Lower respiratory tract infection	12 (3.3%)	11 (3.0%)
Urinary tract infection	7 (1.9%)	10 (2.7%)
Sepsis	10 (2.7%)	11 (3.0%)
Musculoskeletal and connective tissue disorders	43 (11.8%)	53 (14.6%)
Back pain	9 (2.5%)	14 (3.8%)
Gastrointestinal disorders	44 (12.1%)	54 (14.8%)
Diarrhoea	7 (1.9%)	11 (3.0%)
Cardiac disorders	47 (12.9%)	45 (12.4%)
Atrial fibrillation	15 (4.1%)	10 (2.7%)
Cardiac failure	11 (3.0%)	5 (1.4%)

	Proportion of patients, n (%)	
	Rd (n=365)	Dara+Rd (n=364)
General disorders and administration site conditions	42 (11.5%)	39 (10.7%)
Pyrexia	11 (3.0%)	19 (5.2%)
General physical health deterioration	12 (3.3%)	3 (0.8%)
Respiratory, thoracic, and mediastinal disorders	32 (8.8%)	39 (10.7%)
Pulmonary embolism	14 (3.8%)	16 (4.4%)
Renal and urinary disorders	25 (6.8%)	28 (7.7%)
Acute kidney injury	14 (3.8%)	14 (3.8%)
Vascular disorders	22 (6.0%)	20 (5.5%)
Deep vein thrombosis	10 (2.7%)	6 (1.6%)
Blood and lymphatic system disorders	23 (6.3%)	19 (5.2%)
Febrile neutropenia	9 (2.5%)	11 (3.0%)
Anaemia	12 (3.3%)	6 (1.6%)

Dara+Rd = daratumumab, lenalidomide and dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; TEAE = treatment-emergent adverse event; Source: Facon et al. 2021 [19]

7.1.2.9.5 Infections and infestations

A higher frequency of infections and infestations was observed in the Dara+Rd group compared with the Rd group (90% vs. 78%, respectively; Grade 3 or 4 infections: 42% and 29%, respectively) [19, 21]. Patients in the Dara+Rd group were observed to have higher rates of Grade 3 or 4 pneumonia (19%) compared with the Rd group (11%) [19].

7.1.2.9.6 Discontinuations

Discontinuation of study treatment (i.e., all study drugs) due to TEAEs occurred less frequently with Dara+Rd than with Rd (13% and 23%, respectively; statistical comparison not conducted) [19]. Discontinuations due to infection were reported in five patients (1.2%) in the Dara+Rd group and six patients (1.6%) in the Rd group [19]. [redacted]

7.1.2.9.7 Deaths

TEAEs leading to death were reported in 34 (9.3%) patients in the Dara+Rd group and in 32 patients (8.8%) in the Rd group [19]. [redacted]

For detailed efficacy and safety results, refer to Appendix D – Efficacy and safety results per study, and Appendix E – Safety data for intervention and comparators.

7.1.3 Comparative analyses of efficacy and safety

7.1.3.1 Method of synthesis

See section 7.4.1.

7.1.3.2 Results from the comparative analysis

See section 7.4.2.

7.2 Efficacy and safety of Dara+Rd compared to Dara+VMP/VMP for NDMM ASCT-ineligible (TIE) patients

No direct head-to-head studies comparing Dara+Rd and either Dara+VMP or VMP regimens for NDMM ASCT-ineligible (TIE) patients have been identified. One study which compared Dara+VMP and VMP regimens for NDMM ASCT-ineligible (TIE) patients was identified, which provides data supporting the comparisons of Dara+Rd with Dara+VMP and VMP: ALCYONE (MMY3007, NCT02195479) [98]. Efficacy and safety data from this study have been used in an indirect comparison of treatment efficacy (see section 7.4.1), and as a source of safety data for use in the economic analysis.

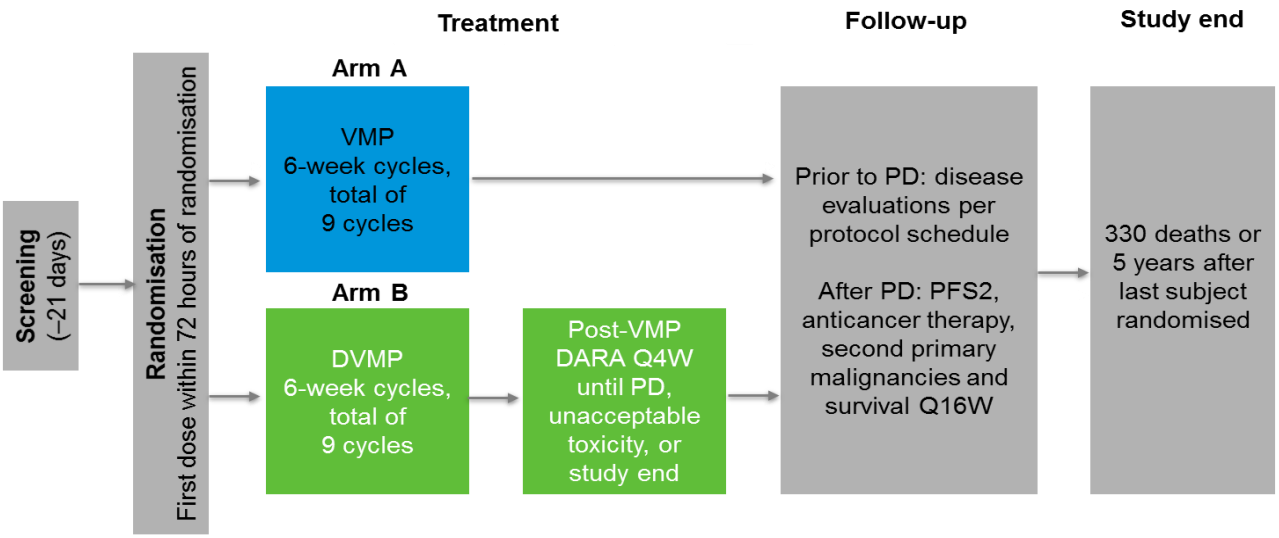
7.2.1 Relevant studies

ALCYONE (MMY3007, NCT02195479) is an ongoing randomized open-label multicentre phase 3 trial with 706 patients randomized, 350 to treatment with Dara+VMP, and 356 to treatment with VMP. Patients were considered to be transplant-ineligible if they were age ≥65 years of age or <65 years of age with comorbid conditions that would have a negative impact on tolerability to high-dose chemotherapy used in ASCT [98].

During screening (based on central laboratory results) eligible patients were stratified by ISS (I, II or III), region (Europe vs. Other) and age (<75 vs. ≥75 years of age) [107]. Patients were randomised to treatment in a 1:1 ratio to either treatment arm A (VMP alone) or treatment arm B (Dara+VMP) [107]. An overview of the ALCYONE study design is presented in Figure 18. The treatment administration schedule, including the frequency of bortezomib administration, is described in detail section 5.2.3.

During the treatment phase, all patients received up to nine cycles of the VMP regimen (one cycle=6 weeks) with or without daratumumab [107]. Patients in both treatment arms received bortezomib 1.3mg/m2 twice weekly in cycle 1 followed by once weekly in cycles 2-9. Melphalan (9mg/m2) and prednisone (60mg/m2) were self-administered on Days 1-4 of each bortezomib cycle [107]. Patients in treatment arm B received daratumumab 16mg/kg once every week for 6 weeks (cycle 1; 1 bortezomib cycle); then once every 3 weeks for 16 additional doses (cycles 2-9) [107]. After completion of the VMP cycles, patients in arm A entered the follow-up phase [107]. Patients in arm B continued to receive daratumumab every 4 weeks until documented progression, unacceptable toxicity, or the study end. Upon discontinuation of daratumumab, patients in arm B entered the follow-up phase [107].

Figure 18. Overview of the ALCYONE study design



Adapted from Figure 1 ALCYONE Clinical Study Report October 2017
DARA: 16mg/kg IV on Days 1, 8, 15, 22, 29 and 36 (cycle 1) and Days 1 and 22 (cycles 2-9 of each 6-week cycle), then Day 1 (cycles 10+ of each 4-week cycle). Bortezomib: 1.3mg/m^2 SC on Days 1, 4, 8, 11, 22, 25, 29 and 32 (cycle 1) and Days 1, 8, 22 and 29 (cycles 2-9 of each 6-week cycle). Melphalan: 9mg/m^2 PO and prednisone: 60mg/m^2 PO on Days 1-4 (cycles 1-9 of each 6-week cycle).
DARA = daratumumab; Dara+VMP = daratumumab-bortezomib-melphalan-prednisone; IV = intravenous; PD = disease progression; PFS2 = time from randomisation to progression on the next line of therapy or death, whichever comes first; Q4W = every 4 weeks; Q16W = every 16 weeks; VMP = bortezomib-melphalan-prednisone. Source: Janssen MMY3007 CSR, October 2017 [107]

For detailed study characteristics refer to Appendix B – Main characteristics of included studies. For baseline characteristics of patients included in each study refer to Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.2.2 Efficacy and safety – ALCYONE (MMY3007, NCT02195479)

Note: Although long-term follow up is ongoing, statistical significance of Dara+VMP vs. VMP in PFS and OS has been demonstrated, and no further hypothesis testing is planned for future data cuts [98].

7.2.2.1 Overall survival

[redacted]

Figure 19. Kaplan-Meier plot for OS among patients treated with either Dara+VMP or VMP (ALCYONE; intent-to-treat analysis set; median follow-up 40.1 months)

7.2.2.2 Progression-free survival

Table 19. PFS among patients treated with Dara+VMP compared with VMP (ALCYONE; intent-to-treat analysis set; median follow-up 40.1 months)

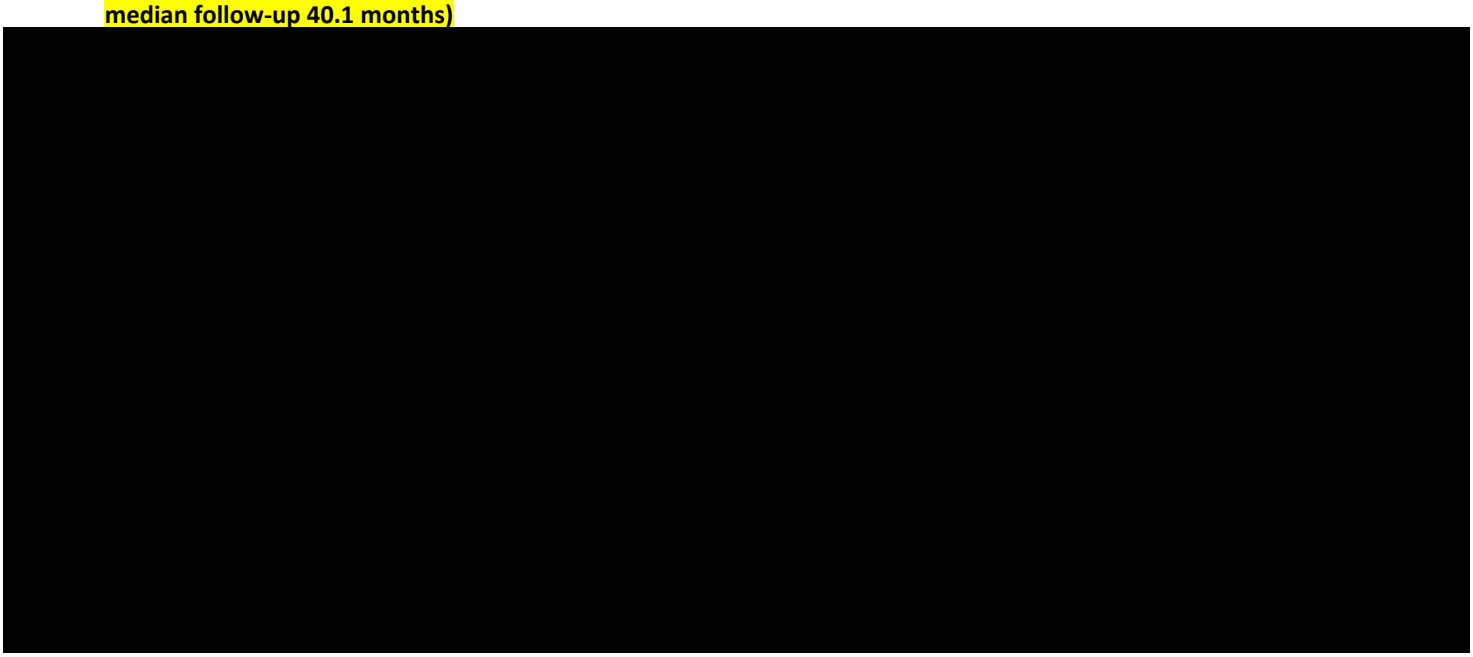


Figure 20. Kaplan-Meier plot for PFS among patients treated with Dara+VMP compared with VMP (ALCYONE; intent-to-treat analysis set; median follow-up 40.1 months)

[redacted]

7.2.2.3 Safety

[redacted]

7.2.2.3.1 Exposure data

[redacted]

Table 20. Treatment exposure (ALCYONE; safety analysis set; 40.1 months follow-up)

[redacted]

[redacted]

7.2.2.3.2 Treatment-emergent AEs

[redacted]

108].

7.2.2.3.3 Grade 3 or 4 TEAEs

[redacted]

Table 21. Most common (≥5%) Grade 3 or 4 TEAEs by MedDRA system organ class and preferred term (ALCYONE; 40.1 months follow-up)

[redacted]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

[redacted]

7.2.2.3.4 Serious TEAEs

[redacted]

7.2.2.3.5 Infections and infestations

[redacted]

7.2.2.3.6 Discontinuations

[redacted]

7.2.2.3.7 Deaths

[redacted]

For detailed efficacy and safety results, refer to Appendix D – Efficacy and safety results per study, and Appendix E – Safety data for intervention and comparators.

7.2.3 Comparative analyses of efficacy and safety

7.2.3.1 Method of synthesis

See section 7.4.1.

7.2.3.2 Results from the comparative analysis

See section 7.4.2.

7.3 Efficacy and safety of Dara+Rd compared to VRd for NDMM ASCT-ineligible (TIE) patients

No direct head-to-head studies comparing Dara+Rd and VRd regimens for NDMM ASCT-ineligible (TIE) patients have been identified. One study which compared VRd and Rd regimens for NDMM patients was identified, and which provides useful information for the facilitating the comparisons of Dara+Rd with VRd: SWOG S0777 (NCT00644228) [99]

[100]. Efficacy and safety data from this study have been used in an indirect comparison of treatment efficacy (see section 7.4.1), and as a source of safety data for use in the economic analysis.

7.3.1 Relevant studies

SWOG S0777 is an ongoing randomized open-label phase 3 trial with 525 NDMM patients randomized, 264 to treatment with VRd, and 261 to treatment with Rd [99] [100].

For detailed study characteristics refer to Appendix B – Main characteristics of included studies. For baseline characteristics of patients included in each study refer to Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.3.2 Efficacy and safety – SWOG S0777 (NCT00644228)

As of the longest follow-up currently available for the SWOG S0777 study, the median follow-up of 84 months has been reported amongst 460 evaluable for survival endpoints [100].

The median OS for VRd was not reached, with median OS for Rd being 69 months: stratified hazard ratio (96% Wald Confidence Interval) was 0.709 (0.543, 0.926) and stratified two-sided P-value was 0.0114.

The median PFS of 41 months was reached for VRd, longer than the 29 months for Rd: stratified hazard ratio (96% Wald Confidence Interval) was 0.742 (0.594, 0.928) and one-sided stratified log-rank P-value 0.003.

However, the SWOG S0777 patient population of newly diagnosed patients with multiple myeloma was not restricted to patients who were considered ineligible for ASCT. Therefore, for the purpose of estimating the relative efficacy of VRd and Rd, the subpopulation of patients who did not have an intent for immediate ASCT, 65 years and older, at baseline has been taken as the best available proxy patient population for the relevant patient population in this submission [20]. Amongst the 65+ subgroup, the PFS HR was estimated as 0.77 (95% CI: 0.55, 1.08) for VRd vs. Rd, and the OS HR was estimated as 0.77 (95% CI: 0.52, 1.14) [20].

7.3.2.1 Safety

While the overall population of patients in the SWOG S0777 study is broader than the patient population of interest for this submission, the SWOG S0777 study provides the best safety data available for treatment with VRd.

Table 22. Grade 3 or 4 TEAEs reported in at least 5% of dubjects in any treatment arm - initialt treatment - SWOG S0777 (safety population)

System Organ Class Preferred Term[a]	RVd (3-week cycles × 8 = 24 weeks) (N = 62) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Subjects With ≥ 1 Grade 3 or 4 TEAE[d]	200 (76.3)	176 (68.8)
Blood and Lymphatic System Disorders	**104 (39.7)**	**106 (41.4)**
Neutropenia	26 (9.9)	42 (16.4)
Thrombocytopenia	45 (17.2)	24 (9.4)
Anaemia	32 (12.2)	41 (16.0)
Lymphopenia	49 (18.7)	39 (15.2)
Leukopenia	23 (8.8)	29 (11.3)
Infections and Infestations	**36 (13.7)**	**24 (9.4)**
Infections	1 (0.4)	0

System Organ Class Preferred Term[a]	RVd (3-week cycles × 8 = 24 weeks) (N = 62) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Lung infection	19 (7.3)	14 (5.5)
Nervous system Disorders	**89 (34.0)**	**24 (9.4)**
Syncope	23 (8.8)	7 (2.7)
Peripheral sensory neuropathy	54 (20.6)	4 (1.6)
Peripheral motor neuropathy	17 (6.5)	3 (1.2)
Respiratory, Thoracic, and Mediastinal Disorders	**26 (9.9)**	**9 (3.5)**
Dyspnoea	16 (6.1)	3 (1.2)
Vascular Disorders	**41 (15.6)**	**18 (7.0)**
Hypotension	20 (7.6)	0
Embolism	18 (6.9)	16 (6.3)
Gastrointestinal Disorders	**46 (17.6)**	**18 (7.0)**
Diarrheal	24 (9.2)	4 (1.6)
General Disorders and Administration Site Conditions	**49 (18.7)**	**29 (11.3)**
Fatigue	38 (14.5)	26 (10.2)
Investigations	**29 (11.1)**	**22 (8.6)**
Alanine aminotransferase increased	13 (5.0)	4 (1.6)
Renal and Urinary Disorders	**8 (3.1)**	**17 (6.6)**
Renal Failure Acute	7 (2.7)	14 (5.5)
Musculoskeletal and Connective Tissue Disorders	**45 (17.2)**	**30 (11.7)**
Muscular weakness	22 (8.4)	11 (4.3)
Metabolism and Nutrition Disorders	**85 (32.4)**	**70 (27.3)**
Hyperglycaemia	19 (7.3)	24 (9.4)
Hypokalaemia	30 (11.5)	12 (4.7)
Hypocalcaemia	17 (6.5)	21 (8.2)
Dehydration	22 (8.4)	6 (2.3)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event. [a] System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column in the PETHEMA GEM2012 study. [b] Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment. [c] For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment." [d] Graded using CTCAE Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the IFM 2009 and SWOG S0777 studies. Note: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study. Data cutoff date = 01 Dec 2016 for the SWOG S0777 studies. [111].

For detailed efficacy and safety results, refer to Appendix D – Efficacy and safety results per study, and Appendix E – Safety data for intervention and comparators.

7.3.3 Comparative analyses of efficacy and safety

7.3.3.1 Method of synthesis

See section 7.4.1.

7.3.3.2 Results from the comparative analysis

See section 7.4.2.

7.4 Comparative analyses of efficacy and safety

7.4.1 Method of synthesis

In the absence of head-to-head RCTs comparing Dara+Rd with each of the relevant comparators for NDMM patients who are ineligible for ASCT, an NMA was conducted to synthesize the relevant efficacy evidence. An NMA is an indirect treatment comparison which can be applied when there are more than two possible interventions for a specific indication and those interventions are linked through a network anchored in a common comparator. Through an NMA, a pooled treatment effect is estimated for each intervention, making a comparison between interventions more reliable.

The NMA was not relevant for the comparison of Dara+Rd and Rd, since the head-to-head RCT, MAIA was conducted.

A bayesian network meta analysis (NMA) was conducted based on efficacy outomes from the 11 studies identified as relevant to the European context [20], which informs the relative efficacy of the relevant treatment comparators in Denmark. The outcomes that were evaluated in the NMA are PFS and OS, which are the key efficacy outcomes considered in this submission, and are key drivers of the cost-effectiveness model.

In addition to the three studies presented in section 7.1 (MAIA), section 7.2 (ALYCONE), and section 7.3 (SWOG S0777), eight additional studies were included in the network of treatments relevant in Europe, which enables the indirect comparison between treatments relevant in Denmark (Table 23). The overall network structure is represented in Figure 21.

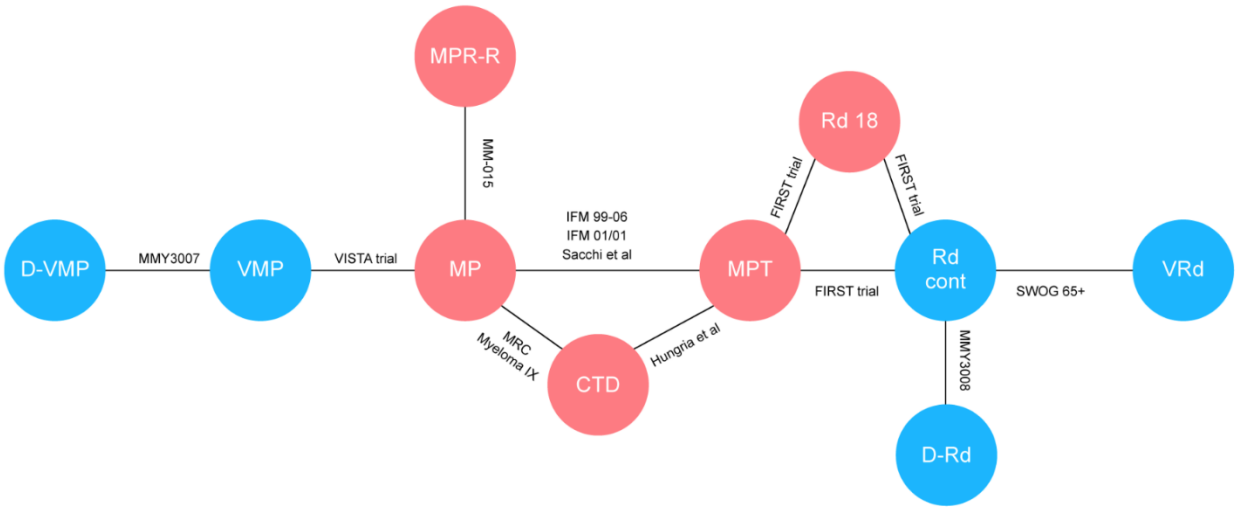
Table 23. Additional studies included in NMA for indirect treatment comparison

Trials	Treatment arms
VISTA trial [112]	VMP MP
MRC Myeloma IX [113]	MP CTd
Hungria et al. [114]	MPT CTd Td
IFM 99–06 [115]	MP MPT
IFM 01/01 [116]	MP MPT
Sacchi et al. [117]	MP MPT

Trials	Treatment arms
FIRST trial [118]	Rd cont Rd18 MPT
UPFRONT [119]	Vd VTd VMP

Abbreviation: Rd = lenalidomide, dexamethasone; DVMP = daratumumab, bortezomib, melphalan-prednisone; Rd continuous = lenalidomide, dexamethasone continuous; Rd 18 = lenalidomide, dexamethasone 18 months; CTd = cyclophosphamide, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; Vd = bortezomib, dexamethasone; MP = melphalan, prednisone; MPT = melphalan, prednisone, thalidomide; VMP = bortezomib, melphalan, prednisone

Figure 21. Evidence network for (A) PFS and (B) OS and (C) PFS and OS using main relevant comparators in Europe[a]



[a]Blue colour indicates EHA-ESMO recommended treatments. CMP, carfilzomib/melphalan/prednisone; CPR, cyclophosphamide/prednisone/lenalidomide; CTd, cyclophosphamide/thalidomide/dexamethasone; Dara+Rd, daratumumab/lenalidomide/dexamethasone; Dara+VMP, daratumumab/bortezomib/melphalan/prednisone; DEX, dexamethasone; DEX-IFN, dexamethasone/interferon alfa 2b; EHA-ESMO, European Hematology Association-European Society for Medical Oncology; KRd, carfilzomib/lenalidomide/dexamethasone; M-DEX, melphalan/dexamethasone; MP, melphalan/prednisone; MPR, melphalan/prednisone/lenalidomide; MPR-R, melphalan/prednisone/lenalidomide as induction, and lenalidomide as maintenance; MPT, melphalan/prednisone/thalidomide; MPT-T, melphalan/prednisone/thalidomide as induction, and thalidomide as maintenance; NCCN, National Comprehensive Cancer Network; OS, overall survival; Pembro-Rd, pembrolizumab/lenalidomide/dexamethasone; PFS, progression-free survival; Rd cont, lenalidomide/dexamethasone, continuous; Rd9, lenalidomide/dexamethasone, 9 cycles; Rd18, lenalidomide/dexamethasone, 18 cycles; Td, thalidomide/dexamethasone; Vd, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisone; VMP-S, bortezomib/melphalanprednisone/siltuximab; VMPT-VT, bortezomib/melphalan/prednisone/thalidomide as induction, and bortezomib/thalidomide as maintenance; VRd, bortezomib/lenalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone.

The NMA was performed using WinBUGS according to the NICE Decision Support Unit guidelines [120]. Three NMA assumptions (homogeneity, similarity, and consistency) were assessed across all studies. Reported hazard ratios (HRs) from relevant RCTs were applied in the NMA, assuming no violation of the proportional hazards assumption. All analyses were performed using fixed- and random-effects models. The choice between fixed- and random-effects models was based on deviance information criterion (DIC) score and/or the presence of observed heterogeneity in the network

[121] [122]. If HRs and associated confidence intervals (CIs) were not reported but Kaplan-Meier curves with corresponding numbers of patients at risk were available, the HRs and CIs were estimated based on the Guyot methodology [123], as recommended by NICE and assuming no violation of proportional hazards. If HRs were reported with only p-values, the CIs associated with the reported HR were also estimated [124].

7.4.2 Results from the comparative analysis

A random-effects model was preferred over a fixed-effects model for OS and PFS because heterogeneity was observed in both networks of evidence. Additionally, the DIC score for these models was lower compared with the fixed-effects model. Results from all studies that included VMP were pooled, as matching-adjusted indirect comparison indicated noninferiority in PFS and OS outcomes regardless of bortezomib dose intensity [125]. A normal likelihood with identity link model was used for PFS. Rd continuous was selected as the referent comparator for the current analysis because it is approved and included in key treatment guidelines across regions [126] [85].

7.4.2.1 Progression-free survival

The regimens with improved PFS compared with Rd continuous were Dara+Rd (HR: 0.53; 95% CrI: 0.43, 0.66), Dara+VMP (HR: 0.58; 95% CrI: 0.37, 0.93), and VRd (HR: 0.77; 95% CrI: 0.55, 1.08; Figure 37A). These regimens also had the highest probability of being more effective than Rd continuous (100%, 98.9%, and 93.2%, respectively). Dara+Rd had the highest probability of being ranked first in terms of PFS, (62%) followed by Dara+VMP (35%) and VRd (2%).

7.4.2.2 Overall survival

The regimens with improved OS compared with Rd continuous were Dara+Rd (HR: 0.68; 95% CrI: 0.54, 0.86), VRd (HR: 0.77; 95% CrI: 0.52, 1.14), and Dara+VMP (HR: 0.79; 95% CrI: 0.50, 1.23). The regimens with the highest probability of being more effective than Rd continuous with respect to OS included Dara+Rd (99.9%), VRd (90.1%), and Dara+VMP (85.5%; Figure 38A). Similarly, Dara+Rd had the highest chance of being ranked first with respect to OS, (53%) followed by VRd (24%) and then Dara+VMP (23%).

For further details of the NMA, refer to Appendix F – Comparative analysis of efficacy and safety.

8 Health economic analysis

An economic model was developed in Microsoft Excel® to assess the cost-effectiveness of Dara+Rd versus Rd, Dara+VMP, VRd, and VMP. In the following sections the model is described in section 8.1 the outcomes and inputs in the model are described in sections 8.2-8.5 and section 8.6 presents the results.

8.1 Model

A state-transition cohort model structure with three health states was selected to follow patients from an initial line of treatment after diagnosis into later lines until death. The three health states modelled were pre-progression, post-progression, and death. For the adequate modelling of treatment-related costs, it was necessary to keep track of treatment status in both the pre- and post-progression health states.

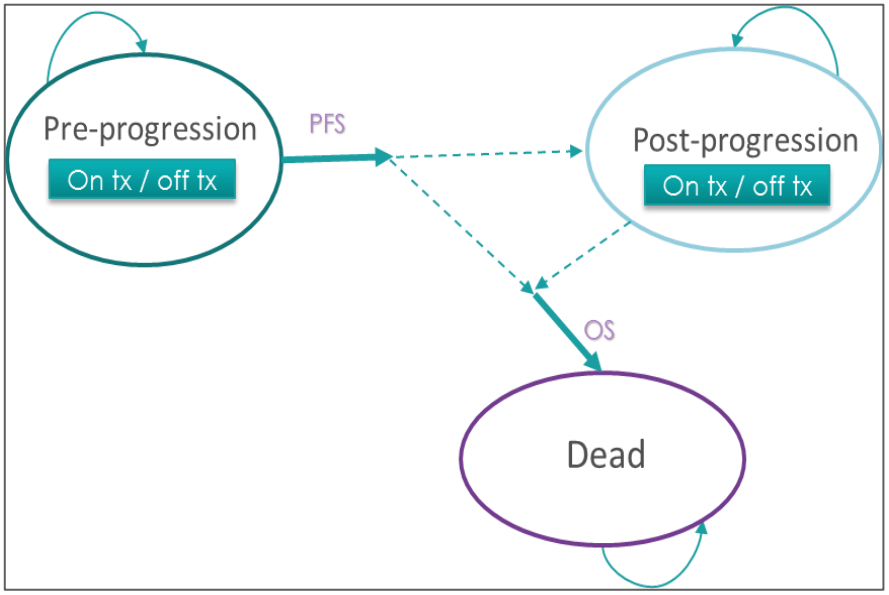
- Progression-free
  - On treatment
  - Off treatment
- Post-progression
  - On subsequent treatment(s)
  - Off treatment
- Death

atients with NDMM who are ineligible for ASCT enter the model, initiate front-line treatment, and experience an interval of PFS. Patients who experience disease progression and do not die during the initial modelled line of treatment continue to the post-progression health state, in which they may receive subsequent treatments. Patients may discontinue treatment or die at any time in the model.

Costs were assigned to each health state, and utilities are applied according to the patients' disease progression status. Costs and utilities were accrued and summarized for each cycle of the model (one week) so the difference in cumulative cost and utilities could be analysed and compared between comparators.

Figure 22 illustrates the survival partition health states for the model. This approach applies treatment-specific and independent OS and PFS curves for each comparator.

Figure 22. Model structure

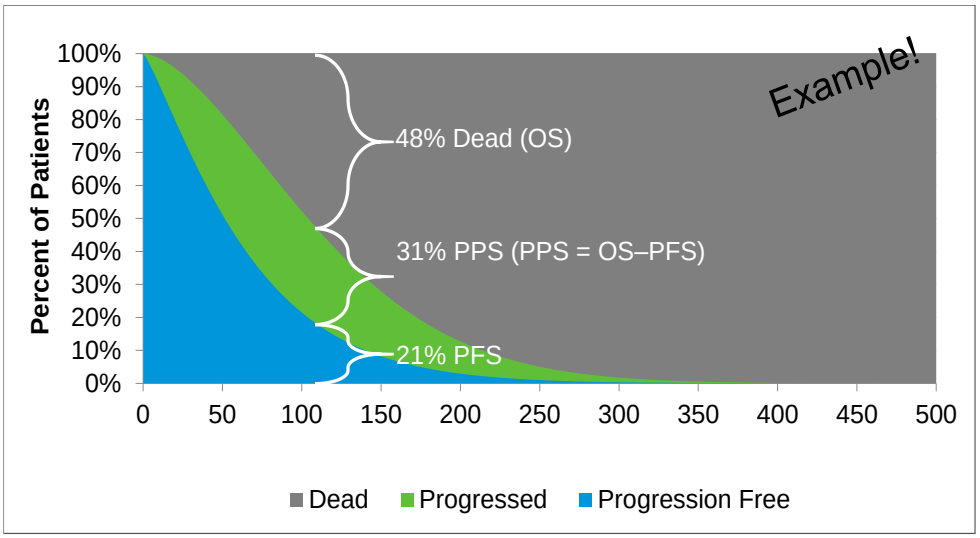


Legend: Dotted lines represent the fact the transitions between health states are not directly tracked, but proportions of patients in each health state are calculated through the partition approach at each time point.

Abbreviation: OS = overall survival; PFS = progression-free survival; tx = treatment

The partitionned survival model (PSM) does not directly calculate transitions between the three health states; instead, it partitions the population into groups. The method postulates that at any time point, the proportion of patients falling under the PFS curve is in the progression-free health state, the proportion of patients falling above the OS curve is in the death health state and those remaining are in the post-progression health state (Figure 23). In the PSM, the efficacy of treatment with respect to PFS does not directly impact OS (PFS and OS are independent).

Figure 23. Partitioned survival approach



Abbreviation: OS = overall survival; PFS = progression-free survival; PPS = post-progression survival

The model captures the proportion of patients on and off treatment within each health state using the same partition approach: patients falling under the time-to-treatment discontinuation (TTTD) curve are on treatment, while the proportion of patients between the TTTD and PFS curves must be in the pre-progression health state but off treatment.

8.1.1 Modelling approach to track progression and survival

The model captures the proportion of patients on and off treatment within each health state using the same partition approach: patients falling under the time-to-treatment discontinuation (TTTD) curve are on treatment, while the proportion of patients between the TTTD and PFS curves must be in the pre-progression health state but off treatment.

8.1.1.1 Progression-free

The PFS curve for each treatment is assumed to track the proportion of patients in the progression-free health state. During pre-progression, patients could stop receiving front-line treatment based on the treatment duration and stop accruing treatment-related costs; however, these patients will not switch to second-line treatments unless they progress.

8.1.1.2 Post-progression

In the post-progression health state, a proportion of patients can receive second-line treatment. PFS and TTTD can be modelled explicitly for second-line treatment, or treatment-to-progression can be assumed. Treatment-related costs are accrued based on the treatment duration of the second-line treatments; however, these patients will not switch to

third-line treatment unless they progress for a second time. Once patients experience progression after receiving second-line treatment, a proportion can receive third-line treatment. However, unlike with first- and second-line treatment, progression is not explicitly modelled for third-line treatment; only treatment costs are accrued while the patient is receiving third-line treatment based on the duration for this line.

8.1.1.3 Overall survival

In the survival partition approach, the efficacy of treatment with respect to PFS does not directly impact OS. Another implication is that the efficacy of subsequent treatments is already captured by the OS data, while their costs need to be captured explicitly and consistently with the actual subsequent treatments applied in the OS of the source trial. However, the subsequent treatments included in the OS of the source trial might not reflect treatments approved or used in clinical practice in Denmark, creating a potential mismatch between the subsequent treatments included in the OS and those for which is cost is captured.

8.1.1.4 Treatment duration – pre-progression

TTTD curves were included for all treatment regimens to account for the fact that patients may stop treatment before progression due to other causes, such as intolerable AEs. TTTD was modelled independently from PFS in the reference scenario since the reasons behind discontinuation were not necessarily linked to efficacy. If patients stop treatment before progression, they stop accruing treatment-related costs (e.g., drug acquisition, administration, monitoring while on treatment); however, patients only start receiving second-line treatment when progression occurs.

The model also includes the option to apply a rule for treatment discontinuation according to the product labels (e.g., until progression for treatments such as Dara+Rd and Rd). Alternatively, it is possible to use the reported median treatment duration from the trials and assume an exponential distribution to predict and extrapolate duration over time. Assuming that treatments are administered according to product labels may overestimate treatment costs; in clinical practice, patients may discontinue treatment before progression. However, using the median treatment duration may underestimate TTTD.

Comparators with fixed duration of treatment were assumed to be discontinued at their specified maximum duration. Due to lack of data on TTTD for other comparators, they were assumed to continue to progression.

8.1.1.5 Subsequent treatments – post-progression

Patients with MM receive multiple lines of treatment. Therefore, subsequent treatments represent a significant component of costs and health benefits, and modelling is a critical aspect of the cost-effectiveness assessment. The choice and efficacy of treatment in subsequent lines may depend on the options selected and efficacy obtained in prior lines. This dependency creates a difficult modelling challenge, as there is little information available from clinical trials regarding:

- The number of subsequent treatment lines
- The treatments applied in subsequent lines
- The duration of subsequent treatments
- The clinical efficacy of subsequent treatment options, especially regarding prior treatment history

For second-line treatments, if there is a lack of TTTD data, treat-to-progression is assumed. The median treatment duration for the comparators was not selected as it would underestimate their actual TTTD. Once progressed, patients start receiving third-line treatment.

Once patients experience progression after receiving second-line treatment, a proportion can receive third-line treatment. Patients accrue treatment-related costs based on the median duration as reported in the literature. However, disease progression and switch to subsequent lines (i.e., fourth line and above) were not considered in the model.

8.1.1.6 Death during PFS

The incidence of progression in each model cycle (one week) is calculated to track patients receiving second-line treatment and PPS. Some patients may die in the pre-progression state; therefore, to avoid over-estimating the incidence of progression, pre-progression death was explicitly incorporated.

Death during the pre-progression state can be modelled in two ways: by assuming a constant mortality rate, or by assuming a constant ratio of death to progression among PFS events.

The ratio and rate of mortality were calculated based on data from the Dara+Rd arm of the MMY3008 for Dara+Rd, and from the Rd arm of the MMY3008 trial for Rd. For other comparators, the ratio and rate of mortality were assumed the mean of Rd from MMY3008 and VMP from MMY3007 (Table 24).

The base case assumption is a constant mortality rate for Dara+Rd and all comparators, as it is more in line with the understanding of the role of progression in MM. The constant mortality rate can be thought of as a reflection of a background mortality, which is not necessarily directly MM-related.

- Using a constant rate of mortality:

$$Pre-progression\ Deaths(t) = PFS(t-1) \times Rate\ of\ Death\ during\ PFS$$

- Using a constant ratio of death and progression:

$$Pre-progression\ Deaths(t) = [PFS(t-1) - PFS(t)] \times Ratio\ of\ Death\ during\ PFS$$

Table 24. PFS Mortality

Comparators	Constant Ratio of Death and Progression	Source	Constant Mortality Rate (weekly)	Source
Dara+Rd	30.00%	MMY3008*	0.000756	MMY3008*
Comparators	21.20%		0.000995	

* Clinical cut-off date of 19 February 2021; median follow-up 56.2 months

Abbreviations: Dara+Rd = daratumumab, lenalidomide, dexamethasone; PFS = progression-free survival; Rd= lenalidomide, dexamethasone; VMP = bortezomib, melphalan, prednisone

8.1.2 Model outcome measures

The model aggregates the health outcomes and costs from each health state and reports the discounted outcomes (costs and health-related outcomes discounted at 3.5% and 3.5% per annum, respectively):

- Life years (LYs), progression-free life years (PFLYs), post-progression life years (PPLYs)
- Quality-adjusted progression-free life years (QAPFLYs), quality-adjusted post-progression life years (QAPPLYs), QALYs
- Disutility associated with AEs
- First-, second-, and third-line drug acquisition, administration, and monitoring (on and off treatment) costs, AE management costs (for first-line treatment only), and patient and transportation costs (all treatment lines)
- ICERs: cost per QALY gained, cost per QAPFLY gained, cost per LY gained

The costs of subsequent treatments are accrued in the model explicitly and consistent with the assumed market shares of the subsequent treatments used by patients in the Danish setting.

The life-table method for half-cycle correction was used to calculate all model outcomes in the base case.

The base case analysis was conducted from a restricted societal perspective. The time horizon of the model is flexible, ranging from one year to a maximum of 30 years. A 30-year time horizon was used in the reference scenario, reflecting a lifetime for patients in the target population. This time horizon was considered long enough to capture the long-term clinical and economic consequences of MM for patients who are ineligible for ASCT, an incurable disease requiring treatment until the end of life. Given the median age of 74.1 years in the MMY3008 trial, 30 years was considered as a fair approximation of a lifetime time horizon.

All costs and health outcomes were discounted at a rate of 3.5% per year in the base case analysis.

The model was developed based on the clinical and treatment pathways for patients with NDMM who are ineligible for ASCT; consideration of key clinical aspects (progression-free survival [PFS], overall survival [OS], post-progression survival [PPS], treatment duration) that affect clinical outcomes, costs, and treatment decisions; a thorough review of published economic modelling approaches and available HTA submission reports; and recommendations from a panel of expert health economists was used to validate the model approach. The model inputs and key structural assumptions have been validated by an internal Janssen Danish clinical expert within MM.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

This section presents and describes the input data used in the model. Table 25 provides a summary of the key inputs and assumptions.

8.2.1 Presentation of input data used in the model and how they were obtained

Table 25. Input data used in the model

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Overall Survival (OS)	See in section 19.1. Observed ITT OS curves for treatments included in the MAIA trial (i.e., Dara+Rd, Rd) shows a clear, increasing separation between Dara+Rd vs. Rd. Treatment-specific HR versus Rd OS (obtained from the NMA) for comparators not included in the MAIA trial [20]	See in section 19.1. Individual ITT OS curves (Gompertz) for treatments included in the MAIA trial (i.e., Dara+Rd, Rd). Treatment-specific HR versus Rd (obtained from the NMA) for comparators not included in the MAIA trial [20]	See in section 19.1.
Progression-free survival (PFS)	See in section 19.2. Observed ITT PFS curves for treatments included in the MAIA trial (i.e., Dara+Rd, Rd) shows a clear, increasing separation between Dara+Rd vs. Rd. Treatment-specific HR versus Rd PFS (obtained from the NMA) for comparators not included in the MAIA trial [20]	See in section 19.2. Individual ITT PFS curves (Exponential) for treatments included in the MAIA trial (i.e., Dara+Rd, Rd). Treatment-specific HR versus Rd PFS (obtained from the NMA) for comparators not included in the MAIA trial [20]	See in section 19.2.
Time-to-treatment discontinuation (TTD) **(in progression-free health state)**	See in section 19.3. Observed TTD curves for treatments included in the MAIA trial (i.e., Dara+Rd, Rd). Treatment until progression for Dara + VMP, VRd, and VMP. For second- line treatment (post-progression), treatment until progression was assumed. For third- line treatment (post-progression), median treatment duration is assumed as equal to median PFS amongst patients treated with PanBorDex following at least two previous lines of treatment for patients reported by Richardson et al 2016 [127] (assumed similar for all third-line treatments)	See in section 19.3. Observed TTD curves (Exponential) for treatments included in the MAIA trial (i.e., Dara+Rd, Rd). Treatment until progression for Dara + VMP, VRd, and VMP. For second- line treatment (post-progression), treatment until progression was assumed. For third- line treatment (post-progression), median treatment duration is assumed as equal to median PFS amongst patients treated with PanBorDex following at least two previous lines of treatment for patients reported by Richardson et al 2016 [127] (assumed similar for all third-line treatments)	See in section 19.3. Second- and third-line PFS was collected from the respective clinical trials

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Adverse Events	Refer to section **Error! R eference source not found.** and 8.5.4 where AEs in the clinical trials are described.	Refer to section 8.2.2.5 for the included AE and Table 38 the disutilities.	Based on reported AEs from clinical trials and disutilities primarily based on previous NICE evaluations
Utilities			
Pre-Progression			The utility values were derived from an analysis of EuroQoL Five-Dimension Five-Level (EQ-5D-5L) data from the MAIA trial. Danish population weights applied to estimate health state utility values (refer to Appendix I – Mapping of HRQoL data)
Post-Progression			

Abbreviations: AE = adverse event; EQ-5D-5L = EuroQoL Five-Dimension Five-Level; TTD = time-to-treatment discontinuation

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The target population of this application of Dara+Rd is the approximately 240 patients per year with documented NDMM who are ineligible for ASCT. Refer to section 5.1 for a description of the Danish population.

Patient population in the clinical documentation submitted: The intention-to-treat (ITT) population in the MAIA trial was patients with newly diagnosed, documented MM, who were not eligible for high-dose chemotherapy with stem-cell transplantation owing to coexisting conditions or an age of 65 years or older [103]. The mean age at baseline of the ITT population was 74.1 years.

Patient population in the health economic analysis submitted: The patient population characteristics are based of the MAIA trial, described above. Relevant patient characteristics for the model are presented in Table 26.

Table 26. Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Mean age, years	[redacted]		Similar mean age expected in Danish clinical practice see 5.1, Epidemiological information. Impact of alternative mean age was tested a in scenario analysis.
Mean weight, kg			Similar mean weight expected in Danish clinical practice. Impact of alternative mean weight (Capital Region) was tested a in scenario analysis.
Body surface area, m^2			Similar body surface area expected in Danish clinical practice. Impact of alternative body surface area (Capital Region) was tested a in scenario analysis.

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice: refer to section 5.3. Inputs regarding Dara+Rd in the model are informed by the clinical trial MAIA [104] . The intervention is described below in Table 27.

Table 27. Intervention

Intervention: Dara+Rd	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	[redacted]		

Intervention: Dara+Rd	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
	[redacted]		
Length of treatment (time on treatment)/ criteria for discontinuation	Treatment until documented progression or unacceptable toxicity	Treatment until documented progression or unacceptable toxicity	Treatment until documented progression or unacceptable toxicity
The pharmaceutical's position in Danish clinical practice	NA	First-line treatment for NDMM	First-line treatment for NDMM

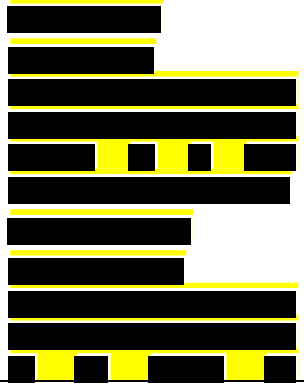
8.2.2.3 Comparators

The current Danish clinical practice: In current Danish clinical practice VRd, Rd, Dara+VMP, and VMP are all recommended as by the DMC (refer to section 5.2.1), and are consequently considered relevant treatment options.

Comparator(s) in the clinical documentation submitted: The comparators presented in the clinical documentation submitted are MAIA (Dara+Rd and RD), (DVTd and VTd), ALCYONE (Dara+VMP and VMP), and SWOG S0777 (VRd) trials. Refer to section 7.1, 7.2, and 7.3 where these clinical trials has been described as well a related appendences.

Comparator(s) in the health economic analysis submitted: The different comparators included in the model are Rd, Dara+VMP, VRd, and VMP, which is in line with treatment options in Danish clinical practice. The clinical inputs are mainly collected from the clinical trials MAIA (Dara+Rd and Rd), ALCYONE (Dara+VMP and VMP), and SWOG S0777 trial (VRd).

Table 28. Comparators

Comparator		Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Rd	Posology		Same as in clinical documentation	Expected to be similar in Danish clinical practice

Comparator		Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
		[redacted]		
	Length of treatment	Treatment until documented progression or unacceptable toxicity	Treatment until documented progression or unacceptable toxicity	Treatment until documented progression or unacceptable toxicity
	The comparator's position in the Danish clinical practice	First-line treatment	First-line treatment	First-line treatment
Dara+VMP	Posology	Daratumumab IV: 16 mg/kg as intravenous infusion, once weekly, for 6 weeks in Cycle 1 and then once every 3 weeks, in Cycle 2 to 9 and thereafter, once every 4 weeks until documented progression, unacceptable toxicity, or until the end of study Or Daratumumab SC: SC Injection at a fixed dose of 1800 mg once every 4 weeks until documented progression, unacceptable toxicity, or until the end of study. Participants can switch from daratumumab IV to daratumumab SC. Bortezomib: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9. Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9. Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9. [18]	1.800 mg of daratumumab solution for subcutaneous injection administered over approximately 3-5 minutes weekly (week 1-6), every three weeks (week 7-54), and every four weeks (week 55 until disease progression) Bortezomib: Bortezomib: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9. Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9. Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9.	1.800 mg of daratumumab solution for subcutaneous injection administered over approximately 3-5 minutes weekly (week 1-6), every three weeks (week 7-54), and every four weeks (week 55 until disease progression) Bortezomib: Bortezomib: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9. Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9. Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9. [128]

Comparator		Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
	Length of treatment	Treatment until documented progression or unacceptable toxicity	Treatment until documented progression or unacceptable toxicity	Treatment until documented progression or unacceptable toxicity
	The comparator's position in the Danish clinical practice	First-line treatment	First-line treatment	First-line treatment
VRd	Posology	First eight cycles of 21 days: Bortezomib: 1.3 mg/m^2, as subcutaneous injection, on day 1, 4, 8, and 11 of each treatment cycle. Lenalidomide: Administered at a dose of 25 mg orally on Days 1 through 14 of each treatment cycle. Dexamethasone: Administered as a total dose of 20 mg p.o. on day 1,2, 4, 5, 8, 9, 11, and 12. Subsequent cycles of 28 days: Lenalidomide: Administered at a dose of 25 mg orally on Days 1 through 21 of each treatment cycle. Administered as a total dose of 40 mg p.o. pm day 1, 8, 15, and 22 of each cycle. [18]	First eight cycles of 21 days: Bortezomib: 1.3 mg/m^2, as subcutaneous injection, on day 1, 4, 8, and 11 of each treatment cycle. Lenalidomide: Administered at a dose of 25 mg orally on Days 1 through 14 of each treatment cycle. Dexamethasone: Administered as a total dose of 20 mg p.o. on day 1,2, 4, 5, 8, 9, 11, and 12. Subsequent cycles of 28 days: Lenalidomide: Administered at a dose of 25 mg orally on Days 1 through 21 of each treatment cycle. Administered as a total dose of 40 mg p.o. pm day 1, 8, 15, and 22 of each cycle.	First eight cycles of 21 days: Bortezomib: 1.3 mg/m^2, as subcutaneous injection, on day 1, 4, 8, and 11 of each treatment cycle. Lenalidomide: Administered at a dose of 25 mg orally on Days 1 through 14 of each treatment cycle. Dexamethasone: Administered as a total dose of 20 mg p.o. on day 1,2, 4, 5, 8, 9, 11, and 12. Subsequent cycles of 28 days: Lenalidomide: Administered at a dose of 25 mg orally on Days 1 through 21 of each treatment cycle. Administered as a total dose of 40 mg p.o. pm day 1, 8, 15, and 22 of each cycle.
	Length of treatment	Treatment until documented progression or unacceptable toxicity	Treatment until documented progression or unacceptable toxicity	Treatment until documented progression or unacceptable toxicity
	The comparator's position in the Danish clinical practice	First-line treatment	First-line treatment	First-line treatment

Comparator		Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
VMP	Posology	Series of 42 days Bortezomib: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4, and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9. Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9. Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9. [18]	Series of 35 days Bortezomib: 1.3 mg/m^2, as subcutaneous on day 1, 8, 15, and 22 in Cycles 1 to 9. Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9. Prednisone: 100 mg, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9.	Series of 35 days Bortezomib: 1.3 mg/m^2, as subcutaneous on day 1, 8, 15, and 22 in Cycles 1 to 9. Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9. Prednisone: 100 mg, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9. [129] [128]
	Length of treatment	Treatment up to 9 cycles or until documented progression or unacceptable toxicity	Treatment up to 9 cycles or until documented progression or unacceptable toxicity	Treatment up to 9 cycles or until documented progression or unacceptable toxicity
	The comparator's position in the Danish clinical practice	First-line treatment	First-line treatment	First-line treatment

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: The relative efficacy outcomes are summarized in section 0. A head to head trial is available for Dara+Rd vs. Rd [19] and efficacy results for each intervention compared to the reference treatment (Rd) have been estimated through a NMA [20]. Efficacy results for the included trials were OS and PFS.

Relevance of the documentation for Danish clinical practice: The clinical documentation is relevant to the Danish population as it presents efficacy results for the proposed treatment in Denmark using relevant efficacy measures (refer to section 7.4).

The relative efficacy outcomes in the submitted health economic analysis: The key efficacy inputs in the model are OS, PFS. These are derived from a direct comparison (Dara+Rd vs. Rd) and via indirect comparisons (Dara+VMP, VRd, and VMP) (refer to section 0). The economic analysis uses the modelled efficacy results (survival curves) presented in section 19.1 and section 19.2.

Table 29. Summary of text regarding value

Clinical efficacy outcome	Clinical documentation	Valuese used in the model
Dara+Rd		
PFS	MAIA derived survival curve [19]	Refer to [redacted]
OS	MAIA derived survival curve [19]	Refer to [redacted]
Rd		
PFS	MAIA derived survival curve	Refer to [redacted]
OS	MAIA derived survival curve	Refer to [redacted]
Dara+VMP vs. Rd		
PFS	HR from NMA [20].	
OS	HR from NMA [20].	HR: 0.79; 95% CrI, 0.50–1.23
VRd vs. Rd		
PFS	HR from NMA [20].	
OS	HR from NMA [20].	HR, 0.77; 95% CrI, 0.52–1.14
VMP vs. Rd		
PFS	HR from NMA [20].	
OS	HR from NMA [20].	HR: 1.31; 95% CrI: 0.92-1.86

Table 30. Summary of text regarding relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
OS	See Table 80	Very relevant, traditionally used in evaluations of drugs in oncology	Very relevant, traditionally used in evaluations of drugs in oncology
PFS	See Table 80	Very relevant, traditionally used in evaluations of drugs in oncology	Very relevant, traditionally used in evaluations of drugs in oncology

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: The clinical documentation for the adverse events included in the cost-effectiveness model are the MAIA, ALCYONE, and SWOG trials. For more details of the adverse events refer to sections 8.4.2 and 8.5.4.

Adverse reaction outcomes in the health economic analysis submitted: Only grade ≥3 AEs occurring in ≥5% of study subjects in the Dara+Rd or Rd arms of MAIA were considered in the model. AEs for second- and third-line treatments were not considered.

This inclusion criterion was considered appropriate and sufficient to capture AEs that would impact patients with any consistency; this is to maintain validity in a real-world setting where AEs are monitored in a less strict manner compared

with a clinical trial setting. It is also a conservative approach, because it ignores AEs that would have a higher occurrence for comparators in the model; these criteria underestimate relative treatment costs in favour of the comparators.

In the model, AEs affect costs and utilities of patients receiving treatment. AEs are assumed to occur only in the first year of treatment. Therefore, patients who remain 'on treatment' for subsequent years do not incur further AE-related costs. In addition, only AEs associated with initial (i.e., front line) treatment were considered.

The model uses the cumulative probabilities of AE occurrence during the treatment period. The cumulative probabilities of AEs are assumed to be independent of PFS and treatment duration. To account for differences in exposure time, treatment-specific cumulative probabilities for the ITT population over the entire trial duration are used to calculate an overall cost of AEs. A per-patient overall AE cost and utility decrement is applied as an on-off lump sum at the start of treatment.

The cumulative probabilities of AE occurrence during the treatment period are shown in Table 31. For VRd although the reference case population for OS is the 65+ population, the only information on AE incidence available from the SWOG S0777 trial is for ITT from the EMA EPAR. Therefore, the ITT incidence rates are used in the reference case.

Table 31. Cumulative probability of AEs (grade 3+)

Adverse reaction outcome	Dara+Rd	Rd	Dara+VMP	VRd	VMP
Anemia	16.8%	21.6%	17.3%	12.2%	19.8%
Asthenia	5.2%	4.7%	0.0%	0.0%	0.0%
Cataract	11.0%	10.7%	0.0%	0.0%	0.0%
Diarrhea	8.8%	6.0%	0.0%	9.2%	0.0%
Fatigue	8.8%	4.7%	0.0%	14.5%	0.0%
Hyperglycemia	7.7%	3.8%	0.0%	7.3%	0.0%
Hypokalemia	12.6%	9.9%	0.0%	11.5%	0.0%
Leukocytopenia	11.5%	6.3%	8.1%	8.8%	8.5%
Lymphopenia	16.5%	11.2%	7.8%	18.7%	6.2%
Neutropenia	54.1%	37.0%	40.2%	9.9%	39.0%
Pneumonia	19.2%	10.7%	13.0%	0.0%	4.2%
Thrombocytopenia	8.8%	9.3%	0.0%	17.2%	0.0%
Hypertension	8.5%	4.4%	0.0%	0.0%	0.0%
Pulmonary embolism	7.1%	5.2%	0.0%	6.9%	0.0%
Clinical documentation	MAIA [19]	MAIA [19]	ALCYONE [130]	SWOG S0777 [131]	ALCYONE [130]
Used in model	Yes	Yes	Yes	Yes	Yes

Abbreviations: Dara+Rd = daratumumab, lenalidomid, dexamethasone; Rd = lenalidomid, dexamethasone; Dara+VMP = daratumumab, bortezomib, melphalan, prednisone; VRd = bortezomib, lenalidomid, dexamethasone; VMP = bortezomib, melphalan, prednisone

8.3 Extrapolation of relative efficacy

The key efficacy inputs in the model are OS are PFS. The MAIA trial was used to derive clinical data for Dara+Rd and Rd, as patient-level. Although not an efficacy outcome in the model, TTTD was also modelled explicitly to appropriately

estimate the treatment costs. For Dara+Rd and Rd, TTD was explicitly extrapolated based on PLD from MAIA, where TTTD from the comparators not included in the MAIA trial were sources from the individual clinical trials.

Extrapolations of PFS and OS based on patient-level data were aligned with recommendations in the NICE Decision Support Unit (DSU) Report 14 and six parametric distributions were fitted to model OS and PFS data and implemented in the model [132]. These are the exponential distribution, the Weibull and Gompertz distributions, the log-logistic and log-normal distributions and the generalized gamma distribution. The process of selecting a 'best-fitting' distribution involved considerations based on the observed data regarding goodness-of-fit and plausibility of results

- Hazard behaviour e.g., proportional hazards (PH) assumptions assessment
- Graphical assessment of fits
- Goodness-of-fit statistics (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]). Statistically, the best fit to the observed data is the curve with the lowest AIC and BIC.
- Clinical plausibility of long-term projections
- Comparison of long-term projections with external sources (if available)

'Best fitting' does not necessarily imply good fit; the best-fitting distribution may still deviate from the observed data or produce clinically implausible long-term projections. When standard parametric survival analysis was not enough to appropriately fit the observed data from the MAIA trial, segmented parametric survival analysis was considered where appropriate. Following considerations based on the above criteria, the most appropriate distribution was selected for the base case analysis (refer to Appendix G – Extrapolation section 19.1 (OS) and section 19.2 PFS)) [132] [133].

8.3.1 Time to event data – summarized

The full method used and results are provided in Appendix G – Extrapolation where OS Appendix G – Extrapolation (section 19.1), PFS (section 19.2), and TTTD (19.3) are presented (including relevant smoothed hazard plots). A short summary of the selected curves for each parameter is presented hereafter.

8.3.1.1 OS extrapolations

For the base case analysis, individual Gompertz distributions were applied for OS for both Dara+Rd (Figure 24) and Rd (Figure 25). Firstly, PH was assessed. A relatively flat line in the Schoenfeld residuals plot and parallel lines in the log-cumulative hazard plots would indicate adequate proportionality between the OS curves of Dara+Rd and Rd. However, this is not the case as the lines cross, indicating a violation of proportional hazards. For this reason, individual, treatment-specific parametric distributions were used to extrapolate OS for Dara+Rd. The Gompertz distribution was selected for both treatment arms based on the following criteria:

- Statistical fit:
  - As illustrated in Table 32 the Exponential, Weibull, Generalized Gamma, and Gompertz curves for Dara+Rd and Rd all had a similar statistical fit to the observed data. Log-logistic and log-normal had a worse statistical fit.
  - The parameters of the Gamma distribution for Dara+Rd and Rd did not converge during the curve fitting exercises, resulting in unrealistic variability estimates. This limits the use of the Gamma distribution in the

model to conduct deterministic and probabilistic sensitivity analyses varying the parameters of this distribution.

- The Exponential distribution is never appropriate to use for OS since we know that the hazard for death is not constant over time.

- Visual fit:
  - Both Weibull and Gompertz provide middle of the range predictions for Dara+Rd. For Rd, Weibull provide middle of the range predictions, whereas Gompertz provide the most conservative long-term survival predictions.
  - The long-term survival predictions for all curves overestimate survival compared with the expected Danish background mortality, and consequently more conservative survival predictions should be assumed to align with Danish background mortality.
- Validation against RWE:
  - The clinical plausibility of the OS longer-term extrapolations for Rd was assessed by comparing them to the OS reported from the FIRST trial (Figure 26) [134]. The FIRST trial was selected because the target population (i.e., patients enrolled) was similar to that of the MAIA trial—patients with NDMM who are ineligible for ASCT, because it reports KM curves for OS after at least five years of follow-up, and because the dosing schedule for Rd was the same to that of the MAIA trial. As shown in Figure 26 the shape of the Gompertz distributions is supported by the data from the OS reported in the FIRST trial, while the extrapolation of OS for Rd in MAIA with Weibull may be too optimistic. As shown in Table 32 the median OS and four- and five-year OS for Rd extrapolated using Gompertz are in line with those from Rd in the FIRST trial, followed by Weibull. Consequently, the Gompertz distribution is considered to be the most appropriate distribution to extrapolate OS.

Figure 24. OS long-term extrapolations using individual curves - Dara+Rd

Figure 25. OS long-term extrapolations using individual curves - Rd

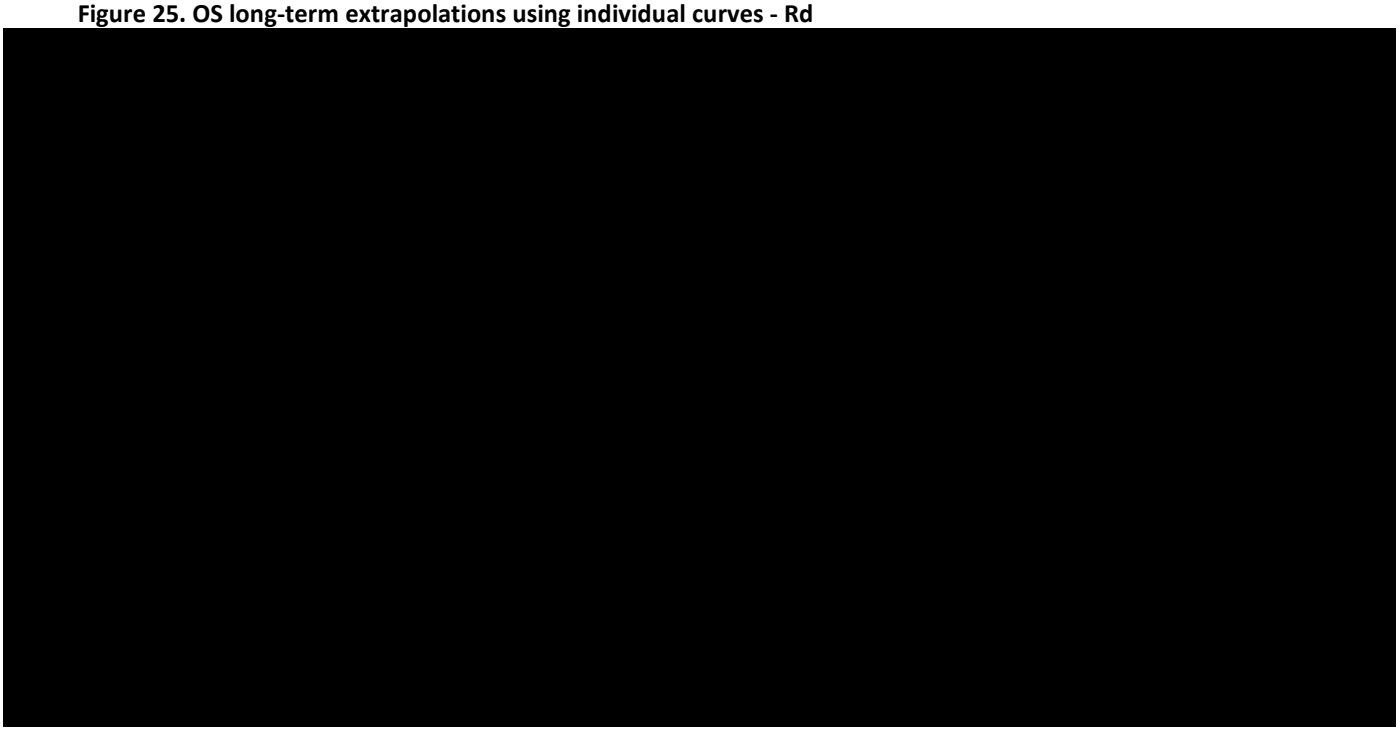


Table 32. OS Dara+Rd and Rd fit statistics using individual curves

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 26. OS comparison with external long-term clinical trial data - Rd

Table 33. OS outcomes Rd in MAIA vs. Rd in FIRST

8.3.1.2 PFS extrapolations

For the base case analysis, individual Exponential distributions were applied for PFS for both Dara+Rd (Figure 27) and Rd (Figure 28). Firstly, PH was assessed. A relatively flat line in the Schoenfeld residuals plot and parallel lines in the log-cumulative hazard plots would indicate adequate proportionality between the OS curves of Dara+Rd and Rd. However, this is not the case as the lines cross, indicating a violation of proportional hazards. For this reason, individual, treatment-specific parametric distributions were used to extrapolate PFS for Dara+Rd. The Exponential distribution was selected for both treatment arms based on the following criteria:

- Statistical fit:
  - Based on the fits statistics AIC and BIC (Table 34), the exponential and log-logistic distributions fit the observed data for Dara+Rd and Rd, respectively, better (i.e., have the lowest AIC and BIC) than the other four distributions. Exponential generally have the best fit for both treatment arms.
  - The parameters of the Gamma distribution for Dara+Rd and Rd did not converge during the curve fitting exercises, resulting in unrealistic variability estimates. This limits the use of the Gamma distribution in the model to conduct deterministic and probabilistic sensitivity analyses varying the parameters of this distribution.
- Visual fit:
  - Based on graphical assessment (Figure 27 and Figure 28) all distributions are close to each other during the trial period for Dara+Rd and Rd. Due to the limited follow-up in the MAIA trial, there is uncertainty in the long-term extrapolations, particularly for Dara+Rd. To be conservative in favour of the comparators in the model, the Exponential distribution was selected for both arms as this provides the most conservative long-term predictions for Dara+Rd and middle-of-the-range estimates for Rd.

Table 34. PFS Dara+Rd and Rd fit statistics using individual curves

Figure 27. PFS long-term extrapolations using individual curves - Dara+Rd

Figure 28. PFS long-term extrapolations using individual curves - Rd

8.3.1.3 First-line treatment duration

Treatment duration is a key driver of costs and thus, cost-effectiveness. If patients stop treatment, they stop accruing treatment-related costs (e.g., drug acquisition, administration, monitoring while on treatment, and patient time). There is a high positive correlation between TTTD and efficacy outcomes, especially for PFS. For Dara+Rd and Rd IPD was available, and consequently treatment duration was modelled independently from efficacy, although the input parameters of the PFS and TTTD curves remain naturally correlated. For the remaining comparators, TTTD is modelled

as treat-to-progression, where TTTD is directly linked to PFS. In the model, stopping treatment affects only cost outcomes, and not efficacy outcomes, which are determined by PFS/OS. It should also be noted that where treatments are fixed duration, the model caps TTTD at the maximum fixed duration; although, it is possible for patients to discontinue treatment before the fixed duration.

For the base case analysis, individual Exponential distributions were applied for TTTD for both Dara+Rd (Figure 27) and Rd (Figure 28).

The Exponential distribution was selected for both treatment arms based on the following criteria:

- Statistical fit:
  - Based on the fits statistics AIC and BIC (), the exponential and Generalized Gamma distributions fit the observed data for Dara+Rd better (i.e., have the lowest AIC and BIC) than the other four distributions. For Rd the Exponential and Weibull distributions fit the observed data best. Exponential generally have the best fit for both treatment arms.
  - The parameters of the Gamma distribution for Dara+Rd and Rd did not converge during the curve fitting exercises, resulting in unrealistic variability estimates. This limits the use of the Gamma distribution in the model to conduct deterministic and probabilistic sensitivity analyses varying the parameters of this distribution.
- Visual fit:
  - Based on graphical assessment (Figure 29 and Figure 30) all distributions are close to each other during the trial period for Dara+Rd and Rd. Due to the limited follow-up in the MAIA trial, there is uncertainty in the long-term extrapolations. The Exponential and Weilbull distributions predicts almost identical results for both Dara+Rd and Rd, and consequently the exponential distribution was selected for both treatment arms since this has the best overall statistical fit and applies the same hazard assumptions as the PFS curves.

Table 35. TTTD Dara+Rd and Rd fit statistics using individual curves

Figure 29. TTTD long-term extrapolations using individual curves - Dara+Rd

Figure 30. TTTD long-term extrapolations using individual curves - Rd

8.3.1.4 Second-line treatment duration

In the model, it assumes that second-line treatments are treat to progression. Median PFS for second-line treatment options is based on the NMAs for the CASTOR trial (MMY3004) and the POLLUX trial (MMY3003) for adults with relapsed/refractory MM who received at least one prior line of therapy. There are two NMAs available, one with Rd as the reference and another with Vd as the reference, as these backbones have separate populations. The HRs from the second-line NMAs are applied to the medians for Rd and Vd. The median for Vd is taken from ITT population in the

POLLUX trial, and the median for Rd is taken from the ASPIRE trial [135]. ASPIRE was selected as the source for median PFS for Rd as it had been reached in this trial, whereas it has not been reached in POLLUX trial (i.e., the median would need to be extrapolated, which would add uncertainty). This allows consistent comparative efficacy for second-line treatments and aligns with the 1-prior line (1PL) models. However, it should be noted that the populations included in the second-line trials do not match those included in the MAIA trial, as they include patients that will have received transplant and appear to be healthier than MAIA patients. For pomalidomide+Vd the HR vs. Vd and median PFS from the OPTIMISMM study [136] has been applied separately. This potentially creates additional uncertainty in the estimates.

Where treatments are fixed duration, TTTD is capped at the maximum duration; however, prior to this timepoint, TTTD is extrapolated based on the median PFS.

Table 36. Second-line TTTD and PFS

Second-line Treatment	Median Duration (Reported per Trial)		Median PFS (Calculated using HRs)		
	Months	Source	Months	HR	Source
Dara+Rd	34.0	MMY3003 IA3* [137]	37.7	0.44	1PL NMA ASCO 2017 data, versus Rd
Dara+Vd	13.3	MMY3004 IA3† [138]	24.1	0.32	1PL NMA ASCO 2017 data, versus Vd
Carfilzomib+ Dexamethasone	9.2	ENDEAVOR study, Dimopoulos et al. 2016 [137]	14.5	0.53	1PL NMA ASCO 2017 data, versus Vd
Carfilzomib+Rd	20.2	ASPIRE study, Stewart et al. 2015 [135]	24.1	0.69	1PL NMA ASCO 2017 data, versus Rd
CVD	4.5	Kropff et al. 2007[139]	10.9	0.71	1PL NMA ASCO 2017 data, versus Vd
Elotuzumab+Rd	17.0	ELOQUENT-2 study, Lonial et al. 2015 [140]	23.4	0.71	1PL NMA ASCO 2017 data, versus Rd
Elotuzumab+Vd	9.2	Jakubowiak et al. 2016 [141]	10.4	0.74	1PL NMA ASCO 2017 data, versus Vd
Ixazomib+Rd	15.6	TOURMALINE study, Moreau et al. 2016 [142]	22.3	0.75	1PL NMA ASCO 2017 data, versus Rd
Panobinostat+Vd	5.0	PANORAMA1 study, San Miguel et al. 2014 [143]	11.1	0.70	1PL NMA ASCO 2017 data, versus Vd
Pomalidomide+ Dexamethasone	4.2	Dimopoulus et al. 2013 [144]	12.1	1.38	1PL NMA ASCO 2017 data, versus Rd
Rd	15.9	MMY3003 IA3* [137]	16.6	1.00	ASPIRE study, Stewart et al. 2015[135]
Td	5.1	Nordic Myeloma study, Hjorth et al. 2012 [145]	8.7	0.89	1PL NMA ASCO 2017 data, versus Vd
Vd	5.9	MMY3004 IA3† [138]	7.7	1.00	MMY3004[138]

Second-line Treatment	Median Duration (Reported per Trial)		Median PFS (Calculated using HRs)		
	Months	Source	Months	HR	Source
VTD	5.2	MMVAR-Velcade, Garderet et al. 2012 [146]	14.0	0.55	1PL NMA ASCO 2017 data, versus Vd
Pomalidomide+Vd	11.2	OPTIMISMM [136]	11.2	0.61	OPTIMISMM data, versus Vd

*Median follow-up 32.9 months; †Median follow-up 26.9 months; Treatment length is capped based on weeks or number of treatment cycles. Dara+Vd: Vd administered for up to 54 weeks maximum; Carfilzomib+Rd: Carfilzomib administered for up to 72 weeks maximum; CVD administered for up to 27 weeks maximum; Panobinostat+Vd administered for up to 48 weeks maximum; VD administered for up to 24 weeks maximum; VTD administered for up to 24 weeks maximum; Abbreviations: 1PL = one prior line; ASCO = American Society of Clinical Oncology; CVD = cyclophosphamide, bortezomib, and dexamethasone; Dara+Rd = daratumumab in combination with lenalidomide and dexamethasone; Dara+Vd = daratumumab in combination with bortezomib and dexamethasone; HR = hazard ratio; NMA = network meta-analysis; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; Td = thalidomide and dexamethasone; TTTD = time-to-treatment discontinuation; Vd = bortezomib and dexamethasone; VTD = bortezomib, thalidomide, and dexamethasone

8.3.1.5 Third-line treatment duration

A median treatment discontinuation of 12.5 months was used for all third-line treatment options, based on the study Richardson et al. (2016) [127]. The TTTD curves are Exponential (i.e., with a constant rate of treatment discontinuation).

In the model, patients accrue treatment-related costs only while they are receiving treatment. In addition, being off treatment does not mean that patients switch to subsequent therapies; treatment switch happens only when progression occurs. However, the model does not model the switch from third- to fourth-line treatment or beyond.

Once patients receive third-line treatment, they stay on treatment based on the median treatment duration of nine months, after which they continue to accrue non-treatment-related costs (e.g., monitoring) until they die, or the end of the model time horizon is reached.

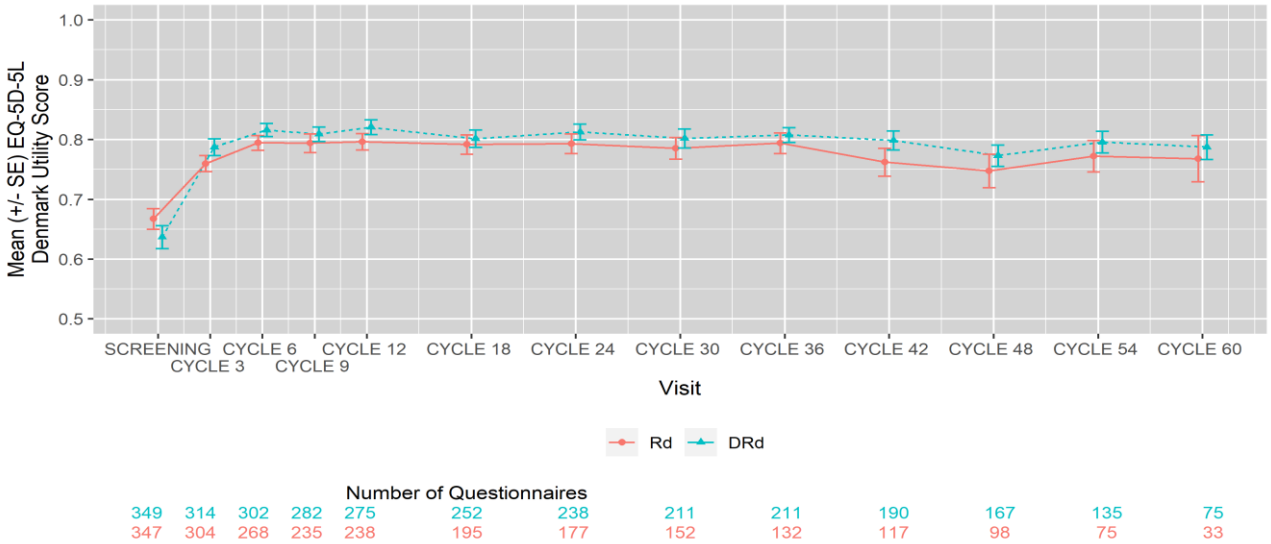
8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

HRQoL for modelled health states was based on the EuroQoL Five-Dimension Five-Level (EQ-5D-5L) data from the MAIA trial. Refer to Appendix I – Mapping of HRQoL data for the full results of the utility data analysis. The literature search did not result in findings that could be used in the comparative analysis. Refer to Appendix H – Literature search for HRQoL data for detailed finding from the literature search.

Utility data (EQ-5D-5L) from the MAIA trial collected prior to progression and at the end-of-treatment (EOT) assessment visit were included in this analysis. One record per patient per visit was created, with observed change from baseline in utility values and time-dependent predictor, such as progression. Time-dependent indicators were derived to reflect the status at each visit (Figure 31).

Figure 31. EQ-5D-5L Utility Score Over Scheduled Visits



Abbreviations: Dara+Rd = daratumumab, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone; SE = standard error

A repeated measures mixed-effect model with a random intercept and slope (i.e., time since randomisation) was fitted to assess the change from baseline in utilities as a function of time since randomisation and progression by including them as time-dependent predictors. Covariance structures, including autoregressive, compound symmetric, Toeplitz, and one unspecified, were tested, and the covariance structure with the lowest AIC/BIC was used for the analyses. If subjects were missing an EQ-5D score at any timepoint in the study, the missing value was removed from the analyses. No imputation was performed for missing utility data.

In this analysis, change in utility values in the post-progression phase was defined relative to the EOT visit (i.e., EOT utility was defined as a baseline utility for the post-progression utility model). One record per patient per visit was created, with observed change from baseline (i.e., EOT visit) in utility values and a time-dependent predictor for on/off subsequent treatment (yes/no). A time-dependent indicator of on/off visit was derived to reflect the status at each visit.

Table 37. Overview of the HSUV measured during clinical trials forming the basis for the relative efficacy

Health state	Estimate	SE	95% CI (mean +/- 1.96 x SE)	Source	Tariff
Pre-progression	0.785	0.007	0.771-0.799	EQ-5D-5L, MAIA trial	Danish EQ-5D-5L utility weights [147]
Post-progression	0.712	0.017	0.679-0.745		

Abbreviations: SE = Standard Error; CI = Confidence Interval; EQ-5D-5L = EuroQoL Five-Dimension Five-Level.

8.4.2 Health state utility values used in the health economic model

Utility values were applied to progression-free and post-progression health states in the model to capture the quality of life associated with treatment and disease outcomes. The utility values were derived from an analysis of EuroQoL Five-Dimension Five-Level (EQ-5D-5L) data from the MAIA trial. The analysis was conducted using the Danish EQ-5D-5L

utility value set [147]. The mean and standard error of the utility pre-progression and post-progression states are shown above in Table 37.The state utilities applied in the model were age-adjusted according to the methodology prescribed by the DMC in section 7.3 of the guideline [148]. Since the mean starting age of the cohort at baseline is 74.1 years, this adjustment has a very minor impact on the results of the analysis.

Adverse event disutility data inputs were obtained from the NICE technology appraisal (TA) 510 for daratumumab monotherapy for treatment of relapsed and refractory multiple myeloma [149], which were based values identified in the literature, including previous HTA submissions. In NICE TA 510, as study by Brown et al., which evaluated lenalidomide plus dexamethasone compared with dexamethasone alone in rrMM reported associated AE disutilities [150]. This was used as the primary source of AE disutilities in the base-case analysis as it provided a degree of internal consistency between the AE disutility values. In an effort to maintain consistency, where disutilities were not reported by Brown et al., values were sought from the NICE technology appraisal for lenalidomide treatment for MM patients who have received at least one prior therapy with bortezomib (TA171) [152], which drew upon the same trial data. Not all utility decrements were available from either source, and therefore the literature was assessed, identifying Lloyd et al. [151]. In support of the NICE TA 510 submission, clinical opinion was also sought for disutilities which were not reported in the literature and to validate those that were. Where the utility duration was not reported, a duration of one month (28 days) was assumed for each AE disutility. The disutility and duration were used to estimate the utility decrement over one year, and this QALY decrement was applied in the first model cycle only. Table 38 shows the disutility and duration associated with each AE included in the model. Standard errors and confidence intervals were not available for the adverse events. The model considers uncertainty of adverse events disutilities by assuming a standard error = 10% of the absolute value and drawing samples from the normal distributions around the mean. An internal Janssen clinical expert with experience in MM in Denmark also validated these inputs.

Table 38. AE duration and disutility

Adverse event	Disutility	Duration (Days)	Source
Anaemia	-0.310	180.0	Brown 2013 Partial review T171 [150]
Asthenia	-0.115	14.6	A conservative assumption
Cataract	-0.070	28.0	Lloyd 2006 [151]
Diarrhoea	-0.103	12.0	Lloyd 2006 [151]
Fatigue	-0.115	14.6	A conservative assumption
Hyperglycaemia	0.000	14.7	(Partial Review TA171) [152]
Hypokalaemia	-0.065	11.4	(Partial Review TA171) [152]
Leukocytopenia	-0.065	14.7	(Partial Review TA171) [152]
Lymphopenia	-0.065	15.5	Brown 2013 Partial review T171 [150]
Neutropenia	-0.145	7.0	Brown 2013 Partial review T171 [150]
Pneumonia	-0.190	7.0	Brown 2013 Partial review T171 [150]
Thrombocytopenia	-0.310	7.0	A conservative assumption
Hypertension	-0.065	11.4	A conservative assumption
Pulmonary embolism	-0.310	7.0	Brown 2013 Partial review T171 [150]

8.5 Resource use and costs

Disease- and treatment-related costs are applied to each health state and event in the model. Cost categories include drug acquisition and administration applied for the duration of active treatment (determined by dosing regimen and treatment duration); costs of routine follow-up care, cost AEs, patient costs, and transportation costs.

8.5.1 Drug acquisition costs

Drug acquisition cost for the treatment options included in the model, including first-, second-, and third-line treatments are shown in Table 39. The model utilizes daratumumab subcutaneous formulation across the daratumumab indications, since this what is used in Danish clinical practice. In line with the DMC guidelines, all drug costs used are pharmaceutical purchasing prices (AIP) and sourced from Medicinpriser.dk [90].

Table 39. Drug acquisition costs

Treatment	Units per Pack	Strength (mg)	Price per Pack (DKK)	Pack (number)
Daratumumab	1	1,800.0	38,901	Darzalex (185054)
Carfilzomib	1	60.0	8,229	Kyprolis (534401)
Carfilzomib	1	30.0	4,115	Kyprolis (090435)
Carfilzomib	1	10.0	1,372	Kyprolis (542915)
Elotuzumab	1	400.0	9,239	Empliciti (187742)
Elotuzumab	1	300.0	6,929	Empliciti (572429)
Ixazomib	3	4.0	48,000	Ninlaro (479991)
Ixazomib	3	3.0	48,000	Ninlaro (086649)
Ixazomib	3	2.3	48,000	Ninlaro (590825)
Bortezomib	1	3.5	1,940	Bortezomib "Stada" (179371)
Lenalidomide	21	25.0	38,829	Revlimid (096515)
Lenalidomide	21	10.0	33,636	Revlimid (096497)
Melphalan	25	2.0	305	Melphalan (396938)
Cyclophosphamide	1	500.0	224	Sendoxan (020307)
Dexamethasone	20	4.0	127	Dexametason "Abcur" (188988)
Dexamethasone	100	4.0	322	Dexamethason "2care4" (112198)
Dexamethasone	20	1.0	196	Dexametason "Abcur" (039413)
Dexamethasone	100	1.0	720	Dexametason "Abcur" (126955)
Thalidomide	28	50.0	2,239	Thalidomide "Celgene" (025917)
Prednisone	100	5.0	93	Prednison "DAK" (057675)
Prednisone	100	25.0	296	Prednison "DAK" (566088)
Panobinostat	6	20.0	29,725	Farydak (480761)
Panobinostat	6	15.0	29,725	Farydak (450215)
Panobinostat	6	10.0	29,725	Farydak (171592)
Pomalidomide	21	4.0	55,581	Imnovid (461441)
Pomalidomide	21	3.0	54,748	Imnovid (554720)
Pomalidomide	21	2.0	53,914	Imnovid (455325)

Treatment	Units per Pack	Strength (mg)	Price per Pack (DKK)	Pack (number)
Pomalidomide	21	1.0	53,080	Imnovid (576123)

Source: Medicinpriser.dk [90], Accessed 07-02-2022, All prices DKK AIP (Pharmacy Purchasing Price).
Abbreviations: mg = milligram; DKK = Danish Kroner

Dosing regimens for the front-line comparators included in the model are shown in Table 40. Dosing is based on the respective clinical trials, SmPCs and Danish clinical guidelines [148].

Table 40. Treatment dosing regimens (first-line)

Treatment Regimens		Dose/Admin	Admin/Cycle	Cycle Length (days)	Relative Dose Intensity	Source
Dara+Rd						
Daratumumab	Cycles 1–2	1800 mg	4	28	90.74%	MAIA study; MMY3008* [19]
	Cycles 3–6	1800 mg	2	28	99.40%	
	Cycles 7+	1800 mg	1	28	99.67%	
Lenalidomide	All cycles	25 mg	21	28	71.51%	
Dexamethasone	All cycles	40 mg	4	28	76.83%	
Rd						
Lenalidomide	All cycles	25 mg	21	28	82.46%	MAIA study; MMY3008* [19]
Dexamethasone	All cycles	40 mg	4	28	81.31%	
Dara+VMP						
Daratumumab	Cycle 1	1800 mg	6	42	90.45%	ALCYONE study; MMY3007† [153]
	Cycles 2–9	1800 mg	2	42	97.49%	
	Cycles 10+	1800 mg	1	28	99.59%	
Bortezomib	Cycle 1	1.3 mg/m^2	8	42	91.52%	
	Cycles 2–9	1.3 mg/m^2	4	42	87.83%	
Melphalan	Cycles 1–9	9 mg/m^2	4	42	92.96%	
Prednisone	Cycles 1–9	60 mg/m^2	4	42	97.40%	
VMP						
Bortezomib	Cycle 1	1.3 mg/m^2	4	35	93.50%	ALCYONE study; MMY3007† [153];
	Cycles 2–9	1.3 mg/m^2	4	35	86.35%	
Melphalan	Cycles 1–9	9 mg/m^2	4	35	92.88%	
Prednisone	Cycles 1–9	100 mg	4	35	97.05%	
VRd						
Bortezomib	Cycles 1–8	1.3 mg/m^2	4	21	88.31%[5]	SWOG S0777 study; [131]
Lenalidomide	Cycles 1–8	25 mg	4	21	82.46%[2]	
Lenalidomide	Cycles 9+	25 mg	14	21	82.46%[2]	
Dexamethasone	Cycles 1–8	20 mg	8	21	81.31%[3]	
Dexamethasone	Cycles 9+	40 mg	4	28	81.31%[3]	

* Clinical cut-off date of 24 September 2019; median follow-up 28 months; † Clinical cut-off date of 12 June 2018; median follow-up 27.5 months; [2]Assumed the same as Lenalidomide in Rd; [3]Assumed the same as dexamethasone in Dara+Rd, [5] Assumed the same as Velcade in Dara+VMP; Abbreviations: Dara+Rd = daratumumab, lenalidomide, dexamethasone; Dara+VMP = daratumumab,

bortezomib, melphalan, prednisone; Rd = lenalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VMP = bortezomib, melphalan, prednisone

8.5.1.1 Drug wastage and dose intensity

For treatments that are dependent on weight or body surface area (BSA), there is the potential that some of the drug will be wasted if perfect vial sharing is not practiced. When vial sharing is used, the model calculates the exact dose needed for the patients, depending on their weight or BSA, and multiplies it by the per milligram cost of the drug.

A mean weight of 74.5 kg and BSA of 1.85 m2 (obtained from the baseline characteristics of patients in the MAIA clinical study) was utilised for therapies that depend on patient weight and BSA [19].

The model is flexible regarding whether to consider wastage. The reference scenario considers wastage (i.e., vial sharing is not allowed), and, therefore, the dosing consumption per administration is rounded up to the closest integer number of vials.

As in the real world, patients in clinical trials do not always receive the full doses of their assigned treatments. Data from clinical trials, therefore, may best reflect the efficacy of the received dose rather than the intended dose. To account for this, dose intensity is considered in the model. This enables the possibility of using a lower number of vials/capsules for certain drug regimens where prescribed dosing intensity was less than 100% and is used to adjust the drug cost in proportion to the doses received in the trial – separately from considering wastage.

The model considers dose intensity and treatment discontinuation in the drug cost calculation. Treatment discontinuation accounts for discontinuation due to progression, AEs, maximum treatment duration, or other non-clinical reasons. Patients' exposure to the regimen during the on-treatment period is reflected via relative dose intensity. Relative dose intensity is calculated as the average of doses per treatment cycle received, divided by doses per cycle, according to the trial design. Applying both factors in the calculation of drug cost ensures that the drug exposure is consistent with the efficacy data from the MAIA trial.

The model is flexible regarding whether to consider dose intensity. In the reference scenario, dose intensity is considered for all treatments. While dosing intensity for daratumumab from the MAIA study [19] was based on IV-treatment, SC treatment is considered in the model for daratumumab, which uses the full 1800mg vial. Dose intensity has no effect on costs of daratumumab for the Dara+Rd treatment arm in these analyses.

Dose intensity was considered separately for each component of each combination treatment (Table 40). For the components of Dara+Rd, Dara+VMP, Rd, and VMP the dose intensity was available from the MAIA and ALCYONE CSRs, cut-off date of July 2019 and 19 February 2021, respectively. For VRd which dose intensity data were not available from trial publications, the same dose intensities were assumed as for the components of Dara+Rd, Dara+VMP, Rd, and VMP (Table 40). Dose intensity is also applicable for subsequent treatment lines (see Appendix L – Dosing schedules of subsequent treatments).

8.5.2 Drug administration costs

Administration of intravenous (IV) and subcutaneous (SC) treatments within oncology requires administration in a hospital setting in Denmark. Consequently, the resource use for administration of IV and SC treatments have been in included in this analysis. No resource use is assumed for treatments administered PO. In line with the DMC guidance,

DRG 2022 cost have been used to estimate the unit costs per administration mode. The same DRG code was applied by the DRG grouper, and consequently, the same unit cost has been applied for both IV and SC. Given that IV is generally a more invasive administration form than SC this approach may be conservative in favour of IV treatment combination containing IV formulations.

The cost by mode of administration is shown in Table 41.

Table 41. Drug administration costs

Mode of Administration	Unit Cost (DKK)	Reference
IV	3,225	DRG 2022, 17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC900: Myelomatose Procedure: BWAA62 Medicingivning ved intravenøs infusion
SC	3,225	DRG 2022, 17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC900: Myelomatose Procedure: BWAA62 Medicingivning ved injektion
Oral Initiation	0	Assumed to be included in regular follow-up visits

Source: Sundhedsdatastyrelsen 2022 [154] Abbreviations: IV = intravenous; SC = subcutaneous

8.5.2.1 Concomitant medications

Co-medication drug costs are calculated separately from the drug acquisition and administration cost for each treatment regimen. The drug costs of concomitant medications included in the model are shown in Table 42. Concomitant medication costs are calculated according to the percentage of patients on front-line treatment who receive each of the co-medications specified in Table 43. The distribution is based on the respective SmPCs and validated by an internal Janssen Danish clinical expert within MM.

Table 42. Concomitant medication drug costs (DKK)

	Drug Units per Pack	Strength (mg)	Price per Pack (AIP)	Dosage per admin (mg)	Cost per admin	Pack (number)
Corticosteroid	1	125	64	100.0	51	Solu-medrol (397856)
Antipyretic	300	500	25	825.0	0	Paracetamol "Orifarm" (064318)
Antihistamines	100	25	139	25.0	1	Phenergan (166611)
Antithrombotic	100	75	12	300.0	0	Acetylsalicylsyre (199371)
Bisphosphonates	1	4	70	4.0	70	Zoledronsyre "Fresenius Kabi"
Antiviral	35	800	44	800.0	1	Aciclovir "1A Farma" (445715)

Source: Medicinpriser.dk [90], Accessed 07-02-2022, All prices DKK AIP (Pharmacy Purchasing Price).
Abbreviations: mg = milligram; DKK = Danish Kroner

Table 43. Percentage of patients receiving concomitant medications

	Dara+Rd	Rd	Dara+VMP	VRd	VMP	Reference
Corticosteroid	100%	0%	100%	0%	0%	SmPCs and opinon by an internal Janssen Danish clinical expert within MM
Antipyretic	100%	0%	100%	0%	0%	
Antihistamines	100%	0%	100%	0%	0%	
Antithrombotic	100%	100%	0%	100%	0%	

	Dara+Rd	Rd	Dara+VMP	VRd	VMP	Reference
Bisphosphonates	100%	100%	100%	100%	100%	
Antiviral	0%	0%	100%	100%	100%	

8.5.3 Monitoring and disease management costs

Routine follow-up care costs were accrued in each health state (i.e., pre- and post-progression) separately in the model. The types and frequencies of healthcare resource and laboratory tests included were based on those used in the NICE assessment for first-line treatment of MM (NICE TA228: bortezomib and thalidomide, [155]). The types of tests and frequency was subsequently validated with an internal Janssen Danish clinical expert within MM.

In the reference scenario, the routine monitoring frequency and use is assumed to be the same for Dara+Rd and all comparators (Table 44).

Table 44. Frequency of medical resource use (every 4 weeks)

IItem	Pre-progression		Post-progression: On subsequent treatment		Post-progression: Off subsequent treatment	
	Freq	% Pts	Freq	% Pts	Freq	% Pts
Haematologist visit (30 min)	0.58	100.00%	0.53	96.54%	0.19	85.00%
Liver function test	0.12	27.50%	0.12	27.50%	0.12	22.50%
Complete blood count test	0.40	100.00%	0.53	100.00%	0.46	88.75%
Chest radiograph + Bone radiograph	0.17	7.50%	0.18	7.50%	0.17	1.25%
Neurological examination + examination for neuropathy	0.00	0.00%	0.05	9.62%	0.00	0.00%
Proteinuria + Urinary protein electrophoresis	0.19	77.50%	0.21	77.50%	0.19	52.50%
Cardiac imaging	0.00	0.00%	0.01	2.31%	0.00	0.00%
Blood chemistry/electrolytes test	0.17	75.00%	0.28	77.31%	0.17	63.75%
C reactive protein	0.06	100.00%	0.06	20.00%	0.06	20.00%
Total protein + Electrophoresis serum protein	0.19	100.00%	0.21	96.54%	0.19	72.50%
Spine or pelvic MRI+ Spine CT	0.12	5.00%	0.12	5.00%	0.12	0.00%
Calcium	0.23	100.00%	0.34	100.00%	0.29	88.75%
ECG	0.00	0.00%	0.01	2.31%	0.00	0.00%
Creatinine	0.40	100.00%	0.53	100.00%	0.46	88.75%
Total cycle cost (DKK)	201.39		202.42		83.10	
Reference	Danish clinical expert opinion*		NICE TA228; [155]		NICE TA228; [155]	

Abbreviations: CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

* Validated by an internal Janssen Danish clinical expert within MM, based on a prior physician survey considering daratumumab in relapsed/refractory MM (one prior line data (1PL)

Table 45 shows the unit costs for the routine follow-up monitoring and laboratory tests.

Table 45. Unit costs of routine monitoring and laboratory tests

Item	Unit cost (DKK)	Reference
Hematologist visit (30 min)	1066	Værdisætning af enhedsomkostninger, version 1.6; https://www.krl.dk/sirka/sirkaApi/tableApi; Lønniveau 2022 Assumed as Overlæger, lægelie chefer m.v.: Montly income = 99637 DKK * 12 months = 1195644 DKK per year. Annual hours = 1122. Hourly income = 1066 DKK. Half hour visit = 533 DKK. Assumed x2 to account for overheads/capital.
Liver function test	108	"LMV 2022"- Albumin;Plv, Alanintransaminase [ALAT];P, Bilirubiner;P, Bilirubin konjugeret;P, Aspartattransaminase [ASAT];P, Protein;P. (NPU19674, NPU19651, NPU01370, NPU17194, NPU19654, NPU03278)
Complete blood count test	300	"LMV 2022"- Hæmoglobin;B, Erytrocytter, vol.fr.;B, Leukocytter;B, C-reaktivt protein [CRP];P, Albumin;Plv, Urat;P, Methæmoglobin;Hb(B), Trombocytter;B, Reticulocytter;B, Kreatinin;P. (NPU02319, NPU01961, NPU02593, NPU19748, NPU19674, NPU03688, NPU02725, NPU03568, NPU08694, NPU04998)
Chest radiograph + Bone radiograph	1,640	DRG 2022, 30PR18, Diagnosis: DC900: Myelomatose Procedure: UXRC10 Røntgenundersøgelse af thorax, inkl. specialprojektion
Neurological examination + examination for neuropathy	3,225	DRG 2022, 17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC900: Myelomatose Procedure: ZZ0149AI Neurologisk undersøgelse
Proteinuria + Urinary protein electrophoresis	16	"LMV 2022"- Albumin;U, (NPU19677)
Cardiac imaging	2,411	DRG 2022, 30PR06, Diagnosis: DC900: Myelomatose Procedure: UXCC00A CT-skanning af hjertet
Blood chemistry/electrolytes test	129	"LMV 2022"- Klorid;P, Kalium;P, Natrium;P,.(NPU01536, NPU03230, NPU03429)
C-reactive protein	16	"LMV 2022"- C-reaktivt protein [CRP];P (NPU19748)
Total protein + Electrophoresis serum protein	16	"LMV 2022"- Albumin;P,.(NPU19673)
Spine or pelvic MRI+ Spine CT	1,979	DRG 2022, 30PR07, Diagnosis: DC900: Myelomatose Procedure: UXCE10 CT-skanning af columna cervicalis
Calcium	16	"LMV 2022"- Calcium;P (NPU01443)
ECG	3,225	DRG 2022, 17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DC900: Myelomatose Procedure: ZZ3925 EKG
Creatinine	16	"LMV 2022"- Kreatinin;U,.(NPU09102)

Abbreviations: CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging

8.5.4 AE management costs

The AEs included in the economic model are previously described in section 8.2.2.5. The unit costs related to the management of AE events were derived from the Danish DRG tariff list using the DRG grouper 'Interaktiv DRG' [154]. AE costs used in the base-case analysis are summarized in Table 46.

Table 46. Adverse events and associated costs

Adverse Event	Cost (DKK)	Reference
Anaemia	3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel
Asthenia	4,460	DRG 2022, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Asteni
Cataract	1,095	DRG 2022, 02MA01 Øvrige indlæggelser eller besøg ved øjensygdomme, Diagnosis: DH263 Grå stær forårsaget af lægemiddel
Diarrhea	6,756	DRG 2022, 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B Ikke-infektiøs diaré UNS
Fatigue	4,460	DRG 2022, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Hyperglycaemia	4,460	DRG 2022, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR739 Hyperglykæmi UNS
Hypokalaemia	1,954	DRG 2022, 10MA98 MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE875 Hyperkaliæmi
Leukocytopenia	3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Leukocytopeni
Lymphopenia	3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728D: Lymfopeni
Neutropenia	3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS
Pneumonia	2,180	DRG 2022, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DJ189: Pneumoni UNS
Thrombocytopenia	3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD696: Trombocytopeni UNS
Hypertension	1,318	DRG 2022, 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension
Pulmonary embolism	2,180	DRG 2022, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI269A Lungeemboli UNS

8.5.5 Patient and transportation cost

Patient costs and transportation costs are included in the model in line with the DMC method guidelines [148]. The unit cost per patient hour is assumed to be DKK 181 and the transportation cost per visit was assumed to be DKK 140 in line with the DMC guidelines [148] (see Table 47). Patient and transportation costs were applied at every visit to the hospital according to the dosing schedule of each individual treatment regimen. 15 minutes of administrations time was assumed for SC treatments and 30 minutes, where two SC treatments were administered at the same visit (e.g., daratumumab and bortezomib). 30 minutes of waiting time was assumed for each hospital visit. The cost patient- and transportation costs per visit for each treatment regimen are illustrated in Table 48.

Table 47. Unit cost for estimation of patient cost and transportation cost

Resource	Unit cost (DKK)	Reference
Average hourly wage	181.00	Medicinrådet - "Værdisætning af enhedsomkostninger v.1.6" [156]
Transportation cost per visit	140.00	Medicinrådet - "Værdisætning af enhedsomkostninger v.1.6" [156]

Table 48. Patient- and transportation costs per administration

Treatment	Drug	Waiting time (min)	Waiting time cost (DKK)	Transporation costs (DKK)	Admin minutes	Admin costs (DKK)	Total costs (DKK)
Dara+VMP	Dara	30.00	90.50	140.00	15	45.25	275.75
	V	30.00	90.50	140.00	15	45.25	275.75
	M		0.00	0.00	0	0.00	0.00
	P		0.00	0.00	0	0.00	0.00
	Dara+V	30.00	90.50	140.00	30	90.50	321.00
VMP	V	30.00	90.50	140.00	15	45.25	275.75
	M		0.00	0.00	0	0.00	0.00
	P		0.00	0.00	0	0.00	0.00
Dara+Rd	Dara	30.00	90.50	140.00	15	45.25	275.75
	R		0.00	0.00	0	0.00	0.00
	d		0.00	0.00	0	0.00	0.00
Rd	R		0.00	0.00	0	0.00	0.00
	d		0.00	0.00	0	0.00	0.00
VRd	V	30.00	90.50	140.00	15	45.25	275.75
	R		0.00	0.00	0	0.00	0.00
	d		0.00	0.00	0	0.00	0.00

Abbreviations: Dara+Rd = daratumumab, lenalidomide, dexamethasone; Dara+VMP = daratumumab, bortezomib, melphalan, prednisone; Rd = lenalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VMP = bortezomib, melphalan, prednisone

8.5.6 Subsequent treatment costs

Drug costs for second- and third-line treatment after progression are included in the model as this reflect the treatment approach in the clinical trials (determining OS in the trials) and because this aligns with the clinical pathway in Denmark. Hence, to provide meaningful results relevant for decision making, subsequent treatments must be included in the analysis.

These post-progression costs are a combination of drug costs (Table 39), administration costs (Table 41), and the monitoring costs (Table 44 and Table 45), which were assumed to be the same regardless of prior treatment. Wastage and dose intensity consideration for subsequent treatments are consistent with those selected by the user for front-line treatments. In the reference scenarios, wastage (i.e., no vial sharing) and dose intensity are considered.

Dose intensity was considered separately for each component of each combination treatment. Dose intensity for Dara+Rd and Dara+Vd was available from the MMY3003/MMY3004 (ASCO 2017 update), respectively. Dose intensity for daratumumab monotherapy was available from the integrated analysis of MMY2002/GEN501 (cut-off date of 31 December 2015) [157]. For other front-line comparator therapies for which dose intensity data were not available from trial publications, the same dose intensities were assumed as for the components of Dara+Rd for lenalidomide-containing regimens, or as for the components of Dara+Vd for bortezomib-containing regimens.

The dosing schedules for subsequent treatments are shown in Appendix L – Dosing schedules of subsequent treatments.

8.5.6.1 Second-line treatment costs

After patients progress from any first-line treatment, a proportion of patients will receive second-line treatment. In the reference scenario, it is assumed that 67% of patients progressing from first-line treatment would receive second-line treatment, regardless of their first-line treatment. Table 49 illustrates how patients are distributed among the second-line treatment options. The proportion of patients receiving subsequent treatment and the treatment mix in second-line has been validated by an internal Janssen Danish clinical expert within MM.

Table 49. Second-line treatment distributions based on first-line treatment received

	First-line Treatment				
Second-line Treatment	**Dara+Rd**	**Rd**	**Dara+VMP**	**VRd**	**VMP**
Dara+Rd	0%	0%	0%	40%	80%
Dara+Vd	0%	80%	0%	0%	0%
Carfilzomib+d	20%	0%	0%	40%	0%
Carfilzomib+Rd	10%	0%	70%	0%	10%
CVD	0%	0%	0%	0%	0%
Elotuzumab+Rd	0%	0%	15%	0%	0%
Elotuzumab+Vd	0%	0%	0%	0%	0%
Ixazomib+Rd	0%	0%	0%	0%	0%
Panobinostat+Vd	0%	0%	0%	0%	0%
Pomalidomide+d	0%	0%	0%	20%	0%
Rd	0%	0%	15%	0%	10%
Td	0%	0%	0%	0%	0%
Vd	0%	0%	0%	0%	0%
VTd	0%	0%	0%	0%	0%
VRd	10%	0%	0%	0%	0%
Pomalidomide+Vd	60%	20%	0%	0%	0%
Total	**100%**	**100%**	**100%**	**100%**	**100%**
Reference	An internal Janssen Danish clinical expert				

Abbreviations: Dara+Rd = daratumumab, lenalidomide, dexamethasone; Dara+VMP = daratumumab, bortezomib, melphalan, prednisone; Rd = lenalidomide, dexamethasone; Vd = bortezomib, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VMP = bortezomib, melphalan, prednisone

8.5.6.2 Third-line treatment costs

After patients progress from any second-line treatment, a proportion of patients will receive second-line treatment. In the reference scenario, it is assumed that 37% of patients progressing from first-line treatment would receive second-line treatment, regardless of their first-line treatment. This assumption reflects the severity of disease, and the expectation that fewer patients would be healthy enough to move to third-line treatment than from first line to second line. Table 50 illustrates how patients are distributed among the third-line treatment options. The proportion of patients receiving subsequent treatment and the treatment mix in third-line has been validated by an internal Janssen Danish clinical expert within MM.

Table 50. Third-line treatment distribution based on first-line treatment received

	First-line Treatment				
Third-line Treatment	**Dara+Rd**	**Rd**	**Dara+VMP**	**VRd**	**VMP**
Dara	0%	0%	0%	0%	0%
Dara+Rd	0%	0%	0%	20%	0%
Dara+Vd	0%	0%	0%	20%	0%
Carfilzomib+d	60%	10%	30%	20%	0%
Carfilzomib+Rd	0%	0%	0%	10%	0%
CVD	0%	10%	0%	0%	0%
Elotuzumab+Rd	0%	0%	0%	0%	0%
Elotuzumab+Vd	0%	0%	0%	0%	0%
Ixazomib+Rd	0%	0%	0%	0%	0%
Panobinostat+Vd	0%	0%	0%	0%	50%
Pomalidomide+d	0%	80%	40%	30%	50%
Rd	0%	0%	0%	0%	0%
Td	0%	0%	0%	0%	0%
Vd	0%	0%	0%	0%	0%
VTd	0%	0%	0%	0%	0%
Pomalidomide+vd	40%	0%	30%	0%	0%
Total	**100%**	**100%**	**100%**	**100%**	**100%**
Reference	An internal Janssen Danish clinical expert				

Abbreviations: Dara+Rd = daratumumab, lenalidomide, dexamethasone; Dara+VMP = daratumumab, bortezomib, melphalan, prednisone; Rd = lenalidomide, dexamethasone; Vd = bortezomib, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VMP = bortezomib, melphalan, prednisone

8.6 Results

8.6.1 Base case overview

Table 51. Summary of model base-case and rationale

Category	Base-case analysis		Rationale
Comparators	Rd Dara+VMP VRd VMP		Reflect the treatment regimens primarily used in Denmark for patients NDMM who are ineligible for ASCT
Type of model	Partitioned Survival		Reflects the three most relevant disease health states which capture the clinical events experienced by patients with NDMM who are ineligible for ASCT. The structure is the most widely used within MM and oncology modelling and has been used in several previous DMC assessments within MM
Time horizon	30 years (life time)		The time horizon was considered sufficient to capture all costs and benefits over the lifetime of the modelled population
Perspective	Restricted Societal		In line with the DMC guidance
Discount rates	Cost and Health benefits: 3.5%		In line with the DMC guidance
Mean age, mean BSA, mean weight	Mean age: 74.1; mean BSA: 1.85m^2; mean weight: 74.5kg		Reflects the patients in the MAIA trial. These numbers are similar to the numbers expected for Danish patients
Parametric function for PFS (pre-progression)	Dara+Rd	Exponential function (individual curve) based on IPD from the MAIA trial	Statistically and clinically plausible extrapolation curve for both Dara+Rd and Rd. Most conservative projections for Dara+Rd and middle-of-range for Rd. Reflect the patients in the MAIA trial most accurately as this relies on IPD
	Rd	Exponential function (individual curve) based on IPD from the MAIA trial	Statistically and clinically plausible extrapolation curve for both Dara+Rd and Rd. Most conservative projections for Dara+Rd and middle-of-range for Rd. Reflect the patients in the MAIA trial most accurately as this relies on IPD
	Dara+VMP, VRd, VMP	HR vs. Rd PFS curve (output from the NMA)	Summary data (HRs) only available for comparators outside of the MAIA trial. Most common approach for modelling indirect efficacy based on summary data
Parametric function for OS	Dara+Rd	Gompertz function (individual curve) based on IPD from the MAIA trial	Statistically and clinically plausible extrapolation curve for both Dara+Rd and Rd. Aligns with RWE data estimates. Reflect the patients in the MAIA trial most accurately as this relies on IPD
	Rd	Gompertz function (individual curve) based on IPD from the MAIA trial	Statistically and clinically plausible extrapolation curve for both Dara+Rd and Rd. Aligns with RWE data estimates. Reflect the patients in the MAIA trial most accurately as this relies on IPD
	Dara+VMP, VRd, VMP	HR vs. Rd OS curve (output from the NMA [20])	Summary data (HRs) only available for comparators outside of the MAIA trial. Most

Category	Base-case analysis		Rationale
			common approach for modelling indirect efficacy based on summary data
Parametric function for TTTD	Dara+Rd	Exponential function (individual curve) based on IPD from the MAIA trial	Reflect the actual treatment duration of patients in the MAIA trial. Statistically and clinically plausible extrapolation curve for both Dara+Rd and Rd. Same hazard assumptions as the PFS curves
	Rd	Exponential function (individual curve) based on IPD from the MAIA trial	Reflect the actual treatment duration of patients in the MAIA trial. Statistically and clinically plausible extrapolation curve for both Dara+Rd and Rd. Same hazard assumptions as the PFS curves
	Dara+VMP, VRd, VMP	Treatment until progression	Only PFS data available for the comparators outside of the MAIA trial. Treatment until progression aligns with the clinical practice in Denmark
Second-line treatment costs (post-progression)	Included, treatment until progression (individually per subsequent treatment). TTTD curves are Exponential (i.e., with a constant rate of treatment discontinuation)		In line with Danish clinical practice for second-line treatments. Most widely used approach to model subsequent treatment durations. Only the Exponential curve is possible to generate with only one observation (median PFS).
Third-line treatment costs (post-progression)	Median treatment duration assumed equal to PFS under treatment with PanBorDex following at least two previous treatment lines reported by Richardson et al (2016) [127] (assumed similar for all third-line treatments). TTTD curves are Exponential (i.e., with a constant rate of treatment discontinuation		Third-line treatment efficacy relies on the sequence of prior treatments. Data is not available for the included treatments conditioned on specific prior regimens. With the objective of model parsimony the same treatment duration was assumed for all third line treatments. Only the Exponential curve is possible to generate with only one observation (median PFS)
Source of utilities	EQ-5D-5L from MAIA. Danish population weights were used to estimate health-state utility values		Data specific to the efficacy data and patients in the MAIA trial
HRQoL	Quality of life is captured using health-state based utilities		Most widely used method in economic modelling. EQ-5D-5L data from MAIA did show numerical utility improvements for Dara+Rd vs. Rd for PFS and OS. However, these were not significant, so the same utility was applied for all included therapies
HRQoL	AE specific disutilities applied		AE specific disutilies were applied to capture the impact of differences in AE events between the included therapies. Although this will potentially double count AE disutilities within the MAIA trial, this more appropriately captures the AE impact on utility for the comparators outside of the MAIA trial.
Adverse events	Grade 3+ TRAEs		Only severe AEs are considered to impact utility and costs
Included costs	Drug acquisition costs Administration costs Concomitant medication costs Routine monitoring costs Costs of adverse events Patient- and transportation costs		In line with the DMC guidance

Category	Base-case analysis		Rationale
Dosage of pharmaceutical	See drug dosing schedule in section 8.5		In line with the SmPC and expected use in Danish clinical practice
Drug wastage	Included		Reflects Danish clinical practice
Relative dose intensity	Dara+Rd	Based on the MAIA trial	Reflect the actual dosing from the trial and not intended dosing
	Rd	Based on the MAIA trial	
	Dara+VMP	Based on the ALCYONE trial	
	VMP	Based on the ALCYONE trial	
	VRd	Based on the SWOG S0777 trial	

Abbreviations: AE = Adverse Event; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; TTTD = time to treatment discontinuation; HRQoL = Health-related Quality of Life; Dara+Rd = daratumumab, lenalidomide, dexamethasone; Dara+VMP = daratumumab, bortezomib, melphalan, prednisone; Rd = lenalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VMP = bortezomib, melphalan, prednisone

8.6.2 Base case results

Table 52 shows the results for the base case analysis. Patients on Dara+Rd had improved survival compared with all the other treatments and spent more time progression-free. Consequently, Dara+Rd was associated with the highest LYs and QALYs. In the base case, Dara+Rd was associated with higher costs than all the other comparators over the patient's lifetime, however the recent introduction of generic lenalidomide will significantly impact these conclusions since these prices are expected to be significantly lower than the current list price. The impact of this introduction will be most significant versus the treatment arms not containing lenalidomide, however this will also generally reduce the incremental costs of Dara+Rd since the average treatment duration of lenalidomide is highest in the Dara+Rd arm.

In second line, savings were expected for Dara+Rd versus the other comparators mainly due to daratumumab will not be used in subsequent lines following initial treatment with daratumumab. Similar costs were estimated for all therapies in third line.

The base case analysis showed that Dara+Rd yielded better survival outcomes and was associated with longer LYs and QALYs vs. other comparators (incremental QALYs for Dara+Rd vs. Rd (+2.14), vs. Dara+VMP (+1.63), vs. VRd (+1.63), and vs. VMP (+2.66).

Based on list prices the ICER for Dara+Rd vs. Rd 1,847,098 DKK/QALY, vs. Dara+VMP 969,505 DKK/QALY, vs. VRd 1,463,974 DKK/QALY, and vs. VMP 1,468,509 DKK/QALY.

Table 52. Base case results

Health outcomes (discounted, per patient)	Dara+Rd	Rd	Dara+VMP	VRd	VMP
Quality life years (QALYs)					
QAPFLYs	4.47	2.69	3.77	3.27	2.06
QAPPLYs	1.34	0.98	0.42	0.92	1.10
Adverse Event	-0.03	-0.04	-0.03	-0.02	-0.03
Total	**5.82**	3.67	**4.19**	4.19	**3.16**
Life years (LYs)					
PFLYs	5.95	3.50	4.95	4.28	2.65
PPLYs	2.06	1.42	0.60	1.34	1.59
Total	**8.01**	4.92	**5.55**	5.62	**4.24**
Costs (discounted, per patient)	**Dara+Rd**	**Rd**	**Dara+VMP**	**VRd**	**VMP**
Pre-Progression					
Drug acquisition	5,214,715	1,290,709	3,273,880	2,322,024	64,183
Drug administration	231,865	-	384,478	99,212	99,951
Concomitant and prophylactic medications	8,771	2,296	10,108	4,178	2,155
Routine monitoring	62,491	36,741	52,058	44,970	27,852
Adverse event management	6,035	4,422	2,615	4,091	2,426
Post-Progression					
Second-line Treatment					
Drug acquisition, administration, on-treatment monitoring	546,164	842,404	809,694	1,235,771	2,065,379
Routine monitoring (off-treatment)	2,377	3,988	2,050	3,323	6,067
Third-line Treatment					
Drug acquisition, administration, on-treatment monitoring	218,201	170,369	179,603	214,023	136,458
Routine monitoring (off-treatment)	6,566	2,184	532	2,489	838
Patient Cost (pre- and post-progression)	25,900	10,553	32,145	13,279	17,899
Total	6,323,086	2,363,664	4,747,164	3,943,360	2,423,209
Incremental results (discounted, per patient)	**Dara+Rd**	**Rd**	**Dara+VMP**	**VRd**	**VMP**
QALYs	-	2.14	1.63	1.63	2.66
QAPFLYs	-	1.78	0.70	1.20	2.42
LYs	-	3.09	2.46	2.39	3.77
Costs	-	3,959,421	1,575,922	2,379,726	3,899,876
Cost per QALY gained	**-**	**1,847,098**	**969,505**	**1,463,974**	**1,468,509**
Cost per QAPFLY gained	-	2,220,476	2,252,858	1,977,689	1,612,939
Cost per LY gained	-	1,281,506	640,673	996,000	1,035,413

Abbreviations: LY = life-years; PFLY = progression-free life-years, PPLY = post-progression life-years QALY = quality-adjusted life years; QAPFLY = quality-adjusted progression-free life-years; QAPPLY = quality-adjusted post-progression life-years.

8.7 Sensitivity analyses

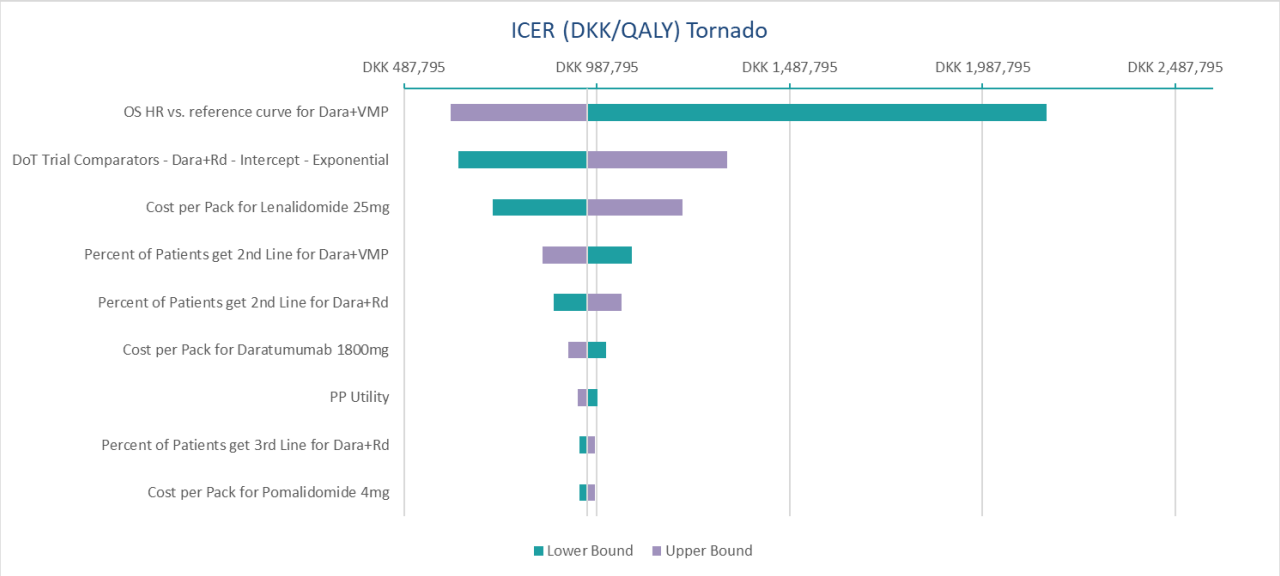
The sensitivity analyses consists of deterministic sensitivity analyses (DSA), refer to section 8.7.1; scenario analyses, refer to section 8.7.2; and probabilistic sensitivity analyses (PSA), refer to section 8.7.3.

8.7.1 Deterministic sensitivity analyses

All major model variables were tested in a one-way DSA to identify model drivers and examine key areas of uncertainty. Where possible, CIs or published ranges were used as alternative values. In the absence of Cis or published ranges, upper and lower bounds tested in the one-way sensitivity analysis were calculated as ± 20% of the mean base case value. The parameters were varied as shown in Appendix K – Deterministic sensitivity analyses.

Figure 32 below present univariate sensitivity analysis results for the comparison of Dara+Rd and Dara+VMP. The figure presents the 10 parameters that had the largest impact on the ICER when they were increased or decreased (upper or lower bounds, respectively). According to the result of the analyses, the inputs that most strongly influenced results were overall survival with Dara+Rd, OS HR vs. reference curve for Dara+VMP, PFS HR vs. reference curve for Dara+VMP unit cost of daratumumab, treatment duration with Dara+Rd, and cost of lenalidomide. In this pairwise comparison the impact on the ICER of the price of daratumumab is minimal, since daratumumab is included in both treatment arms. The results vs. the remaining comparators are illustrated in Appendix K – Deterministic sensitivity analyses.

Figure 32. DSA results (Dara+Rd vs. Dara+VMP)



Abbreviations: ICER = Incremental cost-effectiveness ratio; HR= Hazard Ratio; PFS = Progression-free survival; PP = Post-progression; QALY = quality-adjusted life years; Dara+Rd = daratumumab, lenalidomide, dexamethasone; Dara+VMP = daratumumab, bortezomib, melphalan, prednisone

8.7.2 Scenario analyses

Scenario analyses were conducted to assess the impact of alternative input parameters, settings, or assumptions on the model results. Table 53 summarizes the scenarios considered and Table 54 presents the results of the scenario analyses.

Table 53. Description of scenario analyses

No.	Scenario	Base-case Assumption	Rationale
1	Time horizon 20 years	Time horizon 30 years (lifetime)	Impact of reducing time horizon
2	Time horizon 10 years		
3	Discount rate 0%	Discount rate 3.5%	Impact of increasing or reducing the discount rate
4	Discount rate 5%		
5	Weibull PFS distribution for Dara+Rd	Exponential distribution for PFS	2nd best statistical fit for Dara+Rd
6	Weibull distribution for PFS		2nd best fit overall for both arms
7	Rd log-logistic distribution for PFS		2nd best statistical fit for Rd
8	Dara+Rd Weibull for OS	Gompertz distribution for OS	Best statistical fit for Dara+Rd
9	Weibull distribution for OS		2nd best fit overall for both arms
10	Rd generalised gamma for OS		3rd best statistical fit for Rd
11	Weibull distribution for TTTD	Exponential distribution for TTTD	2nd best fit overall for both arms
12	TTTD = PFS for Dara+Rd and Rd	TTTD individual curves from the MAIA trial	In line with the SmPC, however does not account for treatment due to other reasons than PFS
13	TTTD = Median treatment duration from the MAIA trial for Dara+Rd and Rd		Based only on observed data, however inappropriate use for estimating mean costs
14	UK utility tariffs	DK utility tariffs	Impact of using alternative utility tariffs
15	BW = 73.4 kg (Region H)	Baseline BW from the MAIA trial (74.5 kg)	Impact of reducing the BW to correspond to the BW in Region H
16	BSA = 1.84 m^2 (Region H)	Baseline BSA from the MAIA trial (1.83m^2)	Impact of increasing the BSA to correspond to the BSA in Region H
17	Cost of SC administration -50%	Same cost as IV administration (3,225 DKK)	Impact of assuming a lower administration cost for SC treatments
18	Cost of hematologist visit -50%	1,066 DKK per hour	Impact of assuming a lower cost of physician visits
19	Exclude wastage	Wastage included	Impact of not accounting for drug wastage
20	Exclude RDI	Relative dose intensity of drug is taken from clinical trials	Impact of patients receiving 100% of the intended drug dosage

Abbreviations: BSA = Body Surface Area; BW = Bodyweight; DK = Denmark; IV = Intravenous; OS = overall survival; PFS = progression-free survival; RDI, relative dose intensity; SC = Subcutaneous; TTTD, time to treatment discontinuation; UK = United Kingdom

Table 54. Results of scenario analyses

		ICER vs. Dara+Rd			
	Base case results	**Rd**	**Dara+VMP**	**VRd**	**VMP**
	Base Case	1,847,098	969,505	1,463,974	1,468,509
No.	**Scenario**				
1	Time horizon 20 years	1,921,391	1,044,892	1,561,094	1,516,196
2	Time horizon 10 years	3,893,894	3,799,464	5,025,656	2,652,563
3	Discount rate 0%	1,484,382	672,507	1,059,442	1,176,733
4	Discount rate 5%	2,027,622	1,363,019	1,678,384	1,610,487
5	Weibull PFS distribution for Dara+Rd	1,812,291	935,556	1,423,375	1,443,491
6	Weibull distribution for PFS	1,805,223	1,027,826	1,466,570	1,439,303
7	Rd log-logistic distribution for PFS	1,865,688	449,370	1,144,770	1,482,918
8	Dara+Rd Weibull for OS	1,780,665	924,202	1,395,397	1,425,620
9	Weibull distribution for OS	2,298,573	1,723,293	2,471,723	1,608,269
10	Rd generalised gamma for OS	1,980,677	1,141,253	1,701,707	1,519,322
11	Weibull distribution for TTTD	1,884,588	1,037,852	1,532,319	1,510,343
12	TTTD = PFS for Dara+Rd and Rd	2,218,191	1,793,124	2,287,575	1,972,632
13	TTTD = Median treatment duration from the MAIA trial for Dara+Rd and Rd	1,873,993	994,616	1,489,084	1,483,879
14	UK utility tariffs	2,060,985	1,086,414	1,635,120	1,637,201
15	BW = 73.4 kg (Region H)	1,847,098	969,505	1,463,974	1,468,509
16	BSA = 1.84 m2 (Region H)	1,847,098	969,505	1,463,974	1,468,509
17	Cost of SC administration -50%	1,792,563	1,001,317	1,406,349	1,434,819
18	Cost of hematologist visit -50%	1,840,293	964,826	1,457,781	1,462,215
19	Exclude wastage	1,842,908	988,686	1,459,509	1,469,906
20	Exclude RDI	1,858,453	983,092	1,459,453	1,479,064

8.7.3 Probabilistic sensitivity analyses

To account for the joint uncertainty of the underlying parameter estimates, a second-order stochastic sensitivity analysis (i.e., PSA) was performed. The parameters included in the PSA and how they were varied are shown in the model sheet PSA inputs and in Appendix J – Probabilistic sensitivity analyses.

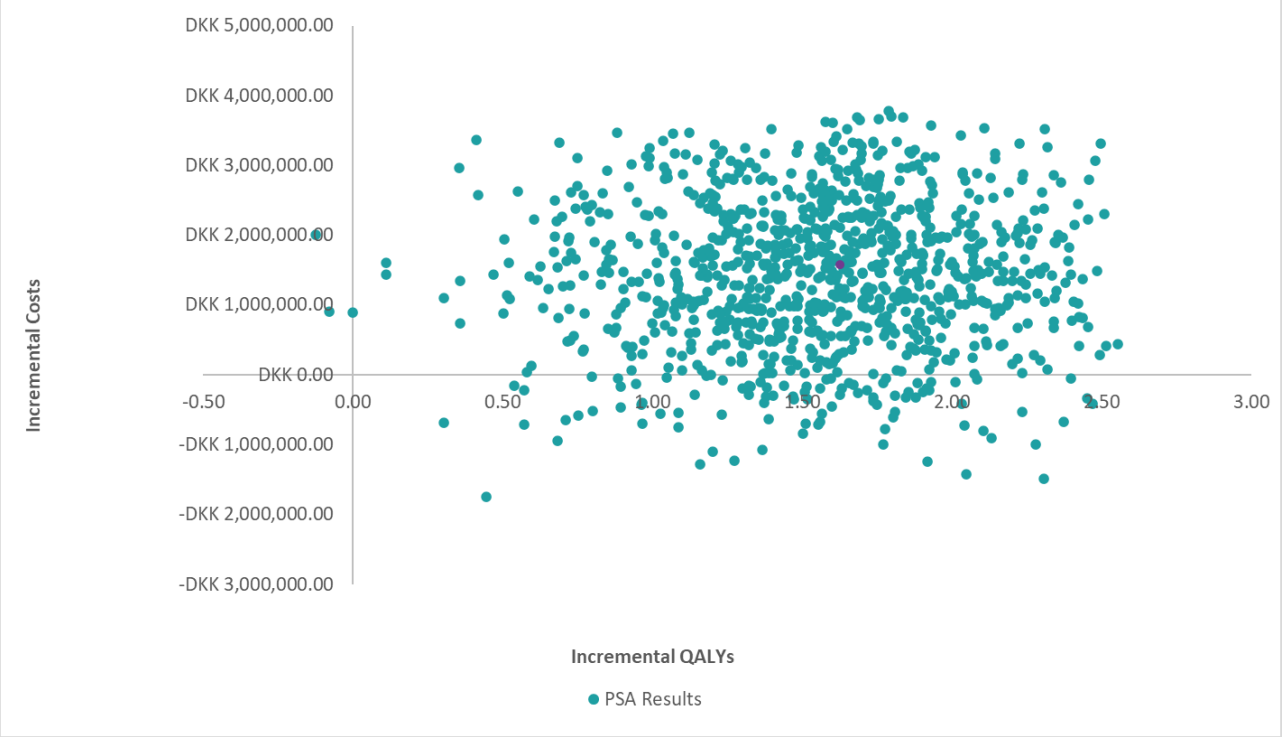
The PSA was performed using 1,000 iterations to ensure convergence. The total costs and QALYs were recorded for each iteration and averaged. PSA results for the comparison to Dara+Rd are presented in Table 55. The probabilistic ICER for Dara+Rd vs. Rd was 1,825,202 DKK/QALY, vs. Dara+VMP 928,309 DKK/QALY, vs. VRd 1,429,326 DKK/QALY, and vs. VMP 1,460,325 DKK/QALY. The probabilistic ICERs for Dara+Rd versus each comparator are in line with the deterministic results, confirming that the results are robust to the expected parameter uncertainty. It must be noted that the PSA ICERs are slightly lower than the deterministic ICERs, which indicate that the base case result may be somewhat conservative in favor of the comparators.

Table 55. Probabilistic base-case results

Health outcomes (discounted, per patient)	Dara+Rd	Rd	Dara+VMP	VRd	VMP
Total costs (DKK)	6,214,698	2,331,202	4,782,810	3,932,045	2,393,495
Lys	8.01	4.95	5.68	5.66	4.30
QALYs	5.82	3.69	4.27	4.22	3.20
Incr. costs (DKK)	-	3883496	1,431,888	2282653	3,821,203
Incr. QALYs	-	2.13	1.54	1.60	2.62
ICER (Dara+Rd vs.) (DKK/QALY)	**-**	1,825,407	928,309	1,429,326	1,460,325

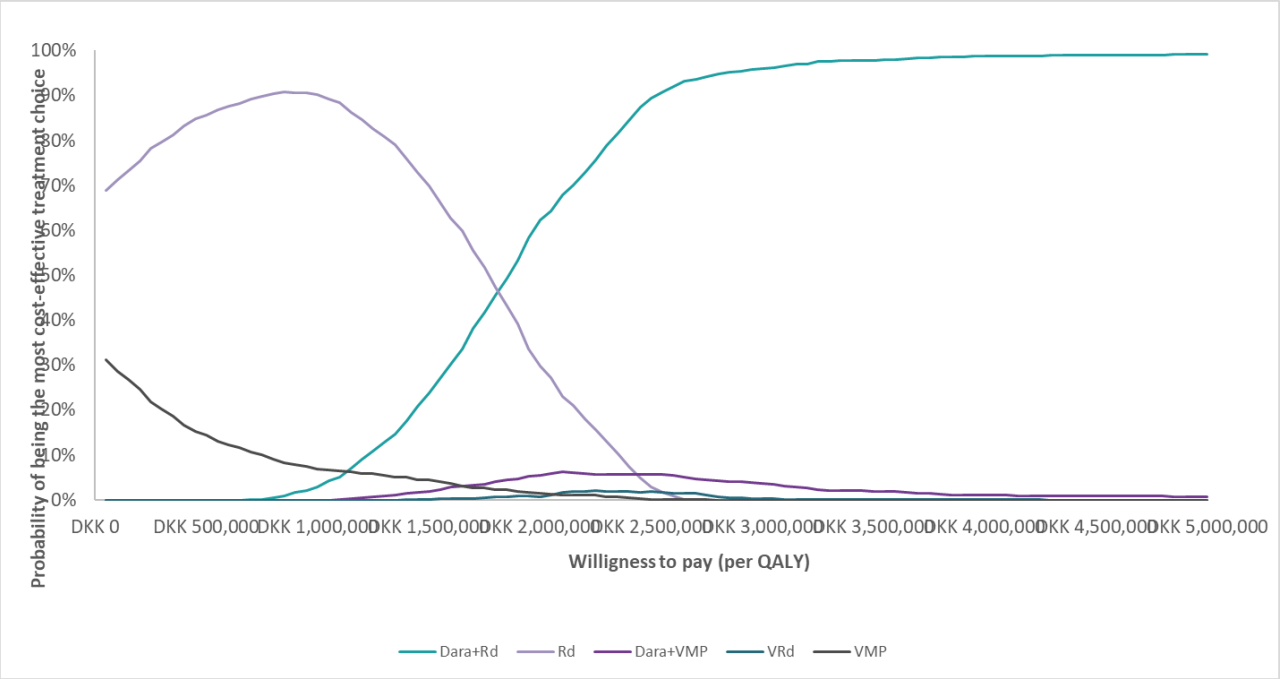
Figure 33 represents the scatter plot of the incremental costs and QALYs from the PSA results based on 1,000 iterations. As shown in the cost-effectiveness acceptability curve (Figure 34), Dara+Rd has a 43.9% probability of being cost-effective versus Dara+VMP, assuming a DKK 800,000 WTP threshold.

Figure 33. PSA Scatter Plot vs. Dara+VMP



Abbreviations: Dara+Rd = daratumumab, lenalidomide, dexamethasone; Dara+VMP = daratumumab, bortezomib, melphalan, prednisone; QALY = quality-adjusted life-years

Figure 34. Cost-effectiveness acceptability curve



Abbreviations: Dara+Rd = daratumumab, lenalidomide, dexamethasone; Dara+VMP = daratumumab, bortezomib, melphalan, prednisone; Rd = lenalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VMP = bortezomib, melphalan, prednisone; QALY = quality-adjusted life-years

9 Budget impact analysis

The budget impact model (BIM) was developed to estimate the expected budget impact of recommending Dara+Rd as a possible standard treatment in Denmark. The budget impact was estimated per year for the first 5 years after the introduction of Dara+Rd in Denmark.

The budget impact model was partially nested within the cost-effectiveness model, and therefore any changes in the settings of the cost-effectiveness model would affect the results of the BIM. The budget impact result is representative of the population in the cost-effectiveness model and the survival outcome of this population.

The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where Dara+Rd is recommended as standard treatment and the scenario where Dara+Rd is not recommended as standard treatment in the relevant treatment comparison. The total budget impact per year is the difference between the two scenarios.

9.1 Number of patients

As described in section 5.1.9, approximately 240 patients are expected to be eligible for 1st line treatment with Dara+Rd each year. For the budget impact analysis, 240 patients have been assumed in year 1 with an expected 1.5% increase in the eligible population size per year.

In the scenario, where Dara+Rd is not recommended, it is assumed that Dara+Rd will not be used, i.e., a market uptake of 0% in the first 5 years. In this scenario, patients are assumed to primarily receive VRd (75%) as this is currently the recommended first-choice treatment regimen by the DMC. 25% of the patients are expected to receive Dara+VMP and

only 5% are expected to receive Rd. No patients are expected to receive VMP in any of the scenarios and Dara+VMP is considered a more efficacious treatment regimen. See Table 56 for the patient numbers in this scenario.

In the scenario, where Dara+Rd is recommended, it is assumed that Dara+Rd will have 20% market uptake in year 1, increasing to 35% in year 5. Dara+Rd is expected to primarily take market shares from Dara+VMP since this regimen also contains a daratumumab component, and Dara+Rd is expected to be preferred to Dara+VMP. Consequently, it is not expected that Dara+Rd will have a much higher market share than Dara+VMP currently has. See Table 57 for the patient numbers in this scenario.

Table 56. Number of patients expected to be treated over the next five-year period – if Dara+Rd is not recommended as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Dara+Rd	0	0	0	0	0
Rd	12	12	12	12	13
Dara+VMP	60	61	62	63	64
VRd	168	171	173	176	178
VMP	0	0	0	0	0
Total number of patients	240	244	247	251	255

Table 57. Number of patients expected to be treated over the next five-year period – if Dara+Rd is recommended as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Dara+Rd	48	73	79	88	89
Rd	12	3	3	3	3
Dara+VMP	24	24	22	20	20
VRd	156	144	143	140	143
VMP	0	0	0	0	0
Total number of patients	240	244	247	251	255

9.2 Budget impact

Based on the base-case settings, the estimated budget impact of recommending Dara+Rd as standard treatment in Denmark was DKK 22,263,765 in year 1 and DKK 139,351,625 in year 5 as shown in Table 58.

Table 58. Budget impact (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario without recommendation of Dara+Rd	188,000,257	313,111,888	429,401,369	536,727,305	645,120,444
Scenario with recommendation of Dara+Rd	210,264,022	373,858,518	517,512,842	652,170,851	784,472,069
Budget impact of the recommendation	22,263,765	60,746,630	88,111,473	115,443,545	139,351,625

10 Discussion on the submitted documentation

Multiple myeloma is a rare cancer of the bone marrow. Despite numerous treatment options and the recent launches of novel therapies, patients with MM eventually become refractory to treatment or suffer relapse. There remains a substantial unmet need for new treatment options that induce deep remission, delay progression, and prolong survival, while improving or maintaining quality of life. Daratumumab operates through novel, multifactorial mechanisms of action, different other therapies including proteasome inhibitors and immunomodulatory drugs. In the phase 3 MAIA (MMY3008) trial, in comparison with Rd, Dara+Rd shows significant benefits in PFS, and OS for the treatment of patients with previously untreated MM who are ineligible for ASCT [19]. MAIA enrolled participants generally expected to be representative of NDMM who are ineligible for ASCT in Denmark, and therefore the efficacy results demonstrated in the MAIA trial are expected to be applicable to the Danish context. As the MAIA study is ongoing, the confidence of efficacy results for Dara+Rd amongst transplant-ineligible NDMM patients is likely to become stronger with subsequent datacuts. The median PFS for Dara+Rd has not yet been established in the MAIA trial, and median OS has not been established for either Dara+Rd or Rd treatment arms.

In order to compare Dara+Rd to the other relevant comparators in Denmark (VMP, Dara+VMP, VRd), a network meta-analysis [20] was conducted exploiting data from the ALCYONE (VMP, Dara+VMP) and SWOG S0777 (VRd) studies. This NMA demonstrated that the Dara+Rd treatment was most likely to provide the best survival outcomes (PFS and OS). It is noted that compared with the MAIA study, the ALYCONE study population included a wider range of ages, including more patients who were under 65 at baseline (see Table 77 and Table 78). Also, it is noted that the SWOG S0777 study was not conducted specifically with transplant-ineligible NDMM patients, so that efficacy evidence specifically from the subgroup of 65+ year old NDMM patients has been used. It is a limitation that the baseline patient characteristics of the 65+ subgroup of patients are not known, and the adverse events evidence from the SWOG S0777 study were from the full population of patients rather than the 65+ year old subset.

The three state partitionned survival model is very commonly used in cancer models, and while a simplificaition which does not allow for differences in efficacy of subsequent treatment lines, the common use of the three state partitionned model does facilitate comparability of models developed for different treatments. The base-case ICERs are: 1) Dara+Rd vs. Rd was 1,847,098 DKK/QALY; 2) Dara+Rd vs. Dara+VMP 969,505 DKK/QALY; 3) Dara+Rd vs. VRd 1,463,974 DKK/QALY; 4) and Dara+Rd vs. VMP 1,468,509 DKK/QALY.

While not reflected in the economic models, if Dara+Rd was approved in first-line treatment with a lower price than the current list price, this would also affect costs of daratumumab in further treatment lines and other indications. Therefore, the estimated cost-effectiveness results and budget impacts should be considered as conservative.

11 List of experts

No external KOL contributed to this submission. An internal Janssen clinical expert with experience with MM in Denmark was consulted.

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13 Appendix A – Literature search for efficacy and safety of intervention and comparators

The literature search aimed to address the following research questions:

- According to the evidence from RCTs, what is the efficacy of Dara+Rd and relevant comparators in ASCT-ineligible patients with NDMM?
- According to the evidence from RCTs, what is the safety of Dara+Rd and relevant comparators in ASCT-ineligible patients with NDMM?

The review was conducted in accordance with the Cochrane handbook [158].

As detailed in Table 59, the initial SLR searches were conducted on 16 June 2017 considering an unlimited time period, with 5 subsequent SLR searches conducted to capture more recently published evidence:

- 1st update, Jun 6, 2018
- 2nd update, Jan 7, 2019
- 3rd update, Jul 24, 2019
- 4th update, Jul 16, 2020
- 5th update, Mar 24, 2021

Searches were performed in the following indexed databases:

- MEDLINE via Pubmed
- Embase
- Cochrane

The following conference websites were manually searched to capture potentially relevant studies:

- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)
- European Society for Medical Oncology (ESMO)
- European Hematology Association (EHA)

Table 59. Bibliographic databases and conference websites included in the clinical literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	Unlimited - 16 June 2017	16 June 2017
		16 June 2017 - 6 June 2018	1st update, 6 June 2018
		6 June 2018 - 7 January 2019	2nd update, 7 January 2019
		7 January 2019 - 24 July 2019	3rd update, 24 July 2019
		24 July 2019 - 16 July 2020	4th update, 16 July 2020
		16 July 2020 - 24 March 2021	5th update, 24 March 2021
Medline	Pubmed	Unlimited - 16 June 2017	16 June 2017
		16 June 2017 - 6 June 2018	1st update, 6 June 2018

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Database	Platform	Relevant period for the search	Date of search completion
		6 June 2018 - 7 January 2019	2nd update, 7 January 2019
		7 January 2019 - 24 July 2019	3rd update, 24 July 2019
		24 July 2019 - 16 July 2020	4th update, 16 July 2020
		16 July 2020 - 24 March 2021	5th update, 24 March 2021
Cochrane	Cochrane Library	Unlimited - 16 June 2017	16 June 2017
		16 June 2017 - 6 June 2018	1st update, 6 June 2018
		6 June 2018 - 7 January 2019	2nd update, 7 January 2019
		7 January 2019 - 24 July 2019	3rd update, 24 July 2019
		24 July 2019 - 16 July 2020	4th update, 16 July 2020
		16 July 2020 - 24 March 2021	5th update, 24 March 2021
ASCO	ASCO	2018-2021	4 March 2021
ASH	ASH	2018-2021	4 March 2021
ESMO	ESMO	2018-2020	4 March 2021
EHA	EHA	1 Jan 2018 - 4 March 2021	4 March 2021

Abbreviations: ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; ESMO = European Society for Medical Oncology; EHA = European Hematology Association

13.1 Search strategy

In the literature reviews, each abstract was reviewed against the defined inclusion and exclusion criteria by two independent investigators to determine its suitability for inclusion in the SLR. Discrepancies between these investigators were addressed via discussion, with any remaining disagreements being resolved by a third investigator. For abstracts that are deemed relevant, the corresponding full-text articles was retrieved for further evaluation. Each full paper was reviewed by two independent investigators. All publications rejected at this stage was assigned a reason for exclusion. Discrepancies between investigators were addressed via discussion; remaining disagreements was resolved by a third investigator. Studies were initially screened and selected for inclusion based on the Population, Intervention, Comparison, Outcome, Study Design (PICOS) criteria outlined in Table 60.

Table 60. Eligibility criteria used in systematic review for RCTs

Criteria	Inclusion criteria	Exclusion criteria	Brief rationale
Population	Newly diagnosed multiple myeloma patient's ineligible for autologous cell transplant (ASCT)	Indications other than MM; transplant eligible population; relapsed/refractory MM.	Only studies on newly diagnosed MM who are ASCT-ineligible are relevant for the purposes of this submission.
Intervention[a]	MPT, CTD, BMP, Ld, BCD, BD, Dara+VMP	Any other treatment regimen; non-anticancer treatment	Only the listed treatment regimens are regarded relevant for the Danish setting.
Outcomes	Clinical outcomes, including OS, PFS, response (overall response, very good partial response, complete response etc.)	HRQoL, economic evaluation, other clinical outcomes, e.g., PFS2 etc.	Only studies reported listed clinical outcomes, which will be used for indirect comparison, are regarded as relevant.

Criteria	Inclusion criteria	Exclusion criteria	Brief rationale
Study design	Randomised Controlled Trials	Observational studies, single-arm trials, pharmacokinetic or pharmacodynamic studies	The study design specified as eligible for inclusion were those considered most likely to report relevant data for this submission.
Publication type	NA	Editorials, reviews, letters	
Language	English	Any other language	The vast majority of the research in the field is published in English
Time	No time restriction for full-text publication; conference abstracts from 2018 onwards	N/A	Conference abstracts published 1 year ahead of search were included in Embase database. Manual search was conducted to ensure the latest publications were identified in the review.

Abbreviations: Ld = lenalidomide, dexamethasone; Dara+VMP = daratumumab, bortezomib, melphalan, prednisone; CTD = cyclophosphamide, thalidomide, dexamethasone; BCD = bortezomib, cyclophosphamide, dexamethasone; BD = bortezomib, dexamethasone; MPT = melphalan, prednisone, thalidomide; BMP = bortezomib, melphalan, prednisone. [a] the initial SLR is a comprehensive review that contains a broad scope of treatment regimens. In this submission, the intervention and comparator are narrowed to focus on those relevant to the Scottish clinical practice.

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Table 61 to Table 67 present the search hits in PubMed, Embase, Cochrane, and each conference website.

Table 61. PubMed search terms

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#1	"Multiple myeloma" [Mesh]	35,865	37,454	38,359	39,455	41,069	42,225
#2	Multiple myeloma [tiab]	30,615	32,552	33,889	35,085	37,463	39,394
#3	Kahler disease [tiab]	17	19	19	19	19	19
#4	Kahler's disease [tiab]	198	198	198	199	199	210
#5	Myelomatosis [tiab]	752	755	761	764	767	774
#6	Plasma cell myeloma [tiab]	633	673	707	743	786	826
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)	44,494	46,653	48,160	49,544	52,142	54,245
#8	Randomised controlled trial [ptyp]	433,457	460,244	474,353	486,714	510,619	526,754
#9	randomised controlled trial [tiab]	47,199	54,113	58,942	63,547	78,689	85,980
#10	allocated random [tiab]	1,949	2,077	2,158	2,236	10,846	11,336
#11	single blind method [tiab]	78	84	87	87	90	92
#12	controlled clinical trial [tiab]	11,093	12,011	12,666	13,258	14,977	15,923
#13	randomised [tiab]	409,127	442,553	465,302	486,487	525,557	557,813
#14	placebo [tiab]	184,546	193,693	199,750	205,029	214,837	222,416
#15	drug therapy [tiab]	44,238	45,521	46,459	47,207	48,662	49,847
#16	randomly [tiab]	271,062	290,228	303,594	315,765	336,884	354,386
#17	trial [tiab]	465,702	504,690	531,757	556,988	603,125	642,502
#18	groups [tiab]	1,706,072	1,817,939	1,894,523	1,964,362	2,093,376	2,200,389
#19	clinical trial [tiab]	108,448	119,458	127,019	134,120	147,626	159,191
#20	phase I [tiab]	36,860	38,668	39,955	41,015	43,353	44,890
#21	phase II [tiab]	47,775	50,126	516,63	53,035	55,584	57,621
#22	phase III [tiab]	27,713	29,678	30,946	32,033	33,978	35,538

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#23	phase IV [tiab]	1,791	1,945	2,041	2,126	2,285	2,409
#24	multicenter study [tiab]	19,731	21,377	22,513	23,616	25,624	27,452
#25	(singl$ OR doubl$ OR treb$ OR tripl$ OR blind$ OR mask$ [tiab])	289,339	303,403	312,229	320,466	334,356	349,086
#26	(#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)	2,640,652	2,810,864	2,927,219	3,033,612	3,246,076	3,410,779
#27	("bortezomib"[Mesh] OR bortezomib [tiab] OR "ldp 341"[tiab] OR "mg 341"[tiab] OR "mln 341"[tiab] OR "ps 341"[tiab] OR velcade [tiab])	6,997	7,620	8,035	8,380	9,096	9,587
#28	("prednisone" [Mesh] OR prednisone [tiab])	48,887	50,218	51,120	51,885	53,330	54,391
#29	("lenalidomide" [Mesh] OR lenalidomide [tiab] OR revlimid [tiab] OR "cc 5013" [tiab] OR "cdc 501"[tiab] OR "cdc 5013" [tiab] OR "enmd 0997" [tiab] OR "imid 1" [tiab] OR "imid 3" [tiab] OR "revimid" [tiab])	3,035	3,401	3,975	4,208	4,654	5,010
#30	("dexamethasone" [Mesh] OR dexamethasone [tiab] OR (9[tiab] AND fluoro[tiab] AND 16[tiab] AND alpha[tiab] AND methylprednisolone[tiab])	64,410	66,549	68,028	69,293	71,634	73,846
#31	("thalidomide" [Mesh] OR thalidomide [tiab] OR Immunoprin [tiab] OR Talidex [tiab] OR Talizer [tiab] OR Thalomid [tiab] OR Alpha-Phthalimidoglutarimide [tiab] OR Contergan [tiab] OR Beta thalidomide [tiab] OR Distaval [tiab] OR Isomin [tiab] OR "k 17"[tiab] OR Kevadon [tiab] OR N-Phthaloylglutamimide [tiab] OR N-Phthalyl-Glutamic Acid Imide [tiab] OR Neurosendin [tiab] OR Neurosedyn [tiab] OR Neurosedyne [tiab] OR "nsc 66847"[tiab] OR Pantosediv [tiab] OR Sedalis [tiab] OR Sedoval [tiab] OR Shin naito [tiab] OR Softenon [tiab] OR synovir [tiab] or Talimol [tiab] OR Talizer [tiab] OR Telagan [tiab] OR 3Phthalimidoglutarimide [tiab])	10,047	10,621	10,942	11,186	11,655	11,975
#32	("cyclophosphamide" [Mesh] OR cyclophosphamide [tiab])	67,261	69,429	70,703	71,777	73,834	75,456

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#33	("bendamustine" [Mesh] OR bendamustine [tiab] OR bendamustine hydrochloride [tiab] OR "cimet 3393"[tiab] OR cytostasan [tiab] OR cytostasan [tiab] OR cytostasane [tiab] OR "imet 3393"[tiab] OR levact [tiab] OR ribomustin [tiab] OR treanda [tiab] OR "SDX-105"[tiab])	834	953	1,044	1,102	1,221	1,322
#34	("interferon" [Mesh] OR interferon [tiab])	131,823	137,364	140,777	143780	149,540	154,277
#35	("vincristine" [Mesh] OR vincristine [tiab] OR vin cristine [tiab] OR vincristin [tiab] OR cellcristin [tiab] OR oncovin [tiab] OR oncovine [tiab] OR kyocristine [tiab] OR leurocristine [tiab] OR marqibo [tiab] OR vincasar [tiab] OR vincosid [tiab] OR vincrex [tiab] OR vincrisul [tiab] OR 22-Oxovincaleukoblastine [tiab])	29,174	29,998	30,512	30,919	31,699	32,309
#36	("Daratumumab" [Mesh] OR Daratumumab [tiab] OR Darzalex® [tiab] OR Anti-CD38 Monoclonal Antibody [tiab] OR HuMax-CD38 [tiab])	158	258	355	429	622	828
#37	(BCD [tiab] OR VD [tiab] OR BLD [tiab] OR CTD [tiab] OR CTDa [tiab] OR MPT [tiab] OR MP [tiab] OR MPB [tiab] OR MPL [tiab] OR MPR [tiab] OR MPV [tiab] OR VMP [tiab] OR VMCP [tiab] OR Rd [tiab] OR Rd18 [tiab] OR PCAB [tiab])	59,552	64,489	67,934	71,096	79,187	84,553
#38	("Melphalan" [Mesh] OR Melphalan [tiab] OR Alkeran [tiab] OR Phenylalanine Mustard [tiab] OR L-PAM [tiab] OR sarcolysin [tiab] OR CB-3025 [tiab] OR Alanine Nitrogen Mustard [tiab] OR Melphalanum [tiab] OR phenylalanine nitrogen mustard [tiab] OR WR-19813 [tiab] OR Melfalan [tiab] OR Evomela [tiab])	10,277	10,543	10,706	10,848	11,159	11,341
#39	("doxorubicin" [Mesh] OR doxorubicin [tiab] OR hydroxydaunorubicin [tiab] OR Adriamycin [tiab] OR Lipsomal doxorubicin [tiab] OR Doxil [tiab])	65,780	69,256	71,645	73,700	77,809	80,724
#40	("carfilzomib" [Mesh] OR carfilzomib [tiab] OR Kyprolis [tiab])	511	634	719	785	929	1,046
#41	("cisplatin" [Mesh] OR cisplatin [tiab])	64,408	67,885	70,155	72,114	75,945	78,718

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#42	("elotuzumab" [Mesh] OR elotuzumab [tiab] OR BMS-901608 [tiab] OR HuLuc63 [tiab] OR Empliciti [tiab])	118	167	197	205	245	294
#43	("etoposide" [Mesh] OR etoposide [tiab] OR VP-16 [tiab] OR Vepesid [tiab] OR etopophos [tiab] OR Toposar [tiab] OR Lastet [tiab] OR Eposin [tiab] OR NSC 141540: [tiab] OR VP-16213 [tiab])	23,773	24,512	25,001	25,386	26,146	26,750
#44	("ixazomib" [Mesh] OR ixazomib [tiab] OR MLN9708 [tiab] OR Ninlaro [tiab] OR MLN2238 [tiab])	142	211	258	282	349	405
#45	("panobinostat" [Mesh] OR panobinostat [tiab] OR LBH 589 [tiab] OR Farydak [tiab])	467	543	718	771	848	894
#46	("pomalidomide" [Mesh] OR pomalidomide [tiab] OR CC 4047 [tiab] OR Pomalyst [tiab] OR Imnovid [tiab] OR actimid [tiab] OR 4-Aminothalidomide [tiab])	419	502	568	614	718	803
#47	("vorinostat" [Mesh] OR vorinostat [tiab] OR Zolinza [tiab] OR suberoylanilide hydroxamic acid [tiab] OR L-001079038 [tiab] OR suberanilohydroxamic acid [tiab] OR N-Hydroxy-N'-phenyl octanediamide [tiab])	1,924	2,130	2,532	2,641	2,822	2,938
#48	(#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47)	484,761	507,673	523,209	536,562	564,338	585,181
#49	(Novo [tiab] OR (first [tiab] AND line [tiab]) OR naïve [tiab] OR first-line [tiab] OR newly diagnosed [tiab] OR frontline [tiab] OR (front [tiab] AND line [tiab]) OR front-line [tiab] OR untreated [tiab])	429,914	459,482	479,763	498193	532,382	560,959
#50	(#7 AND #26 AND #48 AND #49)	795	865	905	955	1042	1,104
#51	"Letter" [ptyp]	949,326	985,958	1,011,203	1,035,358	1,088,575	1,126,694
#52	"Editorial" [ptyp]	427,004	457,374	477,584	496,629	534,117	560,955
#53	"Historical Article" [ptyp]	373,704	380,156	385,012	389,640	397,150	401,522
#54	"Case Reports" [ptyp]	1,834,382	1,877,724	1,916,089	2,033,804	2,108,615	2,163,493

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#55	(#51 OR #52 OR #53 OR #54)	3,371,759	3,484,391	3,567,646	3,727,157	3,891,742	4,011,317
#56	(#50 NOT #55)	783	849	889	939	1,020	1,081
#57	English [lang]	22,618,097	23,769,027	24,572,960	25,260,955	26,521,009	27,564,367
#58	(#56 AND #57)	740	798	837	883	960	1,017
#59	#58 AND (“2017/01/01”[PDAT] : “2018/12/31”[PDAT])	-	82	-	-	-	-
#60	#58 AND (“2018/01/01”[PDAT] : “2019/12/31”[PDAT])	-	-	68	-	-	-
#61	#58 AND (“2019/01/01”[PDAT] : “2019/12/31”[PDAT])			-	51	-	-
#62	#58 AND (“2019/07/01”[PDAT] : “2020/12/31”[PDAT])	-	-	-	-	101	-
#63	#58 AND (“2019/07/01”[PDAT] : “2021/12/31”[PDAT])	-	-	-	-	-	156

Table 62. Embase search terms

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#1	‘multiple myeloma’/exp OR ‘multiple myeloma’:ab,ti OR ‘kahler disease’:ab,ti OR ‘kahlers disease’:ab,ti OR ‘myelomatosis’:ab,ti OR ‘plasma cell myeloma’:ab,ti	69,960	75,399	79,112	81,393	88,329	95,066
#2	‘randomised controlled trial’/de OR ‘randomised controlled trial’:ab,ti OR ‘allocated random’:ab,ti OR ‘single blind method’:ab,ti OR ‘controlled clinical trial’:ab,ti OR ‘randomised’:ab,ti OR ‘placebo’:ab,ti OR ‘drug therapy’:ab,ti OR ‘randomly’:ab,ti OR ‘trial’:ab,ti OR ‘groups’:ab,ti OR ‘clinical trial’:ab,ti OR ‘phase naïve’:ab,ti OR ‘phase ii’:ab,ti OR ‘phase iii’:ab,ti OR ‘phase iv’:ab,ti OR ‘multicenter study’:ab,ti OR ‘singl$ or doubl$ or treb$ or tripl$ or blind$ or mask$’:ab,ti	3,338,649	3,628,818	3,811,202	3,983,073	4,278,827	4,634,108
#3	‘bortezomib’/exp OR ‘bortezomib’:ab,ti OR ‘ldp 341’:ab,ti OR ‘mg 341’:ab,ti OR ‘mln 341’:ab,ti OR ‘ps 341’:ab,ti OR ‘velcade’:ab,ti OR	1,206,591	1,291,485	1,343,786	1,392,395	1,476,995	1,559,890

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
	'prednisone'/exp OR 'prednisone':ab,ti OR 'lenalidomide'/exp OR 'lenalidomide':ab,ti OR 'revlimid':ab,ti OR 'cc 5013':ab,ti OR 'cdc 501':ab,ti OR 'cdc 5013':ab,ti OR 'enmd 0997':ab,ti OR 'imid 1':ab,ti OR 'imid 3':ab,ti OR 'revimid':ab,ti OR 'dexamethasone'/exp OR 'dexamethasone':ab,ti OR (9:ab,ti AND fluoro:ab,ti AND 16:ab,ti AND alpha:ab,ti AND methylprednisolone:ab,ti) OR 'thalidomide'/exp OR 'thalidomide':ab,ti OR 'immunoprin':ab,ti OR 'talidex':ab,ti OR 'thalomid':ab,ti OR 'alpha-phthalimidoglutarimide':ab,ti OR 'contergan':ab,ti OR 'beta thalidomide':ab,ti OR 'distaval':ab,ti OR 'isomin':ab,ti OR 'k 17':ab,ti OR 'kevadon':ab,ti OR 'n-phthaloylglutamimide':ab,ti OR 'n-phthalyl-glutamic acid imide':ab,ti OR 'neurosendin':ab,ti OR 'neurosedyn':ab,ti OR 'neurosedyne':ab,ti OR 'nsc 66847':ab,ti OR 'pantosediv':ab,ti OR 'sedalis':ab,ti OR 'sedoval':ab,ti OR 'shin naito':ab,ti OR 'softenon':ab,ti OR 'synovir':ab,ti OR 'talimol':ab,ti OR 'talizer':ab,ti OR 'telagan':ab,ti OR '3phthalimidoglutarimide':ab,ti OR 'cyclophosphamide'/exp OR 'cyclophosphamide':ab,ti OR 'bendamustine'/exp OR 'bendamustine':ab,ti OR 'bendamustine hydrochloride':ab,ti OR 'cimet 3393':ab,ti OR 'cytostasan':ab,ti OR 'cytostasane':ab,ti OR 'imet 3393':ab,ti OR 'levact':ab,ti OR 'ribomustin':ab,ti OR 'treanda':ab,ti OR 'sdx-105':ab,ti OR 'interferon'/exp OR 'interferon':ab,ti OR 'vincristine'/exp OR 'vincristine':ab,ti OR 'vincristine':ab,ti OR 'vincristin':ab,ti OR 'cellcristin':ab,ti OR 'oncovin':ab,ti OR 'oncovine':ab,ti OR 'kyocristine':ab,ti OR 'leurocristine':ab,ti OR 'marqibo':ab,ti OR 'vincasar':ab,ti OR 'vincosid':ab,ti OR 'vincrex':ab,ti OR 'vincrisul':ab,ti OR '22-oxovincaleukoblastine':ab,ti OR 'daratumumab'/exp OR 'daratumumab':ab,ti OR 'darzalex':ab,ti OR 'anti-cd38 monoclonal antibody':ab,ti OR 'humax-cd38':ab,ti OR 'bcd':ab,ti OR 'VD':ab,ti OR 'bld':ab,ti OR 'ctd':ab,ti OR 'ctda':ab,ti OR 'mpt':ab,ti OR 'mp':ab,ti OR 'mpb':ab,ti OR 'mpl':ab,ti OR 'mpr':ab,ti OR						

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
	'mpv':ab,ti OR 'vmp':ab,ti OR 'vmcp':ab,ti OR 'rd':ab,ti OR 'rd18':ab,ti OR 'pcab':ab,ti OR 'melphalan'/exp OR 'melphalan':ab,ti OR 'alkeran':ab,ti OR 'phenylalanine mustard':ab,ti OR 'lpam':ab,ti OR 'sarcolysin':ab,ti OR 'cb-3025':ab,ti OR 'alanine nitrogen mustard':ab,ti OR 'melphalanum':ab,ti OR 'phenylalanine nitrogen mustard':ab,ti OR 'wr-19813':ab,ti OR 'melfalan':ab,ti OR 'evomela':ab,ti OR 'doxorubicin'/exp OR 'doxorubicin':ab,ti OR 'hydroxydaunorubicin':ab,ti OR 'adriamycin':ab,ti OR 'lipsomal doxorubicin':ab,ti OR 'doxil':ab,ti OR 'carfilzomib'/exp OR 'carfilzomib':ab,ti OR 'kyprolis':ab,ti OR 'cisplatin'/exp OR 'cisplatin':ab,ti OR 'elotuzumab'/exp OR 'elotuzumab':ab,ti OR 'bms-901608':ab,ti OR 'huluc63':ab,ti OR 'empliciti':ab,ti OR 'etoposide'/exp OR 'etoposide':ab,ti OR 'vp-16':ab,ti OR 'vepesid':ab,ti OR 'etopophos':ab,ti OR 'toposar':ab,ti OR 'lastet':ab,ti OR 'eposin':ab,ti OR 'nsc 141540':ab,ti OR 'vp-16213':ab,ti OR 'ixazomib'/exp OR 'ixazomib':ab,ti OR 'mln9708':ab,ti OR 'ninlaro':ab,ti OR 'mln2238':ab,ti OR 'panobinostat'/exp OR 'panobinostat':ab,ti OR 'lbh 589':ab,ti OR 'farydak':ab,ti OR 'pomalidomide'/exp OR 'pomalidomide':ab,ti OR 'cc 4047':ab,ti OR 'pomalyst':ab,ti OR 'imnovid':ab,ti OR 'actimid':ab,ti OR '4aminothalidomide':ab,ti OR 'vorinostat'/exp OR 'vorinostat':ab,ti OR 'zolinza':ab,ti OR 'suberoylanilide hydroxamic acid':ab,ti OR 'l-001079038':ab,ti OR 'suberanilohydroxamic acid':ab,ti OR 'n-hydroxy-n-phenyl oct anediamide':ab,ti						
#4	'novo':ab,ti OR ('first':ab,ti AND 'line':ab,ti) OR 'naïve':ab,ti OR 'first-line':ab,ti OR 'newly diagnosed':ab,ti OR 'frontline':ab,ti OR ('front':ab,ti AND 'line':ab,ti) OR 'frontline':ab,ti OR 'untreated':ab,ti	606,770	665,284	700,499	735,044	794,944	860,683
#5	#1 AND #2 AND #3 AND #4	2,508	2,816	2,926	3,123	3,574	3,877

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#6	'letter'/de OR 'editorial'/de OR 'case report'/de OR 'case study'/de	3,514,724	3,692,679	3,814,311	3,921,970	4,119,968	4,321,816
#7	#5 NOT #6	2,481	2,782	2,892	3,071	3,497	3,774
#8	#7 AND [english]/lim	2,424	2,720	2,824	2,996	3,416	3,683
#9	#8 AND [2017-2018]/py	-	323	-	-	-	-
#10	#8 AND [2018-2019]/py	-	-	109	-	-	-
#11	#8 AND [2019-2020]/py	-	-	-	73	467	-
#12	#8 AND [2020-2021]/py	-	-	-	-	-	350

Table 63. Cochrane search terms

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#1	MeSH descriptor: [Multiple Myeloma] explode all trees	1,009	1,084	1,306	1,362	1569	1624
#2	Multiple myeloma or Kahler disease or Kahler's disease or Myelomatosis or Plasma cell myeloma:ti,ab,kw (Word variations have been searched)	2,895	3,495	3,817	4,841	5037	5298
#3	#1 or #2	2,895	3,495	3,817	4,841	5037	5298
#4	"randomised controlled trial":pt (Word variations have been searched)	421,861	449,078	460,717	473,216	488547	504184
#5	randomised controlled trial or allocated random or single blind method or controlled clinical trial or randomised or placebo or drug therapy or randomly or trial or groups or clinical trial or phase I or phase II or phase III or phase IV or multicenter study or singl$ or doubl* or treb* or tripl* or blind* or mask*:ti,ab,kw (Word variations have been searched)	837,890	925,190	1,073,198	1,284,838	1410409	1493011
#6	#4 or #5	874,299	962,746	1,073,198	1,284,838	1410409	453

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#7	MeSH descriptor: [Bortezomib] explode all trees	152	180	316	339	430	4,016
#8	MeSH descriptor: [Prednisone] explode all trees	2,791	3,051	3,606	3,675	3,942	4,645
#9	MeSH descriptor: [Dexamethasone] explode all trees	2,554	2,802	3,796	3,965	4471	867
#10	MeSH descriptor: [Thalidomide] explode all trees	437	498	725	753	854	5,521
#11	MeSH descriptor: [Cyclophosphamide] explode all trees	4,146	4,282	4,950	5,067	5,432	123
#12	MeSH descriptor: [Bendamustine Hydrochloride] explode all trees	31	40	86	91	116	5,820
#13	MeSH descriptor: [Interferons] explode all trees	5,131	5,259	5,434	5,505	5,769	2,350
#14	MeSH descriptor: [Vincristine] explode all trees	1,904	1,951	2,172	2,208	2,325	2,350
#15	MeSH descriptor: [Melphalan] explode all trees	524	543	626	668	698	704
#16	MeSH descriptor: [Doxorubicin] explode all trees	3,636	3,765	4,304	4,423	4754	4840
#17	MeSH descriptor: [Cisplatin] explode all trees	3,674	3,812	4,394	4,534	4952	5043
#18	MeSH descriptor: [Etoposide] explode all trees	1,267	1,310	1,585	1,625	1768	1791
#19	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18	18,379	19,147	22,237	22,833	24706	25203
#20	Bortezomib or ldp 341 or mg 341 or mln 341 or ps 341 or velcade or prednisone or lenalidomide or revlimid or cc 5013 or cdc 501 or cdc 5013 or enmd 0997 or imid 1 or imid 3 or revimid or dexamethasone or thalidomide or Immunoprin or Talidex or Talizer or Thalomid or Alpha-Phthalimidoglutarimide or Contergan or Beta thalidomide or Distaval or Isomin or k 17 or Kevadon or N-Phthaloylglutamimide or N-Phthalyl-Glutamic Acid Imide or Neurosendin or Neurosedyn or Neurosedyne or nsc 66847 or Pantosediv or Sedalis or Sedoval or Shin naito or Softenon or synovir or Talimol or Talizer or Telagan or Phthalimidoglutarimide or cyclophosphamide or bendamustine or bendamustine hydrochloride or cimet 3393 or cytostasan or cytostasan or	49,687	54,542	98,943	112.905	117290	122788

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
	cytostasane or imet 3393 or levact or ribomustin or treanda or SDX-105 or interferons or vincristine or vin cristine or vincristin or cellcristin or oncovin or oncovine or kyocristine or leurocristine or marqibo or vincasar or vincosid or vincrex or vincrisul or Oxovincaleukoblastine or Daratumumab or Darzalex® or Anti-CD38 Monoclonal Antibody or HuMax-CD38 or BCD or VD or BLD or CTD or CTDa or MPT or MP or MPB or MPL or MPR or MPV or VMP or VMCP or Rd or Rd18 or PCAB or melphalan or alkeran or phenylalanine mustard or l-pam or sarcolysin or cb-3025 or alanine nitrogen mustard or melphalanum or phenylalanine nitrogen mustard or wr-19813 or melfalan or evomela or doxorubicin or hydroxydaunorubicin or adriamycin or lipsomal doxorubicin or doxil or carfilzomib or carfilzomib or Kyprolis or cisplatin or cisplatin or elotuzumab or elotuzumab or BMS901608 or HuLuc63 or Empliciti or etoposide or etoposide or VP-16 or Vepesid or etopophos or Toposar or Lastet or Eposin or NSC 141540 or VP-16213 or ixazomib or ixazomib or MLN9708 or Ninlaro or MLN2238 Orpanobinostat or panobinostat or LBH 589 or Farydak or pomalidomide or pomalidomide or CC 4047 or Pomalyst or Imnovid or actimid or Aminothalidomide or vorinostat or vorinostat or Zolinza or suberoylanilide hydroxamic acid or L-001079038 or suberanilohydroxamic acid or N-Hydroxy-N-phenyl oct anediamide:ti,ab,kw (Word variations have been searched)						
#21	#19 or #20	49,957	54,818	103,234	117,247	117290	127221
#22	Novo or (first and line) or naïve or first-line or newly diagnosed or frontline or (front and line) or front-line or untreated:ti,ab,kw (Word variations have been searched)	40,470	47,294	60,594	74,678	79860	84664
#23	#3 and #6 and #21 and #22	730	947	1050	1,286	1454	1553
#24	Letter or Editorial or Historical Article or Case Reports:pt (Word variations have been searched)	9,653	9,974	10,532	15,206	37968	40220

Nr	Syntax	Hits: Jun 16, 2017 update	Hits: Jun 6, 2018 update	Hits: Jan 7, 2019 update	Hits: Jul 24, 2019 update	Hits: Jul 16, 2020 update	Hits: Mar 25, 2021 update
#25	#23 not #24	715	942	969	1,280	1360	1451
#26	limit #25 to yr="2017 -2018"	-	195	-	-	-	-
#27	limit #25 to yr="2018 -2019"	-	-	22	-	-	-
#28	limit #25 to yr="2019 -2019"	-	-	-	18	-	-
#29	limit #25 to Jul 2019 to Dec 2020	-	-	-	-	199	-
#30	limit #25 to July 2020 to March 2021	-	-	-	-	-	91

Table 64. ASCO search terms

Nr	Syntax	Hits: 4 March 2021
#1	"multiple myeloma" published 2018-2021	1,182

Table 65. ASH search terms

Nr	Syntax	Hits: 4 March 2021
#1	"multiple myeloma" AND cost published 2018-2021	186

Table 66. ESMO search terms

Nr	Syntax	Hits: 4 March 2021
#1	Multiple myeloma, Annual congress 2018 - 2020	541

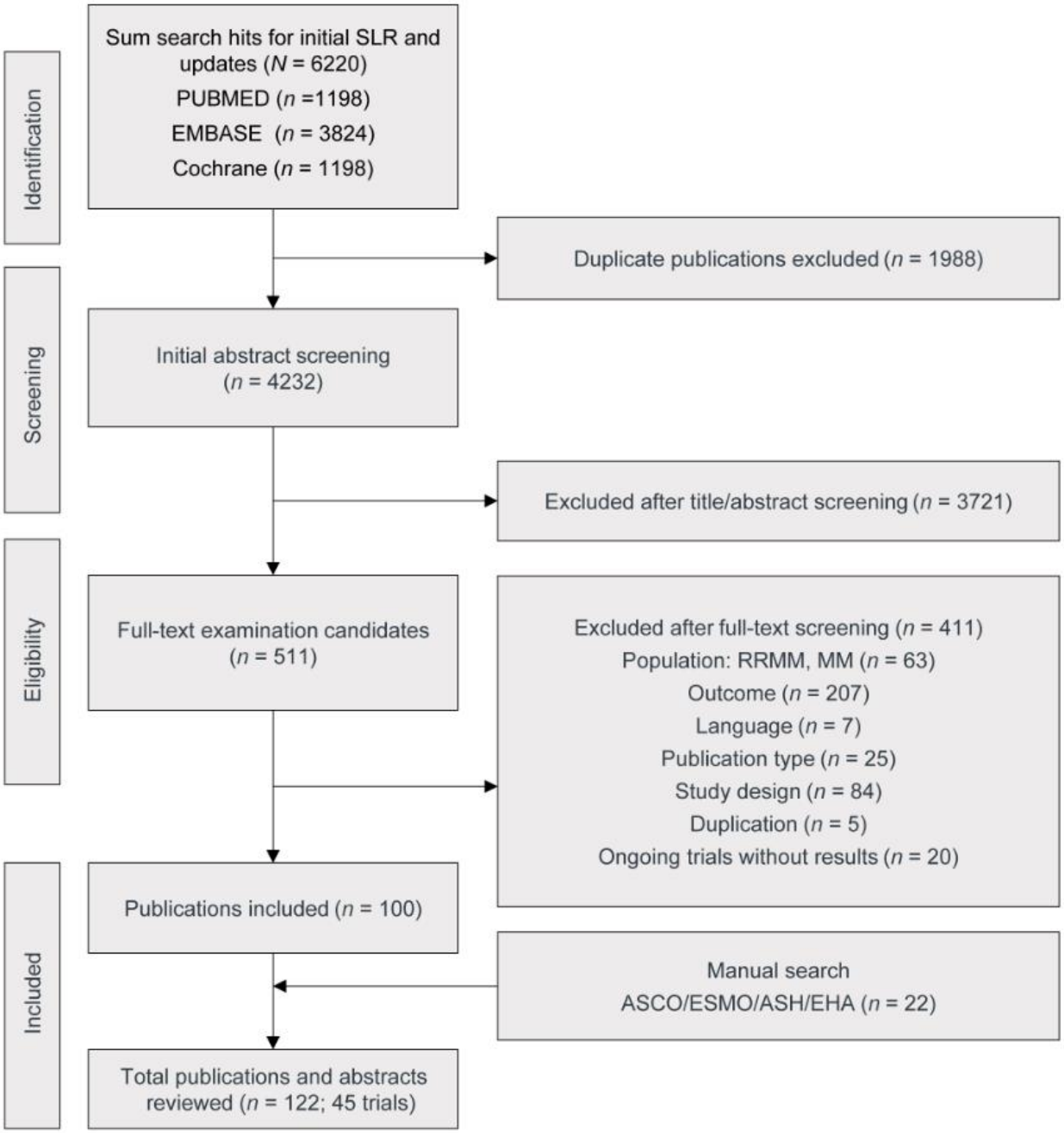
Table 67. EHA search terms

Nr	Syntax	Hits: 4 March 2021
#1	Multiple Myeloma 01/01/2018 to 04/03/2021	51

13.2 Systematic selection of studies

The PRISMA flow diagram of the review process is presented in Figure 35.

Figure 35. PRISMA diagram for randomised controlled trials



A summary of the trials identified in the clinical SLR considered relevant for the decision problem are shown below, in Table 68, with baseline characteristics in Table 69.

Table 68. Summary of trials relevant to the decision problem

Trial	Trial ID	Treatment arm	Location	Recruitment period	Median follow-up length (months)
ALCYONE trial **[159]** **[160]** **[161]** **[162]** **[130]** **[163]** **[164]** **[165]**	NCT02195479	Dara+VMP VMP	Argentina, Australia, Belgium, Brazil, Bulgaria, Croatia, Czech Republic, Georgia, Germany, Greece, Hungary, Japan, Republic of Korea, Macedonia, Poland, Portugal, Romania, Russia, Serbia, Spain, Turkey, Ukraine, UK, US	2015-2016	40.1
VISTA trial **[112]** **[166]** **[167]** **[168]** **[169]** **[170]**	NCT00111319	VMP MP	Argentina, Australia, Austria, Belgium, Canada, China, Czech Republic, Finland, France, Germany, Greece, Hungary, Israel, Italy, Republic of Korea, Poland, Russia, Spain, Sweden, Taiwan, UK and Ireland, US	2004-2006	36.7a
MRC Myeloma IX **[113]**	ISRCTN68454111	MP CTd	Italy	2005-2008	44
Hungria et al. **[114]**	NCT01532856	MPT CTd Td	Brazil, Argentina	N/A	37.5
IFM 99–06[b] **[115]**	NCT00367185	MP MPT	France, Belgium, Switzerland	2000-2005	51.5
IFM 01/01 **[116]**	NCT00644306	MP MPT	France, Belgium	2002-2006	47.5
Sacchi et al. **[117]**	NCT01274403	MP MPT	Australia, Austria, Belarus, Belgium, Czech Republic, Denmark, France, Georgia, Germany, Greece, Ireland, Israel, Italy, Netherlands, Poland, Russian Federation, Spain, Sweden, Switzerland, Turkey, Ukraine, UK	2007-2008	30
FIRST trial **[118]** **[171]** **[172]** **[173]** **[174]**	NCT00689936	Rd cont Rd 18 MPT	Australia, Austria, Belgium, Canada, China, France, Germany, Greece, Ireland, Italy, Republic of Korea, New Zealand, Portugal, Spain, Sweden, Switzerland, Taiwan, UK, US	N/A	67

[175] **[176]** **[177]** **[178]** **[179]** **[134]** **[180]**					
UPFRONT **[119]** **[181]**	NCT00507416	Bd BTd BMP	US	2007-2010	42.7
SWOG-S0777º **[100]**	NCT00644228	VRd Rd cont	Multi country; North America, Asia Pacific	2008 - ?	55 months [99]
MAIA **[103]** **[182]** **[183]** **[184]**	NCT02252172	DRd Rd continuous	Multi country; North America, Europe, Austraila, Israel	2015 - ?	56.2

Abbreviation: Rd = lenalidomide, dexamethasone; DVMP = daratumumab, bortezomib, melphalan-prednisone; Ld continuous = lenalidomide, dexamethasone continuous; Rd 18 = lenalidomide, dexamethasone 18 months; CTd = cyclophosphamide, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; Vd = bortezomib, dexamethasone; MP = melphalan, prednisone; MPT = melphalan, prednisone, thalidomide; VMP = bortezomib, melphalan, prednisone

a. VISTA trial has several data cuts available. The data-cut with a median follow-up time of 36.7 months is used in NMA analysis due to the similar follow-up time as other trials in the network [20]. b. MEL100 arm is not reported

ºPatients without an intent for immediate ASCT were included. A subgroup analysis of patients 65–75 and >75 years old is provided and outcomes of these subgroups are included in this SLR as ASCT-ineligible patients.

Table 69. Baseline characteristics of relevant trials

Trials	Treatment arms	N	Median Age (years)	Female (%)	MM type-IgG (%)	ISS-stage III (%)	High-risk cytogenetic abnormality (%)*	ECOG ≥2 (%)	MRD assessment (threshold; method)
ALCYONE trial **[159]** **[160]** **[161]** **[162]** **[130]** **[163]** **[164]** **[165]**	Dara+VMP VMP	350 356	71	54 53	40.9 39.3	40.6 36.2	16.9 14.9	25.7 23.6	10-5; NGS
VISTA trial **[112]** **[166]** **[167]** **[168]** **[169]**	VMP MP	344 338	71 71	49 51	64 62	35 34	N/A	N/A	N/A

Trials	Treatment arms	N	Median Age (years)	Female (%)	MM type-IgG (%)	ISS-stage III (%)	High-risk cytogenetic abnormality (%)*	ECOG ≥2 (%)	MRD assessment (threshold; method)
[170]									
MRC Myeloma IX [113]	MP CTd	423 426	73 73	45.4 43.2	60.8 58.2	39 39.4	41.9 42.7	423 426	N/A
Hungria et al. [114]	MPT CTd TD	32 32 18	72.2 70 71.6	53.1 65.6 44.4	51.7 55.2 55.6	46.7 41.9 27.8	N/A	53.4 50.4 44.4	N/A
IFM 99–06[b] [115]	MP MPT	196 125	N/A	44 50	N/A	30 29	196 125	N/A	N/A
IFM 01/01 [116]	MP MPT	116 113	78.5	47 62	N/A	30 35	N/A	N/A	N/A
Sacchi et al. [117]	MP MPT	54 64	79 76	52 55	63 73	30 22	N/A	9 12	N/A
FIRST trial [118] [171] [172] [173] [174] [175] [176] [177] [178] [179] [134] [180]	Rd cont Rd18 MPT	535 541 547	73 73 73	45 50 48	62 61 64	40 40 41	17 20 19	22 21 20	N/A
UPFRONT [119] [181]	Vd VTd VMP	168 167 167	74.5 73 72	40 58 46	62 58 62	33 32 36	N/A	N/A	N/A
SWOG-S0777[o] [100]	VRd Rd cont	91 106							
MAIA [103] [182] [183] [184]	Dara+Ld Ld continuous	368 369							

Abbreviation: MRD = minimal residual disease; Dara+Rd = daratumumab plus Ld; Rd = lenalidomide, dexamethasone; DVMP = daratumumab, bortezomib, melphalan-prednisone; Ld continuous = lenalidomide, dexamethasone continuous; Rd 18 = lenalidomide, dexamethasone 18 months; CTd = cyclophosphamide, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; Vd = bortezomib, dexamethasone; MP = melphalan, prednisone; MPT = melphalan, prednisone, thalidomide; VMP = bortezomib, melphalan, prednisone

[b.] MEL100 arm is not reported [o]Patients without an intent for immediate ASCT were included. A subgroup analysis of patients 65–75 and >75 years old is provided and outcomes of these subgroups are included in this SLR as ASCT-ineligible patients.

These 11 trials reported sufficient data for an NMA analysis for clinical endpoints, namely OS, PFS, ORR, CR or better. The analysis is presented in Appendix F – Comparative analysis of efficacy and safety.

Table 70 below lists the 34 trials which were identified in original SLR, but were excluded for indirect treatment comparison as they were not relevant for the decision problem in Denmark.

Table 70. List of studies excluded from indirect treatment comparison

Study	Treatment arms	Reason not to include in ITC
Palumbo et al. [185]	VMPT-VT[a] VMP[a]	Treatments out of decision scope
San-Miguel et al. [162]	VMPS VMP	Treatments out of decision scope
GEM05 [186]	VMP-Lite[b] VTP	Treatments out of decision scope
MM-015 [187]	MPR-R MPR MP	Treatments out of decision scope
TMSG study [188]	MPT-T MP	Treatments out of decision scope
HOVON 49 [189]	MP MPT-T	Treatments out of decision scope
NMSG [190]	MPT-T MP	Treatments out of decision scope
GIMEMA [191] [192]	MPT-T MP	Treatments out of decision scope
Ludwig et al. [193]	VMCP with conv.(P)[c] VMCP with cont. (P)[d]	Treatments out of decision scope
HOVON87/NMSG18 [194]	MPT-T MPR-R	Treatments out of decision scope
IFM 95-01 [195]	MP M-DEX DEX DEX-IFN	Treatments out of decision scope
Magarotto et al. [196]	MPR CPR Rd-9	Treatments out of decision scope
GEM10 [197] [198]	Seq. VMP-Lite[e] + Rd Alt. VMP-Lite[e]+ Rd	Treatments out of decision scope
E1A06 [199]	MPT-T MPR-R	Treatments out of decision scope

Study	Treatment arms	Reason not to include in ITC
Ludwig et al. **[200]**	Td MP	Treatments out of decision scope
Dimopoulos et al. [201] **[202]**	ICd-300[f] ICd-400[f]	Treatments out of decision scope
Takezako et al. **[203]**	ERd Rd continuous	Treatments out of decision scope
CLARION trial **[204]** **[205]**	VMP CMP	Treatments out of decision scope
KEYNOTE 185 trial **[206]** **[207]**	Pembro-Rd Rd continuous	Treatments out of decision scope
IMPROVE MPB-study **[208]**	modified PETHEMA-VMP [g] JCOG-VMP [h]	Treatments out of decision scope
RV-MM-PI-0752 **[209]** **[210]** **[211]**	Rd9-L Rd continuous	Treatments out of decision scope
Myeloma XI [i] **[212]** **[213]** **[214]** **[215]**	CTda-L CTda CLda-L CLda	Treatments out of decision scope
Suzuki et al. **[216]**	MPT MP	Japanese population
GERMAIN **[217]**	VMP-R VMP-placebo	Treatments out of decision scope
ENDURANCE **[218]**	VRd KRd	Treatments out of decision scope
GEM-CLARIDEX **[219]** **[220]**	CRd Rd	Treatments out of decision scope
UNITO-EMN10 **[221]** **[222]**	Id ICd ITd IVd	Treatments out of decision scope
Кирилл Белоусов et al. **[223]**	VMP VLP	Treatments out of decision scope
AGMT MM-02 **[218]** **[224]**	KTd KRd	Treatments out of decision scope
TOURMALINE-MM4[j] **[225]**	Ixazomib Placebo	Treatments out of decision scope
TOURMALINE-MM2 **[226]**	IRd placebo-Rd	Treatments out of decision scope

Study	Treatment arms	Reason not to include in ITC
HOVON126 [227]	ITd-I ITd-placebo	Treatments out of decision scope
SWOG 1211 [228]	VRd-Elo VRd	Treatments out of decision scope
AMARC 03-16 [229]	Dara-VCD VCD	Insufficient data for analysis

Vd = bortezomib, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VRP = bortezomib, lenalidomide, prednisone; VMP = bortezomib, melphalan, prednisone; VMPS = VMP plus siltuximab; VMPT-VT = bortezomib, melphalan, prednisone, thalidomide that followed by maintenance with bortezomib plus thalidomide; VTd = bortezomib, thalidomide, dexamethasone; CRd = cyclophosphamide, lenalidomide, dexamethasone; CRda = attenuated cyclophosphamide, lenalidomide, dexamethasone; CMP = carfilzomib, melphalan, prednisone; CPR = cyclophosphamide, prednisone, lenalidomide; CTda = attenuated cyclophosphamide, thalidomide, dexamethasone; CTda-R/CLda-R = CTDa/CLDa plus lenalidomide mainenance; Dara+VMP = daratumumab plus VMP; DEX-IFN = dexamethasone-Interferon alpha; Dara+Rd = daratumumab plus Rd; ERd = elotuzumab plus Rd; Id = ixazomib, dexamethasone; IVd = ixazomib, bortezomib, dexamethasone; ICd = ixazomib, Cyclophosphamide, dexamethasone; IRd = ixazomib, lenalidomide, dexamethasone; ITd = ixazomib, thalidomide, dexamethasone; ITdI = ITd plus ixazomib maintenance; JCOG = Japan Clinical Oncology Group; KRd = carfilzomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone; Rd 18 = lenalidomide, dexamethasone 18 months; Rd 9 = lenalidomide, dexamethasone 9 months; Rd 9-R = Rd 9 with lenalidomide maintenace; Rd continuous = lenalidomide, dexamethasone continuous; M-DEX = melphalan, dexamethasone; MP = melphalan, prednisone; MPR = melphalan, prednisone, lenalidomide; MPR-R = MPR plus lenalidomide maintenance; MPT = melphalan, prednisone, thalidomide; MPT-T = MPT plus thalidomide maintenance; placebo-Rd = placebo followed with Rd maintenance; VRd-Elo = VRd plus elotuzumab.; VMCP = vincristin, melphalan, cyclophosphamide and prednisolone; [a] Velcade twice weekly during cycles 1 to 4 and once weekly during cycles 5 to 9 (all 6-week cycles). After the inclusion of the first 139 patients, Velcade therapy was modified to once weekly during cycles 1 to 9 (all 5-week cycles); [b] Velcade twice weekly during cycle 1, once weekly during cycles 2-6; [c] 14 days of prednisolone treatment in the induction phase per cycle; [d] 28 days of prednisolone treatment in the induction phase per cycle; [e] Velcade twice weekly during cycle 1, once weekly during cycles 2-9; [f] 13 x 28-day cycles of induction therapy with ixazomib 4.0 mg PO on days 1, 8, and 15, plus cyclophosphamide 300 mg/m2 (ICd-300 arm) or 400 mg/m2 (ICd-400 arm) PO on days 1, 8, and 15, plus dexamethasone 40 mg PO (20 mg in pts aged >75 years) on days 1, 8, 15, and 22; [g] Velcade is administered twice weekly in Cycle 1 (6-week cycle) followed by four weekly doses in cycles 2 to 9; 5-week cycles; [h] Velcade is administered in three weekly doses in cycles 1 to 9; 4-week cycles; [i] Outcomes related to transplant-ineligible patients is included in this SLR. Patients considered ineligible for transplantation at trial entry were randomly assigned (1:1) to induction with either attenuated CTD or attenuated CRD. Patients with a suboptimal response to induction treatment were randomly assigned (1:1) to cyclophosphamide, bortezomib and dexamethasone (CVD) or no CVD. Patients completing induction and intensification treatment (where applicable) and eligible were randomly assigned (1:1) to lenalidomide maintenance or observation; [j] The TOURMALINE-MM4 trial is designed designed to compare single-agent ixazomib maintenance to placebo for patients received a major positive response to initial therapy and have not undergone SCT; [k] Patients without an Intent for immediate ASCT were included. A subgroup analysis of 65-75 and >75 years old is provided and outcomes of these subgroups are included in this SLR as ASCT ineligible patients.

In the initial SLR and its subsequent updates, 411 publications were excluded at full-text screening stage. 169 out of the 411 publications were conference abstracts without relevant data. These publications are not listed in the table below for simplicity and were recorded as excluded on the basis of outcome of interest in the PRSMA flow diagram. In addition, 20 ongoing trials without results were listed in Table 72. In the end, 222 publications were recorded in Table 71.

Table 71. Publications excluded at full-text screening from the RCT review

Citation	Exclusion reason
Merz, Maximilian; Salwender, Hans; Haenel, Mathias; Mai, Elias K.; Bertsch, Uta; Kunz, Christina i wsp. (2015): Subcutaneous versus intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: an interim analysis from the prospective GMMG-MM5 trial. w: Haematologica 100 (7), s. 964–969. DOI: 10.3324/haematol.2015.124347.	Population out of scope

Citation	Exclusion reason
Song, Moo-Kon, Joo-Seop Chung, Ho-Jin Shin, Joon-Ho Moon, Je-Jung Lee, Sung-Soo Yoon, Jin-Seok Kim et al. "Cyclophosphamide-containing regimen (TCD) is superior to melphalan-containing regimen (MPT) in elderly multiple myeloma patients with renal impairment." Annals of hematology 91, no. 6 (2012): 889-896.	Study design out of scope
Delforge, Michel; Minuk, Leonard; Eisenmann, Jean-Claude; Arnulf, Bertrand; Canepa, Letizia; Fragasso, Alberto i wsp. (2015): Health related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. w: Haematologica 100 (6), s. 826–833. DOI: 10.3324/haematol.2014.120121.	Outcomes out of scope
Dimopoulos, Meletios A.; Palumbo, Antonio; Hajek, Roman; Kropff, Martin; Petrucci, Maria Teresa; Lewis, Philip i wsp. (2014): Factors that influence health-related quality of life in newly diagnosed patients with multiple myeloma aged ≥ 65 years treated with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance: results of a randomised trial. w: Leukemia & lymphoma 55 (7), s. 1489–1497. DOI: 10.3109/10428194.2013.847933.	Outcomes out of scope
Scheid, Christof; Sonneveld, Pieter; Schmidt-Wolf, Ingo G. H.; van der Holt, Bronno; El Jarari, Laila; Bertsch, Uta et al. (2014): Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial. In Haematologica 99 (1), pp. 148–154. DOI: 10.3324/haematol.2013.087585.	Population out of scope
Durie, Brian G. M.; Hoering, Antje; Abidi, Muneer H.; Rajkumar, S. Vincent; Epstein, Joshua; Kahanic, Stephen P. i wsp. (2017): Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. w: Lancet (London, England) 389 (10068), s. 519–527. DOI: 10.1016/S0140-6736(16)31594-X.	Population out of scope
Dimopoulos, Meletios A.; Delforge, Michel; Hájek, Roman; Kropff, Martin; Petrucci, Maria T.; Lewis, Philip i wsp. (2013): Lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance, improves health-related quality of life in newly diagnosed multiple myeloma patients aged 65 years or older: results of a randomised phase III trial. w: Haematologica 98 (5), s. 784–788. DOI: 10.3324/haematol.2012.074534.	Outcomes out of scope
White, Darrell J.; Bahlis, Nizar J.; Marcellus, Deb C.; Belch, Andrew; Stewart, A. Keith; Chen, Christine i wsp. (2013): Lenalidomide plus melphalan without prednisone for previously untreated older patients with multiple myeloma: a phase II trial. w: Clinical lymphoma, myeloma & leukemia 13 (1), s. 19–24. DOI: 10.1016/j.clml.2012.08.009.	Study design out of scope
Sonneveld (2012): Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomised phase III HOVON-65/GMMG-HD4 trial. w: JCO 30 (29), s. 3654. DOI: 10.1200/JCO.2012.46.6912.	Population out of scope
Morgan, Gareth J.; Davies, Faith E.; Gregory, Walter M.; Szubert, Alex J.; Bell, Sue E.; Drayson, Mark T. i wsp. (2012): Effects of induction and maintenance plus long-term bisphosphonates on bone disease in patients with multiple myeloma: the Medical Research Council Myeloma IX Trial. w: Blood 119 (23), s. 5374–5383. DOI: 10.1182/blood-2011-11-392522.	Study design out of scope
Delforge, Michel; Dhawan, Ravinder; Robinson, Don; Meunier, Juliette; Regnault, Antoine; Esseltine, Dixie-Lee i wsp. (2012): Healthrelated quality of life in elderly, newly diagnosed multiple myeloma patients treated with VMP vs. MP: results from the VISTA trial. w: European journal of haematology 89 (1), s. 16–27. DOI: 10.1111/j.1600-0609.2012.01788.x.	Outcomes out of scope
Kumar, Shaji; Flinn, Ian; Richardson, Paul G.; Hari, Parameswaran; Callander, Natalie; Noga, Stephen J. i wsp. (2012): Randomised, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. w: Blood 119 (19), s. 4375–4382. DOI: 10.1182/blood-2011-11-395749.	Population out of scope
Chen, R. A.; Tu, Y.; Cao, Y.; Liu, L.; Liang, Y. (2011): Bortezomib-dexamethasone or vincristine-doxorubicin-dexamethasone as induction therapy followed by thalidomide as maintenance	Population out of scope

Citation	Exclusion reason
therapy in untreated multiple myeloma patients. w: The Journal of international medical research 39 (5), s. 1975–1984. DOI: 10.1177/147323001103900544.	
Mateos, Maria-Victoria; Oriol, Albert; Martínez-López, Joaquín; Teruel, Ana-Isabel; Bengoechea, Enrique; Palomera, Luis i wsp. (2016): Outcomes with two different schedules of bortezomib, melphalan, and prednisone (VMP) for previously untreated multiple myeloma: matched pair analysis using long-term follow-up data from the phase 3 VISTA and PETHEMA/GEM05 trials. w: Annals of hematology 95 (12), s. 2033–2041. DOI: 10.1007/s00277-016-2835-3.	Publication type out of scope
Spicka, Ivan; Mateos, M. V.; Redman, K.; Dimopoulos, M. A.; Richardson, P. G. (2011): An overview of the VISTA trial: newly diagnosed, untreated patients with multiple myeloma ineligible for stem cell transplantation. w: Immunotherapy 3 (9), s. 1033–1040. DOI: 10.2217/imt.11.104.	Duplication
Giaccone, Luisa; Storer, Barry; Patriarca, Francesca; Rotta, Marcello; Sorasio, Roberto; Allione, Bernardino i wsp. (2011): Long-term follow-up of a comparison of nonmyeloablative allografting with autografting for newly diagnosed myeloma. w: Blood 117 (24), s. 6721– 6727. DOI: 10.1182/blood-2011-03-339945.	Population out of scope
Verelst, Silvia G. R.; Termorshuizen, F.; Uyl-de Groot, C. A.; Schaafsma, M. R.; Ammerlaan, A. H. M.; Wittebol, S. i wsp. (2011): Effect of thalidomide with melphalan and prednisone on health-related quality of life (HRQoL) in elderly patients with newly diagnosed multiple myeloma: a prospective analysis in a randomised trial. w: Annals of hematology 90 (12), s. 1427–1439. DOI: 10.1007/s00277-0111224-1.	Outcomes out of scope
Delforge, Michel; Terpos, Evangelos; Richardson, Paul G.; Shpilberg, Ofer; Khuageva, Nuriet K.; Schlag, Rudolf i wsp. (2011): Fewer bone disease events, improvement in bone remodeling, and evidence of bone healing with bortezomib plus melphalan-prednisone vs. melphalan-prednisone in the phase III VISTA trial in multiple myeloma. w: European journal of haematology 86 (5), s. 372–384. DOI: 10.1111/j.1600-0609.2011.01599.x.	Outcomes out of scope
Zonder, Jeffrey A.; Crowley, John; Hussein, Mohamad A.; Bolejack, Vanessa; Moore, Dennis F.; Whittenberger, Brock F. i wsp. (2010): Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomised Southwest Oncology Group trial (S0232). w: Blood 116 (26), s. 5838–5841. DOI: 10.1182/blood-2010-08-303487.	Population out of scope
Broyl, Annemiek; Corthals, Sophie L.; Jongen, Joost Lm; van der Holt, Bronno; Kuiper, Rowan; Knegt, Yvonne de i wsp. (2010): Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed multiple myeloma: a prospective analysis of data from the HOVON-65/GMMG-HD4 trial. w: The Lancet. Oncology 11 (11), s. 1057–1065. DOI: 10.1016/S1470-2045(10)70206-0.	Population out of scope
Roussou, Maria; Kastritis, Efstathios; Christoulas, Dimitrios; Migkou, Magdalini; Gavriatopoulou, Maria; Grapsa, Irini i wsp. (2010): Reversibility of renal failure in newly diagnosed patients with multiple myeloma and the role of novel agents. w: Leukemia research 34 (10), s. 1395–1397. DOI: 10.1016/j.leukres.2010.04.024.	Study design out of scope
Rajkumar, S. Vincent; Jacobus, Susanna; Callander, Natalie S.; Fonseca, Rafael; Vesole, David H.; Williams, Michael E. i wsp. (2010): Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. w: The Lancet. Oncology 11 (1), s. 29–37. DOI: 10.1016/S14702045(09)70284-0.	Population out of scope
Venon, Marie-Dominique; Roccaro, Aldo M.; Gay, Julie; Moreau, Anne-Sophie; Dulery, Remy; Facon, Thierry i wsp. (2009): Front line treatment of elderly multiple myeloma in the era of novel agents. w: Biologics : targets & therapy 3, s. 99–109.	Publication type out of scope

Citation	Exclusion reason
Jagannath, Sundar; Durie, Brian G. M.; Wolf, Jeffrey Lee; Camacho, Elber S.; Irwin, David; Lutzky, Jose i wsp. (2009): Extended follow-up of a phase 2 trial of bortezomib alone and in combination with dexamethasone for the frontline treatment of multiple myeloma. w: British journal of haematology 146 (6), s. 619–626. DOI: 10.1111/j.1365-2141.2009.07803.x.	Study design out of scope
Kyle, Robert A.; Jacobus, Susanna; Friedenberg, William R.; Slabber, Coenraad Frederik; Rajkumar, S. Vincent; Greipp, Philip R. (2009): The treatment of multiple myeloma using vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP) alternating with high-dose cyclophosphamide and alpha(2)beta interferon versus VBMCP: results of a phase III Eastern Cooperative Oncology Group Study E5A93. w: Cancer 115 (10), s. 2155–2164. DOI: 10.1002/cncr.24221.	Population out of scope
Breitkreutz, I.; Raab, M. S.; Vallet, S.; Hideshima, T.; Raje, N.; Mitsiades, C. i wsp. (2008): Lenalidomide inhibits osteoclastogenesis, survival factors and bone-remodeling markers in multiple myeloma. w: Leukemia 22 (10), s. 1925–1932. DOI: 10.1038/leu.2008.174.	Study design out of scope
Barlogie, Bart; Pineda-Roman, Mauricio; van Rhee, Frits; Haessler, Jeff; Anaissie, Elias; Hollmig, Klaus i wsp. (2008): Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. w: Blood 112 (8), s. 3115–3121. DOI: 10.1182/blood-2008-03-145235.	Population out of scope
Rajkumar, S. Vincent; Rosiñol, Laura; Hussein, Mohamad; Catalano, John; Jedrzejczak, Wieslaw; Lucy, Lela i wsp. (2008): Multicenter, randomised, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. w: Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26 (13), s. 2171–2177. DOI: 10.1200/JCO.2007.14.1853.	Population out of scope
Pineda-Roman, Mauricio; Zangari, Maurizio; Haessler, Jeff; Anaissie, Elias; Tricot, Guido; van Rhee, Frits i wsp. (2008): Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2. w: British journal of haematology 140 (6), s. 625–634. DOI: 10.1111/j.1365-2141.2007.06921.x.	Study design out of scope
Lokhorst, Henk M.; Schmidt-Wolf, Ingo; Sonneveld, Pieter; van der Holt, Bronno; Martin, Hans; Barge, Rene i wsp. (2008): Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. w: Haematologica 93 (1), s. 124–127. DOI: 10.3324/haematol.11644.	Population out of scope
Facon, Thierry; Darre, Stéphane (2007): Frontline treatment in multiple myeloma patients not eligible for stem-cell transplantation. w: Best practice & research. Clinical haematology 20 (4), s. 737–746. DOI: 10.1016/j.beha.2007.09.004.	Publication type out of scope
Zangari, Maurizio; Barlogie, Bart; Cavallo, Federica; Bolejack, Vanessa; Fink, Louis; Tricot, Guido (2007): Effect on survival of treatment-associated venous thromboembolism in newly diagnosed multiple myeloma patients. w: Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 18 (7), s. 595–598. DOI: 10.1097/MBC.0b013e3281067fb2.	Population out of scope
Avilés, Agustin; Nambo, María J.; Neri, Natividad; Castañeda, Claudia; Cleto, Sergio; Huerta-Guzmán, Judith (2007): Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. w: Medical oncology (Northwood, London, England) 24 (2), s. 227–230.	Population out of scope
Zervas, K.; Mihou, D.; Katodritou, E.; Pouli, A.; Mitsouli, C. H.; Anagnostopoulos, A. i wsp. (2007): VAD-doxil versus VAD-doxil plus thalidomide as initial treatment for multiple myeloma: results of a multicenter randomised trial of the Greek Myeloma Study Group. w: Annals of oncology : official journal of the European Society for Medical Oncology 18 (8), s. 1369–1375. DOI: 10.1093/annonc/mdm178.	Population out of scope
Sonneveld, Pieter; van der Holt, Bronno; Segeren, Christine M.; Vellenga, Edo; Croockewit, Alexandra J.; Verhoe, Gregor E. G. i wsp. (2007): Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. w: Haematologica 92 (7), s. 928–935.	Population out of scope

Citation	Exclusion reason
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Pönisch, W.; Mitrou, P. S.; Merkle, K.; Herold, M.; Assmann, M.; Wilhelm, G. i wsp. (2006): Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone--a randomised phase III study of the East German Study Group of Hematology and Oncology (OSHO). w: Journal of cancer research and clinical oncology 132 (4), s. 205–212. DOI: 10.1007/s00432-005-0074-4.	Population out of scope
Rajkumar, S. Vincent; Blood, Emily; Vesole, David; Fonseca, Rafael; Greipp, Philip R. (2006): Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. w: Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24 (3), s. 431–436. DOI: 10.1200/JCO.2005.03.0221.	Population out of scope
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Cook, G.; Clark, R. E.; Morris, T. C. M.; Robertson, M.; Lucie, N. P.; Anderson, S. i wsp. (2004): A randomised study (WOS MM1) comparing the oral regime Z-Dex (idarubicin and dexamethasone) with vincristine, adriamycin and dexamethasone as induction therapy for newly diagnosed patients with multiple myeloma. w: British journal of haematology 126 (6), s. 792–798. DOI: 10.1111/j.1365-2141.2004.05127.x	Population out of scope
Lund, Johan; Gruber, Astrid; Lauri, Birgitta; Duru, Adil Doganay; Blimark, Cecilie; Swedin, Agneta et al. (2018): Lenalidomide versus lenalidomide + dexamethasone prolonged treatment after second-line lenalidomide + dexamethasone induction in multiple myeloma. In Cancer medicine 7 (6), pp. 2256–2268. DOI: 10.1002/cam4.1422.	Population out of scope
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Tuchman, Sascha A.; Moore, Joseph O.; DeCastro, Carlos D.; Li, Zhiguo; Sellars, Emily; Kang, Yubin et al. (2017): Phase II study of dose-attenuated bortezomib, cyclophosphamide and dexamethasone ("VCD-Lite") in very old or otherwise toxicity-vulnerable adults with newly diagnosed multiple myeloma. In Journal of geriatric oncology 8 (3), pp. 165–169. DOI: 10.1016/j.jgo.2017.02.004.	Study design out of scope
Raza, Shahzad; Safyan, Rachael A.; Lentzsch, Suzanne (2017): Immunomodulatory Drugs (IMiDs) in Multiple Myeloma. In Current cancer drug targets 17 (9), pp. 846–857. DOI: 10.2174/1568009617666170214104426.	Publication type out of scope

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Berdeja, Jesus G.; Bauer, Todd; Arrowsmith, Edward; Essell, James; Murphy, Patrick; Reeves, James A. et al. (2017): Phase II study of bendamustine, bortezomib and dexamethasone (BBD) in the first-line treatment of patients with multiple myeloma who are not candidates for high dose chemotherapy. In British journal of haematology 177 (2), pp. 254–262. DOI: 10.1111/bjh.14536.	Study design out of scope
Lu, Jin; Lee, Jae H.; Huang, Shang-Yi; Qiu, Lugui; Lee, Je-Jung; Liu, Ting et al. (2017): Continuous treatment with lenalidomide and low-dose dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma in Asia: subanalysis of the FIRST trial. In British journal of haematology 176 (5), pp. 743–749. DOI: 10.1111/bjh.14465.	Duplication
Mian, Hira S.; Wildes, Tanya M. (2018): Novel Treatments for Multiple Myeloma: What Role Do They Have in Older Adults? In Drugs & aging 35 (4), pp. 289–302. DOI: 10.1007/s40266-018-0539-1.	Publication type out of scope
Remya S., Sudha M.J., Nair R.B., Jayakumar K.L. (2017): A prospective comparative study of safety of lenalidomide plus dexamethasone combination therapy versus VAD (Vincristine, Doxorubicin and Dexamethasone) regimen in the treatment of multiple myeloma. In IJPSR 8 (11). DOI: 10.13040/IJPSR.0975-8232.8(11).4645-52.	Study design out of scope
Lin J., Chen J., Zeng Z., Qiu D., Wang J.: Efficacy and safety of pegylated liposomal doxorubicin for multiple myeloma: A systematic review and meta-analysis of randomised controlled trials International Journal of Clinical and Experimental Medicine 2017 10:6.	Publication type out of scope
Wang, Yan; Xu, Wenbin; Shen, Yang; Xu, Pengpeng; Mi, Jianqing; Yan, Hua; Li, Junmin (2017): Treatment outcome and prognostic factor in fit elderly patients with multiple myeloma received frontline induction of bortezomib based regimen (PAD or VCD). In Transl. Cancer Res. 6 (3), pp. 502–510. DOI: 10.21037/tcr.2017.06.17.	Study design out of scope
Tandon, Nidhi; Kumar, Shaji K. (2017): Highlights of Multiple Myeloma at the Annual Meeting of American Society of Hematology, 2016. In Indian journal of hematology & blood transfusion: an official journal of Indian Society of Hematology and Blood Transfusion 33 (2), pp. 153–158. DOI: 10.1007/s12288-017-0796-x.	Publication type out of scope
Berenson, James; Manges, Robert; Badarinath, Suprith; Cartmell, Alan; McIntyre, Kristi; Lyons, Roger et al. (2017): A phase 2 safety study of accelerated elotuzumab infusion, over less than 1 h, in combination with lenalidomide and dexamethasone, in patients with multiple myeloma. In American journal of hematology 92 (5), pp. 460–466. DOI: 10.1002/ajh.24687.	Study design out of scope
Blommestein, Hedwig M.; van Beurden-Tan, Chrissy H. Y.; Franken, Margreet G.; Uyl-de Groot, Carin A.; Sonneveld, Pieter; Zweegman, Sonja (2019): Efficacy of first-line treatments for multiple myeloma patients not eligible for stem cell transplantation - A Network Meta-analysis. In Haematologica. DOI: 10.3324/haematol.2018.206912.	Publication type out of scope
Gambella, Manuela; Omedé, Paola; Spada, Stefano; Muccio, Vittorio Emanuele; Gilestro, Milena; Saraci, Elona et al. (2018): Minimal residual disease by flow cytometry and allelic-specific oligonucleotide real-time quantitative polymerase chain reaction in patients with myeloma receiving lenalidomide maintenance. A pooled analysis. In Cancer. DOI: 10.1002/cncr.31854.	Study design out of scope
Baz, Rachid; Naqvi, Syeda Mahrukh Hussnain; Lee, Jae-Hoon; Brayer, Jason; Hillgruber, Nancy; Fridley, Brooke L. et al. (2018): Lenalidomide-based response-adapted therapy for older adults without high risk myeloma. In British journal of haematology. DOI: 10.1111/bjh.15700.	Study design out of scope
Elizabeth; Figg, William D.; Roschewski, Mark; Landgren, Ola (2018): Remission and Progression-Free Survival in Patients With Newly Diagnosed Multiple Myeloma Treated With Carfilzomib, Lenalidomide, and Dexamethasone. Five-Year Follow-up of a Phase 2 Clinical Trial. In JAMA oncology 4 (12), pp. 1781–1783. DOI: 10.1001/jamaoncol.2018.5457.	Study design out of scope
Royle, Kara-Louise; Gregory, Walter M.; Cairns, David A.; Bell, Sue E.; Cook, Gordon; Owen, Roger G. et al. (2018): Quality of life during and following sequential treatment of previously untreated patients with multiple myeloma. Findings of the Medical Research Council Myeloma IX randomised study. In British journal of haematology 182 (6), pp. 816–829. DOI: 10.1111/bjh.15459.	Outcomes out of scope

Citation	Exclusion reason
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Lund, Johan; Gruber, Astrid; Lauri, Birgitta; Duru, Adil Doganay; Blimark, Cecilie; Swedin, Agneta et al. (2018): Lenalidomide versus lenalidomide + dexamethasone prolonged treatment after second-line lenalidomide + dexamethasone induction in multiple myeloma. In Cancer medicine 7 (6), pp. 2256–2268. DOI: 10.1002/cam4.1422.	Population out of scope
Isoda, Atsushi; Murayama, Kayoko; Ito, Shigeki; Kohara, Yoichi; Iino, Masaki; Miyazawa, Yuri et al. (2018): Bortezomib maintenance therapy in transplant-ineligible myeloma patients who plateaued after bortezomib-based induction therapy. A multicenter phase II clinical trial. In International journal of hematology 108 (1), pp. 39–46. DOI: 10.1007/s12185-018-2448-9.	Study design out of scope
D'Agostino, Mattia; Paoli, Lorenzo de; Conticello, Concetta; Offidani, Massimo; Ria, Roberto; Petrucci, Maria Teresa et al. (2018): Continuous therapy in standard- and high-risk newly-diagnosed multiple myeloma. A pooled analysis of 2 phase III trials. In Critical reviews in oncology/hematology 132, pp. 9–16. DOI: 10.1016/j.critrevonc.2018.09.008.	Study design out of scope
Heaney, Jennifer L. J.; Campbell, John P.; Iqbal, Gulnaz; Cairns, David; Richter, Alex; Child, J. Anthony et al. (2018): Characterisation of immunoparesis in newly diagnosed myeloma and its impact on progression-free and overall survival in both old and recent myeloma trials. In Leukemia 32 (8), pp. 1727–1738. DOI: 10.1038/s41375-018-0163-4.	Study design out of scope
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Li, Feng; Yao, Fu-Sheng; Zhu, Xi-Jun; Gu, Wei-Ying; Wang, Xiao-Hua; Chen, Bing et al. (2019): A randomised phase II, open-label and multicenter study of combination regimens of bortezomib at two doses by subcutaneous injection for newly diagnosed multiple myeloma patients. In Journal of cancer research and clinical oncology. DOI: 10.1007/s00432-019-02967-3.	Population out of scope
Larocca, Alessandra; Mina, Roberto; Offidani, Massimo; Liberati, Anna Marina; Ledda, Antonio; Patriarca, Francesca et al. (2019): First-line therapy with either bortezomib-melphalan-prednisone or lenalidomide-dexamethasone followed by lenalidomide for transplant-ineligible multiple myeloma patients. A pooled analysis of two randomised trials. In Haematologica. DOI: 10.3324/haematol.2019.220657.	Study design out of scope
Straka, Christian; Knop, Stefan; Vogel, Martin; Müller, Jürgen; Kropff, Martin; Metzner, Bernd et al. (2019): Bortezomib consolidation following autologous transplant in younger and older patients with newly diagnosed multiple myeloma in two phase III trials. In European journal of haematology 103 (3), pp. 255–267. DOI: 10.1111/ejh.13281.	Population out of scope
Leleu, Xavier; Fouquet, Guillemette; Richez, Valentine; Guidez, Stéphanie; Duhamel, Alain; Machuron, François et al. (2019): Carfilzomib Weekly plus Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Multiple Myeloma (IFM 2012-03). A Phase I Trial. In Clinical cancer research : an official journal of the American Association for Cancer Research 25 (14), pp. 4224–4230. DOI: 10.1158/1078-0432.CCR-18-3642.	Study design out of scope
Dimopoulos, Meletios A.; Laubach, Jacob P.; Echeveste Gutierrez, Maria Asunción; Grzasko, Norbert; Hofmeister, Craig C.; SanMiguel, Jesus F. et al. (2019): Ixazomib maintenance therapy in newly diagnosed multiple myeloma. An integrated analysis of four phase I/II studies. In European journal of haematology 102 (6), pp. 494–503. DOI: 10.1111/ejh.13231.	Study design out of scope
Syed, Yahiya Y. (2019): Daratumumab. A Review in Combination Therapy for Transplant-Ineligible Newly Diagnosed Multiple Myeloma. In Drugs 79 (4), pp. 447–454. DOI: 10.1007/s40265-019-01080-6.	Publication type out of scope

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Xie, Jingmei; Wan, Ning; Liang, Zhuoru; Zhang, Tiantian; Jiang, Jie (2019): Ixazomib - the first oral proteasome inhibitor. In Leukemia & lymphoma 60 (3), pp. 610–618. DOI: 10.1080/10428194.2018.1523398.	Publication type out of scope
Baz, Rachid; Naqvi, Syeda Mahrukh Hussnain; Lee, Jae-Hoon; Brayer, Jason; Hillgruber, Nancy; Fridley, Brooke L. et al. (2018): Lenalidomide-based response-adapted therapy for older adults without high risk myeloma. In British journal of haematology. DOI: 10.1111/bjh.15700.	Study design out of scope
Rodríguez-Otero, Paula; Mateos, María Victoria; Martínez-López, Joaquín; Hernández, Miguel-Teodoro; Ocio, Enrique M.; Rosiñol, Laura et al. (2019): Predicting long-term disease control in transplant-ineligible patients with multiple myeloma. Impact of an MGUS-like signature. In Blood cancer journal 9 (4), p. 36. DOI: 10.1038/s41408-019-0176-x.	Outcome out of scope
Binder, Moritz; Rajkumar, S. Vincent; Ketterling, Rhett P.; Dispenzieri, Angela; Lacy, Martha Q.; Gertz, Morie A. et al. (2019): Substratification of patients with newly diagnosed standard-risk multiple myeloma. In British journal of haematology 185 (2), pp. 254– 260. DOI: 10.1111/bjh.15800.	Outcome out of scope
Cook, Gordon; Royle, Kara-Louise; Pawlyn, Charlotte; Hockaday, Anna; Shah, Vallari; Kaiser, Martin F. et al. (2019): A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance Risk Profile). A development and validation study. In The Lancet. Haematology 6 (3), e154-e166. DOI: 10.1016/S2352-3026(18)30220-5.	Outcome out of scope
Klausen, Tobias W.; Gregersen, Henrik; Abildgaard, Niels; Andersen, Niels Frost; Frølund, Ulf Christian; Gimsing, Peter et al. (2019): The majority of newly diagnosed myeloma patients do not fulfill the inclusion criteria in clinical phase III trials. In Leukemia 33 (2), pp. 546–549. DOI: 10.1038/s41375-018-0272-0.	Outcome out of scope
Huang PA, Beedie SL, Chau CH, Venzon DJ, Gere S, Kazandjian D, Korde N, Mailankody S, Landgren O, Figg WD. Cereblon gene variants and clinical outcome in multiple myeloma patients treated with lenalidomide. Sci Rep. 2019 Oct 16;9(1):14884. doi: 10.1038/s41598-019-51446-9. PMID: 31619706; PMCID: PMC6795854.	Population out of scope
Usmani SZ, Schjesvold F, Oriol A, Karlin L, Cavo M, Rifkin RM, Yimer HA, LeBlanc R, Takezako N, McCroskey RD, Lim ABM, Suzuki K, Kosugi H, Grigoriadis G, Avivi I, Facon T, Jagannath S, Lonial S, Ghori RU, Farooqui MZH, Marinello P, San-Miguel J; KEYNOTE-185 Investigators. Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomised, open-label, phase 3 trial. Lancet Haematol. 2019 Sep;6(9):e448-e458. doi: 10.1016/S23523026(19)30109-7. Epub 2019 Jul 18. PMID: 31327689.	Duplication
Li F, Yao FS, Zhu XJ, Gu WY, Wang XH, Chen B, Huang DP, Ding JH, Wu TQ, Zhu Y, Zhao Q, Tang YM, Song P, Zhou XG, An ZM, Guo X, Wang XL, Zhong L, Xie XB, Zhai YP. A randomised phase II, open-label and multicenter study of combination regimens of bortezomib at two doses by subcutaneous injection for newly diagnosed multiple myeloma patients. J Cancer Res Clin Oncol. 2019 Sep;145(9):2343-2355. doi: 10.1007/s00432-019-02967-3. Epub 2019 Jul 6. PMID: 31280348.	Population out of scope
Suzuki K, Doki N, Meguro K, Sunami K, Kosugi H, Sasaki O, Takagi T, Murakami H, Shimizu K. Report of phase I and II trials of melphalan, prednisolone, and thalidomide triplet combination therapy versus melphalan and prednisolone doublet combination therapy in Japanese patients with newly diagnosed multiple myeloma ineligible for autologous stem cell	Duplication

Citation	Exclusion reason
transplantation. Int J Hematol. 2019 Oct;110(4):447-457. doi: 10.1007/s12185-019-02700-3. Epub 2019 Jul 19. PMID: 31325152.	
Leleu X, Fouquet G, Richez V, Guidez S, Duhamel A, Machuron F, Karlin L, Kolb B, Tiab M, Araujo C, Meuleman N, Malfuson JV, Bourquard P, Lenain P, Roussel M, Jaccard A, Pétillon MO, Belhadj-Merzoug K, Lepeu G, Chrétien ML, Fontan J, Rodon P, Schmitt A, Offner F, Voillat L, Cereja S, Kuhnowski F, Rigaudeau S, Decaux O, Humbrecht-Kraut C, Frayfer J, Fitoussi O, Roos-Weil D, Eisenmann JC, Dorvaux V, Voog EG, Attal M, Moreau P, Avet-Loiseau H, Hulin C, Facon T. Carfilzomib Weekly plus Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Multiple Myeloma (IFM 2012-03): A Phase I Trial. Clin Cancer Res. 2019 Jul 15;25(14):4224-4230. doi: 10.1158/1078-0432.CCR-18-3642. Epub 2019 May 3. PMID: 31053600.	Study design out of scope
Yokoyama A, Kada A, Saito AM, Sawamura M, Komeno T, Sunami K, Takezako N. Phase II Study of Treatment for Newly Diagnosed Multiple Myeloma Patients Over 75 Years Old with Alternating Bortezomib/dexamethasone and Lenalidomide/dexamethasone: the MARBLE Trial. Acta Med Okayama. 2019 Dec;73(6):547-552. doi: 10.18926/AMO/57722. PMID: 31871340.	Study design out of scope
Ishida T, Kimura H, Ozaki S, Kubo K, Sunami K, Takezako N, Fujita H, Hayashi T, Kiguchi T, Ohashi K, Yamamoto S, Takamatsu H, Kosugi H, Ohta K, Sakai R, Handa H, Kondo S, Abe Y, Omoto E, Mitani K, Morita S, Murakami H, Shimizu K. Continuous lenalidomide treatment after bortezomib-melphalan-prednisolone therapy for newly diagnosed multiple myeloma. Ann Hematol. 2020 May;99(5):1063-1072. doi: 10.1007/s00277-020-03988-6. Epub 2020 Apr 4. PMID: 32248251.	Study design out of scope
Stork M, Sandecká V, Boichuk I, Adam Z, Krejci M, Brozova L, Sevcikova S, Pour L. Bortezomib and Thalidomide Treatment Results in Newly Diagnosed Transplant-Ineligible Multiple Myeloma Patients are Comparable in Long-Term Follow-Up. Klin Onkol. 2019 Fall;32(6):445-452. English. doi: 10.14735/amko2019445. PMID: 31842563.	Study design out of scope
Schepers AJ, Jones AR, Reeves BN, Tuchman SA, Bates JS. A comparison of response in the presence or absence of a delay in induction therapy with bortezomib, lenalidomide, and dexamethasone. J Oncol Pharm Pract. 2019 Oct;25(7):1692-1698. doi: 10.1177/1078155218815283. Epub 2018 Nov 30. PMID: 30501382.	Study design out of scope
Facon T, Dimopoulos MA, Meuleman N, Belch A, Mohty M, Chen WM, Kim K, Zamagni E, Rodriguez-Otero P, Renwick W, Rose C, Tempescul A, Boyle E, Manier S, Attal M, Moreau P, Macro M, Leleu X, Lorraine Chretien M, Ludwig H, Guo S, Sturniolo M, Tinel A, Silvia Monzini M, Costa B, Houck V, Hulin C, Yves Mary J. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. Leukemia. 2020 Jan;34(1):224-233. doi: 10.1038/s41375019-0539-0. Epub 2019 Aug 19. PMID: 31427722; PMCID: PMC7214253.	Study design out of scope
Takamatsu H, Iida S, Shibayama H, Shibayama K, Yamazaki H, Suzuki K. Daratumumab, lenalidomide, and dexamethasone in Japanese patients with transplant-ineligible newly diagnosed multiple myeloma: a phase 1b study. Int J Hematol. 2020 May;111(5):692-701. doi: 10.1007/s12185-020-02825-w. Epub 2020 Jan 30. PMID: 32002821.	Study design out of scope
Knauf W, Dingeldein G, Schlag R, Welslau M, Moehler T, Terzer T, Walter S, Habermehl C, Kunz C, Goldschmidt H, Raab MS; BPV trial group. First-line therapy with bendamustine/prednisone/bortezomib-A GMMG trial for non-transplant eligible symptomatic multiple myeloma patients. Eur J Haematol. 2020 Aug;105(2):116-125. doi: 10.1111/ejh.13409. Epub 2020 May 26. PMID: 32155662.	Study design out of scope
Bradbury CA, Craig Z, Cook G, Pawlyn C, Cairns DA, Hockaday A, Paterson A, Jenner MW, Jones JR, Drayson MT, Owen RG, Kaiser MF, Gregory WM, Davies FE, Child JA, Morgan GJ, Jackson GH. Thrombosis in patients with myeloma treated in the Myeloma IX and Myeloma XI phase 3 randomised controlled trials. Blood. 2020 Aug 27;136(9):1091-1104. doi: 10.1182/blood.2020005125. Erratum in: Blood. 2020 Oct 22;136(17):1994. PMID: 32438407; PMCID: PMC7453153.	Outcome out of scope

Citation	Exclusion reason
Merz M, Dechow T, Scheytt M, Schmidt C, Hackanson B, Knop S. The clinical management of lenalidomide-based therapy in patients with newly diagnosed multiple myeloma. Ann Hematol. 2020 Aug;99(8):1709-1725. doi: 10.1007/s00277-020-04023-4. Epub 2020 Apr 16. PMID: 32296915; PMCID: PMC7340649.	Publication type out of scope
Anne Bird, S., Cairns, D., Davies, F. E., Boyd, K., Cook, G., Drayson, M. T., . . . Pawlyn, C. (2019). Sex differences in multiple myeloma biology and clinical outcomes: Results from 3894 patients in the myeloma XI trial. Blood, 134. doi:10.1182/blood-2019-128041	Outcome out of scope
Baysal, M., Demirci, U., Bas, V., Gulsaran, S. K., Umit, E., Kirkizlar, H. O., . . . Demir, A. M. (2020). Could ratio of hemoglobin to red cell distribution width and ratio of absolute lymphocyte count to absolute monocyte count be a prognostic tool in newly diagnosed multiple myeloma patients? Acta Haematologica Polonica, 51(2), 81-87. doi:10.2478/ahp-2020-0016	Study design out of scope
Baz, R., Naqvi, S. M. H., Lee, J. H., Brayer, J., Hillgruber, N., Fridley, B. L., . . . Alsina, M. (2019). Lenalidomide-based responseadapted therapy for older adults without high risk myeloma. British journal of haematology, 184(5), 735-743. doi:10.1111/bjh.15700	Study design out of scope
Belch, A., Bahlis, N. J., White, D., Cheung, M., Chen, C., Shustik, C., . . . Facon, T. (2019). Phase 3 FIRST Trial in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Subgroup Analysis of Patients From Canada and the United States. Clinical Lymphoma, Myeloma and Leukemia, 19(10), e225. doi:10.1016/j.clml.2019.09.374	Outcome out of scope
Bhutani, M., & Usmani, S. Z. (2020). Quadruplets come of age for newly diagnosed multiple myeloma. The Lancet, 395(10218), 94-96. doi:10.1016/S0140-6736(19)33063-6	Study design out of scope
Binder, M., Rajkumar, S. V., Ketterling, R. P., Dispenzieri, A., Lacy, M. Q., Gertz, M. A., . . . Kumar, S. K. (2019). Substratification of patients with newly diagnosed standard-risk multiple myeloma. British journal of haematology, 185(2), 254-260. doi:10.1111/bjh.15800	Study design out of scope
Bobin, A., Fouquet, G., Duhamel, A., Labreuche, J., Manier, S., Karlin, L., . . . Leleu, X. (2020). IFM 2012-03 final analysis, carfilzomib maintenance for non-transplant eligible newly diagnosed multiple myeloma. HemaSphere, 4, 444. doi:10.1097/HS9.0000000000000404	Study design out of scope
Bobin, A., Fouquet, G., Manier, S., Karlin, L., Kolb, B., Tiab, M., . . . Leleu, X. (2019). Maintenance with Weekly Carfilzomib in Elderly newly Diagnosed Multiple Myeloma (IFM 2012-03). Clinical Lymphoma, Myeloma and Leukemia, 19(10), e44. doi:10.1016/j.clml.2019.09.066	Study design out of scope
Cairns, D., Pawlyn, C., Royle, K. L., Best, P., Bird, J., Bowcock, S., . . . Cook, G. (2019). Frailty-adjusted therapy in transplant noneligible patients with newly diagnosed multiple myeloma (fitness): A UK myeloma research alliance study, myeloma XIV. Blood, 134. doi:10.1182/blood-2019-126207	Study design out of scope
Chari, A., Goldschmidt, H., San-Miguel, J., McCarthy, H., Suzuki, K., Hungria, V., . . . Moreau, P. (2019). Subcutaneous (SC) Daratumumab (DARA) in Combination With Standard Multiple Myeloma (MM) Treatment Regimens: An Open-label, Multicenter Phase 2 Study (PLEIADES). Clinical Lymphoma, Myeloma and Leukemia, 19(10), e16-e17. doi:10.1016/j.clml.2019.09.023	Study design out of scope
Chari, A., Rodriguez-Otero, P., McCarthy, H., Suzuki, K., Hungria, V., Sureda Balari, A., . . . Touzeau, C. (2020). Subcutaneous daratumumab plus standard treatment regimens in patients with multiple myeloma across lines of therapy (PLEIADES): an open-label Phase II study. British journal of haematology. doi:10.1111/bjh.16980	Study design out of scope
Chari, A., San-Miguel, J., McCarthy, H., Suzuki, K., Hungria, V. T. M., Sureda, A., . . . Touzeau, C. (2019). Subcutaneous daratumumab plus standard treatment regimens in patients with multiple myeloma across lines of therapy: Pleiades study update. Blood, 134. doi:10.1182/blood-2019-123560	Study design out of scope
Covut, F., Ahmed, R., Samaras, C. J., Anwer, F., Mejia Garcia, A. V., Angelini, D. E., . . . Khouri, J. (2019). External validation of the impede VTE risk score in newly diagnosed multiple myeloma (MM) patients. Blood, 134. doi:10.1182/blood-2019-131400	Outcome out of scope

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Engelhardt, M., Yong, K., Bringhen, S., & Wäsch, R. (2019). Carfilzomib combination treatment as first-line therapy in multiple myeloma: Where do we go from the Carthadex (KTd)-trial update? Haematologica, 104(11), 2128-2131. doi:10.3324/haematol.2019.228684	Study design out of scope
Facon, T., Kotey, S., Tinel, A., Srinivasan, S., & Sturniolo, M. (2019). Impact of Early vs. Late Relapse in Patients With Newly Diagnosed Multiple Myeloma Ineligible for Transplant: A Phase 3 FIRST Trial Subanalysis. Clinical Lymphoma, Myeloma and Leukemia, 19(10), e228. doi:10.1016/j.clml.2019.09.378	Outcome out of scope
Facon, T., Kumar, S., Plesner, T., Orlowski, R. Z., Moreau, P., Bahlis, N., . . . Usmani, S. Z. (2019). Daratumumab plus lenalidomide and dexamethasone for untreated Myeloma. New England Journal of Medicine, 380(22), 2104-2115. doi:10.1056/NEJMoa1817249	Duplication
Facon, T., Lee, J. H., Moreau, P., Niesvizky, R., Dimopoulos, M., Hajek, R., . . . San-Miguel, J. (2019). Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma. Blood, 133(18), 1953-1963. doi:10.1182/blood-2018-09-874396	Duplication
Gries, K., Facon, T., Plesner, T., Usmani, S., Kumar, S., Orlowski, R. Z., . . . Perrot, A. (2019). Daratumumab, Lenalidomide, and Dexamethasone (D-Rd) Delivers a Reduction and Delay in Worsening of Pain Symptoms for Patients with Newly Diagnosed Multiple Myeloma Ineligible for Transplant. Clinical Lymphoma, Myeloma and Leukemia, 19(10), e225-e226. doi:10.1016/j.clml.2019.09.375	Outcome out of scope
Hagiwara, M., Panjabi, S., Delea, T., Yucel, E., & Fonseca, R. (2020). Burden of disease progression in patients with multiple myeloma in the US. Leukemia and Lymphoma, 61(1), 47-55. doi:10.1080/10428194.2019.1648802	Outcome out of scope
Hamadeh, I., Reese, E., Schneider, M., Williams, A., Arnall, J., Kachur, E., . . . Usmani, S. (2019). Patient tolerability and Estimation of Direct/Productivity costs associated with rapid infusion of daratumumab. Clinical Lymphoma, Myeloma and Leukemia, 19(10), e149. doi:10.1016/j.clml.2019.09.248	Outcome out of scope
Jackson, G. H., Davies, F. E., Pawlyn, C., Cairns, D. A., Striha, A., Collett, C., . . . Morgan, G. J. (2019). Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology, 20(1), 57-73. doi:10.1016/S1470-2045(18)30687-9	Duplication
Jones, J. R., Cairns, D., Pawlyn, C., Davies, F. E., Sigsworth, R., Jenner, M., . . . Morgan, G. (2019). Myeloma XI trial for newly diagnosed multiple myeloma (NDMM); long term second primary malignancy (SPM) incidence in the context of lenalidomide maintenance. Blood, 134. doi:10.1182/blood-2019-127469	Outcome out of scope
Kapoor, P., Gertz, M. A., Laplant, B., Malave, G. C., Wolfe, E., Muchtar, E., . . . Kumar, S. K. (2019). Phase 2 trial of daratumumab, ixazomib, lenalidomide and modified dose dexamethasone in patients with newly diagnosed multiple myeloma. Blood, 134. doi:10.1182/blood-2019-131476	Population out of scope
Klausen, T. W., Gregersen, H., Abildgaard, N., Andersen, N. F., Frølund, U. C., Gimsing, P., . . . Vangsted, A. J. (2019). The majority of newly diagnosed myeloma patients do not fulfill the inclusion criteria in clinical phase III trials. Leukemia, 33(2), 546-549. doi:10.1038/s41375-018-0272-0	Outcome out of scope
Kuiper, R., Broijl, A., van Duin, M., van Vliet, M. H., Levin, M. D., van Beers, E. H., . . . Zweegman, S. (2019). Prognostic and Predictive Performance of SKY92 Combined with R-ISS in Elderly Multiple Myeloma Patients in The Hovon-87/NMSG-18 Study. Clinical Lymphoma, Myeloma and Leukemia, 19(10), e10-e11. doi:10.1016/j.clml.2019.09.014	Outcome out of scope
Landgren, O., Hultcrantz, M., Lesokhin, A. M., Mailankody, S., Hassoun, H., Smith, E. L., . . . Korde, N. (2019). Weekly carfilzomib, lenalidomide, dexamethasone and daratumumab (wKRd-D) combination therapy provides unprecedented MRD negativity rates in newly diagnosed multiple myeloma: A clinical and correlative phase 2 study. Blood, 134. doi:10.1182/blood-2019-126378	Study design out of scope

Citation	Exclusion reason
Lee, J. H., Kim, S. H., Lee, H. S., Yoon, S. S., Shin, D. Y., Byun, J. M., . . . Lee, Y. J. (2019). Prognostic implication of inflammatory factor-based staging system in multiple myeloma in the new agent era. Blood, 134. doi:10.1182/blood-2019-127707	Study design out of scope
Manier, S., Dimopoulos, M. A., Hulin, C., Leleu, X., Delforge, M., Weisel, K. C., . . . Facon, T. (2019). Characterization of relapse and second-line therapy in lenalidomide-refractory, transplant-ineligible patients with newly diagnosed multiple myeloma: A subanalysis of the phase 3 first trial. Blood, 134. doi:10.1182/blood-2019-124557	Population out of scope
Perez Persona, E., Oiartzabal Ormategui, I., Diez Angulo, R., Unamunzaga Cilaurren, A., Parra Salinas, I. M., Santamaria Lopez, A., . . . Guinea De Castro, J. M. (2019). Velcadito. a phase II trial with low doses of bortezomib plus melphalan and prednisone for elderly patients (>75y) with newly diagnosed multiple myeloma. HemaSphere, 3, 955-956.	Outcome out of scope
Perrot, A., Facon, T., Plesner, T., Usmani, S. Z., Kumar, S., Bahlis, N. J., . . . Weisel, K. (2019). Faster and sustained improvement in health-related quality of life (HRQoL) for newly diagnosed multiple myeloma (NDMM) patients ineligible for transplant treated with daratumumab, lenalidomide, and dexamethasone (D-Rd) versus Rd alone: MAIA. Journal of Clinical Oncology, 37. doi:10.1200/JCO.2019.37.15_suppl.8016	Outcome out of scope
Qian, W., Wang, L., Li, P., Hu, Y., Wang, Q., Yi, K., . . . Xie, Y. (2020). Efficiency and tolerability of induction and consolidation therapy with arsenic trioxide/ bortezomib/ascorbic acid/dexamethasone (ABCD) regimen compared to bortezomib/ dexamethasone (BD) regimen in newly diagnosed myeloma patients. Cancer Management and Research, 12, 431-441. doi:10.2147/CMAR.S212455	Study design out of scope
Redder, L., Klausen, T. W., Vangsted, A. J., Gregersen, H., Andersen, N. F., Pedersen, R. S., . . . Abildgaard, N. (2019). Validation of a new clinical prediction model for outcome in newly diagnosed multiple myeloma patients not eligible for autologous stem-cell transplantation; a population-based study from the danish national multiple myeloma registry. Blood, 134. doi:10.1182/blood-2019128074	Study design out of scope
Ri, M., Iida, S., Maruyama, D., Saito, K., Saito, Y., Osaga, S., . . . Nagai, H. (2019). Lipidomic profiling of plasma samples in patients with newly diagnosed multiple myeloma; a biomarker study for predicting the response and toxicities of melphalan, prednisolone and bortezomib (MPB) regimen : An ancillary study of the JCOG1105 (JCOG1105A1). Blood, 134. doi:10.1182/blood-2019-122218	Study design out of scope
Sebag, M., Stakiw, J., Stephens, T. J., Padhiar, A., Kim, T., Shum, J., . . . Trudel, S. (2019). Lenalidomide plus bortezomib and dexamethasone in the treatment of newly diagnosed multiple myeloma: Results from a Canadian cost-effectiveness analysis. Blood, 134. doi:10.1182/blood-2019-123636	Study design out of scope
Stege, C. A. M., Nasserinejad, K., Van Der Spek, E., Van Kampen, R. J. W., Sohne, M., Thielen, N., . . . Zweegman, S. (2019). Efficacy and tolerability of ixazomib, daratumumab and low dose dexamethasone (Ixa Dara dex) in unfit and frail newly diagnosed multiple myeloma (NDMM) patients; Results of the interim efficacy analysis of the phase II HOVON 143 study. Blood, 134. doi:10.1182/blood2019-121694	Study design out of scope
Ulaner, G., Sobo, N., aO'Donoghue, J., Burnazi, E., Staton, K., Weber, W., . . . Landgren, C. O. (2019). Preclinical development and first-inhuman imaging of 89Zr-daratumumab for CD38 targeted imaging of myeloma. Journal of Nuclear Medicine, 60.	Outcome out of scope
Usmani, S. Z., Facon, T., Kumar, S., Plesner, T., Moreau, P., Basu, S., . . . Hulin, C. (2019). Impact of age on efficacy and safety of daratumumab in combination with lenalidomide and dexamethasone (D-Rd) in patients (pts) with transplant-ineligible newly diagnosed multiple myeloma (NDMM): MAIA. Journal of Clinical Oncology, 37. doi:10.1200/JCO.2019.37.15_suppl.8035	Outcome out of scope
Van Rhee, F., Zangari, M., Schinke, C. D., Tricot, G. J., Steward, D., Panozzo, S., . . . Barlogie, B. (2019). Long-term outcome of total therapy regimens: Impact of molecular subgroups. Blood, 134. doi:10.1182/blood-2019-131870	Study design out of scope

Citation	Exclusion reason
Weisel, K., Asemissen, A. M., Besemer, B., Hanel, M., Blau, W., Goerner, M., . . . Goldschmidt, H. (2020). Depth of response to isatuximab, carfilzomib, lenalidomide and dexamethasone (ISA-KRD) in frontline treatment of high-risk multiple myeloma: Interim analysis of the GMMG-concept trial. HemaSphere, 4, 58-59. doi:10.1097/HS9.0000000000000404	Study design out of scope
Yang, Y., Liu, Z., & Wang, H. (2020). Peripheral absolute lymphocyte count: An economical and clinical available immune-related prognostic marker for newly diagnosed multiple myeloma. Medical Science Monitor, 26. doi:10.12659/MSM.923716	Outcome out of scope
Zweegman, S., Usmani, S. Z., Chastain, K., Carey, J., Ren, K., Smith, E., . . . Facon, T. (2019). Bortezomib, lenalidomide, and dexamethasone (VRd) ± daratumumab (DARA) in patients (pts) with newly diagnosed multiple myeloma (NDMM) for whom transplant is not planned as initial therapy: A multicenter, randomised, phase III study (CEPHEUS). Journal of Clinical Oncology, 37. doi:10.1200/JCO.2019.37.15_suppl.TPS8056	Outcome out of scope
Durie BGM, Kumar SK, Usmani SZ, Nonyane BAS, Ammann EM, Lam A, Kobos R, Maiese EM, Facon T. Daratumumab-lenalidomidedexamethasone vs. standard-of-care regimens: Efficacy in transplant-ineligible untreated myeloma. Am J Hematol. 2020 Dec;95(12):1486-1494. doi: 10.1002/ajh.25963. Epub 2020 Sep 5. PMID: 32804408; PMCID: PMC7754114.	Outcome out of scope
Li J, Bao L, Xia Z, Wang S, Zhou X, Ding K, Zhang W, Yang W, Li B, Fu C, Chen B, Hua L, Wang L, Luo J, Yang Y, Xu T, Wang W, Huang Y, Wu G, Liu P. Ixazomib-based frontline therapy in patients with newly diagnosed multiple myeloma in real-life practice showed comparable efficacy and safety profile with those reported in clinical trial: a multi-center study. Ann Hematol. 2020 Nov;99(11):25892598. doi: 10.1007/s00277-020-04234-9. Epub 2020 Sep 6. PMID: 32892275; PMCID: PMC7474576.	Study design out of scope
Perrot A, Facon T, Plesner T, Usmani SZ, Kumar S, Bahlis NJ, Hulin C, Orlowski RZ, Nahi H, Mollee P, Ramasamy K, Roussel M, Jaccard A, Delforge M, Karlin L, Arnulf B, Chari A, He J, Ho KF, Van Rampelbergh R, Uhlar CM, Wang J, Kobos R, Gries KS, Fastenau J, Weisel K. Health-Related Quality of Life in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma: **Findings From the Phase III MAIA Trial. J Clin Oncol. 2021 Jan 20;39(3):227-237. doi: 10.1200/JCO.20.01370. Epub 2020 Dec 16. PMID: 33326255; PMCID: PMC8078427.**	Outcome out of scope
Chari A, Rodriguez-Otero P, McCarthy H, Suzuki K, Hungria V, Sureda Balari A, Perrot A, Hulin C, Magen H, Iida S, Maisnar V, Karlin L, Pour L, Parasrampuria DA, Masterson T, Kosh M, Yang S, Delioukina M, Qi M, Carson R, Touzeau C. Subcutaneous daratumumab plus standard treatment regimens in patients with multiple myeloma across lines of therapy (PLEIADES): an open-label Phase II study. Br J Haematol. 2021 Mar;192(5):869-878. doi: 10.1111/bjh.16980. Epub 2020 Jul 30. PMID: 33216361.	Study design out of scope
Michaleas S, Penninga E, Hovgaard D, Dalseg AM, Rosso A, Sarac SB, Jimenez JC, Fernández LL, Fernández CP, Mangas-SanJuan V, Garcia I, Payares-Herrera C, Sancho-López A, Enzmann H, de Castro Lopes Silva MSS, Duarte S, Pignatti F. EMA Review of Daratumumab (Darzalex) for the Treatment of Adult Patients Newly Diagnosed with Multiple Myeloma. Oncologist. 2020 Dec;25(12):1067-1074. doi: 10.1002/onco.13554. Epub 2020 Oct 16. PMID: 33026700; PMCID: PMC7938407.	Publication type out of scope
Hungria V, Martínez-Baños DM, Mateos MV, Dimopoulos MA, Cavo M, Heeg B, Garcia A, Lam A, Machnicki G, He J, Fernandez M. Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Standard of Care in Latin America for Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Propensity Score Matching Analysis. Adv Ther. 2020 Dec;37(12):4996-5009. doi: 10.1007/s12325-02001521-9. Epub 2020 Oct 16. PMID: 33067698; PMCID: PMC7595972.	Outcome out of scope
Rana R, Cockwell P, Drayson M, Cook M, Pratt G, Cairns DA, Pawlyn C, Jackson G, Davies F, Morgan G, Pinney JH. Renal outcome in patients with newly diagnosed multiple myeloma: results from the UK NCRI Myeloma XI trial. Blood Adv. 2020 Nov 24;4(22):58365845. doi: 10.1182/bloodadvances.2020002872. PMID: 33232472; PMCID: PMC7686889.	Outcome out of scope
Croft J, Ellis S, Sherborne AL, Sharp K, Price A, Jenner MW, Drayson MT, Owen RG, Chown S, Lindsay J, Karunanithi K, Hunter H, Gregory WM, Davies FE, Morgan GJ, Cook G, Atanesyan L,	Outcome out of scope

Citation	Exclusion reason
Savola S, Cairns DA, Jackson G, Houlston RS, Kaiser MF. Copy number evolution and its relationship with patient outcome-an analysis of 178 matched presentation-relapse tumor pairs from the Myeloma XI trial. Leukemia. 2020 Dec 1. doi: 10.1038/s41375-020-01096-y. Epub ahead of print. PMID: 33262523.	
Terpos E, Raje N, Croucher P, Garcia-Sanz R, Leleu X, Pasteiner W, Wang Y, Glennane A, Canon J, Pawlyn C. Denosumab compared with zoledronic acid on PFS in multiple myeloma: exploratory results of an international phase 3 study. Blood Adv. 2021 Feb 9;5(3):725-736. doi: 10.1182/bloodadvances.2020002378. PMID: 33560384; PMCID: PMC7876889.	Study design out of scope
Denosumab Versus Zoledronic Acid in Bone Disease Treatment of Newly Diagnosed Multiple Myeloma: an International, Double-Blind, Randomised Controlled Phase 3 Study-Asian Subgroup Analysis	Outcome out of scope
A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial	Duplication
Alaterre, E., Herviou, L., De Boussac, H., Papadopoulos, G., Boireau, S., Robert, N., . . . Moreaux, J. (2020). Comprehensive characterization of the epigenetic landscape in multiple myeloma. Blood, 136(SUPPL 1), 2-3. doi:10.1182/blood-2020-138801	Outcome out of scope
Chakraborty, R., Rybicki, L., Valent, J., Mejia Garcia, A. V., Faiman, B. M., Khouri, J., . . . Khorana, A. A. (2020). Abnormal metaphase cytogenetics adds to currently known risk- factors for venous thromboembolism in multiple myeloma: Derivation of the prism score. Blood, 136(SUPPL 1), 29-30. doi:10.1182/blood-2020-137525	Study design out of scope
Gil-Sierra, M. D., Fenix-Caballero, S., Briceño-Casado, M. D. P., Dominguez-Cantero, M., & Alegre-Del Rey, E. J. (2020). Economic comparison of therapeutic alternatives for firstline treatment of multiple myeloma. European Journal of Hospital Pharmacy, 27(SUPPL 1), A2. doi:10.1136/ejhpharm-2020-eahpconf.4	Outcome out of scope
Jasrotia, S., Gupta, R., Sharma, A., Halder, A., & Kumar, L. (2020). Cytokine profile in multiple myeloma. Cytokine, 136. doi:10.1016/j.cyto.2020.155271	Study design out of scope
Lebioda, A., Popfinger, K., Weiß, V., & Scheider, M. (2020). PRO143 Costs of Multiple Myeloma Patients Diagnosed with Peripheral Neuropathy in Germany. Value in Health, 23, S715. doi:10.1016/j.jval.2020.08.1879	Outcome out of scope
Manrique, I., Greil, R., Andel, J., Sormann, S., Hartmann, B. L., Podar, K., . . . Ludwig, H. (2020). Immunophenotyping of baseline bone marrow reveals a specificpattern of immune cells associated with greater depth and sustained response in newly diagnosed patients randomised tokrd or ktd followed by carfilzomib maintenance or control (AGMTMM 02 study). Blood, 136(SUPPL 1), 29-30. doi:10.1182/blood-2020-140918	Outcome out of scope
Mina, R., Larocca, A., Oidani, M., Innao, V., Cellini, C., Galli, M., . . . Bringhen, S. (2020). Efficacy and safety of ixazomib induction and maintenance innewly diagnosed multiple myeloma patients according to theimwg frailty score: A post-hoc analysis of the EMN10-unito trial. Blood, 136(SUPPL 1), 44-45. doi:10.1182/blood-2020-136292	Outcome out of scope
Moreau, P., Facon, T., Usmani, S. Z., Dimopoulos, M., Kumar, S., Plesner, T., . . . Bahlis, N. (2020). MM-339: Effect of Lenalidomide (R) ± Dexamethasone (d) Discontinuation on Daratumumab Efficacy in Multiple Myeloma (MM): Subgroup Analysis of the Phase 3 MAIA and POLLUX Studies. Clinical Lymphoma, Myeloma and Leukemia, 20, S306-S307. doi:10.1016/S2152-2650(20)30953-8	Outcome out of scope
Sanfilippo, K. M., Fiala, M. A., Tathireddy, H., Feinberg, D., Vij, R., & Gage, B. F. (2020). D-dimer improves risk prediction of venous thromboembolism in patients with multiple myeloma. Blood, 136(SUPPL 1), 26-27. doi:10.1182/blood-2020-142762	Study design out of scope
Soekojo, C. Y., Chung, T. H., Furqan, M. S., & Chng, W. J. (2020). Identifying the genomic profile of functional high-risk multiplemyeloma patients. Blood, 136(SUPPL 1), 51-52. doi:10.1182/blood-2020-136553	Study design out of scope
White, D. J., LeBlanc, R., Baljevic, M., Bahlis, N. J., Lentzsch, S., Venner, C. P., . . . Schiller, G. J. (2020). Selinexor, lenalidomide and dexamethasone (SRD) for patients with	Population out of scope

Citation	Exclusion reason
relapsed/refractory and newly diagnosed multiple myeloma. Blood, 136(SUPPL 1), 45-46. doi:10.1182/blood-2020-140141	
Zhao, R., Xie, Y., Yang, B., Wang, C., Huang, Q., Han, Y., . . . Wu, X. (2020). Identification of metabolic biomarkers to predict treatment outcome and disease progression in multiple myeloma. American Journal of Cancer Research, 10(11), 3935-3946.	Study design out of scope

Table 72 below presents the planned and ongoing randomised clinical trials.

Table 72. Planned and ongoing RCTs

Trial ID	Study Name	Status
NCT03759093	CURATE.AI-optimized modulation for multiple myeloma: an N-of-1 randomised trial	Not yet recruiting
EUCTR2019-00304730-ES	A clinical trial of belantamab mafodotin plus standard of care treatments compared with standard of care treatments alone for patients with newly diagnosed multiple myeloma not eligible for transplant	No Results Available
EUCTR2018-002068-15-IT	A randomised trial that compare carfilzomib - lenalidomide - dexamethasone versus lenalidomide - dexamethasone in newly diagnosed myeloma patients not eligible for autologous stem cell transplantation (asct)	No Results Available
ChiCTR2000029863	A multicenter, prospective, randomised, study for Ixazomib plus Cyclophosphamide and Dexamethasone compared with Lenalidomide plus Cyclophosphamide and Dexamethasone in transplant-ineligible newly diagnosed multiple myeloma	No Results Available
CTRI/2019/07/020397	A comparison of Bortezomib, Pomalidomide with low-dose Dexamethasone and Bortezomib, Lenalidomide with low-dose dexamethasone for newly-diagnosed multiple myeloma patients- A randomised phase III study	Not yet recruiting
NCT04277845	Randomised phase II study of bortezomib, lenalidomide and dexamethasone versus lenalidomide and dexamethasone in elderly patients with newly diagnosed multiple myeloma	Not yet recruiting
NCT03993912	Compare Lenalidomide and Subcutaneous Daratumumab vs. Lenalidomide and Dexamethasone in Frail Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High Dose Therapy	No Results Available
NCT04091126	Bortezomib, Lenalidomide and Dexamethasone (VRd) With Belantamab Mafodotin Versus VRd Alone in Transplant Ineligible Multiple Myeloma	No Results Available
NCT04096066	A Trial That Compare Two Treatments in Newly Diagnosed Myeloma Patients Not Eligible for Transplant	No Results Available
NCT04009109	Study of Lenalidomide/Ixazomib/Dexamethasone/Daratumumab in Transplant-Ineligible Patients With Newly Diagnosed MM	Not yet recruiting
NCT02312258	Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Participants With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation (SCT)	No Results Available
NCT04277845	Randomised Phase II Study in Elderly Patients With Newly Diagnosed Multiple	Not yet recruiting
NCT04268498	A Study of Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma	No Results Available
NCT02891811	Patients With Newly Diagnosed Multiple Myeloma Comparing KTd vs. KRd Induction Therapy and Investigating a K-mono Maintenance Strategy	No Results Available

NCT04808037	Blmf, Lenalidomide and Dexamethasone in Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma (BelaRd)	No Results Available
NCT04717700	Selinexor With Alternating Bortezomib or Lenalidomide Plus Dexamethasone in TIE Newly Diagnosed MM Patients (SABLe)	Not yet recruiting
NCT04751877	Study of Isatuximab+Lenalidomide+Dexamethasone With/Without Bortezomib in de Novo Non Frail NTE Multiple Myeloma Elderly Patients (IFM2020-05)	Not yet recruiting
NCT04635189	Steroid Sparing Treatment With in Newly Diagnosed Transplant Ineligible Patients With Multiple Myeloma	Not yet recruiting
NCT03993912	Compare Lenalidomide and Subcutaneous Daratumumab vs. Lenalidomide and Dexamethasone in Frail Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High Dose Therapy (IFM2017_03)	No Results Available

13.3 Quality assessment

The clinical SLR that has been conducted, including 5 updates, has been extensive and thorough, conducted in line with Cochrane guidance best practices. A risk of bias assessment has been conducted using the Cochrane risk of bias tool, and is reported for or the 9 published trials relevant to the decision problem in Table 73. The Cochrane risk of bias tool is a qualitative tool, leaving room for interpretation. The Cochrane risk of bias tool consists of six elements: random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, complete outcome assessment, and selective reporting [158]. Each item is assessed and indicated as either a high risk, low risk or unclear risk for bias.

Table 73. Risk of bias assessment

TRIAL	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND RESEARCHERS	BLINDING OF OUTCOME ASSESSMENT	COMPLETE OUTCOME ASSESSMENT	SELECTIVE REPORTING
ALCYONE trial [159] [160] [161] [162] [130] [163] [164] [165]	Low	Low	Unclear	Unclear	Low	Unclear
VISTA trial [112] [166] [167] [168] [169] [170]	Unclear	Unclear	High	High	Low	Low
MRC Myeloma IX	Low	Low	High	High	Low	Low

[113]						
Hungria et al. [114]	Unclear	Unclear	High	Unclear	Unclear	High
IFM 99–06 [b] **[115]**	Unclear	Unclear	High	High	Unclear	Unclear
IFM 01/01 [116]	Unclear	Low	Low	Unclear	Unclear	Unclear
Sacchi et al. [117]	Unclear	Low	High	High	Low	Low
FIRST trial [118] [171] [172] [173] [174] [175] [176] [177] [178] [179] [134] [180]	Low	Low	High	Unclear	Low	Unclear
UPFRONT [119] [181]	Low	Low	High	Unclear	Low	Unclear
SWOG-S0777 [100]	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

13.4 Unpublished data

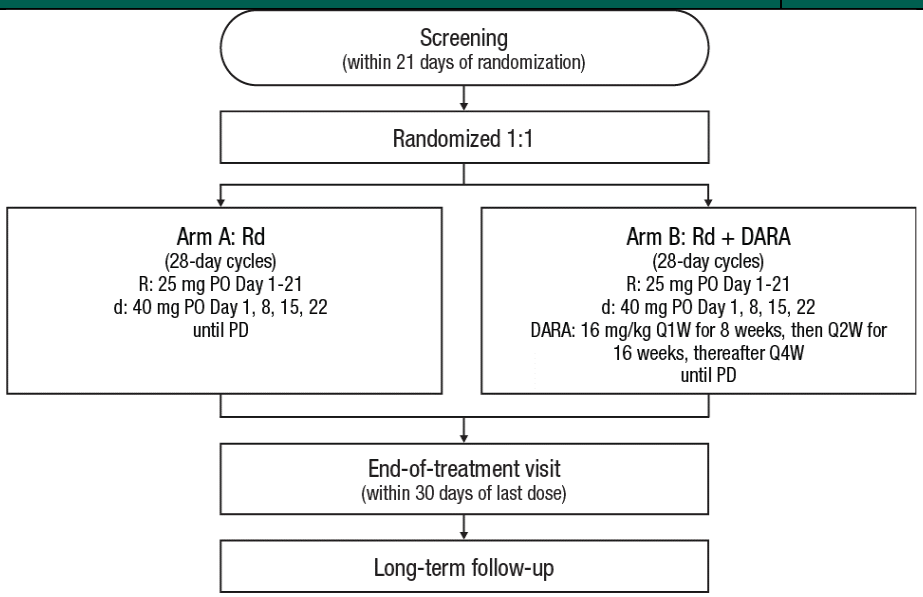
No unpublished data is considered in this assessment of clinical efficacy.

14 Appendix B – Main characteristics of included studies

Table 74. Main characteristics of MAIA (MMY3008, NCT02252172) study

Trial name: MAIA (MMY3008): Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma	**NCT number: NCT02252172**
Objective	The purpose of this study is to compare the efficacy of daratumumab in combination with lenalidomide and dexamethasone to that of lenalidomide and dexamethasone in terms of progression-free survival (PFS) in participants with newly diagnosed multiple myeloma (a blood cancer of plasma cells) who are not candidates for high dose chemotherapy (treatment of disease, usually cancer, by chemical agents) and autologous stem cell transplant (ASCT).

Trial name: MAIA (MMY3008): Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02252172
Publications – title, author, journal, year	**Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, Goldschmidt H, O'Dwyer M, Perrot A, Venner CP, Weisel K, Mace JR, Raje N, Tiab M, Macro M, Frenzel L, Leleu X, Ahmadi T, Wang J, Van Rampelbergh R, Uhlar CM, Tromp B, Delioukina M, Vermeulen J, Usmani SZ. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2021 Nov;22(11):1582-1596. doi: 10.1016/S1470-2045(21)00466-6. Epub 2021 Oct 13.** Cavo M, San-Miguel JFF, Usmani SZ, Weisel KC, Dimopoulos MAA, Avet-Loiseau H, Paiva B, Bahlis NJ, Plesner T, Hungria VTM, Moreau P, Mateos MV, Perrot A, Iida S, Facon T, Kumar SK, van de Donk NWCJ, Sonneveld P, Spencer A, Krevvata M, Heuck C, Wang J, Ukropec J, Kobos R, Sun S, Qi M, Munshi NC. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, MAIA. Blood. 2021 Jul 21. pii: blood.2021011101. doi: 10.1182/blood.2021011101. [Epub ahead of print] San-Miguel J, Avet-Loiseau H, Paiva B, Kumar S, Dimopoulos MA, Facon T, Mateos MV, Touzeau C, Jakubowiak A, Usmani SZ, Cook G, Cavo M, Quach H, Ukropec J, Ramaswami P, Pei H, Qi M, Sun S, Wang J, Krevvata M, DeAngelis N, Heuck C, Van Rampelbergh R, Kudva A, Kobos R, Qi M, Bahlis NJ. Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE. Blood. 2022 Jan 27;139(4):492-501. doi: 10.1182/blood.2020010439. Perrot A, Facon T, Plesner T, Usmani SZ, Kumar S, Bahlis NJ, Hulin C, Orlowski RZ, Nahi H, Mollee P, Ramasamy K, Roussel M, Jaccard A, Delforge M, Karlin L, Arnulf B, Chari A, He J, Ho KF, Van Rampelbergh R, Uhlar CM, Wang J, Kobos R, Gries KS, Fastenau J, Weisel K. Health-Related Quality of Life in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma: Findings From the Phase III MAIA Trial. J Clin Oncol. 2021 Jan 20;39(3):227-237. doi: 10.1200/JCO.20.01370. Epub 2020 Dec 16. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, Goldschmidt H, O'Dwyer M, Perrot A, Venner CP, Weisel K, Mace JR, Raje N, Attal M, Tiab M, Macro M, Frenzel L, Leleu X, Ahmadi T, Chiu C, Wang J, Van Rampelbergh R, Uhlar CM, Kobos R, Qi M, Usmani SZ; MAIA Trial Investigators. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019 May 30;380(22):2104-2115. doi: 10.1056/NEJMoa1817249.
Study type and design	This is a Phase 3, randomized (study drug assigned by chance), open-label (participants and researchers are aware about the treatment, participants are receiving), active-controlled (study in which the experimental treatment or procedure is compared to a standard treatment or procedure), parallel-group (each group of participants will be treated at the same time), and multicenter (when more than one hospital or medical school team work on a medical research study) study in participants with newly diagnosed multiple myeloma and who are not candidates for high dose chemotherapy and ASCT.

Trial name: MAIA (MMY3008): Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02252172
	 Rd, lenalidomide and dexamethasone; R, lenalidomide; PO, orally; d, dexamethasone; PD, progressive disease; DARA, daratumumab; Q1W, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks. All the eligible participants will be randomly assigned to receive either lenalidomide and dexamethasone (Rd) (Arm A) or daratumumab in combination with lenalidomide and dexamethasone (Dara+Rd) (Arm B). Daratumumab (16 milligram per kilogram [mg/kg]) will be administered weekly for first 8 weeks (Cycles 1 to 2) of treatment and then every other week for 16 weeks (Cycles 3 to 6), then every 4 weeks (from Cycle 7 and beyond) until progression of disease or unacceptable toxicity. Lenalidomide will be administered at a dose of 25 mg orally on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg once a week for both treatment arms. Participants in both treatment arms will continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity. All participants randomized to Treatment Arm B (Dara+Rd) in this study initially received daratumumab IV formulation; however, following implementation of protocol amendment 8, participants still receiving treatment with daratumumab IV will have the option to switch to daratumumab SC on Day 1 of any cycle, at the discretion of the investigator. Daratumumab subcutaneous (SC) will be administered by SC injection at a fixed dose of 1800 mg once every 4 weeks until documented progression, unacceptable toxicity, or study completion. Participants in Arm A who have sponsor-confirmed disease progression may have the option to receive daratumumab provided by the sponsor (in any subsequent line of therapy) in the Follow-up phase. The study consists of 3 phases: Screening Phase (within 21 days prior to the first dose administration on Day 1), Treatment Phase (Day 1 up to discontinuation of all study treatment), and Follow-up Phase (from discontinuation of all study treatment up to death, lost to follow up, consent withdrawal, or study end, whichever occurs first). The maximum duration of study will be 7 years after last participant is randomized. Efficacy will primarily be evaluated by PFS. Participants' safety will be monitored throughout the study.
Sample size (n)	737
Main inclusion and exclusion criteria	Inclusion Criteria:

Trial name: MAIA (MMY3008): Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02252172

- Participant must have documented multiple myeloma satisfying the CRAB (calcium elevation, renal insufficiency, anemia and bone abnormalities) criteria, monoclonal plasma cells in the bone marrow greater than or equal to (>=) 10 percent (%) or presence of a biopsy proven plasmacytoma and measurable disease as defined by any of the following: (a) immunoglobulin (Ig) G myeloma (serum monoclonal paraprotein [M-protein] level >=1.0 gram/deciliter [g/dL] or urine M-protein level >=200 milligram[mg]/24 hours[hrs]; or (b) IgA, IgM, IgD, or IgE multiple myeloma (serum M-protein level >=0.5 g/dL or urine M-protein level >=200 mg/24 hrs); or (c) light chain multiple myeloma without measurable disease in serum or urine (serum immunoglobulin free light chain >=10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio).
- Participant must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
- Participants who are newly diagnosed and not considered for high-dose chemotherapy due to: being age >=65 years; or participants less than (<) 65 years with presence of important comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. Sponsor review and approval of participants below 65 years of age is required before randomization.
- Women of childbearing potential must commit to either abstain continuously from sexual intercourse or to use 2 methods of reliable birth control simultaneously as deemed appropriate by the Investigator. Contraception must begin 4 weeks prior to dosing and must continue for 3 months after the last dose of daratumumab.
- Man, who is sexually active with a woman of child-bearing potential must agree to use a latex or synthetic condom, even if he had a successful vasectomy, must agree to use an adequate contraception method as deemed appropriate by the Investigator, and must also agree to not donate sperm during the study and for 4 weeks after last dose of lenalidomide and 4 months after last dose of daratumumab.

Exclusion Criteria:

- Participant has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance (presence of serum M-protein <3 g/dL; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein), or smoldering multiple myeloma (asymptomatic multiple myeloma with absence of related organ or tissue impairment end organ damage).
- Participant has a diagnosis of Waldenström's disease, or other conditions in which IgM M protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.
- Participant has a history of malignancy (other than multiple myeloma) within 5 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy 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).
- Participant has prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids before treatment.
- Participant has had radiation therapy within 14 days of randomization.
- Participant has known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume in 1 second [FEV1] <50% of predicted normal), persistent asthma, or a history of asthma within the last 2 years (controlled intermittent asthma or controlled mild persistent asthma is allowed).
- Participants with known or suspected COPD must have a FEV1 test during Screening.

Trial name: MAIA (MMY3008): Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02252172
	• Participant is known to be seropositive for human immunodeficiency virus (HIV) or hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg] or antibodies to hepatitis B surface and core antigens [anti-HBs and anti-HBc, respectively]) or hepatitis C (anti-HCV antibody positive or HCV-ribonucleic acid [RNA] quantitation positive).
Intervention	Daratumumab + Lenalidomide + Dexamethasone (Dara+Rd) Participants will receive Daratumumab 16 milligram per kilogram (mg/kg) by intravenous infusion, once a week for 8 weeks, then once every other week for 16 weeks, thereafter once every 4 weeks, Lenalidomide 25 mg capsule orally on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or intravenously once a week. Following implementation of protocol amendment 8, participants still receiving treatment with daratumumab IV will have the option to switch to daratumumab SC on Day 1 of any cycle, at the discretion of the investigator. Daratumumab subcutaneous (SC) will be administered by SC injection at a fixed dose of 1800 mg once every 4 weeks until documented progression, unacceptable toxicity, or study completion. Study treatment continues until disease progression, unacceptable toxicity, or end of study (maximum up to 7 years after last subject is randomized) whichever comes first.
Comparator(s)	Lenalidomide and Dexamethasone (Rd) Participants will receive Lenalidomide 25 mg capsule orally on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or intravenously once a week. Study treatment continues until disease progression, unacceptable toxicity, or end of study (maximum up to 7 years after last subject is randomized) whichever comes first.
Follow-up time	Study is ongoing: current data cut reports a median follow-up of 56.2 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary Outcome Measures: 1. Primary: Progression-free Survival (PFS) [Time Frame: From randomization to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or clinical cut-off (CCO) whichever occurs first (up to 3.5 years)] • PFS is defined as time from date of randomization to either progressive disease (PD) or death, whichever occurs first based on computerized algorithm as per International Myeloma Working Group (IMWG) criteria. PD is defined as an increase of 25 percent (%) from the lowest response value in one of the following: serum and urine M-component (absolute increase must be greater than or equal to [>=] 0.5 gram per deciliter [g/dL] and >=200 milligram [mg]/24 hours respectively); Only in participants without measurable serum and urine M-protein levels the difference between involved and uninvolved free light chain (FLC) levels (absolute increase must be greater than [>]10 mg/dL); Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas; Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to Plasma cell (PC) proliferative disorder. Secondary Outcome Measures: 1. Percentage of Participants With Complete Response (CR) or Better [Time Frame: From randomization to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or CCO whichever occurs first (up to 7.8 years)]

Trial name: MAIA (MMY3008): Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02252172

- CR or better is defined as percentage of participants with a CR or better (CR or stringent complete response [sCR]) based on computerized algorithm as per IMWG criteria. CR is defined as negative immunofixation on the serum and urine, and disappearance of any soft tissue plasmacytomas, and less than (<) 5 percent (%) PCs in bone marrow. In participants with only measurable disease by serum FLC levels a normal serum FLC ratio is required. sCR is defined as in addition to CR a normal FLC ratio, and absence of clonal PCs by immunohistochemistry or immunofluorescence or 2 to 4-color flow cytometry.

2. Percentage of Participants With Very Good Partial Response (VGPR) or Better [Time Frame: From randomization to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or CCO whichever occurs first (up to 7.8 years)]

- VGPR or better is defined as the percentage of participants with a response of VGPR or better (VGPR, CR or sCR) based on computerized algorithm as per IMWG criteria. VGPR is defined as serum and urine M-component detectable by immunofixation but not on electrophoresis or >=90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours. In participants with only measurable disease by serum FLC levels a >90% decrease in the difference between involved and uninvolved FLC levels is required.

3. Percentage of Participants With Negative Minimal Residual Disease (MRD) [Time Frame: From randomization to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or CCO whichever occurs first (up to 7.8 years)]

MRD negativity rate is defined as the percentage of participants who had negative MRD (detection of less than 1 malignant cell among 100,000 normal cells) assessment at any timepoint after the date of randomization by evaluation of bone marrow aspirates. MRD was assessed in participants who achieved CR or better.

4. Overall Response Rate (ORR) [Time Frame: From randomization to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or CCO whichever occurs first (up to 7.8 years)]

- ORR is defined as the percentage of participants who achieved partial response (PR) or better (PR, VGPR, CR or sCR) based on computerized algorithm as per IMWG criteria. PR is defined as >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg/24 hours. If the serum and urine M-protein are not measurable, a decrease of >=50% in the difference between involved and uninvolved FLC levels is required. A >=50% reduction in the size of soft tissue plasmacytomas is also required.

5. Overall Survival (OS) [Time Frame: From randomization to death, withdrawal of consent to study participation or CCO whichever occurs first (up to 7.8 years)]

- OS was measured from the date of randomization to the date of the death.

6. Time to Disease Progression (TTP) [Time Frame: From randomization to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or CCO whichever occurs first (up to 7.8 years)]

- TTP is defined as the time from the date of randomization to the date of PD based on computerized algorithm as per IMWG criteria, or death due to PD.

7. Time to Response [Time Frame: From randomization to first response (PR or better) (up to 7.8 years)]

Trial name: MAIA (MMY3008): Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02252172

- Time to response is defined as the time from the date of randomization to the first efficacy evaluation that met criteria for PR or better based on computerized algorithm as per IMWG criteria. PR: >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg/24 hours. If the serum and urine M-protein are not measurable, a decrease of >=50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, >=50% reduction in bone marrow PCs is required. A >=50% reduction in the size of soft tissue plasmacytomas is also required.

8. Duration of Response (DoR) [Time Frame: From first response (PR of better) to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or CCO whichever occurs first (up to 7.8 years)]

- DoR is defined as the time from the date of initial response (PR or better) to the date of PD, based on computerized algorithm as per IMWG criteria.

9. Time to Subsequent Anti-myeloma Treatment [Time Frame: From randomization to start of first subsequent anti-myeloma treatment, death, withdrawal of consent to study participation or CCO whichever is first (up to 7.8 years)]

- Time to subsequent anti-myeloma treatment is defined as the time from randomization to the start of first line of subsequent anti-myeloma treatment or death, whichever occurs first.

10. Progression-free Survival on Next Line of Therapy (PFS2) [Time Frame: From randomization to disease progression on first line of subsequent anti-myeloma therapy, death, withdrawal of consent to study participation or CCO whichever occurs first (up to 7.8 years)]

- PFS2 is defined as the time from randomization to progression on the first line of subsequent anti-myeloma therapy or death, whichever occurs first. Disease progression on first line of subsequent anti-myeloma treatment was based on investigator judgment. Participants that were censored for PFS1 were also censored for PFS2.

11. Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 Global Health Status Score to Day 1 of Cycle 3, 6, 9 and 12 [Time Frame: Baseline and Day 1 of Cycle 3, 6, 9 and 12 (each Cycle of 28 days)]

- EORTC QLQ-C30 is 30 items self-reporting questionnaire, with 1 week recall period, resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status (GHS) scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Questionnaire includes 28 items with 4-point Likert type responses from "1-not at all" to "4-very much" to assess functioning and symptoms; 2 items with 7-point Likert scales (1= poor and 7= excellent) for global health and overall health related QoL. Scores are transformed to 0 to 100 scale, with higher scores representing better GHS, better functioning, and more symptoms. Negative change from baseline values shows deterioration in quality of life or functioning and reduction in symptom and positive values indicate improvement and worsening of symptoms.

12. Change From Baseline in EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analogue Scale (VAS) to Day 1 of Cycle 3, 6, 9 and 12 [Time Frame: Baseline and Day 1 of Cycle 3, 6, 9 and 12 (each Cycle of 28 days)]

Trial name: MAIA (MMY3008): Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02252172
	• EQ-5D-5L is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L Visual Analog Scale. The Visual Analogue Scale is designed to rate the participant's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. 13. Change From Baseline in EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Utility Score to Day 1 of Cycle 3, 6, 9 and 12 [Time Frame: Baseline and Day 1 of Cycle 3, 6, 9 and 12 (each Cycle of 28 days)] • EQ-5D-5L is standardized, participant-reported questionnaire to assess health-related quality of life. EQ-5D-5L includes 2 components: EQ-5D-5L health state profile (descriptive system) and EQ-5D-5L VAS. EQ-5D-5L descriptive system provides a profile of participant's health state 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems and extreme problems) that reflect increasing levels of difficulty. The participant was asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. Responses to the 5-dimension scores were combined and converted into single preference-weighted health utility index score 0 (0.0- worst health state) to 1 (1.0- better health state) representing the general health status of individual (but allows for values less than 0 by United kingdom [UK] scoring algorithm). Endpoints included in this application: This application includes the primary outcome measure progression-free survival, and secondary outcome measure overall survival endpoints, which are detailed in Appendix D – Efficacy and safety results per study Other endpoints: No other secondary end points in the study are included in this application.
Method of analysis	All efficacy analyses were intention-to-treat analyses. Progression-free Survival: For the primary endpoint of PFS, the primary analysis consisted of a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment arms. The Kaplan-Meier method was to be used to estimate the distribution of overall PFS for each treatment. The treatment effect (HR) and its two-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable. The PFS2 was analysed similarly. Overall Survival: OS was measured from the date of randomization to the date of death. Data for subjects who were alive at the date of the last contact or had an unknown vital status were censored at the date when last known alive at the updated CCO of 19 February 2021. The distribution of OS for the 2 treatment groups were compared based on a log-rank test stratified. with International Staging System (ISS) staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. Hazard ratio and its 95% CI were estimated based on a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. A HR<1 indicates an advantage for Dara+Rd. A modified linear alpha spending function was used to

Trial name: MAIA (MMY3008): Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02252172
	determine the alpha level at this interim analysis; the pre-specified stopping boundary was p=0.0414. Deaths: The number of subjects who died during the study and within 30 days of last study treatment dose, and the primary cause of death were summarized as of the CCO of 19 February 2021. The primary cause of death was collected on the case report form page.
Subgroup analyses	• Sex (male, female) • Age (<75 years, ≥75 years) • Race (White, Other) • Region (North America, Other) • Baseline renal function (Creatine Clearance) (>60 mL/min, ≤60 mL/min) • Baseline hepatic function (normal, impaired) • ISS staging (I, II, III) • Type of MM (IgG, non-IgG) • Cytogenetic risk (high risk, standard risk) • ECOG performance score (0, 1, ≥2)
Other relevant information	COVID-19 Related Changes in Conduct Protocol Amendment 8 was issued on 3 April 2020. The primary reason for Amendment 8 was to provide flexibility for study investigators during the global coronavirus (COVID-19) pandemic. The Amendment allowed subjects who were receiving daratumumab IV (16 mg/kg), the option to switch to daratumumab SC (1800 mg). The overall impact of the COVID-19 pandemic on this study was minor and did not affect the integrity, safety, data quality, or interpretation of results. Study recruitment and the analysis performed for the primary CSR were completed before the start of the COVID-19 pandemic and not impacted. Further, there was no impact on the study power for the primary and the major secondary analysis or for this interim OS analyses. Overall, there was no specific impact of COVID-19 to the study population that would require cessation of study treatment.

Table 75. Main characteristics of ALCYONE (MMY3007, NCT02195479) study

Trial name: ALCYONE (MMY3007): A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (Dara+VMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02195479
Objective	The purpose of this study is to determine if the addition of daratumumab to velcade (bortezomib) melphalan-prednisone (VMP) will prolong progression-free survival (PFS) compared with VMP alone in participants with previously untreated multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant (ASCT).
Publications – title, author, journal, year	**Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Knop S, Doyen C, Lucio P, Nagy Z, Pour L, Grosicki S, Crepaldi A, Liberati AM, Campbell P, Yoon SS, Iosava G, Fujisaki T, Garg M, Iida S, Bladé J, Ukropec J, Pei H, Van Rampelbergh R, Kudva A, Qi M, San-Miguel J. Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Frailty Subgroup Analysis of ALCYONE. Clin Lymphoma Myeloma Leuk. 2021 Nov;21(11):785-798. doi: 10.1016/j.clml.2021.06.005. Epub 2021 Jun 18.**

Trial name: ALCYONE (MMY3007): A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (Dara+VMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02195479
	Cavo M, San-Miguel JFF, Usmani SZ, Weisel KC, Dimopoulos MAA, Avet-Loiseau H, Paiva B, Bahlis NJ, Plesner T, Hungria VTM, Moreau P, Mateos MV, Perrot A, Iida S, Facon T, Kumar SK, van de Donk NWCJ, Sonneveld P, Spencer A, Krevvata M, Heuck C, Wang J, Ukropec J, Kobos R, Sun S, Qi M, Munshi NC. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, MAIA. Blood. 2021 Jul 21. pii: blood.2021011101. doi: 10.1182/blood.2021011101. [Epub ahead of print] San-Miguel J, Avet-Loiseau H, Paiva B, Kumar S, Dimopoulos MA, Facon T, Mateos MV, Touzeau C, Jakubowiak A, Usmani SZ, Cook G, Cavo M, Quach H, Ukropec J, Ramaswami P, Pei H, Qi M, Sun S, Wang J, Krevvata M, DeAngelis N, Heuck C, Van Rampelbergh R, Kudva A, Kobos R, Qi M, Bahlis NJ. Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE. Blood. 2022 Jan 27;139(4):492-501. doi: 10.1182/blood.2020010439. Knop S, Mateos MV, Dimopoulos MA, Suzuki K, Jakubowiak A, Doyen C, Lucio P, Nagy Z, Usenko G, Pour L, Cook M, Grosicki S, Crepaldi A, Liberati AM, Campbell P, Shelekhova T, Yoon SS, Losava G, Fujisaki T, Garg M, Wang J, Wroblewski S, Kudva A, Gries KS, Fastenau J, San-Miguel J, Cavo M. Health-related quality of life in patients with newly diagnosed multiple myeloma ineligible for stem cell transplantation: results from the randomized phase III ALCYONE trial. BMC Cancer. 2021 Jun 2;21(1):659. doi: 10.1186/s12885-021-08325-2. **Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, Knop S, Doyen C, Lucio P, Nagy Z, Pour L, Cook M, Grosicki S, Crepaldi A, Liberati AM, Campbell P, Shelekhova T, Yoon SS, Iosava G, Fujisaki T, Garg M, Krevvata M, Chen Y, Wang J, Kudva A, Ukropec J, Wroblewski S, Qi M, Kobos R, San-Miguel J. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020 Jan 11;395(10218):132-141. doi: 10.1016/S0140-6736(19)32956-3. Epub 2019 Dec 10.** Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, Doyen C, Lucio P, Nagy Z, Kaplan P, Pour L, Cook M, Grosicki S, Crepaldi A, Liberati AM, Campbell P, Shelekhova T, Yoon SS, Iosava G, Fujisaki T, Garg M, Chiu C, Wang J, Carson R, Crist W, Deraedt W, Nguyen H, Qi M, San-Miguel J; ALCYONE Trial Investigators. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018 Feb 8;378(6):518-528. doi: 10.1056/NEJMoa1714678. Epub 2017 Dec 12.
Study type and design	The study consists of 3 phases: Screening Phase (within 21 days prior to randomization), Treatment Phase (Cycle 1 Day 1 to discontinuation of all study treatment), and Follow-up Phase (from discontinuation of all study treatment up to death, lost to follow up, withdrawal of consent, or the study ends, whichever occurs first). Treatment phase will include 2 treatments (Treatment A: participants will receive Velcade Melphalan Prednisone (VMP) alone and Treatment B: participants will receive daratumumab in combination with VMP). Two interim analyses are planned. The first will be to evaluate safety after a total of approximately 100 participants have been treated for at least 2 cycles or discontinued the study treatment. The second will be to evaluate cumulative interim safety and efficacy data, and will be performed when approximately 216 PFS events have been accumulated. The final OS analysis will occur when approximately 382 deaths have occurred. Efficacy will be primarily measured by comparison of PFS between the two treatment arms. Participants' safety will be monitored throughout the study.
Sample size (n)	706
Main inclusion and exclusion criteria	Inclusion Criteria:

Trial name: ALCYONE (MMY3007): A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (Dara+VMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02195479

- Participant must have documented multiple myeloma satisfying the calcium elevation, renal insufficiency, anemia, and bone abnormalities (CRAB) diagnostic criteria, monoclonal plasma cells in the bone marrow greater than or equal to 10 percent (%) or presence of a biopsy proven plasmacytoma, and measurable secretory disease, as assessed by the central laboratory, and defined in protocol
- Participants who are newly diagnosed and not considered candidate for high-dose chemotherapy with stem cell transplantation (SCT) due to: being age >=65 years, or in participants <65 years: presence of important comorbid conditions likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation
- Participant must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2
- Meet the clinical laboratory criteria as specified in the protocol
- A woman of childbearing potential must have a negative serum pregnancy test at screening within 14 days prior to randomization
- Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy

Exclusion Criteria:

- Participant has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma
- Participant has a diagnosis of Waldenstrom's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions
- Participant has prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids before treatment
- Participant has peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the national cancer institute common terminology criteria for adverse events (NCI CTCAE) Version 4
- Participant has a history of malignancy (other than multiple myeloma) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years)
- Participant has had radiation therapy within 14 days of randomization
- Participant has had plasmapheresis within 28 days of randomization
- Participant has known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume in 1 second [FEV1] <50% of predicted normal), known moderate or severe persistent asthma within the last 2 years or currently has uncontrolled asthma of any classification (controlled intermittent asthma or controlled mild persistent asthma is allowed)
- Participants with known or suspected COPD must have a FEV1 test during screening
- Participant is known to be seropositive for human immunodeficiency virus (HIV), known to have hepatitis B surface antigen positivity, or history of to have a history of hepatitis C

Trial name: ALCYONE (MMY3007): A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (Dara+VMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02195479
	• Participant has any concurrent medical or psychiatric condition or disease (example active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study
Intervention	Daratumumab + Velcade + Melphalan + Prednisone (Dara+VMP) Participants will receive velcade 1.3 mg/m^2 as SC injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9, melphalan 9 mg/m^2, orally, once daily (on Days 1-4) and prednisone 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9. In addition participants will also receive daratumumab 16 mg/kg as IV infusion, once weekly, for 6 weeks in Cycle 1 and then every 3 weeks, in Cycle 2 to 9 and thereafter, once every 4 weeks until documented progression, unacceptable toxicity, or until the end of study. On days when daratumumab is given, dexamethasone 20 mg IV or PO is given 1 hour or less prior to daratumumab administration as pre medication and prednisone substitute, and prednisone 60 mg/m2 once daily will be given on Days 2-4. Following amendment 7, participants will have the option to switch to daratumumab subcutaneous (SC) on Day 1 of any cycle, at the discretion of the investigator.
Comparator(s)	Velcade + Melphalan + Prednisone (VMP) Participants will receive velcade (bortezomib) 1.3 milligram per square meter (mg/m^2) as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9, melphalan 9 mg/m^2 , orally, once daily (on Days 1-4) and prednisone 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9.
Follow-up time	Median follow-up 40.1 months (longest follow-up time)
Is the study used in the health economic model?	Yes. Integrated into NMA for relative efficacy estimates (PFS, OS) and adverse events.
Primary, secondary and exploratory endpoints	Primary Outcome Measures: 1. Progression Free Survival (PFS) [Time Frame: From randomization to either disease progression or death whichever occurs first (up to 2.4 years)] • PFS- duration from date of randomization to Progressive disease (PD)/death, whichever occurs first. PD per IMWG criteria-Increase of 25% from lowest response value in one of following: Serum and urine M-component (absolute increase >=0.5 gram per deciliter [g/dL] and >=200 milligram [mg]/24 hours respectively); Only participants without measurable serum and urine M-protein levels: difference between involved and uninvolved free light chain (FLC) levels (absolute increase>10 mg/dL); Only participants without measurable serum and urine M-protein levels,without measurable disease by FLC levels,bone marrow Plasma cells (PC) %(absolute % >=10%);Bone marrow PC%: absolute% >10%; Definite development of new bone lesions/soft tissue plasmacytomas/definite increase in size of existing bone lesions/soft tissue plasmacytomas and Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder. Secondary Outcome Measures: 1. Overall Response Rate (ORR) [Time Frame: From randomization to disease progression (up to 2.4 years)]

Trial name: ALCYONE (MMY3007): A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (Dara+VMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02195479

- The Overall response rate was defined as the percentage of participants who achieved a partial response (PR) or better, according to the International Myeloma Working Group (IMWG) criteria, during the study or during follow up. IMWG criteria for PR: greater than or equal to (>=) 50 percentage(%) reduction of serum M-protein and reduction in 24 hour urinary M-protein by >=90% or to <200 mg/24 hours, if the serum and urine M-protein are not measurable, a decrease of >=50% in the difference between involved and uninvolved free light chain (FLC) levels is required in place of the M-protein criteria, If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, >=50% reduction in bone marrow plasma cells (PCs) is required in place of M-protein, provided baseline bone marrow plasma cell percentage was >=30%, in addition to the above criteria, if present at baseline, a >=50% reduction in the size of soft tissue plasmacytomas is also required.

2. Percentage of Participants With Very Good Partial Response (VGPR) or Better [Time Frame: From randomization to disease progression (up to 2.4 years)]

- VGPR or better rate was defined as the percentage of participants who achieved VGPR or complete response (CR) (including stringent complete response[sCR]) according to the IMWG criteria during or after the study treatment. VGPR: Serum and urine component detectable by immunofixation but not on electrophoresis, or >= 90% reduction in serum M-protein plus urine M-protein level less than (<) 100 milligram (mg) per 24 hour; CR: negative immunofixation on the serum and urine, Disappearance of any soft tissue plasmacytomas and < 5% plasms cells (PCs) in bone marrow; sCR: CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry.

3. Percentage of Participants With Complete Response (CR) or Better [Time Frame: From randomization to disease progression (up to 2.4 years)]

- CR or better rate was defined as the percentage of participants with a CR or better (i.e., CR and sCR) as per IMWG criteria. CR: as negative immunofixation on the serum and urine and disappearance of soft tissue plasmacytomas and less than (<) 5 percent plasma cells in bone marrow; sCR: CR plus normal free light chain (FLC) ratio and absence of clonal PCs by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry.

4. Percentage of Participants With Negative Minimal Residual Disease (MRD) [Time Frame: From randomization to disease progression (up to 2.4 years)]

- The Minimal Residual Disease negativity rate was defined as the percentage of participants who had negative MRD (detection of less than 1 malignant cell among 100,000 normal cells) assessment at any timepoint after the first dose of study drugs by evaluation of bone marrow aspirates or whole blood at 10^-5 threshold. MRD was evaluated by using Deoxyribonucleic acid (DNA) sequencing of immunoglobulin genes. MRD was assessed in participants who achieved complete response or stringent complete response (CR/sCR).

5. Overall Survival (OS) [Time Frame: From randomization to death (up to approximately 2.4 years)]

- Overall Survival (OS) was defined as the number of days the date of randomization to date of death. Median Overall Survival was estimated by using the Kaplan-Meier method.

6. Progression Free Survival on Next Line of Therapy (PFS2) [Time Frame: From randomization to either disease progression or death whichever occurs first (up to 2.4 years)]

- Progression-free survival after next-line therapy is defined as the time from randomization to progression on the next line of subsequent antimyeloma therapy or death due to any cause (prior to start of second line of antimyeloma therapy), whichever comes first. Disease progression on next line of treatment was based on investigator judgment.

Trial name: ALCYONE (MMY3007): A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (Dara+VMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02195479

7. Percentage of Participants With Stringent Complete Response (sCR) [Time Frame: From randomization to disease progression (up to 2.4 years)]

- sCR as per IMWG criteria is CR plus normal free light chain (FLC) ratio and absence of clonal PCs by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry. CR: Negative immunofixation on the serum and urine; Disappearance of any soft tissue plasmacytomas; <5% plasma cells (PCs) in bone marrow.

8. Time to Disease Progression (TTP) [Time Frame: From randomization to either disease progression or death due to PD whichever occurs first (up to 2.4 years)]

- TTP: Time from date of randomization to date of first documented evidence of PD or death due to PD, whichever occurs first. PD per IMWG criteria- Increase of 25 % from lowest response value in one of following: Serum and urine M-component (absolute increase >=0.5 gram per deciliter [g/dL] and >=200 mg/24 hours respectively); Only in participants without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase >10 milligram per deciliter [mg/dL]); Only in participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cells (PC)% (absolute % >=10%); Bone marrow PC %: absolute % >10%; Definite development of new bone lesions/soft tissue plasmacytomas or definite increase in size of existing bone lesions/soft tissue plasmacytomas and Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder.

9. Time to Response [Time Frame: From randomization to first documented PR or better (up to 2.4 years)]

- Time to response, defined as the time between the date of randomization and the first efficacy evaluation that the participant has met all criteria for PR or better. PR: >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg/24 hours; If the serum and urine M-protein are not measurable, a decrease of >=50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, >=50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was >=30%.

10. Duration of Response (DOR) [Time Frame: Up to 2.4 years]

- DOR: participants with a confirmed response (PR or better) as time between first documentation of response and disease progression, IMWG response criteria, or death due to PD, whichever occurs first. PD: Increase of 25% from lowest response value in any one of following: Serum M-component (absolute increase>=0.5 g/dL); Urine M-component (absolute increase>=200 mg/24 hours); Only participants without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase >10 mg/dL); Only participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC%(absolute%>=10%); Bone marrow PC's %: absolute%>10%; Definite development of new bone lesions/soft tissue plasmacytomas/definite increase in the size of existing bone lesions or soft tissue plasmacytomas and Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to PC proliferative disorder.

11. Time to Next Treatment (TNT) [Time Frame: Approximately up to 2.4 years]

- Time to next treatment is defined as the time from randomization to the start of the next-line treatment.

12. Percentage of Participants With Best M-protein Response [Time Frame: Approximately up to 2.4 years]

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- Percentage of participants with Best M- protein response of 100% reduction and >=90% to < 100% reduction were assessed. Best M-protein response was defined as the maximal percent reduction or the lowest percent increase from baseline in serum M-protein for participants with measurable heavy chain at baseline or urine M-protein for participants without measurable heavy chain, but with measurable light chain disease at baseline. For participants without measurable heavy chain and light chain disease at baseline, best response in serum free light chain (FLC) was defined as the maximal percent reduction or the lowest percent increase from baseline in the difference between involved and uninvolved serum FLC level (dFLC).

13. Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30: Emotional Functioning Score [Time Frame: Baseline, Months 3, 6, 9, 12 and 18]

- The EORTC QLQ-C30 is a 30 items self-reporting questionnaire, with a 1 week recall period, resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status (GHS) scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The questionnaire includes 28 items with 4-point Likert type responses from "1-not at all" to "4-very much" to assess functioning and symptoms; 2 items with 7-point Likert scales (1= poor and 7= excellent) for global health and overall QoL. Scores are transformed to a 0 to 100 scale, with higher scores representing better GHS, better functioning, and more symptoms. Negative change from baseline values indicate deterioration in quality of life or functioning and positive values indicate improvement.

14. Change From Baseline in EuroQol-5 Dimensions-5 Levels (EQ-5D-5L): Visual Analogue Scale (VAS) [Time Frame: Baseline, Months 3, 6, 9, 12 and 18]

- EQ-5D-5L is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L Visual Analog Scale. The Visual Analogue Scale is designed to rate the participant's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state.

15. Change From Baseline in EuroQol 5 Dimensions-5 Level (EQ-5D-5L) Utility Score [Time Frame: Baseline, Months 3, 6, 9, 12 and 18]

- EQ-5D-5L is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L Visual Analog Scale. The EQ-5D-5L descriptive system provides a profile of the participant's health state 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems and extreme problems) that reflect increasing levels of difficulty. The participant was asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. Responses to the 5 dimension scores were combined and converted into a single preference-weighted health utility index score 0 (0.0- worst health state) to 1 (1.0- better health state) representing the general health status of the individual based on the UK scoring algorithm.

Endpoints included in this application:

This application includes the primary outcome measure progression-free survival, and secondary outcome measure overall survival endpoints, which are detailed in Appendix D – Efficacy and safety results per study

Other endpoints:

Trial name: ALCYONE (MMY3007): A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (Dara+VMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma	NCT number: NCT02195479
	No other secondary end points in the study are included in this application.
Method of analysis	All efficacy analyses were intention-to-treat analyses. Continuous variables were summarized with descriptive statistics, and categorical variables were summarized in frequency tables. Time-to-event variables were evaluated with the Kaplan–Meier method. Binary end points, such as response rate, were assessed with a stratified Cochran–Mantel– Haenszel test, and an odds ratio and two-sided 95% confidence interval were calculated. The primary efficacy end point was estimated with the Kaplan– Meier method, and the treatment effect (hazard ratio) and its two-sided 95% confidence interval were estimated with a stratified Cox regression model. Statistical significance was evaluated with a stratified log-rank test based on the predetermined alpha level at the clinical cut-off date.
Subgroup analyses	• Sex (male, female) • Age (<75 years, ≥75 years) • Race (White, Other) • Region (Europe, Other) • Baseline renal function (Creatine Clearance) (>60 mL/min, ≤60 mL/min) • Baseline hepatic function (normal, impaired) • ISS staging (I, II, III) • Type of MM (IgG, non-IgG) • Cytogenetic risk (high risk, standard risk) • ECOG performance score (0, 1, ≥2)
Other relevant information	NA

Table 76. Main characteristics of SWOG S0777 (NCT00644228) study

Trial name: SWOG S0777: Lenalidomide and Dexamethasone With or Without Bortezomib in Treating Patients With Previously Untreated Multiple Myeloma	NCT number: NCT00644228
Objective	This randomized phase III trial studies lenalidomide, dexamethasone, and bortezomib to see how well it works compared to dexamethasone and lenalidomide alone in treating patients with previously untreated multiple myeloma. Biological therapies, such as lenalidomide, may stimulate the immune system in different ways and stop cancer cells from growing. Drugs used in chemotherapy, such as dexamethasone, work in different ways to stop the growth of cancer cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Bortezomib may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth or by blocking blood flow to the cancer. It is not yet known whether lenalidomide and dexamethasone is more effective with or without bortezomib in treating multiple myeloma.
Publications – title, author, journal, year	Unger JM, LeBlanc M, Blanke CD. The Effect of Positive SWOG Treatment Trials on Survival of Patients With Cancer in the US Population. JAMA Oncol. 2017 Oct 1;3(10):1345-1351. doi: 10.1001/jamaoncol.2017.0762. **Durie BGM, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, Thakuri M, Reu F, Reynolds CM, Sexton R, Orlowski RZ, Barlogie B, Dispenzieri A. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017 Feb 4;389(10068):519-527. doi: 10.1016/S0140-6736(16)31594-X. Epub 2016 Dec 23** [99].

Trial name: SWOG S0777: Lenalidomide and Dexamethasone With or Without Bortezomib in Treating Patients With Previously Untreated Multiple Myeloma	NCT number: NCT00644228
	Usmani SZ, Heuck C, Mitchell A, Szymonifka J, Nair B, Hoering A, Alsayed Y, Waheed S, Haider S, Restrepo A, Van Rhee F, Crowley J, Barlogie B. Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. Haematologica. 2012 Nov;97(11):1761-7. doi: 10.3324/haematol.2012.065698. Epub 2012 Jun 11. **Durie BG, Hoering A, Sexton R, Abidi MH, Epstein J, Rajkumar SV, et al. Longer term followup of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J. 2020;10:1-11 [100]**
Study type and design	Interventional (Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)
Sample size (n)	525
Main inclusion and exclusion criteria	Inclusion Criteria: • Patients must have newly diagnosed multiple myeloma with measurable disease; patients with non-secretory multiple myeloma (MM) based upon standard M-component criteria (i.e., measurable serum/urine M-component) are not eligible for this study; exception: patients with non-secretory MM will be eligible only if the baseline serum Freelite is elevated (Note that serum Freelite must be drawn; serum light chains are not acceptable); all tests for establishing baseline disease status must be completed within 28 days prior to registration and documented on the baseline and follow-up tumor assessment form for multiple myeloma • Patients must have received no prior chemotherapy for this disease; patients must have received no prior radiotherapy to a large area of the pelvis (more than half of the pelvis); prior steroid treatment is allowed provided treatment was not more than 2 weeks in duration; patients must not have received any prior treatment with bortezomib or lenalidomide • Patients must have a Zubrod performance status (PS) of 0 - 3; NOTE: patients with PS 3 are eligible only if it is documented by the treating physician that the patient's multiple myeloma is the central cause of his/her disability; patients who have a PS of 3 due to other concurrent medical conditions are not eligible for this trial • Platelet count >= 80 x 10^3/mcL; must be obtained within 28 days prior to registration; exception: patients with biopsy-proven heavy-marrow involvement, as defined by having at least 30% marrow cellularity, with > 50% of the cells being malignant plasma cells (documented marrow results required); in this case, although there are no required lower limits of normal for the blood counts, the treating physician must use his/her medical judgment as to the appropriateness of this study therapy for these patients • Absolute neutrophil count (ANC) >= 1 x 10^3/mcL; must be obtained within 28 days prior to registration; exception: patients with biopsy-proven heavy-marrow involvement, as defined by having at least 30% marrow cellularity, with > 50% of the cells being malignant plasma cells (documented marrow results required); in this case, although there are no required lower limits of normal for the blood counts, the treating physician must use his/her medical judgment as to the appropriateness of this study therapy for these patients

Trial name: SWOG S0777: Lenalidomide and Dexamethasone With or Without Bortezomib in Treating Patients With Previously Untreated Multiple Myeloma	NCT number: NCT00644228

- Hemoglobin (including patients who have been either transfused or treated with erythropoietin [EPO]) >= 9 g/dL; must be obtained within 28 days prior to registration; exception: patients with biopsy-proven heavy-marrow involvement, as defined by having at least 30% marrow cellularity, with > 50% of the cells being malignant plasma cells (documented marrow results required); in this case, although there are no required lower limits of normal for the blood counts, the treating physician must use his/her medical judgment as to the appropriateness of this study therapy for these patients
- Patients must be offered participation in the Myeloma Specimen Repository for banking and future research; with the patient's consent, bone marrow aspirates and serum specimens will be submitted to the Myeloma Specimen Repository for additional testing and banking (including SNP testing); patient consent must be obtained before specimens may be submitted
- Patients must have baseline skeletal survey to include lateral skull, anterior-posterior (AP) pelvis and posterior-anterior (PA) chest within 28 days prior to registration
- Institutions must submit a local cytogenetics report and fluorescence in situ hybridization (FISH) analysis report obtained prior to enrollment to S0777; for FISH analysis two probes will be utilized: LSI 13 (RBI) 13q14 SpectrumOrange Probe for detection of chromosome 13 deletion and LSI p53 (17p13.1) SpectrumOrange probe for detection of tumor protein (p)53 locus on chromosome 17; if these exact probes are not available locally, it is acceptable to submit results using local protocol; this must be noted on the prestudy form; NOTE: it is not required that the results of the FISH analysis be known prior to registration, only that pre-registration specimens be drawn and sent for analysis prior to registration, and the FISH analysis report be submitted
- Patients with pathologic fractures, pneumonia at diagnosis or symptomatic hyperviscosity must have these conditions attended to prior to registration (i.e., intramedullary rod, I.V. antibiotics, plasmapheresis)
- Patients must have a calculated or measured creatinine clearance > 30 cc/min; measured creatinine clearance or serum creatinine used in calculation must be obtained within 28 days prior to registration

Exclusion Criteria:

- Patients must not have uncontrolled, active infection requiring intravenous antibiotics, New York Heart Association (NYHA) class III or class IV heart failure, myocardial infarction within the last 6 months, history of treatment for clinically significant ventricular cardiac arrhythmias, poorly controlled hypertension, or poorly controlled diabetes mellitus; patients must have undergone an electrocardiogram (EKG) within 28 days prior to registration
- Patients must not have any psychiatric illness that could potentially interfere with the completion of treatment according to this protocol
- Patients must not be hepatitis B, hepatitis C or human immunodeficiency virus (HIV) positive; patients must have a negative hepatitis B and HIV test performed within 28 days prior to registration; exception: treatment-sensitive HIV infection patients will be eligible provided that immunological and virologic indices are indicative of favorable long-term survival prospects on the basis of HIV infection, but whose life expectancy is limited predominantly by multiple myeloma rather than HIV infection in the judgment of the treating physician
- Patients must not have a history of cerebral vascular accident with persistent neurologic deficits
- Patients must be able to take aspirin 325 mg daily (or enoxaparin 40 mg subcutaneously [SQ] daily if patient is unable to take aspirin) as prophylactic anticoagulation; exception: patients receiving anticoagulation therapy such as Coumadin or heparin will NOT receive aspirin, and therefore need not be able to take it

Trial name: SWOG S0777: Lenalidomide and Dexamethasone With or Without Bortezomib in Treating Patients With Previously Untreated Multiple Myeloma	NCT number: NCT00644228
	• Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 - 14 days and again within 24 hours prior to starting cycle 1 of lenalidomide; further, they must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control: one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting lenalidomide; FCBP must also agree to ongoing pregnancy testing; men must agree to use a latex condom during sexual contact with a FCBP, even if they have had a successful vasectomy; a FCBP is a sexually mature woman who: has not undergone a hysterectomy or bilateral oophorectomy; or has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months); all patients must be counseled by a trained counselor every 28 days about pregnancy precautions and risks of fetal exposure • No prior malignancy is allowed except for adequately treated basal cell (or squamous cell) skin cancer, in situ cervical cancer or other cancer for which the patient has been disease-free for five years • Patients must be offered participation in gene expression profiling (GEP) molecular studies for the evaluation of genetic polymorphisms • All patients must be informed of the investigational nature of this study and must sign and give written consent in accordance with institutional federal guidelines • At the time of patient registration, the treating institution's name and identification (ID) number must be provided to the statistical center in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base
Intervention	Bortezomib + lenalidomide + dexamethasone (VRd) Patients receive dexamethasone PO QD on days 1, 2, 4, 5, 8, 9, 11, and 12; lenalidomide PO QD on days 1-14; and bortezomib IV over 3-5 seconds on days 1, 4, 8, and 11. Treatment repeats every 21 days for 8 courses in the absence of disease progression or unacceptable toxicity.
Comparator(s)	Lenalidomide + dexamethasone (Rd) Patients receive dexamethasone PO QD on days 1, 8, 15, and 22 and lenalidomide PO QD on days 1-21. Treatment repeats every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity.
Follow-up time	Overall median follow-up: 55 months [99]
Is the study used in the health economic model?	Yes. Integrated into NMA for relative efficacy estimates (PFS, OS) and adverse events.
Primary, secondary and exploratory endpoints	Primary Outcome Measures: 1. Progression-free Survival [Time Frame: From date of registration to date of first documentation of progression or symptomatic deterioration, or death due to any cause, assessed up to 6 years] • Unstratified median progression-free survival in months. Secondary Outcome Measures: 1. Progression-free Survival [Time Frame: From date of registration to date of first documentation of progression or symptomatic deterioration, or death due to any cause, assessed up to 6 years] • Unstratified median progression-free survival in months. 2. Progression-free Survival [Time Frame: From date of registration to date of first documentation of progression or symptomatic deterioration, or death due to any cause, assessed up to 6 years] • Unstratified median progression-free survival in months.

Trial name: SWOG S0777: Lenalidomide and Dexamethasone With or Without Bortezomib in Treating Patients With Previously Untreated Multiple Myeloma	NCT number: NCT00644228
	Endpoints included in this application: This application includes the primary outcome measure progression-free survival, and secondary outcome measure overall survival endpoints, which are detailed in Appendix D – Efficacy and safety results per study Other endpoints: No other secondary end points in the study are included in this application.
Method of analysis	The sample size was based on the assumption of an eligible patient accrual rate of 110 patients per year (440 eligible patients over 4 years), a median progression-free survival of about 3 years in the control group, exponential distribution of progression-free survival, and roughly 2·5 years of additional follow up. The study was designed to detect a hazard ratio of 1·5, with approximately 87% power and an overall study alpha of 0·05. Thus, to allow for an interim analysis, a one-sided 0·02 significance level was used to assess the primary progression-free survival endpoint. The primary endpoint was evaluated with the use of a group-sequential design, with two planned interim analyses at 1/3 and 2/3 of the total number of events. A Haybittle–Peto approach was used for alpha spending and a one-sided alpha of 0·0025 was used for each interim analysis. At the final analysis, a one-sided stratified log-rank test was done at the 0·02 significance level for an overall one-sided alpha of 0·025. We compared progression-free survival and overall survival between treatment groups using a log-rank test stratified according to the factors used for randomisation. Hazard ratios were estimated by means of a stratified Cox proportional-hazards model. The multivariate analysis were done with a model that was not stratified by, rather adjusted for stratification factors, to provide some idea as to how the stratification factors were associated with outcome. We used the Kolmogorov-Smirnov test to assess assumptions of proportional hazards. There was no evidence of violation of proportional hazards for any of the covariates. Survival curves were based on the Kaplan-Meier method. We compared the overall response rate between groups using a stratified Cochran-Mantel-Haenszel test. The odds ratio and corresponding 95% confidence interval were estimated with the use of the Mantel-Haenszel method. Duration of response was summarised by means of the Kaplan-Meier method. All primary and secondary endpoint analyses were predefined within the protocol. Analyses were done on an intention to treat basis that incorporated all eligible patients. Patients with missing parameters of interest were excluded from multivariate analyses. We used SAS (version 4) for all analyses. Baseline variables were compared using Fisher's exact test. The safety analysis included all eligible patients who received at least one dose of study treatment and who were evaluated for toxic effects.
Subgroup analyses	NA
Other relevant information	NA

15 Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 77. Baseline characteristics of patients in MAIA (MMY3008, NCT02252172)

	MAIA (MMY3008, NCT02252172)	
	Dara+Rd (n=368)	Rd (n=369)
Mean age, years (SD)	74.0 (5.44)	74.2 (5.66)
Median age, years (range)	73 (70–78)	74 (70–78)

	MAIA (MMY3008, NCT02252172)	
	Dara+Rd (n=368)	Rd (n=369)
Age category, years		
<65	4 (1%)	4 (1%)
65–<70	74 (20%)	73 (20%)
70–<75	130 (35%)	131 (36%)
≥75	160 (43%)	161 (44%)
Male / Female	189 (51.4%) / 179 (48.6%)	195 (52.8%) / 174 (47.2%)
Eastern Cooperative Oncology Group (ECOG) performance status†		
0	127 (35%)	123 (33%)
1	178 (48%)	187 (51%)
2†	63 (17%)	59 (16%)
International Staging System disease stage‡		
I	98 (27%)	103 (28%)
II	163 (44%)	156 (42%)
III	107 (29%)	110 (30%)
Type of measurable disease		
IgG	225 (61%)	231 (63%)
IgA	65 (18%)	66 (18%)
Other§	9 (2%)	10 (3%)
Detected in urine only	40 (11%)	34 (9%)
Detected as serum free light-chain only	29 (8%)	28 (8%)
Cytogenetic profile¶		
Standard risk	271/319 (85%)	279/323 (86%)
High risk	48/319 (15%)	44/323 (14%)
Median time since the initial diagnosis of multiple myeloma, months	0·95 (0·53–1·46) 0·89 (0·59–1·45)	0·95 (0·53–1·46) 0·89 (0·59–1·45)

Data are median (IQR), n (%), or n/N (%). The intention-to-treat population included all patients who underwent random assignment. Post hoc analyses showed no significant differences between the two groups in the characteristics evaluated at baseline. *Eastern Cooperative Oncology Group performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. †Two patients had a score of greater than 2 (one patient had a score of 3, and another patient had a score of 4). ‡The International Staging System disease stage, which is based on the combination of serum β2 microglobulin and albumin levels, consists of three stages; higher stages indicate more severe disease. §This category includes IgD, IgE, IgM, and biclonal gammopathies. ¶Cytogenetic risk was based on fluorescence in-situ hybridisation or karyotype analysis; patients who had a high-risk cytogenetic profile had at least one high-risk abnormality (deletion 17p, translocation [14;16], or translocation [4;14]).

Table 78. Baseline characteristics of patients in ALCYONE (MMY3007, NCT02195479)

	ALCYONE (MMY3007, NCT02195479)	
	Dara+VMP (n=350)	VMP (n=356)
Median age, years (range)	71.0 (40–93)	71.0 (50–91)
Age category, years		
<65	36 (10.3)	24 (6.7)
65–<74	210 (60.0)	225 (63.2)

	ALCYONE (MMY3007, NCT02195479)	
	Dara+VMP (n=350)	VMP (n=356)
≥75	104 (29.7)	107 (30.1)
Male / Female	160 (45.7%) / 190 (54.3%)	167 (46.9%) / 189 (53.1%)
Eastern Cooperative Oncology Group (ECOG) performance status*		
0	78 (22.3)	99 (27.8)
1	182 (52.0)	173 (48.6)
2†	90 (25.7)	84 (23.6)
International Staging System disease stage‡		
I	69 (19.7)	67 (18.8)
II	139 (39.7)	160 (44.9)
III	142 (40.6)	129 (36.2)
Cytogenetic profile¶		
Standard risk	261/314 (83.1)	257/302 (85.1)
High risk	53/314 (16.9)	45/302 (14.9)
Median time since the initial diagnosis of multiple myeloma, months	0.8 (0.1–11.4)	0.8 (0.1–25.3) ‖

* The intention-to-treat population was defined as all the patients who had undergone randomization. Post hoc analyses showed no significant differences between the two groups in the characteristics evaluated at baseline. Percentages may not sum to 100 because of rounding.

† Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.

‡ The International Staging System (ISS) disease stage is derived on the basis of the combination of serum β2-microglobulin and albumin levels. Higher stages indicate more severe disease.

§ Cytogenetic risk was based on fluorescence in situ hybridization or karyotype testing. Cytogenetic data assessed by means of next-generation sequencing for the total intention-to-treat population were not available at the data cut-off date, and analysis is ongoing.

¶ These patients had at least one high-risk abnormality: del17p, t (4;14), or t(14;16).

‖ At the time of initial diagnosis, the patient with a time since initial diagnosis of multiple myeloma of 25.3 months did meet International Myeloma Working Group diagnostic criteria for multiple myeloma with a haemoglobin level of less than 10 g per decilitre and at least 10% plasma cells on examination of the bone marrow. A decision was made by the physician not to initiate treatment at the time of diagnosis. The patient's disease was stable and actively monitored until treatment was begun at a later date.

Table 79. Baseline characteristics of patients in SWOG S0777 (NCT00644228)

	SWOG S0777 (NCT00644228)	
Parameter	RVd (N = 263)	Rd (N = 260)
Age (years)		
Median	63.0	63.0
Min, Max	35.0, 85.0	28.0, 87.0
Age Group 1 (years), n (%)		
≤ 65	167 (63.5)	150 (57.7)
> 65	96 (36.5)	110 (42.3)
Age Group 2 (years), n (%)		
≤ 65	167 (63.5)	150 (57.7)
> 65 and ≤ 75	68 (25.9)	85 (32.7)
> 75	28 (10.6)	25 (9.6)

	SWOG S0777 (NCT00644228)	
Parameter	RVd (N = 263)	Rd (N = 260)
Sex, n (%)		
Male	164 (62.4)	137 (52.7)
Female	99 (37.6)	123 (47.3)
Race Group, n (%)		
Caucasian	210 (79.8)	207 (79.6)
Non-Caucasian	46 (17.5)	47 (18.1)
Unknown	7 (2.7)	6 (2.3)
ISS Stage, n (%)		
I	78 (29.7)	75 (28.8)
II	99 (37.6)	98 (37.7)
III	86 (32.7)	87 (33.5)
Revised ISS Stage, n (%)		
I	54 (20.5)	55 (21.2)
II	155 (58.9)	161 (61.9)
III	26 (9.9)	23 (8.8)
Missing	28 (10.6)	21 (8.1)
Intent to Transplant at Progression (Stratification Factor), n (%)		
No	81 (30.8)	81 (31.2)
Yes	182 (69.2)	179 (68.8)
Cytogenetic Risk, n (%)		
High[a]	30 (11.4)	36 (13.8)
Not High	210 (79.8)	207 (79.6)
Missing[b]	23 (8.7)	17 (6.5)
Frailty Group, n (%)		
Not Frail	206 (78.3)	188 (72.3)
Frail	56 (21.3)	72 (27.7)
Missing	1 (0.4)	0 (0.0)
Frailty and Age Group, n (%)		
Age ≤ 65 years and Not Frail	142 (54.0)	120 (46.2)
Age > 65 years and/or Frail	121 (46.0)[c]	140 (53.8)
Performance Status (ECOG) Category 1, n (%)		
0 - Fully active	106 (40.3)	101 (38.8)
1 - Restricted activity	128 (48.7)	120 (46.2)
2 - No work, ambulatory	19 (7.2)	32 (12.3)
3 - Limited self-care	10 (3.8)	7 (2.7)
Creatinine Clearance Group 1, n (%)		
< 60 mL/min	78 (29.7)	79 (30.4)
≥ 60 mL/min	185 (70.3)	180 (69.2)
Missing	0 (0.0)	1 (0.4)
Creatinine Clearance Group 2, n (%)		
< 50 mL/min	46 (17.5)	45 (17.3)

	SWOG S0777 (NCT00644228)	
Parameter	RVd (N = 263)	Rd (N = 260)
≥ 50 mL/min	217 (82.5)	214 (82.3)
Missing	0 (0.0)	1 (0.4)
Hemoglobin Group, n (%)		
< 10 g/dL	89 (33.8)	76 (29.2)
≥ 10 g/dL	174 (66.2)	184 (70.8)
B2 Microglobulin Group, n (%)		
≤ 5.5 mg/L	176 (66.9)	174 (66.9)
> 5.5 mg/L	85 (32.3)	84 (32.3)
Missing	2 (0.8)	2 (0.8)
Lactate Dehydrogenase Group, n (%)		
Not High (LDH ≤ 280 IU/L and not missing)	214 (81.4)	224 (86.2)
High (LDH > 280 IU/L)	44 (16.7)	32 (12.3)
Missing	5 (1.9)	4 (1.5)
Albumin Group, n (%)		
≤ 35 g/L	128 (48.7)	129 (49.6)
> 35 g/L	135 (51.3)	128 (49.2)
Missing	0 (0.0)	3 (1.2)

ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; ITT = intent-to-treat; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; t(4;14) = translocation involving chromosomes 4 and 14; t(14;16) = translocation involving chromosomes 14 and 16. [a] High Risk: t(4;14), t(14;16) or del(17p). [b] Cytogenetic risk assessment was not required by the protocol. [c] One subject in the RVd arm with a missing frailty is counted in the category age > 65 years and/or frail. Data cut-off date = 1 Dec 2016. [111]

15.1 Comparability of patients across studies

The MAIA and ALCYONE studies patient groups have similar median ages, although the ALCYONE trial did include a greater proportion of patients who were below age 65 at baseline, as well as having a higher maximum age at baseline (93 vs. 78). The SWOG S0777 study included a much broader group of patients, but the efficacy evidence which was used from this study is from the subset of patients who were above 65. Further details of the above 65 patient population are not available.

The baseline cytogenetic risk profiles were very similar between the MAIA and ALCYONE trials.

15.2 Comparability of the study populations with Danish patients eligible for treatment

In terms of age distribution and patient weight, the patient population from the MAIA study is believed to be similar to the Danish population of newly diagnosed patients with multiple myeloma who are inelligible for autologous stem cell transplantation.

16 Appendix D – Efficacy and safety results per study

16.1 Definition, validity and clinical relevance of included outcome measures

Table 80 presents the main outcomes that are relevant for this application. PFS, OS, and the safety endpoints listed below are the most commonly used, reliable and interpretable ones in multiple myeloma trials, as well as cancer trials more generally. For validity and clinical relevance of endpoints, refer to section 5.1.7 and 5.1.8.

Table 80. Efficacy and safety outcomes in MAIA (MMY3008, NCT02252172), ALCYONE (MMY3007, NCT02195479), and SWOG S0777

Outcome measure	**Definition**	**Validity**	**Clinical relevance**
Efficacy endpoints			
PFS	Time remaining alive without experiencing further disease progression.	Critical for driving the cost-effectiveness model.	In MM, the EMA has accepted PFS as a suitable primary endpoint for marketing authorization, (e.g., carfilzomib [Kyprolis] [67], elotuzumab [Empliciti] [68], ixazomib [Ninlaro] [69], panobinostat [Farydak] [70], and pomalidomide [Imnovid] [71]). Similarly, daratumumab (Darzalex) was initially approved in the Relapsed/refractory multiple myeloma setting based on overall response rate (ORR) data (with PFS as a secondary endpoint) in 2016, and later the indication was extended to newly diagnosed MM (NDMM) using PFS data in 2018 [93].
OS	Overall survival (OS) is measured from the date of randomization to the date of death due to any cause. Subjects who are lost to follow-up will be censored at the time of lost to follow-up. Subjects who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.	Gold Standard measure of treatment efficacy. Critical for driving the cost-effectiveness model.	Overall survival is the gold-standard for treatment efficacy.

Outcome measure	Definition	Validity	Clinical relevance
Safety endpoints			
Any AE	Number/proportion of patients with at least one adverse event for any reason		
Discontinuation due to AE	TEAE leading to discontinuation of study treatment		
Serious AEs (SAEs)	Number/proportion of patients with at least one serious adverse event for any reason		
Grade 3/4 AEs	Any grade 3/4 adverse event		

16.2 Results per study

Table 81. Results of MAIA (MMY3008, NCT02252172), median follow-up time 56.2 months

				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% CrI**	***P* value**		
PFS	Dara +Rd	368	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	The Kaplan-Meier method was to be used to estimate the distribution of overall PFS for each treatment. The treatment effect (HR) and its two-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable.	MAIA abbreviated CSR Clinical cut-off date 19 February 2021 [104]
	Rd	369	[redacted]								

				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% CrI**	***P* value**		
OS	Dara +Rd	368	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	The Kaplan-Meier method was to be used to estimate the distribution of overall PFS for each treatment. The treatment effect (HR) and its two-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable.	MAIA abbreviated CSR Clinical cut-off date 19 February 2021 [104]
	Rd	369	[redacted]								
Overall Response Rate (ORR)	Dara +Rd	368	342 (92·9%; 89·8–95·3)	NA	NA	NA	Odds ratio (Dara+Rd vs. Rd) = 3.00	1.85, 4.86	<0.0001	Stratified CMH test used to test treatment difference. The CMH estimate of odds ratio and its 95% confidence interval and p-value for testing treatment difference reported. Stratification factors used in the analysis include ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years).	Facon et al., 2021 [19]
	Rd	369	301 (81·6%; 77·2–85.4)	NA	NA	NA					
Complete response or better	Dara +Rd	368	188 (51%)	NA	NA	NA	Odds ratio (Dara+Rd vs. Rd) = 2.44	1.80, 3.30	<0.0001		
	Rd	369	111 (30%)	NA	NA	NA					
Very good partial response or better	Dara +Rd	368	298 (81%)	NA	NA	NA	Odds ratio (Dara+Rd vs. Rd) = 3.28	2.34, 4.59	<0.0001		
	Rd	369	210 (57%)	NA	NA	NA					

				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% CrI**	***P* value**		
Negative Minimal residual disease (MRD)	Dara +Rd	368	114 (31%)	NA	NA	NA	Odds ratio (Dara+Rd vs. Rd) = 3.28	2.62, 5.84	<0.0001		
	Rd	369	38 (10%)	NA	NA	NA					

Table 82. Results of ALCYONE (MMY3007, NCT02195479)

				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% CrI	*P* value		
PFS	Dara+ VMP	350	NA	NA	NA	NA	HR (Dara+VMP vs. Rd) = 0.58	0.37, 0.93	NR	Bayesian NMA. See Appendix F – Comparative analysis of efficacy and safety	Facon et al 2022 (Facon et al., 2022)
	VMP	356	NA				HR (VMP vs. Rd) = 1.39	0.92, 2.11			
OS	Dara+ VMP	350	NA	NA	NA	NA	HR (Dara+VMP vs. Rd) = 0.79	0.50, 1.23	NR	Bayesian NMA. See Appendix F – Comparative	Facon et al 2022 (Facon et al., 2022)

				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% CrI	*P* value		
	VMP	356	NA				HR (VMP vs. Rd) = 1.31	0.92, 1.86		analysis of efficacy and safety	

Table 83. Results of SWOG S0777 (NCT00644228) (65+)[a]

				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% CrI**	***P* value**		
PFS[a]	VRd	91	NA	NA	NA	NA	HR (VRd vs. Rd) = 0.77	0.55, 1.08	NR	Bayesian NMA. See Appendix F – Comparative analysis of efficacy and safety	Facon et al 2022 (Facon et al., 2022)
	Rd	106	NA								
OS[a]	VRd	91	NA	NA	NA	NA	HR (VRd vs. Rd) = 0.77	0.52,1.14	NR	Bayesian NMA. See Appendix F – Comparative analysis of efficacy and safety	Facon et al 2022 (Facon et al., 2022)
	Rd	106	NA								

[a]Patients without an intent for immediate ASCT were included. A subgroup analysis of patients 65–75 and >75 years old is provided and outcomes of these subgroups are included in this SLR as ASCT-ineligible patients.

17 Appendix E – Safety data for intervention and comparators

Safety data for treatment with Dara+Rd and Rd amongst newly diagnosed patients with multiple myeloma who are ineligible for autologous stem cell transplantation come from the MAIA (MMY3008, NCT02252172) study. An overview of patients affected by adverse events is presented in Table 84, with rates of the most common treatment-emergent adverse events presented in Table 85.

Table 84. Overall summary of adverse events amongst the MAIA (MMY3008, NCT02252172) safety population, median follow-up time 56.2 months

Number of patients	Dara+Rd (n=364)	Rd (n=365)
With at least one adverse event	364 (100%)	362 (99.2%)
With at least one serious adverse event	281 (77%)	257 (70%)
Who discontinued study treatment for any reason	209 (57.4%)	298 (81.6%)
Who discontinued study treatment due to adverse events	49 (13.5%)	84 (23.0%)

Sources: Facon et al 2021 [19], MAIA abbreviated CSR Clinical cut-off date 19 February 2021 [104]

Table 85. Most common treatment-emergent adverse events amongst the MAIA (MMY3008, NCT02252172) safety population, median follow-up time 56.2 months

	Dara+Rd (n=364)				Rd (n=365)			
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Anaemia	93 (26%)	60 (16%)	1 (<1%)	0	71 (19%)	79 (22%)	0	0
Thrombocytopenia	47 (13%)	23 (6%)	9 (2%)	0	43 (12%)	23 (6%)	11 (3%)	0
Leukopenia	31 (9%)	37 (10%)	5 (1%)	0	18 (5%)	20 (5%)	3 (1%)	0
Neutropenia	26 (7%)	136 (37%)	61 (17%)	0	30 (8%)	97 (27%)	38 (10%)	0
Lymphopenia	12 (3%)	41 (11%)	19 (5%)	0	7 (2%)	35 (10%)	6 (2%)	0
Diarrhoea	207 (57%)	32 (9%)	0	0	165 (45%)	22 (6%)	0	0

	Dara+Rd (n=364)				Rd (n=365)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Constipation	151 (41%)	5 (1%)	1 (<1%)	0	135 (37%)	2 (1%)	0	0
Peripheral oedema	146 (40%)	8 (2%)	1 (<1%)	0	112 (31%)	3 (1%)	0	0
Back pain	135 (37%)	13 (4%)	1 (<1%)	0	95 (26%)	13 (4%)	1 (<1%)	0
Fatigue	130 (36%)	32 (9%)	0	0	97 (27%)	17 (5%)	0	0
Nausea	125 (34%)	7 (2%)	0	0	86 (24%)	2 (1%)	0	0
Cough	120 (33%)	2 (1%)	0	0	64 (18%)	0	0	0
Asthenia	115 (32%)	18 (5%)	1 (<1%)	0	83 (23%)	16 (4%)	1 (<1%)	0
Bronchitis	112 (31%)	12 (3%)	0	0	79 (22%)	6 (2%)	0	0
Insomnia	111 (30%)	11 (3%)	0	0	102 (28%)	14 (4%)	0	0
Muscle spasms	108 (30%)	2 (1%)	0	0	80 (22%)	4 (1%)	0	0
Dyspnoea	105 (29%)	11 (3%)	1 (<1%)	0	59 (16%)	4 (1%)	0	0
Weight decreased	101 (28%)	10 (3%)	0	0	58 (16%)	11 (3%)	0	0
Peripheral sensory neuropathy	101 (28%)	9 (2%)	0	0	64 (18%)	1 (<1%)	0	0
Arthralgia	94 (26%)	11 (3%)	0	0	71 (19%)	8 (2%)	0	0
Nasopharyngitis	92 (25%)	0	0	0	66 (18%)	0	0	0
Decreased appetite	90 (25%)	3 (1%)	0	0	63 (17%)	2 (1%)	1 (<1%)	0
Upper respiratory tract infection	89 (24%)	6 (2%)	0	0	50 (14%)	4 (1%)	0	0
Pyrexia	86 (24%)	10 (3%)	0	0	58 (16%)	9 (2%)	0	0
Headache	75 (21%)	2 (1%)	0	0	43 (12%)	0	0	0
Pain in extremity	74 (20%)	6 (2%)	0	0	57 (16%)	1 (<1%)	0	0
Dizziness	74 (20%)	4 (1%)	0	0	64 (18%)	2 (1%)	0	0
Vomiting	71 (20%)	4 (1%)	0	0	48 (13%)	2 (1%)	0	0
Cataract	50 (14%)	40 (11%)	0	0	43 (12%)	39 (11%)	0	0
Hypokalaemia	49 (13%)	41 (11%)	5 (1%)	0	34 (9%)	28 (8%)	8 (2%)	0
Pneumonia	40 (11%)	62 (17%)	5 (1%)	3 (1%)	27 (7%)	31 (8%)	5 (1%)	3 (1%)
Hypertension	30 (8%)	29 (8%)	2 (1%)	0	14 (4%)	16 (4%)	0	0

	Dara+Rd (n=364)				Rd (n=365)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Hyperglycaemia	25 (7%)	24 (7%)	4 (1%)	0	14 (4%)	12 (3%)	2 (1%)	0
Pulmonary embolism	0	23 (6%)	3 (1%)	0	0	16 (4%)	3 (1%)	1 (<1%)
Second primary malignancy*	74 (20%)	--	--	--	46 (13%)	--	--	--

Data are n (%). Grade 1–2 treatment-emergent adverse events that occurred in 20% or more of patients and grade 3, 4, and 5 treatment-emergent adverse events that occurred in more than 5% of patients in either treatment group are shown. Appendix pp 14–26 shows grade 1–2 treatment-emergent adverse events that occurred in 10% or more of patients in either treatment group and all grade 3, 4, and 5 treatment-emergent adverse events. *Second primary malignancies were prespecified in the statistical analysis plan as adverse events of clinical interest. Source: [19]

Safety data for treatment with Dara+VMP and VMP amongst newly diagnosed patients with multiple myeloma who are ineligible for autologous stem cell transplantation come from the ALCYONE (MMY3007, NCT02195479) study. An overview of patients affected by adverse events is presented in Table 86 with rates of the most common treatment-emergent adverse events of any grade presented in Table 87, and most common grade 3 and 4 adverse events presented in Table 88.

Table 86. Overall summary of treatment-emergent adverse events amongst the ALCYONE (MMY3007, NCT02195479) safety population

Number of patients	Dara+VMP (n=346) n (%)	VMP (n=354) n (%)
With at least one adverse event	337 (97.4%)	342 (96.6%)
With at least one serious adverse event	277 (80.1%)	274 (77.4%)
Who discontinued study treatment for any reason	NR	NR
Who discontinued study treatment due to adverse events	33 (9.3%)	24 (6.9%)

Source: Janssen data-on-file Dara+VMP DMC submission [98]; NR = not reported

Table 87. Most common treatment-emergent adverse events of any grade (≥10%) amongst the ALCYONE (MMY3007, NCT02195479) safety population

	Dara+VMP (n=346) n (%)	VMP (n=354) n (%)
Any TEAE	337 (97.4%)	342 (96.6%)
Blood and lymphatic system disorders	256 (74.0%)	269 (76.0%)
Neutropenia	174 (50.3%)	186 (52.5%)

	Dara+VMP (n=346) n (%)	VMP (n=354) n (%)
Thrombocytopenia	172 (49.7%)	190 (53.7%)
Anaemia	107 (30.9%)	131 (37.0%)
Leukopenia	47 (13.6%)	53 (15.0%)
Lymphopenia	39 (11.3%)	36 (10.2%)
Infections and infestations	256 (74.0%)	171 (48.3%)
Upper respiratory tract infection	106 (30.6%)	50 (14.1%)
Pneumonia	63 (18.2%)	18 (5.1%)
Bronchitis	72 (20.8%)	27 (7.6%)
Viral upper respiratory tract infection	49 (14.2%)	23 (6.5%)
Urinary tract infection	39 (11.3%)	12 (3.4%)
General disorders and administration site conditions	212 (61.3%)	184 (52.0%)
Pyrexia	89 (25 7%)	74 (20.9%)
Oedema peripheral	68 (19.7%)	39 (11.0%)
Fatigue	60 (17.3%)	51 (14.4%)
Asthenia	48 (13.9%)	43 (12.1%)
Gastrointestinal disorders	195 (56.4%)	192 (54.2%)
Diarrhoea	96 (27.7%)	87 (24.6%)
Nausea	75 (21.7%)	76 (21.5%)
Constipation	64 (18.5%)	65 (18.4%)
Vomiting	61 (17.6%)	55 (15.5%)
Nervous system disorders	178 (51.4%)	181 (51.1%)
Peripheral sensory neuropathy	100 (28.9%)	122 (34.5%)
Musculoskeletal and connective tissue disorders	159 (46.0%)	116 (32.8%)
Back pain	61 (17.6%)	42 (11.9%)
Arthralgia	39 (11.3%)	22 (6.2%)
Pain in extremity	38 (11.0%)	22 (6.2%)
Respiratory, thoracic and mediastinal disorders	149 (43.1%)	74 (20.9%)

	Dara+VMP (n=346) n (%)	VMP (n=354) n (%)
Cough	68 (19.7%)	27 (7.6%)
Dyspnoea	44 (12.7%)	16 (4.5%)
Metabolism and nutrition disorders	131 (37.9%)	125 (35.3%)
Decreased appetite	40 (11.6%)	46 (13.0%)
Skin and subcutaneous tissue disorders	95 (27.5%)	97 (27.4%)
Rash	32 (9.2%)	38 (10.7%)
Vascular disorders	94 (27.2%)	52 (14.7%)
Hypertension	45 (13.0%)	11 (3.1%)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; Most Common (At Least 10%) Treatment-emergent Adverse Events by Treatment Cycle (New Onset), MedDRA System Organ Class and Preferred Term; Safety Analysis Set. ALCYONE; safety analysis set from median follow-up 40.1 months) Janssen, data-on-file Dara+VMP DMC submission [98]

Table 88. Most common treatment-emergent adverse events grade 3 or 4 amongst the ALCYONE (MMY3007, NCT02195479) safety population

	Dara+VMP (n=346) n (%)	VMP (n=354) n (%)
Patients with Grade 3 or 4 TEAEs	277 (80.1%)	274 (77.4%)
Blood and lymphatic system disorders	211 (61.0%)	219 (61.9%)
Neutropenia	139 (40.2%)	138 (39.0%)
Anaemia	60 (17.3%)	70 (19.8%)
Thrombocytopenia	120 (34.7%)	134 (37.9%)
Lymphopenia	27 (7.8%)	22 (6.2%)
Leukopenia	28 (8.1%)	30 (8.5%)
Infections and infestations	92 (26.6%)	53 (15.0%)
Pneumonia	45 (13.0%)	15 (4.2%)
Respiratory, thoracic and mediastinal disorders	30 (8.7%)	13 (3.7%)
Hypertension	19 (5.5%)	6 (1.7%)

Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by Treatment Cycle (New Onset), MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set. ALCYONE; safety analysis set from median follow-up 40.1 months; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; Janssen data-on-file Dara+VMP DMC submission [98]

The patient population participating in the SWOG S0777 study do not perfectly match up with the patients with newly diagnosed multiple myeloma who are ineligible for ASCT. Safety data for treatment with VRd comes from the SWOG S0777 study. An overview of patients affected by adverse events is presented in Table 89 with rates of the most common treatment-emergent adverse events presented in Table 90.

Table 89. Overall summary of adverse events amongst the SWOG S0777 (NCT00644228) safety population, by age group

	RVd (3-week cycles × 8 = 24 weeks)	Rd (4-week cycles × 6 = 24 weeks)	RVd (3-week cycles × 8 = 24 weeks)	Rd (4-week cycles × 6 = 24 weeks)
Subjects with at least 1:	≤ 65 years		≤ 75 years	
	N = 167 n (%)	N = 149 n (%)	N = 234 n (%)	N = 232 n (%)
TEAE	164 (98.2)	141 (94.6)	228 (97.4)	226 (97.4)
Grade 3 or 4 TEAE [a]	120 (71.9)	89 (59.7)	178 (76.1)	157 (67.7)
Grade 5 TEAE [a]	5 (3.0)	1 (0.7)	10 (4.3)	6 (2.6)
Treatment-emergent SAE	57 (34.1)	35 (23.5)	90 (38.5)	63 (27.2)
Treatment Discontinuation Due to TEAE[b]	32 (19.2)	11 (7.4)	51 (21.8)	19 (8.2)
Subjects with at least 1:	> 65 years		> 75 years	
	N = 95 n (%)	N = 107 n (%)	N = 28 n (%)	N = 24 n (%)
TEAE	91 (95.8)	104 (97.2)	27 (96.4)	24 (100.0)
Grade 3 or 4 TEAE [a]	80 (84.2)	87 (81.3)	22 (78.6)	19 (79.2)
Grade 5 TEAE [a]	1 (1.1)	2 (1.9)	0 (0.0)	1 (4.2)
Treatment-emergent SAE	48 (50.5)	38 (35.5)	15 (53.6)	10 (41.7)
Treatment Discontinuation Due to TEAE[b]	28 (29.5)	13 (12.1)	9 (32.1)	5 (20.8)

Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event. [a] Graded using Common Terminology Criteria for Adverse Events, Version 4.0; [b] The adverse events leading to treatment discontinuation were recorded on the Off Treatment Notice Form. Note: Treatment-emergent adverse events include adverse events that started between the date of first dose and 30 days after the date of last dose. Data cut-off date = 01 Dec 2016. [111].

Table 90. Most common treatment-emergent adverse events amongst the SWOG S0777 (NCT00644228) safety population reported in at least 20% of subjects in any treatment arm by transplant eligibility

System Organ Class Preferred Term[a]	TNE		TE	
	RVd (3-week cycles × 8 = 24 weeks) (N = 120) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 137) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 142) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 119) n (%)
Subjects With ≥ 1 TEAE	115 (95.8)	133 (97.1)	140 (98.6)	112 (94.1)
Nervous System Disorders	100 (83.3)	82 (59.9)	119 (83.8)	63 (52.9)
Peripheral sensory neuropathy	80 (66.7)	47 (34.3)	104 (73.2)	38 (31.9)
Dizziness	36 (30.0)	23 (16.8)	40 (28.2)	18 (15.1)
Dysgeusia	35 (29.2)	29 (21.2)	44 (31.0)	19 (16.0)
Gastrointestinal Disorders	99 (82.5)	93 (67.9)	112 (78.9)	73 (61.3)
Constipation	63 (52.5)	69 (50.4)	84 (59.2)	46 (38.7)
Diarrhea	52 (43.3)	45 (32.8)	52 (36.6)	34 (28.6)
Nausea	40 (33.3)	36 (26.3)	58 (40.8)	33 (27.7)
Dyspepsia	19 (15.8)	17 (12.4)	31 (21.8)	16 (13.4)
General Disorders and Administration Site Conditions	99 (82.5)	103 (75.2)	122 (85.9)	88 (73.9)
Fatigue	84 (70.0)	90 (65.7)	109 (76.8)	77 (64.7)
Edema peripheral	57 (47.5)	41 (29.9)	65 (45.8)	24 (20.2)
Blood and Lymphatic System Disorders	96 (80.0)	118 (86.1)	112 (78.9)	85 (71.4)
Anemia	82 (68.3)	101 (73.7)	97 (68.3)	74 (62.2)
Thrombocytopenia	77 (64.2)	77 (56.2)	74 (52.1)	40 (33.6)
Leukopenia	46 (38.3)	76 (55.5)	63 (44.4)	50 (42.0)
Neutropenia	35 (29.2)	58 (42.3)	42 (29.6)	41 (34.5)
Lymphopenia	34 (28.3)	37 (27.0)	33 (23.2)	25 (21.0)
Metabolism and Nutrition Disorders	93 (77.5)	111 (81.0)	108 (76.1)	91 (76.5)
Hypocalcemia	66 (55.0)	63 (46.0)	65 (45.8)	48 (40.3)
Hyperglycemia	58 (48.3)	81 (59.1)	69 (48.6)	61 (51.3)
Decreased appetite	43 (35.8)	35 (25.5)	47 (33.1)	24 (20.2)
Hypoalbuminemia	43 (35.8)	40 (29.2)	35 (24.6)	27 (22.7)
Hyponatremia	41 (34.2)	42 (30.7)	39 (27.5)	23 (19.3)
Hypokalemia	36 (30.0)	31 (22.6)	40 (28.2)	22 (18.5)

System Organ Class Preferred Term[a]	TNE		TE	
	RVd (3-week cycles × 8 = 24 weeks) (N = 120) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 137) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 142) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 119) n (%)
Dehydration	25 (20.8)	13 (9.5)	18 (12.7)	4 (3.4)
Musculoskeletal and Connective Tissue Disorders	87 (72.5)	96 (70.1)	98 (69.0)	70 (58.8)
Muscular weakness	36 (30.0)	29 (21.2)	28 (19.7)	16 (13.4)
Back pain	35 (29.2)	37 (27.0)	52 (36.6)	34 (28.6)
Investigations	73 (60.8)	83 (60.6)	90 (63.4)	61 (51.3)
Blood AP increased	31 (25.8)	29 (21.2)	35 (24.6)	19 (16.0)
Blood creatinine increased	30 (25.0)	38 (27.7)	18 (12.7)	26 (21.8)
Weight decreased	26 (21.7)	41 (29.9)	27 (19.0)	13 (10.9)
ALT increased	24 (20.0)	21 (15.3)	43 (30.3)	28 (23.5)
AST increased	18 (15.0)	21 (15.3)	38 (26.8)	17 (14.3)
Respiratory, Thoracic, and Mediastinal Disorders	69 (57.5)	74 (54.0)	81 (57.0)	43 (36.1)
Dyspnea	43 (35.8)	38 (27.7)	37 (26.1)	27 (22.7)
Cough	36 (30.0)	30 (21.9)	41 (28.9)	21 (17.6)
Skin and Subcutaneous Tissue Disorders	47 (39.2)	55 (40.1)	66 (46.5)	49 (41.2)
Rash	20 (16.7)	25 (18.2)	29 (20.4)	27 (22.7)
Vascular Disorders	47 (39.2)	44 (32.1)	54 (38.0)	29 (24.4)
Hypotension	24 (20.0)	11 (8.0)	19 (13.4)	2 (1.7)
Psychiatric Disorders	45 (37.5)	64 (46.7)	68 (47.9)	46 (38.7)
Insomnia	35 (29.2)	40 (29.2)	51 (35.9)	34 (28.6)

AE = adverse event; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TE = transplant eligible; TEAE = treatment-emergent adverse event; TNE = transplant non-eligible. a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency by the TNE RVd column. [111].

Table 91. Grade 3 or 4 TEAEs reported in at least 5% of subjects in any treatment arm – Initial treatment – SWOG S0777 (safety population)

System Organ Class Preferred Term[a]	RVd (3-week cycles × 8 = 24 weeks) (N = 62) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Subjects With ≥ 1 Grade 3 or 4 TEAE[d]	200 (76.3)	176 (68.8)
Blood and Lymphatic System Disorders	**104 (39.7)**	**106 (41.4)**
Neutropenia	26 (9.9)	42 (16.4)
Thrombocytopenia	45 (17.2)	24 (9.4)
Anaemia	32 (12.2)	41 (16.0)
Lymphopenia	49 (18.7)	39 (15.2)
Leukopenia	23 (8.8)	29 (11.3)
Infections and Infestations	**36 (13.7)**	**24 (9.4)**
Infections	1 (0.4)	0
Lung infection	19 (7.3)	14 (5.5)
Nervous system Disorders	**89 (34.0)**	**24 (9.4)**
Syncope	23 (8.8)	7 (2.7)
Peripheral sensory neuropathy	54 (20.6)	4 (1.6)
Peripheral motor neuropathy	17 (6.5)	3 (1.2)
Respiratory, Thoracic, and Mediastinal Disorders	**26 (9.9)**	**9 (3.5)**
Dyspnoea	16 (6.1)	3 (1.2)
Vascular Disorders	**41 (15.6)**	**18 (7.0)**
Hypotension	20 (7.6)	0
Embolism	18 (6.9)	16 (6.3)
Gastrointestinal Disorders	**46 (17.6)**	**18 (7.0)**
Diarrheal	24 (9.2)	4 (1.6)
General Disorders and Administration Site Conditions	**49 (18.7)**	**29 (11.3)**
Fatigue	38 (14.5)	26 (10.2)
Investigations	**29 (11.1)**	**22 (8.6)**
Alanine aminotransferase increased	13 (5.0)	4 (1.6)
Renal and Urinary Disorders	**8 (3.1)**	**17 (6.6)**
Renal Failure Acute	7 (2.7)	14 (5.5)

System Organ Class Preferred Term[a]	RVd (3-week cycles × 8 = 24 weeks) (N = 62) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)
Musculoskeletal and Connective Tissue Disorders	**45 (17.2)**	**30 (11.7)**
Muscular weakness	22 (8.4)	11 (4.3)
Metabolism and Nutrition Disorders	**85 (32.4)**	**70 (27.3)**
Hyperglycaemia	19 (7.3)	24 (9.4)
Hypokalaemia	30 (11.5)	12 (4.7)
Hypocalcaemia	17 (6.5)	21 (8.2)
Dehydration	22 (8.4)	6 (2.3)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event. a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency for the RVd column in the PETHEMA GEM2012 study. b Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment. c For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment." d Graded using CTCAE Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the IFM 2009 and SWOG S0777 studies. Note: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study. Data cutoff date = 01 Dec 2016 for the SWOG S0777 studies. [111].

18 Appendix F – Comparative analysis of efficacy and safety

Based on the results of a the clinical SLR (Appendix A – Literature search for efficacy and safety of intervention and comparators), a Bayesian NMA was conducted [20].

18.1 Methods

The NMA was performed using WinBUGS according to the NICE Decision Support Unit guidelines [120]. Three NMA assumptions (homogeneity, similarity, and consistency) were assessed across all studies. Reported hazard ratios (HRs) from relevant RCTs were applied in the NMA, assuming no violation of the proportional hazards assumption. All analyses were performed using fixed- and random-effects models. The choice between fixed- and random-effects models was based on deviance information criterion (DIC) score and/or the presence of observed heterogeneity in the network [121] [122]. If HRs and associated confidence intervals (CIs) were not reported but Kaplan-Meier curves with corresponding numbers of patients at risk were available, the HRs and CIs were estimated based on the Guyot methodology [123], as recommended by NICE and assuming no violation of proportional hazards. If HRs were reported with only P values, the CIs associated with the reported HR were also estimated [124].

18.2 Results

Outcomes for efficacy (PFS and OS) were compared across all studies relevant in Europe (see evidence network in Figure 36). The network included 10 unique treatment regimens. A random-effects model was preferred over a fixed-effects model for OS and PFS because heterogeneity was observed in both networks of evidence. Additionally, the DIC score for these models was lower compared with the fixed-effects model. Results from all studies that included VMP were pooled, as matching-adjusted indirect comparison indicated noninferiority in PFS and OS outcomes regardless of bortezomib dose intensity [125]. A normal likelihood with identity link model was used for PFS. Rd continuous was selected as the referent comparator for the current analysis because it is approved and included in key treatment guidelines across regions [126] [85].

18.3 Progression-free survival

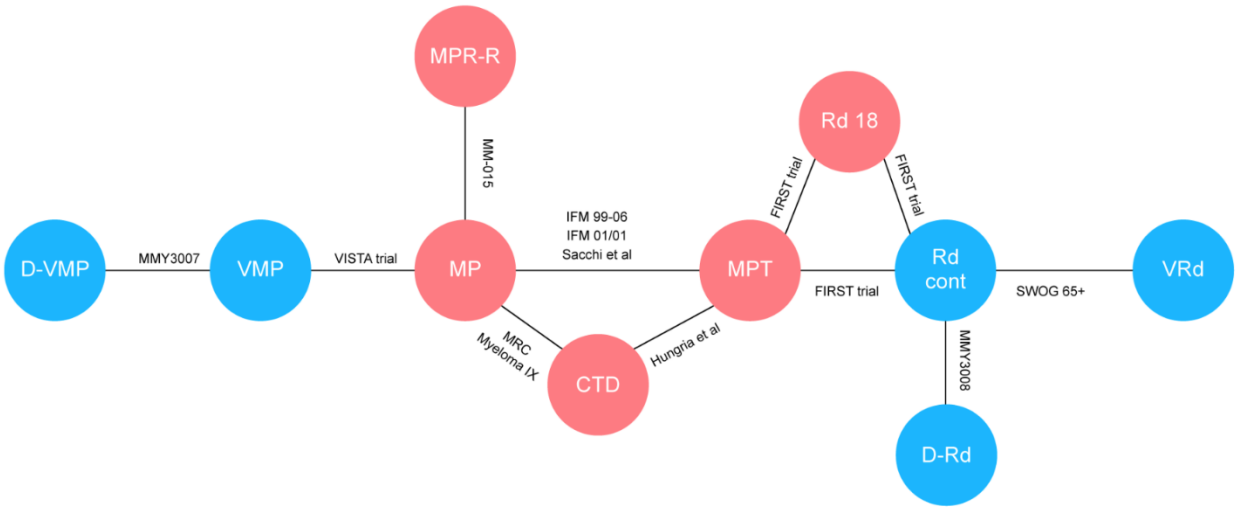
The regimens with improved PFS compared with Rd continuous were Dara+Rd (HR, 0.53; 95% CrI, 0.43–0.66), Dara+VMP (HR, 0.58; 95% CrI, 0.37–0.93), and VRd (HR, 0.77; 95% CrI, 0.55–1.08; Figure 37A). These regimens also had the highest probability of being more effective than Rd continuous (100%, 98.9%, and 93.2%, respectively; Figure 37A). Dara+Rd had the highest probability of being ranked first in terms of PFS, (62%) followed by Dara+VMP (35%) and VRd (2%; Figure 37B).

18.4 Overall survival

The regimens with improved OS compared with Rd continuous were Dara+Rd (HR, 0.68; 95% CrI, 0.54–0.86), VRd (HR, 0.77; 95% CrI, 0.52–1.14), and Dara+VMP (HR, 0.79; 95% Crl, 0.50–1.23; Figure 38A). The regimens with the highest probability of being more effective than Rd continuous with respect to OS included Dara+Rd (99.9%), VRd (90.1%), and Dara+VMP (85.5%; Figure 38A). Similarly, Dara+Rd had the highest chance of being ranked first with respect to OS, (53%) followed by VRd (24%) and then Dara+VMP (23%; Figure 38B).

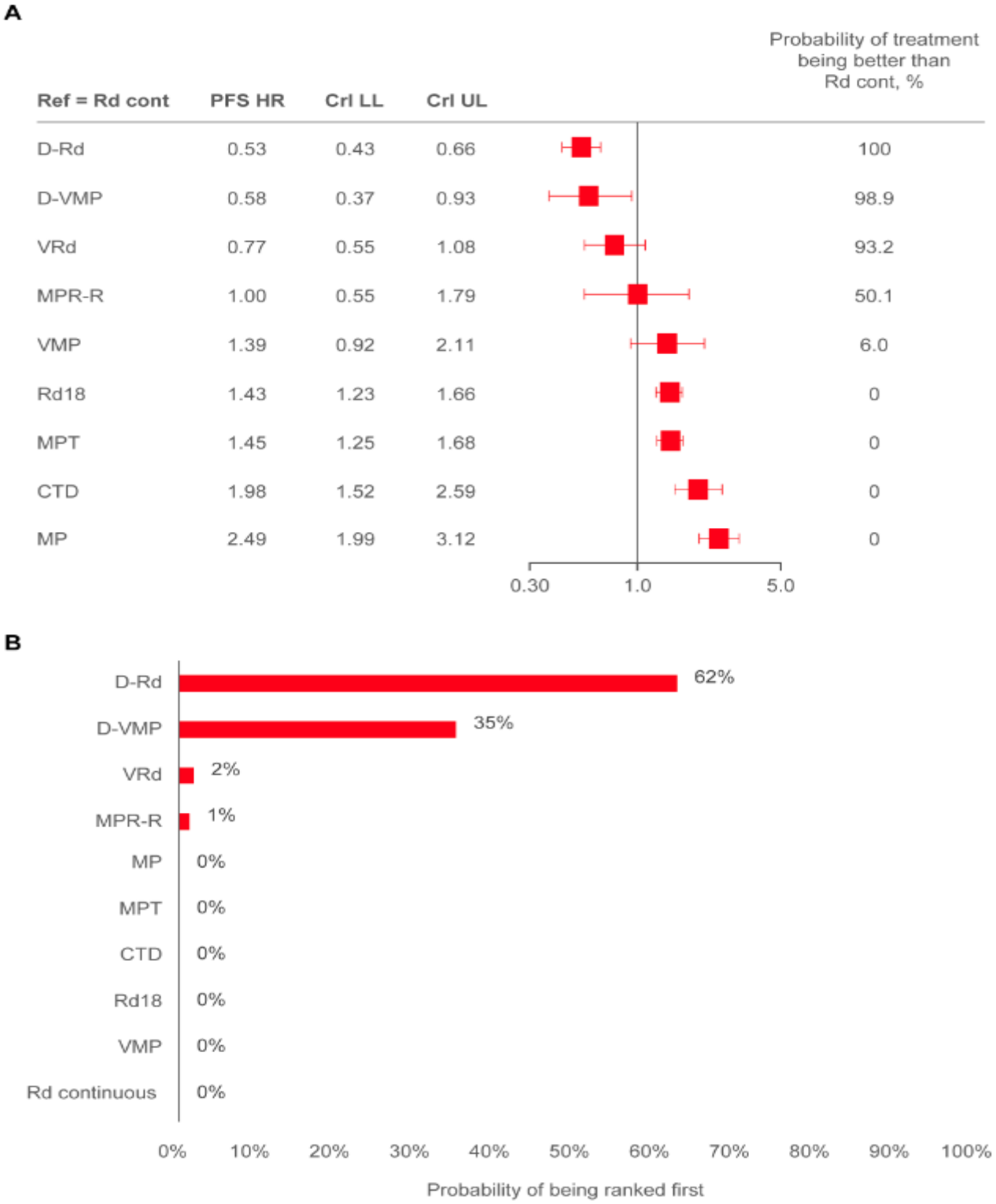
The present NMA incorporated the most recently published data evaluating SOC treatments from RCTs with more mature data including the daratumumab-containing regimens from the ALCYONE and MAIA trials. The results demonstrated that, compared with other relevant treatment options, Dara+Rd, Dara+VMP, and VRd are most effective in improving PFS and OS in TIE patients 305 with NDMM. Overall, Dara+Rd had the highest chance of being ranked as the most effective treatment with respect to both PFS and OS. Findings from the European NMA were consistent with the global NMA. Results of this study may help guide choice of treatment for this patient population.

Figure 36. Evidence network for (A) PFS and (B) OS and (C) PFS and OS using main relevant comparators in Europe[a]



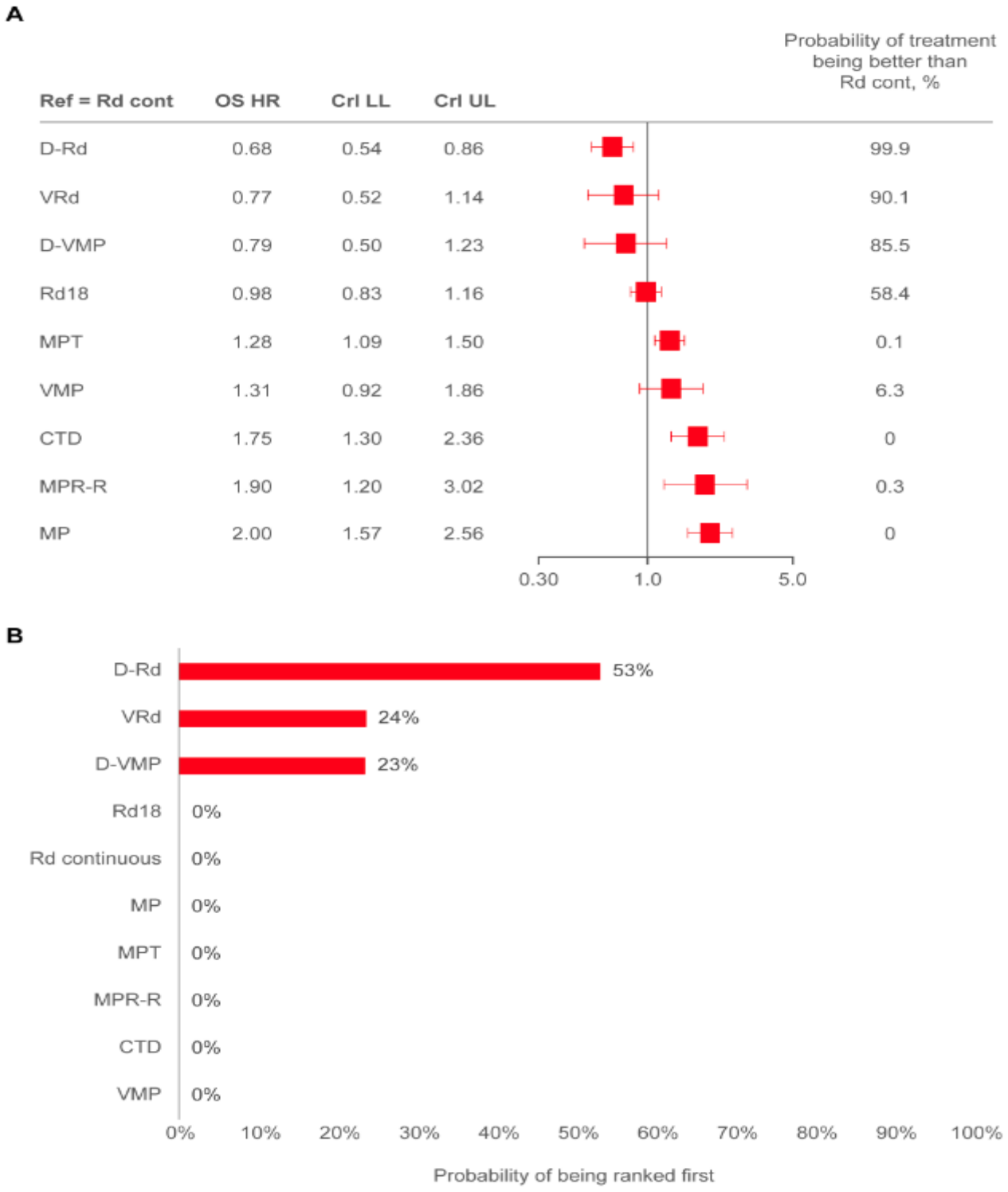
[a]Blue colour indicates EHA-ESMO recommended treatments. CMP, carfilzomib/melphalan/prednisone; CPR, cyclophosphamide/prednisone/lenalidomide; CTD, cyclophosphamide/thalidomide/dexamethasone; Dara+Rd, daratumumab/lenalidomide/dexamethasone; Dara+VMP, daratumumab/bortezomib/melphalan/prednisone; DEX, dexamethasone; DEX-IFN, dexamethasone/interferon alfa 2b; EHA-ESMO, European Hematology Association-European Society for Medical Oncology; KRd, carfilzomib/lenalidomide/dexamethasone; M-DEX, melphalan/dexamethasone; MP, melphalan/prednisone; MPR, melphalan/prednisone/lenalidomide; MPR-R, melphalan/prednisone/lenalidomide as induction, and lenalidomide as maintenance; MPT, melphalan/prednisone/thalidomide; MPT-T, melphalan/prednisone/thalidomide as induction, and thalidomide as maintenance; NCCN, National Comprehensive Cancer Network; OS, overall survival; Pembro-Rd, pembrolizumab/lenalidomide/dexamethasone; PFS, progression-free survival; Rd cont, lenalidomide/dexamethasone, continuous; Rd9, lenalidomide/dexamethasone, 9 cycles; Rd18, lenalidomide/dexamethasone, 18 cycles; TD, thalidomide/dexamethasone; VD, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisone; VMP-S, bortezomib/melphalanprednisone/siltuximab; VMPT-VT, bortezomib/melphalan/prednisone/thalidomide as induction, and bortezomib/thalidomide as maintenance; VRd, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

Figure 37. Progression-free survival (using simplified evidence network of main relevant comparators in Europe)



(A) Forest plot of PFS HRs of treatments versus Rd continuous by efficacy and probability of being better than Rd continuous, and (B) rankogram presenting probability of being ranked first in PFS. CMP, carfilzomib/melphalan/prednisone; CPR, cyclophosphamide/prednisone/lenalidomide; CrI LL, credible interval lower limit; CrI UL, credible interval upper limit; CTD, cyclophosphamide/thalidomide/dexamethasone; Dara+Rd, daratumumab/lenalidomide/dexamethasone; Dara+VMP, daratumumab/bortezomib/melphalan/prednisone; DEX, dexamethasone; DEX-IFN, dexamethasone/interferon alfa 2b; HR, hazard ratio; MP, melphalan/prednisone; MPR-R, melphalan/prednisone/lenalidomide as induction, and lenalidomide as maintenance; MPT, melphalan/prednisone/thalidomide; OS, overall survival; Rd cont, lenalidomide/dexamethasone, continuous; Rd18, lenalidomide/dexamethasone, 18 cycles; VMP, bortezomib/melphalan/prednisone; VRd, bortezomib/lenalidomide/dexamethasone.

Figure 38. Overall survival (using simplified evidence network of main relevant comparators in Europe)



(A) Forest plot of OS HRs of treatments versus Rd continuous by efficacy and probability of being better than Rd continuous, and (B) rankogram presenting probability of being ranked first in OS. CMP, carfilzomib/melphalan/prednisone; CPR, cyclophosphamide/prednisone/lenalidomide; CrI LL, credible interval lower limit; CrI UL, credible interval upper limit; CTD, cyclophosphamide/thalidomide/dexamethasone; Dara+Rd, daratumumab/lenalidomide/dexamethasone; Dara+VMP, daratumumab/bortezomib/melphalan/prednisone; DEX, dexamethasone; DEX-IFN, dexamethasone/interferon alfa 2b; HR, hazard ratio; MP, melphalan/prednisone; MPR-R, melphalan/prednisone/lenalidomide as induction, and lenalidomide as maintenance; MPT, melphalan/prednisone/thalidomide; OS, overall survival; Rd cont, lenalidomide/dexamethasone, continuous; Rd18, lenalidomide/dexamethasone, 18 cycles; VMP, bortezomib/melphalan/prednisone; VRd, bortezomib/lenalidomide/dexamethasone.

19 Appendix G – Extrapolation

Extrapolations of time-to-event data (OS, PFS, TTTD) were performed in line with DMC Guideline recommendations, which are in line with the NICE Decision Support Unit guidelines [230]. Six parametric distributions were fitted to model OS, PFS, PPS, and TTTD data, and were implemented in the model [132].

- The Exponential distribution is a one-parameter function that is considered the simplest parametric model. The Exponential model is a proportional hazards model, meaning it is assumed that the HR for the two groups being compared is constant over time.
- The Weibull and Gompertz distributions are functions with two parameters—a shape and scale. Therefore, these two distributions are more flexible than the Exponential distribution. Both distributions are proportional hazards models.
- The Log-logistic and Log-normal distributions share many similarities. They have a hazard function that can be non-monotonic with respect to time. Therefore, neither of the distributions can be parameterised as a proportional hazards model. Furthermore, due to their functional forms, the Log-logistic and Log-normal models typically produce long tails in the survivor function. As a result, the clinical validity of Log-logistic and Log-normal survival models must be carefully assessed.
- The Generalised Gamma distribution is a flexible three-parameter model. The Weibull, Exponential, and Log-normal distributions are special cases of the Generalised Gamma distribution. However, due to its flexibility, the long-term projections may be unduly influenced by the end of the Kaplan-Meier (KM) curves, which are based on a small number of patients. Therefore, similar to the Log-normal and Log-logistic distributions, the clinical validity of the projected survival must be assessed.

The process of selecting a 'best-fitting' distribution involves considerations based on the observed data regarding goodness-of-fit and plausibility of results [132, 133]:

- Graphical assessment of fits
- Goodness-of-fit statistics (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]). Statistically, the best fit to the observed data is the curve with the lowest AIC and BIC.
- Clinical plausibility of long-term projections
- Comparison of long-term projections with external sources (if available)

'Best fitting' does not necessarily imply good fit; the best-fitting distribution may still deviate from the observed data or produce clinically implausible long-term projections.

The following sections list the relevant data from the fitting exercises, including predicted versus observed curves, parameters of the survival distributions and the covariance matrix (used to correlate the parameters of the distributions in the DSA and PSA), AIC and BIC values, diagnostic plots for each fit, and HRs for the comparators.

All parametric fits to survival data discussed in this section were obtained using the LIFETEST and LIFEREG procedures from Statistical Analysis System (SAS) version 9.4.

19.1 Overall survival (OS)

[redacted]

Figure 39. OS observed - Dara+Rd and Rd

[redacted]

Figure 40. OS Schoenfeld residuals plot - Dara+Rd and Rd

Figure 41. OS long-cumulative hazard plots - Dara+Rd and Rd

19.1.1 Parametric survival analysis using individual parametric distributions for Dara+Rd and Rd

[redacted]

[redacted]

[redacted]

Figure 42. OS long-term extrapolations using individual curves - Dara+Rd

[redacted]

Figure 43. OS Long-term extrapolations using individual curves - Rd

19.1.2 Smoothed hazard plots

Figure 44. OS – ITT – Rd

Figure 45. OS – ITT – Rd (stratified)

Figure 46. OS – ITT – Rd (as predictor)

Figure 47. OS – ITT – Dara+Rd

Figure 48. OS – ITT – Dara+Rd (stratified)

Figure 49. OS – ITT – Dara+Rd (as predictor)

19.1.3 Goodness-of-fit statistics and graphical assessment of fits

Table 92. OS Dara+Rd and Rd parametric distribution parameters and fit statistics using individual curves

[redacted]

Table 93. OS Dara+Rd and Rd covariance matrix using individual curves

[redacted]

19.1.4 General population mortality

[redacted]

19.1.5 Clinical trials and RWE

[redacted]

Figure 50. OS comparison with external long-term clinical trial data - Rd

Table 94. OS outcomes Rd in MMY3008 vs. Rd in FIRST

19.2 Progression-free survival (PFS)

Figure 51. PFS observed - Dara+Rd and Rd

Figure 52. PFS Schoenfeld residuals plot - Dara+Rd and Rd

Figure 53. PFS long-cumulative hazard plots - Dara+Rd and Rd

19.2.1 Parametric survival analysis using individual parametric distributions for Dara+Rd and Rd

[redacted]

Figure 54. PFS long-term extrapolations using individual curves - Dara+Rd

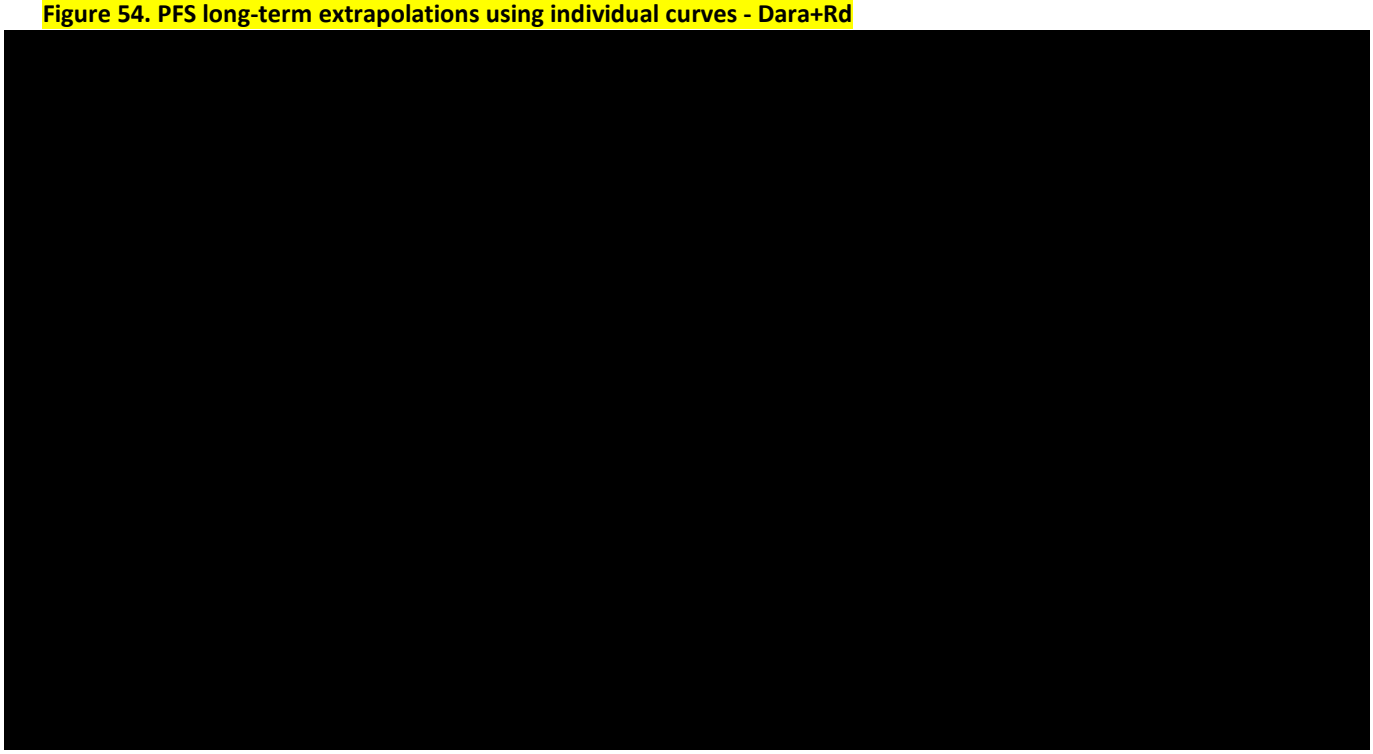


Figure 55. PFS long-term extrapolations using individual curves - Rd

19.2.2 Smoothed hazard plots

[redacted]

Figure 56. PFS – ITT – Rd

Figure 57. PFS – ITT – Rd (stratified)

Figure 58. PFS – ITT – Rd (as predictor)

Figure 59. PFS – ITT – Dara+Rd

Figure 60. PFS – ITT – Dara+Rd (stratified)

Figure 61. PFS – ITT – Dara+Rd (as predictor)

19.2.3 Goodness-of-fit statistics and graphical assessment of fits

[redacted]

Table 95. PFS Dara+Rd and Rd parametric distribution parameters and fit statistics using individual curves

[redacted]

Table 96. PFS Dara+Rd and Rd covariance matrix using individual curves

[redacted]

19.3 Time to treatment discontinuation (TTTD)

[redacted]

19.3.1 First-line treatment duration

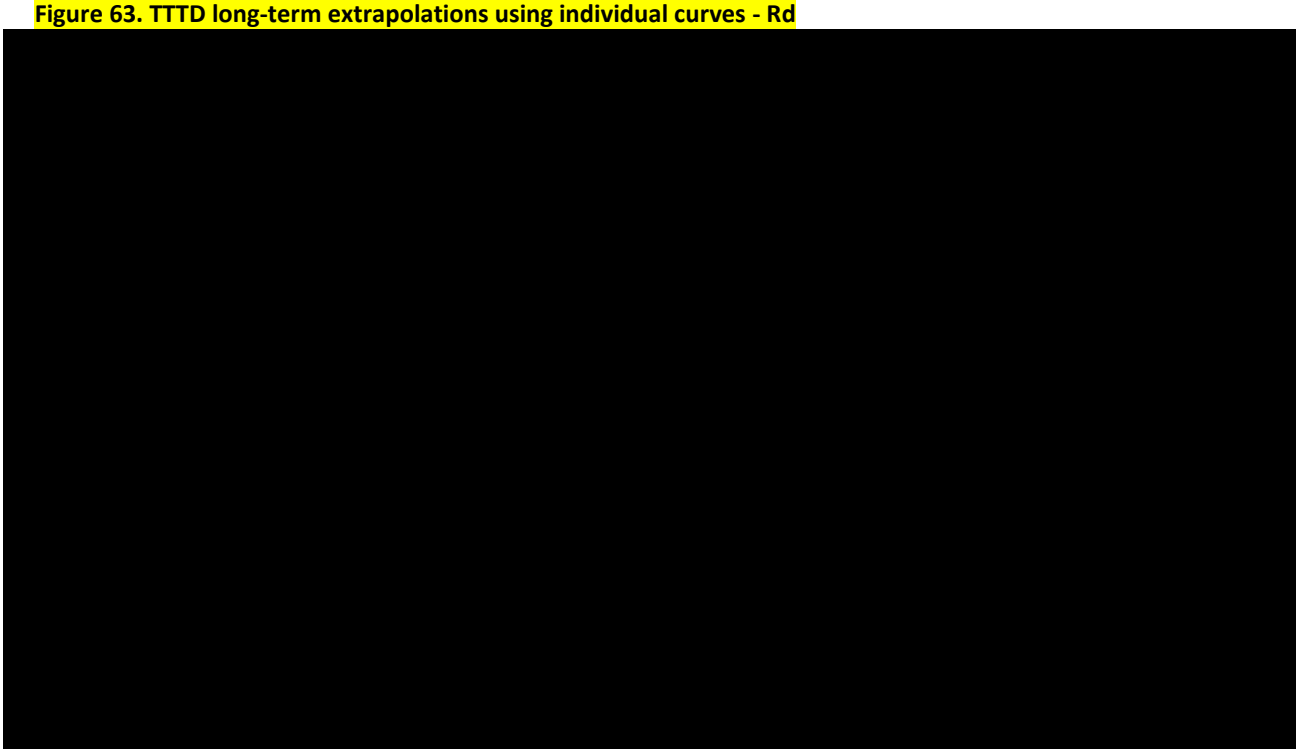
[redacted]

Table 97. Dara+Rd network: TTTD curve options

[redacted]

Figure 62. TTTD long-term extrapolations using individual curves - Dara+Rd

Figure 63. TTTD long-term extrapolations using individual curves - Rd



19.3.2 Smoothed hazard plots

Figure 64. TTTD – ITT – Rd

Figure 65. TTTD – ITT – Rd (stratified)

Figure 66. TTTD – ITT – Rd (as predictor)

Figure 67. TTTD – ITT – Dara+Rd

Figure 68. TTTD – ITT – Dara+Rd (stratified)

Figure 69. TTTD – ITT – Dara+Rd (as predictor)

19.3.3 Goodness-of-fit statistics and graphical assessment of fits

[redacted]

Table 98. TTTD Dara+Rd and Rd parametric distribution parameters and fit statistics using individual curves

Table 99. TTTD Dara+Rd and Rd covariance matrix using individual curves

[redacted]

19.3.4 Median treatment duration and treat-to-progression approaches

[redacted]

Table 100. First-line median treatment duration

[redacted]

[redacted]

[redacted]

19.3.5 Second-line TTTD and PFS

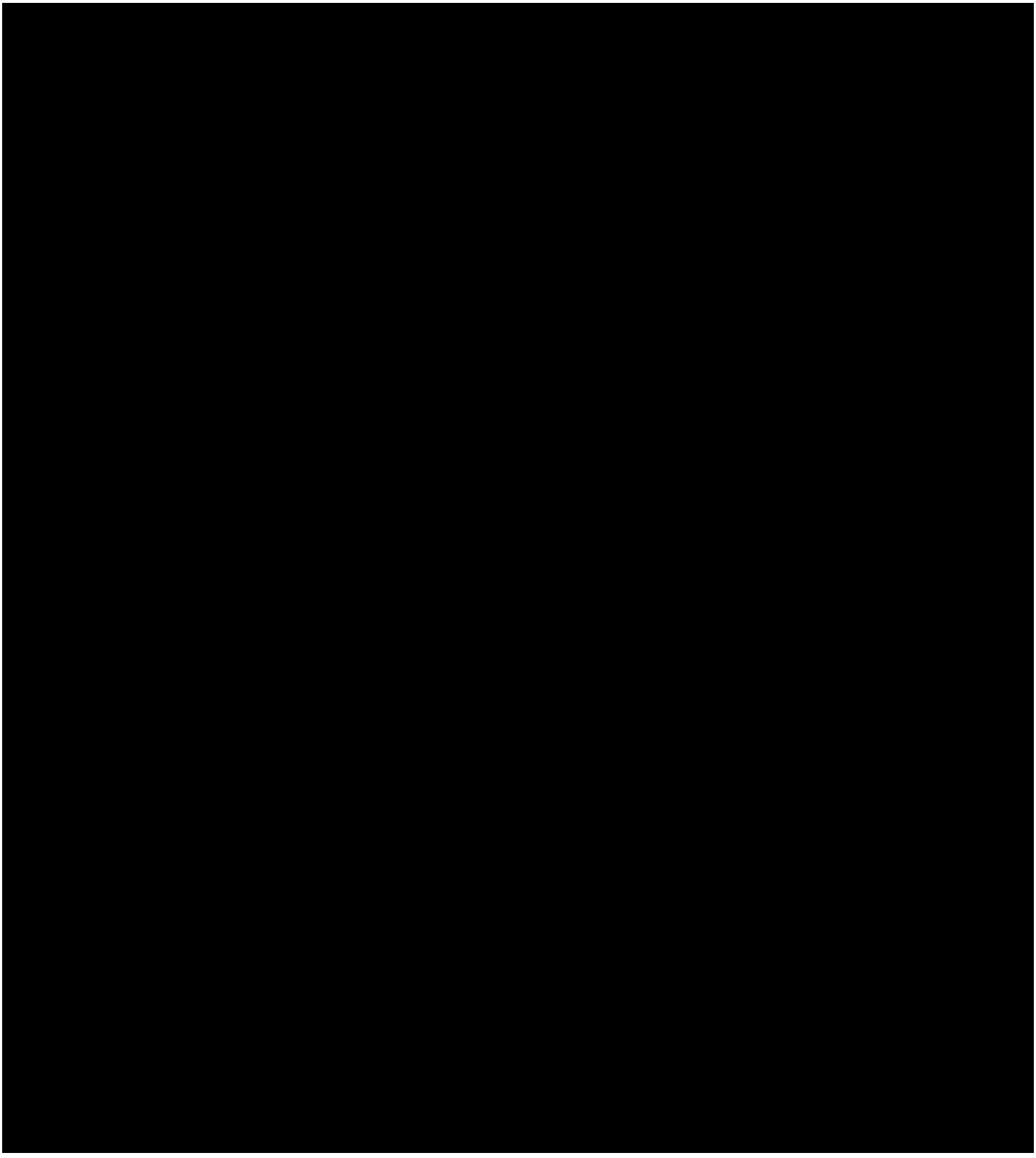
[redacted]

19.3.6 Treat-to-progression: using second-line PFS estimates

[redacted]

Table 101. Second-line TTTD and PFS

[redacted]



[redacted]

19.3.7 Third-line treatment duration

[redacted]

20 Appendix H – Literature search for HRQoL data

The literature search aimed to address the following research question:

- What is the evidence for HRQoL (i.e., utility) associated with NDMM, particularly in ACST-ineligible patients?

Utility values for relevant health states were identified from a systematic review of the published literature from a number of databases (Table 102). Relevant studies were identified by searching Medline (via PubMed) and Embase (via Embase) with an unlimited look-back period, and with searches run on April 5, 2021. In addition, other sources (e.g., CRD, ISPOR, and HTA authorities) were manually searched for potentially relevant studies, with a three year look back period.

Table 102. Bibliographic databases, conference websites, and HTA bodies included in the HRQoL literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	Unlimited – 5 April 2021	5 April 2021
Medline	Pubmed	Unlimited – 5 April 2021	5 April 2021
Centre for Reviews and Dissemination	CRD Web page	4 March 2018 - 4 March 2021	4 March 2021
ISPOR	ISPOR Web page	4 March 2018 - 4 March 2021	4 March 2021
NICE	NICE Web page	5 April 2018 – 5 April 2021	5 April 2021
SMC	SMC Web page	5 April 2018 – 5 April 2021	5 April 2021
PBAC	PBAC Web page	5 April 2018 – 5 April 2021	5 April 2021
CADTH	CADTH Web page	5 April 2018 – 5 April 2021	5 April 2021

Abbreviations: ISPOR = Professional Society for Health Economics and Outcomes Research (formerly International Society for Pharmacoeconomics and Outcomes Research); NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Council; PBAC =Pharmaceutical Benefits Advisory Committee; CADTH = Canadian Agency for Drugs and Technologies in Health

20.1 Search strategy

Explicit criteria were used to select studies for inclusion with two reviewers independently selecting studies at the title/abstract level, and full-text level, with any disagreements resolved by a third reviewer. For those studies that met inclusion criteria, they underwent data extraction using a piloted form, with all data checked for accuracy by a second reviewer. Studies were initially screened and selected for inclusion based on the Population, Intervention, Comparison, Outcome, Study Design (PICOS) criteria outlined in Table 103.

Additional publications such as those reporting of the previously conducted RCT SLRs were searched to identify additional relevant publications or relevant data not captured in the database search. Bibliographies of articles and grey literature sources were also searched. Searches were restricted to English language. Conference abstracts were included in the review if: 1) results of the respective study were not reported in any other full-text publication; and 2) relevant data could be extracted from the abstract. In the case of full-text studies, where values were reported in figures, HRQoL values were extracted by digitizing the curves using Engauge digitizer.

Table 103. Eligibility criteria for the health-related quality of life systematic review

Domain	Inclusion criteria	Exclusion criteria	Brief rationale
Population	Frontline ASCT-ineligible MM	The population does not include frontline ASCT-ineligible multiple myeloma; Relapsed/refractory MM; alternatively, relevant outcomes are not presented separately for this patient population	Only studies on frontline ASCT-ineligible multiple myeloma are relevant for the purposes of this submission
Intervention/ Comparator	Any or none	N/A	Both non-treatment specific and treatment specific utility values are relevant for the purposes of this submission
Outcomes	Original health state utility data obtained using any methodology (e.g., TTO, SG, VAS, EQ-5D, SF-6D, HUI, QWB, or disease-specific utility instruments)	HSUV data not reported No useful HSUV data reported. For example: The article presents only previously published data, or the study is methodological only	A broad approach was taken with regard to the methodology for obtaining HSUVs, in case insufficient studies were identified (EQ5D measured in the patient population of interest and valued using the UK general population)
Study design	Experimental studies including RCTs and non-RCTs, observational studies, economic evaluations	Comments, letters, editorials and non-systematic or narrative reviews, case studies, case reports or case series	The study designs specified as eligible for inclusion were those considered most likely to report relevant data for this submission
	Systematic reviews were included at the title/abstract screening stage and used for identification of any additional primary studies not identified through the database searches, but were excluded during the full-text review if not presenting a novel analysis		

Domain	Inclusion criteria	Exclusion criteria	Brief rationale
Language	English	Any other language	The vast majority of the research in the field is published in English

Abbreviations: EQ-5D, EuroQoL-5 Dimension; HSUV, health state utility value; HUI, Health Utilities Index; NICE, National Institute for Health and Care Excellence; QWB, Quality of Well-Being; RCT, randomised controlled trial; SF-6D, Short Form-6 Dimension; SG, standard gamble; TTO, time trade-off; VAS, visual analogue scale.

Table 104 to Table 107 present the search hits in PubMed, Embase, the CRD and ISPOR.

Table 104. Medline search syntax for health-related quality of life review

Number	Syntax	Hits, Apr 5, 2021
#1	"Multiple myeloma" [Mesh] OR "Multiple myeloma"[tiab] OR "Kahler disease"[tiab] OR "Kahler's disease"[tiab] OR Myelomatosis[tiab] OR "Plasma cell myeloma" [tiab]	54,214
#2	(Quality of life [MeSH Terms] OR Quality of life [tiab] OR Life quality [tiab] OR Hql [tiab] OR qol [tiab] OR euroqol[tiab] OR eq5d OR eq 5d [tiab] OR Qaly* [tiab] OR Quality adjusted life year* [tiab] OR Hye* [tiab] OR Health* year* equivalent* [tiab] OR Health utility* [tiab] OR hui [tiab] OR Quality of wellbeing* [tiab] OR Quality of wellbeing [tiab] OR qwb [tiab] OR qald*[tiab] or qale*[tiab] or qtime*[tiab] OR Standard gamble* [tiab] OR Time trade off [tiab] OR Time tradeoff [tiab] OR tto [tiab] OR Visual analog* scale* [tiab] OR Discrete choice experiment* [tiab] OR Health state* utilit* [tiab] OR Health state* value* [tiab] OR health state* preference* [tiab])	399,776
#3	(("short form" OR sf OR "short-form" OR shortform) AND (12 OR 36 OR 6D OR 6 OR six OR twelve OR "thirty six" OR "thirtysix")) OR SF-6D OR SF6D OR SF-12 OR SF12 OR SF-36 OR SF36 OR "SF 6" OR "SF 12" OR "SF 36"	32,409
#4	("european organization for research and treatment of cancer quality of life questionnaire" AND "core 30"[tiab]) OR "eortc quality of life questionnaire"[tiab] OR (eortc AND ('qlq c30' OR QLQ-C30 OR core))[tiab] OR QLQ-C30[tiab]	4,817
#5	#2 OR #3 OR #4	410,171
#6	#1 AND #5	1,119
#7	"Letter" [ptyp] OR "Editorial" [ptyp] OR "Historical Article" [ptyp] OR "Case Reports" [ptyp]	4,009,876
#8	#6 NOT #7	1,056
#9	English [lang]	27,550,495
#10	#8 AND #9	971

Table 105. Embase search syntax for health-related quality of life review

Number	Syntax	Hits, Apr 5,2021
#1	'multiple myeloma'/exp OR 'multiple myeloma' OR 'multiple myeloma':ab,ti OR 'kahler disease':ab,ti OR 'kahlers disease':ab,ti OR 'myelomatosis':ab,ti OR 'plasma cell myeloma':ab,ti	93,379

#2	'quality of life'/exp OR 'quality of life':ab,ti OR 'life quality':ab,ti OR 'hql':ab,ti OR 'euroqol':ab,ti OR 'eq5d':ab,ti OR 'eq 5d':ab,ti OR 'qaly$':ab,ti OR 'quality adjusted life year$':ab,ti OR 'hye$':ab,ti OR 'health$ year$ equivalent$':ab,ti OR 'health utilit*':ab,ti OR 'hui':ab,ti OR 'quality of wellbeing$':ab,ti OR 'quality of well being':ab,ti OR 'gwb':ab,ti OR 'qald$':ab,ti OR 'qale$':ab,ti OR 'qtime$':ab,ti OR 'standard gamble$':ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR 'tto':ab,ti OR 'visual analog$ scale$':ab,ti OR 'discrete choice experiment$':ab,ti OR 'health state$ utilit*':ab,ti OR 'health state$ value$':ab,ti OR 'health state$ preference$':ab,ti	675,853
#3	(('short form' OR 'short-form' OR sf OR shortform) NEAR/1 (12 OR 36 OR 6d OR 6 OR six OR twelve OR 'thirty six' OR 'thirtysix')) OR 'sf 6d':ab,ti OR sf6d:ab,ti OR sf12:ab,ti OR sf36:ab,ti OR 'sf 6':ab,ti OR 'sf 12':ab,ti OR 'sf 36':ab,ti	64,853
#4	'european organization for research and treatment of cancer quality of life questionnaire core 30'/exp OR 'european organization for research and treatment of cancer quality of life questionnaire core 30' OR 'eortc quality of life questionnaire'/exp OR 'eortc quality of life questionnaire' OR (eortc NEAR/1 ('qlq c30' OR core))	8,288
#5	#2 OR #3 OR #4	694,992
#6	#1 AND #5	3,347
#7	'letter'/de OR 'editorial'/de OR 'case report'/de OR 'case study'/de	4,289,704
#8	#7 NOT #8	3,045
#9	#8 AND [english]/lim	2,903

Table 106. CRD registry search strategy Mar 2021

Number	Syntax	Hits, Mar 4, 2021
#1	Multiple myeloma (keyword search), 2018 to 2021	0

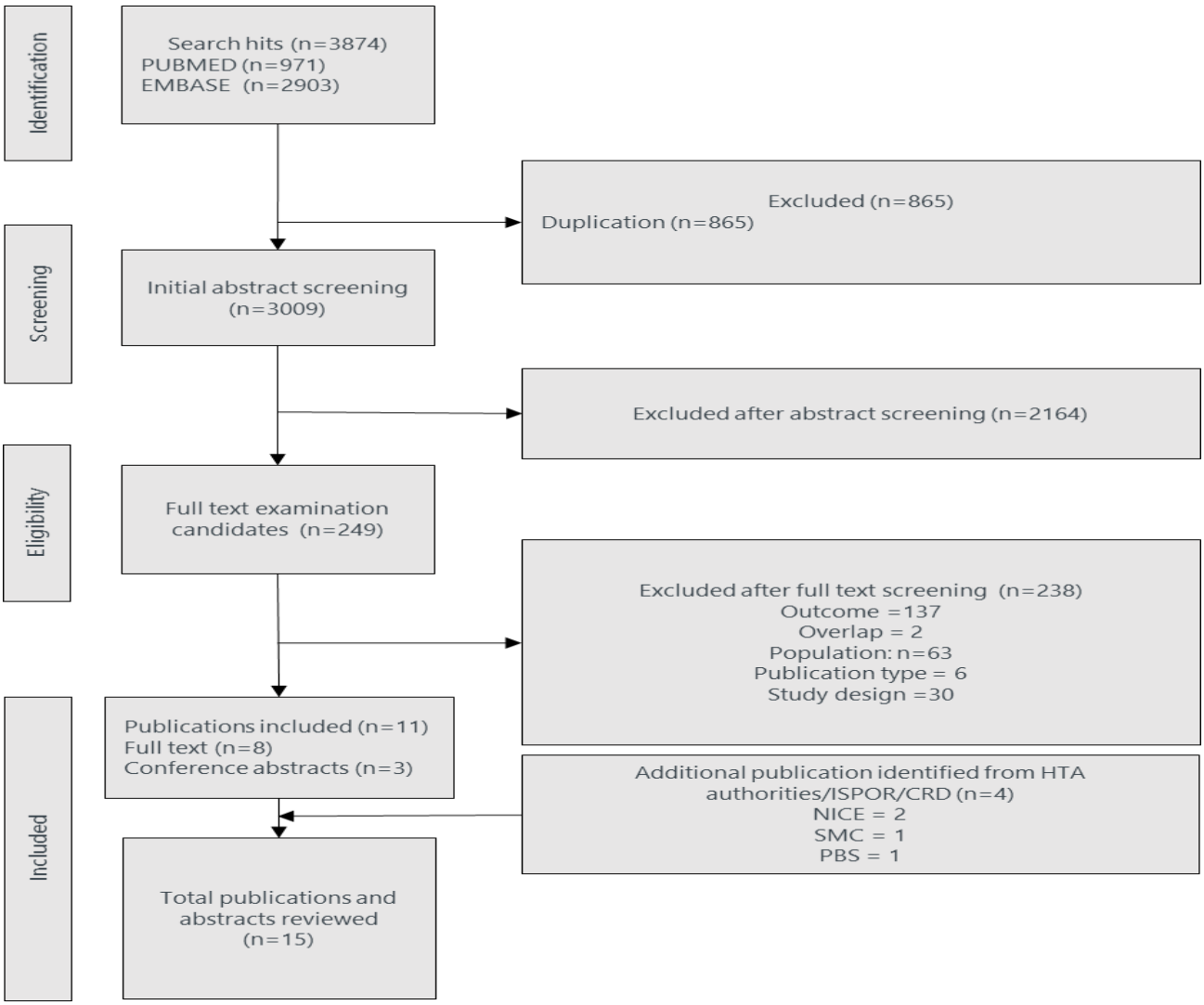
Table 107. ISPOR search strategy Mar 2021

Number	Syntax	Hits, Mar 4, 2021
#1	Multiple myeloma, 2018 to 2020	177

20.2 Systematic selection of studies

The PRISMA flow diagram of the review process for health-related quality of life is presented in Figure 70.

Figure 70. PRISMA diagram for health-related quality of life



In total, 15 relevant publications were identified, including 8 full-text articles, 3 conference posters and 4 health technology assessment (HTA) appraisals. Among which, 4 clinical trials (FIRST, VISTA, ALCYONE, and MAIA) and one publication reported EQ-5D utility values for health states, which are summarised below in Table 108, while the rest publications presented utilities that were derived from these original values.

In the FIRST trial, Delforge et al. (2015) collected HRQoL data from international patients, 68.7% of whom were from Europe [232]. The percentage of patients from the UK was not reported. The data gathered from the EQ-5D-3L instrument was converted to utilities using the UK value set based on the TTO valuation method. This approach to obtaining utility values conforms to the NPAF guidance and is in keeping with the use of EQ-5D in multinational clinical trials [233] [234]. This method was also applied in the paper by Rowen and colleagues [235]. Notably, utility values in ALCYONE and MAIA were generated with a Dutch EQ-5D-5L value set [234] [236].

The systematic review also identified one additional publication that reported utility values from a cost-utility model of Ld compared with BMP as first-line therapy in ASCT-ineligible multiple myeloma in the USA [237]. Usmani et al., (2016)

[237] applied the mapping algorithms by Proskorovsky et al. (2014) [238] in the models, converting quality-of-life measured by QLQ-C30 to the value of EQ-5D.

Table 108. Summary of utilities for relevant health states from clinical trials

Summary of utilities for relevant health states	
Progression-free disease (baseline)	FIRST [232]: 0.50 VISTA [235]: 0.52 ALCYONE [236] 0.59 (Dara+VMP) 0.57 (BMP) MAIA [236] : 0.58 (DRd) 0.6 (Ld) Usmani et al, 2016 [237]: 0.53
Progression-free disease (on treatment)	FIRST trial [235], [232]: 1 month: 0.60 (Rd)/ 0.60 (MPT) 3 months: 0.70 (Rd)/ 0.60 (MPT) 6 months: 0.70 (Rd)/ 0.70 (MPT) 12 months: 0.70 (Rd)/ 0.70 (MPT) 18 months: 0.70 (Rd)/ 0.70 (MPT) At study discontinuation: 0.60 (Rd)/ 0.60 (MPT) VISTA [235]: 1.5 months: 0.60 3 months: 0.64 4.5 months: 0.64 6 months: 0.65 7.5 months: 0.67 9 months: 0.69 10.5 months: 0.72 12 months: 0.72
Progression-free disease (off treatment)	VISTA [235]: 14 months: 0.64 16 months: 0.69 18 months: 0.70 20 months: 0.72 22 months: 0.73 24 months: 0.70 26 months: 0.64 Usmani et al, 2016 [237]: PFS on treatment varied over time with a maximum value of 0.67 for Rd and 0.65 for VMP.
Progression- free disease by MRD status	None reported.
Progression-free disease by response status	None reported.
Progressed disease	Usmani et al, 2016 [237]: 0.59
Adverse event disutilities	None reported.
Age-related disutilities	None reported.

Table 109 lists study designs for the 11 publications included in review.

Table 109. Studies included in the health-related quality of life review reporting EQ-5D utility values

Study	Description of population and recruitment method	Country	Sample size and response rate	Description of health states and adverse events	Methods of elicitations and valuation	Results
Delforge 2015 (FIRST trial) [232]	NDMM aged transplant-ineligible; Median age of 73 in both treatment arms and approximately 52% male Intervention Ld(n=1076) /MPT(n=547) Recruitment Recruited from the population of the FIRST trial	Europe, North America	Total sample size, n=1476 of ITT population of n=1623; Total respondents in first 6 months (≥84%); Total respondents lower in MPT arm (64.5%75.4%) compared to Ld arm (79.8%-85.5%) after 12 months.	Health states PFS on treatment; Study discontinuation; Adverse events not reported	One EQ-5D-3L questionnaire was completed by each respondent at each of the timepoints UK general population weights algorithm generated using the time-trade-off (TTO) method used to estimate EQ-5D index utilities	Time / Ld (EQ-5D) / MPT (EQ-5D) Baseline: 0.5 (0.36) / 0.5 (0.37) 1 month: 0.6 (0.34) / 0.6 (0.32) 3 months: 0.7 (0.27) / 0.6 (0.31) 6 months: 0.7 (0.25) / 0.7 (0.26) 12 months: 0.7 (0.23) / 0.7 (0.28) 18 months: 0.7 (0.24) / 0.7 (0.22) At study discontinuation: 0.6 (0.35) / 0.6 (0.35) Value in brackets are standard deviations
Rowen 2012 (VISTA trial) [235]	NDMM transplant-ineligible patients; Mean age of 71.58 and 49.2% male	Europe, North America, Australia	Total sample size, n=682; Dataset used contained 674 individuals and 16-time periods (all	Health states PFS on treatment; PFS	Patients completed EQ-5D at their screening visit, day 1 of each of the nine cycles of treatment,	Observed EQ-5D utilities Time (BMP/MP): Pooled On treatment

Study	Description of population and recruitment method	Country	Sample size and response rate	Description of health states and adverse events	Methods of elicitations and valuation	Results	
	Intervention Non-interventional mapping study Recruitment Recruited from the VISTA trial population		periods in the VISTA trial where n>65)); Total respondents, 98% for at least one timepoint	treatment-free interval; Study discontinuation Adverse events not reported	end of treatment visit, and during the posttreatment phase (every 6 or 8 weeks) until disease progression UK general population weights algorithm used to estimate EQ-5D utilities	Baseline 0 weeks 6 weeks 12 weeks 18 weeks 24 weeks 30 weeks 36 weeks 42 weeks 48 weeks	0.52 0.54 0.60 0.64 0.64 0.65 0.67 0.69 0.72 0.72
						Post-treatment	
						56 weeks 64 weeks 72 weeks 80 weeks 88 weeks 96 weeks 104 weeks	0.64 0.69 0.70 0.72 0.73 0.70 0.64

Study	Description of population and recruitment method	Country	Sample size and response rate	Description of health states and adverse events	Methods of elicitations and valuation	Results
Young 2015 [239]	NDMM transplant-ineligible patients; Mean age of 71.79 (SD 5.45) and 50% male patients Intervention Non-interventional mapping study Recruitment Myeloma dataset based on VISTA trial population	Europe, North America, Australia	Total sample size, n=527 of original trial population (n=682); Total respondents 77%; reason data from only 572 patients not stated	Health state No defined health states; Adverse events not reported	Methods of elicitation and valuation are as in Rowen et al.	Mean observed EQ-5D utility value: 0.519 (SD. 0.36) with 7.9% of patients in perfect health; number of observations is not stated/not clear what timepoint this refers to.

<table>
<tr><th>Study</th><th>Description of population and recruitment method</th><th>Country</th><th>Sample size and response rate</th><th>Description of health states and adverse events</th><th>Methods of elicitations and valuation</th><th>Results</th></tr>
<tr>
<td>Picot 2011 [155]</td>
<td>NDMM patients from two trials; <60 years for people treated with HDM with ABSCS, >60 years for those treated with MP and 18–93 years for reference population

Intervention
Cost-effectiveness study of BMP/MP/MPT/CT Da

Recruitment
EORTC values are taken from Gulbrandsen et al. [240]</td>
<td>Denmark, Sweden, Norway</td>
<td>Total sample size, n=203 In Gulbrandsen et al. [240] there are 203 from over 60 population, and 221 from under 60; Total respondents not reported</td>
<td>Health state PFS ontreatment; PFS posttreatment; Postprogression;

Adverse events not reported</td>
<td>EORTC-QLQ-C30 values from over 60 trial population in Gulbrandsen et al. mapped to UK EQ-5D3L values using mapping model of McKenzie [241]

In Gulbrandsen et al., EORTC questionnaire was administered QoL was assessed at baseline, 1, 6, 12, 24 and 36 months</td>
<td>Authors suggest most appropriate utility estimates as follows
<table>
<tr><th>Time</th><th>Mapped EQ-5D</th></tr>
<tr><td>0 months</td><td>0.55</td></tr>
<tr><td>1 months</td><td>0.58</td></tr>
<tr><td>6 months</td><td>0.68</td></tr>
<tr><td>12 months</td><td>0.68</td></tr>
<tr><td>24 months</td><td>0.68</td></tr>
<tr><td>36 months</td><td>0.69</td></tr>
<tr><td colspan="2">Health-state utilities are estimated at:</td></tr>
<tr><td>PFS on treatment</td><td>0.58</td></tr>
<tr><td>PFS post treatment</td><td>0.68</td></tr>
<tr><td>PPS</td><td>0.68</td></tr>
</table>
</td>
</tr>
</table>

Study	Description of population and recruitment method	Country	Sample size and response rate	Description of health states and adverse events	Methods of elicitations and valuation	Results
Blommestein 2016 [242]	MM patients 66 years or older as any patient over 65 was considered ASCT-ineligible Intervention Cost-effectiveness study of MP, T, B, L Recruitment Patients who filled in a preliminary version of 5Q-5D-5L from the real-world Dutch PROFILES database	The Netherlands	Total sample size n=101 with 61 patients responding; Total respondents 60%	Health state No defined health states; Adverse events not reported	Crosssectional study conducted in PROFILES registry. Each patient received preliminary version of EQ-5D-5L (Dutch value set)	Mean observed EQ-5D utility value 0.76 (SD 0.21)
Usmani 2016 [237]	NDMM ASCT-ineligible patients participating in VISTA/FIRST trials Intervention Cost-effectiveness study of Ld and BMP Recruitment Pre-progression	Europe, North America, Australia	Total sample size not reported; Total respondents not reported	Health state PFS at baseline PFS ontreatment PPS; Adverse events not reported; Impact of AE was captured in utilities.	For Ld, HSUVs associated with PFS were calculated based on patient-level responses to EQ-5D (UK value set) in the FIRST trial. Predictive equation estimated Ld-specific health state utilities over duration of PFS. PFS utilities for BMP were calculated by	Mapped EQ-5D utilities in the model were as follows: PFS at baseline for both treatment arms: 0.53 PFS on treatment varied over time with a maximum value of 0.67 for Ld and 0.65 for BMP PPS for both treatment arms: 0.59

Study	Description of population and recruitment method	Country	Sample size and response rate	Description of health states and adverse events	Methods of elicitations and valuation	Results
	HSUVs for Ld and BMP were based on information collected during FIRST and VISTA				mapping patient-level EORTC-QLQ-C30 from VISTA to EQ5D (UK value set) using the mapping algorithm by Proskorovsky et al. **[238]** Pre-progression HSUV was assumed to be same for both treatments based on patients enrolled in FIRST. Post-progression HSUV was also calculated using information from FIRST and was assumed to be invariant over time	
Hatswell 2016 [243]	MM patients at all stages of disease Intervention Non-interventional registry analysis	22 countries including Europe, Russia, Turkey, South	Total sample size, n=2445 with 9,080 EQ-5D questionnaire s across all disease stage including	Health state Baseline (no treatment); On 1st treatment; On 2nd treatment; 3rd	Analysed EQ-5D utility (UK value set) using Generalised Estimating Equations (GEE) to account for multiple observations per	<table><tr><th>Time</th><th>Predicted EQ-5D</th></tr><tr><td>Baseline</td><td>0.46</td></tr><tr><td>On 1st tx</td><td>0.59</td></tr><tr><td>On 2nd tx</td><td>0.59</td></tr></table>

<table>
<tr><th>Study</th><th>Description of population and recruitment method</th><th>Country</th><th>Sample size and response rate</th><th>Description of health states and adverse events</th><th>Methods of elicitations and valuation</th><th>Results</th></tr>
<tr><td></td><td><u>Recruitment</u> Patients participating in the EMMOS registry database</td><td>Africa</td><td>302 newly diagnosed patients, 867 in first-line, 570 in second-line, and 205 in third-line; Total respondents not reported</td><td>treatment or beyond

Adverse events not reported</td><td>patient and adding SCT as a dummy variable

Covariates included treatment line and dummy variable for Post-ASCT</td><td><table><tr><td>3rd tx or beyond</td><td>0.51</td></tr></table></td></tr>
<tr><td>Hatswell 2017 [244]</td><td>MM patients all disease stages including NDMM, RRMM

Intervention
Non-interventional methodological study

Recruitment
Patients from EMMOS registry, APEX clinical trial, and data identified through an SLR</td><td>Europe (Germany, France, Spain, Austria), Russia, Turkey, South Africa, USA</td><td>Total sample size, not reported; Total respondents, not reported</td><td>Health state
Newly diagnosed;
After 1st line
After 2nd line
After 3rd line
After 4th line

Adverse events not reported</td><td>Meta regressions were performed to predict EQ-5D utilities from the datasets using five models with meta regression and Bayesian methodologies.

Covariates included treatment line and dummy variable for Post-ASCT

Fixed-effects inverse variance meta-analysis was used to combine multiple values informing these parameters. In the absence of data,</td><td>Results from the second and fourth models are presented, however, no preference is implied:

<table><tr><th>Time</th><th>Model 2 (Meta regression</th><th>Model 4 (Bayesian)</th></tr><tr><td>Baseline</td><td>0.529 (0.459-0.600)</td><td>0.530 (0.510 - 0.550)</td></tr><tr><td>1st tx</td><td>0.635 (0.564-0.707)</td><td>0.620 (0.456-0.786)</td></tr><tr><td>2nd tx</td><td>0.597 (0.535-0.631)</td><td>0.590 (0.568-0.612)</td></tr><tr><td>3rd tx</td><td>0.574 (0.490-0.616)</td><td>0.578 (0.275-0.880)</td></tr></table></td></tr>
</table>

Study	Description of population and recruitment method	Country	Sample size and response rate	Description of health states and adverse events	Methods of elicitations and valuation	Results
					SCT percentage was assumed to be the mean of data from other studies for that stage of treatment.	4th tx: 0.457 (0.312-0.539); 0.469 (0.021-0.016) Value in brackets above are 95% CI
Lu 2019 [245]	NDMM patients ineligible for transplant Intervention Cost-effectiveness study of Ld and bortezomib contained therapy The model variables for patient age and gender distribution were estimated through a singlearm meta-analysis of the reported age and gender from identified observational studies including Chinese NDMM	China	Total sample size not reported; Total respondents not reported	Health state: On-treatment; PFS; PDS Adverse events not reported	Utilities were calculated by mapping patient-level EORTC-QLQ-C30 from VISTA to EQ5D (UK value set) using the mapping algorithm by Proskorovsky et al. **[238]**	Mapped EQ-5D utilities in the model were as follows: Utility under Ld treatment: 0.641 (95%CI: 0.481, 0.802) Utility under bortezomib contained therapy: 0.558 (95%CI: 0.419, 0.698) PFS utility for both arms: 0.897 (95%CI: 0.672, 1.121) PDS utility for both arms: 0.766 (95%CI: 0.575, 0.958)

Study	Description of population and recruitment method	Country	Sample size and response rate	Description of health states and adverse events	Methods of elicitations and valuation	Results
	patients					
Cao 2021 [246]	NDMM transplant-ineligible patients participating in ALCYONE trial Intervention Cost-effectiveness study of Dara+VMP and BMP Recruitment Pre-progression HSUVs for Dara+VMP and BMP	Europe, Asia, North America, South America	Total sample size not reported; Total respondents not reported	Health state: PFS; progression disease Adverse events not reported	Utility for Dara+VMP in PFS stage was calculated by combining the mean of first-line utility of MM with a pooled utility from three daratumumab trials in RRMM population;	PFS for Dara+VMP: 0.685
Penaloza-Ramos [236]	Transplantineligible patients participating in ALCYONE and MAIA trials Intervention Dara+VMP/BMP; DRd/Ld Recruitment Recruited from the population of the ALCYONE/MAIA trial	Europe, Asia, North America, South America	Dara+VMP/BMP n=706 DRd/Ld n=737	Baseline utility value; Adverse events not reported	EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire is applied.	Mean baseline utility (SD) Dara+VMP: 0.59 (0.30) VMP: 0.57 (0.29) DRd: 0.58 (0.32) Rd: 0.60 (0.29)

Table 110 presents the 4 HTA appraisals that contain utility information for NDMM transplant-ineligible population.

Table 110. Summary of HTA appraisals from health-related quality of life review

<table>
<tr><th>HTA institute/submission</th><th>Description of population and recruitment methods</th><th>Country of study</th><th>Methods of elicitations and valuation</th><th>Results</th></tr>
<tr>
<td>NICE (UK)

TA228
Assessment Group Report
[247]</td>
<td>NDMM patients;
> 60 years of age

Intervention
Non-interventional mapping study

Recruitment
Myeloma dataset based on a prospective Nordic Myeloma Study group trial (MP group).
Also, a myeloma dataset from MMIX study for complete response data (CTDa and MP groups).</td>
<td>Nordic
Myeloma Study
group trial included population from Denmark,
Sweden and Norway.
MMIX study included population from the UK.</td>
<td>The 30-item questionnaire was administered by postal questionnaire to the reference population. EORTC QLQ-C30 was used. Methods of elicitation and evaluation are as in Gulbrandsen et al. (2004) [240] and MMIX clinical data (confidential data).
Method for mapping as
McKenzie et al. (2009) [241]</td>
<td>Assessment Report (Picot 2011195)
<table>
<tr><th>Time</th><th>MP (EQ-5D)</th></tr>
<tr><td>Reference population</td><td>0.81</td></tr>
<tr><td>Baseline</td><td>0.58</td></tr>
<tr><td>1 month</td><td>0.58</td></tr>
<tr><td>6 months</td><td>0.68</td></tr>
<tr><td>12 months</td><td>0.68</td></tr>
<tr><td>24 months</td><td>0.68</td></tr>
<tr><td>36 months</td><td>0.69</td></tr>
</table>
The utility estimates for the treatment period are for the one month time-point, i.e., 0.58, and for the post treatment is an average of the 6 month to 36 month timepoints, i.e., 0.68.
(2) The MMIX utility estimates for complete response are not reported (confidential data)
Status of submission: accepted</td>
</tr>
</table>

HTA institute/submission	Description of population and recruitment methods	Country of study	Methods of elicitations and valuation	Results
NICE (UK) **TA228** **Janssen-Cilag submission on Bortezomib** **[248]**	Submission objective is to provide evaluation of costs and benefits of Bortezomib with MP compared to MPT, CTDa and MP in NDMM patients ineligible to receive SCT. Intervention HRQoL for this model based on published cost utility analysis with HOVON 24 study data. Recruitment Patients <65 years of age with previously untreated MM, and stage II or III A/B disease were eligible for the study.	Netherlands and Belgium. The preference weights used in this study was obtained from a sample of the general population of the United Kingdom	In the QoL questionnaires, the EuroQol-5D instrument was included with the aim of calculating utility values.	For the response state, a utility value of 0.81 was used, based on the utility of the general public at an age (median 54 years) corresponding to that of the patients in the study. A utility value of 0.64 was applied to the post- progression disease state. A utility value of 0.77 was applied to patients prior to the response to treatment. Status of submission: accepted

HTA institute/submission	Description of population and recruitment methods	Country of study	Methods of elicitations and valuation	Results
NICE (UK) **TA587 Celgene submission on Thalidomide** **[118]**	Submission objective is to provide evaluation of costs and benefits of MPT with those of BMP and MP in NDMM patients ineligible to receive HDT who are >65 years of age. Intervention HRQoL for this model based on cost utility analysis with HOVON 24 study data. Recruitment Patients <65 years of age with previously untreated MM, and stage II or III A/B disease were eligible for the study.	Netherlands and Belgium. The preference weights used in this study were obtained from a sample of the general population of the United Kingdom	In the QoL questionnaires, the EuroQol-5D instrument was included with the aim of calculating utility values.	The utility values used in the submission were 0.64 for people not responding to treatment and 0.81 for people who did respond (using general public utility for same age group). A utility value of 0.77 at 24 months was used for those who continue to respond to treatment with intensive chemotherapy and had not progressed. An assumption was made that pre-progression patients and post-progression patients matched responders and non-responders in the HOVON trial. Status of submission: accepted

<table>
<tr><th>HTA institute/submission</th><th>Description of population and recruitment methods</th><th>Country of study</th><th>Methods of elicitations and valuation</th><th>Results</th></tr>
<tr>
<td>NICE (UK)

TA587
Celgene submission on Lenalidomide
[118]</td>
<td>Submission objective is to provide evaluation of costs and benefits of Ld and BMP in adults with previously untreated multiple myeloma for whom stem-cell transplantation is considered inappropriate.

Intervention
The utility values for the
Ld arm were derived from EQ-5D data collected in the MM-020 study, and for the BMP arm HRQoL data from the VISTA study

Recruitment
MM-020: 1,623 patients from 18 countries either ≥65 or < 65 years of age and ineligible for stem cell transplant were randomised 1:1:1 into three arms.
VISTA: evaluated the effect of MP combination with or without the first-inclass proteasome inhibitor bortezomib in newly diagnosed myeloma patients who were not candidates for autologous stem cell transplantation.</td>
<td>The MM-020 trial was a randomised, open-label, Phase III study carried out in 18 countries. Of the patients randomised, 72 patients were recruited from 16 centres in the UK.

The VISTA trial was a randomised, open-label, Phase III study carried out in 151 centers across 22 countries</td>
<td>Progression-free:
Regression model with treatment coefficient using EQ-5D data from FIRST trial provides utility for LEN+DEX and MPT. BMP calculated by mapping EORTC from VISTA
trial to EQ-5D

Post-progression:
Based on FIRST EQ5D, independent of treatment</td>
<td>Progression-free:

<table>
<tr><th rowspan="2">Time</th><th rowspan="2">BMP</th><th colspan="2">Modelled change from baseline</th></tr>
<tr><th>Ld</th><th>MPT</th></tr>
<tr><td>Baseline</td><td>0.53</td><td>0.53</td><td>0.53</td></tr>
<tr><td>Cycle 1</td><td>0.521</td><td>+0.037</td><td>+0.05</td></tr>
<tr><td>Cycle 2</td><td>0.541</td><td>+0.037</td><td>+0.05</td></tr>
<tr><td>Cycle 3</td><td>0.527</td><td>+0.108</td><td>+0.09</td></tr>
<tr><td>Cycle 4</td><td>0.517</td><td>+0.108</td><td>+0.09</td></tr>
<tr><td>Cycle 5</td><td>0.549</td><td>+0.135</td><td>+0.127</td></tr>
<tr><td>Cycle 6</td><td>0.592</td><td>+0.135</td><td>+0.127</td></tr>
<tr><td>Cycle 7</td><td>0.619</td><td>+0.135</td><td>+0.127</td></tr>
<tr><td>Cycle 8</td><td>0.634</td><td>+0.135</td><td>+0.127</td></tr>
<tr><td>Thereafter</td><td>0.645</td><td>+0.037</td><td>+0.05</td></tr>
</table>
Progression disease:
< Year 2: 0.5574
> Year 2: 0.51
Disutilities were not included as the company assumed any disutility from adverse events would be captured in the quality of life data collected in the studies.

Status of submission: restricted to for use in patients unsuitable for thalidomide-containing regimens</td>
</tr>
</table>

HTA institute/submission	Description of population and recruitment methods	Country of study	Methods of elicitations and valuation	Results
SMC (Scotland) **1096/15 (2015)** **[249]**	Submission objective is to provide evaluation of costs and benefits of Ld compared to BMP in patients with previously untreated multiple myeloma who are not eligible for transplant and are unable to tolerate or have contradictions to thalidomide. Intervention/Recruitment Same as NICE TA587	The MM-020 trial was a randomised, open-label, Phase III study carried out in 18 countries. The VISTA trial was a randomised, open-label, Phase III study carried out in 151 centers across 22 countries	The utility values for the Ld arm were derived from EQ-5D data collected in the MM-020 study, and for the BMP arm HRQoL data from the VISTA study were used based on the EORTC QLQC30 mean functional and symptom scores mapped to the EQ-5D using a published mapping algorithm;	The utility value for patients at baseline was 0.53 and for the PF state the utility score was 0.59. Disutilities were not included as the company assumed any disutility from adverse events would be captured in the quality of life data collected in the studies. The company supplied additional analysis applying the utility values from the Ld submission where patients have been previously treated, using utility values as follows; stable disease 0.81, stable after 2 years 0.77 and progressed disease 0.64. Status of submission: restricted to for use in patients unsuitable for thalidomide-containing regimens
PBS (Australia) **Revlimid (2019 08)** **[250]**	The submission requested BLd for treatment of patients with newly diagnosed multiple myeloma who are ineligible for an autologous stem cell transplant Intervention BLd versus Ld Recruitment	(1) The MM-020 trial was a randomised, open-label, Phase III study carried out in 18 countries.	The trial-based utility values were derived from EQ-5D data collected within the MM-020 trial	The PSCR provided revised utility values using 0.51 at baseline, 0.73 best score prior to progressive disease and 0.59 at progressive disease. Status of submission Recommended

Abbreviation: PSCR = pre-Sub-Committee response; HDT = high dose therapy; Ld = lenalidomide, dexamethasone; BLd = bortezomib, lenalidomide, dexamethasone; MPT = melphalan, prednisone, thalidomide

Table 111 below lists the studies which did not meet inclusion criteria in the utility review.

Table 111. Publications excluded at full-text screening from the health-related quality of life review

Citation	Exclusion reason
Anonymous (2000). "Multiple myeloma: QALY gains from optimal therapy." Drugs and Therapy Perspectives 16(9): 12-16.	Study design out of scope
Abonour, R., Rifkin, R.M., Gasparetto, C., et al. (2020). "Effect of initial treatment on health-related quality of life in patients with newly diagnosed multiple myeloma without immediate stem cell transplant intent: results from the Connect® MM Registry." British Journal of Haematology.	Outcomes out of scope
Abonour, R., Rifkin, R.M., Gasparetto, C., et al. (2018). "Impact of initial treatment (tx) on HRQoL and outcomes in patients (pts) with newly diagnosed multiple myeloma (NDMM) without intent for immediate transplant (SCT): Results from the Connect® MM registry." Annals of Oncology 29: viii360.	Outcomes out of scope
Acaster, S., Gaugris, S., Lloyd, A., et al. (2010). "The impact of a treatment free interval on multiple myeloma patients quality of life: A UK cross-sectional observational survey." Haematologica 95: 187.	Population out of scope
Ahmadzadeh, A., Yekaninejad, M.S., Saffari, M., et al. (2016). "Reliability and Validity of an Iranian Version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Multiple Myeloma: the EORTC QLQ-MY20." Asian Pacific journal of cancer prevention : APJCP 17(1): 255-259.	Population out of scope
Akechi, T., Aiki, S., Sugano, K., et al. (2017). "Does cognitive decline decrease health utility value in older adult patients with cancer?" Psychogeriatrics 17(3): 149-154.	Outcomes out of scope
Aoki, N., Moore, E.M., Wood, E.M., et al. (2019). "Real-world treatment patterns and clinical outcomes in multiple myeloma in the Asia-pacific region: Methodology and preliminary results of the Asia-pacific myeloma and related diseases registry (APAC MRDR)." Blood 134.	Outcomes out of scope
Asrar, M., Bansal, D. and Lad, D.P. (2020). "PCN38 A REAL WORLD EVIDENCE OF EFFECTIVENESS, SAFETY AND COST IMPLICATIONS OF TREATMENT REGIMENS IN MULTIPLE MYELOMA." Value in Health 23: S29.	Population out of scope
Asrar, M.M., Bansal, D. and Lad, D.P. (2020). "Treatment effectiveness, safety and health related quality of life in multiple myeloma: Evidence from the real world." Pharmacoepidemiology and Drug Safety 29(SUPPL 3): 104.	Population out of scope
Astolfi, S., Scaramuzzo, L. and Logroscino, C.A. (2009). "A minimally invasive surgical treatment possibility of osteolytic vertebral collapse in multiple myeloma." European Spine Journal 18(SUPPL. 1): S115-S121.	Population out of scope
Avaronnan, M., Raghavan, V., Shenoy, P., et al. (2018). "Health related quality of life in patients with multiple myeloma on novel agents : Experience from a tertiary cancer centre in south India." Indian Journal of Hematology and Blood Transfusion 34(1): 376.	Population out of scope
Balderas-Peña, L.M., Miranda-Ruvalcaba, C., Robles-Espinoza, A.I., et al. (2019). "Health-Related Quality of Life and Satisfaction With Health Care: Relation to Clinical Stage in Mexican Patients With Multiple Myeloma." Cancer Control 26(1): 1073274819831281.	Population out of scope
Beall, D.P., Chambers, M.R., Thomas, S., et al. (2019). "Prospective and multicenter evaluation of outcomes for quality of life and activities of daily living for balloon kyphoplasty in the treatment of vertebral compression fractures: The Evolve trial." Neurosurgery 84(1): 169-178.	Population out of scope
Beijers, A., Vreugdenhil, G., Oerlemans, S., et al. (2015). "Chemotherapy-induced peripheral neuropathy in multiple myeloma patients: Influence on quality of life and validation of aquestionnaire for daily clinical practice." Supportive Care in Cancer 23(1): S150.	Study design out of scope

Citation	Exclusion reason
Beijers, A.J., Vreugdenhil, G., Oerlemans, S., et al. (2016). "Chemotherapy-induced neuropathy in multiple myeloma: influence on quality of life and development of a questionnaire to compose common toxicity criteria grading for use in daily clinical practice." Support Care Cancer 24(6): 2411-20.	Population out of scope
Blommestein, H., van Beurden-Tan, C., de Groot, S., et al. (2018). "COMBINING INTERNALLY VALID TRIAL EVIDENCE WITH GENERALIZABLE REAL-WORLD DATA: INSIGHTS INTO EFFECTS, COSTS, AND COST-EFFECTIVENESS OF NOVEL TREATMENT SEQUENCES IN PATIENTS WITH MULTIPLE MYELOMA." Value in Health 21: S10-S11.	Outcomes out of scope
Blommestein, H., Verelst, S., De Groot, S., et al. (2013). "One line does not make a picture: Real-world cost-effectiveness of multiple myeloma treatments using a full disease model." Value in Health 16(7): A408.	Stud design out of scope
Boeckler, J., Haas, K., Heuschmann, P.U., et al. (2014). "Evaluation of individual Quality of Life in patients diagnosed with Multiple Myeloma by using standardized questionnaires of the European Organization for Research and Treatment of Cancer." Oncology Research and Treatment 37: 140.	Outcomes out of scope
Booker, R., Olson, K., Pilarski, L.M., et al. (2009). "The relationships among physiologic variables, quality of life, and fatigue in patients with multiple myeloma." Oncology nursing forum 36(2): 209-216.	Outcomes out of scope
Butler, J.S., Malhotra, K., Patel, A., et al. (2015). "Pathologic sternal involvement is a potential risk factor for severe sagittal plane deformity in multiple myeloma with concomitant thoracic fractures." Spine Journal 15(12): 2503-2508.	Study design out of scope
Cavenagh, J.D., Belch, A.R., Hulin, C., et al. (2014). "Cost-effectiveness in newly diagnosed multiple myeloma (NDMM): Lenalidomide plus low-dose dexamethasone (Rd) versus bortezomib plus melphalan and prednisone (VMP)." Haematologica 99: 379.	Outcomes out of scope
Cenic, O., Schützl, P., Jank, R., et al. (2010). "Neurocognitive impairment in patients with multiple myeloma following chemotherapy." Onkologie 33(6): 248.	Outcomes out of scope
Chalayer, E., Bourmaud, A., Tinquaut, F., et al. (2016). "Cost-effectiveness analysis of low-molecular-weight heparin versus aspirin thromboprophylaxis in patients newly diagnosed with multiple myeloma." Thrombosis Research 145: 119-125.	Outcomes out of scope
Chen, L.H., Hsieh, M.K., Niu, C.C., et al. (2012). "Percutaneous vertebroplasty for pathological vertebral compression fractures secondary to multiple myeloma." Archives of Orthopaedic and Trauma Surgery 132(6): 759-764.	Population out of scope
Chen, W., Yang, Y., Du, F., et al. (2015). "Cost-effectiveness of bortizomib for multiple myeloma: A systematic review." Value in Health 18(7): A456.	Outcomes out of scope
Cizova, D., Panjabi, S., Abbas, Z., et al. (2019). "PCN467 THE HUMANISTIC BURDEN OF MULTIPLE MYELOMA IN NEWLY DIAGNOSED PATIENTS: A SYSTEMATIC LITERATURE REVIEW." Value in Health 22: S527.	Population out of scope
Cocks, K., Cohen, D., Wisløff, F., et al. (2007). "An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma." European Journal of Cancer 43(11): 1670-1678.	Outcomes out of scope
Coluzzi, F., Raffa, R.B., Pergolizzi, J., et al. (2015). "Tapentadol prolonged release for patients with multiple myeloma suffering from moderate-to-severe cancer pain due to bone disease." Journal of Pain Research 8: 229-238.	Outcomes out of scope
Crott, R., Versteegh, M. and Uyl-de-Groot, C. (2013). "An assessment of the external validity of mapping QLQ-C30 to EQ-5D preferences." Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 22(5): 1045-1054.	Study design out of scope
Das, M. (2016). "Carfilzomib therapy improves quality of life in multiple myeloma." The Lancet. Oncology 17(10): e427.	Publication type out of scope

Citation	Exclusion reason
De Abreu Lourenco, R., Colman, S. and Lee, C. (2009). "Thalidomide plus melphalan and prednisone for australian patients newly diagnosed with multiple myeloma is cost-effective when compared with melphalan and prednisone alone." Value in Health 12(7): A381.	Outcomes out of scope
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Niesvizky, R., Flinn, I.W., Rifkin, R., et al. (2011). "Patient-reported quality of life (QoL) in elderly, newly diagnosed multiple myeloma (MM) patients receiving bortezomib-based combinations: Results from all randomised patients in the community-based, phase 3b UPFRONT Study." Blood 118(21).	Outcomes out of scope
Niesvizky, R., Flinn, I.W., Rifkin, R.M., et al. (2010). "Patient-reported quality of life in elderly, newly diagnosed multiple myeloma patients treated with bortezomib-based regimens: Results from the phase 3B upfront study." Blood 116(21).	Outcomes out of scope
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Osborne, T., Ramsenthaler, C., Siegert, R., et al. (2011). "Health related quality of life instruments for use in people with multiple myeloma: A systematic literature review." Haematologica 96: 366.	Publication type out of scope
Osborne, T.R., Ramsenthaler, C., Siegert, R.J., et al. (2012). "What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools." European Journal of Haematology 89(6): 437-457.	Study design out of scope
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Pamuk, G.E., Uyanik, M.S. and Demir, M. (2013). "Assessment of quality of life in turkish multiple myeloma patients by using EORTCQLQ-C30 and EORTC-QLQ-MY20." Clinical Lymphoma, Myeloma and Leukemia 13: S220-S221.	Population out of scope
Pashos, C.L., Durie, B.G., Mehta, J., et al. (2011). "Association of health-related quality of life (HRQOL) with ISS stage and ECOG status in multiple myeloma." Value in Health 14(3): A175-A176.	Study design out of scope
Pashos, C.L., Durie, B.G., Rifkin, R., et al. (2011). "Association of Race with Health-Related Quality of Life (HRQOL) among multiple myeloma patients." Blood 118(21).	Study design out of scope
Pashos, C.L., Durie, B.G., Rifkin, R.M., et al. (2012). "Association of health-related quality of life among patients with multiple myeloma with insurance coverage." Value in Health 15(4): A233-A234.	Study design out of scope
Pashos, C.L., Durie, B.G., Rifkin, R.M., et al. (2012). "Race- and health-related quality of life among patients newly diagnosed with multiple myeloma." Journal of Clinical Oncology 30(15).	Study design out of scope
Pashos, C.L., Durie, B.G., Rifkin, R.M., et al. (2011). "Association of health-related quality of life (HRQOL) with bone disease in multiple myeloma (MM)." Haematologica 96: S139-S140.	Study design out of scope
Pashos, C.L., Durie, B.G.M., Rifkin, R., et al. (2011). "Variation in health-related quality of life (HRQOL) among multiple myeloma patients by insurance coverage." Blood 118(21).	Study design out of scope
Pashos, C.L., Durie, B.G.M., Rifkin, R.M., et al. (2010). "Variation in health-related quality of life (HRQOL) by ISS stage and ECOG status among multiple myeloma patients." Blood 116(21).	Outcomes out of scope
Pashos, C.L., Shah, J.J., Terebelo, H.R., et al. (2013). "Change in patient-reported outcomes during the first year postdiagnosis of multiple myeloma." Value in Health 16(3): A146.	Outcomes out of scope
Pashos, C.L., Shah, J.J., Terebelo, H.R., et al. (2013). "Changes in patient-reported outcomes in patients diagnosed with and treated for multiple myeloma in the Connect MM registry." Journal of Clinical Oncology 31(15).	Outcomes out of scope
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Perrot, A., Facon, T., Plesner, T., et al. (2019). "Faster and sustained improvement in health-related quality of life (HRQoL) for newly diagnosed multiple myeloma (NDMM) patients ineligible for transplant treated with daratumumab, lenalidomide, and dexamethasone (D-Rd) versus Rd alone: MAIA." Journal of Clinical Oncology 37.	Outcomes out of scope
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Porcher, R., Lévy, V., Fermand, J.P., et al. (2002). "Evaluating high dose therapy in multiple myeloma: Use of quality-adjusted survival analysis." Quality of Life Research 11(2): 91-99.	Outcomes out of scope
Priscilla, D., Hamidin, A., Azhar, M.Z., et al. (2011). "The socio-demographic and clinical factors associated with quality of life among patients with haematological cancer in a large government hospital in Malaysia." Malaysian Journal of Medical Sciences 18(3): 49-56.	Population out of scope
Priscilla, D., Hamidin, A., Azhar, M.Z., et al. (2011). "Quality of life among patients with hematological cancer in a Malaysian hospital." Med J Malaysia 66(2): 117-20.	Population out of scope
Raje, N., Roodman, G.D., Willenbacher, W., et al. (2018). "A cost-effectiveness analysis of denosumab for the prevention of skeletalrelated events in patients with multiple myeloma in the United States of America." Journal of Medical Economics 21(5): 525-536.	Intervention
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Rickert, J.B., Hornberger, J., Liwing, J., et al. (2010). "Bortezomib is cost-effective for first-line treatment of multiple myeloma in Sweden." Value in Health 13(3): A40.	Outcomes out of scope
Robinson, D., Esseltine, D.L., Regnault, A., et al. (2016). "The influence of baseline characteristics and disease stage on healthrelated quality of life in multiple myeloma: findings from six randomised controlled trials." British Journal of Haematology 174(3): 368381.	Study design out of scope
Roussel, M., Moreau, P., Hebraud, B., et al. (2020). "Bortezomib, thalidomide, and dexamethasone with or without daratumumab for transplantation-eligible patients with newly diagnosed multiple myeloma (CASSIOPEIA): health-related quality of life outcomes of a randomised, open-label, phase 3 trial." The Lancet Haematology 7(12): e874-e883.	Outcomes out of scope
Royle, K.L., Gregory, W.M., Cairns, D.A., et al. (2018). "Quality of life during and following sequential treatment of previously untreated patients with multiple myeloma: findings of the Medical Research Council Myeloma IX randomised study." British Journal of Haematology 182(6): 816-829.	Outcomes out of scope
Rudzianskiene, M., Inciura, A., Gerbutavicius, R., et al. (2015). "The impact of palliative radiotherapy on quality of life in multiple myeloma patients with painful bone destructions." Haematologica 100: 578-579.	Study design out of scope
Sabatelli, L., Jamotte, A., Giannopoulou, C., et al. (2017). "Estimation of the health benefit associated with a potential denosumabinduced extension of progression free survival in multiple myeloma patients." Value in Health 20(9): A414-A415.	Outcomes out of scope
Santos, F.R., Kozasa, E.H., Chauffaille Mde, L., et al. (2006). "Psychosocial adaptation and quality of life among Brazilian patients with different hematological malignancies." J Psychosom Res 60(5): 505-11.	Outcomes out of scope
Sayuti, N.A., Andayani, T.M., Endarti, D., et al. (2019). "Health- Related Quality of Life for Multiple Myeloma Patients with Bone Metastases in Indonesia: A Cross-Sectional Study." Asian Pacific journal of cancer prevention : APJCP 20(10): 3161-3166.	Population out of scope
Schoormans, D., Mols, F. and Husson, O. (2018). "Health-related quality of life among 8807 longterm cancer survivors with and without cardiovascular disease at time of cancer	Population out of scope

Citation	Exclusion reason
diagnosis: Results from the population-based profiles registry." Supportive Care in Cancer 26(2): S272.	
Sebag, M., Stakiw, J., Stephens, T.J., et al. (2019). "Lenalidomide plus bortezomib and dexamethasone in the treatment of newly diagnosed multiple myeloma: Results from a Canadian cost-effectiveness analysis." Blood 134.	Outcomes out of scope
Sevindik, O.G., Alacacioglu, I., Payzin, K.B., et al. (2015). "Quality of life in multiple myeloma: Validation of the Turkish version of the QLQ-MY20 instrument." Haematologica 100: 579.	Outcomes out of scope
Shi, Q., Mendoza, T.R., Wang, X.S., et al. (2016). "Using a symptom-specific instrument to measure patient-reported daily functioning in patients with cancer." European Journal of Cancer 67: 83-90.	Study design out of scope
Sidi Mohamed El Amine, B., Asma, H., Fouzia, O., et al. (2017). "Financial toxicity of the management of multiple myeloma." Haematologica 102: 603.	Study design out of scope
Sidi Mohamed El Amine, B., Asma, H., Fouzia, O., et al. (2017). "Evaluation of treatment induced neuropathy in multiple myeloma and its influence on physical and role functioning." Haematologica 102: 523.	Outcomes out of scope
Sloot, S., Boland, J., Snowden, J.A., et al. (2014). "Side effects of analgesia may significantly reduce quality of life in symptomatic multiple myeloma: a cross-sectional prevalence study." Supportive Care in Cancer.	Population out of scope
Smith, A.G., Soutar, R.L., Schey, S., et al. (2004). "Home care versus hospital care in patients with multiple myeloma treated with pamidronate." International journal of palliative nursing 10(3): 144-149.	Study design out of scope
Stead, M.L., Brown, J.M., Velikova, G., et al. (1999). "Development of an EORTC questionnaire module to be used in health- related quality-of-life assessment for patients with multiple myeloma." British Journal of Haematology 104(3): 605-611.	Study design out of scope
Sungailaite, S., Aziz, F. and Hekal, W. (2016). Balloon kyphoplasty in multiple myeloma patients. 30: 486.	Outcomes out of scope
Szeinbach, S.L., Barnes, J.H., McGhan, W.F., et al. (1999). "Using conjoint analysis to evaluate health state preferences." Drug Information Journal 33(3): 849-858.	Population out of scope
Sztankay, M., Neppl, L., Wintner, L.M., et al. (2019). "Complementing clinical cancer registry data with patient reported outcomes: A feasibility study on routine electronic patient-reported outcome assessment for the Austrian Myelome Registry." European journal of cancer care 28(6): e13154.	Population out of scope
Tamburrelli, F.C., Proietti, L., Scaramuzzo, L., et al. (2012). "Bisphosphonate therapy in multiple myeloma in preventing vertebral collapses: Preliminary report." European Spine Journal 21(SUPPL. 1): S141-S145.	Publication type out of scope
Terebelo, H., Srinivasan, S., Narang, M., et al. (2017). "Recognition of early mortality in multiple myeloma by a prediction matrix." American Journal of Hematology 92(9): 915-923.	Study design out of scope
Terebelo, H.R., Abonour, R., Gasparetto, C.J., et al. (2017). "Development of a prognostic model that predicts 3-and 5-year overall survival in multiple myeloma using the connect MM patient registry." Blood 130.	Outcomes out of scope
Terpos, E., Jamotte, A., Christodoulopoulou, A., et al. (2019). "A cost-effectiveness analysis of denosumab for the prevention of skeletal-related events in patients with multiple myeloma in four European countries: Austria, Belgium, Greece, and Italy." Journal of Medical Economics 22(8): 766-776.	Population out of scope
Trajkovska-Anchevska, Z., Pivkova, A., Genadieva-Stavrich, S., et al. (2017). "Early complications and late effects and quality of life at myeloma multiplex patients." Bone Marrow Transplantation 52: 461.	Population out of scope

Citation	Exclusion reason
van der Poel, M.W., Oerlemans, S., Schouten, H.C., et al. (2015). "Elderly multiple myeloma patients experience less deterioration in health-related quality of life than younger patients compared to a normative population: a study from the population-based PROFILES registry." Ann Hematol 94(4): 651-61.	Population out of scope
van Gelder, T., Mulhern, B., Schoormans, D., et al. (2020). "Assessing health-related quality of life in cancer survivors: factors impacting on EORTC QLU-C10D-derived utility values." Quality of Life Research 29(6): 1483-1494.	Outcomes out of scope
Velasco, R., Postma, T.J., Aaronson, N., et al. (2010). "Preliminary validation of the EORTC chemotherapy-induced peripheral neuropathy quality of life questionnaire (QLQ-CIPN20) Spanish version in a series of multiple myeloma patients treated with bortezomib." Neuro-Oncology 12: iii26.	Study design out of scope
Verelst, S., Termorshuizen, F., Uyl-de Groot, C., et al. (2010). "Effect of thalidomide with melphalan and prednisone on health-related quality of life (HRQoL) in elderly patients with newly diagnosed multiple myeloma: A prospective analysis in a randomised trial." Blood 116(21).	Outcomes out of scope
Verelst, S., Termorshuizen, F., Uyl-De Groot, C., et al. (2011). "Effect of thalidomide with melphalan and prednisone on health-related quality of life (HRQOL) in elderly patients with newly diagnosed multiple myeloma: A prospective analysis in a randomised trial (HOVON 49)." Haematologica 96: S135.	Outcomes out of scope
Vogl, D.T., Delforge, M., Song, K., et al. (2016). "Effect of lenalidomide plus low-dose dexamethasone treatment until progression on health-related quality of life over time in transplant-ineligible patients with newly diagnosed multiple myeloma." Haematologica 101: 145.	Outcomes out of scope
Vogl, D.T., Delforge, M., Song, K., et al. (2018). "Long-term health-related quality of life in transplant-ineligible patients with newly diagnosed multiple myeloma receiving lenalidomide and dexamethasone." Leukemia and Lymphoma 59(2): 398-405.	Outcomes out of scope
Vogl, D.T., Delforge, M., Song, K.W., et al. (2016). "Health-related quality of life over time in transplant-ineligible patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone until progression." Journal of Clinical Oncology 34.	Outcomes out of scope
Wagner, I., Durie, B.G., Jagannath, S., et al. (2018). "Health-related quality of life assessments predict relapse or death in patients with newly diagnosed multiple myeloma (MM): Results from the Connect® MM registry." Value in Health 21: S6.	Outcomes out of scope
Wagner, L.I., Toomey, K., Ailawadhi, S., et al. (2019). "Clinical outcomes and health-related quality of life (HRQoL) among randomised clinical trial (rct)-eligible and rct-ineligible patients: Results from the connect® mm registry." Blood 134.	Outcomes out of scope
Wang, S.T., Huang, H., Ba-mancini, A., et al. (2011). "The cost-effectiveness of bortezomib plus melphalan and prednisone versus lenalidomide plus melphalan and prednisone with continuous LENALIDOMIDE MAINTENANCE TREATMENT FOR THE INITIAL TREATMENT OF MULTIPLE MYELOMA IN THE UNITED STATES." Value in Health 14(3): A62.	Outcomes out of scope
Wang, S.T., Huang, H., Shi, H., et al. (2009). "The cost-effectiveness of bortezomib for the initial treatment of multiple myeloma in the United States." Blood 114(22).	Outcomes out of scope
Wang, S.T., Huang, H., Shi, H., et al. (2010). "Modeling the cost-effectiveness of bortezomib for the initial treatment of multiple myeloma in the United States." Value in Health 13(3): A210.	Outcomes out of scope
Wisløff, F., Eika, S., Hippe, E., et al. (1996). "Measurement of health-related quality of life in multiple myeloma. Nordic Myeloma Study Group." Br J Haematol 92(3): 604-13.	Outcomes out of scope
Wisløff, F., Gulbrandsen, N., Hjorth, M., et al. (2005). "Quality of life may be affected more by disease parameters and response to therapy than by haemoglobin changes." European Journal of Haematology 75(4): 293-298.	Outcomes out of scope

Citation	Exclusion reason
Wisløff, F. and Hjorth, M. (1997). "Health-related quality of life assessed before and during chemotherapy predicts for survival in multiple myeloma." British Journal of Haematology 97(1): 29-37.	Outcomes out of scope
Wisløff, F., Hjorth, M., Kaasa, S., et al. (1996). "Effect of interferon on the health-related quality of life of multiple myeloma patients: Results of a Nordic randomised trial comparing melphalan-prednisone to melphalan-prednisone + α-interferon." British Journal of Haematology 94(2): 324-332.	Outcomes out of scope
Wisløff, F., Kvam, A.K., Hjorth, M., et al. (2007). "Serum calcium is an independent predictor of quality of life in multiple myeloma." European Journal of Haematology 78(1): 29-34.	Outcomes out of scope
Yao, Y., Zou, D., Liao, A., et al. (2019). "Comprehensive geriatric assessment in consecutive newly-diagnosed elderly multiple myeloma patients in China: A multicentered, prospective, non-interventional study." Blood 134.	Outcomes out of scope
Yoong, K., Attard, C., Jivraj, F., et al. (2009). "Cost effectiveness analysis of bortezomib in previously untreated multiple myeloma patients in Canada." Value in Health 12(7): A272.	Outcomes out of scope
Yu, H.M., Malhotra, K., Butler, J.S., et al. (2016). "The relationship between spinopelvic measurements and patient-reported outcome scores in patients with multiple myeloma of the spine." Bone and Joint Journal 98-B(9): 1234-1239.	Outcomes out of scope
Zaleta, A.K., Miller, M.F., Olson, J.S., et al. (2020). "Symptom burden, perceived control, and quality of life among patients living with multiple myeloma." JNCCN Journal of the National Comprehensive Cancer Network 18(8): 1087-1095.	Outcomes out of scope
Zee, B., Cole, B., Li, T., et al. (1998). "Quality-adjusted time without symptoms or toxicity analysis of interferon maintenance in multiple myeloma." Journal of Clinical Oncology 16(8): 2834-2839.	Study design out of scope
Zober, A., Möller, M., Dold, S.M., et al. (2015). "Impact of comorbidities and prospective functional geriatric assessment tools (CF-GA) as an aide to understand outcome, therapy tolerance, side effects and clinical trial eligibility in multiple myeloma (MM) patients (pts)." Blood 126(23): 5616.	Outcomes out of scope
Zou, J., Mei, X., Gan, M., et al. (2010). "Kyphoplasty for spinal fractures from multiple myeloma." Journal of Surgical Oncology 102(1): 43-47.	Outcomes out of scope
Engelhardt, M., Knauf, W., Lipke, J., et al. (2020). "Dynamics in the choice of treatment for patients with multiple myeloma-results from the myriam registry." HemaSphere 4: 454-455.	Outcomes out of scope
Fleming, S., Eremenco, S., Gleeson, S., et al. (2017). "Incorporating patient input in selecting patient reported outcomes instruments for clinical studies in multiple myeloma." Value in Health 20(5): A225-A226.	Outcomes out of scope
Gimsing, P. (2011). "Pamidronate: Can the dose be lowered?" Haematologica 96: S13-S14.	Intervention
Knauf, W., Engelhardt, M., Lipke, J., et al. (2018). "MYRIAM: Prospective, intersectoral Real World cohort study for treatment and outcome of myeloma patients in Germany." Oncology Research and Treatment 41: 190.	Outcomes out of scope
Knauf, W., Engelhardt, M., Losem, C., et al. (2018). "The prospective intersectoral national cohort study myriam to study characteristics, treatment and outcome of patients with multiple myeloma in germany." HemaSphere 2: 967.	Duplication
Knauf, W., Engelhardt, M., Losem, C., et al. (2020). "The prospective intersectoral national cohort study myriam to study characteristics, treatment and outcome of patients with multiple myeloma in Germany." Oncology Research and Treatment 43: 130.	Outcomes out of scope
Oerlemans, S., Schagen, S.B., van den Hurk, C.J., et al. (2021). "Self-perceived cognitive functioning and quality of life among cancer survivors: results from the PROFILES registry." J Cancer Surviv.	Population out of scope
Roydhouse, J., Lee, H., Cheng, J., et al. (2019). "Evaluating time to physical function deterioration in multiple myeloma." Quality of Life Research 28(SUPPL 1): S50-S51.	Outcomes out of scope

Citation	Exclusion reason
Roydhouse, J., Mishra-Kalyani, P., Bhatnagar, V., et al. (2019). "Does knowledge of treatment assignment affect patientreported outcomes? An evaluation of open-label bias in multiple myeloma." Quality of Life Research 28(SUPPL 1): S69.	Outcomes out of scope
Scheubeck, S., Dold, S.M., Ihorst, G., et al. (2016). "Functional geriatric assessment (F-GA) in multiple myeloma patients: Results from a prospective multicenter study group (DSMM) trial and changes from baseline to follow-up assessment." Blood 128(22).	Outcomes out of scope
Scheubeck, S., Ihorst, G., Dold, S.M., et al. (2017). "Functional assessment (FA) in multiple myeloma (MM) patients predicts survival: Use of most valuable comorbidity scores and functional tests in a German study group (deutsche studiengruppe multiples myelom [DSMM]) incentive." Blood 130.	Outcomes out of scope
Smith, A.B., Taylor, M. and Parry, D. (2011). "Methodological limitations of patient-reported outcome measures (PROMS) in oncology: A meta-review." Value in Health 14(7): A460.	Outcomes out of scope
Viala, M., Bhakar, A.L., de la Loge, C., et al. (2007). "Patient-reported outcomes helped predict survival in multiple myeloma using partial least squares analysis." Journal of Clinical Epidemiology 60(7): 670-679.e3.	Population out of scope
Yucel, E., Sully, K., Trigg, A., et al. (2019). "A mixed methods approach to generate meaningful change estimates for the EORTC QLQ-MY20." Quality of Life Research 28(SUPPL 1): S28.	Population out of scope
Acaster, S., Gaugris, S., Velikova, G., et al. (2013). "Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: A UK cross-sectional survey." Supportive Care in Cancer 21(2): 599-607.	Population out of scope
Aoki, N., Moore, E., Wellard, C., et al. (2020). "Real-world treatment patterns and clinical outcomes in multiple myeloma in the asiapacific region: Preliminary results of the asia-pacific myeloma and related diseases registry." HemaSphere 4: 923-924.	Population out of scope
De La Rubia, J., Domingo, A., Delgado, O., et al. (2020). "Assessment of disease burden in terms of health-related quality of life in patients with multiple myeloma not eligible for asct in spain: Update of the qolmmbus study." HemaSphere 4: 469-470.	Outcomes out of scope
Dold, S.M., Zober, A., Ihorst, G., et al. (2016). "Prospective comorbidity and functional geriatric assessment (CF-GA) in multiple Myeloma (MM) patients (pts): Results from a multicenter German study group MM (DSMM) trial." Oncology Research and Treatment 39: 159.	Outcomes out of scope
Dold, S.M., Zober, A., Pantic, M., et al. (2016). "Prospective comorbidity and functional geriatric assessment (CF-GA) in multiple myeloma (MM) patients (PTS): Results from a multicenter german study group mm (DSMM) trial." Haematologica 101: 257-258.	Outcomes out of scope
Engelhardt, M., Ihorst, G., Singh, M., et al. (2020). "Health-related quality of life (HRQOL) reported by patients with multiple myeloma (MM) in Germany." Oncology Research and Treatment 43: 157.	Outcomes out of scope
Espinoza-Zamora, J.R., Portilla-Espinosa, C.M., Labardini-Méndez, J.R., et al. (2015). "Quality of life in multiple myeloma: clinical validation of the Mexican-Spanish version of the QLQ-MY20 instrument." Annals of Hematology.	Population out of scope
Gimsing, P., Carlson, K., Turesson, I., et al. (2010). "Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial." Lancet Oncol 11(10): 973-82.	Population out of scope
Gulbrandsen, N., Hjermstad, M.J. and Wisløff, F. (2004). "Interpretation of quality of life scores in multiple myeloma by comparison with a reference population and assessment of the clinical importance of score differences." European Journal of Haematology 72(3): 172-180.	Outcomes out of scope
Husson, O., Oerlemans, S., Mols, F., et al. (2013). "Satisfaction with information is associated with baseline and follow-up quality of life among lymphoma and multiple myeloma survivors: Results from the profiles registry." Supportive Care in Cancer 21: S37-S38.	Population out of scope
Jordan, K., Proskorovsky, I., Lewis, P., et al. (2014). "Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of	Population out of scope

Citation	Exclusion reason
life in patients with multiple myeloma: Results of a European, multicenter cohort study." Supportive Care in Cancer 22(2): 417-426.	
Kharroubi, S.A., Edlin, R., Meads, D., et al. (2015). "Use of Bayesian Markov chain Monte Carlo methods to estimate EQ-5D utility scores from EORTC QLQ data in myeloma for use in cost-effectiveness analysis." Medical decision making : an international journal of the Society for Medical Decision Making 35(3): 351-360.	Population out of scope
Kvam, A.K., Fayers, P.M. and Wisloff, F. (2011). "Responsiveness and minimal important score differences in quality-of-life questionnaires: A comparison of the EORTC QLQ-C30 cancer-specific questionnaire to the generic utility questionnaires EQ-5D and 15D in patients with multiple myeloma." European Journal of Haematology 87(4): 330-337.	Population out of scope
Kvam, A.K., Wisløff, F. and Fayers, P.M. (2010). "Minimal important differences and response shift in health-related quality of life; a longitudinal study in patients with multiple myeloma." Health and Quality of Life Outcomes 8.	Population out of scope
Laribi, K., Rodon, P., Kfoury, E., et al. (2018). "Evaluating the correlation between fatigue and quality of life in patients with hematological malignancies and treated with biosimilar epoetin alfa for chemotherapy induced anemia: The ciroco study." HemaSphere 2: 302.	Outcomes out of scope
Larsen, R.F., Jarden, M., Minet, L.R., et al. (2020). "Exercise in newly diagnosed patients with multiple myeloma-a randomised, controlled trial of effects on physical function, physical activity, pain and quality of life." HemaSphere 4: 808-809.	Outcomes out of scope
Manda, S., Yimer, H.A., Girnius, S.K., et al. (2020). "Long-term proteasome inhibition in multiple myeloma (MM) following an in-class transition from bortezomib (BTZ) to ixazomib (IXA): Updated realworld (RW) data from the us MM-6 community-based study." HemaSphere 4: 127.	Outcomes out of scope
Mendoza, T.R., Dueck, A.C., Shi, Q., et al. (2015). "The significant contribution of pain in determining the health status of patients with multiple myeloma (MM)." Blood 126(23): 4495.	Outcomes out of scope
Mols, F., Oerlemans, S., Vos, A.H., et al. (2012). "Multiple myeloma survivors experience a low quality of life and many diseasespecific complaints: Results from a prospective population-based study." Psycho-Oncology 21: 25-26.	Population out of scope
Proskorovsky, I., Lewis, P., Williams, C.D., et al. (2014). "Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma." Health and Quality of Life Outcomes 12(1).	Population out of scope
Ramsenthaler, C., Osborne, T.R., Gao, W., et al. (2016). "The impact of disease-related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: A multi-centre study." BMC Cancer 16(1).	Population out of scope
Rowen, D., Brazier, J., Young, T., et al. (2011). "Deriving a preference-based measure for cancer using the EORTC QLQ-C30." Value in Health 14(5): 721-731.	Outcomes out of scope
Sevindik, O.G., Alacacioglu, I., Payzin, K.B., et al. (2015). "Quality of life in multiple myeloma: Validation of the Turkish version of the Qlq-My20 instrument." Clinical Lymphoma, Myeloma and Leukemia 15: e202.	Outcomes out of scope
Sidi Mohamed El Amine, B., Asma, H., Fouzia, O., et al. (2017). "Quality of life and symptom burden in patients with multiple myeloma." Haematologica 102: 843.	Population out of scope
Stewart, A.K., Jacobus, S., Fonseca, R., et al. (2015). "Melphalan, prednisone, and thalidomide vs. melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma." Blood 126(11): 1294-1301.	Outcomes out of scope
Sztankay, M., Neppl, L., Wintner, L., et al. (2018). "Complementing clinical cancer registries with patientreported outcome data-a feasibility study on routine ePRO assessment for the Austrian Myeloma Registry." Quality of Life Research 27: S101.	Outcomes out of scope
Toomey, K., Durie, B.G., Rifkin, R.M., et al. (2012). "Variation of health-related quality of life by gender among patients newly diagnosed with multiple myeloma." Supportive Care in Cancer 20: S264-S265.	Outcomes out of scope

Citation	Exclusion reason
Tu, H., Zhang, L., Ding, L., et al. (2018). "Effect of compound kushen injection on immune function for patients with newly diagnosed multiple myeloma undergoing chemotherapy." HemaSphere 2: 970-971.	Outcomes out of scope
Verelst, S.G., Termorshuizen, F., Uyl-de Groot, C.A., et al. (2011). "Effect of thalidomide with melphalan and prednisone on healthrelated quality of life (HRQoL) in elderly patients with newly diagnosed multiple myeloma: a prospective analysis in a randomised trial." Ann Hematol 90(12): 1427-39.	Outcomes out of scope
Versteegh, M.M., Leunis, A., Luime, J.J., et al. (2012). "Mapping QLQ-C30, HAQ, and MSIS-29 on EQ-5D." Medical decision making : an international journal of the Society for Medical Decision Making 32(4): 554-568.	Outcomes out of scope
Wagner, L.I., Toomey, K., Ailawadhi, S., et al. (2020). "Clinical outcomes and health-related quality of life (HRQoL) among randomised clinical trial (RCT)-eligible and RCT-ineligible patients: Results from the Connect® MM registry." HemaSphere 4: 460461.	Outcomes out of scope
Wang, S.T., Huang, H., Ba-Mancini, A., et al. (2010). "The cost-effectiveness of bortezomib plus melphalan and prednisone versus lenalidomide plus melphalan and prednisone with continuous lenalidomide maintenance treatment for the initial treatment of multiple myeloma in the United States." Blood 116(21).	Outcomes out of scope
Weger, R., Willenbacher, W., Loth, F., et al. (2016). "“Routine assessment of patient-reported outcomes (PROs) in patients with multiple myeloma” An analysis of the Austrian Myeloma Registry (AMR)." Oncology Research and Treatment 39: 159.	Outcomes out of scope
Wisloff, F. and Gulbrandsen, N. (2000). "Health-related quality of life and patients' perceptions in interferon-treated multiple myeloma patients." Acta Oncologica 39(7): 809-813.	Outcomes out of scope
Witherall, R., Garg, M. and Rennie, R. (2014). "Association of myeloma treatment on health outcomes following vertebroplasty: A pipe dream?" British Journal of Haematology 165: 51.	Study design out of scope

The utility estimates for pre- and post-progression health states are based on application of the Danish EQ-5D-5L tariffs to HRQoL measures of patients enrolled in the MMY3008 MAIA trial and are not based on estimates from the literature. Only disutilities associated with adverse events identified in the literature are used in the model. There is no particular concern that the disutilities associated with specific adverse events would be significantly different amongst the Danish population.

20.3 Quality assessment and generalizability of estimates

To evaluate the quality of the seven studies included in the review, the assessment criteria for individual HUSV studies outlined by the NICE Decision Support Unit was used [251]. A comparative overview of the quality of each study is presented below in Table 112.

Table 112. Quality assessment of individual health-related quality of life studies

Study name	Sample size	Respondent selection and recruitment	Response rate to instruments	Loss to follow-up	Missing data
Delforge 2015					
Rowen 2012					
Young 2015					
Usmani 2015					

Study name	Sample size	Respondent selection and recruitment	Response rate to instruments	Loss to follow-up	Missing data
Picot 2011					
Blommestein 2016					
Hatswell 2016					
Hatswell 2017					
Lu 2019					
Cao 2021					
Penaloza-Ramos 2020					
PBS Revlimid 2019 08					
NICE TA587					
NICE TA228					
SMC 1096/15					

Green – satisfactory; Yellow – interpret with caution; Red – not satisfactory; Grey – Not adequately reported.

20.4 Unpublished data

The only unpublished HRQoL data used in this analysis are the MMY3008 MAIA trial's Danish EQ-5D-5L utilities, which are discussed in Appendix I – Mapping of HRQoL data.

21 Appendix I – Mapping of HRQoL data

21.1 Objective

Utility analyses used in the cost-effectiveness model were done for the intent-to-treat (ITT) population using the February 2021 data cut of the MAIA (MMY3008, NCT02252172) trial.

The analyses consisted of descriptive statistics, a repeated-measures linear mixed-effects regression model to estimate pre-progression utility, and a linear regression model to estimate post-progression utility.

21.2 Description of Instruments

The MAIA trial collected patient-reported outcomes using the EQ-5D-5L instrument. The EQ-5D-5L is a five-item questionnaire that assesses five domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression plus a visual analogue scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the five separate questions are categorical and are cannot be analysed as cardinal numbers. However, the scores for the five dimensions are used to compute a single utility score ranging from -0.758 to 1 representing the general health status of the individual. A value of 0 is equivalent to death, negative values represent a health status worse than death, and 1 is equivalent to a perfect health state.

EQ-5D-5L assessments were made at the following time points per the MAIA clinical protocol: at baseline, every three months for the first 12 months, and every six months thereafter while on treatment and progression-free as well as post-PD week 8, and post-PD week 16.

21.3 Analysis methods

21.3.1 Deriving health utility scores

The Danish EQ-5D-5L value set used to analyse the trial's health utility scores was sourced from Jensen et al. 2021[6] hybrid model. If one or more questions were not answered on the five dimensions of the EQ-5D, the health utility score was set to missing.

21.3.2 Missing data

If subjects were missing an EQ-5D score at any timepoint in the study, the missing value was removed from the analyses. No imputation was performed for missing utility data.

21.3.3 Descriptive analyses

The number of observations with non-missing utility values and the distribution of observed utility values (i.e., mean, mean standard error, standard deviation, median, interquartile range, minimum, and maximum) were summarized by scheduled visits and by treatment arm. Observations that were not mapped to any scheduled visit were not considered.

21.3.4 Pre-progression utility

Pre-progression utility was defined as the average utility for subjects before the date of progression based on a computerized algorithm. Average utility was calculated using a repeated-measures linear mixed-effects model. A subject random intercept was used to account for repeated measures of individuals over multiple cycles before progression.

All post-baseline observations before the date of progression were used in these analyses regardless of whether they were per-protocol scheduled or unscheduled visits.

As the aim of this analysis was to derive an equation to be used in the economic analysis, only predictors that were relevant for the economic model were considered. Covariates to identify utility increment were:

- Treatment arm: daratumumab, lenalidomide, and dexamethasone (Dara+Rd) vs. lenalidomide and dexamethasone (Rd)
- Baseline utility
- Time in weeks (log-scale)

The decision to include time in a log-scale was made to capture the initial rapid increase in utility that slows down over time.

[6] Jensen, Cathrine Elgaard, et al. "The Danish EQ-5D-5L value set: a hybrid model using cTTO and DCE data." Applied Health Economics and Health Policy 19.4 (2021): 579-591.

21.3.5 Post-progression utility

For patients who progressed and whose progression was not death, post-progression utility was defined as the average utility at the date of confirmed progression based on computerized algorithm or after.

All post-progression observations before the date of confirmed progression were used in these analyses regardless of whether they were per-protocol scheduled or unscheduled visits.

Similar as pre-progression analyses, a subject random intercept was used to account for repeated measures of individuals over multiple cycles and post-PD assessments.

Given the limited number of subjects and post-PD assessments only treatment arm was considered as a potential covariate.

21.4 Statistical analysis

21.4.1 Patient characteristics of analysis data sets

The characteristics of patients having at least a baseline EQ-5D for the overall population is presented in Table 113. Patient characteristics are comparable for the ITT data set and those with baseline EQ-5D-5L.

Table 113. Baseline characteristics of analysis sets

	ITT set		Baseline EQ-5D data subset	
Baseline Characteristic	**Dara+Rd**	**Rd**	**Dara+Rd**	**Rd**
N	368	369	349	347
Age - Median (Range)	73 (50, 89)	74 (45, 89)	73 (50, 89)	74 (45, 89)
Age < 65 – n (%)	4 (1.1)	4 (1.1)	4 (1.1)	4 (1.2)
Age 65 to 74 – n (%)	204 (55.4)	204 (55.3)	193 (55.3)	189 (54.5)
Age ≥ 75 – n (%)	160 (43.5)	161 (43.6)	152 (43.6)	154 (44.4)
Race				
White	336 (91.3)	339 (91.9)	318 (91.1)	320 (92.2)
Black	12 (3.3)	16 (4.3)	12 (3.4)	14 (4)
Asian	3 (0.8)	2 (0.5)	3 (0.9)	2 (0.6)
Other*	17 (4.6)	12 (3.3)	16 (4.6)	11 (3.2)
ECOG = 0 – n (%)	127 (34.5)	123 (33.3)	123 (35.2)	120 (34.6)
ECOG = 1 – n (%)	178 (48.4)	187 (50.7)	167 (47.9)	171 (49.3)
ECOG = 2 – n (%)	62 (16.8)	58 (15.7)	58 (16.6)	55 (15.9)
ISS stage I – n (%)	103 (28)	105 (28.5)	101 (28.9)	102 (29.4)
ISS stage II – n (%)	157 (42.7)	155 (42)	148 (42.4)	143 (41.2)
ISS stage III – n (%)	108 (29.3)	109 (29.5)	100 (28.7)	102 (29.4)
Cytogenic Risk				
Standard	271 (73.6)	279 (75.6)	258 (73.9)	259 (74.6)
High	48 (13)	44 (11.9)	44 (12.6)	44 (12.7)

*Other category includes the following race categories: “Other”, “Unknown”, “Not Reported” and “Multiple”

Abbreviations: Dara+Rd = daratumumab, lenalidomide, and dexamethasone; ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; ITT = intent-to-treat; Rd = lenalidomide and dexamethasone

21.5 Summary of results

[redacted]

Table 114. Mean utility at baseline and pre/post-progression [1]

[redacted]

[redacted]

Table 115. Descriptive utility over scheduled visits [1]

[redacted]

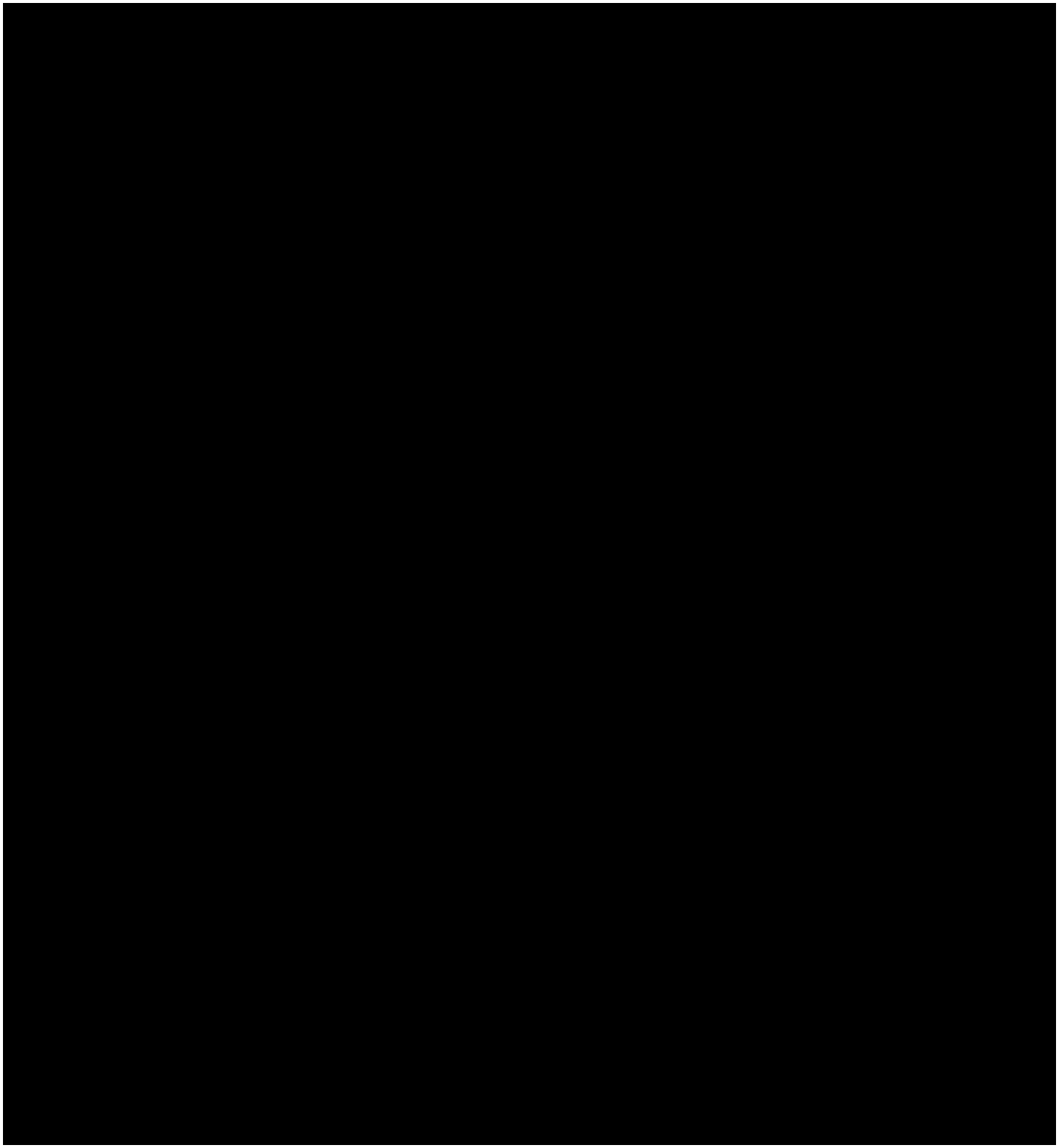


Figure 71. EQ-5D-5L Utility Score Over Scheduled Visits

21.5.1 Pre-progression utility

Table 116. Pre-progression utility with no coefficient

Table 117. Pre-progression utility with treatment arm as coefficient

[redacted]

[redacted]

Table 118. Pre-progression utility – time-dependent

[redacted]

21.5.2 Post-progression utility

[redacted]

Table 119. Post-progression utility with no coefficient

[redacted]

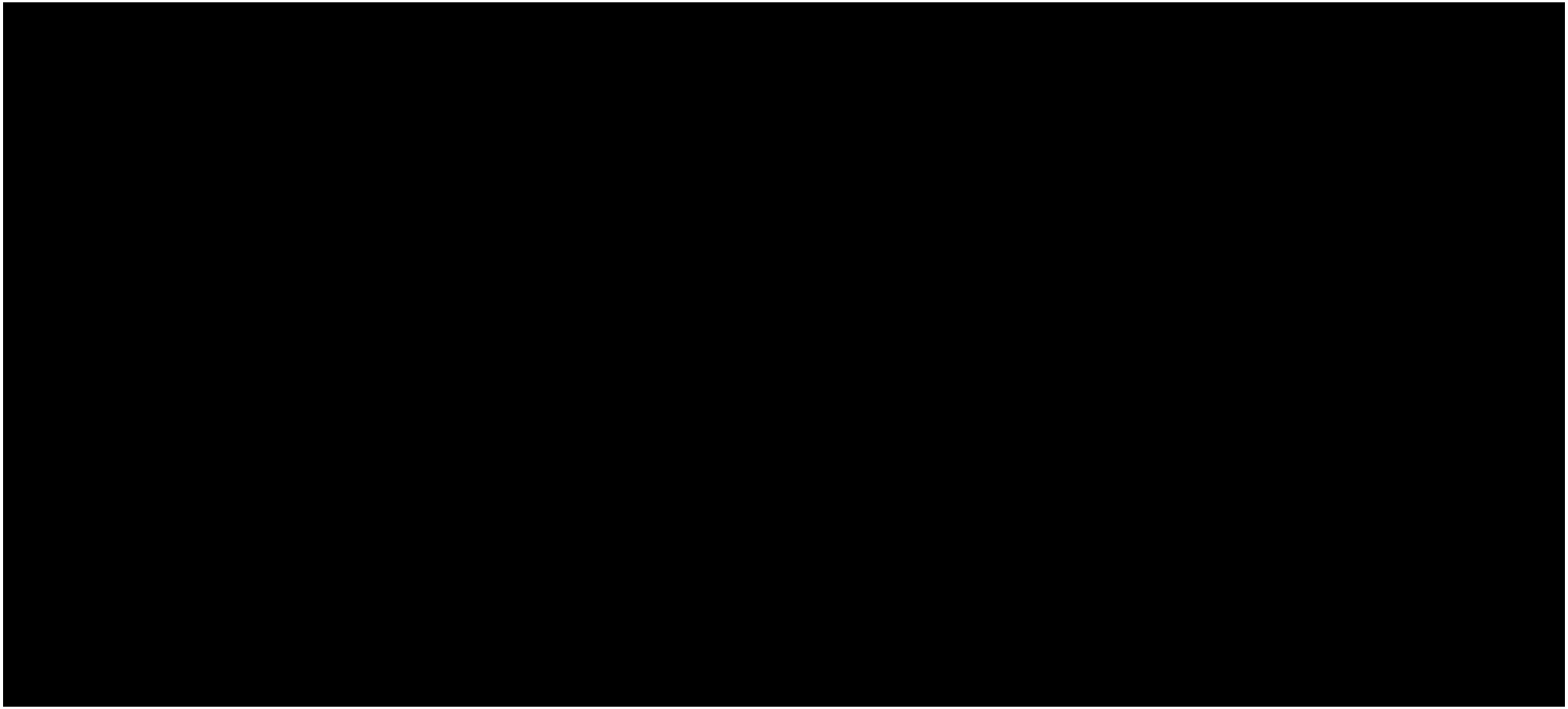
[redacted]

Table 120. Post-progression utility with treatment arm as coefficient

22 Appendix J – Probabilistic sensitivity analyses

All model parameters used to inform the probabalistic sensitivity analysis (PSA) are found in the "*Parameters*" sheet in the model. All parameters included in the PSA, their numerical values, lower- and upper CE value, distribution type and standard error are presented in Table 121.

Table 121. List of model parameters and parameter values included in the probabilistic sensitivity analysis



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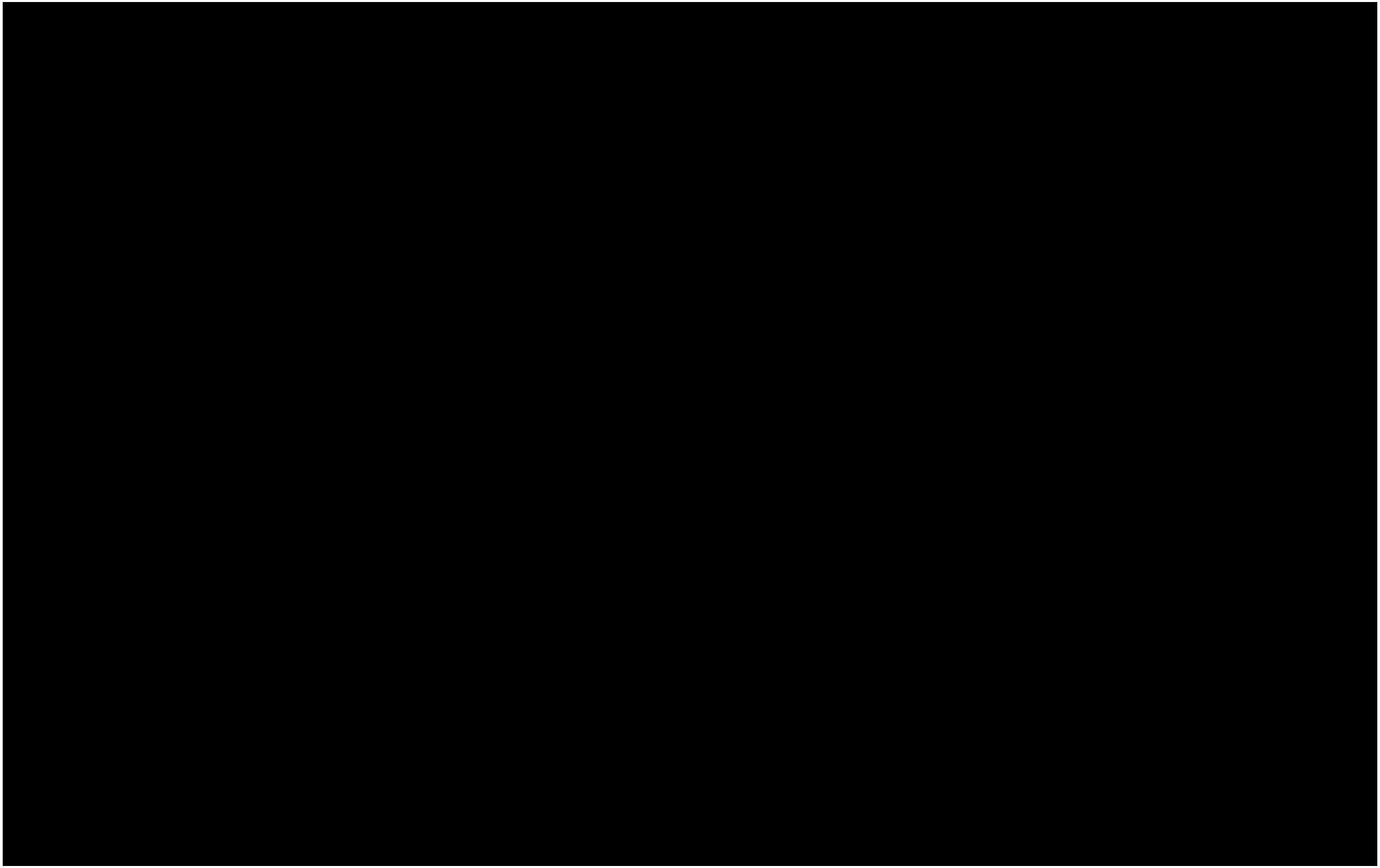

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Figure 72. PSA Scatter Plot vs. Rd

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Figure 73. PSA Scatter Plot vs. VRd

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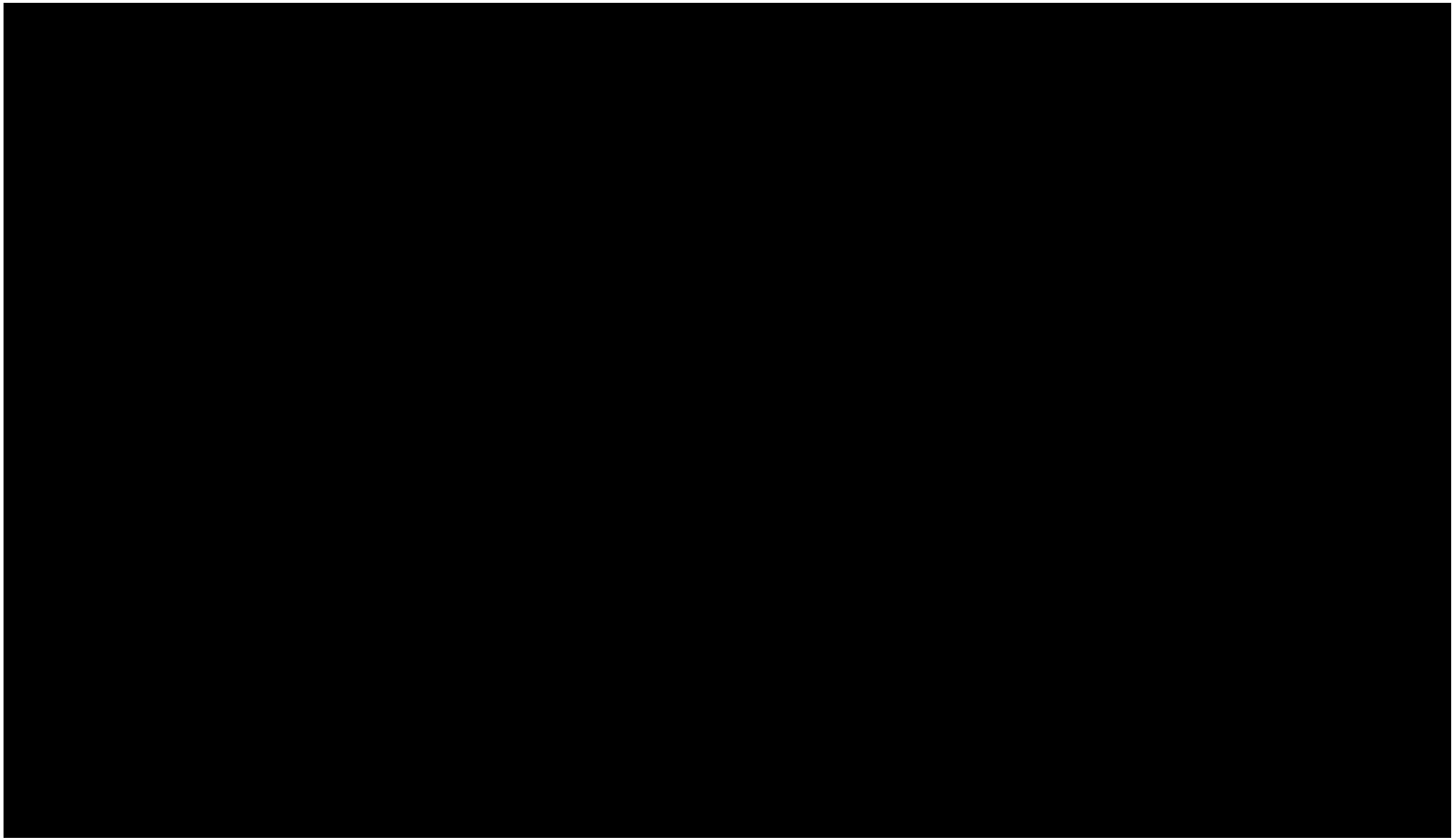
Figure 74. PSA Scatter Plot vs. VMP



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23 Appendix K – Deterministic sensitivity analyses

Figure 75. DSA results (Dara+Rd vs. Rd)

Figure 76. DSA results (Dara+Rd vs. VRd)

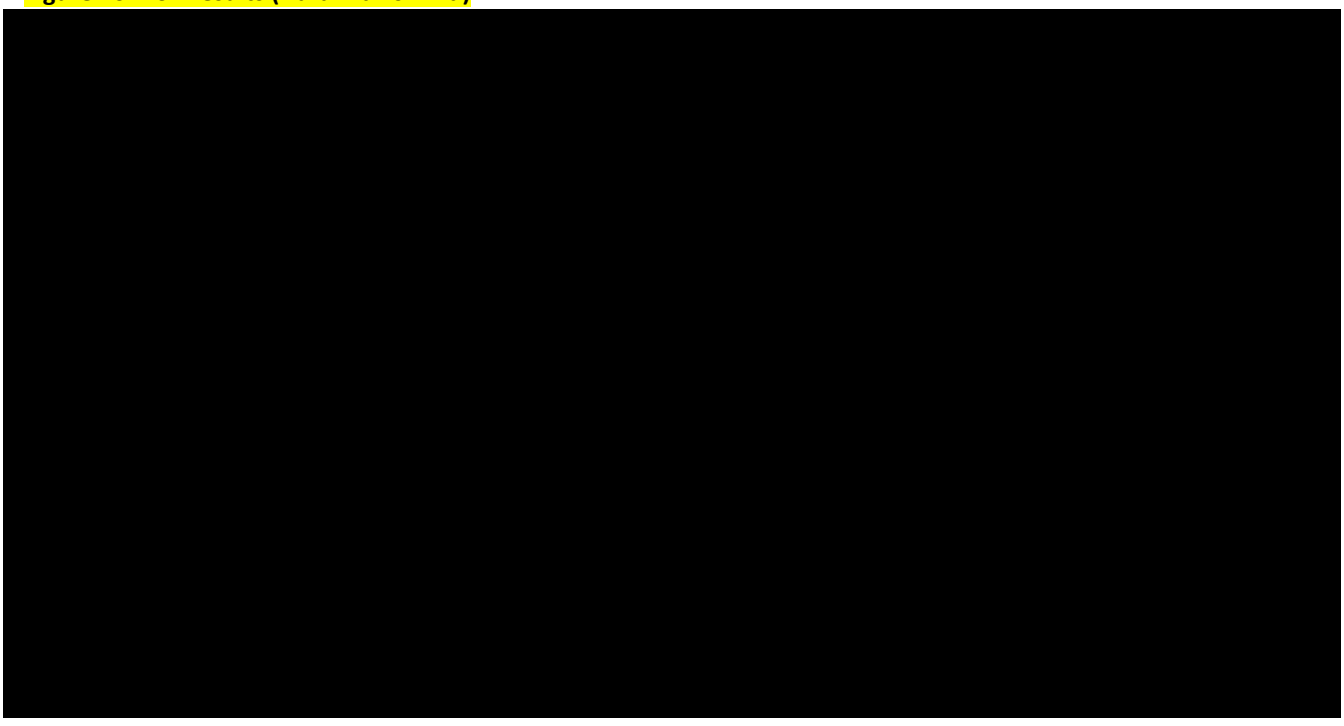

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Figure 77. DSA results (Dara+Rd vs. VMP)

24 Appendix L – Dosing schedules of subsequent treatments

Table 122. Summary of Subsequent Treatment Regimen Dosing (Part 1)

Treatment Regimens		Dose/Admin	Admin/Cycle	Cycle Length (days)	Relative Dose Intensity	Source
Carfilzomib+Dexamethasone						
Carfilzomib	Cycle 1 (Days 1 & 2)	20 mg/m^2	2	7	93.80%*	ENDEAVOR study, Dimopoulos et al. 2016 [137]
	Cycle 1 (post Days 1 & 2)	56 mg/m^2	4	21	93.80%*	
	Cycles 2+	56 mg/m^2	6	28	93.80%*	
Dexamethasone	All cycles	20 mg/m^2	8	28	87.25%†	
Carfilzomib+Rd						
Carfilzomib	Cycle 1 (Days 1 & 2)	20 mg/m^2	2	7	96.63%‡	ASPIRE study, Stewart et al. 2015 [135]
	Cycle 1 (post Days 1 & 2)	27 mg/m^2	4	21	96.63%‡	
	Cycles 2–12	27 mg/m^2	6	28	96.63%‡	
	Cycles 13–18	27 mg/m^2	4	28	96.63%‡	
Lenalidomide	All cycles	25 mg	21	28	73.60%¶	
Dexamethasone	All cycles	40 mg	4	28	99.80%¥	
CVD						
Cyclophosphamide	Cycles 1–8	50 mg	21	21	93.80%*	

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Treatment Regimens		Dose/Admin	Admin/Cycle	Cycle Length (days)	Relative Dose Intensity	Source
Cyclophosphamide	Cycles 9–11	50 mg	35	35	93.80%*	Kropff, et al. 2007 [139]
Bortezomib	Cycles 1–8	1.3 mg/m^2	4	21	81.70%¶	
Bortezomib	Cycles 9–11	1.3 mg/m^2	4	35	81.70%¶	
Dexamethasone	Cycles 1–8	20 mg	8	21	87.25%†	
Dexamethasone	Cycles 9-11	20 mg	8	35	87.25%†	
Daratumumab						
Daratumumab	Cycles 1–2	1800 mg	4	28	95.22%	MMY2002 [157]
	Cycles 3–6	1800 mg	2	28	95.22%	
	Cycles 7+	1800 mg	1	28	95.22%	
Dara+Rd						
Daratumumab	Cycles 1–2	1800 mg	4	28	96.63%	MMY3003 [137]
	Cycles 3–6	1800 mg	2	28	96.63%	
	Cycles 7+	1800 mg	1	28	96.63%	
Lenalidomide	All cycles	25 mg	21	28	73.60%	
Dexamethasone	All cycles	40 mg	4	28	99.08%	

*Assumed the same as daratumumab in Dara+Vd; †Assumed the same as dexamethasone in Dara+Vd; ‡ Assumed the same as daratumumab in Dara+Rd; ₸ Assumed the same as lenalidomide in Dara+Rd; ¥ Assumed the same as dexamethasone in Dara+Rd; ¶ Assumed the same as bortezomib in Dara+Vd. Abbreviations: CVD = cyclophosphamide, bortezomib, and dexamethasone; Dara+Rd = daratumumab in combination with lenalidomide and dexamethasone; Rd = lenalidomide and dexamethasone

Table 123. Summary of Subsequent Treatment Regimen Dosing (Part 2)

Treatment Regimens		Dose/ Admin	Admin/Cycle	Cycle Length (days)	Relative Dose Intensity	Source
Dara+Vd						
Daratumumab	Cycles 1–3	1800 mg	3	21	93.80%	MMY3004 [138]
	Cycles 4–8	1800 mg	1	21	93.80%	
	Cycles 9+	1800 mg	1	28	93.80%	
Bortezomib	Cycles 1–8	1.3 mg/m^2	4	21	81.70%	
Dexamethasone	Cycles 1–8	20 mg	8	21	87.25%	
Elotuzumab+Rd						
Elotuzumab	Cycles 1–2	10 mg/kg	4	28	96.63%	ELOQUENT-2 study, Lonial 2015 [140]
	Cycles 3+	10 mg/kg	2	28	96.63%	
Lenalidomide	All Cycles	25 mg	21	28	73.60%	
Dexamethasone	All Cycles (elotuzumab weeks)	28 mg	4	28	99.08%	
		8 mg	4	28	99.08%	
Dexamethasone	All Cycles	40 mg	4	28	99.08%	

Treatment Regimens		Dose/ Admin	Admin/Cycle	Cycle Length (days)	Relative Dose Intensity	Source
	(non-elotuzumab weeks)					
Elotuzumab+Vd						
Elotuzumab	Cycles 1–2	10 mg/kg	3	21	93.80%*	Palumbo et al. 2015 [252]
	Cycles 3–8	10 mg/kg	2	21	93.80%*	
	Cycles 9+	10 mg/kg	2	28	93.80%*	
Bortezomib	Cycles 1–8	1.3 mg/m^2	4	21	81.70%¶	
	Cycles 9+	1.3 mg/m^2	3	28	81.70%¶	
Dexamethasone	Cycles 1–8 (elotuzumab weeks)	28 mg	4	21	87.25%†	
		8 mg	4	21	87.25%†	
	Cycles 1–8 (non-elotuzumab weeks)	20 mg	4	21	87.25%†	
	Cycles 9+ (elotuzumab weeks)	28 mg	4	28	87.25%†	
		8 mg	4	28	87.25%†	
	Cycles 9+ (non-elotuzumab weeks)	20 mg	4	28	87.25%†	
Ixazomib+Rd						
Ixazomib	All cycles	4 mg	3	28	96.63%‡	TOURMALINE study, Moreau et al. 2016 [142]
Lenalidomide	All cycles	25 mg	21	28	73.60%₸	
Dexamethasone	All cycles	40 mg	4	28	99.08%¥	

*Assumed the same as daratumumab in Dara+Vd; †Assumed the same as dexamethasone in Dara+Vd; ‡ Assumed the same as daratumumab in Dara+Rd; ₸ Assumed the same as lenalidomide in Dara+Rd; ¥ Assumed the same as dexamethasone in Dara+Rd; ¶ Assumed the same as bortezomib in Dara+Vd

Abbreviations: Dara+Vd = daratumumab in combination with bortezomib, dexamethasone; Rd = lenalidomide and dexamethasone; Vd = bortezomib and dexamethasone

Table 124. Summary of Subsequent Treatment Regimen Dosing (Part 3)

Treatment Regimens		Dose/Admin	Admin/Cycle	Cycle Length (days)	Relative Dose Intensity	Source
Panobinostat+Vd						
Panobinostat	Cycles 1–8	20 mg	6	21	93.80%*	

Treatment Regimens		Dose/Admin	Admin/Cycle	Cycle Length (days)	Relative Dose Intensity	Source
	Cycles 9–12	20 mg	12	42	93.80%*	PANORAMA1 study, San Miguel et al. 2014 [143]
Bortezomib	Cycles 1–8	1.3 mg/m^2	4	21	81.70%¶	
	Cycles 9–12	1.3 mg/m^2	4	42	81.70%¶	
Dexamethasone	Cycles 1–8	20 mg	8	21	87.25%†	
	Cycles 9–12	20 mg	8	42	87.25%†	
Pomalidomide+Dexamethasone						
Pomalidomide	All cycles	4 mg	21	28	96.63%‡	Weisel, et al. 2013 [253]
Dexamethasone (aged ≤75)	All cycles	40 mg	4	28	99.08%¥	
Dexamethasone (aged >75)	All cycles	20 mg	4	28	99.08%¥	
Rd						
Lenalidomide	All cycles	25 mg	21	28	85.02%	MMY3003 [137]
Dexamethasone	Cycles 1–4	40 mg	12	28	99.38%	
	Cycles 5+	40 mg	4	28	99.38%	
Td						
Thalidomide	Cycles 1–4	200 mg	28	28	85.02%§	Nordic Myeloma study, Hjorth, et al. 2012 [145]
Dexamethasone	Cycles 1–4	40 mg	4	21	99.38%Ⱦ	
Vd						
Bortezomib	Cycles 1–8	1.3 mg/m^2	4	21	87.18%	MMY3004 [138]
Dexamethasone	Cycles 1–8	20 mg	8	21	90.94%	
VTD						
Bortezomib	Cycles 1–8	1.3 mg/m^2	4	21	81.70%¶	MMVAR-velcade, Garderet, et al. 2012 [146]
Bortezomib	Cycles 9–12	1.3 mg/m^2	4	42	81.70%¶	
Thalidomide	Cycles 1–16	200 mg	21	21	93.80%*	
Dexamethasone	Cycles 1–16	40 mg	4	21	87.25%†	

*Assumed the same as daratumumab in Dara+Vd; †Assumed the same as dexamethasone in Dara+Vd; ‡ Assumed the same as daratumumab in Dara+Rd; Ⱦ Assumed the same as lenalidomide in Dara+Rd; ¥ Assumed the same as dexamethasone in Dara+Rd; ¶ Assumed the same as bortezomib in Dara+Vd; § Assumed the same as lenalidomide in Rd; Ⱦ Assumed the same as dexamethasone in Rd

Abbreviation: Rd = lenalidomide and dexamethasone; Td = thalidomide and dexamethasone; Vd = bortezomib and dexamethasone; VTD = bortezomib, thalidomide, and dexamethasone

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